

# Electroencephalographic Alpha Measures Predict Therapeutic Response to a Selective Serotonin Reuptake Inhibitor Antidepressant: Pre- and Post-Treatment Findings

Gerard E. Bruder, James P. Sedoruk, Jonathan W. Stewart, Patrick J. McGrath, Frederic M. Quitkin, and Craig E. Tenke

**Background:** There is growing evidence that individual differences among depressed patients on electrophysiologic (EEG), neuroimaging, and neurocognitive measures are predictive of therapeutic response to antidepressant drugs. This study replicates prior findings of pretreatment differences between selective serotonin reuptake inhibitor (SSRI) responders and nonresponders in EEG alpha power or asymmetry and examines whether these differences normalize or are stable after treatment.

**Methods:** Resting EEG (eyes open and closed) was recorded from 28 electrodes (nose reference) in 18 depressed patients when off medication and at the end of 12 weeks of fluoxetine treatment. Clinical response was assessed by an independent rater with the Clinical Global Impression Improvement scale. The EEG data were also obtained for 18 healthy adults matched to patients in gender and age.

**Results:** Treatment responders had greater alpha power compared with nonresponders and healthy control subjects, with largest differences at occipital sites where alpha was largest. There were also differences in alpha asymmetry between responders and nonresponders at occipital sites. Responders showed greater alpha (less activity) over right than left hemisphere, whereas nonresponders tended to show the opposite asymmetry. Neither alpha power nor asymmetry changed after treatment, and test-retest correlations were high, particularly for alpha power. Alpha power and asymmetry showed reasonable positive predictive value but less negative predictive value.

**Conclusions:** The findings confirm reports of alpha differences between antidepressant responders and nonresponders and raise hopes for developing EEG tests for selecting effective treatments for patients. The stability of alpha power and asymmetry differences between SSRI responders and nonresponders after treatment suggests that they represent state-independent characteristics.

**Key Words:** Alpha power, depression, EEG, hemispheric asymmetry, SSRI

An abundance of antidepressant drugs with distinct pharmacologic profiles are available for treating depression, and yet clinicians have no way of knowing whether a patient will benefit from a specific medication. Studies using neuroimaging (1–4), neurocognitive (5–7), and electrophysiologic (8–12) measures have found that pretreatment differences among depressed patients are related to subsequent clinical response to antidepressant drugs.

The ability of quantitative electroencephalographic (qEEG) measures of “spontaneous” brain electrical activity in a resting state to predict response to a selective serotonin reuptake inhibitor (SSRI) or other antidepressant drugs has been suggested in several studies. Ulrich *et al.* (13) found increased posterior alpha in patients who eventually responded to amitriptyline, suggesting that there might be two subtypes of depression having different pathophysiology and antidepressant response. Prichep *et al.* (14) similarly found evidence for two subgroups of

patients having an obsessive-compulsive disorder; one with relative excess of alpha responded well to an SSRI, and one with increased relative theta showed little treatment response. Knott *et al.* (15) found that depressed patients who responded to imipramine showed a trend for more alpha but had significantly less theta compared with nonresponders. Cook *et al.* (16) did not find pretreatment differences between fluoxetine responders and nonresponders in theta but did find group differences in “cordance,” a measure based on a form of surface Laplacian (see [17] for methodological issues). We found a difference in alpha asymmetry between fluoxetine responders and nonresponders (8), which was predicted on the basis of dichotic listening findings (18). Fluoxetine nonresponders showed greater alpha power (less activity) over the left hemisphere than the right, whereas responders tended to have the opposite asymmetry. Two studies have used tomographic (LORETA) analyses to infer theta current density in specific brain regions. Pizzagalli *et al.* (12) localized pretreatment theta increases to rostral anterior cingulate cortex (ACC) in responders to nortriptyline. Similarly, Mulert *et al.* (19) reported that depressed patients responding to either citalopram or reboxetine had increased pretreatment activity localizable to rostral ACC. These findings suggest that pretreatment alpha or theta measures might be of value as predictors of clinical response to SSRI or other antidepressant drugs.

The EEG in healthy adults has high test-retest reliability for power in the alpha and theta bands (20), whereas it is somewhat lower for alpha asymmetry (21). Less is known about stability of qEEG in depressed patients during treatment with antidepressant drugs. Studies have reported changes in qEEG after acute administration of antidepressant drugs and suggested that they

From the Department of Psychiatry (GEB, JWS, PJM, FMQ, CET), College of Physicians and Surgeons of Columbia University; and Division of Cognitive Neuroscience (GEB, JPS, CET) and Depression Evaluation Service (JWS, PJM, FMQ), New York State Psychiatric Institute, New York, New York.

Address reprint requests to Gerard E. Bruder, Ph.D., Division of Cognitive Neuroscience, 1051 Riverside Drive, New York, NY 10032; E-mail: [bruder@pi.cpmc.columbia.edu](mailto:bruder@pi.cpmc.columbia.edu).

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might be of value for identifying patients who are most likely to benefit from treatment. Knott *et al.* (15) found that depressed patients who responded to 2 weeks of imipramine treatment differed from nonresponders in showing acute increases in theta 3 hours after a test dose as well as an increase in frontal theta 2 weeks after treatment. In contrast, Cook *et al.* (9) measured qEEG during treatment with fluoxetine or venlafaxine and found no difference between responders and nonresponders in either baseline or acute change in theta power. Patients who responded to 8 weeks of treatment did show an acute decrease in prefrontal “cordance” after 48 hours and 1 week of treatment. Fewer studies have examined longer-term effects of treatments on qEEG. Knott *et al.* (22) reported that male depressed patients showed a decrease in alpha power and an increase in relative theta/delta after 6 weeks of treatment with the SSRI paroxetine. Deldin and Chiu (23) did not find changes in alpha power or asymmetry in depressed patients after a cognitive intervention to improve mood.

The present study measured resting EEG in a new sample of depressed patients before and after 12 weeks of treatment with the SSRI fluoxetine. The purpose was twofold: 1) to replicate prior findings of pretreatment differences in alpha power and asymmetry between SSRI responders and nonresponders as well as to examine differences in their theta power. We hypothesized that responders would differ from nonresponders in showing greater alpha power and the opposite alpha asymmetry; and 2) to determine whether pretreatment differences between responders and nonresponders normalize during treatment or are stable, state-independent characteristics.

## Methods and Materials

### Subjects

Outpatients between the ages of 20 and 56 attending a university-affiliated depression research clinic were included. Patients were excluded for any of the following reasons: serious suicide risk, seizure disorder, mental disorders secondary to a general medical condition, substance use disorders (including alcohol abuse) within the last 6 months, psychotic disorders, history of significant head trauma, or other neurologic disorder. All patients signed informed consent forms before participating in the study. All aspects of their diagnostic assessment and treatment were carried out by research psychiatrists.

The EEG was obtained for 18 depressed patients at baseline and again after 12 weeks of open treatment with fluoxetine. All but one patient were treated as part of a clinical trial in which they received 10 mg of fluoxetine during week 1, 20 mg during weeks 2–4, and 40 mg during weeks 5–8, and if still no response, a further increase to 60 mg was permitted during weeks 9–12. Dose increases after week 2 were optional, on the basis of clinical response and tolerability of medication. The end dose of fluoxetine at week 12 was 60 mg—except for 2 patients whose end dose was 40 mg (one treatment responder and one nonresponder). The remaining patient was tested before receiving a 6-week single-blind placebo period and, after not responding to placebo, received 12 weeks of fluoxetine treatment beginning at 20 mg and increasing biweekly up to a final dose of 60 mg. A clinician, blind to the patient's EEG data, rated each patient at the end of 12 weeks of treatment with the Clinical Global Impression Improvement scale (CGI-I) (24). Patients who had a CGI-I rating of “much or very much” improved were considered to be responders, and all other patients were considered as nonresponders. A 21-item Hamilton Depression scale (HAM-D<sub>21</sub>) (25)

**Table 1.** Characteristics of Treatment Responders, Nonresponders, and Healthy Control Subjects

	Responders	Nonresponders	Control Subjects
Gender			
M/F	7/4	6/1	13/5
Age (yrs)			
Mean	38.0	33.7	31.7
SD	9.4	9.7	7.6
Education (yrs) <sup>a</sup>			
Mean	16.5	13.4	15.5
SD	2.6	1.6	1.8
Handedness (Laterality Quotient)			
Mean	61.8	19.7	72.9
SD	64.5	91.1	19.9
Pre-treatment HAM-D			
M	19.0	19.7	
SD	2.1	6.6	
Post-Treatment HAM-D <sup>b</sup>			
Mean	5.4	15.4	
SD	2.5	8.6	

<sup>a</sup>*n* = 10 for responders. Significant difference among groups in education [ $F(2,32) = 4.27, p < .05$ ]. Newman-Keuls post hoc test, nonresponders < responders = control subjects.

<sup>b</sup>Responders differ significantly from nonresponders in post-treatment Hamilton Depression scale (HAM-D) [ $t(16) = 3.57, p < .01$ ].

was obtained before and during treatment. The EEG was also obtained for 18 right-handed healthy adults matched to the depressed patients in gender and age. They were screened to exclude those having current or past Axis I psychopathology, substance abuse, history of significant head trauma, and neurological disorders.

Table 1 gives the characteristics of the responders, nonresponders, and healthy control subjects. These groups did not differ significantly in gender or age, but nonresponders had somewhat less education than responders and healthy control subjects ( $p < .05$ ). Education was not, however, significantly associated with alpha power ( $r = .11, ns$ ) or asymmetry ( $r = .32, ns$ ). Also, group differences in alpha power and asymmetry reported in the following text remained the same when education was included as a covariate. The groups did not differ significantly in handedness, as indicated by their laterality quotient (LQ) on the Edinburgh Inventory (26). Two responders and three nonresponders were left-handed, and the remaining patients and control subjects were right-handed (LQ > 0). Handedness LQ scores were not significantly associated with either alpha power ( $r = .07, ns$ ) or asymmetry ( $r = -.22, ns$ ). There was no difference between responders and nonresponders in pretreatment severity of depression on the HAM-D<sub>21</sub>. After treatment, responders had markedly lower HAM-D<sub>21</sub> scores than nonresponders [ $t(16) = 3.57, p < .01$ ] and were essentially in remission (i.e., all had HAM-D<sub>21</sub> score  $\leq 7$  except for one patient who had a score of 8). Among responders, eight met DSM-IV criteria for major depressive disorder (MDD), two for both MDD plus dysthymia, and one for dysthymia with past MDD. Among nonresponders, six met criteria for MDD and one for MDD plus dysthymia. Three responders also met DSM-IV criteria for an anxiety disorder (one social phobia, one panic disorder, and one obsessive-compulsive disorder). Two nonresponders met criteria for panic disorder.

## Procedures

Patients were initially tested during a baseline session after being unmedicated for a minimum of 7 days (6 weeks if receiving fluoxetine), but most patients were drug-free for considerably longer. Four responders and four nonresponders were not previously treated with an antidepressant, and three responders and two nonresponders had not received an antidepressant for over 8 months. All patients were retested at the end of the 12th week of fluoxetine treatment with the same procedures as the baseline session. Resting EEG was recorded while subjects sat quietly in a sound-attenuated booth. The EEGs were recorded during four 2-min periods, one-half with eyes open (O), and one-half with eyes closed (C), in a counterbalanced order (OCCO or COOC). Subjects were instructed to remain still and avoid blinks or eye movements during the recording period. During the O condition, subjects fixated on a central cross.

## Electrophysiologic Recording

Scalp EEG was recorded with a 30-channel electrode cap (Electro Cap International, Eaton, Ohio) with a nose reference. Ag/AgCl electrodes (Grass, West Warwick, Rhode Island) at supra- and infraorbital sites surrounding the right eye were used to monitor eye blinks and vertical eye movements (bipolar), and electrodes at right and left outer canthi monitored horizontal eye movements (bipolar). All electrode impedances were below 5 kilo-ohms ( $k\Omega$ ). The EEG was recorded through a Grass Neurodata acquisition system at a gain of 10,000 (5000 and 2000 for horizontal and vertical eye channels), with a bandpass of .1–30 Hz. A PC-based EEG acquisition system (NeuroScan, Sterling, Virginia) acquired and digitized the data continuously at 200 samples/sec over each recording period.

## Electrophysiologic Analyses

Data were segmented into consecutive 1.28-sec epochs (50% overlap), yielding a frequency resolution of .78 Hz. Epochs contaminated by blinks, eye movements, and movement-related artifacts were excluded from analyses by direct visual inspection of the raw data. The DC offset of each epoch was then removed, and the EEG was tapered over the entire 1.28 sec with a Hanning window to suppress spectral side lobes (27). By overlapping epochs by 50%, the attenuated data are restored in the adjacent record, preserving data with minimal redundancy. The EEG data were subjected to a power spectrum analysis with a Fast-Fourier Transform. At each electrode, alpha power was averaged for artifact-free epochs spanning each recording period for each subject and subsequently integrated over 7.8–12.5 Hz. Common logarithms of alpha power were computed to normalize the data. Secondary analyses also examined group differences in theta power (4–7 Hz). There was a difference among groups in total number of minutes of artifact-free EEG data [ $F(2,33) = 3.31, p < .05$ ]. Normal control subjects (mean =  $3.4 \pm 1.1$ ) had fewer minutes of EEG than responders (mean =  $4.8 \pm 2.1; p < .05$ ), but there was no significant difference between responders and nonresponders (mean =  $4.3 \pm 1.0$ ). However, number of minutes of EEG was not significantly related to either alpha power ( $r = .22, ns$ ) or asymmetry ( $r = -.14, ns$ ).

## Statistical Analyses

Analyses focused on alpha because of its inverse relation to cortical activity (28) and prior findings of differences between antidepressant responders and nonresponders. Previous EEG studies have indicated the importance of regional (e.g., anterior versus posterior) and hemispheric (left versus right) differences

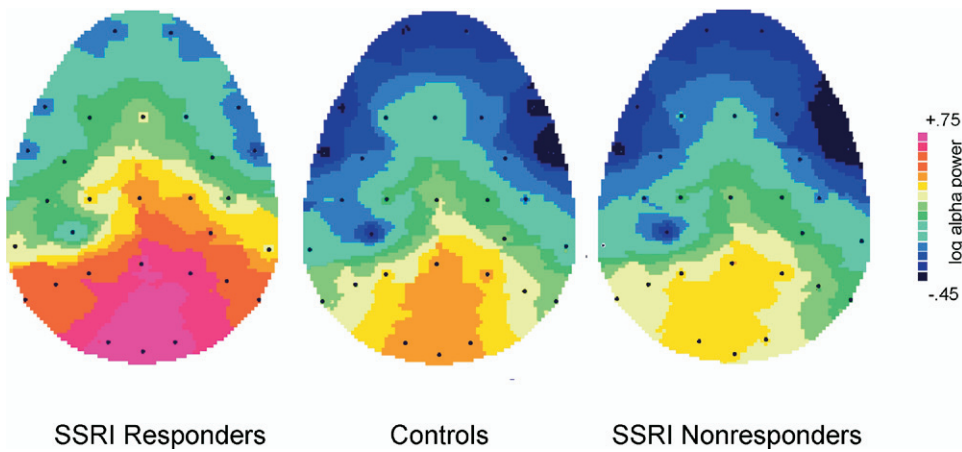
when comparing alpha in depressed and nondepressed subjects. To examine these regional differences, log alpha power during pretreatment session was computed at medial sites over each hemisphere at frontal (left, F3; right, F4), central (C3; C4), parietal (P3; P4), and occipital (O1; O2) regions. These topographic measures were then used as orthogonal factors in a repeated-measures analysis of variance (ANOVA), with three within-subject factors, Hemisphere (left, right), Region (F, C, P, O), and Condition (eyes open, eyes closed); and one between-subjects factor, Group (responder, nonresponder, control subjects). The sources of significant interactions were further examined by analysis of simple effects. The  $F$  ratios were evaluated with degrees of freedom computed with the Greenhouse–Geisser  $\epsilon$  correction (29) where appropriate to counteract heterogeneity of variance–covariance matrices associated with repeated measures. The same ANOVA model was also used to examine theta power. To determine whether pretreatment differences in alpha between responders and nonresponders remained stable or changed after fluoxetine treatment, a repeated-measures ANOVA was performed on log alpha power at occipital sites, where pretreatment differences were maximal. This ANOVA used three within-subject factors, Hemisphere (left, right), Condition (eyes open, eyes closed), and session (pretreatment, fluoxetine); and one between-subjects factor, Group (responder, nonresponder).

## Results

### Pretreatment Session in Responders, Nonresponders, and Control Subjects

There was a difference in overall alpha power among groups [ $F(2,33) = 3.19, p = .05$ ], with responders having significantly greater alpha when compared with control subjects ( $p = .02$ ). The enhanced alpha in responders was most evident at posterior sites where alpha is typically largest (Figure 1). When separately examined at frontal, central, parietal, and occipital regions, the difference in alpha among groups was significant only at occipital sites [ $F(2,33) = 3.51, p = .04$ ]. Responders had significantly greater alpha when compared with control subjects ( $p = .02$ ) at occipital sites and also tended to have greater alpha than nonresponders ( $p = .06$ ) (Figure 2, top). Although only approaching a conventional level of significance, the alpha difference between responders and nonresponders had a relatively large effect size of .98. There was also a trend for the predicted difference in alpha asymmetry among groups at occipital sites [Group  $\times$  Hemisphere interaction,  $F(2,33) = 2.68, p = .08$ ]. Responders differed significantly from nonresponders in alpha asymmetry ( $p = .02$ ), with responders showing greater alpha (less activity) over right than left occipital sites and nonresponders tending to show the opposite asymmetry (Figure 2, bottom). Healthy control subjects had essentially no alpha asymmetry and did not differ significantly from either patient group.

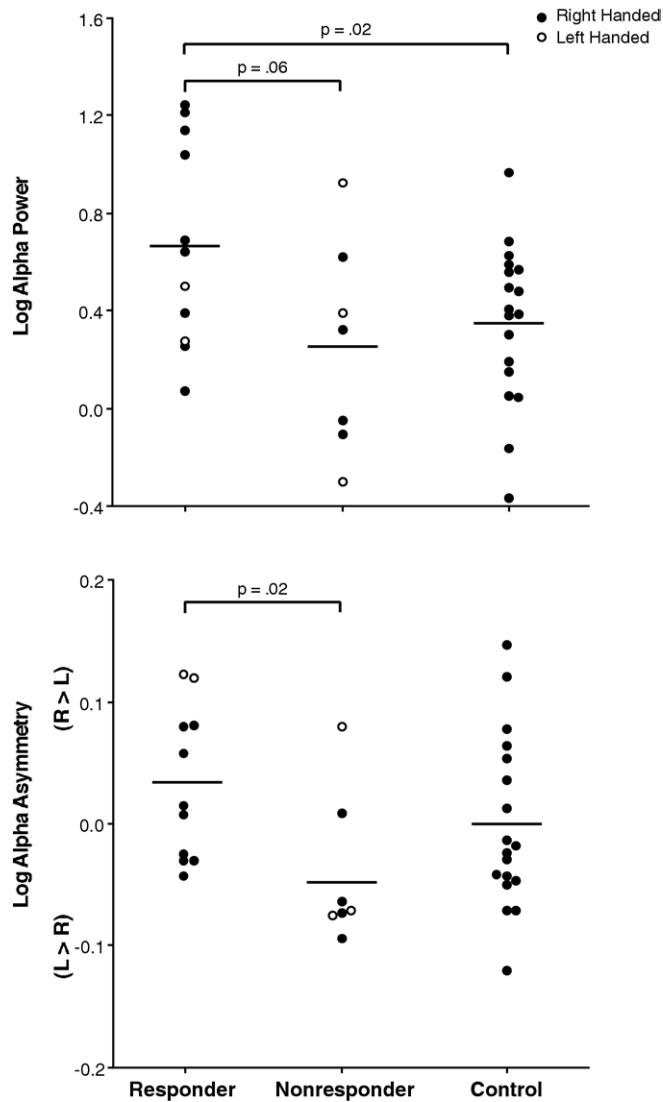
There was also a difference among the responder, nonresponder, and control groups in theta power at occipital sites [ $F(2,33) = 3.26, p = .05$ ]. Responders had greater theta power (mean =  $.29 \pm .22$ ) when compared with control subjects (mean =  $.13 \pm .18; p = .02$ ), whereas nonresponders (mean =  $.25 \pm .20$ ) did not differ significantly from the other groups. The difference in theta between responders and control subjects was also significant at the midline occipital site ( $p = .02$ ) but not at other midline sites. Although there was a difference in theta across left and right occipital sites [ $F(1,33) = 6.88, p = .01$ ], there was no significant group difference in the theta asymmetry.



**Figure 1.** Topography of pretreatment alpha power for responders, nonresponders, and healthy control subjects, illustrating that group differences in alpha are most evident over posterior sites (bottom portion of maps). SSRI, selective serotonin reuptake inhibitor.

**Pretreatment Versus Fluoxetine Treatment Sessions in Responders and Nonresponders**

At occipital sites, where group differences in alpha were most evident, responders tended to have greater alpha power than

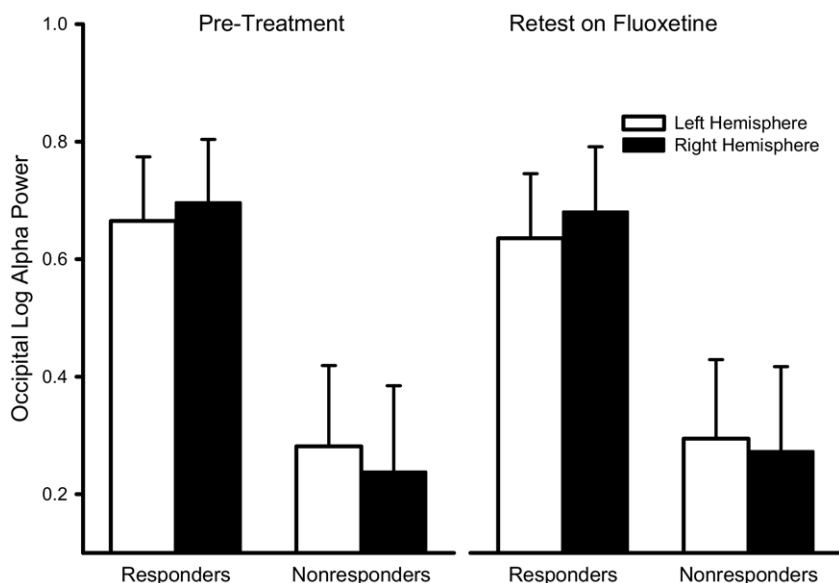


**Figure 2.** Log alpha power and asymmetry for the responders, nonresponders, and healthy control subjects.

nonresponders across the pre- and post-treatment sessions [Figure 3;  $F(1,16) = 3.85, p = .07$ ]. There was no significant change in alpha power across sessions, and the difference in alpha between responders and nonresponders did not change (i.e., no Group  $\times$  Session interaction). There was a Group  $\times$  Hemisphere interaction [ $F(1,16) = 6.66, p = .02$ ], with responders showing greater alpha (less activity) over right than left occipital site [ $F(1,16) = 5.09, p = .04$ ] and nonresponders showing a nonsignificant asymmetry in opposite direction. This group difference in occipital asymmetry did not change across sessions, which is indicated by the lack of a Group  $\times$  Hemisphere  $\times$  Session interaction. There was a significant group difference in occipital alpha asymmetry in both pretreatment [ $F(1,16) = 6.16, p = .02$ ] and fluoxetine treatment [ $F(1,16) = 5.83, p = .03$ ] sessions. Test-retest correlations confirmed that alpha power was extremely stable across pretreatment and fluoxetine treatment sessions, ranging from  $r = .92$  at frontal to  $r = .97$  at occipital sites. Test-retest correlations were lower for alpha asymmetry, being  $r = .63$  at frontal,  $r = .56$  at central,  $r = .73$  at parietal, and  $r = .86$  at occipital sites.

**Prediction of Treatment Response**

We examined the value of alpha power and asymmetry at occipital sites for predicting treatment response. As in our prior studies, we used the mean asymmetry for healthy control subjects (Figure 2) as a cut-off to divide patients into those having alpha asymmetry  $>$  normal (predicted to be responders) or  $<$  normal (predicted to be nonresponders). Similarly, we used mean alpha power for healthy control subjects as a cut-off for dividing patients into those with  $>$  or  $<$  normal alpha. Indices evaluating predictions of treatment response are given in Table 2. Both alpha power and asymmetry showed reasonable positive predictive value (i.e., response rate of 72.7% and 77.8%, respectively, for patients predicted to be responders) but less negative predictive value (i.e., nonresponse rate of 57.1% and 55.6%, respectively, for patients who were predicted to be nonresponders). Although alpha power and asymmetry were positively correlated ( $r = .34, p = .04$ ), the small magnitude of this correlation suggests that each provides somewhat independent information for predicting treatment response. Therefore we evaluated whether combined use of both would improve the predictive value. In two-thirds of the patients, there was agreement as to the prediction of treatment response across the alpha power and asymmetry measures (i.e., both above versus below normal). In these cases, using agreement across measures improved the sensitivity and negative predictive value to 83.3% and 80.0%, respectively.



**Figure 3.** Mean log alpha power over right and left hemisphere for responders and nonresponders before treatment and after 12 weeks on fluoxetine (bars = SEs).

### Right-Handed Responders, Nonresponders, and Control Subjects

Although there were too few left-handed patients to allow meaningful conclusions as to the impact of handedness (Figure 2), a comparison was made of the data for only right-handed responders, nonresponders, and control subjects. Overall, all findings reported for the full samples were as strong or stronger for right-handers only. Thus, there was a significant difference among groups in alpha power [ $F(2,28) = 5.50, p < .01$ ], with responders having greater alpha when compared with both nonresponders ( $p = .04$ ) and control subjects ( $p < .01$ ). Group differences in alpha were present at only occipital sites [Figure 2, top;  $F(2,28) = 4.56, p = .02$ ], where responders had greater alpha than nonresponders ( $p = .05$ ) and control subjects ( $p = .02$ ). At these sites, responders also differed from nonresponders in alpha asymmetry [Figure 2, bottom;  $F(1,11) = 5.65, p = .04$ ]. At occipital sites, the same group difference in theta power evident for the full samples was seen for right-handers [ $F(2,28) = 3.54, p = .04$ ]. Responders had greater theta than control subjects ( $p = .01$ ) but did not differ significantly from nonresponders.

### Discussion

Patients who responded to fluoxetine had greater EEG alpha when compared with healthy control subjects, whereas nonre-

**Table 2.** Indices Evaluating Predictions of Response With Log Alpha Power and Log Alpha Asymmetry at Occipital Sites

	Alpha Power	Alpha Asymmetry	Combined
Sensitivity <sup>a</sup>	72.7	63.6	83.3
Specificity <sup>b</sup>	57.5	71.4	67.7
Positive Predictive Value <sup>c</sup>	72.7	77.8	71.4
Negative Predictive Value <sup>d</sup>	57.1	55.6	80.0

<sup>a</sup>Sensitivity = percentage of responders who were predicted to be responders.

<sup>b</sup>Specificity = percentage of nonresponders who were predicted to be nonresponders.

<sup>c</sup>Positive predictive value = response rate for patients who were predicted to be responders.

<sup>d</sup>Negative predictive value = nonresponse rate for patients who were predicted to be nonresponders.

sponders did not differ from control subjects. An excess of alpha has previously been reported for patients having an obsessive-compulsive disorder who responded to an SSRI (14) and in affectively disordered patients who responded to treatment with an antidepressant or secondary treatment with an anticonvulsant or lithium (13,30). Early studies of resting EEG reported finding greater alpha with eyes closed in depressed patients when compared with control subjects (31,32). Given the inverse relation of alpha power and cortical activity, increased alpha was viewed as evidence of reduced activity in depressed patients. Our findings indicate that this reduced cortical activity is evident in a subgroup of depressed patients who respond to an SSRI and is a predictor of those who most benefit from this treatment. This might not, however, be specific to SSRI antidepressant drugs, in that depressed patients who responded to tricyclic antidepressant drugs also showed increased alpha (13,15). In contrast, decreased alpha has been found to be predictive of improvement in mood after cognitive restructuring (23). The increase in occipital power in fluoxetine responders was also found in the theta band, which suggests that this qEEG difference is not specific to alpha but includes somewhat lower frequencies as well. It is noteworthy that a distinct spectral component with a peak that spans both the alpha and theta bands is identifiable in the resting EEG with a reference-free approach (17).

The SSRI responders also differed from nonresponders in their alpha asymmetry, which is in accord with our prior findings (8). At occipital sites, where alpha is largest, responders showed an asymmetry indicative of greater activity over left than right hemisphere, whereas nonresponders had the opposite direction of asymmetry. The favoring of left over right hemisphere activity in responders is the asymmetry seen for patients having a "pure" MDD in EEG studies (33,34) and SSRI responders in dichotic listening studies (5). Although the specificity of the posterior alpha asymmetry to SSRI responders is unknown, alpha asymmetry at frontal but not posterior sites predicted mood improvement after cognitive restructuring (23). In the present study, frontal alpha asymmetry did not differ between fluoxetine responders and nonresponders.

Neither alpha power nor asymmetry changed after 12 weeks of treatment with fluoxetine. The extremely high test-retest correlations for alpha power in depressed patients ( $r \geq .90$ ) are

comparable to those previously reported for healthy adults for retest periods over 1 year, and twin studies indicate that alpha power is a stable, heritable trait (20). Elevated alpha power has been found in recovered depressed patients in a euthymic state, which led Pollock and Schneider (35) to hypothesize that it reflects a trait difference in a subgroup of depressed patients. Our findings suggest that this trait is present in patients who respond favorably to an SSRI.

Although there was no significant change in alpha asymmetry after 12 weeks of treatment, test-retest correlations were lower than that seen for alpha power but were still moderately high ( $r = .56-.86$ ), particularly at occipital sites. Test-retest correlations in healthy adults are also lower for alpha asymmetry than alpha power, with about 60% of the variance of alpha asymmetry attributed to a temporally stable trait (21). The alpha asymmetry in SSRI responders at occipital sites has been found in depressed adolescents and adults (33,34,36,37), in remitted depressed patients (38), and in offspring of parents concordant for MDD who have increased risk for developing a depressive disorder (39). This alpha asymmetry might therefore be a trait marker of vulnerability to a familial form of depression that responds to an SSRI.

It is known that serotonergic activity is closely related to arousal. In an awake state, serotonergic cells in raphé nuclei display a constant pattern of discharge that decreases in firing rate as arousal decreases to a sleep state (40). We hypothesize that increased alpha in depressed patients who respond to an SSRI reflects low arousal associated with low serotonergic activity. Evidence for the role of right temporoparietal and subcortical regions in mediating arousal (41,42) suggests a possible mechanism that could account not only for increased alpha in SSRI responders but also their alpha asymmetry. Heller *et al.* (42) presented a model suggesting that depression is related to dysfunction of right temporoparietal mechanisms mediating emotional arousal. Thus, low serotonergic activity, presumably related to reduced activity of mesencephalic raphé nuclei and cortical afferents, could play a role in both the increased alpha and alpha asymmetry in SSRI responders.

A question remains as to why clinical improvement in SSRI responders did not normalize their alpha. Although a common serotonergic mechanism might underlie both depression and EEG abnormalities in responders, they need not have the same pharmacological properties. A preclinical study (43) found that spontaneous firing of serotonin neurons in dorsal raphé of rats was not altered after 2 weeks of escitalopram administration, whereas combined treatment with this SSRI plus bupropion resulted in a marked increase in firing rates. Moreover, persistence of alpha abnormalities in treatment responders is compatible with their being an endophenotypic marker of vulnerability to MDD (39).

This study has limitations. First, the sample of SSRI nonresponders was small ( $n = 7$ ). It was, however, larger in our prior study (8), and the difference in alpha asymmetry between fluoxetine responders ( $n = 34$ ) and nonresponders ( $n = 19$ ) was the same as the present study. Also, heightened alpha in responders ( $n = 11$ ) was seen not only when compared with nonresponders but also compared with healthy control subjects ( $n = 18$ ). The stability of differences between responders and nonresponders across pre- and post-treatment sessions also increases confidence in the findings. A second limitation is that patients in this study were predominately men, which might raise a question as to whether findings generalize to women. The number of women was larger in our prior studies (5,8), and the

difference in hemispheric asymmetry between responders and nonresponders was even stronger among women than men. Third, the EEG findings were obtained during open-label treatment, and placebo effects are unknown. In a study in which a placebo control group was included (44), we found no difference between placebo responders and nonresponders in hemispheric asymmetry for dichotic listening. Last, although differences between responders and nonresponders in alpha power and asymmetry seem to represent stable, state-independent traits, their biological basis is unknown. An ongoing study is using a high-density electrode array and current source density measures (17) to provide spatial resolution to more adequately address the neuroanatomical origin of these differences. Studies are also needed to determine their relation to genetic and neurochemical mechanisms that might underlie responsiveness to antidepressant drugs. The findings do raise hopes for developing qEEG tests for selecting effective treatments for depressed patients.

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