Electroencephalographic and Perceptual Asymmetry Differences between Responders and Nonresponders to an SSRI Antidepressant

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Background: *Recent reports suggest the value of electroencephalographic and dichotic listening measures as predictors of response to antidepressants. This study examines the potential of electroencephalographic alpha asymmetry and dichotic measures of perceptual asymmetry as predictors of clinical response to 12 weeks of treatment with fluoxetine (Prozac).*

Methods: *Resting electroencephalography (eyes open and eyes closed) and dichotic listening with word or complex tone stimuli were assessed in depressed outpatients during a pretreatment period.*

Results: *Fluoxetine responders (*n *= 34) differed from nonresponders (*n *= 19) in favoring left over right hemisphere processing of dichotic stimuli. They also differed in their resting electroencephalographic alpha asymmetry, particularly in the eyes open condition. Nonresponders showed an alpha asymmetry indicative of overall greater activation of the right hemisphere than the left, whereas responders did not. The relationship between hemispheric asymmetry and treatment response interacted with gender, being evident among depressed women but not men.*

Conclusions: *The results are consistent with the hypothesis that a characteristic tendency toward greater left than right hemisphere activation is associated with favorable response to fluoxetine, whereas the opposite hemispheric asymmetry predicts poor response.* Biol Psychiatry 2001; 49:416–425 © *2001 Society of Biological Psychiatry*

Key Words: Depression, electroencephalograph, dichotic listening, antidepressant, SSRI, treatment response

Introduction

Selective serotonin reuptake inhibitors (SSRIs) are the most frequently prescribed antidepressant medications, and yet, they are effective in less than two thirds of depressed patients. The reason why they work in some patients but not in others is poorly understood, and there are no clinical predictors of whether or not patients will benefit from an SSRI. Although some studies have reported evidence of biological predictors of response to antidepressants (Figueras et al 1999; Ko et al 1997), there are no established markers available for clinical use. Studies using neuroimaging (Baxter et al 1989; George et al 1994), electrophysiologic measures (Bruder et al 1997a; Henriques and Davidson 1991), and behavioral laterality tests (Bruder 1995) indicate that asymmetric activation of right-left brain regions plays a role in depressive disorders. There have also been recent reports suggesting the potential value of these measures as predictors of response to treatments for depression (Bruder et al 1999; Ketter et al 1999).

Individual differences among depressed patients on dichotic listening tests of brain laterality and on electroencephalographic (EEG) measures have been found to be related to antidepressant response (for a review, see Bruder et al 1999). In dichotic listening tests, different words, syllables, or tones are simultaneously presented to the two ears and the difference in accuracy for reporting right and left ear items provides a measure of perceptual asymmetry (PA). In a collaborative study of the SSRI fluoxetine (Prozac), unmedicated depressed patients who subsequently responded to fluoxetine had a greater right ear (left hemisphere) advantage for dichotic words and less left ear (right hemisphere) advantage for complex tones when compared with treatment nonresponders (Bruder et al 1996). There were no changes in PAs following treatment, which suggests that these differences between fluoxetine responders and nonresponders represent stable, state-independent characteristics. These findings support the hypothesis that a characteristic tendency

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for relatively greater left than right hemisphere activation during dichotic listening is associated with better outcome of treatment with fluoxetine.

Electroencephalographic studies of regional hemispheric activity in depressed patients have focused on measures of alpha power because of its inverse relation to cortical activation (Shagass 1972). Studies measuring resting EEG have found greater alpha power over left frontal sites than over right in unipolar major depression (Bell et al 1998; Henriques and Davidson 1991) and bipolar seasonal affective disorder (Allen et al 1993), which is indicative of relatively less left frontal activation or greater right frontal activation. There have, however, been some inconsistent findings concerning resting frontal alpha asymmetry in depression (e.g., Reid et al 1998), which may be related to methodological factors or the comorbidity and clinical heterogeneity typical of depressive disorders (Davidson 1998). Some studies have also found the opposite pattern of greater alpha power (less activation) over right parietal sites than over left in depressed patients (Bruder et al 1997a; Reid et al 1998) or previously depressed subjects (Henriques and Davidson 1990), whereas other studies have not found this posterior asymmetry in depressed subjects (Henriques and Davidson 1991; Schaffer et al 1983). Heller et al (1995) suggested that inconsistent findings for parietal alpha asymmetry may be due to the opposing effects of depression and anxious arousal on right parietotemporal activity. This is supported by the findings of Bruder et al (1997a), who compared the alpha asymmetry of depressed patients with or without a comorbid anxiety disorder. Patients having a "pure" major depression showed an alpha asymmetry indicative of less activation over right parietal sites than over left, whereas patients having a comorbid anxious depression showed evidence of greater activation over right frontal and parietal sites.

The above EEG studies suggest that depression is associated with reduced left frontal and right parietal activation. The presence of abnormal frontal and parietal alpha asymmetries in previously depressed patients supports the view that they represent state-independent markers of vulnerability to negative affect and depressive disorders (Henriques and Davidson 1990). There are, however, marked individual differences in alpha asymmetry among depressed patients, which appear to be related to their clinical features, including comorbidity and diagnostic subtype. In this study we examine whether or not individual differences in resting alpha asymmetry are related to outcome of treatment with an SSRI antidepressant. If the differences in PA observed between fluoxetine responders and nonresponders reflect characteristic, state-independent differences in regional hemispheric activation (Bruder et al 1996), one would predict that these subgroups would also differ in their resting alpha asymmetry patterns. Moreover, the PA scores for these patients should correlate with their alpha asymmetry (Davidson and Hugdahl 1996). To test these predictions, the depressed patients in this study were tested on both resting EEG and the dichotic listening tests used in our prior study.

A secondary purpose of this study was to begin to examine the possible role of gender in this context. The greater incidence of depression in women and gender differences in hemispheric asymmetries for cognitive processing underscore the importance of examining this variable (Heller 1993). Electroencephalographic studies of depression have primarily used female participants or have not examined gender differences in regional hemispheric asymmetries. In this study we examine whether gender is of importance when examining differences in hemispheric activation between fluoxetine responders and nonresponders.

Methods and Materials

Subjects

Patients between the ages of 18 and 65 who met DSM-IV criteria for major depression, dysthymia, or depression not otherwise specified were included in the study. Patients were excluded for any of the following reasons: serious suicide risk, seizure disorder, organic mental disorders, substance use disorders (including alcohol abuse) within the last 6 months, psychotic disorders, antisocial personality disorder, history of head trauma, or other neurologic disorder. In addition, patients were excluded from participation in the dichotic tests if they had a hearing loss greater than 30 dB in either ear at 500, 1000, or 2000 Hz or if they had an ear difference greater than 10 dB. All patients signed informed consent forms before participating in the study.

Electroencephalograms were recorded from 64 right-handed depressed outpatients who were attending a university-affiliated Depression Evaluation Service at the New York State Psychiatric Institute. All aspects of the diagnostic assessment and treatment of patients were carried out by research psychiatrists. The patients were participants in two ongoing treatment protocols. In one protocol, 37 patients were tested before receiving a 6-week single-blind placebo period and then received 12 weeks of treatment with fluoxetine. Only patients who were placebo nonresponders entered the fluoxetine treatment phase, which provides some control over nonspecific, placebo response. Seven patients who were tested at baseline and subsequently responded to placebos were not included in this report. Patients began fluoxetine treatment at 20 mg, and the dose was increased biweekly up to a maximum of 80 mg depending on clinical need and tolerance. In a second protocol, 27 patients were tested before receiving 12 weeks of fluoxetine treatment. There was no initial placebo period in this study and patients were aware of receiving active treatment during the 12-week period. Patients received 10 mg of fluoxetine during week 1, 20 mg during weeks 2–4, and 40 mg during weeks 5–8, and if there was still no

Table 1. Patient Characteristics

	Responders	Nonresponders
Gender		
F	21	7
M	13	12
Age (years)		
Mean	40.6	38.6
SD	13.5	13.4
Education (years)		
Mean	15.8	15.5
SD	1.9	2.6
Handedness (LQ)		
Mean	79.3	91.8
SD	24.4	12.0
Beck Depression Inventory		
Mean	20.6[a]	22.4
SD	8.1	9.3
Trait Anxiety Scale		
Mean	75.2[a]	73.9
SD	9.0	6.3
Anxious Arousal Scale		
Mean	27.0[b]	24.9[c]
SD	10.9	6.6

F, female; M, male; LQ, laterality quotient.
[a] $n = 33$.
[b] $n = 32$.
[c] $n = 17$.

response, a further increase to 60 mg was permitted during weeks 9–12. Patients who responded to open treatment were then randomized either to continue their dose of fluoxetine or to be switched to a placebo for a follow-up period of 24 weeks. Four patients who initially responded to fluoxetine but relapsed during the additional weeks of fluoxetine treatment were not included in this report because they were presumed to have had a nonspecific, "placebo" response. An independent evaluator, blind to the patient's EEG and dichotic listening data, rated each patient at the end of 12 weeks of treatment using the Clinical Global Impression Improvement (CGI-I) scale. Patients who had a CGI-I rating of "much improved" or "very much improved" were considered to be responders and all other patients were considered as nonresponders.[1]

Table 1 gives the characteristics of 34 patients who were classified as fluoxetine responders and the 19 patients who were nonresponders. There was a smaller proportion of females in the nonresponder group and gender was therefore entered as a variable in the statistical analyses. The responder and nonresponder groups did not differ significantly in age or education level. All patients in each group were right-handed, as indicated by their positive laterality quotient (LQ) on the Edinburgh Handedness Inventory (Oldfield 1971). There was no difference between responders and nonresponders in pretreatment scores on the Beck Depression Inventory (Beck et al 1961). Among responders, 24 met DSM-IV criteria for major depression, 15 met criteria for dysthymia, and five met criteria for depression not otherwise specified. Among nonresponders, 13 met criteria for major depression and eight met criteria for dysthymia. Two responders also met DSM-IV criteria for panic disorder and one for social phobia. One nonresponder met criteria for panic disorder, two for social phobia, and one for generalized anxiety disorder. Given evidence of the opposing effects of depression and anxiety or anxious arousal on parietal alpha asymmetry (Bruder et al 1997; Heller et al 1995), it is important to note that there was no significance difference between responders and nonresponders in pretreatment scores on the trait anxiety scale of the State-Trait Anxiety Inventory (Spielberger et al 1983) or on the anxious arousal scale of the Mood and Anxiety Symptom Questionnaire (Watson and Clark 1991).

[1] Data from two treatment protocols were combined so as to yield sufficient samples of female and male fluoxetine responders and nonresponders. With the exception of the initial placebo period in one study, the treatment protocols were comparable in terms of both fluoxetine doses and the raters evaluating treatment response. Most importantly, the differences between fluoxetine responders and nonresponders reported for the total samples were also evident when only the data for the placebo-controlled protocol were analyzed; however, the larger total sample allowed us to also take patient gender into account.

Procedures

Patients were tested during an initial drug-free period between a baseline evaluation and the beginning of the treatment protocol. This period was a minimum of 7 days, but most patients were drug free for a considerably longer period or were not previously treated with an antidepressant. No patient was tested within 6 weeks of receiving fluoxetine. Resting EEGs were recorded while subjects sat quietly in a sound-attenuated booth. For most patients, an EEG was recorded during two 3-min periods (eyes open and eyes closed), with the order of these conditions alternated across subjects. For eight patients (five responders and three nonresponders), EEGs were recorded during four 2-min periods, half with eyes open (O) and half with eyes closed (C) in a counterbalanced order (OCCO or COOC). Subjects were instructed to remain still and to avoid blinks or eye movements during the recording period. During the O condition, subjects fixated on a central cross. All but two patients were also tested on dichotic fused word and complex tone tests, with the order counterbalanced across patients.

Electrophysiologic Recording

Scalp EEGs were recorded from 13 lateral pairs of electrodes (Fp1, Fp2; F3, F4; F7, F8; FC5, FC6; FT9, FT10; C3, C4; T7, T8; CP5, CP6; TP9, TP10; P3, P4; P7, P8; P9, P10; O1, O2) using an electrode cap (Electro Cap International, Eaton, OH) with a nose reference. Ag/AgCl electrodes (Grass, West Warwick, RI) 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 KΩ. Electroencephalograms were recorded through a Grass Neurodata (West Warwick, RI) acquisition system at a gain of 10 K (5 K and 2 K for horizontal and vertical eye channels), with a bandpass of 0.01–30 Hz. A PC-based EEG acquisition system (NeuroScan, Sterling, VA) acquired and digitized the data continuously at 100 samples/sec over each eyes open and eyes closed recording period.

Electrophysiologic Analyses

Data were segmented into consecutive 1.28-sec epochs every 0.64 sec (50% overlap). 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 using a Hanning window to suppress spectral side lobes (Bendat and Piesol 1971). The Hanning window de-emphasizes data near the beginning and end of each epoch. By overlapping the epochs by 50% the attenuated data are restored in the record. This acts to preserve data and introduces minimal redundancy.

Electroencephalographic data were subjected to a power spectrum analysis using a Fast-Fourier Transform. Analyses focused on the alpha band because this is the band in which differences in hemispheric asymmetries have been found for depressed subjects (Bruder et al 1997a; Davidson et al 1987; Henriques and Davidson 1990, 1991). 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. Secondary analyses also examined whether group differences in alpha were evident in the low alpha (7.8–10 Hz) or high alpha (10–12.5 Hz) band. Common logarithms of alpha power were computed to normalize the data.

The total number of recording epochs entering into each average did not differ for the responder and nonresponder groups in the eyes open [$t(51) = 0.10$, ns] or eyes closed [$t(51) = 1.22$, ns] conditions. In the eyes open condition, the mean numbers of epochs were 172 (SD = 75) for responders and 174 (SD = 81) for nonresponders. In the eyes closed condition, the mean numbers of epochs were 150 (SD = 84) for responders and 123 (SD = 70) for nonresponders.

Dichotic Listening Tests

The Fused Rhymed Words Test (Wexler and Halwes 1983) consists of 15 different single-syllable word pairs in which each member of every pair differs from the other only in the initial consonant (e.g., *coat, goat*). All words begin with one of six stop consonants (*b, d, p, t, g, k*) and are natural speech spoken by a male voice. When presented dichotically, the members of each pair fuse into a single percept. Participants indicate what word they heard by marking a line through it on a prepared answer sheet that has four possible responses, both members of the dichotic pair and two other words differing from the dichotic stimuli only in the initial consonant. Following practice trials, each participant received four 30-item blocks for a total of 120 trials. Orientation of headphones was reversed after the first and third quarters to control for channel differences and ear of presentation. The words were presented via a matched pair of TDH-49 headphones at a comfortable level of 75 dB sound pressure level (SPL).

The Complex Tone Test (Sidtis 1981) requires participants to compare the pitch of a binaural complex tone with the pitches of a dichotic pair of complex tones presented 1 sec earlier. Subjects point to a response card labeled *Yes* when the probe tone is the same as either member of the previous dichotic pair or to a card labeled *No* when it differs from both. The complex tones are square waves with fundamental frequencies corresponding to eight notes in the octave between C4 and C5. After 16 binaural and 16 dichotic practice trails, participants were tested on four blocks of 28 trials in which half of the probe tones matched a member of the dichotic pair and half did not. Orientation of headphones was reversed after the first two blocks. The tones were presented at 74 dB SPL.

Statistical Analyses

Previous EEG studies have indicated the importance of regional (e.g., anterior vs. posterior) differences when comparing alpha asymmetry in depressed and nondepressed subjects (Bruder et al 1997a; Davidson et al 1985; Henriques and Davidson 1991). To examine these regional differences, $\log_{10}$ alpha powers were independently computed at medial and lateral sites over each hemisphere at anterior (left, F3, F7; right, F4, F8), central (left, C3, T7; right, C4, T8), and posterior (left, P3, P7; right, P4, P8) regions. These topographic measures were then used as orthogonal factors in a repeated-measures analysis of variance (ANOVA), using four within-subject factors: Hemisphere (left, right), Region (anterior, central, posterior), Medial-Lateral, and Condition (eyes open, eyes closed). Between-subject factors were Treatment Response (responder, nonresponder) and Gender (female, male). The sources of significant interactions were further examined by analysis of simple effects. *F* ratios were evaluated using degrees of freedom computed using the Greenhouse–Geisser ϵ correction (Jennings and Wood 1976) where appropriate to counteract heterogeneity of variance–covariance matrices associated with repeated measures.

In the dichotic word and complex tone tests, the number of correct responses was computed for right (R) and left (L) ear presentations. These scores were used to compute a measure of PA for each task, where $PA = 100\ (R - L)/(R + L)$. An ANOVA of PA scores included the variables of Treatment Response (responder, nonresponder), Gender (female, male), and the repeated-measure factor of Task (words, tones). Differences between responders and nonresponders on each task were examined with *t* tests.

Results

Dichotic Listening

The pretreatment differences in PA between fluoxetine responders and nonresponders replicate those seen in our prior study (Bruder et al 1996). There was an overall trend for responders to have a larger right ear (left hemisphere) advantage for words and a smaller left ear (right hemisphere) advantage for complex tones relative to nonresponders. The common direction of this group difference in asymmetry for the word and tone tests was reflected in a main effect of Treatment Response [$F(1,47) = 3.98$, $p = .05$]. The difference in asymmetry between responders and nonresponders on each test was, however, dependent on gender, as indicated by a Treatment Response by Gender

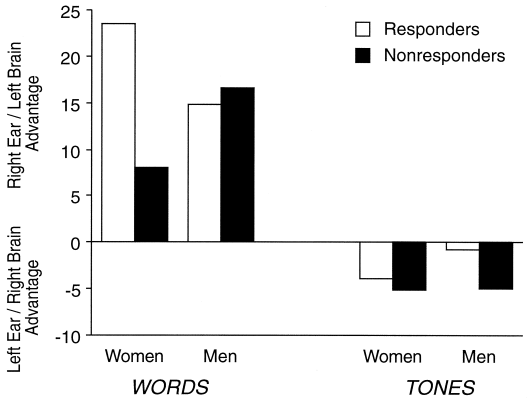

Figure 1. Mean perceptual asymmetry scores for female and male fluoxetine responders and nonresponders on the dichotic word and complex tone tests. Perceptual asymmetry score = 100 (R − L)/(R + L), where R = right ear score and L = left ear score.

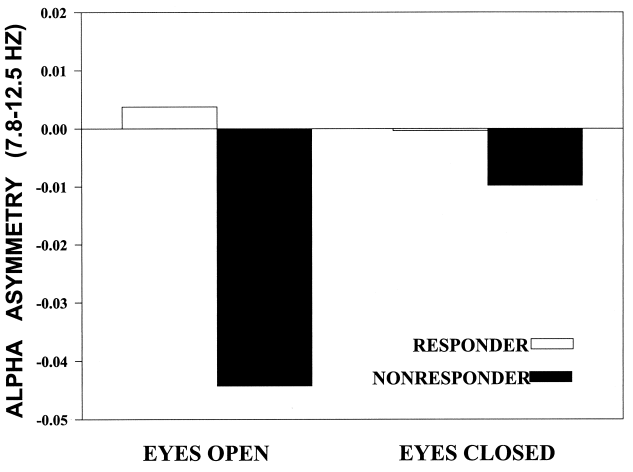

Figure 2. Mean alpha asymmetry scores [log(Right Hemisphere) − log(Left Hemisphere)] for responders and nonresponders in the eyes open and eyes closed conditions. Positive scores indicate greater activation (less alpha) over the left hemisphere than the right, and negative scores indicate greater activation (less alpha) over the right hemisphere.

by Test interaction [$F(1,47) = 4.48$, $p < .05$]. On the words test (Figure 1), female responders had a larger right ear/left hemisphere advantage (mean = 23.5, SD = 13.1) relative to nonresponders [mean = 8.0, SD = 9.3; $t(24) = 3.36$, $p < .005$], but there was no significant difference between male responders and nonresponders. The mean right ear/left hemisphere advantage for the 19 female responders is more than twice as large as seen for 18 healthy, right-handed women [mean = 11.2, SD = 15.6; $t(35) = 2.60$, $p = .01$] who were tested in our laboratory over the same time period.[2] On the complex tone test (Figure 1), the tendency for responders to have a smaller left ear/right hemisphere advantage relative to nonresponders was primarily evident for male patients, but these group differences were not statistically significant.

EEG Alpha Asymmetries

Our analyses of resting EEGs focused on power in the alpha band (7.8–12.5 Hz) because of its inverse relation to cortical activation and prior findings of abnormalities of alpha asymmetries in depressed patients. Alpha suppression was evident in the reduced power for the eyes open condition relative to eyes closed [$F(1,49) = 85.33$, $p < .001$]. Although there was no significant difference in overall alpha power between fluoxetine responders and nonresponders, the groups did differ in their hemispheric asymmetry of alpha, and this was greatest in the eyes open condition [Treatment Response by Hemisphere by Condition interaction, $F(1,49) = 5.60$, $p < .05$]. This interaction is illustrated in Figure 2, which shows the overall alpha asymmetry (averaged over homologous sites of the anterior, central, and posterior regions) for responders and nonresponders in the eyes open and eyes closed conditions. Positive scores are indicative of greater activation (less alpha) over the left hemisphere than over the right, whereas negative scores are indicative of relatively greater activation (less alpha) over the right hemisphere. Analyses of simple effects indicated that there was a significant difference in alpha asymmetry between responders and nonresponders in the eyes open condition [$F(1,49) = 5.69$, $p < .05$] but not in the eyes closed condition. In the eyes open condition, nonresponders showed greater activation (less alpha) over the right hemisphere, but responders did not. Analyses of simple effects for the eyes open condition also revealed that this difference in alpha asymmetry between fluoxetine responders and nonresponders interacted with gender [Treatment Response by Hemisphere by Gender interaction, $F(1,49) = 4.49$, $p < .05$]. There was a significant difference in alpha asymmetry between female responders (mean = .003, SD = .057) and nonresponders [mean = −.087, SD = .088; $t(21) = 3.16$, $p < .005$] but not between male responders and nonresponders.

Analyses of alpha power in the low alpha (7.8–10 Hz) and high alpha (10–12.5 Hz) frequency bands indicated that the above group differences in alpha asymmetry were most evident in the high alpha range (Figure 3). With eyes open, nonresponders showed greater activation (less alpha) over the right hemisphere than over the left, but

[2] The 18 healthy women were screened for psychopathology using a structured interview schedule and were excluded if they had a hearing loss, substance abuse, a history of head trauma, or other neurologic disorder. They did not differ significantly from the female patients in education (mean = 15.8, SD = 1.3) or handedness (LQ = 84.7, SD = 20.6), but they were somewhat younger than the female patients [mean age = 27.6, SD = 6.9; $t(35) = 3.21$, $p = .001$]. Age was not, however, related to perceptual asymmetry scores of either female patients ($r = -.01$, ns) or male patients ($r = -.02$, ns) on the fused words test. Nor was age significantly correlated with alpha asymmetry scores of female patients ($r = -.09$, ns) or male patients ($r = .11$, ns).

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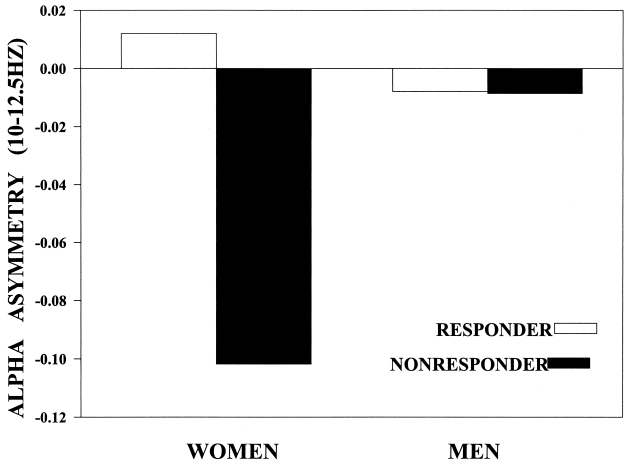

Figure 3. Mean high alpha (10–12.5 Hz) asymmetry scores [log(Right Hemisphere) − log(Left Hemisphere)] for female and male responders and nonresponders in the eyes open condition. Positive scores indicate greater activation (less alpha) over the left hemisphere than the right, and negative scores indicate greater activation (less alpha) over the right hemisphere than the left.

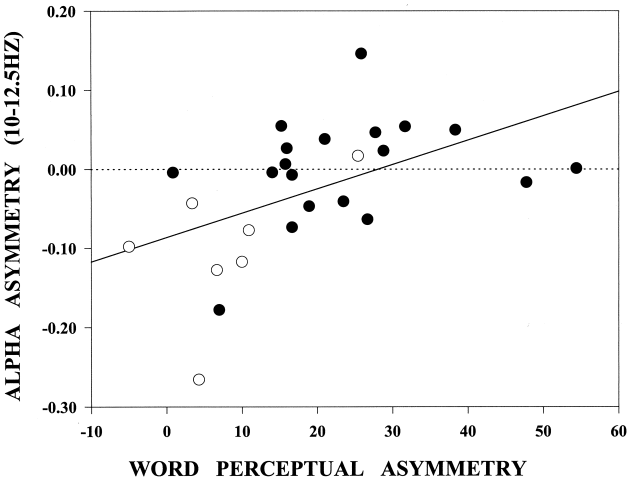

Figure 4. Scattergram illustrating the relationship between perceptual asymmetry for dichotic words and high alpha (10–12.5 Hz) asymmetry for women (●, responders; ○, nonresponders). $r = .51$, $p < .01$.

responders did not [Treatment Response by Hemisphere interaction, $F(1,49) = 6.53$, $p = .01$], and this was again evident for female patients but not for male patients [Treatment Response by Hemisphere by Gender interaction, $F(1,49) = 6.38$, $p = .01$]. Female nonresponders showed relatively greater activation over the right hemisphere (mean = −.102, SD = .087), whereas female responders tended to show the opposite alpha asymmetry [mean = .012, SD = .073; $t(26) = 3.10$, $p < .005$]. The mean alpha asymmetry for female nonresponders was also significantly different from that for 18 right-handed, healthy women [mean = −.002, SD = .086; $t(23) = 2.59$, $p < .05$].

Relation of Dichotic and EEG Asymmetries

Correlations were performed between the dichotic listening and EEG measures that best differentiated fluoxetine responders and nonresponders—that is, PA for the fused words test and alpha asymmetry (10–12.5 Hz) for the eyes open condition. Given the interactions with gender in the above analyses, separate correlations examined the relationship of dichotic and EEG asymmetries for female and male patients. There was a significant correlation between PA for words and alpha asymmetry for female patients ($r = .51$, $p < .01$) but not for male patients ($r = -.15$, ns). Figure 4 shows the PA scores for female responders and nonresponders plotted against their alpha asymmetry scores. More positive scores for the word test indicate greater right ear (left hemisphere) advantage and positive alpha asymmetry scores indicate relatively greater left hemisphere activation. All but one of the female nonresponders had an alpha asymmetry indicating relatively greater right hemisphere activation and also showed little or no left hemisphere advantage for perceiving dichotic words.

Prediction of Treatment Response

Inspection of the distribution of PA scores for female responders and nonresponders on the dichotic fused words test (Figure 4) suggests its possible value for predicting outcome of treatment with fluoxetine. The mean PA for healthy women (mean = 11.2) was used as a cutoff score for dividing female patients into those with relatively large or small right ear (left hemisphere) advantages, and a comparison was made of their treatment response. Patients with a large right ear advantage above the normal mean had a 94% response rate (17/18) to fluoxetine, whereas patients with a right ear advantage less than normal had only a 25% response rate (2/8) to fluoxetine [$\chi^2(1) = 13.6$, $p < .001$]. Using this cutoff score on the fused words test would therefore have a sensitivity of 89% and a specificity of 86% for predicting outcome of fluoxetine treatment among women.

Perceptual asymmetry for women on the dichotic word and tone tests and alpha asymmetry (10–12.5 Hz) for the eyes open condition were also examined as combined and individual predictors of treatment outcome in hierarchical logistic regression equations. The three asymmetry measures significantly improved prediction of treatment outcome over a constant alone [$\chi^2(3) = 12.26$, $p < .01$]. Asymmetry for the fused words test was a significant predictor of treatment outcome on its own [Wald test(1) =

5.10, $p < .05$]. The dichotic tone test and alpha asymmetry measures did not contribute significant additional prediction over the asymmetry for the fused words test. Alpha asymmetry was a significant predictor of treatment outcome on its own [Wald test(1) = 4.96, $p < .05$], and the dichotic tests did not result in a significant increment in predictability after alpha asymmetry was entered in the regression equation.

Discussion

Individual differences in hemispheric asymmetries among depressed patients, as measured by dichotic listening or resting EEG, were related to therapeutic response to an SSRI antidepressant. In accordance with our prior study (Bruder et al 1996), fluoxetine responders differed from nonresponders in favoring left over right hemispheric processing of dichotic stimuli. Moreover, fluoxetine nonresponders differed from responders in showing a resting EEG alpha asymmetry indicative of overall greater right than left hemispheric activation. The relationship between hemispheric asymmetries and treatment response was evident among depressed women but not among men. Given the relatively small sample sizes, the influence of gender in this context will need replication.

Depressed women who respond to fluoxetine had a marked right ear (left hemisphere) advantage for perceiving dichotic words, which is the predominant PA seen among depressed patients. In our prior studies, both adults and adolescents having a major depressive disorder showed an abnormally large right ear (left hemisphere) advantage on the dichotic fused words test (Pine et al, 2000). In contrast, depressed women who fail to respond to fluoxetine had a relatively small right ear (left hemisphere) advantage for dichotic words and also had an EEG alpha asymmetry in a resting state favoring right hemisphere activation over left (Figure 4). Thus, enhanced right hemispheric activation in nonresponders may act to counter the left hemispheric favoring for processing dichotic words typically seen among depressed patients. The significant correlation observed between PA and resting alpha asymmetry among women is in accord with the hypothesis that fluoxetine responders differ from nonresponders in their characteristic, state-independent hemispheric activation patterns.

The tendency for fluoxetine responders to favor left hemisphere processing over right during dichotic listening might appear to be at odds with evidence that depression involves reduced left prefrontal activation (Baxter et al 1989; Henriques and Davidson 1991). However, dichotic listening involves perceptual processes in more posterior temporoparietal regions (Coffey et al 1989; Davidson and Hugdahl 1996). We have previously suggested that decreased left prefrontal activation in depression may release left temporoparietal regions from inhibition, resulting in the enhanced left hemisphere advantage for dichotic perception in fluoxetine responders (Bruder et al 1996). This is consistent with electrophysiologic evidence of an inhibitory relationship between frontal and temporoparietal regions (Knight et al 1980; Tucker et al 1981) and with the inverse pattern of frontal and parietal alpha asymmetries in depression (Davidson et al 1985; Henriques and Davidson 1990). Fluoxetine nonresponders did not show this left hemisphere favoring for dichotic perception and also had a global alpha asymmetry indicative of relatively greater right hemisphere activation in frontal and more posterior regions.

The alpha asymmetry of fluoxetine nonresponders resembles that seen in patients having a major depression with comorbid anxiety disorder (Bruder et al 1997a). There was, however, no difference between fluoxetine responders and nonresponders in self-ratings of trait anxiety or anxious arousal. It is, of course, possible that more direct measures of somatic arousal (e.g., electrodermal activity) might reveal differences in overall arousal related to right temporoparietal activity (Heller et al 1995). The importance of arousal level is supported by the finding that differences between responders and nonresponders were less evident in the least arousing eyes closed, resting EEG condition.

Why should individual differences among depressed patients in left-right hemispheric activation be associated with therapeutic response to an SSRI antidepressant? One possible reason is that the serotonergic neurotransmitter system, implicated in depressive disorders and affected by SSRI antidepressants, may have a lateralized distribution in the brain and may be asymmetrically disrupted in a subtype of depressed patients. Although it has been suggested that serotonin pathways are asymmetric for homologous regions of the right and left brain (Mandell and Knapp 1979; Tucker and Williamson 1984), postmortem studies have not found consistent evidence of serotonin uptake asymmetries as measured by imipramine binding in the left and right frontal cortices (Arato et al 1991; Arora and Meltzer 1991). A positron emission tomography (PET) study measuring regional glucose metabolism found that the serotonin-releasing drug D,L-fenfluramine increased metabolism in the left prefrontal cortex and temporoparietal areas and decreased metabolism in the right prefrontal cortex in healthy adults, but not in depressed patients (Mann et al 1996). However, Meyer et al (1998) found that changes in regional cerebral blood flow following intravenous D-fenfluramine were similar in depressed patients and healthy subjects. This discrepancy could result from the use of oral D,L-fenfluramine in the Mann et al study, which is less selective for serotonin

release than D-fenfluramine, or of other study differences, including the timing of the PET scans or differences in patient characteristics (e.g., suicidal attempts or gender).

Positron emission tomography studies have provided preliminary evidence that pretreatment regional brain metabolism is linked to response to antidepressant treatments (Ketter et al 1999; Little et al 1996; Mayberg et al 1997). Unipolar depressed outpatients who subsequently responded to venlafaxine or bupropion showed decreased left middle frontal gyral and bilateral prefrontal and temporal metabolism relative to healthy control subjects (Little et al 1996). Rostral anterior cingulate metabolism at baseline differentiated responders to treatment with an SSRI, tricyclic antidepressant, or bupropion from nonresponders, and these cingulate differences tended to be right lateralized (Mayberg et al 1997). Most recently, Ketter et al (1999) found pretreatment paralimbic (left insular) and prefrontal metabolism was differentially related to response to carbamazepine and nimodipine. Although the relation of these neuroimaging findings to the dichotic listening and EEG findings of the current study is unclear, they do argue that responsiveness to antidepressants depends, at least in part, on the patient's pretreatment pattern of regional hemispheric activation. Application of new dense-electrode array EEG and source localization techniques, in conjunction with neuroimaging, should help define the neural structures that contribute to the differences in hemispheric asymmetry between treatment responsive and nonresponsive subtypes of depression.

Electrophysiologic studies of depression have predominantly tested women. This is one of the first studies to examine the role of gender in this context. Differences in dichotic listening and EEG alpha asymmetry between fluoxetine responders and nonresponders were found among depressed women but not among men. Women who responded to fluoxetine had a marked right ear (left hemisphere) advantage for dichotic words, more than twice as large as nonresponders or healthy women. This is remarkable when one considers that women typically exhibit *less* asymmetry than men on verbal laterality tests, including the fused words test (McGlone 1980; Pine et al, 2000). Also, there was a significant correlation between dichotic word and EEG alpha asymmetries among depressed women but not among men. What might account for these gender differences? Heller (1993) reviewed evidence for gender differences in neuropsychologic function and hemispheric organization and speculated on their relation to gender differences in depression. A maturational advantage for the left hemisphere in girls and the right hemisphere in boys may lead to tendencies for females to use verbal strategies and males to use nonverbal strategies. Women may therefore be more likely to ruminate when depressed, which would involve increased activity of the left posterior region. Following Heller (1993), we speculate that one form of depression in women is characterized by heightened left posterior activation for verbal processing and favorable response to the SSRI fluoxetine or to cognitive-behavioral therapy (Bruder et al 1997b). Other women who are prone toward right posterior activation may have a different form of depression characterized by poor response to these treatments.

The findings for women also suggest that the dichotic fused words test may be of value for predicting therapeutic response to fluoxetine. All but one of 18 depressed women with above normal left hemisphere advantage for words responded to fluoxetine. In contrast, only two of eight women with a left hemisphere advantage below normal responded to fluoxetine, a response rate no better than typically seen for a placebo. What, then, would be an alternative treatment for depressed women who exhibit pervasive right hemisphere activation and are not likely to respond to fluoxetine? Two experimental treatments might ultimately be of some value in shifting their asymmetry toward left hemisphere activation and reducing their depression. First, repetitive transcranial magnetic stimulation is being explored as a means for altering regional brain activity and thereby reducing depression in patients who are refractory to antidepressant treatments (Post et al 1999). Second, there is preliminary evidence that EEG alpha asymmetries can be shifted using neurofeedback training, and this is associated with the expected changes in mood (Baehr et al 1999; Rosenfeld et al 1995). Further study of the potential value of dichotic and electrophysiologic asymmetry measures for selecting patients who might most benefit from these alternative treatments would seem to be in order.

Lastly, although the direction of alpha asymmetry differences between fluoxetine responders and nonresponders was consistent across the eyes open and eyes closed conditions, differences were more marked in the eyes open condition (Figure 2). Since differences in alpha asymmetry between depressed patients and control subjects have not generally been reported to differ across these conditions (Bruder et al 1997a; Henriques and Davidson 1991), the alpha asymmetry differences between fluoxetine responders and nonresponders may reflect a separable mechanism. One possibility is that hemispheric asymmetry differences between fluoxetine responders and nonresponders may depend upon level of arousal. Eyes closed during resting EEG is the least arousing condition, whereas eyes open leads to an increase in arousal and dichotic listening requires active task performance. Additional research is needed to determine the importance of these condition-dependent alpha asymmetries in this context.

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