

Brain event-related potentials to complex tones in depressed patients: Relations to perceptual asymmetry and clinical features

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Abstract

Brain event-related potentials (ERPs) to probe tones in a dichotic complex tone test were recorded from right-handed depressed patients ($n = 44$) and normal subjects ($n = 19$) at homologous sites over left and right hemispheres (F3, F4; C3, C4; P3, P4; O1, O2). There were no differences between groups in N1 or P2 amplitude, but patients had smaller P3 amplitude than did normal subjects. Depressed patients failed to show either the left ear advantage or behavior-related hemispheric asymmetry of P3 seen for normal subjects. Depressed patients also showed less difference in hemispheric asymmetry between *same* and *different* judgments. These findings indicate that the abnormal behavioral asymmetry for dichotic pitch discrimination in depressed patients reflects a reduction in hemispheric asymmetry and is related to relatively late stages of cognitive processing.

Descriptors: Depressive disorders, Event-related potentials, P300 (P3), Dichotic listening, Laterality, Pitch discrimination

Event-related potentials (ERPs) recorded during the performance of a discrimination task provide a means of examining electrophysiologic correlates of sensory and cognitive processing. ERPs have a temporal resolution that surpasses that of other functional imaging techniques, enabling the investigator to monitor physiologic activity related to sequential information processing. Early ERP components, for example, N1, primarily reflect sensory and attentional processing (Näätänen & Picton, 1987), whereas later ERP components, for example, P3, are more associated with cognitive processes such as stimulus evaluation and working memory (Donchin & Coles, 1988).

Although schizophrenia is typically associated with a reduction in amplitude of both early and late ERP components, findings for depressed patients have been less consistent. Studies

measuring ERPs during passive listening to tones or clicks have found some evidence of reduced N1 or P2 amplitude in depressed patients when compared with normal controls (Roth, Pfefferbaum, Kelly, Berger, & Kopell, 1981; Shagass, 1981). This reduction in depressed patients was reported to be more evident with psychotic than with neurotic disorders (Shagass, 1981), but a recent study found reduced N1–P2 amplitude in dysthymic subjects (Yee, Deldin, & Miller, 1992). Although these findings raise the possibility that abnormalities of early sensory-attentional processing may exist in depressive disorders, the nature of these abnormalities and the type of depressed patients who display them remain unclear. Studies measuring P3 in depressed patients during oddball tone detection tasks have yielded inconsistent findings, with studies being about equally divided between those reporting a reduction in P3 amplitude when compared with controls and those that do not (Roth, Duncan, Pfefferbaum, & Timsit-Berthier, 1986). In those studies where depressed patients did have smaller P3 amplitude, the reduction was not as large as that seen for schizophrenic patients (Blackwood et al., 1987; Roth et al., 1981).

ERP tasks involving passive listening provide little or no control over what patients are attending to during the test and relatively little information concerning later stages of cognitive processing. Furthermore, the oddball task may be too simple to reveal consistently cognitive dysfunctions that exist in depressive disorders. Roth et al. (1986) argued for the need to move

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beyond the oddball paradigm and investigate specific hypotheses concerning information processing in psychopathology. Measurement of ERPs in depressed patients during more cognitively challenging tasks, selected on the basis of existing theories concerning cognitive or neurophysiologic deficits in depressive disorders, might yield more consistent and revealing findings than previously found for passive listening or oddball tasks.

Support for a hypothesis of right hemisphere dysfunction in depressive disorders was initially provided by studies finding abnormal lateral asymmetries of skin conductance responses (Gruzelić & Venables, 1976) or performance deficits on neuropsychological tests of visuospatial function (Flor-Henry, 1976). More recently, studies measuring performance asymmetries or hemispatial bias in visual tasks have similarly found evidence suggestive of right hemisphere dysfunction in depressed patients (Bruder et al., 1992; Jaeger, Borod, & Peselow, 1987; Liotti, Sava, Rizzolatti, & Caffarra, 1991). Additional evidence for this hypothesis has come from studies using dichotic listening tests, in which different nonverbal sounds were simultaneously presented to the two ears (Bruder, 1988, 1995; Bruder et al., 1989; Johnson & Crockett, 1982; Overby, Harris, & Leek, 1989). In these dichotic tests, normal adults show a mean left ear (right hemisphere) advantage, whereas groups of depressed patients generally fail to show this behavioral asymmetry.

The present study measured both behavioral ear advantages and ERPs of depressed patients during a dichotic complex tone test (Sidtis, 1981; Tenke, Bruder, Towey, Leite, & Sidtis, 1993). These measurements should provide an adequate test of the hypothesis that depressed patients have reduced P3 amplitude during a cognitively challenging tone discrimination task. It was also predicted that depressed patients would have reduced or absent left ear (right hemisphere) advantage on this nonverbal dichotic task. Moreover, measurement of ERPs at corresponding sites over the right and left hemispheres provides a means for determining the correspondence between abnormal behavioral asymmetry in depressed patients and hemispheric asymmetry of early and late ERPs, which typically reflect sensory-attentional (N1) and later cognitive (P3) processing.

A further purpose of this study was to examine the relation of ERP abnormalities to the specific clinical features of a large sample of depressed patients. For instance, some depressed patients may have reduced P3 amplitude whereas others do not, but the clinical features that might characterize patients who have an abnormal P3 are presently unknown. Hence, this study examined the relation of both P3 amplitude and asymmetry to severity of depression and outcome of treatment.

Method

Subjects

ERPs were recorded from 44 right-handed depressed patients (28 women, 16 men) between the ages of 18 and 60 years ($M = 36.1$ years, $SD = 9.8$ years) who were attending an outpatient depression research clinic at New York State Psychiatric Institute. All aspects of the diagnostic assessment and evaluation of treatment outcome were carried out by research psychiatrists in this clinic. There were 39 patients who met DSM-III-R criteria for major depressive disorder and the remaining 5 patients met criteria for a dysthymic disorder. All but 3 patients, who met DSM-III-R criteria for Bipolar Disorder Not Otherwise Specified, had unipolar disorders. The patients were tested after a minimum drug-free period of 7–10 days, with most patients drug

free for a considerably longer period. The patients were moderately depressed as indicated by their mean Hamilton Depression Scale score of 17.5 ($SD = 4.7$). The normal controls were 19 right-handed volunteers (from Tenke et al., 1993) who were recruited from hospital personnel, local colleges, and families of laboratory staff. Controls were screened using a modified version of the Schedule for Affective Disorders and Schizophrenia–Lifetime version (Spitzer & Endicott, 1975) to exclude those with current or past psychopathology. Controls did not differ significantly from the patients in their gender (11 women, 8 men) or age ($M = 31.2$ years, $SD = 8.9$).

All subjects were screened for hearing loss using a standard audiometric evaluation. Subjects were required to have less than a 10-dB difference between ears and a hearing loss no greater than 30 dB at 500, 1000, or 2000 Hz. Subjects were excluded if they had a current or past neurological problem or substance abuse disorder.

The handedness of subjects was evaluated using the Edinburgh Inventory (Oldfield, 1971). Ten items concerning hand preference for writing, drawing, holding a spoon, and so forth, were used to compute a laterality quotient score, $100(R - L)/(R + L)$. A score of 100 equals completely right handed, and -100 equals completely left handed. Only subjects with a positive score were included in this report. There was no difference in handedness scores between the patients ($M = 80.6$, $SD = 23.6$) and normal subjects ($M = 80.1$, $SD = 17.3$).

Complex Tone Test

In this S1–S2–R matching task, a different complex tone was presented simultaneously to the two ears (S1), followed by a binaurally presented probe tone (S2). The probe tone was either the same as one member of the dichotic pair or different from both. The subject pressed a response button (R) when the probe matched one of the dichotic tones. Each trial was 7.5 s in duration and was signalled by the onset of a fixation light 1 s prior to the initial dichotic pair of complex tones. The dichotic pair was followed 2 s later by the probe tone. The subject was required to respond during a 3-s response period that was signalled by the offset of the fixation light, 1.5 s after the probe tone.

A digitally synthesized version of the complex tone test was used in this study (for details, see Tenke et al., 1993). There were eight complex tones with fundamental frequencies corresponding to the major notes in the octave between middle C (264 Hz) and C5 (528 Hz). Each tone was synthesized using sinusoids at the fundamental frequency and the first three harmonics to approximate a square wave. These stimulus characteristics were selected on the basis of the findings of Sidtis (1980). He found that square waves, containing the fundamental frequency and its odd harmonics, yielded a left-ear (right hemisphere) advantage in normal right-handed adults, whereas pure tones at the fundamental frequencies did not. Tones were 250 ms in duration, with rise and decay times of 25 ms. Trials were arranged in six 28-trial blocks. In each block, half of the probe stimuli matched a member of the dichotic pair, and there were equal numbers of left- and right-ear matches. Two practice blocks (binaural and dichotic) were also included. Stimuli were presented at 72 dB SPL through a matched pair of TDH-49 earphones. Earphone orientation and response hand were randomized across subjects within each group.

Behavioral Asymmetry

A behavioral asymmetry score was computed for each subject from the percentage of correct responses to probe stimuli

that matched right (R) or left (L) stimuli in the dichotic pair, $100(R - L)/(R + L)$. A positive score indicates a right-ear advantage, whereas a negative score indicates a left-ear advantage. To determine whether or not behavioral ear advantages were related to ERP measures, the patient and normal groups were divided into subjects with a strong left-ear advantage and subjects with little or no left-ear advantage. The median ear advantage for normal subjects was used to split the patient and normal groups in two subgroups: (a) subjects with a left-ear advantage equal to or greater than the median and (b) the remaining subjects who had a weak left-ear advantage or a right-ear advantage. Our rationale for using the median score to form subgroups with different ear advantages was the same as described elsewhere (Tenke et al., 1993).

ERP Recording

Scalp recordings were made from four lateral pairs of electrodes (F4, F3; C4, C3; P4, P3; O2, O1) using a commercially available electrode cap (Electro Cap International, Inc.). Electroencephalograms (EEGs) were recorded with a nose tip reference and a mastoid ground. A nose reference was chosen for this study because it is inherently symmetric and has been used successfully in prior studies (e.g., Vaughan & Ritter, 1970; Vaughan, Ritter, & Simson, 1980). Electrodes at supra- and infraorbital sites surrounding the right eye were used to monitor eyeblinks and vertical eye movements (bipolar), and electrodes at right and left outer canthi monitored horizontal eye movements (bipolar). The cap and reference electrodes were composed of tin, and all other electrodes were standard Beckman Ag/AgCl electrodes. The EEG and electrooculogram (EOG) were recorded from amplifiers with a band pass of 0.032–50 Hz. Gains were set at 10,000 for EEG channels and 5,000 for EOG channels. A PDP 11/34 minicomputer acquired the ERP data (100 Hz sampling rate) along with the behavioral responses and stored them on hard disk. Data were acquired over 1,200-ms recording epochs for dichotic pairs and probe stimuli, with a 170-ms prestimulus period.

ERP Analyses

Artifact removal. Subjects were instructed to inhibit blinks or eye movements whenever the fixation light was on. Trials contaminated by blinks or large amplitude eye movements were excluded from analysis by using a 50- μ V RMS rejection criterion for EOG channels. Smaller eye movements were corrected on a trial-by-trial basis whenever the RMS amplitude of the EOG exceeded the RMS amplitude at Fz. This procedure prevents overcorrection when eye movement is minimal and the ERP has a frontal distribution. After removal of DC offsets, transfer coefficients between the EOG channels and the EEG channels were computed from the corresponding correlation coefficients (Gratton, Coles, & Donchin, 1983; Verleger, Gasser, & Möcks, 1982). In our implementation, transfer coefficients were computed independently for each trial to minimize the effect of state-related changes in EEG variance (e.g., alpha) on transfer coefficient estimates. After eye movement correction, trials in which EEG RMS amplitude exceeded 50 μ V were excluded from analysis. The eye movement correction procedure was implemented only after an initial empirical validation period, in which corrected averages were compared with uncorrected waveforms produced using a 25- μ V RMS rejection criterion.

Loss of trials was mostly due to blinks. Of the total of 168 trials, the mean number of trials remaining following artifact rejection was 140 ($SD = 28.1$) for patients and 160 ($SD = 10.7$) for normal controls. Despite the greater loss of trials for patients, the number of remaining trials was sufficient to yield ERP waveforms of quality comparable to that for normal subjects. Examination of the data for individuals indicated that loss of trials was not related to the findings presented below. Most importantly, there was no significant correlation between the number of trials remaining after rejection for artifacts and either P3 amplitude ($r = -.01$ to $.20$ at frontal to occipital sites) or hemispheric asymmetry of P3 ($r = -.16$ to $.02$) for patients.

ERP averages. This report presents ERPs recorded at lateral electrodes to probe stimuli that were correctly identified as being the same as a tone in the dichotic pair or as being different (correct rejection). Averaged ERP waveforms were computed for each subject and across subjects on the basis of electrode site (frontal, central, parietal, occipital), hemisphere (left, right), and condition (different, same). Because our analyses have not revealed differences in ERPs to probe tones as a function of the ear to which the matching stimulus was presented in the dichotic pair (e.g., Tenke et al., 1993), ERPs to probe tones were computed as the mean of the waveforms for correct left and right matches. The ERP waveforms were filtered to an equivalent upper cutoff frequency (-3 dB) of 9 Hz (Ruchkin & Glaser, 1978). Although this filter attenuated N1 by approximately one-third, it did not affect the resolution of relative amplitude differences across conditions, hemispheres, or groups.

Amplitude measurements. ERP amplitudes were measured as average values within the following windows: (a) N1, a negative component between 70 and 150 ms poststimulus; (b) P2, a positive component between 160 and 250 ms; (c) P3, a late positive component between 260 and 700 ms; and (d) positive slow wave, computed as the average value between 710 and 1,030 ms. The 170-ms prestimulus interval was used as the baseline for amplitude measurements. Average values within these time windows were used because of the variable and smaller amplitude of the late positive components for patients.

Statistical Methods

Behavioral data. The percentage of correct responses to probe tones was subjected to an analysis of variance (ANOVA) with group (patient, control) and ear (right, left). Paired t tests were used to evaluate the significance of ear advantages for each group, and a t test was used to compare the mean ear asymmetry score of the patient and control groups.

ERP data. Average amplitudes for each of the ERP components were subjected to a repeated-measures ANOVA with group (patient, control), ear advantage (strong left-ear advantage, no left-ear advantage), electrode (frontal, central, parietal, occipital), hemisphere (right, left), and condition (different, same). Significant interactions involving electrode or hemisphere were also evaluated after scaling the amplitudes for each condition by the vector amplitude measured across electrodes in each subject (McCarthy & Wood, 1985). F ratios were evaluated using degrees of freedom computed using the Greenhouse-Geisser epsilon correction (Jennings & Wood, 1976) where appropriate to counteract heterogeneity of variance-covariance matrices

associated with repeated measures. Only findings that reached a .05 significance level are considered in this report.

Correlations between ear advantages and ERP asymmetries were also computed to provide a measure of the strength of the relationship between these continuous variables. For each ERP component, a hemispheric difference (right hemisphere – left hemisphere amplitude) was computed as a measure of physiological asymmetry at each of the lateral pairs of electrodes. Product-moment correlations between these hemispheric differences and behavioral asymmetry scores were calculated separately for the patient and normal groups. Correlations were also checked for statistical significance using Spearman rank-order correlations.

Results

Behavioral Data

Table 1 gives the mean percentage of correct responses to probe tones and mean asymmetry score for patient and normal groups. There was no significant difference between patient and normal groups in accuracy levels, but the groups did differ in ear advantages. An ANOVA of the accuracy data revealed an overall left-ear advantage ($F[1,59] = 10.79, p < .005$), and an interaction between ear advantage and subject group ($F[1,59] = 3.89, p = .05$). Normal subjects showed significantly greater accuracy for matching left- than right-ear tones in the dichotic pair (paired $t[18] = 3.02, p < .01$), whereas the ear advantage for patients was not statistically significant (paired $t[43] = 1.37, n.s.$). A comparison of asymmetry scores across groups indicated that the left-ear advantage was significantly greater for normals than for patients ($t[61] = 2.21, p < .05$). Nonparametric analyses confirmed the above findings: a significant left-ear advantage in normal controls (Wilcoxon matched-pairs test, $z = 2.78, p < .01$) but not in patients ($z = 1.14, n.s.$) and a significant difference in asymmetry scores between these groups (Mann-Whitney U test, $z = 2.01, p < .05$).

Table 2 gives the mean asymmetry scores and subject characteristics for subgroups formed by dividing the normal and patient groups at the median asymmetry score for normal subjects. The median split was successful in yielding subgroups having a strong left-ear advantage or no left-ear advantage. Comparison of the characteristics for these subgroups, using chi-square or ANOVA, showed that there were no significant differences among subgroups in gender, age, or handedness scores.

Table 1. Correct Responses and Asymmetry Scores

Group	% Correct		Asymmetry ^a
	Left ear	Right ear	
Normal ($n = 19$)			
<i>M</i>	86.4	75.6	-7.7
<i>SD</i>	9.1	17.4	10.9
Patients ($n = 44$)			
<i>M</i>	83.5	80.6	-1.7
<i>SD</i>	12.1	11.8	9.3

^aScore = $100(\text{right} - \text{left})/(\text{right} + \text{left})$; negative score = left-ear advantage.

Table 2. Asymmetry Scores and Subject Characteristics

Variable	Normal		Patient	
	Strong LEA ($n = 10$)	No LEA ($n = 9$)	Strong LEA ($n = 15$)	No LEA ($n = 29$)
Asymmetry score				
<i>M</i>	-14.9	0.3	-11.4	3.2
<i>SD</i>	10.1	4.0	7.6	5.4
Gender				
F	6	5	10	18
M	4	4	5	11
Age (years)				
<i>M</i>	30.3	32.1	34.8	36.7
<i>SD</i>	9.5	8.6	9.8	9.8
Handedness score				
<i>M</i>	74.4	86.4	81.3	80.2
<i>SD</i>	16.4	16.8	22.2	24.7

Note: Negative asymmetry score = left-ear advantage (LEA).

ERP Waveforms for Patients and Normals

Figure 1 shows the average ERP waveforms for patient and normal groups at electrode sites over each hemisphere for correct responses to probe tones. N1 and P2 components are most prominent at frontal and central sites. A late positive complex is also evident, which is small frontally and maximum parietally.

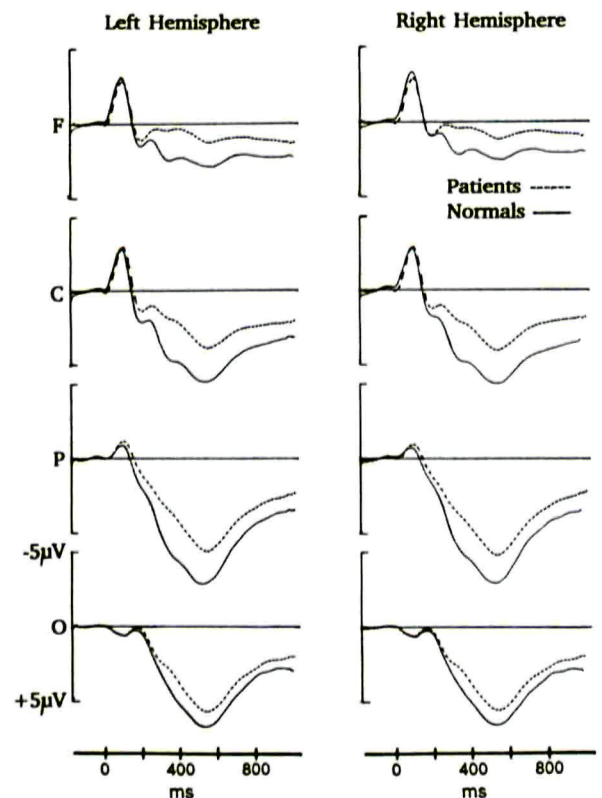


Figure 1. Average waveforms for probe stimuli for patient and normal groups at left and right frontal (F), central (C), parietal (P), and occipital (O) sites averaged over correct *same* and *different* judgments.

It consists of a peak at about 550 ms, referred to hereafter as P3, followed by a sustained slow wave. There was essentially no difference between patient and normal groups in N1 or P2 amplitude (Figure 1). Patients did show consistently smaller P3 amplitude than did normal controls, which was confirmed in the statistical analyses presented below. This group difference in P3 amplitude was widespread, being present at each electrode site over the left and right hemispheres.

N1 and P2 Amplitude

ANOVAs of the average amplitude in the N1 and P2 windows indicated that there was no significant difference between patient and normal groups in the amplitude of these components. P2 also showed no significant interactions involving group. N1 showed only a Group \times Ear Advantage \times Condition interaction ($F[1,59] = 6.33, p < .025$). Further analyses indicated that this three-way interaction was due to the presence of a significant Ear Advantage \times Stimulus Condition interaction for normals ($F[1,17] = 17.56, p < .001$) but not for patients ($F[1,42] = 0.21, n.s.$). The nature of the three-way interaction is illustrated in Figure 2. Normals with a strong left-ear advantage had greater N1 amplitude when the probe tone was the same as a member of the dichotic pair than when it was different from the dichotic pair ($F[1,9] = 5.20, p < .05$), whereas the opposite effect of stimulus condition was evident for normals with little or no left-ear advantage ($F[1,8] = 11.82, p < .001$). This differential effect of stimulus condition on N1 amplitude for normal subjects with different ear advantages was not, however, seen for the patient subgroups.

P3 Amplitude

The ANOVA of average amplitude in the P3 window confirmed that patients had overall smaller P3 amplitude than did normal controls ($F[1,59] = 5.87, p < .025$). There was no significant Group \times Electrode, Group \times Hemisphere, or Group \times Hemisphere \times Electrode interaction, which indicates that the difference in P3 amplitude between groups was not dependent on electrode site.

P3 showed hemispheric asymmetries that differed across groups and were related to behavioral ear advantages. Figure 3 illustrates the Group \times Ear Advantage \times Hemisphere interaction in the ANOVA of P3 amplitude ($F[1,59] = 12.30, p < .001$), which was also present after vector scaling to remove the overall amplitude difference between groups. Normal subjects

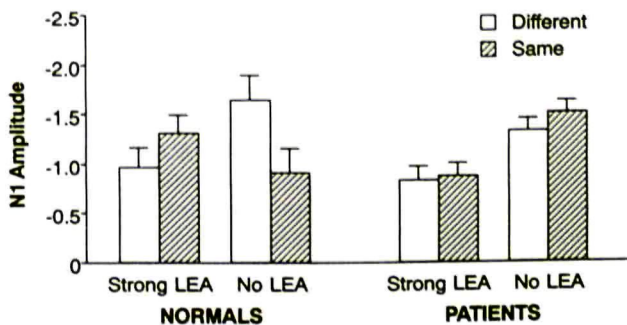


Figure 2. Mean amplitude of N1 for patients and normals with a strong left-ear advantage (Strong LEA) or no left-ear advantage (No LEA) plotted separately for probe tones that were correctly judged to be different or same.

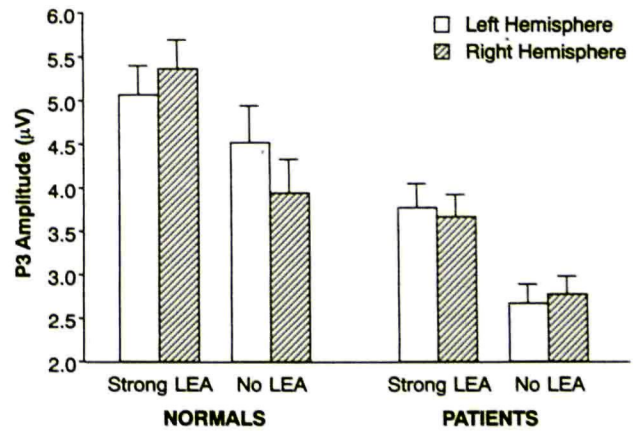


Figure 3. Mean amplitude of P3 over the left and right hemispheres for patients and normals with a strong left-ear advantage (Strong LEA) or no left-ear advantage (No LEA).

showed behavior-related hemispheric asymmetries of P3. Normals with a strong left-ear advantage had greater amplitude over the right than left hemisphere, whereas normals with little or no left-ear advantage had the opposite hemispheric asymmetry. These behavior-related hemispheric asymmetries of P3 were not seen for patients. Further analyses confirmed that there was a significant Ear Advantage \times Hemisphere interaction for normal subjects ($F[1,17] = 7.80, p = .01$) but not for patients ($F[1,42] = 1.95, n.s.$).

The ANOVA of P3 amplitude also revealed a significant Group \times Stimulus Condition \times Hemisphere interaction ($F[1,59] = 11.19, p = .001$) and Stimulus Condition \times Hemisphere \times Electrode interaction ($F[3,177] = 19.46, p < .0001, \epsilon = 0.76$), which remained significant after vector scaling. The nature of these interactions can be seen in Figure 4, which shows the hemispheric asymmetry of P3 at each electrode site for patients and normals plotted separately for trials on which the probe tone was correctly judged to be the same or different when compared with the dichotic pair. In normals, P3 was greater over the left than right hemisphere when the probe was different from

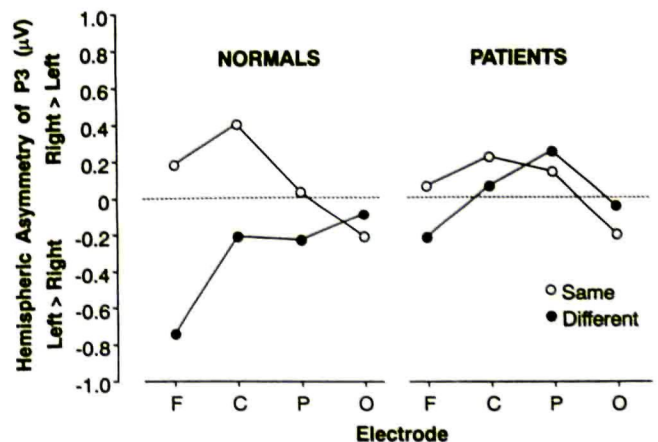


Figure 4. Mean hemispheric asymmetries (right minus left hemisphere) of P3 at frontal (F), central (C), parietal (P), and occipital (O) sites for patients and normals plotted separately for probe tones that were correctly judged to be different or same.

the dichotic pair, but the opposite hemispheric asymmetry was present when the probe was the same as a member of the dichotic pair. This was reflected in a Stimulus Condition \times Hemisphere interaction in an analysis of the P3 data for normal subjects ($F[1,17] = 16.01, p < .001$). In contrast, the patients did not show this Stimulus Condition \times Hemisphere interaction ($F[1,42] = 0.43, n.s.$). Figure 4 also shows that the difference in hemispheric asymmetry for *same* and *different* conditions was largest at frontocentral sites, which was reflected in the Stimulus Condition \times Hemisphere \times Electrode interaction.

Given the finding of overall smaller P3 amplitude in patients than in normal controls, an important question is whether the lack of hemispheric asymmetries of P3 for patients could be due to a floor effect. Smaller amplitudes could limit the magnitude of the P3 asymmetry. To examine this question, the median P3 amplitude of patients at parietal sites was used to split patient group into two subgroups, those with P3 amplitudes less than the median ($M = 1.31, SD = 1.92$) or greater than the median ($M = 4.80, SD = 3.18$). An ANOVA of the P3 amplitude for these subgroups, including the same variables and electrode sites as in the previous analyses, confirmed the subgroup difference in P3 amplitude ($F[1,40] = 54.0, p < .0001$) but did not show either a Subgroup \times Hemisphere or Subgroup \times Ear Advantage \times Hemisphere interaction. There was no trend for depressed patients with higher P3 amplitudes to show the hemispheric asymmetries of P3 that were seen for normal controls. For instance, among the subgroup of patients with higher P3 amplitude, the nine patients with a strong left-ear advantage failed to show evidence of greater P3 amplitude over the right than left hemisphere (right = $4.78 \mu\text{V}$, left = $5.06 \mu\text{V}$). It is therefore very unlikely that the lack of P3 asymmetry in patients is related to a floor effect.

Slow Wave Amplitude

Although it appears in Figure 1 that patients have less late positive slow wave amplitude than do normal adults, the ANOVA of average amplitude in the slow wave window indicated that this group difference was not statistically significant ($F[1,59] = 2.58, n.s.$). Likewise, there were no behavior-related hemispheric asymmetries of slow wave amplitude for either patients or normal subjects. However, the same difference between patient and normal groups in the effects of stimulus condition on hemispheric asymmetry of P3 was evident in the slow wave region. There was a significant Group \times Stimulus Condition \times Hemisphere interaction for slow wave amplitude ($F[1,59] = 4.49, p < .05$). The nature of this interaction is essentially the same as that for P3 in Figure 4. In normal subjects, slow wave amplitude at frontocentral sites was greater over the left than right hemisphere for the *different* condition, but the opposite hemispheric asymmetry was present for the *same* condition (Stimulus Condition \times Hemisphere interaction: $F[1,17] = 10.92, p < .005$; see also Tenke et al., 1993, Figure 4). Patients did not show this Stimulus Condition \times Hemisphere interaction ($F[1,42] = 0.49, n.s.$). The Stimulus Condition \times Hemisphere \times Electrode interaction seen for P3 was also found for slow wave amplitude ($F[3,177] = 22.0, p < .0001, \epsilon = 0.82$), which again reflected the difference in hemispheric asymmetry between *same* and *different* conditions and its dependence on electrode site.

Correlational Analyses

The relationship between hemispheric asymmetry of P3 and behavioral ear advantage was also examined by computing product-

moment correlations of these variables within the patient and normal groups. Normal subjects displayed significant correlations between behavioral ear advantage and hemispheric asymmetry of P3 at parietal and occipital sites (Table 3). The negative sign of these correlations indicates that larger left-ear advantage was associated with greater P3 over the right than over the left hemisphere. In contrast, depressed patients showed positive correlations that attained significance only at the parietal site.

Correlational analyses were also used to determine whether or not reduced P3 amplitude in patients was related to their abnormal ear advantage. No significant correlations were found between overall amplitude of P3 and behavioral asymmetry scores for either patients ($r = -.22$ to $.09$ at frontal to occipital sites) or normals ($r = -.04$ to $.14$).

Clinical Correlates

The relation of both P3 amplitude and asymmetry to clinical features of patients was examined in two ways. First, the relation to severity of depression was evaluated using pretreatment Hamilton Depression Scale scores. No significant relationship was found between severity of depression and P3 amplitude ($r = -.12$ to $-.01$ at frontal to occipital sites). Greater severity was associated with relatively larger P3 over the right than over the left frontal site ($r = .32, p < .05$). However, no significant correlation between severity and P3 asymmetry was found for more posterior sites where P3 is maximum ($r = -.05$ to $.08$ at central to occipital sites). Second, the relation to treatment outcome was evaluated using the difference in Hamilton Depression Scale scores before and after treatment as an index of clinical improvement. A subset of 27 patients received 6–12 weeks of treatment, as part of ongoing drug studies, with one of the following: fluoxetine ($n = 17$), tricyclic antidepressant ($n = 2$), or placebo ($n = 8$). Clinical improvement was significantly correlated with pretreatment P3 amplitude at occipital sites ($r = .41, p < .05$) but not at more anterior sites. Smaller P3 amplitude was associated with less clinical improvement. There was, however, no significant relationship between pretreatment P3 asymmetry and this index of clinical improvement ($r = .07$ to $.22$ at frontal to occipital sites).

Discussion

P3 Reduction in Depression

Depressed patients had smaller P3 amplitude than did normal controls in a cognitively demanding dichotic pitch discrimination task. This result is consistent with prior findings of reduced P3 amplitude in depressed patients during auditory or visual oddball tasks (Blackwood et al., 1987; Diner, Holcomb, & Dyk-

Table 3. Correlations Between Hemispheric Asymmetry of P3 and Behavioral Asymmetry Scores

Electrodes	Normals	Patients
Frontal	-.15	.09
Central	-.35	.20
Parietal	-.63**	.39**
Occipital	-.65**	.09
Overall	-.58**	.28

** $p < .01$.

man, 1985; Roth et al., 1981). The reduction of P3 amplitude in depressed patients was not lateralized but was present equally at electrode sites over each hemisphere. Reduced P3 amplitude was also unrelated to the abnormal behavioral asymmetry observed for dichotic pitch discrimination. This study, therefore, provided no evidence that P3 reduction in depressed patients is related to a lateralized dysfunction.

Although the basis for the P3 reduction in depressed patients remains unclear, the findings of this study provide some clues. The lack of a difference in N1 amplitude between depressed patients and controls suggests that the P3 reduction was not due to a deficit in early sensory-attentional processing. Moreover, all patients were carefully screened to exclude those with a hearing loss, and patients did not differ from normal controls in overall accuracy of dichotic pitch discrimination. The normal performance level of depressed patients also argues that their P3 reduction did not result from a generalized deficit, for example, due to reduced motivation or effort. The findings for depressed patients are more consistent with an alteration in later cognitive processes that are thought to modulate P3 amplitude, for example, stimulus evaluation, working memory, or judgmental processes.

Abnormal Behavioral and P3 Asymmetries in Depression

Depressed patients differed from normal controls in both their behavioral ear advantages and P3 asymmetries in response to complex tones. Patients failed to show the left-ear (right hemisphere) advantage seen for normal adults (Sidtis, 1981; Tenke et al., 1993), which replicates the findings of several other studies that have used nonverbal dichotic listening tests (Bruder, 1988; Bruder et al., 1989; Johnson & Crockett, 1982; Overby et al., 1989). Depressed patients also did not show the behavior-related hemispheric asymmetries of P3 seen for normal subjects. In normal adults, behavioral ear advantages for complex tones were associated with hemispheric asymmetries of P3 amplitude over posterior sites. Normal subjects with a strong left-ear advantage had greater P3 amplitude over the right than left hemisphere sites, whereas normal subjects with little or no left-ear advantage had the opposite hemispheric asymmetries of P3. In contrast, depressed patients showed essentially no hemispheric asymmetry of P3 amplitude, regardless of their behavioral ear advantages. These findings, together with the absence of behavior-related hemispheric asymmetries of earlier ERP components (N1 or P2), support the conclusion that the abnormal perceptual asymmetry for dichotic pitch discrimination in depressed patients is related to a relatively late stage of cognitive processing, which is reflected in the P3 component.

There is evidence that behavioral ear advantages for dichotic listening tests are mediated by asymmetric cognitive processing. Greater P3 amplitude over the right than the left hemisphere in normal adults with a left-ear advantage on the complex tone test may reflect greater activation of right hemisphere sites that are thought to be involved in complex pitch discrimination (Sidtis, 1980; Sidtis & Volpe, 1988; Tenke et al., 1993). This possibility is supported by the findings of an imaging study that recorded regional cerebral blood flow during a dichotic pitch discrimination task (Coffey, Bryden, Schroering, Wilson, & Mathew, 1989). Coffey et al. found that subjects with a left-ear advantage showed greater activation of right posterior temporal cortex, whereas subjects with the opposite ear advantage showed greater activation of the left temporal region. Studies measur-

ing ERPs during verbal dichotic listening tasks have likewise found that behavioral ear advantages are accompanied by greater amplitudes of late positive potentials over the contralateral hemisphere (Ahonniska, Cantell, Tolvanen, & Lyytinen, 1993; van de Vijver, Kok, Bakker, & Bouma, 1984).

One interpretation of the lack of a left-ear advantage and associated P3 asymmetry in depressed patients is that it results from a failure to activate right hemisphere mechanisms for complex pitch discrimination. Sidtis (1980) presented evidence that the magnitude of left-ear (right hemisphere) advantage for dichotic pitch discrimination depends on the number of overtones present in the tonal stimuli and that the right hemisphere is specialized for the analysis of this harmonic information. He also suggested that complex pitch perception typically involves tonotopic analysis for which temporal lobe function is necessary. An abnormality of this process in depressed patients may therefore arise from a disturbance of right hemisphere function comparable to that which is presumed to underlie visuospatial deficits in depressed patients (Bruder et al., 1992; Flor-Henry, 1976). A problem with this interpretation is that depressed patients did not show poorer dichotic pitch discrimination than did controls. They may, however, have been able to compensate by using alternative processing strategies that rely more on the left hemisphere. This tentative interpretation will require empirical support.

Same and Different Judgments in Depression

Depressed patients also showed less difference between hemispheric asymmetries for *same* and *different* conditions when compared with normal subjects. Given that these hemispheric asymmetries were found for both P3 and slow wave and were maximal at frontocentral rather than at posterior sites, it is likely that they reflect a component that overlaps P3, such as frontal slow wave activity. In normal subjects, P3 and slow wave amplitude at frontocentral sites was greater over the left than over the right hemisphere when the probe tone was different from the dichotic pair, but the opposite hemispheric asymmetry was present when the probe tone was the same as a member of the dichotic pair. This finding is consistent with the view that *different* and *same* judgments are mediated by distinct hemispheric processes (Magnani, Mazzucchi, & Parma, 1984; Taylor, 1976). This differential pattern of hemispheric asymmetry for *same* and *different* judgments was less evident in depressed patients.

Normal subjects also showed a difference in N1 amplitude for *same* and *different* conditions, which depended on the subject's behavioral ear advantage. Normal subjects with a strong left-ear advantage had greater N1 amplitude when the probe tone was the same as a member of the dichotic pair, whereas those with no left-ear advantage had greater N1 amplitude when the probe tone was different from the dichotic pair. One possibility is that subjects with a strong left-ear advantage were more attentive or responsive to a match between the dichotic pair and probe tone, and subjects with no left-ear advantage were more attentive or responsive to a difference between these stimuli. This difference in response could in turn be related to a difference in hemispheric activation between these subjects, with strong-left-ear-advantage subjects being more likely to activate their right hemisphere and no-left-ear-advantage subjects being more likely to activate their left hemisphere. The lack of this pattern of asymmetric hemispheric activation in depressed patients could likewise account for the absence of these N1 effects in patients. The main difficulty with this tentative interpretation

is the short latency of the effect (i.e., 100 ms), which may precede the point at which subjects can behaviorally discriminate a difference between *same* and *different* conditions. Clearly, further research is needed to determine the nature of the differences in N1 amplitude for *same* and *different* conditions.

Clinical Correlates of P3 Amplitude and Asymmetry in Depression

P3 amplitude reduction was not related to severity of depressive illness as measured by the Hamilton Depression Scale, which is in accord with prior findings (Diner et al., 1985; Roth et al., 1981). A significant correlation was found between severity of depression and hemispheric asymmetry of P3 at frontal sites. Because amplitude of P3 is smallest at these sites, this relationship may be due to an overlapping ERP component or to an asymmetry of frontal EEG alpha (Davidson, 1992). A study is now

underway to examine the relationship of P3 and alpha asymmetries in depressed patients.

Pretreatment P3 amplitude was related to subsequent treatment outcome, with smaller P3 amplitude at occipital sites being associated with less clinical improvement. A similar situation may also exist in schizophrenic patients, where smaller P3 amplitude was related to poorer outcome of treatment with an antipsychotic (Ford et al., 1994). Although preliminary, such findings are of potential clinical importance because they could lead to the development of psychophysiological measures of value for selecting optimal treatments for individual patients. Hemispheric asymmetry of P3 was not, however, related to treatment outcome. Further research with larger samples of patients treated with fixed doses of specific antidepressants will need to be done before conclusions can be drawn about the clinical utility of P3 measures as predictors of treatment outcome.

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