Hearing Loss and Asymmetry in Major Depression

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To assess patterns of hearing loss and asymmetry in major depressive disorder (MDD), pure-tone and brief-click audiometric thresholds were measured in 59 inpatients with MDD and 40 normal control subjects. For both tasks, patients had higher bilateral thresholds, with marked hearing loss for the highest pure-tone frequency. At lower frequencies, patients displayed significant asymmetry, with poorer hearing in the left ear. After ECT, patients maintained the bilateral hearing losses; however, the baseline asymmetry resolved. These findings suggest that bilateral hearing loss may be a stable characteristic in severe depression. Poorer left ear pure-tone hearing may be present during the depressed state. The baseline asymmetry in audiometric deficits suggests right-hemisphere dysfunction in severe MDD.

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Impaired auditory acuity has long been noted in psychiatric patients.[1] Several studies have documented hearing loss in mood disorders.[2–4] Recent evidence also suggests that individuals with depressive disorders show atypical patterns of lateralization as measured by auditory and visual performance asymmetries.[5–9]

The visual pathways are essentially fully lateralized to the level of the primary visual cortex, such that input from each visual hemifield projects only to the contralateral hemisphere. In contrast, afferents to the primary auditory cortex are characterized by ipsilateral as well as contralateral projection. Despite this lack of full anatomic lateralization, several lines of evidence indicate that contralateral auditory connections predominate over ipsilateral connections. First, patients with unilateral lesions in the auditory cortex have increased reaction time and elevated monaural brief-click threshold for stimuli presented to the contralateral ear.[10] Second, right hemispherectomy has been shown to result in a 5–10-dB pure-tone hearing loss in the left relative to the right ear.[11] Third, evoked potential and single cell recording studies

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indicate greater responses in the contralateral auditory cortex (compared with the ipsilateral auditory cortex) to monaural auditory stimuli.[12,13] Fourth, in normal adults, dichotic listening tests, which involve the simultaneous presentation of different stimuli to each ear, typically show a right ear advantage for verbal stimuli[14,15] and a left ear advantage for nonlinguistic or musical stimuli.[16–18] Similar ear advantages have also been found with monaural presentation of information-processing tasks. Structural right and left temporal lesions may result in the loss of the normal left and right ear advantages for nonverbal and verbal dichotic listening tasks, respectively.[19,20] In this light, it appears reasonable to use monaural auditory thresholds as indirect measures of contralateral hemispheric function.

Studies of hearing abnormalities in depressed patients may be complicated by nonsensory variables such as apathy, poor attention, and low motivation. Forced-choice paradigms and audiometric threshold testing over a range of frequencies may help minimize these effects. Given the results of previous investigations,[2–4] we hypothesized that patients with major depression have bilateral hearing deficits, as evidenced by elevated pure-tone and brief-click thresholds for monaural stimuli. However, it is as yet unclear whether this is a stable characteristic or a state-dependent phenomenon. It is also unclear whether depressed patients display auditory asymmetry in monaural tests and whether such asymmetry, if present, changes with treatment. For example, on a nonverbal dichotic test, Bruder et al.[7] found that melancholic depressed patients lacked the normal left ear (right hemisphere) advantage. Williams et al.[8] found that electroconvulsive therapy (ECT) led to a restoration of the normal asymmetry pattern for verbal dichotic listening tests. Longitudinal study is required to evaluate the stability of lateralization abnormalities in depressive disorders.

To assess patterns of hearing loss and asymmetry in major depression, as well as the effects of state change on these measures, we tested 59 severely depressed inpatients and 40 matched, healthy normal control subjects for pure-tone and brief-click thresholds.

METHODS

Subjects

On evaluation with the Schedule for Affective Disorders and Schizophrenia,[21] the patients ($n = 59$) met the Research Diagnostic Criteria[22] (RDC) for major depressive disorder (MDD), endogenous subtype. They all had pretreatment scores greater than 18 (mean ± SD = 30.4 ± 8.2) on the 24-item Hamilton Rating Scale for Depression[23] (Ham-D) and had a negative lifetime history for neurological illness, schizophrenia, schizoaffective disorder, other functional psychoses, rapid-cycling bipolar disorder, and organic mental disorders. They had been free of alcohol or substance abuse for at least 1 year and had a negative lifetime history for alcohol or substance dependence. Following informed consent, subjects were maintained medication free for at least 5 days before baseline auditory testing, with the exception of lorazepam (up to 3 mg/day as needed). All were inpatients at the New York State Psychiatric Institute, where the Institutional Review Board approved the study.

Control subjects ($n = 40$), recruited from the community, had a negative lifetime history for all RDC disorders and for neurological illness, and they had no current medical illnesses. They were medication free for at least 4 weeks before each assessment. They were matched to the patient sample with respect to age, gender, education, socioeconomic status, and verbal IQ. Patient and control characteristics are presented in Table 1. All patients and control subjects were right-handed.[24]

Audiometric Procedures

A Maico MA27 audiometer and standard audiological evaluation procedures were used. One-second pure tones at frequencies of 250, 500, 1,000, 2,000, 4,000, and 8,000 Hz were presented monaurally. Sound intensity at each frequency was changed in 5-dB steps, following standard up-and-down-staircase procedures, with the order of the threshold measurement for each frequency being random across blocks. Subjects whose mean pure-tone threshold was greater than 35 dB (across both ears and all frequencies) were excluded from the study. Four patients and no control subjects were excluded for this reason.

TABLE 1. Subject characteristics

	Control Subjects ($n = 40$)	Patients ($n = 59$)
Age (years)	54.2 ± 12.3	52.3 ± 14.4
Gender (% female)	70	56
Education (years)	14.9 ± 2.4	13.6 ± 3.0
Socioeconomic status[a]	2.6 ± 1.2	2.5 ± 1.3
Verbal IQ	105.6 ± 12.0	103.1 ± 16.0
Psychotic (%)		45
Bipolar (%)		25
Age at onset (years)		39.1 ± 15.8
Previous affective episodes		3 ± 3
Baseline Ham-D score		30.4 ± 8.2

Note: Values are means ± SD except where otherwise noted. Ham-D = Hamilton Rating Scale for Depression.
[a]Scored according to the Hollingshead Four-Factor Index, with 1 indicating the highest status and 5 the lowest status.

Brief-click thresholds were measured by using a three-interval temporal forced-choice paradigm, following the procedure of Bruder et al.[2] A saw-tooth click of 0.2 ms duration was presented to either left or right ear during 1 of 3 intervals denoted by lighted diodes. Subjects chose which interval coincided with the click by pointing to the appropriate diode. Click intensity was adjusted in 1-dB steps until a level of 67% accuracy was achieved over 30 trials, using a block up-and-down-staircase procedure. This defined the threshold. Threshold at each ear was assessed separately, with the order randomized across subjects. Subjects whose mean brief click threshold was greater than 55 dB (across both ears) were excluded from the study. Two patients and no control subjects were excluded for this reason.

Treatment and Clinical Evaluation

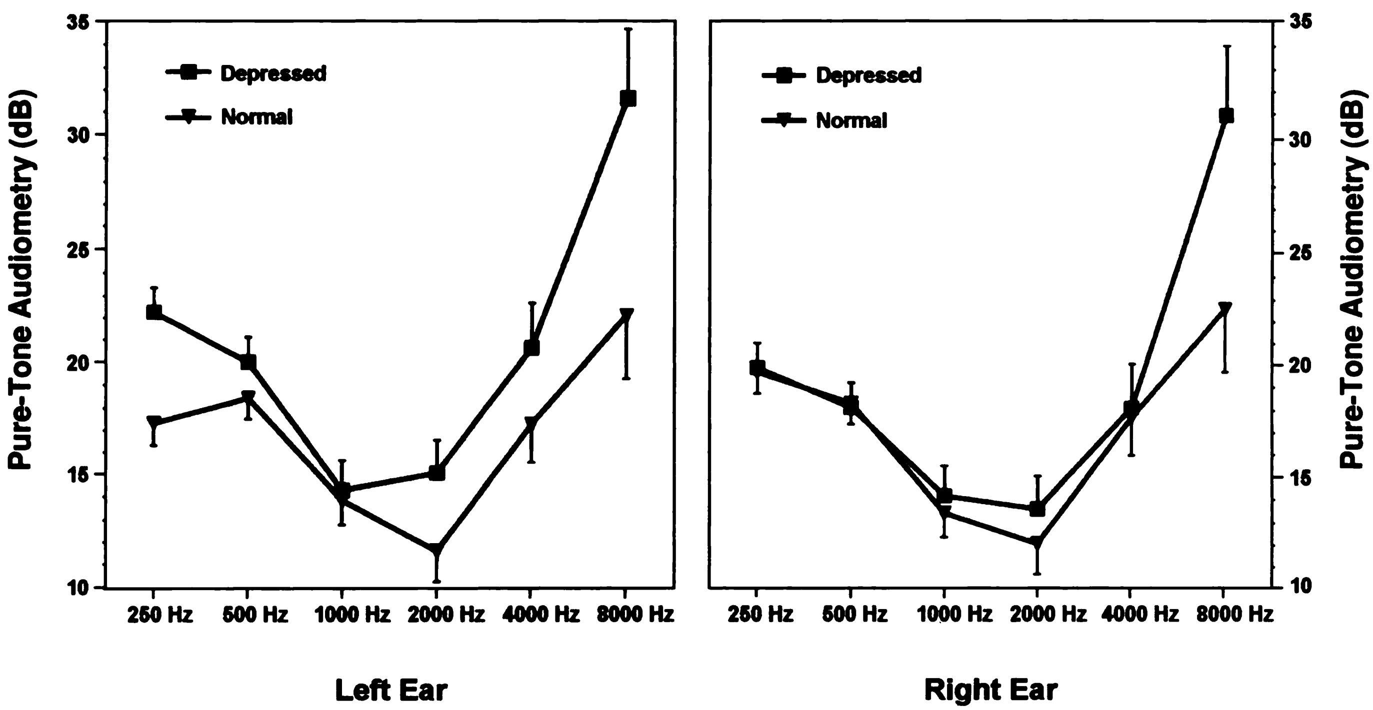
Patients participated in one of two consecutive ECT research protocols.[25,26] In both studies, treatments were given with either unilateral or bilateral electrode placement. The ECT procedures are detailed in Sackeim et al.[26] Patients were evaluated with the Ham-D before their first treatment, at least twice weekly during treatment, and within a week after their last treatment. They were considered to have responded if they had a reduction of more than 60% in their Ham-D scores that was maintained for at least 1 medication-free week and a total Ham-D score of 16 or lower. Patients underwent auditory testing before their first treatment and within a week of their last treatment. A subgroup of patients were also retested 2 months after completion of ECT. During the follow-up period, all patients received maintenance pharmacotherapy with antidepressant medications. Control subjects were assessed at comparable intervals.

RESULTS

Pure-Tone Audiometry

Figure 1 presents the baseline pure-tone audiometric thresholds for the patient and control groups. A repeated-measures analysis of covariance (ANCOVA), with diagnostic group and gender as between-subject variables, frequency (6 levels) and ear as repeated measures, and age as a covariate, yielded main effects of diagnostic group ($F = 9.07$, df = 1,465, $P < 0.005$), frequency ($F = 11.97$, df = 5,93, $P < 0.0001$), and age ($F = 71.15$, df = 1,93, $P < 0.0001$). There was also a significant interaction between diagnostic group and frequency ($F = 2.70$, df = 5,465, $P = 0.02$) and a trend for an interaction between diagnostic group and ear ($F = 3.31$, df = 1,93, $P = 0.07$). To follow up the interaction between diagnostic group and frequency, ANCOVAs were conducted on thresholds at each frequency averaged across both ears,

FIGURE 1. Pure-tone audiometric thresholds in depressed and control subjects at baseline. Error bars indicate standard error of the mean.



with diagnostic group and gender as between-subject variables and age as a covariate. There was a main effect of diagnostic group at 8,000 Hz ($F = 7.45$, df = 1,93, $P < 0.01$), and there were trends toward a main effect of diagnostic group at 250 Hz ($F = 3.41$, df = 1,93, $P = 0.07$), 2,000 Hz ($F = 3.33$, df = 1,93, $P = 0.07$), and 4,000 Hz ($F = 7.06$, df = 1,93, $P = 0.08$).

As illustrated in Figure 1, the depressed group had exceptionally poor hearing in both ears at 8,000 Hz, whereas group differences were smaller at the other frequencies. The original repeated-measures ANCOVA was conducted again, dropping the 8,000-Hz frequency. The main effect of diagnostic group was still significant ($F = 4.42$, df = 1,93, $P < 0.05$). The only substantive changes in the findings were that the interaction between group and frequency no longer approached significance ($P = 0.85$) and the interaction between group and ear was significant ($F = 7.29$, df = 1,93, $P < 0.01$).

Across the 250–4,000-Hz frequency range, the patient group had 1.7 ± 3.7 dB poorer hearing in the left than the right ear ($t = 3.55$, df = 58, $P < 0.001$). Normal subjects evidenced no asymmetry, averaging 0.5 ± 3.0 dB better hearing in the left ear ($t = -1.05$, df = 39, $P = 0.3$). To explore further the interaction between diagnostic group and ear, we conducted post hoc paired *t*-tests at each frequency. Among the depressed patients, we found a significant asymmetry in the direction of higher left ear thresholds at 250 Hz ($t = 3.51$, df = 58, $P < 0.001$), 500 Hz ($t = 2.81$, df = 58, $P < 0.01$), and 4,000 Hz ($t = 2.38$, df = 58, $P = 0.02$) but not at other frequencies. Among normal subjects, we found significant asymmetry only at 250 Hz, with better hearing in the left ear ($t = -2.71$, df = 39, $P = 0.01$).

Forty-four depressed patients and 33 control subjects were retested at the post-ECT time point. Given the findings at baseline, we analyzed separately the posttreatment audiometric data for 8,000 Hz and all other frequencies. As illustrated in Figure 2, the bilateral high-frequency hearing loss at 8,000 Hz did not resolve after treatment. A repeated-measures ANCOVA on bilaterally averaged thresholds at 8,000 Hz, with diagnostic group as between-subject factor, age as a covariate, and time point (pre- or posttreatment) as the repeated-measures factor, yielded only a main effect of diagnosis ($F = 9.99$, df = 1,71, $P < 0.005$) and of age ($F = 38.89$, df = 1,71, $P < 0.0001$). Hearing loss at the lower frequencies, although less marked than at 8,000 Hz, also did not resolve after treatment. However, the threshold asymmetry noted in depressed patients at the lower frequencies did resolve. A repeated-measures ANCOVA on threshold values between 250 and 4,000 Hz, with diagnostic group and gender as between-subject factors, age as a covariate, and time point and ear as repeated measures, yielded a main effect of diagnostic group ($F = 5.64$, df = 1,72, $P = 0.02$) and age ($F = 22.7$, df = 1,72, $P < 0.0001$). The only effect involving time point was the interaction between diagnostic group, ear, and time point ($F = 8.07$, df = 1,72, $P < 0.01$). This finding indicated that threshold asymmetry changed over time as a function of diagnostic group.

Auditory threshold asymmetry values were computed at each time point across the 250–4,000-Hz frequency range. As in the previous analysis, the depressed group had significantly poorer hearing in the left ear at baseline (2.1 ± 3.9 dB, $t = 3.54$, df = 43, $P = 0.001$). However, as illustrated in Figure 3, the depressed patients lost their baseline hearing asymmetry after treatment (0.3 ± 4.8 dB, $t = 0.41$, df = 43, $P = 0.69$). The change in asymmetry was significant within the depressed group ($t = 2.57$, df = 43, $P < 0.02$). In contrast, normal subjects showed no asymmetry at either baseline (–0.4 ± 3.1 dB, $t = -0.67$, df = 32, $P = 0.51$) or follow-up (0.8 ± 3.7 dB, $t = 1.33$, df = 32, $P = 0.19$).

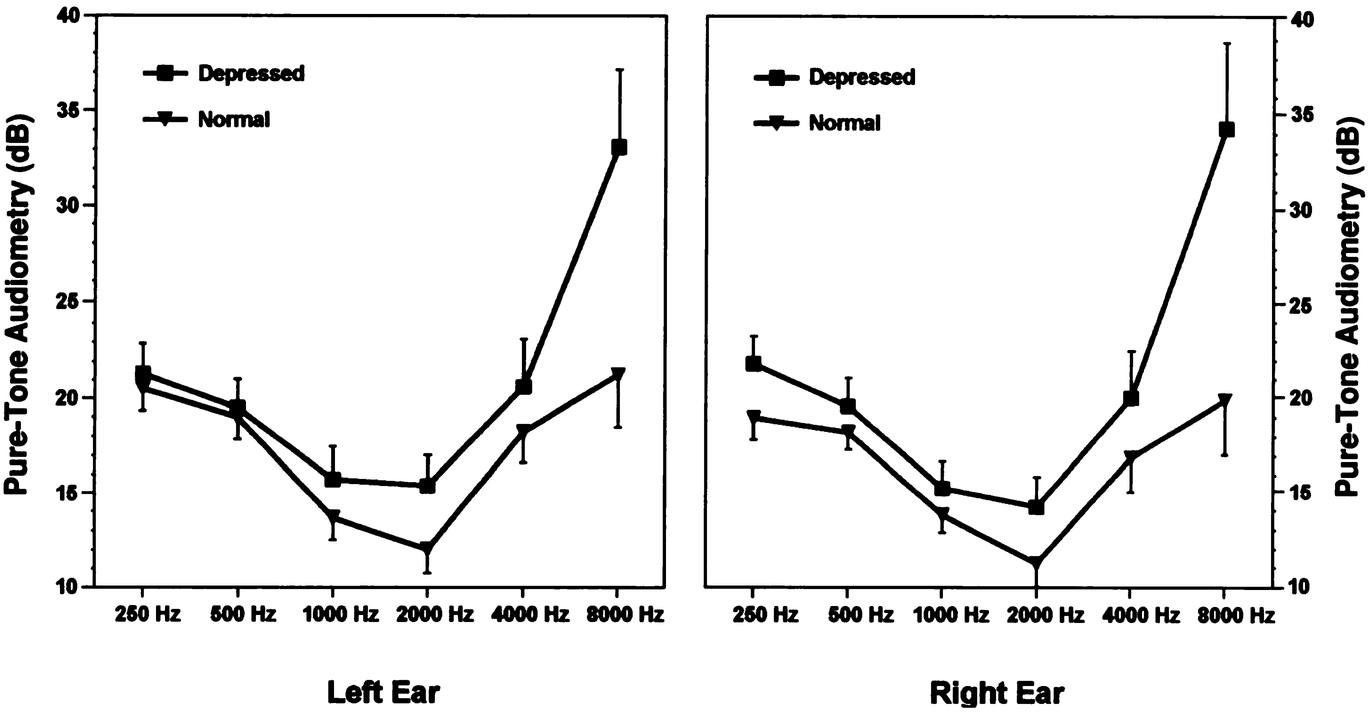
Subsequent analyses indicated that neither clinical outcome nor electrode placement (right unilateral versus bilateral) during ECT were related to the changes in bilateral thresholds or in asymmetry in the depressed group. For example, an ANCOVA on the change in asymmetry in the 250–4,000-Hz range, with response status and electrode placement as between-subject variables, yielded no significant effects.

At 2-month follow-up, euthymic patients still evidenced high-frequency hearing loss. A repeated-measures ANCOVA, with gender as between-subject variable, time point at baseline and 2 months in remission as the repeated measures, and age as a covariate, was conducted on the bilaterally averaged auditory thresholds at 8,000 Hz for 20 successfully treated patients. Only a main effect of age was significant ($F = 21.83$, df = 1,17, $P = 0.0002$). The baseline threshold asymmetry at the lower frequencies, which had resolved immediately following ECT, remained resolved at 2-month follow-up. A repeated-measures ANCOVA on averaged auditory thresholds of patients in the 250–4,000-Hz range, with gender as between-subject variable, time point (baseline and 2 months in remission) and ear as repeated measures, and age as a covariate, yielded a main effect of age ($F = 6.47$, df = 1,17, $P < 0.05$) and an interaction between time point and ear ($F = 6.03$, df = 1,17, $P < 0.05$). In this subgroup, poorer hearing in the left ear at baseline (mean = 1.20 dB, SD = 4.28) was reduced by half at 2-month follow-up (mean = 0.65 dB, SD = 3.20).

Brief-Click Thresholds

Table 2 presents baseline brief-click thresholds for the patient group ($n = 44$) and the control group ($n = 39$). A repeated-measures ANCOVA on click thresholds, with

FIGURE 2. Pure-tone audiometric thresholds in patients and control subjects after completion of ECT course. Control subjects were retested at a comparable interval (about 3 weeks). Error bars indicate standard error of the mean.



diagnostic group and gender as between-subject variables, ear as a repeated-measures factor, and age as a covariate, yielded a main effect of diagnostic group (F = 10.78, df = 1,78, $P < 0.002$), with patients having an average threshold 4 dB higher than control subjects, a main effect of age (F = 19.59, df = 1,78, $P < 0.0001$), and a significant interaction between diagnostic group, gender, and ear (F = 6.30, df = 1,78, $P < 0.02$). Within-group analyses indicated that the only subgroup to show significant asymmetry were depressed females (t = 2.10, $P < 0.05$), whose brief-click threshold averaged 2.7 ± 5.9 dB higher in the left than the right ear.

Thirty-one depressed patients and 39 control subjects were retested at the post-ECT time point. As in the case of pure-tone audiometry, the bilateral elevated click thresholds in the depressed subjects did not resolve after treatment. A repeated-measures ANCOVA on click thresholds, with diagnostic group and gender as between-subject factors, age as a covariate, and time point (pre- or posttreatment) and ear as the repeated measures, yielded main effects of diagnosis (F = 14.27, df = 1,65, $P < 0.0005$) and age (F = 8.65, df = 1,65, $P < 0.005$), as well as interactions between ear, diagnosis, and gender (F = 4.87, df = 1,65, $P < 0.05$) and between time point, ear, diagnosis, and gender (F = 4.08, df = 1,65, $P < 0.05$). Unlike the control subjects, whose brief-click thresholds improved slightly on their second testing (1.4 ± 3.3 dB, t = 2.66, $P < 0.02$), the depressed patients maintained their elevated bilateral thresholds after treatment (–0.1 ± 8.3 dB, t = –0.05, P = 0.96). Among the depressed patients, men and women differed in the direction of threshold asymmetry changes. However, despite the significant four-way interaction, none of the changes in asymmetry as a function of gender and diagnosis were significant. As in pure-tone audiometry, clinical response and ECT modality did not influence the pattern of asymmetry.

At 2-month follow-up, 13 euthymic patients still evidenced elevated binaural brief-click thresholds. A repeated-measures ANCOVA on bilaterally averaged brief-click thresholds, with gender as between-subject variable, time point at baseline and 2 months in remission as the repeated measures, and age as a covariate, yielded no significant effects or interactions.

Baseline Clinical Correlates

Potential clinical correlates of baseline audiometric thresholds in the depressed group were examined. We conducted a series of simultaneous multiple regressions with age, pretreatment Ham-D score, diagnosis of unipolar or bipolar depression, and diagnosis of psychotic or nonpsychotic depression as predictor variables. The de-

FIGURE 3. Pure-tone audiometric hearing asymmetries in depressed patients and control subjects at baseline and after completion of ECT course. Control subjects were retested at a comparable interval (about 3 weeks). Values are left ear minus right ear averaged thresholds at 250 to 4,000 Hz. Error bars indicate standard error of the mean.

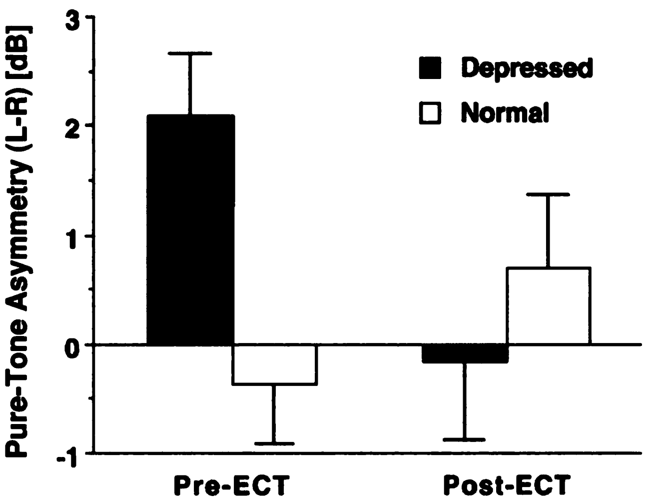


TABLE 2. Brief-click thresholds at baseline

Group	Decibels (Mean ± SD) Left Ear	Right Ear	Asymmetry
Patients			
Male ($n = 22$)	35.8 ± 9.3	36.9 ± 8.3	−1.2 ± 4.6
Female ($n = 22$)	39.3 ± 10.7	36.7 ± 10.5	2.7 ± 5.9
Control subjects			
Male ($n = 12$)	31.3 ± 4.0	30.1 ± 5.9	1.3 ± 4.8
Female ($n = 27$)	34.1 ± 5.8	34.6 ± 6.3	−0.5 ± 4.3

pendent variables were bilaterally averaged audiometric thresholds across the 250–4,000-Hz frequency range, bilateral thresholds at 8,000 Hz, bilateral brief-click thresholds, and asymmetry in audiometric (250–4,000 Hz) and click thresholds. Other than an effect of age for all bilateral parameters, there was only one other significant effect. Patients with bipolar depression had significantly higher bilateral brief-click thresholds (41.0 ± 10.4 dB) than patients with unipolar depression (36.0 ± 8.9 dB), ($t = 2.59$, df = 1,37, $P = 0.01$).

DISCUSSION

By use of two independent methods, this study documented hearing deficits in a population of severely depressed, neurologically intact patients compared with matched normal control subjects. The study has two main findings. First, depressed patients had bilateral hearing loss that did not resolve with treatment. Second, depressed patients evidenced state-dependent hearing asymmetries, with poorer hearing in the left ear. *A priori* audiometric criteria were used to exclude subjects who evidenced gross hearing impairment at baseline. Several depressed patients but no control subjects were excluded, further underscoring the validity of the findings.

The pattern of bilateral pure-tone hearing loss was specific; that is, the highest frequency (8,000 Hz) was more affected than the lower frequencies. The frequency specificity suggests that the bilateral hearing loss is not likely to be attributable to attentional or motivational variables. This high-frequency pure-tone hearing loss resembles the sensorineural hearing loss observed in normal aging.[27]

The pure-tone and brief-click binaural hearing losses did not improve with treatment, regardless of clinical outcome. This finding suggests that binaural hearing loss may be a stable characteristic in severe major depression. The pattern of hearing losses resembles that of "normal" aging, which suggests that it may reflect accelerated aging effects or other subtle neurological impairment. In the subgroup of patients who were euthymic for 2 months at the time of follow-up, bilateral pure-tone and brief-click deficits remained unresolved. This finding lends further support to the hypothesis that the bilateral deficits observed at baseline were not the result of attentional or motivational variables associated with a depressed mood, but rather may reflect a stable characteristic of patients with severe major depression.

In contrast, the pure-tone hearing asymmetry in the depressed group was notable for its resolution after treatment. At baseline, the brief-click hearing asymmetry in depressed patients was contingent upon female gender. Female patients had approximately 3 dB poorer hearing in the left ear, and this asymmetry also resolved after treatment. Our findings suggest that asymmetry in pure-tone and brief-click hearing (left worse than right) may be a state characteristic in severe major depression. The finding that the baseline brief-click asymmetry, but not the pure-tone asymmetry, was contingent upon female gender suggests that reception and processing of brief and longer duration auditory stimuli are subserved by different neural systems, in accordance with the findings of Karasseva.[10]

In this study, we found state-dependent auditory asymmetries with poorer left ear hearing in depressed patients. Several published studies[5,8,28,29] (and G. E. Bruder et al., submitted for publication) have suggested that abnormal patterns of perceptual asymmetry in mood disorders may change as a function of affective state. On the other hand, the normal left ear advantage for dichotic complex tones was found to be absent in nonmelancholic depression,[7] and this abnormality did not resolve after treatment with tricyclic antidepressants.[30] Our findings suggest that there is an asymmetry in auditory perception in major depression, indicative of right hemispheric dysfunction, and that it resolves with ECT treatment regardless of clinical outcome for depression. Our baseline findings are in agreement with two lines of evidence that have documented right hemispheric dysfunction in MDD. Classic neuropsychological testing revealed right hemispheric cognitive deficits in MDD,[31–33] and dichotic listening tests and tachistoscopic split-field tests have documented left sensory field perceptual deficits in major depression.[5–8,34,35]

Curiously, we found that auditory asymmetries in depressed patients resolved after electroconvulsive therapy, even among patients who did not respond to treatment. This finding raises the question of whether or not the baseline asymmetry is indeed state dependent. Here it is noteworthy that there were no significant changes in asymmetry on retesting normal control subjects and that even the nonresponders to ECT showed partial clinical improvement.[25,26] Thus, it is possible that the auditory asymmetry is a state-dependent abnormality that is present in severe depression and resolves with small improvements in clinical status. Overall, our findings support the hypothesis, which was suggested by neuropsychological testing, dichotic listening, and tachistoscopic viewing tasks, that severe major depression is accompanied by reversible deficits in right hemispheric function.

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