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Do Tricyclic Responders Have Different Brain Laterality?

Jonathan W. Stewart, Frederic M. Quitkin, Patrick J. McGrath, and Gerard E. Bruder
New York State Psychiatric Institute and Columbia University

A previous study showed that depressed patients who improved with tricyclic antidepressant medication had dichotic complex tones test results suggesting right-hemisphere dysfunction relative to nonresponders and controls (G. E. Bruder et al., 1990). A new sample of 68 depressed patients completed dichotic consonant–vowel (CV) and complex tones (CT) tests and then were treated with imipramine or placebo. A significant Ear × Test × Treatment × Response interaction was accounted for by significantly poorer left-ear accuracy for CVs among imipramine responders compared with nonresponders, placebo responders, and controls. CV left-ear accuracy was also significantly greater among placebo responders than placebo nonresponders and controls. The results only partially replicate the prior study in that evidence of right-hemisphere dysfunction in tricyclic responders was seen for the CV test but not the CT test.

Bruder et al. (1990) reported that depressed patients who responded to a tricyclic antidepressant lacked the left-ear advantage for dichotic complex tones seen in both tricyclic nonresponders and controls. Because stimuli presented to the left ear are preferentially processed in the right temporoparietal region (Coffey, Bryden, Schroering, Wilson, and Mathew, 1989; Gordon, 1970; Zatorre, Evans, Meyer, & Gjedde, 1992), these data suggest that imipramine responsive patients have a relative right-hemisphere dysfunction. This conclusion must be tempered because the study lacked a placebo comparison group and a variety of tricyclic antidepressants were used.

The present study was designed to determine whether the earlier results would replicate. We also included a depressed control group treated with placebo to identify whether differences found in responders could be attributed to patients who improved due to specific drug effects, or to those improving due to nonspecific benefits. Finally, all drug-treated patients were treated with imipramine.

Method

Dichotic listening testing was offered to a consecutive series of depressed outpatients seeking treatment at an outpatient research clinic at the New York State Psychiatric Institute. A never-depressed control group was also recruited. Testing was limited to those with essentially normal hearing, defined as less than 30-dB hearing loss at 500, 1000, and 2000 Hz and no ear difference greater than 10 dB. Entry into a treatment protocol was not dependent on completion of the testing. Patients were aged 18–65, met *Diagnostic and Statistical Manual of Mental Disorders* (3rd ed., rev.; *DSM–III–R;* American Psychiatric Association, 1987) criteria for a depressive disorder, were physically healthy, and signed informed consent.

Description of Patients

The 68 new depressed outpatients included 28 men (41%) and 40 women (59%). Mean age was 35 ± 9 years. Fifty-seven (84%) had major depression and 25 (37%) had dysthymia, including 14 (21%) with double depression (major depression superimposed on dysthymia). Edinburgh Handedness Inventory (Oldfield, 1971) scores indicated that 85% were right handed. Age, sex, and handedness did not differ significantly among treatment-response groups or between treatment-response groups and controls.

Treatment

Most patients were treated in double-blind treatment protocols, including 30 who received imipramine and 31 who were treated with placebo. Randomly assigned placebo capsules were identical to imipramine, which was given in 50 mg capsules. The dose was raised once or twice weekly, depending on protocol, to a maximum of six capsules daily (300 mg if on imipramine), with maximum tolerated dose maintained for the remainder of the trial. Outcome was determined after 6 weeks in three studies (n = 42), and after 12 weeks in one study (n = 19). An additional 7 patients were treated with imipramine following nonresponse to other medication in a formal study, with judgment of improvement made after 12 weeks. Outcome of patients who received at least 4 weeks of treatment but withdrew before the 6- or 12-week final assessment was determined from their last rating. Judgments of treatment response or nonresponse were always made independently of knowledge of dichotic testing results. Responders were patients whose end of study Clinical Global Impression (CGI) Scale (Guy, 1976) Global Improvement rating was "much improved" or "very much improved" compared with pretreatment baseline. All others were considered nonresponders. Analyses (not shown) failed to find a different relationship between testing and outcome in the blindly versus openly treated patients or between 6- and 12-week protocols.

Jonathan W. Stewart, Frederic M. Quitkin, and Patrick J. McGrath, Depression Evaluation Service, New York State Psychiatric Institute and Department of Psychiatry, College of Physicians and Surgeons, Columbia University; Gerard E. Bruder, Department of Biopsychology, New York State Psychiatric Institute and Department of Psychiatry, College of Physicians and Surgeons, Columbia University.

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Correspondence concerning this article should be addressed to Jonathan W. Stewart, Depression Evaluation Service, New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York 10032.

Controls

A sample of 55 medication-free controls also underwent dichotic testing. All controls were without known medical disorders that could affect hearing or brain function and were judged to be free of lifetime *DSM–III–R* Axis I disorder following a screening interview using the schedule for Affective Disorders and Schizophrenia (Endicott & Spitzer, 1978).

Dichotic Listening Testing

The consonant–vowel (CV) test (Berlin, Hughs, Lowe-Bell, & Berlin, 1973) simultaneously presents a different nonsense CV syllable (e.g., "ga," "ba") to each ear; the participant then indicates which CV was heard in each ear. The complex tones (CT) test (Sidtis, 1981) simultaneously presents a CT of different fundamental frequency to each ear. The participant reports whether a subsequent comparison tone is the same as one of the test tones or different from both.

Scoring

Absolute accuracy in each ear was computed for each test from the number of accurate responses divided by the number of presentations times 100. A perceptual asymmetry was also computed for each test: PA = $100 \times (R - L)/(R + L)$, where PA indicates perceptual asymmetry, R indicates right-ear accuracy, and L indicates left-ear accuracy.

Statistical Analyses

Repeated measures analysis of variance (ANOVA) investigated whether ear accuracy differed by treatment and outcome. Test and ear were within-subject factors, and treatment (imipramine or placebo) and response (responder, nonresponder) were between-subject grouping variables. Significant interactions were further investigated by analyses limited to a single ear, test, treatment, or response.

PA scores were also investigated using repeated measures ANOVA. Test was the within-subject repeated measure, and treatment and response were between-subject grouping variables. Significant interactions were further investigated by analyses limited to a single test, treatment, or response.

Treatment–response groups were also compared with the control group by means of *t* tests.

Results

Accuracy

Repeated measures ANOVA of accuracy scores revealed a significant interaction among ear, test, treatment, and response, $F(1, 64) = 5.40$, $p = .023$. Within test, there was a significant Ear × Treatment × Response interaction on the CV test, $F(1, 64) = 4.97$, $p = .029$, but not on the CT test, $F(1, 64) = 0.14$, $p = .713$. Holding ear constant, within the CV test there was a significant Treatment × Response interaction for the left ear, $F(1, 64) = 7.83$, $p = .007$, but not for the right ear, $F(1, 64) = .04$, $p = .847$. As Figure 1 shows, there was little difference in mean right-ear accuracy, while a clear interaction existed for left-ear accuracy. Responders to imipramine had significantly poorer left-ear CV accuracy than placebo responders, $t(9) = 2.68$, $p = .025$. The two nonresponding groups did not differ in left-ear CV accuracy, $t(39) = 1.29$, $p = .204$. Within treatment, imipramine responders had significantly poorer left-ear accuracy on the CV test than did nonresponders, $t(24) = 2.60$, $p = .016$, while placebo responders and nonresponders did not differ, $t(29) = 1.56$, $p = .13$.

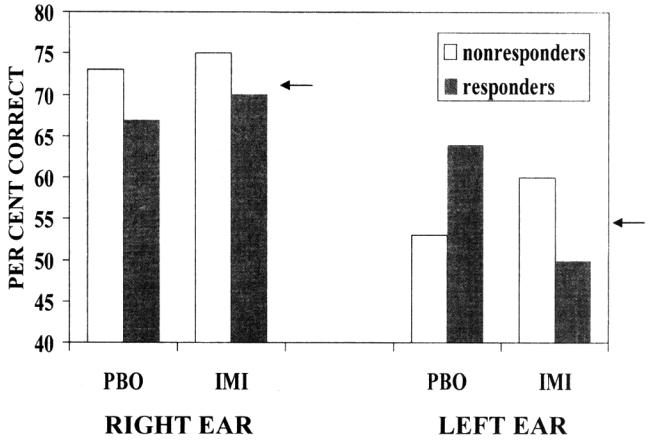

Figure 1. Mean percentage of correct responses on the consonant–vowel test in responders and nonresponders to treatment with imipramine (IMI) or placebo (PBO). Arrow indicates the mean accuracy for each ear for controls.

Asymmetry

Repeated measures ANOVA revealed a significant Test × Treatment × Response interaction, $F(1, 64) = 6.82$, $p = .011$. Holding test constant, there was a significant Treatment × Response interaction for the CV test, $F(1, 64) = 5.42$, $p = .023$, but not for the CT test, $F(1, 64) = .19$, $p = .665$. The significant interaction within the CV test was accounted for by a significantly smaller right-ear advantage among placebo responders compared with both imipramine responders, $t(27) = 2.74$, $p = .011$, and placebo nonresponders, $t(22) = 2.24$, $p = .036$.

Comparisons With Controls

Responders to imipramine or placebo, but not nonresponders to either treatment, differed from controls on the CV test. Left-ear accuracy was significantly better on the CV test for controls than for imipramine responders, $t(49) = 2.27$, $p = .028$. Compared with placebo responders, controls had larger CV asymmetry scores, $t(61) = 2.03$, $p = .047$, with a trend toward poorer left-ear accuracy on the CV test, $t(61) = 1.94$, $p = .057$.

Use of Dichotic Testing to Predict Treatment Outcome

To examine the value of left-ear accuracy on the CV test for predicting treatment outcome, we split the sample at the mean of the controls, as had been done with the earlier sample of patients. Patients with relatively poorer left-ear accuracy on the CV test (below the mean of controls) showed a significant difference between response rates to imipramine and placebo—64% responded to imipramine and 13% responded to placebo, $\chi^2(1, N = 43) = 8.25$, $p = .004$. Patients with CV left-ear accuracy above the control mean responded about equally to imipramine and placebo—33% responded to imipramine and 38% to placebo, $\chi^2(1, N = 25) = .043$, $p = .84$. Individual left-ear accuracy scores are shown in Figure 2.

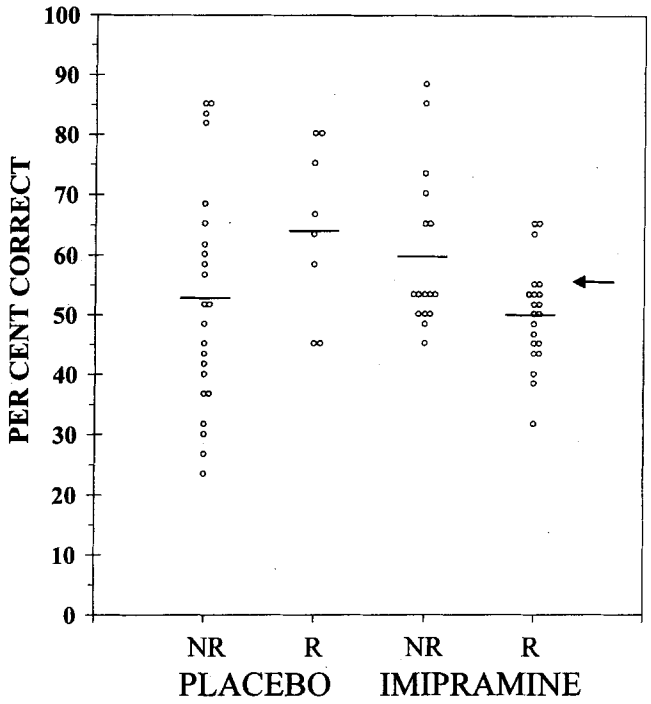

Figure 2. Left-ear accuracy on the consonant–vowel test for responders (R) and nonresponders (NR) to treatment with imipramine or placebo. Horizontal lines indicate group means. Arrow indicates the mean accuracy for controls.

Discussion

In an earlier study (Bruder et al., 1990), patients who responded to a tricyclic antidepressant differed from nonresponders and healthy controls in failing to show a left-ear advantage for dichotic CTs, which was interpreted as suggesting right-hemisphere dysfunction. This specific finding was not replicated in the present study. There were, however, significant differences between these groups in their left-ear accuracy on the dichotic CV test. Namely, patients who improved when given a tricyclic antidepressant had significantly poorer left-ear accuracy on this test when compared with nonresponders, placebo responders, or controls. Although this finding also provides evidence for a dysfunction in tricyclic responders involving the right hemisphere, the absence of between-group differences on the CT test raises questions about the validity of this interpretation. One possible reason for the difference in findings across studies for the CT test may relate to the smaller perceptual asymmetries and lower reliabilities generally found for nonverbal than for verbal dichotic listening tests (Bruder, 1991). Also, while tricyclic responders tended to have poorer left-ear performance than nonresponders on both the CT and CV tests, the effect sizes were smaller for the CT test in both the present study (.75 vs. .14) and the earlier study (.66 vs. .49). The smaller effect size for the CT test would limit the power to detect between-groups differences.

Levy, Heller, Banich, and Burton (1983) suggested a unifying theory that might bring together the seemingly disparate findings of the earlier study with those of the current study. These authors suggested that each individual has a characteristic perceptual asymmetry that influences performance across both verbal and nonverbal perceptual tests. Some individuals show increased left-hemisphere dominance for verbally presented information together with decreased right-hemisphere advantage for nonverbal information, while others have the opposite direction of characteristic perceptual asymmetry. Kim and Levine (1992) validated this theory by applying a principal components analysis to results from several perceptual tests demonstrating a common factor that accounted for about half the between-subject variation in perceptual asymmetry. Indeed, in the current study, significant correlations were found for left-ear accuracy on the CT and CV tests ($r = .41$, $p < .001$), for asymmetry scores on the two tests ($r = .29$, $p < .02$), and between CV asymmetry score and left-ear accuracy on the CT test ($r = .38$, $p < .005$). The other four correlations of interest were not significant. Thus, the direction of asymmetry shift may be critical in identifying specific tricyclic responders rather than the specific test demonstrating this effect. Support for this interpretation is provided by a study of perceptual asymmetry differences between responders and nonresponders to treatment with the antidepressant fluoxetine (Bruder et al., 1996). Treatment responders differed from nonresponders in showing a characteristic perceptual asymmetry favoring the left over the right hemisphere across dichotic word and CT tests.

Because the earlier study did not include a group treated with placebo, it was ambiguous whether to attribute differences between treatment responders and nonresponders to specific medication effects or to nonspecific factors. The current study found relatively poor left-ear accuracy in imipramine responders but not in placebo responders, indicating that relative right-hemisphere dysfunction characterizes patients who require specific imipramine effects in order to improve.

The predictive value of dichotic testing was demonstrated by splitting the sample at the mean of the controls. Left-ear accuracy on the CV test separated patients into one subgroup that fared no better on drug than on placebo, and another that had a fairly robust drug response while infrequently benefiting from placebo. Presumably, the group that is as likely to benefit from placebo as from drug is not experiencing a true drug effect and therefore should not receive it. Conversely, the group that showed relative right-hemisphere dysfunction presumably required the drug in order to improve. If replicated in prospective studies, this methodology may serve in the future to separate depressed patients into those for whom tricyclic antidepressants ought to be considered and those for whom this treatment should not be considered.

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