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Abnormal functional brain asymmetry in depression: Evidence of biologic commonality between major depression and dysthymia

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ABSTRACT

Prior studies have found abnormalities of functional brain asymmetry in patients having a major depressive disorder (MDD). This study aimed to replicate findings of reduced right hemisphere advantage for perceiving dichotic complex tones in depressed patients, and to determine whether patients having "pure" dysthymia show the same abnormality of perceptual asymmetry as MDD. It also examined gender differences in lateralization, and the extent to which abnormalities of perceptual asymmetry in depressed patients are dependent on gender. Unmedicated patients having either a MDD ($n=96$) or "pure" dysthymic disorder ($n=42$) and healthy controls ($n=114$) were tested on dichotic fused-words and complex-tone tests. Patient and control groups differed in right hemisphere advantage for complex tones, but not left hemisphere advantage for words. Reduced right hemisphere advantage for tones was equally present in MDD and dysthymia, but was more evident among depressed men than depressed women. Also, healthy men had greater hemispheric asymmetry than healthy women for both words and tones, whereas this gender difference was not seen for depressed patients. Dysthymia and MDD share a common abnormality of hemispheric asymmetry for dichotic listening.

1. Introduction

Studies using neurocognitive, electrophysiologic, and neuroimaging measures have found evidence of abnormalities of functional brain asymmetry in depressed patients, most of whom had major depressive or bipolar disorders (Henriques and Davidson, 1991; George et al., 1994; Heller et al., 1995; Reid et al., 1998; Deldin et al., 2000; Kayser et al., 2000; Bruder, 2003; Rabe et al., 2005; Moratti et al., 2008; Stewart et al., 2011). Our studies of cerebral laterality using dichotic listening tests demonstrated that major depression is characterized by abnormal laterality, which is related to the patient's diagnostic subtype and response to antidepressants (Bruder, 2003). In dichotic tests, a different stimulus (e.g., word or tone) is simultaneously presented to the left and right ear, and the accuracy for perceiving stimuli in the right and left ear provides a measure of perceptual asymmetry (PA). Dichotic listening tests have been shown to provide reliable and valid measures of left hemisphere dominance for language processing (Wexler and Halwes, 1983; Zatorre, 1989; Hugdahl et al., 2003) and right hemisphere dominance for complex pitch perception (Sidtis, 1981; Zatorre, 2003). The most consistent finding for patients having depressive disorders has been a reduction or absence of the normal right hemisphere advantage for nonverbal dichotic listening (Johnson and Crockett, 1982; Bruder et al., 1989; Overby et al., 1989; Bruder et al., 1995). This agrees with evidence of right hemisphere dysfunction in depression in neurocognitive tests (Flor-Henry, 1976; Heller et al., 1995; Miller et al., 1995) and decreased right parietotemporal activity in neurophysiologic tests (Post et al., 1987; Henriques and Davidson, 1991; Bruder et al., 1995; Reid et al., 1998; Deldin et al., 2000; Kayser et al., 2000; Moratti et al., 2008; Stewart et al., 2011). Findings for verbal dichotic listening tests have been more variable and some studies have found a normal left hemisphere advantage in depressed patients (Hugdahl et al., 2003). The present study further examined cerebral laterality for both verbal and nonverbal dichotic listening in relatively large samples of depressed patients and healthy controls, which enabled us to also address diagnostic and gender issues not adequately studied in this area.

An important question addressed in this report is whether patients having a "pure" dysthymic disorder display the same abnormality of dichotic listening as patients having a major depressive disorder (MDD). If so, this would provide new evidence that they share a common abnormality of functional brain asymmetry. The diagnosis of dysthymic disorder was added to DSM-III in 1980 to categorize mild chronic depressions, which were less severe than major depression and were previously termed "neurotic depression" in DSM-II (Keller and Russell, 1996). It is a common disorder, affecting

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3–6% of people during a lifetime and appears strongly associated with major depression, which supervenes in about 77% of the cases (Klein et al., 2000). Systematic review of controlled trial evidence has shown that antidepressant medications of various classes are effective in treating dysthymia (De Lima and Hotopf, 2003). Biological studies of "pure" dysthymia, that is dysthymia uncomplicated by major depression, have been few and, apart from its response to antidepressant medication, it is unclear whether dysthymia shares biologic characteristics with major depression (Howland and Thase, 1991).

A further purpose was to evaluate gender differences in dichotic listening asymmetry among patients having depressive disorders. Gender differences in the prevalence of depressive disorders (Weissman et al., 1984) and in hemispheric lateralization (McGlone, 1980; Kimura, 1999) point to the potential importance of gender. Epidemiological studies have consistently found greater lifetime prevalence of major depression and dysthymia in women than men, although the gender difference in dysthymia was smaller in some studies (Hasin et al., 2011). Studies have found gender differences in dichotic listening, with men generally having greater lateralization than women (Bryden, 1988; Hiscock et al., 1995). The extent to which differences in dichotic listening among patients having a depressive disorder and healthy controls are dependent on gender is therefore evaluated.

The following hypotheses were tested in this study: (1) depressed patients will show decreased right hemisphere advantage for perceiving dichotic tones, but will not differ from healthy controls in PA for dichotic words; (2) patients with a dysthymic disorder will show the same abnormalities of PA as patients having MDD; (3) men will show greater PA than women; and (4) differences in right hemisphere advantage for tones between depressed patients and controls will be more evident among men than women.

2. Method

2.1. Subjects

Patients were right-handed outpatients between the ages of 18 and 65 who were attending a university-affiliated research clinic at New York State Psychiatric Institute. Patients were excluded for any of the following: serious suicide risk, substance abuse disorders (including alcohol abuse) within the last 6 months, psychotic disorders, antisocial personality disorder, seizure disorder, organic mental disorder, unstable medical disorder, taking psychoactive medication, history of head trauma, or other neurological disorder. Diagnostic assessment was by Structured Interview for Clinical Diagnosis, patient version (SCID-P; First et al., 1994) conducted by research psychiatrists before dichotic listening tests. Patients met DSM-IV criteria for *either* current MDD without a lifetime history of dysthymia ($n=96$) or current "pure" dysthymic disorder, without a lifetime history of MDD ($n=42$). All cases were reviewed after structured interview to compare the clinical history with the SCID-P diagnosis, and dysthymic patients with a history of major depression were removed from the sample.

Right-handed controls ($n=114$) were recruited through notices to hospital staff and college students and through advertisements in local newspapers. Potential participants were screened with a semistructured interview to exclude those with current or past psychopathology. They were also excluded if they had current substance abuse or a history of head trauma or other neurological disorder. Control subjects and patients were excluded 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. The study was approved by the Institution Review Board at New York State Psychiatric Institute and Columbia University Department of Psychiatry. All participants gave written informed consent before participating in the study. Both patients and controls received $15 per hour for their participation.

2.2. Procedure

Patients were unmedicated a minimum of 7 days before testing, although 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. Handedness was determined with the Edinburgh Inventory (Oldfield, 1971) and severity of depression was assessed using the Beck Depression Inventory (BDI; Beck et al., 1961). All patients and controls were tested on the dichotic fused words and complex tones tests described below, with the order of the tests counterbalanced across subjects.

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 dichotically presented, 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 s 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 and third blocks. The tones were presented at 74 dB SPL.

2.3. Statistical analyses

Correct responses in the fused words and complex tones tests were computed for right- and left-ear presentations. These scores were used to compute an index of perceptual asymmetry, PA = 100 (Right Correct − Left Correct)/(Right Correct + Left Correct). An initial 2 by 2 ANOVA of PA scores included the between-subject variables of Group (MDD, controls) and Gender (women, men) and one repeated-measure factor of Test (words, tones). Given significant interactions involving Group, Gender and Test, a separate ANOVA was performed to evaluate the significance of group differences on each test in women and men. Analyses were also performed on the absolute accuracy scores for the right and left ear for the complex tone test, with the variables being Group (MDD, controls), Gender (women, men) and one repeated-measure factor of Ear (right, left). This analysis was not performed on the data for the fused-words test because overall accuracy was close to 100% for the single response required on each trial. Correlational analyses were also used to examine the relationship of PA scores to Beck Depression Inventory scores, age and education.

An ANOVA was also used to compare the PA scores for patients having a MDD and those having a dysthymic disorder with the between subject variables of Group (MDD, dysthymia), Gender (women, men) and Test (words, tones). An ANOVA also compared accuracy scores for MDD and dysthymic patients using Group, Gender and Ear as the variables. Parallel analyses were also performed to compare the PA scores for patients having a MDD and controls or those having a dysthymic disorder and controls.

3. Results

3.1. Depressed patients and healthy controls

Table 1 summarizes the characteristics of depressed patients and healthy controls. Although the groups differed significantly in gender, the impact of gender on group differences in PA is examined below.

Table 1
Characteristics of depressed patients and healthy controls.

Variable	Patients ($n=138$)	Controls ($n=114$)
Gender[a]		
Women	63	67
Men	75	47
Age (years)[b]		
M	36.4	30.6
S.D.	11.3	8.3
Education (years)[c]	15.2	15.8
	2.3	1.9
Handedness laterality quotient	83.0	80.9
	19.4	19.5
Beck Depression Inventory[d]	22.2	1.9
	8.5	2.6

[a] Significant difference in gender between groups ($x^2=14.6$, d.f. = 1, $P<0.001$).
[b] Significant difference in age between groups ($t=4.59$, d.f. = 250, $P<0.001$).
[c] $n=135$ for patients; $n=112$ for controls; significant difference in education between groups ($t=2.40$, d.f. = 245, $P<0.05$).
[d] $n=134$ for patients; $n=110$ for controls; significant difference in depression between groups ($t=24.08$, d.f. = 242, $P<0.001$).