

Atypical Depression: Enhanced Right Hemispheric Dominance for Perceiving Emotional Chimeric Faces

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Two studies compared hemispatial bias for perceiving chimeric faces in patients having either atypical or typical depression and healthy controls. A total of 245 patients having major depressive disorder (MDD) or dysthymia (164 with atypical features) and 115 controls were tested on the Chimeric Faces Test. Atypical depression differed from typical depression and controls in showing abnormally large right hemisphere bias. This was present in patients having either MDD or dysthymia and was not related to anxiety, physical anhedonia, or vegetative symptoms. In contrast, patients having MDD with melancholia showed essentially no right hemisphere bias. This is further evidence that atypical depression is a biologically distinct subtype and underscores the importance of this diagnostic distinction for neurophysiologic studies.

Despite evidence for the heterogeneity of depression, there remains a lack of biological markers to define subtypes for neurophysiologic, genetic, and treatment studies. Melancholia, one of the most well-established subtypes of depression, is characterized by anhedonia, nonreactivity of mood, and vegetative symptoms such as insomnia, anorexia, and psychomotor retardation. Klein (1974) originally hypothesized that pervasive anhedonia is a central feature of *endogenomorphic depression*, which was thought to be associated with a central nervous system deficit. There is, however, a need to delineate nonmelancholic subtypes of depression and to study their neurocognitive features (Parker, 2000). Atypical depression is a nonmelancholic subtype, which is included in the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; *DSM-IV*; American Psychiatric Association, 1994) as a specifier for mood disorders. It is characterized by symptom features that are in some respects opposite of those for melanco-

lia, including reactivity of mood with preserved pleasure capacity and reversed vegetative features such as hypersomnia and overeating. The superior response of atypical depression to monoamine oxidase inhibitors (MOAIs) compared with tricyclic antidepressants, as well as evidence from epidemiologic, neuroendocrine, and sleep studies, suggests that this may be a biologically distinct subtype of mood disorder (Asnis, McGinn, & Sanderson, 1995; McGrath et al., 2000; Rabkin et al., 1996; Stewart, McGrath, Rabkin, & Quitkin, 1993).

Measures of hemispheric asymmetry for processing auditory or visual stimuli represent potential biological markers for distinguishing subtypes of depression (Bruder, 1995). Dichotic listening tests, in which a different complex tone or syllable is simultaneously presented to the two ears, have revealed evidence of right temporal lobe dysfunction in melancholia (Bruder et al., 1989). In contrast, patients having atypical depression were less likely to display abnormal asymmetries on dichotic listening tests (Bruder et al., 1989, 1995). Similarly, abnormally long latency of the P3 event-related brain potential in an auditory spatial localization task, which presumably draws on right parietotemporal processes, was found for typical or melancholic depression but not for atypical depression (Bruder et al., 1991). Longer P3 latency for audio-spatial discrimination was associated with higher ratings of early, middle, and late insomnia. This suggests that reduced right parietotemporal processing in typical or melancholic depression may be associated with vegetative symptoms, in particular, insomnia. Moreover, Postolache et al. (1999) found that poorer identification of odors by the right nostril in patients having a seasonal affective disorder was associated with severity of typical depressive symptoms but not atypical symptoms. Given the predominance of ipsilateral olfactory projections, this is consistent with dichotic listening and electrophysiologic evidence that right hemisphere

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dysfunction is more evident in typical than atypical depression (Bruder et al., 1989, 1991).

In the visual modality, there is evidence from behavioral, electrophysiologic, and neuroimaging studies that the processing of affective facial stimuli involves regions of right parietotemporal cortex and that depressed patients display abnormalities in processing emotional stimuli (Deldin, Keller, Gergen, & Miller, 2000; Kayser, Bruder, Tenke, Stewart, & Quitkin, 2000). Levy, Heller, Banich and Burton (1983) introduced a free-vision Chimeric Faces Test (CFT), using split (chimeric) faces with one half of the face smiling and the other half with a neutral expression. Two faces, the original and its mirror image, are mounted on a page, one above the other, with the smiling half either on the left or right side; the subject's task is to choose the face (top or bottom) that looks happier. Right-handed healthy adults have a bias for choosing the face with the smile on the left side (Levy et al., 1983), which reflects right parietotemporal advantage for processing the facial and/or emotional content of these stimuli. Right-handed men having a unipolar major depression showed reduced right hemisphere bias on this test when compared with healthy controls (Jaeger, Borod, & Peselow, 1987). Opposing biases have been observed for depression and anxiety in students, with depression being associated with decreased right hemisphere bias and anxiety with increased right hemisphere bias (Heller, Etienne, & Miller, 1995). Similar opposing effects of depression and anxiety were observed by Keller et al. (2000), who used the Beck Depression Inventory (BDI; Beck, Ward, Mendelson, & Erbaugh, 1961), the Trait scale of the State-Trait Anxiety Inventory (STAI-T; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983), and their interaction as predictors of hemispatial bias for chimeric faces. Participants in their study who met criteria for major depressive episode did not, however, differ from healthy controls in their right hemisphere bias. Thus, although there is evidence of reduced right parietotemporal dominance for perceiving emotional chimeric faces in depression, this is not a universal finding among depressed patients. The present study extends previous studies by examining whether atypical and typical subtypes of depression differ in hemispatial bias for perceiving emotional chimeric faces.

Electrophysiologic studies measuring resting EEG have also reported evidence implicating right parietal regions in depression. Depressed adults and adolescents have been reported to exhibit abnormal alpha asymmetries indicative of less right than left parietal activation (Bruder et al., 1997; Henriques & Davidson, 1990; Kentgen et al., 2000; Reid, Duke, & Allen, 1998). Other studies have not, however, found evidence of this parietal asymmetry in depressed subjects (Henriques & Davidson, 1991; Schaffer, Davidson, & Saron, 1983). One hypothesis advanced to account for this inconsistency is that right parietal activation accompanying comorbid anxiety may counteract or neutralize the effects of depression, resulting in normal parietal asymmetry (Heller et al., 1995; Heller & Nitschke, 1998). In support of this hypothesis, the EEG of depressed adults and adolescents having a comorbid anxiety disorder did not show evidence of the reduced right parietal activation seen for those having "pure" major depression (Bruder et al., 1997; Kentgen et al., 2000). It is also possible that some subtypes of depression—in particular, atypical depression—may not display evidence of right parietal hypoactivation. In a model proposed by Heller (1993), a right parietotemporal system is hypothesized to be involved in the arousal com-

ponent of emotion and regulation of autonomic activity. The preserved pleasure capacity, mood reactivity, and rejection sensitivity seen in patients having atypical depression may make them more likely to show activation of this right parietotemporal system during processing of emotional faces when compared with patients having typical or melancholic depressions.

This report presents the findings for two studies that compared the performance of patients having atypical versus typical depressive disorders and healthy controls on the CFT. We predicted that depressed patients having atypical depressions would show greater right hemisphere bias when compared with patients having typical depressive disorders and that patients having a melancholic depression would show the least right hemisphere bias, consistent with dichotic listening findings of right hemisphere dysfunction in melancholia (Bruder et al., 1989). We also examined whether physical anhedonia and vegetative symptoms typically seen in melancholia are associated with reduced right hemisphere bias in depressed patients. A secondary purpose was to determine whether comorbidity with an anxiety disorder or ratings of trait or state anxiety are associated with increased right hemisphere bias. Finally, the large sample of patients enabled us for the first time to examine whether or not patients meeting *DSM-IV* criteria for dysthymia display the same abnormalities of right hemisphere bias as seen for patients having a major depressive disorder (MDD).

Method

Participants

Study 1 was a collaborative study conducted at both the New York State Psychiatric Institute (NYSPI) and the Connecticut Mental Health Center. The sample included 129 outpatients (75 women) who met *DSM-IV* criteria for current MDD or dysthymia as determined by an initial semi-structured interview. The diagnostic assessments were carried out by research psychiatrists at these clinical centers. Eighty-five of these outpatients met Columbia criteria for atypical depression (Liebowitz et al., 1984), which include the essential feature of reactivity of mood and a rating of moderate-to-severe on at least one of four associated features: hypersomnia, overeating, extreme bodily inertia, and rejection sensitivity. These criteria differ from *DSM-IV* criteria, which require two associated features. Our justification for requiring only one associated feature has been detailed elsewhere (McGrath et al., 2000). Sixty-eight of the atypical patients met criteria for MDD, and the remaining 17 met criteria for a dysthymic disorder. Of the patients having typical depressions, 40 met criteria for MDD and 4 had a dysthymic disorder. Fifty-five healthy controls (32 women) were recruited from hospital staff, colleges, and communities surrounding the hospitals. They were screened to exclude those with current or past psychopathology, using a modified version of the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (Spitzer & Endicott, 1975).

Study 2 included 116 outpatients (57 women) from NYSPI who met criteria for MDD or dysthymia and 60 healthy controls (38 women). The participants received the same assessments as in Study 1. Seventy-nine of these outpatients met Columbia criteria for atypical depression, of whom 62 had MDD and 17 had a dysthymic disorder. Of the patients having typical depressions, 24 met criteria for MDD and 13 had a dysthymic disorder. Six patients in Study 1 and 3 patients in Study 2 who had typical MDDs also met *DSM-IV* criteria for melancholia. Participants in both studies were excluded if they had current substance abuse or a history of head trauma or other neurological disorder.

Table 1 gives the participant characteristics and self-rating scale measures for the atypical depression, typical depression, and healthy control

Table 1
 Characteristics of Atypical, Typical, and Control Participants in Study 1 and Study 2

Characteristic	Study 1			Study 2		
	Atypical	Typical	Controls	Atypical	Typical	Controls
Gender						
Women	52	23	32	42	17	38
Men	33	21	23	37	20	22
Age (years)						
<i>M</i>	40.6	39.5	35.5	36.9	38.0	30.7
<i>SD</i>	10.5	10.9	10.6	11.0	12.6	8.8
Education (years)						
<i>M</i>	15.3 ^a	14.3	15.8	14.9 ^b	15.1 ^c	15.7
<i>SD</i>	2.3	2.5	2.2	2.4	2.0	1.6
Handedness (LQ)						
<i>M</i>	85.7	88.9	88.6	83.2	85.6	80.3
<i>SD</i>	18.5	15.9	19.2	23.0	20.4	21.3
Beck Depression Inventory						
<i>M</i>	21.0 ^d	22.7	2.2 ^e	21.8	22.9	2.0
<i>SD</i>	9.0	9.4	3.1	8.7	11.3	2.4
STAI Trait Anxiety						
<i>M</i>	76.5 ^f	79.5 ^g	47.2	76.1 ^a	76.0	45.6
<i>SD</i>	10.1	11.7	9.2	8.0	9.9	9.9
STAI State Anxiety						
<i>M</i>	58.5 ^f	64.1 ^g	42.6	60.5 ^a	61.6	42.1
<i>SD</i>	12.8	12.6	5.7	11.6	14.3	6.5
Chapman Physical Anhedonia						
<i>M</i>	15.4 ^a	20.0 ^h	10.4 ⁱ	15.3 ^j	16.4 ^c	10.2 ^k
<i>SD</i>	9.6	9.2	6.0	8.1	9.4	6.9

Note. A laterality quotient (LQ) score of 100 indicates complete right-hand preference and -100 indicates complete left-hand preference. STAI = State-Trait Anxiety Inventory.

^a $n = 77$. ^b $n = 75$. ^c $n = 35$. ^d $n = 83$. ^e $n = 52$. ^f $n = 82$. ^g $n = 40$. ^h $n = 41$. ⁱ $n = 54$. ^j $n = 73$. ^k $n = 59$.

groups in Studies 1 and 2. Education level and self-rating scales were not obtained for a few participants, and the exact sample sizes in these cases are therefore given in footnotes. A 3 (Group) \times 2 (Study) analysis of variance (ANOVA) was used to compare the characteristics of these groups. There was a difference among groups in age, $F(2, 354) = 10.98$, $p < .001$, which was due to the somewhat younger age of controls. There was, however, no difference in age between the atypical and typical patients, and age was not associated with asymmetry scores on the CFT in either patients ($r = .12$) or controls ($r = .03$). There was also a difference among groups in education, $F(2, 345) = 5.48$, $p < .01$, with controls having slightly greater education. Again, there was no difference in education between the atypical and typical patients, and education was not associated with asymmetry scores in either patients ($r = -.07$) or controls ($r = .07$). All participants were right-handed, and there was no difference among groups in handedness on the Edinburgh Inventory (Oldfield, 1971). There was a significant difference among groups in BDI, $F(2, 352) = 246.62$, $p < .001$; STAI-T, $F(2, 348) = 381.77$, $p < .001$; and STAI-S (State Anxiety) scores, $F(2, 348) = 109.25$, $p < .001$, which was clearly due to the lower scores of controls. The atypical and typical patients did not differ in severity of depression or anxiety. Most participants also completed the Revised Physical Anhedonia Scale (Chapman & Chapman, 1978). There was a significant difference among the atypical, typical, and control groups' physical anhedonia scores, $F(2, 336) = 23.17$, $p < .001$. Newman-Keuls post hoc tests indicated that controls had less physical anhedonia than the patient groups, and typical patients had greater physical anhedonia than atypical patients ($p < .05$).

To examine the influence of comorbidity with an anxiety disorder on the findings for atypical and typical depression, Studies 1 and 2 were combined to yield adequate sample sizes. A total of 49 patients having atypical depression also met *DSM-IV* criteria for one or more of the following

anxiety disorders: panic disorder ($n = 20$), social phobia ($n = 28$), generalized anxiety disorder ($n = 3$), or obsessive-compulsive disorder ($n = 7$). Similarly, 22 patients having typical depression also met criteria for one or more of the following: panic disorder ($n = 13$), social phobia ($n = 9$), generalized anxiety disorder ($n = 1$), or obsessive-compulsive disorder ($n = 2$). These patients are referred to as having an *anxious depression*, whereas the remaining patients in each group who did not meet criteria for an anxiety disorder are referred to as having a *nonanxious depression*. Table 2 gives the characteristics of the atypical and typical patients who had anxious or nonanxious depression. A 2 (anxious, non-anxious) \times 2 (atypical, typical) ANOVA revealed a significant difference between the anxious and nonanxious groups in age. Patients having an anxious depression were slightly younger than the nonanxious patients, $F(1, 244) = 5.62$, $p < .05$. Otherwise, there were no significant group differences in these subject characteristics.

The hemispatial bias of atypical and typical patients was also examined separately for patients having either MDD or dysthymia. Patients who met criteria for MDD but not dysthymia (present or past) and patients who met criteria for dysthymia but not MDD (present or past) entered into this analysis. Seventeen atypical patients (4 women) and 15 typical patients (4 women) met criteria for dysthymia. Because these dysthymic patients were predominantly male and were generally older than the MDD patients, they were compared with an equal number of atypical and typical patients having MDD who were selected to match the dysthymic patients in gender, age, and education. As can be seen in Table 3, the resulting subgroups of atypical and typical patients having MDD or dysthymic disorder did not differ in gender, age, education, or handedness. A 2 (atypical, typical) \times 2 (MDD, dysthymia) ANOVA did indicate that the MDD patients had significantly higher BDI, $F(1, 60) = 20.52$, $p < .001$; STAI-T, $F(1, 58) = 5.93$, $p < .05$; and STAI-S scores, $F(1, 57) = 7.15$, $p = .01$, when

Table 2
Characteristics of Atypical and Typical Patients With or Without an Anxiety Disorder

Characteristic	Anxious depression		Nonanxious depression	
	Atypical	Typical	Atypical	Typical
Gender				
Women	34	10	60	30
Men	15	12	55	29
Age (years)				
<i>M</i>	37.1	34.8	39.5	40.3
<i>SD</i>	10.2	10.3	11.1	11.8
Education (years)				
<i>M</i>	15.1 ^a	14.5 ^b	15.1 ^c	14.7 ^d
<i>SD</i>	2.5	2.5	2.3	2.3
Handedness (LQ)				
<i>M</i>	84.7	86.8	84.5	87.6
<i>SD</i>	19.6	15.3	21.4	19.0
Beck Depression Inventory				
<i>M</i>	21.8	23.3	21.2 ^e	22.6
<i>SD</i>	9.3	8.3	8.7	11.0
STAI Trait Anxiety				
<i>M</i>	78.3 ^a	77.4 ^f	75.4 ^g	78.0 ^h
<i>SD</i>	8.7	10.0	9.2	11.3
STAI State Anxiety				
<i>M</i>	63.4 ^a	62.0 ^f	57.8 ^g	63.2 ^h
<i>SD</i>	12.6	12.4	11.8	13.9

Note. A laterality quotient (LQ) score of 100 indicates complete right-hand preference and -100 indicates complete left-hand preference. STAI = State-Trait Anxiety Inventory. ^a*n* = 47. ^b*n* = 21. ^c*n* = 105. ^d*n* = 58. ^e*n* = 113. ^f*n* = 20. ^g*n* = 112. ^h*n* = 57.

compared with dysthymic patients, but there was no significant difference in these scores between the atypical and typical subgroups.

Procedure

Patients were tested on the CFT after a minimum drug-free period of 7 days, although most patients were unmedicated for a considerably longer period. All participants were administered the CFT (see Levy et al., 1983, for details). It consists of 36 bound pages, each containing pairs of chimeric faces with one half of the face smiling and the other half with a neutral expression. Two faces are mounted, one above the other, with the smiling half either on the left or right side. The stimulus booklet was placed directly in front of the participant, and each was asked to look at each page (at their own pace) and choose the face that looked happier. Participants marked their responses (top or bottom) for each of the 36 pages on an answer sheet. To compute an asymmetry index, (R - L)/36, the number of responses in which the smile was in the participant's left hemispace (L) was subtracted from the number of responses in which the smile was in the right hemispace (R), and this was divided by the total number of trials. Negative asymmetry scores equal a left hemispatial (right hemisphere) bias.

A 3 × 2 × 2 ANOVA was performed on the asymmetry scores for the atypical, typical, and control groups, with study and gender serving as additional factors. Newman-Keuls post hoc tests were used to evaluate differences in asymmetry between each group. To examine the influence of comorbidity with an anxiety disorder, a 2 (anxious, nonanxious) × 2 (atypical, typical) × 2 (Gender) ANOVA was also performed on the asymmetry scores. A 2 (atypical, typical) × 2 (MDD, dysthymia) ANOVA was used to evaluate differences in asymmetry scores between atypical and typical patients having MDD or dysthymic disorder. A hierarchical linear regression analysis, modeled after that used by Keller et al. (2000), was

performed to determine the relationship of anxiety and depression scores to hemispatial bias for chimeric faces. The BDI, STAI-T, and their interaction were used as predictors of asymmetry scores. Separate regression analyses were performed for Studies 1 and 2, using the data for all atypical, typical, and control subjects who had ratings on the BDI and STAI-T scales (Table 1). Correlational analyses were also used to examine the relationship of asymmetry scores to STAI-S scores and physical anhedonia scores on the Chapman scale. Ratings on the 21-item version of the Hamilton Rating Scale for Depression (HAM-D₂₁; Hamilton, 1960) were also available for a subsample of 100 patients (70 atypical, 30 typical). These were obtained by the patients' research psychiatrists during the baseline pretreatment period, typically within a week of the Chimeric Faces Test. This enabled an analysis of the correlations between asymmetry scores and key vegetative symptoms in these patients.

Results

Atypical Depression, Typical Depression, and Healthy Controls

As shown in Figure 1, the three groups in Studies 1 and 2 showed negative asymmetry scores indicative of a right hemisphere bias for perceiving chimeric faces. A 3 × 2 × 2 ANOVA indicated that there was a difference in asymmetry scores among the atypical, typical, and control groups, *F*(2, 348) = 6.72, *p* = .001, but no significant effects were found for study or gender. The differences in right hemisphere bias among groups were highly similar across Studies 1 and 2, which was reflected in the absence of a Group × Study interaction, *F*(2, 348) = 0.13, *p* = .87. In the

Table 3
Characteristics of Atypical and Typical Patients Having MDD or Dysthymia

Characteristic	MDD		Dysthymia	
	Atypical	Typical	Atypical	Typical
Gender				
Women	4	4	4	4
Men	13	11	13	11
Age (years)				
<i>M</i>	45.2	41.6	45.2	42.1
<i>SD</i>	8.4	10.9	8.1	11.1
Education (years)				
<i>M</i>	15.4	15.1	15.5 ^a	15.0
<i>SD</i>	2.1	2.3	2.5	1.7
Handedness (LQ)				
<i>M</i>	90.1	87.3	87.4	80.0
<i>SD</i>	12.2	18.0	14.6	26.9
Beck Depression Inventory				
<i>M</i>	21.7	24.2	13.9	14.4
<i>SD</i>	5.8	11.3	6.1	6.9
STAI Trait Anxiety				
<i>M</i>	80.1	77.4 ^b	71.1	73.9 ^b
<i>SD</i>	8.9	13.0	5.4	12.2
STAI State Anxiety				
<i>M</i>	60.5	66.9 ^b	56.5	54.5 ^c
<i>SD</i>	10.8	13.9	9.4	13.7

Note. A laterality quotient (LQ) score of 100 indicates complete right-hand preference and -100 indicates complete left-hand preference. MDD = major depressive disorder; STAI = State-Trait Anxiety Inventory. ^a*n* = 16. ^b*n* = 14. ^c*n* = 13.

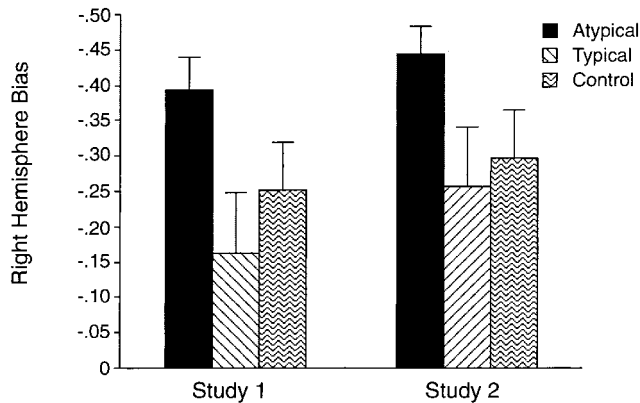


Figure 1. Mean right hemisphere bias on the Chimeric Faces Test for 85 atypical patients, 44 typical patients, and 55 controls in Study 1 and for 79 atypical patients, 37 typical patients, and 60 controls in Study 2 (error bars = standard errors of the mean).

remaining analyses, we therefore collapsed the samples from Studies 1 and 2. A one-way ANOVA of asymmetry scores for the three groups, followed by post hoc tests, indicated that patients having atypical depression had significantly larger right hemisphere bias when compared with either typical patients or healthy controls ($p < .05$), but there was no significant difference between typical patients and controls. The percentage of participants having a right hemisphere bias also differed among groups, with 86% of atypical patients, 63% of typical patients, and 70% of controls having a negative asymmetry score, $\chi^2(2, N = 184) = 18.35, p < .001$. The percentage for controls agrees with the original findings of Levy et al. (1983), who found that 74% of 111 right-handed adults had a right hemisphere bias for chimeric faces.

Only 9 of the patients having typical depressions met *DSM-IV* criteria for melancholia. These 9 melancholic patients did not significantly differ from the remaining 72 typical patients in the demographic characteristics given in Table 1. Although the sample was small, the melancholic patients showed essentially no right hemisphere bias. Less than half of the melancholic patients (44%) had a negative asymmetry score indicative of right hemisphere bias. There was a significant difference in the mean asymmetry scores for melancholic patients ($M = 0.07, SD = 0.48$), atypical patients ($M = -0.42, SD = 0.42$), and healthy controls ($M = -0.27, SD = 0.52$), $F(2, 282) = 6.88, p = .001$. Post hoc tests indicated that the melancholic patients differed significantly from both atypical patients and healthy controls ($p < .05$). The 72 typical patients who did not meet criteria for melancholia had a mean right hemisphere bias ($M = -0.24, SD = 0.54$) comparable to healthy controls. They did have a smaller right hemisphere bias than atypical patients ($p < .05$) and tended to have a larger right hemisphere bias than melancholic patients, but this difference was not statistically significant ($p = .10$).

Comorbidity of Anxiety Disorders With Atypical and Typical Depression

An $2 \times 2 \times 2$ ANOVA was performed to evaluate the effects of comorbidity with an anxiety disorder on right hemisphere bias in atypical and typical depression, with gender serving as a third

factor. Right hemisphere bias was larger for atypical than typical depression, $F(1, 237) = 8.89, p = .005$, but there was no significant difference between depressed patients with versus without an anxiety disorder, $F(1, 237) = 0.34, p = .56$, and no significant gender effect, $F(1, 237) = 0.92, p = .34$. The difference in right hemisphere bias between atypical and typical patients was the same for those having an anxious or nonanxious depression (see Figure 2), which was reflected in the absence of a significant interaction for these group variables, $F(1, 237) = 0.02, p = .89$.

The patients in the anxious depression subgroups had a variety of anxiety disorders, primarily social phobia or panic disorders. The question arises as to whether there is a difference in right hemisphere bias depending on the type of anxiety disorder. Across studies, there was a sufficient number of patients to allow a comparison of asymmetry scores for patients having comorbidity with social phobia versus panic disorder. There were 30 depressed patients who had social phobia but no panic disorder (23 atypical, 7 typical) and 25 patients who had a panic disorder but no social phobia (15 atypical, 10 typical). There was no significant difference in the mean asymmetry scores for patients having social phobia ($M = -0.38, SD = 0.43$) or panic disorder ($M = -0.43, SD = 0.38$), $t(53) = 0.54, p = .59$.

MDD Versus Dysthymia

As shown in Figure 3, patients who met *DSM-IV* criteria for dysthymia had essentially the same right hemisphere bias for chimeric faces as seen for patients having MDD. A 2×2 ANOVA of these data indicated that atypical patients had a larger right hemisphere bias than typical patients, $F(1, 60) = 4.37, p < .05$, but there was no significant difference between patients having MDD or dysthymia, $F(1, 60) = 0.08, p = .78$. The difference in right hemisphere bias between atypical and typical depression was comparable for MDD and dysthymia, which is reflected in the lack of a significant interaction involving these group variables, $F(1, 60) = 0.01, p = .98$.

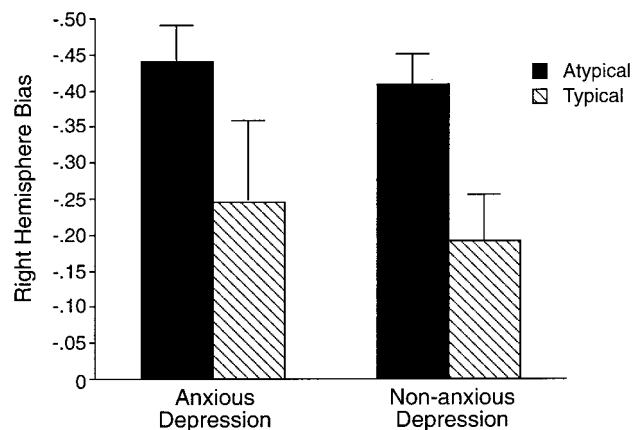


Figure 2. Mean right hemisphere bias on the Chimeric Faces Test for 49 atypical patients and 22 typical patients having an anxiety disorder and for 115 atypical patients and 59 typical patients with no anxiety disorder (error bars = standard errors of the mean).

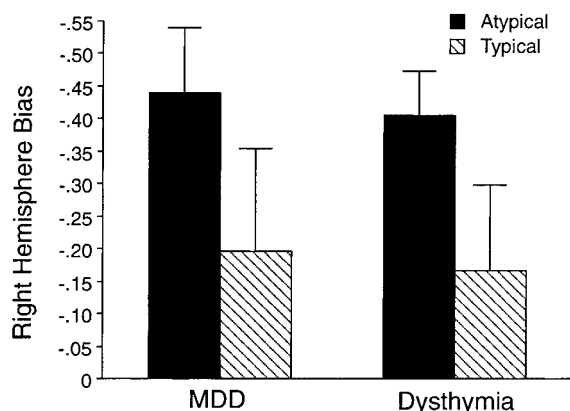


Figure 3. Mean right hemisphere bias on the Chimeric Faces Test for 17 atypical patients and 15 typical patients having major depressive disorder (MDD) and for 17 atypical patients and 15 typical patients having dysthymia (error bars = standard errors of the mean).

Hierarchical Regression Analyses

As in the prior study by Keller et al. (2000), a hierarchical linear regression used the BDI, STAI-T, and their interaction as predictors of the right hemisphere bias for chimeric faces. No significant relationship was found between either BDI scores alone or STAI-T scores alone and asymmetry scores for all participants in either Study 1 or Study 2 (Table 4). BDI and STAI-T scores were also examined after the variance associated with the other predictor was removed, but there were still no significant relationships between these scores (added second) and asymmetry scores, nor was there a significant interaction of BDI and STAI-T. Overall, the three predictors in the model accounted for little of the variance in asymmetry scores. STAI-S scores for all participants were highly correlated with both STAI-T scores ($r = .70, p < .001$) and BDI scores ($r = .70, p < .001$) but were not significantly correlated with asymmetry scores ($r = -.04$).

Physical Anhedonia and Vegetative Symptoms

It is possible that the difference in right hemisphere bias between atypical and typical depression could, in part, stem from greater physical anhedonia in typical (or melancholic) depression (Table 1). We therefore examined whether or not physical anhe-

donia scores on the Chapman scale were associated with asymmetry scores. There was no significant correlation between physical anhedonia and asymmetry scores for the total sample of participants ($r = .06$). Separate analyses for each group also showed no significant correlation for atypical patients ($r = .03$), typical patients ($r = .06$), or controls ($r = .12$).

In 100 patients for whom symptom ratings were available on the HAM-D₂₁, there was no significant correlation between total HAM-D₂₁ scores and asymmetry scores ($r = .10$). One question is whether the difference in right hemisphere bias between atypical and typical patients could be due to a difference in their vegetative symptoms. A vegetative subtotal score was therefore computed by summing ratings for six vegetative symptoms in the HAM-D₂₁ scale: genital symptoms, somatic symptoms gastrointestinal, insomnia late, diurnal variation severity, retardation, and loss of weight. The vegetative subtotal scores were not significantly correlated with asymmetry scores for the 100 patients ($r = -.01$), for atypical patients alone ($r = -.05$), or for typical patients alone ($r = -.01$). Neither were there significant correlations between the individual vegetative symptoms and asymmetry scores for the 100 patients ($r = -.12$ to $.08$), atypical patients ($r = -.14$ to $.12$), or typical patients ($r = -.20$ to $.20$).

Discussion

The findings support previous epidemiological, neuroendocrine, dichotic listening, and electrophysiologic studies suggesting that atypical depression is a biologically distinct subtype of depression (Asnis et al., 1995; Bruder et al., 1989, 1991; McGrath et al., 2000; Stewart et al., 1993). Although previous studies have found differences between atypical and typical subtypes, this is the first study in which atypical depression was associated with a distinctive abnormality of hemispheric laterality. Patients in two studies having atypical depression showed larger right hemisphere bias for perceiving chimeric faces when compared with either healthy adults or patients having typical depression. The enhanced right hemisphere bias in atypical depression was present in patients having either MDD or dysthymic disorder and was present whether or not they had a comorbid anxiety disorder. In contrast, a subgroup of patients having typical depressions who met DSM-IV criteria for MDD with melancholia showed essentially no right hemisphere bias. This agrees with previous dichotic listening findings, in which melancholic patients did not show the right

Table 4
Regression Analyses for Study 1 and Study 2

Variable	Study 1				Study 2			
	R ²	ΔR ²	Test	p	R ²	ΔR ²	Test	p
BDI alone	.012		$t(177) = -1.48$.14	.006		$t(174) = -1.10$.27
BDI added second		.019	$t(169) = -1.81$.07		.0002	$t(171) = 0.16$.87
STAI-T alone	.002		$t(175) = 0.54$.59	.016		$t(172) = -1.68$.09
STAI-T added second		.008	$t(169) = 1.18$.24		.0090	$t(171) = -1.13$.26
BDI × STAI-T		.005	$t(168) = 0.91$.36		.0004	$t(170) = 0.26$.79
Full model	.025		$F(3, 168) = 1.45$.23	.017		$F(3, 170) = 0.97$.41

Note. Probability values are two-tailed. BDI = Beck Depression Inventory; STAI-T = State-Trait Anxiety Inventory, Trait Scale.

hemisphere advantage seen in healthy adults or atypically depressed patients (Bruder et al., 1989).

The findings of this study have implications for neuropsychological models of regional hemispheric activation in depression. Heller et al. (1995) suggested that differences among right-handers in magnitude of hemispatial bias for chimeric faces provide a measure of characteristic asymmetry of parietotemporal activation. They found depression to be associated with reduced right hemisphere bias for processing chimeric faces, consistent with evidence of impairments of right parietotemporal function in depressed patients (Bruder et al., 1989; Jaeger et al., 1987; Miller, Fujioka, Chapman, & Chapman, 1995). In a model proposed by Heller (1993), a right parietotemporal system is involved in the arousal component of emotion and in regulation of autonomic functions. Hypoactivation of this arousal system in melancholic depression could be responsible for the lack of right hemisphere bias for perceiving emotional chimeric faces. There are, however, other possible explanations. Heller et al. (1995) raised the possibility that failure of depressed people to perceive chimeric faces as happy could influence their hemispatial bias. One could argue that reduced perception of happiness in faces contributed to the lack of a right hemisphere bias in melancholic depression. Although we previously found evidence supporting an association of physical anhedonia in depressed patients and reduced right hemispheric activation to complex tones (Bruder et al., 1998), hemispatial bias for chimeric faces was not related to physical anhedonia scores on the Chapman scale. However, without direct ratings of the extent to which the faces were perceived as happy, one cannot dismiss this possibility. Researchers have also suggested that right parietal hypoactivation in depression is associated with spatial cognitive deficits that have been reported to occur in depressed patients (Heller & Nitschke, 1997; Henriques & Davidson, 1997). It is therefore possible that the lack of right hemisphere bias in melancholic depression is not related to emotional processing but rather to a deficit in visuospatial processing. To address these possibilities, researchers would do well in future studies to include a chimeric faces test in which the faces have a neutral expression and the task does not involve judgment of emotional content, for example, the gender chimeric faces test developed by Luh, Rueckert, and Levy (1991).

The findings of this study also indicate that hemispatial bias for chimeric faces is dependent on the diagnostic subtype of depression. Atypical depression is not associated with evidence of right hemisphere hypoactivation on either chimeric faces or dichotic listening tests (Bruder et al., 1989). The abnormally large right hemisphere bias exhibited by patients having atypical depression suggests hyperactivation of right parietotemporal sites involved in the processing of emotional chimeric faces. In terms of the model proposed by Heller (1993), atypical depression may be characterized by increased activation of the right parietotemporal system involved in the arousal component of emotion. It is tempting to speculate that the mood reactivity and rejection sensitivity seen in atypical depression may be related to the tendency to activate this right parietotemporal system during emotional processing. There is, however, no evidence that behavioral or autonomic arousal to emotional stimuli is enhanced in atypical depression. To test this model further, it would be important in future studies to include physiologic measures of arousal (e.g., skin conductance) as well as more direct electrophysiologic or hemodynamic measures of re-

gional hemispheric activation. One could also argue that patients having atypical depression are more responsive to the emotional content of the faces and thereby activate the right parietotemporal region more. Inclusion of a nonemotional CFT in future studies would help to determine whether the greater right hemisphere bias in atypical as compared with typical depression is present for all chimeric faces tests or only those requiring emotional judgments.

The dominance of the right hemisphere extends beyond the perception and evaluation of emotional stimuli to include physiologic and neuroendocrine functions (e.g., Heller et al., 1995; Kayser et al., 2000; Wittling & Pflüger, 1990). The right hemisphere plays a predominant role in regulating autonomic activity, as measured by skin conductance and cardiac activity (Heller, Nitschke, & Lindsay, 1997). The P300 event-related brain potential is larger to emotional stimuli, particularly over right parietotemporal sites (Kayser et al., 2000). Moreover, when the right hemisphere viewed an emotionally arousing film, this resulted in greater cortisol secretion than when viewed by the left hemisphere (Wittling & Pflüger, 1990). The dominant role of the right parietotemporal region in mediating physiologic responses in emotionally arousing situations raises the possibility that vegetative symptoms of melancholic depression, or the reverse vegetative symptoms in atypical depression, might be related to abnormally reduced or heightened activity in this region. Ratings of vegetative symptoms for a subsample of patients in this study did not, however, show any relationship to right hemisphere bias for perceiving chimeric faces. The absence of a relationship between hemispatial bias and vegetative symptoms or physical anhedonia suggests that the global diagnostic distinction between atypical and melancholic depression is more closely related to asymmetric hemispheric activation than ratings of these symptoms. However, the small number of patients meeting criteria for melancholia may have limited our ability to detect relationships of hemispatial bias to vegetative symptoms and anhedonia. In addition, other symptom features characteristic of atypical depression, such as mood reactivity and rejection sensitivity, may be related to the enhanced right hemisphere bias in this form of depression.

Although the main findings for depressed patients on the CFT are similar to those seen for dichotic listening tests, there are some differences worthy of comment. First, patients meeting criteria for atypical depression showed greater right hemisphere bias than healthy controls on the CFT but did not differ significantly from controls on dichotic listening tests (Bruder et al., 1989). Second, depressed patients having a comorbid anxiety disorder differed from those having nonanxious depression in showing dichotic listening asymmetries favoring right over left hemisphere processing (Bruder, Wexler, Stewart, Price, & Quitkin, 1999), whereas this was not seen for the CFT. The difference in findings may stem from modality specificity of perceptual asymmetries. Kim and Levine (1992) examined asymmetry scores of healthy adults on visual half-field and dichotic listening tests. The correlations of asymmetry scores across modalities were generally very small. Principal components analysis indicated that both modality-specific and modality-general factors contribute to perceptual asymmetries, with the modality specific component accounting for more variance. In addition to modality, the CFT differs from dichotic tests in its emotional and cognitive content. Choosing the chimeric face that looks happier involves emotional and spatial processes not active during dichotic listening. Whereas CFT is

likely to reflect asymmetric activation of parietotemporal regions involved in processing emotional faces, dichotic listening tests involve auditory processes mediated by distinct temporal lobe regions. It should, however, be mentioned that the CFT findings also differ from those for resting EEG measures, in which patients having anxious MDD differed from those having nonanxious MDD in their alpha asymmetry at parietal sites (Bruder et al., 1997). Thus, there are differences in findings for the CFT and dichotic listening or resting EEG, which could, in part, stem from differences in emotional or cognitive task demands, but this will require further study to confirm.

A hierarchical regression analysis using the BDI, STAI-T, and their interaction as predictors of hemispatial bias for chimeric faces did not reveal evidence of an inverse relationship for depression and anxiety, which was previously reported by Keller et al. (2000) in two studies. The reason for this difference in findings is unclear. Note, however, that the significant relationship between depression or anxiety scores and hemispatial bias in the Keller et al. study was present only after removing the variance associated with the other predictor; even then, the BDI and STAI-T scores accounted for relatively little of the variance in asymmetry scores. The findings of the present study suggest that melancholia at one extreme, and atypical depression at the other, may define a dimension related to right hemisphere bias for perceiving chimeric faces. The items on the BDI are not, however, well suited for assessing the symptoms of melancholia or atypical depression. Moreover, subjects in Keller et al. (2000) were depressed patients medicated with antidepressants in one study and college students in the other study. They were therefore considerably different from the unmedicated, depressed patients in the current study.

In summary, patients having atypical depression showed abnormally large right hemispheric dominance for perceiving chimeric faces, which was not related to patient gender, comorbidity with anxiety disorders, vegetative symptoms, or self-ratings of depression, anxiety, or physical anhedonia. Atypical depression not only differs in this regard from typical depression but shows the opposite right hemispheric abnormality seen for melancholia. The enhanced right hemispheric activation in atypical depression may be of importance for understanding mood reactivity, rejection sensitivity, and other atypical features of this form of depression. These findings provide further support for inclusion of atypical depression in *DSM-IV* criteria as a distinct subtype of mood disorder and also underscore the importance of this diagnostic distinction for neurophysiological studies of depression. Further study should be conducted to determine the origins of heightened right hemisphere activation in atypical depression and the potential value of hemispheric asymmetry measures as biological markers for this diagnostic subtype.

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