

The Asymmetrical Brain

edited by Kenneth Hugdahl and
Richard J. Davidson



The MIT Press

From The MIT Press



MITCogNet

© 2003 Massachusetts Institute of Technology

All rights reserved. No part of this book may be reproduced in any form by any electronic or mechanical means (including photocopying, recording, or information storage and retrieval) without permission in writing from the publisher.

This book was set in Palatino on 3B2 by Asco Typesetters, Hong Kong and was printed and bound in the United States of America.

Library of Congress Cataloging-in-Publication Data

The asymmetrical brain / edited by Kenneth Hugdahl and Richard J. Davidson.

p.; cm.

Rev. ed. of: Brain asymmetry / edited by Richard J. Davidson and Kenneth Hugdahl. c1995.

"A Bradford book."

Includes bibliographical references and index.

ISBN 0-262-08309-4 (alk. paper)

1. Cerebral dominance. 2. Laterality. I. Hugdahl, Kenneth. II. Davidson, Richard J. III. Brain asymmetry.

[DNLM: 1. Dominance, Cerebral. 2. Brain—physiology. 3. Laterality. WL 335 A8608 2003]

QP385.5 .B725 2003

612.8'2—dc21

2002025092

10 9 8 7 6 5 4 3 2 1

20 Frontal and Parietotemporal Asymmetries in Depressive Disorders: Behavioral, Electrophysiologic, and Neuroimaging Findings

Gerard E. Bruder

My chapter in *Brain Asymmetry*, edited by Davidson and Hugdahl (1995), reviewed findings from behavioral and electrophysiologic studies giving evidence of lateralized hemispheric abnormalities in affective disorders and schizophrenia (Bruder, 1995). Abnormalities of cerebral laterality in depression were shown to be related to the patient's clinical features (i.e., diagnostic subtype and outcome of treatment with antidepressants). An examination of the marked individual differences in laterality data among depressed patients suggested that multiple factors contribute to these abnormalities. The findings were generally supportive of a hypothesis postulating the existence of *both* left frontal and right parietotemporal hypoactivation in depressive disorders (Kinsbourne & Bemporad, 1984). This chapter will focus on recent findings not only from behavioral laterality and electrophysiologic studies, but also from neuroimaging studies, which have provided new evidence of abnormal frontal and parietotemporal asymmetries in depressive disorders. New findings also highlight the importance of taking comorbidity with anxiety disorders into account in studies of brain asymmetry in depression. On a more clinical level, differences in brain asymmetry between responders and nonresponders to antidepressant medications are reviewed for behavioral, electrophysiologic, and neuroimaging measures. The findings suggest the potential value of these measures as predictors of therapeutic responsiveness to treatments for depression.

FRONTAL ASYMMETRIES IN DEPRESSION

Early evidence of left prefrontal hypoactivation in depression was provided by electroencephalographic (EEG) studies of resting alpha

asymmetries. Patients having a unipolar major depression (Bell et al., 1998; Henriques & Davidson, 1991) or a bipolar seasonal affective disorder (Allen et al., 1993) showed an abnormal alpha asymmetry indicative of less left frontal activation or greater right frontal activation. Davidson (1992) suggested that this frontal asymmetry identifies a diathesis predisposing individuals to respond predominantly with negative affect. Studies of EEG in infants have revealed that those who cry during maternal separation show less left than right frontal activation when compared to noncriers (Davidson & Fox, 1989; Fox et al., 1992). The hypothesis that left frontal hypoactivation represents a state-independent marker of vulnerability to depression is supported by the presence of this alpha asymmetry in previously depressed adults in a euthymic state (Henrique & Davidson, 1990) and in infants of depressed mothers (Dawson et al., 1997; Field et al., 1995). Some recent EEG studies have not, however, found evidence of decreased left frontal activation in depressed adults (Reid et al., 1998) or adolescents (Kentgen et al., 2000), which has led to a search for possible mediating variables. In addition to methodological issues, such as test-retest reliability and reference electrode site (Debener et al., 2000; Reid et al., 1998), a possible mediating variable discussed below is the presence of comorbid anxiety disorders (Bruder, Fong, et al., 1997).

One of the most consistent findings in neuroimaging studies of depression has been reduced metabolism or regional cerebral blood flow in the left dorsolateral prefrontal cortex (for reviews see George et al., 1994; Grasby, 1999; Videbech, 2000). Reduced metabolism in depressed patients has been found in additional prefrontal regions, including the anterior cingulate (Mayberg, 1994; Drevets et al., 1997). There are, however, other regions of prefrontal cortex (i.e., ventral and orbital regions), in which metabolism was *increased* in depressed patients (Biver et al., 1994; Brody et al., 1999). There is also strong evidence that alterations of prefrontal metabolism in depression are state-dependent. Reduced left dorsolateral prefrontal and anterior cingulate metabolism tends to normalize following clinical recovery from depression (Baxter et al., 1989; Bench et al., 1995). Moreover, normalization of activity in dorsolateral (Mayberg et al., 1999) or ventrolateral prefrontal cortex (Brody et al., 1999) was reported to be even stronger in the right than in the left hemisphere.

Thus, both EEG alpha asymmetry and neuroimaging studies have found evidence of reduced left prefrontal activation in depressed

patients. However, it is not clear that these measures converge on a common neurophysiologic deficit in depression. Abnormal prefrontal alpha asymmetry in depression has been hypothesized to be a stable (trait) characteristic, whereas abnormalities of prefrontal metabolism were state-dependent. Studies measuring both EEG alpha asymmetries and glucose metabolism, or other neuroimaging measures (e.g., fMRI), in the same depressed patients and controls are needed to clarify this issue. Further study is also needed to determine how reduced left prefrontal activation impacts on the clinical symptoms and cognitive function of depressed patients.

Davidson and Tomarken (1989) suggested that the abnormal frontal asymmetry in depression reflects a deficit in left prefrontal mechanisms that regulate approach behaviors, which may clinically be manifested in symptoms such as psychomotor retardation and low energy level. This is supported by neuroimaging findings linking left dorsolateral hypoactivation in depression to psychomotor retardation or poverty of speech (Bench et al., 1993; Dolan et al., 1993). In our prior chapter (Bruder, 1995), we presented the results of a principal components analysis (PCA) of event-related brain potential (ERP) and perceptual asymmetry data for depressed patients and controls who were tested on several cognitive tasks. One PCA-derived factor was associated with having longer latency of the P3 potential to auditory stimuli in the right than in the left hemifield and reduced right visual field advantage for perceiving syllables. A slowing of cognitive processing for stimuli in the right hemifield is consistent with the hypothesis of left frontal hypoactivation depression.

PARIETOTEMPORAL ASYMMETRIES IN DEPRESSION

In dichotic listening tasks in which complex tones or musical chords are simultaneously presented to the two ears, healthy adults typically show an advantage for perceiving the stimulus in the left ear. This is thought to reflect the dominance of right temporal cortex for pitch discrimination (Coffey et al., 1989; Sidtis, 1981). Depressed patients have been reported to show reduced left ear (right hemisphere) advantage in nonverbal dichotic listening tasks (Bruder, 1988; Johnson & Crockett, 1982; Overby et al., 1989). Also, Bruder et al. (1995) measured brain ERPs of depressed patients and healthy controls during a dichotic complex tone test. Healthy adults showed the expected left ear advantage for

perceiving complex tones, which was associated with having greater P3 amplitude over right than over left hemisphere sites. Depressed patients did not show either this perceptual asymmetry or the associated hemispheric asymmetry of P3, which is consistent with other evidence of right hemisphere dysfunction in depression (Flor-Henry, 1976; Heller et al., 1995; Miller et al., 1995; Liotti et al., 1991). Reduced left ear (right hemisphere) advantage was also found to be related to important clinical features of depression, including diagnostic subtype. Patients having a melancholic depression with pervasive anhedonia and vegetative symptoms such as insomnia, anorexia, or psychomotor retardation had no left ear advantage for complex tones, whereas patients having a nonmelancholic, atypical depression with preserved pleasure capacity and reversed vegetative features showed a normal left ear advantage (Bruder et al., 1989; Bruder, 1995).

Patients having a melancholic depression also had an abnormally large right ear advantage for perceiving dichotic consonant-vowel syllables (Bruder et al., 1989). Accuracy scores indicated that this was due to poorer left ear performance in melancholia, which again points to dysfunction of the right temporal region. Although findings for depressed patients on verbal dichotic listening tests have been inconsistent (for a review, see Bruder, 1988), both adolescents and adults having a major depressive disorder were found to have an abnormally large right ear advantage on the Fused Rhymed Words Test (Pine et al., 2000). This is one of the most reliable and valid dichotic listening tests for assessing hemispheric dominance for language (Wexler & Halwes, 1983; Zatorre, 1989).

A study by Davidson and Hugdahl (1996) suggests that the enhanced right ear advantage may be related to both parietotemporal and prefrontal activational asymmetries. They examined in healthy adults the relationship of right ear advantage for perceiving dichotic consonant vowels and resting EEG alpha asymmetry measured 4 months prior to the dichotic test. As might be expected, individuals with greater activation (less EEG alpha) over left parietotemporal regions had a larger right ear advantage for perceiving dichotic syllables. The larger right ear advantage in depressed patients could therefore stem from greater activation of left than of right parietotemporal regions, which is consistent with the resting alpha asymmetry seen for depressed adults and adolescents in most studies (Davidson et al., 1987; Henriques & David-

son, 1990; Kentgen et al., 2000; Reid et al., 1998; but see Henriques & Davidson, 1991 and Schaffer et al., 1983 for negative findings). Most interestingly, Davidson & Hugdahl (1996) found that alpha asymmetry in the prefrontal region was also related to dichotic listening asymmetry, but in the *opposite* direction. Decreased activation of the left prefrontal region (i.e., the asymmetry seen in depressed adults; Davidson, 1992) and increased activation of the right prefrontal region were associated with greater right ear advantage. Thus, the same pattern of prefrontal and parietotemporal activation asymmetries typically seen in depression were predictive of enhanced right ear advantage for dichotic syllables.

Studies measuring visual field asymmetries for nonverbal stimuli have also found evidence of right parietotemporal dysfunction in patients having a unipolar depressive disorder (Jaeger et al., 1987; Liotti et al., 1991) or bipolar depressive disorders (Bruder et al., 1989, 1992). Moreover, two recent studies measuring brain ERPs to face stimuli have provided direct evidence of right parietal hypoactivation in depressed patients (Deldin et al., 2000; Kayser et al., 2000). Deldin et al. (2000) measured ERPs of depressed patients and healthy controls while they performed a recognition memory task with positive, negative, and neutral face and word stimuli. Amplitude of the N2 potential was reduced in depressed patients, with the greatest reduction over right parietal cortex. This right-lateralized N2 reduction was specific to face stimuli with a positive affective valence.

One of the most consistent findings of ERP studies using emotional stimuli has been the larger amplitude of the late P3 potential to positive or negative affective stimuli when compared to neutral stimuli, and this P3 enhancement was greatest over right parietotemporal sites (see Kayser et al., 1997 for a review). Given the hypothesis of right parietotemporal hypoactivation in depression, Kayser et al. (2000) predicted that depressed patients would be less likely to show an enhancement of late P3 amplitude to emotional stimuli. They measured the ERPs of unmedicated depressed patients and healthy controls to pictures of dermatological patients showing disordered facial areas (negative stimuli) or healed facial areas after cosmetic surgery (neutral stimuli). The pictures were briefly exposed (250 ms) to the right or left visual field so as to directly stimulate the contralateral hemisphere. One of the distinct advantages of this paradigm is that the pictures depicting negative and

neutral affective content are highly similar in physical characteristics, so as to reduce the influence of visuospatial processing. Also, no overt response is required to the affective stimuli, thus reducing the influence of cognitive processing and response-related potentials. In agreement with prior studies, healthy adults showed greater late P3 amplitude to the negative than to the neutral pictures, and this was most marked over the right parietotemporal region. In contrast to the healthy adults, depressed patients had a marked reduction of late P3 amplitude and failed to show the enhancement of late P3 to negative as compared to neutral stimuli.

Although these findings are supportive of the hypothesis of right parietotemporal hypoactivation in depression, the depressed patients did show a transient increase of an early P3 subcomponent in response to negative as compared to neutral stimuli, particularly over the right parietal region. The enhancement of this early P3 to negative stimuli in depressed patients and the absence of enhancement of late P3 suggested to Kayser et al. the possibility that early stimulus classification in depressed patients was followed by an inhibition of the later affective processing. In accordance with this suggestion, they found that depressed patients showed the same N2 amplitude and topography as healthy controls, with greatest N2 over the right parietal region. The lack of the N2 reduction seen for depressed patients in the Deldin et al. (2000) study may stem from the different ERP paradigms in these studies. Deldin et al. measured ERPs during a recognition memory task that entails more cognitive and response-related processing than the passive viewing of affective pictures in the Kayser et al. study.

Although neuroimaging studies of depression have focused predominantly on prefrontal regions of interest, there are reports of decreased metabolism in right temporal lobe (Post et al., 1987) and bilaterally in parietal regions (Biver et al., 1994; Cohen et al., 1992). A weakness of most neuroimaging studies of depression has been the failure to control for comorbidity with anxiety disorders. The opposing effects of depression and anxiety or anxious arousal on activation asymmetries in the parietotemporal region could account for why more imaging studies in depressed patients have not reported abnormal asymmetries in this region (Heller et al., 1995). Also, neuroimaging studies often report findings for small samples and generally have not dealt adequately with the issue of diagnostic heterogeneity of depression.

COMORBIDITY OF DEPRESSIVE AND ANXIETY DISORDERS

Anxiety is a common symptom in depressive disorders, and about half of patients having a major depressive disorder exhibit comorbidity with an anxiety disorder (Gulley & Nemeroff, 1993; Zimmerman et al., 2000). This is a potential problem for studies of brain asymmetry in depressive disorders because depression and anxiety appear to be associated with *opposite* abnormalities of lateralized hemispheric function. Findings of reduced left hemifield advantages on visual half-field or dichotic listening tests in depressed patients (Bruder et al., 1989; Jaeger et al., 1987; Overby et al., 1989) or students with high depression scores (Heller et al., 1995) have supported the hypothesis of right hemisphere dysfunction in depression. In contrast, visual hemifield findings suggestive of left hemisphere dysfunction or right hemisphere hyperactivation have been reported for patients having anxiety disorders (Liotti et al., 1991) and for students with high trait anxiety (Heller et al., 1995; Tucker et al., 1981). Similarly, neuroimaging studies have found decreased metabolism or regional cerebral blood flow in the left temporoparietal cortex of patients having a panic disorder (Meyer et al., 2000; Nordahl et al., 1998). A recent study using hierarchical regression analyses of visual perceptual asymmetries for depressed patients and nonpatients has reported further evidence of the opposing patterns of hemispheric asymmetries associated with depression and anxiety (Keller et al., 2000).

The impact of comorbidity of depression and anxiety on regional brain asymmetries was demonstrated in a study in which resting EEG was recorded in depressed patients with or without an anxiety disorder and healthy controls (Bruder, Fong, et al., 1997). Patients with comorbidity of major depressive and anxiety disorders (primarily a panic disorder or social phobia) had the *opposite* alpha asymmetry pattern at parietal sites when compared to patients having a major depression without an anxiety disorder. Patients having an anxious depression showed an alpha asymmetry indicative of greater activation over right than left parietal sites, whereas those having a "pure" depressive disorder showed less activation over right than left parietal sites. This is consistent with the opposite direction of perceptual asymmetries seen in depression and anxiety (Heller et al., 1995; Keller et al., 2000). Depressed patients with an anxiety disorder also showed evidence of

greater activation over right than left frontal sites, whereas this was not seen in depressed patients without an anxiety disorder or in healthy controls. Comorbidity of depressive and anxiety disorders may therefore act to heighten the abnormal frontal alpha asymmetry that has been reported to occur in depressive disorders (Davidson, 1992).

Given the relationship of EEG alpha asymmetry at prefrontal and parietotemporal sites to perceptual asymmetry on a dichotic listening task (Davidson & Hugdahl, 1996), we predicted that depressed patients with or without a comorbid anxiety disorder would also differ in their dichotic listening performance (Bruder et al., 1999). Patients having an anxious depression did differ from nonanxious depressed patients and controls in showing a larger left ear (right hemisphere) advantage for complex tones, whereas nonanxious depressed patients differed in showing a larger right ear (left hemisphere) advantage for fused words. An index of characteristic perceptual asymmetry (Levy et al., 1983) indicated that the anxious depressed patients had a bias favoring right hemisphere activation, whereas the nonanxious depressed patients had a bias favoring left hemisphere activation. This difference in characteristic perceptual asymmetry between the anxious and nonanxious depressed patients agrees with the different direction of parietal alpha asymmetries seen for these groups (Bruder, Fong, et al., 1997).

The favoring of right over left hemispheric activation in anxious depression could stem from hyperactivation of right parietotemporal cortex due to anxious arousal (Heller et al., 1995), from left parietotemporal hypoactivation seen in anxiety disorders (Meyer et al., 2000; Nordahl et al., 1998), or from some combination of both. Examination of the absolute accuracy scores indicated that the enhanced left ear advantage of anxious depressed patients was clearly due to their poorer right ear accuracy (Bruder et al., 1999). Given the contralateral nature of the projections from the ear to auditory cortex, this finding may suggest left parietotemporal hypofunction in anxious depression. However, a study of the effects of arousal level on dichotic listening in students suggests an alternative explanation (Asbjørnsen et al., 1992). They observed that a highly arousing negative condition (threat of electric shock) reduced the right ear advantage for perceiving dichotic consonant-vowel syllables, and suggested that threat of a shock not only primes the right hemisphere but also facilitates callosal transfer of the left ear input, and as a result the left ear stimulus interferes with the processing of the right ear stimulus. Thus, heightened right parieto-

temporal activation in anxious depressed patients may increase left ear stimulus interference with the right ear stimulus and result in reduced right ear accuracy.

A number of studies have reported that the presence of comorbid depressive and anxiety disorders is associated with poorer outcome of treatment with medication or interpersonal therapy (Fava et al., 1997; Feske et al., 2000; Frank et al., 2000), although some studies have not found this relationship (Tollefson et al., 1994). The characteristic perceptual asymmetry observed for depressed patients with a comorbid anxiety disorder (i.e., a favoring of right hemisphere activation) resembles that seen for nonresponders to the antidepressant fluoxetine (Prozac), whereas the opposite asymmetry in patients having a “pure” depressive disorder (i.e., a favoring of left hemisphere activation) resembles that seen for treatment responders (Bruder et al., 1996). Below we review evidence from dichotic listening, EEG, and neuroimaging studies that point to differences in regional brain asymmetry between treatment-responsive and nonresponsive subgroups of depressed patients.

RELATIONS OF BRAIN ASYMMETRY IN DEPRESSION TO TREATMENT OUTCOME

Several studies suggest that individual differences in perceptual asymmetry on dichotic listening tests are related to the therapeutic response to antidepressants or cognitive-behavioral therapy. Our initial study found a difference in pretreatment perceptual asymmetry between subgroups of depressed patients formed on the basis of their subsequent clinical response to a tricyclic antidepressant (Bruder et al., 1990). Patients who showed a favorable response to treatment—a Clinical Global Improvement (CGI) rating of “much improved” or “very much improved”—failed to show the left ear (right hemisphere) advantage for dichotic complex tones seen for both tricyclic nonresponders and healthy controls. This supported our hypothesis that tricyclic responders would show evidence of right hemisphere dysfunction similar to that seen for patients having a melancholic depression, a diagnostic subtype that typically responds well to this type of antidepressant. The findings of this study were, however, only partially replicated in a follow-up study (Stewart et al., 1999). Although there was no difference between tricyclic responders and nonresponders on the complex tone test, there

were significant differences between these groups in their left ear accuracy on the dichotic consonant-vowel test. Patients who responded to treatment with a tricyclic antidepressant had poorer left ear accuracy when compared to treatment nonresponders, placebo responders, and healthy controls. Although their poorer left ear accuracy provides evidence of right hemisphere dysfunction in tricyclic responders, the absence of a group difference on the complex tone test weakens this conclusion.

In a multisite study of the selective serotonin reuptake inhibitor (SSRI) fluoxetine, unmedicated depressed patients who subsequently responded to fluoxetine had a greater right ear (left hemisphere) advantage for dichotic fused words and less left ear (right hemisphere) advantage for complex tones when compared to treatment nonresponders (Bruder et al., 1996). There was no change in perceptual asymmetries following treatment, which suggests that these laterality differences between fluoxetine responders and nonresponders represent stable, state-independent characteristics. These findings from two clinical centers support the conclusion that a characteristic perceptual asymmetry favoring greater left than right hemispheric activation during dichotic listening is associated with better outcome of treatment with an SSRI antidepressant.

We also investigated the potential value of dichotic listening tests in predicting outcome of cognitive-behavioral therapy for depression (Bruder, Stewart, et al., 1997). Depressed patients were tested before receiving 16 weekly sessions of standard cognitive therapy. Following treatment, outcome was evaluated, using the CGI scale, by a rater who was unaware of the dichotic listening results. Patients who responded to cognitive therapy had twice the right ear (left hemisphere) advantage compared to nonresponders and healthy controls. Although this resembles the larger right ear advantage observed for fluoxetine responders, the cognitive therapy responders did not show the reduced left ear (right hemisphere) advantage seen for fluoxetine responders. The larger right ear advantage for syllables in cognitive therapy responders was clearly due to their *better* right ear accuracy when compared to nonresponders or healthy controls. This suggests that the abnormal perceptual asymmetry for dichotic syllables in cognitive therapy responders was due to their superior left hemisphere processing of phonetic stimuli, which is likely to involve left parietotemporal activation (Davidson & Hugdahl, 1996). Patients with greater left hemi-

sphere superiority may be better able to use their verbal skills in learning cognitive strategies for relieving depression.

In an ongoing project, we are examining the value of dichotic listening and more direct electrophysiologic measures of hemispheric activation as predictors of response to treatment with an SSRI antidepressive. If differences in perceptual asymmetry observed between fluoxetine responders and nonresponders reflect characteristic, state-independent differences in regional hemispheric activation (Bruder et al., 1996), we predict that these subgroups will also differ in their resting EEG alpha asymmetry patterns. Moreover, perceptual asymmetry scores for these patients should correlate with their alpha asymmetry (Davidson & Hugdahl, 1996). We have also begun to examine whether gender is of importance when studying differences in EEG alpha asymmetry between responders and nonresponders to antidepressants. The greater incidence of depression in women and gender differences in hemispheric asymmetries for cognitive processing underscore the importance of examining the influence of gender in this context (Heller, 1993).

Preliminary dichotic listening and EEG data were analyzed for 34 patients (21 female) who were classified as fluoxetine responders and 19 patients (7 female) who were nonresponders (Bruder et al., 2001). The depressed outpatients in this study were tested during a drug-free phase prior to receiving 12 weeks of treatment with fluoxetine. An independent evaluator, blind to the patient's EEG and dichotic listening data, rated each patient at the end of the 12 weeks of treatment, using the CGI scale. Patients with ratings of "much improved" or "very much improved" were considered to be responders and all other patients were considered as nonresponders. The difference in perceptual asymmetry between treatment responders and nonresponders on the dichotic fused words and complex tone tests replicated those seen in our prior study (Bruder et al., 1996). As can be seen in figure 20.1, there was an overall trend for responders to have a larger right ear (left hemisphere) advantage for words and a smaller left ear (right hemisphere) advantage for complex tones when compared to nonresponders. The differences in asymmetry between responders and nonresponders were, however, dependent on gender. On the words test, female responders showed a markedly larger right ear advantage when compared to female nonresponders, but there was no significant difference between male responders and nonresponders. On the complex tone test, the

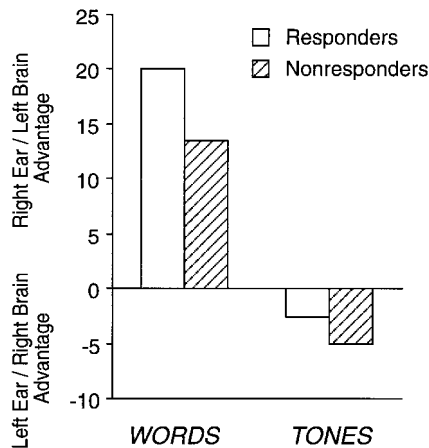


Figure 20.1 Mean perceptual asymmetry for fluoxetine responders and nonresponders on dichotic fused word and complex tone tests. Perceptual asymmetry score = $100(R - L)/(R + L)$, where R = right ear score and L = left ear score.

tendency for responders to have a smaller left ear advantage when compared to nonresponders was primarily seen for males.

Analyses of the resting EEG focused on alpha power because of its inverse relation to cortical activation and prior findings of abnormalities of alpha asymmetries in depressed patients (Davidson, 1992). Although there was no significant difference in overall alpha power between fluoxetine responders and nonresponders, these groups did differ in their alpha asymmetry, and this was greatest in the eyes open condition. Figure 20.2 shows the overall alpha asymmetry (averaged over homologous anterior, central and posterior sites) for responders and nonresponders in the eyes open and closed conditions. Positive scores indicate greater activation (less alpha) over the left than the right hemisphere, whereas negative scores indicate greater activation (less alpha) over the right hemisphere. In the eyes open condition, nonresponders showed overall greater activation (less alpha) over the right than the left hemisphere, but responders did not. Further analyses indicated that the difference in alpha asymmetry between responders and nonresponders in the eyes open condition was statistically significant for females but not for males. Also, there was a significant correlation between the perceptual asymmetry for fused words and EEG alpha asymmetry in the eyes open condition for female patients ($r = .51$,

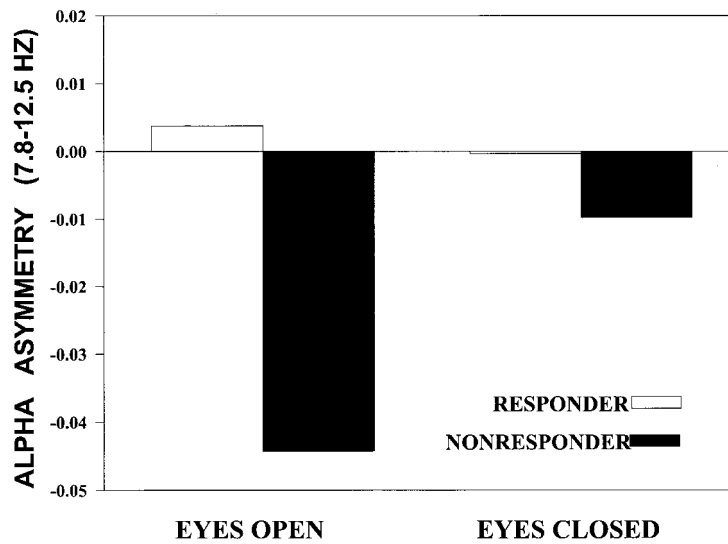


Figure 20.2 Mean EEG alpha asymmetry ($\log[\text{right hemisphere}] - \log[\text{left hemisphere}]$) for fluoxetine responders and nonresponders in the eyes open and eyes closed conditions. Positive scores indicate greater activation (less alpha) over the left than the right hemisphere, and negative scores indicate greater activation (less alpha) over the right than the left hemisphere.

$p < .01$), but not male patients ($r = -.15$, ns). Greater activation (less alpha) over the right than the left hemisphere in female patients was associated with smaller left hemisphere advantage for perceiving dichotic words.

The above findings indicate that individual differences among depressed patients in hemispheric asymmetries, as measured by dichotic listening or resting EEG, were related to outcome of treatment with an SSRI antidepressant. In accordance with our prior study (Bruder et al., 1996), patients who responded to fluoxetine differed from nonresponders in favoring left over right hemisphere processing of dichotic stimuli. Also, fluoxetine nonresponders differed from responders in showing an EEG alpha asymmetry indicative of overall greater right than left hemisphere activation. These relationships between hemispheric asymmetries and treatment response were more evident among depressed women than men. However, given the relatively small samples, the influence of gender in this context will need replication.

Neuroimaging studies have also provided preliminary evidence that pretreatment regional brain metabolism is related to response to antidepressants (Little et al., 1996; Mayberg et al., 1997; Ketter et al., 1999). Unipolar depressed patients who subsequently responded to venlafaxine or bupropion had decreased left middle frontal gyrus and bilateral prefrontal and temporal metabolism compared to healthy controls (Little et al., 1996). Hypermetabolism of the rostral anterior cingulate was associated with favorable response to treatment with a SSRI, tricyclic antidepressant, or bupropion, whereas hypometabolism was associated with poorer response to these treatments. Interestingly, these anterior cingulate differences tended to be right-lateralized (Mayberg et al., 1997). Most recently, Ketter et al. (1999) found pretreatment frontal and left insular metabolism were differentially related to response to carbamazepine and nimodipine. The large variety of medications used in these imaging studies makes it difficult, however, to compare their findings with those reviewed above for perceptual and electrophysiologic studies.

OVERVIEW AND THEORETICAL INTEGRATION OF BRAIN ASYMMETRY FINDINGS FOR DEPRESSION

EEG measures of alpha asymmetry and neuroimaging measures of regional cerebral metabolism or blood flow in a resting state have provided evidence of left prefrontal hypoactivation in depressive disorders. On the other hand, behavioral laterality tests assessing perceptual asymmetry and brain ERP measures of regional hemispheric activity, and to a lesser extent resting EEG and neuroimaging measures, have provided evidence of relative hypoactivation of right parietotemporal regions in depressive disorders. The converging evidence from behavioral, electrophysiologic, and neuroimaging studies therefore gives further support to the hypothesis that *both* left prefrontal and right parietotemporal inactivation are involved in depression (Kinsbourne & Bemporad, 1984). Moreover, recent findings confirm that mood disorders following stroke are associated with both left frontal and right posterior lesions (Shimoda & Robinson, 1999).

There is also increasing evidence that individual differences among depressed patients in perceptual, EEG, and ERP asymmetries are related to their clinical features (e.g., diagnostic subtype, comorbidity with anxiety disorders, and responsiveness to treatments for depression).

Right parietotemporal dysfunction (e.g., as evidenced by poor left ear accuracy during dichotic listening) is most evident in major depression with melancholia, but is also seen among patients having a non-melancholic depression who respond favorably to treatment with a tricyclic antidepressant. Also, patients having a "pure" major depression show heightened right ear (left hemisphere) advantage for perceiving dichotic fused words and resting EEG alpha asymmetries indicative of greater left than right parietotemporal activation, which is not seen in depressed patients having a comorbid anxiety disorder. This is consistent with evidence that depression and anxiety are associated with opposing patterns of perceptual asymmetry (Heller et al., 1995; Keller et al., 2000), and underscores the need to take comorbidity with anxiety into account in studies of brain asymmetry in depression. Similarly, depressed patients who respond favorably to the SSRI antidepressant fluoxetine (Prozac) show perceptual asymmetries indicative of a characteristic favoring of left over right parietotemporal activation, whereas nonresponders show perceptual and EEG asymmetries indicative of overall greater right than left hemisphere activation. The right hemispheric favoring in fluoxetine nonresponders resembles that seen in depressed adults having a comorbid anxiety disorder, which is of particular interest, given reports of poor treatment outcome in patients having an anxious depression. Also, neuroimaging studies have begun to emerge suggesting that metabolism of right or left prefrontal structures is related to clinical response to antidepressants (Ketter et al., 1999; Mayberg et al., 1997).

Davidson (1992) has proposed that prefrontal asymmetries are related to an approach/withdrawal dimension, with left frontal activation being related to approach behaviors and right frontal activation to withdrawal behaviors. Left frontal hypoactivation could therefore be manifested clinically in symptoms of depression, such as psychomotor retardation, poverty of speech, or absence of motivation, whereas right frontal hypoactivation could be manifested in anxious behaviors or negative affect. This model does not, however, deal with the role of asymmetries in more posterior brain regions. A model developed by Heller (1990) similarly hypothesizes that activity in the frontal region is associated with the valence dimension of emotion and, in addition, proposes that activity in the right posterior region is associated with the arousal dimension of emotion. Low levels of arousal in depression would be associated with decreased activity in right parietotemporal

cortex. This model could therefore account for why “pure” depression is accompanied by both left frontal and right parietotemporal hypoactivation. Moreover, as Heller et al. (1995) suggest, panic or other anxious states that increase right parietotemporal activation will act to cancel out the tendency for depression to be associated with decreased right parietotemporal activation. The high incidence of comorbidity with anxiety disorders could thereby account for why some EEG and imaging studies have not found evidence of right parietotemporal hypoactivation in depression. These models are, however, limited because they fail to deal with the clinical heterogeneity of depression and its relationship to brain asymmetry.

Several lines of evidence suggest the existence of treatment-responsive and nonresponsive subtypes of depression that differ in brain asymmetry. First, patients who respond to a tricyclic antidepressant show evidence of right parietotemporal dysfunction similar to that seen in major depression with melancholia. Thus, there appears to be a subtype of depression that responds favorably to a tricyclic and shares some of the biologic and clinical features commonly seen in melancholia. Second, patients who respond favorably to an SSRI antidepressant show a characteristic perceptual asymmetry consistent with a favoring of left over right parietotemporal activation. This SSRI responsive subtype includes patients having an “atypical depression” but is less likely to include patients having an “anxious depression” with a comorbid anxiety disorder. Third, patients who do not respond to an SSRI antidepressant show perceptual and electrophysiologic asymmetries consistent with a pervasive favoring of right parietotemporal activation. This SSRI nonresponsive subtype appears to be most common among depressed women and may be characterized by heightened psychological distress and negative affectivity. Depressed patients showing evidence of greater right than left parietotemporal activation would also be expected to respond poorly to a tricyclic antidepressant (Bruder et al., 1990) or to standard cognitive-behavioral therapy for depression (Bruder, Stewart, et al., 1997), and may therefore represent a general category of treatment-nonresponsive depression.

An important question that needs further research is why right-left brain asymmetries should be related to outcome of treatments for depression. One possibility is that the neurotransmitter systems implicated in depressive disorders and affected by antidepressants may have a lateralized distribution in the brain or may be asymmetrically dis-

rupted in a particular subtype of depression. It has, for instance, been suggested that serotonin pathways are asymmetrically distributed in the brain (Mandell & Knapp, 1979; Tucker & Williamson, 1984), although postmortem studies have not found consistent evidence of asymmetries of serotonin uptake (Arato et al., 1991; Arora & Meltzer, 1991). A study measuring glucose metabolism did find that the serotonin-releasing drug *d,l*-fenfluramine increased metabolism in left prefrontal cortex and temporoparietal areas, and decreased metabolism in right prefrontal cortex in healthy adults (Mann et al., 1996). Moreover, recent neuroimaging studies have reported lateralized differences in regional brain metabolism between responders and nonresponders to antidepressants (Ketter et al., 1999; Mayberg et al., 1997). Studies that compare treatment responders and nonresponders not only on behavioral laterality and electrophysiologic measures but also on neuroimaging measures are needed to specify the biological basis for the relation of brain asymmetries to treatment outcome.

Further study is also needed to determine the role of gender in abnormalities of brain asymmetry in depression. Given the greater incidence of depression among women, most studies in this area have predominantly tested women. Our initial findings suggest that differences in perceptual asymmetry and EEG alpha asymmetry between fluoxetine responders and nonresponders are more evident among women than men (Bruder et al., 2001). Also, Heller (1993) has speculated on the relation of gender differences in hemispheric organization to gender differences in depression. One of the distinct advantages of behavioral laterality tests and electrophysiologic measures of regional hemispheric activity is that they can be economically administered to relatively large samples, which will be necessary for determining how gender modulates differences in brain asymmetry not only between depressed patients and healthy controls but also between treatment-responsive and nonresponsive subgroups of depression.

ACKNOWLEDGMENTS

Preparation of this chapter was supported in part by grant MH-36295 from the National Institute of Mental Health, National Institute of Health, Bethesda, Maryland. Findings are reviewed for several studies conducted with the collaboration and help of many people at New York State Psychiatric Institute. They include my colleagues in the

Psychophysiology Laboratory: Craig Tenke, Jürgen Kayser, Paul Leite, Barbara Stuart, Nil Bhattacharya, and James Towey, and my collaborators in the Depression Evaluation Service: Jonathan Stewart, Frederic Quitkin, Patrick McGrath, and Deborah Deliyannides.

REFERENCES

- Allen, J. J., Iacono, W. G., Depue, R. A., & Arbisi, P. (1993). Regional electroencephalographic asymmetries in bipolar seasonal affective disorders before and after exposure to bright light. *Biological Psychiatry*, 33, 642–646.
- Arato, M., Frecska, E., MacCrimmon, D. J., Guscott, R., Saxena, B., Tekes, K., & Tothfalusi, L. (1991). Serotonergic interhemispheric asymmetry: Neurochemical and pharmac-EEG evidence. *Progress in Neuro-Psychopharmacological & Biological Psychiatry*, 15, 759–764.
- Arora, R. C., & Meltzer, H. Y. (1991). Laterality and ^3H -imipramine binding: Studies in the frontal cortex of normal controls and suicide victims. *Biological Psychiatry*, 29, 1016–1022.
- Asbjørnsen, A., Hugdahl, K., & Bryden, M. P. (1992). Manipulations of subjects' level of arousal in dichotic listening. *Brain and Cognition*, 19, 183–194.
- Baxter, L. R., Schwartz, J. M., Phelps, M. E., Mazziotta, J. C., Guze, B. H., Selin, C. E., Gerner, R. H., & Sumida, R. M. (1989). Reduction of prefrontal cortex glucose metabolism common to three types of depression. *Archives of General Psychiatry*, 46, 243–250.
- Bell, I. R., Schwartz, G. E., Hardin, E. E., Baldwin, C. M., & Kline, J. P. (1998). Differential resting quantitative electroencephalographic alpha patterns in women with environmental chemical intolerance, depressives, and normals. *Biological Psychiatry*, 43, 376–388.
- Bench, C. J., Frackowiak, R. S. J., & Dolan, L. J. (1993). Regional cerebral blood flow (rCBF) in depression, measured by position emission tomography (PET): The relationship with clinical dimensions. *Psychological Medicine*, 23, 570–590.
- Bench, C. J., Frackowiak, R. S. J., & Dolan, R. J. (1995). Changes in regional cerebral blood flow on recovery from depression. *Psychological Medicine*, 25, 247–251.
- Biver, F., Goldman, S., Delvenne, V., Luxen, A., De Maertelaer, V., Hubain, P., Mendlewicz, J., & Lotstra, F. (1994). Frontal and parietal metabolic disturbances in unipolar depression. *Biological Psychiatry*, 36, 381–388.
- Brody, A. L., Saxena, S., Silverman, D. H. S., Alborzian, S., Fairbanks, L. A., Phelps, M. E., Huang, S. C., Wu, H. M., Maidment, K., & Baxter, L. R., Jr. (1999). Brain metabolic changes in major depressive disorder from pre- to post-treatment with paroxetine. *Psychiatry Research: Neuroimaging*, 91, 127–139.
- Bruder, G. E. (1988). Dichotic listening in psychiatric patients. In K. Hugdahl (Ed.), *Handbook of dichotic listening: Theory, methods and research* (pp. 527–563). New York: John Wiley & Sons.

- Bruder, G. E. (1995). Cerebral laterality and psychopathology: Perceptual and event-related potential asymmetries in affective and schizophrenic disorders. In R. Davidson & K. Hugdahl (Eds.), *Brain asymmetry* (pp. 661–691). Cambridge, MA: MIT Press.
- Bruder, G. E., Fong, R., Tenke, C. E., Leite, P., Towey, J. P., Stewart, J. W., McGrath, P. J., & Quitkin, F. M. (1997). Regional brain asymmetries in major depression with or without an anxiety disorder: A quantitative electroencephalographic study. *Biological Psychiatry*, 41, 939–948.
- Bruder, G. E., Otto, M. W., Stewart, J. W., McGrath, P., Fava, M., Rosenbaum, J. F., & Quitkin, F. M. (1996). Dichotic listening before and after fluoxetine treatment for major depression: Relations of laterality to therapeutic response. *Neuropsychopharmacology*, 15, 171–179.
- Bruder, G. E., Quitkin, F. M., Stewart, J. W., Martin, C., Voglmaier, M., & Harrison, W. M. (1989). Cerebral laterality and depression: Differences in perceptual asymmetry among diagnostic subtypes. *Journal of Abnormal Psychology*, 98, 177–186.
- Bruder, G. E., Stewart, J. W., Mercier, M. A., Agosti, V., Leite, P., Donovan, S., & Quitkin, F. M. (1997). Outcome of cognitive-behavioral therapy for depression: Relation to hemispheric dominance for verbal processing. *Journal of Abnormal Psychology*, 106, 138–144.
- Bruder, G. E., Stewart, J. W., Tenke, C. E., McGrath, P. J., Leite, P., Bhattacharya, N., & Quitkin, F. M. (2001). Electroencephalographic and perceptual asymmetry differences between responders and nonresponders to an SSRI antidepressant. *Biological Psychiatry*, 48, 416–425.
- Bruder, G. E., Stewart, J. W., Towey, J. P., Friedman, D., Tenke, C. E., Voglmaier, M. M., Leite, P., Cohen, P., & Quitkin, F. M. (1992). Abnormal cerebral laterality in bipolar depression: Convergence of behavioral and brain event-related potential findings. *Biological Psychiatry*, 32, 33–47.
- Bruder, G. E., Stewart, J. W., Voglmaier, M. M., Harrison, W. M., McGrath, P., Tricamo, E., & Quitkin, F. M. (1990). Cerebral laterality and depression: Relations of perceptual asymmetry to outcome of treatment with tricyclic antidepressants. *Neuropsychopharmacology*, 3, 1–10.
- Bruder, G. E., Tenke, C. E., Stewart, J. W., Towey, J. P., Leite, P., Voglmaier, M., & Quitkin, F. M. (1995). Brain event-related potentials to complex tones in depressed patients: Relations to perceptual asymmetry and clinical features. *Psychophysiology*, 32, 373–381.
- Bruder, G. E., Wexler, B. E., Stewart, J. W., Price, L. H., & Quitkin, F. M. (1999). Perceptual asymmetry differences between major depression with or without a comorbid anxiety disorder: A dichotic listening study. *Journal of Abnormal Psychology*, 108(2), 233–239.
- Coffey, C. E., Bryden, M. P., Schroering, E. S., Wilson, W. H., & Mathew, R. J. (1989). Regional cerebral blood flow correlates of a dichotic listening task. *Journal of Neuropsychiatry*, 1, 46–52.
- Cohen, R. M., Gross, M., Nordahl, T. E., Semple, W. E., & Oren, D. A. (1992). Preliminary data on the metabolic brain pattern of patients with winter seasonal affective disorder. *Archives of General Psychiatry*, 49, 545–552.

- Davidson, R. J. (1992). Anterior cerebral asymmetry and the nature of emotion. *Brain & Cognition*, 20, 125–151.
- Davidson, R. J., Chapman, J. P., & Chapman, L. J. (1987). Task-dependent EEG asymmetry discriminates between depressed and non-depressed subjects. *Psychophysiology*, 24, 585.
- Davidson, R. J., & Fox, N. A. (1989). Frontal brain asymmetry predicts infants' response to maternal separation. *Journal of Abnormal Psychology*, 98(2), 127–131.
- Davidson, R. J., & Hugdahl, K. (Eds.). (1995). *Brain asymmetry*. Cambridge, MA: MIT Press.
- Davidson, R. J., & Hugdahl, K. (1996). Baseline asymmetries in brain electrical activity predict dichotic listening performance. *Neuropsychology*, 10, 241–246.
- Davidson, R. J., & Tomarken, A. J. (1989). Laterality and emotion: An electrophysiological approach. In F. Boller & J. Grafman (Eds.), *Handbook of neuropsychology* (pp. 419–441). Amsterdam: Elsevier.
- Dawson, G., Frey, K., Panagiotides, H., Osterling, J., & Hessler, D. (1997). Infants of depressed mothers exhibit atypical frontal brain activity: A replication and extension of previous findings. *Journal of Child Psychology & Psychiatry*, 38(2), 179–186.
- Debener, S., Beauducel, A., Nessler, D., Brocke, B., Heilemann, H., & Kayser, J. (2000). Is resting anterior EEG alpha asymmetry a trait marker for depression? *Neuropsychobiology*, 41, 31–37.
- Deldin, P. J., Keller, J., Gergen, J. A., & Miller, G. A. (2000). Right-posterior face processing anomaly in depression. *Journal of Abnormal Psychology*, 109, 116–121.
- Dolan, R. J., Bench, C. J., Liddle, P. F., Friston, K. J., Frith, C. D., Grasby, P. M., & Frackowiak, R. S. J. (1993). Dorsolateral prefrontal cortex dysfunction in the major psychoses: Symptom or disease specificity? *Journal of Neurology, Neurosurgery and Psychiatry*, 56, 1290–1294.
- Drevets, W. C., Price, J. L., Simpson, J. R., Jr., Todd, R. D., Reich, T., Vannier, M., & Raichle, M. E. (1997). Subgenual prefrontal cortex abnormalities in mood disorders, *Nature*, 386, 824–827.
- Fava, M., Uebelacker, L. A., Alpert, J. E., Nierenberg, A. A., Pava, J. A., & Rosenbaum, J. F. (1997). Major depressive subtypes and treatment response. *Biological Psychiatry*, 42, 568–576.
- Feske, U., Frank, E., Mallinger, A. G., Houck, P. R., Fagiolini, A., Shear, M. K., Grochowski, V. J., & Kupfer, D. J. (2000). Anxiety as a correlate of response to the acute treatment of bipolar I disorder. *American Journal of Psychiatry*, 157, 956–962.
- Field, T., Fox, N. A., Pickens, J., & Nawrocki, T. (1995). Relative right frontal EEG activation in 3- to 6-month old infants of “depressed mothers.” *Developmental Psychology*, 31(3), 358–363.
- Flor-Henry, P. (1976). Lateralized temporal-limbic dysfunction and psychopathology. *Annals of the New York Academy of Sciences*, 280, 777–795.

- Fox, N. A., Bell, M. A., & Jones, N. A. (1992). Individual differences in response to stress and cerebral asymmetry. *Developmental Neuropsychology*, 8(2,3), 161–184.
- Frank, E., Shear, M. K., Rucci, P., Cyranoski, J. M., Endicott, J., Fagiolini, A., Grochocinski, V. J., Houck, P., Kupfer, D. J., Maser, J. D., & Cassano, G. B. (2000). Influence of panic-agoraphobic spectrum symptoms on treatment response in patients with recurrent major depression. *American Journal of Psychiatry*, 157, 1101–1107.
- George, M. S., Ketter, T. A., & Post, R. M. (1994). Prefrontal cortex dysfunction in clinical depression. *Depression*, 2, 59–72.
- Grasby, P. M. (1999). Imaging strategies in depression. *Journal of Psychopharmacology*, 13(4), 346–351.
- Gulley, L. R., & Nemeroff, C. B. (1993). The neurobiological basis of mixed depression-anxiety states. *Journal of Clinical Psychiatry*, 54, 16–19.
- Heller, W. (1990). The neuropsychology of emotion: Developmental patterns and implications for psychopathology. In N. Stein, B. L. Leventhal, & T. Trabasso (Eds.), *Psychological and biological approaches to emotion* (pp. 167–211). Hillsdale, NJ: Lawrence Erlbaum Associates.
- Heller, W. (1993). Gender differences in depression: Perspectives from neuropsychology. *Journal of Affective Disorders*, 29, 129–143.
- Heller, W., Etienne, M. A., & Miller, G. A. (1995). Patterns of perceptual asymmetry in depression and anxiety: Implications for neuropsychological models of emotion and psychopathology. *Journal of Abnormal Psychology*, 104, 327–333.
- Henriques, J. B., & Davidson, R. J. (1990). Regional brain electrical asymmetries discriminate between previously depressed and healthy control subjects. *Journal of Abnormal Psychology*, 99, 22–31.
- Henriques, J. B., & Davidson, R. J. (1991). Left frontal hypoactivation in depression. *Journal of Abnormal Psychology*, 100, 535–545.
- Jaeger, J., Borod, J. C., & Peselow, E. (1987). Depressed patients have atypical hemispace biases in the perception of emotional chimeric faces. *Journal of Abnormal Psychology*, 96, 321–324.
- Johnson, O., & Crockett, D. (1982). Changes in perceptual asymmetries with clinical improvement of depression and schizophrenia. *Journal of Abnormal Psychology*, 91, 45–54.
- Kayser, J., Bruder, G. E., Tenke, C. E., Stewart, J. W., & Quitkin, F. M. (2000). Event-related potentials (ERPs) to hemifield presentations of emotional stimuli: Differences between depressed patients and healthy adults in P3 amplitude and asymmetry. *International Journal of Psychophysiology*, 36, 211–236.
- Kayser, J., Tenke, C., Nordby, H., Hammerborg, D., Hugdahl, K., & Erdmann, G. (1997). Event-related potential (ERP) asymmetries to emotional stimuli in a visual half-field paradigm. *Psychophysiology*, 34(4), 414–426.

- Keller, J., Nitschke, J. B., Bhargava, T., Deldin, P. J., Gergen, J. A., Miller, G. A., & Heller, W. (2000). Neuropsychological differentiation of depression and anxiety. *Journal of Abnormal Psychology, 109*(1), 3–10.
- Kentgen, L. M., Tenke, C. E., Pine, D. S., Fong, R., Klein, R. G., & Bruder, G. E. (2000). Electroencephalographic asymmetries in adolescents with major depression: Influence of comorbidity with anxiety disorders. *Journal of Abnormal Psychology, 109*, 797–802.
- Ketter, T. A., Kimbrell, T. A., George, M. S., Willis, M. W., Benson, B. E., Danielson, A., Frye, H. A., Herscovitch, P., & Post, R. M. (1999). Baseline cerebral hypermetabolism associated with carbamazepine response, and hypometabolism with nimodipine response in mood disorders. *Biological Psychiatry, 46*, 1364–1374.
- Kinsbourne, M., & Bemporad, B. (1984). Lateralization of emotion: A model and the evidence. In N. A. Fox and R. J. Davidson (Eds.), *The psychobiology of affective development*. Hillsdale, NJ: Lawrence Erlbaum Associates.
- Levy, J., Heller, W., Banich, M., & Burton, L. A. (1983). Are variations among right handed individuals in perceptual asymmetries caused by characteristic arousal differences between hemispheres? *Journal of Experimental Psychology: Human Perception and Performance, 9*, 329–359.
- Liotti, M., Sava, D., Rizzolatti, G., & Caffarra, P. (1991). Differential hemispheric asymmetries in depression and anxiety: A reaction-time study. *Biological Psychiatry, 29*, 887–899.
- Little, J. T., Ketter, T. A., Kimbrell, T. A., Danielson, A., Benson, B., Willis, M. W., & Post, R. M. (1996). Venlafaxine or bupropion responders by not nonresponders show baseline prefrontal and paralimbic hypometabolism compared with controls. *Psychopharmacology Bulletin, 32*, 629–635.
- Mandell, A. J., & Knapp, S. (1979). Asymmetry and mood, emergent properties of serotonin regulation. *Archives of General Psychiatry, 36*, 909–916.
- Mann, J. J., Malone, K. M., Diehl, D. J., Perel, J., Cooper, T. B., & Mintun, M. A. (1996). Demonstration in vivo of reduced serotonin responsivity in the brain of untreated depressed patients. *American Journal of Psychiatry, 153*, 174–182.
- Mayberg, H. S. (1994). Frontal lobe dysfunction in secondary depression. *Journal of Neuropsychiatry & Clinical Neuroscience, 6*, 428–442.
- Mayberg, H. S., Brannan, S. K., Mahurin, R. K., Jerabek, P. A., Brickman, J. S., Tekell, J. L., Silva, A., McGinnis, S., Glass, T. G., Martin, C. C., & Fox, P. T. (1997). Cingulate function in depression: A potential predictor of treatment response. *NeuroReport, 8*, 1057–1061.
- Mayberg, H. S., Liotti, M., Brannan, S. K., McGinnis, S., Mahurin, R. K., Jerabek, P. A., Silva, J. A., Tekell, J. L., Martin, C. C., Lancaster, J. L., & Fox, P. T. (1999). Reciprocal limbic-cortical function and negative mood: Converging PET findings in depression and normal sadness. *American Journal of Psychiatry, 156*, 675–682.
- Meyer, J. H., Swinson, R., Kennedy, S. H., Houle, S., & Brown, G. M. (2000). Increased left posterior parietal-temporal cortex activation after D-fenfluramine in women with panic disorder. *Psychiatry Research: Neuroimaging, 98*, 133–143.

- Miller, E. N., Fujioka, T. A. T., Chapman, L. J., & Chapman, J. P. (1995). Hemispheric asymmetries of function in patients with major affective disorders. *Journal of Psychiatric Research*, 29, 173–183.
- Nordahl, T. E., Stein, M. B., Benkelfat, C., Semple, W. E., Andreason, P., Zametkin, A., Uhde, T. W., & Cohen, R. M. (1998). Regional cerebral metabolic asymmetries replicated in an independent group of patients with panic disorders. *Biological Psychiatry*, 44, 998–1006.
- Overby, L. A. III, Harris, A. E., & Leck, M. R. (1989). Perceptual asymmetry in schizophrenia and affective disorder: Implications from a right hemisphere task. *Neuropsychologia*, 27, 861–870.
- Pine, D. S., Kentgen, L. M., Bruder, G. E., Leite, P., Bearman, K., Ma, Y., & Klein, R. G. (2000). Cerebral laterality in adolescent major depression. *Psychiatry Research*, 93, 135–144.
- Post, R. M., DeLisi, L. E., Holcomb, H. H., Uhde, T. W., Cohen, R., & Buchsbaum, M. S. (1987). Glucose utilization in the temporal cortex of affectively ill patients: Positron emission tomography. *Biological Psychiatry*, 22, 545–553.
- Reid, S. A., Duke, L. M., & Allen, J. J. B. (1998). Resting frontal electroencephalographic asymmetry in depression: Inconsistencies suggest the need to identify mediating factors. *Psychophysiology*, 35, 389–404.
- Schaffer, C. E., Davidson, R. J., & Saron, C. (1983). Frontal and parietal electroencephalogram asymmetry in depressed and nondepressed subjects. *Biological Psychiatry*, 18, 753–762.
- Shimoda, K., & Robinson, R. G. (1999). The relationship between poststroke depression and lesion location in long-term follow-up. *Biological Psychiatry*, 45, 187–192.
- Sidtis, J. J. (1981). The complex tone test: Implications for the assessment of auditory laterality effects. *Neuropsychologia*, 19, 103–112.
- Stewart, J. W., Quitkin, F. M., McGrath, P. J., & Bruder, G. E. (1999). Do tricyclic responders have different brain laterality? *Journal of Abnormal Psychology*, 108(4), 707–710.
- Tollefson, G. D., Holman, S. L., Sayler, M. E., & Potvin, J. H. (1994). Fluoxetine, placebo, and tricyclic antidepressants in major depression with and without anxious features. *Journal of Clinical Psychiatry*, 55(2), 50–59.
- Tucker, D. M., Stenslie, C. E., Roth, R. S., & Shearer, S. L. (1981). Right frontal activation and right hemisphere performance: Decrement during a depressed mood. *Archives of General Psychiatry*, 38, 169–174.
- Tucker, D. M., & Williamson, P. A. (1984). Asymmetric neural control systems in human self-regulation. *Psychological Bulletin*, 91, 185–215.
- Videbech, P. (2000). PET measurements of brain glucose metabolism and blood flow in major depressive disorder: A critical review. *Acta Psychiatrica Scandinavica*, 101, 11–20.

- Wexler, B. E., & Halwes, T. (1983). Increasing the power of dichotic methods: The fused rhymed words test. *Neuropsychologia*, 21, 59–66.
- Zatorre, R. J. (1989). Perceptual asymmetry on the dichotic fused words test and cerebral speech lateralization determined by the carotid sodium amytal test. *Neuropsychologia*, 27, 1207–1219.
- Zimmerman, M., McDermut, W., & Mattia, J. I. (2000). Frequency of anxiety disorders in psychiatric outpatients with major depressive disorder. *American Journal of Psychiatry*, 157, 1337–1340.