

Neuroimaging Abnormalities in the Amygdala in Mood Disorders

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ABSTRACT: Neuroimaging technology has been applied to investigate the pathophysiology of mood disorders in studies aimed at characterizing the anatomical correlates of depressive symptoms, the neurophysiological effects of antidepressant treatments, and the trait-like abnormalities that persist despite symptom remission. These studies have identified cerebral blood flow and metabolic differences between depressives and controls in the amygdala and anatomically related areas of the prefrontal cortex, striatum, and thalamus. Taken together with converging evidence from neuroendocrine, lesion analysis, and postmortem studies of clinically depressed subjects, these data suggest that emotional/stress-response systems that include the amygdala are pathologically activated in major depression and that this activity is associated with dysfunction of the prefrontal cortex and monoamine neurotransmitter systems that normally modulate such responses.

KEYWORDS: amygdala; neuroimaging; mood disorders

CLINICAL PHENOMENOLOGY OF MOOD DISORDERS

Major depressive episodes (MDEs) are characterized by persistent dysphoric, anxious, and irritable emotional experiences and thought that coexist with disturbances of motivation, social behavior, sleep, and psychomotor activity.¹ The psychological manifestations include preoccupation with death, suicide, guilt, self-depreciation, and hopelessness. The intrusive and perseverative nature of such thoughts and their responsiveness to antidepressant drugs suggest that abnormal brain processes underlie and maintain such symptoms. MDEs may arise as primary, idiopathic disorders in the absence of clear medical or psychiatric antecedents (termed MDD when only depressive episodes occur or BD when manic as well as depressive episodes occur), or as syndromes that occur secondary to specific neurological, endocrinological, or psychiatric disorders or pharmacological substances.

The etiology of primary MDD and BD is unknown. Twin, adoption, and family studies indicate that genetic factors contribute substantially to the liability for devel-

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oping both disorders.¹ Nevertheless, the varied nature of the antecedents to depressive syndromes (genetic, medical, and psychosocial), the diversity of responses to somatic or psychological therapies, and the variable presence of neuroendocrine, neurochemical, and circadian rhythm disturbances in depressive samples imply that the MDE criteria encompass a group of disorders that are heterogeneous with respect to pathophysiology and etiology.¹ Since the MDE symptoms resemble those of a severe stress response (such as bereavement), stressful events are expected to constitute acquired factors that interact with genetic susceptibility in the development of mood disorders. A link between stressors and MDEs is commonly hypothesized for the initial MDE. However, such a link is generally not apparent for subsequent episodes, as individuals with recurrent MDEs commonly report that their pattern of depressive symptoms is inappropriate to and not explained by stressful life situations. Life events that clearly increase the risk for developing MDEs include pregnancy and delivery (that is, the postpartum period comprises the epoch of greatest risk in females), perimenopause, and acquisition of lesions involving the prefrontal cortex or striatum.¹⁻³

MDD is one of the most common illnesses encountered in primary health care. Illness onset can occur throughout the lifespan, although the first MDE most commonly occurs after puberty.¹ The usual course of MDD consists of recurrent MDEs separated, early in the illness course, by returns to the premorbid level of function. Later returns to the premorbid baseline, however, are often incomplete, and depressive symptoms and functional impairment may become chronic or intermittent. Antidepressant drug treatment shortens the duration of depressive episodes, reduces the likelihood of chronicity, and, if continued, decreases the risk of recurrence. Mortality risks from suicide, accidental death, and cardiovascular disease are elevated in MDD.^{1,4}

NEUROIMAGING ABNORMALITIES IN THE AMYGDALA IN MOOD DISORDERS

Neurophysiological Abnormalities

During MDEs, the resting cerebral blood flow (CBF) and glucose metabolism are abnormally elevated in the amygdala, and CBF responses to emotionally valenced stimuli are abnormal in at least some depressive subgroups (FIGS. 1 and 2). Resting CBF and metabolism are elevated in subgroups that meet criteria for familial pure depressive disease (FPDD)⁵⁻⁹; conform to the MDD-melancholic subtype¹⁰; display Type II BD or nonpsychotic, Type I BD^{8,11}; or prove responsive to sleep deprivation.¹² By contrast, metabolism has usually not been found abnormal in unipolar depressives who meet criteria for depression spectrum disease^{8,9,13} or who meet MDD criteria as the only entrance criterion.¹⁴⁻¹⁶ Nevertheless, data analysis for these latter studies suffered from technical difficulties (see below) that limited interpretation of whether these discrepant findings reflect pathophysiological differences across depressive subtypes.

Relation to Mood State and Illness Severity

The resting CBF and metabolism in the amygdala correlate positively with ratings of depression severity that assess both the emotional and the neurovegetative

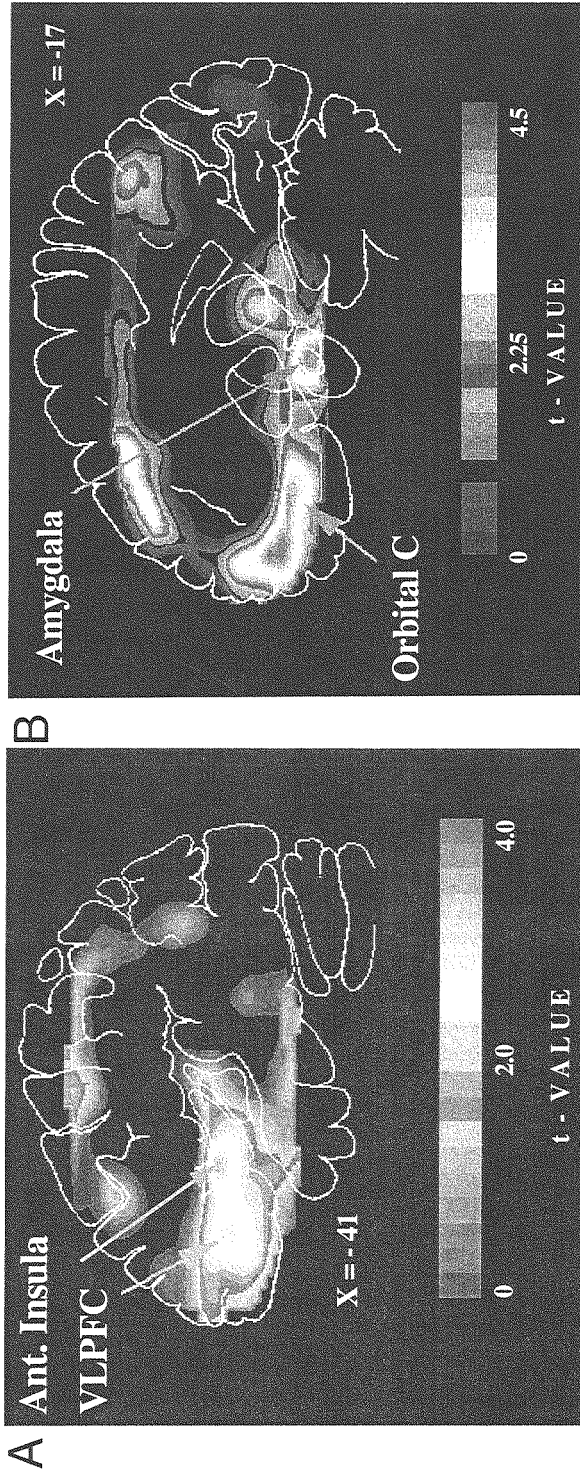


FIGURE 1. (A and B) Areas of abnormally increased blood flow in subjects with major depressive disorder. The image sections shown are from an image of t values, produced by a voxel-by-voxel computation of the unpaired t statistic to compare regional CBF between a depressed sample selected according to criteria for familial pure depressive disease ($n = 13$) and a healthy control sample ($n = 33$).⁵ The positive t values shown correspond to areas where flow is increased in the depressives relative to the controls. The abnormal activity in these regions was replicated using glucose metabolism imaging in independent subject samples.^{7,8,13} (A) Sagittal section at 17 mm left of midline illustrating areas of increased CBF in depression in the amygdala and medial (MED) orbital cortex. (B) This area of increased flow in the orbital cortex extended laterally to involve lateral orbital and ventrolateral prefrontal cortical (VLPFC) areas as well.^{5,7} The x coordinate locates sagittal sections in mm to the left of midline. (A and B) The PET images from which the t image was generated have been stereotactically transformed to the coordinate system of Talairach and Tournoux,¹⁴⁵ from which the corresponding atlas outline is shown. Anterior is left. FIGURE 1A is modified from Price *et al.*⁹⁰ and FIGURE 1B is reproduced from Drevets *et al.*¹⁴⁶ with permission.

aspects of MDE (that is, Hamilton Depression Rating Scale^{5,8,13,14}). In addition, the left amygdala glucose metabolism correlated positively with plasma cortisol concentrations measured under stressed conditions in both MDD and BD.⁸ Although the magnitude of amygdala activity in depression is partly modulated by illness severity, preliminary data also suggest that left amygdala activity is abnormally elevated (albeit to a lesser extent) in asymptomatic (that is, between MDEs), familial depressives who are not taking antidepressant drugs,⁵ and remitted BD subjects who were not taking mood stabilizers.⁸ Notably, Bremner *et al.*¹⁷ reported that AD-medicated, remitted MDD subjects who relapsed in response to serotonin depletion had a higher amygdala metabolism prior to depletion than did similar subjects who did not relapse, suggesting that abnormal amygdala activity may be involved in the susceptibility to symptom recurrence as well as to episode severity.

Hemodynamic Responses to Emotional Stimuli

Functional imaging data acquired as subjects view emotionally valenced visual stimuli demonstrate altered physiological responses in MDD. In the left amygdala, healthy humans increase CBF in the amygdala during exposure to pictures of faces expressing fear (relative to viewing either smiling or neutral faces), but this response is blunted in both depressed children¹⁸ and depressed adults.¹⁹ This finding was potentially consistent with the elevation of basal CBF and metabolism in the *left* amygdala in such cases, since tissue that is physiologically activated is expected to show an attenuation of further rises in metabolic activity in response to tasks that normally engage the same tissue because of the relationship between glutamate transmission and glucose utilization.^{20–26} Nevertheless, Sheline *et al.*²⁷ reported that hemodynamic responses in the left amygdala were exaggerated in MDD subjects exposed to fearful or smiling faces that were displayed briefly (40 ms) and then masked by faces with neutral expressions (such that subjects were not consciously aware of having seen the emotional faces).

The duration of the amygdala response to emotionally valenced stimuli is also abnormal in depression. Siegle *et al.*²⁸ reported that the elevation in hemodynamic activity occurring in the amygdala during exposure to sadly valenced words persisted for an abnormally long time in depressives relative to controls. Moreover, it has been observed that although depressives with MDD or BD do not differ from controls with respect to their hemodynamic response to initial exposures to sad faces, repeated presentation of the same sad faces resulted in habituation of the amygdala response in healthy controls, but not in depressives (that is, the amygdala CBF response persisted during exposure to repeated blocks of sad faces in depressives, but not in controls).¹⁹ This deficit in habituation of the hemodynamic response in the amygdala appeared specific to sad faces, as the corresponding rate of habituation to fearful-face stimuli did not differ between depressives and controls.

Specificity of Neuroimaging Abnormalities in the Amygdala to Mood Disorders

Elevation of *resting* amygdala CBF metabolism may prove specific to primary mood disorders, insofar as this abnormality has not been reported in obsessive-compulsive disorder, panic disorder, phobic disorders, schizophrenia, or other neuropsychiatric conditions.²⁹ In either healthy or anxiety-disordered human subjects, hemodynamic activity in the amygdala increases during exposure to emotionally sa-

lient sensory stimuli, but not during anxiety or sadness states elicited by internally generated thought (reviewed in Ref. 29). Thus, elevation of amygdala flow and metabolism in depressives with MDD or BD is not expected to relate to nonspecific aspects of MDE, such as anxiety, worrying, or sadness. The lack of association between abnormal amygdala activity in depression and overt exposure to emotionally valenced sensory stimuli would appear to imply a pathological process that may be specific to mood disorders. Consistent with this observation, Nofzinger *et al.*¹⁰ reported that while amygdala metabolism was increased in depressives versus controls during wakefulness, the increase in metabolism occurring in the amygdaloid complex during rapid eye movement sleep was also greater in depressives than controls, suggesting that amygdala hypermetabolism exists in MDD even when conscious processing of stressors is dormant. It is nevertheless conceivable that the elevated amygdala activity in mood disorders reflects an exaggerated response to the stress of scanning,⁸ that may be mediated by the positive feedback between amygdala neuronal activity and secretion of CRH, cortisol, and norepinephrine, which appear dysregulated in primary mood disorders.³⁰

Antidepressant Treatment Effects on Amygdala Activity

During chronic, effective antidepressant treatment, the resting amygdala metabolism decreases towards normal in MDD.^{7,31,32} The magnitude of the mean metabolic reduction in these studies was similar to that of the abnormal elevation of activity found in depressives prior to treatment (FIG. 2). The reduction in amygdala metabolism during treatment correlated positively with both clinical improvement (as measured by the decrement in depression ratings) and reduction in stressed plasma cortisol concentrations.⁷ This reduction in amygdala metabolism has been demonstrated for chronic treatment with citalopram and sertraline (selective serotonin reuptake inhibitors^{7,32}) and desipramine (a tricyclic antidepressant that is relatively selective as a norepinephrine transporter inhibitor³¹). Moreover, Sheline *et al.*²⁷ showed that the left amygdala's hemodynamic response to emotionally valenced stimuli was also attenuated in MDD subjects following chronic sertraline treatment.

These data are compatible with preclinical evidence that chronic antidepressant drug treatments suppress amygdala function.^{33–36} Horovitz³⁵ observed that direct injection of antidepressant drugs (ADs) into and specific lesions of the centromedial amygdaloid nucleus produced identical effects in animal models used to predict AD efficacy. Gerber *et al.*³⁴ found that 2-deoxyglucose uptake decreased in the amygdala after chronic desipramine administration in rats. Finally, the downregulation of beta-adrenergic receptors that occurs in experimental animals following chronic AD administration is most prominently and consistently observed (that is, relative to other brain regions and across the widest variety of AD classes) in the amygdala.³⁶ This effect occurs after 21 days of AD administration in the amygdala, coinciding with the usual 3-week latency prior to clinical improvement during AD treatment of MDD, although in most other brain structures this effect occurs after less than 2 weeks of AD administration.³⁷ Norepinephrine release increases in the amygdala during emotional behaviors in animals³⁸ (reviewed in Charney and Drevets²⁹), and microinjection of beta-adrenergic antagonists into the amygdala prevents such behaviors.^{38,39} The reduced beta-adrenergic receptor sensitivity induced by AD administration may thus suppress amygdala function. Finally, the AD-induced

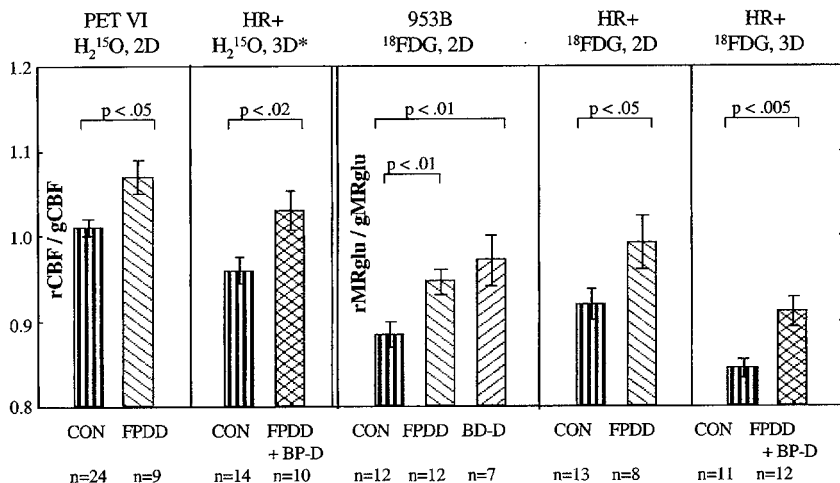


FIGURE 2. Elevation of mean normalized physiological activity ($\pm$ SEM) in the left amygdala, measured in terms of CBF or glucose metabolism, in mid-life depressed subjects relative to healthy controls. The five consecutive studies obtained using different PET cameras (PETT VI, HR+, and 953B are PET scanner model numbers—the latter two manufactured by Siemens/CTI; 2D and 3D refer to distinct image acquisition modes) in different laboratories in independent subject samples are summarized in Refs. 5–8 and Ref. 141. Because the first glucose metabolism study (*center*) showed that FPDD and BD-D samples both significantly differed from controls, but not from each other, subjects from these categories were combined for two subsequent studies (panels 2 and 4). The amygdala activity was assessed using a stereotaxic approach in the PETT VI study, and with an MRI-based ROI approach (FIG. 3) in the other four studies. Abbreviations: rCBF/gCBF, regional-to-global CBF ratio; rMRglu/gMRglu, ratio of regional-to-global metabolic rates for glucose; CON, healthy controls; FPDD, familial pure depressive disease; BD-D, depressed phase of bipolar disorder.

enhancement of serotonin (5-HT) transmission has been associated with inhibition of postsynaptic neuronal firing activity in the amygdala and hippocampus (but not in some other brain structures^{31,40–42}).

Technical Limitations of Neuroimaging Methods: Implications for Literature Review

Elevation of resting amygdala CBF or metabolism in MDD has proven highly reproducible under certain experimental conditions (FIG. 2). Nevertheless, few published studies of depression have employed methods with adequate sensitivity to detect this abnormality, so amygdala function has not been addressed by much of the psychiatric neuroimaging literature. Issues of experimental design that must be taken into account to sensitively assess amygdala function in depression are reviewed below (as detailed in Ref. 2).

Behavioral State during Scanning

Because CBF and metabolism are sensitive to changes in neural activity, the behavioral state in which subjects are imaged profoundly influences neurophysiological image data. Limbic and paralimbic structures such as the amygdala, ventral anterior cingulate cortex (ACC), lateral orbital cortex, and posterior cingulate cortex normally *deactivate* (that is, decrease hemodynamic activity) during performance of attentionally demanding tasks.^{7,43,44} Possibly related to this phenomenon, the elevations of CBF and metabolism seen in these areas, in depressed subjects scanned while they are resting with eyes closed, have been less often replicated in studies of MDD subjects imaged while engaging in attentionally demanding tasks (see, for example, Ref. 45). Nevertheless, a PET study in which bipolar depressives were imaged while performing a continuous performance task did identify abnormally elevated resting metabolism in the right amygdala.¹¹ Differential changes in CBF or metabolism between depressives and controls that arise specifically in association with performing continuous performance tasks or other attentionally demanding tasks have thus far not been characterized.

Spatial Resolution Effects: Implications for Image Acquisition and Analysis

The small size of the amygdala relative to the spatial resolution of functional imaging technology constitutes a major limitation to the sensitivity for detecting neuroimaging differences in this structure between depressives and controls and has thus far precluded resolution of specific amygdala nuclei. For example, computer simulations that correct PET measures obtained from a structure with the amygdala's size, geometry, and spatial location for the resolution (partial volume) effects of PET suggest that a difference of the 6–8% magnitude measured between depressives with FPDD or BD and healthy controls (FIG. 2) would correspond to an actual increase in CBF and metabolism of 50–70% in the depressives.^{5,46} This value is within the expected physiological range, as CBF increases ~50% in the rat amygdala during exposure to fear-conditioned stimuli as measured by tissue autoradiography.⁴⁷

The spatial resolution of functional brain images is improving with refinements of technology (to 4 mm for the newest generation of PET camera and to <1 mm for MRI), techniques for c-registering PET and MRI images, and image analysis methods. However, most of the extant literature in depression consists of image data acquired using PET, SPECT, and nontomographic techniques that more severely constrain the spatial resolution and the sensitivity for assessing amygdala function. For example, perfusion images acquired using ¹³³Xe administration provide measures limited to the cortical gray matter lying near the scalp, precluding measures from medial temporal lobe structures.⁴⁸ Moreover, perfusion measures obtained using SPECT and either ^{99m}Tc-HMPAO or ¹³³I-iodoamphetamine, agents that do not freely diffuse across the blood-brain barrier, are relatively insensitive to CBF increases within the upper end of the physiological range. Consequently, SPECT studies rarely detect the elevation of amygdala flow in depression.⁴⁹ Although PET affords relatively higher spatial resolution and sensitivity for deep structures, early PET studies used tomographs with limited axial fields-of-view (FOV) that did not sample the entire brain. When such images were analyzed using statistical parametric mapping techniques⁵⁰ that excluded voxels not sampled by all subjects from analysis, the effective FOV was further restricted (to 6 or 7 cm). Many of these studies

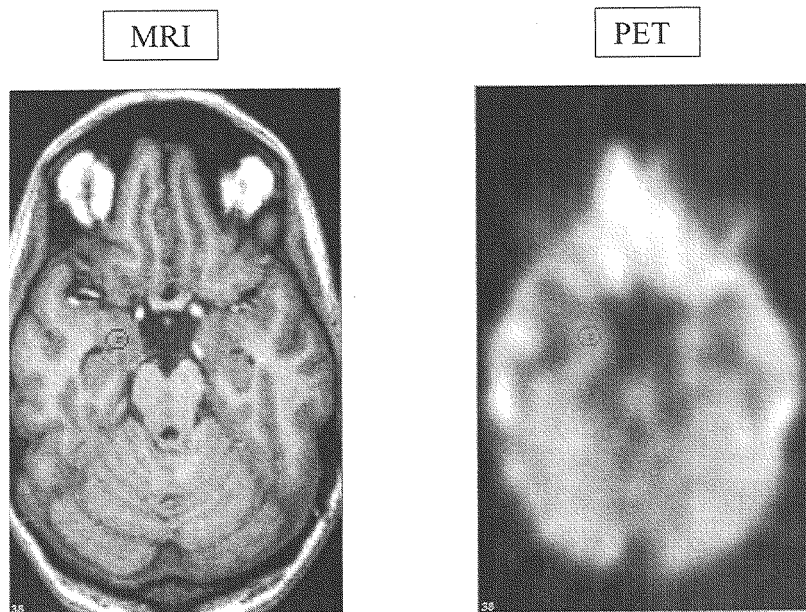


FIGURE 3. Aligned anatomical magnetic resonance image (*left*) and PET image of glucose metabolism (*right*) showing placement of the region-of-interest in the amygdala, an approach that has proven sensitive for detecting neurophysiological differences between depressives and controls (FIG. 2). The ROI in which amygdala metabolism was measured was approximately positioned over the basal/accessory basal nuclei, which form the largest nuclear complex within the amygdala. The location of this nuclear complex can easily be approximated in high-resolution MRI images, and ROI centered in the basal nuclear complex are predominantly surrounded by tissue belonging to other portions of the amygdaloid complex. The PET image shown had a final, reconstructed FWHM resolution of 8 mm and a three-dimensional resolution volume for each voxel of 0.5 mL. This compares to the average anatomical volume of the amygdala of 1.22 ± 0.17 mL (*left*) and 1.11 ± 0.21 mL (*right*) measured in the healthy controls from the same study measured using MRI.⁶³ The metabolism was measured within a small number of voxels situated deep within the amygdala to eliminate from the average amygdala voxel value those voxels lying on the outer boundary of the amygdala that would be partly comprised of tissue from structures adjacent to the amygdala.⁵² Reproduced with permission from Ref. 19.

positioned the scanner gantry over dorsal brain regions and consequently did not sample ventral areas such as the amygdala.⁵¹

Even among PET studies that sampled the amygdala, the image analysis approaches applied limited the sensitivity for detecting differences between depressives and controls in most studies. The technique that currently provides optimal sensitivity and precision involves MRI-based ROI analysis, in which ROI are pre-defined on each subject's anatomical MRI scans and then transferred to co-registered, lower-resolution functional images (FIG. 3). The sensitivity for assessing amygdala physiology using this technique depends on adherence to technical prin-

ciples for ROI definition in PET images, as discussed in Drevets *et al.*³² To preserve the specificity of measures for the amygdala, voxels lying on the outer boundary of this structure must be excluded from the average regional voxel value, because they will be composed of heterogeneous mixtures of neighboring structures, and will increase the influence of radioactivity spilling in from tissues surrounding the structure.^{46,52} Thus, in the MRI-based ROI shown in FIGURE 3, metabolism would reflect activity from the basal/accessory basal nuclear tissue over which the ROI is centered, but it would also be influenced by spilling in of radioactivity from the remainder of the basal and accessory basal nuclei anteriorly, dorsally, and ventrally; the cortical and central nuclei dorsally; the lateral nucleus laterally; the paralaminar nucleus ventrally; the periamygdaloid cortex anteriorly and medially; and the head of the hippocampus posteriorly.⁵³ Measured activity would also be reduced by dilutional effects from the CSF spaces located medially and posteriorly and the white matter situated ventrally and laterally.^{46,52} Because the structure extrinsic to the amygdaloid complex that would influence PET measures in the amygdala by spilling in of radioactivity is the anterior head of the hippocampus,^{46,52} a control ROI was placed in this region in the studies reviewed in FIGURE 2 to address the specificity of findings to the amygdala.⁸ Demonstrating an effect of depression on amygdala metabolism depended on showing that the magnitude of the difference with respect to controls in the amygdala was not exceeded by an even greater difference in the adjacent hippocampus.

Notably, the three studies of MDD that employed MRI-based ROI but did not detect significant differences between depressives and controls defined ROI that were excessively large, by outlining the entire amygdaloid complex. These studies thus included all image voxels through which the edge of the amygdala passed, substantially diluting the proportion of measured radioactivity actually emanating from the amygdala.¹⁴⁻¹⁶ It has therefore remained unclear whether this technical limitation or the sample selection criteria employed (these studies were also the only three to report data for samples selected according to MDD criteria in the absence of other, more specific entrance criteria) may have accounted for the negative results from these studies with respect to amygdala function.

Limitations of ROI-based approaches for image analysis include their inability to localize the peak difference between conditions and their tendency to dilute an intergroup difference if the ROI defined is larger than the area of actual difference.^{8,52} To address these issues, voxel-by-voxel analysis techniques (such as statistical parametric mapping, or SPM) were developed to survey large volumes and localize inherent differences between conditions (FIG. 1) (see, for example, Refs. 5 and 10). Studies employing voxel-by-voxel approaches have localized the stereotaxic centroid of the peak difference of abnormal CBF or metabolism in depression to the amygdala in both MDD^{5,10,54} (FIG. 1) and BD.¹¹

Nevertheless, voxel-by-voxel approaches are relatively insensitive for detecting abnormalities in small structures such as the amygdala because they depend on spatial transformation of the primary tomographs into a standardized stereotaxic space using algorithms that imprecisely address anatomical variability across subjects. Small structures such as the amygdala can, therefore, be misaligned across subjects. To reduce the effects of misalignment error, PET or fMRI images are blurred (filtered) prior to analysis to a lower spatial resolution. Both the reduction of spatial resolution from blurring and the imprecision in overlaying brain structures

across subjects decrease sensitivity for detecting abnormalities in the amygdala. For example, Abercrombie *et al.*⁵⁵ demonstrated that while a positive correlation between depression severity and right amygdala metabolism was evident in MDD when images were analyzed using MRI-based ROI analysis, this relation was not detected when the same image set was analyzed using a voxel-by-voxel analysis. The reduction in sensitivity for detecting abnormalities of amygdala activity encountered during application of techniques that rely upon spatial transformation may account for the negative results in some studies of depression.

Inaccuracies involved in spatial transformation procedures may also lead to error in localizing differences between depressives and controls in voxel-by-voxel analyses. These algorithms currently align external brain surfaces across subjects, but do not specifically align internal structures, assuming instead that the proportionate distances of such structures along orthogonal brain axes are identical across individuals. Regional differences in radioactivity between depressives and controls may thus have errors in their stereotaxic location relative to the actual anatomy, particularly if abnormalities of brain structure exist in depression. For example, Videbech *et al.*⁵⁶ localized an abnormal elevation of CBF in MDD to the junction of the amygdala and hippocampus. The locus implicated was within the area expected to reflect amygdala activity in SPM images, but could not be resolved from the adjacent hippocampus. Interpretation of these data must, therefore, consider the results reviewed in FIGURE 2, which used MRI-based ROI analysis (FIG. 3) to demonstrate both that metabolism and CBF were significantly elevated in MDD and BD and that activity did not significantly differ between depressives and controls in the head of the hippocampus (see, for example, Ref. 8—although activity may be abnormal in other regions of the hippocampus, as shown, for example, in Ref. 5).

Clinical Sources of Variability in Image Data from Depressed Samples

A major source of variability in functional imaging studies is the clinical heterogeneity inherent within the major depressive syndrome, as diverse signs and symptoms may have distinct neurophysiological correlates.¹ Depressives with prominent anxiety, obsessive ruminations, insomnia, and psychomotor agitation may, for example, show distinct imaging findings from subjects who are instead apathetic, hypersomnolent, and psychomotor slowed.⁵⁷ Nevertheless, the relative contributions of these factors to the variability of image data has not been established.

A related challenge for imaging studies is the likelihood that the major depressive syndrome encompasses a group of disorders that are heterogeneous with respect to pathophysiology and etiology. Biological heterogeneity is evidenced by the variety of antecedents to MDE onset (for example, genetic, medical, and psychosocial), the diversity of responses to somatic or psychological therapies, and the variable presence of neuroendocrine, neurochemical, and circadian rhythm disturbances in depressive samples.¹ If depression is associated with multiple pathophysiologic states, it will presumably be characterized by an assortment of functional imaging abnormalities. The literature supports this hypothesis, as the reproducibility of some imaging findings appears to depend upon subtyping subjects *a priori*.

Subtyping strategies that increase sensitivity for detecting neuroimaging abnormalities in mood disorders have been ones which more generally appear to enrich depressed samples for subjects likely to have biological markers for depression in

previous studies using other biological assessments. For example, depressives with FPDD and BD have been more likely to have some imaging abnormalities, such as elevated CBF and metabolism in the amygdala, than unipolar depressives who lack a family history of a mood disorder or who have first-degree relatives with alcoholism or sociopathy (FIG. 2).^{8,58} The FPDD and BD subgroups had previously been shown to be more likely to respond to biological therapies and to manifest abnormalities of hypothalamic-pituitary-adrenal (HPA) axis function, sleep EEG, and serotonergic binding sites than other depressive subtypes (reviewed in Ref. 8). It is conceivable that the FPDD and BD subgroups may have a common set of pathophysiologically linked abnormalities (for example, through interactions between the amygdala and corticotrophin-releasing hormone (CRH)/glucocorticoid secretion). Other subtyping strategies that have increased the likelihood of having elevated amygdala, anterior cingulate cortex, and orbital cortex activity involve selecting depressed subjects whose symptoms remit following sleep deprivation,^{12,59,60} or remitted depressives whose symptoms exacerbate following serotonin depletion.¹⁷

Other subtyping approaches for subject selection that are critical for reducing the variability of imaging data relate to the likelihood of neuromorphological abnormalities that can influence functional imaging measures. Depressives who are elderly with a late age-of-depression onset or who are bipolar or psychotic have been shown to have ventricular and sulcal enlargement and reductions in some lobar or gyral volumes. The reductions in gray matter that accompany these abnormalities would decrease the magnitude of tomographic imaging measures from the corresponding regions via "partial volume averaging" effects.⁵² Elderly depressives with a late age-of-depression-onset also have a markedly increased likelihood of having patches of MR signal hyperintensity in the frontal lobe white matter and striatal lacunae relative to age-matched controls who are either healthy or are depressed but with an early age-of-depression-onset. Postmortem, clinical, and functional neuroimaging studies have shown that these abnormalities generally reflect cerebrovascular disease (reviewed in Ref. 2). Since the relationship between regional BF, metabolism, and local synaptic transmission is altered by cerebrovascular disease, functional imaging studies of elderly depressives cannot be interpreted unless such subjects have been excluded.^{54,61} Although these gross abnormalities are generally not evident in non-delusional, unipolar depressives with a young age-of-onset, even these groups have focal areas of reduced gray matter volume that require partial volume correction and neuromorphometric/neuropathological evaluation of areas where CBF and metabolism appear irreversibly *decreased* in depressives relative to controls (FIG. 3).^{62,63}

Finally, medication effects constitute an important source of clinical variability in functional imaging studies of depression. Metabolism and CBF in the prefrontal cortical and limbic areas of interest in depression can be reduced by antidepressant, antipsychotic, and antianxiety drugs (reviewed in Refs. 2 and 64). Image data acquired in depressives medicated with these agents are thus difficult to interpret if scans in the unmedicated-baseline condition are not available for comparison. Nevertheless, most published studies of depression report data confounded by medication effects, potentially obscuring neurobiological differences with respect to controls. Most studies of depressives confounded by medication effects have failed to detect the areas of abnormally elevated metabolism seen in unmedicated subjects (such as in the amygdala), and have instead reported regional reductions in flow or metabolism that cannot be replicated in unmedicated samples (reviewed in Ref. 64).

Structural Neuroimaging Abnormalities of the Amygdala in Mood Disorders

Neuromorphometric MRI studies have reported abnormalities of amygdala volume in mood disorders, but this literature is in disagreement. In MDD, the amygdala volume is reported to be decreased,⁶⁵ not different⁶⁶ except for an abnormal asymmetry, and increased⁶⁷ relative to healthy controls. Similarly, the amygdala volume in BD is reported to be decreased,⁶⁸ not different,⁶⁹ or increased^{70,71} relative to healthy controls. Technical limitations, medication effects, and age differences may all contribute to differences across studies. The reliability of amygdala volumetric MRI data has been low in images with voxel size $\geq 1 \text{ mm}^3$ (as is the case in all published studies) because some of this structure's boundaries are ambiguous in images of this spatial resolution, potentially contributing to Type I error. In BD, the conflicting results may reflect medication effects, because some mood stabilizer treatments exert neurotrophic/neuroprotective effects.^{72,73}

Postmortem Histopathological Studies of the Amygdala in Mood Disorders

A postmortem study of the amygdala in mood disorders reported that the mean glia-to-neuron ratio was decreased in MDD relative to healthy control subjects.⁷³ Although the corresponding measure in a BD sample did not significantly differ from that of controls, inspection of the data from individual cases suggested that this abnormality may extend to bipolar subjects who were not taking mood stabilizers prior to death. The neuronal count and density did not significantly differ across the MDD, BD, and control groups.

The finding of reduced glial cell counts without an equivalent loss of neurons has also been demonstrated in the lateral orbital cortex and the anterior cingulate cortex ventral to the genu of the corpus callosum (subgenual) in MDD and/or BD.^{43,63,74,75} These brain structures had also been shown to have reduced gray matter volume in *in vivo* MRI and/or postmortem studies of MDD and BD.^{2,62,76,77} Similar neuropathological findings have also been reported in anatomically related structures. In the ventral striatum, Baumann *et al.*⁷⁸ reported that the volume of the accumbens area was decreased in both MDD and BD samples relative to a healthy control sample. In the hippocampus, postmortem studies of BD have additionally found reduced mRNA concentrations for synaptic proteins and spine density on apical dendrites of pyramidal neurons in the subiculum, and reductions in the numbers of glutamate acid decarboxylase (GAD)-staining neurons in the dentate gyrus and CA 2, 3 (GAD₆₅ only), and 4 (GAD₆₇ only) in BD relative to control samples.^{79–81} Notably, Berretta *et al.*⁸² observed that activation of the excitatory amygdalar afferents to hippocampus induced reductions in GAD-staining neurons in CA2 and 3, which partly resembled the changes found postmortem in BD.

While the pathogenesis of these histopathological changes in mood disorders has not been established, it is noteworthy that many of these structures appear homologous to regions where histopathological changes occur during repeated stress in rodents. The dendritic arborization of pyramidal cells has been shown to undergo reshaping in limbic structures of adult rodents in the hippocampus, medial prefrontal cortex (PFC), and amygdala during repeated or chronic stress applied over several

weeks to adult rats.^{83,84} In the hippocampus, this effect has been shown to depend upon an interaction between NMDA glutamate receptor stimulation and elevated glucocorticoid secretion.⁸³

Interpreting the Possible Nature of Amygdala Hypermetabolism in Depression

The critical involvement of EAA transmission in the pathogenesis of dendritic re-shaping is noteworthy because the elevation of glucose metabolism in the amygdala suggests that afferent glutamatergic transmission is increased. Local cerebral CBF and glucose metabolism predominantly reflect a summation of metabolic activity associated with terminal field synaptic transmission within each image volume element, or voxel.^{48,85} The glucose metabolic signal in particular is dominated by the energy utilization associated with synaptic transmission within the neuropil that is glutamatergic in nature.^{22–26} Elevated regional CBF and metabolism in the amygdala may thus signify increased neurotransmission from afferent.⁴⁸

One source of afferent glutamatergic transmission that may influence amygdala metabolism originates from the orbital and medial PFC areas that share substantial, reciprocal connections with the basal nuclear complex of the amygdala, and that have elevated metabolic activity in MDD.^{53,86–90} In rats and monkeys, the prefronto-amygdalar projection appears predominantly glutamatergic, and both AMPA and NMDA glutamatergic receptors exist on neurons in the basolateral amygdala (BLA), the major target of the prefronto-amygdalar projections.^{88,91} The majority of the PFC afferents to the BLA form synaptic contacts with dendritic spines of the spiny pyramidal neurons which have a morphology that implies they are excitatory.^{92,93} In the lateral amygdala as well, electrophysiological characterization of the EPSPs revealed that the EPSPs consisted of dual, fast and slow, glutamatergic components.⁹⁴ However, electrical stimulation of the medial PFC evokes IPSP in amygdalar projection neurons through apparently polysynaptic monosynaptic events that are initially mediated through excitatory connections synapsing onto inhibitory interneurons.⁹⁵ While individual amygdala nuclei are too small to resolve using PET, the ROI in which amygdala metabolism was measured for the studies reviewed in FIGURE 2 was positioned over the basal/ accessory basal nuclei for technical and scientific reasons, and was thus most influenced by metabolic activity within these nuclei (FIG. 3). The elevation of amygdala metabolism in FPDD and BD-D could thus reflect increased glutamatergic transmission from the caudal orbital cortex, anterior insula, and ventral anterior cingulate cortex, which are also hypermetabolic in primary MDD (reviewed in Refs. 2 and 5).

Reduced inhibitory transmission within the amygdala or increased firing activity of amygdala neurons may also contribute to the elevated metabolism in the amygdala, albeit to a lesser extent.^{48,85} Shekhar *et al.* (this volume) observed that repeated CRH infusion into the amygdala markedly shifts the EPSP-to-IPSP ratio for amygdala neurons in favor of EPSP, an effect which can persist for several months. Such a phenomenon could conceivably contribute to the elevation of amygdala metabolism in depressives from mood-disordered subgroups who have elevated CRH secretion (reviewed in Refs. 30 and 96), as well for the temporal duration of depressive signs and symptoms of MDE that may be driven by amygdala hyperexcitability (see below).

The differences in neural transmission between depressives and controls reflected in CBF or metabolic images may additionally reflect neurophysiological correlates of emotional, behavioral, or cognitive symptoms associated with MDE, pathophysiological changes that predispose to or result from affective disease, or compensatory mechanisms invoked to modulate or inhibit pathological processes. Physiological correlates of depressive symptoms and behaviors would putatively appear in the depressed phase, but normalize following symptom resolution, and may to some extent be reproduced in healthy subjects imaged while performing tasks that mimic corresponding depressive manifestations. In contrast, neuroimaging abnormalities that reflect pathological changes in synaptic transmission associated with altered neurotransmitter synthesis, receptor sensitivity/binding, or neuronal arborization (see, for example, Ref. 97) may in some cases be evident as trait-like abnormalities that persist whether subjects are symptomatic or asymptomatic.^{2,5,62}

Implications of Amygdala Dysfunction for the Pathogenesis of Depressive Symptoms

The observation of Siegle *et al.*²⁸ that amygdala activity persists for an abnormally prolonged period during contemplation of sad words is noteworthy in light of neuroimaging, electrophysiological, and lesion analysis studies in humans and experimental animals that demonstrate the amygdala's involvement in the acquisition and recall of emotional or arousing memories.^{98,99} In humans, bursts of EEG activity occur in the amygdala during recollection of specific emotional events,¹⁰⁰ and electrical stimulation of the amygdala can evoke emotional experiences (fear, anxiety, and dysphoria) and recall of emotionally charged life events from remote memory.^{101,102} Taken together with the finding of elevated amygdala metabolism in MDD, these observations suggest the hypothesis that excessive amygdala stimulation of cortical structures involved in declarative memory may account for the tendency of depressed subjects to ruminate about memories of emotionally aversive or guilt-provoking life events.¹⁰³

Amygdala dysfunction may also conceivably alter the initial evaluation and memory consolidation related to social or sensory stimuli with respect to their emotional significance in mood disorders. The amygdala is involved in recognizing sadness and fear in facial expression and fear and anger in spoken language (reviewed in Ref. 104). Norepinephrine (NE) release in the amygdala plays a critical role in at least some types of emotional learning, and the activation of NE release is facilitated by glucocorticoid secretion.⁹⁹ At least some depressed subjects have abnormally elevated secretion of both NE and cortisol,¹⁰⁵ which in the presence of amygdala activation may conceivably increase the likelihood that sensory or social stimuli are perceived or remembered as emotionally arousing or aversive.^{29,104}

The amygdala plays an important role in organizing other emotional, behavioral, neuroendocrine, and autonomic aspects of emotional/stress responses as well, potentially compatible with reports that amygdala CBF and metabolism correlate positively with ratings of depression severity that assess neurovegetative, as well as emotional, aspects of MDEs.^{5,6,8,14} For example, the amygdala facilitates stress-related CRH release¹⁰⁶ and electrical stimulation of the amygdala in humans increases cortisol secretion,¹⁰⁷ suggesting a mechanism via which excessive amygdala activity may play a role in inducing CRH hypersecretion in MDD.^{96,108} In both MDD and

BD, glucose metabolism in the left amygdala correlated positively with stressed plasma cortisol secretion, which may conceivably reflect either the effect of amygdala activity on CRH secretion or the effect of cortisol on amygdala function.⁸

Imaging Abnormalities in Anatomically Related Areas of the Prefrontal Cortex

The neuroimaging abnormalities in the amygdala in mood disorders coexist with abnormalities of the PFC, striatal, medial thalamic, and brain-stem areas that participate in the modulation of emotion and of amygdala function. For example, the posterior orbital cortex and amygdala send overlapping projections to each other as well as to hypothalamic, periaqueductal gray matter, and brain-stem structures that subserve the autonomic, behavioral, and neuroendocrine expressions of emotion, through which they appear to modulate each other's neural transmission.^{89,109,110} Thus, concomitant electrical stimulation of the orbital C and the amygdala attenuates all aspects of the defense responses evoked by amygdala stimulation alone.¹¹¹ In the medial PFC of rats, firing activity of most mPFC neurons can be inhibited by BLA stimulation,¹¹² and during exposure to fear-conditioned stimuli, firing activity of mPFC neurons decreases immediately after the increase in amygdala neuronal activity.¹⁰⁹ The nature of the neuroimaging and neuropathological abnormalities found in these medial and orbital PFC areas in mood disorders suggests mechanisms through which behavioral, autonomic, and neuroendocrine responses driven by excessive amygdala activity may be disinhibited.

Lateral Orbital/Ventrolateral Prefrontal Cortex

In the lateral orbital cortex, ventrolateral PFC, and anterior insula, CBF and metabolism have been abnormally increased in most studies of *unmedicated* depressives with primary MDD scanned while resting (reviewed in Ref. 2) and in some studies of unmedicated BD subjects.¹¹ The elevated activity in these areas in MDD appears mood-state dependent.^{2,5,113} Flow and metabolism also increase in these areas during induced sadness and anxiety in healthy subjects and induced anxiety and obsessional states in subjects with anxiety disorders (reviewed in Refs. 29 and 43). Many studies also report that flow or metabolism decrease during antidepressant treatment in the orbital cortex, ventrolateral PFC, and/or anterior insula (reviewed in Ref. 2).

A complex relationship exists between depression severity and physiological activity in the orbital cortex and ventrolateral PFC. While CBF and metabolism increase in these areas in the depressed relative to the remitted phase of MDD, the magnitude of these measures correlates inversely with ratings of depressive ideation and severity.^{5,6,114} This inverse relationship between orbital cortex/ventrolateral PFC activity and ratings of depression severity appears compatible with similar assessments in other conditions. Posterior orbital cortex flow also increases in obsessive-compulsive disorder and animal phobic subjects during exposure to phobic stimuli and in healthy subjects during induced sadness,^{115–117} and the change in posterior orbital CBF correlated inversely with changes in obsessive thinking, anxiety, and sadness, respectively.

These data appear consistent with electrophysiological and lesion analysis data showing that parts of the orbital cortex participate in modulating behavioral and visceral responses associated with defensive, fear, and reward-directed behavior as re-

inforcement contingencies change.¹¹⁸ The lateral orbital cortex area implicated in depression includes BA 47 (corresponding to caudal area 12 in monkeys), which receives projections from sensory association cortices and shares extensive, reciprocal, anatomical connections with the amygdala, ACC, ventral striatum, hippocampal subiculum, hypothalamus, periaqueductal gray, and brainstem monoaminergic and autonomic nuclei⁸⁹ through which they participate in extinguishing unreinforced responses to aversive or appetitive stimuli.^{89,110,118} The lateral orbital cortex thus plays a role in integrating experiential stimuli with emotional salience and in associating reward-directed behavioral responses with the outcome of such responses, allowing redirection of behavior as reinforcement contingencies change.^{118,119}

Activation of the orbital cortex during depression may thus reflect endogenous attempts to attenuate emotional expression or interrupt unreinforced aversive thought and emotion. Nevertheless, the abnormal reduction in gray matter found in this area in MDD⁷⁵ suggests that the orbital cortices' role in modulating motivated and emotional behavior may be impaired during depression. Consistent with this hypothesis, cerebrovascular lesions and tumors involving the frontal lobe increase the risk for developing major depression,¹²⁰ with the orbital cortex having been more specifically implicated as the area where such lesions induce depression.¹²¹ Finally, serotonin depletion^{17,122} and Parkinson's disease appear to impair orbital cortex function,^{123,124} suggesting other mechanisms through which deficits in orbital cortex function may increase risk for depression.

Ventral Anterior Cingulate Cortex

The anterior cingulate cortex (ACC) situated ventral and anterior to the genu of the corpus callosum (termed subgenual and pregenual, respectively) has also been consistently implicated in the pathophysiology of MDD and BD. In the subgenual PFC, a complex relation between CBF, metabolism, and illness state exists that appears accounted for by a left-lateralized, volumetric reduction of the corresponding cortex, initially demonstrated by MRI-based morphometric measures^{62,125–127} (Fig. 2) and later by postmortem neuropathological studies of familial BD and MDD.⁶³ This reduction in volume exists early in the illness in familial BD¹²⁶ and MDD,¹²⁷ but may follow illness-onset based upon preliminary evidence in twins discordant for MDD.¹²⁸

Effective antidepressant pharmacotherapy results in a *decrease* in metabolic activity in this region in MDD (reviewed in Ref. 2). Furthermore, during depressive episodes, metabolism shows a positive relationship with depression severity.^{7,8,129} This mood-state-dependency of subgenual ACC metabolism thus appears consistent with PET studies showing that flow increases in this region in healthy, non-depressed humans during sadness internally induced via contemplation of sad thoughts or memories.^{130–132}

In the pregenual ACC, Drevets and colleagues initially found increased CBF in MDD. While other laboratories also reported abnormalities of CBF and metabolism in this area during depression, these data have been inconsistent (reviewed in Ref. 2). The effects of treatment on pregenual ACC flow and metabolism have also differed across studies, with activity decreasing in some, but increasing in others in post- relative to pre-treatment scans (reviewed in Ref. 2). Nevertheless, the variability of the neuroimaging results in this region may have clinical relevance, as several

studies report relationships between pregenual ACC activity and subsequent antidepressant treatment outcome (reviewed in Ref. 2). The pregenual ACC shows elevated CBF during a greater variety of emotional conditions elicited in healthy or anxiety-disordered humans (reviewed in Refs. 29 and 43), and electrical stimulation of this region elicits fear, panic, or a sense of foreboding in humans, and vocalization in experimental animals (reviewed in Ref. 90).

In rodents and nonhuman primates, the cortex that appears homologous to human subgenual ACC has extensive reciprocal connections with the orbital cortex, lateral hypothalamus, amygdala, accumbens, subiculum, ventral tegmental area, raphe, locus coeruleus, periaqueductal gray, and nucleus tractus solitarius (NTS) (reviewed in Refs. 89 and 133). The pregenual ACC is similar in its anatomical connectivity as subgenual ACC, except that the projections to NTS become relatively sparse. Humans with lesions that include these ventromedial PFC regions show abnormal autonomic responses to emotionally provocative stimuli, inability to experience emotion related to concepts that ordinarily evoke emotion, and inability to use information regarding the likelihood of punishment and reward in guiding social behavior.¹³⁴ Similarly, rats with experimental lesions of the putatively homologous cortex demonstrate altered autonomic, neuroendocrine, and behavioral responses to stress and fear-conditioned stimuli. For example, Diorio *et al.*¹³⁵ demonstrated glucocorticoid receptors in these regions, which when stimulated by corticosterone (CORT), reduced stress-related HPA activity and showed that lesioning the prelimbic and infralimbic cortex resulted in elevated plasma ACTH and CORT responses to restraint stress. In rats, bilateral or *right*-lateralized lesions of the ACC, prelimbic, and infralimbic cortices *attenuate* sympathetic autonomic responses, stress-induced corticosterone secretion, and gastric stress pathology during restraint stress or exposure to fear-conditioned stimuli.^{136–138} In contrast, *left*-sided lesions of this area *increase* sympathetic autonomic arousal and corticosterone responses to restraint stress.¹³⁸ These data suggest the hypothesis that the right ventral ACC facilitates expression of visceral responses during emotional processing, whereas the left ventral ACC modulates such responses.¹³⁸ If so, then the left-lateralized gray matter reduction of the subgenual ACC in MDD and BD may dysregulate neuroendocrine and autonomic function in depression.^{4,8,135,139}

The pre- and subgenual ACC may also participate in evaluating the reward-related significance of stimuli. These areas send efferent projections to the VTA and substantia nigra, and receive dense dopaminergic innervation from VTA.^{89,140} In rats, electrical or glutamatergic stimulation of medial PFC areas that include prelimbic cortex elicits burst firing patterns from DA cells in the VTA and increases DA release in the accumbens (reviewed in Ref. 141). Because these phasic, burst firing patterns of DA neurons are thought to encode information regarding stimuli that predict reward and deviations between such predictions and occurrence of reward,¹¹⁹ ventral ACC dysfunction may conceivably contribute to disturbances of hedonic perception and motivated behavior in mood disorders.

Dorsomedial/Dorsal Anterolateral Prefrontal Cortex

Many studies reported decreased CBF and metabolism in areas of the dorsolateral and dorsomedial PFC in unipolar and bipolar depressives relative to controls

(FIG. 3). The dorsomedial region where flow and metabolism are decreased in MDD appears to include the dorsal ACC and an area rostral to the dorsal ACC involving cortex on the medial and lateral surface of the superior frontal gyrus (approximately corresponding to Brodmann areas 9 and 32) (reviewed in Ref. 2). Postmortem studies of MDD and BD have found abnormal reductions in the size of neurons and/or the density of glia in this portion of BA 9.^{75,142,143} The reduction in metabolism in this region in the unmedicated-depressed condition may thus reflect these histopathological changes.^{7,144}

Flow normally increases in the dorsomedial PFC in healthy humans as they perform tasks that elicit emotional responses or require emotional evaluations (reviewed in Ref. 2). In healthy humans scanned during anxious anticipation of an electrical shock, CBF increases in this region correlated inversely with changes in anxiety ratings and heart rate, suggesting this region functions to attenuate emotional expression. In rats, lesions of the dorsomedial PFC result in exaggerated heart rate responses to fear-conditioned stimuli, and stimulation of these sites attenuate defensive behavior and cardiovascular responses evoked by amygdala stimulation,¹³⁶ although the homologue to these areas in primates has not been established. In primates, the BA 9 cortex sends efferent projections to the lateral periaqueductal gray and the dorsal hypothalamus, through which it may modulate cardiovascular responses associated with emotional behavior.⁸⁹ Projections from the amygdala to BA 9 are relatively sparse.⁸⁹

Striatum and Thalamus

The amygdala and the ventrolateral, anterior cingulate, and orbital PFC areas where CBF and metabolism are abnormal in major depression share extensive interconnections with the mediodorsal nucleus of the thalamus, ventral striatum, and medial caudate.⁸⁹ In both the medial thalamus and ventral striatum, CBF and metabolism are abnormally increased in unipolar and bipolar depression, and decreased during antidepressant drug treatment (reviewed in Ref. 2).

In the caudate, early PET studies that acquired lower-resolution images reported that CBF and metabolism were abnormally reduced in MDD (reviewed in Ref. 2). These abnormalities may conceivably have reflected a partial volume averaging effect of abnormally reduced caudate volume in MDD.⁷⁸ In the dorsal striatum, Brody *et al.*¹⁵ reported that metabolism was abnormally increased in MDD, and decreased during both paroxetine treatment and interpersonal psychotherapy.

Abnormalities in Other Brain Areas

Neurophysiological activity has been reported to be abnormally elevated in other brain areas as well in depression, including the posterior cingulate cortex, the medial cerebellum, and the somatosensory association cortices in posterior insula and parietal operculum (reviewed in Ref. 2). Flow increases in the former regions in experimentally induced states of anxiety or sadness in healthy subjects and in anxiety states elicited in subjects with anxiety disorders (reviewed in Ref. 29).

CONCLUDING REMARKS

The convergent results from studies of mood disorders conducted using neuroimaging, lesion analysis and postmortem techniques support a model in which the signs and symptoms of some mood-disordered subtypes emanate from dysfunction within limbic, PFC, striatal, and brainstem systems that modulate emotional behavior. These structures form an extended anatomical network in which dysfunction may result in the emotional, cognitive, psychomotor, neurovegetative, neuroendocrine, and neurochemical disturbances associated with depression. Antidepressant therapies may compensate for this dysfunction by attenuating the pathological limbic activity that mediates such symptoms,^{7,32} and by increasing genetic transmission of neurotrophic factors that exert neuroplastic effects within the pathways modulating emotional expression.⁷²

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