

# Clinical research

## *Neuroplasticity in mood disorders*

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The recent development of neuroimaging technologies that permit in vivo characterization of the anatomical, physiological, and receptor pharmacological correlates of mood disorders have enabled significant advances toward delineating the neurobiological correlates of mood disorders. Because these conditions were not associated with gross brain pathology or with clear animal models for spontaneous, recurrent mood episodes, the availability of tools allowing noninvasive assessment of the human brain proved critical to illuminating the pathophysiology of major depressive disorder (MDD) and bipolar disorder (BD). The results of studies applying imaging technologies and postmortem studies have

*Neuroimaging and neuropathological studies of major depressive disorder (MDD) and bipolar disorder (BD) have identified abnormalities of brain structure in areas of the prefrontal cortex, amygdala, striatum, hippocampus, parahippocampal gyrus, and raphe nucleus. These structural imaging abnormalities persist across illness episodes, and preliminary evidence suggests they may in some cases arise prior to the onset of depressive episodes in subjects at high familial risk for MDD. In other cases, the magnitude of abnormality is reportedly correlated with time spent depressed. Postmortem histopathological studies of these regions have shown abnormal reductions of synaptic markers and glial cells, and, in rare cases, reductions in neurons in MDD and BD. Many of the regions affected by these structural abnormalities show increased glucose metabolism during depressive episodes. Because the glucose metabolic signal is dominated by glutamatergic transmission, these data support other evidence that excitatory amino acid transmission is elevated in limbic-cortical-striatal-pallidal-thalamic circuits during depression. Some of the subject samples in which these metabolic abnormalities have been demonstrated were also shown to manifest abnormally elevated stressed plasma cortisol levels. The co-occurrence of increased glutamatergic transmission and cortisol hypersecretion raises the possibility that the gray matter volumetric reductions in these depressed subjects are partly accounted for by processes homologous to the dendritic atrophy induced by chronic stress in adult rodents, which depends upon interactions between elevated glucocorticoid secretion and N-methyl-D-aspartate (NMDA)-glutamate receptor stimulation. Some mood-stabilizing and antidepressant drugs that exert neurotrophic effects in rodents appear to reverse or attenuate the gray matter volume abnormalities in humans with mood disorders. These neurotrophic effects may be integrally related to the therapeutic effects of such agents, because the regions affected by structural abnormalities in mood disorders are known to play major roles in modulating the endocrine, autonomic, behavioral, and emotional experiential responses to stressors.*

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## Selected abbreviations and acronyms

<b>ACC</b>	<i>anterior cingulate cortex</i>
<b>BD</b>	<i>bipolar disorder</i>
<b>FPDD</b>	<i>familial pure depressive disease</i>
<b>5-HT</b>	<i>5-hydroxytryptamine (serotonin)</i>
<b>MDD</b>	<i>major depressive disorder</i>
<b>NMDA</b>	<i>N-methyl-D-aspartate</i>
<b>PFC</b>	<i>prefrontal cortex</i>
<b>VTA</b>	<i>ventral tegmental area</i>

guided clinical neuroscience toward models in which both functional and structural brain pathology play roles in the pathogenesis of mood disorders.

Longitudinal positron emission tomography (PET) imaging studies of MDD and BD identified abnormalities of regional cerebral glucose metabolism and cerebral blood flow (CBF), which, in some cases, persisted beyond symptom remission, and in other cases appeared mood state-dependent (reviewed in reference 1; *Figure 1*). These reversible abnormalities presumably reflect areas where metabolic activity increases or decreases to mediate or respond to emotional and cognitive manifestations of the depressive syndrome, because local glucose metabolism and CBF (which is tightly coupled to glucose metabolism) reflect summations of the energy utilization associated with terminal field synaptic transmission during neural activity.<sup>2-4</sup> In contrast, abnormalities that persist independently of the mood state may instead reflect neuropathological sequelae of recurrent illness or neurodevelopmental abnormalities that may confer vulnerability to MDD (eg, in cases where they are evident in otherwise healthy individuals at high familial risk for developing mood disorders). Such abnormalities in CBF and metabolism may reflect pathological changes in synaptic transmission associated with altered neurotransmitter receptor function, cerebrovascular disease, changes in neuronal arborization or synapse formation, or abnormalities in cellular viability or proliferation.<sup>5</sup> For example, areas where CBF and metabolism appeared irreversibly decreased in depressives relative to controls in PET studies of MDD and BD were subsequently associated with focal tissue reductions in magnetic resonance imaging (MRI)-based morphometric and postmortem histopathological studies of MDD and BD.<sup>6-10</sup>

Abnormalities of gray matter volume and histology have now been identified in several brain structures using volumetric MRI and postmortem neuropathological assessments, which in many cases were guided by initial appli-

cation of functional imaging approaches. The regions affected by these abnormalities have been shown to play major roles in modulating emotional behavior by electrophysiological, lesion analysis, and functional neuroimaging studies in experimental animals and healthy humans. Thus, the structural abnormalities in these regions may prove relevant to the emotional dysregulation that is clinically manifest in mood disorders.

## Sensitivity for detecting neuroimaging abnormalities in depression

The neuroimaging abnormalities discovered to date have not had effect sizes sufficient to permit sensitive or specific classification of individual cases. Moreover, the psychiatric imaging literature is in disagreement regarding the specific location and direction of some abnormalities. Many limitations in the sensitivity in reproducing findings across studies appear to be accounted for simply by technical issues of image acquisition and/or analysis.<sup>1</sup> In other cases, however, disagreements within the literature appear to reflect differences in subject selection criteria applied across studies, because the conditions encompassed by the diagnostic criteria for MDD appear to be heterogeneous with respect to pathophysiology and etiology.

It is noteworthy that neuroimaging laboratories selecting depressed subjects according to MDD criteria alone have rarely been able to replicate their own previous findings in independent subject samples. Instead, neuroimaging abnormalities appear to be specific to subsets of MDD subjects.<sup>1</sup> For example, requiring that subjects have familial aggregation of illness and an early age at illness onset improved sensitivity for identifying subject samples with reproducible neuroimaging abnormalities. Clinical differences related to the capacity for developing mania or psychosis or having a late age at illness onset have also been shown to influence neuroimaging data. For example, elderly MDD subjects with a late age at depression onset have an elevated prevalence of MRI signal hyperintensities (in T<sub>2</sub>-weighted MRI scans, as putative correlates of cerebrovascular disease) in the deep and periventricular white matter, which is not the case for elderly depressives with an early age at depression onset. Similarly, elderly MDD cases with a late-life onset and delusional MDD cases have been shown to have lateral ventricular enlargement—a feature which is generally not present in MDD cases who are elderly but have an

early age of MDD onset, or in midlife depressives who are not delusional. In addition, enlargement of the third ventricle has been consistently reported in BD, but not in MDD.

A major technical issue that influences the sensitivity for detecting neuroimaging abnormalities across studies is the low spatial resolution of imaging technology relative to the size of brain structures of primary interest. With respect to morphometric assessments of gray matter volume, the volumetric resolution of state-of-the-art image data has recently been about 1 mm<sup>3</sup>, compared with the cortex thickness of only 3 to 4 mm. MRI studies involving images of this resolution have been able to reproducibly show regionally specific reductions in mean gray matter volume across groups of clinically similar depres-

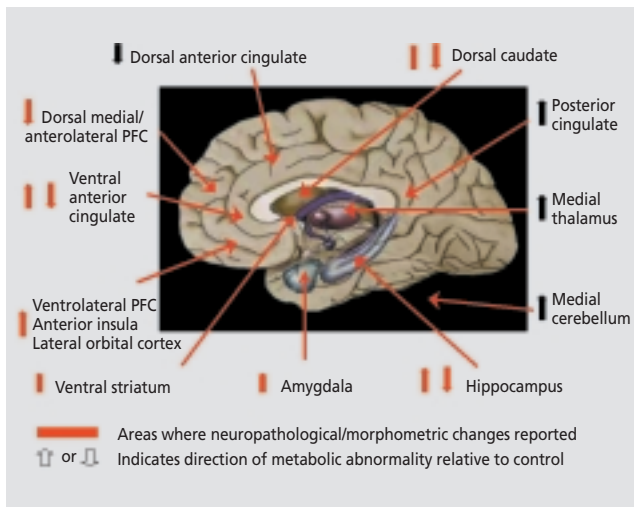
sives versus controls. However, they have lacked sensitivity to detect the relatively subtle tissue reductions extant in mood disorders in individual subjects. Moreover, studies attempting to replicate such findings using data acquired at lower spatial resolutions (ie, voxel sizes  $\geq 1.5$  mm<sup>3</sup>) have commonly been negative because of the substantial partial volume effects that arise when attempting to segment regions of only 3- to 4-mm cortex thickness in such low-resolution MRI images.

## Volumetric MRI imaging abnormalities in mood disorders

### Frontal lobe structures

Volumes of the whole brain and entire frontal lobe generally have not differed between depressed and healthy control samples. In contrast, volumetric abnormalities have been identified in specific prefrontal cortical (PFC), mesiotemporal, and basal ganglia structures in mood disorders. The most prominent reductions in the cortex have been identified in the anterior cingulate gyrus ventral to the genu of the corpus callosum, where gray matter volume has been abnormally decreased 20% to 40% in depressed subjects with familial pure depressive disease (FPDD), familial BD, and psychotic depression<sup>6,11-13</sup> relative to healthy controls or mood-disordered subjects with no first-degree relatives with mood disorders. These findings were confirmed by postmortem studies of clinically similar samples (see below). Effective treatment with selective serotonin (5-hydroxytryptamine [5-HT]) reuptake inhibitors did not alter the subgenual PFC volume in MDD,<sup>6</sup> although the PFC appeared significantly larger in BD subjects chronically medicated with lithium or divalproex than BD subjects who were either unmedicated or medicated with other agents,<sup>1</sup> compatible with evidence that chronic administration of these mood stabilizers increases expression of the neurotrophic factors in rodents.<sup>14</sup>

In the posterior orbital, cortex, and ventrolateral PFC, volume has also been shown to be reduced in *in vivo* volumetric MRI studies<sup>15,16</sup> and in postmortem neuropathological studies of MDD.<sup>17,18</sup> Reductions in gray matter volume were also found in the dorsomedial/dorsal anterolateral PFC in MDD subjects versus controls,<sup>19</sup> and postmortem studies of MDD and BD reported abnormal reductions in the size of neurons and/or the density of glia.<sup>18,20,21</sup>



**Figure 1.** Summary of neuroimaging abnormalities in early-onset, primary, major depressive disorder (MDD). The regions where neurophysiological imaging abnormalities have been consistently reported in unmedicated MDD samples are listed and approximately shown on this midsagittal brain diagram in which subcortical structures are highlighted onto the medial surface. Because only the medial wall of the cortex is shown, the location of the lateral orbital/ventrolateral prefrontal cortex (PFC)/anterior insular region is better illustrated in Figure 2B. The “ventral anterior cingulate” region refers to both pregenual and subgenual portions (see text and Figure 2). The arrows in front of each region name indicate the direction of resting state abnormalities in glucose metabolism in unmedicated, depressed MDD samples relative to healthy control samples. In some cases, abnormalities in both directions have been reported which may depend either on the specific region involved or on the clinical state (eg, treatment responsive vs nonresponsive; see text). The red arrows have indicated histopathological and/or gray matter volumetric abnormalities in postmortem studies of primary mood disorders.

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## Temporal lobe structures

Morphometric MRI studies of specific temporal lobe structures reported significant reductions in the hippocampal volume in MDD, with magnitudes of difference ranging from 8% to 19% with respect to healthy controls.<sup>22-28</sup> Sheline et al<sup>23</sup> and MacQueen et al<sup>28</sup> reported that the hippocampal volume was negatively correlated with the total time spent depressed or with the number of depressive episodes in MDD. Other groups found no significant differences between MDD and control samples.<sup>29-35</sup> The inconsistency in the results of MDD studies may reflect pathophysiological heterogeneity within the MDD samples studied. For example, Vythilingam et al<sup>36</sup> reported that the hippocampal volume was abnormally decreased in depressed women who also had suffered early-life trauma, but not in women who had depression without early-life trauma.

In BD, reductions in hippocampal volume were identified by Noga et al<sup>37</sup> and Swayze et al<sup>38</sup> relative to healthy controls, although Pearson et al<sup>39</sup> and Nugent et al<sup>27</sup> found no differences between BD and control samples. In postmortem studies of BD, abnormal reductions in the mRNA concentrations of synaptic proteins<sup>40</sup> and in apical dendritic spines of pyramidal cells<sup>41</sup> were specifically observed in the subicular and ventral CA1 subregions of the hippocampus. A recent study using high-resolution MRI scans found that the volume of the subiculum, but not the remainder of the hippocampus, was decreased in BD relative to control samples.<sup>27</sup>

Two studies reported abnormalities of the hippocampal T<sub>1</sub> MRI signal in MDD. Krishnan et al<sup>42</sup> observed that the T<sub>1</sub> relaxation time was reduced in the hippocampus, but not in the entire temporal lobe, in unipolar depressives relative to healthy controls, and Sheline et al<sup>23</sup> observed that elderly subjects with MDD have a higher number of areas with a low MRI signal than age-matched controls in T<sub>1</sub>-weighted images. The significance of such abnormalities remains unclear.

In the amygdala, the literature is in disagreement. Studies of MDD have reported that amygdala volume is decreased,<sup>43,44</sup> increased,<sup>45</sup> or not different<sup>26</sup> in depressives relative to healthy controls. Similarly, in BD, amygdala volume was reported to be increased,<sup>46-48</sup> decreased,<sup>39,49,50</sup> or not different<sup>38</sup> relative to healthy controls. Although the extent to which disagreements in the results across studies are accounted for by confounding factors (such as medication effects) remains unclear, it appears more

likely that MRI images acquired at  $\leq 1.5$  tesla lack the spatial and tissue contrast resolution needed to measure amygdala volumes with sufficient validity and reliability. The amygdala's small size and proximity to other gray matter structures seriously limits the specificity (accuracy) for delimiting amygdala boundaries in images acquired using MRI scanners of  $\leq 1.5$ -tesla field strength. High-resolution MRI images acquired at 3-tesla magnetic field strength, in contrast, permit valid and reliable volumetric measures of the human amygdala. A recent study employing this technique established that mean amygdala volumes are decreased bilaterally ( $P < 0.001$ ) in MDD relative to healthy control samples.<sup>51</sup> Amygdala volumes were decreased both in currently depressed and currently remitted MDD subsamples. Although mean amygdala volumes did not differ between BD and control samples, they were smaller in BD subjects who had not been recently medicated with mood stabilizers than in BD subjects who had been taking such agents, consistent with evidence that some mood stabilizers exert neurotrophic effects.<sup>14</sup>

## Basal ganglia

Volumes of some basal ganglia structures have also been reported to be abnormally decreased in mood disorders. Husain et al<sup>52</sup> reported that the putamen was smaller in depressives (mean age 55) than controls, and Krishnan et al<sup>53</sup> found a smaller caudate nucleus volume in depressives (mean age 48) than controls. In a sample limited to elderly depressives, Krishnan et al<sup>54</sup> also reported smaller putamen and caudate volumes relative to controls. These findings were consistent with the postmortem study of Baumann et al,<sup>55</sup> which found that caudate and accumbens area volumes were markedly decreased in both MDD and BD samples relative to control samples. Nevertheless, Dupont et al<sup>56</sup> and Lenze et al<sup>57</sup> failed to find significant differences in caudate or lentiform nucleus (putamen plus globus pallidus) volumes between younger MDD subjects and controls. The factors accounting for the discrepant results across studies remain unclear.

## Abnormalities of corpus callosal volume in mood disorders

The genual subsection of the corpus callosum was reduced in volume in both depressed women with MDD and their high-risk, female offspring (insufficient num-

bers of males were studied to determine whether the abnormality extends to males).<sup>58,59</sup> These white matter regions contain the transcallosal fibers connecting the orbital cortex, anterior cingulate cortex (ACC), and medial PFC with their homologous cortices in the contralateral hemisphere. The volumes of the splenial sub-region of the corpus callosum was also decreased in mood-disordered versus control samples, which contains transcallosal fibers from the posterior cingulate cortex.

### Other cerebral structures

Morphometric studies of other brain structures in depression have produced less consistent results. Of MRI studies of the thalamus, Dupont et al<sup>56</sup> reported that the thalamic volume was decreased in unipolar depressives relative to controls, but Krishnan et al<sup>42,54</sup> found no differences between depressives and controls. Two studies of thalamic volume in BD also have reported conflicting results. Of MRI studies of the cerebellum, two reported that the vermal volume is reduced in depressives relative to controls,<sup>60,61</sup> while a third did not.<sup>62</sup>

Consistent with evidence that the hypothalamic-pituitary-adrenal (HPA) axis function is elevated in some mood-disordered subgroups, enlargement of the pituitary and adrenal glands has been reported in MDD. Krishnan et al<sup>63</sup> showed that MRI-based measures of cross-sectional area and volume of the pituitary were increased (by 34% and 41%, respectively) in depressives (n=19) versus controls (n=19). This observation is consistent with evidence that the adrenal gland is also abnormally enlarged in MDD,<sup>1</sup> which would putatively result from chronically elevated stimulation of the adrenal cortex by adrenocorticotrophic hormone (ACTH).

### Postmortem neuropathological assessments of mood disorders

Most of the regions where MRI studies demonstrated volumetric abnormalities in mood disorders were also shown to contain histopathological changes or gray matter volumetric reductions in postmortem studies of MDD and BD. Reductions in gray matter volume, thickness, or wet weight have been reported in the subgenual ACC, posterolateral orbital cortex, and ventral striatum in MDD and/or BD subjects relative to controls.<sup>7,9,18,55</sup> The histopathological correlates of these abnormalities included reductions in glial cells with no equivalent loss

of neurons, reductions in synapses or synaptic proteins, elevations in neuronal density, and reductions in neuronal size.<sup>9,17,18,20,40,64,65</sup> Abnormal reductions in glial cell counts and density, and/or glia-to-neuron ratios have also been found in MDD in Brodmann area (BA) 24 cortex of the pregenual ACC,<sup>20</sup> the dorsal anterolateral PFC (BA9),<sup>21,66</sup> and the amygdala.<sup>1,67</sup> Finally, the mean size of neurons was reduced in the dorsal anterolateral PFC (BA9) in MDD subjects relative to controls,<sup>18</sup> and the density of neurons was decreased in the ACC in BD.<sup>68</sup> In several of these studies, the decreases were largely accounted for by differences in the left hemisphere.<sup>1,7,9,17,67</sup> In the amygdala and the dorsal anterolateral PFC (BA9), the glial type that specifically differed between MDD and control samples was the oligodendrocytes. In contrast, astrocyte and microglial cell counts did not differ significantly between MDD or BD samples and healthy control samples in the amygdala.<sup>1</sup> Oligodendroglia are best characterized for their role in myelination, and the reduction in oligodendrocytes may conceivably arise secondary to an effect on myelin, either through demyelination, abnormal development, or atrophy in the number of myelinated axons. Notably, the myelin basic protein concentration was found to be decreased in the frontal polar cortex (BA10) in MDD subjects.<sup>69</sup> Compatible with these data, the concentration of white matter within the vicinity of the amygdala<sup>27</sup> and the white matter volume of the genu and splenial portions of the corpus callosum are abnormally reduced in MDD and BD.<sup>58,59</sup> These regions of the corpus callosum were also smaller in child and adolescent offspring of women with MDD who had not yet experienced a major depressive episode, in comparison to age-matched controls, suggesting that the reduction in white matter in MDD reflects a developmental defect that exists prior to the onset of depressive episodes.<sup>58</sup> All of these observations support the hypothesis that the glial cell loss in mood disorders is accounted for by a reduction in myelinating oligodendrocytes.

Further evidence supporting this hypothesis comes from several reports that deficits in glia in the cerebral cortex depend upon laminar analysis, with the greatest effects in layers III, V, and VI.<sup>18,20,70,71</sup> The intracortical plexuses of myelinated fibers known as “bands of Baillarger” are generally concentrated in layers III and V. The size of these plexuses varies across cortical areas, so if the oligodendrocytes related to these plexuses were affected, different areas would be expected to show greater or lesser deficits. Layer VI in particular has a relatively large component of

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myelinated fibers running between the gray and white matter.

Finally, a population of satellite oligodendrocytes exists next to neuronal cell bodies that have largely unknown functions, but do not appear to have a role in myelination under normal conditions.<sup>72</sup> An electron microscopic study of the PFC in BD revealed decreased nuclear size, clumping of chromatin, and other types of damage to satellite oligodendrocytes, including indications of both apoptotic and necrotic degeneration.<sup>73</sup> Fewer signs of degeneration were seen in myelin-related oligodendrocytes in white matter. Satellite oligodendrocytes may play a role in maintaining the extracellular environment for the surrounding neurons, which resembles the functions mediated by astrocytes. These oligodendrocytes are immunohistochemically reactive for glutamine synthetase, suggesting that they function like astrocytes and take up synaptically released glutamate for conversion to glutamine and cycling back into neurons.<sup>74</sup> Many studies of glial function have not distinguished astrocytes from oligodendrocytes, and the two glial types may share several functions.

In other brain regions, reductions in astroglia have been reported by postmortem studies of mood disorders. In the frontal cortex, Johnston-Wilson et al<sup>75</sup> found that four forms of the astrocytic product glial fibrillary acidic protein (GFAP) were decreased in mood-disordered subjects relative to controls, although it remained unclear whether this decrement reflected a reduction in the astrocyte density or in GFAP expression. Using immunohistochemical staining for GFAP, Webster et al<sup>76</sup> did not find significant differences in cortical astrocytes between controls, and MDD or BD cases. Other studies also did not find differences in GFAP between mood disorder cases and controls.<sup>66</sup>

Factors that may conceivably contribute to a loss of oligodendroglia in mood disorders include the elevated glucocorticoid secretion and glutamatergic transmission evident during depression and mania. Glucocorticoids affect glia as well as neurons,<sup>77</sup> and elevated glucocorticoid levels decrease the proliferation of oligodendrocyte precursors.<sup>78</sup> Moreover, oligodendrocytes express  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) and kainate-type glutamate receptors, and are sensitive to excitotoxic damage from excess glutamate as well as to oxidative stress.<sup>1</sup> These vulnerabilities putatively contribute to oligodendrocyte degeneration in ischemic brain injury and demyelinating diseases,<sup>79,80</sup> although no data exist to establish a similar role in mood disorders. The targeted nature

of the reductions in gray matter volume and glial cells to specific areas of the limbic-cortical circuits that show increased glucose metabolism during depressive episodes is noteworthy given the evidence reviewed below that the glucose metabolic signal is dominated by glutamatergic transmission. The hypothesis that glutamate transmission is elevated in these areas in depression was also supported by a postmortem study in depressed suicide victims.<sup>81</sup>

Elevations of glutamate transmission and cortisol secretion in mood disorders may also contribute to reductions in gray matter volume and synaptic markers by inducing dendritic atrophy in some brain structures. In the medial PFC and parts of the hippocampus and amygdala of adult rodents, the dendritic arbors undergo atrophy or debranching in response to specific types of repeated or chronic stress.<sup>82</sup> The effects of stress on dendritic arborization depend both upon the type of stress applied and anatomical location. For example, chronic unpredictable stress produces dendritic atrophy in the basolateral amygdala, whereas chronic immobilization stress increased dendritic branching in pyramidal and stellate neurons within the basolateral amygdala, but did not affect dendritic arborization in the central nucleus of the amygdala.<sup>83,84</sup> These dendritic reshaping processes depend upon interactions between *N*-methyl-D-aspartate (NMDA) glutamatergic receptor stimulation and glucocorticoid secretion associated with repeated stress.<sup>82</sup>

The depressives with BD and FPDD who show regional reductions in gray matter volume also show evidence of having increased cortisol secretion and glutamate transmission. Specifically, depressives with FPDD or BD are more likely to show abnormal suppression of cortisol secretion by dexamethasone and blunted hypoglycemic response to insulin<sup>8</sup> and to release excessive amounts of cortisol during stress.<sup>8,85</sup> Subjects with FPDD or familial BD also show elevations of glucose metabolism, which largely reflects glutamate transmission, in the medial and orbital PFC, amygdala, ventral striatum, and cingulate cortex regions that show reductions in gray matter volume and cellular elements.

## Association between structural and metabolic abnormalities

The glucose metabolic signal is dominated by changes in glutamate transmission, and so the findings that gray matter reductions appear to occur specifically in regions that show hypermetabolism during depression raise the possi-

bility that excitatory amino acid transmission plays a role in the neuropathology of mood disorders. At least 85% to 90% of the glucose metabolic measure is accounted for by glutamate transmission from afferent projections originating within the same structure or from distal structures.<sup>4,86-89</sup> In the depressed phase of familial MDD and BD, regional cerebral metabolism and CBF are abnormally increased in the amygdala, lateral orbital/ventrolateral PFC, ACC anterior to the genu of the corpus callosum ("pregenual" ACC), posterior cingulate cortex, ventral striatum, medial thalamus, and medial cerebellum.<sup>1</sup> During effective antidepressant drug or electroconvulsive therapy, metabolic activity decreases in all of these regions,<sup>1,8</sup> compatible with evidence that these treatments result in desensitization of NMDA glutamatergic receptors in the frontal cortex.<sup>90</sup> In addition to these areas of increased metabolic activity, areas of reduced CBF and metabolism in depressives relative to controls were found in the ACC ventral to the genu of the corpus callosum (ie, "subgenual" ACC) and the dorsomedial/ dorsal anterolateral PFC.<sup>19,91,92</sup> Yet even in these regions, metabolic activity increases during the depressive relapse induced by tryptophan depletion (a dietary challenge that depletes central 5-HT transmission),<sup>93</sup> and metabolism is increased in the subgenual ACC in the unmedicated-depressed phase relative to the unmedicated-remitted phase. In all of these regions where glucose metabolism is increased in the depressed phase relative to the remitted phase, reductions in cortex volume and/or histopathological changes have been found in *in vivo* MRI studies and/or postmortem studies of MDD and/or BD.

The hypothesis that the elevations in glucose metabolism seen in these circuits reflect elevations in glutamatergic transmission is supported by evidence that the anatomical projections between affected areas are excitatory in nature. The abnormally increased CBF and metabolism in the ventrolateral and orbital PFC, ventral ACC, amygdala, ventral striatum, and medial thalamus evident in depression (*Figure 2*) implicate a limbic-thalamo-cortical circuit involving the amygdala, the mediodorsal nucleus of the thalamus and the orbital and medial PFC, and a limbic-striatal-pallidal-thalamic circuit involving related parts of the striatum and the ventral pallidum along with the components of the other circuit.<sup>95</sup> The first of these circuits can be conceptualized as an excitatory triangular circuit, whereby the basolateral nucleus of the amygdala and the orbital and medial prefrontal regions are interconnected by excitatory (especially glutamatergic) projections with

each other and with the mediodorsal nucleus.<sup>96-100</sup> This means that increased metabolic activity in these structures would presumably reflect increased synaptic transmission through the limbic-thalamo-cortical circuit. The limbic-striatal-pallidal-thalamic circuit constitutes a disinhibitory side loop between the amygdala or PFC and the mediodorsal nucleus. The amygdala and the PFC send excitatory projections to overlapping parts of the ventromedial striatum.<sup>101</sup> This part of the striatum sends an inhibitory projection to the ventral pallidum,<sup>102</sup> which in turn sends GABAergic (GABA,  $\gamma$ -aminobutyric acid), inhibitory fibers to the mediodorsal nucleus.<sup>99</sup>

### Implications for the pathogenesis of emotion dysregulation

The circuits described above have also been implicated in the depressive syndromes arising secondary to lesions or degenerative illnesses. Lesions involving the PFC (eg, tumors or infarctions) and the diseases of the basal ganglia (eg, Parkinson's disease or Huntington's disease) are associated with higher rates of depression than other similarly debilitating conditions and result in dysfunction at distinct points within these circuits and affect synaptic transmission in diverse ways.<sup>103</sup> Consistent with this hypothesis, imaging studies of depressive syndromes arising secondary to neurological disorders have generally shown results that differ from those reported for primary mood disorders. For example, in contrast to the findings of increased CBF or metabolism in parts of the orbital cortex in primary depressives, orbital cortex flow is reportedly decreased or not significantly different in subjects with depressive syndromes arising secondary to Parkinson's disease, Huntington's disease, or basal ganglia infarction relative to nondepressed subjects with the same illnesses.<sup>104-107</sup> Primary and secondary depressive syndromes may thus involve the same neural network, although the direction of the physiological abnormalities within individual structures may differ across conditions. A common substrate in these cases may be dysfunction of the PFC-striatal modulation of limbic and visceral functions, because the idiopathic neuropathological changes evident in the orbital and medial PFC and ventral striatum in primary mood disorders (see above) and those found in neurodegenerative conditions all appear to be capable of inducing depressive syndromes (eg, Parkinson's disease, Huntington's disease, and cerebrovascular disease).

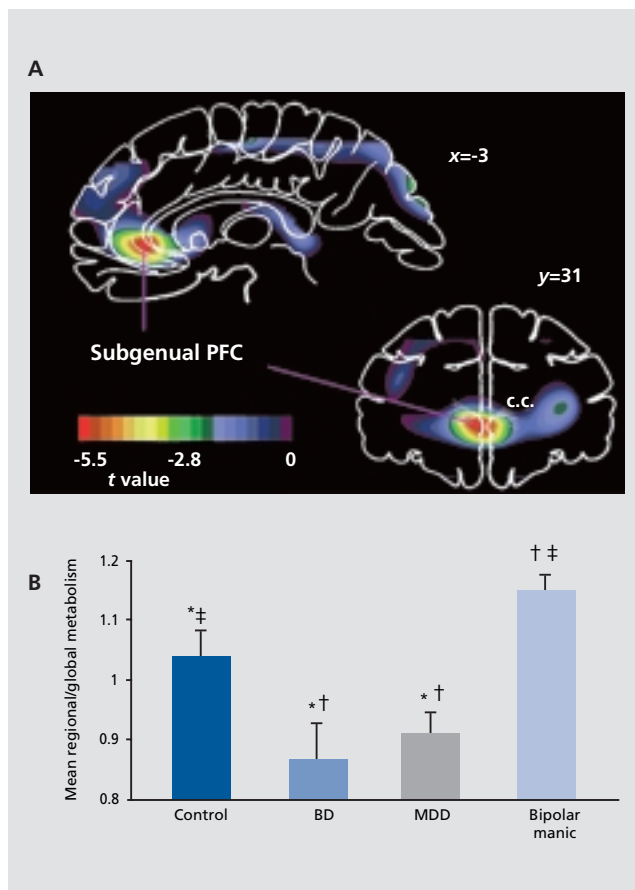
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PFC-amygdalar projections may also play a role in the pathogenesis of depressive and anxiety symptoms in mood disorders. Although the reciprocal PFC-amygdalar projections are excitatory in nature, these connections ultimately appear to activate inhibitory interneurons, which, in turn, lead to functional inhibition in the projected field of the amygdala (for PFC-amygdalar projections) or the medial PFC and ventrolateral PFC.<sup>96,108-110</sup> The function of the PFC in modulating the amygdala appears to be impaired in mood disorders, according to functional MRI data showing that abnormally sustained amygdala activity in response to aversive words or sad faces in MDD is associated with blunted activation of PFC areas.<sup>108,111</sup> Thus, the volumetric and/or histopathological changes evident in the subgenual and pregenual ACC, lateral orbital cortex, dorsomedial/dorsal anterolateral PFC, hippocampal subiculum, amygdala, and ventral striatum may interfere with the modulation of emotional behavior, as discussed below.

**Figure 2.** Altered metabolism in the prefrontal cortex (PFC) ventral to the genu of the corpus callosum (c.c.) (ie, subgenual PFC) in mood disorders. **A.** Negative voxel  $t$  values where glucose metabolism is decreased in depressives relative to controls in coronal (31 mm anterior to the anterior commissure, or  $y=31$ ) and sagittal (3 mm left of midline, or  $x=-3$ ) planes of a statistical parametric image comparing depressives relative to controls.<sup>7</sup> This image localized an abnormality in the subgenual portion of the anterior cingulate cortex (subgenual ACC<sup>7</sup>), which was subsequently shown to be accounted for by a corresponding reduction in cortex volume on the left side (see text). Anterior (or left) is to the left of the image. **B.** Mean, normalized, glucose metabolic values for the left subgenual ACC measured using magnetic resonance imaging (MRI)-based region-of-interest analysis. Metabolism is decreased in depressed subjects with either bipolar disorder (BD) or major depressive disorder (MDD) relative to healthy controls. In contrast, subjects scanned in the manic phase of BD ("bipolar manic") have higher metabolism than either depressed or control subjects in this region. \* $P<0.025$  controls versus depressed; † $P<0.01$  depressed versus manic; ‡ $P<0.05$  controls versus manic. Although none of these subjects were involved in the study that generated the images shown in Figure 3, the mean glucose metabolism in this independent sample of depressives and controls also confirmed the areas of abnormally increased activity in the depressives in the amygdala, lateral orbital cortex, ventrolateral PFC, and medial thalamus (not shown in A, which only illustrates negative  $t$  values corresponding to hypometabolic areas in the depressives). Figure 2A reproduced with permission from reference 6: Drevets WC, Price JL, Simpson JR, et al. Subgenual prefrontal cortex abnormalities in mood disorders. *Nature*. 1997;386:824-827. Copyright © 1997, Nature Publishing Group. Figure 2B reproduced with permission from reference 94: Drevets WC. Neuroimaging and neuropathological studies of depression: Implications for the cognitive emotional manifestations of mood disorders. *Curr Opin Neurobiol*. 2001;11:240-249. Copyright © 2001, Elsevier.

## Ventral ACC

The ACC ventral and anterior to the genu of the corpus callosum ("subgenual" and "pregenual," respectively; Figure 2) shows complex relationships between CBF, metabolism, and illness state, which appear to be accounted for by a left-lateralized reduction in the corresponding cortex, initially demonstrated by MRI-based morphometric measures<sup>6,12-16,112</sup> and later by postmortem neuropathological studies of familial BD and MDD.<sup>9</sup> Thus, computer simulations that correct the PET data acquired from this region for the partial volume effect of the reduction in gray matter volume measured in MRI scans of the same subject conclude the "actual" metabolic activity in the remaining subgenual PFC tissue is increased in depressives relative to controls, and decreases to normative levels during effective treatment.<sup>113</sup> This hypothesis appears to be compatible with the observations that effective antidepressant pharmacotherapy results in a decrease in meta-





bolic activity in this region in MDD,<sup>8,10,114</sup> that during depressive episodes metabolism shows a positive relationship with depression severity,<sup>8,115,116</sup> and that flow increases in this region in healthy, nondepressed humans during sadness induced via contemplation of sad thoughts or memories.<sup>114,117,118</sup>

The reduction in volume in this region exists early in the illness in familial MDD<sup>11</sup> and BD.<sup>12</sup> The gray matter deficit may nevertheless worsen or initially become apparent following illness onset based upon preliminary evidence in twins discordant for MDD that the affected twin has a smaller volume than their unaffected cotwin.<sup>119</sup> Kimbrell et al<sup>120</sup> reported that the subgenual ACC metabolism correlated inversely with the number of lifetime depressive episodes, compatible with the possibility that the reduction in metabolism in this region measured via PET reflects a partial volume effect of a gray matter reduction that worsens with repeated illness.

In the pregenual ACC, Drevets et al<sup>95</sup> initially found increased CBF in MDD, and subsequent studies extended this observation by demonstrating complex relationships between pregenual ACC activity and subsequent antidepressant treatment outcome. Wu et al<sup>121</sup> reported that depressed subjects whose mood improved during sleep deprivation showed elevated metabolism in the pregenual ACC and amygdala in their pretreatment scans. Mayberg et al<sup>122</sup> reported that, while metabolism in the pregenual ACC was abnormally increased in depressives who subsequently responded to antidepressant drugs, metabolism was decreased in depressives who later had poor treatment response. Finally, in a tomographic electroencephalographic (EEG) analysis, Pizzagalli et al<sup>123</sup> reported that depressives who ultimately showed the best response to nortriptyline showed hyperactivity (higher theta activity) in the pregenual ACC at baseline, compared with subjects showing the poorer response. During effective antidepressant treatment, most PET studies have shown that pregenual ACC flow and metabolism decrease in post-treatment scans relative to pretreatment scans.<sup>1</sup> The finding that this region contains histopathological changes in MDD and BD<sup>20,64,68</sup> suggests the hypothesis that the abnormal reduction in metabolism in treatment-nonresponsive cases reflects more severe reductions in cortex.

In rodents and nonhuman primates, the regions that appear homologous to human subgenual and pregenual ACC, namely the infralimbic, prelimbic, and ventral ACCs, have extensive reciprocal connections with areas implicated in the expression of behavioral, autonomic, and

endocrine responses to threat, stress, or reward/nonreward, such as the orbital cortex, lateral hypothalamus, amygdala, accumbens, subiculum, ventral tegmental area (VTA), raphe, locus ceruleus, periaqueductal grey (PAG), and nucleus tractus solitarius.<sup>7,124</sup> Humans with lesions that include these ventromedial PFC structures show abnormal autonomic responses to emotionally provocative stimuli and an inability to experience emotion related to concepts that ordinarily evoke emotion.<sup>125</sup> Electrical stimulation of the ACC elicits fear, panic, or a sense of foreboding in humans, and vocalization in experimental animals.<sup>126</sup> Similarly, rats with experimental lesions of pre- and infralimbic cortex demonstrate altered autonomic, behavioral, and neuroendocrine responses to stress and fear-conditioned stimuli. The pre- and infralimbic cortices contain abundant concentrations of glucocorticoid receptors, which, when stimulated by corticosterone (CORT), reduce stress-related HPA activity.<sup>127</sup> Lesions of these cortices consequently result in exaggerated plasma ACTH and CORT responses to restraint stress.<sup>127</sup> In rats, bilateral or right-lateralized lesions of the ACC and pre- and infralimbic cortex attenuate sympathetic autonomic responses, stress-induced CORT secretion, and gastric stress pathology during restraint stress or exposure to fear-conditioned stimuli.<sup>128-130</sup> In contrast, left-sided lesions of this area increase sympathetic autonomic arousal and CORT responses to restraint stress.<sup>130</sup> These data suggest that the right subgenual PFC facilitates expression of visceral responses during emotional processing, while the left subgenual PFC inhibits or modulates such responses.<sup>130</sup> It is thus noteworthy that the gray matter reduction in this region in MDD and BD was lateralized to the left side, suggesting that it may contribute to disinhibition of neuroendocrine and autonomic function in depression.<sup>127,131,132</sup>

The ventral ACC also appears to participate in processing of behavioral incentive and motivated behavior. These areas send efferent projections to the VTA and substantia nigra, and receive dense dopaminergic innervation from VTA.<sup>124</sup> In rats, electrical or glutamatergic stimulation of medial PFC areas that include pre- and infralimbic cortex elicits burst firing patterns from dopamine (DA) cells in the VTA and increases DA release in the accumbens.<sup>113</sup> These phasic, burst firing patterns of DA neurons appear to encode information regarding stimuli that predict reward and deviations between such predictions and actual occurrence of reward.<sup>133</sup> Ventral ACC dysfunction may thus conceivably contribute to disturbances of motivated behavior and hedonic perception in mood disorders.

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## *Dorsomedial/dorsal anterolateral PFC*

Metabolism and CBF are abnormally decreased in the dorsolateral and dorsomedial PFC in MDD.<sup>1</sup> The dorsomedial PFC region includes the dorsal ACC<sup>92</sup> and an area rostral to the dorsal ACC involving cortex on the medial and lateral surface of the superior frontal gyrus (approximately corresponding to BA9 and BA32).<sup>8,19,91</sup> Postmortem studies of MDD and BD found abnormal reductions in the size of neurons and/or the density of glia in this portion of BA9,<sup>18,20,134</sup> which may account for the reduction in metabolism in this region in MDD, and for the failure of antidepressant drug treatment to correct metabolism in these areas.<sup>8,19</sup> Nevertheless, currently remitted MDD subjects who experience depressive relapse during tryptophan depletion show increased metabolic activity within these areas in the depressed versus the remitted conditions,<sup>93</sup> similar to other structures where histopathological and gray matter volume changes exist in MDD.

Flow normally increases in the vicinity of this dorsomedial/dorsal anterolateral PFC in healthy humans as they perform tasks that elicit emotional responses or require emotional evaluations.<sup>1</sup> In healthy humans, CBF increases in this region during anxious anticipation of an electrical shock to an extent that correlates inversely with changes in anxiety ratings and heart rate, suggesting that 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,<sup>128</sup> although the homologue to these areas in primates has not been clearly established. In primates, the BA9 cortex sends efferent projections to the lateral PAG and the dorsal hypothalamus through which it may modulate cardiovascular responses associated with emotional behavior.<sup>124</sup> It is thus conceivable that dysfunction of the dorsomedial/dorsal anterolateral PFC may contribute to impairments in the ability to modulate emotional responses in mood disorders.

## *Lateral orbital/ventrolateral PFC*

In the lateral orbital cortex, ventrolateral PFC, and anterior insula, the resting CBF and metabolism have been abnormally increased in unmedicated subjects with primary MDD (*Figure 3*).<sup>1</sup> The elevated activity in these

areas in MDD appears to be mood-state dependent,<sup>95</sup> and, during treatment with somatic antidepressant therapies, flow and metabolism decreases in these regions.<sup>1</sup> The relationship between depression severity and physiological activity in the lateral orbital cortex/ventrolateral PFC is complex. While CBF and metabolism increase in these areas in the depressed phase relative to the remitted phase of MDD, the magnitude of these measures is inversely correlated with ratings of depressive ideation and severity.<sup>95,116,135</sup> Moreover, while metabolic activity is abnormally increased in these areas in treatment-responsive unipolar and bipolar depressives, more severely ill or treatment-refractory samples show CBF and metabolic values lower than or not different from those of controls.<sup>81,139</sup> This inverse relationship between orbital cortex/ventrolateral PFC activity and ratings of depression severity extends to some other emotional states as well. Posterior orbital cortex flow also increases in subjects with obsessive-compulsive disorder or simple animal phobias during exposure to phobic stimuli and in healthy subjects during induced sadness,<sup>140-142</sup> with the change in posterior orbital CBF correlating inversely with changes in obsessive thinking, anxiety, and sadness, respectively.

These data appear to be consistent with electrophysiological and lesion analysis data showing that parts of the orbital cortex participate in modulating behavioral and visceral responses associated with defensive, emotional, and reward-directed behavior as reinforcement contingencies change.<sup>124,143,144</sup> The orbital cortex and amygdala send overlapping projections to each of these structures and to each other through which they appear to modulate each other's neural transmission.<sup>124,143,145</sup>

Activation of the orbital cortex during depression may thus reflect compensatory attempts to attenuate emotional expression or interrupt unreinforced aversive thought and emotion. Consistent with this hypothesis, cerebrovascular lesions of the orbital cortex are associated with an increased risk for depression.<sup>146</sup> These observations also suggest that the reduction of CBF and metabolism in the orbital cortex and ventrolateral PFC during antidepressant drug treatment may not be a primary mechanism through which such agents ameliorate depressive symptoms. Instead, direct inhibition of pathological limbic activity in areas such as the amygdala and ventral ACC may attenuate the mediation of depressive symptoms.<sup>8</sup> The orbital cortex neurons may thus "relax," as reflected by the return of metabolism to normal lev-

els, as antidepressant drug therapy attenuates the pathological limbic activity to which these neurons putatively respond.<sup>145</sup>

### The amygdala

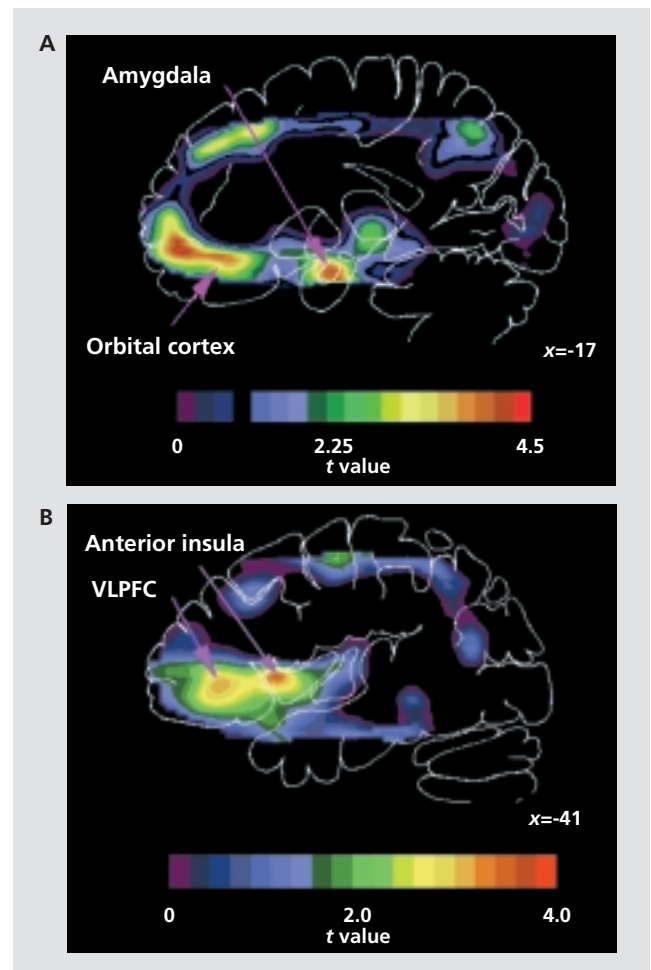
In the amygdala, neurophysiological activity is altered both at rest and during exposure to emotionally valenced stimuli in some depressive subgroups. The basal CBF and metabolism are elevated in mood-disordered subgroups who meet criteria for FPDD (Figure 3),<sup>8,95,135,136</sup> for MDD melancholic subtype,<sup>148</sup> type II or nonpsychotic type I BD,<sup>136,149</sup> or for those who are responsive to sleep deprivation.<sup>121</sup> In contrast, metabolism has not been abnormal in unipolar depressives meeting criteria for depression spectrum disease,<sup>136,137</sup> or in MDD samples meeting *Diagnostic and Statistical Manual of Mental Health Disorders (DSM)* criteria,<sup>150-152</sup> although the interpretation of the latter results was confounded by technical problems that reduced sensitivity for measuring amygdala activity.<sup>136</sup> During antidepressant treatment that both attenuates depressive symptoms and prevents relapse, amygdala metabolism decreases toward normative levels.<sup>8</sup>

**Figure 3.** Areas of abnormally increased blood flow in subjects with major depressive disorder (MDD). 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 (FPDD) ( $n=13$ ) and a healthy control sample ( $n=33$ ).<sup>95</sup> The positive  $t$  values 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.<sup>8,135,136</sup> **A.** Sagittal section at 17 mm left of midline illustrating areas of increased CBF in depression in the amygdala and orbital cortex. **B.** Area of increased flow extended through the lateral orbital cortex to the ventrolateral prefrontal cortex (VLPFC) and anterior insula.<sup>8,95</sup> The  $x$  coordinate locates sagittal sections in millimeters to the left of midline. The PET images in **A** and **B** from which the  $t$  image was generated have been stereotaxically transformed to the coordinate system of Talairach and Tournoux,<sup>137</sup> from which the corresponding atlas outline is shown. Anterior is left.

Figure 3A reproduced with permission from reference 126: Price JL, Carmichael ST, Drevets WC. Networks related to the orbital and medial prefrontal cortex: a substrate for emotional behavior? *Prog Brain Res.* 1996;107:523-536. Copyright © 1996, Elsevier.

Figure 3B reproduced with permission from reference 138: Drevets WC, Videen TO, Snyder AZ, MacLeod AK, Raichle ME. Regional cerebral blood flow changes during anticipatory anxiety. *Soc Neurosci Abstr.* 1994;20:368. Copyright © 1994, Society for Neuroscience.

Functional imaging data acquired as subjects view emotionally valenced stimuli that normally activate the amygdala also demonstrate altered physiological responses in MDD. In the left amygdala, the hemodynamic response to viewing fearful faces was blunted in depressed children<sup>153</sup> and depressed adults,<sup>94</sup> consistent with the elevation of basal CBF and metabolism in the left amygdala in such cases (physiologically activated tissue is expected to show an attenuation of further rises in the hemodynamic/metabolic signal in response to tasks that normally engage the same tissue). The duration of the amygdala response to emotionally valenced stimuli is also abnormally prolonged in response to sad stimuli in depression. Drevets et al<sup>94</sup> observed that, although the initial amygdala CBF response to sad faces was similar in depressives and controls, this response habituated during repeated



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exposure to the same stimuli in the controls, but not in the depressives over the imaging period. Similarly, Siegle et al<sup>44</sup> reported that hemodynamic activity increased in the amygdala during exposure to negatively valenced words to a similar extent in depressives and controls, but, while the hemodynamic response rapidly fell to baseline in the controls, it remained elevated in the depressives. The amygdala plays major roles in organizing other behavioral, neuroendocrine, and autonomic aspects of emotional and stress responses to experiential stimuli. For example, the amygdala facilitates stress-related corticotropin-releasing hormone (CRH) release<sup>154</sup> and electrical stimulation of the amygdala in humans increases cortisol secretion,<sup>155</sup> suggesting a mechanism via which excessive amygdala activity may participate in inducing the CRH and cortisol hypersecretion that is evident in MDD. In PET studies of MDD and BD, CBF and metabolism in the left amygdala correlates positively with stressed plasma cortisol secretion, which may reflect the effect of either amygdala activity on CRH secretion or cortisol or CRH on amygdala function.<sup>136</sup>

If the reduction in amygdala volume is associated with reductions in synaptic contacts formed by afferent projections from regions known to modulate amygdala function, then amygdala neuronal activity may become disinhibited. The above reports that amygdala blood flow and metabolism are abnormally elevated and hemodynamic responses to emotional stimuli are abnormally persistent in MDD support this hypothesis. Notably, Siegle et al<sup>44</sup> reported that the abnormally prolonged hemodynamic responses of the amygdala to sad words occurred particularly in the MDD subjects who had reduced amygdala volumes. If the neurotrophic effects of mood-stabilizing drugs restore and protect modulatory connections formed between the amygdala and cortex,<sup>1</sup> then the volumetric changes observed during treatment may contribute to their therapeutic effects in mood disorders.

## **Abnormalities in anatomically related limbic and subcortical structures**

In the medial thalamus and ventral striatum, CBF and metabolism are abnormally elevated in the depressed phase of MDD and BD, and decrease during antidepressant pharmacotherapy.<sup>8,95,134,136,154,156,157</sup> Several groups also reported abnormally increased CBF in the posterior cingulate cortex in the unmedicated, depressed phase of MDD.<sup>8,112,158</sup> Bench et al<sup>158</sup> specifically reported that the

elevation of posterior cingulate flow in depressives relative to controls correlated positively with anxiety ratings. Exposure to aversive stimuli of various types results in increased physiological activity in the posterior cingulate cortex.<sup>159</sup> The posterior cingulate cortex sends major anatomical projections to the pregenual ACC.<sup>160</sup>

## **Neuroreceptor imaging abnormalities in mood disorders**

Neuroreceptor imaging studies of mood disorders have demonstrated reductions in 5-HT<sub>1A</sub> receptor binding in mood disorders, which would appear to hold major implications for alterations in neuroplasticity in these conditions. Both presynaptic (in the raphe) and postsynaptic (insula, anterior, and posterior cingulate cortices, parieto-occipital cortex, orbital/ventrolateral PFC) 5-HT<sub>1A</sub> binding is abnormally decreased in MDD and panic disorder (irrespective of the current presence of comorbid depression), and postsynaptic 5-HT<sub>1A</sub> receptor binding is also decreased in BD.<sup>85,116,161-165</sup> The magnitudes of these differences have been similar to those found by postmortem studies of primary mood-disordered samples<sup>17,165</sup> and depressed suicide victims.<sup>166</sup> These data are also compatible with results of studies showing that MDD and panic disorder subjects show blunted thermic and adrenocorticotropin/cortisol responses to 5-HT<sub>1A</sub> receptor agonist challenge.<sup>85,162</sup>

The 5-HT<sub>1A</sub> receptor plays major roles in the neuroplasticity involving serotonergic and other neurons.<sup>167,168</sup> In addition, during fetal development and subsequently during 5-HT neuronal injury, stimulation of astrocyte and radial glial cell-based 5-HT<sub>1A</sub> receptors results in release of the trophic factor S100 $\beta$ , which promotes 5-HT neuronal arborization.<sup>168,169</sup> If glial function is reduced during 5-HT system development in BD and MDD, it is conceivable that arborization of the 5-HT neurons may be attenuated, potentially reflected by the widespread reductions of 5-HT transporter and postsynaptic 5-HT<sub>1A</sub> receptor expression seen in MDD.<sup>17,85,116,163,166,170</sup> Such a hypoplastic process may also underlie the finding that the area expressing 5-HT<sub>1A</sub> receptors in the dorsal raphe nucleus is abnormally decreased in depressed suicides.<sup>166</sup> It is conceivable that the persistently increased anxiety behaviors and the exaggerated fear and behavioral despair responses shown by 5-HT<sub>1A</sub> receptor knockout mice at least partly reflect effects of deficient 5-HT<sub>1A</sub> receptor function on neuroplasticity during neurodevel-

opment.<sup>162</sup> It remains unclear, however, whether the reduction in 5-HT<sub>1A</sub> receptor function and expression constitutes a neurodevelopmental or an acquired abnormality in mood disorders.<sup>165</sup>

### Concluding remarks

The convergent results from studies of mood disorders conducted using neuroimaging, lesion analysis, and post-

mortem techniques support models in which the signs and symptoms of major depression can emanate from dysfunction within PFC, striatal, and brain stem systems that modulate emotional behavior. Antidepressant therapies may compensate for this dysfunction by attenuating the pathological limbic activity that mediates such symptoms,<sup>9</sup> and by increasing genetic transmission of neurotrophic factors that exert neuroplastic effects within the pathways modulating emotional expression.<sup>14</sup> □

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## Neuroplasticidad en los trastornos afectivos

Los estudios neuropatológicos y de neuroimágenes en la depresión mayor (DM) y en el trastorno bipolar (TB) han identificado anomalías de la estructura cerebral en áreas de la corteza prefrontal, la amígdala, el cuerpo estriado, el hipocampo, el giro parahipocámpico y el núcleo del rafe. Estas anomalías estructurales en las neuroimágenes se mantienen más allá de los episodios de la enfermedad y las evidencias preliminares sugieren que en algunos casos ellas pueden aparecer antes del inicio de los episodios depresivos en sujetos con alto riesgo familiar de DM. En otros casos, la magnitud de la anomalía se correlaciona con el tiempo que lleva la depresión. Estudios histopatológicos postmortem de estas regiones han mostrado disminuciones anormales de marcadores sinápticos y de células gliales y, en raros casos, disminución de neuronas en la DM y el TB. Muchas de las regiones afectadas por estas alteraciones estructurales muestran un aumento del metabolismo de la glucosa durante los episodios depresivos. Dado que la señal metabólica de glucosa está comandada por la transmisión glutamatérgica, estos datos sustentan el argumento a favor del incremento de la transmisión del aminoácido excitatorio en los circuitos límbico-córtico-estriato-pálido-talámicos durante la depresión. Algunos de los sujetos de las muestras en que se encontraron estas anomalías metabólicas también tuvieron cifras elevadas de cortisol plasmático en respuesta al estrés. La aparición concomitante del aumento de la transmisión glutamatérgica y de la hipersecreción de cortisol incrementa la probabilidad que las disminuciones del volumen de sustancia gris en los sujetos con depresión se deba en parte a los procesos equivalentes a los de la atrofia dendrítica inducida por el estrés crónico en roedores adultos, lo que depende de las interacciones entre el aumento de la secreción de glucocorticoides y la estimulación del receptor de glutamato N-metil-D-aspartico (NMDA). Algunos antidepresivos y estabilizadores del ánimo que ejercen efectos neurotróficos en roedores parece que revierten o disminuyen las anomalías del volumen de sustancia gris en humanos con trastornos afectivos. Estos efectos neurotróficos pueden estar relacionados íntegramente con los efectos terapéuticos de dichos fármacos, ya que se sabe que las regiones afectadas por alteraciones estructurales en los trastornos afectivos tienen un papel importante en la modulación de las respuestas endocrina, autonómica, conductual y emocional que se experimenta frente al estrés.

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## Neuroplasticité dans les troubles de l'humeur

Les études de neuropathologie et de neuro-imagerie des troubles dépressifs majeurs (TDM) et des troubles bipolaires (TB) ont identifié des anomalies de la structure cérébrale dans les aires du cortex préfrontal, de l'amygdale, du striatum, de l'hippocampe, du gyrus parahippocampique et du noyau du raphé. Ces anomalies structurelles à l'image persistent à travers les épisodes de la maladie et des arguments antérieurs suggèrent qu'elles peuvent se produire avant l'apparition des épisodes dépressifs chez les sujets à haut risque familial de TDM. Dans d'autres cas, l'importance des anomalies serait liée à la durée de la dépression. Des études histopathologiques post mortem de ces régions ont montré des réductions anormales des marqueurs synaptiques et des cellules gliales et, dans quelques rares cas, des diminutions du nombre des neurones dans les TDM et les TB. De nombreuses régions atteintes par ces anomalies structurelles présentent un métabolisme du glucose augmenté pendant ces épisodes dépressifs. La transmission glutamatergique dominant le signal métabolique du glucose, ces données confortent un autre argument à savoir que la transmission de l'acide aminé excitateur est élevée dans les circuits limbiques-corticaux-striataux-pallidiaux-thalamiques pendant la dépression. Certains échantillons, chez des sujets chez qui on a trouvé des anomalies métaboliques, ont également montré des concentrations anormalement élevées de cortisol plasmatique en réponse au stress. L'apparition concomitante de l'augmentation de la transmission glutamatergique et de l'hypersécrétion de cortisol accroît la possibilité que les réductions de volume de la substance grise chez ces personnes dépressives soient en partie justifiées par des processus identiques à ceux de l'atrophie dendritique induite par le stress chronique chez les rongeurs adultes, qui dépend des interactions entre la sécrétion élevée des glucocorticoïdes et la stimulation du récepteur glutamatergique N-méthyl-D-aspartate (NMDA). Certains médicaments anti-dépresseurs et thymorégulateurs exerçant des effets neurotrophiques chez les rongeurs semblent inverser ou atténuer les anomalies du volume de la substance grise chez les humains atteints de troubles de l'humeur. Ces effets neurotrophiques peuvent être intégralement liés aux effets thérapeutiques de tels médicaments, parce qu'il est reconnu que les régions affectées par des anomalies structurelles au cours des troubles de l'humeur jouent un rôle majeur dans la modulation des réponses aux agents stressants au niveau de l'expérience endocrine, autonome, comportementale et émotionnelle.

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