Bipolar Depression: Molecular Neurobiology, Clinical Diagnosis and Pharmacotherapy
Edited by C.A. Zarate and H.K. Manji

Neuroimaging studies of bipolar depression: therapeutic implications

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Abstract

Bipolar disorder (BPD) is characterized by pathophysiological changes to the visceromotor network, disrupting the regulation of endocrine and autonomic responses to stress, and hence emotion and behavior. Specifically, reductions in gray matter volume and a concomitant increase in glutamatergic neurotransmission, is observed in the pregenual (pgACC) and subgenual anterior cingulate cortex (sgACC), the orbitofrontal, frontal polar and ventrolateral prefrontal cortex (PFC), the posterior cingulate, ventral striatum, and hippocampus. While increased glutamatergic signaling is equally salient in the amygdala, the data are conflicting on the nature of volumetric changes in this region. Neuroreceptor imaging data provide preliminary evidence for serotonin, serotonin transporter (5-HTT), dopamine receptor, and cholinergic system dysfunction in BPD. Oft-reported abnormalities of the deep frontal and basal ganglia white matter, and enlargement of the third and lateral ventricles are likely associated with cerebrovascular disease. Mood stabilizers and antidepressant drugs may attenuate pathological limbic activity, and increase neurotrophic processes, restoring balance to the system.

Introduction

The World Health Organization ranks bipolar disorder (BPD) as the fifth leading cause of disability [1], yet almost nothing is known about this condition's pathogenesis. Because BPD is 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 elucidating its neurobiology. The recent development of neuroimaging technologies that permit *in vivo* characterization of the anatomical, physiological, and neurochemical correlates of BPD thus has enabled significant advances toward illuminating the pathophysiology of this condition. Notably, the results of neuroimaging studies and the *post mortem* studies that have been guided by neuroimaging results have given rise to neurocircuitry-based models in which both functional and structural brain pathology play roles in the development of BPD.

To date, none of these abnormalities has shown sufficient sensitivity and specificity to prove useful as a diagnostic test. The variable presence and mag-

nitude of such abnormalities in mood disorders likely reflects the heterogeneity encompassed within the BPD syndrome with respect to pathophysiology and etiology. As long as psychiatric nosology depends on syndrome-based classifications, diagnosing BPD may continue to encompass patients with a range of conditions that appear clinically related but are neurobiologically distinct. This lack of precise and biologically verifiable definition of illness presumably contributes to the inconsistencies extant within the literature pertaining to neurobiological abnormalities associated with BPD, and to the variable responses of BPD patients to psychopharmacological treatment options. Ultimately the discovery of illness subtypes that are associated with specific genotypes is expected to improve the sensitivity and specificity of research findings as well as therapeutic approaches.

Neural circuits implicated in BPD

Evidence from neuroimaging, neuropathological, and lesion analysis studies implicates brain networks that normally regulate the evaluative, expressive, and experiential aspects of emotional behavior in the pathophysiology of BPD [3]. These circuits include the limbic-cortical-striatal-pallidal-thalamic circuits (LCSPT) formed by the orbital and medial prefrontal cortex (OMPFC), amygdala, hippocampal subiculum, ventromedial striatum, mediodorsal thalamic nucleus, and ventral pallidum [4]. The LCSPT circuits initially were related to *emotional behavior* on the basis of their anatomical connectivity with limbic structures that mediate emotional expression, such as the hypothalamus and periaqueductal grey (PAG) [5]. They were also initially implicated in the *pathophysiology of depression* by the observations that degenerative basal ganglia diseases and lesions of the striatum and orbitofrontal cortex (OFC) increased the risk of developing major depressive or manic syndromes [6].

In addition to involving LCSPT circuitry, the functional and structural brain abnormalities associated with mood disorders also affect an extended anatomical network formed by neural projections linking the LCSPT components to areas of the mid- and posterior cingulate cortex, superior and medial temporal gyrus, parahippocampal cortex, medial thalamic nuclei, and habenula [4]. This extended 'visceromotor' network functions to regulate autonomic, endocrine, neurotransmitter, and behavioral responses to aversive and rewarding stimuli and contexts by modulating neuronal activity within the limbic and brainstem structures that mediate and organize emotional expression (e.g., amygdala, bed nucleus of the stria terminalis (BNST), PAG, hypothalamus) [4]. Thus, impaired function within this network could disinhibit or alter emotional expression and experience, conceivably giving rise to the clinical manifestations of depression or mania. Compatible with this hypothesis, pharmacological, neurosurgical, and electrical stimulation treatments for mood disorders appear to inhibit pathological activity within visceromotor network structures such as the amygdala and subgenual anterior cingulate cortex (sgACC) [7–9].

Structural neuroimaging in BPD

Patients with BPD show abnormalities of morphology or morphometry in multiple structures that form the extended visceromotor network [7] (Tab. 1). The extent or prevalence of these abnormalities depends partly on clinical characteristics such as age at onset of illness, risk for developing psychosis as well as mania, and evidence for familial aggregation of illness. For example, elderly BPD or major depressive disorder (MDD) subjects with late-onset mood disorders show an increased prevalence of neuroimaging correlates of cerebrovascular disease, relative to both age-matched, healthy controls and to eld-

Table 1. Neuroimaging and histopathological abnormalities evident in the visceromotor network [4] in early-onset, recurrent MDD and/or BPD

Brain region	Grey matter volume	Cell counts, cell markers	Glucose metabolism, CBF	
	Dep *versus* Con	Dep *versus* Con	Dep *versus* Con	Dep *versus* Rem
Dorsal medial/anterolateral PFC (BA9)	Decreased	Decreased	Decreased	Increased
Frontal polar cortex (BA 10)		Decreased	Increased	Increased
Subgenual anterior cingulate cortex	Decreased	Decreased	Mixed findings[a]	Increased
Pregenual anterior cingulate cortex	Decreased	Decreased	Increased	Increased
Orbital C/Ventrolateral PFC	Decreased	Decreased	Increased	Increased
Posterior cingulate	Decreased		Increased	Increased
Parahippocampal cortex	Decreased	Decreased in BPD	Increased	Increased
Amygdala	Mixed findings[b]	Decreased in MDD	Increased	Increased
Ventromedial striatum	Decreased		Increased	Increased
Hippocampus	Decreased	Decreased in BPD	n.s.	n.s.
Superior temporal gyrus/ Temporopolar cortex	Decreased			Increased
Medial thalamus			Increased	Increased

[a] In the sgACC, the apparent reduction in CBF and metabolism in PET images of subjects with MDD is thought to be accounted for by the reduction in tissue volume in the corresponding cortex. After partial volume correction for the reduction in grey matter, the metabolism appears increased relative to controls.

[b] The literature disagrees with respect to amygdala volume in mood disorders (see text).

Abbreviations: Dep *versus* Con: Unmedicated individuals with MDD *versus* healthy controls; Dep *versus* Rem: Unmedicated individuals with MDD *versus* themselves in either the medicated or unmedicated remitted phases; n.s.: differences generally not significant; PFC – prefrontal cortex. Empty cells indicate insufficient data. Modified from [188].

erly individuals with MDD with an early age of onset [10]. Similarly, individuals with MDD and BPD who manifest either psychosis (delusions and/or hallucinations) or a late-life onset of illness show nonspecific signs of atrophy, such as lateral ventricle enlargement, that are absent in early-onset, non-psychotic MDD cases.

Volumetric MRI abnormalities identified in BPD

Early-onset, non-psychotic BPD cases also show volumetric abnormalities that are localized to some prefrontal cortex (PFC), cingulate, temporal lobe and striatal structures (Tab. 1). The most prominent volumetric abnormality reported to date has been a reduction in grey matter in the *left* anterior cingulate cortex (ACC) ventral to the corpus callosum *genu* (i.e., 'subgenual'), which is evident in MDD and BPD with evidence of familial clustering or with psychotic features [11–14]. This volumetric reduction exists early in the course of the illness and in young adults at high familial risk for BPD or MDD [11, 14]. In BPD this abnormality is evident for both BPD I and BPD II samples [15, 16]. Conventional antidepressant drug treatment and symptom remission do not appear to alter the reductions in grey matter volume in the sgACC [13], but chronic lithium treatment, which exerts robust neurotrophic effects in animal models, has been associated with increasing grey matter volume in treatment responders in the sgACC and other PFC areas [10, 17] (Fig. 1).

Grey matter volume also is reduced in the OFC (BA 11, 47) and ventrolateral PFC (VLPFC; BA 45, 47) in MDD [18] and BPD [16], in the frontal polar/dorsal anterolateral PFC (BA 9, 10) in MDD [10], and in the posterior cingulate cortex and superior temporal gyrus in BPD [19] (Fig. 2, see page 131). In BPD the peak difference in grey matter loss in the lateral OFC was found in the sulcal BA47 cortex [19], a region that appears to function as part of both the visceromotor and 'sensory' networks within the OMPFC [4]. Compatible with these data, the MRS study by Cecil and colleagues [20] found reduced NAA and choline concentrations in the orbitofrontal GM in BPD, suggesting decreased neuronal integrity.

Decreases in the volume of the dorsal PFC have also been reported in BPD and MDD [21]. For example, Frangou and colleagues [22] and Haznedar and colleagues [15] described GM volume reductions of the DLPFC (BA 8, 9, 45, 46) in medicated and remitted BPD I patients, and partially medicated, 'stable' bipolar-spectrum individuals, respectively. More circumscribed volume reductions of BA 9 also were reported in a medicated, euthymic pediatric BPD sample [23]. In a mixed BPD I and BPD II sample Lochhead and colleagues [24] reported reduced GM volume of the ACC immediately dorsal to the corpus callosum (CC).

In the hippocampus, at least half of the studies reported reductions in the volume of the whole hippocampus in MDD; in BPD, however, the volumetric reductions appear more specific to the anterior subiculum/ventral CA1 region

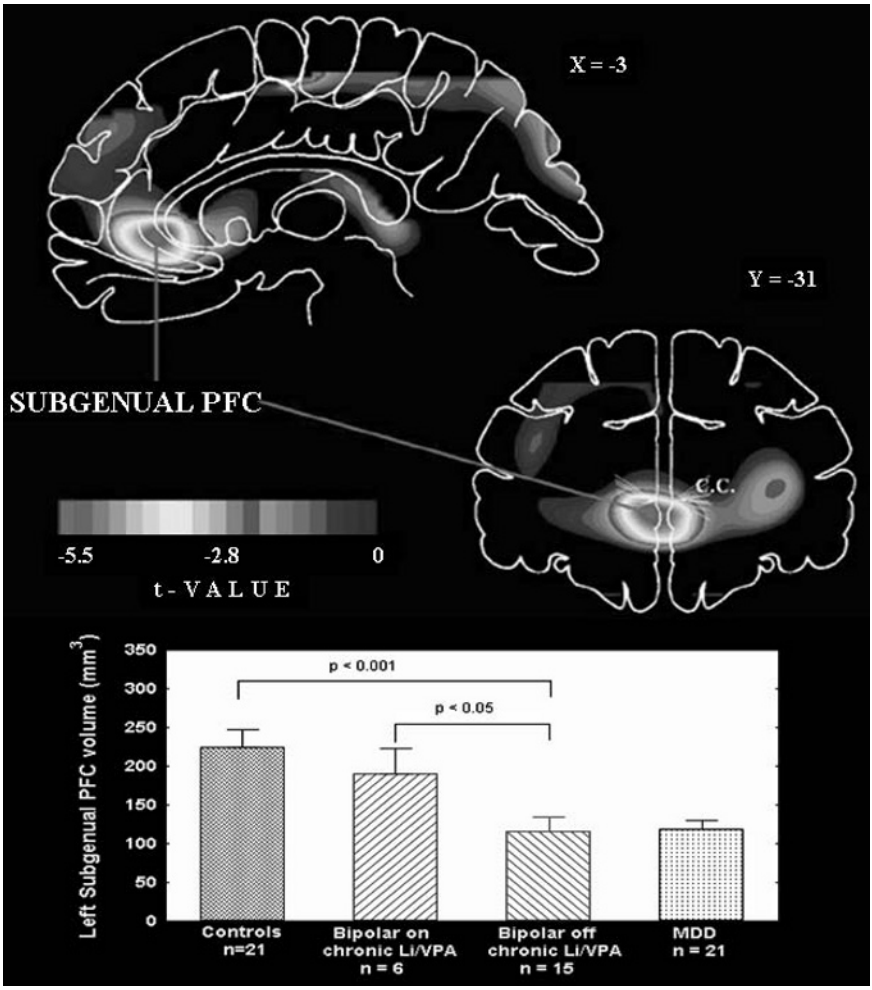

Figure 1. *Upper panel:* Coronal (31 mm anterior to the anterior commissure; y = 31) and sagittal (3 mm left of midline; x = –3) sections showing negative voxel t-values where glucose metabolism is decreased in depressives relative to controls. The reduction in activity in this prefrontal cortex (PFC) region located in the anterior cingulate gyrus ventral to the genu of the corpus callosum (i.e., subgenual) appeared to be accounted for by a corresponding reduction in cortex volume (Tab. 1; reproduced from [13]). Anterior or left is to left. *Lower Panel:* Although the PET data shown in the upper panel were obtained exclusively in unmedicated subjects, the volumetric MRI data from this study were obtained in a larger sample that included six cases who had been chronically receiving lithium or valproate prior to scanning. The bar histogram shows the mean subgenual ACC volumes in mm^3 for the healthy controls, individuals with MDD, unmedicated individuals with bipolar depression, and BPD subjects chronically medicated with lithium or valproate. Reproduced with permission from [17].

[10]. In contrast, the whole hippocampal volume was reported to be smaller in BPD subjects than controls in some studies, but not different from controls in most studies (reviewed in [21]). The reasons for this apparent difference in the

results between neuromorphometric studies of MDD *versus* BPD remain unclear. In MDD the reduction in hippocampal volume was limited to depressed women who suffered early-life trauma in some studies [25] and was correlated inversely with time spent depressed in other studies (e.g., [26]), but it remains unclear whether these relationships also extend to BPD.

One potential reason for the apparent discrepancies between MDD and BPD may be the neurotrophic/neuroprotective effects associated with mood stabilizing treatments. Animal studies demonstrate that lithium promotes hippocampal neurogenesis [27] and long-term potentiation (LTP) [28]. A sample of BPD patients treated for 4 weeks with lithium showed a 3% (24 cm^3) increase in whole brain gray matter volumes from baseline [29], an effect that appeared to result from the neurotrophic effect of the drug [30]. Four more recent studies [31–34] comparing lithium-treated and non-lithium treated groups demonstrated similar effects in large cortical areas, including the hippocampus. The phenomenon may not be restricted to lithium; comparable effects have been noted with other classes of mood stabilizers, especially valproate [35, 36]. In contrast, with the exception of the as yet rarely prescribed tianeptine [37–39], the neurotrophic properties of antidepressants are less persuasive (although see [40] and [41]).

Amygdala volume has been reported to be increased in some studies but decreased in others in individuals with MDD relative to controls [10]. In general these data suggest that the amygdala volume in patients with BPD shows an age-related dichotomy of findings. In adults, the predominant pattern is one of increased amygdala volume while in children and adolescents the reverse is true (reviewed in [21]). The findings in adults seem to hold even in samples with a long history of illness [22, 42, 43]. Parallels have been drawn with the temporal lobe epilepsy (TLE) literature, which suggests increased or preserved amygdala volume [44] despite the presence of hippocampal sclerosis in TLE patients with co-morbid affective illness [45–48].

In the basal ganglia (i.e., caudate, putamen, or globus pallidus) subjects with BPD generally have not shown morphometric differences relative to controls (reviewed in [21]). These data appear consistent with the reported absence of N-acetyl-aspartate (NAA) abnormalities in the basal ganglia of BPD samples [49–51]. Nevertheless, a *post mortem* study of a combined MDD and BPD sample reported volumetric reductions of the left accumbens, bilateral pallidum, and right putamen [52].

There has, however, been some suggestion of striatal enlargement in adult and pediatric samples with BPD (reviewed in [21]). As in the case of the hippocampus, these analyses may conceivably be confounded by treatment effects. Enlargement of basal ganglia structures is a well-known effect of antipsychotic drugs [53–56], and notably three of the studies reporting basal ganglia enlargement made use of partially manic samples treated with antipsychotic medication [57–59].

Enlargement of the third and lateral ventricles has commonly been observed in BPD (reviewed in [21]). Many studies reporting ventriculomegaly

included subjects with early age of onset. Nevertheless, the extent to which chronic alcohol abuse [60], incipient neurological disorders with prodromal depression, or cerebrovascular disease [61–63] (see ensuing section on white matter abnormalities) contributed to ventricular enlargement has not been established.

Neuromorphological MRI abnormalities in BPD: white matter pathology

In morphological MRI studies, an elevation in the incidence of white matter hyperintensities (WMH), especially in the deep frontal cortex and basal ganglia, commonly has been reported in BPD and in late-onset MDD samples [64–68]. Seen as high intensity signals on T2-weighted MRI scans, WMH are caused by circumscribed increases in water content, that putatively indicate a decrease in white matter density due to demyelination, atrophy of the neuropil, ischemia-associated microangiopathy, or other causes [69]. This phenomenon normally is prevalent in elderly, non-depressed populations [70], but shows an abnormally high prevalence in MDD cases with a late age of onset and in BPD samples of all ages.

The incidence of WMH may relate in part to cerebrovascular disease (reviewed in [71]). BPD is associated with a significantly increased prevalence of cardiovascular disease risk factors such as smoking, obesity, diabetes mellitus (DM), hypertension, and dyslipidemia (reviewed in [72,73]). Hypertension [74, 75], obesity [76], smoking [77] and diabetes mellitus [78] have in turn been directly associated with the development of WMH. Although most published studies of BPD attempt to exclude patients with such potentially confounding conditions, the whole gamut of risk conditions is rarely controlled for, raising the possibility that WMH in BPD are an artifact of medical co-morbidity or some obscure ischemic risk factor. Moreover, drug abuse is prevalent in BPD populations and stimulant drug-induced vasoconstriction may lead to WMH [79, 80]. Notably, marijuana use also may interact in an additive fashion with WMH to predispose to depressive symptomatology [81]. In addition, Lenze and colleagues [82] and Nemeroff and colleagues [83] speculated that excess depression-associated secretion of serotonin by blood platelets [84, 85] facilitates platelet aggregation and thereby predisposes to thrombotic events and vasoconstriction. Finally, cerebrovascular reactivity, which describes the compensatory dilatory capacity of arterioles to dilatory stimuli, is reportedly reduced in acutely depressed patients without any neurological, cardiac, or vascular risk factors [86], raising the possibility that impaired regulation of vascular tone also plays a role in the pathogenesis of WMH in BPD.

Nevertheless, studies that attempted to match patients and controls for the presence of cardiovascular risk factors still find elevated rates of WMH in their depressed samples (reviewed in [21]). Moreover, the hypothesis that WMH reflect cerebrovascular disease fails to account for the white matter pathology

noted in pediatric BPD samples [87–89] as well as the high concentration of WMH in both BPD subjects and their unaffected relatives [90]. A significant minority of young BPD patients with a relatively typical age-of-onset show white matter abnormalities on MRI scans (reviewed in [21]). Thus, while a proportion of adults with BPD with significant white matter pathology will present with risk factors for cerebrovascular disease, WMH may also less commonly arise in pediatric or young adult BPD samples due to developmental insults or via some as yet unknown pathophysiological mechanism.

Obstetric complications are well known to be associated with schizophrenia [91], but with a few exceptions [92, 93], appear less salient in BPD. Nevertheless, it is possible that perinatal hypoxic events precipitate BPD in a vulnerable minority [94].

Another possible explanation for demyelination as evidenced by WMH in BPD may be changes in oligodendrocyte function. *Post mortem* studies have reported a down-regulation of oligodendrocyte-related gene expression of genes impacting myelin or oligodendrocyte function and decreased oligodendrocyte density in both BPD and MDD [95–100]. As reviewed in [101–103] variants of some of these genes such as oligodendrocyte lineage transcription factor 2 (*OLIG2*) [NCBI accession number 10215], Neuregulin 1 (*NRG1*) [3084], and v-erb-a erythroblastic leukemia viral oncogene homolog 4 (*ERBB4*) [2066] have been directly associated with mood disorders and may determine how resilient these cells are to environmental stressors. White matter is decreased in the genu of the corpus callosum in both adults with BPD or MDD and their high-risk child and adolescent offspring (particularly in females), and is also decreased in the splenium of the corpus callosum in adults with BPD or MDD. Finally, the high incidence of familial WMH seen in the Ahearn and colleagues [90] sample supports a role for genetic factors, and suggests that genetic variance in genes related to oligodendrocyte function may contribute to the development of WMH in BPD.

An unresolved issue is whether the relationship between white matter pathology and mood disorders is one of cause or effect. Certainly, new cases of BPD may be precipitated by subcortical infarcts [104]. Moreover, depressive and bipolar syndromes are relatively common sequelae of the genetic disorder cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) [105, 106]. The deep frontal white matter pathology commonly seen in mood disorders conceivably may result in a disruption of the pathways linking subcortical regions such as the striatum to functionally homologous regions of the PFC, giving rise to dysregulation of emotional behavior in BPD [107–109].

Neurophysiological imaging in bipolar depression

Many regions where structural abnormalities are apparent in mood disorders also contain abnormalities of cerebral blood flow (CBF) and glucose metabo-

lism (Tab. 1; Fig. 1). In most of these structures, and particularly those that form the extended visceromotor network, the basal activity appears abnormally increased during the depressed phase of BPD. In MDD this pattern of differences also has been demonstrated in cross-sectional studies of depressed MDD subjects relative to controls, longitudinal studies of patients imaged before *versus* after treatment (e.g., [8], and challenge studies of remitted patients scanned before *versus* during depressive relapse (e.g., [110, 111]).

Nevertheless, the reduction in gray matter volume in some structures is sufficiently prominent to produce partial volume effects in functional brain images due to their relatively low spatial resolution, yielding complex relationships between physiological measures and depression severity. For example, relative to controls, depressed BPD and MDD subjects show metabolic activity that appears *reduced* in the sgACC [13, 112]. However, when this volumetric deficit is taken into account by correcting the metabolic data for the partial volume averaging effect associated with the corresponding gray matter reduction (which range in magnitude from ~20% to ~50% across studies of MDD and BPD), metabolism instead appears *increased* in the sgACC in the unmedicated-depressed phase and normal in the medicated-remitted phase [7]. Consistent with these data, activity is decreased in the remitted *versus* the depressed phase of mood disorders in the sgACC, as assessed following effective treatment [8, 9, 113, 114]. Conversely, metabolic activity is increased in the sgACC in remitted MDD cases during depressive relapse induced by tryptophan depletion or catecholamine depletion [110, 111]. The volumetric reductions in the OFC and VLPFC may also contribute to the complexity of relationships observed between metabolism and illness severity, as metabolism appears elevated in depressed samples of mild-to-moderate severity, but reduced in more severe, treatment-refractory cases (reviewed in [115]).

Although the pattern of activity in the extended visceromotor network generally is one in which metabolism is elevated during the depressed *versus* the remitted phases, the relationship between activity and symptom severity differs in valence across some structures, compatible with preclinical evidence that distinct structures are involved in opponent processes with respect to emotion modulation [116]. Regions where metabolism correlates positively with depression severity include the amygdala, sgACC, and ventromedial frontal polar cortex [7, 111]. Metabolism and flow decrease in these regions during effective treatment [8, 9]. Conversely, in recovered MDD cases who experience depressive relapse under serotonin or catecholamine depletion, metabolic activity generally increases in these regions as depressive symptoms return [110, 111, 117], although such studies have not been extended to BPD.

In the amygdala, abnormal elevations of resting metabolism can be seen in depressed samples categorized as having BPD, familial pure depressive disease (FPDD), MDD-melancholic type, or MDD that responds to a night of total sleep deprivation (reviewed in [118]). In such cases amygdala metabolism decreases toward normative levels during effective antidepressant treat-

ment [8]. In BPD these findings of increased baseline amygdalar activity have largely been limited to adults [119–123], in whom resting activity has correlated positively with severity of depression [119]. Furthermore, increased hemodynamic responses of the amygdala to negatively valenced faces have been reported in BPD subjects relative to healthy controls [124–127].

In the accumbens, medial thalamus, and posterior cingulate cortex the metabolism is abnormally elevated in the depressed phase of MDD and BPD [10, 121,123]. In the OFC, Blumberg and colleagues [128] showed that manic patients have reduced rCBF, while induction of a sad mood through psychological means resulted in decreased rCBF to the medial OFC in euthymic but not depressed BPD subjects *versus* controls [129]. Finally, reductions in metabolism and in the hemodynamic responses to various cognitive-behavioral tasks have been reported in dorsolateral PFC regions located outside the OMPFC (reviewed in [3]).

Implications for treatment mechanisms

Elevated glutamatergic function is thought to support the neurophysiological activation of visceromotor networks in depression. The anatomical projections between the OMPFC, striatum, and amygdala implicated in mood disorders are formed by predominantly excitatory projections [4]. Because cerebral glucose metabolism largely reflects the energy requirements associated with glutamatergic transmission [130], the elevated metabolism evident in limbic-thalamo-cortical circuits in depression implies that glutamatergic transmission is increased in these circuits [131]. Compatible with this hypothesis, *post mortem* studies of the NMDA receptor complex in suicide victims found evidence suggesting that glutamatergic transmission had been increased in the PFC *antemortem*, and implicated disturbances in glutamate metabolism, NMDA, and mGluR1,5 receptors in depression and suicide [132].

Notably, antidepressant and mood stabilizing drugs that have diverse primary pharmacological actions are hypothesized to have a final common pathway of reducing NMDA receptor sensitivity and/or transmission, and many of these agents also increase GABA levels or transmission [132, 133]. Compatible with these data, during effective antidepressant drug or electroconvulsive therapy, glucose metabolic activity decreases in the regions of the extended visceromotor network (Tab. 1; reviewed in [10, 121]), which would be expected if treatment-induced NMDA receptor desensitization resulted in reduced glutamatergic transmission [132]. As described in the ensuing sections, elevated glutamatergic transmission within discrete anatomical circuits may partly explain the targeted nature of grey matter changes within mood disorders (e.g., affecting left more than right sgACC) [7, 134], so one important mechanism of effective treatment in bipolar depression may involve the reduction of excessive excitatory transmission mediated via NMDA receptor stimulation [134].

Neuropathological correlations in mood disorders

Most regions where MRI studies demonstrated volumetric abnormalities in BPD also have been shown to contain histopathological changes or grey matter volumetric reductions in *post mortem* studies of MDD and BPD. For example, reductions of grey matter volume, thickness, or wet weight have been reported in the subgenual ACC, posterolateral orbital cortex, and ventral striatum in MDD and/or BPD subjects relative to controls [52, 135–137]. 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 in MDD and/or BPD samples [99, 136, 138, 139]. Reductions in glial cell counts and density, and/or glia-to-neuron ratios additionally were found in MDD subjects *versus* controls in the pregenual ACC (pgACC [BA24]) [140], the dorsal anterolateral PFC (BA9) [97, 99], and the amygdala [98, 141]. Finally, the density of non-pyramidal neurons was decreased in the ACC and hippocampus in BPD [142, 143], and in the dorsal anterolateral PFC (BA9) of MDD [139]. Reductions in synapses and synaptic proteins were evident in BPD subjects in the hippocampal subiculum/ventral CA1 region [138, 144].

The glial type that specifically differed between mood disordered and control samples in many of these studies was the oligodendrocyte (e.g., [98, 99]). 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, myelin basic protein concentration was found to be decreased in the frontal polar cortex (BA 10) [145], and the expression of genes related to oligodendrocyte function (i.e., genes that encoded structural components of myelin, enzymes involved in the synthesis of myelin constituents or in the regulation of myelin formation, transcription factors regulating other myelination-related genes, or factors involved in oligodendrocyte differentiation) was decreased in the middle temporal gyrus in MDD subjects relative to controls [96].

Compatible with these data, myelin staining was decreased in the deep white matter of the dorsolateral PFC in MDD and BPD subjects [146], and the white matter volume of the genual and splenial portions of the corpus callosum were abnormally reduced in MDD and BPD (e.g., [147]). These regions of the corpus callosum were also smaller in child and adolescent offspring of women with MDD who had not yet developed a mood disorder, relative to age-matched controls, suggesting that the reduction in white matter in MDD reflects a developmental defect that exists prior to illness onset [148].

Finally, satellite oligodendrocytes were also implicated in the pathophysiology of mood disorders by an electron microscopic study of the PFC in BPD, which revealed decreased nuclear size, clumping of chromatin, and other types of damage to satellite oligodendrocytes, including indications of both apoptotic and necrotic degeneration [100, 149]. Satellite oligodendrocytes are

immunohistochemically reactive for glutamine synthetase, suggesting that they function like astrocytes to take up synaptically released glutamate for conversion to glutamine and cycling back into neurons [150].

In other brain regions, reductions in astroglia have been reported by *post mortem* studies of mood disorders. In the frontal cortex one study found that four forms of the astrocytic product glial fibrillary acidic protein (GFAP) were decreased in mood disordered subjects relative to controls, although it was not determined whether this decrement reflected a reduction in astrocyte density or GFAP expression [151]. However, another study that used immunohistochemical staining for GFAP did not find significant differences in cortical astrocytes between controls and MDD or BPD cases [152]. Other studies also did not find differences in GFAP between mood disorder cases and controls (reviewed in [153]).

Factors that may conceivably contribute to a loss of oligodendroglia in mood disorders include elevated glucocorticoid secretion and glutamatergic transmission evident during depression and mania. Glucocorticoids affect both glia and neurons [154] and elevated glucocorticoid concentrations and repeated stress decrease the proliferation of oligodendrocyte precursors [155, 156]. Moreover, oligodendrocytes express AMPA and kainate type glutamate receptors, and are sensitive to excitotoxic damage from excess glutamate (reviewed in [98]). The targeted nature of the reductions in grey 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.

Correlations with rodent models of chronic and repeated stress

In regions that appear homologous to the areas where grey matter reductions are evident in humans with BPD (i.e., medial PFC, hippocampus), repeated stress results in dendritic atrophy and reductions in glial cell counts or proliferation in rodents [134, 156–159]. In contrast, in the basolateral amygdala (BLA), chronic, unpredictable stress also produced dendritic atrophy, but chronic immobilization stress instead *increased* dendritic branching [160, 161].

Dendritic atrophy would be reflected by a decrease in the volume of the neuropil, which occupies most of the grey matter volume. The similarities between the histopathogical changes that accompany stress-induced dendritic atrophy in rats and those found in humans suffering from depression thus led to hypotheses that homologous processes underlie the reductions in grey matter volume in hippocampal and PFC structures in MDD and BPD [134]. In rats the stress-induced dendritic atrophy in the medial PFC was associated with impaired modulation (i.e., extinction) of behavioral responses to fear-conditioned stimuli [162, 163]. Notably, healthy humans with thinner ventromedial

PFC tissue also show a greater galvanic skin response to conditioned stimuli during extinction learning [164]. Finally, when rats were subjected to repeated stress beyond 4 weeks, the dendritic atrophy could be reversed by lithium [134], resembling the effects on sgACC volume in depressed humans.

In rodent stress models, these dendritic reshaping processes depend on interactions between increased N-methyl-D-aspartate (NMDA) receptor stimulation and glucocorticoid secretion associated with repeated stress [134, 158]. Elevations of glutamate transmission and cortisol secretion in mood disorders also may contribute to reductions in gray matter volume and synaptic markers by inducing dendritic atrophy in some brain structures, as the depressive subtypes (e.g., BPD, FPDD) who show regional reductions in grey matter volume also show evidence of cortisol hypersecretion (reviewed in [8]) and increased glutamate transmission. Subjects with familial BPD also show elevations of glucose metabolism, which largely reflect glutamate transmission (see above), in the medial and orbital PFC, amygdala, and cingulate cortex regions that show reductions in grey matter volume and cellular elements. The findings that grey matter reductions appear to occur specifically in regions that show hypermetabolism during BPD thus raise the possibility that excitatory amino acid transmission plays a role in the neuropathology of BPD.

Neuroreceptor imaging in bipolar depression

Of the neurochemical systems that modulate neural transmission within the visceromotor network, mood disorders have been associated with abnormalities of serotonergic, dopaminergic, noradrenergic, cholinergic, glutamatergic, GABA-ergic, glucocorticoid, and peptidergic (e.g., corticotrophin releasing factor (CRF)) function. Some receptors of the monoaminergic neurotransmitter systems have been imaged in BPD using PET or SPECT and radioligands.

Serotonergic system

The central serotonin (5-HT) system has received particular interest in depression research because selective serotonin reuptake inhibitors (SSRIs) exert antidepressant effects, and most other antidepressant drugs also increase serotonin (especially post-synaptic 5-HT_{1A} receptor) transmission [165]. This effect of antidepressant drugs may augment an endogenous elevation of serotonin release during the stress of depression, analogous to the enhanced serotonergic transmission that occurs in some brain regions during stress in rodents (reviewed in [166, 167]). Enhancement of serotonin transmission in MDD also may compensate for abnormalities in density and sensitivity of some serotonin receptor subtypes evidenced by *post mortem*, neuroimaging, and pharmacological challenge studies of depression [165, 168]. For example, *postsynaptic* 5-HT_{1A} receptor binding or mRNA expression is decreased in the insula, cin-

gulate, parieto-occipital, and orbital/ventrolateral prefrontal cortices in some neuroimaging studies of MDD and BPD (reviewed in [165]).

It remains unclear whether the reduction in 5-HT_{1A} receptor function and expression in mood disorders constitutes a neurodevelopmental or an acquired abnormality. This issue is of interest because interruption of 5-HT_{1A} receptor function during neurodevelopment persistently alters the function of emotion-modulating systems in genetically engineered mice [169]. Nevertheless, the reduction in 5-HT_{1A} receptor binding and mRNA expression in depression may arise secondarily to cortisol hypersecretion [170], as 5-HT_{1A} receptor mRNA expression and density are tonically inhibited by glucocorticoid receptor stimulation. In experimental animals the elevated CORT secretion during chronic or repeated stress results in reduced 5-HT_{1A} receptor density and mRNA expression [170, 171]. Moreover, the mood disordered subgroups with reduced 5-HT_{1A} receptor binding may be limited to those with a diathesis to hypersecrete cortisol (e.g., [165, 170, 172]).

Altered serotonin transporter (5-HTT) function is also thought to play a role in the pathophysiology of mood disorders (reviewed in [168, 173]). For example, depressed BPD subjects showed elevated 5-HTT binding in the striatum, thalamus, and insula, as well as reduced binding in the vicinity of the pontine raphe [166, 173] (Fig. 3). PET studies performed using 5-HTT radioligands with high selectivity for 5-HTT sites, such as [^{11}C]DASB, similarly reported abnormally increased 5-HTT binding in the striatum, thalamus, insula, and ACC of individuals with early-onset MDD and/or those MDD patients with negativistic attitudes; however, the reduction in 5HTT binding in the pontine raphe found in individuals with bipolar depression did not extend to MDD cases [166]. Finally, genetic polymorphisms involving 5-HTT regulatory sites reportedly increase the vulnerability for developing BPD as well as MDD (reviewed in [166]).

Dopamine receptor imaging

Neuroimaging studies have discovered abnormalities involving multiple aspects of the central dopaminergic system in depression, which converge with other types of evidence to implicate this system in the pathophysiology of mood disorders. However, few of these studies specifically assessed bipolar depression. With respect to dopamine D1 receptors, Suhara and colleagues [174] reported that binding of [^{11}C]SCH-23990 was decreased in the frontal cortex of BPD subjects studied in various illness phases, a finding that awaits replication using more selective D_1 receptor ligands. In addition, Pearlson and colleagues [175] showed that *psychotic* individuals with BPD had increased striatal uptake of the dopamine D2/D3 receptor ligand [^{11}C]- N-methylspiperone relative to healthy controls and non-psychotic individuals with BPD, but that the non-psychotic BPD cases did not differ from healthy controls. Similarly, a SPECT-[^{123}I]IBZM study found no difference in striatal dopamine

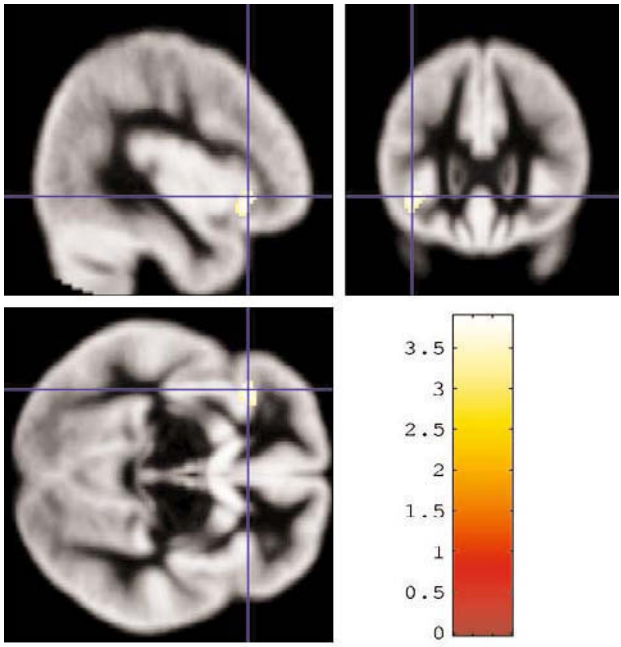

Figure 2. Lateral orbitofrontal cortical area (approximately sulcal BA 47 l/47 s) [4] where peak effect size of grey matter reduction was located in BPD. The image sections shown are from a voxel-based morphometric analysis that compared MRI measures of grey matter volume between depressed subjects with BPD and healthy controls. Anterior or left is to left. Reproduced with permission from [19].

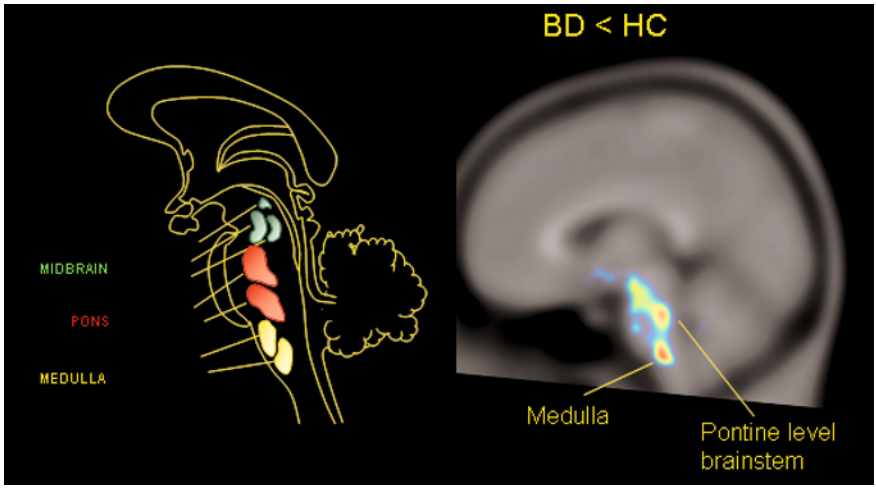

Figure 3. Serotonin transporter binding is reduced in bipolar depression. This section from a voxel-wise analysis of [^{11}C]DASB parametric binding potential images shows regions where individuals with BPD have reduced serotonin transporter (5-HTT) binding relative to controls at $p < 0.05$ (right panel), together with a schematic illustration showing approximate locations of the raphe-nuclei within the brainstem (left panel; after [190]). Reproduced with permission from [173].

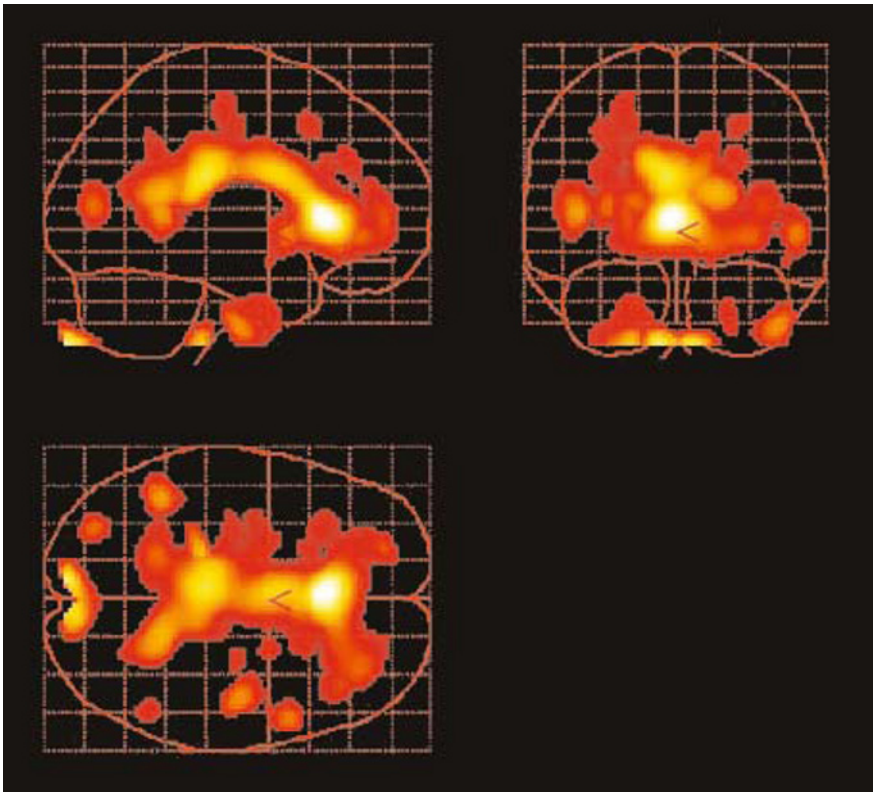

Figure 4. Reduced muscarinic type 2 (M2) receptor binding in the cingulate cortex in individuals with bipolar depression relative to healthy controls. The statistical parametric map shows voxel t-values corresponding to areas where the uptake of [^{18}F]FP-TZTP, a PET radioligand that selectively binds M2 receptors, was significantly reduced (at $p < 0.005$) in individuals with bipolar depression relative to healthy controls. The areas of maximal difference between groups were located in the anterior cingulate cortex. Reproduced from [180].

D2/D3 receptor binding at baseline, and no difference in the change in [^{123}I]IBZM binding under amphetamine challenge between medicated, euthymic BPD patients and healthy controls [176].

Cholinergic system

The cholinergic system is also implicated in the pathophysiology of mood disorders, with evidence indicating that the muscarinic cholinergic system is overactive or hyper-responsive in depression. Janowsky and colleagues [177] reported that increasing cholinergic activity using the acetylcholine-esterase inhibitor physostigmine, resulted in the rapid induction of depressive symptoms in currently manic BPD subjects, and in a worsening of symptoms in

individuals with MDD. The administration of the M_2R antagonist, procaine, elicits emotional responses in humans ranging from sadness, fear, and severe anxiety to euphoria, and results in increased physiological activity of the cingulate cortex [178, 179], a region densely innervated by cholinergic projections. Moreover, in individuals with bipolar depression, decreased M_2R binding has been reported in the cingulate cortex [180] (Fig. 4). Multiple M_2R gene polymorphisms are associated with increased risk for developing major depressive episodes (reviewed in [180]), but thus far these SNPs have not been associated with BPD. Finally, the muscarinic cholinergic receptor antagonist, scopolamine, exerts rapid and robust antidepressant effects in depressed MDD and BPD patients, although the ~24 h delay in onset of these effects raises the possibility that a secondary mechanism of action underlies the antidepressant response [181].

Implications for neurocircuitry models of depression

The neuropathological, neurochemical, and neurophysiological abnormalities extant within the extended visceromotor network may impair this network's modulation of autonomic, endocrine, neurotransmitter, emotional, and behavioral responses to aversive and reward-related stimuli or contexts [4], potentially accounting for the disturbances within these domains seen in BPD (Fig. 5). The neuroimaging abnormalities in the VLPFC, OFC, sgACC, pgACC, amygdala, ventral striatum, and medial thalamus evident in BPD implicate a limbic-thalamo-cortical circuit involving the amygdala, the mediodorsal nucleus of the thalamus (MD), and the OMPFC, and a limbic-striatal-pallidal-thalamic circuit involving related parts of the striatum and ventral pallidum along with the components of the other circuit [131].

The first of these circuits can be conceptualized as an excitatory triangular circuit (Fig. 5) whereby the BLA and the OMPFC are interconnected by excitatory (especially glutamatergic) projections with each other and with the MD [7], so increased glucose metabolism 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 MD. The amygdala and the PFC send excitatory projections to overlapping parts of the ventromedial striatum [182]. This part of the striatum sends an inhibitory projection to the ventral pallidum which in turn sends GABA-ergic, inhibitory fibers to the MD (reviewed in [131]). Because the pallidal neurons have relatively high spontaneous firing rates, activity in the PFC or amygdala that activates the striatum and in turn activates the ventral pallidum may release the MD from the inhibitory pallidal influence, potentially disinhibiting transmission through the limbic-thalamo-cortical circuitry (reviewed in [131]). Notably, repeated stress results in hyperexcitability in the BLA in rodents [183], although whether the mechanisms underlying these changes involve changes

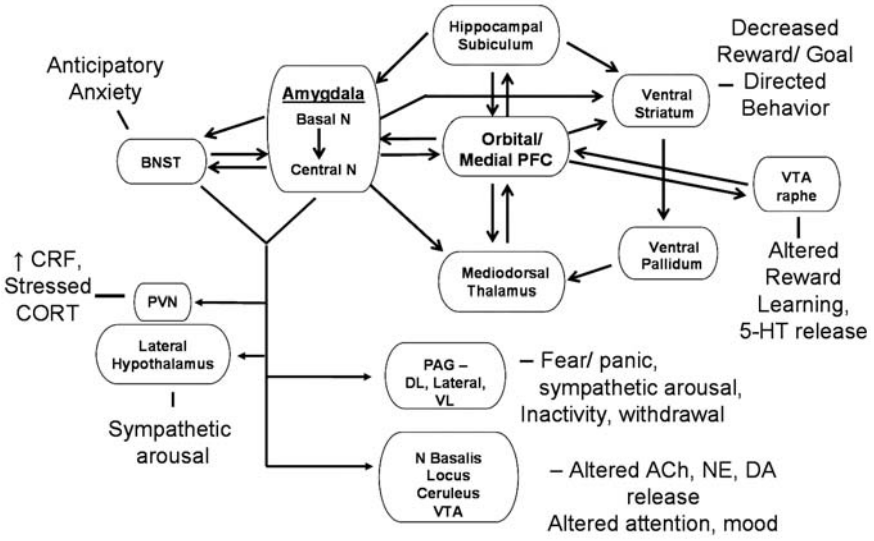

Figure 5. Anatomical circuits involving the orbitomedial PFC (OMPFC) and amygdala reviewed within the context of a model in which OMPFC dysfunction results in disinhibition of limbic transmission through the amygdala, yielding the emotional, cognitive, endocrine, autonomic, and neurochemical manifestations of depression. The basolateral amygdala sends efferent projections to the central nucleus of the amygdala (ACe) and the bed nucleus of the stria terminalis (BNST). The efferent projections from these structures to the hypothalamus, periaqueductal grey (PAG), nucleus basalis, locus coeruleus, raphe, and other diencencephalic and brainstem nuclei then organize the neuroendocrine, neurotransmitter, autonomic, and behavioral responses to stressors and emotional stimuli [184, 185]. The OMPFC shares reciprocal projections with all of these structures (although only the connections with the amygdala are illustrated), which function to modulate each component of emotional expression [4]. Impaired OMPFC function thus may disinhibit or dysregulate limbic outflow through the ACe and BNST. Solid white lines indicate some of the major anatomical connections between structures, with closed arrowheads indicating the direction of projecting axons. Solid yellow lines show efferent pathways of the ACe and BNST, which are generally monosynaptic, but in some cases are bisynaptic connections (e.g., [189]). Other abbreviations: 5-HT – serotonin; ACh – acetylcholine; DA – dopamine; DL – dorsolateral column of PAG; N – nucleus, NE – norepinephrine; NTS – nucleus tractus solitarius; PVN – paraventricular N of the hypothalamus; VL – ventrolateral column of PAG; VTA – ventral tegmental area. Reproduced with permission from [188].

in afferent modulation of the amygdala or alterations in synaptic plasticity remains unclear.

The BLA sends anatomical projections to the central nucleus of the amygdala (ACe) and the BNST, and projections from these structures to the hypothalamus, PAG, locus coeruleus, raphe, nucleus basalis, and other diencencephalic and brainstem nuclei play major roles in organizing neuroendocrine, neurotransmitter, autonomic, and behavioral responses to stressors and emotional stimuli [184, 185]. The OMPFC sends overlapping projections to each of these structures and to the amygdala that function to modulate each component of emotional expression [186]. The neuropathological changes evident in the OMPFC in BPD and mood disorders arising secondary to neurological

disorders thus may impair the modulatory role of the OMPFC over emotional expression, disinhibiting, or dysregulating limbic responses to stressors and emotional stimuli (reviewed in [7]). These data suggest that during depressive episodes the increased activity seen within some OMPFC areas reflects a compensatory response that modulates depressive symptoms, and impaired function of these regions (possibly due to the neuropathological changes in BPD) may result in more severe and treatment-refractory illness.

Summary

Convergent results from studies conducted using neuroimaging, lesion analysis and *post mortem* techniques support models in which the signs of BPD emanate from dysfunction within an extended visceromotor network that interferes with this system's modulation of emotional behavior. Mood stabilizing and antidepressant therapies may compensate for this dysfunction by attenuating the pathological limbic activity that putatively mediates depressive symptoms [8] and increasing expression of neurotrophic/neuroprotective factors that preserve the function of the OMPFC [187].

References

1 The World Health Organization (WHO) (2001) *The World Health Report 2001*. Geneva, Switzerland
2 Kessler RC, Chiu WT, Demler O, Walters EE (2005) Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey replication. *Arch Gen Psychiatry* 62: 617–627
3 Phillips ML, Drevets WC, Rauch SL, Lane R (2003) Neurobiology of emotion perception II: Implications for major psychiatric disorders. *Biol Psychiatry* 54: 515–528
4 Ongur D, Ferry AT, Price JL (2003) Architectonic subdivision of the human orbital and medial prefrontal cortex. *J Comp Neurol* 460: 425–449
5 Nauta WJH, Domesick V (1984) Afferent and efferent relationships of the basal ganglia. In: D Evered, M O'Conner (eds): *Function of the basal ganglia*. Pitman Press, London
6 Folstein MF, Robinson R, Folstein S, McHugh PR (1985) Depression and neurological disorders. New treatment opportunities for elderly depressed patients. *J Affect Disord* Suppl 1: S11–14
7 Drevets WC, Price JL (2005) Neuroimaging and neuropathological studies of mood disorders. In: JWM Licinio (ed.): *Biology of depression: from novel insights to therapeutic strategies*. Wiley-VCH Verlag GmbH & Co., Weinheim, Germany, 427–466
8 Drevets WC, Bogers W, Raichle ME (2002) Functional anatomical correlates of antidepressant drug treatment assessed using PET measures of regional glucose metabolism. *Eur Neuropsychopharmacol* 12: 527–544
9 Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, Schwalb JM, Kennedy SH (2005) Deep brain stimulation for treatment-resistant depression. *Neuron* 45: 651–660
10 Drevets WC, Gadde K, Krishnan KRR (2004) Neuroimaging studies of depression. In: DS Charney, BJ Bunney (eds): *The neurobiological foundation of mental illness: Second Edition*. Oxford University Press, New York, 461–490
11 Botteron KN, Raichle ME, Drevets WC, Heath AC, Todd RD (2002) Volumetric reduction in left subgenual prefrontal cortex in early onset depression. *Biol Psychiatry* 51: 342–344
12 Coryell W, Nopoulos P, Drevets W, Wilson T, Andreasen NC (2005) Subgenual prefrontal cortex

volumes in major depressive disorder and schizophrenia: diagnostic specificity and prognostic implications. *Am J Psychiatry* 162: 1706–1712
13 Drevets WC, Price JL, Simpson JR Jr, Todd RD, Reich T, Vannier M, Raichle ME (1997) Subgenual prefrontal cortex abnormalities in mood disorders. *Nature* 386: 824–847
14 Hirayasu Y, Shenton ME, Salisbury DF, Kwon JS, Wible CG, Fischer IA, Yurgelun-Todd D, Zarate C, Kikinis R, Jolesz FA et al (1999) Subgenual cingulate cortex volume in first-episode psychosis. *Am J Psychiatry* 156: 1091–1093
15 Haznedar MM, Roversi F, Pallanti S, Baldini-Rossi N, Schnur DB, Licalzi EM, Tang C, Hof PR, Hollander E, Buchsbaum MS (2005) Fronto-thalamo-striatal gray and white matter volumes and anisotropy of their connections in bipolar spectrum illnesses. *Biol Psychiatry* 57: 733–742
16 Lyoo IK, Kim MJ, Stoll AL, Demopulos CM, Parow AM, Dager SR, Friedman SD, Dunner DL, Renshaw PF (2004) Frontal lobe gray matter density decreases in bipolar I disorder. *Biol Psychiatry* 55: 648–651
17 Drevets WC, Savitz J (2008) Mood disorders and the subgenual anterior cingulate cortex. *CNS Spectr* 13: 663–681
18 Drevets WC, Todd RD (2005) Depression, mania and related disorders. In: E Rubin, C Zorumski (eds): *Adult psychiatry, Second Ed.* Blackwell Publishing, Oxford, 91–129
19 Nugent AC, Milham MP, Bain EE, Mah L, Cannon DM, Marrett S, Zarate CA, Pine DS, Price JL, Drevets WC (2006) Cortical abnormalities in bipolar disorder investigated with MRI and voxel-based morphometry. *Neuroimage* 30: 485–497
20 Cecil KM, DelBello MP, Morey R, Strakowski SM (2002) Frontal lobe differences in bipolar disorder as determined by proton MR spectroscopy. *Bipolar Disord* 4: 357–365
21 Savitz J, Drevets WC. Bipolar and major depressive disorder: Neuroimaging the developmental-degenerative divide. *Neurosci Biobehav Rev*; *in press*
22 Frangou S, Donaldson S, Hadjulis M, Landau S, Goldstein LH (2005) The Maudsley Bipolar Disorder Project: executive dysfunction in bipolar disorder I and its clinical correlates. *Biol Psychiatry* 58: 859–864
23 Dickstein DP, Milham MP, Nugent AC, Drevets WC, Charney DS, Pine DS, Leibenluft E (2005) Frontotemporal alterations in pediatric bipolar disorder: results of a voxel-based morphometry study. *Arch Gen Psychiatry* 62: 734–741
24 Lochhead RA, Parsey RV, Oquendo MA, Mann JJ (2004) Regional brain gray matter volume differences in patients with bipolar disorder as assessed by optimized voxel-based morphometry. *Biol Psychiatry* 55: 1154–1162
25 Vythilingam M, Heim C, Newport J, Miller AH, Anderson E, Bronen R, Brummer M, Staib L, Vermetten E, Charney DS et al (2002) Childhood trauma associated with smaller hippocampal volume in women with major depression. *Am J Psychiatry* 159: 2072–2080
26 Sheline YI, Gado MH, Kraemer HC (2003) Untreated depression and hippocampal volume loss. *Am J Psychiatry* 160: 1516–1518
27 Kim JS, Chang MY, Yu IT, Kim JH, Lee SH, Lee YS, Son H (2004) Lithium selectively increases neuronal differentiation of hippocampal neural progenitor cells both *in vitro* and *in vivo*. *J Neurochem* 89: 324–336
28 Son H, Yu IT, Hwang SJ, Kim JS, Lee SH, Lee YS, Kaang BK (2003) Lithium enhances long-term potentiation independently of hippocampal neurogenesis in the rat dentate gyrus. *J Neurochem* 85: 872–881
29 Moore GJ, Bebchuk JM, Wilds IB, Chen G, Manji HK (2000) Lithium-induced increase in human brain grey matter. *Lancet* 356: 1241–1242
30 Manji HK, Moore GJ, Chen G (2000) Clinical and preclinical evidence for the neurotrophic effects of mood stabilizers: implications for the pathophysiology and treatment of manic-depressive illness. *Biol Psychiatry* 48: 740–754
31 Bearden CE, Thompson PM, Dalwani M, Hayashi KM, Lee AD, Nicoletti M, Trakhtenbroit M, Glahn DC, Brambilla P, Sassi RB et al (2007) Greater cortical gray matter density in lithium-treated patients with bipolar disorder. *Biol Psychiatry* 62: 7–16
32 Beyer JL, Kuchibhatla M, Payne ME, Moo-Young M, Cassidy F, Macfall J, Krishnan KR (2004) Hippocampal volume measurement in older adults with bipolar disorder. *Am J Geriatr Psychiatry* 12: 613–620
33 Sassi RB, Brambilla P, Hatch JP, Nicoletti MA, Mallinger AG, Frank E, Kupfer DJ, Keshavan MS, Soares JC (2004) Reduced left anterior cingulate volumes in untreated bipolar patients. *Biol Psychiatry* 56: 467–475

34 Yucel K, Taylor VH, McKinnon MC, Macdonald K, Alda M, Young LT, Macqueen GM (2008) Bilateral hippocampal volume increase in patients with bipolar disorder and short-term lithium treatment. *Neuropsychopharmacology* 33: 361–367
35 Hao Y, Creson T, Zhang L, Li P, Du F, Yuan P, Gould TD, Manji HK, Chen G (2004) Mood stabilizer valproate promotes ERK pathway-dependent cortical neuronal growth and neurogenesis. *J Neurosci* 24: 6590–6599
36 Mark RJ, Ashford JW, Goodman Y, Mattson MP (1995) Anticonvulsants attenuate amyloid beta-peptide neurotoxicity, Ca^{2+} deregulation, and cytoskeletal pathology. *Neurobiol Aging* 16: 187–198
37 McEwen BS, Magarinos AM, Reagan LP (2002) Structural plasticity and tianeptine: cellular and molecular targets. *Eur Psychiatry* 17 Suppl 3: 318–330
38 McEwen BS, Olie JP (2005) Neurobiology of mood, anxiety, and emotions as revealed by studies of a unique antidepressant: tianeptine. *Mol Psychiatry* 10: 525–537
39 Watanabe Y, Gould E, Daniels DC, Cameron H, McEwen BS (1992) Tianeptine attenuates stress-induced morphological changes in the hippocampus. *Eur J Pharmacol* 222: 157–162
40 Stewart CA, Reid IC (2000) Repeated ECS and fluoxetine administration have equivalent effects on hippocampal synaptic plasticity. *Psychopharmacology (Berl)* 148: 217–223
41 Duman RS, Monteggia LM (2006) A neurotrophic model for stress-related mood disorders. *Biol Psychiatry* 59: 1116–1127
42 Altshuler LL, Bartzokis G, Grieder T, Curran J, Jimenez T, Leight K, Wilkins J, Gerner R, Mintz J (2000) An MRI study of temporal lobe structures in men with bipolar disorder or schizophrenia. *Biol Psychiatry* 48: 147–162
43 Brambilla P, Harenski K, Nicoletti M, Sassi RB, Mallinger AG, Frank E, Kupfer DJ, Keshavan MS, Soares JC (2003) MRI investigation of temporal lobe structures in bipolar patients. *J Psychiatr Res* 37: 287–295
44 Krishnamoorthy ES (2007) A differential role for the hippocampus and amygdala in neuropsychiatric disorders. *J Neurol Neurosurg Psychiatry* 78: 1165–1166
45 Tebartz Van Elst L, Baeumer D, Lemieux L, Woermann FG, Koepp M, Krishnamoorthy S, Thompson PJ, Ebert D, Trimble MR (2002) Amygdala pathology in psychosis of epilepsy: A magnetic resonance imaging study in patients with temporal lobe epilepsy. *Brain* 125: 140–149
46 Baxendale SA, Thompson PJ, Duncan JS (2005) Epilepsy & depression: the effects of comorbidity on hippocampal volume – a pilot study. *Seizure* 14: 435–438
47 Briellmann RS, Hopwood MJ, Jackson GD (2007) Major depression in temporal lobe epilepsy with hippocampal sclerosis: clinical and imaging correlates. *J Neurol Neurosurg Psychiatry* 78: 1226–1230
48 Richardson EJ, Griffith HR, Martin RC, Paige AL, Stewart CC, Jones J, Hermann BP, Seidenberg M (2007) Structural and functional neuroimaging correlates of depression in temporal lobe epilepsy. *Epilepsy Behav* 10: 242–249
49 Kato T, Hamakawa H, Shioiri T, Murashita J, Takahashi Y, Takahashi S, Inubushi T (1996) Choline-containing compounds detected by proton magnetic resonance spectroscopy in the basal ganglia in bipolar disorder. *J Psychiatry Neurosci* 21: 248–254
50 Hamakawa H, Kato T, Murashita J, Kato N (1998) Quantitative proton magnetic resonance spectroscopy of the basal ganglia in patients with affective disorders. *Eur Arch Psychiatry Clin Neurosci* 248: 53–58
51 Ohara K, Isoda H, Suzuki Y, Takehara Y, Ochiai M, Takeda H, Igarashi Y, Ohara K (1998) Proton magnetic resonance spectroscopy of the lenticular nuclei in bipolar I affective disorder. *Psychiatry Res* 84: 55–60
52 Baumann B, Danos P, Krell D, Diekmann S, Leschinger A, Stauch R, Wurthmann C, Bernstein HG, Bogerts B (1999) Reduced volume of limbic system-affiliated basal ganglia in mood disorders: preliminary data from a postmortem study. *J Neuropsychiatry Clin Neurosci* 11: 71–78
53 Jernigan TL, Zisook S, Heaton RK, Moranville JT, Hesselink JR, Braff DL (1991) Magnetic resonance imaging abnormalities in lenticular nuclei and cerebral cortex in schizophrenia. *Arch Gen Psychiatry* 48: 881–890
54 Swayze VW, Andreasen NC, Alliger RJ, Yuh WT, Ehrhartdt JC (1992) Subcortical and temporal lobe structures in affective disorder and schizophrenia: A magnetic resonance imaging study. *Biol Psychiatry* 31: 221–240
55 Chakos MH, Lieberman JA, Alvir J, Bilder R, Ashtari M (1995) Caudate nuclei volumes in schizophrenic patients treated with typical antipsychotics or clozapine. *Lancet* 345: 456–457
56 Frazier JA, Giedd JN, Kaysen D, Albus K, Hamburger S, Alaghband-Rad J, Lenane MC,

McKenna K, Breier A, Rapoport JL (1996) Childhood-onset schizophrenia: brain MRI rescan after 2 years of clozapine maintenance treatment. *Am J Psychiatry* 153: 564–566
57 Strakowski SM, DelBello MP, Zimmerman ME, Getz GE, Mills NP, Ret J, Shear P, Adler CM (2002) Ventricular and periventricular structural volumes in first- *versus* multiple-episode bipolar disorder. *Am J Psychiatry* 159: 1841–1847
58 DelBello MP, Zimmerman ME, Mills NP, Getz GE, Strakowski SM (2004) Magnetic resonance imaging analysis of amygdala and other subcortical brain regions in adolescents with bipolar disorder. *Bipolar Disord* 6: 43–52
59 Wilke M, Kowatch RA, DelBello MP, Mills NP, Holland SK (2004) Voxel-based morphometry in adolescents with bipolar disorder: first results. *Psychiatry Res* 131: 57–69
60 Anstey KJ, Jorm AF, Reglade-Meslin C, Maller J, Kumar R, von Sanden C, Windsor TD, Rodgers B, Wen W, Sachdev P (2006) Weekly alcohol consumption, brain atrophy, and white matter hyperintensities in a community-based sample aged 60 to 64 years. *Psychosom Med* 68: 778–785
61 Salerno JA, Murphy DG, Horwitz B, DeCarli C, Haxby JV, Rapoport SI, Schapiro MB (1992) Brain atrophy in hypertension. A volumetric magnetic resonance imaging study. *Hypertension* 20: 340–348
62 Goldstein IB, Bartzokis G, Guthrie D, Shapiro D (2002) Ambulatory blood pressure and brain atrophy in the healthy elderly. *Neurology* 59: 713–719
63 Knopman DS, Mosley TH, Catellier DJ, Sharrett AR (2005) Cardiovascular risk factors and cerebral atrophy in a middle-aged cohort. *Neurology* 65: 876–881
64 Krishnan KR, Doraiswamy PM, Figiel GS, Husain MM, Shah SA, Na C, Boyko OB, McDonald WM, Nemeroff CB, Ellinwood EH Jr (1991) Hippocampal abnormalities in depression. *J Neuropsychiatry Clin Neurosci* 3: 387–391
65 Figiel GS, Krishnan KR, Rao VP, Doraiswamy M, Ellinwood EH Jr, Nemeroff CB, Evans D, Boyko O (1991) Subcortical hyperintensities on brain magnetic resonance imaging: a comparison of normal and bipolar subjects. *J Neuropsychiatry Clin Neurosci* 3: 18–22
66 Hickie I, Scott E, Mitchell P, Wilhelm K, Austin MP, Bennett B (1995) Subcortical hyperintensities on magnetic resonance imaging: clinical correlates and prognostic significance in patients with severe depression. *Biol Psychiatry* 37: 151–160
67 Steffens DC, Helms MJ, Krishnan KR, Burke GL (1999) Cerebrovascular disease and depression symptoms in the cardiovascular health study. *Stroke* 30: 2159–2166
68 Hannestad J, Taylor WD, McQuoid DR, Payne ME, Krishnan KR, Steffens DC, Macfall JR (2006) White matter lesion volumes and caudate volumes in late-life depression. *Int J Geriatr Psychiatry* 21: 1193–1198
69 Ovbiagele B, Saver JL (2006) Cerebral white matter hyperintensities on MRI: Current concepts and therapeutic implications. *Cerebrovasc Dis* 22: 83–90
70 Kertesz A, Black SE, Tokar G, Benke T, Carr T, Nicholson L (1988) Periventricular and subcortical hyperintensities on magnetic resonance imaging. 'Rims, caps, and unidentified bright objects'. *Arch Neurol* 45: 404–408
71 Drevets WC, Gadde K, Krishnan KRR (2008) Neuroimaging studies in depression. In: DS Charney, EJ Nestler (eds): *The neurobiological foundation of mental illness*. Oxford University Press, New York, 461–490
72 Kilbourne AM, Cornelius JR, Han X, Pincus HA, Shad M, Salloum I, Conigliaro J, Haas GL (2004) Burden of general medical conditions among individuals with bipolar disorder. *Bipolar Disord* 6: 368–373
73 Newcomer JW (2006) Medical risk in patients with bipolar disorder and schizophrenia. *J Clin Psychiatry* 67 Suppl 9: 25–30; discussion 36–42
74 Dufouil C, de Kersaint-Gilly A, Besancon V, Levy C, Auffray E, Brunnereau L, Alperovitch A, Tzourio C (2001) Longitudinal study of blood pressure and white matter hyperintensities: the EVA MRI Cohort. *Neurology* 56: 921–926
75 Gunstad J, Cohen RA, Tate DF, Paul RH, Poppas A, Hoth K, Macgregor KL, Jefferson AL (2005) Blood pressure variability and white matter hyperintensities in older adults with cardiovascular disease. *Blood Press* 14: 353–358
76 Gustafson DR, Steen B, Skoog I (2004) Body mass index and white matter lesions in elderly women. An 18-year longitudinal study. *Int Psychogeriatr* 16: 327–336
77 Dager SR, Friedman SD (2000) Brain imaging and the effects of caffeine and nicotine. *Ann Med* 32: 592–599
78 Novak V, Last D, Alsop DC, Abduljalil AM, Hu K, Lepicovsky L, Cavallerano J, Lipsitz LA

(2006) Cerebral blood flow velocity and periventricular white matter hyperintensities in type 2 diabetes. *Diabetes Care* 29: 1529–1534
79 Dupont RM, Jernigan TL, Butters N, Delis D, Hesselink JR, Heindel W, Gillin JC (1990) Subcortical abnormalities detected in bipolar affective disorder using magnetic resonance imaging. Clinical and neuropsychological significance. *Arch Gen Psychiatry* 47: 55–59
80 Lyoo IK, Streeter CC, Ahn KH, Lee HK, Pollack MH, Silveri MM, Nassar L, Levin JM, Sarid-Segal O, Ciraulo DA et al (2004) White matter hyperintensities in subjects with cocaine and opiate dependence and healthy comparison subjects. *Psychiatry Res* 131: 135–145
81 Medina KL, Nagel BJ, Park A, McQueeny T, Tapert SF (2007) Depressive symptoms in adolescents: associations with white matter volume and marijuana use. *J Child Psychol Psychiatry* 48: 592–600
82 Lenze E, Cross D, McKeel D, Neuman RJ, Sheline YI (1999) White matter hyperintensities and gray matter lesions in physically healthy depressed subjects. *Am J Psychiatry* 156: 1602–1607
83 Nemeroff CB, Musselman DL (2000) Are platelets the link between depression and ischemic heart disease? *Am Heart J* 140: 57–62
84 Biegon A, Essar N, Israeli M, Elizur A, Bruch S, Bar-Nathan AA (1990) Serotonin 5-HT2 receptor binding on blood platelets as a state dependent marker in major affective disorder. *Psychopharmacology (Berl)* 102: 73–75
85 Musselman DL, Tomer A, Manatunga AK, Knight BT, Porter MR, Kasey S, Marzec U, Harker LA, Nemeroff CB (1996) Exaggerated platelet reactivity in major depression. *Am J Psychiatry* 153: 1313–1317
86 de Castro AG, Bajbouj M, Schlattmann P, Lemke H, Heuser I, Neu P (2008) Cerebrovascular reactivity in depressed patients without vascular risk factors. *J Psychiatr Res* 42: 78–82
87 Botteron KN, Vannier MW, Geller B, Todd RD, Lee BC (1995) Preliminary study of magnetic resonance imaging characteristics in 8- to 16-year-olds with mania. *J Am Acad Child Adolesc Psychiatry* 34: 742–749
88 Lyoo IK, Lee HK, Jung JH, Noam GG, Renshaw PF (2002) White matter hyperintensities on magnetic resonance imaging of the brain in children with psychiatric disorders. *Compr Psychiatry* 43: 361–368
89 Pillai JJ, Friedman L, Stuve TA, Trinidad S, Jesberger JA, Lewin JS, Findling RL, Swales TP, Schulz SC (2002) Increased presence of white matter hyperintensities in adolescent patients with bipolar disorder. *Psychiatry Res* 114: 51–56
90 Ahearn EP, Steffens DC, Cassidy F, Van Meter SA, Provenzale JM, Seldin MF, Weisler RH, Krishnan KR (1998) Familial leukoencephalopathy in bipolar disorder. *Am J Psychiatry* 155: 1605–1607
91 Cannon M, Jones PB, Murray RM (2002) Obstetric complications and schizophrenia: historical and meta-analytic review. *Am J Psychiatry* 159: 1080–1092
92 Kinney DK, Yurgelun-Todd DA, Levy DL, Medoff D, Lajonchere CM, Radford-Paregol M (1993) Obstetrical complications in patients with bipolar disorder and their siblings. *Psychiatry Res* 48: 47–56
93 Kinney DK, Yurgelun-Todd DA, Tohen M, Tramer S (1998) Pre- and perinatal complications and risk for bipolar disorder: a retrospective study. *J Affect Disord* 50: 117–124
94 Pavuluri MN, Henry DB, Nadimpalli SS, O'Connor MM, Sweeney JA (2006) Biological risk factors in pediatric bipolar disorder. *Biol Psychiatry* 60: 936–941
95 Tkachev D, Mimmack ML, Ryan MM, Wayland M, Freeman T, Jones PB, Starkey M, Webster MJ, Yolken RH, Bahn S (2003) Oligodendrocyte dysfunction in schizophrenia and bipolar disorder. *Lancet* 362: 798–805
96 Aston C, Jiang L, Sokolov BP (2005) Transcriptional profiling reveals evidence for signaling and oligodendroglial abnormalities in the temporal cortex from patients with major depressive disorder. *Mol Psychiatry* 10: 309–322
97 Cotter D, Mackay D, Chana G, Beasley C, Landau S, Everall IP (2002) Reduced neuronal size and glial cell density in area 9 of the dorsolateral prefrontal cortex in subjects with major depressive disorder. *Cereb Cortex* 12: 386–394
98 Hamidi M, Drevets WC, Price JL (2004) Glial reduction in amygdala in major depressive disorder is due to oligodendrocytes. *Biol Psychiatry* 55: 563–569
99 Uranova NA, Vostrikov VM, Orlovskaya DD, Rachmanova VI (2004) Oligodendroglial density in the prefrontal cortex in schizophrenia and mood disorders: a study from the Stanley Neuropathology Consortium. *Schizophr Res* 67: 269–275

100 Vostrikov VM, Uranova NA, Orlovskaya DD (2007) Deficit of perineuronal oligodendrocytes in the prefrontal cortex in schizophrenia and mood disorders. *Schizophr Res* 94: 273–280
101 Carter CJ (2007) EIF2B and oligodendrocyte survival: where nature and nurture meet in bipolar disorder and schizophrenia? *Schizophr Bull* 33: 1343–1353
102 Carter CJ (2007) Multiple genes and factors associated with bipolar disorder converge on growth factor and stress activated kinase pathways controlling translation initiation: implications for oligodendrocyte viability. *Neurochem Int* 50: 461–490
103 Sokolov BP (2007) Oligodendroglial abnormalities in schizophrenia, mood disorders and substance abuse. Comorbidity, shared traits, or molecular phenocopies? *Int J Neuropsychopharmacol* 1–9
104 Starkstein SE, Robinson RG (1989) Affective disorders and cerebral vascular disease. *Br J Psychiatry* 154: 170–182
105 Chabriat H, Vahedi K, Iba-Zizen MT, Joutel A, Nibbio A, Nagy TG, Krebs MO, Julien J, Dubois B, Ducrocq X et al (1995) Clinical spectrum of CADASIL: a study of 7 families. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. *Lancet* 346: 934–939
106 Desmond DW, Moroney JT, Lynch T, Chan S, Chin SS, Mohr JP (1999) The natural history of CADASIL: a pooled analysis of previously published cases. *Stroke* 30: 1230–1233
107 Adler CM, Holland SK, Schmithorst V, Wilke M, Weiss KL, Pan H, Strakowski SM (2004) Abnormal frontal white matter tracts in bipolar disorder: a diffusion tensor imaging study. *Bipolar Disord* 6: 197–203
108 Geschwind N (1965) Disconnexion syndromes in animals and man. I. *Brain* 88: 237–294
109 Geschwind N (1965) Disconnexion syndromes in animals and man. II. *Brain* 88: 585–644
110 Neumeister A, Nugent AC, Waldeck T, Geraci M, Schwarz M, Bonne O, Bain EE, Luckenbaugh DA, Herscovitch P, Charney DS et al (2004) Neural and behavioral responses to tryptophan depletion in unmedicated patients with remitted major depressive disorder and controls. *Arch Gen Psychiatry* 61: 765–773
111 Hasler G, Fromm S, Carlson PJ, Luckenbaugh DA, Waldeck T, Geraci M, Roiser JP, Neumeister A, Meyers N, Charney DS, Drevets WC (2008) Neural response to catecholamine depletion in unmedicated subjects with major depressive disorder in remission and health subjects. *Arch Gen Psychiatry* 65: 521–531
112 Kegeles LS, Malone KM, Slifstein M, Ellis SP, Xanthopoulos E, Keilp JG, Campbell C, Oquendo M, Van Heertum RL, Mann JJ (2003) Response of cortical metabolic deficits to serotonergic challenge in familial mood disorders. *Am J Psychiatry* 160: 76–82
113 Holthoff VA, Beuthien-Baumann B, Zundorf G, Triemer A, Ludecke S, Winiecki P, Koch R, Fuchtner F, Herholz K (2004) Changes in brain metabolism associated with remission in unipolar major depression. *Acta Psychiatr Scand* 110: 184–194
114 Nobler MS, Oquendo MA, Kegeles LS, Malone KM, Campbell CC, Sackeim HA, Mann JJ (2001) Decreased regional brain metabolism after ect. *Am J Psychiatry* 158: 305–308
115 Ketter TA, Drevets WC (2002) Neuroimaging studies of bipolar depression: functional neuropathology, treatment effects, and predictors of clinical response. *Clinical Neuroscience Research* 2: 182–192
116 Vidal-Gonzalez I, Vidal-Gonzalez B, Rauch SL, Quirk GJ (2006) Microstimulation reveals opposing influences of prelimbic and infralimbic cortex on the expression of conditioned fear. *Learn Mem* 13: 728–733
117 Neumeister A, Hu XZ, Luckenbaugh DA, Schwarz M, Nugent AC, Bonne O, Herscovitch P, Goldman D, Drevets WC, Charney DS (2006) Differential effects of 5-HTTLPR genotypes on the behavioral and neural responses to tryptophan depletion in patients with major depression and controls. *Arch Gen Psychiatry* 63: 978–986
118 Drevets WC (2001) Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features of mood disorders. *Curr Opin Neurobiol* 11: 240–249
119 Ketter TA, Kimbrell TA, George MS, Dunn RT, Speer AM, Benson BE, Willis MW, Danielson A, Frye MA, Herscovitch P et al (2001) Effects of mood and subtype on cerebral glucose metabolism in treatment-resistant bipolar disorder. *Biol Psychiatry* 49: 97–109
120 Sheline YI, Barch DM, Donnelly JM, Ollinger JM, Snyder AZ, Mintun MA (2001) Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. *Biol Psychiatry* 50: 651–658
121 Drevets WC, Price JL, Bardgett ME, Reich T, Todd RD, Raichle ME (2002) Glucose metabolism

in the amygdala in depression: relationship to diagnostic subtype and plasma cortisol levels. *Pharmacol Biochem Behav* 71: 431–447
122 Bauer M, London ED, Rasgon N, Berman SM, Frye MA, Altshuler LL, Mandelkern MA, Bramen J, Voytek B, Woods R et al (2005) Supraphysiological doses of levothyroxine alter regional cerebral metabolism and improve mood in bipolar depression. *Mol Psychiatry* 10: 456–469
123 Mah L, Zarate CA Jr, Singh J, Duan YF, Luckenbaugh DA, Manji HK, Drevets WC (2007) Regional cerebral glucose metabolic abnormalities in bipolar II depression. *Biol Psychiatry* 61: 765–775
124 Yurgelun-Todd DA, Gruber SA, Kanayama G, Killgore WD, Baird AA, Young AD (2000) fMRI during affect discrimination in bipolar affective disorder. *Bipolar Disord* 2: 237–248
125 Lawrence NS, Williams AM, Surguladze S, Giampietro V, Brammer MJ, Andrew C, Frangou S, Ecker C, Phillips ML (2004) Subcortical and ventral prefrontal cortical neural responses to facial expressions distinguish patients with bipolar disorder and major depression. *Biol Psychiatry* 55: 578–587
126 Rich BA, Vinton DT, Roberson-Nay R, Hommer RE, Berghorst LH, McClure EB, Fromm SJ, Pine DS, Leibenluft E (2006) Limbic hyperactivation during processing of neutral facial expressions in children with bipolar disorder. *Proc Natl Acad Sci USA* 103: 8900–8905
127 Pavuluri MN, O'Connor MM, Harral E, Sweeney JA (2007) Affective neural circuitry during facial emotion processing in pediatric bipolar disorder. *Biol Psychiatry* 62: 158–167
128 Blumberg HP, Stern E, Ricketts S, Martinez D, de Asis J, White T, Epstein J, Isenberg N, McBride PA, Kemperman I et al (1999) Rostral and orbital prefrontal cortex dysfunction in the manic state of bipolar disorder. *Am J Psychiatry* 156: 1986–1988
129 Kruger S, Seminowicz D, Goldapple K, Kennedy SH, Mayberg HS (2003) State and trait influences on mood regulation in bipolar disorder: blood flow differences with an acute mood challenge. *Biol Psychiatry* 54: 1274–1283
130 Shulman RG, Rothman DL, Behar KL, Hyder F (2004) Energetic basis of brain activity: implications for neuroimaging. *Trends Neurosci* 27: 489–495
131 Drevets WC, Videen TO, Price JL, Preskorn SH, Carmichael ST, Raichle ME (1992) A functional anatomical study of unipolar depression. *J Neurosci* 12: 3628–3641
132 Paul IA, Skolnick P (2003) Glutamate and depression: clinical and preclinical studies. *Ann N Y Acad Sci* 1003: 250–272
133 Krystal JH, Sanacora G, Blumberg H, Anand A, Charney DS, Marek G, Epperson CN, Goddard A, Mason GF (2002) Glutamate and GABA systems as targets for novel antidepressant and mood-stabilizing treatments. *Mol Psychiatry* 7 Suppl 1: S71–80
134 McEwen BS, Magarinos AM (2001) Stress and hippocampal plasticity: implications for the pathophysiology of affective disorders. *Hum Psychopharmacol* 16: S7–S19
135 Bowen DM, Najlerahim A, Procter AW, Francis PT, Murphy E (1989) Circumscribed changes of the cerebral cortex in neuropsychiatric disorders of later life. *Proc Natl Acad Sci USA* 86: 9504–9508
136 Ongur D, Drevets WC, Price JL (1998) Glial reduction in the subgenual prefrontal cortex in mood disorders. *Proc Natl Acad Sci USA* 95: 13290–13295
137 Rajkowska G, Miguel-Hidalgo JJ, Wei J, Dilley G, Pittman SD, Meltzer HY, Overholser JC, Roth BL, Stockmeier CA (1999) Morphometric evidence for neuronal and glial prefrontal cell pathology in major depression. *Biol Psychiatry* 45: 1085–1098
138 Eastwood SL, Harrison PJ (2000) Hippocampal synaptic pathology in schizophrenia, bipolar disorder and major depression: a study of complexin mRNAs. *Mol Psychiatry* 5: 425–432
139 Rajkowska G, Miguel-Hidalgo JJ (2007) Gliogenesis and glial pathology in depression. *CNS Neurol Disord Drug Targets* 6: 219–233
140 Cotter D, Mackay D, Landau S, Kerwin R, Everall I (2001) Reduced glial cell density and neuronal size in the anterior cingulate cortex in major depressive disorder. *Arch Gen Psychiatry* 58: 545–553
141 Bowley MP, Drevets WC, Ongur D, Price JL (2002) Low glial numbers in the amygdala in major depressive disorder. *Biol Psychiatry* 52: 404–412
142 Benes FM, Vincent SL, Todtenkopf M (2001) The density of pyramidal and nonpyramidal neurons in anterior cingulate cortex of schizophrenic and bipolar subjects. *Biol Psychiatry* 50: 395–406
143 Todtenkopf MS, Vincent SL, Benes FM (2005) A cross-study meta-analysis and three-dimensional comparison of cell counting in the anterior cingulate cortex of schizophrenic and bipolar brain. *Schizophr Res* 73: 79–89

144 Czeh B, Lucassen PJ (2007) What causes the hippocampal volume decrease in depression? Are neurogenesis, glial changes and apoptosis implicated? *Eur Arch Psychiatry Clin Neurosci* 257: 250–260
145 Honer WG, Falkai P, Chen C, Arango V, Mann JJ, Dwork AJ (1999) Synaptic and plasticity-associated proteins in anterior frontal cortex in severe mental illness. *Neuroscience* 91: 1247–1255
146 Regenold WT, Phatak P, Marano CM, Gearhart L, Viens CH, Hisley KC (2007) Myelin staining of deep white matter in the dorsolateral prefrontal cortex in schizophrenia, bipolar disorder, and unipolar major depression. *Psychiatry Res* 151: 179–188
147 Brambilla P, Nicoletti M, Sassi RB, Mallinger AG, Frank E, Keshavan MS, Soares JC (2004) Corpus callosum signal intensity in patients with bipolar and unipolar disorder. *J Neurol Neurosurg Psychiatry* 75: 221–225
148 Martinez P, Ronsaville D, Gold PW, Hauser P, Drevets WC (2002) Morphometric abnormalities in adolescent offspring of depressed mothers. *Soc Neurosci Abstr* 32: 498–504
149 Uranova N, Orlovskaya D, Vikhreva O, Zimina I, Kolomeets N, Vostrikov V, Rachmanova V (2001) Electron microscopy of oligodendroglia in severe mental illness. *Brain Res Bull* 55: 597–610
150 Janus C, D'Amelio S, Amitay O, Chishti MA, Strome R, Fraser P, Carlson GA, Roder JC, St George-Hyslop P, Westaway D (2000) Spatial learning in transgenic mice expressing human presenilin 1 (PS1) transgenes. *Neurobiol Aging* 21: 541–549
151 Johnston-Wilson NL, Sims CD, Hofmann JP, Anderson L, Shore AD, Torrey EF, Yolken RH (2000) Disease-specific alterations in frontal cortex brain proteins in schizophrenia, bipolar disorder, and major depressive disorder. The Stanley Neuropathology Consortium. *Mol Psychiatry* 5: 142–149
152 Webster MJ, Knable MB, Johnston-Wilson N, Nagata K, Inagaki M, Yolken RH (2001) Immunohistochemical localization of phosphorylated glial fibrillary acidic protein in the prefrontal cortex and hippocampus from patients with schizophrenia, bipolar disorder, and depression. *Brain Behav Immun* 15: 388–400
153 Cotter DR, Pariante CM, Everall IP (2001) Glial cell abnormalities in major psychiatric disorders: the evidence and implications. *Brain Res Bull* 55: 585–595
154 Cheng JD, de Vellis J (2000) Oligodendrocytes as glucocorticoids target cells: functional analysis of the glycerol phosphate dehydrogenase gene. *J Neurosci Res* 59: 436–445
155 Alonso G (2000) Prolonged corticosterone treatment of adult rats inhibits the proliferation of oligodendrocyte progenitors present throughout white and gray matter regions of the brain. *Glia* 31: 219–231
156 Banasr M, Hery M, Printemps R, Daszuta A (2004) Serotonin-induced increases in adult cell proliferation and neurogenesis are mediated through different and common 5-HT receptor subtypes in the dentate gyrus and the subventricular zone. *Neuropsychopharmacology* 29: 450–460
157 Czeh B, Pudovkina O, van der Hart MG, Simon M, Heilbronner U, Michaelis T, Watanabe T, Frahm J, Fuchs E (2005) Examining SLV-323, a novel NK1 receptor antagonist, in a chronic psychosocial stress model for depression. *Psychopharmacology (Berl)* 180: 548–557
158 Wellman CL (2001) Dendritic reorganization in pyramidal neurons in medial prefrontal cortex after chronic corticosterone administration. *J Neurobiol* 49: 245–253
159 Radley JJ, Rocher AB, Rodriguez A, Ehlenberger DB, Dammann M, McEwen BS, Morrison JH, Wearne SL, Hof PR (2008) Repeated stress alters dendritic spine morphology in the rat medial prefrontal cortex. *J Comp Neurol* 507: 1141–1150
160 Vyas A, Bernal S, Chattarji S (2003) Effects of chronic stress on dendritic arborization in the central and extended amygdala. *Brain Res* 965: 290–294
161 Vyas A, Mitra R, Shankaranarayana Rao BS, Chattarji S (2002) Chronic stress induces contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons. *J Neurosci* 22: 6810–6818
162 Izquierdo A, Wellman CL, Holmes A (2006) Brief uncontrollable stress causes dendritic retraction in infralimbic cortex and resistance to fear extinction in mice. *J Neurosci* 26: 5733–5738
163 Miracle AD, Brace MF, Huyck KD, Singler SA, Wellman CL (2006) Chronic stress impairs recall of extinction of conditioned fear. *Neurobiol Learn Mem* 85: 213–218
164 Milad MR, Quinn BT, Pitman RK, Orr SP, Fischl B, Rauch SL (2005) Thickness of ventromedial prefrontal cortex in humans is correlated with extinction memory. *Proc Natl Acad Sci USA* 102: 10706–10711
165 Drevets WC, Thase ME, Moses-Kolko EL, Price J, Frank E, Kupfer DJ, Mathis C (2007)

Serotonin-1A receptor imaging in recurrent depression: replication and literature review. *Nucl Med Biol* 34: 865–877
166 Cannon DM, Ichise M, Rollis D, Klaver JM, Gandhi SK, Charney DS, Manji HK, Drevets WC (2007) Elevated serotonin transporter binding in major depressive disorder assessed using positron emission tomography and [^{11}C]DASB; comparison with bipolar disorder. *Biol Psychiatry* 62: 870–877
167 Barton DA, Esler MD, Dawood T, Lambert EA, Haikerwal D, Brenchley C, Socratous F, Hastings J, Guo L, Wiesner G et al (2008) Elevated brain serotonin turnover in patients with depression: effect of genotype and therapy. *Arch Gen Psychiatry* 65: 38–46
168 Stockmeier CA (2003) Involvement of serotonin in depression: evidence from postmortem and imaging studies of serotonin receptors and the serotonin transporter. *J Psychiatr Res* 37: 357–373
169 Gross C, Zhuang X, Stark K, Ramboz S, Oosting R, Kirby L, Santarelli L, Beck S, Hen R (2002) Serotonin1A receptor acts during development to establish normal anxiety-like behaviour in the adult. *Nature* 416: 396–400
170 Lopez JF, Chalmers DT, Little KY, Watson SJ (1998) A.E. Bennett Research Award. Regulation of serotonin1A, glucocorticoid, and mineralocorticoid receptor in rat and human hippocampus: implications for the neurobiology of depression. *Biol Psychiatry* 43: 547–573
171 Flugge G (1995) Dynamics of central nervous 5-HT1A-receptors under psychosocial stress. *J Neurosci* 15: 7132–7140
172 Drevets WC, Frank E, Price JC, Kupfer DJ, Holt D, Greer PJ, Huang Y, Gautier C, Mathis C (1999) PET imaging of serotonin 1A receptor binding in depression. *Biol Psychiatry* 46: 1375–1387
173 Cannon DM, Ichise M, Fromm SJ, Nugent AC, Rollis D, Gandhi SK, Klaver JM, Charney DS, Manji HK, Drevets WC (2006) Serotonin transporter binding in bipolar disorder assessed using [^{11}C]DASB and positron emission tomography. *Biol Psychiatry* 60: 207–217
174 Suhara T, Nakayama K, Inoue O, Fukuda H, Shimizu M, Mori A, Tateno Y (1992) D1 dopamine receptor binding in mood disorders measured by positron emission tomography. *Psychopharmacology (Berl)* 106: 14–18
175 Pearlson GD, Wong DF, Tune LE, Ross CA, Chase GA, Links JM, Dannals RF, Wilson AA, Ravert HT, Wagner HN Jr, et al (1995) *In vivo* D2 dopamine receptor density in psychotic and nonpsychotic patients with bipolar disorder. *Arch Gen Psychiatry* 52: 471–477
176 Anand A, Verhoeff P, Seneca N, Zoghbi SS, Seibyl JP, Charney DS, Innis RB (2000) Brain SPECT imaging of amphetamine-induced dopamine release in euthymic bipolar disorder patients. *Am J Psychiatry* 157: 1108–1114
177 Janowsky DS, Overstreet DH, Nurnberger JIJ (1994) Is cholinergic sensitivity a genetic marker for the affective disorders? *Am J Med Genet* 54: 335–344
178 Benson BE, Carson RE, Kiesewetter DO, Herscovitch P, Eckelman WC, Post RM, Ketter TA (2004) A potential cholinergic mechanism of procaine's limbic activation. *Neuropsychopharmacology* 29: 1239–1250
179 Ketter TA, Andreason PJ, George MS, Lee C, Gill DS, Parekh PI, Willis MW, Herscovitch P, Post RM (1996) Anterior paralimbic mediation of procaine-induced emotional and psychosensory experiences. *Arch Gen Psychiatry* 53: 59–69
180 Cannon DM, Carson RE, Nugent AC, Eckelman WC, Kiesewetter DO, Williams J, Rollis D, Drevets M, Gandhi S, Solorio G et al (2006) Reduced muscarinic type 2 receptor binding in subjects with bipolar disorder. *Arch Gen Psychiatry* 63: 741–747
181 Furey ML, Drevets WC (2006) Antidepressant efficacy of the antimuscarinic drug scopolamine: a randomized, placebo-controlled clinical trial. *Arch Gen Psychiatry* 63: 1121–1129
182 Russchen FT, Bakst I, Amaral DG, Price JL (1985) The amygdalostriatal projections in the monkey. An anterograde tracing study. *Brain Res* 329: 241–257
183 Shekhar A, Truitt W, Rainnie D, Sajdyk T (2005) Role of stress, corticotrophin releasing factor (CRF) and amygdala plasticity in chronic anxiety. *Stress* 8: 209–219
184 Davis M, Shi C (1999) The extended amygdala: are the central nucleus of the amygdala and the bed nucleus of the stria terminalis differentially involved in fear *versus* anxiety? *Ann N Y Acad Sci* 877: 281–291
185 LeDoux J (2003) The emotional brain, fear, and the amygdala. *Cell Mol Neurobiol* 23: 727–738
186 Drevets WC, Price JL, Furey ML (2008) Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. *Brain Struct Function* 213: 93–118

187 Manji HK, Drevets WC, Charney DS (2001) The cellular neurobiology of depression. *Nature Medicine* 7: 541–547
188 Drevets WC (2007) Orbitofrontal cortex function and structure in depression. *Ann N Y Acad Sci* 1121: 499–527
189 Herman JP, Cullinan WE (1997) Neurocircuitry of stress: central control of the hypothalamo-pituitary-adrenocortical axis. *Trends Neurosci* 20: 78–84
190 Carpenter M, Sutin J (1983) *Human Neuroanatomy, Eighth Edition*. Williams and Wilkins, Baltimore, MD