Chapter 8
Neuroimaging Studies of Bipolar Depression: Therapeutic Implications

Jonathan Savitz, Harvey M. Morris, and Wayne C. Drevets

Abstract Bipolar disorder (BD) 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/or cortical thickness and a concomitant increase in glutamatergic neurotransmission are observed in the pregenual (pgACC) and subgenual anterior cingulate cortex (sgACC); the orbitofrontal, frontal polar, and ventrolateral prefrontal cortex (PFC); and the posterior cingulate, ventral striatum, and hippocampus. Neuroreceptor imaging data provide preliminary evidence for serotonin, serotonin transporter (5-HTT), dopamine receptor, and cholinergic system dysfunction in BD. Recent PET imaging data also suggest microglial cell activation in mood disorders. 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, increase neurotrophic processes, and decrease inflammation, restoring balance to the system.

Keywords Bipolar disorder (BD) • Neuroimaging • Amygdala • Hippocampus • Prefrontal cortex • Glutamate

J. Savitz, PhD (✉)
Laureate Institute for Brain Research, 6655 S. Yale Avenue, Tulsa, OK 74136, USA

Faculty of Community Medicine, The University of Tulsa, Tulsa, OK, USA
e-mail: jsavitz@laureateinstitute.org

H.M. Morris, PhD
Laureate Institute for Brain Research, 6655 S. Yale Avenue, Tulsa, OK 74136, USA

W.C. Drevets, MD
Janssen Pharmaceuticals of J&J, Inc., Titusville, NJ, USA

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8.1 Introduction

Since this chapter's first edition in 2010, the field of neuroimaging studies in bipolar disorder (BD) has rapidly evolved. Some of the major changes include: a reduced emphasis on structural magnetic resonance imaging (MRI) studies, as advances in technology have led to greater interest in techniques such as magnetic resonance spectroscopy (MRS), diffusion tensor imaging (DTI), and functional MRI (fMRI) assessment of the blood oxygen level dependence (BOLD) signal during the resting state to investigate the functional connectivity across brain regions. One exception to this trend, however, has been the development of automated techniques that allow for the measurement of cortical thickness and gyrification. The past five years have also seen a general increase in the number of fMRI studies, a greater interest in correlating molecular-level phenotypes with imaging data, and a quest to identify transdiagnostic biomarkers of psychiatric illness. The evolution of the research trajectory has been influenced in part by the development of new classes of antidepressant medication underlined by the promising results of ketamine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist, for the treatment of bipolar depression (Ionescu et al. 2015; Zarate et al. 2012). Here, we incorporate some of the results from these new areas into our review of the neuroimaging and neuropathological abnormalities in BD.

The World Health Organization ranks BD as one of the leading causes of disability (The World Health Organization (WHO) 2001); yet, our knowledge about this condition's pathogenesis remains modest. Because BD 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 is critical to elucidating its neurobiology. The development of neuroimaging technologies that permit in vivo characterization of the anatomical, physiological, and neurochemical correlates of BD has thus enabled advances toward illuminating the pathophysiology of this condition. Notably, the results of neuroimaging studies and the postmortem studies that have been guided by neuroimaging results have given rise to neurocircuitry-based models in which both functional and structural brain pathologies play roles in the development of BD.

The symptomatology of the clinical syndromes that manifest in BD, namely, the major depressive and manic episodes, implicates brain systems involved in the regulation of mood and emotional expression, reward processing, attention, motivation, stress response, social cognition, and neurovegetative function (e.g., sleep, appetite, energy, libido). The symptomatology of mania thus implicates the same domains of brain function as those underlying depressive episodes but generally with opposite valence. Anxiety symptoms are also prominent during the depressed phase of BD, and this disorder commonly occurs comorbidly with anxiety disorders such as panic disorder, social phobia, posttraumatic stress disorder (PTSD), and obsessive–compulsive disorder (OCD) (Kessler et al. 2005). Consistent with the clinical phenomenology of BD, a variety of neurophysiological, neuropathological,

and neurochemical abnormalities have been discovered in BD within the neural systems that modulate emotional behavior.

To date, none of these abnormalities have shown sufficient sensitivity and specificity to prove useful as a diagnostic test, and neuroimaging is not recommended within either the USA or the European practice guidelines for positively defining diagnosis of any primary psychiatric disorder (Savitz et al. 2013). The variable presence and magnitude of such abnormalities in mood disorders likely reflects the heterogeneity encompassed within the BD syndrome with respect to pathophysiology and etiology. As long as psychiatric nosology depends on syndrome-based classifications, diagnosing BD 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 extant inconsistencies within the literature pertaining to neurobiological abnormalities associated with BD and to the variable responses of BD 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 of therapeutic approaches.

8.2 Neural Circuits Implicated in Bipolar Disorder

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 BD (Phillips et al. 2003). These circuits include the limbic–cortical–striatal–pallidal–thalamic (LCSPT) circuits formed by the orbital and medial prefrontal cortex (OMPFC), amygdala, hippocampal subiculum, ventromedial striatum, mediodorsal thalamic nucleus, and ventral pallidum (Ongur et al. 2003). 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 gray (PAG) (Nauta and Domesick 1984). They were also initially implicated in the *pathophysiology of depression* by the observation that degenerative basal ganglia diseases and lesions of the striatum and orbitofrontal cortex (OFC) increased the risk of developing major depressive or manic syndromes (Folstein et al. 1985).

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 (Ongur et al. 2003). 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) (Ongur et al. 2003). 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) (Price and Drevets 2012).

8.3 Structural Neuroimaging in Bipolar Disorder

Patients with BD show abnormalities of morphology or morphometry in multiple structures that form the extended visceromotor network (Drevets and Price 2005) (Tables 8.1 and 8.2). 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 BD 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 elderly individuals with MDD with an early age of onset (Drevets et al. 2004). Similarly, individuals with MDD or BD 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, which are absent in early onset, nonpsychotic MDD cases.

8.3.1 Volumetric MRI Abnormalities Identified in Bipolar Disorder

Early onset, nonpsychotic BD cases also show volumetric abnormalities that are localized to some PFC, cingulate, temporal lobe, and striatal structures (Tables 8.1 and 8.2). The most prominent volumetric abnormality reported to date has been a reduction in gray matter (GM) in the *left* anterior cingulate cortex (ACC) ventral to the corpus callosum *genu* (i.e., "subgenual"), which is evident in MDD and BD with evidence of familial clustering or with psychotic features (Botteron et al. 2002; Coryell et al. 2005; Drevets et al. 1997; Hirayasu et al. 1999). This volumetric reduction exists early in the course of the illness and in young adults at high familial risk for BD or MDD (Botteron et al. 2002; Hirayasu et al. 1999). This abnormality is also evident for both BD-I and BD-II samples (Haznedar et al. 2005; Lyoo et al. 2004a). Reductions in cortical thickness of the sgACC and the rostral ACC

Table 8.1 Neuroimaging and histopathological abnormalities evident in the visceromotor network in early onset, recurrent MDD, and/or BD

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

[a]In the sgACC, the apparent reduction in cerebral blood flow 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 gray matter, the metabolism appears increased relative to controls

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

Abbreviations: BD: bipolar disorder; Dep vs. Con: unmedicated individuals with MDD versus healthy controls; Dep vs. 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 Drevets (2007)

more generally have also been reported using automated analysis software such as FreeSurfer, which is able to distinguish cortical area and cortical thickness (Elvsashagen et al. 2013; Foland-Ross et al. 2011) (Table 8.2).

Conventional antidepressant drug treatment and symptom remission do not appear to alter the reductions in GM volume in the sgACC (Drevets et al. 1997). Interestingly, chronic lithium treatment, which exerts robust neurotrophic effects in animal models (Moore et al. 2000), largely normalizes sgACC volume in treatment responders (Moore et al. 2009). These data are supported by MRS studies, which find that higher levels of *N*-acetylaspartate (NAA) in the sgACC, a marker of neuronal integrity, are associated with lithium treatment (Moore and Galloway 2002; Forester et al. 2008) (Fig. 8.1).

Also consistent with the structural MRI literature are the results of postmortem studies. Notably, a reduction in the number of Nissl-stained glia identified

Table 8.2 Summary of cortical thickness measurements in adult BD

Study	Regions of decreased thickness	Sample size	Mood state	Mean age
Giakoumatos et al. (2015)	LOC (B), lingual (R) in BD-no Li versus HC	186 BD, 342 HC	Psychotic	37, 36
Oertel-Knochel et al. (2015)	MOG (L), IFG (B), precuneus (B), STG (L), rACC (R)	32 BD, 35 HC	Remitted	44, 42
Janssen et al. (2014)	Frontal cortex	20 BD, 52 HC	Psychotic	16, 15
Lan et al. (2014)	IPC (B), caudal middle-frontal (R), SPC (L), PCC (R), supramarginal (R)	18 BD, 54 HC	Depressed	38, 32
Maller et al. (2014)	Parietal cortex (L), supramarginal gyrus (R), SFG (R), precuneus (R)	31 BD, 31 HC	Depressed	43, 40
Elvsashagen et al. (2013)	sgACC (L), dorsomedial PFC (B), DLPFC (B), temporal gyrus (L)	36 BD II, 42 HC	Depressed, remitted, hypomanic	33, 31
Hatton et al. (2013)	Calcarine sulcus (L), angular gyrus (L), supramarginal gyrus (R), SPC (R), precuneus (R), precentral gyrus (R), fusiform gyrus (R)	73 BD, 49 HC	Psychotic	22, 24
Foland-Ross et al. (2011)	ACC (L), pregenual ACC (L), OFC (B), frontopolar (L), dorsomedial PFC (L), temporal pole (L)	34 BD, 31 HC	Euthymic	31, 38
Rimol et al. (2010)	Frontal lobe, posterior temporal, and temporoparietal regions	139 BD, 207 HC	NS	35, 36
Fornito et al. (2009)	Male patients had increased thickness in sgACC (R)	26 BD, 26 HC	Manic (1st episode)	22, 22
Lyoo et al. (2006)	Postcentral cortex (B), dorsal ACC (L), pregenual ACC (L), PCC (L), occipital cortex (L), OFC (R), fusiform gyrus (R)	25 BD, 21 HC	Depressed	34, 32

(L) = left, (B) = bilateral, (R) = right, NS = not stated, LOC = lateral occipital cortex, MOG = medial orbital gyrus, STG = superior temporal gyrus, rACC = rostral anterior cingulate cortex, SFG = superior frontal gyrus, IFG = inferior frontal gyrus, IPC = inferior parietal cortex, SPC = superior parietal cortex, PCC = posterior cingulate cortex, sgACC = subgenual anterior cingulate cortex, DLPFC = dorsolateral prefrontal cortex, ICV = intracranial volume, Li = lithium, OFC = orbital frontal cortex, PFC = prefrontal cortex, BD = bipolar disorder, HC = healthy control

morphometrically together with an increase in neuronal density in the sgACC was found in two independent samples of patients with familial BD as well as familial MDD (Ongur et al. 1998). The reported reduction in glial cells most clearly implicated the perineuronal and myelinating oligodendroglia and may, thus, compromise the structural integrity of white matter (WM) fibers. Certainly, DTI studies have produced evidence of structural abnormalities of WM tracts connecting the sgACC with limbic nuclei (Wang et al. 2008, 2009).

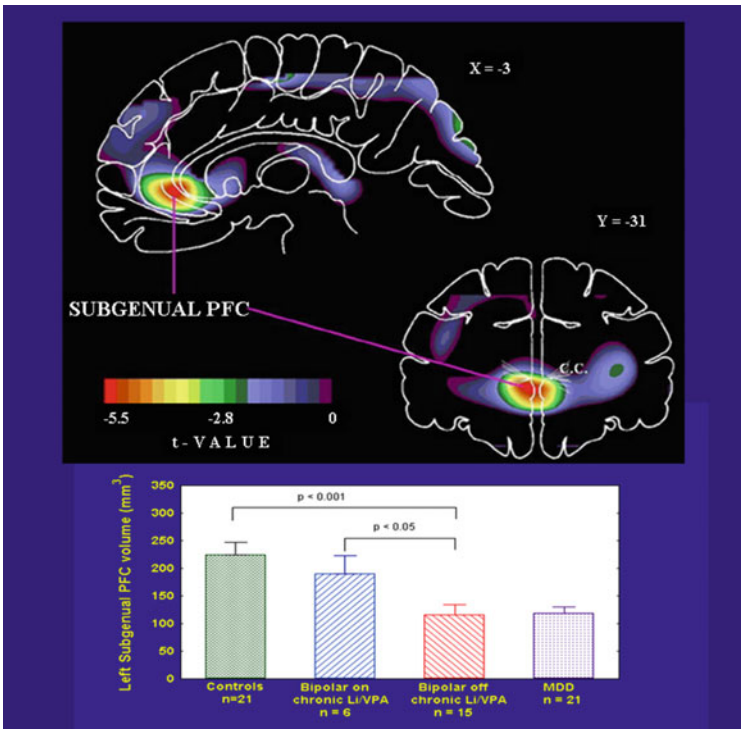

Fig. 8.1 *Upper panel:* Coronal (31 mm anterior to the anterior commissure; $y = 31$) and sagittal (3 mm left of midline; $x = -3$) sections showing negative voxel *t*-values where glucose metabolism is decreased in individuals with depression relative to controls. The reduction in activity in this prefrontal 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 (Table 8.1; reproduced from Drevets et al. (1997)). 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 anterior cingulate cortex (sgACC) volumes in mm^3 for the healthy controls, individuals with major depressive disorder (MDD), unmedicated individuals with bipolar depression, and subjects with bipolar disorder (BD) chronically medicated with lithium or valproate

GM volume and cortical thickness is also reduced in the OFC (BA 11, 47) and ventrolateral PFC (VLPFC; BA 45, 47) in MDD (Drevets and Todd 2005) and BD (Lyoo et al. 2004a; Foland-Ross et al. 2011; Oertel-Knochel et al. 2015), in the frontal polar/dorsal anterolateral PFC (BA 9, 10) in MDD (Drevets et al. 2004), and in the posterior cingulate cortex and superior temporal gyrus in BD (Nugent et al. 2006; Oertel-Knochel et al. 2015). In BD, the peak difference in GM loss in the lateral OFC was found in the sulcal BA47 cortex (Nugent et al. 2006), a region that appears to function as part of both the visceromotor and "sensory" networks within the OMPFC (Ongur et al. 2003). Compatible with these data, the MRS study

by Cecil and colleagues found reduced NAA and choline concentrations in the orbitofrontal GM in BD, suggesting decreased neuronal integrity (Cecil et al. 2002).

Decreases in the volume of the dorsal PFC have also been reported in BD and MDD (Savitz and Drevets 2009a). For example, Frangou and colleagues (2005) and Haznedar and colleagues (2005) described GM volume reductions of the dorsolateral PFC (DLPFC) (BA 8, 9, 45, 46) in medicated and remitted BD-I patients and partially medicated, "stable" bipolar-spectrum individuals, respectively. More circumscribed volume reductions of BA 9 were also reported in a medicated, euthymic pediatric BD sample (Dickstein et al. 2005). In a mixed BD-I and BD-II sample, Lochhead and colleagues reported reduced GM volume of the ACC immediately dorsal to the corpus callosum (CC) (Lochhead et al. 2004). Reductions in cortical thickness of the dorsomedial PFC and DLPFC were also reported in a lithium-free sample of BD subjects (Foland-Ross et al. 2011).

In the hippocampus, at least half of the studies reported reductions in the volume of the whole hippocampus in MDD. In BD, however, the volumetric reductions appear more specific to the anterior subiculum/ventral CA1 region (Drevets et al. 2004). In contrast, the whole hippocampal volume was reported to be smaller in BD subjects than controls in some studies, but not different from controls in most studies (Savitz and Drevets 2009a). The reasons for these apparent differences between neuromorphometric studies of MDD versus BD remain unclear. In MDD, the reduction in hippocampal volume was limited to depressed women who suffered early life trauma in some studies (Vythilingam et al. 2002) and was correlated inversely with time spent depressed in other studies (e.g., Sheline et al. (2003)), but it remains unclear whether these relationships also extend to BD. Regarding the postmortem literature, Fatemi and colleagues reported a 39 % decrease in CA4 volume together with a decreased density of reelin-expressing gamma aminobutyric acid (GABA)ergic neurons (Fatemi et al. 2000). Similarly, Pantazopoulos and colleagues detected a decrease in both the total number and the density of inhibitory, GABAergic neurons in the superficial layers of the entorhinal cortex in a BD sample (Pantazopoulos et al. 2007).

One potential reason for the apparent discrepant imaging findings between MDD and BD may be the neurotrophic/neuroprotective effects associated with mood stabilizing treatments. Animal studies demonstrate that lithium promotes hippocampal neurogenesis (Kim et al. 2004) and long-term potentiation (LTP) (Son et al. 2003). A sample of BD patients treated for four weeks with lithium showed a 3 % (24 cm^3) increase in whole brain GM volumes from baseline (Moore et al. 2000), an effect that appeared to result from the neurotrophic effect of the drug (Manji et al. 2000). Four more recent studies (Bearden et al. 2007; Beyer et al. 2004; Sassi et al. 2004; Yucel et al. 2008) 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 (Hao et al. 2004; Mark et al. 1995). In contrast, with the exception of the as yet rarely prescribed tianeptine (McEwen et al. 2002; McEwen and Olie 2005; Watanabe et al. 1992), the neurotrophic properties of antidepressants are less

persuasive (although see Stewart and Reid (2000)) and Duman and Monteggia (2006)). The potential effects of lithium on hippocampal volume are supported by a recent meta-analysis that found that in aggregate, hippocampal volume is reduced in BD after controlling for the effects of lithium (Hajek et al. 2012).

Amygdala volume has been reported to be increased in some studies but decreased in others in individuals with MDD relative to controls (Drevets et al. 2004). In general, these data suggest that the amygdala volume in patients with BD 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 (Savitz and Drevets 2009a). The findings in adults seem to hold even in samples with a long history of illness (Altshuler et al. 2000; Brambilla et al. 2003; Frangou et al. 2005). As in the case of the hippocampus, reports of increased GM volume in BD subjects versus healthy controls may be an artifact of treatment with medications. Relative to healthy controls, we found larger amygdalar volumes in lithium or valproate-treated BD patients but smaller amygdalar volumes in unmedicated subjects with BD (Savitz et al. 2010). These data are supported by the postmortem literature: a 19 % reduction in oligodendrocyte density in the amygdala that reached trend level significance was found in one study (Hamidi et al. 2004), and in another study, the density of glial cells in the amygdala was significantly reduced in MDD but not in BD (Bowley et al. 2002). However, samples from two unmedicated patients with BD were indicative of reduced oligodendrocyte density (Bowley et al. 2002).

In the basal ganglia (i.e., caudate, putamen, or globus pallidus), subjects with BD generally have not shown morphometric differences relative to controls (Savitz and Drevets 2009a). These data appear consistent with the reported absence of NAA abnormalities in the basal ganglia of BD samples (Kato et al. 1996; Hamakawa et al. 1998; Ohara et al. 1998). Nevertheless, a postmortem study of a combined MDD and BD sample reported volumetric reductions of the left accumbens, bilateral pallidum, and right putamen (Baumann et al. 1999).

There has, however, been some suggestion of striatal enlargement in adult and pediatric samples with BD (Savitz and Drevets 2009a). As in the case of the hippocampus, treatment effects may conceivably confound these analyses. Enlargement of basal ganglia structures is a well-known effect of antipsychotic drugs (Jernigan et al. 1991; Swayze et al. 1992; Chakos et al. 1995; Frazier et al. 1996) and, notably, three of the studies reporting basal ganglia enlargement used samples that included subjects who were manic and treated with antipsychotic medications (Strakowski et al. 2002; DelBello et al. 2004; Wilke et al. 2004).

Enlargement of the third and lateral ventricles has commonly been observed in BD (Savitz and Drevets 2009a). Many studies reporting ventriculomegaly included subjects with early age of onset. Nevertheless, the extent to which chronic alcohol abuse (Anstey et al. 2006), incipient neurological disorders with prodromal depression, or cerebrovascular disease (Salerno et al. 1992; Goldstein et al. 2002; Knopman et al. 2005) (see ensuing section on WM abnormalities) contributes to ventricular enlargement has not been established. Notably, Strakowski and colleagues found that the lateral ventricles were significantly larger in patients with

multiple-episode BD than in first-episode BD patients or healthy controls, and larger lateral ventricles were associated with a higher number of prior manic episodes (Strakowski et al. 2002). The multiple-episode patients in this study also had a smaller total cerebral volume than the healthy subjects, but not the first-episode patients. These cross-sectional data imply that a progressive loss of cerebral tissue volume occurs during repeated manic episodes, although this observation requires confirmation in longitudinal studies.

8.3.1.1 Lithium's Effects on T1 Signal Intensity of Gray Matter in MRI Image Analysis

In considering the design and interpretation of studies reporting lithium's effects on regional GM volume, the nonspecific effect of lithium on T1 signal intensity merits comment. Cousins and colleagues showed that lithium reduced T1 relaxation in cerebral GM (but not in WM), and that this effect could distort measures of GM volume obtained using analysis techniques that depend heavily or exclusively on MRI signal intensity, such as voxel-based morphometry (VBM) (Cousins et al. 2013). In this study, MRI scans were obtained in healthy controls before and after receiving lithium for 11 days. Analysis of cerebral volumes performed using VBM showed an increase in total GM volume by a mean of 1.1 % versus placebo (along with a corresponding reduction in CSF volume and no significant change in WM volume). In contrast, no significant difference between lithium and placebo was noted when the same images were analyzed using Structural Image Evaluation using Normalization of Atrophy (SIENA), a technique that additionally employed paired edge finding methods (analogous to the boundary finding capabilities of the human eye). This effect of lithium on the T1 signal must, therefore, be considered in the design and interpretation of volumetric studies of lithium's effects on GM volume.

One study that used a semi-automated segmentation approach (analogous to VBM) addressed this limitation by including a relevant control group that enabled controlling for lithium's nonspecific effects on T1 signal intensity. Moore and colleagues imaged 28 BD patients before and following a four-week course of lithium. Although in the entire sample the total brain GM volume increased significantly in the post- versus pre-treatment condition, the separate comparisons of lithium responders ($n = 11$) and nonresponders ($n = 17$) proved most instructive (Moore et al. 2009). These subgroups did not differ significantly in lithium level, age, sex, or baseline total brain volume. In the nonresponders, the treatment-associated changes in GM volume were not statistically significant but were nominally in the 0.5–1 % range in the entire PFC and subgenual PFC regions, respectively, compatible with the findings of Cousins and colleagues (2013). In the lithium responders, however, GM volume increased *significantly* in the PFC; moreover, the magnitude of the GM changes was greater in the treatment responder group, being >4 % in the PFC more broadly and 8 % in the sgPFC specifically. Thus, the nonresponder group controlled for the nonspecific effects of lithium on

MR signal intensity and enabled a compelling demonstration that, in treatment responders, lithium increased GM volume in regions where GM had been reported in previous studies to be abnormally decreased in BD.

Another useful approach was exemplified by Savitz and colleagues, who applied two useful approaches for dealing with the nonspecific effect of lithium on T1 signal in a study employing a cross-sectional design (Savitz et al. 2010). First, in addition to examining the effects of lithium on amygdala volume, this study also investigated the effects of another mood stabilizing medication, divalproex, which showed neuroprotective effects similar to those of lithium in preclinical models, but has not been associated with confounding effects on MRI signal intensity. Second, this study used a manual segmentation technique in images that were high in both spatial and tissue contrast resolution. The manual segmentation technique relies on the capabilities of the human eye to implement information about both signal intensity and boundary shape, analogous to the SIENA approach. In *unmedicated* BD subjects, the mean right amygdala volume was significantly smaller than in matched healthy controls. In contrast, the mean right amygdala volume was significantly greater (with a similar trend on the left) in BD patients treated with either lithium or divalproex, relative to the BD subjects who were unmedicated. In a post hoc analysis, the effect was at least as robust for divalproex as for lithium (the volumes were nominally larger in the divalproex-treated subsample). Since preclinical data showed that lithium and divalproex exert similar neuroplasticity effects under a variety of physiological and psychological stress models in rodents, these data appear compatible with the hypothesis that these neuroplasticity effects extend to humans with BD. Notably, the medicated BD subjects did not show any difference relative to matched healthy controls in whole brain volume, suggesting that mood stabilizer treatment may correct an abnormal reduction in amygdala volume in BD without nonspecifically changing GM volume all over the brain.

8.3.2 Neuromorphological MRI Abnormalities in BD: White Matter Pathology

Abnormalities of WM tracts in BD as indexed by reduced fractional anisotropy (FA) and increased radial diffusivity (RD) have been reported in regions such as the cingulum, genu, and splenium of the corpus callosum and inferior and superior longitudinal fasciculi (Emsell et al. 2014; Torgerson et al. 2013; Barysheva et al. 2013; Versace et al. 2014). FA is a measure of the degree to which the diffusion process is constrained by the WM fibers, such that a low FA may indicate decreases in fiber density and/or myelination in WM. Interestingly, a recent study reported that psychotic BD patients showed similar WM connectivity abnormalities to schizophrenics with decreases in FA of the callosal, posterior thalamic/optic, paralimbic, and fronto-occipital tracts (Kumar et al. 2015). These findings were partially consistent with a previous study reporting reduced FA in the anterior limb

of the internal capsule, anterior thalamic radiation, and in the region of the uncinate fasciculus in patients with BD and those with schizophrenia compared with controls (Sussmann et al. 2009), thus suggesting that the presence of WM abnormalities may cut across traditional diagnostic boundaries.

In morphological MRI studies, an elevation in the incidence of WM hyperintensities (WMH), especially in the deep frontal cortex and basal ganglia, has commonly been reported in BD and in late-onset MDD samples (Krishnan et al. 1991; Figiel et al. 1991; Hickie et al. 1995; Steffens et al. 1999; Hannestad et al. 2006). 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 WM density due to demyelination, atrophy of the neuropil, ischemia-associated microangiopathy, or other causes (Ovbiagele and Saver 2006). This phenomenon normally is prevalent in elderly, nondepressed populations (Kertesz et al. 1988) but shows an abnormally high prevalence in MDD cases with a late age of onset and in BD samples of all ages.

The incidence of WMH may relate in part to cerebrovascular disease. BD is associated with a significantly increased prevalence of cardiovascular disease risk factors such as smoking, obesity, diabetes mellitus (DM), hypertension, and dyslipidemia (reviewed in Kilbourne et al. (2004) and Newcomer (2006)). Hypertension (Dufouil et al. 2001; Gunstad et al. 2005), obesity (Gustafson et al. 2004), smoking (Dager and Friedman 2000), and diabetes mellitus (Novak et al. 2006) have in turn been directly associated with the development of WMH. Although most published studies of BD 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 BD are an artifact of medical comorbidity or some obscure ischemic risk factor. Moreover, drug abuse is prevalent in BD populations and stimulant drug-induced vasoconstriction may lead to WMH (Dupont et al. 1990; Lyoo et al. 2004b). Notably, marijuana use also may interact in an additive fashion with WMH to predispose to depressive symptomatology (Medina et al. 2007). In addition, Lenze and colleagues (1999) and Nemeroff and colleagues (2000) speculated that excess depression-associated secretion of serotonin by blood platelets (Biegon et al. 1990; Musselman et al. 1996) 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 (de Castro et al. 2008), raising the possibility that impaired regulation of vascular tone also plays a role in the pathogenesis of WMH in BD.

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 Savitz and Drevets (2009a)). Moreover, the hypothesis that WMH reflect cerebrovascular disease fails to account for the WM pathology noted in pediatric BD samples (Botteron et al. 1995; Lyoo et al. 2002; Pillai et al. 2002) as well as the high concentration of WMH in both BD subjects and their unaffected relatives (Ahearn et al. 1998). A significant minority of young

BD patients with a relatively typical age of onset show WM abnormalities on MRI scans (Savitz and Drevets 2009b). Thus, while a proportion of adults with BD with significant WM pathology will present with risk factors for cerebrovascular disease, WMH may also less commonly arise in pediatric or young adult BD samples due to developmental insults or via some as yet unknown pathophysiological mechanism.

Obstetric complications are well known to be associated with schizophrenia (Cannon et al. 2002), but with a few exceptions (Kinney et al. 1993, 1998), appear less salient in BD. Nevertheless, it is possible that perinatal hypoxic events precipitate BD in a vulnerable minority (Pavuluri et al. 2006).

Another possible explanation for demyelination as evidenced by WMH in BD may be changes in oligodendrocyte function. Postmortem studies have reported a downregulation of oligodendrocyte-related expression of genes impacting myelin or oligodendrocyte function and decreased oligodendrocyte density in both BD and MDD (Tkachev et al. 2003; Aston et al. 2005; Cotter et al. 2002; Hamidi et al. 2004; Uranova et al. 2004; Vostrikov et al. 2007). Conversely, oligodendrocyte density and 2′,3′-cyclic-nucleotide 3′-phosphodiesterase (CNPase), a putative marker of oligodendrocytes, were increased in the WM underlying the DLPFC of individuals with BD prescribed mood stabilizers, suggesting a treatment effect (Hercher et al. 2014). 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 (see Carter (2007a, b) and Sokolov (2007) for a review). WM is decreased in the genu of the corpus callosum in both adults with BD or MDD, their high-risk children, and their adolescent offspring (particularly in females), and is also decreased in the splenium of the corpus callosum in adults with BD or MDD. Finally, the high incidence of familial WMH seen in the Ahearn and colleagues 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 BD (Ahearn et al. 1998).

An unresolved issue is whether the relationship between WM pathology and mood disorders is one of cause or effect. Certainly, new cases of BD may be precipitated by subcortical infarcts (Starkstein and Robinson 1989). Moreover, depressive and bipolar syndromes are relatively common sequelae of the genetic disorder, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) (Chabriat et al. 1995; Desmond et al. 1999). The deep frontal WM pathology commonly seen in mood disorders may conceivably disrupt the pathways linking subcortical regions such as the striatum to functionally homologous regions of the PFC, giving rise to dysregulation of emotional behavior in BD (Adler et al. 2004; Geschwind 1965a, b).

8.4 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 metabolism (Table 8.1; Fig. 8.1). 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 BD. In MDD, this pattern of differences has also been demonstrated in cross-sectional studies of depressed MDD subjects relative to controls, longitudinal studies of patients imaged before versus after treatment (Drevets et al. 2002a), and challenge studies of remitted patients scanned before versus during depressive relapse (Neumeister et al. 2004; Hasler et al. 2008).

Nevertheless, the reduction in GM 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 BD and MDD subjects show metabolic activity that appears *reduced* in the sgACC (Drevets et al. 1997; Kegeles et al. 2003). However, this abnormal reduction in flow and metabolism may be partly attributable to the partial volume averaging effect associated with the reduction in the corresponding GM (Drevets and Price 2005). This effect may contribute to the complex relationship observed between metabolic activity and clinical state, as activity is decreased further in the remitted versus the depressed phase of mood disorders in the sgACC, as assessed following effective treatment (Drevets et al. 2002a; Holthoff et al. 2004; Nobler et al. 2001; Mayberg et al. 2005). Conversely, metabolic activity is increased in the sgACC in remitted MDD cases during depressive relapse induced by tryptophan depletion or catecholamine depletion (Neumeister et al. 2004; Hasler et al. 2008). 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 (Ketter and Drevets 2002).

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 (Vidal-Gonzalez et al. 2006). Regions where metabolism correlates positively with depression severity include the amygdala, sgACC, and ventromedial frontal polar cortex (Hasler et al. 2008; Drevets et al. 2002a). Metabolism and flow decrease in these regions during effective treatment (Mayberg et al. 2005; Drevets et al. 2002a). 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 (Neumeister et al. 2004, 2006; Hasler et al. 2008).

In the amygdala, abnormal elevations of resting metabolism can be seen in depressed samples categorized as having BD, familial pure depressive disease (FPDD), MDD-melancholic type, or MDD that responds to a night of total sleep deprivation (Drevets 2001). In such cases, amygdala metabolism decreases toward normative levels during effective antidepressant treatment (Drevets et al. 2002a). In BD, these findings of increased baseline amygdalar activity have largely been limited to adults (Ketter et al. 2001; Sheline et al. 2001; Drevets et al. 2002b; Bauer et al. 2005; Mah et al. 2007), in whom resting activity has correlated positively with severity of depression (Ketter et al. 2001). Furthermore, increased hemodynamic responses of the amygdala to negatively valenced faces have been reported in BD subjects relative to healthy controls (Yurgelun-Todd et al. 2000; Lawrence et al. 2004; Rich et al. 2006; Pavuluri et al. 2007). Notably, both adolescents with BD and unaffected adolescents with a family history of BD showed an elevated hemodynamic response in the amygdala when presented with faces expressing negatively valenced emotion, implying that this abnormality either arises very early in the illness or reflects a heritable trait-like biomarker (Olsavsky et al. 2012; Manelis et al. 2015). This finding extended to the offspring of parents with non-bipolar mood disorder as well; however, in the functional connectivity analysis from the same study, an increased amygdala–VLPFC and reduced amygdala–ACC functional connectivity pattern previously shown in individuals with BD also differentiated the offspring of BD parents from those of non-bipolar mood disorders (Manelis et al. 2015). If these findings prove reproducible, they would imply that these abnormalities may constitute risk markers for the development of BD.

In the accumbens, medial thalamus, and posterior cingulate cortex, resting metabolism and perfusion appear abnormally elevated in the depressed phase of MDD and BD (Drevets et al. 2002b, 2004; Mah et al. 2007). In the OFC, Blumberg and colleagues showed that manic patients have reduced rCBF (Blumberg et al. 1999), while induction of a sad mood through psychological means resulted in decreased rCBF to the medial OFC in euthymic but not depressed BD subjects versus controls (Kruger et al. 2003). Finally, reductions in metabolism have been reported in the dorsolateral PFC, and abnormalities in the hemodynamic responses to various cognitive–behavioral tasks have been reported in BD in both the OMPFC and the DLPFC (Phillips et al. 2003).

The patterns of hemodynamic response to a variety of positively or negatively valenced stimuli have consistently differed between mood disordered and healthy control samples and, in some cases, between depressed subjects with MDD versus BD; these consistently highlight altered function within the limbic–cortical circuits that involve the OMPFC (Phillips and Swartz 2014). For example, in an fMRI study that compared patterns of hemodynamic change during a reward anticipation task between BD-I, MDD, and healthy control groups, the reward expectancy-related activation in the ACC observed in healthy individuals was significantly reduced in depressed patients with either BD-I or MDD, despite showing no significant difference in the ventral striatum across the three groups (Chase et al. 2013). Notably, the anticipation-related increase in hemodynamic activity in the left

VLPFC was significantly exaggerated in the BD-I depressed group compared to the other two groups. While medication effects have been a confounding factor in most fMRI studies of BD, some have begun to take such factors into account in the study design. For example, Hafeman and colleagues studied the impact of medication in youth with BD and reported an area in the right VLPFC in which unmedicated BD youth showed decreased activation relative to both healthy and psychiatric controls during the processing of negative face stimuli; a separate sample of medicated BD subjects also showed decreased activation in this cluster relative to healthy controls and non-BD youth, but the magnitude of this differences was diminished in the medicated BD group compared to the unmedicated group with respect to the control groups (Hafeman et al. 2014).

8.4.1 Patterning Hemodynamic Responses to Classify Individual Subjects with BD or Those at High Risk for BD

The pattern of hemodynamic abnormalities within and outside the medial prefrontal network detected in BD using fMRI has been explored for its potential as a biomarker signature capable of classifying individual subjects. For example, in one study, the hemodynamic response of the default mode and temporal lobe networks during an auditory oddball paradigm was applied a priori to a sample of 14 medicated patients with BD-I, 21 medicated patients with schizophrenia, and 26 healthy controls (Calhoun et al. 2008). The authors were able to distinguish BD patients from patients with schizophrenia and healthy controls with 83 % sensitivity and 100 % specificity. The accuracy of the BD versus healthy control classification was not provided, however. Similarly, Hahn and colleagues used three independent fMRI paradigms in an attempt to maximize classification accuracy: the passive viewing of emotionally valenced faces and two different versions of the monetary incentive delay task emphasizing potential winnings and potential losses, respectively (Hahn et al. 2011). A decision tree algorithm derived from the combination of the imaging task classifiers produced a diagnostic sensitivity of 80 % and a specificity of 87 % in a sample of 30 patients with depression (both MDD and BD) and 30 healthy controls. The algorithm's ability to distinguish subjects with MDD from BD was not reported.

Another study applied a Gaussian Process Classifiers (GPCs) machine-based learning approach to distinguish healthy adolescents with and without a parent with BD from each other with 75 % sensitivity and 75 % specificity (Mourao-Miranda et al. 2012). A discriminating pattern of BOLD activation was found in the superior temporal sulcus and ventromedial PFC when subjects were presented with neutral faces in the context of happy faces. Six out of 13 of the high-risk adolescents who were followed clinically subsequently met DSM-IV criteria for MDD or an anxiety disorder. These six individuals had higher GPC risk scores than the seven high-risk

subjects who did not become ill. Conversely, three out of the four high-risk subjects that the GPC algorithm incorrectly classified as low-risk remained healthy at follow-up. While these sample sizes are small, the study highlights the potential utility of such approaches for developing predictive biomarkers in samples at high familial risk for BD.

8.4.2 Neuropathological Correlations in Mood Disorders

Most regions where MRI studies demonstrated volumetric abnormalities in BD have also been shown to contain histopathological changes or GM volumetric reductions in postmortem studies of MDD and BD. For example, reductions of GM volume, thickness, or wet weight have been reported in the sgACC, posterolateral orbital cortex, and ventral striatum in MDD and/or BD subjects relative to controls (Baumann et al. 1999; Bowen et al. 1989; Ongur et al. 1998; Rajkowska et al. 1999). The histopathological correlates of these abnormalities included reductions in synapses or synaptic proteins, reductions in glial cells, elevations in neuronal density in some regions, and reductions in neuronal size in MDD and/or BD samples (Ongur et al. 1998; Eastwood and Harrison 2000; Uranova et al. 2004; Rajkowska and Miguel-Hidalgo 2007). Reductions in glial cell counts and density and/or glia-to-neuron ratios were also found in MDD subjects versus controls in the pgACC [BA24] (Cotter et al. 2001a), the dorsal anterolateral PFC (BA9) (Cotter et al. 2002; Uranova et al. 2004), and the amygdala (Bowley et al. 2002; Hamidi et al. 2004). Finally, the density of non-pyramidal neurons was decreased in the ACC and hippocampus in BD (Benes et al. 2001; Todtenkopf et al. 2005), and in the dorsal anterolateral PFC (BA9) of individuals with MDD (Rajkowska and Miguel-Hidalgo 2007). Reductions in synapses and synaptic proteins were evident in BD subjects in the hippocampal subiculum/ventral CA1 region (Eastwood and Harrison 2000; Czeh and Lucassen 2007).

The glial type that specifically differed between mood disordered and control samples in many of these studies was the oligodendrocyte (Uranova et al. 2004; Hamidi et al. 2004). 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) (Honer et al. 1999), 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 (Aston et al. 2005). Similarly, a quantitative PCR analysis of BA 9 demonstrated a significant reduction in mRNA expression of protein markers of myelination and oligodendrocyte function (Tkachev et al. 2003).

Expression of proteolipid protein 1 (PLP1), myelin associated glycoprotein (MAG), oligodendrocyte specific protein (CLDN11), myelin oligodendrocyte glycoprotein (MOG), and transferrin (TF) were reduced by approximately two- to four-fold in BD patients relative to psychiatrically healthy controls (Tkachev et al. 2003). Further, expression of the OLIG2 and SOX10 genes, which code for transcription factors involved in oligodendrocyte differentiation and maturation, was downregulated by two- to three-fold in BD. Similarly, MacDonald and colleagues reported that mRNA transcripts of oligodendrocyte-specific proteins such as gelsolin, MAG, and ERBB3 were downregulated in BD (MacDonald et al. 2006).

Compatible with these data, myelin staining was decreased in the deep WM of the DLPFC in MDD and BD subjects (Regenold et al. 2007), and the WM volume of the genual and splenial portions of the corpus callosum was abnormally reduced in MDD and BD (Brambilla et al. 2004). 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 WM in MDD reflects a developmental defect that exists prior to illness onset (Martinez et al. 2002).

Finally, satellite oligodendrocytes were also implicated in the pathophysiology of mood disorders by an electron microscopic study of the PFC in BD, which revealed decreased nuclear size, clumping of chromatin, and other types of damage to satellite oligodendrocytes, including indications of both apoptotic and necrotic degeneration (Uranova et al. 2001; Vostrikov et al. 2007). 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 (Janus et al. 2000).

In other brain regions, reductions in astroglia have been reported by postmortem 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 subjects with mood disorders relative to controls, although it was not determined whether this decrement reflected a reduction in astrocyte density or GFAP expression (Johnston-Wilson et al. 2000). However, another study that used immunohistochemical staining for GFAP found no significant differences in cortical astrocytes between controls and MDD or BD cases (Webster et al. 2001). Other studies also found no differences in GFAP between mood disorder cases and controls (Cotter et al. 2001b).

Factors that may conceivably contribute to a loss of oligodendroglia in mood disorders include elevated glucocorticoid secretion, microglial activation, and glutamatergic transmission evident during depression and mania. Glucocorticoids affect both glia and neurons (Cheng and de Vellis 2000), and elevated glucocorticoid concentrations and repeated stress decrease the proliferation of oligodendrocyte precursors (Alonso 2000; Banasr et al. 2004). Recent PET studies have found evidence for microglial activation in the PFC and ACC of patients with MDD and the hippocampus in patients with BD as indexed by an increase in the distribution of volume of the ligand for the translocator protein ligand, TPSO (Setiawan et al. 2015; Haarman et al. 2014). Activated microglia, in turn, releases the

neurotoxin and NMDA receptor agonist quinolinic acid (QA) (Dantzer et al. 2008). In line with these data, a postmortem immunohistochemistry study showed that relative to controls, a mixed sample of MDD and BD subjects had increased QA-positive cell densities in the anterior mid-cingulate cortex and sgACC, suggesting microglial cell activation (Steiner et al. 2011). Activation of the kynurenine pathway may affect the structure of regions such as the hippocampus and medial PFC. We previously reported that the ratio of QA to kynurenic acid (KynA) in the serum is inversely correlated with hippocampal and amygdalar volume in both unmedicated and medicated patients with BD and have as yet unpublished data showing an inverse correlation between QA and thickness of the BA32 (Savitz et al. 2014a). Moreover, oligodendrocytes express α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate type glutamate receptors and are sensitive to excitotoxic damage from excess glutamate (Hamidi et al. 2004). The targeted nature of the reductions in GM 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.

8.4.3 Correlations with Rodent Models of Chronic and Repeated Stress

In regions that appear homologous to the areas where GM reductions are evident in humans with BD (i.e., medial PFC, hippocampus), repeated stress results in dendritic atrophy and reductions in glial cell counts or proliferation in rodents (Banasr et al. 2004; Czeh et al. 2005; McEwen and Magarinos 2001; Wellman 2001; Radley et al. 2008). In contrast, in the basolateral amygdala (BLA), chronic, unpredictable stress also produced dendritic atrophy, but chronic immobilization stress instead *increased* dendritic branching (Vyas et al. 2002, 2003).

Dendritic atrophy would be reflected by a decrease in the volume of the neuropil, which occupies most of the GM volume. The similarities between the histopathological changes that accompany stress-induced dendritic atrophy in rats and those found in humans suffering from depression thus led to the hypotheses that homologous processes underlie the reductions in GM volume in hippocampal and PFC structures in MDD and BD (McEwen and Magarinos 2001). 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 (Izquierdo et al. 2006; Miracle et al. 2006). Notably, healthy humans with thinner ventromedial PFC tissue also showed a greater galvanic skin response to conditioned stimuli during extinction learning (Milad et al. 2005). Finally, when rats were subjected to repeated stress beyond four weeks, the dendritic atrophy could be reversed by lithium (McEwen and Magarinos 2001), resembling the effects on sgACC volume in depressed humans.

In rodent stress models, these dendritic reshaping processes depend on interactions between increased NMDA receptor stimulation and glucocorticoid secretion associated with repeated stress (Wellman 2001; McEwen and Magarinos 2001). Elevations of glutamate transmission and cortisol secretion in mood disorders also may contribute to reductions in GM volume and synaptic markers by inducing dendritic atrophy in some brain structures, given that the depressive subtypes (e.g., BD, FPDD) who show regional reductions in GM volume also show evidence of cortisol hypersecretion under stressed conditions (reviewed in Drevets et al. (2002a)) and increased glutamate transmission. Subjects with familial BD 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 GM volume and cellular elements. The findings that GM reductions appear to occur specifically in regions that show hypermetabolism during BD thus raise the possibility that excitatory amino acid transmission plays a role in the neuropathology of BD.

8.4.4 Implications for Treatment Mechanisms that Target Plasticity Around the Glutamatergic Synapse

Reverberatory glutamatergic transmission is thought to underlie the pathophysiological activation of limbic-thalamo-cortical circuits of the medial prefrontal (visceromotor) network in BD and MDD (Savitz et al. 2014a, b). The anatomical projections between the OMPFC, striatum, and amygdala implicated in mood disorders are formed by predominantly excitatory projections (Ongur et al. 2003). Because cerebral glucose metabolism largely reflects the energy requirements associated with glutamatergic transmission (Shulman et al. 2004), elevated metabolism in limbic-thalamo-cortical circuits in depression would imply that glutamatergic transmission is increased in these circuits (Drevets et al. 1992). Compatible with this hypothesis, postmortem studies of the NMDA receptor complex and other elements of the glutamatergic synapse in suicide victims show changes in synaptic gene expression and sensitivity that putatively reflect compensatory responses to abnormally elevated excitatory signaling in depression; these data implicate disturbances in glutamate metabolism, NMDA, and mGluR1,5 receptors in depression and suicide and suggest that glutamatergic transmission is increased in the PFC antemortem (Paul and Skolnick 2003; Duric et al. 2013). Furthermore, increased levels of glutamate have been found in postmortem tissue of the frontal cortex of individuals with MDD or BD (Hashimoto et al. 2007).

Additional postmortem data suggest that the impairment in glutamate transport results in excessive or dysregulated glutamate receptor signaling. Glutamate reuptake is critical for regulating glutamate concentrations in the synaptic cleft and maintaining normal synaptic activity. Evidence for impaired glutamate reuptake in mood disorders has been obtained in postmortem studies of mood disorders by

direct measures of reduced glutamate transport by astroglia (Chandley et al. 2013; Rajkowska and Stockmeier 2013), reduced expression of glial excitatory amino acid transporters 1 and 2 (EAAT1 and EAAT2), and reductions in cell counts, density, and gene expression of the astrocyte and perineuronal oligodendroglia that express EAATs and glutamine synthetase (Miguel-Hidalgo et al. 2010; Kim and Webster 2010; Pitt et al. 2003). Microarray analysis of anterior cingulate and dorsolateral PFC (BA9, 46) tissue obtained from MDD patients postmortem demonstrated concomitant downregulation of EAAT1 (SLC1A3) and EAAT2 (SLC1A2) along with decreased expression of glutamine synthetase (L-glutamate–ammonia ligase), the enzyme that converts glutamate to glutamine (Choudary et al. 2005). The mechanisms that may potentially impair EAAT function in patients with mood disorders include glial cell dysfunction and loss, which some evidence suggests may arise secondary to the elevated release of glucocorticoid hormones and proinflammatory cytokines extant in subgroups of patients with mood disorders (Pitt et al. 2003; Boehmer et al. 2006; Boycott et al. 2008).

Notably, the astrocyte-based glutamate transporter GLT-1 (aka. EAAT-2) is thought to be responsible for nearly 90 % of glutamate uptake in the brain, and the importance of this and other glial-based glutamate transporters in the development of depressive behaviors is supported by preclinical models. In rodents, the local infusion of the astrocyte-specific toxin L-alpha-aminoadipic acid into the medial PFC induced depression-like behaviors (in contrast, infusion of ibotenic acid, a neuronal toxin, had no effect in this model) and pharmacological blockade of astrocytic glutamate uptake by dihydrokainic acid, an EAAT2 (GLT-1) inhibitor, induced anhedonia-like behavior (Banasr and Duman 2008). Moreover, Banasr and colleagues showed that chronic stress impairs cortical glial function in rodents in association with depression-like behaviors and impaired glutamate metabolism and that the cellular, metabolic, and behavioral alterations induced by chronic unpredictable stress were reversed and/or prevented by chronic administration of riluzole, which increases the expression of the astrocyte-based glutamate transporter GLT-1 (aka. EAAT-2) (Banasr et al. 2010). Riluzole also reversed depressive-like symptoms induced by chronic stress and in the olfactory bulbectomy model (reviewed in Pilc et al. (2013)).

Reverberatory glutamatergic transmission may also be a downstream effect of circuits being released from inhibition. For example, mRNA expression of parvalbumin (PV), a putative marker for a subset of GABA neurons that powerfully inhibits pyramidal cells via innervation at the cell soma and axon initial segment (Markram et al. 2004; Lewis et al. 2012), was reduced in postmortem samples of DLPFC from individuals with BD (Sibille et al. 2011). This study suggests that GABA neurotransmission in at least a subset of local circuit neurons is attenuated; however, the functional implications are not well understood. In addition to disinhibition of pyramidal neurons, other studies found that PV-containing interneurons are critical for generating gamma oscillations (Gonzalez-Burgos et al. 2015; Gonzalez-Burgos and Lewis 2008), which are implicated in normal cortical function (e.g., working memory (Yamamoto et al. 2014)). Interestingly, expression of mRNA for neuronal activity-regulated pentraxin (NARP), a protein that is secreted

at presynaptic glutamate synapses that terminate on PV-containing interneurons, is reduced in the DLPFC of subjects with BD (Kimoto et al. 2015), suggesting that excitatory drive onto this interneuron subclass is disrupted; this, in turn, could lead to a disruption of gamma oscillations and associated cortical function.

Such a pathophysiological process may contribute to reverberatory excitatory transmission, which in the presence of the diminished excitatory amino acid transporter function and expression found in MDD and BD postmortem, may conceivably result in glutamate-induced excitotoxicity. Such a mechanism could account for the GM loss and accompanying histopathological changes in mood disorders, such as losses of neuropil (Stockmeier et al. 2004) and glial cells (Ongur et al. 1998). Chronic activation of AMPA receptors is neurotoxic and could be related to the reduced volume of the hippocampus and medial PFC that appears early in the course of depression but then becomes more prominent over the course of chronic or recurrent depressive episodes (Price and Drevets 2012; Stockmeier et al. 2004). Clinical correlations with these MRI data indicate that GM reductions are associated with disease recurrence and chronicity. The findings of reduced GM volume in association with impaired glutamate transport, dendritic atrophy, synapse loss, and cellular loss (especially of glia and interneurons) have led to hypotheses that dysregulation of glutamatergic signaling results in reverberatory activity in limbic-thalamo-cortical circuits implicated in mood disorders (Price and Drevets 2012).

The in vivo MRS literature highlights intriguing differences between MDD and BD within the glutamatergic system. The results of proton MRS studies have largely shown a decrease in Glx (which is constituted predominantly by the intracellular components of glutamate and glutamine), particularly within the medial PFC and DLPFC in depressed patients with MDD, but an increase in the Glx signal in BD (Yuksel and Ongur 2010; Taylor et al. 2009; Hasler et al. 2007). In addition, the MRS data differentiate depression from mania based on the ratio of glutamine to glutamate, which is abnormally reduced in studies of depression (both MDD and BD) but elevated in mania. These patterns suggest that the glutamate-related metabolite pool (only part of which is relevant to neurotransmission) is constricted in MDD and expanded in BD, but that depressive and manic episodes may be characterized by modulation of the glutamine/glutamate ratio in opposite directions, possibly suggesting reduced versus elevated glutamate conversion to glutamine by glial cells, respectively (Yuksel and Ongur 2010). Finally, studies showing that MRS measures of GABA are abnormally decreased in MDD suggest a decrease in GABAergic signaling (Sanacora et al. 1999; Hasler et al. 2007).

8.4.4.1 Antidepressant and Mood Stabilizing Drug Effects on Glutamatergic Transmission

In mood disorders, several experimental and conventional treatments may exert their clinical effects via mechanisms that depend on altering glutamatergic transmission. As described above, riluzole, which increases the expression of the

astrocyte-based glutamate transporter GLT-1 (EAAT-2), appeared effective as adjunctive and monotherapy for treatment-resistant depression and as adjunctive therapy for bipolar depression, mainly in open-label studies (Zarate et al. 2004; Yuksel and Ongur 2010). In addition, lamotrigine is an anticonvulsant that reduces glutamate release via sodium, calcium, and potassium channel modulation and has shown efficacy as a mood stabilizer in BD, especially for prevention of depressive episodes and as adjunctive therapy for both BD and MDD (Yuksel and Ongur 2010). Notably, a single, subanesthetic dose infusion of ketamine has been shown to have rapid and potent antidepressant effects in treatment-resistant MDD and BD patients (Lee et al. 2015; Ionescu et al. 2015; McGirr et al. 2015; Zarate et al. 2012). Further, 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 (Krystal et al. 2002; Paul and Skolnick 2003). For example, chronic treatment with some conventional antidepressant drugs reduces both glutamate release in the rat brain and NMDA receptor subunit expression in depressed humans (Bonanno et al. 2005; Golembiowska and Dziubina 2000; Paul and Skolnick 2003), suggesting that a persistent effect that modulates dysregulation of glutamate release can maintain antidepressant effects. Compatible with these data, during effective antidepressant drug or electroconvulsive therapy, glucose metabolic activity decreases in the regions of the extended visceromotor network (Table 8.1; (Drevets et al. 2002b, 2004)), which would be expected if treatment-induced NMDA receptor desensitization modulated glutamatergic transmission (Paul and Skolnick 2003). As described in the ensuing sections, elevated glutamatergic transmission within discrete anatomical circuits may partly explain the targeted nature of GM changes within mood disorders (e.g., affecting left more than right sgACC) (McEwen and Magarinos 2001; Drevets and Price 2005), so one important mechanism of effective treatment in bipolar depression may involve modulation of excessive excitatory transmission (McEwen and Magarinos 2001).

In contrast, preclinical data suggest that the mechanism underlying the antidepressant effect of acute administration of ketamine and some other NMDA receptor antagonists, which persist for at least several days beyond the clearance of the drug from the plasma in some BD and MDD patients, instead may depend on a transient disinhibition of glutamate release that stimulates a persistent effect on synaptic plasticity. Duman and colleagues found that a single administration of ketamine can reverse the loss of synapses and synaptic function induced by repeated stress by inducing synaptogenesis in the medial PFC (Abdallah et al. 2015). Conceivably, ketamine's antidepressant effect in MDD and BD may reflect such an effect on synaptic plasticity that addresses the histopathological changes in mood disorders, but that may be initiated and potentially maintained by acute administration followed by pulsed, as opposed to chronic, treatment.

8.5 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, GABAergic, glucocorticoid, and peptidergic (e.g., corticotrophin releasing factor, CRF) functions. Some receptors of the monoaminergic neurotransmitter systems have been imaged in BD using PET or SPECT.

8.5.1 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 because some other antidepressant drug classes also increase postsynaptic 5-HT_{1A} receptor transmission (Drevets et al. 2007). This effect of antidepressant drugs may augment endogenous serotonin release during the stress of depression, analogous to the enhanced serotonergic transmission that occurs in some brain regions during stress in rodents (Cannon et al. 2007; Barton et al. 2008). Enhancement of serotonin transmission in MDD also may compensate for abnormalities in density and sensitivity of some serotonin receptor subtypes evidenced by postmortem, neuroimaging, and pharmacological challenge studies of depression (Stockmeier 2003; Drevets et al. 2007). For example, postsynaptic 5-HT_{1A} receptor binding or mRNA expression is decreased in the insula, hippocampus, cingulate, parieto-occipital, and orbital/ventrolateral prefrontal cortices in some neuroimaging studies of MDD and BD (Drevets et al. 2007; Bhagwagar et al. 2004; Sargent et al. 2000; Hirvonen et al. 2008). Of note is our group's recent replication of our previous findings using a slightly different methodology. Specifically, we found that mean 5-HT_{1A} receptor binding potential (measured by BP_P as well as BP_{ND}) was significantly lower in BD subjects compared to controls in cortical regions where 5-HT_{1A} receptors are expressed postsynaptically, most prominently in the mesiotemporal cortex (Nugent et al. 2013). Further, BP_P in the mesiotemporal cortex was inversely correlated with trough plasma cortisol levels, consistent with preclinical literature indicating that hippocampal 5-HT_{1A} receptor expression is inhibited by glucocorticoid receptor stimulation (Nugent et al. 2013).

These data receive support from a PET study of previously healthy subjects exposed to a severe recent stressor. Compared with nonstressed subjects, stressed subjects displayed reduced binding in the ACC, insula, and hippocampus, with a trend toward significance in the amygdala, DLPFC, parietal cortex, temporal cortex, and raphe (Jovanovic et al. 2011). In addition, a reduction in 5-HT_{1A} receptor distribution volume (V_T) was found in the raphe nuclei, amygdala, hippocampus, and ACC in a PET study of subordinate cynomolgus monkeys who showed behavioral signs of depression after exposure to social defeat (Shively et al. 2006).

In postmortem studies, 5-HT_{1A} receptor binding was increased in the rostral, ventrolateral, and dorsal subnuclei of the raphe but decreased in the caudal subnucleus of the raphe (Boldrini et al. 2008; Stockmeier et al. 1998).

Although the interruption of 5-HT_{1A} receptor function during neurodevelopment has been shown to persistently alter the function of emotion-modulating systems in genetically engineered mice (Gross et al. 2002), the reduction in postsynaptic 5-HT_{1A} receptor binding and mRNA expression in mood disorders may arise secondary to cortisol hypersecretion (Lopez et al. 1998). 5-HT_{1A} receptor mRNA expression and density are tonically inhibited by glucocorticoid receptor stimulation. In experimental animals, elevated CORT secretion during chronic or repeated stress resulted in reduced 5-HT_{1A} receptor density and mRNA expression (Lopez et al. 1998; Flugge 1995). Thus, the mood disordered subgroups with reduced postsynaptic 5-HT_{1A} receptor binding may be limited to those with a diathesis to hypersecrete cortisol (e.g., Lopez et al. (1998), Drevets et al. (1999, 2007)).

Altered serotonin transporter (5-HTT) function is also thought to play a role in the pathophysiology of mood disorders (Cannon et al. 2006b; Stockmeier 2003). For example, depressed BD subjects showed elevated 5-HTT binding in the striatum, thalamus, and insula, as well as reduced binding in the vicinity of the pontine raphe (Cannon et al. 2006b, 2007) (Fig. 8.2). PET studies performed using 5-HTT radioligands with high selectivity for 5-HTT sites, such as [^{11}C]DASB, similarly

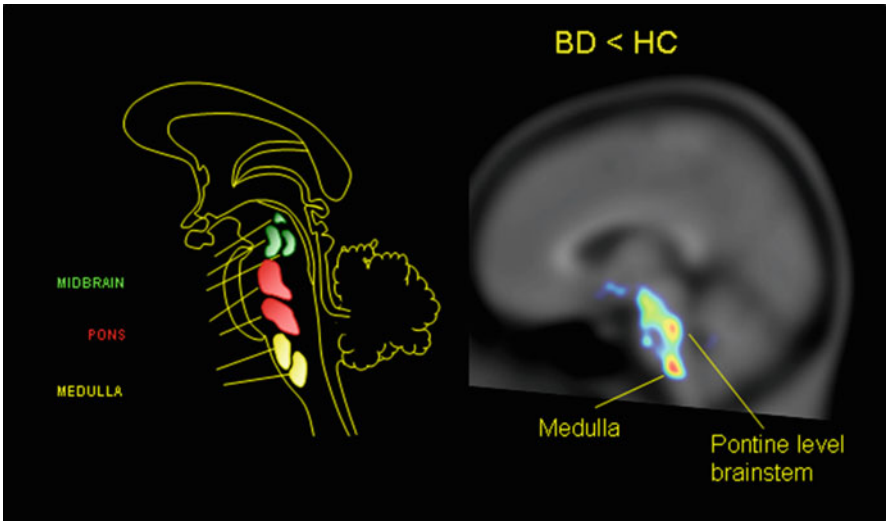

Fig. 8.2 Serotonin transporter binding is reduced in bipolar depression. This section from a voxel-wise analysis of [^{11}C]DASB parametric binding potential images shows regions where individuals with bipolar disorder (BD) have reduced serotonin transporter (5-HTT) binding relative to controls at $p < 0.05$ (*right panel*), together with a schematic illustration showing approximate locations of the raphe nuclei within the brainstem (*left panel*; after Carpenter and Sutin (1983)). Reproduced with permission from Cannon et al. (2006b)

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 5-HTT binding in the pontine raphe found in individuals with bipolar depression did not extend to MDD cases (Cannon et al. 2007). Nevertheless, although another study found no difference in 5-HTT binding between MDD patients and healthy controls, scores on the Dysfunctional Attitude Scale were correlated positively with 5-HTT binding in the PFC, ACC, putamen, and thalamus (Meyer et al. 2004). The possible increase in 5-HTT binding in BD is also consistent with increases in 5-HTT binding in the DLPFC, amygdala, hypothalamus, raphe, and posterior cingulate cortex in clinically depressed patients with Parkinson's disease (PD) (Politis et al. 2010; Boileau et al. 2008).

8.5.2 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 reported that binding of [^{11}C]SCH-23990 was decreased in the frontal cortex of BD subjects studied in various illness phases, a finding that awaits replication using more selective D_1 receptor ligands (Suhara et al. 1992). [^{11}C]SCH-23390 displays poor specificity, which potentially compromises the reliability of the D_1 receptor measurement in extrastriatal areas such as the frontal cortex, where the density of these receptors is significantly lower than in the striatum. In a postmortem study, the percentage of D1-expressing neurons together with D1 mRNA expression was reported to be increased by 25 % in the CA3 region of the hippocampus (Pantazopoulos et al. 2004) in BD subjects versus controls, but did not differ from controls in the amygdala of MDD subjects (Xiang et al. 2008).

Pearlson and colleagues showed that *psychotic* individuals with BD had increased striatal uptake of the dopamine D2/D3 receptor ligand, [^{11}C]-*N*-methylspiperone, relative to healthy controls and nonpsychotic individuals with BD but that the nonpsychotic BD cases did not differ from healthy controls (Pearlson et al. 1995). In contrast, no difference in the binding of the more selective ligand, [^{11}C]raclopride, was found between manic patients with BD and healthy controls (Yatham et al. 2002). Similarly, a SPECT-[^{123}I]IBZM study found no difference in striatal dopamine D2/D3 receptor binding at baseline, and no difference in change in [^{123}I]IBZM binding under amphetamine challenge between medicated, euthymic BD patients and healthy controls (Anand et al. 2000). It is unclear if D2 receptor binding differs in subjects with MDD compared to BD. Unmedicated MDD patients with motor retardation displayed increased binding in the caudate and striatum compared with healthy controls (Meyer et al. 2006).

Regarding the dopamine transporter, DAT, decreased binding was reported in the caudate, but not the putamen of BD patients relative to healthy controls (Anand et al. 2011), raising the possibility that abnormalities of dopamine reuptake constitute a risk factor for the development of BD.

8.5.3 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 hyperresponsive in depression. Janowsky and colleagues (1994) reported that increasing cholinergic activity using the acetylcholinesterase inhibitor, physostigmine, resulted in the rapid induction of depressive symptoms in currently manic BD subjects and in a worsening of symptoms in individuals with MDD. The administration of the M_2R antagonist, procaine, elicited emotional responses in humans ranging from sadness, fear, and severe anxiety to euphoria and increased the physiological activity of the cingulate cortex (Benson et al. 2004; Ketter et al. 1996), a region densely innervated by cholinergic projections. In individuals with bipolar depression, decreased M_2R binding has been reported in the cingulate cortex (Cannon et al. 2006a) (Fig. 8.3). This finding appeared attributable to an interaction involving genetic variation in the cholinergic-muscarinic type 2 (M2) receptor gene (CHRM2). A differential impact of the M2-receptor polymorphism at rs324650 on the V_T of the M2 receptor was evident in individuals with BD versus healthy controls, such that the BD subjects homozygous for the T-allele showed markedly lower V_T (by 27–37 % across regions) than healthy controls of the same genotype (Cannon et al. 2011). Post hoc analyses suggested that within the BD sample, T homozygosity was associated with a more severe illness course. Multiple M_2R gene polymorphisms have been associated with increased risk for developing major depressive episodes (Cannon et al. 2011), but thus far, these single nucleotide polymorphisms (SNPs) have not been associated with BD. Finally, the muscarinic cholinergic receptor antagonist, scopolamine, exerts rapid and robust antidepressant effects in depressed MDD and BD patients, although the ~24 hour delay in onset of these effects raises the possibility that a secondary mechanism of action underlies the antidepressant response (Furey and Drevets 2006). Preclinical evidence suggests that this antidepressant effect depends on the induction of synaptic plasticity changes analogous to those induced by ketamine administration (Duman 2014).

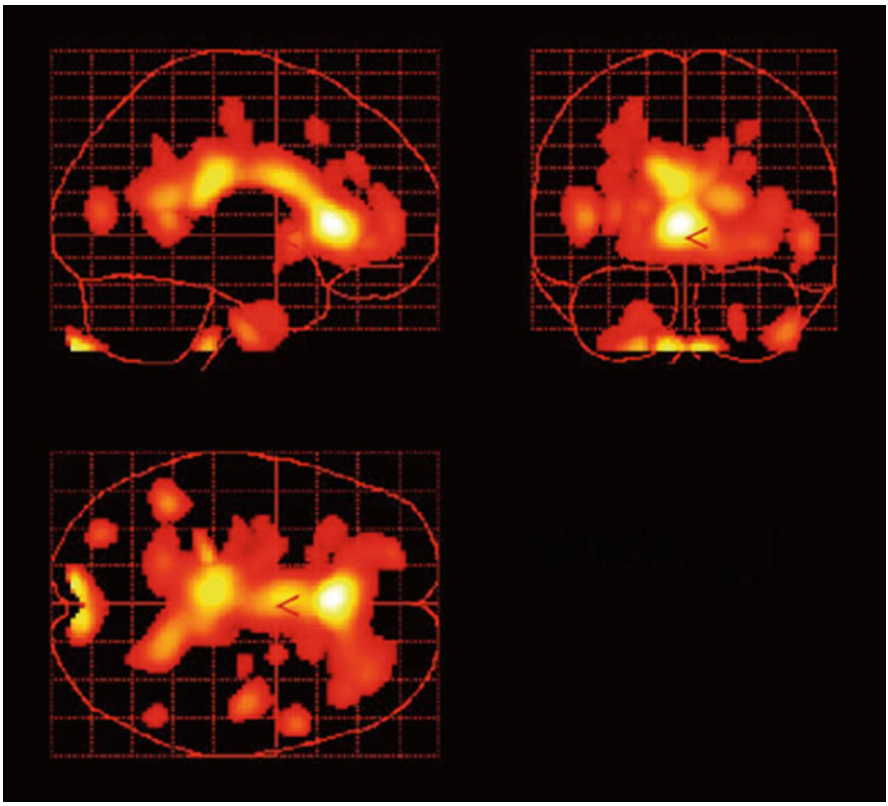

Fig. 8.3 Reduced muscarinic type 2 (M2) receptor binding in the cingulate cortex in individuals with bipolar depression relative to healthy controls. The statistical parametric map shows voxel *t*-values corresponding to areas where the uptake of [^{18}F]FP-TZTP, a PET radioligand that selectively binds 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 Cannon et al. (2006a)

8.6 Implications for Neurocircuitry Models of Depression

Taken together, the neuropathological, neurochemical, and neurophysiological abnormalities extant within the extended visceromotor network may impair this network's modulation of autonomic, endocrine, immune, neurotransmitter, emotional, and cognitive responses to aversive and reward-related stimuli or contexts (Ongur et al. 2003), potentially accounting for the disturbances within these domains seen in BD (Fig. 8.4). The neuroimaging abnormalities in the VLPFC, OFC, sgACC, pgACC, amygdala, ventral striatum, and medial thalamus evident in BD 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

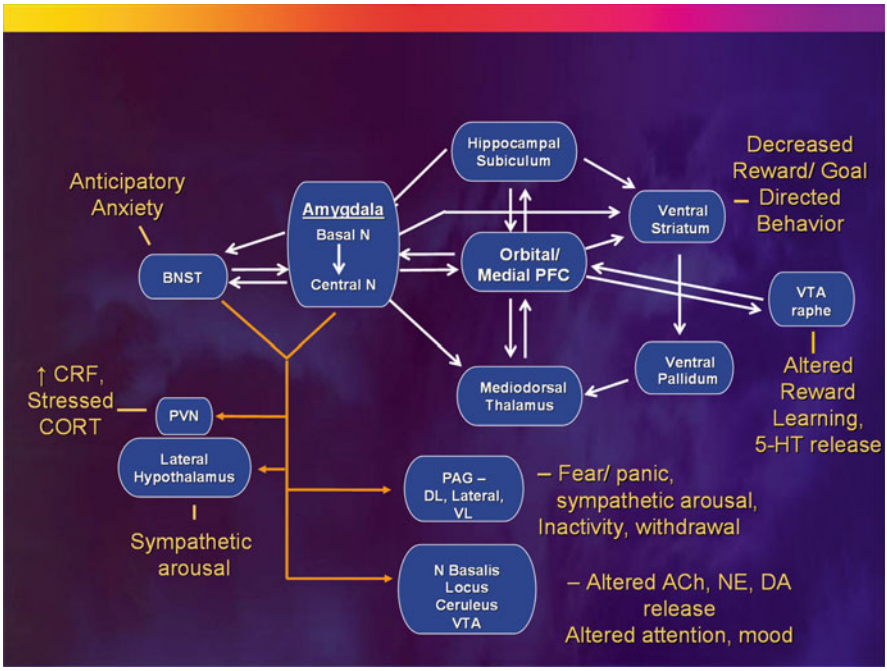

Fig. 8.4 Anatomical circuits involving the orbitomedial PFC (OMPFC) and amygdala reviewed within the context of a model in which OMPFC dysfunction results in disinhibition of limbic transmission through the amygdala, yielding the emotional, cognitive, endocrine, autonomic, and neurochemical manifestations 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 gray (PAG), nucleus basalis, locus coeruleus, raphe, and other diencephalic and brainstem nuclei then organize the neuroendocrine, neurotransmitter, autonomic, and behavioral responses to stressors and emotional stimuli (Davis and Shi 1999; LeDoux 2003). 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 (Ongur et al. 2003). Impaired OMPFC function may thus 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., Herman and Cullinan (1997)). 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 Drevets (2007)

pallidum along with the components of the other circuit (Drevets et al. 1992). The first of these circuits can be conceptualized as an excitatory triangular circuit (Fig. 8.4), whereby the BLA and the OMPFC are interconnected by excitatory (especially glutamatergic) projections with each other and with the MD (Drevets and Price 2005), so increased glucose metabolism in these structures would

presumably reflect increased synaptic transmission through the limbic-thalamocortical circuit.

The basolateral nuclei of the amygdala send 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 diencephalic and brainstem nuclei play major roles in organizing neuroendocrine, neurotransmitter, autonomic, and behavioral responses to stressors and emotional stimuli (Davis and Shi 1999; LeDoux 2003). The OMPFC sends overlapping projections to each of these structures and to the amygdala that function to modulate each component of emotional expression (Price and Drevets 2010). The neuropathological changes evident in the OMPFC in BD and mood disorders arising secondary to neurological disorders may thus impair the modulatory role of the OMPFC over emotional expression, disinhibiting or dysregulating limbic responses to stressors and to social and emotional stimuli (Drevets and Price 2005; Price and Drevets 2012). These data suggest that during depressive episodes, the increased activity seen within some OMPFC areas reflects a compensatory response that modulates depressive symptoms and that impaired function of these emotion regulatory regions (possibly due to the neuropathological changes in BD) may result in more severe and treatment-refractory illness (Phillips et al. 2008).

8.7 Summary

Convergent results from studies conducted using neuroimaging, lesion analysis, and postmortem techniques support models in which the clinical phenomenology of BD emanates from dysfunction affecting the extended medial prefrontal network that interferes with this system's modulation of visceromotor and emotional behavior (Savitz et al. 2014b). At a molecular level, these abnormalities may be partly driven by a dysregulation of glutamatergic neurotransmission that in turn may ultimately be related to inflammatory processes. Mood stabilizing and antidepressant therapies may compensate for this dysfunction by attenuating pathological excitatory transmission in cortico-limbic circuits (Drevets et al. 2002a) and increasing expression of neurotrophic/neuroprotective factors that preserve the structure and function of the OMPFC (Manji et al. 2001).

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