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Review

Bipolar and major depressive disorder: Neuroimaging the developmental-degenerative divide

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ABSTRACT

Both major depressive disorder and bipolar disorder are the subject of a voluminous imaging and genetics literature. Here, we attempt a comprehensive review of MRI and metabolic PET studies conducted to date on these two disorders, and interpret our findings from the perspective of developmental and degenerative models of illness. Elevated activity and volume loss of the hippocampus, orbital and ventral prefrontal cortex are recurrent themes in the literature. In contrast, dorsal aspects of the PFC tend to display hypometabolism. Ventriculomegaly and white matter hyperintensities are intimately associated with depression in elderly populations and likely have a vascular origin. Important confounding influences are medication, phenotypic and genetic heterogeneity, and technological limitations. We suggest that environmental stress and genetic risk variants interact with each other in a complex manner to alter neural circuitry and precipitate illness. Imaging genetic approaches hold out promise for advancing our understanding of affective illness.

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1. Background

Depression is arguably the epidemic of our time. The lifetime prevalence of major depressive disorder (MDD) ranges from 10 to 30% (Kessler et al., 2003) and depression arising within the context of bipolar disorder (BD) has equally serious implications for morbidity and mortality (Pini et al., 2005).

Understanding the etiological and pathophysiological basis of affective illness is clearly an international imperative. Current nosological systems are based on symptomatology rather than etiology, and robust biological correlates of depression have not been identified. The identification of biomarkers of depression is crucial not only in the ascent towards etiological understanding, but also in evaluating the efficacy of treatment interventions.

While the limited resolution of previous generation neuroimaging paradigms blunted the sensitivity and specificity of preceding investigations; with the advent of new technology, glints of understanding are beginning to emerge. Neuroimaging data implicate a key emotion-regulating circuit, the visceromotor network, encompassing the medial prefrontal cortex (mPFC) and its reciprocal connections to the amygdala, hippocampus, ventral striatum, hypothalamus and brain-stem in the pathophysiology of both MDD and BD (Ongur and Price, 2000).

More specifically, regions of orbitofrontal cortex (OFC) and the mPFC have shown MRI and post-mortem-derived evidence of tissue loss. Parallel metabolic and volumetric changes to the limbic components of the visceromotor network such as the amygdala, hippocampus and ventral striatum have been widely recorded, although the data are often conflicting. Unfortunately, diminutive structures such as the habenula and periaqueductal gray (PAG), which play a prominent role in emotional behavior, remain largely unstudied because of technological limitations.

Here we review the biological correlates of MDD and BD as evinced by neuroimaging paradigms, and interpret these data from the perspective of neurodevelopmental and neurodegenerative pathoetiology. We attempt to integrate the conclusions drawn from the literature into a heuristic framework which characterizes affective illness as the consequence of a loss of top–down control (especially mPFC) over limbic structures such as the amygdala; or alternatively, the consequence of disinhibited limbic drive which overrides cortical regulation (Fig. 1).

2. Methodology

A literature search of the PUBMED database up until September 2007 was carried out using the following keywords: depression, bipolar disorder, neuroimaging, MRI, PET, fMRI, amygdala, hippocampus, basal ganglia, caudate, prefrontal cortex, orbital frontal cortex, dorsolateral prefrontal cortex, anterior cingulate, subgenual prefrontal cortex, white matter, and ventricle. Furthermore, review articles were searched, and other publications cross-referenced for additional published articles. Our inclusion criteria were heavily biased towards analyses of resting state metabolism rather than responses to cognitive, emotional or biochemical challenges. Thus, although we highlight the result of certain fMRI studies (primarily in Section 4), we make no attempt to cover the substantial, but as yet inchoate, functional magnetic resonance imaging (fMRI) and magnetic resonance spectroscopy (MRS) literature comprehensively. Positron emission tomography

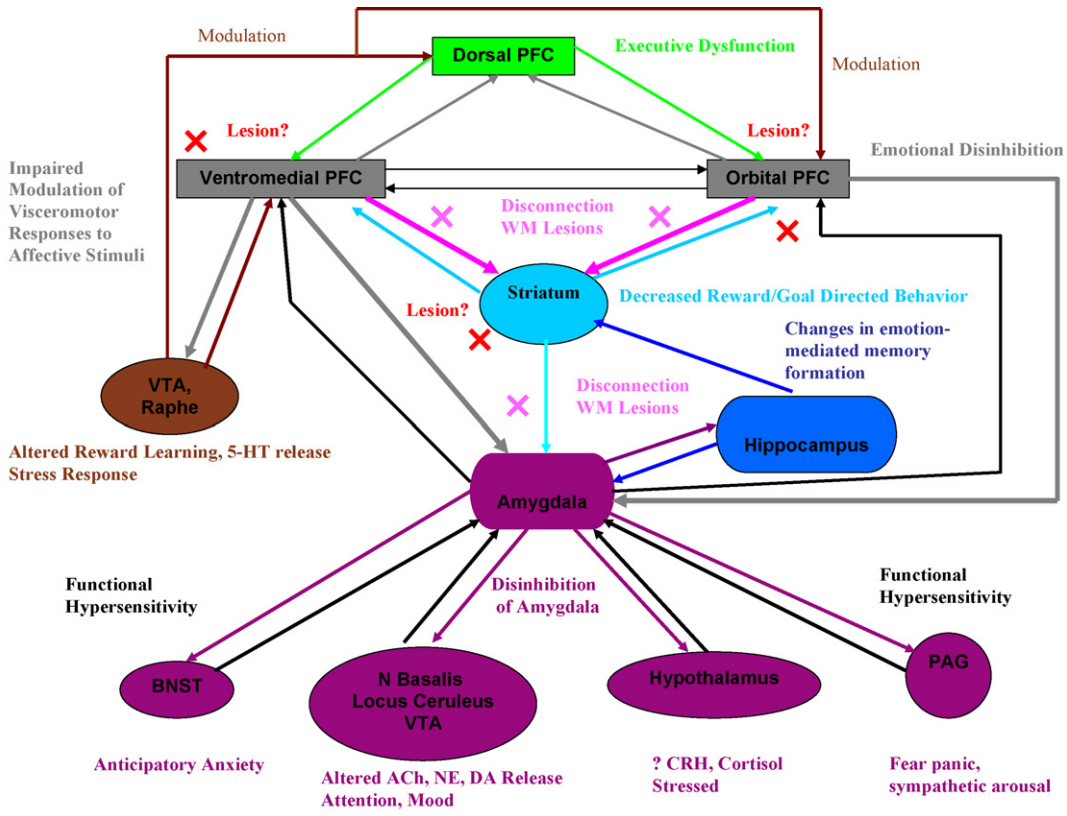

Fig. 1. Amygdala-centric model of potential pathophysiological changes in BD and MDD. Lesions (red crosses) to the ventromedial, orbital PFC or basal ganglia may abrogate top-down control over the amygdala and deeper limbic structures (gray and purple lines). A similar PFC-limbic disconnection effect may result from white matter pathology (pink crosses). Alternatively, functional hypersensitivity of deeper limbic structures and/or the amygdala may disrupt prefrontal emotional regulation (black lines). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

(PET) neuroreceptor studies are also beyond the scope of this review.

Further, the following exclusion criteria obtained: papers that were not written in English, book chapters, conference abstracts, and case studies were not reviewed. Computerised tomography (CT) and single photon emission tomography (SPECT) studies were omitted. CT has a significantly lower tissue contrast and spatial resolution than MRI, and is also subject to bony artifacts in brain structures situated near the skull. SPECT has reduced sensitivity for detecting areas of increased perfusion due to its reliance on radioligands that are not freely diffusible across the blood–brain barrier. Analyses of gross neuroanatomical structures such as the entire frontal or temporal cortices were generally not discussed.

Extensive inter-connecting neural networks are involved in the generation and regulation of affect. These networks can be at least partly subsumed under the iterative activity of three cortical–striatal–limbic circuits encompassing a dorsolateral/dorsomedial prefrontal circuit, an orbital prefrontal circuit, and a ventromedial prefrontal circuit, including the anterior cingulate cortex (ACC) (Tekin and Cummings, 2002; Drevets, 2001; Price, 1999). These circuits operate in parallel with prefrontal cortex-originating bidirectional projections to different nuclei of the perirhinal and entorhinal cortices, striatum, pallidum, thalamus, amygdala, hippocampus, hypothalamus, habenula, and periaqueductal gray (Tekin and Cummings, 2002; Price, 1999).

Nevertheless, the limitations of current neuroimaging modalities make it unfeasible to reliably discriminate between individual nuclei within these structures. The amygdala, for example, is a heterogeneous structure of at least 14 different nuclei (Bachevalier and Loveland, 2006). We will therefore discuss imaging studies of the amygdala, hippocampus, and striatum, separately, rather than placing them under the rubric of the dorsal prefrontal, orbital frontal, and ventromedial cortical–striatal–limbic circuits described above.

3. Results

3.1. The Amygdala

Despite its apparent heterogeneity of function, a degree of consensus that the amygdala plays a pivotal role in evaluating the emotional significance of perceptual data has been reached (Phillips et al., 2003). In coloring perceptual stimuli with emotion, however, the amygdala appears to emphasize the hues of fear, anger and sadness (Gloor et al., 1982; Davidson, 2002), providing *prima facie* evidence for its involvement in depression.

3.1.1. BD

Neuroimaging studies of the amygdala in patients with BD (Tables 1 and 2) are characterized by an interesting age-related dichotomy of findings. In adults, the predominant pattern is one of increased amygdala volume while in children and adolescents the reverse applies (Table 1). The findings in adults seem to hold even in samples with a long history of illness (Altshuler et al., 2000; Brambilla et al., 2003a; Frangou, 2005).

Resting state functional analyses have been largely limited to the adult population (Table 2) and are indicative of increased baseline amygdalar activity (Ketter et al., 2001; Sheline et al., 2001; Drevets et al., 2002b; Bauer et al., 2005; Mah et al., 2007) which correlates positively with severity of depression (Drevets et al., 1992; Ketter et al., 2001).

Table 1
Morphometric studies of the amygdala in bipolar disorder.

Study	Sample	Age	Method	Age of onset	Duration of illness/# episodes	Family history of illness	Clinical status at testing	Medication status	Comorbidity	Findings
Pearlson et al. (1996)	27 BD 60 HC	34.9 ± 8.6 31.6 ± 8	1.5 T 3 mm ROI	NR	NR	NR	NR	NR	No substance abuse, other axis I conditions	L amygdala volume decreased in BD
Altshuler et al. (1998)	12 BD 18 HC	50.8 ± 13.3 53.4 ± 11.1	1.5 T 1.4 mm ROI	NR	NR	NR	Remitted	NR	No other axis I disorders	Bilateral enlargement of the amygdalae in BD
Strakowski et al. (1999)	24 BD 22 HC	27 ± 6 28 ± 6	MRI 1.5 T 1 mm ROI	NR	6 ± 6	NR	14 manic, 10 mixed episode	MS + AP	No substance abuse for 3+ months	Enlarged amygdala in BD
Altshuler et al. (2000)	24 BD 18 HC	50.2 ± 12.7 53.4 ± 11.1	1.5 T 1.5 mm ROI	26.6 ± 10.4	23.6 ± 11.4	NR	Euthymic	AP, AD + MS	No substance dependence, alcohol abuse for 9+ months	Enlarged amygdala in BD
Brambilla et al. (2003a)	24 BD 36 HC	35 ± 10 37 ± 10	1.5 T 1.5 mm ROI	19 ± 7	15 ± 9	11 with family history, 13 without	13 euthymic, 10 depressed, 1 hypomanic	15 patients on lithium. 9 not medicated	No co-morbid conditions, including substance abuse	Enlarged L amygdala in BD
Blumberg et al. (2003a)	36 BD I 56 HC	31 ± 14.1 28.3 ± 13.7	1.5 T 1.2 mm ROI	Adults: 17.4 ± 8 Adolescents: 13.1 ± 9.5	NR	Yes	Adults: 32% manic, 23% depressed. Adolescents symptomatic	±33% of adults + half of adolescents medication free. Balance on MS, AD + AP	±33% of BD cohort with substance dependence. Adolescent BD with ADHD, ODD, PTSD, PD	Reduced BL amygdala volume in adolescents + adults with BD
Chen et al. (2004)	16 BD (12 BD I, 3 BD II, 1 BD NOS) 21 HC	16 ± 3 17 ± 4	1.5 T 1.5 mm ROI	NR	NR	Yes	14 euthymic, 2 mildly depresses	MS	5 ADHD, 1 CD, 1 ODD	Trend for decreased L amygdala volume in BD. Patients with co-morbid diagnosis had smaller L amygdala than non-comorbid subjects
DelBello et al. (2004)	23 BD 20 HC	16 ± 2 17 ± 2	1.5 T 1.5 mm ROI	14 ± 3	2.4 ± 2.1	NR	Mixed or manic episode	20 subjects on MS, 11 on AP. Minority on AD or stimulants	No substance abuse in last 3 months. 10 subjects with ADHD. No head trauma or medical or neurological condition	Decreased amygdala volume in BD
Lyoo et al. (2004a)	39 BD I 43 HC	38.3 ± 11.6 35.7 ± 10.1	1.5 T 1.5 mm VBM	18.6 ± 7.0	18.1 ± 11.0 10.5 ± 9.2 (manic episodes) 13.5 ± 7.2 (depressive)	NR	22 depressed, 17 hypomanic/ manic	±50% on medication including lithium + MS	No substance abuse in last 3 months, other axis I diagnosis, no antisocial PD, ADHD	No difference in amygdala volume
Blumberg et al. (2005b)	10 BD 8 HC	15.0 ± 4.0 15.3 ± 2.8	1.5 T 1.2 mm ROI	NR	2.5 ± 0.4	Yes	Both depressed + manic	Half of subjects on medication at first scan and 30% on medication at second scan. AP, MS, stimulants	1 ADHD, 2 LD, 1 social phobia, 1 ODD, 1 substance abuse	Reduced amygdala volume in BD at both scans 1 and 2 (2-year interval). No longitudinal changes
Chang et al. (2005b)	20 BD 20 HC	14.6 ± 2.8 14.1 ± 2.8	3 T 1.5 mm ROI	NR	NR	Yes	Depressed + hypomanic	Patients on medication (MS, AD + AP) except stimulants which were discontinued 24 h prior to scan	No pervasive developmental disorders, substance abuse. 16 ADHD, 7 anxiety disorder, 11 ODD	Reduced BL amygdala volume in BD. Subjects with past lithium or valproate exposure had greater amygdala volumes

Dickstein et al. (2005)	20 BD 20 HC	13.4 ± 2.5 13.3 ± 2.3	1.5 T 1.2 mm VBM	10.1 ± 3.2	NR	NR	Euthymic	AP, MS, AD	ADHD, psychosis, anxiety	Volume reduction of L amygdala in BD. 24; 5; −15
(Frangou, 2005)	43 BD 43 HC	42.9 ± 11	1.5 T 1.5 mm VBM	25.5 ± 9.2	16.0 ± 19.0	Mixed	Remitted	MS + AP	NR	BL enlargement of amygdala in BD
Rosso et al. (2007)	20 psychotic BD 23 HC	23 ± 3 25 ± 3	1.5 T 3 mm ROI	6 patients with family history.	1st episode	23 ± 3	14 manic, 4 mixed, 2 depressed	40% lithium, 65% AP, 25% MS, 10% AD	No substance abuse	Reduction in amygdala volume. More pronounced in RH and patients with a family history of illness
Velakoulis et al. (2006)	34 affective psychosis 87 HC	22.0 ± 3.1 21.7 ± 4.2 26.9 ± 10	1.5 T 1.5 mm ROI	NR	1st episode	NR	NR	AP	No alcohol abuse, neurological disorders, head injuries	Enlargement of R amygdala in both MDD and BD

AD = antidepressants; ADHD = attention deficit hyperactivity disorder; AP = anti-psychotics; BA = Brodmann's area; BD = bipolar disorder; Benz = benzodiazepines; BL = bilateral; CD = conduct disorder; DM = diabetes mellitus; HC = healthy control; Hosp = hospitalizations; L = left; LD = learning disorder; Lith = lithium; MS = mood stabilizers; NR = not reported; OCD = obsessive compulsive disorder; ODD = oppositional defiant disorder; PD = personality disorder; PDD = pervasive developmental disorder; PTSD = post-traumatic stress disorder; R = right; RH = right hemisphere; ROI = region of interest; TD = tryptophan depletion; MDD = unipolar depression; VBM = voxel-based method. Slice thickness is shown in methodology column. Stereotaxic coordinates are shown as *x*, *y* and *z* axes. For functional scans ^{18}F-FDG = [^{18}F]-fluorodeoxyglucose; ^{15}O-H_2O = ^{15}O-Water.

Table 2
Functional studies of the amygdala in bipolar disorder.

Study	Sample	Age	Method	Age of onset	Duration of illness/# episodes	Family history of illness	Clinical status at testing	Medication status	Comorbidity	Findings	Brodmann map/stereotaxic coordinates
al-Mousawi et al. (1996)	15 manic psychosis 10 depressed (6 psychotic) 10 HC	44.4 ± 11.7 50.5 ± 20.5 40.1 ± 12.4	^{18}F-FDG MRI 0.08 T 12 mm ROI	NR	119.47 months 137 months	NR	Psychotic mania/ depression	Benz, AD, MS + AP	No current substance abuse	Decreased metabolism of L amygdala in manic group	NR
Yurgelun-Todd et al. (2000)	14 BD 10 HC	31.5 NR	fMRI 1.5 T 6 mm ROI	22	NR	NR	Stable out-patients	85% MS 60% lith 92% AP	No neurological disorder, head trauma, current substance abuse 30% with past history of substance abuse	Increased activation of L amygdala in response to fearful but not happy faces in BD	NR
Ketter et al. (2001)	43 BD 43 HC	37.5 ± 10.6 38.1 ± 10.4	^{18}F-FDG	18.8 ± 9.9	18.3 ± 10.4	NR	Depressed, mildly depressed + euthymic	Unmedicated for 2+ weeks	NR	Increased metabolism of R amygdala in depressed BD patients only	NR
Drevets et al. (2002b)	15 BD 12 HC	35 ± 7.4 35 ± 9.8	^{18}F-FDG 3.4 mm MRI 1.5 T ROI	NR	NR	NR	7 depressed, 7 remitted	No medication for 3+ weeks before study in depressed BD group Euthymic patients medicated with MS or AP	No substance abusers	Elevated activity of the L amygdala in depressed BD. Remitted BD patients showed intermediate activity levels	−21; −7; 18

Table 2 (*Continued*)

Study	Sample	Age	Method	Age of onset	Duration of illness/# episodes	Family history of illness	Clinical status at testing	Medication status	Comorbidity	Findings	Brodmann map/stereotaxic coordinates
Lawrence et al. (2004)	12 BD 9 MDD 11 HC	41 ± 11 for full sample	fMRI 1.5 T 7 mm Voxel-wise	NR	15.4 ± 13.4 years (BD) 8 ± 5 (MDD)	NR	Mildly depressed (BD) Significantly depressed (MDD)	BD: 5 AD, 5 AP, 7 MS, 3 lith MDD: 9 AD	No head injury, substance abuse, comorbid conditions	BD patients showed a greater response to fearful and happy, but not sad faces in L amygdala	−25; 10; −18 −15; 6; 16
Lennox et al. (2004)	10 BD 12 HC	37.3 ± 12.8 32.6 ± 10.7	fMRI 3 T Voxel-wise	NR	NR	NR	Manic	8 lith, 7 MS, 3 haloperidol, 4 olanzapine	NR	BD patients had attenuated BL activation of amygdala in response to sad faces	NR
Altshuler et al. (2005a)	9 BD 9HC	34.6 ± 8 30.4 ± 7.6	fMRI 3 T 4 mm (1 mm gap) ROI	NR	14.8 years 4.2 manic episodes	NR	Manic	6 MS, 2 lith, 1 olanzapine	No left-handednesss, hypertension, head trauma	L amygdala overactivated in manic group in response to emotional faces	NR
Bauer et al. (2005)	10 BD I 10 HC	39.3 ± 7.8 35.0 ± 9.3	^{18}F-FDG Voxel-wise	NR	20.4 ± 7.0	NR	Depressed	AD, MS, AP	NR	Activity in R amygdala and hippocampus decreased with levothyroxine treatment	26; −2; −24
Blumberg et al. (2005a)	5 unmedicated BD 12 medicated BD 17 HC	40.0 ± 12.3 45 ± 9.4 33.2 ± 10.8	fMRI 7 mm ROI	NR	NR	NR	Various	8 MS, 4 lith, 3 AD, 1 AP	2 left-handers No comorbidity except 1 person with hypothyroidism	Increased amygdala response to happy faces in unmedicated BD but decreased response in medicated BD	NR
Rich et al. (2006)	22 BD 21 HC	14.2 ± 3.1 14.5 ± 2.5	fMRI 3 T ROI	NR	NR	NR	Half euthymic, half depressed or hypomanic	80% medicated	No pervasive developmental disorder, IQ < 70, unstable medical illness, substance abuse for 2+ months	BD patients rated neutral faces as more hostile + fearful and showed greater activation of the L amygdala	−22; 4; −18
Mah et al. (2007)	13 BD II 18 HC	43.0 ± 8.4 39.0 ± 8.0	^{18}F-FDG 4.25 mm MRI 3 T ROI	20 ± 10.5	22.9 ± 12	NR	Depressed	Lithium only	No substance abuse, psychotic features, rapid-cycling	Increased metabolism of BL amygdala	−24; −1; −20 22; −1; −18
Pavuluri et al. (2007)	10 BD 14 HC	14.9 ± 1.8 14.3 ± 2.4	fMRI 3 T 5 mm (1 mm gap) ROI	NR	NR	NR	Euthymic	No medication for 1+ week. Previously on AP, MS and stimulants	No DSM comorbidity except ADHD. No neurological disorder, head trauma, substance use, IQ < 80, medication affecting CBF	Increased activation of R amygdala in response to angry faces in BD	NR

See legend of Table 1.

3.1.2. MDD

The literature regarding the structural and functional changes of this region in MDD is in disagreement (Tables 3 and 4). Several studies have reported gray matter (GM) volume loss in euthymic (Sheline et al., 1998) and depressed (von Gunten et al., 2000; Caetano et al., 2004; Hickie et al., 2006), or psychotic (Keller et al., 2008) patients, but many negative results have also been published. Resting state functional data are largely suggestive of hypermetabolism (Drevets et al., 1992, 2002b; Anand et al., 2005).

3.2. The hippocampus

The hippocampus, a key structure for the encoding of emotionally relevant data into memory, interacts with the amygdala to provide input regarding the context in which stimuli occur (LaBar and Cabeza, 2006). This process is influenced by the hypothalamic–pituitary–adrenal (HPA) axis through the modulation of arousal (LaBar and Cabeza, 2006; Roozendaal et al., 2006). In rodents the hippocampus in turn plays an inhibitory role in the regulation of the amygdala, and HPA axis activity (Jacobson and Sapolsky, 1991).

3.2.1. MDD

Hippocampal volume reduction has been widely reported (Table 5). The authors of an earlier meta-analysis of the literature also came to the conclusion that hippocampal GM loss is characteristic of depression (Campbell et al., 2004); an effect that (Stockmeier et al., 2004) attribute to a decrease in neuropil—although see (Lucassen et al., 2001).

A significant number of studies have, however, failed to find evidence of hippocampal atrophy in depressed patients (Table 5) and based on these data we suggest that the following caveat obtains: the majority of studies reporting evidence of hippocampal atrophy have made use of elderly, middle-aged or chronically ill populations (see Section 4) (Table 5).

3.2.2. BD

Regarding BD, although a few studies have indeed reported volumetric decrements, the majority of studies report preservation of hippocampal tissue (Table 7). Once again, pediatric and adult samples appear to produce different results with more evidence of volume loss in the former; although see (Ladouceur et al., 2008) who found increased GM volume in the left hippocampus of the healthy offspring of parents with BD.

3.3. The basal ganglia

The basal ganglia (BG), made up of the caudate, putamen, globus pallidus (GP), subthalamic nucleus (STN), and substantia nigra (SN) were traditionally conceptualized as a center of motoric integration (Pollack, 2001; DeLong and Wichmann, 2007). This view evolved over time as the neuropsychiatric symptoms of Parkinson's (Lieberman, 2006) and Huntington's disease (PD and HD) (Slaughter et al., 2001) patients became clear, and neuropsychological case studies of affectively disturbed patients with BG lesions began to surface in the literature (Lauterbach et al., 1997). More recently, deep brain stimulation of the STN, nucleus accumbens, ventromedial caudate, and GP has provided some relief to patients with obsessive-compulsive disorder and PD-related depression (Kopell and Greenberg, 2008). The current understanding is that motor, sensory and emotional data travel in parallel but segregated pathways between cortical and subcortical structures such as the BG.

For example, the dorsal and orbitofrontal aspects of the prefrontal cortex send major efferent projections to the dorsal, and anterior caudate, respectively, while the anterior cingulate

Table 3
Morphometric studies implicating the amygdala in unipolar depression.

Study	Sample	Age	Method	Age of onset	Duration of illness/# episodes	Family history of illness	Clinical status at testing	Medication status	Comorbidity	Findings
Sheline et al. (1998)	20 MDD 20 HC	54 ± 18 53 ± 17	1.5 T 1.25 mm	NR	NR	NR	Largely euthymic	14 patients on AD	No comorbid conditions	No group differences in overall amygdala volumes but BL reduction in core nuclei volumes in MDD
Bremner et al. (2000)	16 MDD 16 HC	43 ± 8 45 ± 10	ROI	NR	2 ± 3 (episodes)	NR	Remitted	AD	No PTSD. 5 patients with history of substance abuse/dependence. 1 PD	No between group differences
von Gunten et al. (2000)	14 MDD (with memory complaints) 14 HC	57.6 58.1	1.5 T 5 mm	NR	±6.5	NR	Depressed	7 AD, 2 BZ	No neurological disorders, substance abuse	Smaller L amygdala volume in MDD
Caetano et al. (2004)	31 MDD 31 HC	39.2 ± 11.9 36.7 ± 10.7	1.5 T 1.5 mm ROI	30.5 ± 12.5 (remitted) 26.7 ± 11.4 (depressed)	12.3 ± 8.4 (remitted) 11.0 ± 11.7 (depressed)	NR	21 depressed; 10 remitted	All patients off psychotropics for 2+ weeks	No comorbid disorders except substance abuse in remission for 6+ months	Trend towards smaller L amygdala volume in MDD
Frodl et al. (2004)	30 MDD 30 HC	48.4 ± 13.4 45.7 ± 12.9	1.5 T 1.5 mm ROI	39.3 ± 13.4	9.1 ± 10.2	NR	Depressed	AD + lithium	No co-morbid disorders	No differences in amygdala volumes

Table 3 (*Continued*)

Study	Sample	Age	Method	Age of onset	Duration of illness/# episodes	Family history of illness	Clinical status at testing	Medication status	Comorbidity	Findings
Inagaki et al. (2004)	17 MDD 51 HC	47.1 ± 6 48.6 ± 5	1.5 T 1.5 mm	NR	1.1 ± 1.0 (episodes)	No	Remitted	No psychotropic medication for 1+ month but 29 on tamoxifen which may have anti-manic properties (Zarate et al., 2007)	No substance abuse	No amygdala volume differences in cancer survivors
Lange and Irle (2004)	17 female MDD 17 female HC	34 ± 10 34 ± 6	1.5 T 1.3 mm ROI	29 ± 10	5 ± 5	Yes—in 7 cases but no history of BD	Depressed	No history of psychosis. No PTSD, borderline PD	AD	Enlarged amygdala in MDD
Hickie et al. (2006)	45 MDD 16 HC	52.0 ± 12.8 55.8 ± 10.3	1.5 T 1.5 mm	36.1 ± 17.2	15.6 ± 16.1 6.9 ± 9.8 episodes	NR	Depressed	29/45 AD	No substance abuse but comorbid axis II disorders. No head injury, neurological illness, stroke, dementia	Smaller amygdala volume in MDD
Frodl et al. (2007)	60 MDD 60 HC	44.2 ± 11.8 41.6 ± 12.3	1.5 T 1 mm ROI	37.7 ± 11.7	6.7 ± 8.7	NR	Depressed	AD	No head injury, neurological disorders, substance abuse, and personality disorders	No group differences
Macmaster et al. (2007)	32 MDD 35 HC	14.08 ± 2.08 14.51 ± 2.72	1.5 T 1.5 mm ROI	11.77 ± 2.92	27.70 ± 27.68 months	Yes	Depressed	Medication naive	No psychosis, BD, OCD, PTSD, eating disorders, substance abuse, autism, LD, medical or neurological conditions	No group differences
Tang et al. (2007)	14 MDD 13 HC	29.5 ± 6.84 29.46 ± 6.86	1.5 T 1.6 mm ROI	1st episode	5.44 ± 5.22 months	NR	Depressed	Medication naive	No medical or neurological disorder, head injury, substance abuse. 4 with GAD	Decreased volume of R amygdala in MDD. 22; 0; −16
Keller et al. (2008)	23 MDD (with psychosis)	36.5 ± 13.2 36.6 ± 11.9 32.2 ± 11.5	3 T 1.5 mm ROI	27.6 ± 11.7 27.0 ± 14.0	2.9 ± 4.4 4.0 ± 9.3 (episodes)	NR	Depressed	AD, MS, AP, 4 no med 8 no med, 8 AD, 3 other	No major medical illness, seizures, head trauma, unstable cerebrovascular, endocrine conditions. No treatment with steroids, hormone replacement therapy. No substance abuse within last 6 months	Smaller BL amygdala in psychotic but not non-psychotic MDD

See legend of Table 1.

Table 4
Functional Studies implicating the amygdala in unipolar depression.

Study	Sample	Age	Method	Age of onset	Duration of illness/# episodes	Family history of illness	Clinical status at testing	Medication status	Comorbidity	Findings	Brodmann map/stereotaxic coordinates
Drevets et al. (1992)	13 depressed MDD 10 remitted MDD 33 HC	36.2 ± 8.9 33.6 ± 10.0 30.1 ± 7.8	^{15}O-H_2O	NR	NR	Yes	Depressed/ Remitted	Depressed sample unmediated for 3+ weeks before scan. Remitted sample unmedicated for at least 4 months	No substance abusers, anti-social PD. No other axis I diagnoses	Elevated activity of L amygdala in both remitted + depressed groups	21; 5; −14
Abercrombie et al. (1998)	Sample 1: 10 MDD 11 HC Sample 2: 17 MDD 13 HC	31.1 ± 10.7 38.0 ± 14.0 34.6 ± 9.9 34.3 ± 11.6	^{18}F-FDG ROI	NR	NR	NR	Depressed	Medication free	No other axis I disorders except phobia and dysthymia. No DM, brain injury or thyroid disease	No significant differences	NR
Sheline et al. (2001)	11 MDD 11 HC	40.3 39.8	fMRI 1.5 T 8 mm ROI	NR	NR	NR	Depressed	Free of medication for 4+ weeks	No neurological trauma or disorder, physical illness, comorbid psychiatric disorder, substance abuse	MDD showed greater L amygdala activation to all faces, especially fearful faces which normalized with AD treatment	NR
Thomas et al. (2001)	5 MDD 12 GAD 12 HC	12.3 ± 2.7 12.8 ± 2.1 12.2 ± 2.6	fMRI 5 mm (2.5 mm gap) ROI	NR	NR	NR	Depressed	No medication for 2+ weeks	No nicotine, alcohol, drugs, psychotropic medication for 2+ weeks, medical or neurological illness, extreme obesity, eating disorders, schiz, LD, PTSD, IQ < 80	Compared with HC, anxious children showed exaggerated response to fearful faces while MDD showed blunted response in L amygdala	−13; −4; −16
Drevets et al. (2002b)	12 MDD 12 HC	36 ± 8.7 35 ± 9.8	^{18}F-FDG 3.4 mm MRI 1.5 T ROI	NR	NR	Yes	Depressed	No medication for 3+ weeks before study in depressed BD group but euthymic patients medicated with MS or AP	No substance abusers	Elevated activity of the L amygdala in MDD	−21; −7; 18
Siegle et al. (2002)	7 MDD 10 HC	34.3 ± 8.8 36.1 ± 6.7	fMRI 1.5 T 3.8 mm	NR	4 episodes	NR	Depressed	No tricyclics or nefazodone	No substance in last 6 months. No history of psychosis	Sustained amygdala response to negative words in MDD relative to HC	−15; −4; −6
Davidson et al. (2003)	12 MDD 5 HC	38.17 ± 9.3 27.8 ± 10.4	fMRI 1.5 T 1 mm ROI	NR	NR	NR	Depressed	NR for baseline	No other axis I disorders except specific phobia or dysthymia. No neurological disorders	No group differences in BL amygdala activity in response to aversive visual stimuli	−18; −6; −10 20; −4; −14
Canli et al. (2004)	15 MDD 15 HC	35.1 30.7	fMRI 3 T Voxel-wise	NR	NR	NR	Depressed	7 patients on AD	No history of psychosis, substance abuse in last 6 months, social anxiety disorder	Decreased activity in R amygdala in response to happy stimuli	22; −6; −13
Fu et al. (2004)	21 MDD 19 HC	43.2 ± 8.8 42.8 ± 6.7	fMRI 1.5 T 8 mm ROI	NR	NR	NR	Depressed	No medication for 4+ weeks	No neurological trauma, disorder, comorbid axis I condition, substance within 2 months	Exaggerated response to sad faces in L amygdala which improved after treatment	−12; −5; −8 −11; −10; −12

Table 4 (*Continued*)

Study	Sample	Age	Method	Age of onset	Duration of illness/# episodes	Family history of illness	Clinical status at testing	Medication status	Comorbidity	Findings	Brodmann map/stereotaxic coordinates
Irwin et al. (2004)	12 MDD 14 HC	38 ± 3 28 ± 2	fMRI 1.5 T 7 mm ^{18}F-FDG ROI	NR	NR	NR	Depressed	Medication free	No axis I comorbidity, neurological trauma, disorder	Reduced connectivity between L + R amygdala in MDD	20; −4; −10 −21; −6; −9
Anand et al. (2005)	15 MDD 15 HC	28 ± 9 28 ± 7	fMRI 1.5 T	NR	19	NR	Euthymic	Lithium	No medical illness	Increased activation of amygdala and insula in MDD	NR
Gotlib et al. (2005)	18 MDD 18 HC	35.2 30.8	fMRI 3 T Voxel-wise	NR	NR	NR	Depressed	9 on AD	No brain injury, psychosis, social phobia, panic disorder + substance abuse in last 6 months	No significant differences in response to facial stimuli	NR
Surguladze et al. (2005)	16 MDD 14 HC	42.3 ± 8.4 35.1 ± 13.2	fMRI 1.5 T	NR	7.5 ± 5.1	NR	Depressed	AD	No head injury, substance abuse, dementia	MDD: increased activation in amygdala to sad faces which was correlated with severity of depression	−14; −7; −18
Neumeister et al. (2006a)	27 MDD 26 HC	39.7 ± 12.8 34.2 ± 12.2	^{15}O-H_2O ROI	NR	NR	NR	Remitted	Unmedicated	No medical illness	Greater rCBF in response to sad faces in MDD	NR
Chen et al. (2007b)	19 MDD 19 HC	43.3 ± 8.6 42.8 ± 6.7	fMRI 1.5 T 7 mm	NR	NR	NR	Depressed	No medication for 4+ weeks prior to baseline scan	No axis I comorbidity, neurological trauma, disorder, substance abuse within 2 months	At baseline reduced functional coupling of amygdala with hippocampus, putamen, caudate, insula, temporal cortices, inferior and middle cortex in MDD. After 8 week treatment with fluoxetine no group differences	44; 42; 22 31; 32; 32 47; 37; 1 54; 18; 4 13; 49; 18 15; 22; 29 39; 30; 7 24; −1; 14 15; 14; 20
Dannlowski et al. (2007)	35 MDD	38.6 ± 12.2	fMRI 3 T ROI	NR	125 ± 125.5 months 4.7 episodes	NR	Depressed	AD	No history of mania, neurological illness, ECT, Benz treatment, age > 60,	Amygdala reactivity to masked negative faces predicted negative judgemental bias towards consciously viewed faces.	−18; −4; −12 22; 2; −20
Fales et al. (2008b)	27 MDD 24 HC	33.4 ± 8 36.4 ± 9	fMRI 3 T 3.2 mm	NR	NR	NR	Depressed	No medication for 4+ weeks	No axis I comorbidity, physical or neurological illness, brain trauma	Enhanced response of L amygdala to unattended fearful faces in MDD	−18; −5; −19
Siegle et al. (2007)	27 MDD 25 HC	38 ± 12.7 31.5 ± 9.0	fMRI 3 T 3.2 mm	NR	Median # episodes = 15+	NR	Depressed	No medication for 2+ weeks	No excessive alcohol use. No physical illness, drug abuse for 6+ months. IQ > 80	MDD patients showed greater BL amygdala activity during the processing of emotionally valenced verbal stimuli.	−22; −5; −15

See legend of Table 1.

Table 5
Morphometric studies of the hippocampal complex in MDD.

Study	Sample	Age	Method	Age of onset	Duration of illness/# episodes	Family history of illness	Clinical status at testing	Medication status	Comorbidity	Findings
Axelson et al. (1993)	19 MDD 30 HC	46.7 ± 7.4 56.6 ± 19.1	1.5 T 5 mm ROI	34 ± 17	12.7 ± 13.1	NR	Depressed	NR	NR	No difference in hippocampal-amygdala complex volumes. Age negatively correlated with volume
Sheline et al. (1996)	10 MDD 10 HC	68.5 ± 10.4 68.0 ± 9.5	1.5 T 1.25 mm ROI	NR	1293 ± 1067 (days)	NR	Partially remitted	8 AD	No drug or alcohol abuse	Smaller BL hippocampal volumes in MDD. Volume correlated negatively with duration of depression
Pantel et al. (1997)	19 MDD 13 HC	72.4 ± 8.8 68.2 ± 5.3	1.5 T 1.25 mm	64.2 ± 9.2	26.7 ± 6.6 (months)	NR	Depressed	NR	NR	No difference in hippocampal-amygdala complex volumes
Shah et al. (1998)	20 MDD (chronic) 20 MDD (remitted) 20 HC	21–65	VBM	NR	NR	NR	Depressed and remitted	AD	No mania, significant substance abuse, organic pathology or neurological illness	Chronic MDD group showed trend towards reduced GM density in the L hippocampus −29; −18; −16
Ashtari et al. (1999))	40 MDD 40 HC	74.3 ± 6.0 71.4 ± 0.3	1 T 3.1 mm ROI	61.5 ± 5.5	1.8 ± 0.5	NR	Depressed	NR	NR	No difference in hippocampal volumes. No relationship between # episodes + volume
Sheline et al. (1999)	24 MDD 24 HC	52.8 ± 18.4 52.8 ± 17.8	1.5 T 1.25 mm ROI	NR	1058 ± 1032 (days) 4.8 (episodes)	NR	Depressed	16 on AD	No substance abuse, medical or neurological conditions	Smaller BL hippocampal volumes in MDD. No correlation between volume and age but duration of depression associated with volume
Bremner et al. (2000)	16 MDD 16 HC	43 ± 8 45 ± 10	ROI	NR	2 ± 3 (episodes)	NR	Remitted	AD	No PTSD. 5 patients with history of substance abuse/dependence. 1 PD	Reduced L hippocampal volume in MDD. Trend for R hippocampus. No association between volume and # episodes or hospitalisations
Mervaala et al. (2000)	34 MDD (6 BD) 17 HC	42.2 ± 12.2 42.1 ± 14.6	1.5 T 8 mm ROI	NR	31 months	NR	Depressed	AD	No substance abuse	Smaller L hippocampal volumes in MDD. Trend for R hippocampus
Steffens et al. (2000)	66 MDD 18 HC	71.74 ± 8.42 67.11 ± 5.04	1.5 T 3 mm	25.6 (N = 28) 65.2 (N = 38)	NR	NR	Depressed	NR	No other "major" psychiatric illnesses	Smaller BL hippocampal volumes in MDD. Weak negative association between age of onset and volume. No association between # of episodes + volume
Vakili et al. (2000)	38 MDD 20 HC	38.5 ± 10.0 40.3 ± 10.4	1.5 T 3 mm ROI	NR	NR	NR	Depressed	Fluoxetine	No active substance abuse	No significant differences in hippocampal volume. Negative correlation between severity of depression and volume
von Gunten et al. (2000)	14 MDD (with memory complaints) 14 HC	57.6 58.1	1.5 T 5 mm	NR	± 6.5	NR	Depressed	7 AD, 2 BZ	No neurological disorders, substance abuse	No difference in hippocampal volumes

Table 5 (*Continued*)

Study	Sample	Age	Method	Age of onset	Duration of illness/# episodes	Family history of illness	Clinical status at testing	Medication status	Comorbidity	Findings
Rusch et al. (2001)	25 MDD 15 HC	33.2 ± 9.5 37.4 ± 14.4	1.5 T 1.2 mm ROI	NR	NR	Yes but not BD	Depressed	Free of medication for 4+ weeks	No history of mania, psychosis or any other axis I disorder except dysthymia	No hippocampal volume differences
Bell-McGinty et al. (2002)	30 MDD 47 HC	69.3 ± 5.7 66.9 ± 7.3	1.5 T VBM	NR	1.8 ± 0.9 (episodes)	NR	Depressed	NR	No other axis I disorders or substance abuse. No neurological disorders, untreated DM or hypertension	Smaller R hippocampal volume in MDD. Volume inversely correlated with age of onset
Frodl et al. (2002)	30 FE MDD 30 HC	40.3 ± 12.6 40.6 ± 12.5	1.5 T 3 mm ROI	40 ± 12.5	0.71 ± 0.9	NR	Depressed	AD	No other axis I conditions, neurological disorders or had injury	Smaller L hippocampal GM volumes in male MDD. No association between illness duration or age and volume
Vythilingam et al. (2002)	21 MDD with history of childhood abuse 12 MDD without abuse 14 HC	33 ± 6 34 ± 8 27 ± 5	1.5 T 1.5 mm ROI	NR	NR	NR	Depressed	NR	Anxiety disorders, especially PTSD more prevalent in abused MDD sample	Smaller L hippocampal volume in MDD group with history of childhood abuse
MacQueen et al. (2003)	20 FE MDD. 17 multi-episode MDD. 20 HC 17HC	28.4 ± 11.8 35.9 ± 11.1 28.4 ± 11.5 36.2 ± 11.9	1.5 T 1.2 mm ROI	26.3 ± 12 24.9 ± 11.6	10 years 6 (episodes)	Mixed	Depressed	FE MDD group medication naive. AD in multi-episode group	No substance abuse, anxiety disorders	Hippocampal volume reduction in multi-episode patients. Correlation between duration of depression and hippocampal volume
Posener et al. (2003)	27 MDD 42 HC	33.0 ± 10.7 33.2 ± 10.8	1.5 T 1 mm ROI	NR	0.8 ± 1.2 (episodes)	NR	Depressed	Yes—not specified	No substance abuse in last 3 months. No other axes I or II disorders. No neurological disorders, cardiovascular risk factors	No differences in hippocampal volume but surface deformation
Caetano et al. (2004)	31 MDD 31 HC	39.2 ± 11.9 36.7 ± 10.7	1.5 T 1.5 mm ROI	30.5 ± 12.5 (remitted) 26.7 ± 11.4	12.3 ± 8.4 (remitted) 11.0 ± 11.7 (depressed)	Both	21 depressed; 10 remitted	All patients off psychotropics for 2+ weeks	No comorbid disorders except substance abuse in remission for 6+ months	Depressed patients had smaller hippocampal volumes than remitted patients. Inverse correlation between length of illness and L hippocampus
Frodl et al. (2004)	30 MDD 30 HC	48.4 ± 13.4 45.7 ± 12.9	1.5 T 1.5 mm ROI	39.3 ± 13.4	9.1 ± 10.2	NR	Depressed	AD + lithium	No co-morbid disorders	No differences between hippocampal volumes in remitted group. Smaller R hippocampal volume in non-remitted group ($N = 12$) at baseline and follow-up. No change in volumes over 1 year
Hastings et al. (2004)	18 MDD 18 HC	38.9 ± 11.4 34.8 ± 13.6	1.5 T 1.5 mm ROI	23 ± 12.3	4.7 ± 4.4	Mixed	Depressed	NR	No current drug abuse	No volume changes of hippocampus
Inagaki et al. (2004)	17 MDD 51 HC	47.1 ± 6 48.6 ± 5	1.5 T 1.5 mm	NR	1.1 ± 1.0	No	Remitted	No psychotropic medication for 1+ month. Tamoxifen	No substance abuse	No hippocampal volume differences in cancer survivors

Janssen et al. (2004)	28 MDD 41 HC	64.04 ± 10.9 62.37 ± 11.38	1.5 T 1.2-5 mm ROI	33.04 ± 9.48	93.5 ± 17.5 months	NR	Depressed	22 AD, 4 lithium, 1 BZ	NR	Smaller R hippocampal volume in MDD
Lange and Irle (2004)	17 female MDD 17 female HC	34 ± 10 34 ± 6	1.5 T 1.3 mm ROI	29 ± 10	5 ± 5	Yes—in 7 cases but no history of BD	Depressed	AD	No history of psychosis. No PTSD, borderline PD	Reduction in hippocampal volume in MDD
Lloyd et al. (2004)	51 MDD (23 early onset; 28 late-onset) 39 HC	72.7 ± 6.7 75.1 ± 5.8 73.1 ± 6.7	1 T 1 mm	38.7 (N = 23) 72.0 (N = 28)	88.3 weeks; 5.1 (episodes) 24.3 weeks; 2.0 (episodes)	NR	Depressed	AD	No drug or alcohol abuse	BL hippocampal atrophy in late-onset MDD compared with early-onset MDD + HC. No relationship between volume + lifetime duration of depression
MacMaster and Kusumakar (2004)	17 MDD 17 HC	16.67 ± 1.83 16.23 ± 1.61	1.5 T 1.5 mm ROI	14.06 ± 1.98	2.89 ± 1.71	Yes in 9/17	Depressed	14 treatment naive. 3 AD or methyphenidate	No neurological or serious medical illness. 2 substance abuse, 1 ODD	BL (especially L) reduction in hippocampal volume in MDD
O'Brien et al. (2004)	61 MDD 40 HC	73.9 ± 6.7 73.3 ± 6.7	1 T 1 mm ROI	NR	2.2 ± 2.7 (episodes)	NR	Depressed. 20% with psychotic features	51 AD, 7 lithium	No substance abuse, stroke, unstable medical illness	Decreased volume of hippocampus in MDD
Hickie et al. (2005)	66 (14 BD) MDD 20 HC	53.5 ± 13.5 55.8 ± 10.8	1.5 T 1.5 mm ROI	38.4 ± 16.3	15 ± 15.8	NR	Depressed	NR	No substance abuse	Reduced hippocampal volume. Effect stronger in late onset patients. Increasing age associated with smaller volumes
Neumeister et al. (2005)	31 MDD 57 HC	40.1 ± 101 38.0 ± 10.9	3 T 0.6 mm	24.6 ± 10.3	3.2 ± 2.1 (episodes)	NR	Remitted	Unmedicated	No history of trauma or substance abuse	Total + posterior hippocampal volume reductions in MDD
Frodl et al. (2006)	34 MDD 34 HC	45.5 ± 11.9 43.6 ± 13.2	1.5–3 mm ROI	38.8 ± 12.4	6.8 ± 8.8	NR	Depressed	AD, 4 AP	No comorbidity	BL hippocampal GM + WM volume reductions in MDD. No correlation between illness duration + hippocampal volume
Hickie et al. (2006)	45 MDD 16 HC	52.0 ± 12.8 55.8 ± 10.3	1.5 T 1.5 mm	36.1 ± 17.2	15.6 ± 16.1 6.9 ± 9.8 episodes	NR	Depressed	29/45 AD	No substance abuse but comorbid axis II disorders. No head injury, neurological illness, stroke, dementia	Smaller hippocampal volume in MDD
Rydmark et al. (2006)	29 female MDD 28 HC	47.7 ± 4.9 47.6 ± 4.2	1.5 T VBM	44.1 ± 8.4	Mostly 1st episode	NR	Partially remitted	AD	No hazardous alcohol or illicit drug use	No hippocampal differences
Frodl et al. (2007)	60 MDD 60 HC	44.2 ± 11.8 41.6 ± 12.3	1.5 T 1 mm ROI	37.7 ± 11.7	6.7 ± 8.7	NR	Depressed	AD	No head injury, neurological disorders, cortisol medication, substance abuse, and personality disorders	Smaller hippocampal volumes in MDD. No association between duration of illness and volume
Janssen et al. (2007)	13 early onset MDD 15 late-onset depression 22 HC	70.38 ± 8.3 72.67 ± 6.7 71.05 ± 7.5	1.5 T	33.62 ± 8.8 69.93 ± 6.4	NR	NR	Depressed	4 lithium	Cerebrovascular risk factors not exclusion criterion. No neurological disorders, dementia, substance abuse	Smaller hippocampus in early-onset group only
Macmaster et al. (2007)	32 MDD 35 HC	14.08 ± 2.08 14.51 ± 2.72	1.5 T 1.5 mm ROI	11.77 ± 2.92	27.70 ± 27.68 months	Yes	Depressed	Medication naive	No psychosis, BD, OCD, PTSD, eating disorders, substance abuse, autism, learning disorders, medical or neurological conditions	Smaller L + R hippocampal volumes in MDD

Table 5 (*Continued*)

Study	Sample	Age	Method	Age of onset	Duration of illness/# episodes	Family history of illness	Clinical status at testing	Medication status	Comorbidity	Findings
Keller et al. (2008)	23 MDD (with psychosis) 19 MDD (without psychosis 22 HC	36.5 ± 13.2 36.6 ± 11.9 32.2 ± 11.5	3 T 1.5 mm ROI	27.6 ± 11.7 27.0 ± 14.0	2.9 ± 4.4 4.0 ± 9.3 (episodes)	NR	Depressed	AD, MS, AP, 4 no med 8 no med, 8 AD, 3 other	No major medical illness, seizures, head trauma, unstable cerebrovascular, endocrine conditions. No treatment with steroids, hormone replacement therapy. No substance abuse within last 6 months	No significant differences
Tae et al. (2008)	21 MDD 20 HC	41.7 ± 11.0 41.9 ± 10.3	1.5 T 1.3 mm ROI VBM	33.2 ± 13.0	3.9 ± 3.3 (episodes) 80.0 ± 67.0 months (duration)	4+ 17−	Depressed	AD only	No childhood trauma, other axis I disorder, no current or past history of substance abuse/ dependence, major medical illness, head trauma, steroid meds	Smaller L hippocampus in MDD using both manual and VBM methods

See legend of Table 1.

Table 6
Functional studies reporting a significant difference in the hippocampus in MDD.

Study	Sample	Age	Method	Age of onset	Duration of illness/# episodes	Family history of illness	Clinical status at testing	Medication status	Comorbidity	Findings
Kennedy et al. (2001)	13 MDD 24 HC	36 ± 10 31.7 ± 6.7	^{18}F-FDG	NR	2.84 ± 3.95 episodes	NR	Depressed	Scanned before and after treatment with paroxetine. Off medication of 4+ weeks prior to study	No patients with concurrent DSM diagnosis	Recovery associated with decreased hippocampal metabolism 30; −28; −12
Videbech et al. (2001)	42 MDD 47 HC	42 ± 13 41 ± 12	^{15}O-H_2O	NR	2 episodes	NR	Moderately to severely depressed	AD	No substance abuse	Increased activity of R hippocampus in MDD. 29; −9; −20
Goldapple et al. (2004)	17 MDD	41 ± 9	^{18}F-FDG Voxel-wise	NR	NR	NR	Depressed	Unmedicated	No psychotic symptoms, axis I disorders and substance abuse	Response to cognitive behavior therapy associated with increased metabolism of hippocampus −26; −36; −8 38; −10; −14

See legend of Table 1.

Table 7
Morphometric studies of the hippocampus in BD.

Study	Sample	Age	Method	Age of onset	Illness duration/# episodes	Family history of illness	Clinical status at testing	Medication status	Comorbidity	Findings
Altshuler et al. (1991)	10 BD I 10 HC	39.8 ± 9 37 ± 12	0.5 T 10 mm	NR	2–39 years	NR	Euthymic	MS	NR	Decreased BL TL volume in BD. Duration of illness inversely correlated with TL volume in males
Swayze et al. (1992)	48 BD 47 HC	33.41 (M) 33.61 (F)	0.5 T 10 mm ROI	22.86 ± 7.82	5.89 ± 6.15 hospitalization	NR	NR	NR	NR	Volume of R hippocampus decreased in BD
Pearlson et al. (1996)	27 BD 60 HC	34.9 ± 8.6 31.6 ± 8	1.5 T 3 mm ROI	NR	NR	NR	NR	NR	No substance abuse, other axis I conditions	No hippocampal volume changes
Altshuler et al. (1998)	12 BD 18 HC	50.8 ± 13.3 53.4 ± 11.1	1.5 T 1.4 mm ROI	NR	NR	NR	Remitted	NR	No other axis I disorders	No hippocampal volume changes
Hirayasu et al. (1998)	16 FE affective psychosis (12 BD) 18 HC	23.7 ± 4 24.0 ± 4.5	1.5 T 1.5 mm ROI	NR	1st episode	NR	12 manic, 2 mixed, 2 depressed	Medication naive	No substance abuse, head trauma, neurological disorders	Normal amygdala-hippocampal complex volume
Sax et al. (1999)	17 BD 12HC	27 ± 6 27 ± 5	1.5 T 1 mm ROI	NR	NR	NR	Manic + mixed	5 medication free. 12 on MS. 5 on AP	NR	No change in hippocampal volume
Strakowski et al. (1999)	24 BD 22 HC	27 ± 6 28 ± 6	MRI 1.5 T 1 mm ROI	NR	6 ± 6	NR	14 manic, 10 mixed episode	MS + AP	No substance abuse for 3+ months	No change in hippocampal volume or association between length of illness and volume
Altshuler et al. (2000)	24 BD 18 HC	50.2 ± 12.7 53.4 ± 11.1	1.5 T 1.5 mm ROI	26.6 ± 10.4	23.6 ± 11.4	NR	Euthymic	AP, AD + MS	No substance abusers but alcohol dependence included if patients sober for 9+ months	No hippocampal volumes differences
Hauser et al. (2000)	25 BD I 22 BD II 19 HC	41.8 ± 10.5 39.4 ± 10.2 33.2 ± 7.1	0.5 T 5 mm ROI	24 for BD I and 18 for BD II.	18.2 ± 11.8 (BD I) 21.1 ± 9.1 (BD II)	NR	Euthymic	NR	No substance abuse, chronic medical or neurological disorder	No change in hippocampal volume
Strakowski et al. (2002)	^{18}FE BD 17 multiple episode BD 32 HC	22 ± 6 25 ± 6 24 ± 6	1.5 T 1.5 mm ROI	1st episode: 20 ± 5. Multiple episode: 15 ± 4.	2 ± 3 10 ± 5	NR	32 psychotic, 16 mixed state	No prior treatment with medication in FE group. Multiple episode group on MS + AP	No substance abuse within 3+ months of scan	No difference in hippocampal volume across groups
Blumberg et al. (2003a)	36 BD I 56 HC	31 ± 14.1 28.3 ± 13.7	1.5 T 1.2 mm ROI	Adults: 17.4 ± 8 Adolescents: 13.1 ± 9.5	NR	Yes	Adults: 45% euthymic, 32% hypomanic/manic, 23% depressed. All adolescents symptomatic	± 33% of adults + half of adolescents medication free. Balance of sample on MS, AD + AP	± 33% of BD cohort with substance dependence. # of adolescent BD with ADHD, ODD, learning disorders, PTSD + avoidant PD	Trend for reduced BL hippocampal volume in adolescents + adults with BD
Brambilla et al. (2003a)	24 BD 36 HC	35 ± 10 37 ± 10	1.5 T 1.5 mm ROI	NR	15 ± 9	11 with family history. 13 without	NR	15 patients on lithium mono-therapy. 9 not medicated	No comorbid disorders and substance abuse within last 6 months	Normal hippocampal volume. Controlling for family history did not alter results

Table 7 (*Continued*)

Study	Sample	Age	Method	Age of onset	Illness duration/# episodes	Family history of illness	Clinical status at testing	Medication status	Comorbidity	Findings
Beyer et al. (2004b)	36 BD 29 HC	58.2 ± 7.80 61.0 ± 5.49	1.5 T 3 mm ROI	NR	NR	NR	NR	12 lithium, 5 valproate, 15 lithium-valpoate combination	No major psychiatric disorders, substance abuse	Enlargement of L hippocampus in late-onset BD group
Lochhead et al. (2004)	11 (BD (7 BD I 4 BD II) 31 HC	38.2 ± 10 36 ± 14	1.5 T 1.5 mm VBM	24.3 ± 9.2	9.0 ± 6.4 episodes	NR	Depressed	No medication for 2+ weeks	No comorbid disorders	Decrease in volume of L parahippocampal gyrus −20; −21; −21
McDonald et al. (2004a)	38 BD 52 unaffected relatives 54 HC	41 ± 11.7 44 ± 15.5 40.2 ± 15.3	1.5 T 1.5 mm ROI	22.6 ± 5.5	NR	Yes	NR	33 BD on MS. 10 on AP	No organic brain disease, head trauma, substance abuse in last 12 months	Hippocampal volume preserved in BD
Wilke et al. (2004)	10 BD 52 HC	14.5 ± 1.8 15 ± 1	3 T 1.5 mm VBM	NR	NR	NR	Six mixed and 4 manic	No medication 72 h before scan. No data on medication type	No schizophrenia, learning disabilities or pervasive developmental disorders	Reduced GM volume of BL medial TL
Chang et al. (2005b)	20 BD 20 HC	14.6 ± 2.8 14.1 ± 2.8	3 T 1.5 mm ROI	NR	NR	Yes	Depressed + hypomanic	Patients on medication (MS, AD+ AP) except stimulants which were discontinued 24 h prior to scan	No pervasive developmental disorders, substance abuse. 16 ADHD, 7 anxiety disorder, 11 ODD	No hippocampal volume differences between groups
Frazier et al. (2005)	43 BD 20 HC	11.3 ± 2.7 11.0 ± 2.6	1.5 T 1.5 mm ROI	7.0 ± 3.8	2.8 ± 3.1	NR	50% mixed, 16% manic, 11% depressed, 20% euthymic	MS, AP, AD, stimulants, anticholinergics	No substance abuse for 2+ months. No schizophrenia, autism, bulimia, anorexia or learning disorders. 27 ODD, 22 ADHD	Reduced hippocampal volume in BD. Effect stronger in females
Strasser et al. (2005)	23 psychotic BD 15 non-psychotic BD 44 HC	36.39 ± 11.6 40.80 ± 14.1 39.61 ± 11.7	1.5 T 1.5 mm ROI	NR	NR	Yes	NR	NR	No substance abuse	Significantly smaller L hippocampal volumes in psychotic BD
McDonald et al. (2006)	38 BD 52 unaffected relatives 54 healthy controls	41 ± 11.7 44 ± 15.5 40.2 ± 15.3	1.5 T 1.5 mm ROI	22.6 ± 5.5	5.4 ± 5.6 (hospitalizations)	Yes	NR	33 MS. 10 AP	No substance abuse in last 12 months	Hippocampal volume preserved in BD relatives
Velakoulis et al. (2006)	34 affective psychosis (22 BD, 12 MDD) 87 HC	22.0 ± 3.1 21.7 ± 4.2 26.9 ± 10	1.5 T 1.5 mm ROI	NR	1st episode	NR	NR	AP	No alcohol abuse	No hippocampal volume differences
Chen et al. (2007c)	24 BD I 25 HC	38.2 ± 11.0 38.4 ± 11.1	1.5 T 1.6 mm VBM	NR	14.2 ± 10.3	Yes—in 14 subjects	NR	12 Lith 12 MS	No current substance use, neurological disease, head injury, other DSM diagnosis	Increased L parahippocampal gyrus but smaller L middle temporal gyrus (BA 39) in BD −17; −19; −22 −44; −74; −13
Moorhead et al. (2007)	20 BD I 21 HC	41.5 ± 8.9 38.5 ± 12.6	1.5 T 1.7 mm TBM	NR	14 ± 8.4	NR	45% euthymic (first round) 85% euthymic (second round)	10 Lith 5 AP 7 MS	No head injury, neurological disorder, drug dependence, LD	Longitudinal study over 4 years. GM decline in L hippocampus in BD −39; −14;−18

Yucel et al. (2007)	28 BD 12 Lith+ 7 other MS 9 no meds 30 HC	25.73 ± 6.2 25.55 ± 8.5 24.36 ± 8.4 25.3 ± 7.8	1.5 T 1.2 mm	19.3 ± 8.7 16 ± 4.5 15.5 ± 7.7	7 ± 7.1 9.6 ± 15.2 (episodes) 9.4 ± 7.0 8.6 ± 7.1 (episodes) 9.4 ± 7.2 6.4 ± 3.6 (episodes)	NR	Mixed	12 lith 7 MS 9 no med/AD	No substance abuse, PTSD, untreated medical illness, head injury, neurological disorders, past history of drug treatment	Larger hippocampal volume in Lith+ compared with untreated group. No difference between untreated group + HC
Chepenik et al. (2008)	20 BD 18 HC	40 ± 9 28 ± 12	1.5 T 1.2 mm ROI	21 ± 8	18 years (duration)	NR	6 euthymic, 8 depressed, 5 manic	6 no meds, 15 MS or AD	2 panic disorder, 14 history of substance abuse. No medical neurological illness, head trauma	Smaller volume in BD

See legend of Table 1.

cortex projects to the ventral surface of the striatum, respectively (Ferry et al., 2000). In addition, the ventral or limbic striatum (ventral caudate, accumbens and olfactory tubercle), receives dopaminergic input from the SN and ventral tegmental area (VTA) (Utter and Basso, 2007), glutamatergic input from the amygdala and thalamus, and serotonergic input from the dorsal raphe nucleus (Pollack, 2001; Bonelli et al., 2006).

3.3.1. MDD

Several early studies raised the possibility of BG volume reductions in MDD, although with the exception of a recent pediatric study (Matsuo et al., 2008), these data have generally not been replicated in subsequent analyses (Table 9). As in the case of BD there has been some suggestion that volume loss is associated with late age-of-onset (Greenwald et al., 1997) and chronicity or severity of illness (Pillay et al., 1998; Lacerda et al., 2003)—although see (Sheline et al., 1999). Most recently (Hickie et al., 2006) failed to detect a MDD-associated decrease in striatal volumes. However, when the sample was stratified by serotonin transporter promoter polymorphism genotype (5-HTTLPR), striatal volume loss was observed in short allele carriers; indicating that genetic factors may contribute to the heterogeneity characteristic of the literature.

At least five studies (Table 10) have reported decreased activity of the striatum in MDD, and a tryptophan depletion study reported that severity of depression was associated with diminished activity of the caudate (Smith et al., 1999).

3.3.2. BD

Compared to healthy controls, subjects with BD generally have not shown morphometric differences in the caudate or putamen (Table 11). These data are congruent with the reported absence of *N*-acetyl-aspartate (NAA) abnormalities in the BG of BD populations (Kato et al., 1996; Hamakawa et al., 1998; Ohara et al., 1998). Nevertheless, a post-mortem study of a combined MDD and BD sample has reported volumetric reductions of the left nucleus accumbens, the bilateral pallidum, and the right putamen (Baumann et al., 1999).

There has however, been some suggestion of BD-associated striatal enlargement in adult (Aylward et al., 1994; Noga et al., 2001; Strakowski et al., 2002) and pediatric (DelBello et al., 2004; Wilke et al., 2004) samples, a point we will return to in Section 4.

To complicate matters further, reduced striatal volumes have been associated with length of bipolar illness (Brambilla et al., 2001b) and an older age of onset (Beyer et al., 2004a) suggesting a potential role for chronicity or cerebrovascular disease. This notion is consistent with reports of white matter lesions of the BG in elderly patients with MDD (Murphy et al., 1992; Greenwald et al., 1996; Iidaka et al., 1996) although striatal volume reductions have also been reported to be a marker of disease-diathesis in the relatives of BD probands (McDonald et al., 2004a; McIntosh et al., 2004).

Finally, metabolic activity or blood flow in the BG has been reported to be both increased and decreased in BD samples (Table 12). In manic or hypomanic samples striatal activity appears more generally increased relative to controls during tasks that normally activate the striatum (Blumberg et al., 2000; Caligiuri et al., 2003, 2006). For example, a recent fMRI study using a monetary incentive task noted that the expected differences in functional activity of the nucleus accumbens and ventral tegmentum in response to trials where a reward is received, compared to trials where a reward is not received, are attenuated in patients with mania (Abler et al., 2008). In other words, subjects with mania show an inappropriate, generalized activation of reward circuitry. In bipolar depressed samples activity also is increased in the ventral striatum (Ketter et al., 2001; Bauer et al.,

Table 8
Functional analyses reporting differences in the hippocampus in BD.

Study	Sample	Age	Method	Age of onset	Illness duration/# episodes	Family history of illness	Clinical status at testing	Medication status	Comorbidity	Findings	Brodmann map/stereotaxic coordinates
Bauer et al. (2005)	10 BD I	39.3 ± 7.8	^{18}F-FDG	NR	20.4 ± 7.0	NR	Depressed	AD + MS	No psychosis	Activity in R hippocampus decreased with successful treatment with thyroxine. BD group still showed elevated metabolism of R hippocampus after treatment	34; −26; −8
	10 HC	35.0 ± 9.3	Voxel-wise								
Mah et al. (2007)	13 BD II	43.0 ± 8.4	^{18}F-FDG	20 ± 10.5	22.9 ± 12	NR	Depressed	Lithium	No substance abuse within 90 days, substance dependence within 5 years. No current psychotic features. 1 OCD, 1 eating disorder	Increased metabolism of L parahippocampal gyrus	−22; −35; −7
	18 HC	39.0 ± 8.0									

See legend of Table 1.

2005; Dunn et al., 2002; Mah et al., 2007), but the direction and existence of physiological abnormalities in the remainder of the striatum has been more variable across studies (Table 12).

3.4. Ventricular abnormalities

Substantial tissue loss in the medial–temporal lobe, lateral PFC or BG in MDD or BD may be reflected by enlargement of the adjacent ventricular system. The evidence for ventricular enlargement (mostly of the third or lateral ventricles) in MDD and BD is mixed. Almost all reports of ventricular enlargement have been obtained in elderly or chonically depressed samples with late-onset illness (Coffey et al., 1989; Rabins et al., 1991; Salloway, 1996; Dahabra et al., 1998; Simpson et al., 2001) and given the evidence that familial MDD usually manifests early in life (Kovacs et al., 1997; Kendler et al., 2005; Nierenberg et al., 2007), this suggests that periventricular tissue loss does not have a purely genetic etiology. One possibility is cerebrovascular disease, as discussed in the following section.

3.5. White matter changes

A higher than normal incidence of deep frontal white matter hyperintensities (WMH), especially WMH of the deep frontal cortex and BG, appears characteristic of MDD and BD samples who manifest with late age-of-illness onset (Krishnan et al., 1991; Figiel et al., 1991; Hickie et al., 1995; Steffens et al., 1999; Hannestad et al., 2006).

WMH appear as bright high intensity signals seen on T2-weighted MRI scans that are caused by circumscribed increases in water content (Ovbiagele and Saver, 2006). As discussed by Ovbiagele and Saver (2006) they are most likely indicative of leukoaraiosis: a decrease in the density of white matter due to demyelination, atrophy of the neuropil, and ischemia-associated microangiopathy, among others. The phenomenon is non-specific, being prevalent in elderly populations, generally. According to Kertesz et al. (1988) almost all individuals will display WMH by the age of 85.

Diffusion tensor imaging (DTI) is another method of assessing WM integrity. Theoretically, damage to cellular tissue causes parallel changes in the rate of diffusion of water across the affected cellular membranes, and this so-called proton diffusibility can be measured with DTI (Bammer, 2003).

3.5.1. MDD

While the onset of MDD peaks in adolescence and young adulthood, an increased incidence is also seen in elderly individuals (Paykel et al., 2005), contributing to the idea that vascular pathology plays a role. The term "vascular depression" was initially proposed to describe depressive symptomatology associated with multiple subcortical infarcts of an ischemic origin (Alexopoulos et al., 1997; Krishnan et al., 1997).

With few exceptions (Dupont et al., 1995a; Greenwald et al., 1996; Sassi et al., 2003; Rainer et al., 2006), extant evidence supports the existence of vascular depression. Both epidemiological studies of elderly community-based samples and cross-sectional analyses of matched control and MDD groups detail the intimate relationship between late-onset depression and WM lesions (Table 13).

3.5.2. BD

In BD most studies suggestive of WM pathology involve DTI. Changes in diffusion coefficients, which are believed to reflect the integrity of WM fibres, have been reported in the WM bundles connecting the PFC (particularly BA 9 and 10) to subcortical regions (Adler et al., 2004), OFC (Beyer et al., 2005), internal capsule

Table 9
Morphometric studies of the basal ganglia in unipolar depression.

Study	Sample	Age	Method	Age of onset	Duration of illness/# episodes	Family history of illness	Clinical status at testing	Medication status	Comorbidity	Findings
Husain et al. (1991)	41 MDD 44 BD	55.3 ± 18.8 56.4 ± 19.2	1.5 T 5 mm (2.5 mm gap)	NR	NR	NR	Depressed	NR	No major medical illness	Smaller putamen in MDD. Age negatively correlated with putamen size
Krishnan et al. (1992)	50 MDD	48.3 ± 17 49.3 ± 18	1.5 T 5 mm (2.5 mm gap)	NR	NR	NR	Depressed	NR	NR	BL reduction in caudate nucleus volumes in MDD
Greenwald et al. (1997)	30 MDD 36 HC	75.9 ± 6.7 72.8 ± 6.6	1 T 3.1 mm ROI	45.7 ± 14.1 (EO) 73.2 ± 3.7 (LO)	1.8 ± 1.5 episodes	NR	Depressed	NR	No stroke, degenerative illness, other DSM diagnoses	Greater L caudate atrophy in late-onset (>60) compared with early-onset (<60) MDD
Sheline et al. (1998)	20 MDD 20 HC	54 ± 18 53 ± 17	1.5 T 1.25 mm	NR	NR	NR	Largely euthymic	14 patients on AD	No comorbid conditions	No differences in caudate
Parashos et al. (1998)	72 MDD 38 HC	55.4 ± 16.8 55.1 ± 17.1	1.5 T 5 mm ROI	38.5 ± 19.0	NR	NR	Depressed	NR	NR	Reduced volume of caudate + putamen in MDD. Significant positive association between caudate volume + age of onset
Pillay et al. (1998)	38 MDD 20 HC	38.5 ± 10.0 40.3 ± 10.4	1.5 T 3 mm ROI	NR	NR	NR	Mild to moderately depressed	No medication for 1+ week prior to study	No axis I disorders except phobias. No substance abuse, medical or neurological illness	No differences in caudate + lenticular nuclei. Severity of depression negatively correlated with L caudate volume
Kim et al. (1999)	45 MDD	65 ± 7	1.5 T 1.5 mm ROI	NR	NR	NR	Depressed	None	No other axis I disorders or substance abuse. No seizures, head trauma, cerebrovascular disease, neurological or medical illness	No significant differences between deluded + non-deluded MDD
Lenze and Sheline (1999)	24 MDD 24 HC	53 53	1.25 mm ROI	NR	NR	NR	Depressed	AD	No history of psychosis, psychiatric or medical conditions affecting the CNS	No significant differences in caudate + putamen. No effect of age of onset, severity of depression
Bremner et al. (2000)	16 MDD 16 HC	43 ± 8 45 ± 10	ROI	NR	2 ± 3	NR	Remitted	AD	No PTSD. 5 patients with history of substance abuse/dependence. 1 PD	No caudate volume differences
Lacerda et al. (2003)	25 MDD 48 HC	41 ± 11 35 ± 10	1.5 T 5 mm (1 mm gap) ROI	29.44 ± 11.67	11.88 ± 11.54 4.21 ± 3.76 episodes	NR	10 euthymic, 15 depressed	Drug-free for 2+ weeks before scan	No other axis I disorders, no substance abuse	No differences in caudate, putamen + GP volumes. Inverse correlation between length of illness + L putamen volume
Hannestad et al. (2006)	182 MDD 62 HC	70.2 ± 5.8 70.0 ± 7.7	1.5 T 3 mm (3 mm gap) ROI	43.7 ± 20.8	NR	NR	Depressed	NR	No other DSM disorders, substance abuse, neurological illness	No differences in caudate volume
Hickie et al. (2006)	45 MDD 16 HC	52.0 ± 12.8 55.8 ± 10.3	1.5 T 1.5 mm	36.1 ± 17.2	15.6 ± 16.1 6.9 ± 9.8 episodes	NR	Depressed	29/45 AD	No substance abuse but comorbid axis II disorders. No head injury, neurological illness, stroke, dementia	No differences in caudate + putamen but smaller caudate volumes in MDD subjects with S allele of 5-HTTLPR

See legend of Table 1.

Table 10
Functional studies of the basal ganglia in unipolar depression.

Study	Sample	Age	Method	Age of onset	Duration of illness/# episodes	Family history of illness	Clinical status at testing	Medication status	Comorbidity	Findings	Brodmann map/stereotaxic coordinates
Baxter et al. (1985)	11 MDD 9 HC	34.7 30.8	^{18}F-FDG	NR	NR	NR	Depressed	Drug-free for 1+ week prior to scanning	NR	Lower metabolic rate of caudate (normalized to whole hemisphere volume) in MDD	NR
Baxter et al. (1987)	14 MDD 14 HC	35.3 ± 12.3 31.6 ± 4.5	^{18}F-FDG	NR	NR	NR	Depressed	Free of drugs for 1+ week	NR	No significant differences in head of caudate	NR
Drevets et al. (1992)	13 depressed MDD 10 remitted MDD 33 HC	36.2 ± 8.9 33.6 ± 10.0 30.1 ± 7.8	^{15}O-H_2O Voxel-wise	NR	NR	Yes	Depressed + euthymic	Depressed sample unmediated for 3+ weeks before scan. Remitted sample unmedicated for 4+ months	No co-morbid conditions	Decreased activity in L caudate of depressed MDD	8; 25; 16
Wu et al. (1999)	12 MDD responders 24 MDD non-responders 26 HC	28.8 ± 9.2 30.8 ± 9.9 29.4 ± 9.5	^{18}F-FDG	NR	NR	NR	Depressed	No medication for 2+ weeks	No axis I diagnoses or physical disorders	Decreased striatal metabolism in depressed patients	−31; 21; 10 −22; −4; 10
Mayberg et al. (2000)	17 MDD	49 ± 9	^{18}F-FDG	NR	2 ± 1episodes	NR	Depressed	Scanned before and after treatment with fluoxetine	No history of psychosis or substance abuse. No other axis I disorders. No dementia, head injury, cerebrovascular illness	Decreased metabolism of caudate associated with treatment	−18; 16; 0 −16; 16; 2 18; 16; 0
Brody et al. (2001)	24 MDD 16 HC	35.6 ± 18.3 38.3 ± 11.4	^{18}F-FDG	± 20	NR	± 50%	Depressed	Scanned before and after treatment with paroxetine or psychotherapy. No medications for 2+ weeks prior to start of study	Patients with history of substance abuse excluded. No other axis I disorders	At baseline MDD group had greater activity in caudate	−16; 4; 16 14; −4; 14
Kennedy et al. (2001)	13 MDD 24 HC	36 ± 10 31.7 ± 6.7	^{18}F-FDG	NR	2.84 ± 3.95 episodes	NR	Depressed	Scanned before and after treatment with paroxetine. Off medication of 4+ weeks prior to study	No patients with concurrent DSM diagnosis	Decreased metabolism of ventral striatum at baseline. Increase after treatment	12; 20; −6
Videbech et al. (2001)	42 MDD 47 HC	42 ± 13 41 ± 12	^{15}O-H_2O	NR	2 episodes	NR	Moderately to severely depressed	AD	No substance abuse	No significant differences	NR
Dunn et al. (2002)	31 MDD	42.4 ± 13.6	^{18}F-FDG	15.9 ± 13.1	26.7 ± 14.6	NR	Mildly to severely depressed	Unmedicated for 2+ weeks	No active substance abuse, eating disorder, OCD, dementia, medical illness	Anhedonia associated with decreased activity of the R striatum	14; 16; −4 32; 0; −4
Kegeles et al. (2003)	19 (14 MDD, 5 BD) 10 HC	36 ± 11 39 ± 19	^{18}F-FDG	NR	NR	Yes	Depressed	BZ discontinued 24 h before study in 12 cases. 7 subjects on BZ. Patients free of other medication for 2+ weeks	3 panic disorder, 2 dysthymia, 1 each with social phobia, simple phobia, anorexia + PTSD. No medical illness	Lower activity of L putamen in MDD	−26; 8; −4

Table 10 (*Continued*)

Study	Sample	Age	Method	Age of onset	Duration of illness/# episodes	Family history of illness	Clinical status at testing	Medication status	Comorbidity	Findings	Brodmann map/stereotaxic coordinates
Saxena et al. (2003)	27 MDD	38.1 ± 11.3	^{18}F-FDG	NR	NR	NR	Depressed	Unmedicated for 4+ weeks	No axis I disorders,	Caudate activity not associated with response to paroxetine	NA
Fu et al. (2004)	21 MDD	43.2 ± 8.8	fMRI	NR	NR	NR	Depressed	No medication for 4+ weeks	No neurological trauma, disorder, comorbid axis I condition, substance within 2 months	Exaggerated response to sad faces in L ventral striatum + caudate which improved after treatment	−21; −5; 12
	19 HC	42.8 ± 6.7	1.5 T 8 mm ROI								−15; −4; −4 −20; 17; 16 −22; 12; 4
Holthoff et al. (2004)	41 MDD	45.1 ± 15.66	^{18}F-FDG Voxel-wise	NR	1st episode in 54% of sample. 10 patients had more than 2 episodes	NR	Moderate to severely depressed	Treated with AD. BZ discontinued 3 days before baseline	No substance abusers, axis II disorders	Decreased metabolism of the putamen upon recovery from depression	−24; 6; 14 26; 4; 14
Neumeister et al. (2004)	27 MDD	39.8 ± 12.7	TD	23.8 ± 8.4	3.6 ± 2.6 (episodes)	23/27	Euthymic	Unmedicated	No medical illness	TD associated with increased metabolism of ventral striatum	NR
	19 HC	34.4 ± 11.5	^{18}F-FDG								
Mayberg et al. (2005)	6 MDD	46 ± 8	^{15}O-H_2O	29.5 ± 12	4.7 ± 5 (episodes)	Yes—in 5 out of 6 subjects	Depressed	NR	No psychotic symptoms, substance abuse in last 3 months	Decreased metabolism of R caudate in MDD	14; 2; 12
Neumeister et al. (2006a)	27 MDD	39.7 ± 12.8	^{15}O-H_2O	NR	NR	NR	Remitted	Unmedicated	No medical illness	Reduced rCBF in ventral striatum in response to sad faces in MDD	NR
	26 HC	34.2 ± 12.2	ROI								
Chen et al. (2007a)	17 MDD	44.06 ± 8.36	fMRI 1.5 T 3 mm	NR	NR	NR	Depressed	Scanned before and after treatment with fluoxetine. Patients off medication 4+ weeks before study	No current axis I comorbidity or substance abuse within 2 months of study. Personality disorders not assessed	Increased functional activation of caudate associated with decreased symptom severity at baseline	−11; 25; 1

See legend of Table 1.

Table 11
Morphometric studies of the basal ganglia in BD.

Study	Sample	Age	Method	Age of onset	Illness duration/# episodes	Family history of illness	Clinical status at testing	Medication status	Comorbidity	Findings
Swayze et al. (1992)	48 BD 47 HC	33.41 (M)/33.61 (F)	0.5 T 10 mm ROI	22.86 ± 7.82	5.89 ± 6.15 (hosp)	NR	NR	NR	NR	No significant differences
Strakowski et al. (1993)	17 BD 16 HC	28.4 ± 6.8 30.9 ± 7.3	1.5 T 6 mm ROI	NR	1st episode	NR	Manic	Medication naive	No substance abuse for 1+ month	No significant differences
Dupont et al. (1995b)	48 BD 47 HC	33.41 (M)/33.61 (F)	0.5 T 10 mm ROI	22.86 ± 7.82	NR	NR	NR	NR	NR	No significant differences in the volume of caudate and putamen
Aylward et al. (1994)	30 BD 30 HC	39.3 ± 11.1 37.6 ± 9.0	1.5 T 5 mm	24.6 ± 8.4	NR	NR	1 depressed, 2 manic, 2 mixed, 27 euthymic	AD	No "substantial" substance abuse. No CNS illness, head injury, oral steroids	Larger caudate in male BD
Harvey et al. (1994)	26 BD 34 HC	35.6 31.6	0.5 T 5 mm ROI	23.2	4.1 (hosp)	NR	NR	10 AD, 18 lithium	History of psychosis. No anorexia, alcohol abuse or hypertension	No difference in size of caudate
Sax et al. (1999)	17 BD 12 HC	27 ± 6 27 ± 5	1.5 T 1 mm ROI	NR	NR	NR	Manic + mixed	5 medication free, 12 MS, 5 AP	NR	No significant differences in caudate volume
Strakowski et al. (1999)	24 BD 22 HC	27 ± 6 28 ± 6	1.5 T 1 mm ROI	NR	6 ± 6	NR	14 manic, 10 mixed episode	MS + AP	No substance abuse for 3+ months	No significant differences in striatal volume
Brambilla et al. (2001b)	22 BD 22 HC	36 ± 10 38 ± 10	1.5 T 1.5 mm	20 ± 7	16 ± 9.15	10/12	10 depressed, 11 euthymic, 1 hypomanic	14 lithium, 8 drug-free	No substance abuse for 6+ months	No differences in caudate, putamen or GP volumes. Length of illness predicted smaller L putamen
Noga et al. (2001)	6 discordant BD TP 6 HC TP	34.5 ± 10.5 34.7 ± 11	1.5 T 2 mm ROI	23 ± 9	NR	Yes	NR	AP	No other axis I disorders	Larger L caudate in affected and unaffected twins. Larger R caudate in affected BD twin compared to unaffected twin
Strakowski et al. (2002)	^{18}FE BD 17 multiple episode BD 32 HC	22 ± 6 25 ± 6 24 ± 6	1.5 T 1.5 mm ROI	First episode: 20 ± 5. Multiple episode: 15 ± 4.	2 ± 3 10 ± 5	NR	32 psychotic, 16 mixed state	No prior treatment with medication in FE group. Multiple episode group on MS + AP	No substance abuse within 3+ months of scan	No significant differences in putamen volume. Larger putamen in BD
Beyer et al. (2004a)	36 BD 35 HC	58.8 ± 7.91 63.2 ± 5.25	1.5 T 3 mm (3 mm gap) ROI	NR	15.92 ± 16.58	NR	NR	NR	NR	Smaller R caudate in BD. Effect stronger in late-onset cases, defined as >45 years
DelBello et al. (2004)	23 BD 20 HC	16 ± 2 17 ± 2	1.5 T 1.5 mm ROI	14 ± 3	2.4 ± 2.1	NR	Mixed or manic episode	20 subjects on MS, 11 on AP. Minority on AD or stimulants	No substance abuse in last 3 months or lifetime substance abuse of more than 1 year. 10 subjects with ADHD	Enlarged putamen in BD

Lochhead et al. (2004)	11 (BD (7 BD I 4 BD II) 31 HC	38.2 ± 10 36 ± 14	1.5 T 1.5 mm VBM	24.3 ± 9.2	9.0 ± 6.4 episodes	NR	Depressed	No medication for 2+ weeks	No comorbid disorders	No volumetric changes in BG
McDonald et al. (2004a)	38 BD 52 unaffected relatives 54 HC	41 ± 11.7 44 ± 15.5 40.2 ± 15.3	1.5 T 1.5 mm ROI	22.6 ± 5.5	NR	Yes	NR	33 BD on MS. 10 on AP	No organic brain disease, head trauma, substance abuse in last 12 months	Increased genetic risk for BD associated with reduced volume of ventral striatum
McIntosh et al. (2004)	26 BD 22 unaffected relatives 50 HC	40.5 ± 12.1 34.73 ± 12.6	1.5 T VBM	NR	NR	Yes	NR	NR	NR	GM volume reductions in caudate in both BD subjects and their unaffected relatives 2; −3; 13 −5; −1; 12
Wilke et al. (2004)	10 BD 52 HC	14.5 ± 1.8 15 ± 1	3 T 1.5 mm VBM	NR	NR	NR	Six mixed and 4 manic	No medication 72 h before scan. No data on medication type	No schizophrenia, learning disabilities or pervasive developmental disorders	Enlarged caudate + putamen in BD
Chang et al. (2005b)	20 BD 20 HC	14.6 ± 2.8 14.1 ± 2.8	3 T 1.5 mm ROI	NR	NR	Yes	Depressed + hypomanic	Patients on medication (MS, AD+ AP) except stimulants which were discontinued 24 h prior to scan	No pervasive developmental disorders, substance abuse. 16 ADHD, 7 anxiety disorder, 11 ODD	No difference in caudate volumes
Dickstein et al. (2005)	20 BD 20 HC	13.4 ± 2.5 13.3 ± 2.3	1.5 T 1.2 mm VBM	10.1 ± 3.2	NR	NR	Euthymic	AP, MS, AD	No ADHD, psychosis, anxiety	Gray matter reduction in L nucleus accumbens −6; 9; −7
Haznedar et al. (2005)	40 BD (BD I 17; BD II; 7 cyclothymia 16) 36 HC	39.8 ± 13.4 43.8 ± 6.7 43.9 ± 9.2 40.7 ± 11.6	1.5 T 1.2 mm ROI	NR	NR	Yes (10)	NR	BD II + cyclothymia samples medication free. BD I on MS + AP	"pathological gambling disorder", 1 OCD, 1 panic disorder, 1 PTSD. No concurrent substance dependence, but previous history of abuse	No differences in BG structures
Sanches et al. (2005a)	15 BD 21 HC	15.9 ± 3.2 16.9 ± 3.8	1.5 T 1.5 mm ROI	12 ± 4.17	3.83 ± 2.45 6.87 ± 6.15 (episodes)	Yes	Euthymic	6 lithium, 4 valproate, 4 combination	No substance abuse in last 6 months	No differences in caudate and putamen volumes
Hwang et al. (2006)	21 drug-naive BD 28 drug-treated BD 37 HC	29.9 ± 9.3 34.2 ± 9.5 34.4 ± 11.1	1.5 T 1.5 mm ROI	NR	NR	NR	Depressed	11 lithium, 7 MS, 10 AP	No axis I or axis II disorders, substance abuse within last 3 months	No differences in striatal volumes. R-sided shape differences in drug-free BD
Ahn et al. (2007)	46 BD 22 HC	11.3 ± 2.7 11.1 ± 2.7	1.5 T 1.5 mm ROI	6.8 ± 4.1	2.6 ± 2.9	NR	24 mixed, 8 manic, 9 euthymic, 5 depressed	35 AP, 11 Lith, 18 MS, 15 AD, 11 stimulants, 7 alpha agonists, 2 benz	35 ADHD, 18 psychosis, 12 anxiety. No LD, autism, eating disorders, schiz, current substance abuse, active medical or neurological disease	No significant differences in caudate, putamen, GP

See legend of Table 1.

Table 12
Functional studies of the basal ganglia in BD.

Study	Sample	Age	Method	Age of onset	Illness duration/# episodes	Family history of illness	Clinical status at testing	Medication status	Comorbidity	Findings	Brodmann map/stereotaxic coordinates
Buchsbaum et al. (1986)	20 (16 BD + 4 MDD) 24 HC	39 ± 12.2 31 ± 10.4	^{18}F-FDG	24.8 ± 10	16.8 ± 11.5	NR	NR	Unmedicated for 2+ weeks	NR	Decreased metabolism of the BG	NR
Schwartz et al. (1987)	9 MDD 13 HC	NR	^{18}F-FDG	NR	NR	NR	Depressed	Drug-free for 1+ week prior to scanning	NR	No difference in metabolic rate of caudate (normalized to whole hemisphere volume) in BD	NR
Martinot et al. (1990)	7 BD 10 HC	49 ± 15 38 ± 11	^{18}F-FDG	NR	NR	NR	Severely depressed	At baseline medicated with AP + BZ. Incomplete drug washout for other medications	Substance abusers excluded	No significant metabolic differences in striatal regions	NR
Blumberg et al. (2000)	11 BD	33.4 ± 11.6	^{15}O-H_2O	NR	14.2 ± 14.9 (manic) 12.0 ± 5.6 (euthymic)	NR	5 manic BD; 6 euthymic	MS, AP, AD, BZ	No comorbid axis I or II conditions. Substance abuse taking place >5 years previously was allowed	Increased L caudate activity in manic patients	−16; 20; 0
Ketter et al. (2001)	43 BD I + II (treatment resistant) 43 HC	37.5 ± 10.6 38.1 ± 10.4	^{18}F-FDG	18.8 ± 9.9	18.3 ± 10.4	NR	Depressed, mildly depressed + euthymic	Unmedicated for 2+ weeks	NR	Increased metabolism of ventral striatum in BD	NR
Dunn et al. (2002)	27 BD	36.7 ± 11.3	^{18}F-FDG	18.0 ± 9.9	16.7 ± 14.6	NR	Mildly to severely depressed	Unmedicated for 2+ weeks	No active substance abuse, eating disorder, OCD, dementia, medical illness	Anhedonia associated with decreased activity of the R striatum increased activity of L nucleus accumbens + caudate	12; 18; 0 −4; 6; −4
Blumberg et al. (2003c)	10 BD 10 HC	13.6 ± 2.8 14.6 ± 2.8	fMRI	NR	NR	Yes	Depressed	4 lithium, 3 MS, 3 AD, 2 AP, 1 stimulant	No substance use within 24 h of scan. 2 ADHD, 2 ODD, 2 substance abuse, 1 OCD, 1 anxiety, 1 phobia	Elevated activity of L putamen during Stroop. Greater depression associated with signal increase in ventral striatum	NR
Caligiuri et al. (2003)	24 BD 13 HC	45.7 ± 11.8 35.6 ± 15.7	1.5 T ROI Motor Probe	NR	NR	NR	Manic + depressed	AP, MS, AD	No co-morbidity. Family history of illness not exclusion criterion for HC	Manic but not depressed patients showed elevated BOLD response in L GP + lower activity of R GP. Depressed subjects showed increases in caudate relative to manic patients	NR

Chang et al. (2004)	12 BD (I+II)	14.7 ± 3.0	fMRI	NR	3.1	Yes—56%	Euthymic	MS + AD. Stimulants discontinued 24 h before screening	11/12 with ADHD. No substance abuse, pervasive developmental disorders	Increased activation of L caudate in BD after working memory task	−4; 14; 0
	10 HC	14.4 ± 3.2	3 T Voxel-wise								
Bauer et al. (2005)	10 BD I	39.3 ± 7.8	^{18}F-FDG	NR	20.4 ± 7.0	NR	Depressed	AD, MS, AP	NR	Higher activity of the R ventral striatum at baseline in BD	18; 8; −8
	10 HC	35.0 ± 9.3	Voxel-wise								
Caligiuri et al. (2006)	10 BD	49.5 ± 11.9	1.5 T	NR	NR	NR	10 depressed, 2 manic, 1 mixed	7 AD, 6 MS, 3 AP	NR	Greater caudate + L GP activity in euthymic + hypomanic subjects compared to normative sample. Negative correlation between severity of depression + activity of R GP	NR
			ROI Motor Probe								
Mah et al. (2007)	13 BD II	43.0 ± 8.4	^{18}F-FDG	20 ± 10.5	22.9 ± 12	NR	Depressed	Lithium	No substance abuse within 90 days, substance dependence within 5 years. No current psychotic features. 1 OCD, 1 eating disorder	Increased activity in the ventral striatum in BD	−14; 11; −7
	18 HC	39.0 ± 8.0									16; 11; −6 −10; 10; 1 14; 10; 5 −22; 8; −2 26; 8; −2 30; 4; 0 18; 8; 5

See legend of Table 1.

Table 13
White matter hyperintensities in MDD.

Study	Sample	Age	Method	Age of onset	Illness duration/# episodes	Family history of illness	Clinical status at testing	Medication status	Comorbidity	Findings
Coffey et al. (1988)	67 MDD referred for ECT	71.6 (60–86)	Both MRI + CT MRI: 5 mm (2.5 mm gap). CT: 10 mm	After age 60 in 58% of cases	NR	Yes—43%	Depressed	Tapered off medication	35 heart disease or hypertension, 8 DM, 4 COPD, 2 DVT, 2 dementia	WMH found in 44 MDD
Krishnan et al. (1988)	35 MDD	NR	1.5 T 10 mm	12 < 45 23 > 45	NR	NR	Depressed	AD	No dementia. Greater incidence of medical problems in older group	Higher rate of PVH in late-onset group
Coffey et al. (1989)	51 MDD	71.3	1.5 T 5 mm (2.5 mm gap)	80% > 60	NR	NR	Depressed	Variety of medication for medical illness. 27% with a previous course of ECT	10 patients with history of dementia, 4 alcohol abuse. Cardiovascular risk factors in 58% of sample	PVH in 100% of sample. WMH in 86% of sample
Dolan et al. (1990)	10 MDD 13 HC	47 ± 11 46 ± 7	0.08 T 12 mm ROI	31 ± 9	11 ± 7	NR	Depressed	AD, BZ	No significant medical illness or alcohol abuse	Greater mean T1 relaxation times in frontal WH in MDD
Zubenko et al. (1990)	67 MDD 44 HC	73.2 ± 6.5 68.0 ± 6.2	1.5 T 5 mm (1–2.5 mm gap)	62.5 ± 16.0	NR	NR	Depressed	NR	NR	Increased incidence of infarcts + leukoencephalopathy in MDD
Deicken et al. (1991)	90 psychiatric patients (31 MDD)	43.9 ± 21.5 46.7 ± 21.9	0.5 T 5 mm (2.6 mm gap)	NR	NR	NR	NR	NR	Large variety of cardiovascular risk factors	42% of patients + 12% of HC showed deep WMH. Mean age for patients with and without WMH was 62 and 32
Rabins et al. (1991)	21 MDD 14 HC	23–79 60+	1.5 T ROI	54.2 ± 17.1	NR	NR	Depressed	NR	No neurological disease or head trauma	Greater severity of WMH but not PVH in MDD
Guze and Szuba (1992)	119 MDD (44 young + 75 old) 60 HC (30 young + 30 old).	33.4 66.2 34.1 68.7	0.3 T 7 mm (3 mm gap)	21 (young) 43 (old)	11.6 (young) 24.2 (old)	NR	Depressed	NR	NR	Old MDD group had more WMH than young MDD and old HC. Young defined as less than 45 years of age
Coffey et al. (1993)	48 MDD 76 HC	62.4 ± 16.4 61.6 ± 15.9	1.5 T 5 mm (2.5 mm gap) ROI	NR	NR	NR	Severely depressed	30 free of medication for 2.5 days (median). Remainder on Benz, AD + AP	No substance abuse, neurological disorder. 13 with hypertension or heart disease, 2 with COPD	Greater number of PVH in MDD
Fujikawa et al. (1993)	(1) 31 young, early-onset MDD (2) 70 young, late-onset MDD	56.7 ± 3.6 58.2 ± 3.6	0.5 T 10 mm	Early-onset < 50 Late-onset > 50	NR	NR	Depressed	NR	NR	Frequency of silent cortical infarcts: (1) 22.6% (2) 51.4%

	(3) 41 old, early-onset depression (4). 63 old, late-onset depression	67.6 ± 2.4 72.8 ± 5.3								(3) 65.9% (4) 93.7%
Howard et al. (1993)	12 MDD 12 HC	76.0 ± 6.5 77.7 ± 7.9	1.5 T 8 mm (0.8 mm gap)	>45	NR	NR	Severely depressed	NR	No neurological disorders, stroke or alcohol abuse. Groups matched for cardiovascular risk factors	Trend for PVH + WMH to be more severe in MDD
Dupont et al. (1995b)	33 MDD 32 HC	38.9 ± 10.2 39.2 ± 8.9	1.5 T 5 mm (2.5 mm gap)	±25	NR	Mixed	Depressed	13 AD, 18 no medication	No substance abuse in last 5 years. No hypertension, head injury	No significant differences
Hickie et al. (1995)	39 MDD	64.4	1.5 T 5 mm (2.5 mm gap)	NR	63 ± 54.9 weeks	19/39	Severe depression with history of psychosis	AD, lithium, ECT	Positive history of hypertension + cerebrovascular risk factors. 6/39 with alcohol abuse	Late-onset group (>50) showed more WM changes than earlier onset group. WMH associated with negative family history of depression + poor response to treatment
Lewine et al. (1995)	27 MDD 150 HC	40 ± 11 33 ± 9	1.5 T 5–8 mm	±35	NR	NR	NR	NR	No neurological or medical disorders. No current substance abuse	Deep WMH more common in MDD
Greenwald et al. (1996)	48 MDD 39 HC	74.6 ± 6.1 72.6 ± 6.4	1 T 7 mm (0.7 mm gap)	62.4 ± 15.2	NR	NR	Depressed	NR	No dementia, history of stroke or other DSM diagnosis. 19 MDD with hypertension, 7 heart disease, 6 DM. Similar rates in HC	No significant differences in WMH
Iidaka et al. (1996)	30 MDD 30 HC	67.7 ± 5.4 66.3 ± 4.7	1.5 T 5 mm	61.8 ± 9.4	NR	9/30	Depressed	NR	Matched for cerebrovascular risk factors	More PVH but not WMH in frontal lobes + BG in MDD
O'Brien et al. (1996)	60 MDD 39 HC	71.2 ± 7.9 71.4 ± 11.0	0.3 T 5 mm (0.5–2.5 mm gap)	NR	NR	NR	Depressed	NR	No PD, epilepsy, substance abuse, insulin-dependent DM	Deep WMH in BG and frontal lobes more common in MDD group. Patients with late-onset MDD had more WMH than early-onset MDD
Salloway et al. (1996)	30 MDD	Early-onset: 73.3 ± 7.8 Late-onset: 77.5 ± 4.4	1.5 T 5 mm (2.5 mm gap)	"Early" onset: 35.8 ± 16.4 "Late" onset: 72.4 ± 7.1	±37 (early-onset) ±5 (late-onset)	NR	Depressed	NR	No neurological disorders or substance abuse	More deep WMH + PVH in late-onset group

Table 13 (*Continued*)

Study	Sample	Age	Method	Age of onset	Illness duration/# episodes	Family history of illness	Clinical status at testing	Medication status	Comorbidity	Findings
Dahabra et al. (1998)	23 MDD	66.2 ± 5.1	0.5 T 7 mm (1 mm gap)	12 > 55 11 < 50	NR	NR	Euthymic	AD, 7 lithium	No substance abuse, epilepsy, heart disease, neurological or endocrine disorders	Greater severity of WMH in late-onset MDD
Greenwald et al. (1998)	35 MDD 31 HC	74.7 ± 6.4 72.9 ± 4.7	1 T 5 mm (2.5 mm gap) ROI	56.5 ± 17.1	NR	NR	Depressed	NR	No dementia, stroke, other DSM diagnoses. Patients and controls matched for other cerebrovascular risk factors	Depression associated with L deep frontal and L putaminal WMH
Lenze et al. (1999)	24 MDD	52.7 ± 18.4	1.5 T	19 early-onset (25.4 ± 6.4). 5 late-onset (59.2 ± 6.6)	151 ± 147 (weeks)	Yes—75% (79% early-onset; 60% late-onset)	Depressed	AD	No neurological, endocrine and cerebrovascular disorders. No hypertension	No significant differences in total number of lesions
	24 HC		5 mm							
Sato et al. (1999)	3371 people drawn from background population	72.2	1.5 T 5 mm	NR	NR	NR	NR	NR	No cancer but a variety of cardiovascular risk factors	WMH associated with depressive symptomatology
Steffens et al. (1999)	3660 people drawn from background population	Approximately 75	1.5 T	NR	NR	NR	NR	NR	NR	Number of WMH in BG associated with depressive symptoms as measured with a psychometric scale after controlling for hypertension + cardiovascular disease
de Groot et al. (2000)	1077 non-demented adults	60–90	1.5 T 5–6 mm (20% gap)	NR	NR	NR	NR	NR	No dementia	People with severe WMH were 3–5 times more likely to have symptoms of depression. WMH associated with older age of onset (>60)
Kumar et al. (2000)	51 MDD 30 HC	74.3 ± 6.56 69.43 ± 6.09	1.5 T 5 mm	35 patients had onset after age 60	NR	NR	Depressed	AD, BZ	No neurological disorders, dementia or substance abuse. Both MDD + HC had heart disease, DM	Increase in lesion volume in MDD
MacFall et al. (2001)	88 MDD 47 HC	72.6 ± 7.9 72.2 ± 6.3	1.5 T 3 mm VBM	49.3 ± 22.6	NR	NR	Depressed	NR	NR	Trend towards more deep WMH in MDD

Murata et al. (2001)	20 early-onset MDD 27 late-onset MDD	62.7 ± 6.7 60.3 ± 6.9	1.5 T 5 mm	Early-onset: 39.7 ± 8.8 Late-onset: 65.6 ± 5.4	2.78 ± 0.89 episodes (early) 1.47 ± 0.68 episodes (late)	NR	Depressed	AD, BZ	Incidence of cardiovascular risk factors not different across groups	More severe WMH in late-onset group
Nebes et al. (2001)	92 healthy volunteers	73.6 ± 3.4	1.5 T 5 mm (1 mm gap)	NR	NR	NR	NR	1 person on AD	No PD, HD, AD, schizophrenia, BD, alcoholism, head injury	Deep WMH but not PVH associated with level of depression
Tupler et al. (2002)	115 MDD (69 late-onset, 46 early-onset) 37 HC	66.7 ± 10.9 65.9 ± 9.4	1.5 T 5 mm (2.5 mm gap)	NR	NR	NR	Depressed	NR	No exclusion for comorbid medical illness except dementia	More severe WMH rating in deep frontal regions in late-onset cases. Early-onset defined as <50
Sassi et al. (2003)	17 MDD 38 HC	42.8 ± 9.2 36.8 ± 9.7	1.5 T 5 mm	7/17 < 30 10/17 > 30	NR	Mixed	NR	No medication for 2+ weeks before scan	No neurological disorders, axis I co-morbidity or substance abuse	MDD patients with longer illness duration had more WMH. The early-onset group had more WMH than HC. MDD subjects with a positive-family history had more WMH than their counterparts with no history
Silverstone et al. (2003)	11 MDD 19 HC	34.4 35.9	0.5 T 5 mm (2.5 mm gaps)	26.6	7.8	NR	Depressed	NR	No neurological disorders, cardiovascular disease, DM or head injury	No between group differences
Firbank et al. (2004)	29 MDD 32 HC	75.7 ± 5.9 74.9 ± 7.0	1.0 T 5 mm (1.5 mm gap) VBM	NR	±21.5 ±4 episodes	NR	Depressed	NR	No dementia, substance abuse, history of stroke, ischemic attack. Other vascular risk factors allowed	Greater frontal lobe WM lesion volume in MDD. Differences between groups greater after exclusion of subjects with hypertension, DM and heart disease
Janssen et al. (2004)	28 MDD 41 HC	64.04 ± 10.9 62.37 ± 11.38	1.5 T 1.2–5 mm ROI	33.04 ± 9.48	93.5 ± 17.5 months	NR	Depressed	22 AD, 4 lithium, 1 BZ	NR	No differences in WMH
Kumar et al. (2004)	8 MDD 8 HC	71.5 ± 5.13 74.1 ± 8.90	MT-MRI 1.5 T 3 mm ROI	NR	NR	NR	Depressed	Off medication for 2+ weeks	No neurological disorders including dementia	Abnormalities in the WM of the R caudate + R putamen in MDD
Lloyd et al. (2004)	51 MDD (23 early-onset; 28 late-onset) 39 HC	72.7 ± 6.7 75.1 ± 5.8 73.1 ± 6.7	1 T 1 mm	38.7 (N = 23) 72.0 (N = 28)	88.3 weeks; 5.1 (episodes) 24.3 weeks; 2.0 (episodes)	NR	Depressed	AD	No drug or alcohol abuse, neurological or serious medical disorders	No differences between groups

Table 13 (*Continued*)

Study	Sample	Age	Method	Age of onset	Illness duration/# episodes	Family history of illness	Clinical status at testing	Medication status	Comorbidity	Findings
Firbank et al. (2005)	629 subjects from background population	NR	5 mm	NR	NR	NR	NR	NR	439 with hypertension, 184 with history of stroke	Level of depression associated with severity of WMH
Heiden et al. (2005)	31 MDD	68.0 ± 6.5	1.5 T 6 mm (0.6 mm gap)	47–51	NR	NR	NR	AD	NR	Extent of WMH associated with severity of depression after 5 year follow-up. Severity of WMH associated with poorer outcome
Jorm et al. (2005)	475 background volunteers. 17 classified as MDD	60–64	1.5 T 2 mm	NR	NR	NR	Depressed	NR	NR	Association between total brain WMH + depression. Remitted subjects taking AD intermediate to depressed patients + HC
Minett et al. (2005)	60 patients attending memory clinic (12 MDD)	72.6 ± 4.7	1.5 T 5 mm (0.5 mm gap)	NR	NR	NR	NR	NR	No dementia, severe medical or neurological disease, current psychiatric disorders or alcohol abuse	Late-onset depression associated with WMH severity
Taylor et al. (2005)	253 MDD 146 HC	70.48 ± 6.23 69.85 ± 7.54	1.5 T 3 mm	NR	NR	NR	Depressed	NR	No other major psychiatric disorders such as BD. No substance abuse or neurological disorders. Hypertension + heart disease more common in MDD	Greater WM lesion volumes in MDD
Bae et al. (2006)	106 MDD 84 HC	70.4 ± 6.4 71.7 ± 6.0	DTI 1.5 T 3 mm ROI	NR	NR	NR	Depressed	NR	NR	Loss of WM integrity in middle + superior frontal gyri + ACC
Chen et al. (2006)	164 MDD 126 HC	68.93 ± 7.04 69.83 ± 6.25	1.5 T 3 mm (3 mm gap)	NR	NR	NR	Depressed	Yes—not specified	No current substance abuse, psychiatric or neurological illness	Greater volume of WM lesions at baseline + at 2-year + 4-year follow-up in MDD
Hannestad et al. (2006)	182 MDD 62 HC	70.2 ± 5.8 70.0 ± 7.7	1.5 T 3 mm (3 mm gap) ROI	43.7 ± 20.8	NR	NR	Depressed	NR	No other DSM disorders, substance abuse, neurological illness	Greater volume of WML in MDD
Iosifescu et al. (2006)	84 MDD 35 HC	40.7 ± 10.2 39.3 ± 9.8	1.5 T 3 mm	NR	NR	NR	Depressed	No medication	No BD, psychosis, substance abuse within last 21 months, organic mental disorder, seizure disorder, unstable medical illness	No difference in prevalence of WMH. WMH correlated with cardiovascular risk score

Nobuhara et al. (2006)	13 MDD 13 HC	62.8 ± 6.6 61.5 ± 4.8	DTI 1.5 T 6 mm (2 mm gap) ROI	52.9 ± 7.3	4.0 ± 2.6	NR	Depressed	AD	No dementia, severe medical illness, neurological disorders	Loss of integrity of WM frontal and temporal tracts
Rainer et al. (2006)	51 MDD 204 HC	75.8 (whole sample)	1 T	>65—not specified	NR	NR	Depressed	AD, BZ	Groups matched for cardiovascular risk factors	No differences in incidence of WMH
Versluis et al. (2006)	527 background population	74.9	1.5 T 3 mm	NR	NR	NR	NR	NR	Cerebrovascular risk factors not exclusion criterion	Presence of WMH at baseline was not predictive of depression at 33-month follow-up
Godin et al. (2007)	1214 subjects followed for 4 years. 14.5% depressed at baseline	72.5 ± 4.1	1.5 T 3.5 mm (0.5 mm gap)	NR	NR	NR	Depressed	AD—not specified	No pacemaker, vulvular prosthesis, history of neurosurgery or aneurysm	Patients with baseline depression had more WMH at follow-up. Among non-depressed subjects at baseline, the higher the rate of WMH, the greater the risk of depression at follow-up
Janssen et al. (2007)	13 early-onset MDD 15 late-onset depression 22 HC	70.38 ± 8.3 72.67 ± 6.7 71.05 ± 7.5	1.5 T	33.62 ± 8.8 69.93 ± 6.4	NR	NR	Depressed	4 lithium	Cerebrovascular risk factors not exclusion criterion. No neurological disorders, dementia, substance abuse	Greater severity of WMH in late-onset group
Ma et al. (2007)	14 MDD 14 HC	28.9 ± 8.0 27.1 ± 6.7	1.5 T 2 mm DTI	28.1 ± 7.8	10.3 ± 8.3 (months)	NR	Depressed	Treatment naive	No LOC, substance abuse in last 9 months, mental retardation, serious medical or neurological illness	Lower FA in WM of R middle frontal gyrus (dorsal PFC), parietal + occipito-temporal lobes
Yang et al. (2007)	31 MDD 15 HC	64.6 ± 5.21 64.3 ± 4.22	1.5 T DTI 3 mm ROI	NR	NR	NR	Depressed	24 AD, 7 drug-free	No substance abuse, major psychiatric or neurological disorders	Decreased FA values in middle, superior frontal gyri + R parahippocampal gyrus
Zanetti et al. (2008)	28 MDD 102 HC	30.5 30.4	1.5 T 3 mm	NR	34.1 (28.5) weeks	NR	Psychotic	16 AP, 14 AD, 4 MS, 7 drug-free	No organic, neurological illness, head injury, mental retardation. 6 individuals with substance abuse/ dependence, 2 individuals with hypertension	No significant differences in prevalence or severity of WMH between groups

See legend of Table 1.

adjacent to the striatum and thalamus (Haznedar et al., 2005), genu of the corpus callosum (Yurgelun-Todd et al., 2007), and prefrontal and temporal cortex (Bruno et al., 2008). Further, a DTI tractography (allows for the measurement of entire WM pathways) study reported a higher incidence of reconstructed WM fibres linking the left sgACC and the amygdalo-hippocampal complex in remitted adults with BD (Houenou et al., 2007).

Most MRI-based reports of BD-associated WMH are, however, derived from pediatric samples. A significant minority of young BD patients with a relatively typical age-of-onset show WM abnormalities on MRI (Table 14).

Adler et al. (2004) has hypothesized that the pattern of deep frontal WM pathology commonly seen in affective illness, results in a disruption of the pathways linking subcortical regions such as the striatum to functionally homologous regions of the prefrontal cortex—a version of the so-called "disconnection syndrome" (Geschwind, 1965). In the following three sections, we discuss key areas of the PFC involved in the regulation of emotional behavior.

3.6. The orbital frontal cortex

The orbital frontal cortex (OFC) on the ventral surface of the frontal lobe receives inputs from the ventrolateral amygdala and other limbic structures such as the entorhinal and perirhinal cortices, and the hippocampal subiculum (Price, 1999). The OFC also projects directly to the amygdala, hypothalamus, and brainstem, modulating limbic-driven behavior (Ongur and Price, 2000). More specifically, it acts to integrate limbic data with sensory input thus providing a first-pass analysis of the reward or aversive value of stimuli (Price, 1999; Kringelbach, 2005). These data then feed into higher level processing circuits such as that of the mPFC (*vide infra*) which act together with the OFC to guide behavior in terms of these expected contingencies (Kringelbach and Rolls, 2004; Amodio and Frith, 2006).

3.6.1. MDD

Functional imaging analyses of the OFC in MDD (Table 15) are generally suggestive of increased metabolism or blood flow in the eyes closed or resting state in young to middle-aged samples (Drevets et al., 1992, 2002a; Biver et al., 1994)—particularly acutely depressed subjects (Drevets, 2007). In contrast, while performing a probabilistic reversal learning task, MDD patients demonstrated attenuated hemodynamic activity in the lateral OFC/ventrolateral PFC and dorsomedial PFC relative to both healthy controls and BD subjects on trials in which misleading negative feedback triggered a behavioral response reversal, compared to trials in which misleading negative feedback did not precipitate reversal (Taylor Tavares et al., 2008). This physiological difference was associated with an increased likelihood for the MDD subjects to switch their behavioral responses as a result of the misleading negative feedback, although basic object reversal learning is intact in depression. Another study showed an increased hemodynamic response in the posterior orbital cortex in depressed versus non-depressed BD subjects imaged while performing a color-word Stroop task (Blumberg et al., 2003b).

Concerning the structural neuroimaging data, a sample of elderly MDD patients was first reported by Lai et al. (2000) to show bilateral volume reduction of the OFC. This finding has been replicated a number of times in elderly populations with later-onset depression (Table 16) and a negative association between the integrity of the white matter tracts of the OFC and severity of depression in a late-onset MDD group has also been recorded (Nobuhara et al., 2006). Lacerda et al. (2004) reported a reduction of right medial and left lateral OFC volume in a younger sample (mean age 39) although the effect was more pronounced in depressed compared with euthymic patients. Similar to the (Nobuhara et al., 2006) report, Chen et al. (2007a) found that severity of depression correlated negatively with right OFC volume.

3.6.2. BD

GM volume reductions of the OFC have also been reported in adult (Frangou, 2005; Haznedar et al., 2005; Lyoo et al., 2006; Nugent et al., 2006) and pediatric BD samples (Wilke et al., 2004; Najt et al., 2007); although see (Lopez-Larson et al., 2002) and (Dickstein et al., 2005). Thus unlike MDD, BD-associated volume reduction of the OFC appears to occur in individuals with a more typical age-of-onset (Table 18).

Concerning functional imaging studies of the OFC in BD (Table 17) (Blumberg et al., 1999) showed that manic patients have reduced rCBF in this region while induction of a sad mood through psychological means resulted in decreased rCBF to the medial OFC in euthymic but not depressed patients compared with controls (Kruger et al., 2003). A study using an affective Go/NoGo paradigm to examine neural activity during voluntary attentional control of emotion found that despite intact task performance, euthymic BD adults demonstrated abnormally increased activity in bilateral OFC and left dorsal ACC, together with increased activity in some subcortical limbic regions, when inhibiting responses to emotional versus neutral distractors (Wessa et al., 2007).

Other studies showed reduced activity in euthymic BD relative to healthy adults during automatic attentional control paradigms, such as the non-emotional Stroop color-word or counting task, in the left OFC/VLPFC and mPFC (Blumberg et al., 2003b; Kronhaus et al., 2006), and the right mPFC (Strakowski et al., 2005) and dorsal ACG, but also increased activity in right dorsolateral PFC (Gruber et al., 2004). Subjects imaged during the depressed or manic phases of BD while performing similar paradigms also showed reduced left OFC activity relative to healthy controls (Blumberg et al., 2003b), although these findings were not replicated by others (Marchand et al., 2007). Most of these studies showed intact task performance in BD adults, although in other cases performance was impaired relative to healthy controls (Strakowski et al., 2005).

3.7. The ventro-medial "Emotion" circuit

Neuroimaging data suggest that the peri-callosal tissue of the ventro-medial prefrontal cortex known as the anterior cingulate cortex (BA 24, 25, and 32)[1] (Fig. 2) plays a pivotal role in translating OFC-derived valenced data into actions and behavior (Bush et al., 2000; Devinsky et al., 1995; Drevets, 2000a).

Drevets et al. (1997) carried out the first well-controlled imaging study of the medial prefrontal cortex in affective illness. Both depressed BD and MDD patients with a family history of affective illness showed left hemisphere gray matter loss in a region immediately ventral to the genu of the corpus callosum—the subgenual anterior cingulate cortex (sgACC). Further, the medication free patients displayed reduced metabolism of the left sgACC as demonstrated by PET.

In the interim, at least seven other studies have provided further evidence for MDD or BD-associated GM loss in the sgACC (Hirayasu et al., 1999; Botteron et al., 2002; Sharma et al., 2003; Hastings et al., 2004; Boes et al., 2007; Koo et al., 2008; Yucel et al., 2008) (Tables 20 and 22). The recent meta-analysis of Hajek et al.

[1] Perhaps because of inadequate differentiation between non-human primate and human neuroanatomy, the literature is characterized by inconsistent usage of Brodmann map areas which make up the sgACC. We recommend the human anatomical schema of Price and colleagues which can be found in Figure 3. Nevertheless, in Tables 21–24 we have cited the authors' original anatomical descriptions, verbatim.

Table 14
White matter hyperintensities in BD.

Study	Sample	Age	Method	Age of onset	Illness duration/# episodes	Family history of illness	Clinical status at testing	Medication status	Medical + psychiatric comorbidity	Findings
Dolan et al. (1990)	14 BD 13 HC	39 ± 9 46 ± 7	0.08 T 12 mm ROI	31 ± 9	11 ± 7	NR	Depressed	Lith, AD, BZ	No significant medical illness or alcohol abuse	No group differences
Dupont et al. (1990)	19 BD 10 HC	36.5 ± 10 41 ± 10	1.5 T 5 mm (2.5 mm gap)	25 ± 7.5	NR	Mixed—not specified	Mixed—not specified	Lith, MS. No Benz, ECT, antihypertensives	No poorly controlled hypertension, head injury with neurological sequelae, substance abuse of greater than 5 years duration	9 out of 19 BD subjects and no HC showed deep frontal WMH. No differences in age, age of onset, family history of BD between those patients with WMH and those without, but WMH associated with more hospitalizations
Swayze et al. (1990)	48 BD 47 HC	33.9 34.4	0.5 T 10 mm	22.86 ± 7.82	5.89 ± 6.15 (hosp)	NR	Manic	Lithium, AP, ECT	27 with drug abuse, 33 with alcohol abuse	9 out of 48 BD and 2 out of 47 HC showed WMH
Figiel et al. (1991)	18 BD 18 HC	37.5 (26–56) 34.7	1.5 T 5 mm (2.5 mm gap)	NR	±28	NR	12 manic, 6 depressed	NR	No dementia, neurological illnesses. Presence of atherosclerotic risk factors similar in BD and HC	WMH in 8 out of 18 BD, 1 out of 18 HC
McDonald et al. (1991)	12 BD 12 HC	68.3 ± 7 67.7 ± 7	1.5 T 5 mm (2.5 mm gap)	62 ± 6	NR	3/12	manic	NR	1 patient with ataxia, 1 with peripheral neuropathy, 1 with tardive dyskinesia. All patients had cognitive dysfunction	More BL subcortical WMH in BD group
Brown et al. (1992)	22 BD 154 HC	37.7 ± 7.6 34 ± 9.5	0.5 T and 1.5 T 7 mm	NR	NR	NR	NR	NR	No history of cardiovascular risk factors, current drug abuse	No inter-group differences in WMH
Strakowski et al. (1993)	18 BD 15 HC	31 ± 11.8 32.4 ± 8.8	1.5 T 5 mm (2 mm gap)	NR	1st episode	NR	Manic	Majority of patients medication naive	5 BD with drug abuse. No major neurological or medical illness	More WMH in BD but not statistically significant
Aylward et al. (1994)	30 BD 30 HC	39.3 ± 11.1 37.6 ± 9.0	1.5 T 5 mm	24.6 ± 8.4	NR	NR	1 depressed, 2 manic, 2 mixed, 27 euthymic	AD	No "substantial" substance abuse. 7 hypertension, 12 smokers, 3 cardiovascular disease, 3 elevated cholesterol, 1 DM	Greater prevalence of deep WMH in BD but significant differences due to older BD group
Altshuler et al. (1995)	29 BD I 26 BD II 20 HC	41.6 ± 11.6 40.0 ± 10.0 35.2 ± 9.9	0.5 T 10 mm	28.3 ± 10.9 for BD I, 19.2 ± 7 for BD II	14.2 ± 8.7 (BD I) 18.9 ± 7.7 (BD II)	NR	Euthymic	30 lithium, 10 carbamazepine, 3 AD	1 DM, 4 hypertension	No significant difference between groups in deep frontal WMH. Trend (2×) towards more PVH in BD I. Greater number of PVH was due to BD I subsample >30 years of age

Table 14 (*Continued*)

Study	Sample	Age	Method	Age of onset	Illness duration/# episodes	Family history of illness	Clinical status at testing	Medication status	Medical + psychiatric comorbidity	Findings
Botteron et al. (1995)	11 BD 5 HC	11.3 ± 3.1 11.8 ± 2.9	1.5 T 4–5 mm	NR	NR	NR	Manic	NR	No autism, pervasive developmental disorder, anorexia, bulimia, major medical or neurological illness, head injury	WMH in 2 BD patients
Dupont et al. (1995b)	44 BD 32 HC	36.6 ± 10.7 39.2 ± 8.9	1.5 T 5 mm (2.5 mm gaps)	23 ± 8.0	NR	Mixed	28 BD in remission, others depressed or manic	26 lithium, 6 AD, 6 AP, 2 anticholinergics	No substance abuse in last 5 years. No hypertension, head injury	Greater number of WMH in BD (46% vs. 22%). Not accounted for by age of onset. Higher (but not significant) rate of WMH in subjects with family history
Lewine et al. (1995)	20 BD 150 HC	36 ± 7	1.5 T 5–8 mm	±30	NR	NR	NR	NR	No neurological or medical disorders. No current substance abuse	No significant differences
Woods et al. (1995)	52 BD 38 HC	36.3 ± 15.1 36.3 ± 11.4	1.5 T 5 mm (2.5 mm gap)	NR	2.1 ± 1.8 (hosp)	NR	NR	NR	NR	More deep WMH and PVH in BD
Persaud et al. (1997)	26 BD 34 HC	35.6 31.6	0.5 T 5 mm	25	NR	NR	Manic	NR	No hypertensives, anorexics, heavy drinkers	No significant differences
Ahearn et al. (1998)	21 family members (9 BD, 2 MDD, 10 unaffected)	41 (range 12–66)	1.5 T 4–6 mm	18	NR	Yes	NR	NR	No substantial artherosclerotic risk factors	WMH in 9 affecteds and 6 unaffecteds
McDonald et al. (1999)	79 BD 70 HC	49.9 ± 19.7 53.2 ± 18.1	1.5 T 5 mm (2.5 mm gap)	38 ± 17	NR	NR	NR	NR	NR	16% of young BD (35.9 ± 11) vs. 0% HC showed WMH. No difference between old (68.2 ± 9) BD and old HC
Krabbendam et al. (2000)	21 BD 22 HC	38.3 ± 7.9 41.4 ± 11.3	1.5 T 5 mm (0.5 mm gap)	32.2 ± 9.4	6.2 ± 5.1 dep episodes 3.9 ± 3.7 manic episodes	NR	Remitted	16 Lith 6 MS	No cerebrovascular disease; head injury, DM, hypertension; substance abuse in last year	No significant differences
Moore et al. (2001)	14 BD (good outcome) 15 BD (poor outcome) 15 HC	47.4 ± 10.10 42.1 ± 13.9 41.9 ± 12.6	0.5 T 7 mm (1 mm gap)	31.4 in good outcome and 26.3 in poor outcome groups	16 ± 7.9 8.6 ± 6.0 episodes (good outcome) 15.8 ± 10.8 8.9 ± 4.3 episodes (poor outcome)	4 in each group	Good outcome group euthymic Poor outcome group depressed	Lithium in good outcome group, not specified in poor outcome	No axis I comorbidity, learning disorders, neurological or cerebrovascular disease, head injury, hypertension, cardiovascular illness, drug abuse	Greater number of subcortical WMH in poor outcome BD (7/15) group than good outcome sample (1/14) or controls (0/15)

Lopez-Larson et al. (2002)	17 BD 12 HC	29 ± 8 31 ± 8	1.5 T 1 mm ROI	NR	7 ± 6	NR	Manic	9 MS, 4 AP, 3 AD	No medical or neurological disorders, head injury, substance abuse in previous 3 months	No WM differences
Lyoo et al. (2002b)	56 BD 83 HC	13.6 ± 2.1 9.9 ± 3.3	1.5 T 5 mm (2.5 mm gap)	NR	NR	NR	NR	NR	NR	Greater number of frontal WMH in BD (17.9%) compared with HC (1.2%)
Pillai et al. (2002)	15 BD 16 HC	15.0 ± 2.4 16.0 ± 1.8	1.5 T 5 mm (2 mm gap)	10 ± 4.2	5 ± 3.4	NR	NR	NR	No significant neurological disorder, head injury with loss of consciousness for more than 20 min. No substance abuse	WMH present in 10 BD (67%) and 5 HC (31%)
Sassi et al. (2003)	24 BD 17 MDD 38 HC	34.2 ± 9.9 42.8 ± 9.2 36.8 ± 9.7	1.5 T 5 mm	14/24 < 20 10/24 > 21	NR	12/24	NR	Lithium	No neurological disorders, axis I comorbidity or substance abuse	No significant differences
Silverstone et al. (2003)	13 BD 19 HC	40.2 35.9	0.5 T 5 mm (2.5 mm gap)	25.9	14.2	NR	Depressed	NR	No neurological disorders, cardiovascular disease, DM or head injury	More BD subjects (56%) had deep frontal WMH than HC (26%). Effect strongest in older subjects. No differences in PVH
Adler et al. (2004)	9 BD 9 HC	32 ± 8 31 ± 7	3 T 5 mm ROI	NR	NR	NR	NR	MS, AP	No concurrent psychiatric or medical illness including substance abuse	Reduced fractional anisotropy in frontal regions of BD indicative of loss of bundle coherence of WM tracts
Ahn et al. (2004)	43 BD 39 HC	36.9 ± 11.9 35.1 ± 9.7	1.5 T 3 mm	NR	NR	NR	NR	NR	No axis I disorders, substance abuse within 3 months of study, anti-social PD, neurological illnesses, head injury, seizure, ADHD	Greater number of deep frontal WMH in BD (27.9%) compared with HC (7.7%)
Beyer et al. (2005)	14 BD 21 HC	44.0 ± 17.6 44.6 ± 13.5	1.5 T 5 mm (2.5 mm gap) ROI	NR	13.6 ± 12.1	NR	6 depressed, 5 manic, 3 euthymic	NR	No dementia, neurological or medical illnesses, other primary psychiatric diagnosis or recent substance abuse	WM of OFC exhibited higher apparent diffusion coefficients but not FA in BD
Chang et al. (2005a)	20 BD 20 HC	14.6 ± 2.8 14.1 ± 2.8	3 T 1.5 mm	NR	1.7 ± 1.8	NR	3 manic, 3 mixed, 1 depressed, 13 euthymic	MS, AD, AP. Psychostimulants discontinued 24 h before scan	No pervasive developmental disorders, neurological conditions, substance abuse. 85% had ADHD, 35% anxiety disorder, 60% ODD	No difference between groups in prevalence of WMH
Adler et al. (2006a)	11 BD 17 HC	14 ± 2	3 T 5 mm ROI	11 ± 3	1st episode	NR	Manic or mixed episode	Nil	No substance abuse in last 3 months. No head trauma, unstable neurological or medical conditions	No differences in FA of medial and inferior frontal regions but FA of superior frontal cortex lower in BD

Table 14 (*Continued*)

Study	Sample	Age	Method	Age of onset	Illness duration/# episodes	Family history of illness	Clinical status at testing	Medication status	Medical + psychiatric comorbidity	Findings
de Asis et al. (2006)	40 BD 15 HC	69.8 ± 6.7 66.9 ± 6.5	1.5 T 5 mm	51.8 ± 18.3	NR	NR	Manic	NR	No dementia, medical illness	More severe deep frontal WMH in BD. Positive association between age of onset of mania + WMH
El-Badri et al. (2006)	50 BD 26 HC	30.2 ± 6.2 30.2 ± 6.2	0.5 T	NR	8.9 ± 3.3	NR	Euthymic	NR	No axis I comorbidity, learning disorders, neurological or cerebrovascular disease, head injury, hypertension, cardiovascular illness, drug abuse	Deep WMH found in 5 BD but no HC
Gulseren et al. (2006)	12 BD 1 12 siblings 12 HC	30.9 ± 3.6 29.5 ± 5.8 30.4 ± 3.6	0.5 T 5 mm	24.8 ± 3.6	6.1 ± 3.2	Yes—2/12	NR	Lithium	No substance abuse, hypertension, history of neurological disorders or head trauma. All subjects <45 years old	No difference in frequencies of WMH. Number of WMH correlated with # manic episodes
Regenold et al. (2006)	8 severe BD 8 controls with neurological illness	58.4 ± 12.9 54.5 ± 12.8	1.5 T 5 mm (1 mm gap) DTI ROI	32	25 ± 7.2 (episodes)	NR	4 manic, 3 mixed, 1 depressed	7 MS, 7 AP, 2 AD, 2 Benz	6 BD, 1 control smokers. No substance abuse	Elevated apparent diffusion coefficient as evinced by DTI—indicative of decreased integrity of WM in the frontal lobes of BD patients
Houenou et al. (2007)	16 BD 16 HC	41.88 ± 12.82 40.50 ± 12.82	1.5 T 1.3 mm DTI	18.13 ± 3.77	NR	NR	Euthymic	Lithium, AD	No neurological conditions, substance abuse, head injury. 1 patient with comorbid PD	Increased number of white matter tracts between the L sgACC and the amygdala-hippocampal complex. This result was not influenced by illness duration
Yurgelun-Todd et al. (2007)	11 BPD 1 10 HC	32.9 ± 10.5 32.4 ± 9.1	1.5 T 5 mm DTI	21.7 ± 5.4	12.0 ± 9.8	NR	Euthymic	Lith, MS, AP	No organic mental disorder, head injury, CNS disease, substance abuse in previous 6 months	BD patients had significantly higher FA in the midline of the genu but not splenium indicating changes in WM microstructure
Zanetti et al. (2008)	25 BD 102 HC	28.7 30.4	1.5 T 3 mm	NR	27.1 ± 19.3 weeks	NR	Psychotic	12 AP, 2 AD, 13 MS, 6 drug-free	No organic, neurological illness, head injury, mental retardation. 5 individuals with substance abuse/dependence, 2 individuals with hypertension	No significant differences in prevalence or severity of WMH between groups

See legend of Table 1.

Table 15
Functional analyses of the orbitofrontal cortex in MDD.

Study	Sample	Age	Method	Age of onset	Duration of illness/# episodes	Family history of illness	Clinical status at testing	Medication status	Comorbidity	Findings	Brodmann map/stereotaxic coordinates
Baxter et al. (1987)	14 MDD 14 HC	35.3 ± 12.3 31.6 ± 4.5	^{18}F-FDG	NR	NR	NR	Depressed	Free of drugs for 1+ week	NR	No significant differences	NR
Drevets et al. (1992)	13 depressed MDD 10 remitted MDD 33 HC	36.2 ± 8.9 33.6 ± 10.0 30.1 ± 7.8	^{15}O-H_2O Voxel-wise	NR	NR	Yes	Depressed + euthymic	Depressed sample unmediated for 3+ weeks before scan. Remitted sample unmedicated for 4+ months	No co-morbid conditions	Elevated BF in L PFC (which included a portion of the lateral OFC) of depressed MDD	47; 41; 6
Biver et al. (1994)	12 MDD 12 HC	37.6 ± 13.2 31.08 ± 5.4	^{18}F-FDG ROI	NR	NR	NR	Depressed	Unmediated for 10+ days prior to scan	No neurological disorders or other medical conditions	Metabolic rate increased in OFC of MDD	NR
Brody et al. (1999)	16 MDD	39.3 ± 9.5	^{18}F-FDG ROI	NR	±1 ± 1 (episodes)	NR	Depressed	No medication for 2+ weeks prior to scan	No axis I disorders, substance abuse, medical conditions	Decrease in metabolism from baseline of OFC in patients who responded to paroxetine	NR
Drevets et al. (2002a)	20 MDD 14 HC	36 ± 10 34 ± 9.1	^{18}F-FDG	NR	NR	NR	Depressed	Patients medication free for 3+ weeks prior to study	No other psychiatric disorders or substance abuse	Greater baseline metabolic rate of lateral OFC in MDD	BA 47
Liotti et al. (2002)	10 remitted MDD 7 ill MDD 8 HC	37 ± 9 42 ± 15 36 ± 6	^{15}O-H_2O 6.5 mm	NR	NR	NR	Euthymic	AD	No other primary psychiatric or neurological disorder. No head injury, substance abuse	Mood provocation led to rCBF decreases in medial OFC in both MDD groups	BA 10+32 −4; 40; −2 4; 56; 8 4; 36; −10 2; 60; −2 0; 34; −14
Goldapple et al. (2004)	17 MDD	41 ± 9	^{18}F-FDG Voxel-wise	NR	NR	NR	Depressed	Unmedicated	No psychotic symptoms, axis I disorders and substance abuse	Successful treatment with CBT associated with decreased metabolism of medial OFC	BA 11 20; 52; −22
Mayberg et al. (2005)	6 MDD	46 ± 8	^{15}O-H_2O	29.5 ± 12	4.7 ± 5 (episodes)	Yes—in 5 out of 6 subjects	Depressed	NR	No psychotic symptoms, substance abuse in last 3 months	Treatment with deep brain stimulation produced decreased metabolism of the OFC	BA 11 0; 34; −8 6; 46; 2 22; 60; −10
Chen et al. (2007a)	17 MDD	44.06 ± 8.36	MRI 1.5 T 3 mm	NR	NR	NR	Depressed	Scanned before and after treatment with fluoxetine. Patients off medication 4+ weeks before study	No current axis I comorbidity or substance abuse within 2 months of study. Personality disorders not assessed	Functional activation of OFC negatively associated with severity of depression at baseline	BA 11 5; 46; −14 −20; 46; −17

See legend of Table 1.

Table 16
Morphometric analyses of the orbitofrontal cortex in MDD.

Study	Sample	Age	Method	Age of onset	Duration of illness/# episodes	Family history of illness	Clinical status at testing	Medication status	Comorbidity	Findings
Parashos et al. (1998)	72 MDD 38 HC	55.4 ± 16.8 55.1 ± 17.1	1.5 T 5 mm ROI	38.5 ± 19.0	NR	NR	Depressed	NR	NR	No differences in OFC volume
Lai et al. (2000)	20 MDD 20 HC	66.65 ± 5.65 71.79 ± 4.44	1.5 T 3 mm ROI	44.75 ± 18.03	3.75 (hosp)	NR	Moderately depressed	15 AD	No major psychiatric disorder, substance dependence, primary neurological illness	Bilateral reduction of orbital PFC in MDD
MacFall et al. (2001)	88 MDD 47 HC	72.6 ± 7.9 72.2 ± 6.3	1.5 3 mm VBM	49.3 ± 22.6	NR	NR	Depressed	NR	NR	Increased lesion density of medial OFC which correlated with severity of depression −18, 40, −10
Bremner et al. (2002)	15 MDD 20 HC	43 ± 8 45 ± 11	1.5 T 3 mm ROI	NR	2 ± 3 (episodes)	NR	Remitted	AD	Current substance abusers excluded. No history of schizophrenia, PTSD. About 20% of sample had past history of substance abuse	Medial OFC (gyrus rectus) reduced by 32% in MDD
Steffens et al. (2003)	30 MDD 40 HC	69.60 ± 7.15 70.90 ± 6.13	1.5 T 3 mm ROI	NR	NR	NR	NR	NR	No other major psychiatric illness, substance dependence, primary neurological illness	Bilateral reduction of orbital PFC in MDD
Taylor et al. (2003)	41 MDD 40 HC	68.73 ± 6.98 71.42 ± 6.07	1.5 T 3 mm ROI	NR	NR	NR	Depressed	AD	No other major psychiatric illness, substance dependence, primary neurological illness	Smaller medial orbitofrontal gyri volume in MDD. OFC volume also associated with functional impairment
Ballmaier et al. (2004)	24 MDD 19 HC	65.85 ± 8.18 66.24 ± 7.25	1.5 T 1.4 mm ROI	35.0 ± 3.45	2 ± 3 (episodes)	NR	Depressed	No medication for 2+ weeks before imaging	No history of dementia, neurological disorder, BD, alcohol abuse	BL volume reduction of OFC (12%) + gyrus rectus (19–24%) in MDD
Hastings et al. (2004)	18 MDD 18 HC	38.9 ± 11.4 34.8 ± 13.6	1.5 T 1.5 mm ROI	23 ± 12.3	4.7 ± 4.4 (episodes)	Mixed	Depressed	Not medicated at time of scan	No other axis I disorders. No current drug abuse	No significant differences
Janssen et al. (2004)	28 MDD 41 HC	64.04 ± 10.9 62.37 ± 11.38	1.5 T 1.2–5 mm ROI	33.04 ± 9.48	93.5 ± 17.5 months	NR	Depressed	22 AD, 4 lithium, 1 BZ	NR	No significant differences in orbitofrontal volume
Lacerda et al. (2004)	31 MDD 34 HC	39.26 ± 11.9 37.03 ± 11.88	1.5 T 1.5 mm ROI	27.94 ± 11.64	11.42 ± 10.47	NR	19 depressed, 12 euthymic	Patients drug-free for 2+ weeks	No axis I comorbidity, head injury, substance abuse in last 6 months	GM decrease in R medial OFC + L lateral OFC in MDD. Trends for L medial + R lateral OFC. No volume differences between euthymic + acutely ill patients
Lavretsky et al. (2004)	41 MDD 41 HC	70.5 ± 7.6 72.2 ± 7.3	1.5 T 1.4 mm	48.5 ± 23.5	2.7 ± 2.7 (episodes)	NR	Depressed	No medication for 2+ weeks	No substance abuse, dementia or other neurological disorder	Smaller total and GM volumes of OFC in MDD

Nobuhara et al. (2006)	13 MDD 13 HC	62.8 ± 6.6 61.5 ± 4.8	DTI 1.5 T 6 mm (2 mm gap) ROI	52.9 ± 7.3	4.0 ± 2.6	NR	Depressed	AD	No dementia, severe medical illness, neurological disorders	Negative association between integrity of WM tracts in medial orbital cortex + severity of depression
Chen et al. (2007a)	17 MDD	44.06 ± 8.36	MRI 1.5 T 3 mm	NR	NR	NR	Depressed	Scanned before and after treatment with fluoxetine. Patients off medication 4+ weeks before study	No current axis I comorbidity or substance abuse within 2 months of study. Personality disorders not assessed	Baseline severity of depression negatively correlated with GM volume of R OFC BA 11 34; 60; −6

See legend of Table 1.

Fig. 2. Architectonic subdivisions of the medial surface of the human brain Ongur et al. (2003).

(2008) confirms that on average both left and right sgACC volumes are decreased in mood disorders although interestingly, the effect (especially in the left hemisphere) appears to be driven by cases with a family history of illness.

Similarly, decreased activity of in particular, the left sgACC has been recorded in other studies of MDD and BD samples (Tables 19 and 21). These data apply equally to males (Hastings et al., 2004) and females (Botteron et al., 2002) as well as psychotic (Hirayasu et al., 1999; Coryell et al., 2005; Adler et al., 2006b) and bipolar-spectrum illness (Haznedar et al., 2005), respectively. There are also data to suggest that metabolic changes predate the onset of clinical symptoms. Kumano et al. (2006) followed a cohort of cancer patients and found that those individuals who went on to develop depression had lower baseline metabolic rates of the subgenual PFC compared to their counterparts who did not become depressed during the course of the study.

Other researchers have however, produced evidence of increased MDD and BD-associated metabolic activity of the ventral emotion circuit (Tables 19 and 21). A highly consistent finding across the literature has been that activity is elevated in the sgACC in the depressed phase relative to the remitted phase of MDD (Drevets et al., 2002a; Mayberg et al., 2005; Clark et al., 2006; Neumeister et al., 2006b; Hasler et al., 2008). Consistent with these data, an fMRI study reported decreased response to sad facial stimuli in the right sgACC after AD treatment (Keedwell et al., 2008).

An anatomical region more rostral to the sgACC (24/25), BA 32 (Fig. 2), is also an integral part of the ventral "emotion" circuit, and has been implicated in affective illness. A voxel-based morphometry (VBM) study reported a 7.3% decrease of the GM density of the left ventral aspect of this region in a sample of patients with BD I (Lyoo et al., 2004a). The partially medicated BD I, BD II, and cyclothymic sample of Haznedar et al. (2005) yielded similar results with decreased white and GM volume of the BA 32 area,

Table 17
Functional analyses of the orbitofrontal cortex in BD.

Study	Sample	Age	Method	Age of onset	Duration of illness/# episodes	Family history of illness	Clinical status at testing	Medication status	Comorbidity	Findings	Brodmann map/stereotaxic coordinates
Cohen et al. (1992)	7 SAD (5 BD II, 2 MDD) 38 HC	44.9 ± 11.1 36.2 ± 11	^{18}F-FDG	NR	NR	No MDD in relatives	Depressed	No medication for 3+ weeks	No serious medical or psychiatric history	Increased activity of medial OFC in MDD	NR
Blumberg et al. (1999)	5 manic 6 euthymic 5 HC	34.2 ± 12.2 32.5 ± 11.0 30.0 ± 6.7	^{15}O-H_2O	NR	NR	NR	5 manic, 6 euthymic	AD, AP, MS, Benz	No axis I and II disorders or neurological/ medical illness	Decreased rCBF to OFC at rest in manic sample	BA 11 −2, 46, −28
Kruger et al. (2003)	11 depressed BD 9 remitted BD	43 ± 9 38 ± 12	^{15}O-H_2O Voxel-wise	22 ± 6	8 ± 3 (dep episodes) 3 ± 2 (manic episodes) 8 ± 5 (dep episodes) 3 ± 2 (manic episodes)	NR	Depressed/ Remitted	MS	No axis I or II disorders. No substance abusers	rCBF decreases to R orbitofrontal region after sadness induction in both BD groups	BA 10/11 6; 42; −10 14; 46; −20 8; 56; −6
Rich et al. (2006) In L orbital cortex BD patients showed greater activation when rating the hostility of neutral face stimuli	22 BD −32; 20; −16 21 HC	14.2 ± 3.1 14.5 ± 2.5	Voxel-wise ROI used for amygdala, VPFC and ventral striatum Facial processing task	NR	NR	NR	Half euthymic, half depressed or hypomanic	80% medicated	No pervasive		developmental disorder, IQ < 70, unstable medical illness, substance abuse for 2+ months

See legend of Table 1.

Table 18
Morphometric analyses of the orbitofrontal cortex in BD.

Study	Sample	Age	Method	Age of onset	Duration of illness/# episodes	Family history of illness	Clinical status at testing	Medication status	Comorbidity	Findings
Lopez-Larson et al. (2002)	17 BD 12 HC	29 ± 8 31 ± 8	1.5 T 1 mm ROI	NR	7 ± 6	NR	Manic	9 MS, 4 AP, 3 AD	No medical disorders, head injury, substance abuse for 3 months	No difference
Wilke et al. (2004)	10 BD 52 HC	14.5 ± 1.8 15 ± 1	3 T 1.5 mm VBM	NR	NR	NR	Six mixed and 4 manic	No medication 72 h before scan	No schizophrenia, LD or PDD	Reduction in OFC GM in BD
Beyer et al. (2005)	14 BD 21 HC	44.0 ± 17.6 44.6 ± 13.5	1.5 T 5 mm ROI	NR	13.6 ± 12.1	NR	6 depressed, 5 manic, 3 euthymic	NR	No dementia, medical illnesses, other primary psychiatric diagnosis, recent substance abuse	WM of OFC—higher diffusion coefficients, but not FA, in BD
Dickstein et al. (2005)	20 BD 20 HC	13.4 ± 2.5 13.3 ± 2.3	1.5 T 1.2 mm VBM	10.1 ± 3.2	NR	NR	Euthymic	AP, MS, AD	ADHD, psychosis, anxiety	No significant differences
Frangou (2005)	43 BD 43 HC	42.9 ± 11	1.5 T 1.5 mm VBM	25.5 ± 9.2	16.0 ± 19.0	Mixed	Remitted	MS + AP	NR	Reduced GM in orbitofrontal gyrus of BD BA 11
Haznedar et al. (2005)	40 BD (17 BD I 7 BD II, 17 sub-threshold) 36 HC	39.8 ± 13.4 43.8 ± 6.7 43.9 ± 9.2 40.7 ± 11.6	1.5 T 1.2 mm ROI	NR	NR	10 yes	NR	BD II + cyclothymia samples medication free. BD I on MS, AP	1 OCD, 1 panic disorder, 1 PTSD. No concurrent substance dependence	Reduced GM in OFC in BD BA 11 + 12
Lyoo et al. (2006)	25 BD (18 BD I, 7 BD II) HC	33.8 ± 9.6 31.5 ± 9.7	1.5 T 1.5 mm	17.9 ± 5.4	16.5 ± 11.5 years	NR	Mixed	6 Lith, 4 valproate, 8 others	No substance abuse; comorbid axis I disorder in last 3 months, ASPD; medical illness, LD, ADHD	Reduced cortical thickness of the R OFC in BD 10; 55; 0
Nugent et al. (2006)	36 BD 65 HC	39 ± 8.1 38 ± 11.8	3 T 1.2 mm VBM	Medicated: 18 ± 8.8 Unmedicated: 21 ± 6.5	23 ± 9.0 17 ± 10.0	NR	NR	16 off medication for 4+ months. Rest on lithium or valproate	No neurological disorders, medical illnesses, substance abuse within last 90 days	GM volume reduction in L lateral OFC in BD −40, 52, −14
Najt et al. (2007)	14 BD 20 HC	15.5 ± 3.2 16.9 ± 3.8	1.5 T 1.5 mm	11.9	3.6 ± 2.4	Yes	Euthymic	Lithium + valproate	NR	Male BD smaller OFC volumes. Female BD large OFC volumes

See legend of Table 1.

Table 19
Functional analyses of the ventromedial prefrontal cortex in MDD.

Study	Sample	Age	Method	Age of onset	Duration of illness/# episodes	Family history of illness	Clinical status at testing	Medication status	Comorbidity	Findings	Brodmann map/stereotaxic coordinates
Drevets et al. (1992)	13 depressed MDD 10 remitted MDD 33 HC	36.2 ± 8.9 33.6 ± 10.0 30.1 ± 7.8	^{15}O-H_2O Voxel-wise	NR	NR	Yes	Depressed + euthymic	Depressed unmediated for 3+ weeks before scan. Remitted unmedicated for 4+ months	No co-morbid conditions	Depressed patients showed increased rCBF of L pregenual ACC. Effects not seen in remitted group	BA 32 7; 55; 6
Drevets et al. (1997)	10 MDD 21 HC	39 ± 7.3 34 ± 8.2 30.8 ± 9.9	1.5 T 1 mm slice ROI	NR	NR	Yes	Depressed	Not treated for 4 weeks prior to scans	NR	Decreased metabolism of L sgACC in MDD group	BA 24 1; 25; −6
Wu et al. (1999)	12 MDD responders 24 MDD non-responders 26 HC	28.8 ± 9.2 29.4 ± 9.5	^{18}F-FDG	NR	NR	NR	Depressed	No medication for 2+ weeks	No axis I diagnoses or physical disorders	Responders had higher metabolic rates in sgACC at baseline. Change in metabolic rate of L mPFC correlated with Ham-D scores after sleep deprivation, i.e. metabolism = improved symptoms	BA 24; 25 3; 25; −4 5; 48; −4
Mayberg et al. (2000)	17 MDD	49 ± 9	^{18}F-FDG	NR	2 ± 1 episodes	NR	Depressed	Scanned before and after treatment with fluoxetine	No history of psychosis or substance abuse. No other axis I disorders. No dementia, head injury, cerebrovascular illness	Improvement associated with decreased activity of sgACC. No subgenual cingulate changes in non-responders to fluoxetine	BA 25 4; 2; −4 2; 26; −8
Kennedy et al. (2001)	13 MDD 24 HC	36 ± 10 31.7 ± 6.7	^{18}F-FDG	NR	2.84 ± 3.95 episodes	NR	Depressed	Scanned before and after treatment with paroxetine	No patients with concurrent DSM diagnosis	Depressed group had higher activity in R pregenual cingulate which increased further with treatment	BA 24 8; 36; −4
Drevets et al. (2002a)	20 MDD 14 HC	36 ± 10 34 ± 9.1	^{18}F-FDG	NR	NR	NR	Depressed	Patients medication free for 3+ weeks prior to study	No other psychiatric disorders or substance abuse	At baseline metabolism decreased in sgACC anteromedial PFC. After treatment with sertraline significant decreases in activity of L sgACC	3; 31; −10
Dunn et al. (2002)	31 MDD	42.4 ± 13.6	^{18}F-FDG	15.9 ± 13.1	26.7 ± 14.6	NR	Mildly to severely depressed	Unmedicated for 2+ weeks	No active substance abuse, eating disorder, OCD, dementia, medical illness	Anhedonia associated with greater activity of the L pgACC and mPFC	pgACC BA 24, 25, 32 −16; 44; 4 BA 10
Liotti et al. (2002)	10 remitted MDD 7 ill MDD 8 HC	37 ± 9 42 ± 15 36 ± 6	^{15}O-H_2O 6.5 mm	NR	NR	NR	Euthymic	AD	No other primary psychiatric or neurological disorder. No head injury, substance abuse	Decrease in rCBF to medial PFC and pregenual cingulate in acutely depressed and remitted group, respectively	BA 9 + 10 8; 54; 12 6; 40; 27 BA 24 12; 38; 16

Davidson et al. (2003)	12 MDD 5 HC	38.17 ± 9.3 27.8 ± 10.4	fMRI 1.5 T 1 mm ROI Block design with alternating negative-neutral or positive-neutral visual stimuli	NR	NR	NR	Depressed	NR for baseline	No other axis I disorders except specific phobia or dysthymia. No neurological disorders	Less activation of the L ACC at baseline which improved with treatment	NR
Holthoff et al. (2004)	41 MDD No Controls	45.1 ± 15.66	^{18}F-FDG Voxel-wise ROI	NR	1st episode in 54% of sample. 10 patients had more than 2 episodes	NR	Moderate to severely depressed	Treated with AD. BZ discontinued 3 days before baseline	No substance abusers, axis II disorders	Remission associated with decreased metabolism of L ventral PFC	−16; 40; −2 −14; 70; 0 −14; 68; −12
Pizzagalli et al. (2004)	38 MDD (20 melancholic) 18 non-melancholic 18 HC	33.1 ± 8.8 36.5 ± 12.9 38.1 ± 13.6	^{18}F-FDG MRI 1.5 T Voxel-wise	NR	NR	Yes—in 12 melancholic + 7 non-melancholic subjects	Depressed	Free of medication for 2+ months	No other axis I disorders except simple phobias and dysthymia. No history of psychosis + current substance abuse. No axis II assessment	Decreased (16%) metabolism of sgACC in melancholic patients only	BA 25 −3; 9; −6
Gotlib et al. (2005)	18 MDD 18 HC	35.2 30.8	3 T Voxel-wise	NR	NR	NR	Depressed	9 on AD	No brain injury, psychosis, social phobia, panic disorder + substance abuse in last 6 months	Greater BOLD response to sad faces in L sgACC (BA 25) in MDD. Also greater perfusion of L BA 32/24 in response to happy faces	BA 25—coordinates not given BA 32/24 −8; 31; 7
Mayberg et al. (2005)	6 MDD	46 ± 8	^{15}O-H_2O	29.5 ± 12	4.7 ± 5 (episodes)	Yes—in 5 out of 6 subjects	Depressed	NR	No psychotic symptoms, substance abuse in last 3 months	Elevated CBF to the sgACC but decreased CBF BA 24b at baseline in MDD. Treatment with deep brain stimulation associated with reduced activity of BA 25 and elevated metabolism of BA 24b	Baseline: sgACC ~BA 24 −10; 28; −12 −2; 18; 28 Treatment: 3 months sgACC BA 25 −2; 8; −10 BA 24 −2; 10; 28 6 months BA 25 10; 20; −4 BA 24 −4; 4; 34
Clark et al. (2006)	5 MDD responders 17 MDD non-responders 8 HC	43.4 ± 6.1 42.0 ± 10.8 35.0 ± 9.5	fMRI 1.5 T ASL At rest	NR	NR	NR	Depressed	Patients medication free for 2+ weeks prior to study; rescanned after sleep deprivation	No patients with history of substance abuse, concurrent axis I disorders	At baseline, responders had higher activity of L ventral ACC (including sgACC) that correlated with depressed mood. After sleep deprivation perfusion decreased in L + R ventral ACC cingulate in responders	NR

Table 19 (*Continued*)

Study	Sample	Age	Method	Age of onset	Duration of illness/# episodes	Family history of illness	Clinical status at testing	Medication status	Comorbidity	Findings	Brodmann map/stereotaxic coordinates
Kumano et al. (2006)	19 cancer patients followed longitudinally	58.4 ± 15.7 (deterioration group) 57.9 ± 16.4 (no change sample)	^{18}F-FDG	NR	NR	No	Depressed + euthymic	Cancer medication	NR	Patients who became more depressed over time showed prodromal hypermetabolism of R ACC + L subcallosal gyrus	BA 25 −4; 9; −12 2; 11; −7
Chen et al. (2007a)	17 MDD No controls	44.06 ± 8.36	MRI 1.5 T 3 mm Sad facial stimuli	NR	NR	NR	Depressed	Scanned before and after treatment with fluoxetine. Patients off medication 4+ weeks before study	No current axis I comorbidity or substance abuse within 2 months of study. Personality disorders not assessed	Increased functional activation of pregenual ACC and medial frontal cortex associated with decreased symptom severity at baseline	BA 32 −2; 40; 15 BA 10 −1; 53; 4
Fales et al. (2008b)	27 MDD 24 HC	33.4 ± 8 36.4 ± 9	3 T fMRI ROI Emotional interference task: houses and faces	NR	NR	NR	Depressed	No medication for 4+ weeks	No axis I disorders preceding onset of MDD, acute physical illness, trauma with loss of consciousness, current neurological disorder	Elevated activity of sgACC in MDD	BA 24: −10; 35; −2 0; 13; 29 0; 13; 34
Nahas et al. (2007)	17 MDD	46.8 ± 6.3	fMRI 1.5 T	NR	71.2 ± 57.3 months (current episode)	NR	Depressed	Yes—not specified	NR	VNS decreased activity of the R sgACC	BA 25 0; 8; −16

See legend of Table 1.

Table 20
Morphometric analyses of the ventral–medial prefrontal cortex in MDD.

Study	Sample	Age	Method	Age of onset	Duration of illness/# episodes	Family history of illness	Clinical status at testing	Medication status	Comorbidity	Findings	Brodmann map/stereotaxic coordinates
Drevets et al. (1997)	10 MDD 21 HC	39 ± 7.3 34 ± 8.2	1.5 T 1 mm slice ROI	NR	NR	Yes	Depressed	Cohort not treated for 4 weeks prior to scans	NR	Decreased volume of L sgACC in MDD group	1; 25; −6
Shah et al. (1998)	20 MDD (chronic) 20 MDD (remitted) 20 HC	21–65	VBM	NR	NR	NR	Depressed and remitted	AD	No mania, significant substance abuse, organic pathology or neurological illness	Reduced GM volume of L inferior lateral frontal gyrus in chronic MDD	−55; 14; 14
Botteron et al. (2002)	30 MDD 8 HC	20.2 ± 1.6	1.5 T 1 mm ROI	15.2 ± 2.3	NR	Yes	Depressed	Less than 10% of MDD sample on medication	NR	Decreased volume of L sgACC in MDD	NR
Bremner et al. (2002)	15 MDD 20 HC	43 ± 8 45 ± 11	1.5 T 3 mm ROI	NR	2 ± 3 (episodes)	NR	Remitted	AD	Current substance abusers excluded. No history of schizophrenia, PTSD. About 20% of sample had past history of substance abuse	No volumetric changes of peri-callosal tissue	BA 24, 25 and 32
Kegeles et al. (2003)	19 (14 MDD, 5 BD) 10 HC	36 ± 11 39 ± 19	1.5 T 1.5 mm ROI	NR	NR	Yes	Depressed	BZ discontinued 24 h before study in 12 cases. 7 subjects on BZ. Patients free of other medication for 2+ weeks	3 panic disorder, 2 dysthymia, 1 each with social phobia, simple phobia, anorexia + PTSD. No medical illness	No sgACC volumetric differences across groups	NA
Hastings et al. (2004)	18 MDD 18 HC	38.9 ± 11.4 34.8 ± 13.6	1.5 T 1.5 mm ROI	23 ± 12.3	4.7 ± 4.4	Mixed	Depressed	No medicated at time of scan	No other axis I disorders. No current drug abuse	Volume reduction in L inferior ACC in males only	NR
Coryell et al. (2005)	10 MDD 10 HC	21.9 ± 4.9 22.1 ± 6.0	1.5 T 1 mm ROI	NR	4.7 ± 5.7	NR	Depressed	NR	History of psychosis	Volume reductions in L posterior sgACC but not anterior sgACC in MDD	NR
Lacerda et al. (2005)	22 MDD 39 HC	41.4 ± 11.1 35.8 ± 10.5	1.5 T 3 mm ROI	NR	11.6 ± 12.2	11 with family history, 11 without	NR	Drug-free for 2+ weeks	No comorbid disorders except substance abuse in remission for 6+ months. No medical problems	Patients with family history of depression had larger genu and splenium volumes than HC and non-familial depressives	NR
Caetano et al. (2006)	31 MDD 31 HC	39.2 ± 11.9 36.7 ± 10.7	1.5 T 1.5 mm ROI	27.9 ± 11.7	11.4 ± 10.6 5.1 ± 6.1 (episodes)	NR	21 depressed, 10 remitted	Unmedicated	No comorbid disorders except substance abuse in remission for 6+ months	Currently depressed patients had smaller BL ACC volume. Remitted group had smaller L ACC volumes than HC	NR
Boes et al. (2007)	31 HC—no family history 28 HC + family history	12.02 ± 2.72 12.14 ± 2.13	1.5 T 1.5 mm ROI	NA	No DSM-IV-defined episodes	Mixed	Mixed	NR	No serious medial or neurological illness, psychiatric illness, learning disorder (but no clinical interview).	In boys (but not girls) with subclinical depression smaller L sgACC and pregenual PFC volumes. Similar effect in family history + group	BA 24, 33 but not 25

Table 20 (*Continued*)

Study	Sample	Age	Method	Age of onset	Duration of illness/# episodes	Family history of illness	Clinical status at testing	Medication status	Comorbidity	Findings	Brodmann map/stereotaxic coordinates
Chen et al. (2007a)	17 MDD	44.06 ± 8.36	MRI 1.5 T 3 mm	NR	NR	NR	Depressed	Scanned before and after treatment with fluoxetine. Patients off medication 4+ weeks before study	No current axis I comorbidity or substance abuse within 2 months of study. Personality disorders not assessed	Increased GM volume of pregenual ACC associated with lower symptom severity at baseline	BA 32 5; 44; 1
Tang et al. (2007)	14 MDD 13 HC	29.5 ± 6.84 29.46 ± 6.86	1.5 T 1.6 mm ROI	1st episode	5.44 ± 5.22 months	NR	Depressed	Medication naive	No medical or neurological disorder, head injury, substance abuse. 4 with GAD	Decreased volume of pregenual PFC in MDD	2; 30; −2

See legend of Table 1.

noted. In line with these data, Kegeles et al. (2003) noted hypometabolism of BA 32 in depression. In contrast, Holthoff et al. (2004) reported a remission-associated decrease in the activity of this region and Nobler et al. (2001) obtained analogous results after ECT administration.

Individuals with MDD display a predominantly left sided hypometabolism of the ventro-medial circuit (Table 19) (Drevets et al., 1997; Kumano et al., 2006). Compatible with these findings, Smith et al. (2002) found that decreased metabolism of the right sgACC at baseline was predictive of an improved response to antidepressant therapy. Similarly, higher baseline activity of the left sgACC at baseline was positively correlated with response to sleep deprivation therapy; although after treatment, responders showed a drop in perfusion of the left ventral cingulate (Clark et al., 2006). Parallel findings of volume reductions of the ventral aspects of the left ACC are observed in morphometric analyses (Table 20).

The volumetric reductions seen in the left SGACC in some mood-disordered subgroups may contribute to the complex relationship between clinical state and sgACC metabolism. Partial volume effects may have contributed to the original suggestions of hypometabolism (see Mah et al., 2007 and discussion below).

A similar pattern obtains in BD with left-sided hypometabolism or right-sided hypermetabolism (Drevets et al., 1997; Bauer et al., 2005; Mah et al., 2007), and left-sided tissue loss (Drevets et al., 1997; Hirayasu et al., 1999; Sassi et al., 2004; Wilke et al., 2004; Kaur et al., 2005) of the broader ventral ACC region (Tables 21 and 22). One might hypothesize the reverse pattern to apply to the manic state (Drevets et al., 1997), a phenomenon observed in the sample of Blumberg et al. (2000) which was characterized by elevated rCBF in the left sgACC.

During functional brain mapping studies of BD a study employing an Affective Go/No Go task showed greater activity to happy distracters in left sgACC, medial PFC and bilateral DLPFC, and greater activity in response to sad relative to neutral distracters in right ventrolateral PFC and DLPFC, in manic BD versus healthy adults (Elliott et al., 2004).

3.8. The dorsal "Cognitive" circuit

Davidson and Irwin (1999) illustrate how the line between cognition and emotion is becoming increasingly blurred in their description of the DLPFC as mediator of "affective working memory" (Davidson and Irwin, 1999) (p. 11). The DLPFC allows for the initially "raw" limbic-derived emotional stimuli which is refined through rounds of ever more comprehensive processing in the orbital and ventromedial circuits to be represented "online" so that it can drive goal directed behavior (Davidson and Irwin, 1999). In this sense, the dorsal aspects of the PFC discharge traditionally characterized executive processes such as response selection, inhibition, and error detection—the monitoring of actions to insure that they match intentions.

As reviewed by Davidson (2002), in depression, a deficit in the top–down inhibitory control of the DLPFC over the amygdala and sundry limbic tissue may result in chronic limbic over-activity and negative emotions. Implicit in this deliberately over-simplified description of the above model is the notion that positive affect is primarily a consequence of the suppression of negative emotions.

3.8.1. MDD

Hypometabolism of the dorsal PFC is one of the most robust findings in both MDD (Hurwitz et al., 1990; Cohen et al., 1989; Biver et al., 1994; Bench et al., 1995; Dunn et al., 2002; Davidson et al., 2003; Chen et al., 2007a) and BD (Buchsbaum et al., 1986; Baxter et al., 1989; Drevets et al., 2002a; Kruger et al., 2003), and in some studies appears to normalize with successful treatment (Mayberg et al., 1999, 2000, 2005; Kennedy et al., 2001; Fales et al.,

Table 21
Functional anatomical studies of the ventromedial prefrontal cortex in BD.

Stud	Sample	Age	Method	Age of onset	Illness duration/# episodes	Family history of illness	Clinical status at testing	Medication status	Comorbidity	Findings	Brodmann map/stereotaxic coordinates
Drevets et al. (1997)	21 BD 21 HC	35 ± 8.2 34 ± 8.2	1.5 T 1 mm slice ROI	NR	NR	Yes	Depressed	Cohort not treated for 4 weeks prior to scans	NR	Decreased metabolism of L sgACC in BD group	1; 25; −6
Blumberg et al. (2000)	11 BD	33.4 ± 11.6	^{15}O-H_2O	NR	14.2 ± 14.9 (manic) 12.0 ± 5.6 (euthymic)	NR	5 manic BD; 6 euthymic	MS, AP, AD, BZ	No comorbid axis I or II conditions. Substance abuse taking place >5 years previously was allowed	Manic patients had greater rCBF in R ventral ACC than remitted subjects	BA 32 10; 26; −8
Ketter et al. (2001)	43 BD I + II (treatment resistant) 43 HC	37.5 ± 10.6 38.1 ± 10.4	^{18}F-FDG	18.8 ± 9.9	18.3 ± 10.4	NR	Depressed, mildly depressed + euthymic	Unmedicated for 2+ weeks	NR	Decreased metabolism of L middle frontal and inferior frontal gyri in depressed BD patients only. Global cerebral metabolism decreased in depressed BD too	BA 9 + 44 No coordinates given
Drevets et al. (2002a)	20 MDD 14 HC	36 ± 10 34 ± 9.1	^{18}F-FDG	NR	NR	NR	Depressed	Patients medication free for 3+ weeks prior to study	No other psychiatric disorders or substance abuse	Reduced baseline metabolism of L sgACC PFC in MDD	NR
Dunn et al. (2002)	27 BD	36.7 ± 11.3	^{18}F-FDG	18.0 ± 9.9	26.7 ± 14.6	NR	Mildly to severely depressed	Unmedicated for 2+ weeks	No active substance abuse, eating disorder, OCD, dementia, medical illness	Anhedonia associated with greater metabolism of R sgACC	10; 42; −4
Kegeles et al. (2003)	19 (14 MDD, 5 BD) 10 HC	36 ± 11 39 ± 19	^{18}F-FDG	NR	NR	Yes	Depressed	BZ discontinued 24 h before study in 12 cases. 7 subjects on BZ. Patients free of other medication for 2+ weeks	3 panic disorder, 2 dysthymia, 1 each with social phobia, simple phobia, anorexia + PTSD. No medical illness	Lower metabolic activity of the R pregenual ACC in MDD	BA 32 4; 34; −12
Kruger et al. (2003)	11 depressed BD 9 remitted BD	43 ± 9 38 ± 12	^{15}O-H_2O Voxel-wise	22 ± 6	8 ± 3 (dep episodes) 3 ± 2 (manic episodes) 8 ± 5 (dep episodes) 3 ± 2 (manic episodes)	NR	Depressed/ remitted	MS	No axis I or II disorders. No substance abusers	BL decreases in rCBF to ventral–medial PFC after sadness induction in both BD groups	In remitted group increased rCBF to dorsal anterior cingulated—BA 24a: 10; 20; 24. Decreased rCBF to orbitomedial and ventromedial cortex—BA 11: 6; 42; −10 14; 46; −20 20; 62; −4 −18; 54; 10 −14; 64; 0

Table 21 (*Continued*)

Stud	Sample	Age	Method	Age of onset	Illness duration/# episodes	Family history of illness	Clinical status at testing	Medication status	Comorbidity	Findings	Brodmann map/stereotaxic coordinates
											In depressed group: decreased orbitomedial and ventromedial rCBF: 8; 56; −6 4; 58; 9
Lennox et al. (2004)	10 BD 12 HC	37.3 ± 12.8 32.6 ± 10.7	fMRI 3 T Voxel-wise	NR	NR	NR	Manic	8 Lith, 7 MS, 3 haloperidol, 4 olanzapine	NR	BD patients had attenuated BL activation of sgACC in response to sad faces	−2; 20; −14 BA 25
Bauer et al. (2005)	10 BD I 10 HC	39.3 ± 7.8 35.0 ± 9.3	^{18}F-FDG	NR	20.4 ± 7.0	NR	Depressed	AD + MS	No psychosis	Higher activity in R sgACC which decreased with treatment	8; 24; −6
Haldane et al. (2007)	8 BD I	42.1 ± 11.8	fMRI 1.5 T 7 mm (0.7 mm gap)	23.1 ± 5.6	10.1 ± 6.5 episodes	NR	Mildly depressed	Lamotrigine	No alcohol or substance abuse, significant medical or neurological disorder, treatment resistance, suicide attempts, axis I comorbidity	Greater activation of L medial frontal gyrus + R ACC in response to angry faces after lamotrigine therapy relative to baseline	BA 10 −4; 46; 10 BA 32/24 10; 36; 6
Mah et al. (2007)	13 BD II 18 HC	43.0 ± 8.4 39.0 ± 8.0	^{18}F-FDG	20 ± 10.5	22.9 ± 12	NR	Depressed	Lithium	No substance abuse within 90 days, substance dependence within 5 years. No current psychotic features. 1 OCD, 1 eating disorder	Increased metabolism of R pregenual ACC in BD	12; 47; 5

See legend of Table 1.

Table 22
Morphometric studies of the ventromedial prefrontal cortex in BD.

Study	Sample	Age	Method	Age of onset	Illness duration/ # episodes	Family history of illness	Clinical status at testing	Medication status	Comorbidity	Findings	Brodmann map/ stereotaxic coordinates
Drevets et al. (1997)	21 BD 21 HC	35 ± 8.2 34 ± 8.2	1.5 T 1 mm slice ROI	NR	NR	Yes	Depressed	Cohort not treated for 4 weeks prior to scans	NR	Decreased volume of L sgACC in BD group	1; 25; −6
Hirayasu et al. (1999)	21 BD 17 SZ 20 HC	23.7 ± 5.1 24.0 ± 4.3	1.5 T 1.5 mm ROI	23.7 ± 5.1	1st hosp	14 familial subjects	First episode manic psychosis (BD and SZ)	AP	No substance abuse within last 5 years	Decreased volume of L sgACC in familial BD patients. No significant changes in SZ	NR
Brambilla et al. (2002)	27 BD 38 HC	35 ± 11 37 ± 10	1.5 T 1.5 mm ROI	NR	NR	12 familial, 12 non-familial	11 mildly depressed, 1 hypomanic, 15 euthymic	No medication for 2+ weeks in 11 subjects, other 16 on lithium monotherapy	No co-morbid psychiatric conditions. No current medical problems	No difference in sgACC volumes. No difference between familial and non-familial subjects	NR
Sharma et al. (2003)	12 BD 8 HC	38 ± 6 38 ± 7	4 T 3.3 mm gap	21.1 ± 6.4	12 ± 17.2	6 with family history, 6 without	Euthymic	MS, AD	No substance abuse in last 5 years	Decreased volume of R sgACC in BD	NR
Doris et al. (2004)	11 BD I 11 HC	40.5 ± 11.6 38.1 ± 10.8	2 T 1 mm VBM	24.3 ± 5.1	16.2 ± 11.1 7.8 ± 3.4 (hosp)	NR	Relatively euthymic	MS, AD, AP	No comorbid conditions	Decreases in gray matter density of R medial frontal gyri	BA 10 9; 52; −2
Lyoo et al. (2004a)	39 BD I 43 HC	38.3 ± 11.6 35.7 ± 10.1	1.5 T 1.5 mm VBM	18.6 ± 7.0	18.1 ± 11.0 10.5 ± 9.2 (manic episodes) 13.5 ± 7.2 (depressive episodes)	NR	Mixed manic and depressed	Treated with lithium and other medications	No axis I disorders, substance abuse within last 3 months, anti-social PD	GM volume reduction of L medial frontal gyrus + R inferior frontal gyrus	BA 10 + BA 47 −8; 54; 16 39; 26; −11
McDonald et al. (2004a)	38 BD 52 unaffected relatives 54 HC	41 ± 11.7 44 ± 15.5 40.2 ± 15.3	1.5 T 1.5 mm ROI	22.6 ± 5.5	NR	Yes	NR	33 BD on MS. 10 on AP	No organic brain disease, head trauma, substance abuse in last 12 months	Increased genetic risk for BD associated with reduced volume of R ACC	BA 11, 24, 25.
Sassi et al. (2004)	11 BD (unmedicated) 16 BD (medicated) 39 HC	38 ± 11 33 ± 11 39 ± 10	1.5 T 1.5 mm ROI	20 ± 6	16.9 ± 10.7 16 ± 16 (episodes) 12.67 ± 7.4 17.8 ± 19.5 (episodes)	14 yes, 13 no	11 depressed, 16 euthymic	11 free of medication; 16 treated with lithium	No comorbid conditions	Decrease in volume of L ACC in untreated BD sample compared with both HC and lithium group. Family history and mood at scan did not alter results	NR

Table 22 (*Continued*)

Study	Sample	Age	Method	Age of onset	Illness duration/ # episodes	Family history of illness	Clinical status at testing	Medication status	Comorbidity	Findings	Brodmann map/ stereotaxic coordinates
Wilke et al. (2004)	10 BD 52 HC	14.5 ± 1.8 15 ± 1	3 T 1.5 mm VBM	NR	NR	NR	Six mixed and 4 manic	No medication 72 h before scan. No data on medication type	No schizophrenia, learning disabilities or pervasive developmental disorders	Reduced gray matter volume of L sgACC	NR
Adler et al. (2005)	32 BD 27 HC	31.2 ± 9.4 30.5 ± 9.7	3 T 1 mm VBM	22.5 ± 7.7	8.7 ± 9.2 2.9 ± 3.2 (depressive episodes) 2.0 ± 1.5 (manic episodes)	Majority of patients on a range of medication	25 euthymic. 7 manic or depressed	9 unmedicated, others on AP, MS, AD + BZ	No comorbid conditions	Increased GM volume of ACC in BD	BA 32 −3; 47; 6 3; 47; 6
Haznedar et al. (2005)	40 BD (BD I 17; BD II; 7 cyclothymia 16) 36 HC	39.8 ± 13.4 43.8 ± 6.7 43.9 ± 9.2 40.7 ± 11.6	1.5 T 1.2 mm ROI	NR	NR	10 yes	NR	BD II + cyclothymia samples medication free. BD I on MS + AP	"pathological gambling disorder", 1 OCD, 1 panic disorder, 1 PTSD. No concurrent substance dependence, but previous history of abuse	BL loss of GM in inferior cingulate	BA 25 and 32
Kaur et al. (2005)	16 BD 21 HC	15.5 ± 3.4 16.9 ± 3.8	1.5 T 1.5 mm ROI	NR	NR	Yes	2 depressed, 14 euthymic	10 lithium, 3 AD, 1 AP, 1 stimulant, 1 BZ	No substance abuse. 5 ADHD, 1 ODD, 1 CD	Decrease in volume of L ACC which includes BA 24	NR
Sanches et al. (2005b)	15 BD (3 BD II, 1 BD NOS) 21 HC	15.5 ± 3.5 16.9 ± 3.8	1.5 T 1.5 mm ROI	NR	3.8 ± 2.4	Yes	13 euthymic, 2 mildly depressed	13 on MS	No substance abuse. 5 ADHD, 1 ODD, 1 CD	No group differences in sgACC volumes No differences between patients on and off medication	NR
Zimmerman et al. (2006)	27 BD 22 HC	24.0 ± 6.4 23.5 ± 6.5	1.5 T 1.5 mm ROI	NR	NR	NR	Manic or mixed episode	28 MS, 3 AD, 18 AP, 7 BZ	NR	No volume differences between groups	NR

Bearden et al. (2007)	28 BD (70% on lithium) 28 HC	36.1 ± 10.5 35.9 ± 8.5	1.5 T	18.6 ± 6.1	15.1 ± 18.2	NR	30% depressed 70% euthymic	Lithium for 2+ weeks (treated group). No lithium for 1+ month (untreated group)	No neurological, medical problems. No substance abuse, other psychiatric disorders	Greater volumes of the anterior cingulate, including the sgACC in lithium treated group compared to HC and lithium negative BD	NR
Chiu et al. (2007)	16 BP 15 HC	10.63 ± 4.56 10.94 ± 1.65	1.5 T 1.5 mm	NR	NR	NR	NR	12 AD, 9 MS, 8 AP, 3 adrenergic agents	No CNS disease, serious medical problems, IQ < 70	Smaller L ACG (included both dorsal + ventral aspects) in BD	NR
Koo et al. (2008)	41 first-episode affective psychosis (38 BD) 40 HC	22.8 ± 4.5 23 ± 3.2	1.5 T ROI	First Episode	8.2 ± 13.2 weeks	30 +ve 10 −ve	Manic	Median of 1 week duration of AP treatment prior to scan. Range 0–26 weeks	No seizures, head trauma, sinistrality, neurological disorders, lifetime drug or alcohol dependence	Volume of L + R sgACC smaller in patients than HC. Decrease in sgACC volume over 1.5 year follow-up period	NR

See legend of Table 1.

2008a), lending support to the veridicality of the above-mentioned model of depression.

Consistent with these data, Chen et al. (2007a) found that severity of depression correlated negatively with GM volume of DLPFC and Davis et al. (2004) reported global decrements of both GM and WM volume, including areas of the DLPFC. We note that there are conflicting reports in the literature—see (Brody et al., 1999; Brody et al., 2001; Drevets et al., 2002a) (Table 24).

Nevertheless, the vast area of cortex that is subsumed under the term dorsal or DLPFC makes the functional data difficult to interpret. The dorsal PFC consists of distinct functional units, some of which play the traditionally described cognitive role, while others have closer ties to the more medial and ventral aspects of the PFC. For example, part of BA 9 in the medio-dorsal PFC is probably an important constituent of the viscero-motor network with projections to the lateral column of the PAG in macaques (An et al., 1998).

3.8.2. BD

Decreases in the volume of the dorsal cortex, although not always the lateral convexity, have been reported in BD (Table 23). More recently Frangou (2005) and Haznedar et al. (2005) described GM volume reductions of the 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 have also reported in a medicated, euthymic pediatric sample (Dickstein et al., 2005). An optimized VBM analysis of a mixed BD I and BD II sample Lochhead et al. (2004) reported reduced GM volume of the ACC immediately dorsal to the corpus callosum (CC).

3.9. The corpus callosum

There is some preliminary evidence for decreased volume of the corpus callosum (CC) in BD (Coffman et al., 1990; Brambilla et al., 2003b; Atmaca et al., 2007) and MDD (Lyoo et al., 2002a) (Table 25). A meta-analysis of the BD studies supported the hypothesis that the collosal region is reduced in volume in BD (Arnone et al., 2008). Congruent with these data, Yurgelun-Todd et al. (2007) reported BD-associated WM changes in the genu of the CC as measured by DTI.

It is unclear from the above studies, however, whether the genu or splenium is preferentially affected. Ballmaier et al. (2007) have proposed that the effect is age of onset-specific: they reported genu-specific thinning in early-onset depressed patients but evidence of thinning of both the genu and splenium in late-onset MDD.

4. Discussion

4.1. The amygdala

4.1.1. MDD

The finding of increased amygdala reactivity to negative stimuli is one of the most consistent findings in the literature (Thomas et al., 2001; Fu et al., 2004; Surguladze et al., 2005; Neumeister et al., 2006a). In addition, Siegle et al. (2002) found that amygdalar responses to negative words were no longer visible after 10 s in healthy controls but persisted in depressed patients for at least 25 s, on average. Similarly, patients with MDD reportedly remember negative words better than positive words (Watkins et al., 1992), a finding that correlates with increased BOLD activity of the right amygdala (Hamilton and Gotlib, 2008).

The phenomenon may be reversed by antidepressant treatment. Sheline et al. (2001) showed that the elevated BOLD response seen in the left amygdala of depressed patients in response to masked fearful faces was reduced by sertraline. The apparent efficacy of

Table 23
Structural imaging analyses of dorsal PFC in BD.

Study	Sample	Age	Method	Age of onset	Illness duration/ # episodes	Family history of illness	Clinical status at testing	Medication status	Comorbidity	Findings	Brodmann map/ stereotaxic coordinates
Lopez-Larson et al. (2002)	17 BD 12 HC	29 ± 8 31 ± 8	1.5 T 1 mm ROI	NR	7 ± 6	NR	Manic	9 MS, 4 AP, 3 AD	No medical disorders, head injury, substance abuse in previous 3 months	Smaller L middle + superior GM volumes in BD	NR
Doris et al. (2004)	11 BD I 11 HC	40.5 ± 11.6 38.1 ± 10.8	2 T 1 mm VBM	24.3 ± 5.1	16.2 ± 11.1 7.8 ± 3.4 (hosp)	NR	Relatively euthymic	MS, AD, AP	No comorbid conditions	Decreases in GM density of dorsal-medial frontal gyri	45; 30; 28
Lochhead et al. (2004)	11 (BD (7 BD I 4 BD II) 31 HC	38.2 ± 10 36 ± 14	1.5 T 1.5 mm VBM	24.3 ± 9.2	9.0 ± 6.4 episodes	NR	Depressed	No medication for 2+ weeks	No co-morbid disorders	Decrease in volume of BL dorsomedial ACC	0; 27; 21
Dickstein et al. (2005)	20 BD 20 HC	13.4 ± 2.5 13.3 ± 2.3	1.5 T 1.2 mm VBM	10.1 ± 3.2	NR	NR	Euthymic	AP, MS, AD	ADHD, psychosis, anxiety	GM volume reduction of L DLPFC	BA 9 −32; 42; 32
Frangou (2005)	43 BD 43 HC	42.9 ± 11	1.5 T 1.5 mm VBM	25.5 ± 9.2	16.0 ± 19.0	Mixed	Remitted	MS + AP	NR	Volume reduction of L DLPFC in BD	BA 9/46
Haznedar et al. (2005)	40 BD (BD I 17; BD II; 7 cyclothymia 16) 36 HC	39.8 ± 13.4 43.8 ± 6.7 43.9 ± 9.2 40.7 ± 11.6	1.5 T 1.2 mm ROI	NR	NR	± 50%	"Stable"	BD I but not BD II, cyclothymia on MS + AP	4 anxiety disorders 19 substance abuse	BL loss of GM and WM in DLPFC	BA 8, 9, 45, 46
Soares et al. (2005)	32 BD I 32 HC	34 ± 10.5 NR	Deformation-field morphometry 1.5 T 1.5 mm	NR	NR	NR	NR	NR	No axis I diagnoses, substance abuse in previous 6 months + serious medical conditions	Smaller L DLPFC in males only	NR
Yatham et al. (2007)	15 BD 15 HC	36 ± 13 36 ± 13	1.5 T 1.5 mm VBM	NR	3.9 ± 8.1	NR	Manic	8 medication naive, rest AD	No medical or neurological illness, substance abuse	6% reduction (not significant) in L ACC of BD	BA 32 −6; 36; 17

See legend of Table 1.

Table 24
Volumetric changes of dorsal PFC in MDD.

Study	Sample	Age	Method	Age of onset	Illness duration/ # episodes	Family history of illness	Clinical status at testing	Medication status	Psychiatric comorbidity	Findings	Brodmann map/ stereotaxic coordinates
Shah et al. (1998)	20 MDD (chronic) 20 MDD (remitted) 20 HC	21–65	VBM	NR	NR	NR	Depressed and remitted	AD	No mania, significant substance abuse, organic pathology or neurological illness	Reduced GM volume of L DLPFC chronic MDD	−56; 1; 32
Chen et al. (2007a)	17 MDD	44.06 ± 8.36	MRI 1.5 T 3 mm	NR	NR	NR	Depressed	Scanned before and after treatment with fluoxetine. Patients off medication 4+ weeks before study	No current axis I comorbidity or substance abuse within 2 months of study. Personality disorders not assessed	Severity of depression negatively correlated with GM volume of DLPFC	BA 46 31; 53; 15 −31; 45; 17 BA 9 32; 34; 30 −15; 35; 42

See legend of Table 1.

antidepressant medications in attenuating this hyper-reactivity has received support from more recent studies (Fu et al., 2004; Chen et al., 2007b). There is some suggestion that rather than being a stable trait, baseline hypermetabolic activity seen in MDD samples may be reflective of acute depression (Abercrombie et al., 1998; Drevets et al., 2002b; Surguladze et al., 2005).

The inconsistency in the volumetric MRI literature in MDD may reflect the intrinsic problem that all analyses of the amygdala conducted to date were acquired using 1.5 T scanners, which do not have the resolution to allow for the adequate definition of the boundaries of this diminutive region because of its proximity to other gray matter structures such as the claustrum, entorhinal cortex, hippocampus, and basal forebrain.

4.1.2. BD

Increased metabolism of the amygdala – both at base-line, and in response to emotional challenges such as negatively valenced faces (Yurgelun-Todd et al., 2000; Lawrence et al., 2004; Rich et al., 2006; Pavuluri et al., 2007) – is commonly reported in BD samples, and may be attenuated by lamotrigine (Chang et al., 2008). This increase in amygdala activity is often associated with greater MRI volume.

The amygdala may be an exception to this pattern with neuronal and dendritic hypertrophy reported in parallel to hypermetabolism (Vyas et al., 2002). Elevated activity may be an adaptive mechanism that enhances sensitivity to aversive stimuli, thereby facilitating fear conditioning and anxiety-related phenomenology (McEwen and Chattarji, 2004; Radley and Morrison, 2005).

Nevertheless, this hypothetical phenomenon cannot explain the decreased neuronal somal size (suggestive of reduced axo-dendritic connections) in the lateral amygdaloid and accessory basal parvocellular nuclei (Bezchlibnyk et al., 2007), and the decreased number and density of lateral amygdaloid nucleus neurons (Berretta et al., 2007) reported in post-mortem BD subjects. The postulated hypertrophy of the amygdala is also inconsistent with the putative volume decrements seen in childhood BD, and a minority of adult samples (Pearlson et al., 1996; Blumberg et al., 2003a).

One possibility is that studies reporting enlarged amygdala volumes in BD may be at least partly confounded by medication effects. Chang et al. (2005b) have suggested that hypertrophy of the amygdala may be related to exposure to mood stabilizers. This topic is addressed in detail below.

4.1.3. Amygdala abnormalities and the signs and symptoms of MDD and BD

The amygdala plays a central role in the modulation of monoamine and corticosteroid release in response to aversive or novel stimuli. Disruption of the amygdala's afferent and efferent connections may thus have negative implications for the regulation of mood and affect (Fig. 1).

4.2. The hippocampus

4.2.1. MDD

Hippocampal volume loss appears to be a sequala of depression, particularly in elderly or chronically ill samples. Further, hippocampal volume has been reported to be negatively related to risk of depressive relapse in patients followed over 2 years (Kronmuller et al., 2008). Recurrent depressive illness appears to exert an insidious pathological effect on neural, and in particular, hippocampal tissue. Stress-induced dendritic atrophy has been shown to be mediated by an interaction of glucocorticoid receptor stimulation and excitatory amino acid transmission (specifically NMDA receptor stimulation) (McEwen and Magarinos, 2001).

Table 25
Abnormalities of the corpus callosum in BD and MDD.

Study	Sample	Age	Method	Age of onset	Illness duration/ # episodes	Family history of illness	Clinical status at testing	Medication status	Comorbidity	Findings
Wu et al. (1993)	20 MDD 16 HC	32.9 ± 11.5 30.5 ± 9.8	1.5 T 5 mm ROI	NR	NR	NR	Depressed	Medication free for 2+ weeks	NR	Anterior + posterior CC larger in MDD
Lyoo et al. (2002a)	40 MDD 42 HC	21.4 ± 2.1 20.9 ± 2.8	1.5 T 1.5 mm ROI	16.7 ± 1.7	4.8 ± 1.3	NR	Mildly depressed	Medication naive	No axis I or II disorders. No medical illness, head trauma	Smaller genu and CC in minor depression
Brambilla et al. (2004)	23 MDD 36 HC	41 ± 10 37 ± 10	1.5 T ROI	NR	11 ± 9 4 ± 3 (episodes)	NR	9 euthymic 14 depressed	Off drugs for 2+ weeks	No comorbid disorders. No substance abuse in previous 6 months	No difference in CC signal intensity
Bae et al. (2006)	106 MDD 84 HC	70.4 ± 6.4 71.7 ± 6.0	DTI 1.5 T 3 mm ROI	NR	NR	NR	Depressed	NR	NR	No WM changes in CC
Nobuhara et al. (2006)	13 MDD 13 HC	62.8 ± 6.6 61.5 ± 4.8	DTI 1.5 T 6 mm ROI	52.9 ± 7.3	4.0 ± 2.6	NR	Depressed	AD	No dementia, severe medical illness, neurological disorders	No WM changes in CC
Yasar et al. (2006)	16 BD 21 HC	15.5 ± 3.4 16.9 ± 3.8	1.5 T 3 mm ROI	NR	NR	Yes	2 depressed, 14 euthymic	Yes—not specified	5 ADHD, 1 CD, 1 ODD. No substance abuse	No difference in CC
Atmaca et al. (2007)	12 BD I 12 HC	28.2 ± 6.5 26.8 ± 7.6	1.5 T 2.4 mm ROI	27.4 ± 6.1	0.3 ± 0.4	NR	10 manic, 2 mixed	medication-naive	No axis I conditions, substance abuse for 6+ months. 2 OCD, 2 PD	CC significantly smaller in BD
Ballmaier et al. (2007)	24 early-onset 24 late-onset 34 HC	68.00 ± 5.83 74.50 ± 8.09 72.38 ± 6.93	1.5 T 1.4 mm ROI	33.25 ± 16.05 71.27 ± 7.23	4.80 ± 4.13 episodes 0.50 ± 0.90 episodes	NR	Depressed	Free of medication for 2+ weeks	No neurological illness, alcohol abuse/dependence, long-term AD use, comorbidity	CC thinning in genu of early-onset MDD and genu and splenium of late-onset MDD
Yurgelun-Todd et al. (2007)	11 BPD 10 HC	32.9 ± 10.5 32.4 ± 9.1	1.5 T 5 mm DTI	21.7 ± 5.4	12.0 ± 9.8	NR	Euthymic	Lith, MS, AP	No head injury, CNS disease, substance abuse for 6+ months	Higher FA in the midline of the genu but not splenium in BD

See legend of Table 1.

Notably, in rodents, the CA3 region of the dorsal hippocampus is the hippocampal area that shows the greatest vulnerability to excitotoxic processes (Sloviter, 1996; Ben-Ari and Cossart, 2000; Dudek and Sutula, 2007). In humans with MDD and PTSD, the posterior hippocampus (the putative homologue of the rodent dorsal hippocampus) shows the most prominent reduction in volume relative to healthy controls (Neumeister et al., 2005; Bonne et al., 2008).

At sufficiently high concentrations, glutamate acts as an excitotoxin and neuronal death may follow from intra-cellular calcium-driven cytoskeletal degeneration and free radical production (Lee et al., 2002). At lower glutamate concentrations, hippocampal neurogenesis is inhibited and dendritic atrophy occurs in association with stress-induced glucocorticoid hormone secretion (McEwen and Magarinos, 2001).

The latter effect may be mediated at least in part by down-regulated gene expression of brain-derived neurotrophic factor (BDNF) and other neurotrophins (Duman and Monteggia, 2006). Rats exposed to corticosteroids or stressors show decreased expression of BDNF in the hippocampus (Gronli et al., 2006; Jacobsen and Mork, 2006; Tsankova et al., 2006; Xu et al., 2006) although the effect may be limited to particular splice-variants of the protein (Nair et al., 2006; Tsankova et al., 2006). Similarly humans with mood disorders have shown decreased serum (Karege et al., 2002) and hippocampal BDNF levels at post-mortem (Dwivedi et al., 2003; Karege et al., 2005).

Stress-induced plasticity of the hippocampus appears to be crucial for effective learning and memory, maintenance of goal directed behavior, and modulation of emotional behavior by contextual information (LeDoux, 2000; Frank et al., 2006; Morris, 2006; Hasler et al., 2007). Prolonged prenatal and adult stress in primates, rodents and tree shrews leads to selective hippocampal damage including apoptosis, depressed long-term potentiation (LTP) and neurogenesis, as well as, apical dendritic atrophy (Uno et al., 1989; Sapolsky et al., 1990; Watanabe et al., 1992; Magarinos et al., 1996; Czeh et al., 2001). Similar effects have been noted in stress-related psychiatric disorders such as post-traumatic stress disorder (PTSD) (Bremner et al., 1995; Vythilingam et al., 2005).

If the excitotoxic hypothesis holds true in humans then one would expect to see a negative correlation between the duration or severity of illness and hippocampal volume. There is mixed evidence for this potential effect (Table 5).

4.2.2. BD

In BD the data are less clear, perhaps because of the widespread use of mood stabilizers which appear to increase gray matter volume. Animal studies have demonstrated that lithium promotes hippocampal neurogenesis (Kim et al., 2004) and long-term potentiation (Son et al., 2003). A sample of BD patients treated for 4 weeks with lithium showed a 3% (24 cm^3) increase in whole brain gray matter volumes from baseline (Moore et al., 2000), an effect that appears to result from the neurotrophic effect of the drug (Manji et al., 2000). Four more recent studies (Beyer et al., 2004b; Sassi et al., 2004; Bearden et al., 2007; Yucel et al., 2007) 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 with comparable effects noted with other classes of mood stabilizers, especially valproate (Mark et al., 1995; Hao et al., 2004). In contrast, with the exception of tianeptine (Watanabe et al., 1992; McEwen et al., 2002; McEwen and Olie, 2005), the neurotrophic properties of antidepressants are less persuasive—although see (Stewart and Reid, 2000; Duman and Monteggia, 2006).

An alternative explanation for the differential impact of MDD and BD on hippocampal structure is that the two disorders differ in etiology. This hypothesis, however, stands in contradistinction to evidence that MDD tends to aggregate in the relatives of individuals with BD (McGuffin and Katz, 1989).

4.2.3. Hippocampal changes and the signs and symptoms of MDD and BD

A disruption of hippocampal function may contribute to the deficits in executive performance, learning and emotion-mediated memory formation observed in mood disorders (Fig. 1).

4.3. The basal ganglia

4.3.1. MDD

Both hypometabolism or blood flow and reduced gray matter volume have commonly been reported in the MDD literature (Tables 9 and 10). The former result may thus reflect a partial volume averaging effect rather than a genuine diminution in metabolic activity. Interpretation of imaging studies is, however, rendered difficult by the mass of contradictory results yielded through diverse scanning methodologies and population samples. We suggest that medication and age of onset are important confounding factors. In contrast, increased resting metabolic activity of the anteroventral striatum is apparent during depression, and may be linked particularly to anhedonic symptoms (Hasler et al., 2008), consistent with evidence that depressives show blunted caudate activation during exposure to positively valenced sensory stimuli (Epstein et al., 2006).

4.3.2. BD

No clear conclusions can yet be drawn from studies of the BG. There is some suggestion of increased striatal metabolism and volumetric GM increases in BD. As in the case of the hippocampus, it is plausible that these analyses are confounded by treatment effects. Enlargement of the BG nuclei is a well known effect of anti-psychotic drugs (Jernigan et al., 1991; Swayze et al., 1992; Chakos et al., 1995; Frazier et al., 1996) and a perusal of Table 11 indicates that three of the studies reporting BG enlargement made use of partially manic samples treated with anti-psychotic medication (Strakowski et al., 2002; DelBello et al., 2004; Wilke et al., 2004).

Metabolic activity or blood flow was consistently elevated in manic or hypomanic samples (Blumberg et al., 2000; Caligiuri et al., 2003; Caligiuri et al., 2006) (Table 10). Nevertheless, hypermetabolism of the BG has also been reported in depressed samples, specifically in the ventral striatum (Ketter et al., 2001; Bauer et al., 2005; Mah et al., 2007).

4.3.3. Potential relationship of BG changes to the signs and symptoms of BD and MDD

Impaired striatal function may explain the anhedonia and reduction in goal-seeking behavior that is observed in some patients with MDD and depressed BD cases. Conversely, the elevation in psychomotor activity is congruent with reports of increased metabolism or blood flow in more dorsal regions of the striatum in the manic phase of BD.

4.4. Ventriculomegaly and white matter pathology

4.4.1. MDD

Ventricular enlargement, usually of the third or lateral ventricles, is characteristic of older and chronically ill patients with depression, or patients with a late age of depression-onset. The white matter hyperintensities seen concomitantly in these patient groups raise the possibility of a vascular etiology for depression (Krishnan, 2002; Knopman et al., 2005; Sneed et al., 2008).

Clearly, the hypothesized excitotoxic processes which may be operating in medial temporal and striatal tissue could theoretically

cause ventricular enlargement. Nevertheless, the degree of subcortical atrophy needed to manifest as ventricular enlargement remains unclear. If long-term pathological processes are a prerequisite for ventriculomegaly then this may explain why the phenomenon appears to predominate in elderly populations. Factors such as chronic alcohol abuse (Anstey et al., 2006) and incipient neurological disorders with prodromal depression may also contribute to enlargement of ventricles.

These data are congruent with the neuropathological studies of Thomas et al. (2002, 2003) which describe WM disease of the DLPFC in a sample of elderly depressed patients, a result replicated in a middle-aged sample of depressed individuals who showed reduced levels of myelin staining in the deep WM tracts of the DLPFC (Regenold et al., 2007). One possible explanation for this potential demyelination is change in oligodendrocyte function. At least three post-mortem studies have reported a down-regulation of oligodendrocyte-related gene expression in MDD and BD (Hakak et al., 2001; Tkachev et al., 2003; Aston et al., 2005), while decreased oligodendrocyte density has also been noted in several studies (Cotter et al., 2002; Hamidi et al., 2004; Uranova et al., 2004; Vostrikov et al., 2007).

An unresolved issue is whether the WM pathology-depression relationship is one of cause or effect. Certainly, there appear to be cases that are precipitated by subcortical infarcts. For example, depression is a relatively common sequala of the genetic disorder, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) (Chabriat et al., 1995; Desmond et al., 1999). Similarly, given the increased rate of risk factors for cerebrovascular disease observed in MDD samples (Steffens et al., 1999; Lyness et al., 2000; Wassertheil-Smoller et al., 2004), it is likely that subcortical ischemic events play a role in the development of late-onset MDD.

Nevertheless, some studies have made attempts to match patients and controls (or statistically control) for the presence of cerebrovascular risk factors and still find elevated rates of WMH in their MDD samples (Table 13). A possible explanation is that depression may predispose to the development of small WM lesions via some as yet occult pathophysiological mechanism.

Based on extant evidence in the literature (Biegon et al., 1990; Musselman et al., 1996; Lenze et al., 1999), Nemeroff and Musselman (2000) have speculated that excess depression-associated secretion of serotonin by blood platelet cells facilitates cellular aggregation and therefore predisposes to atherosclerosis, thrombosis and vasoconstriction. Another possibility is impaired regulation of vascular tone. Cerebrovascular reactivity, which describes the compensatory dilatory capacity of arterioles to dilatory stimuli, has been reported to be reduced in acutely depressed patients without any neurological, cardiac or vascular risk factors (de Castro et al., 2006).

4.4.2. BD

Ventriculomegaly is more commonly observed in BD across different age groups (Swayze et al., 1990; Figiel et al., 1991; Strakowski et al., 1993, 1999, 2002; Botteron et al., 1995; Zipursky et al., 1997; Lim et al., 1999; Hauser et al., 2000; Brambilla et al., 2001a; Davis et al., 2004; Strasser et al., 2005; Soares et al., 2005).

It is plausible that as in the case of MDD, WM abnormalities are a long-term consequence rather than a cause of bipolar illness. One possibility is that people with BD have an excess of atherosclerotic risk factors that lead to microvascular pathology at an even earlier age than MDD. As reviewed by Kilbourne et al. (2004) and Newcomer (2006), BD is associated with a significantly increased prevalence of cardiovascular disease risk factors such as smoking, obesity, diabetes mellitus (DM), hypertension and dyslipidemia. Hypertension (Dufouil et al., 2001; Gunstad et al., 2005), obesity (Gustafson et al., 2004), smoking (Dager and Friedman, 2000) and DM (Novak et al., 2006) have in turn been directly associated with the development of WMH. Further, drug abuse is prevalent in BD populations and stimulant drug-induced vasoconstriction may lead to WMH (Dupont et al., 1990; Lyoo et al., 2004b). Marijuana may also interact in an additive fashion with WMH to predispose to depressive symptomatology (Medina et al., 2007).

Although most published studies make an attempt to exclude patients with potentially confounding conditions, the whole gamut of risk conditions is very rarely controlled for, raising the possibility that WMH in BD are an artifact of co-morbid ischemic risk factors.

Nevertheless, this hypothesis fails to account for the WM pathology noted in pediatric BD samples (Botteron et al., 1995; Lyoo et al., 2002b; Pillai et al., 2002) as well as the high concentration of WMH in both BD subjects and their unaffected relatives reported by Ahearn et al. (1998). We suggest that although a proportion of BD individuals with significant WM pathology will present with cardiovascular risk factors, WMH may less commonly also co-occur with some kind of developmental insult. In other words, the WMH seen in pediatric or young adult BD samples are likely to have a different origin to those seen in older populations.

The etiology of these precocious lesions is unclear. Obstetric complications are well known to be associated with schizophrenia (see meta-analysis of 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 bipolar illness in a vulnerable minority (Pavuluri et al., 2006).

The high incidence of familial WMH seen in the (Ahearn et al., 1998) sample suggests that genetic factors may also be at play. A number of post-mortem analyses provided evidence for the altered gene expression of genes impacting myelin or oligodendrocyte function in both MDD and BD (Tkachev et al., 2003; Aston et al., 2005; Sequeira et al., 2006). As reviewed by Carter (2007a,b) and Sokolov (2007) 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 affective illness and may determine how resilient these cells are to environmental stressors[2]. This hypothesis will be discussed in greater detail below.

4.4.3. Potential relationship of WM lesions to the signs and symptoms of BD and MDD

Lesions to the deep WM tracts of the frontal cortex and BG disrupt communication between key components of the visceromotor network, resulting in a so-called "disconnection syndrome" with sequalae that bear some resemblance to the symptomatology induced by GM lesions to the individual components of the network.

4.5. The OFC

4.5.1. MDD

The evidence for increased metabolism of the OFC in depressed samples receives support from serotonin and catecholamine depletion studies which have elicited a similar effect in remitted patients as they develop depressive relapse (Neumeister et al., 2004; Hasler et al., 2008). Congruent with these data, treatment with antidepressant medication (Brody et al., 1999), psychotherapy (Goldapple et al., 2004), and deep-brain stimulation (Mayberg

[2] Oligodendrocytes have a high density of glutamate receptors and are particularly vulnerable to glutamate-induced excitotoxicity.

et al., 2005) has been associated with decreased metabolism of the OFC. The combination of elevated OFC activity and tissue loss in MDD samples is consistent with the operation of an excitotoxic process.

The structural MRI-derived evidence of OFC volume loss (Table 16) is supported by the post-mortem analysis of Rajkowska et al. (1999) which uncovered a 12% decrease in the thickness of the rostral (but not the caudal) OFC, and a 15% decrease in the middle OFC in depressed patients compared to healthy controls; a finding attributed to neuronal shrinkage with attendant reduction in volume of the neuropil. Further, a 15% decrease in glial cell density was observed in the caudal OFC.

Nevertheless, we note that a significant number of the patients in the samples demonstrating volume reductions became ill after the age of 40, raising the issue of etiological heterogeneity.

4.5.2. BD

BD samples also appear to be characterized by tissue loss in the OFC as measured by MRI. These data are supported by the post-mortem analysis of Cotter et al. (2005) who found evidence of reduced glial cell density and neuronal size in the caudal OFC of patients with BD. Further, the structural integrity of WM tracts in the OFC, as measured by diffusion tensor imaging, may also be compromised in adult (Beyer et al., 2005; Haznedar et al., 2005) and pediatric (Frazier et al., 2007) patients. GM loss secondary to excitatory metabolic disturbances is supported by the MRS study of Cecil et al. (2002) who recorded reduction of NAA and choline concentrations in the orbitofrontal GM of a BD sample.

Too few resting state studies have been conducted to reach a conclusion about BD-associated OFC metabolism. Nevertheless, fMRI studies using cognitive probes of behavioral inhibition and decision-making, have reported decreased OFC BOLD response in patients with mania (Elliott et al., 2004; Altshuler et al., 2005b). Similarly, the passive viewing of emotional material has been associated with a relative decrease in the BOLD response of the left OFC in a patient with post-partum psychosis compared with her monozygotic cotwin (Fahim et al., 2007). It is unclear how these fMRI finding relate to the putative OFC volume loss observed in BD.

4.5.3. Potential relationship of changes in the OFC to the signs and symptoms of BD and MDD

The OFC plays major roles in the regulation of emotional and by implication, social behavior. Lesions to the OFC have been associated with depression, mood instability and anxiety in other clinical case-studies (Grafman et al., 1996; MacFall et al., 2001), providing further evidence that this part of the brain is critical for the self-regulation of emotion and behavior.

Theoretically, therefore, volumetric and perhaps metabolic changes to the OFC may account for the emotional and cognitive disinhibition often characteristic of affective illness. Reduced orbitofrontal activity in BD patients during performance of an emotional go/no-go task (Elliott et al., 2002, 2004) as well as the Stroop task, a measure of cognitive control, Kronhaus et al. (2006) has previously been noted. These data are relevant because impaired performance on the Stroop and go/no-go tasks have been separately demonstrated in MDD and BD samples (Erickson et al., 2005; Savitz et al., 2007b).

4.6. Ventro-medial "Emotion" circuit

The modulation of visceral responses to affective stimuli seems to be crucial for translating OFC-derived valenced data into actions and behavior (Ongur et al., 2003), an idea popularized by Damasio and colleagues (Damasio, 1996; Bechara et al., 1997) as the "somatic marker" (SM) hypothesis.

According to the SM conjecture, a somatic marker, an unpleasant or positive viscerally generated stimulus such as anxiety or reward, is temporally paired with a predicted future outcome. This juxtaposition of cognitive and emotional inputs ensures competent decision-making in complex situations because it allows individuals to anticipate the future positive and negative consequences of their actions. When this process goes awry, as in the case of individuals with lesions to the ventro-medial cortex, impaired judgment results (Damasio, 1996).

Recent studies are indicative of increased metabolism of the sgACC in the depressed phase relative to the remitted phase of MDD patients (Drevets et al., 2008). Congruent with these data, a tryptophan depletion study of healthy subjects showed that serotonin depletion resulted in increased rCBF in the sgACC (BA 24 and 25) (Talbot and Cooper, 2006). Neumeister et al. (2004) had previously reported the same phenomenon using glucose metabolic measures in remitted, unmedicated patients with a history of MDD. Similarly, the depressive relapse associated with alpha-methyl-*para*-tyrosine induced catecholamine depletion in remitted MDD subjects was also associated with increased metabolism in the sgACC (Hasler et al., 2008).

Changes in the metabolic activity of the ventro-medial circuit have also been reported after treatment and improvement in symptomatology. Mayberg et al. (2000) found that people who responded to a trial of fluoxetine showed decreased bilateral activity of the sgACC, while treatment with sertraline resulted in significant decreases in the activity of the left sgACC (Drevets et al., 2002a). Two sleep deprivation studies showed a drop in elevated baseline levels of sgACC activity in depressed patients who responded to treatment (Wu et al., 1999; Clark et al., 2006). In another indication that these changes may be independent of treatment modality, a deep-brain stimulation study (Mayberg et al., 2005) showed reduced perfusion of both the anterior and posterior portions of the sgACC (BA 25 and part of 24, respectively; Fig. 2) in treatment responders.

The ventral ACC has also been demonstrated to mediate fluctuations within the normal range of emotion. For example, Mayberg et al. (1999) asked healthy and depressed subjects to recall sad personal experiences and found that negative mood induction was associated with increased activity of the sgACC. On the other hand, women grieving the break-up of a romantic relationship have been reported to display reduced activity in the left pregenual and sgACC (Najib et al., 2004).

Anatomical MRI studies have provided evidence for decreased sgACC volume in both MDD and BD (Drevets et al., 2008). Moreover, Ongur et al. (1998) found a reduction in the number of glial cells together with an increase in neuronal density in the sgACC of patients with familial BD and MDD, suggesting that the reduction in neuropil is accounted for by the reduction in sgACC volumes reported in the literature. Using the same set of brain tissue, these findings were partially replicated by Cotter et al. (2001) who detected reduced glial density and neuronal size (but not density) in the region of pregenual ACC in patients with major depression. An analogous effect in the sgACC in both familial and non-familial depression with glial cell density reductions of 24% and 41%, respectively (Ongur et al., 1998; Drevets, 2000b). These data receive support from animal models of depression.

Rats subjected to 3 weeks of repeated restraint stress show a 16–20% reduction of apical dendritic spine density in the anterior cingulate region of the medial PFC (Liston et al., 2006; Radley et al., 2006). A corresponding effect has also been noted in the pups of mothers exposed to prenatal stress (Murmu et al., 2006). This dendritic remodeling process has been shown to depend on interactions between NMDA receptor stimulation and glucocorticoid release during chronic or repeated stress, suggesting that the

dendritic atrophy is a type stress-induced, slow excitotoxicity (Reagan and McEwen, 1997).

These anatomical changes may correlate with behavior: restraint stress-associated retraction of apical dendrites in the medial PFC of rodents has been associated with retarded extinction learning (Miracle et al., 2006). The same effect may hold in humans. Healthy individuals with thinner ventromedial PFC tissue show a greater galvanic skin response to conditioned stimuli during extinction learning (Milad et al., 2005). Chronic psychosocial stress may also impact glial cell function: rats exposed to 5 weeks of daily social defeat have been reported to show a suppression of gliogenesis in the medial PFC; an effect reversed by fluoxetine (Czeh et al., 2007).

Interestingly, ibotenic acid-induced lesions of the rat mPFC (infralimbic/prelimbic and ACC cortices) have been shown to produce evidence for a lateralized effect: right but not left-sided lesions were anxiolytic (Sullivan and Gratton, 2002). In contrast, left-sided lesions are anxiogenic, and result in increased sympathetic activity and corticosterone response to stress. This result is reminiscent of an earlier study in which dopamine depletion of the left but not right medial PFC rendered animals vulnerable to stress-associated ulceration (Sullivan and Szechtman, 1995). Further, Sullivan and Gratton (1999) found that left-sided lesions potentiate autonomic stress responses to restraint stress while right-sided lesions diminish these endocrine reactions. The putatively differential effect of the two hemispheres appears to follow a phylogenetic continuum.

Babinski (1914) first discussed the anosognosic and manic sequelae of right-sided lesions while Goldstein (1939) coined the term, "catastrophic reaction" to describe the emotional distress and depressive symptomatology associated with left-hemisphere lesions. More modern structural imaging studies have lent support to the original clinical reports (Robinson et al., 1984; Morris et al., 1996) and studies of idiopathic anxiety, depression, and BD have produced analogous findings (Silberman and Weingartner, 1986; Davidson, 1992; Pascual-Leone et al., 1996; Savitz et al., 2004; McDonald et al., 2004b).

The physiological mechanisms underlying these effects have been extensively debated. Explanations generally circle around the theme of a positive emotion-producing, appetitive, reward-seeking circuit in the left PFC which interacts in a dialectical manner with a mirror neural network in the right-hemisphere (Flor-Henry, 1979; Sackeim et al., 1982; Savitz et al., 2007a). Conceivably, a disruption of the regulatory capacity of these circuits, such as disinhibition of the right hemisphere after left hemisphere damage, may lead to affective illness.

Consistent with the above hypothesis, differential hemispheric functional activity of the mPFC has been reported in the literature. Nevertheless, caution should be exerted in interpreting these data because the PET data are too low in resolution to accurately resolve left from right in regions close to the midline.

Since the vast majority of the studies samples were limited to currently depressed patients, it is unclear whether the possible dichotomy in hemispheric activity is a stable trait which applies to euthymic populations. There is some evidence that it is more likely to be a state-dependent phenomenon. In both the Drevets et al. (1997) and the Blumberg et al. (2000) cohorts, the manic subjects had greater rCBF or metabolism in the ACC than in depressed or remitted individuals (in contrast, the volumetric deficit in the sgACC persisted across illness phases). Further, Liotti et al. (2002) reported that after the execution of a sadness-induction paradigm, rCBF was higher in the sgACC in healthy controls compared to remitted depressives.

It should be noted that a minority of researchers have reported the diametric pattern of right-sided hypometabolism or volume loss and left-sided hypermetabolism in MDD (Drevets et al., 1992; Wu et al., 1999; Kennedy et al., 2001) and BD (Kegeles et al., 2003; Sharma et al., 2003). In the case of the latter study, however, the sample was euthymic while the Kegeles et al. (2003) cohort was composed of both BD and MDD patients with comorbid anxiety disorders and was characterized by benzodiazepine (BZ) use at the time of the scanning. Further, these researchers reported right-sided hypometabolism of the pregenual as opposed to the sgACC and this may have accounted for the discrepancy in results.

Nevertheless, Davidson and Irwin (1999) warn that most claims about hemispheric asymmetry of function are methodologically flawed because they are based on the observation that voxel-based activity in only one hemisphere reaches statistical significance. It does not, however, necessarily follow from this that the two hemispheres are significantly different from each other. This hypothesis needs to be tested by examining group or condition x hemisphere interactions (Davidson and Irwin, 1999).

Fornito et al. (2007) favor a developmental rather than a stress-driven explanation for the sgACC volumetric changes believed to be characteristic of affective illness. These authors examined the folding patterns of the ACC, and reported a lower incidence of the adjacent paracingulate sulcus (PCS) in BD subjects compared with controls. Nevertheless, given the fact that the PCS is absent in many healthy individuals, the functional significance of this pattern of cortical folding is unclear.

4.6.1. Potential relationship of changes in the ventro-medial circuit to the signs and symptoms of BD and MDD

Autonomic, endocrine and metabolic (McIntyre et al., 2007; Rottenberg, 2007; Smolin et al., 2007; Harvey, 2008; Surtees et al., 2008) abnormalities are over-represented in individuals with affective illness. The ventromedial PFC, with its connections to the hypothalamus and brain-stem, modulates visceral output in response emotional stimuli (Price, 2007). Conceivably, therefore, damage to the ventromedial PFC may not only dysregulate emotional function, but may play a pathoetiological role in the development of comorbid medical conditions.

4.7. The DLPFC

4.7.1. MDD

Hypometabolism and to a lesser extent GM volume decrements of particularly the left DLPFC have been widely reported in people suffering from depression. These data are consistent with the executive and working memory deficits characteristic of many such patients (Savitz et al., 2005). They are also congruent with fMRI analyses that have reported altered BOLD signal in the DLPFC of MDD patients challenged with cognitive tasks that require executive control (Harvey et al., 2005; Matsuo et al., 2007; Siegle et al., 2007).

As is the case with other neural networks, one complication of this literature is the potentially lateralized function of the PFC. Based on our rudimentary understanding of how emotional processing is lateralized in the brain, one would expect a preponderance of left dorsal cortex hypoactivation in depression. We are aware of at least nine studies that have recorded left-sided hypofunction or GM loss of the dorsal PFC in MDD (Bench et al., 1995; Shah et al., 1998; Kennedy et al., 2001; Drevets et al., 2002a) and BD (Baxter et al., 1989; Martinot et al., 1990; Lopez-Larson et al., 2002; Frangou, 2005; Dickstein et al., 2005). Furthermore, right hemisphere hypoactiviation in MDD responders to sleep deprivation has been recorded (Clark et al., 2006). Congruent with these reports, Beauregard et al. (2006) found that those individuals who experienced difficulty actively down-regulating sad thoughts showed a greater (presumably compensatory) response in the left mPFC (BA 10). More recently, Grimm et al. (2007) reported left-sided hypoactivity and right-sided hyperactivity in MDD patients,

who as a group, tended to judge pictures as more negatively valenced than healthy controls.

This hypothetical lateralization of function could theoretically explain the minority of studies detailing *increased* activity of the DLPFC in MDD (Brody et al., 2001; Holthoff et al., 2004). Nevertheless, none of these studies reported exclusive hypermetabolism of the right hemisphere. However, in one study the patients were only withdrawn from benzodiazepines 3 days prior to scanning, potentially confounding the metabolic measures (Holthoff et al., 2004). *Decreased* activity of the right (Hurwitz et al., 1990) DLPFC in depressed MDD patients has also been noted but again the withdrawal of benzodiazepines 1 day prior to scanning is a significant limitation.

Consistent with the notion of GM atrophy, histological changes to the DLPFC have been reported. Although no significant differences in cortical density were apparent across their MDD and control groups, Rajkowska et al. (1999) noted a depression-associated decrease in neuronal size with a concomitant decline in large cell density and increase in small neuronal cell density. Further, suicide has been associated with microgliosis of the DLPFC in a post-mortem schizophrenia and MDD sample (Steiner et al., 2008).

4.7.2. BD

BD samples have tended to display evidence of dorsal PFC GM volume loss, and these putative changes are consistent with reports of aberrant dorsal PFC gene expression in patients with BD (Nakatani et al., 2006; Beneyto and Meador-Woodruff, 2007; Kanazawa et al., 2007; Pennington et al., 2007; Pillai, 2008; Shao and Vawter, 2008; Silberberg et al., 2008)—although see (Ryan et al., 2006) for a negative report. The mechanism by which these putative molecular changes impinge on the development of gross anatomical structures such as the DLPFC is not yet understood.

4.8. The corpus callosum

The functional consequences of callosal WM abnormalities are unclear. One proposal is that a disruption to inter-hemispheric transmission impairs cognitive function in people with mood disorders (Brambilla et al., 2004). Damage to the CC, however, may retard the transfer of visual, motor, linguistic and somatosensory information in a regionally specific manner, and moreover, there may be some redundancy in these information highways, both within the CC itself, and subcortical circuitry (Gazzaniga, 2005). Given the absence of salient deficits in these domains in affective illness, it seems likely that any lesions of the CC would preferentially affect cognitive or emotional processing. One possibility is that volume loss of the CC is secondary to abnormalities of the surrounding GM. Further work is needed to clarify the relationship between potential demyelination of the CC and cognitive and/or emotional impairment.

5. Over-arching discussion

5.1. Neurodevelopment versus neurodegeneration

The heritability of BD converges on the 60–80% range (McGuffin et al., 2003; Kieseppa et al., 2004) while the heritability score for MDD is closer to the 40% mark (Agrawal et al., 2004; Boomsma et al., 2005). Thus although genetic factors play an important etiological role in affective disorders, the importance of environmental variables should not be discounted. In fact, the average concordance rate among monozygotic (MZ) and dizygotic (DZ) twins stands at approximately 40% and 10%, respectively, for BD (McGuffin et al., 2003; Kieseppa et al., 2004), and approximately 30% and 20% for MDD (Lyons et al., 1998; Kendler and Prescott, 1999).

One potentially important environmental variable is exposure to adversity: stressful life events are known to precipitate bouts of affective illness in both BD (Kessing et al., 2004; Johnson, 2005) and MDD (Kendler et al., 1999; Hettema et al., 2006) populations.

Current models of pathological change in affective illness are deeply rooted to these environmental contingencies, as functional and anatomical change in depression is often viewed as degenerative: stress-induced, glutamate-mediated excitotoxicity leads to metabolic changes or decreases in GM volume. In contrast, the role of genetically mediated neuroplasticity is not usually explicitly addressed in contemporary models of illness-associated neuropathology. We will first discuss the neurodegenerative hypothesis, which conceptualizes GM or WM volume loss as a downstream effect of an unspecified environmental pathogen, such as psychological stress.

The degenerative model is based on the premise that psychological stress or some other pathophysiological insult is a necessary determinant of affective illness. Given the clustering of MDD and BD in families, and some reports that GM volume loss only occurs in familial cases (Drevets et al., 1997; Hirayasu et al., 1999; Ongur et al., 1998; Brambilla et al., 2001a; Kegeles et al., 2003; Lacerda et al., 2005), one possibility is that psychological stress must also be familial in order for this conceptualization of illness to be valid.

Actually, there may be a familial or genetic component to the experience of life stress because of a phenomenon known as gene–environment correlation (Bergeman et al., 1988; Rutter, 2007). Rowe (1981) first reported this counter-intuitive notion by showing that adolescent twins' reports of their parents' levels of accepting and rejecting behavior were under genetic influence; a finding that has been extended to retrospective measures of family warmth and parental control (Plomin et al., 1988) as well as family cohesion and encouragement of growth (Bouchard et al., 1990).

There are at least three ways in which gene–environment correlation might apply in the case of the degenerative hypothesis. The parental genotype or affective disorder may exert an effect on parental behavior such that their children are reared in a high-stress environment. Here there is a correlation between passing on "stress-provoking" genes and providing a stressful family environment.

Secondly, it can be argued that people are selecting and shaping their environmental experiences on the basis of their genetic heritage, leading to preferential exposure to significantly stressful events and depression-associated neuroplastic changes in a subset of the population. This phenomenon may be related to the way in which individuals perceive or process information in their environment; an intrinsic bias often described as temperament.

Certainly, so-called dysthymic or anxiety-related personality traits have been widely described in MDD individuals, while BD is characterized by various combinations of dysthymic, cyclothymic-unstable and hypomanic traits (Evans et al., 2005; Savitz and Ramesar, 2006; Savitz et al., 2008a; Savitz et al., 2008b). Since these traits are likely underpinned by genetic factors (reviewed in Savitz and Ramesar, 2004; Ebstein, 2006), temperament may mediate the impact of genes on environmental experiences (Savitz and Ramesar, 2006).

Yet a third possibility is that genetic effects play no role in influencing exposure to stressors but moderate the physiological effect of these events on neural tissue.

One class of proteins potentially involved in this type of gene–environment interaction is the neurotrophins.

As reviewed by Poo (2001), one of these enzymes, brain-derived neurotrophic factor (*BDNF*) [627], increases forebrain serotonin fibre density and neurogenesis, prevents spontaneous and neurotoxin-induced cell death, and modulates the formation of synaptic connections, particularly in the PFC and hippocampus.

Recent studies have suggested that the low expression (*met*) allele of a functional single nucleotide polymorphism (SNP) (Val66Met) of the *BDNF* gene may increase the probability of developing depression (Kaufman et al., 2006) and cognitive impairment (Savitz et al., 2007c) after exposure to childhood maltreatment. Perhaps through its reduced ability to protect against neurotoxicity, the *met* allele has also been reported to increase the risk of developing depression after stroke (Kim et al., 2007).

Another potential moderator of the stress-response is central serotonergic activity. As reviewed by Drevets (2000b), the binding of serotonin to post-synaptic 5-HT_{1A} receptors not only enhances the negative feedback inhibition of cortisol release but also prevents dendritic cytoskeletal breakdown by catalyzing the release of the neurotrophic factor, S100β, and indirectly inhibiting protein kinase-induced apoptosis (Szatmari et al., 2007). The regulation of 5-HT_{1A} receptors in the raphe is at least partly controlled by functional variants of the *HTR1A* [3350] (−1019C/G; rs6295) (Lemonde et al., 2003; Parsey et al., 2006) and the *SLC6A4* [6532] (promoter region length polymorphism) (David et al., 2005) genes, respectively.

In contradistinction to the degenerative model, the developmental model advocates that neuroanatomical changes precede the onset of affective illness. An interesting set of animal experiments has lent credence to this hypothesis: a line of rats, genetically bred to suffer from learned helplessness display baseline hypometabolism of the amygdalae, BG, VTA, dorsal–frontal, medial-OFC and ACC, but increased metabolism of the infraradiata (sgACC), hippocampi and habenula (Shumake et al., 2000; Shumake et al., 2002). To further control for the effects of early-life stress, Shumake et al. (2004) examined the brains of this genetic line of rats at birth and again found hypo or hypermetabolism of most of these regions. Moreover, the midbrain and brain-stem regions were found to be disconnected from limbic forebrain regulation, suggesting to the authors that the fundamental disturbance in depression is one of top–down regulatory control (Shumake et al., 2004).

In humans one way of examining this issue is to compare the degree of variation in regions of interest across the life-span. Lupien et al. (2007) found that there was just as much variability in the hippocampal volumes of healthy young adults as in older individuals, implying that volume decrements attributed to aging or stress could be reflective of neurodevelopmental differences. Specifically, a quarter of their subjects in the 18–24-year age group had hippocampal volumes as small as the average hippocampal size in their 60–75-year-old sample, and the mean difference in hippocampal volumes between the upper and lower quartiles of the young age group (12–16%) was greater than volumetric reductions typically seen in depressed samples (Lupien et al., 2007). These data are congruent with an earlier study (Gilbertson et al., 2002) which reported an association between post-traumatic stress disorder and smaller hippocampal volume in war veterans. Intriguingly, the MZ twin brothers of the PTSD cohort who did not serve in the military also presented with smaller hippocampi than the PTSD group, raising the possibility that reduced hippocampal volumes are a contributing cause rather than an effect of PTSD.

Recent findings from the emerging field of imaging genomics also emphasize the importance of genetic influences. A variant of the neuregulin 1 (*NRG1*) [3084] gene, which is involved in the myelination process, and has been implicated in both BD and schizophrenia, may be associated with WM density and integrity of the internal capsule (McIntosh et al., 2007). In another study, the *short* (*s*) allele of the serotonin transporter (5-HTT) gene (*SLC6A4*) [6532] promoter polymorphism has been shown to be associated with increased resting CBF in the amygdala and decreased perfusion of the ventromedial PFC in healthy individuals (Rao et al., 2007).

The neurodevelopmental hypothesis can also be evaluated by searching for neural changes in unaffected family members who presumably share a genetic diathesis for the disorder with their ill relatives. Noga et al. (2001) compared MZ pairs discordant for BD with a control group of unaffected twins, and found that the right hippocampus was smaller in the affected twins, but that both ill and well twins had larger caudate nuclei than the control pairs. McDonald et al. (2004a) reported that genetic risk for BD was associated with reduced volume of the right anterior cingulate gyrus and ventral striatum. Similarly, a compensatory hypermetabolic response to a sadness induction paradigm was observed in the medial PFC of healthy BD relatives compared with background controls (Kruger et al., 2006). Conversely, McIntosh et al. (2006) and Munn et al. (2007) failed to detect any significant neural changes in at-risk BD relatives.

Concerning MDD, Monk et al. (2007) reported that the pediatric offspring of parents with MDD displayed greater amygdala and accumbens area activity in response to fearful faces, and lower accumbens area activation in response to happy faces than a low-risk control group. A small number of serotonin depletion experiments have succeeded in inducing depressive symptoms in otherwise healthy relatives of MDD probands. Six out of 20 healthy males with a family history of affective illness but 0 out of 19 male controls displayed a lowering of mood in response to tryptophan depletion (Benkelfat et al., 1994). More recently, van der Veen et al. (2007) reported a greater lowering of mood, and stronger amygdala response to fearful faces under tryptophan depletion in healthy individuals with a family history of depression compared with controls. Neumeister et al. (2002) showed that this effect may be mediated by the *SLC6A4* promoter length polymorphism: family history-positive heterozygotes showed a greater mood-lowering effect than their heterozygote counterparts without a history of depression.

These potential neuroimaging endophenotypes are most likely genetically driven. For example, serotonergic activity not only plays an important role in modulating the impact of stressful events, but also is a key regulator of neural development influencing neurogenesis, apoptosis and dendritic growth (Gaspar et al., 2003). Fluoxetine-induced suppression of the serotonin transporter during development has been shown to result in abnormalities of emotional behavior in mice (Ansorge et al., 2004). Recent data have also shown the direct effect of the 5-HTT polymorphism on neural tissue with increased hemodynamic response of the amygdala (Hariri et al., 2002; Heinz et al., 2005; Pezawas et al., 2005; Dannlowski et al., 2006) to fearful faces (versus geometric images or neutral faces) in *s* allele carriers.

The distinction between early, developmental, and later-onset stress-induced pathology may be partly artificial. Genetically determined subtleties of brain-wiring may sensitize the individual to the effect of ubiquitous, relatively mild stressors.

The *s* allele of the above-mentioned 5-HTT gene insertion/deletion polymorphism, first associated with anxiety-related personality traits more than a decade ago (Lesch et al., 1996), is now one of the prototypical examples of a risk variant that interacts with adverse life experiences to predispose to psychopathology (Caspi et al., 2003; Kaufman et al., 2004).

Pezawas et al. (2005) investigated the neurobiology behind this process. The authors demonstrated that healthy carriers of the *s* allele of the polymorphism display reduced functional connectivity between the amygdala and the sgACC. The latter structure exerts an inhibitory effect on the amygdala[3] and thus a genetically

[3] The regulation of the amygdala by the sgACC is proving to be increasingly complicated. Recent evidence suggests that although area 25 does indeed exert inhibitory effects, projections from area 24 actually have an excitatory effect on the amygdala (Vidal-Gonzalez et al., 2006).

determined attenuation of this negative-feedback loop may increase sensitivity to environmental adversity and by implication, lead to maladaptive neuroplastic changes (Pezawas et al., 2005).

A nascent trend in the study of psychiatric disorders is a recognition of the potentially important role of epigenetic mechanisms in disease causation (see Mill and Petronis, 2007). Epigenetic inheritance refers to a regulated pattern of gene expression which is transmitted intact from one or other of the parents to their offspring. The process is mediated by the methylation and histone acetylation of cytosine residues and chromatin, respectively, leading to the activation or silencing of particular genes. The phenomenon is epigenetic because it results in phenotypic traits that are inherited independently of the informational content of DNA.

Meaney and Szyf (2005) review rodent studies which demonstrate that stress sensitivity in rat pups is modulated by parental grooming behavior that exerts its effect through a histone modification-driven regulation of glucocorticoid receptor gene expression. If these biological mechanisms generalize to humans then exposure to adversity may modify gene expression in pathways that impact neuroplasticity.

5.2. Methodological and theoretical issues

(1) A common confounding variable is medical treatment. As Drevets (1998) notes, rCBF and metabolism of various neuroanatomical regions may be reduced by antidepressants, anti-psychotics and anxiolytics. Further, psychotropic drugs have been shown to alter both the behavioral and the neurophysiological response to the environmentally valenced stimuli used as neurocognitive probes in fMRI studies.

Recent studies have detailed the neurotrophic effects of lithium and mood stabilizers on hippocampal and other neural tissue. In fact, there has been some suggestion that AD may also exert a neurotrophic effect in particular regions of the brain (Stewart and Reid, 2000; Rocher et al., 2004; Duman and Monteggia, 2006). These data are supported by an fMRI study which showed that depressed patients suffer from reduced functional coupling of the amygdala with diverse brain regions including the hippocampus, caudate, putamen, and ACC; an effect reversed by treatment with fluoxetine (Chen et al., 2007b). Similarly, a decrease in left amygdala activity to normal has been observed after antidepressant treatment (Drevets et al., 2002a). Interestingly, a decrement in amygdala activity in response to aversive stimuli also been observed in healthy individuals treated with citalopram (Harmer et al., 2006) and reboxetine (Norbury et al., 2007).

Neuroleptics, which are commonly used to treat BD, may also exert a neurotrophic effect, with reports of post-treatment increases in basal ganglia volumes (or shape) in patients with BD (Hwang et al., 2006) and schizophrenia (Chakos et al., 1994; Gur et al., 1998; Massana et al., 2005; Glenthoj et al., 2007; Okugawa et al., 2007).

The association between imaging changes and medication is rendered even more complicated by the possibility that treatment may be a proxy variable for genetic etiology. In other words, the hippocampal or sgACC volumetric changes associated with a drug-like lithium, for example, could theoretically be characteristic of a particular subtype of BD that just happens to be responsive to lithium (Moore et al., in press). This is one example of etiological heterogeneity that may be a significant contributor to inter-study variability.

(2) Another example of disease heterogeneity is the difference in the pathophysiological mechanisms underlying early-onset and late-onset depression discussed above. Other hidden etiological differences may be an even more pernicious source of bias. In genetic studies, a distinction is often made between those patients who are recurrently ill and those subjects who have experienced one life-time episode of depression (Zubenko et al., 2002), but this is rarely seen in the imaging literature. Further, the degree to which MDD or BD runs in the families of recruited subjects or whether MDD patients are recruited from BPD families is not always detailed. Differences between psychotic and non-psychotic "subtypes" of BD may also contribute to inter-study variability in findings. Approximately 50% of BD I patients experience psychosis (Keck et al., 2003; Ketter et al., 2004) and recent evidence suggests that working memory deficits may be specific to those patients with a history of psychosis (Glahn et al., 2007; Savitz et al., 2009).

Information about obstetric or other developmental problems is rarely reported. The diagnosis of BD in children has increased sharply (mostly in the United States) in recent years, yet it is unclear as to whether children diagnosed with BD actually suffer from the same disorder as adults (Duffy, 2007). This is particularly true when the broader phenotype of severe mood dysregulation (irritability and hyperarousal), which overlaps with ADHD, is used (Duffy, 2007). A narrower pediatric clinical phenotype may more faithfully represent adult nosological categories (Brotman et al., 2007). Caution should therefore be exerted in extrapolating neuroimaging findings from these pediatric populations to adults and *vice versa*, particularly when broad diagnostic criteria are used. This caveat is illustrated by Biederman et al. (2007) who reported that pediatric BD patients with co-morbid ADHD show additive patterns of MRI-evinced volume loss characteristic of both disorders when studied independently.

(3) State versus trait outcome differences do not always receive the attention that they merit: identification of the neuroanatomical or functional changes associated with the acute effects of depression and mania may serve as a useful means of evaluating the efficacy of treatments. Conversely, mood-independent abnormalities may be endophenotypes that can be exploited for genetic studies.

(4) While functional and morphometric analyses of affective illness often receive separate treatment in the literature, these two factors cannot be divorced from each other on either theoretical or methodological grounds. As alluded to above, GM volume loss may occur secondary to glutamate-driven excitotoxicity, a phenomenon which presumably correlates with elevated glucose metabolic activity (Shulman et al., 2004). Volume loss may however, lead to an underestimation of metabolic activity because of partial voluming effects: the inclusion of hypometabolic WM or CSF in putatively GM-containing voxels.

An example of this potential confound can be found in our own work. Initially, we found evidence of reduced metabolic activity in conjunction with reduced volume of the subgenual ACC in the depressed phase of both MDD and BD (Drevets et al., 1997, 2002a). Compatible with this hypothesis, depressed BD samples treated chronically with lithium indeed showed elevated sgACC metabolism irrespective of correction for partial volume effects (Bauer et al., 2005; Mah et al., 2007), consistent with evidence that lithium treatment is associated increase in the sgACC GM volume (Moore et al., in press).

Another example can be found in studies of the amygdala. Despite reports of volume reductions, hypermetabolism of the amygdala is a consistent feature of the literature, which suggests that the increase in activity, if genuine, may be substantial—in the order of 70%, even though state-of-the-art PET imaging technology

detects this as only a 6% difference between depressives and controls due to spatial resolution (i.e., partial volume) limitations (Drevets et al., 1992). The partial voluming effect can be attenuated to some extent by region of interest (ROI)-based analyses of a small central region of the ROI as implemented by the Drevets group, presumably facilitated their finding of substantially increased amygdalar activity (Drevets et al., 2002b).

Limitations in spatial resolution also have impinged on the efficacy of volumetric MRI measures. Further, most of the older and even current-imaging platforms do not have the necessary spatial resolution to accurately detail volumetric changes in dimunitive anatomical structures such as individual amygdalar nuclei. This limitation may lead to the implicit reification of neuroanatomical function; that is, the notion that gross anatomical structures should be uniformally affected by mood disorders simply because they are imagable units.

If one takes this argument to its logical extreme it becomes questionable as to what constitutes a replication. In other words, how similar do the functional or structural changes reported across studies have to be in order to establish that the identical functional units are affected?

(5) A comparison of the analytical methods used in imaging analysis is beyond the scope of this review. Nevertheless, a brief discussion of the two primary analytical approaches to imaging data analysis bears mentioning. Voxel-based analysis (as implemented in imaging analysis software such as the Statistical Parametric Mapping [SPM] series) is based on a mass-univariate statistical approach that compares the differences between two or more subject groups at each individual voxel in the brain (Ashburner and Friston, 2000). As such, Gaussian random field theory is used to correct for the multiple dependent comparisons that would, if uncorrected, lead to false positive results (Ashburner and Friston, 2000).

Voxel-wise analyses, however, are also highly sensitive to Type II errors because spatial normalization algorithms cannot precisely overlay small structures like the amygdala and sgACC across subjects, exaggerating the statistical variance. Possibly therefore, voxel-wise analyses should not be the method of choice when diminutive, subcortical structures are the subject of study (Bookstein, 2001; Nugent et al., 2006). Despite this limitation, voxel-wise analysis affords the advantage of allowing agnosticism with respect to the pathophysiology of the disorder under investigation.

On the other hand, the region of interest approach relies on extant empirical or theoretical data to identify candidate regions that may show inter-group differences. Thus, assuming the veridicality of the disease model, Bayesian inference suggests that the probability of a significant ROI result being a true positive is higher than in cases where convergent *a priori* data are absent. Nonetheless, the ROI approach is time and resource intensive especially when subject groups are large. The strength of the method is critically dependent on the precision of ROI segmentation, which depends heavily on the reproducibility of the anatomical landmarks chosen to delineate the target structure.

To our knowledge, very few comparisons of ROI and voxel-wise approaches have been made in psychiatrically ill samples. In one such study (Kubicki et al., 2002) that the voxel-wise approach for comparing cerebral volumes, termed "voxel-based morphometry (VBM)", produced an analogous finding (volume of STG) to their previously published ROI study, but also showed changes in other regions, one of which had not been previously implicated in schizophrenia. Later schizophrenia studies produced reasonably convergent results across ROI and VBM analyses in cortical regions (Job et al., 2002; Giuliani et al., 2005). Douaud et al. (2006) extended the correspondence in VBM-ROI results to the striatum in a case–control study of Huntington's disease; although it is unclear whether a VBM analysis would be able to detect the more subtle subcortical changes characteristic of affective illness. In at least one case, however, PTSD-associated hippocampal changes have been obtained in the same sample using both ROI and VBM approaches (Emdad et al., 2006).

We did not identify a clear difference in the results of VBM and ROI analyses in the BD and MDD literature (Tables 1–25), possibly because there are very few published VBM studies of subcortical regions.

(6) Genetic association studies are plagued by false positive results: with approximately 20, 000 genes, and multiple variants within each gene of interest, the *a priori* probability of a true association is low. Sample sizes in analyses which combine genetic and imaging data are by nature small, although this is offset to some extent by the relative precision of the phenotypic data that are collected. The problem can be partially ameliorated by targeted hypotheses.

6. A heuristic model

Top–down and bottom–up disruptions to cortico–striatal–limbic circuits are the most straightforward method of describing the pathophysiological and symptomatological changes associated with affective illness. We have not made any attempt to distinguish between MDD and BD, here. A graphical representation is provided in Fig. 1.

As discussed above, projections from the orbital and medial PFC to the amygdala and its associated limbic and brain-stem nuclei form a "visceromotor network" that modulates endocrine, autonomic, and behavioral aspects of emotion (Ongur et al., 2003).

In the top–down model, impaired PFC function, or cortical–subcortical "disconnection" disinhibits downstream limbic projections, altering emotional behavior. For example, disinhibition of the amygdala projections to the bed nucleus of the stria-terminalus (BNST), hypothalamus and periaqueductal gray matter (Behbehani, 1995; Sah et al., 2003) may increase cortisol releasing hormone (CRH) release and anxiety symptoms. Disinhibition of projections from the amygdala to the nucleus basalis, locus ceruleus and ventral tegmental area (Davis and Whalen, 2001; Sah et al., 2003) could account for the alterations in cholinergic (ACh), noradrenergic (NE) and dopaminergic (DA) transmission which may affect mood and attention. Finally, disinhibition of amygdala projections to the ventral striatum (Cardinal et al., 2002) would attenuate reward-seeking and goal-directed behavior, potentially contributing to the anhedonia and amotivation characteristic of depression. According to the bottom–up model, a functional hypersensitivity of limbic nuclei such as the amygdala, raphe and parahippocampus would predispose to dysregulation of PFC-mediated regulatory mechanisms.

In reality, the distinction between bottom–up and top–down models is artificial. If MDD and BD are polygenic disorders underpinned by many genes of small effect size, affected individuals are likely to possess many different risk variants affecting multiple neuroanatomical pathways and a single point of origin is unlikely.

The etiology of the suspected hypersensitivity or lesions[4] is unclear but most likely involves complex gene–environment interactions. For example, the *s* allele of the 5-HTT promoter variant may predispose to reduced functional connectivity between the amygdala and perigenual PFC (Pezawas et al.,

[4] Here we use the term "lesion", loosely, to signify any illness predisposing change in neurochemical function or neuroanatomical structure.

2005), which may be maladaptive under stress. Similarly, the *NRG1* gene may impact the myelination process and therefore predispose to WM lesions and a disruption to cortical–subcortical connections in the presence of cardiovascular risk factors. Two nonsynonymous SNPs of another gene, proline dehydrogenase (oxidase) 1 (*PRODH*) [5625] have also been associated with frontal WM volume reductions in schizophrenia (Zinkstok et al., 2007).

Other potential examples are the −1019C/G single nucleotide polymorphism (rs6295) of the *HTR1A* gene promoter which disrupts a glucocorticoid binding site and modulates raphe-PFC serotonergic transmission (Lemonde et al., 2003), and the val66met change in the *BDNF* gene which appears to impact hippocampal volumes in schizophrenic (Szeszko et al., 2005; Ho et al., 2006), healthy (Pezawas et al., 2004; Bueller et al., 2006), BD (Chepenik et al., 2008) and depressed (Frodl et al., 2007) individuals.

Many other similar examples are likely to emerge over time and hold out great promise for disinterring the latent pathophysiological basis of affective illness.

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