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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.

Background

Depression is arguably the epidemic of our time. The lifetime prevalence of major depressive disorder (MDD) ranges from 10–30% (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 2000a).

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

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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 (Figure 1).

Methodology

A literature search of the PUBMED database up until September 2007 was carried out using the following key words: 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, we although we highlight the result of certain fMRI studies (primarily in the discussion section), 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 (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 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 grey (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 then placing them under the rubric of the dorsal prefrontal, orbital frontal, and ventromedial cortical-striatal-limbic circuits described above.

Results

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 emphasise the hues of fear, anger and sadness (Gloor et al 1982) (Davidson 2002), providing *prima facie* evidence for its involvement in depression.

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).

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) (Drevets et al 2002b) (Anand et al 2005).

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).

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 discussion).

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.

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 sub-cortical structures such as the BG.

For example, the dorsal and orbito-frontal aspects of the prefrontal cortex send major efferent projections to the dorsal, and anterior caudate, respectively, while the anterior cingulate 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).

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).

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 the discussion.

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) (Caligiuri et al 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 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).

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.

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).

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).

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 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 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.

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 brain stem, modulating limbic-driven behavior (Ongur and Price 2000b). 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 behaviour in terms of these expected contingencies (Kringelbach and Rolls 2004) (Amodio and Frith 2006).

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) (Biver et al 1994) (Drevets et al 2002a) – 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 were 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.

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).

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 (ACC) (BA 24, 25, and 32) [1] (Figure 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 and colleagues (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

[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 through 24 we have cited the authors’ original anatomical descriptions, verbatim.

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 1999b) (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 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 1999a) (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 (Figure 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, 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 1999a) (Sassi et al 2004) (Wilke et al 2004) (Kaur et al 2005) of the broader ventral ACC region (Tables 21 and 22). One might hypothesise 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).

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 behaviour (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.

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) (Mayberg et al 2000) (Kennedy et al 2001) (Mayberg et al 2005) (Fales et al 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 make 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).

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).

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.

Discussion

The Amygdala

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 seconds in healthy controls but persisted in depressed patients for at least 25 seconds, 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 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 1.5T 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 grey matter structures such as the claustrum, entorhinal cortex, hippocampus, and basal forebrain.

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 postmortem 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 1997) (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) has suggested that hypertrophy of the amygdala may be related to exposure to mood stabilizers. This topic is addressed in detail below.

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 (Figure 1).

The Hippocampus

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).

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).

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 (LTP) (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) and (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).

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 (Figure 1).

The Basal Ganglia

MDD—Both hypometabolism or blood flow and reduced grey 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).

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).

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.

Ventriculomegaly and White Matter Pathology

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) and (Thomas et al 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) and (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).

BD—Ventriculomegaly is more commonly observed in BD across different age groups (Swayze et al 1990); (Figiel et al 1991); (Strakowski et al 1993); (Botteron et al 1995); (Zipursky et al 1997); (Lim et al 1999); (Strakowski et al 1999); (Hauser et al 2000); (Brambilla et al 2001a); (Strakowski et al 2002); (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 medical co-morbidity 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); (Kinney et al 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), (Carter 2007b), 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.

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 viscero-motor 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.

The OFC

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 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.

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 (DTI), 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.

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

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.

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 behaviour. 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 behaviour.

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) (Elliott et al 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).

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 behaviour (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; Figure 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 (Babinski 1914) first discussed the anosognosic and manic sequelae of right-sided lesions while Goldstein (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 then 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 × 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.

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.

The DLPFC

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 9 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 three 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 one 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)

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.

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.

Over-Arching Discussion

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 conceptualises 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 1999a) (Ongur et al 1998) (Brambilla et al 2001a) (Kegeles et al 2003) (Lacerda et al 2005) (Kogelnik et al 2006), 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 behaviour 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 behaviour 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 (PTSD) 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 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 behaviour 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 sensitise 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-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.

[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 I, Vidal-Gonzalez B, Rauch SL, Quirk GJ (2006): Microstimulation reveals opposing influences of prelimbic and infralimbic cortex on the expression of conditioned fear. *Learn Mem* 13:728–733.

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 in press).

Information about obstetric or other developmental problems is rarely reported. The diagnosis of BD in children has increased sharply (mostly in the Unites 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) (Drevets et al 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 – on 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 2 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, voxelwise 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 (ROI) 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 through 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.

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 Figure 1.

As discussed above, projections from the orbital and medial PFC to the amygdala and its associated limbic and brainstem 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 (PAG) (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 (VTA) (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 artifical. 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 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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[4]Here we use the term "lesion", loosely, to signify any illness predisposing change in neurochemical function or neuroanatomical structure.

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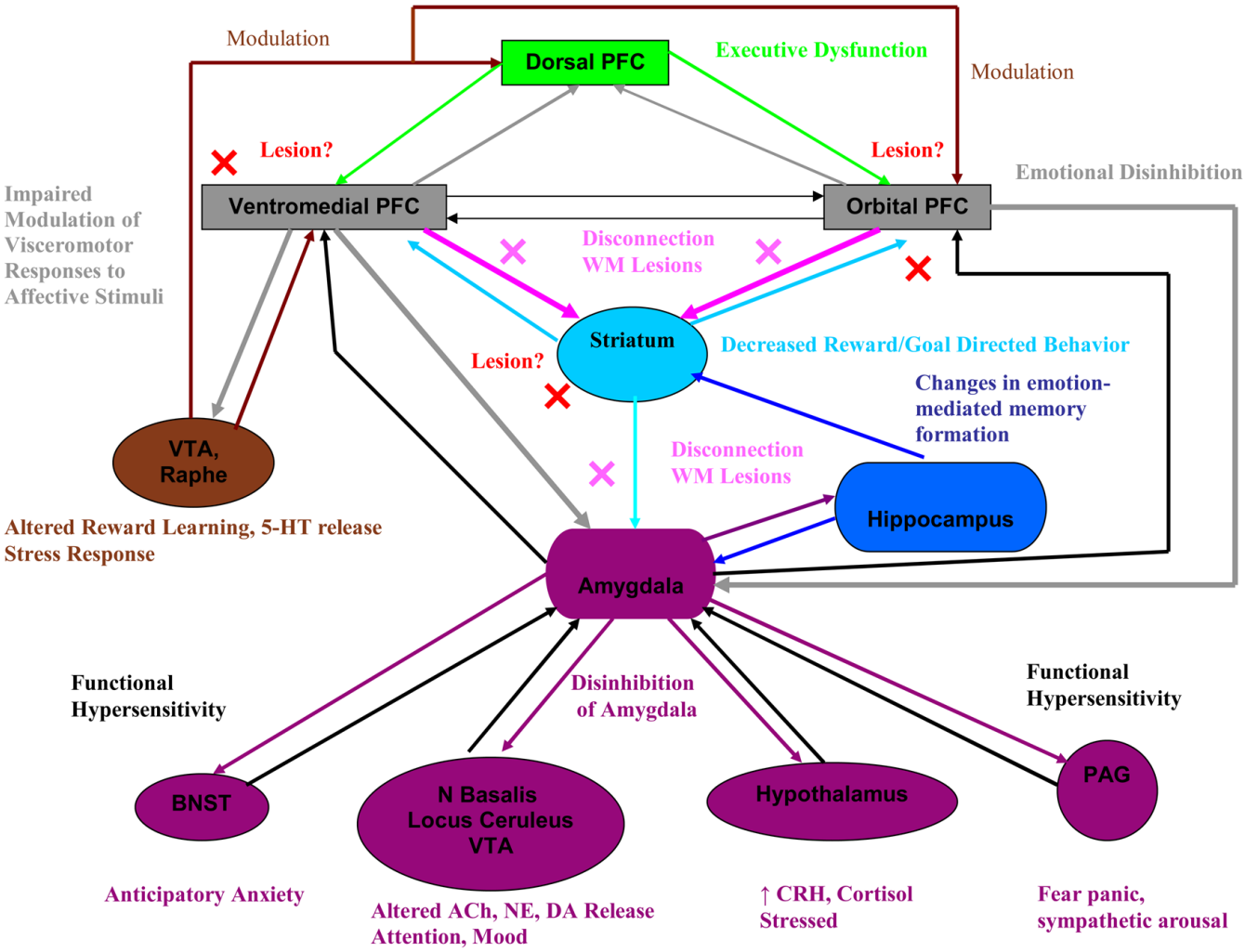

Figure 1. Amygdala-Centric Model of Potential Pathophysiological Changes in BD and MDD

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).

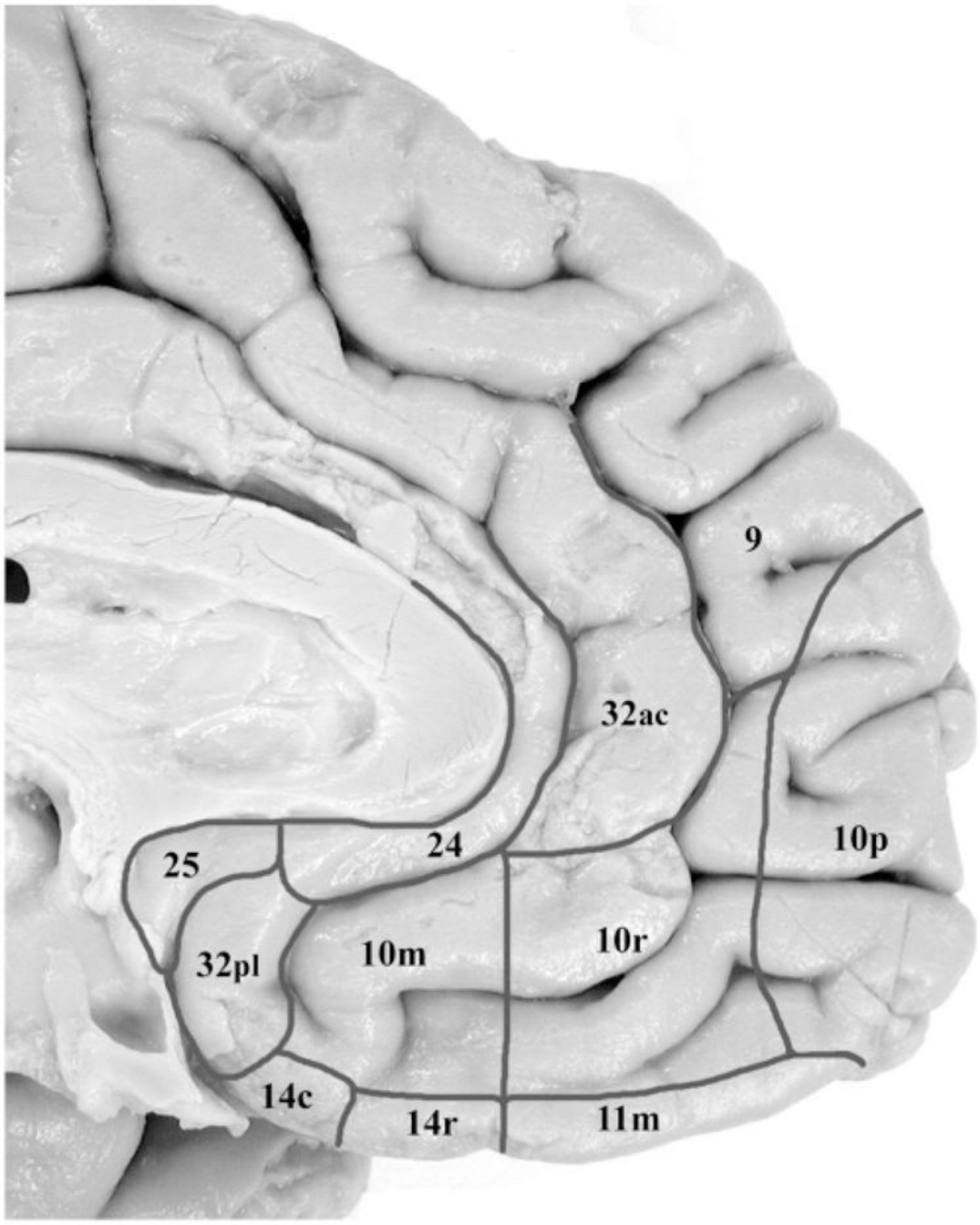

Figure 2. Architectonic subdivisions of the medial surface of the human brain
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Table 1

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 1997)	27 BD 60 HC	34.9±8.6 31.6±8	1.5T 3mm 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	1.5T 1.4mm 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 1.5T 1mm 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	1.5T 1.5mm 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	1.5T 1.5mm 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	1.5T 1.2mm 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	1.5T 1.5mm 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

Study	Sample	Age	Method	Age of Onset	Duration of Illness/# Episodes	Family History of Illness	Clinical Status at Testing	Medication Status	Comorbidity	Findings
(DelBello et al 2004)	23 BD 20 HC	16±2 17±2	1.5T 1.5mm 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	1.5T 1.5mm 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	1.5T 1.2mm 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 scan 2 (2-year interval). No longitudinal changes.
(Chang et al 2005b)	20 BD 20 HC	14.6±2.8 14.1±2.8	3T 1.5mm ROI	NR	NR	Yes	Depressed + hypomanic	Patients on medication (MS, AD+ AP) except stimulants which were discontinued 24 hours 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	1.5T 1.2mm 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	1.5T 1.5mm 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	1.5T 3mm 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

Study	Sample	Age	Method	Age of Onset	Duration of Illness/# Episodes	Family History of Illness	Clinical Status at Testing	Medication Status	Comorbidity	Findings
										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	1.5T 1.5mm ROI	NR	1st episode	NR	NR	AP	No alcohol abuse, neurological disorders, head injuries.	Enlargement of R amygdala in both MDD and BD

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 0.08T 12mm 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 1.5T 6mm 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 3.4mm MRI 1.5T 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
(Lawrence et al 2004)	12 BD 9 MDD 11 HC	41±11 for full sample	fMRI 1.5T 7mm 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 3T 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 3T 4mm (1mm 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 7mm 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

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
(Rich et al 2006)	22 BD 21 HC	14.2±3.1 14.5±2.5	fMRI 3T 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 4.25mm MRI 3T 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 3T 5mm (1mm 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

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	1.5T 1.25mm	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	1.5T 5mm	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	1.5T 1.5mm 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	1.5T 1.5mm ROI	39.3±13.4	9.1±10.2	NR	Depressed	AD + lithium	No co-morbid disorders	No differences in amygdala volumes
(Inagaki et al 2004)	17 MDD 51 HC	47.1±6 48.6±5	1.5T 1.5mm	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	1.5T 1.3mm 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	1.5T 1.5mm	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

Study	Sample	Age	Method	Age of Onset	Duration of Illness/# Episodes	Family History of Illness	Clinical Status at Testing	Medication Status	Comorbidity	Findings
(Frodl et al 2007)	60 MDD 60 HC	44.2±11.8 41.6±12.3	1.5T 1mm 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	1.5T 1.5mm 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	1.5T 1.6mm 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) 19 MDD (without psychosis 22 HC	36.5±13.2 36.6±11.9 32.2±11.5	3T 1.5mm 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

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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 1.5T 8mm 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 5mm (2.5mm 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 3.4mm MRI 1.5T 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 1.5T 3.8mm	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 1.5T 1mm 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 3T 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

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
(Fu et al 2004)	21 MDD 19 HC	43.2±8.8 42.8±6.7	fMRI 1.5T 8mm 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
(Irwin et al 2004)	12 MDD 14 HC	38±3 28±2	fMRI 1.5T 7mm ^{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 1.5T	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 3T 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 1.5T	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 1.5T 7mm	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 3T 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 3T 3.2mm	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 3T 3.2mm	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

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	1.5T 5mm 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	1.5T 1.25mm 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	1.5T 1.25mm	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	1T 3.1mm 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	1.5T 1.25mm 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 associationbetween volume and # episodes or hospitalisations
(Mervaala et al 2000)	34 MDD (6 BD) 17 HC	42.2±12.2 42.1±14.6	1.5T 8mm 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	1.5T 3mm	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	1.5T 3mm 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	1.5T 5mm	NR	±6.5	NR	Depressed	7 AD, 2 BZ	No neurological disorders, substance abuse	No difference in hippocampal volumes

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	1.5T 1.2mm 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	1.5T 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	1.5T 3mm 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	1.5T 1.5mm 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	1.5T 1.2mm ROI	26.3±12 24.9±11.6	10 years 6 (episodes)	Mixed	Depressed	FE MDD group medication naïve. AD in multi-episode group.	No substance abuse, anxiety disorders.	Hippocampal volume reduction in multi-episode patients. Correlation between duration of depression & hippocampal volume.
(Posener et al 2003)	27 MDD 42 HC	33.0±10.7 33.2±10.8	1.5T 1mm ROI	NR	0.8±1.2 (episodes)	NR	Depressed	Yes – not specified.	No substance abuse in last 3 months. No other axis 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	1.5T 1.5mm 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	1.5T 1.5mm 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 base-line 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	1.5T 1.5mm 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	1.5T 1.5mm	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	1.5T 1.2–5mm 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.

Study	Sample	Age	Method	Age of Onset	Duration of Illness/# Episodes	Family History of Illness	Clinical Status at Testing	Medication Status	Comorbidity	Findings
(Lange and Irle 2004)	17 female MDD 17 female HC	34±10 34±6	1.5T 1.3mm 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	1T 1mm	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	1.5T 1.5mm 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	1T 1mm 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	1.5T 1.5mm 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	3T 0.6mm	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	1.5–3mm 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	1.5T 1.5mm	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	1.5T 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	1.5T 1mm 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	1.5T	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	1.5T 1.5mm 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

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	3T 1.5mm 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	1.5T 1.3mm 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

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

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	0.5T 10mm	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)	0.5T 10mm ROI	22.86±7.82	5.89±6.15 hospitalization	NR	NR	NR	NR	Volume of R hippocampus decreased in BD
(Pearlson et al 1997)	27 BD 60 HC	34.9±8.6 31.6±8	1.5T 3mm 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	1.5T 1.4mm 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	1.5T 1.5mm 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	1.5T 1mm 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 1.5T 1mm 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	1.5T 1.5mm 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	0.5T 5mm 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	1.5T 1.5mm 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	1.5T 1.2mm 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

Study	Sample	Age	Method	Age of Onset	Illness Duration/# Episodes	Family History of Illness	Clinical Status at Testing	Medication Status	Comorbidity	Findings
(Brambilla et al 2003a)	24 BD 36 HC	35±10 37±10	1.5T 1.5mm 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.
(Beyer et al 2004b)	36 BD 29 HC	58.2±7.80 61.0±5.49	1.5T 3mm 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	1.5T 1.5mm 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	1.5T 1.5mm 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	3T 1.5mm VBM	NR	NR	NR	Six mixed and 4 manic	No medication 72 hours 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	3T 1.5mm ROI	NR	NR	Yes	Depressed + hypomanic	Patients on medication (MS, AD+ AP) except stimulants which were discontinued 24 hours 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	1.5T 1.5mm 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	1.5T 1.5mm 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	1.5T 1.5mm 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	1.5T 1.5mm 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	1.5T 1.6mm 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

Study	Sample	Age	Method	Age of Onset	Illness Duration/# Episodes	Family History of Illness	Clinical Status at Testing	Medication Status	Comorbidity	Findings
										−44; −74; −13
(Moorhead et al 2007)	20 BD I 21 HC	41.5±8.9 38.5±12.6	1.5T 1.7mm 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	1.5T 1.2mm	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	1.5T 1.2mm 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

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 10 HC	39.3±7.8 35.0±9.3	^{18} F-FDG voxelwise	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
(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 L parahippocampal gyrus.	−22; −35; −7

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	1.5T 5mm (2.5mm 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	1.5T 5mm (2.5mm 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	1T 3.1mm 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	1.5T 1.25mm	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	1.5T 5mm 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

Study	Sample	Age	Method	Age of Onset	Duration of Illness/# Episodes	Family History of Illness	Clinical Status at Testing	Medication Status	Comorbidity	Findings
(Pillay et al 1998)	38 MDD 20 HC	38.5±10.0 40.3±10.4	1.5T 3mm 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	1.5T 1.5mm 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	1.25mm 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	1.5T 5mm (1mm 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

Study	Sample	Age	Method	Age of Onset	Duration of Illness/# Episodes	Family History of Illness	Clinical Status at Testing	Medication Status	Comorbidity	Findings
										putamen volume
(Hannestad et al 2006)	182 MDD 62 HC	70.2±5.8 70.0±7.7	1.5T 3mm (3mm 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	1.5T 1.5mm	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

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 hours before study in 12 cases. 7 subjects on BZ.	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

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
								Patients free of other medication for 2+ weeks.			
(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 19 HC	43.2±8.8 42.8±6.7	fMRI 1.5T 8mm 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 ventral striatum + caudate which improved after treatment	−21; −5; 12 −15; −4; −4 −20; 17; 16 −22; 12; 4
(Holthoff et al 2004)	41 MDD	45.1±15.66	^{18}F-FDG voxelwise	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 19 HC	39.8±12.7 34.4±11.5	TD ^{18}F-FDG	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
(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 26 HC	39.7±12.8 34.2±12.2	^{15}O-H_2O ROI	NR	NR	NR	Remitted	Unmedicated	No medical illness	Reduced rCBF in ventral striatum in response to sad faces in MDD	NR
(Chen et al 2007a)	17 MDD	44.06±8.36	fMRI 1.5T 3mm	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

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)	0.5T 10mm 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	1.5T 6mm 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)	0.5T 10mm ROI	22.86±7.82	NR	NR	NR	NR	NR	No significant differences in the volume of caudate & putamen.
(Aylward et al 1994)	30 BD 30 HC	39.3±11.1 37.6±9.0	1.5T 5mm	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	0.5T 5mm 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	1.5T 1mm 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	1.5T 1mm 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	1.5T 1.5mm	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	1.5T 2mm ROI	23±9	NR	Yes	NR	AP	No other axis I disorders.	Larger L caudate in affected & 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	1.5T 1.5mm 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	1.5T 3mm (3mm 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	1.5T 1.5mm 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	Enlarged putamen in BD

Study	Sample	Age	Method	Age of Onset	Illness Duration/# Episodes	Family History of Illness	Clinical Status at Testing	Medication Status	Comorbidity	Findings
									abuse of more than 1 year. 10 subjects with ADHD.	
(Lochhead et al 2004)	11 (BD (7 BD I 4 BD II) 31 HC	38.2±10 36±14	1.5T 1.5mm 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	1.5T 1.5mm 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	1.5T 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	3T 1.5mm VBM	NR	NR	NR	Six mixed and 4 manic	No medication 72 hours 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	3T 1.5mm ROI	NR	NR	Yes	Depressed + hypomanic	Patients on medication (MS, AD+ AP) except stimulants which were discontinued 24 hours 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	1.5T 1.2mm 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	1.5T 1.2mm 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	1.5T 1.5mm 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 six months	No differences in caudate and putamen volumes.
(Hwang et al 2006)	21 drug-naïve BD 28 drug-treated BD 37 HC	29.9±9.3 34.2±9.5 34.4±11.1	1.5T 1.5mm 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	1.5T 1.5mm 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.

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 hours 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	1.5T 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) 10 HC	14.7±3.0 14.4±3.2	fMRI 3T Voxel-wise	NR	3.1	Yes -56%	Euthymic	MS + AD. Stimulants discontinued 24 hours 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
(Bauer et al 2005)	10 BD I 10 HC	39.3±7.8 35.0±9.3	^{18} F-FDG voxelwise	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

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
(Caligiuri et al 2006)	10 BD	49.5±11.9	1.5T ROI Motor Probe	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
(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 activity in the ventral striatum in BD	−14; 11; −7 16; 11; −6 −10; 10; 1 14; 10; 5 −22; 8; −2 26; 8; −2 30; 4; 0 18; 8; 5

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: 5mm (2.5mm gap). CT: 10mm	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	1.5T 10mm	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	1.5T 5mm (2.5mm 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	0.08T 12mm 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	1.5T 5mm 91-2.5mm 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	0.5T 5mm (2.6mm 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+	1.5T 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	0.3T 7mm (3mm 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	1.5T 5mm (2.5mm 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 67.6±2.4 72.8±5.3	0.5T 10mm	Early-onset < 50 Late-onset > 50	NR	NR	Depressed	NR	NR	Frequency of silent cortical infarcts: (1) 22.6% (2) 51.4%

Study	Sample	Age	Method	Age of Onset	Illness Duration/# Episodes	Family History of Illness	Clinical Status at Testing	Medication Status	Comorbidity	Findings
	(3) 41 old, early onset depression (4). 63 old, late-onset depression									(3) 65.9% (4) 93.7%
(Howard 1993)	12 MDD 12 HC	76.0±6.5 77.7±7.9	1.5T 8mm (0.8mm 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	1.5T 5mm (2.5mm gaps)	±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	1.5T 5mm (2.5mm 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	1.5T 5–8mm	±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	1T 7mm (0.7mm 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	1.5T 5mm	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	0.3T 5mm (0.5–2.5mm 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	1.5T 5mm (2.5mm 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.
(Dahabra et al 1998)	23 MDD	66.2±5.1	0.5T 7mm (1mm gap)	12 >55 11 <50	NR	NR	Euthymic	AD, 7 lithium	No substance abuse, epilepsy, heart	Greater severity of WMH in late-onset MDD

Study	Sample	Age	Method	Age of Onset	Illness Duration/# Episodes	Family History of Illness	Clinical Status at Testing	Medication Status	Comorbidity	Findings
									disease, neurological or endocrine disorders.	
(Greenwald et al 1998)	35 MDD 31 HC	74.7±6.4 72.9±4.7	1T 5mm (2.5mm 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 24 HC	52.7±18.4	1.5T 5mm	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
(Sato et al 1999)	3371 people drawn from background population	72.2	1.5T 5mm	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	1.5T	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	1.5T 5–6mm (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	1.5T 5mm	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 3mm 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	1.5T 5mm	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.

Study	Sample	Age	Method	Age of Onset	Illness Duration/# Episodes	Family History of Illness	Clinical Status at Testing	Medication Status	Comorbidity	Findings
(Nebes et al 2001)	92 healthy volunteers	73.6±3.4	1.5T 5mm (1mm 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	1.5T 5mm (2.5mm 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	1.5T 5mm	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	0.5T 5mm (2.5mm 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	1.0T 5mm (1.5mm 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	1.5T 1.2–5mm 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 1.5T 3mm 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	1T 1mm	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
(Firbank et al 2005)	629 subjects from background population	NR	5mm	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	1.5T 6mm (0.6mm gap)	47–51	NR	NR	NR	AD	NR	Extent of WMH associated with severity of depression after 5 year follow-up. Severity of

Study	Sample	Age	Method	Age of Onset	Illness Duration/# Episodes	Family History of Illness	Clinical Status at Testing	Medication Status	Comorbidity	Findings
										WMH associated with poorer outcome.
(Jorm et al 2005)	475 background volunteers. 17 classified as MDD.	60–64	1.5T 2mm	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	1.5T 5mm (0.5mm 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	1.5T 3mm	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 1.5T 3mm 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	1.5T 3mm (3mm 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	1.5T 3mm (3mm 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	1.5T 3mm	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 1.5T 6mm (2mm 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.

Study	Sample	Age	Method	Age of Onset	Illness Duration/# Episodes	Family History of Illness	Clinical Status at Testing	Medication Status	Comorbidity	Findings
(Rainer et al 2006)	51 MDD 204 HC	75.8 (whole sample)	1T	>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	1.5T 3mm	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	1.5T 3.5mm (0.5mm 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	1.5T	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	1.5T 2mm 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	1.5T DTI 3mm 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	1.5T 3mm	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.

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	0.08T 12mm 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	1.5T 5mm (2.5mm 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	0.5T 10mm	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	1.5T 5mm (2.5mm 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	1.5T 5mm (2.5mm 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	0.5T and 1.5T 7mm	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	1.5T 5mm (2mm 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	1.5T 5mm	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	0.5T 10mm	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 (2x) towards more PVH in BD I. Greater number of PVH was due to BD I subsample >30 years of age.
(Botteron et al 1995)	11 BD 5 HC	11.3±3.1 11.8±2.9	1.5T 4–5mm	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	1.5T 5mm (2.5mm gaps)	23±8.0	NR	Mixed	28 BD in remission, others	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.

Study	Sample	Age	Method	Age of Onset	Illness Duration/# Episodes	Family History of Illness	Clinical Status at Testing	Medication Status	Medical + Psychiatric Comorbidity	Findings
							depressed or manic.			Higher (but not significant) rate of WMH in subjects with family history.
(Lewine et al 1995)	20 BD 150 HC	36±7	1.5T 5–8mm	±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	1.5T 5mm (2.5mm 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	0.5T 5mm	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)	1.5T 4–6mm	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	1.5T 5mm (2.5mm 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	1.5T 5mm (0.5mm 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	0.5T 7mm (1mm 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	1.5T 1mm 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	1.5T 5mm (2.5mm 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	1.5T 5mm (2mm 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	1.5T 5mm	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	0.5T 5mm (2.5mm gaps)	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.

Study	Sample	Age	Method	Age of Onset	Illness Duration/# Episodes	Family History of Illness	Clinical Status at Testing	Medication Status	Medical + Psychiatric Comorbidity	Findings
(Adler et al 2004)	9 BD 9 HC	32±8 31±7	3T 5mm 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	1.5T 3mm	NR	NR	NR	NR	NR	No axis I disorders, substance abuse within 3 months of study, antisocial 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	1.5T 5mm (2.5mm 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	3T 1.5mm	NR	1.7±1.8	NR	3 manic, 3 mixed, 1 depressed, 13 euthymic	MS, AD, AP. Psychostimulants discontinued 24 hrs 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	3T 5mm 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
(de Asis et al 2006)	40 BD 15 HC	69.8±6.7 66.9±6.5	1.5T 5mm	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	0.5T	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	0.5T 5mm	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	1.5T 5mm (1mm gap) ROI DTI	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	1.5T 1.3mm 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	1.5T 5mm 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	1.5T 3mm	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/	No significant differences in prevalence or severity of WMH between groups.

Study	Sample	Age	Method	Age of Onset	Illness Duration/# Episodes	Family History of Illness	Clinical Status at Testing	Medication Status	Medical + Psychiatric Comorbidity	Findings
									dependence, 2 individuals with hypertension	

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 6.5mm	NR	NR	NR	Euthymic	AD	No other primary psychiatric or neurological disorder. No head injury, substance abuse	Mood provocation led to rCBF descreases 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 1.5T 3mm	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

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Table 16

Morphometric Analyses of the Orbito-Frontal 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	1.5T 5mm 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	1.5T 3mm 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 3mm 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	1.5T 3mm 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	1.5T 3mm 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	1.5T 3mm ROI	NR	NR	NR	Depressed	AD	No other major psychiatric illness, substance dependence,	Smaller medial orbitofrontal gyri volume in MDD. OFC volume also associated with functional impairment

Study	Sample	Age	Method	Age of Onset	Duration of Illness/# Episodes	Family History of Illness	Clinical Status at Testing	Medication Status	Comorbidity	Findings
									primary neurological illness	
(Ballmaier et al 2004)	24 MDD 19 HC	65.85±8.18 66.24±7.25	1.5T 1.4mm 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	1.5T 1.5mm 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	1.5T 1.2–5mm 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	1.5T 1.5mm 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	1.5T 1.4mm	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 1.5T 6mm (2mm 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 1.5T 3mm	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

Table 17

Functional Analyses of the Orbito-Frontal 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 acitivity 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-H2O 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)	22 BD 21 HC	14.2±3.1 14.5±2.5	Voxelwise 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	In L orbital cortex BD patients showed greater activation when rating the hostility of neutral face stimuli	−32; 20; −16

Table 18

Morphometric Analyses of the Orbito-Frontal 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	1.5T 1mm 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	3T 1.5mm VBM	NR	NR	NR	Six mixed and 4 manic	No medication 72 hours 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	1.5T 5mm 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	1.5T 1.2mm 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	1.5T 1.5mm 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	1.5T 1.2mm 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) 21 HC	33.8±9.6 31.5±9.7	1.5T 1.5mm	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	3T 1.2mm 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	1.5T 1.5mm	11.9	3.6±2.4	Yes	Euthymic	Lithium + valproate	NR	Male BD smaller OFC volumes. Female BD large OFC volumes

Table 19

Functional Analyses of the Ventro-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 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	1.5T 1mm 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 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	Responders had higher metabolic rates in sgACC at baseline. Change in metabolic rate of L mPFC correlated with Ham-D scores after sleep deprivation. ie 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 6.5mm	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	BA 9 + 10 8; 54; 12 6; 40; 27 BA 24

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
										remitted group, respectively	12; 38; 16
(Davidson et al 2003)	12 MDD 5 HC	38.17±9.3 27.8±10.4	fMRI 1.5T 1mm 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 1.5T 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	BA25 −3; 9; −6
(Gotlib et al 2005)	18 MDD 18 HC	35.2 30.8	3T 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 BA25 −2; 8; −10 BA 24 −2; 10; 28 6 months BA 25 10; 20; −4 BA24 −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 1.5T 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	NR

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
										+ R ventral ACC cingulate in responders	
(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 1.5T 3mm 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	3T 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 1.5T	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

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	1.5T 1mm 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	1.5T 1mm 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	1.5T 3mm 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	1.5T 1.5mm ROI	NR	NR	Yes	Depressed	BZ discontinued 24 hours 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	1.5T 1.5mm 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	1.5T 1mm 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	1.5T 3mm 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	1.5T 1.5mm 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	12.02±2.72 12.14±2.13	1.5T 1.5mm ROI	NA	No DSM-IV-defined episodes	Mixed	Mixed	NR	No serious medial or neurological illness, psychiatric	In boys (but not girls) with subclinical depression smaller L	BA 24, 33 but not 25.

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
	28 HC - + family history								illness, learning disorder (but no clinical interview).	sgACC & pregenual PFC volumes. Similar effect in family-history + group.	
(Chen et al 2007a)	17 MDD	44.06±8.36	MRI 1.5T 3mm	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	1.5T 1.6mm 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

Table 21

Functional Anatomical Studies of the Ventro-Medial 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	1.5T 1mm 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 hours 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-H2O 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 cingulate – BA24a: 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 In depressed group: decreased orbitomedial and ventromedial rCBF:

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
											8; 56; −6 4; 58; 9
(Lennox et al 2004)	10 BD 12 HC	37.3±12.8 32.6±10.7	fMRI 3T 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 BA25
(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 1.5T 7mm (0.7mm 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

Table 22

Morphometric Studies of the Ventro-Medial 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	1.5T 1mm 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 1999a)	21 BD 17 SZ 20 HC	23.7±5.1 24.0±4.3	1.5T 1.5mm 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	1.5T 1.5mm 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	4T 3.3mm 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	2T 1mm 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	1.5T 1.5mm 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, antisocial 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	1.5T 1.5mm 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	1.5T 1.5mm 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
(Wilke et al 2004)	10 BD 52 HC	14.5±1.8 15±1	3T 1.5mm VBM	NR	NR	NR	Six mixed and 4 manic	No medication 72 hours before scan. No data on medication type	No schizophrenia, learning disabilities or pervasive developmental disorders.	Reduced gray matter volume of L sgACC	NR

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
(Adler et al 2005)	32 BD 27 HC	31.2±9.4 30.5±9.7	3T 1mm 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	1.5T 1.2mm 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 & 32
(Kaur et al 2005)	16 BD 21 HC	15.5±3.4 16.9±3.8	1.5T 1.5mm 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	1.5T 1.5mm 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	1.5T 1.5mm 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	1.5T	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	1.5T 1.5mm	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	1.5T 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

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	1.5T 1mm 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	2T 1mm 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	1.5T 1.5mm 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	1.5T 1.2mm 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	1.5T 1.5mm 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	1.5T 1.2mm 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 1.5T 1.5mm	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	1.5T 1.5mm 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

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 1.5T 3mm	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

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	1.5T 5mm 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	1.5T 1.5mm 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	1.5T 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 1.5T 3mm 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 1.5T 6mm 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	1.5T 3mm 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	1.5T 2.4mm ROI	27.4±6.1	0.3±0.4	NR	10 manic, 2 mixed	medication-naïve	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	1.5T 1.4mm 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.

Study	Sample	Age	Method	Age of Onset	Illness Duration/# Episodes	Family History of Illness	Clinical Status at Testing	Medication Status	Comorbidity	Findings
(Yurgelun-Todd et al 2007)	11 BPD 10 HC	32.9±10.5 32.4±9.1	1.5T 5mm 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

Key to Table Abbreviations. 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