Anatomical MRI abnormalities in bipolar disorder: do they exist and do they progress?

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Aim: Morphometric brain imaging studies have revealed regional brain abnormalities in patients with bipolar disorder, which may play a role in illness pathophysiology. It is not known whether such changes are of neurodevelopmental, neurodegenerative, or combined origin. We reviewed the anatomical brain imaging literature in bipolar disorder, in an attempt to determine whether there is evidence to suggest that such abnormalities are progressive.

Method: Literature searches were conducted using MEDLINE for the period from 1966 to June 2004, using specific key words; bipolar disorder and the names of the individual brain structures. Papers were selected according to their salience in relation to whether reported changes are progressive.

Results: Available findings suggest reduced grey matter in prefrontal brain regions such as anterior cingulate and subgenual prefrontal cortex, and abnormalities in amygdala size in adult and paediatric bipolar patients. White matter hyperintensities, which are non-specific abnormalities, are also common in bipolar patients. Bipolar patients may lose more brain grey matter by ageing. There is also evidence for impaired myelination of the corpus callosum in bipolar disorder. Lithium may reverse or prevent grey matter prefrontal cortex abnormalities in bipolar patients by its neuroprotective effects.

Conclusions: Both early developmental and later neurodegenerative processes may play a role in the pathophysiology of bipolar disorder. Findings from anatomical brain imaging studies implicate key regions involved in mood regulation. The evidence for the progressive nature of this illness is tentative, as no follow-up study with bipolar patients has been reported to this date.

Key words: bipolar disorder, magnetic resonance imaging, volumetrics.

An increasing number of magnetic resonance imaging (MRI) morphometric and spectroscopy (MRS) studies have examined the mechanisms involved in bipolar disorder over the last decade. There is evidence from these studies for abnormalities in critical brain regions, namely, prefrontal cortex, medial temporal lobe structures, striatum and cerebellum [1,2]. These regions are components of a neuroanatomic model of mood regulation comprising two interrelated neuronal circuits; a limbic-thalamic-cortical circuit, that includes amygdala, mediodorsal nucleus of thalamus, and medial and ventrolateral prefrontal cortex; and a limbic-striatal-pallidal-thalamic circuit, that includes striatum, ventral pallidum, and regions of the other circuit [1,3]. This review focuses on the neuroanatomic and neurochemical changes in bipolar disorder, with particular attention to studies that may help us address the question as to whether identified abnormalities are progressive.
Method

A MEDLINE search was conducted for the period from 1966 to June 2004 and complemented by manual search of bibliographical cross-referencing. We identified all in vivo human studies that: (i) were published in English; (ii) used research diagnostic criteria (RDC) or DSM-III, DSM-III-R, or DSM-IV criteria to diagnose mood disorders; (iii) had a healthy control group; (iv) included a minimum of 15 patients with bipolar disorder compared with a similarly sized healthy comparison group; and (v) used MRI or MRS to obtain brain measurements. We selected papers according to their pertinence with respect to whether reported abnormalities are progressive.

Results

The results from reviewed studies are considered by anatomical region.

Cerebrum and cortical structures

Several MRI studies [4–7] found significantly increased lateral and third ventricle sizes in bipolar patients. According to a recent review [8] right (but not left) lateral ventricular enlargement is the most consistent MRI abnormality in bipolar disorder (followed by the right prefrontal cortex reduction). Studies also reported decreased cortical grey matter in bipolar patients [9,10], and a more-pronounced age-related decline in total brain grey matter compared to healthy controls [9]. Two studies examining the effects of chronic (4 weeks) lithium treatment found increased total grey matter volumes in lithium-treated bipolar patients [10,11], and recently, chronic lithium treatment has also been shown to increase grey matter volume in cortical brain regions in healthy controls [12,13]. Support for the hypothesis of neurotrophic and neuroprotective effects of lithium also comes from an MRS study that demonstrated increased levels of N-acetyl-aspartate, a putative marker of neuronal viability, myelin formation and maintenance, across several cortical regions, after 4 weeks of lithium treatment [14].

Among specific brain regions of interest, the prefrontal cortex appears to be a key region in the neuroanatomic model of mood regulation. Postmortem histologic studies of patients with bipolar disorder report reduction in glial cells in the subgenual prefrontal cortex [15] and in neuronal and glial cell densities in the dorsolateral prefrontal cortex [16]. Decreased subgenual [17,18] and prefrontal [19] cortical volumes have been reported, although not in all studies [20]. Reduction in anterior cingulate grey matter volumes [21,22] and density [23,24] appears to be a consistently reported finding in recent studies using region-of-interest and voxel-based morphometry methods. Of interest are the presence of cingulate findings in children and adolescents with bipolar disorder [22] and the findings pointing to possible effects of lithium in preventing or reversing grey matter changes [21].

In regard to temporal lobe abnormalities, there are inconsistent findings. Some studies reported decreased [25,26] or increased [27,28] temporal lobe volume, whereas others found no changes [29–32]. One study reported a progressive volume reduction in left posterior superior temporal gyrus grey matter in patients with first-episode schizophrenia, but not in patients with first-episode affective psychoses [33]. Recently, Chen and colleagues reported significantly smaller left total superior temporal gyrus volumes in children and adolescents with bipolar disorder compared to healthy controls [34].

Amygdala and hippocampus

Three different research groups [32,35,36] have reported amygdala enlargement in adult bipolar patients, without hippocampal enlargement, suggesting that hypertrophy of this region might reflect dysfunction underlying the mood lability of bipolar disorder. In children and adolescents with bipolar disorder, although amygdala volumes appear to be reduced [37–39], Caetano and colleagues [40] found a direct correlation between age and length of disease and amygdala volumes, suggestive of neurodevelopmental abnormalities and/or compensatory mechanisms as the disease progresses. One study, using relatively thick (1 cm) image slices, found right hippocampal enlargement in bipolar patients [31], but this finding was not replicated in several other studies [26,28,32,35]. A more recent study [38] found smaller amygdala sizes also in adult bipolar patients, unlike results of the 3 studies cited above [32,35,36]. Discrepancy in results in this patient group has been common, reflecting perhaps sample heterogeneity and emphasizing the importance of sample selection.

Mid-line brain structures

Two studies have identified decreased corpus callosum area in adult bipolar patients [41,42] and recently, abnormally reduced corpus callosum signal intensity was found in adult [43] and young (mean age 16) [44] patients with bipolar disorder. These findings suggest that abnormalities in corpus callosum white matter in bipolar patients are possibly due to altered myelination, which may lead to impaired inter-hemispheric communication.

The thalamus is a key structure in brain anatomic circuits that is potentially involved in the pathophysiology of mood disorders; however, most studies in bipolar patients have failed to identify thalamic abnormalities. Some studies have reported increased [35, 45] or unchanged [46–48] thalamic volumes and two recent studies [39,49] in young patients with bipolar disorder found no abnormalities. Thus, available findings in bipolar disorder suggest that anatomically the thalamus is unimpaired.

Similarly, most studies examining the basal ganglia have reported no abnormalities [27,31,46,50,51], with the exception of two [35,52]. Recently, however, caudate size was shown to be decreased in older (mean age 58) bipolar patients, suggesting that older patients may have more pronounced regional and global brain abnormalities [53].

Cerebellum

The only two published MRI studies [54,55] did not find significantly smaller cerebellar hemispheres or vermis in adult bipolar patients compared with healthy subjects. DelBello and colleagues [54] found that vermis area V3 (the inferior posterior and flocculonodular lobes, lobules VIII-X) was significantly smaller in multiple-episode than in first-episode bipolar patients and healthy volunteers, suggesting that the anatomical changes in the cerebellar vermis may originate from neurodegenerative processes during the course of the illness. This finding was supported by Brambilla and colleagues [55], where a trend (p = 0.075) for an inverse correlation between number of episodes and
vermis area V3 was observed. In bipolar children and adolescents with familial mood disorder, significant inverse correlation between age and vermis area V3 was reported [56], as well as neurochemical abnormalities within the cerebellar vermis [57]. Taken together, these findings suggest that cerebellar vermal abnormalities occur in bipolar disorder, and that these are perhaps neurodegenerative and hence ‘progressive’.

**Hyperintense lesions**

‘White matter hyperintensities’ represent a change in water content in the brain. The vast majority of studies have found higher rates of white matter hyperintensities in bipolar disorder patients compared to healthy controls [58–60], and these have been associated with poor long-term outcome [61], female gender, and multiple psychiatric admissions [61]. Often these foci are related to vascular pathology in older adults, however, bipolar adolescents have been shown to have a statistically significant increase in white matter hyperintensities compared to healthy controls and schizophrenic patients [62]. Increased prevalence and severity of white matter signal hyperintensities have also been reported in children with bipolar disorder, unipolar depression, and conduct disorder/attention deficit disorder [63]. Recently, the presence of an inflammatory response was found in the anterior cingulate cortex in bipolar disorder, and thought to be associated with white matter hyperintensities [64]. It is therefore likely that these lesions are involved in the pathophysiology of bipolar disorder and that they interrupt essential neural pathways in the brain that are involved in mood regulation [1].

**Discussion**

The onset of bipolar disorder is usually during late adolescence. Structural brain abnormalities are common in adult, as well as paediatric patients with bipolar disorder. Abnormalities of cortical and subcortical structures participating in a proposed neuroanatomic model of mood regulation have been described in several studies. Hyperintense lesions in cortical and subcortical regions are the most consistently reported and widely studied structural abnormalities, but their association with multiple events, such as ageing, migraine headaches and cerebrovascular disorders and their diverse aetiology (e.g. astrogliosis, demyelination, encephalomalacia, loss of axons, minute brain cysts, infarction, necrosis) obscure their potential pathophysiologic significance [58]. Right lateral ventricular enlargement is another consistent MRI abnormality in bipolar disorder. Ventricular enlargement is sensitive to factors such as the number of episodes [51,65] and illness severity [30]. Such effects may suggest some neurotoxic process during the active episodes or that those who show (putatively) progressive changes with recurring episodes may also suffer from a more severe, recurrent form of bipolar disorder. Only longitudinal studies would clarify these issues. Smaller prefrontal cortical volume is another common finding in bipolar disorder and in keeping with this, Strakowski and colleagues [66] suggested that diminished prefrontal modulation of subcortical structures within the anterior limbic network (e.g. amygdala, anterior striatum and thalamus) might result in mood dysregulation. Increased volumes of limbic subcortical structures in bipolar disorder have been observed. However, the histopathologic meaning of these changes remains unknown.

The cross-sectional nature of most of the above-mentioned studies precludes causal interpretations. These focal abnormalities may be present early in development, or be a result of neurodegenerative illness-related processes. The reduced volumes could be a result of cell loss or atrophy of neurones or glia, or a decreased density of neuronal processes. Most anatomical brain imaging studies in bipolar disorder support the idea that both early developmental and later atrophic processes play a key role in illness pathophysiology, as has been suggested by Cotter and Pariente [67]. These changes may be primary (disease-related), or secondary to stress-related changes in glucocorticoid hormones. However, confounding variables, such as medication history, mood state, psychiatric comorbidities, and substance abuse may also have influenced the results.

The prevention and/or reversal of these regional brain abnormalities by medication are intriguing areas of research, considering the preclinical and clinical evidence of neurotrophic/neuroprotective effects of lithium. This area of research lacks longitudinal studies that are necessary to draw robust conclusions in regard to the aetiology of neuroanatomical changes, and their relation to treatment and illness course. Studying pediatric bipolar patients at the onset of their illnesses is likely to prove an equally useful strategy, as children and adolescents with bipolar disorder probably represent a population with a higher genetic load for the illness, and are less likely to have as many confounding variables associated with ongoing medication treatment and illness chronicity.

In conclusion, it is not evident, as yet, whether the reported neuroanatomical changes in bipolar disorder are of a neurodevelopmental or neurodegenerative origin. The answer will perhaps be forthcoming from longitudinal imaging studies. The available evidence to date, which is wholly cross-sectional, indicates that brain abnormalities in bipolar disorder are quite likely to involve both neurodevelopmental and neurodegenerative processes. This possibility is of profound potential significance both in terms of understanding the pathophysiology of bipolar disorder and in terms of its clinical consequences.
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