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No change to grey and white matter volumes in bipolar I disorder patients

■ **Abstract** *Background* Structural brain imaging is assumed to be a key method to elucidate the underlying neuropathology of bipolar disorder. However, magnetic resonance imaging studies using region of interest analysis and voxel-based morphometry (VBM) revealed quite inconsistent findings. Hence, there is no clear evidence so far for core regions of cortical or subcortical structural abnormalities in bipolar disorder. The aim of this study was to investigate grey and white matter volumes in a large sample of patients with bipolar I disorder. *Methods* Thirty-five patients with bipolar I disorder and 32 healthy controls matched with respect to gender, handedness and education participated in the study. MRI scanning was performed and an optimized VBM analysis was conducted. *Results* We could not observe any significant differences of grey or white matter volumes between patients with bipolar disorder and healthy control subjects. Additional analyses did not reveal significant correlations between grey or white matter volume with number of manic or depressive episodes, duration of illness, existence of psychotic symptoms, and treatment with lithium or antipsychotics. *Conclusions* With this VBM study we were not able to identify core regions of structural abnormalities in bipolar disorder.

■ **Key words** grey matter volume · white matter volume · bipolar disorder · VBM · MRI

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Introduction

The neurobiological basis of bipolar disorder is still not fully understood. Structural and functional imaging is assumed to be a clue method to elucidate the underlying neuropathology of this disorder. In the last decade conventional magnetic resonance imaging (MRI) studies using region of interest analyses revealed quite inconsistent findings in bipolar disorder [13, 22, 24]. A meta-analytical review indicated merely increased lateral ventricles but no cortical or subcortical differences compared to healthy control subjects [13]. Another recent review summarizes structural and functional neuro-imaging studies [24]. Based on the reviewed studies these authors postulate several functional neuronal networks that modulate mood states and might be causal for bipolar affective disorder. These networks comprise the prefrontal cortex, ventral striatum, thalamus, and the associated limbic regions (amygdala and midline cerebellum). The authors postulate that in bipolar disorder a diminished prefrontal modulation of subcortical and temporal structures within the anterior limbic network results in dysregulation of mood.

The included studies of these reviews used region of interest analysis of brain structures by manually traced regions of interest in predefined brain regions. This method is prone to measurement error and investigator bias. Moreover it is time consuming, and focusing on hypothesized brain regions might lead to overlooking of possible findings in unexpected regions. Voxel-based morphometry (VBM) is a new method which allows the investigation of structural

MRI of the brain that is free from hypotheses and user-bias [2]. VBM is a fully automated whole brain image analysis technique that involves the voxel-wise comparison of segmented grey and white matter between at least two groups of subjects. Therefore, this method does not require manual tracing of regions. In bipolar disorder eight studies investigated structural abnormalities using VBM. Three of them [5, 9, 11] used traditional VBM which results in data of grey and white matter density, whereas the other five [1, 4, 10, 14, 19] used the optimized VBM protocol [7] which allows the determination of grey and white matter volumes.

Investigations of grey matter in bipolar disorder revealed quite inconsistent findings. While two studies reported decreased grey matter density in different cortical regions involving frontal [11], temporal and parietal cortex [5], a further study [9] could not observe any grey matter density changes at usual significance level. One of the five studies investigating grey matter volume could not observe any volume differences between patients with bipolar disorder and healthy control subjects [4] and another reported decreased grey matter volume only in the prefrontal cortex but not in other brain regions [14]. The further three studies reported varying grey matter volume increases or decreases in several brain regions involving frontal regions—in particular anterior cingulate cortex—and temporal and parietal regions but could never replicate prior findings in the same sub-region [1, 10, 19].

Analyses of white matter abnormalities in bipolar disorder are rare. Bruno et al. [4] could not observe any white matter volume differences between patients with bipolar disorder and healthy control subjects, while Nugent et al. [19] found increased white matter volumes in the left orbital cortex between medicated bipolar patients and controls, and in the left posterior cingulate and medial parietal cortex interface between unmedicated bipolar patients and controls. A study on white matter density observed a reduction in the left anterior internal capsule in patients with familial bipolar disorder [14]. Two different studies investigated the influence of the genetic risk of bipolar disorder on structural brain abnormalities. The first study revealed an association of the genetic risk for bipolar disorder with white matter deficits in the anterior corpus callosum and bilateral frontal, left temporoparietal, and right parietal regions [12]. The second study could not observe any white matter deficits which related to an increased genetic liability to bipolar disorder [15].

In summary, the results of studies on grey and white matter abnormalities in patients with bipolar disorder are highly inconsistent and core regions of cortical or subcortical structural abnormality in bipolar disorder are far from evident.

The aim of this study was to re-investigate abnormalities of grey and white matter volumes in a large sample of euthymic patient swith bipolar I disorder. Despite the reported inconsistencies we hypothesized based on postulated neuronal networks that volume abnormality could be expected in the prefrontal cortex, especially in the anterior cingulate cortex, and in subcortical regions (ventral striatum, thalamus and amygdala).

Methods

Subjects

Thirty-five euthymic patients with bipolar I disorder and 32 healthy controls matched with respect to gender, handedness and education participated in the study. The mean age in this sample differed significantly between groups (43.3 ± 12.5 in patients vs. 33.7 ± 11.8 in controls; Table 1). Therefore we used age as a covariate in the further analyses of this sample. In this sample the age of onset was 28.4 (±8.9) years, duration of illness was 14.4 (±10.9) years and patients exhibited on average 3.9 (±5.6) previous manic and 4.8 (±5.6) previous depressive episodes. The scores on the MADRS [17] (4.7 ± 3.4) and YMRS [30] (2.5 ± 2.8) scales indicated patients' euthymic mood state. Twelve patients received lithium, 27 other mood-stabilizers, 3 first and 15 second generation antipsychotics (Table 1). All patients were on stable medication at the time of imaging.

Written informed consent was obtained from all subjects and the study was approved by the local ethical committee. Patients with bipolar disorder were consecutively recruited from the outpatient unit of the Department of Psychiatry and Psychotherapy of the Saarland University Hospital between December 2003 and August 2005. The diagnosis of bipolar I disorder was confirmed by using the German version of the Structural Clinical Interview for DSM-IV [29]. Other axis-I disorders in particular alcohol dependence and medical illnesses that might have influence on brain structure were excluded. The healthy control subjects exhibited no past or present psychiatric, neurological or medical disorder and had no positive family history of psychiatric disorders. They were recruited from the general population via advertising in newspapers.

Imaging

MRI scanning was performed on a 1.5 T Magnetom (Siemens, Erlangen). A T1-weighted, MPRAGE sequence (TE = 4.42 ms, TR

Table 1 Demographical and clinical data of subjects

	Bipolar patients	Healthy controls	P
Number	35	32	
Gender (F/M)	17/18	20/12	
Handedness (R/L/B)	31/2/2	25/5/2	
Age (years ± SD)	43.31 ± 12.48	33.71 ± 11.81	<0.01
Education proband (years ± SD)	13.83 ± 2.60	14.59 ± 2.75	0.25
Education father (years ± SD)	12.94 ± 2.57	13.87 ± 2.85	0.20
Education mother (years ± SD)	10.91 ± 2.22	12.26 ± 2.41	0.02
Age of onset (±SD)	28.38 ± 8.91		
Duration of illness (±SD)	14.38 ± 10.93		
Previous manic episodes (±SD)	3.92 ± 5.64		
Previous depressive episodes (±SD)	4.83 ± 5.61		
MADRS (±SD)	4.71 ± 3.41		
YMRS (±SD)	2.54 ± 2.79		
Lithium	12		
Mood-stabilizer	27		
First generation antipsychotic	3		
Second generation antipsychotic	15		

B both, *F* female, *L* left, *MADRS* Montgomery Asberg depression rating scale, *M* male, *R* right, *SD* standard deviation, *YMRS* Young mania rating scale

= 1,900 ms, TI = 700 ms, flip angle = 15°, FOV 256 × 256 mm) of 176 consecutive slices was acquired with a voxel size of 1 × 1 × 1 mm. The images were re-orientated and aligned parallel to the anterior–posterior commissural axis and the origin was set to the anterior commissure. Image analysis was performed on a PC using MATLAB (Mathworks Inc., Natick, MA, USA) and SPM2 software (Wellcome Department of Cognitive Neurology, London, UK). For analysis we used VBM, a fully automatic technique for computational analysis of differences in local grey and white matter. We applied an optimized method of VBM [3] using SPM extension software.

In a first step we created a customized template using the SPM extention software ''cg_create_template'' [6]. This step involved registration of the 67 images to the International Consortium of Brain Mapping template (Montreal Neurological Institute, Montreal, Canada), which approximates Talairach Space. We applied a 12 parameter affine transformation to correct for image size and position. Regional volumes were preserved while corrections for global differences in whole brain volume were made. The normalized images of all subjects were averaged and smoothed with a Gaussian kernel of 8 mm full-width at half-maximum (FWHM) and then used as a new template which reduced scanner- and population-specific bias. In the second normalization step using the software ''cg_optimized'' [6] we locally deformed each image to the new template using a non-linear spatial transformation. This accounts for the remaining shape differences between the images and the template and improves the overlap of corresponding anatomical structures. Finally, using a modified mixture model cluster analysis, normalized images were corrected for non-uniformities in signal intensity and partitioned into grey and white matter, CSF and background [6]. The following smoothing procedure involved in the VBM process is necessary to obtain a local weighted average of the surrounding pixels. The width of the Gaussian smoothing kernel determines the scale at which morphological changes are most sensitively detected [6]. In VBM studies investigating patients with bipolar disorder Gaussian kernels with a FWHM of 8 [5, 9] or 12 mm [1, 4, 10, 14, 19] were used. Therefore, we decided to smooth the resulting grey and white images with Gaussian kernels of both 8 and 12 mm FWHM for parallel analyses to consider different dimensions of possible morphological abnormalities.

■ Statistical analysis

Processed images were analysed within SPM2. An ANOVA model with age as a covariate was designed for analysing the sample. Four contrasts were calculated, testing for a positive or negative correlation of grey or white matter volume with the parameter of interest. In addition we performed multiple regression analyses testing for a positive or negative correlation of grey and white matter volume with number of manic or depressive episodes, duration of illness, existence of psychotic symptoms, or treatment with lithium or antipsychotics. In all these additional analyses age was used as a covariate. For regions with an a priori hypothesis as laid out in the introduction, significance was set at a P value of 0.001, not corrected for multiple comparisons, as suggested by several authors [19, 28]. An additional extent threshold of 200 contiguous voxels had to be met, excluding smaller clusters possibly arising by chance. For volumetric abnormalities found outside of expected regions, a correction for multiple comparisons was required, and significance was only assumed at a corrected P value of 0.05. Furthermore, we performed analyses with small volume correction to investigate regions which showed abnormal volume in prior studies. For small volume correction we used a 5 mm sphere around the Talairach coordinates originally reported in these studies [1, 5, 9, 10, 19].

Results

The statistical analyses revealed neither significant increases nor decreases of grey or white matter volume between patients with bipolar disorder and healthy control subjects using a Gaussian kernel of FWHM = 8 or 12 mm. Analyses with lower level of significance did not reveal further results. Analyses with small volume correction in previously reported regions of abnormal volume did not reveal significant changes.

The additional analyses revealed no significant correlation between grey or white matter volume and number of manic or depressive episodes, duration of illness, existence of psychotic symptoms, and treatment with lithium or antipsychotics.

Discussion

In this study we could not observe any significant differences of grey or white matter volumes between euthymic patients with bipolar I disorder and healthy control subjects. Firstly we looked at regions with an a priori hypothesis as laid out in the introduction (prefrontal cortex including anterior cingulate cortex, amygdala, ventral striatum and thalamus) with a significance level of $P = 0.001$ and a threshold of 200 contiguous voxels. Secondly we conducted analyses with small volume correction around the Talairach coordinates of all originally reported volume abnormalities in previous studies [1, 5, 9, 10, 19]. Neither the first nor the second analysis revealed significant volume abnormalities of grey or white matter in our samples.

Our results are in accordance with three studies [4, 10, 14] apart from the finding of decreased grey matter volume in the prefrontal lobe in the latter. Our results are in contrast to three studies using the optimized VBM protocol [1, 10, 19] and two using traditional VBM [5, 11]. In these studies decreased grey matter density or decreased and increased grey matter volume in multiple cortical regions were reported. For the most part these differences were observed in frontal cortical regions involving prefrontal and anterior cingulate cortices. But no study could replicate prior findings in exactly the same localization according to the Talairach coordinates. Moreover, some reported abnormalities are contradictory, for example increased and decreased volumes of the anterior cingulate gyrus. Taken together the reported grey matter volume or density abnormalities in bipolar disorder are highly inconsistent. We hypothesize that this inconsistency might be caused by differences in the investigated samples with regard to sample size, clinical outcome, type of bipolar disorder, age range and number of previous manic or depressive episodes.

Three studies investigated small samples with 16 [9] or 11 patients [5, 10]. Significant results in such small samples might be false positive findings. In the present study the sample consisted of 33 patients with bipolar disorder and 30 healthy control subjects. Since we used a rather conservative level of signifi-

cance as compared to previous VBM studies [1, 5, 19] this might have led to a false negative finding. To resolve this problem, we lowered the significance level as suggested by several authors [1, 5, 19, 28] but again we could not find any abnormalities. Nonetheless our sample might be too small to detect hypothesized abnormalities, but to our knowledge there is no study that investigates many more patients.

Previous VBM studies in bipolar disorder also differed from each other with respect to the clinical characteristics of the samples. One study [5] investigated patients with poor outcome whereas the other studies did not mention the outcome of the patients. In the present study we analysed only patients with good outcome that are euthymic and on stable medication.

The majority of studies assessed patients with bipolar I disorder [1, 5, 11, 14] but three included also patients with bipolar II disorder into analysis [4, 10, 19]. Lochhead et al. [10] investigated seven patients with bipolar I and four patients with bipolar II disorder, Bruno et al. [4] included 28 patients with bipolar I and 11 patients with bipolar II disorder and Nugent et al. [19] investigated seven bipolar I and 29 bipolar II patients. In our study we investigated only patients with bipolar I disorder. Clinical differences between patients like recurrent episodes of hypomania or mania might be caused by different structural brain abnormalities or might lead to different structural changes. Therefore, investigations of patient samples that are heterogeneous with respect to clinical criteria might produce inconsistent results.

The age range of the subjects in most studies was between 18 and 65 years. In most studies matching was done with regard to mean age and not pair-wise to single subjects. Because the effect of age on brain structure may be non-linear and may also vary between individuals, matching by mean values alone might not be able to fully control for age effects. We analysed a large sample in which patients with bipolar disorder were significantly older than the controls. When using age as a covariate, we could not observe any changes of grey or white matter volumes.

A meta-analysis of MRI studies revealed that hippocampal volume is reduced in patients with repeated periods of major depressive disorder [27]. Patients with bipolar disorder did not show a reduction of hippocampal volume in that study. Nevertheless, this finding suggests a possible influence of number of affective episodes on brain structure. Therefore, this criterion should be taken into account in discussions of study results of brain volume abnormalities. The majority of previous VBM studies in bipolar disorder did not report number of episodes [4, 5, 9, 14, 19]. Two studies investigated patients with multiple depressive and manic episodes [10, 11]. One study so far [1] and the present study investigated patients with only few previous illness episodes (Table 1). Due to these clear differences regarding number of affec-

tive episodes the comparability of the studies is limited. We performed additional multiple regression analyses concerning number of manic or depressive episodes. In the present study we did not find any significant correlation between number of affective episodes and grey or white matter volume.

There is some evidence that psychiatric medication could influence brain structure. Some studies reported increased grey matter volume due to treatment with lithium in patients with bipolar disorder [18, 21]. So far no data is available on the effect of other mood-stabilizers or antidepressive drugs on grey matter volume. The effect of first and second generation antipsychotics on brain structure in patients with schizophrenia was recently reviewed [23]. First generation antipsychotics seem to increase the volume of nucleus caudatus and to reduce the overall grey matter volume. In contrast to this, second generation antipsychotics seem to affect neither the cortical grey matter nor the basal ganglia volumes except the thalamus whose volume has been reported to be increased. Most patients in the VBM studies in bipolar disorder were treated with mood stabilizers or antipsychotic drugs. However, no study investigated their possible influence on the reported abnormalities of brain structure. In this study, we did not differentiate between patients treated with lithium or other mood stabilizers. We performed however multiple regression analyses regarding treatment with lithium or antipsychotics. This analysis did not reveal any significant correlation of grey or white matter volume with medication.

VBM studies on patients with schizophrenia reported grey matter reductions in frontal and temporal regions [8]. These differences—in particular in the dorsolateral prefrontal cortex and the superior temporal gyrus—were already found at the time of the first psychotic episode [16]. One recent study observed additionally an increased CSF volume in the frontal and temporal lobe of patients with schizophrenia [20]. A recent study on patients with bipolar disorder revealed a ventricular enlargement in patients with psychotic symptoms in contrast to patients without psychotic symptoms [25]. This result suggests that patients with bipolar disorder with psychotic symptoms could be considered a clinically distinguishable sub-group with possibly distinctive neuropathological features. We performed, therefore, an additional multiple regression analysis concerning the existence of prior psychotic symptoms. However, we could not detect a correlation between psychotic symptoms and grey or white matter volume in our sample.

Investigation with VBM allows structural analyses free from hypotheses and user-bias [2]. Despite these advantages, its general application in structural MRI studies might be restricted by a low sensitivity in detecting marginal abnormalities. A recent study concluded that manual tracing of the corpus callosum was more sensitive in detecting discrete structural changes than VBM [26]. Negative findings in VBM-

studies, therefore, could only exclude major structural changes but not minor abnormalities.

The lack of structural abnormality in this study may speak against a structural vulnerability hypothesis in bipolar disorder. Nevertheless, studies using region of interest analyses in patients with bipolar disorder revealed for example consistently a decreased amygdala volume in children and adolescents and more heterogeneous an increased amygdala volume in adult patients [24]. We conclude, therefore, that we need both methods, VBM and region-of-interest analyses to detect major and discrete structural changes in patients with bipolar disorder.

In summary, using the optimized VBM-procedure the present study could not provide any evidence for differences of grey and white matter volume in a sample of patients with bipolar I disorder. This is in contrast to some prior findings. Our negative finding does not eliminate possible grey and white matter volume changes in the longitudinal course of the illness. Perhaps, structural changes emerge only in distinct sub-groups of bipolar patients. Larger well matched samples in consideration of clinical characteristics are needed to examine brain volume abnormalities in longitudinal studies. A combination of structural and functional imaging might reveal more robust data on patho-physiological relevant brain regions in bipolar disorder.

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