Research Paper

Combined analysis of grey matter voxel-based morphometry and white matter tract-based spatial statistics in late-life bipolar disorder

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Background: Previous magnetic resonance imaging (MRI) studies in young patients with bipolar disorder indicated the presence of grey matter concentration changes as well as microstructural alterations in white matter in various neocortical areas and the corpus callosum. Whether these structural changes are also present in elderly patients with bipolar disorder with long-lasting clinical evolution remains unclear. **Methods:** We performed a prospective MRI study of consecutive elderly, euthymic patients with bipolar disorder and healthy, elderly controls. We conducted a voxel-based morphometry (VBM) analysis and a tract-based spatial statistics (TBSS) analysis to assess fractional anisotropy and longitudinal, radial and mean diffusivity derived by diffusion tensor imaging (DTI). **Results:** We included 19 patients with bipolar disorder and 47 controls in our study. Fractional anisotropy was the most sensitive DTI marker and decreased significantly in the ventral part of the corpus callosum in patients with bipolar disorder. Longitudinal, radial and mean diffusivity showed no significant between-group differences. Grey matter concentration was reduced in patients with bipolar disorder in the right anterior insula, head of the caudate nucleus, nucleus accumbens, ventral putamen and frontal orbital cortex. Conversely, there was no grey matter concentration or fractional anisotropy increase in any brain region in patients with bipolar disorder compared with controls. **Limitations:** The major limitation of our study is the small number of patients with bipolar disorder. **Conclusion:** Our data document the concomitant presence of grey matter concentration decreases in the anterior limbic areas and the reduced fibre tract coherence in the corpus callosum of elderly patients with long-lasting bipolar disorder.

Introduction

Bipolar disorder is a severe psychiatric disorder that affects 1.5% of the general population. Onset of the disorder is usually at a young age, and it accounts for 10%–25% of geriatric patients with mood disorders.[1,2] Various structural alterations have been reported in patients with bipolar disorder, supporting both the presence of neurodevelopmental deficits in early life and neurodegenerative changes related to illness chronicity.[3,4] The most widely accepted idea concerns the presence of grey matter changes that affect the anterior limbic network, including the prefrontal cortex, subgenual anterior cingulate cortex, anterior hippocampus, amygdala, thalamus and ventral striatum.[3–7] Voxel-based morphometry (VBM), a fully automated image analysis of the whole brain that is free from a priori hypotheses, partly confirmed this viewpoint by revealing decreased grey matter concentration and volume in the ventrolateral prefrontal, anterior cingulate, temporal and parietal cortices.[6–13] However, negative data were also reported, pointing to the heterogeneity of the bipolar disorder spectrum.[5,14] Severe white matter abnormalities in patients with bipolar disorder have been usually investigated using

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magnetic resonance imaging (MRI) studies of white matter volumes and hyperintensities, magnetization transfer studies and MRI spectroscopy.[11,14–16] More recently, diffusion tensor imaging (DTI), an MRI technique that explores the microstructural integrity of white matter,[17] has been applied in studies of bipolar disorder. Overall, the few previous DTI studies reported reduced fractional anisotropy and increased radial diffusion in the frontal and prefrontal lobes, internal capsule, corpus callosum and uncinate fasciculus of patients with bipolar disorder.[18–24] Tract-based spatial statistics (TBSS) is a recently introduced advanced analysis technique that projects all individual DTI parameters onto a group average white matter skeleton, reducing potential spatial misregistrations.[25] Only 2 TBSS studies were performed in young patients with bipolar disorder, showing a reduction in fractional anisotropy, notably in the corpus callosum and fornix[22] as well as in the right uncinate fasciculus.[26]

Despite the interest in exploring the persistence of neurodevelopmental deficits and possible neurodegenerative changes, MRI studies in middle-aged and elderly patients with bipolar disorder are very rare.[27,28] In particular, to our knowledge, no study explored whether the described changes in the anterior limbic network and white matter microstructure are present in old age. If present, neurodegenerative MRI changes in grey and white matter should be much more pronounced in elderly patients with bipolar disorder with a long duration of illness. To address this issue, we performed a detailed analysis of grey matter (VBM and region of interest [ROI] analyses) and white matter (TBSS analysis of DTI parameters) in euthymic patients with bipolar disorder lasting 2 decades or more and healthy controls, all of whom were older than 65 years.

Methods

Participants

We recruited patients with bipolar disorder either from the psychogeriatric outpatient service of the University Hospitals of Geneva or via advertisements in specialized journals. Controls were also recruited via advertisements in local newspapers. We established the diagnosis of bipolar disorder (patients) or the absence of a psychiatric condition (healthy individuals) using the Mini International Neuropsychiatric Interview,[29] administered by an old-age psychiatrist (A.C.). Euthymia was defined according to the DSM-IV criteria (absence of depressive symptoms for at least 2 months). In addition, all participants had to obtain a score below 5 on the 15-item Geriatric Depression Scale[30] and on the Young Mania Rating Scale[31] at the time of inclusion in the study. Clinical assessment of euthymia and administration of the 2 scales were performed by the same old-age psychiatrist. Exclusion criteria for both groups were history of major neurologic disorders (i.e., dementing conditions, tumours, neuroimmunologic disorders), head trauma, presence of a current or a past DSM-IV psychiatric diagnosis (other than bipolar disorder for the patient group), current systemic medical disease requiring inpatient treatment, fewer than 4 years of formal education, and hearing, vision or motor impairment precluding neuropsychologic testing. After we received formal approval from the Ethics Committee at the University of Geneva, Switzerland, we obtained written informed consent from all participants before inclusion in this study. All participants who regularly used psychotropics, stimulants and β-blockers, as well as those with severe physical illness that precluded participation in either phase of the project, were excluded.

All participants underwent standardized neuropsychologic assessment, including a reaction time test for processing speed,[32] the Letter–Number Sequencing subtest of the Wechsler Memory Scale III for working memory,[33] the cued recall (CR48) items test,[34] the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Word List Memory[35] for episodic memory, the Colour Trails Test (CTT), the French version of the standard Stroop colour–word interference task and the Consonant Updating Test for executive functions.

Group comparisons of demographic and clinical variables were performed using the Wilcoxon test for continuous variables and the χ^2 test for dichotomous variables.

Image acquisition

We obtained MRI scans using a 3.0-T clinical routine whole-body scanner (MAGNETOM Trio; Siemens). On diffusion tensor imaging, 12 diffusion directions were isotropically distributed on a sphere (b value = 1000) and 1 had no diffusion weighting (b value = 0). The acquisition parameters were as follows: matrix $128 \times 128 \times 49$, voxel size $1.8 \times 1.8 \times 3.0$ mm, echo time (TE) 74 ms, repetition time (TR) 5300 ms, 2 averages. On 3-dimensional T_1 magnetization-prepared rapid acquisition with gradient echo (MPRAGE), the acquisition parameters were sagittal acquisition, 192 slices, matrix 240×256, isotropic voxel size $0.9 \times 0.9 \times 0.9$ mm^3, TE 3 ms, TR 2500 ms, 1 average. Additional sequences (T_2-weighted, fluid-attenuated inversion-recovery [FLAIR]) were acquired and analyzed to exclude brain pathology, such as ischemic stroke, subdural hematomas or space-occupying lesions. We assessed white matter lesions in T_2-weighted sequences with the Scheltens semiquantitative scale.[36]

Grey matter VBM analysis of T_1 data

We conducted a VBM analysis using the Oxford Centre for Functional MRI of the Brain's (FMRIB) FSL software package version 4.1 (www.fmrib.ox.ac.uk/fsl/). Standard processing steps were used, as described in detail previously.[25,37] The essential processing steps included using the brain extraction tool (BET; part of FSL), tissue-type segmentation using the FMRIB's Automated Segmentation Tool version 4 (FAST4; part of FSL), nonlinear transformation into Montreal Neurological Institute (MNI) reference space and creation of a study-specific grey matter template, to which the native grey matter images were then nonlinearly reregistered. The modulated segmented images were then smoothed with an isotropic Gaussian kernel with a sigma of 2 mm. Finally, we applied a voxel-wise general linear model (GLM) using permutation-based nonparametric testing (RANDOMIZE,

part of FSL), correcting for multiple comparisons by implementing threshold-free cluster enhancement (TFCE).[38] Age and sex were nonexplanatory coregressors. We considered results to be significant at $p < 0.05$, fully corrected. The entire grey matter template included 239 918 voxels. To assess structural changes within the anterior limbic network, we repeated the VBM analysis with a restricted grey matter mask of 17 065 voxels, which included only the fronto-basal cortex and basal ganglia.[5,6,8,10,12–14,39] The analysis was repeated using medication load as an additional, nonexplanatory coregressor.

White matter TBSS analysis of DTI data

The TBSS analysis of the DTI data was also performed with the FSL software package version 4.1 according to the standard procedure, described in detail elsewhere.[40] Briefly, TBSS projects all participants' fractional anisotropy data onto a mean fractional anisotropy tract skeleton using nonlinear registration. The tract skeleton is the basis for voxel-wise cross-subject statistics and reduces potential misregistrations as the source for false-positive or false-negative results. Our TBSS skeleton mask included 124 297 voxels. The other DTI-derived parameters — longitudinal (also known as axial diffusivity), radial and mean diffusivity — were analyzed in the same way, reusing the spatial transformation parameters that were estimated in the initial fractional anisotropy analysis. Similar to the VBM analysis discussed previously, we performed voxel-wise statistical analysis with TFCE[38] correction for multiple comparisons. We considered results to be significant at $p < 0.05$, fully corrected. Age and sex, again, were coregressors. We repeated the analysis using medication load as an additional coregressor.

To compare our findings to those reported previously,[26] we performed an ROI analysis of the DTI data (fractional anisotropy and longitudinal, radial and mean diffusivity) in the genu, body and splenium of the corpus callosum, bilateral uncinate fasciculus, anterior cingulum and posterior cingulum. These ROIs were defined on the group average skeleton according to previous literature[26] and the Johns Hopkins University white matter tractography atlas, which is implemented in the FSL software package. We compared the ROI average fractional anisotropy and longitudinal, radial and mean diffusivity values between groups using nonpaired parametric group analysis of variance (ANOVA) with post hoc pair-wise Bonferroni-corrected tests.

In contrast to traditional ROI analyses, our ROIs were not manually drawn for each individual; rather, they were defined once on the normalized group-average skeleton. There was consequently no operator dependence, and the ROIs were identical for each participant.

Correlation analyses between MRI and clinical data

We also performed correlation analyses to study the relation between the duration of illness and either grey matter VBM or white matter TBSS data, using duration of illness as a regressor in the framework of a general linear model. As in the analyses described previously, we used age and sex as coregressors. We considered results to be significant at $p < 0.05$, TFCE-corrected. Equivalent analyses were performed to examine the association between the neuropsychologic tests for bipolar disorder and either VBM or DTI data.

Results

Demographic, neuropsychologic and routine radiologic data

We included 19 consecutive euthymic, elderly patients with bipolar disorder (11 with type I and 8 with type II bipolar disorder) and 47 healthy controls in this prospective study. All participants were right-handed and had normal or corrected-to-normal visual acuity. None reported a history of sustained head injury or neurologic or psychiatric disorders.

There were no significant differences in age, education and Charlson Cormorbidity Index[41] score between patients with bipolar disorder and controls. There was a significantly higher percentage of women among the patients than the controls. The scores on the Geriatric Depression Scale (< 4/15 in all patients) and the Young Mania Rating Scale (< 3/44 in all patients) confirmed the patients' euthymic mood state. Duration of illness was quite long in all patients, and the mean age at onset was 39.4 (standard deviation [SD] 15.3) years (Table 1). No patients had early-onset bipolar disorder (first episode before age 18 yr). Older patients had significantly worse performances than controls in the simple reaction time test, Letter–Number Sequencing subtest, cued recall on the CR48 and delayed recall on the CERAD Word List

Table 1: Demographic and clinical characteristics of patients with bipolar disorder and healthy controls

Characteristic	Group; mean (SD)*		Z/χ^2	p value
	Bipolar disorder, $n = 19$	Control, $n = 47$		
Age, yr	68.53 (5.89)	69.77 (6.55)	$Z = -0.60$	0.55
Sex, % women	74	47	$\chi^2_1 = 4.47$	0.034
Education, no. yr	13.00 (3.59)	13.23 (3.32)	$Z = -0.33$	0.74
GDS score (max 15)	1.53 (1.65)	1.40 (1.42)	$Z = -0.01$	0.92
YMRS score (max 44)	0.95 (1.43)	0.06 (0.32)	$Z = -3.89$	0.001
CCI score (max 19)	0.79 (0.71)	0.55 (0.85)	$Z = -1.57$	0.12
Age at onset of illness, yr	39.37 (15.26)	—	—	—

CCI = Charlson Comorbidity Index;[41] GDS = Geriatric Depression Scale;[30] SD = standard deviation; YMRS = Young Mania Rating Scale.[31]
*Unless otherwise indicated.

Memory test. There were no significant differences in the other neuropsychologic tests between the 2 groups (Table 2).

Regarding medication, 79% of patients received mood stabilizers, 26% received antidepressants, 37% received benzodiazepines and 26% received neuroleptics. In 15% of patients, there was no prescription for mood stabilizers, antidepressants, benzodiazepines or neuroleptics (Table 3).

In a routine radiologic assessment of vascular burden, periventricular hyperintensity scores were comparable between patients with bipolar disorder and controls ($Z = 1.40$, $p = 0.10$). This was also the case for hyperintensities in neocortical white matter ($Z = 0.39$, $p = 0.61$), basal ganglia ($Z = 0.39$, $p = 0.54$) and infratentorial areas ($Z = 1.0$, $p = 0.30$).

Grey matter VBM analysis of T_1 data

When the entire grey matter was considered, there were no TFCE-corrected suprathreshold differences between the bipolar disorder and control groups. Restricting the analysis to the fronto-basal cortex and basal ganglia revealed significantly higher grey matter concentration in controls than in patients with bipolar disorder in the right anterior insula, head of caudate nucleus, nucleus accumbens, ventral putamen and frontal orbital cortex (Fig. 1, Table 4). The inverse comparison of the bipolar disorder group versus controls yielded no significant voxels. These differences persisted after controlling for medication effect (data not shown).

Table 2: Neuropsychologic test results of patients with bipolar disorder and healthy controls

Neuropsychologic measure; test	Group; mean (SD)		*t*/*Z*	*p* value
	Bipolar disorder, $n = 19$	Control, $n = 47$		
Processing speed				
Simple reaction time latencies, msec[32]	339.92 (73.67)	299.95 (64.83)	$t_{64} = -2.26$	0.027
Working memory				
Letter–Number Sequence score[33]	7.89 (2.69)	10.47 (2.59)	$t_{64} = 3.89$	< 0.001
Episodic memory				
48-item cued recall score[34]	22.95 (5.958)	28.06 (6.232)	$t_{64} = 3.06$	0.003
CERAD 10-word total recall score[35]	18.84 (4.729)	22.91 (3.222)	$t_{64} = 3.75$	< 0.001
Executive function				
Flexibility				
Colour Trail Making Test relative ratio score	1.04 (0.58)	1.04 (0.54)	$Z = -0.23$	0.82
Inhibition				
Stroop Colour relative ratio sore	0.27 (0.09)	0.26 (0.12)	$t_{64} = -0.59$	0.56
Updating				
Consonant updating				
2 updating cost	–0.22 (0.22)	–0.13 (0.15)	$t_{64} = 1.82$	0.07
4 updating cost	–0.15 (0.28)	–0.12 (0.19)	$t_{64} = 0.48$	0.63

CERAD = Consortium to Establish a Registry for Alzheimer's Disease; SD = standard deviation.

Table 3: Medication load of patients with bipolar disorder*

Patient	Mood stabilizers	Antidepressants	Benzodiazepines	Neuroleptics	Medication load
1	1	0	0	0	1
2	2	2	1	2	7
3	2	0	1	0	3
4	0	1	2	0	3
5	2	0	1	1	4
6	2	0	0	1	3
7	0	0	0	0	0
8	1	0	1	0	2
9	1	0	1	0	2
10	1	1	0	0	2
11	2	2	0	0	4
12	1	0	0	1	2
13	2	1	0	0	3
14	2	0	0	1	3
15	1	0	0	1	2
16	1	0	0	0	1
17	2	0	2	0	4
18	1	0	0	0	1
19	0	0	0	0	0

*0 = no medication; 1 = low dose; 2 = high dose. The overall medication load is calculated as sum of all medication classes.

White matter TBSS analysis of DTI data

Fractional anisotropy was significantly decreased in patients with bipolar disorder compared with controls in the ventral and central portion of the corpus callosum (Fig. 1, Table 5). The analysis of longitudinal, radial and mean diffusivity revealed no TFCE-corrected suprathreshold voxels, although the differences were just below threshold (between $p < 0.06$ and $p < 0.08$, corrected) and had a similar distribution to the reported fractional anisotropy analysis. These differences persisted after controlling for medication effect (data not shown). The additional ROI analyses revealed significant differences between groups in the body of the corpus callosum (fractional anisotropy, $p = 0.033$; mean diffusivity, $p = 0.018$; radial diffusivity, $p = 0.015$). There were no significant group differences in DTI parameters (fractional anisotropy and longitudinal, radial and mean diffusivity) for the bilateral uncinate fasciculus, anterior cingulum and posterior cingulum.

Correlation analyses between MRI data, duration of illness and neuropsychologic tests

The correlation analysis for the duration of illness yielded no TFCE-corrected suprathreshold voxels (VBM, fractional anisotropy and longitudinal, radial and mean diffusivity). There was, however, a clear trend between increasing duration of illness and decreasing fractional anisotropy in a distributed network at the level of the corpus callosum (persisting up to $p < 0.2$, TFCE-corrected). Conversely, there was no trend between increasing duration of disease and increasing fractional anisotropy ($p < 0.95$, TFCE-corrected).

Concerning the correlation analyses between MRI data (VBM, fractional anisotropy and longitudinal, radial and mean diffusivity) and neuropsychologic tests, there were no TFCE-corrected suprathreshold differences.

Discussion

Grey matter changes in patients with bipolar disorder

In our series, the reduction of grey matter concentration was limited to the orbitofrontal cortex bilaterally, right anterior insula, head of the caudate nucleus, nucleus accumbens and ventral putamen in patients with bipolar disorder compared with controls. In fact, and as already reported in elderly patients with bipolar disorder,[28] when the entire brain was considered, no significant differences in VBM concentration data were found between patients and controls. These observations are in line with several previous VBM studies in young patients with bipolar disorder that pointed to a possible involvement of certain parts of the anterior limbic network known to participate in visceromotor and emotion regulation in patients with bipolar disorder.[6–13] However, results show that in elderly patients, this involvement mainly concerns the frontostriatal network. Recent neuropsychologic and functional MRI studies in young[42,43] and elderly patients[44] also postulated the presence of a disconnection in the transfer of information within the frontostriatal network that could affect both cognitive and affective processing. The MRI involvement of the frontal lobe subdivisions in patients with bipolar disorder was first suggested by Lyoo and colleagues,[10] who reported a reduced grey matter concentration that was most pronounced in the right inferior frontal gyrus and, to a lesser degree, in the right precentral gyrus, left medial frontal gyrus and left anterior cingulate cortex in young adults with bipolar disorder. Similarly, Wilke and colleagues[12] found decreased grey matter densities in the bilateral orbitofrontal

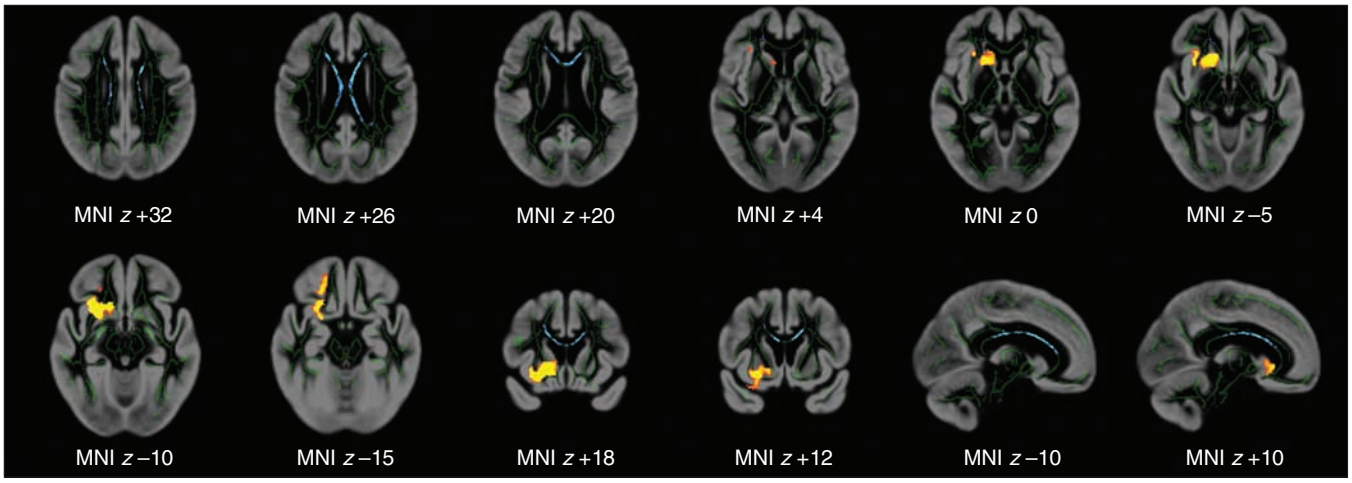

Fig. 1: Voxel-based morphometry (VBM) and tract-based spatial statistics (TBSS) analysis of the bipolar disorder group versus healthy controls illustrates the spatial distribution of threshold-free cluster enhancement–corrected significant differences between patients and controls in the white matter, notably in the corpus callosum, and grey matter, notably in the right anterior insula, head of the caudate nucleus, nucleus accumbens, ventral putamen and frontal orbital cortex. The inverse comparison of patients and controls yielded no suprathreshold activations. Grey areas denote group average grey matter mask. Green areas denote group average white matter skeleton. Red and yellow areas denote significant voxels for the VBM analysis. Blue and light blue areas denote significant voxels for the TBSS fractional anisotropy analysis. The images are presented in accordance with radiologic convention (left is right). MNI = Montreal Neurological Institute.

cortex in 10 adolescents with bipolar disorder. These results were confirmed later on in 36 young patients with bipolar disorder who displayed decreased grey matter concentration in the lateral orbital cortex compared with 65 healthy controls.[13] The presence of decreased grey matter densities in the bilateral orbitofrontal cortex in our patients indicates that the structural abnormalities in this area are also present in old age. Furthermore, they reveal significant reduction of grey matter concentration in the basal ganglia and nucleus accumbens. In their recent VBM study, Almeida and colleagues[6] also reported a reduction of grey matter volume in the left putamen of young, euthymic and depressed patients with type I bipolar disorder. The involvement of these nuclei is compatible with the hypothesis of Strakowski and colleagues[45] and earlier functional imaging studies[46] that postulated the presence of subtle alterations in bipolar disorder affecting the visceromotor network of the brain, a set of highly interconnected cortical and subcortical nuclei involved in the processing of emotionally salient stimuli. One main issue to consider when interpreting these differences is the unusually long duration of illness in the present series. Two earlier studies[8,39] and 2 recent meta-analyses in young adults with bipolar disorder,[47,48] as well as data from patients with early-onset and first-episode bipolar disorder,[3,4] suggested the presence of increased volumes of grey matter in various cortical and subcortical areas, such as the middle and superior temporal and posterior cingulate gyri, left insular/frontoparietal operculum cortex, left ventral occipitotemporal cortex, globus pallidus and cerebellum, and suggested the presence of a neuronal overgrowth or a deficit in the normal pruning process during neuronal maturation in these patients. Our negative data in elderly patients with more than 20 years of clinical evolution did not support this scenario and imply that if present in early adulthood, such an increase of partial brain volumes does not persist in late life.

White matter changes in patients with bipolar disorder

There have been 16 published DTI studies that used ROI analyses to identify subtle white matter changes in adolescents and young adults with bipolar disorder (for a review, see Heng and colleagues[49]). Highly heterogeneous, these studies reported decreased fractional anisotropy values in the frontal, prefrontal and, to a lesser extent, parietal, temporal and occipital lobes,[16,18–21] decreased or increased fractional anisotropy values in several white matter tracts and projection fibres of the internal capsule and thalamic radiations,[23,24,50–52] and decreased fractional anisotropy in association fibres that connect the frontal and prefrontal cortex with various lobes of the cerebral hemisphere.[51,53–55] Only 2 ROI-based studies in young adults examined microstructural changes in the corpus callosum, and they report conflicting data.[56,57]

Three recent studies implemented a TBSS analysis in patients with bipolar disorder. This method avoids some limitations of classic ROI analyses, notably the operator dependency, the time-consuming manual ROI selection and the difficulty of delineating the ROI borders unequivocally. Moreover, the method includes the entire brain and is not restricted to areas defined a priori. As in our study, 2 of these 3 studies showed that fractional anisotropy, but not longitudinal, radial or mean diffusivity, is a sensitive DTI parameter to assess white matter pathology in patients with bipolar

Table 4: Significant clusters for the grey matter voxel-based morphometry analysis between patients with bipolar disorder and healthy controls*

Group comparison; cluster index	Cluster size, mm^3	Maximum *Z* value	Location of maximum *Z* value, MNI space			Centre of gravity, MNI space			Side	Anatomic region
			x	*y*	*z*	*x*	*y*	*z*		
Controls > bipolar disorder										
1	6443	0.988	26	12	–10	22.7	21.8	9.88	Right	Anterior insula, head of the caudate nucleus, nucleus accumbens, ventral putamen, frontal orbital cortex
Bipolar disorder > controls										
No suprathreshold voxels	—	—	—	—	—	—	—	—	—	—

MNI = Montreal Neurological Institute.
*Suprathreshold voxels after threshold-free cluster enhancement (TFCE)–correction for multiple comparisons for the voxel-based morphometry analysis between patients with bipolar disorder and healthy controls.

Table 5: Significant clusters for the white matter tract-based spatial statistics analysis between patients with bipolar disorder and healthy controls*

Group comparison; cluster index	Cluster size, mm^3	Maximum *Z* value	Location of maximum *Z* value, MNI space			Centre of gravity, MNI space			Side	Anatomic region
			x	*y*	*z*	*x*	*y*	*z*		
Controls > bipolar disorder										
1	2494	0.97	–11	15	24	0.269	6.13	24.5	Bilateral	Corpus callosum
Bipolar disorder > controls										
No suprathreshold voxels	—	—	—	—	—	—	—	—	—	—

MNI = Montreal Neurological Institute.
*Suprathreshold voxels after threshold-free cluster enhancement (TFCE)–correction for multiple comparisons for the fractional anisotropy analysis between patients with bipolar disorder and healthy controls.

disorder.[22,26] A first report in 31 young patients with bipolar disorder revealed greater fractional anisotropy in patients versus controls in the left uncinate fasciculus, left optic radiation and right anterothalamic radiation and decreased fractional anisotropy in the right uncinate fasciculus.[26] In contrast, no significant difference was observed in the corpus callosum. However, among the 31 patients included in the study, 14 displayed acute depressive symptoms and 10 had a lifetime history of alcohol or drug abuse. Consistent with our data in strictly selected elderly patients, a recent study by Barnea-Goraly and colleagues[22] reported reduced fractional anisotropy in the corpus callosum but not in these fascicules and radiations in 21 adolescents with bipolar disorder without drug abuse and significant psychiatric comorbidities (other than behavioural and anxiety disorders). In a quite recent study, Chan and colleagues[58] reported lower fractional anisotropy and higher radial diffusivity in most parts of the anterior limbic network, as well as increased radial diffusivity in the left corpus callosum, in young patients with remitted first-episode mania. These latter findings cannot be directly comparable to ours, since the study by Chan and colleagues neither concerned definite bipolar disorder nor applied the strict exclusion criteria that we did. However, the authors also point to the presence of structural changes that affect corticocortical connections, even at very early stages of the disease. Another methodologic difference is related to thresholding. In the present study, we used a more conservative full TFCE-corrected threshold for multiple comparisons at a significance level of $p < 0.05$. In contrast, the study by Chan and colleagues employed a more liberal permutation test for group differences to reduce the margin of error to under 10%, and then considered a cluster significant when it consisted of a group of 5 or more contiguous voxels with a significance of $p < 0.001$.

The corpus callosum is the main interhemispheric commisure that connects most of the neocortical areas and comprises extensive networks subserving various cognitive functions and emotional states.[59] Both in adolescents and young adults with bipolar disorder, the corpus callosum shows reduced signal intensity compared with controls.[60–62] Only 1 previous ROI-based study in adults with bipolar disorder reported an fractional anisotropy increase in the genu of the corpus callosum.[57] Several explanations were proposed to explain this finding, including development of abberant myelination with age, abnormal perivascular structures preventing the antero-posterior flow of extracellular fluid and parallel reduction of fractional anisotropy in 1 fibre tract in regions of crossing fibres. It is possible that within the restricted area of the core of the genu, fibres are more densely packed, with fewer crossing fibres. In this context, the use of TBSS analysis is more likely to detect a true fractional anisotropy decrease since it investigates only the skeleton of the white matter tracts. The decrease of fractional anisotropy in the present study, confirmed both by ROI and TBSS analyses, should be interpreted in conjunction with the relative stability of the diffusivity parameters. As postulated by Adler and colleagues,[63] this dissociation between fractional anisotropy and other DTI parameters supports the idea of a reduced fibre tract coherence rather than myelin or axonal integrity loss in patients with bipolar disorder.

Grey matter versus white matter changes in patients with bipolar disorder

Unlike the studies discussed, we analyzed both grey matter VBM and white matter TBSS in the same patients. We found that TBSS analysis of fractional anisotropy data was the most sensitive marker. Consistent with the 2 previous TBSS studies in patients with bipolar disorder, the other DTI-derived diffusivity parameters — longitudinal, radial and mean diffusivity — were less sensitive.[22,26] In fact, when considering the voxel-wise TBSS analysis, only fractional anisotropy showed significant differences. However, in the ROI analysis, fractional anisotropy and radial and longitudinal diffusivity showed significant differences. There are 2 reasons why the ROI analysis may have been more sentitive than the voxel-wise analysis. First, the signal was averaged across several voxels per participant, potentially increasing the signal-to-noise ratio. Second, the multiple comparisons correction was much less severe for the ROI analysis. Voxel-based morphometry analysis of grey matter was also less sensitive than TBSS analysis of fractional anisotropy when considering the whole brain, and VBM analysis provided significant differences only after restricting the included voxels to the fronto-basal cortex and basal ganglia. As a constraint for the direct comparison between white matter TBSS and grey matter VBM analyses, the TBSS analysis included only about half the voxels (124 297 voxels for the TBSS skeleton v. 239 918 voxels for the grey matter mask); therefore, the effect of multiple comparisons correction was less pronounced for the TBSS analysis. The substantially higher level of TFCE-corrected significance for the TBSS analysis compared with the VBM analysis, however, exceeded this factor of 2 for multiple comparisons. We therefore conclude that the TBSS analysis of fractional anisotropy was more sensitive than the VBM analysis of grey matter in patients with bipolar disorder. This observation is consistent with the few available combined VBM and TBSS studies of multiple sclerosis[64] and ataxia.[65,66] However, in the absence of a gold standard reference for the morphometric differences between patients with bipolar disorder and healthy controls, we cannot determine which method is more valid in this clinical context.

Origin of MRI changes in elderly patients with bipolar disorder

The absence of any increase in grey matter densities and DTI parameters did not support the idea of a massive neurodevelopmental abnormality that is still present later in life. In contrast, the trend indicating a positive relation between duration of illness and a decrease in fractional anisotropy would sustain the neurodegenerative hypothesis. Importantly, even the subtle cognitive deficits that affected processing speed, working memory and episodic memory in the present sample were not related to the MRI findings, excluding a possible contamination of our observations by the inclusion

of patients with incipient dementia. Although one could argue that an early neurodevelopmental abnormality could be compensated by the beneficial effect of psychotropic medication taken over more than 2 decades, this is an unlikely scenario in the absence of any relation between the pharmacologic data and MRI findings in this study. However, the cross-sectional nature of our study does not allow us to draw definite conclusions about the progression of neurodegenerative changes versus the stability of neurodevelopmental deficits in elderly patients with bipolar disorder. Future longitudinal studies with repeated MRI measures and appropriate control for medication in well-documented cases of bipolar disorder are needed to further explore this issue.

Absence of correlation between the cognitive measures and grey or white matter data

In contrast to previous functional MRI observations,[42,43] and as already reported in our earlier work on late-life bipolar disorder,[28] there was no correlation between the patterns of neuropsychologic deficits found in our patients and structural MRI data. There are 2 plausible explanations for this negative finding. First, the relatively low variability in cognitive performances within our patient group increased the likelihood to detect group differences, but also decreased the likelihood of detecting correlations between cognitive tests and MRI data. Second, the limited number of highly selected patients with bipolar disorder may have prevented us from detecting subtle correlations with MRI data. Future studies in elderly cohorts are warranted to further explore this issue.

Limitations

Strengths of the present study include the combined use of various MRI analyses (VBM of grey matter, and TBSS and ROI analyses of white matter); careful exclusion of lifetime psychiatric comorbidities, which could have an impact on structural imaging data in patients with bipolar disorder;[26] comparable somatic comorbidities between the 2 diagnostic groups; and detailed assessment of cognitive abilities related to the anterior limbic network, such as processing spread, working and episodic memory and executive functions. Several limitations should be taken into account when interpreting our data. First, similar to previous studies involving elderly patients with bipolar disorder,[67,68] our sample size was relatively small, so no distinction was made between type I and type II bipolar disorder. Second, our strict inclusion criteria may have favoured the selection of patients with mild cases of bipolar disorder (e.g., lower number of manic episodes) and, as a result, may have underestimated the effect of bipolar illness on brain structure.[69] Third, the relation between MRI data and clinical evolution was established solely on the basis of the duration of illness. Additional clinical parameters, such as the number of previous episodes and history of psychotic symptoms, were not available. Finally, in the absence of a detailed pharmacologic history for our patients with a very long duration of illness, the assessment of medication effect was made on a simple qualitative basis.

Conclusion

The presented combined grey matter and white matter analyses of elderly patients with long-lasting bipolar disorder demonstrates the concomitant presence of grey matter concentration decreases in the anterior limbic areas and reduced fibre tract coherence in the corpus callosum.

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