Longitudinal analysis of cognitive performances and structural brain changes in late-life bipolar disorder


1 Division of Geriatric Psychiatry, University Hospitals of Geneva, Switzerland
2 Faculty of Psychology and Educational Sciences, University of Geneva, Switzerland
3 Department of Imaging and Medical Informatics, University Hospitals of Geneva, Switzerland
4 Department of Rehabilitation and Geriatrics, University Hospitals of Geneva, Switzerland
5 Division of Old Age Psychiatry, University Hospitals of Lausanne, Switzerland

Correspondence to: C. Delaloye, E-mail: christophe.delaloye@hcuge.ch

Objectives: Cross-sectional studies in bipolar disorder (BD) suggested the presence of cognitive deficits and subtle magnetic resonance imaging (MRI) changes in limbic areas that may persist at euthymic stages. Whether or not cognitive and MRI changes represent stable attributes of BD or evolve with time is still matter of debate. To address this issue, we performed a 2-year longitudinal study including detailed neuropsychological and magnetic resonance imaging (MRI) analyses of 15 euthymic older BD patients and 15 controls.

Methods: Neuropsychological evaluation concerned working memory, episodic memory, processing speed, and executive functions. MRI analyses included voxel-based morphometry (VBM) analysis of gray matter including region of interest (ROI) analysis and tract-based spatial statistics (TBSS) analysis of white matter of diffusion tensor imaging derived fractional anisotropy (FA).

Results: BD patients displayed significantly lower performances in processing speed and episodic memory but not in working memory and executive functions compared to controls. However, BD patients did not differ from controls in the mean trajectory of cognitive changes during the 2 years follow-up. In the same line, longitudinal gray matter (VBM, ROI) and white matter (TBSS FA) changes did not differ between BD patients and controls.

Conclusion: The lack of distinction between BD patients and controls in respect to the 2-year changes in cognition and MRI findings supports the notion that this disorder does not have a significant adverse impact on cognitive and brain aging. From this point of view, the present results convey a message of hope for patients suffering from BD. Copyright © 2011 John Wiley & Sons, Ltd.

Key words: bipolar disorder; older adults; longitudinal design; neuropsychology; neuroimaging

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Introduction

There is growing recognition that bipolar disorder (BD) involves cognitive deficits which persist between affective episodes (e.g., Robinson et al., 2006) and account for a substantial portion of the disability associated with this illness (e.g., Depp et al., 2009). Which higher function is mainly affected in BD remains matter of debate. Previous cross-sectional studies reported decreased performances of young and middle-aged euthymic BD patients in processing speed, executive function, attention but also working and episodic memory (for review see Torres et al., 2007). Latter may be a primitive trait of BD (Bearden et al., 2006) or attributable to severe attentional deficits (Deckersbach et al., 2004). In older euthymic BD cases, we recently found processing speed and episodic memory impairment whereas working memory and executive functions were well preserved (Delaloye et al., 2009b). These patients obtained a significantly
reduced cued-recall score compared to controls compatible with an Alzheimer disease related primitive episodic memory (Ivanoiu et al., 2005). In the absence of longitudinal follow-up, this observation raised doubts about the presence of cases with incipient dementia in older BD cases. Whether or not the above-mentioned BD-associated cognitive deficits represent stable attributes or evolve with time is equally controversial. Early cross-sectional observations in younger BD cases indicated a positive relationship between the duration of illness and cognitive measures (Bearden et al., 2001; Schouws et al., 2007), yet two recent investigations in older cohorts did not confirm this point of view (Martino et al., 2008a; Delaloye et al., 2009b).

The structural substrates of these cognitive deficits are still disputed. Besides the neurodevelopmental abnormalities affecting the anterior limbic structures often described in adolescent and adult BD cases (for review see Frazier et al., 2005), progressive pathologic process such as atrophic changes in the ventrolateral prefrontal cortex could appear later as a function of illness chronicity (for review see Adler et al., 2007). In particular, several biological alterations such as stress-induced glucocorticoid-mediated neurotoxicity (Brambilla et al., 2001), decreased inflammatory defense leading to decreased production of brain-derived neurotrophic factors (Kauer-Sant’Anna et al., 2009) and increased deep white matter and periventricular hyperintensities compared to controls (Beyer et al., 2005), all may contribute to the acceleration of cognitive decline in older BD cases (for review see Savitz and Drevets, 2009). However, recent cross-sectional data in euthymic older BD patients did not support the neurodegenerative hypothesis (Delaloye et al., 2009a; Sarnicola et al., 2009).

One main limitation of previous contributions is their cross-sectional design that did not allow for assessing the temporal evolution of cognitive deficits and structural changes in the same BD cases as compared to age-matched controls. This is particularly relevant for older BD patients since it is well known that subtle cognitive alterations affecting both executive functions and memory are also present in healthy controls (for a review see Park and Schwarz, 2008; Salthouse, 2010).

In order to explore whether the cognitive decline and structural brain changes are accelerated in older patients with BD, we performed a longitudinal study of 15 outpatients with long-standing BD and 15 healthy controls. Both groups received within an interval of 2 years two comprehensive neurocognitive assessments as well as MRI investigations. MR images were analyzed combining region of interest (ROI) estimates of the amygdala, hippocampus, entorhinal, and anterior cingulate cortex and voxel-based volumetric analysis as well as diffusion tensor imaging (DTI) analysis of white-matter integrity using tract-based spatial statistics (TBSS).

## Methods

### Participants

At baseline (T0), 22 older BD patients (11 patients with bipolar I and 11 patients with bipolar II disorders) and 22 age-, gender-, and education-matched controls were included in this study. BD patients were recruited either from the psychogeriatric outpatient service of the University Hospitals of Geneva (n = 6) or via advertisements in specialized journals (n = 9). Controls were recruited via advertisements in local newspapers. The diagnosis of BD or the absence of a psychiatric condition (healthy controls) was established using the Mini International Neuropsychiatric Inventory Interview (Sheehan et al., 1998) administered by a senior geropsychiatrist. Euthymia was defined according to DSM-IV criteria, namely absence of symptoms for at least 2 months. In addition, all participants had to obtain a score below 5 both on the 15 item Geriatric Depression Scale (GDS) (Yesavage et al., 1982) and the Young Mania Rating Scale (YMRS) (Young et al., 1978) at inclusion. Exclusion criteria for both groups were: (1) history of major neurological disorders or head trauma, (2) presence of a current or a past DSM-IV psychiatric diagnosis (other than BD), (3) current systemic medical disease requiring inpatient treatment, (4) less than 4 years of formal education, and (5) hearing, vision, or motor impairment precluding neuropsychological testing. Fifteen among the 22 BD patients (68.18%) were followed up at 2 years. Reasons for loss to follow-up were either loss of interest (n = 3) or absence of a euthymic state (n = 4). The 15 matched controls subjects have been also assessed at the 2 years follow-up. Following the formal acceptance of the research protocol by the local ethics committee, written informed consent was obtained from all participants before inclusion in the study.

### Cognitive measures

A cognitive assessment was performed in all cases including reaction time test for processing speed (Hultsch et al., 2000), the reading span test (Delaloye et al., 2009b).
et al., 2008) for working memory, the cued recall 48 items (CR 48) test (Ivanou et al., 2005) for episodic memory, the color trail making test (Maj et al., 1993), the French version of the standard Stroop color-word interference task (Stroop, 1935) and the consonant updating test (de Ribaupierre et al., 2004) for executive functions. All these tasks have been described extensively in our transversal reports (see Delaloye et al., 2009b).

MRI procedures

MR imaging was performed a 3.0T clinical routine whole body scanner (Magnetom Trio, Siemens, Erlangen, Germany). DTI: 12 diffusion directions isotropically distributed on a sphere and $b = 1000$, 180 image with no diffusion weighting, $128 \times 128 \times 49$ matrix, $1.8 \times 1.8 \times 3.0$ mm voxel size, echo time TE 74 ms, repetition time TR 5300 ms, 2 averages. 3D T1 matrix, $1.8/2$, image with no diffusion weighting, $128/2$ matrix following formula: (absolute volume in mm$^3$/ICV brain regions of interest were determined by using the segmented images. Normalized volumes for the cerebrospinal fluid, were measured automatically cerebrum (including cerebellum and stem) as well as the cerebrospinal fluid, were measured automatically without diffusion weighting, $128/2$ image with no diffusion weighting, $128/2$ matrix following formula: (absolute volume in mm$^3$/ICV brain regions of interest were determined by using the segmented images. Normalized volumes for the cerebrospinal fluid, were measured automatically cerebrum (including cerebellum and stem) as well as the cerebrospinal fluid, were measured automatically without diffusion weighting, $128/2$ image with no diffusion weighting, $128/2$ matrix following formula: (absolute volume in mm$^3$/ICV brain regions of interest were determined by using the segmented images. Normalized volumes for the cerebrospinal fluid, were measured automatically cerebrum (including cerebellum and stem) as well as the cerebrospinal fluid, were measured automatically without diffusion weighting, $128/2$ image with no diffusion weighting, $128/2$ matrix following formula: (absolute volume in mm$^3$/ICV brain regions of interest were determined by using the segmented images. Normalized volumes for the cerebrospinal fluid, were measured automatically cerebrum (including cerebellum and stem) as well as the cerebrospinal fluid, were measured automatically without diffusion weighting, $128/2$ image with no diffusion weighting, $128/2$ matrix following formula: (absolute volume in mm$^3$/ICV brain regions of interest were determined by using the segmented images. Normalized volumes for the cerebrospinal fluid, were measured automatically cerebrum (including cerebellum and stem) as well as the cerebrospinal fluid, were measured automatically without diffusion weighting, $128/2$ image with no diffusion weighting, $128/2$ matrix following formula: (absolute volume in mm$^3$/ICV brain regions of interest were determined by using the segmented images. Normalized volumes for the cerebrospinal fluid, were measured automatically cerebrum (including cerebellum and stem) as well as the cerebrospinal fluid, were measured automatically without diffusion weighting, $128/2$ image with no diffusion weighting, $128/2$ matrix following formula: (absolute volume in mm$^3$/ICV brain regions of interest were determined by using the segmented images. Normalized volumes for the cerebrospinal fluid, were measured automatically cerebrum (including cerebellum and stem) as well as the cerebrospinal fluid, were measured automatically without diffusion weighting, $128/2$ image with no diffusion weighting, $128/2$ matrix following formula: (absolute volume in mm$^3$/ICV brain regions of interest were determined by using the segmented images. Normalized volumes for the cerebrospinal fluid, were measured automatically cerebrum (including cerebellum and stem) as well as the cerebrospinal fluid, were measured automatically without diffusion weighting, $128/2$ image with no diffusion weighting, $128/2$ matrix following formula: (absolute volume in mm$^3$/ICV brain regions of interest were determined by using the segmented images. Normalized volumes for the cerebrospinal fluid, were measured automatically cerebrum (including cerebellum and stem) as well as the cerebrospinal fluid, were measured automatically without diffusion weighting, $128/2$ image with no diffusion weighting, $128/2$ matrix following formula: (absolute volume in mm$^3$/ICV

ROI analysis. Anterior cingular and entorhinal cortices, as well as hippocampal and amygdala perimeters were traced manually on each contiguous coronal slice using a ROI procedure of ANALYZE software (version 8, Mayo Foundation). Neuroanatomic boundaries of the hippocampus and amygdala were based on those of Watson et al. (1992). Anatomic guidelines for outlining the entorhinal and anterior cingular cortices were those described by Bernasconi et al. (1999) and Sassi et al. (2004), respectively. References to sagittal and horizontal planes were performed whenever necessary to improve identification of structure boundaries. Each brain structure was delimited by a manual contour from which the corresponding volume was calculated using the Analyze software. The total volume of each structure was then calculated by summing all values obtained from ROIs applied on consecutive slices (slice thickness: 0.9 mm). Intracranial volumes (ICV), defined as all gray and white matter in the cerebrum (including cerebellum and stem) as well as the cerebrospinal fluid, were measured automatically from the segmented images. Normalized volumes for brain regions of interest were determined by using the following formula: (absolute volume in mm$^3$/ICV

WM TBSS analysis of DTI data. The TBSS analysis of the DTI data was again done implementing the FSL software package (http://www.fmrib.ox.ac.uk/fsl/, Version 4.1), according to the standard procedure described in details (Smith et al., 2004). In principle, TBSS projects all subjects’ FA data onto a mean FA 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 negative results. The TBSS skeleton mask included 124297 voxels. Similar to the VBM analysis discussed above, mixed-effects model statistical analysis was performed with TFCE (Smith and Nichols, 2009) correction for multiple comparisons, considering fully corrected $p$-values $<0.05$ as significant. The analysis was again repeated using medication load as additional co-regressor.

Correlation analyses between MRI and clinical data. We also performed correlation analyses to study the relationship between gray-matter VBM (white-matter TBSS, respectively) data and duration of BD illness using duration of illness as regressor in the
Statistical analysis

Differences in cognitive performance and ROI were analyzed using a two-way analysis of variance (ANOVA) for study group and TA with TA as a within-subject repeated factor. To respect assumptions of normality (Shapiro–Wilk) and homogeneity of variance (Levene’s test), data were modified prior to analysis by means of logarithmic transformation whenever needed and possible. Data were analyzed with SPSS statistical computer software, version 17.0.

Results

Demographic and clinical characteristics

Among the 15 BD patients, 5 (30%) presented a depression or a manic episode during the 2 years follow-up. However, they were all at euthymic stages both at inclusion (T0) and second assessment (T1). The demographic and clinical characteristics of the series at T0 are summarized in Table 1. There were no significant differences between the two groups in gender distribution, average age, years of education, and somatic co-morbidity as assessed by the Charlson Comorbidity Index (Charlson et al., 1987). Scores on the GDS and YMRS confirmed the patient’s euthymic mood in all cases.

At T0, 10 patients received mood stabilizers (lithium: 13%, valproic acid: 33%, other anticonvulsants: 20%). This treatment was associated with atypical antipsychotics in 27% of the cases, serotonin or noradrenalin reuptake inhibitors in 20% of the cases, and benzodiazepines in 40% of the cases. In 7% of the cases, there was a concomitant prescription of antipsychotics, antidepressants, and benzodiazepines (see Table 2). One BD patient out of 15 had been treated once by electroconvulsive therapy in a distant past (more than 35 years ago). Control cases did not receive psychotropic medication.

Cognition

Performances on cognitive tests are provided in Table 3.

Processing speed. Older BD patients were statistically slower than the comparison group as a significant group effect was observed for the simple reaction time test $[F(1, 28) = 11.22, p < 0.01, r = 0.29]$. No significant effect of the TA (T0 vs. T1) and no significant interaction between group and TA were obtained.

Working memory. In the reading span test, only a main effect of TA was observed $[F(1, 28) = 5.65, p < 0.05, r = 0.17]$. The simple group effect and the interaction between group and TA were not significant.

Episodic memory. Compared to controls, older BD patients obtained a significantly lower cued recall score on the CR 48 items test $[F(1, 28) = 4.64, p < 0.05, r = 0.14]$. No significant effect of TA and no significant interaction between group and occasion were observed.

Executive functions. There was no significant difference in the executive domain performances between BD patients and controls. Indeed, no significant effect of group and TA as well as no significant interaction between group and TA was observed in the Stroop color test, the trail making test or the consonant updating task.

Importantly, duration of illness had nearly no impact on cognitive performances. Indeed, duration of illness correlated significantly only with one measure of processing speed (letter comparison test) at T0 ($r = 0.56, p < 0.05$). Furthermore, duration of illness did not correlate with the 2-year changes in any cognitive measure. We also did not observe any significant correlations between medication load and cognitive measures.
MRI data

Analyses on MRI data were conducted only on 13 BD patients and matched controls as 1 BD patient refused and another patient could not complete the MRI assessment.

ROI analysis. Table 4 summarizes the mean normalized volumes of each brain ROI by group of participants and measurement time. With respect to the hippocampus, a significant main effect of TA was found \( F(1, 24) = 10.09, p < 0.01, r = 0.30 \) but no main group effect nor interaction between group and measurement time.

Table 2 Medication load at T0

<table>
<thead>
<tr>
<th>Subject</th>
<th>Mood stabilizers</th>
<th>Antidepressants</th>
<th>Benzodiazepines</th>
<th>Neuroleptics</th>
<th>Medication load</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Patient 2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Patient 3</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Patient 4</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Patient 5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Patient 6</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Patient 7</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Patient 8</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Patient 9</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Patient 10</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Patient 11</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Patient 12</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Patient 13</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Patient 14</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Patient 15</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Medication load of BD patients for the different medication classes. For each medication class, scores of 0–2 are given: 0, no medication; 1, low dose; 2, high dose. The overall medication load is calculated as sum of all medication classes.

Table 3 Descriptive and inferential analysis between control’s and patient’s cognitive scores

<table>
<thead>
<tr>
<th></th>
<th>T0</th>
<th>T1</th>
<th>ANALYSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients ((N = 15))</td>
<td>Controls ((N = 15))</td>
<td>Patients ((N = 15))</td>
</tr>
<tr>
<td>Processing speed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple reaction time</td>
<td>(M) 350.00</td>
<td>(SD) 81.91</td>
<td>(M) 357.63</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working memory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reading span (score)</td>
<td>1.22</td>
<td>0.73</td>
<td>1.31</td>
</tr>
<tr>
<td>Episodic memory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cued Recall 48 items</td>
<td>(M) 24.00</td>
<td>(SD) 5.71</td>
<td>(M) 25.67</td>
</tr>
<tr>
<td>Executive functions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroop color</td>
<td>(M) 2.25</td>
<td>(SD) 0.58</td>
<td>(M) 2.30</td>
</tr>
<tr>
<td>Color trail making</td>
<td>(M) 1.21</td>
<td>(SD) 0.72</td>
<td>(M) 1.05</td>
</tr>
<tr>
<td>Consonant updating</td>
<td>(M) -0.07</td>
<td>(SD) 0.26</td>
<td>(M) -0.15</td>
</tr>
</tbody>
</table>

Significant results (\(p < 0.05\)) are indicated in bold.
TA. The same pattern was observed for the entorhinal cortex $[F(1, 24) = 4.28, p = 0.05, r = 0.15]$ and the amygdala $[F(1, 24) = 7.14, p < 0.05, r = 0.23]$. For the anterior cingulate cortex no significant effects of group and TA as well as no significant interaction between group and TA were observed.

Duration of illness had no impact on any ROI either at T0 or T1. Furthermore, no correlation was significant between the duration and the 2-year volume changes in the different ROI. We also did not observe any significant relationships between medication load and the different ROI’s volumes.

Gray matter VBM analysis of T1 data. When the entire gray matter was considered, there were no TFCE corrected supra-threshold differences between BD and healthy cases either at T0 or at T1. The comparison of gray matter over time showed no significant decrease or increase either in BD patients or healthy controls. Finally, TA by group interaction analysis was also negative.

WM TBSS analysis of DTI data. There were no TFCE corrected supra-threshold FA differences between BD and healthy cases either at T0 or at T1. The comparison of FA over time showed a significant decrease in both groups as reported in Table 5 and Figure 1. Controls presented a significant reduction of FA in the anterior thalamic radiation, the corpus callosum, the uncinate fasciculus, and the cerebellum. Finally, time point by group interaction analysis was negative. These results again remained after controlling for the medication effect.

The correlation analysis for the duration of illness yielded no TFCE corrected supra-threshold voxels (VBM, FA).

**Discussion**

This study addressed the longitudinal evolution of neurocognitive and structural MRI deficits in late-life BD. In agreement with our previous cross-sectional reports (Delaloye et al., 2009a, b), euthymic older BD patients have reduced baseline performances in processing and episodic memory compared to healthy controls. In particular, BD patients presented a significantly reduced cued-recall score compared to controls suggesting a primitive episodic memory impairment that could be attributed to incipient dementia (Ivanoiu et al., 2005; Grober et al., 2008), or be a core feature of BD. The longitudinal stability of this parameter does not support the first scenario. More generally, cognitive performances remained impressively stable in both diagnostic groups over the 2-year period. Two previous studies by Depp et al. (2008) and Balanza-Martinez et al. (2005) did not detect any differential age-related decline in middle-aged BD patients assessed longitudinally over a period of 3 years and between 1 and 3 years, respectively. However, others reported a more rapid cognitive decline in middle-aged and older BD patients.

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Table 4 Mean normalized regional brain volumes in older BD and comparison groups

<table>
<thead>
<tr>
<th></th>
<th>T0</th>
<th>T1</th>
<th>ANALYSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients (N = 13)</td>
<td>Controls (N = 13)</td>
<td>Patients (N = 13)</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hippocampus</td>
<td>3.59</td>
<td>0.36</td>
<td>3.81</td>
</tr>
<tr>
<td>Entorhinal cortex</td>
<td>1.16</td>
<td>0.17</td>
<td>1.20</td>
</tr>
<tr>
<td>Anterior cingulate cortex</td>
<td>2.35</td>
<td>0.42</td>
<td>2.35</td>
</tr>
<tr>
<td>Amygdala</td>
<td>1.82</td>
<td>0.24</td>
<td>1.82</td>
</tr>
</tbody>
</table>

Significant results (p < 0.05) are indicated in bold.
compared to healthy controls (Dhingra and Rabins, 1991; Gildengers et al., 2009) pointing to the marked heterogeneity of cognitive profiles in BD (Martino et al., 2008b). In the present series, BD patients were free from lifetime psychiatric comorbidities such as substance abuse that are known to influence cognition (Liappas et al., 2007; Levy et al., 2008).

Our MRI data also pointed to the absence of an active neurodegenerative process in older BD cases. Consistent with recent observations (Delaloye et al.,

<table>
<thead>
<tr>
<th>Cluster index</th>
<th>Cluster size (mm³)</th>
<th>Z-maxᵃ</th>
<th>Z-MAX Xᵇ</th>
<th>Z-MAX Yᵇ</th>
<th>Z-MAX Zᶜ</th>
<th>Z-MAX Xᵇ</th>
<th>Z-MAX Yᵇ</th>
<th>Z-MAX Zᶜ</th>
<th>Side</th>
<th>Anatomic regions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bipolar patients T0 &gt; T1</td>
<td>3669</td>
<td>0.98</td>
<td>−8</td>
<td>29</td>
<td>0</td>
<td>1.44</td>
<td>22.3</td>
<td>20.5</td>
<td>bi</td>
<td>anterior thalamic radiation, cerebellum</td>
</tr>
<tr>
<td>2</td>
<td>65</td>
<td>0.95</td>
<td>−27</td>
<td>36</td>
<td>1</td>
<td>−25.3</td>
<td>36.5</td>
<td>6.09</td>
<td>left</td>
<td>anterior thalamic radiation, uninate fasciculus</td>
</tr>
<tr>
<td>3</td>
<td>34</td>
<td>0.95</td>
<td>−20</td>
<td>7</td>
<td>−12</td>
<td>−22</td>
<td>5.71</td>
<td>−10.6</td>
<td>left</td>
<td>uncinate fasciculus</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>0.95</td>
<td>−8</td>
<td>−11</td>
<td>27</td>
<td>−9.1</td>
<td>−12</td>
<td>28.2</td>
<td>left</td>
<td>corpus callosum</td>
</tr>
<tr>
<td>Controls T0 &gt; T1</td>
<td>31033</td>
<td>1.00</td>
<td>−5</td>
<td>33</td>
<td>−22</td>
<td>3.09</td>
<td>−7.58</td>
<td>19.6</td>
<td>bi</td>
<td>anterior thalamic radiation, superior longitudinal fasciculus, corpus callosum, inferior fronto-occipital fasciculus, uncinate fasciculus, internal capsule, inferior longitudinal fasciculus, cingulum, corticospinal tract</td>
</tr>
<tr>
<td>2</td>
<td>113</td>
<td>0.96</td>
<td>22</td>
<td>−48</td>
<td>−25</td>
<td>19.3</td>
<td>−50.5</td>
<td>−21.2</td>
<td>left</td>
<td>cerebellum</td>
</tr>
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<td>3</td>
<td>79</td>
<td>0.96</td>
<td>23</td>
<td>−38</td>
<td>−28</td>
<td>21.5</td>
<td>−38.5</td>
<td>−24.9</td>
<td>left</td>
<td>cerebellum</td>
</tr>
</tbody>
</table>

ᵃMaximum Z-value.
ᵇLocation of maximum Z-value (Z-MAX) in MNI standard space.
ᶜCenter of gravity (COG) of the cluster in MNI standard space.
ᵈBilateral.

Figure 1 TBSS analysis of BD and controls’ longitudinal changes illustrates the spatial distribution of TFCE corrected significant differences between the 2 years’ assessments (T0 > T1) in the white matter in controls and bipolar patients. Gray: MNI152 image, green: group average white matter skeleton, red-yellow: significant voxels for the TBSS FA analysis. Radiological convention with right hemisphere on left hand side.
2009a; Sarnicola et al., 2009; Usher et al., 2010), the VBM analysis yielded no significant differences in gray-matter volume between euthymic older BD patients and controls at baseline. Interestingly, two studies indicated the presence of regional increases in brain volume in older BD compared to healthy controls raising the question of the association between neurodevelopmental and neurodegenerative deficits in this disorder (Beyer et al., 2004; Usher et al., 2010). In their meta-analysis Usher et al. (2010) reported a positive correlation between mean age and amygdala volume in patients with BD and postulated that early neurodevelopmental abnormalities may be masked by the compensatory effect of medication. (Moore et al., 2000; Yucel et al., 2007; Savitz and Drevets, 2009). However, the absence of relationship between medication load and ROI volumetric data in the present series does not support this hypothesis. Contrasting with certain studies in younger BD cohorts (Blumberg et al., 2005; Farrow et al., 2006; Moorhead et al., 2007), our longitudinal VBM data revealed no significant gray-matter changes over the 2-year follow-up. A finer ROI analysis revealed an effect of time of assessment for the hippocampus, the entorhinal cortex and the amygdala. However, there was no interaction between time of assessment and clinical diagnosis indicating that these changes in gray matter volume were not more marked in our BD cases than controls.

Recent TBSS analyses revealed patterns of loss of white matter integrity in younger BD cohorts (Versace et al., 2008; Barnea-Goraly et al., 2009). A first report in 31 young BD subjects revealed greater FA in BD versus controls in the left uncinate fasciculus, left optic radiation and right anterothalamic radiation and decreased FA in the right uncinate fasciculus (Versace et al., 2008). However, among the 31 BD patients included in this study, 14 displayed acute depressive symptoms, and 10 had a lifetime history of alcohol or drug abuse. Consistent with our data in strictly selected older cases, one recent study by Barnea-Goraly and collaborators (Barnea-Goraly et al., 2009) reported reduced FA in corpus callosum but not in these fascicles and radiations in 21 BD adolescents without drug abuse and significant psychiatric comorbidities (other than behavioral and anxiety disorders). The present data do not replicate these findings suggesting that older BD cases may represent a distinct subgroup less vulnerable to the deficits of corticocortical connectivity. Further supporting this idea, these patients display an FA reduction upon follow-up comparable to that of healthy controls.

Strengths of the present study include the combination of cross-sectional and longitudinal data, careful exclusion of lifetime psychiatric comorbidities (which could affect both cognitive performances and structural imaging data in BD), comparable somatic comorbidities and pairwise matching for demographic variables between the two diagnostic groups, detailed assessment of cognitive performances, and use of various MRI analyses that explore both gray and white matter integrity. Our strict inclusion criteria may have induced a selection of patients with less severe BD disease (e.g., lower number of manic episodes). Although the design adopted in the present study can provide a more precise evaluation of the effect of BD on cognition and structural brain volume, it may also lead to an underestimation of this effect (Bearden et al., 2001). Several limitations should be taken into account when interpreting our data. First, and as in previous studies in older BD cohorts (Schouws et al., 2007; Martino et al., 2008a) the sample size is relatively small. Given this limitation, no distinction was made between BDI and BDII cases. Second, the relationship between cognitive and neuroimaging 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, intensity of stressful life events and history of psychotic symptoms were not available. Finally, in the absence of detailed pharmacological history in our cases with very long duration of illness, the assessment of medication effect was made on a simple qualitative basis.

In summary, the lack of distinction between BD patients and controls with respect to the 2-year changes in gray/white matter and cognition is internally consistent and supports the notion that BD does not have a significant adverse impact on cognitive and brain aging. From this point of view, the present results clearly convey a message of hope for patients suffering from BD.

Key Point
- To examine cognition and its structural correlates in long-standing bipolar disorder (BD), we performed a 2-year longitudinal neuropsychological and MRI analyses revealing that old euthymic BD patients did not differ from controls in the mean trajectory of cognitive, gray matter and white matter changes. Thus, BD does not have a significant adverse impact on cognitive and brain aging. From this point of view, the present results convey a message of hope for BD patients.
Conflict of interest

The authors of this paper do not have any commercial associations that might pose a conflict of interest in connection with this paper.

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