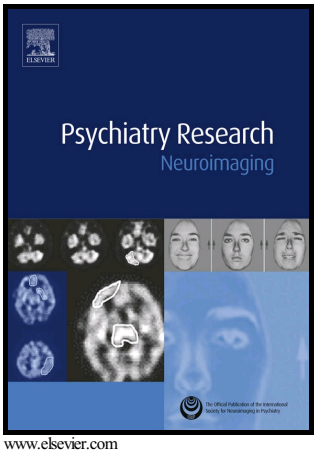

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Longitudinal investigation of the parietal lobe anatomy in bipolar disorder and its association with general functioning

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Abstract

The parietal lobe (PL) supports cognitive domains, including attention and memory, which are impaired in bipolar disorder (BD). Although cross-sectional voxel-based morphometry studies found reduced PL grey matter (GM) in BD, none has longitudinally focused on PL anatomy in BD, relating it to patients' functioning. Thirty-eight right-handed BD patients and 42 matched healthy subjects (HS) underwent a Magnetic Resonance Imaging (MRI) scan at baseline. Seventeen BD patients and 16 matched HS underwent a follow-up MRI. PL white matter (WM) and GM volumes were measured. The trajectory of parietal volumes over time and the possible relation with the global functioning were investigated in both BD patients and HS. At baseline, BD patients showed significant reduced PL WM and GM and different WM

laterality compared with HS. Furthermore, smaller PL WM volumes predicted lower global functioning in BD, but not in HS. At follow-up, although BD patients reported reduced PL WM compared with HS, no different pattern of volume changes over time was detected between groups.

This study suggests the involvement of the PL in the pathophysiology of BD. In particular, PL WM reductions seem to predict an impairment in general functioning in BD and might represent a marker of functional outcome.

Keywords: white matter; grey matter; asymmetry; brain volumes; magnetic resonance imaging

1. **Introduction**

Bipolar disorder (BD) is a severe psychiatric illness characterized by acute episodes of mood disturbance that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning (Hirschfeld et al., 2003; Pope et al., 2007, Altamura et al., 2015). Magnetic Resonance Imaging (MRI) studies have tried to clarify the neuro-anatomical brain abnormalities underlying BD, showing impairments in some specific areas, with particular regards to prefrontal cortex and limbic areas (Strakowski et al., 2012; Arnone et al., 2009). However, the role of the parietal role (PL) in the pathophysiology of BD is surprisingly under-examined. This region, as part of a more extended network, is involved in adaptive control processes (Cole et al., 2014), and in sustaining major cognitive domains, such as attention and working memory (Behrmann et al., 2004; Collette and Van der Linden, 2002; Yantis et al., 2002), abilities consistently found to be altered in BD (Thompson et al., 2007; Najt et al., 2013; Brooks et al., 2015, Cremaschi et al., 2013). Indeed, several functional MRI studies have consistently reported alterations of this frontal-parietal circuitry in BD patients while performing a working memory (Townsend et al., 2010, Frangou et al., 2008) and attention (Cabeza and Nyberg, 2000) tasks. In this perspective, several cross-sectional studies, using voxel-based morphometry (VBM) reported PL volume reduction in both children (Frazier et al., 2005) and adults with BD (Ha et al., 2009; Adler et al., 2005; Haldane et al., 2008; Doris et al., 2004; Cui et al., 2011; Li et al., 2011; Rimol et al., 2010) and they associated this PL reduction with lower global functioning (Frazier et al., 2005; Forcada et al., 2011).

In contrast, some prior longitudinal VBM studies hold inconsistent findings, reporting PL grey matter volume reduction (de Castro-Manglano et al., 2011a), increase (Adleman et al., 2012) or no changes (Farrow et al., 2005; Delaloye et al., 2011; Arango et al., 2012) in BD over time, leading to inconclusive results.

Nevertheless, to the best of our knowledge no prior studies focused on PL in BD using a Region of Interest (ROI) approach. Therefore, the present study, for the first time, aimed to a) assess PL white and grey matter volume differences between BD patients and healthy subjects, b) explore the relationship between PL and global functioning, and c) investigate PL volumes changes over time. Based on the VBM studies in literature, we hypothesized to find abnormal reductions of PL white and grey matter volumes in BD patients compared with healthy subjects, which may reflect an impairment of global functioning.

2. Methods

2.1 Subjects

A sample of patients aged 18-65 with a DSM-IV diagnosis of BD (*N*=38) was recruited from the South Verona Psychiatric Case Register (Tansella et al., 2006; Amaddeo et al., 2009; Amaddeo and Tansella, 2009). Diagnoses were confirmed with the Item Group Checklist (IGC) of the Schedule for Clinical Assessment in Neuropsychiatry (SCAN) (Tansella and Nardini 1996) and by clinical consensus. Comorbid Axis I psychiatric disorders, alcohol or substance abuse within the six months preceding the MRI, an history of traumatic head injury with loss of consciousness, neurological diseases, mental retardation or major medical conditions represented exclusion criteria for the study. Socio-demographic data, including age of onset, duration of illness, number of hospitalizations, handedness and psychopharmacological lifetime treatment, were collected from patients' interviews and medical records. Patients with BD were not at their first episode and continued their psychopharmacological treatment during the course of the study. We calculated the cumulative prescribed daily dose/definitely daily dose ratio for psychotropic drugs (Nosè and Barbui, 2008).

The All BD patients and healthy subjects were right-handed, as determined by the Edinburgh Handedness Inventory (Oldfield, 1971). Clinical symptoms of patients were assessed by using the 24-item version of the Brief Psychiatric Rating Scale (BPRS; Ventura et al., 1993), the Hamilton Depression Rating Scale 21 items (HDRS, Hamilton, 1960) and the Bech–Rafaelsen Mania Rating Scale (BRMRS, Bech et al., 1979). The global functioning in both patients and healthy subjects was assessed with Global Assessment of Functioning (GAF, American Psychiatry Association, 1994).

Furthermore, a sample of healthy subjects (*N*=42) was recruited from the same geographical area, through leaflets and word of mouth. The same exclusion criteria considered for patients were applied to healthy subjects. A history of psychiatric disorders, as determined by an adjusted and abbreviated version of the Structured Clinical Interview for DSM-IV Axis I Disorders, non-patient edition (SCID-I/NP, First et al., 2002), also in first-degree relatives, represent additional exclusion criteria for healthy subjects. Then, they were selected to have a similar distribution in age, gender, laterality index, and years of education to the patients.

After at least one year, 17 patients with BD and 16 healthy subjects accepted to participate in the follow-up phase and underwent a second MRI, representing the sample enrolled in the longitudinal study. The inter-scan interval mean for the patients group was 2.41±1.62 years and for the control group was 3.09±0.76 years.

For socio-demographic and clinical information for both patients and healthy subjects, see Table 1. The Ethics Committee of the Azienda Ospedaliera Universitaria Integrata of Verona approved this study. All participants provided signed informed consent, after having understood the nature and purpose of the study.

2.2 MRI data acquisition

All patients and healthy subjects underwent a MRI scan at the Section of Radiology of the University Hospital of Verona, Policlinico G.B. Rossi, using a 1.5T Siemens Magnetom Symphony Maestro Class, Syngo MR 2002B (Siemens Eerlangen, Germany). Initially, explorative sagittal images series, T1-weighted spin-echo (SE) (*N* = 18 sections, TR = 450 ms, TE = 14 ms, flip angle = 90 °, FOV = 230 * 230, slice thickness = 5 mm, matrix size = 384 * 512, NEX = 2, t = 2 min 52 s acquisition) were obtained to verify the location of the individual and the quality of the images. The median sagittal image allowed the acquisition of

transverse images and coronal. To exclude the presence of focal lesions, it was performed a DP and T2 - weighted turbo spin-echo (TSE) sequence. The parameters applied were: *N* = 20 sections * 2, TR = 2500 ms, TE = 24/121 ms, flip angle = 180°, FOV = 230 * 230, slice thickness = 5 mm, matrix size = 410 * 512, NEX = 2, turbo factor = 5, t = 3 min 25 s acquisition, according to a transverse plane, parallel conducted to the bicommissural line. It was subsequently performed a coronal sequence 3D MPR, according to the plan of Charcot (sections *N* = 144, TR = 2060 ms, TE = 3.9 ms, flip angle = 15th, FOV = 176 * 235, slice thickness = 1.25 mm, matrix size = 270 * 512, TI = 1100, NEX = 1, t acquisition = 5 min 23 s) to obtain images covering the entire brain.

2.3 MRI data post-processing

All the MRI data were transferred to a PC workstation and processed using the BRAINS2 software (http://www.psychiatry.uiowa.edu/mhcrc/IPLpages/BRAINS.htm) (Andreasen et al., 1996; Magnotta et al., 2002).

For the reconstruction of volumetric three-dimensional (3D) whole brain, forebrain, cerebellum and ventricular system images from the 3D MPR sequence were used. The PL was manually traced in sagittal progressive sections, by an operator blind to subjects' identity and to the other variables of the study (A.F.). An inter-rater reliability, defined by 10 randomly selected scans traced by two raters blind to the variables of the study was performed (A.F. and N.D.). Results obtained were r=0.92 and r=0.91 for left and right PL, respectively. To verify the maintenance of tracing methods over time, intra-rater reliability (Interclass Correlation Coefficient, ICC), defined as the degree of concordance among five randomly selected scans performed by the same rater (A.F.), was r=0.97 and r=0.98 for PL left and right, respectively.

As regard the post-processing imaging approach, we chose a manual Region of Interest (ROI)-based analyses rather than a whole brain analyses (i.e. VBM) because although VBM is rapid and fully automated, the ROI approach has more strength, namely anatomic validity (Perlini et al., 2012).

The Intra Cranial Volume (ICV), necessary to compare PL measures of the two groups of subjects by excluding differences in the total volume, was also calculated at baseline and at follow up.

Total volumes were segmented into grey matter and white matter with the *FAST tool* (FMRIB's Automated Segmentation Tool) of the FSL software (FMRIB Software Library, Release 4.1 (c) 2008, The University of Oxford).

2.4 Parietal lobe tracing

The PL was manually traced bilaterally in the sagittal plane. Anatomical boundaries were defined according to literature (Zhou et al., 2007), anatomical atlas (Duvernoy, 1999) and tracing guidelines developed and suggested by the Laboratory of Neuroimaging Resource "LONI-R", USC Mark and Mary Stevens Neuroimaging and Informatics Institute, University of Southern California (http://resource.loni.usc.edu/resources/downloads/research-protocols/masking-regions/parietal-lobe/).

The PL was defined as the portion of the cerebrum superior and anterior to the parieto-occipital sulcus, posterior to the central sulcus, and superior to the corpus callosum. The landmarks for delineating the PL were: central sulcus, parieto-occipital sulcus, lateral ventricle, sylvian fissure, superior temporal sulcus (both horizontal and ascending ramus), anterior calcarine sulcus.

To locate the central sulcus in the axial plane, the superior frontal sulcus, which is perpendicular to the pre-central sulcus, was identified. Immediately posterior to the pre-central sulcus, was the central sulcus. Tracing started slightly off center from midline and proceeded laterally in the sagittal plane.

Moving laterally, the corpus callosum disappeared and the PL was traced as all matter above the lateral ventricle down to the tip of the hippocampus. Next, a line was drawn from the hippocampus to the parieto-occipital sulcus to distinguish the inferior boundary. Once the parieto-occipital sulcus disappeared, the lateral ventricle replaced the hippocampus as the inferior boundary for the lobe. Once the lateral ventricle has disappeared, the most medial segment of the sylvian fissure was connected to the horizontal ramus of the superior temporal sulcus.

2.5 Statistical analyses

All statistical analyses were performed with the Statistical Program for the Social Sciences (SPSS version 21.0, Armonk, NY: IBM Corp 2012). Throughout, a two-tailed alpha-level of 0.05 was used for statistical testing. Chi–square test ($\chi 2$) was used to compare qualitative variables, i.e. gender, while a series of

independent sample *t*-tests were performed in order to compare quantitative variables as age, years of education and global functioning. To examine PL volume differences in white and grey matter between patients and healthy subjects, repeated measures analysis of covariance (repeated measures ANCOVA) were performed. The between-subject factor was the group (BD patients with BD vs. healthy subject) and the within-subject factor was hemisphere (left and right). The interaction effect of group by hemisphere were examined. Age, gender, ICV, years of education were included as covariates. To test the asymmetry in PL white matter and grey matter, we performed paired t-test to compare left and right PL volumes within the group of patients and healthy subjects, respectively. The asymmetry index for each subjects [(right PL– left PL)/ (right PL + left PL)] have been also calculated.

Independent samples t-tests have been performed to investigate possible differences in the PL volumes asymmetry between BD patients and healthy subjects. In this analysis, a multiple comparison correction was applied using Bonferroni criterion: specifically, the threshold p-value was divided for the number of tests, 4 (p=0.013).

To test the hypothesis that patients and healthy subjects would present different pattern of volumes change over time (longitudinal dimension), we performed repeated measures analysis of covariance (repeated measures ANCOVA). The between-subject factor was the group (patients and healthy subjects) and the within-subject factors were hemisphere (left and right volumes) and time (volume at baseline and volume at follow up). The interaction effects of group by time, group by hemisphere and hemisphere by time were examined. Gender, ICV, age, years of education and inter-scan intervals were included as covariates. Moreover, the PL volume change between baseline and follow up (Delta %) for both groups (patients and healthy subjects) was calculated (volume T1 - volume T2/volume T1*100).

Finally, to investigate whether and how PL white matter and grey matter were related to global functioning (GAF scores), we performed simple linear regressions. The GAF scores were considered as dependent variables and PL volumes as independent variables; gender, ICV and group were included as covariates. Similar analysis were performed for left and right, PL white matter and PL grey matter separately. Regression analyses were run at baseline (cross-sectional study) and at follow-up (longitudinal study).

3. Results

3.1 Socio-demographic and clinical results

Socio-demographical and clinical features of the cross-sectional and longitudinal samples are described in Table 1.

At baseline, 38 right-handed patients with BD and 42 right-handed healthy subjects were enrolled in the study. After at least one year, 17 patients with BD and 16 healthy subjects underwent a second MRI, thus representing the sample enrolled in the longitudinal study. The inter-scan interval mean for the patients group was 2.41±1.62 years and for the control group was 3.09±0.76.

Mean length of illness (measured by the mean time from the illness onset) at baseline was 15.95±9.97 years and the number of hospital admissions amounted to 3.84±3.69. No BD patients, except one, and none of healthy subjects had a history of illicit drug use lifetime.

There were no significant differences between the groups of BD patients and healthy subjects with regard to age, gender, ICV, neither at baseline nor at follow up (all $p>0.10$).

However, both at baseline and follow-up there was a significant difference between the GAF scores of BD patients and healthy subjects (all $p\leq0.001$).

Based on the Hamilton Depression Rating Scale (HDRS) and Bech Rafaelsen Mania Rating Scale (BRMRS) scores, at baseline 17 patients were depressed (HDRS score $\geq$ 8), 17 patients were euthymic (HDRS $\leq$ 7; BRMRS $\leq$ 7), and 4 patients were in hypomania/mixed state (HDRS> 7; BRMRS> 7).

All BD patients except one (*N*=37) were on pharmacological treatment with one or more different medications. We calculated the cumulative prescribed daily dose/definitely daily dose ratio for psychotropic drugs (Nosè and Barbui, 2008). Twenty-five patients were treated with antipsychotic drugs (*N*=14 atypical, *N*=8 typical and *N*=3 with a combination of the two antipsychotics), 9 with a mood stabilizer (*N*=4 lithium, *N*=4 valproate and *N*=1 lamotirigine), 15 with antidepressants and one anti-parkinsonian medication. In addition, 12 patients took benzodiazepines.

At the time of the second MRI scan (follow-up), based on the HDRS and BRMRS scores, eight patients were depressed; seven were euthymic and two in a mixed state.

All patients except one (*N*=16) were on psychotropic treatment. Nine of the 17 patients were taking antipsychotic drugs. Specifically, three patients were on atypical (second generation), five on typical and one on a combination of the two antipsychotics. Moreover, ten patients were receiving a mood stabilizer (*N*=4 lithium, *N*=3 valproate, *N*=2 lamotrigine and *N*=1 a combination of lithium and valproate), seven patients took antidepressant, one anti-parkinsonian medication and seven benzodiazepines. In addition, the mean dose of antipsychotic drugs was calculated and expressed in chlorpromazine equivalents. Inter-scan interval did not differ significantly between patients and healthy subjects ($p>0.05$).

3.2 MRI results: Cross-sectional study

PL volumes are presented in Table 2 and in Figure 1a.

Significant differences in bilateral PL white and gray matter were found in BD patients compared with healthy subjects, with patients showing smaller PL white and gray matter ($F(1,74)=13.37$, $p=0.00$ and $F(1,74)=6.20$; $p=0.02$). No significant hemisphere effect was found ($p>0.05$). A significant group by hemisphere interaction was observed only in PL white matter ($F(1,74)=4.17$; $p=0.04$), suggesting a significant difference in laterality between patients and healthy subjects.

Post-hoc comparisons showed that the healthy subjects had the left PL white matter significantly larger than the right ($t(41)=-3.19$; $p=0.001$). In contrast, no significant differences between left and right PL white matter was observed in BD patients ($p>0.05$).

Finally, the comparison of PL white matter asymmetry index between BD patients and healthy subjects reported a significant difference ($t(78)=2.31$; $p=0.02$) (Table 3, Figure 1b), with BD patients showing the lack of typical asymmetry (left>right) found in healthy subjects. No significant differences in the asymmetry index were found in PL grey matter between BD patients compared with healthy subjects ($p>0.05$).

3.3 MRI results: Longitudinal study

Volume changes over time are presented in Table 4 and in Figure 2.

The main effect of group ($F(1,26)=4.27$; $p=0.05$) but not of time ($p>0.05$) was observed on PL white matter. No significant interaction effects of time by group, group by hemisphere and hemisphere by time were detected ($p>0.05$). A significant time but no group ($p>0.05$) effect was detected on PL grey matter ($F(1,26)=6.86$; $p=0.01$). No significant time by group interactions, group by hemisphere and hemisphere by time were found ($p>0.05$).

All PL volumes and percentage differences between baseline and follow-up are reported in Table 5.

The main differences in PL reductions between BD patients and healthy subjects were found in the right PL white matter and the right PL grey matter, being approximately of 6% in BD patients and 4% in healthy subjects. Nevertheless, the reductions of PL white and grey matter were not significantly different between BD patients and healthy subjects (all $p>0.05$).

3.4 Association between PL volumes and GAF scores, pharmacological treatment and clinical state: Cross-sectional study.

A main effect of the group emerged ($F(1, 74)= 59.48$; $p<0.00$) with BD patients reporting lower GAF scores compared to healthy subjects (mean±SD=57.63± 12.33; versus 76.15±5.68, respectively).

The GAF scores were also predicted by the volumes of the right ($F(1,74)=7.69$; $p=0.007$) and the left ($F(1,74)=10.23$; $p=0.002$) PL white matter. No significant right PL white matter by group interaction was observed ($p>0.05$). However, a significant left PL white matter by group interaction in the prediction of GAF scores was detected ($F(1,74)= 4.94$; $p=0.03$) (Figure 3).

Regression analyses within each group have been then performed to clarify the interaction, showing that the prediction was significant only within the group of BD patients ($F(1,35)=4.35$, $p=0.04$) but not within the control group ($p>0.05$).

No significant associations emerged between PL measures (left and right white matter and grey matter), age, gender, scores at BPRS, BRMRS, HDRS, total equivalent dose of antipsychotics drugs, antidepressants and mood stabilizer dose (cumulative prescribed daily dose/definitely daily dose ratio) and clinical mood state (all $p>0.05$).

3.5 Association between PL volumes and GAF scores, pharmacological treatment and clinical state: Longitudinal study

As for the cross-sectional study, the GAF scores at follow-up were predicted by the group ($F(1,23)= 6.56$; $p=0,02$). No main effects of the PL measures (left and right white matter and grey matter) nor interactions emerged (all $p>0.05$). Also, similarly to baseline (cross-sectional study), there were not significant associations between PL measures and age, gender, scores at BPRS, BRMRS, HDRS, total equivalent dose of antipsychotics drugs, antidepressants and mood stabilizer dose (cumulative prescribed daily dose/definitely daily dose ratio) and clinical mood state (all $p>0.05$).

4. Discussion

4.1 Parietal grey and white matter abnormalities in BD

In the cross-sectional study, we observed PL grey and white matter reductions in BD patients compared to healthy subjects at baseline. Our results are in line with other cross-sectional MRI studies, using the VBM approach, which detected a decrease in PL gray matter volume (Doris et al., 2004; Adler et al., 2005; Ha et al., 2009; Haldane et al. 2008; Li et al,. 2011; Lyoo et al., 2006). Furthermore, it is important to remark that the PL is involved in several cognitive functions known to be altered in BD, including working memory (Pomarol-Clotet et al., 2015), episodic memory (Oertel-Knochel et al., 2014) and spatial attention (Najt et al., 2013). Interestingly, it has also been suggested that functional deficits in this area might be considered a common feature characterizing BD patients at different phases of the illness, as reported by several functional MRI studies in BD in manic, depressive and euthymic phase (Fernández-Corcuera et al., 2013; Townsend and Altshuler, 2012).

Similarly, we found PL white matter reductions in BD compared with healthy subjects, both at baseline and follow-up, consistently with previous findings from two independent meta-analyses reporting significant overall reduction in cerebral white matter volume in patients with first episode BD (Vita et al., 2009; De Peri el al., 2012). Additionally, specifically for PL, Farrow et al. (2005) observed white matter reductions in BD

patients compared with healthy subjects in bilateral posterior parieto-temporal junction. Moreover, Diffusion Tensor Imaging (DTI) data reported by Oertel-Knochel et al. (2014) revealed increased radial, axial, and mean diffusivity in the left superior longitudinal fascicle (a bundle of myelinated axons, connecting frontal and occipital lobes, part of parietal and temporal lobes of each hemisphere) in BD patients compared with controls. Similarly, a recent DTI study (Poletti et al., 2015) confirmed the importance of white matter integrity as a neurobiological underpinning of cognitive deficits in BD, reporting that cognitive performances in attention, information processing, working memory, executive functions and psychomotor coordination were associated with disrupted white matter integrity in several association fibers, including the inferior and superior longitudinal fasciculus, inferior fronto-occipital fasciculus, cingulum bundle, corpus callosum, and corona radiate. Therefore, all together these results further support the putative role of white matter abnormalities in the neurobiology of BD, in accordance to previous studies in BD (Mahon et al., 2010; Bellani et al., 2009).

4.2 PL volume changes over time.

In the longitudinal analyses, we observed a significant time effect on left and right PL grey matter, with BD patients and healthy subjects showing the same pattern of grey matter decrease over time. We observed also a group effect on bilateral PL white matter, with BD patients showing smaller PL volumes. It is important to remark that the trajectories of structural brain changes over time in BD patients are still disputed and surprisingly under-examined. Indeed, although it has been consistently hypothesized that BD patients would show significant volume changes over time compared to healthy subjects (Moorhead et al., 2007; Liberg et al., 2016), the direction of these changes are still unclear. Specifically for PL gray matter, Adleman et al. (2012) observed an increased PL gray matter volume in pediatric BD patients compared to healthy subjects, which in turn, showed a decreased PL volume over time, as also reported by Lisy et al. (2011). Similarly, Nakamura et al. (2007) found a significant reduction in parieto-occipital grey matter in BD patients compared to healthy subjects after approximately 1.5 years. In contrast, a 3-years longitudinal study reported grey matter reductions over time in several regions, including the PL, in healthy subjects and a trend towards significance in patients at first episode of affective psychosis but not in patients with schizophrenia (de

Castro-Manglano et al. 2011a). Interestingly, the authors explained the absence of grey mater reductions in patients with schizophrenia as a perturbation of typical processes of brain development, which alter the normal pattern of longitudinal grey matter volume reductions during adolescence and early adulthood (Giedd et al., 1999).

Therefore, our sample of BD patients seemed to follow the normal developmental trajectories of PL volumes, which is in line with the evidence reported by a recent study by Arango et al. (2012), reporting more marked progressive brain changes in patients with a diagnosis of schizophrenia rather than of BD.

Although the potential neuroprotective effects of mood stabilizer, and in particular of lithium, have been reported (Berk et al., 2017, Nakamura et al., 2007), we did not observed significant relationship with PL grey and white matter volumes.

Finally, all together these findings further highlight that:

a) PL white and grey matter volume reductions in BD compared to healthy subjects might be considered a putative biological marker of the disorder;

b) PL grey and white matter volume reductions persist over time in both BD patients and healthy subjects, suggesting that PL volumes follow the normal developmental trajectories.

4.3 Lack of PL white matter asymmetry (left > right) in BD.

The present study showed no typical left>right PL white matter asymmetry in BD patients, which was observed, however, in healthy subjects. This lack of asymmetry observed in BD patients might be due to a reduction of white matter in the left hemisphere, usually considered the dominant hemisphere in right-handed subjects. Indeed, changes in connectivity between the two hemispheres might interfere with the process of lateralization of hemispheric dominance in major psychosis (Crow et al. 1997), such as BD, possibly affecting the cognitive functioning, including language and spatial attention, abilities linked to lateralized cerebral circuitry. Moreover, twin and genetic studies have also suggested the putative role of left white matter abnormalities in the pathophysiology of BD (Noga et al., 2001; McDonalds et al., 2004; Kieseppa et al., 2003). Specifically, a study reported that white matter reduction in the left frontal and

temporo-parietal regions might represent endophenotypic markers associated with genetic risk for BD (McDonalds et al., 2004). Similarly, imaging genetics studies (Kieseppa 2003; Noga et al., 2001), further supported this hypothesis. Specifically, Kieseppa (2003) investigated structural alterations related to BD and to the increased genetic risk on a nationwide sample of twins with BD type I, their unaffected co-twins and control twin subjects. The authors found decreased left hemispheric white matter volumes in BD patients and co-twin compared with control twin subjects, suggesting that left PL white matter reduction may reflect a genetic risk factor for BD type I. Finally, another MRI study (Noga et al., 2001) compared monozygotic twin pairs discordant for BD with control twin pairs, failed to find the typical asymmetry of hemispheres in healthy co-twins of twins with BD compared with control subjects, supporting structural risk factors shared by both bipolar twins of the discordant pairs. Therefore, our findings seem to suggest that structural abnormalities in white matter, especially in the left hemisphere, in BD might be considered as a biological marker of this severe mental illness.

4.4 Association between GAF scores and PL white matter

We found that reduced PL white matter volume was associated with lower global functioning in BD, suggesting that good functioning may represent a protective factor from brain volume loss.

These results suggest that the reduction in PL white matter as well as the lack of asymmetry found among BD patients may contribute to the social impairment characterizing BD and might therefore represent a marker of social outcome. Indeed, it makes sense that the absence of a left hemisphere dominance in BD may affect not only cognitive abilities but also the global functioning. In support to this hypothesis is the study by Forcada et al. (2011), which found that greater total white matter volume, together with higher IQ, predicted higher GAF scores in BD patients, sustaining the role of white matter integrity in relation to functional outcome in BD and suggesting that targeted remediation of such domain-specific impairments, might improve global cognitive function. Finally, the association between cognitive deficits and PL volume loss has been reported to be a common substrate characterizing not only BD but also schizophrenia (Ayesa-Arriola et al., 2013; Zhou et al., 2007) suggesting that white matter volume loss in PL might be a putative predictive marker of functional outcome in major psychosis.

4.5 Limitations

Several limitations should be taken into account when interpreting our results.

First, most of the patients included in the present research had a long history of psychopharmacological treatment, which did not allow us to exclude the role of this confounding variable. Second, the sample studied was relatively small, although it is larger compared with previous studies investigating this brain region at baseline (Doris et al., 2004; Adler et al., 2005) and follow-up (Farrow et al., 2005; Moorhead et al., 2007). Third, the group of healthy subjects reported homogeneous values at GAF scores; therefore, this lack of dispersion could explain why we did not observe significant correlations.

Finally, the interval between the first and the second MRI was heterogeneous, particularly for the patients group, and the possible variation of the scanner during this interval may have affected the results. However, there was no significant difference in inter-scan interval between patients and control.

4.6 Conclusions

In conclusion, the results from our study suggest the involvement of the PL in the pathophysiology of the BD, especially the white matter, possibly sustaining the impairment in psychosocial functioning in patients with BD. Moreover, PL white matter reductions may reflect intra and inter-hemispheric connectivity abnormalities, as a part of a more extended network, including frontal and temporal regions, which might explain cognitive deficits and symptomatology in BD patients. However, further studies are needed to better investigate the role and the developmental course of PL in this severe mental illness in both chronic and first-episode patients. Finally, it would be of interest to investigate common and distinct pattern of PL white and grey matter abnormalities in BD patients compared to other major psychosis, including schizophrenia.

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Contributors

Paolo Brambilla, MD, PhD, designed the study, supervised recruitment and data analyses.

Paolo Brambilla, MD, PhD, and wrote, along with Adele Ferro PsyD, PhD and Giuseppe Delvecchio PhD the first draft of the paper.

Adele Ferro PsyD, PhD, Cinzia Perlini, PsyD, PhD, Nicola Dusi, MD, PhD, and Veronica Marinelli, PsyD, PhD, participated in recruitment, and in collection of clinical and MRI data.

Adele Ferro PsyD, PhD, and Nicola Dusi, MD, PhD, participated in manual tracing.

Carolina Bonivento, Psychologist, PhD, performed statistical analyses.

Marcella Bellani, MD, PhD, coordinated the recruitment of the patients and study's methodology.

Mirella Ruggeri, MD, PhD, Carlo Altamura, MD, PhD, and Benedicto Crespo-Facorro, MD, PhD, participated in the discussion of the results.

All authors participated in the revision of manuscript and approved the final version.

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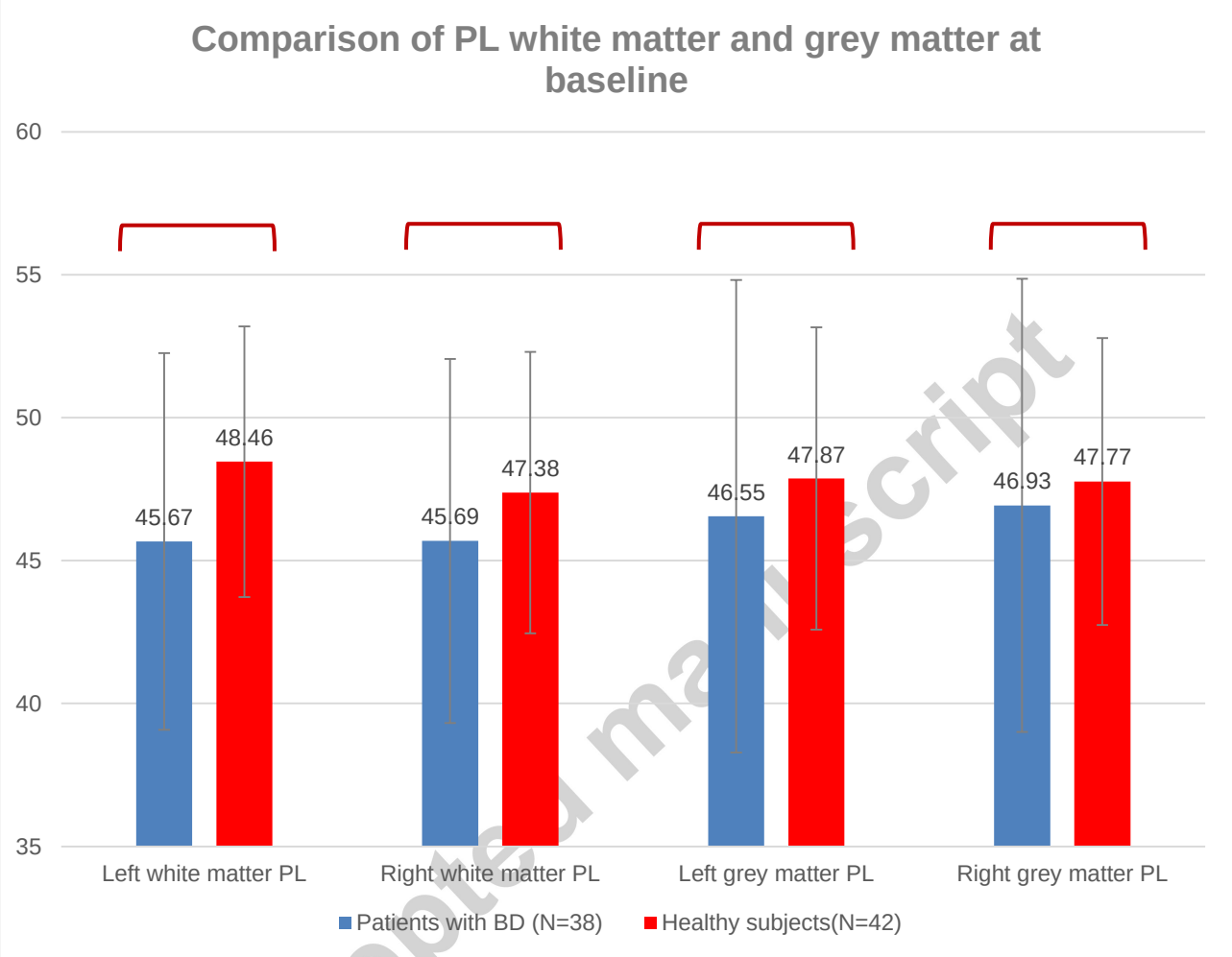
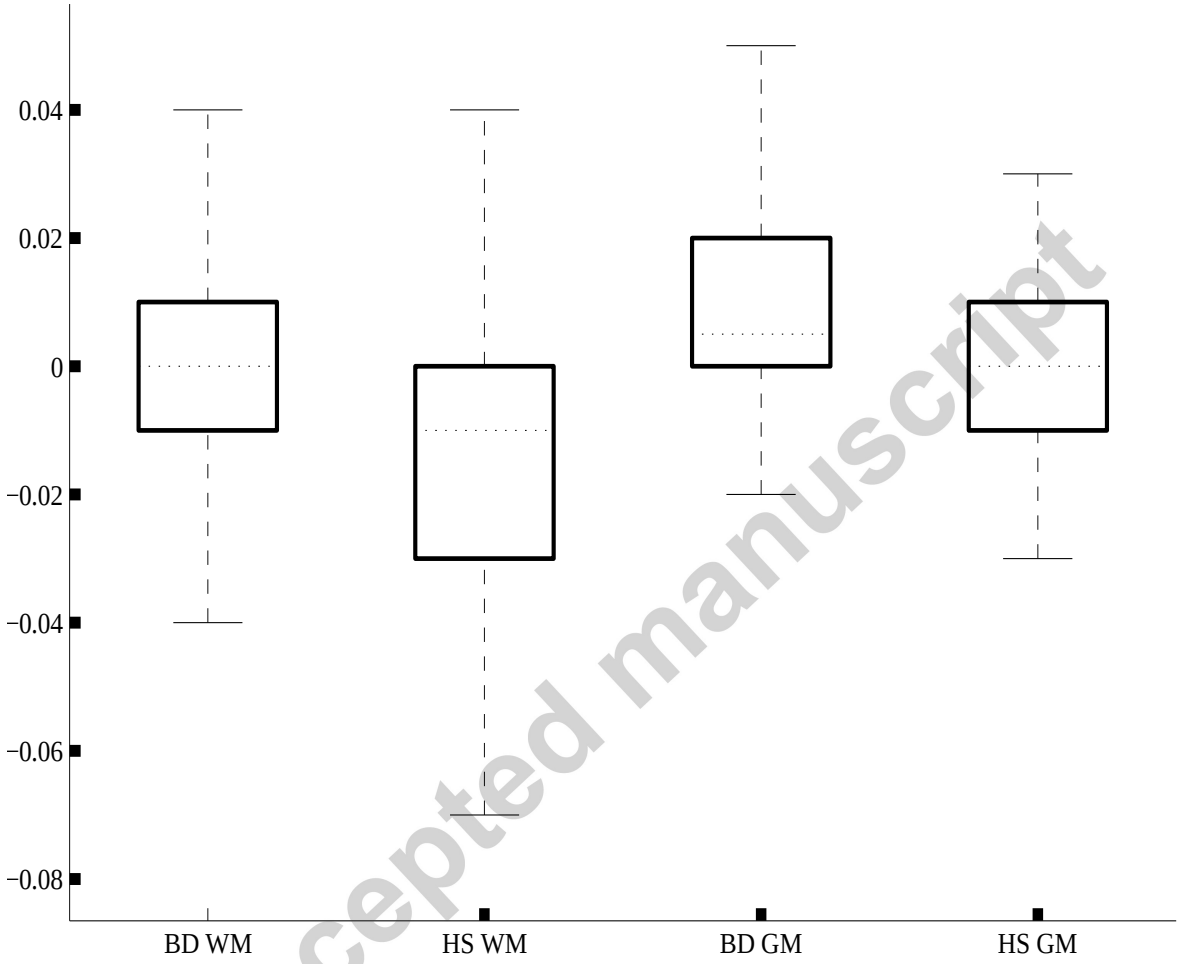
Fig 1a. Differences in parietal lobe (PL) white and grey matter at baseline in bipolar disorder (BD) patients and healthy subjects (HS).



PL=parietal lobe; BD= bipolar disorder; HS=healthy subjects

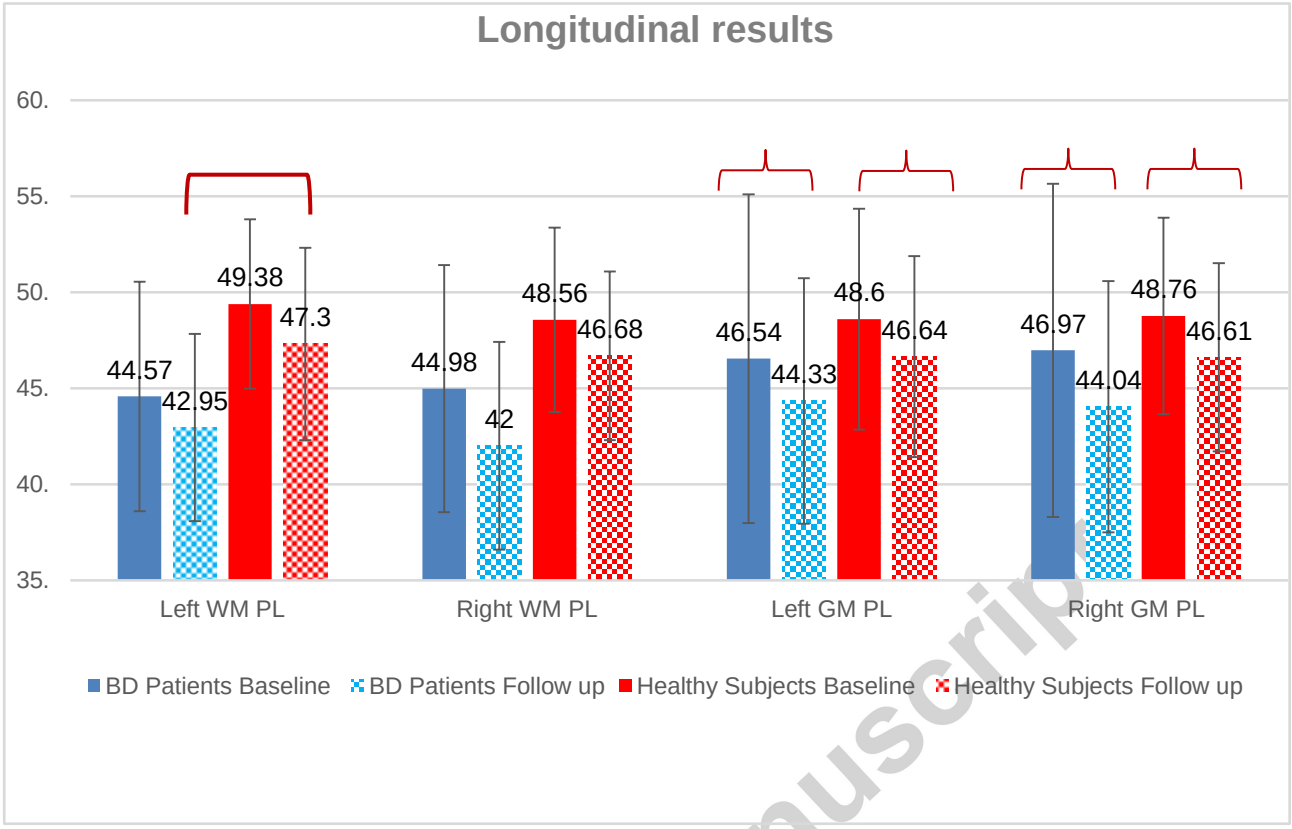
Significant differences in PL white (p=0.00) and grey matter (p=0.02) between BD patients and healthy subjects (BD < HS).

Fig 1b. Asymmetry index of the parietal lobe (PL) at baseline in bipolar disorder patients (BD) and healthy subjects (HS).



BD=bipolar disorder; HS=healthy subjects; WM=white matter; GM=grey matter;

Fig 2. Grey matter (GM) and white matter (WM) parietal lobe (PL) volume changes over time in both BD patients and healthy subjects.

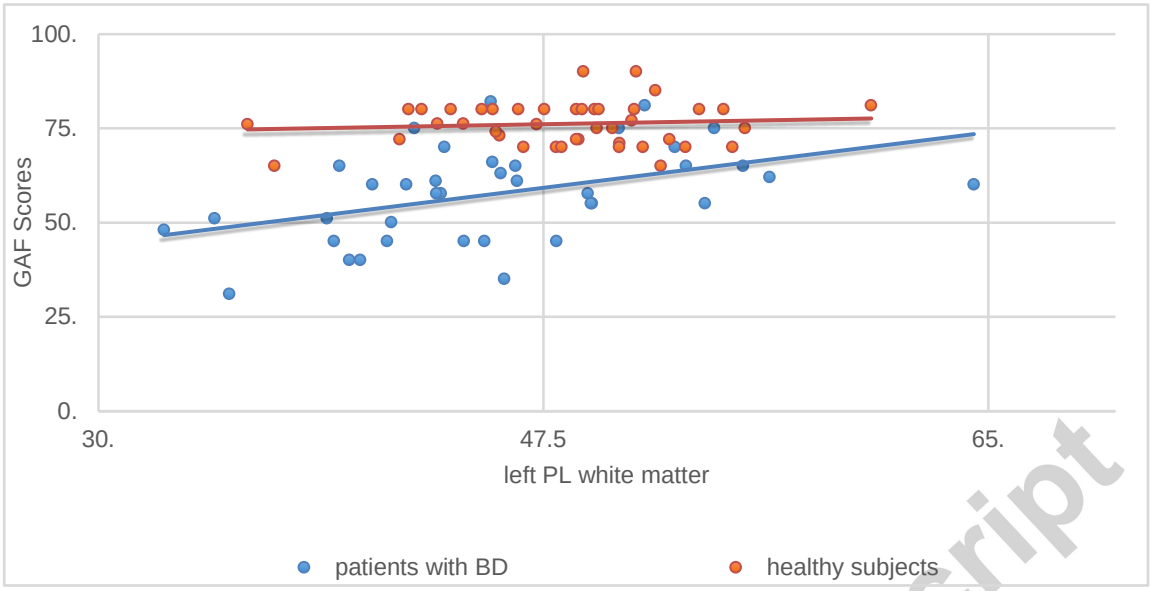


Main effect of time on PL GM (baseline < follow-up, p=0.01)

Main effect of group on PL WM (BD < HS, p=0.05)

GM=grey matter; WM=white matter; PL=parietal lobe; BD= bipolar disorder; HS=healthy subjects

Fig 3. Relationship between left PL white matter and GAF scores in both Bipolar Disorder (BD) patients and healthy subjects.



BD=bipolar disorder; PL=parietal lobe; GAF=global assessment of functioning

Table 1. Socio-demographic and clinical features of the cross-sectional and longitudinal sample.

	Cross-sectional study			
	Patients with BD (*N*=38)	**Healthy subjects (*N*=42)**		
	Mean±SD	**Mean±SD**	**Statistics**	***p***
Age at baseline scan	49.24±9.82	45.74±10.50	$t(78)=1.54$	$p=0.13$
Gender (female/male)	25/13	27/15	$\chi^2(1)=0.02$	$p>0.1$
ICV	1446.02±178.35	1414.90±128.55	$t(66.7)=0.910$	$p=0.37$

Age at onset, years	32.95±11.65			
Length of illness	15.95±9.96			
Bipolar type I/II	23/15			
Mood state(depressed/euthymic/hypomanic or mixed)	17/17/4			
Number of Hospitalizations	3.84±3.69			
Years of education	10.00±3.41	11.67±4.62	*t*(75.1)=-1.85	*p*=0.07
GAF	57.63±12.33	76.15±5.68	*t*(50.9)=-8.481	*p*=0.00
Total Eq AP	120.72±239.06			
Total AD (PDD/DDD)	0.66±1.19			
Total STAB(PDD/DDD)	0.82±0.31			
Total Atypical (PDD/DDD)	0.50±0.82			
Total Typical (PDD/DDD)	0.12±0.22			
BPRS depression/anxiety	10.39±4.66			
BPRS negative symptoms	7.95±1.54			
BPRS positive symptoms	6.26±2.40			
BPRS mania	10.71±1.78			
BRMRS	2.63±4.35			
HDRS 21 items	7.84±6.98			

Longitudinal study

	Patients with BD (N=17)	**Healthy subjects (N=16)**		
	Mean±SD	**Mean±SD**	**Statistics**	***p***
Age at baseline scan	48.88±9.45	42.48±11.91	*t*(31)=1.72	*p*=0.10

Inter-scan interval (years)	2.41±1.62	3.09±0.76	$t(31)=-1.586$	$p=0.13$
ICV (baseline)	1395.81±152.60	1458.71±149.43	$t(30.9)=1.196$	$p=0.24$
Gender (female/male)	13/4	10/6	$\chi 2(1)=0.76$	$p>0.1$
Age at onset, years	34.20±8.21			
Length of illness	17.73±8.12			
Bipolar type I/II	11/6			
Mood state(depressed/euthymic/mixed)	*8/7/2*			
Hospitalization	*4.00±3.37*			
Total Eq AP	*79.41±150.32*			
Total AD (PDD/DDD)	*0.46±0.86*			
Total STAB(PDD/DDD)	*0.48±0.55*			
Total Atypical (PDD/DDD)	*0.22±0.53*			
Total Typical (PDD/DDD)	*0.25±0.62*			
Years of education	11.06±3.31	12.81±4.39		
GAF	55.25±13.79	79.13±4.84	$t(20.1)=-6.55$	$p=0.001$
*BPRS depression/anxiety**	11.53±5.34			
*BPRS negative symptoms**	7.76±1.68			
*BPRS positive symptoms**	6.06±1.95			
*BPRS mania**	10.71±1.86			
*BRMRS**	2.71±4.80			
*HDRS 21 items**	9.35±6.53			

AP= Antipsychotic; GAF=Global Assessment of Functioning; BPRS=Brief Psychiatric Rating Scale; BD= Bipolar Disorder; AP=Antipsychotics; AD= antidepressants; Eq AP= chlorpromazine equivalents; PDD=prescribed daily dose; DDD=defined daily dose; HDRS=Hamilton Rating Scale for Depression; ICV= Intra-cranial Volumes BRMRS=Bech-Rafaelsen Mania Rating Scale; SD= Standard Deviation.
*Scores did not significantly differ in the sub-sample of BD patients at follow up.

Table 2. Comparison of parietal lobe (PL) white matter (WM) and grey matter (GM) at baseline.

	Patients with BD (*N*=38)	**Healthy subjects (*N*=42)**	***Group effect***		***Hemisphere effect***		***Group by hemisphere***	
	Mean(SD)	**Mean(SD)**	***F* (1,74)**	***p***	***F* (1,74)**	***p***	***F* (1,74)**	***p***
Left WM PL	45.67(6.59)	48.46(4.74)	13.37	**0.00**	0.14	0.71	4.17	**0.04**
Right WM PL	45.69(6.37)	47.38(4.92)						
Left GM PL	46.55(8.27)	47.87(5.29)	6.20	**0.02**	0.47	0.50	0.58	0.45
Right GM PL	46.93(7.93)	47.77(5.02)						

BD= bipolar disorder; SD= Standard Deviation; PL= Parietal Lobe; WM= white matter; GM=grey matter. Repeated measure ANOVA, with left and right as within subjects factor, and group as between subjects factor; ICV, gender and age and years of education as covariates.

Table 3. Differences in Parietal Lobe (PL) asymmetry index (Asym Index) =[(right PL– left PL)/ (right PL + left PL)] in white matter (WM) and gray matter (GM) between BD patients compared with healthy subjects.

	Patients with BD (*N*=38)	**Healthy subjects (*N*=42)**	***Statistic***	
	Mean(SD)	**Mean(SD)**	***t*(78)**	***p***
PL WM Asym Index	0.001(0.023)	-0.012(0.024)	2.31	**0.02***
PL GM Asym Index	0.005(0.022)	-0.001(0.019)	1.36	0.18

asymmetry index = [(right PL– left PL)/ (right PL + left PL)]). Independent sample t-tests. SD: standard deviation; WM=white matter; GM=grey matter; PL=parietal lobe; BD=bipolar disorder * This result did not survive Bonferroni corrections (alpha level=0.013).

Table 4. Longitudinal evaluation of parietal lobe (PL) white matter (WM) and gray matter (GM) changes between bipolar disorder (BD) patients and healthy subjects

	Group		**Time**		**Group by Time**		**Hemisphere**		**Group by Hemisphere**		**Hemisphere by Time**	
	***F*(1,26)**	***p***	***F*(1,26)**	***p***	***F*(1,26)**	***p***	***F*(1,26)**	***p***	***F*(1,26)**	***p***	***F*(1,26)**	***p***
PLWM	**4.27**	**0.05**	1.25	0.27	1.53	0.23	0.03	0.86	0.65	0.43	0.04	0.85
PL GM	0.29	0.60	**6.86**	**0.01**	0.33	0.57	0.30	0.59	0.01	0.94	1.42	0.24

Repeated measures ANCOVA, with the group as between-subject factor, hemispheres (left and right) and time (volume at baseline and volume at follow up) as within-subject factors; inter-scans interval, age at follow-up MRI exam, years of education, gender, ICV as covariates. PL=parietal lobe; WM=white matter; GM=grey matter; BD=bipolar disorder

Table 5. All parietal lobe volumes and % differences between baseline and follow-up.

	Patients with BD (*N*=17)		Delta* %	Healthy Subjects (*N*=16)		Delta* %	Paired t test	
	Baseline	Follow-up		Baseline	Follow-up			
	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)		*t*(31)	*p*
Left WM PL	44.57(5.98)	42.95(4.88)	3.29	49.38(4.41)	47.30(5.01)	4.22	-0.56	0.58
Right WM PL	44.98(6.43)	42.00(5.41)	5.96	48.56(4.80)	46.68(4.39)	3.67	0.86	0.40
Left GM PL	46.54(8.56)	44.33(6.39)	3.90	48.60(5.75)	46.64(5.23)	3.34	0.17	0.87
Right GM PL	46.97(8.67)	44.04(6.54)	5.54	48.76(5.12)	46.61(4.90)	3.92	0.56	0.58

PL=parietal lobe; WM=white matter; GM= grey matter; BD=bipolar disorder. P-values reported are uncorrected for multiple comparisons. *Delta% is the mean of delta volumes at baseline – volume at follow-up/baseline*100.

Highlights

- White and grey matter reductions of parietal lobe (PL) in bipolar disorder (BD)
- Lack of PL white matter asymmetry (left > right) in BD
- PL white matter volume reduction as marker of lower global functioning in BD