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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.

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.,

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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., 2011), 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 (Nosé 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 Psychiatric 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 1.5 T 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 Section * 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