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Gray matter deficits in bipolar disorder are associated with genetic variability at interleukin-1 beta gene (2q13)

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Twin, family and recent molecular studies support the hypothesis of genetic overlapping between schizophrenia and bipolar disorder. Brain structural features shared by both psychiatric disorders might be the phenotypic expression of a common genetic risk background. Interleukin-1 (IL-1) cluster (chromosome 2q13) genetic variability, previously associated with an increased risk both for schizophrenia and for bipolar disorder, has been also associated with gray matter (GM) deficits, ventricular enlargement and hypoactivity of prefrontal cortex in schizophrenia. The aim of the present study was to analyze the influence of IL-1 cluster on brain morphology in bipolar disorder. Genetic variability at IL-1B and IL-1RN genes was analyzed in 20 DSM-IV (Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition) bipolar patients. Magnetic resonance imaging (MRI) measurements were obtained for whole-brain GM and white matter, dorsolateral prefrontal cortex (DLPFC), superior temporal gyrus, hippocampus and lateral ventricles. MRI data were corrected for age and cranial size using regression parameters from a group of 45 healthy subjects. A −511C/T polymorphism (rs16944) of IL-1B gene was associated with whole-brain GM deficits ($P = 0.031$) and left DLPFCGM deficits ($P = 0.047$) in bipolar disorder patients. These findings support the hypothesis of IL-1 cluster variability as a shared genetic risk factor contributing to GM deficits both in bipolar disorder and in schizophrenia. Independent replication in larger samples would be of interest to confirm these results.

Keywords: Bipolar disorder, gray matter, interleukin-1, magnetic resonance imaging, schizophrenia

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Bipolar disorder and schizophrenia are severe and disabling psychiatric illnesses with similar lifetime prevalences around 1% (Jablensky *et al.* 1992; Tohen & Angst 2002). Current major diagnostic systems define bipolar disorder and schizophrenia as separate disorders. However, the overlap between both illnesses in relation to clinical, psychopathological, neuropharmacological and epidemiological features disagrees with this categorical distinction (Murray *et al.* 2004).

The important genetic contribution to the etiology of bipolar disorder and schizophrenia has been shown by twin studies reporting heritability estimates of around 80% for both disorders (Cardno *et al.* 1999; McGuffin *et al.* 2003). Moreover, twin studies have also shown the significant degree of overlapping with regard to genetic risk factors contributing to these disorders (Cardno *et al.* 2002). This genetic overlapping implies a genetic heterogeneity within current diagnostic categories, which could account for the clinical and phenotypic similarities observed between some bipolar and schizophrenic patients (Niculescu *et al.* 2006).

Certain brain structural changes have been robustly described in schizophrenic and bipolar patients (Hajek *et al.* 2005; Wright *et al.* 2000). Recent studies have brought up the interest of genetic analyses based on neuroanatomical phenotypes ascertained through neuroimaging techniques (Glahn *et al.* 2007; Gur *et al.* 2007; McDonald *et al.* 2004). According to these data, brain structural abnormalities shared by bipolar and schizophrenic patients might arise from the same genetic predisposition background.

IL-1 cluster is a suggestive candidate that maps to a region (2q13) that has achieved genome-wide significant linkage in a meta-analytic study in schizophrenia (Lewis *et al.* 2003) and in two recent linkage studies in bipolar disorder (Etain *et al.* 2006) (Goes *et al.* 2007). Supporting these data, genetic variability at IL-1 cluster has been associated with an increased risk for both disorders (Katila *et al.* 1999; Papiol *et al.* 2004; Rosa *et al.* 2004; Zanardini *et al.* 2003). Furthermore, gray matter (GM) deficits, hypofrontality and ventricular enlargement, commonly described in schizophrenia (Wright *et al.* 2000), have been associated in these patients with genes mapped to IL-1 cluster: IL-1B gene (Meisenzahl *et al.* 2001; Papiol *et al.* 2007) and IL-1RN gene (Papiol *et al.* 2005).

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These genes encode for interleukin-1 beta (IL-1β) and interleukin-1 receptor antagonist (IL-1Ra). IL-1Ra, an endogenous antagonist at IL-1 receptors, modulates the action of IL-1β by competition for receptor occupancy. Genetic variability mapped to these genes exerts a functional effect on quantitative expression of IL-1β and IL-1Ra (Chen *et al.* 2006; Hurme & Santtila, 1998). An imbalance between these proteins might induce an aberrant IL-1 receptor activation/inhibition, which could affect neurodevelopment (Nawa *et al.* 2000) or promote neurodegeneration (Allan *et al.* 2005). *In vitro* studies have shown that IL-1β has an important role in the induction of the dopaminergic phenotype in mesencephalic neuronal precursors (Potter *et al.* 1999; Rodriguez-Pallares *et al.* 2005) as well as in the regulation of dendrite growth in developing cortical neurons (Gilmore *et al.* 2004). Therefore, it could be suggested that genetic variability promoting changes in IL-1β/IL-1Ra expression might impact upon brain morphology in bipolar patients.

Our aim was to investigate whether the effects of IL-1 cluster genetic variability on brain morphology in bipolar disorder are similar to those previously reported in schizophrenia. Genetic variability with functional repercussion in IL-1B and IL-1RN genes expression was analyzed in a sample of bipolar patients with MRI data available in the context of a hypothesis-driven selection of regions of interest (ROIs).

Table 1: Sociodemographic and clinical characteristics of the sample

	Bipolar patients	Controls
Age in years, mean (SD)	43.3 (11.7)	29.4 (9.0)
Sex, males/females	10/10	24/21
Intracraneal volumes in ml, mean (SD)	1490.6 (184.7)	1401.6 (159.6)
Illness duration in years	13.2 (5.4)	—
Subjects under lithium treatment (as monotherapy)	14 (10)	—
Subjects under valproate treatment	4	—
Subjects under carbamazepine treatment	2	—
Subjects under lamotrigine treatment	2	—
Subjects under quetiapine treatment	1	—
Subjects under risperidone treatment	1	—
Subjects with at least one manic or depressive episode with psychotic symptoms	10	—

Method

Twenty DSM-IV (Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition) bipolar patients were included in the study. All patients were clinically stable, without change in their treatment in the last 6 months. Forty-five healthy subjects enrolled in previous MRI studies (Molina *et al.* 2005) were used as a control group to obtain normalized volume data relative to age and cranial size of a healthy population (see below). All subjects, of Caucasian Spanish origin, provided written informed consent to participate in the study, approved by the hospital ethical committee. See Table 1 for further sociodemographic and clinical details.

Exclusion criteria in all subjects were history of substance abuse, any other current comorbid axis-I diagnosis or psychoactive treatment, history of serious head trauma or diseases with known effects on central nervous system.

MRI scans were acquired on a Philips Gyroscan 1.5-T scanner using T1-weighted three-dimensional (3D) gradient echo sequence (matrix size 256 × 256, pixel size 0.9 × 0.9 mm, flip angle 30°, echo time 4.6 ms and slice thickness 1.5 mm). T2-weighted sequences were acquired for verification of cerebrospinal fluid (CSF) segmentation (Turbo-Spin Echo, turbo factor 15, echo time 120 ms, matrix size 256 × 256 and slice thickness 4.0–5.0 mm).

To obtain volume measurements of the main brain lobes, we used a method for semi-automated segmentation of the brain based on the Talairach proportional grid system, as described in Andreasen *et al.* (1996), Desco *et al.* (2001) and Swayze *et al.* (1996). The Talairach grid system begins with a reorientation centered on the anterior commissure and the interhemispheric plane as the vertical axis, followed by a piecewise linear transformation that produces a tessellation of the brain into a 3D grid of 1056 cells representing homologous brain regions across subjects (Talairach & Tournoux 1988). This subdivision of the brain according to the Talairach grid system allowed us to use it as the basis for a segmentation method for intersubject comparisons by defining brain ROIs as sets of 3D volume grid cells or 'boxels' (Andreasen *et al.* 1996; Desco *et al.* 2001; Swayze *et al.* 1996). This segmentation method is particularly appropriate for our study because there is no registration with templates, thus preserving intact the size and shape of the brains studied. Segmentation of cerebral tissue was performed using an automated method included in the SPM2 (Statistical Parametric Mapping) Program (Ashburner & Friston 1997). The method performs a cluster analysis with modified mixture model and a priori information about the likelihoods of each MRI voxel being one of four tissue types: GM, white matter (WM), CSF and 'other tissues'. The a priori information is based on anatomical templates that represent an 'average' brain and provide information about the spatial distribution of the different brain tissues. The algorithm also removes the effect of radiofrequency field inhomogeneities (Ashburner & Friston 2000). This segmentation was checked for inconsistencies and manually corrected whenever necessary by an experienced radiologist blinded to the diagnosis.

In a primary analysis, we studied whole-brain GM and WM. We planned second-level analyses including only four regions of potential physiopathological interest according to previous findings in schizophrenia and bipolar disorder (Hajek *et al.* 2005; Strakowski *et al.* 2005; Wright *et al.* 2000): dorsolateral prefrontal cortex (DLPFC) GM, superior temporal gyrus (STG) GM and hippocampus and lateral ventricles (LV). Whole-brain GM and WM included both cerebral hemispheres, excepting the cerebellum. The DLPFC was defined as the Talairach grid cells of the GM tissue encompassing Brodmann's areas 8, 9, 10 and 46. The LV were measured as the CSF tissue in the Talairach grid cells encompassing this region (Kates *et al.* 1999; Swayze *et al.* 1996). Hippocampal and STG volume measurements were obtained considering only the GM tissue contained within relevant cells (E2b10 and E3b10 for the hippocampus and Dc9, Dd9, E1c9, E1d8, E2d8, E3d8, E2c8, E3c8, E2d7, E3d7, Fd7 and Fc7 for the STG) as described in the Talairach atlas (Talairach & Tournoux 1988).

The validity of the Talairach-based procedure as a suitable automated segmentation tool has been previously proven (Andreasen *et al.* 1996; Ho *et al.* 2003; Kates *et al.* 1999). In our implementation, all manual procedures were performed by a single operator, thus avoiding any potential inter-rater variability. Reliability of the method was assessed by repeating the whole segmentation procedure in a sample of five cases randomly selected. Values of ICC (Intraclass correlation) ranged from 0.96 to 0.99 for regional GM measurements and from 0.89 to 0.99 for CSF data.

Because age and cranial size are known factors affecting regional cerebral volumes, their effect was removed by using the residuals from the regression models obtained from a group of 45 healthy individuals [see our previous work (Papiol *et al.* 2005) for further details on control sample], following the procedure of Pfefferbaum (Pfefferbaum *et al.* 1992). After this transformation, volume data become expressed as residuals representing excess (if positive) or defect (if negative) relative to healthy controls of their same age and cranial size.

Genomic DNA was extracted from patient's blood samples using standard phenol–chloroform methods. A −511 *Ava*I polymorphic site (rs16944) of IL-1B gene and a variable nucleotide tandem repeat (VNTR) of IL-1RN gene were genotyped as described in Katila *et al.* (1999). Allele*1 (−511C) of IL-1B gene completes an AvaI restriction site, while allele*2 (−511T) gives an intact product. On the other hand, the two commonest alleles (allele*1 and allele*2) of the VNTR in intron 2 of IL-1RN gene were detected in this sample.

Because of the small sample sizes, nonparametric (Mann–Whitney test) analyses were conducted to detect the effect of genotype or lithium treatment on the MRI variables analyzed in the patient sample. This was carried out by comparing the volume residuals for each ROI (global GM and WM measurements and region-specific analyses) between groups of patients defined according to their genotype or the presence/absence of lithium treatment. Moreover, we compared age means (Mann–Whitney test) between patients with both genotypes because ischemia has been reported to play a role in late-onset bipolar disorder. Finally, to test that possible differences in volume were not because of an effect of age and the associated higher risk of ischemia, we planned to repeat the comparisons an analysis of covariance (ANCOVA) with genotype as independent variable and age as a covariable (see *Results*).

Results

Genotypic frequencies in patients showed Hardy–Weinberg equilibrium and were similar to frequencies previously described in Spanish population despite the relative small sample size (Table 2).

In relation to IL-1B gene polymorphism and according to previous reports (Meisenzahl *et al.* 2001), two subgroups were generated: risk allele*2 carriers (genotypes: allele*1/allele*2 and allele*2/allele*2; $n = 12$) and noncarriers (genotype: allele*1/allele*1; $n = 8$). Adjusted structural measurements of neuroanatomical variables according to these subgroups are displayed in Table 3. There were no differences in age (noncarriers: 43.28 ± 13.90; carriers: 43.25 ± 10.66, $U = 45.5$, $Z = -0.19$, $P =$ not significant), sex distribution (noncarriers: four females and four males; carriers: six females and six males) or treatment (noncarriers: six with lithium; carriers: eight with lithium; $\chi^2 = 0.16$, df $= 1$, $P = 0.53$) between both subgroups. Both groups of patients also showed a similar profile in terms of anticonvulsant or antipsychotic treatment. Allele*2 carriers showed a longer time from onset than noncarriers, although this variable did not correlate with MRI measurements (Spearman's rho between GM volume residuals and illness duration $= 0.116$, $P =$ not significant). This coefficient was also nonsignificant for each of the subgroups. Five of 11 allele*2 carriers and 5 of 8 allele*2 noncarriers had a history of psychotic symptoms, while this was unknown for one carrier ($\chi^2 = 0.54$, df $= 1$, $P = 0.46$).

After correction for age and intracranial volume, allele*2 carriers of IL-1B polymorphism showed whole-brain GM deficits ($U = 20$, $z = -2.160$, $n = 20$, $P = 0.031$) with respect to noncarriers (Fig. 1). In secondary analyses, these patients showed a borderline trend toward left DLPFC volume deficits ($U = 22$, $z = -2.006$, $n = 20$, $P = 0.047$; Fig. 1) compared with noncarriers. These comparisons were still significant in an ANCOVA (total GM: $F = 4.84$, df $= 1, 17$, $P = 0.04$; left DLPFC: $F = 4.25$, df $= 1, 17$, $P = 0.05$).

Nonparametric tests showed no effect of lithium treatment on whole-brain GM ($U = 40$, $z = -0.165$, $n = 20$, $P = 0.869$) or left DLPFC GM ($U = 33$, $z = -0.742$, $n = 20$, $P = 0.458$) in the whole bipolar patients sample.

With respect to IL-1RN gene, we did not find any influence of its genetic variability on any of the ROIs.

Discussion

To our knowledge, this is the first study analyzing the relationship between IL-1 cluster and brain morphology in bipolar disorder. We report the association of a genetic variant (allele*2) at IL-1B gene with generalized GM deficits in bipolar patients. The influence of this allele on these deficits seems to be mainly focused on the left DLPFC region. In this vein, it is interesting to highlight that the same allele has been previously associated with bifrontal–temporal GM deficits in schizophrenia (Meisenzahl *et al.* 2001) and that GM deficits in frontal regions have been described by neuroimaging studies both in schizophrenia and in bipolar disorder (Honea *et al.* 2008; Lyoo *et al.* 2004).

A developmental model for functional psychoses (Murray *et al.* 2004) provides a framework for our results. Thereby IL-1 cluster could be a genetic risk factor shared by schizophrenic patients and a subgroup of bipolar patients closely related to schizophrenia picture according to their brain structural features. Association between allele*2 and generalized GM decrease would also support this notion, although these

Table 2: Allelic and genotypic frequencies of −511C/T and 86 base pair VNTR polymorphisms of IL-1B and IL-1RN genes in bipolar disorder patients

	Genotypic frequencies			Allelic frequencies	
IL-1B: −511C/T					
N	Allele*1/allele*1	Allele*1/allele*2	Allele*2/allele*2	Allele*1	Allele*2
20	8 (40.0%)	9 (45.0%)	3 (15.0%)	25 (62.5%)	15 (37.5%)
IL-1RN: VNTR					
N	Allele*1/allele*1	Allele*1/allele*2	Allele*2/allele*2	Allele*1	Allele*2
20	10 (50.0%)	10 (50.0%)	0 (0.0%)	30 (75%)	10 (25%)

Table 3: Structural measurements [mean (SD)] expressed as residuals after adjustment (see *Methods*) of all neuroanatomical variables analyzed in bipolar patients with respect to allele*2 carriage. These volumes represent a quantitative measure with respect to the control sample. Statistically significant differences between groups of patients are also indicated

	Noncarriers	Allele*2 carriers
Total GM*	14.64 (24.52)	−10.67 (24.74)
Total WM	−17.23 (18.82)	−22.64 (16.03)
DLPFC GM left*	0.08 (3.89)	−2.20 (2.88)
DLPFC GM right	−0.43 (2.52)	−2.75 (2.88)
Hippocampus left	0.05 (0.29)	−0.16 (0.30)
Hippocampus right	0.00 (0.33)	−0.09 (0.27)
STG GM left	−0.03 (1.09)	−0.31 (0.89)
STG GM right	−0.27 (0.70)	−0.53 (0.33)
Ventricle left	2.21 (6.21)	1.34 (3.17)
Ventricle right	1.56 (5.45)	1.96 (2.93)

*$P < 0.05$ between allele*2 carriers and noncarriers groups.

generalized deficits have been reported in schizophrenia (Gur *et al.* 1999) but not in bipolar disorder.

However, on the light of imaging evidences in bipolar disorder, the authors do not discard the possibility of progressive processes in the origin of these brain differences driven by early developmental and/or neurodegenerative events (Monkul *et al.* 2005). In this vein, recent follow-up studies are starting to show the neurodevelopmental trajectory of these brain abnormalities in bipolar disorder (Gogtay *et al.* 2007). Considering these hypothetic neurodegenerative processes, it should be noted that IL-1 is a key mediator in the brain damage derived from ischemia and there is evidence of this kind of lesion in at least some bipolar patients, mainly of late onset (Berthier *et al.* 1996). Therefore, the authors cannot discard that the role of IL-1 in the risk to develop bipolar disorder might be mediated through these ischemic processes, although the similar age in both groups argues against this possibility.

Likewise, the authors cannot discard (because of the lack of data regarding environmental stressors in these patients) that the effect of IL-1B genetic polymorphism on bipolar disorder is driven by the role of IL-1 as a modulator of hypothalamus–pituitary–adrenal (HPA) axis because (1) this neuroendocrine pathway is a key mediator of environmental stress and (2) this stress is a triggering event of psychotic symptoms in subjects at risk of developing a psychotic disorder (Post & Leverich 2006; Thompson *et al.* 2007).

A major point is the possibility of the effect of lithium treatment on the GM volumes because lithium has been reported to increase GM volumes in prefrontal regions (Monkul *et al.* 2007). Although our results show no significant effect of lithium treatment on GM volumes in those areas, the authors cannot rule out an neuroprotective/osmotic effect that could not be detected because of the low sample size.

There are some methodological limitations that require additional comments. In first place, sample size of this study may generate type II errors that could lead to a lack of power to detect genetic effects on MRI variables. However, our results suggest that −511C/T polymorphism has a strong influence on certain morphological variables. This influence has allowed us to detect this genetic effect in spite of our sample size. Second, it should be noted that statistical significance of our results would not resist a strict multiple comparisons adjustment. However, this correction seems too conservative in the context of our study because (1) selection of genetic polymorphisms, neuroanatomical areas of interest and their analyses has been performed according to a clear directional hypothesis taking into account previous data, (2) analyses include MRI measurements with an important degree of overlap and (3) only two functional polymorphisms of special interest have been chosen for analyses, avoiding a massive genetic screening of both candidate genes.

In conclusion, our results reinforce the interest of IL-1 cluster as a genetic risk factor shared by different nosological entities, confirming previous results obtained in linkage and association studies. It should be noted, however, that these preliminary results need independent replication because of the small sample size included in this study.

Further research on IL-1 family of cytokines (e.g. receptor regulation and biochemical signaling pathways) is required to identify processes filling the gap between genetic variability

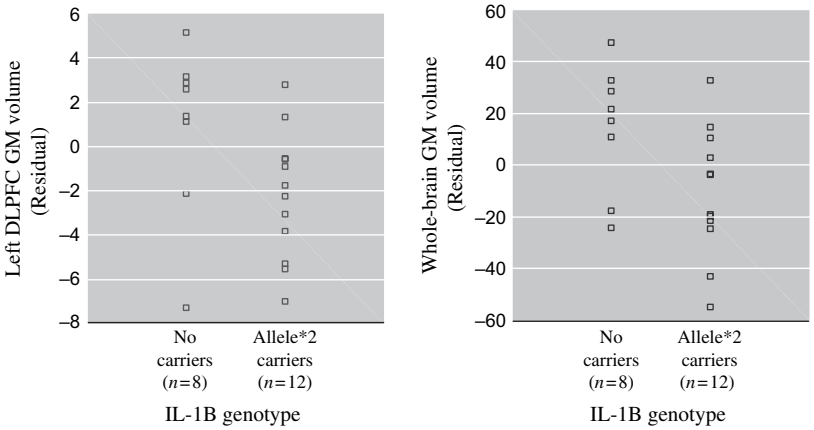

Figure 1: Scatterplot of whole-brain GM and left dorsolateral prefrontal (DLPFC) GM adjusted volumes in bipolar patients. These volumes represent a quantitative measure of GM atrophy (if negative) with respect to a normal sample (see *Methods*). Patients who were allele*2 (−511T) carriers of IL-1B gene polymorphism show a significant decrease in whole-brain GM and left dorsolateral prefrontal GM.

with functional repercussion and brain abnormalities described in functional psychoses. Once these issues were clarified, it would be probably easier to discern some of the elusive mechanisms which link brain structural changes with mental disease symptoms.

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