Gray matter volumes in patients with bipolar disorder and their first-degree relatives

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ABSTRACT

Bipolar disorder (BD) is highly heritable. First-degree relatives of BD patient have an increased risk to develop the disease. We investigated abnormalities in gray matter (GM) volumes in healthy first-degree relatives of BD patients to identify possible brain structural endophenotypes for the disorder. 3D T1-weighted magnetic resonance images were obtained from 25 DSM-IV BD type I patients, 23 unaffected relatives, and 27 healthy controls (HC). A voxel-based morphometry protocol was used to compare differences in GM volumes between groups. BD patients presented reduced GM volumes bilaterally in the thalamus compared with HC. Relatives presented no global or regional GM differences compared with HC. Our negative results do not support the role of GM volume abnormalities as endophenotypes for BD. Thalamic volume abnormalities may be associated the pathophysiology of the disease.

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1. Introduction

Bipolar disorder (BD) is highly heritable (Winokur et al., 1995; McGuffin et al., 2003; Kieseppa et al., 2004). First-degree relatives of BD patients have an approximate 11% risk of developing the disorder compared with 1–3% of the general population (Goodwin and Jamison, 2007). Due to this strong hereditability, first-degree relatives may share genetic underlying influences which can cause brain alterations without the manifestation of the disease. If these alterations are potentially involved in the pathophysiology of the disease, they are called endophenotypes (Gottesman and Gould, 2003; Hasler et al., 2006).

One strategy to identify endophenotypes is to compare BD patients with their relatives and healthy controls. (Brambilla and Tansella, 2009). The aim of this comparisson is to identify biological alterations in nonaffected family members wich are also found in affected members, both at a higher rate than in the general population (Glahn et al., 2014). This design is important to identify brain changes which are a manifestation of the underlying disease liability and separate from those that occur as a consequence of the disease or treatment.

Gray matter (GM) abnormalities, probably associated with the pathophysiology of the disease, have been found in BD patients (Bora et al., 2010). Those findings have stimulated the investigation of GM alterations as endophenotypes in BD. However, the results of the studies in relatives are less consistents and have yielded varying results. They have found, in both patients and relatives, increased volumes of the caudate (Noga et al., 2001; Hajek et al., 2009), left insula (Kempton et al., 2009), and right inferior frontal gyrus (Hajek et al., 2013) and decreased GM volume in the left insula (Matsuo et al., 2012), orbitofrontal cortex and bilateral anterior thalamus (McIntosh et al., 2004). There are also studies which did not find differences between the groups when comparing global, hemispheric, frontal and temporal GM volumes, or subgenual anterior cingulate cortex, amygdala, hippocampus, basal ganglia and pituitary volumes (Noga et al., 2001; Kieseppa et al., 2002, 2003; McDonald et al., 2006; Hajek et al., 2008a, 2008b, 2010; Singh et al., 2008; Takahashi et al., 2010). The significance of these findings is still not clear, mainly because there was no replication among the studies. It is important to notice,

however, that the areas identified have been associated with BD in previous studies.

Thus, the objective of the present study was to further investigate the differences in whole and regional GM volumes among BD patients, their unaffected relatives, and healthy controls (HC) looking for biological alterations that might be identified as endophenotypes. Our hypothesis was that BD patients and their unaffected first-degree relatives would present decreased GM volumes in brain areas pertaining to the anterior limbic network, which is postulated to be disturbed in BD (Strakowski et al., 2012).

2. Patients and methods

2.1. Sample

The sample was comprised of 25 patients with BD, 23 unaffected relatives, and 27 HC. Subjects were recruited from outpatient facilities at the Institute of Psychiatry of the University of Sao Paulo Medical School, or from the community through media advertisements. All subjects gave written informed consent to participate in the study. All the procedures were carried out according to the Declaration of Helsinki and the study was approved by the University of Sao Paulo Medical School Ethics Committee.

Inclusion criteria for patients with BD were a diagnosis of BD type I, according to DSM-IV criteria, age above 18 years old, having at least one first-degree relative older than 18 years old and willing to participate in the study, and being in remission. We defined remission as not meeting criteria for any mood episode in the last 2 months, and presenting Hamilton Depression Rating Scale (HDRS) scores and Young Mania Rating Scale (YMRS) scores below 8 on the day of participation (Tohen et al., 2009). Patients were allowed to be on their current medication. Inclusion criteria for unaffected relatives were being a first-degree relative of the proband, age over 18 years old, and absence of any lifetime Axis I diagnosis. Inclusion criteria for HC were age over 18 years old, absence of any lifetime DSM-IV Axis I diagnosis, and absence of any lifetime DSM-IV Axis I diagnosis among first-degree relatives. Exclusion criteria for all subjects were pregnancy (in female subjects), severe and/or decompensated medical diseases with repercussions in the central nervous system, such as diabetes mellitus, hypertension, or hypothyroidism, and neurological disorders, such as epilepsy or stroke. Additional exclusion criteria for patients with BD were presence of active alcohol/drug use disorders in the last 12 months.

2.2. Psychiatric assessments

We used the Structured Clinical Interview for DSM-IV diagnosis (SCID), versions for patients and non-patients, to confirm the diagnosis of BD type I in patients and to exclude psychiatric diagnosis in unaffected relatives and HC (First et al., 2002). We used the 17-item HDRS (Hamilton, 1976) and the YRMS (Young et al., 1978) to evaluate the presence of depressive and manic symptoms, respectively. Board-certified psychiatrists (FGN, JAA) with extensive research experience in mood disorders administered the SCID, HDRS, and YMRS in all subjects.

2.3. Image acquisition

Imaging data were obtained using a 3T Phillips scanner (Philips Medical Systems, Best, The Netherlands) and an eight-channel head coil. Contiguous sagittal images across the entire brain were acquired using a 3D T1-FFE sequence with the following parameters: TE=3.2 ms, TR=7 ms, flip angle=8°, SENSE=2, acquisition matrix=240 × 240, and voxel size of 1 mm × 1 mm × 1 mm (180 slices).

2.4. Images processing and analysis

The voxel-based morphometry (VBM) analysis was carried out using Statistical Parametric Mapping, version 8 (SPM8; http://www.fil.ion.ucl.ac.uk/spm) running under Matlab r2009b (http://www.mathworks.com/index.html). Briefly, all MRI datasets were first oriented manually to place the anterior commissure at the origin of the three-dimensional Montreal Neurological Institute (MNI) coordinate system. Images were then segmented into gray and white matter partitions using the unified segmentation procedure described in Ashburnerm and Friston (2005). The Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) algorithm (Ashburner, 2007) was then used to spatially normalize the segmented images; this procedure maximizes sensitivity and accuracy of localization by registering individual structural images to an asymmetric custom T1-weighted template derived from the participants' structural images rather than a standard T1-weighted template based on a different sample (Ashburner, 2007). An additional "modulation" step consisted of multiplying each spatially normalized GM image by its relative volume before and after normalization; this ensured that the total amount of GM in each voxel was preserved. Finally, the resulting GM images were smoothed using a 8-mm isotropic kernel at full width half maximum (FWHM) to ensure normal data distribution as required by subsequent parametric tests.

Between-group statistical comparisons of mean GM volumes were performed with the general linear model, based on random Gaussian field theory (Friston et al., 1995). Only voxels with values above an absolute GM threshold of 0.05 entered the analyses, resulting in a search volume of approximately 550,000 voxels. A measure of the total volume of GM of each subject was entered as a covariate in an analysis of covariance. Resulting statistics at each voxel were transformed to Z scores and displayed as SPMs into standard space, at a threshold of $Z=3.09$. Subsequently, the analyses with positive findings were repeated using age and sex as covariates because these variables may affect brain structure (Good et al., 2001; Sowell et al., 2003).

To investigate GM volume differences between groups, three different 2-group comparisons were performed: GM volumes in BD patients versus unaffected relatives, BD patients versus HC, and unaffected relatives versus HC. GM volume differences (increased or decreased) were tested between each group. The voxel-wise set of results for each of the above contrasts constituted an SPM t statistic {SPM (t)} map, using an uncorrected threshold of $p \leq 0.001$. Based on previous literature about GM differences in relatives of BD patients, the following a priori regions of interests (ROIs) were selected for identification of any significant findings on the SPM(t) maps: orbitofrontal cortex, anterior cingulate cortex, amygdala, hippocampus, parahyppocampal gyrus, insula, caudate and thalamus. Such voxel-wise search of each map was performed using the small volume correction (SVC) method with the purpose of constraining the total number of voxels included in the analyses. Each region was circumscribed by merging the spatially normalized ROI masks that are available within the Anatomical Automatic Labeling SPM toolbox. Findings of these hypothesis-driven, SVC-analyses were reported as significant if they survived family-wise error (FWE) correction for multiple comparisons ($p \leq 0.05$), with further criteria for voxel clusters to comprise at least 20 voxels over the respective ROI.

2.5. Statistical analysis

Regarding demographic and clinical data, Chi-square tests were conducted for cross-tabulated qualitative data and analysis of