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Research paper

Subcortical structural volumes in recently remitted first episode mania

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ABSTRACT

Background: Magnetic resonance imaging (MRI) studies have yielded inconsistent findings with regard to subcortical volumetric abnormalities in patients with bipolar I disorder. Duration of illness and long term medication intake could have confounded the findings.

Method: Volumes of nine subcortical structures were compared between 63 patients who recently remitted from their first manic episode and 77 healthy volunteers. The volumetric segmentation was performed with the automated segmentation algorithm Freesurfer version 5.1.

Results: There were no significant volumetric differences between the two groups in any of the structures examined including caudate, putamen, globus pallidum, nucleus accumbens, amygdala, thalamus, cerebellum, hippocampus and lateral ventricles ($q > 0.05$-false discovery rate corrected).

Limitations: All patients were on psychotropic medications at the time of scanning, which might have confounded the results. Sample size may not be large enough to detect small volumetric changes.

Conclusions: Patients with bipolar I disorder do not appear to have any significant subcortical volumetric abnormalities during the early stage of the disease. Thus, early stage bipolar disorder may present an opportunity for intervention to arrest neuroprogression of the disease.

1. Introduction

Structural brain abnormalities in magnetic resonance imaging (MRI) may provide important clues for understanding the pathogenesis of complex neuropsychiatric syndromes like bipolar disorder. Meta-analyses (McDonald et al., 2004; Kempton et al., 2008; Arnone et al., 2009) and mega-analyses (Hallahan et al., 2011; Hibar et al., 2016) of studies comparing the structural MRI of patients with bipolar disorder and healthy controls have consistently reported enlargement of lateral ventricular volumes in patients with bipolar disorders. However, the results with regards to other structures are highly inconsistent, with significant heterogeneity detected in meta-analysis (McDonald et al., 2004). The heterogeneity could be secondary to the variation in sampling and imaging techniques employed in the studies. For example, duration of illness and various medications used for treating bipolar disorder may affect regional brain volumes (Arnone et al., 2009) (Hallahan et al., 2011). Studying patients early in the course of illness would minimize these confounding effects. Further, the structural abnormalities found at disease onset are more likely to be directly related to the pathogenesis of the condition.

There have been attempts to study patients during their first episode of mania, when the diagnosis of bipolar disorder is first established. While earlier imaging studies employed a region of interest (ROI) methodology, recent studies used the more agnostic voxel based morphometry (VBM) to identify structural MRI variations in bipolar disorder. Both methods have their merits and demerits and should be considered complementary to each other (Giuliani et al., 2005). Studies employing VBM in first episode manic patients have shown inconsistent findings with volumetric abnormalities observed in thalamus, basal ganglia (Chen et al., 2012), cerebellum (Watson et al., 2012a), anterior cingulate cortex and other cortical structures (Farrow et al., 2005) (Yatham et al., 2007; Adler et al., 2007). ROI studies have also not been consistent. For example, ROI studies have found increased (Watson et al., 2012b), decreased (Rosso et al., 2007) or no change in amygdala volumes (Bitter et al., 2011) between patients and controls. Most of the studies had a small sample size which might have compromised statistical power to detect meaningful differences.

The objective of the present study, therefore, was to examine the volume of subcortical structures in a large sample of well-characterized bipolar I disorder patients who recently experienced their first manic episode in comparison to matched healthy subjects. We restricted the focus to subcortical structures to limit the number of comparisons. Furthermore, subcortical structures have been frequently found to be affected in first episode manic patients in previous studies and are key

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components of the anterior limbic network which is implicated in the pathogenesis of bipolar disorder (Chen et al., 2012; Adler et al., 2007; Strakowski et al., 2005). Based on previous studies, we hypothesized that patients with bipolar disorder with recent first episode mania would have increased volume of lateral ventricles, amygdala and basal ganglia as well as decreased cerebellar volumes compared to healthy volunteers.

2. Method

2.1. Participants

All subjects provided written informed consent or parental/guardian assent, in accordance with Tri-council policy, as mandated by the UBC Research Ethics Board. Sixty-three subjects who recently remitted from their first manic/mixed episode and 77 healthy volunteers were included in the study. The subjects were recruited as a part of an ongoing longitudinal study (the Systematic Treatment Optimization Program for Early Mania -STOP-EM). The STOP-EM methodology has been described elsewhere (Yatham et al., 2009). Briefly, subjects aged 14–35 years who had experienced their first manic or mixed episode within 3 months prior to recruitment were included. Subjects unable to take part in neuropsychological testing, MRI and those with a previous manic episode were excluded. All the patients received a diagnosis of bipolar I disorder. The diagnosis was made using DSM-IV-TR criteria based on clinical interview and the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). All psychiatric and general medical comorbidities including substance use disorders were permitted to capture the full range of patients seen in clinical practice. Presence of psychotic symptoms was also permitted for the same reason. All patients were assessed with the Young Mania Rating Scale (YMRS), Hamilton Depression Rating Scale (HAM-D), Montgomery–Äsberg Depression Rating Scale (MADRS), Brief Psychiatric Rating Scale (BPRS) and Positive and Negative Syndrome Scale (PANSS) to evaluate the severity of symptoms. Clinical remission was defined with a score of $\leq$ 12 on YMRS and HAM-D.

Forty-seven age and gender matched healthy volunteers were recruited as a part of the STOP-EM program. As the number of patients recruited was greater than that of healthy volunteers, we augmented the healthy sample with the MR images of thirty additional healthy volunteers within the same age range, who were recruited as a part of a first episode psychosis project conducted by two of the authors (DJL, WGH). They were scanned on the same scanner using the same acquisition protocols. All healthy volunteers were also assessed with the MINI to exclude psychiatric disorders.

2.2. MRI acquisition and processing

2.2.1. Scanning

Brain images were acquired for all patients and controls with a Philips Achieva 3.0 T MRI scanner (Amsterdam, The Netherlands) using a three dimensional T-1 weighted axial Turbo Field Echo (TFE) sequence. The MRI was acquired after the patient achieved response or remission from their first manic/mixed episode. The acquisition parameters were as follows: repetition time (TR) = 7.6 ms and echo time (TE) = 3.5 ms, FOV = 256 mm x 200 mm, acquisition matrix = 256 × 200, SENSE factor = 0, isotropic voxels (1 × 1 × 1 mm^3), autoshim, flip angle = 8° and 1 mm thick contiguous 180 slices of the whole brain. The images were obtained with T/R head coil.

2.2.2. Image segmentation

Volumetric segmentation was performed with the automated validated segmentation algorithm Freesurfer version 5.1 (http://surfer.nmr.mgh.harvard.edu/) (Fischl, 2012). The process involves removal of non-brain tissue, Talairach transformation, segmentation of subcortical structures and cortical regions, intensity normalization, tessellation of grey matter/white matter boundary, topology correction and surface deformation. Volume of subcortical regions of interest (ROIs) were measured by automatic whole brain segmentation, where each voxel in the normalized brain volume is assigned one of around 40 labels (http://freesurfer.net/fswiki/SubcorticalSegmentation) (Fischl et al., 2002). Manual quality check of images was conducted with inspection for: motion artifacts, missing brain parts after skull stripping and removal of non-brain tissue, white matter segmentation (adding excluded white matter and removing non-white matter voxels), pial surface and correction of any surface not following the white/grey matter boundary and correction of subcortical segmentation due to enlarged ventricles. Intracranial volume (ICV) and total brain volume were assessed with statistical parametric mapping software (London, UK: Wellcome Department of Imaging Neuroscience Group), with the SPM8-new segment toolbox followed by morphological operations on merged grey matter, white matter and CSF volumes. Intracranial volume is a measure of head size; which can be used as a proxy measure for maximum premorbid brain volume (Malone et al., 2015).

The volumes of the following subcortical structures were extracted and chosen for comparison between patients and healthy controls: thalamus, caudate, putamen pallidum, hippocampus, amygdala, nucleus accumbens. In addition, cerebellar and lateral ventricular volumes were also assessed, as they have been found to be significantly altered in previous studies on patients with bipolar disorder.

2.3. Statistical analysis

All statistical analysis were conducted with the Statistical Package for Social Sciences (SPSS) version 24.0 (SPSS Inc., Chicago, IL). Baseline comparisons were made with $\chi 2$ analysis or *t*-tests as appropriate. Analysis of Covariance (ANCOVA) was used to compare the volume of each subcortical region between subjects and healthy volunteers, with hemisphere as the within-subject factor; group (subjects vs. healthy volunteers) and gender as between subject variable, while age and ICV were entered as covariates. A visual inspection of the normal Q-Q plots of dependent variables revealed that lateral ventricle volumes in both hemispheres were not normally distributed. Hence, they were log-transformed before analysis. As there were nine primary comparisons involved, we corrected for multiple comparisons using the false discovery rate technique at q $\leq$ 0.05 (http://www.sdmproject.com/utilities/?show=FDR) (Benjamini, 2010). This technique allows correction with lesser loss of power compared to the family wise error approach. The significance level (p) for other comparisons was set at $\leq$ 0.05. As lithium intake and presence of previous depressive episodes may act as confounding variables, subgroup analyses were conducted to test the effect of lithium and history of past depressive episodes on the volume of subcortical structures in the bipolar disorder group. ANCOVA was used for these analyses, with the same covariates used as in primary analysis, with correction for multiple comparisons as discussed earlier. To test the effect of duration of affective illness and antipsychotic use, separate ANCOVA analyses were conducted on the bipolar disorder group with duration of illness/antipsychotic use as additional covariate.

3. Results

The baseline characteristics of the sample are as shown in Table 1. The bipolar disorder sample consisted of predominantly young adults [mean age = 22.6 (4.5 years); range −15 to 34], with a near equal gender distribution (percentage of females = 55.6%). Duration of illness at the time of scanning ranged from 0 to 19 years with a mean of 2.9 (4.2) years. Of the 63 patients, 36 (57.1%) had a history of mood episode in the past and 59 (93.65%) were on psychotropic medications at the time of scanning. There were no significant differences between the patients and controls in any of the demographic variables studied.

The bipolar disorder group had lower ICV (p = 0.04) compared to