Brazilian Journal of Psychiatry
BJP
Revista Brasileira de Psiquiatria

BRIEF COMMUNICATION

Smaller left anterior cingulate cortex in non-bipolar relatives of patients with bipolar disorder

Marsal **Sanches**,[1,2] (iD) Edilberto **Amorim**,[3] Benson **Mwangi**,[1] Giovana B. **Zunta-Soares**,[1] Jair C. **Soares**[1]

[1]UT Center of Excellence on Mood Disorders, Department of Psychiatry and Behavioral Sciences, The University of Texas Health Science Center at Houston, Houston, TX, USA. [2]Department of Psychiatry and Behavioral Sciences, University of North Dakota School of Medicine, Bismarck, ND, USA. [3]Massachusetts General Hospital & Brigham and Women's Hospital, Boston, MA, USA.

Objective: Bipolar disorder (BD) is highly heritable. The present study aimed at identifying brain morphometric features that could represent markers of BD vulnerability in non-bipolar relatives of bipolar patients.
Methods: In the present study, structural magnetic resonance imaging brain scans were acquired from a total of 93 subjects, including 31 patients with BD, 31 non-bipolar relatives of BD patients, and 31 healthy controls. Volumetric measurements of the anterior cingulate cortex (ACC), lateral ventricles, amygdala, and hippocampus were completed using the automated software FreeSurfer.
Results: Analysis of covariance (with age, gender, and intracranial volume as covariates) indicated smaller left ACC volumes in unaffected relatives as compared to healthy controls and BD patients ($p = 0.004$ and $p = 0.037$, respectively). No additional statistically significant differences were detected for other brain structures.
Conclusion: Our findings suggest smaller left ACC volume as a viable biomarker candidate for BD.

Keywords: Bipolar disorder; cingulate cortex; magnetic resonance imaging; endophenotypes

Introduction

Bipolar disorder (BD) is highly heritable.[1] The expression of specific susceptibility genes may produce morphological and functional brain abnormalities before the onset of clinically detectable symptoms.[2] Therefore, imaging of brain areas involved in the regulation of emotions in non-bipolar relatives (NB) of bipolar patients may be useful to identify potential biomarkers of increased susceptibility to BD.[3]

The goal of this study was to compare the volumes of key brain regions in BD patients, NB of bipolar patients, and healthy controls (HC) without family history of mental disorder. Since previous neuroimaging findings point to the involvement of the anterior cingulate cortex (ACC) in the pathophysiology of BD,[4] we hypothesized that NB would present a smaller anterior cingulate volumes as compared to HC.

Methods

Participants

The subjects included in this study were recruited from the inpatient and outpatient units of the Department of Psychiatry at the University of Texas Health Science Center at San Antonio (UTHSCSA) and the University of North Carolina at Chapel Hill (UNC), as well as through radio advertisements.

The sample consisted of 31 BD patients (12 males, 19 females, age [mean ± standard deviation] = 34.1± 12.8 years), 31 non-bipolar first-degree relatives of bipolar patients (8 males, 23 females, age = 47.1±10.7 years), and 31 HC (7 males, 24 females, age = 39.5±9.9 years). The three groups were similar with respect to demographic characteristics, except for age, which was higher in NB as compared to BD ($p < 0.001$) and HC ($p = 0.048$). For all groups, the following inclusion criteria were adopted: age ⩾18 years, no family history of hereditary neurological disorder, and absence of current neurological disease or other major medical problems. All subjects meeting DSM-IV criteria for current substance abuse or dependence or who had a positive urine drug screen were excluded.

The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID)[5] was administered to all participants. All patients met DSM-IV criteria for BD (30 patients had BD type I and one patient met criteria for BD type II). As for mood state, 17 BD patients were euthymic, nine were depressed, two were manic, two were hypomanic, and one was in a mixed state. At the time of the MRI scan, only seven patients were receiving treatment with psychotropics: one was on an antidepressant, three on

anticonvulsants, one on an atypical antipsychotic, and two on a combination of lithium, antidepressants, and atypical antipsychotics. However, 28 (90.3%) BD patients had previously used at least one psychotropic medication. NB were characterized as first-degree relatives (parents, siblings, or offspring) of patients with BD who did not meet lifetime DSM-IV criteria for BD or psychotic disorders. However, other axis I disorders were not an exclusion criteria for NB in order to avoid the inclusion of an unusually resilient group of NB. Nine NB met lifetime DSM-IV diagnostic criteria for major depressive disorder, one for alcohol abuse, one for adjustment disorder, and one for anxiety disorder.

This study was approved by the respective Institutional Review Boards. Informed consent was obtained from all participants.

Data acquisition and processing

Magnetic resonance imaging data were collected using similar protocols at UTHSCSA and UNC. However, some technical distinctions should be noted. At UTHSCSA, images were acquired on two different scanners: in the first, a Siemens 3 T Trio scanner, images were acquired using an axial, three-dimensional, T1 weighted MP-RAGE (Magnetization Prepared Rapid Acquisition gradient echo) sequence (repetition time 22 msec; echo time 3 msec; flip angle 13 degrees, slice thickness 0.8 mm); in the second, a Phillips 1.5 T Intera scanner, images were acquired using an axial, three-dimensional, T1 weighted SPGR (spoiled gradient recalled echo) sequence (repetition time 24 msec; echo time 5 msec; flip angle 40 degrees, slice thickness 1 mm). At UNC, images were collected on a Siemens 3 T Allegra scanner using an axial, three-dimensional, T1 weighted MP-RAGE sequence (repetition time 17.5 msec; echo time 4 msec; flip angle 8 degrees, slice thickness 0.8 mm).

The volumes of the ACC, amygdala, hippocampus, and lateral ventricles were obtained using automated parcellation on the FreeSurfer software version 4.5.0.[6] Automatic correction of topological defects was followed by visual inspection and manual correction of inaccurate segmentation for all subjects. The methods used to obtain the volumetric measurements have been described in detail elsewhere.[6]

Statistical analysis

Data analyses were performed using SPSS version 19. The groups were compared regarding age, and years of formal education using analysis of variance, and regarding sex, race/ethnic group, study center, and scanner using exact chi-square tests. Regional brain volume data were analyzed using mixed model analysis of covariance. All these models included group (HC, BD patients, and NB) and scanner (1.5T San Antonio, 3T San Antonio, 3T Chapel Hill) as fixed factors, and subject, age, sex, and total intracranial volume as fixed covariates. ACC volume comprised the a priori variable of primary interest. Pairwise contrasts between adjusted group means were tested with the Dunn-Sidak procedure on an a priori basis to limit Type I errors, and adjusted p-values are reported.

Results

Consistent with our specific hypothesis, left ACC volumes were smaller in NB compared to HC (Sidak, p = 0.004). The same was noted for the comparison between NB and BD, with smaller left ACC volumes in NB (Sidak, p = 0.037). No significant difference was found between HC and BD patients. Volumetric analysis of the right ACC, hippocampus, amygdala, and lateral ventricles failed to detect differences between the BD, NB, and HC groups. The mean non-adjusted region of interest (ROI) volumes and standard deviations for all groups are presented in Table 1.

Discussion

The concept of endophenotype presumes the occurrence of certain biological and behavioral markers not only in patients affected by the disease in question, but also in unaffected individuals at high genetic risk for the same condition.[2] Our analysis showed smaller left ACC volumes in NB compared to HC and BD patients. No significant volume differences were detected in right ACC, hippocampus, amygdala, or lateral ventricles.

Involvement of the ACC in the pathogenesis of BD has received considerable attention.[7] For example, ACC volume and activity have been previously described as being decreased in BD.[4,8] Moreover, postmortem studies

Table 1 Anatomical volumes (mm^3) of selected structures in BD, NB, and HC

Structure	HC (n=31)	BD patients (n=31)	NB (n=31)
Left anterior cingulate	4,172±122	4,123±162	3,551±145*
Right anterior cingulate	4,130±138	3,719±183	3,986±163
Left amygdala	1,505±28	1,550±37	1,493±33
Right amygdala	1,601±29	1,640±38	1,571±34
Left hippocampus	4,125±59	4,155±78	4,053±70
Right hippocampus	4,186±61	4,181±80	4,140±72
Left lateral ventricle	7,403±742	8,676±981	6,253±878
Right lateral ventricle	7,763±826	8,686±1,094	6,035±978

BD = participants with bipolar disorder; HC = healthy controls; NB = non-bipolar relatives of BD.
* Significant differences were observed between HC and NB (Sidak, p = 0.004) and between BD and NB (Sidak, p = 0.037). No significant differences were found across groups with regard to the other structures analyzed.

point to the presence of cytoarchitectural abnormalities in this area, including reduction in glial number.[9]

In contrast, few studies have specifically assessed ACC morphometry in NB, with inconsistent findings. One group demonstrated associations between high genetic risk for BD and decreased right ACC volumes, but no association was found with regard to left ACC.[2] Another group examined the subgenual cingulate cortex among unaffected and affected offspring of BD patients, as well as sporadic BD patients and HC, and failed to demonstrate any differences across groups.[10,11] Regarding other brain structures, an isolated finding of smaller right hippocampus among affected versus unaffected twins discordant for the diagnosis of BD has been described,[12] but several studies failed to identify significant differences between unaffected relatives of BD patients and healthy controls with respect to the amygdala, hippocampus, and lateral ventricles (for a review, see Nery et al).[3]

Our findings must be interpreted with caution. Even though we found smaller left ACC volumes among NB compared to HC, no differences were found between bipolar patients and HC. This finding could challenge decreased ACC volume as an endophenotypic trait of BD. However, medication effects might have contributed to this lack of difference. Most of our BD patients reported a history of treatment with mood stabilizers, which have well-demonstrated neuroprotective properties and may, therefore, cause increases in gray matter volumes.[13] Furthermore, the lack of morphometric differences in the amygdala and hippocampus of BD participants is partially supported by previous literature findings, which describe smaller, normal, or increased amygdala volumes, as well as normal or smaller hippocampal volumes, in patients with BD.[14]

Our study has some methodological limitations that must be acknowledged. The small sample size may have led to type II errors, which could explain the inability to determine significant differences regarding the right ACC and other brain regions in NB. In addition, the fact that we analyzed a heterogeneous group of patients, with different medication histories, may have neutralized some of the putative findings among bipolar patients. Moreover, there were age differences, with NB participants displaying higher mean age than the other two groups, and the brain scans were obtained in two different centers. However, the inclusion of these potential confounders in the statistical analysis did not suggest that these factors impacted our results. Furthermore, the fact that some of the NB also met criteria for lifetime unipolar depression must be taken into consideration, since depression may represent the initial presentation of BD. Nevertheless, only one of these subjects was within the high-risk age range to develop BD (15-40 years old).

In summary, our results suggest that smaller left ACC volumes may represent an endophenotypic trait of BD. These findings provide insight for future studies on genetic liability for BD and the expression of brain imaging biomarkers. Further research focused on identifying underlying neural mechanisms responsible for psychosis, clinical expression, and their interaction with genetic factors are critical to support advances in disease prevention and development of new therapies.

Acknowledgements

Disclosure

References

1 Craddock N, Sklar P. Genetics of bipolar disorder. Lancet. 2013;381: 1654-62.

2 McDonald C, Bullmore ET, Sham PC, Chitnis X, Wickham H, Bramon E, et al. Association of genetic risks for schizophrenia and bipolar disorder with specific and generic brain structural endophenotypes. Arch Gen Psychiatry. 2004;61:974-84.

3 Nery FG, Monkul ES, Lafer B. Gray matter abnormalities as brain structural vulnerability factors for bipolar disorder: a review of neuroimaging studies of individuals at high genetic risk for bipolar disorder. Aust N Z J Psychiatry. 2013;47:1124-35.

4 Kaur S, Sassi RB, Axelson D, Nicoletti M, Brambilla P, Monkul ES, et al. Cingulate cortex anatomical abnormalities in children and adolescents with bipolar disorder. Am J Psychiatry. 2005;162:1637-43.

5 First MB, Spitzer RL, Gibbon M, Janet W. Structured clinical interview for DSM-IV axis I disorders--non-patient edition, version 2.0 [Internet]. 1996 [cited 2018 Sep 14]. eprovide.mapi-trust.org/instruments/structured-clinical-interview-for-dsm-iv-axis-i-disorders

6 Fischl B. FreeSurfer. Neuroimage. 2012;62:774-81.

7 Fountoulakis KN, Giannakopoulos P, Kövari E, Bouras C. Assessing the role of cingulate cortex in bipolar disorder: neuropathological, structural and functional imaging data. Brain Res Rev. 2008;59:9-21.

8 Shah MP, Wang F, Kalmar JH, Chepenik LG, Tie K, Pittman B, et al. Role of variation in the serotonin transporter protein gene (SLC6A4) in trait disturbances in the ventral anterior cingulate in bipolar disorder. Neuropsychopharmacology. 2009;34:1301-10.

9 Ongur D, Drevets WC, Price JL. Glial reduction in the subgenual prefrontal cortex in mood disorders. Proc Natl Acad Sci USA. 1998;95: 13290-5.

10 Hajek T, Gunde E, Bernier D, Slaney C, Propper L, Grof P, et al. Subgenual cingulate volumes in affected and unaffected offspring of bipolar parents. J Affect Disord. 2008;108:263-9.

11 Hajek T, Novak T, Kopecek M, Gunde E, Alda M, Höschl C. Subgenual cingulate volumes in offspring of bipolar parents and in sporadic bipolar patients. Eur Arch Psychiatry Clin Neurosci. 2010;260: 297-304.

12 Noga JT, Vladar K, Torrey EF. A volumetric magnetic resonance imaging study of monozygotic twins discordant for bipolar disorder. Psychiatry Res. 2001;106:25-34.

13 Machado-Vieira R, Andreazza AC, Viale CI, Zanatto V, Cereser V Jr, da Silva Vargas R, et al. Oxidative stress parameters in unmedicated and treated bipolar subjects during initial manic episode: a possible role for lithium antioxidant effects. Neurosci Lett. 2007;421:33-6.

14 DelBello MP, Zimmerman ME, Mills NP, Getz GE, Strakowski SM. Magnetic resonance imaging analysis of amygdala and other subcortical brain regions in adolescents with bipolar disorder. Bipolar Disord. 2004;6:43-52.