Prefrontal gray matter volume in adults bipolar I outpatients is associated with history of suicide attempts?

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Received: 07/06/2020– **Accepted:** 03-09-2020

DOI: 10.15761/0101-60830000000260

Abstract

Background: Patients with Bipolar Disorder (BD) have the highest lifetime risk for suicidal behavior (SB) compared to other psychiatric disorders. Neuroimaging research provides evidence of some structural and functional abnormalities in the brain of BD suicide attempters (SA), but interpretation of these findings may represent a number of features.
Objective: The purpose of this study was to evaluate the volume of the prefrontal cortex in euthymic BD type I outpatients, with and without history of SA.
Methods: 36 euthymic BD I outpatients (18 with and 18 without suicide attempt history) were underwent structural MRI and total and regional gray matter volumes were assessed and compared with 22 healthy controls (HC).
Results: We did not found any differences in all areas between suicidal and non-suicidal BD I patients and BD patients as a group compared to HC as well.
Discussion: our findings suggest that can be a different subgroups of patients in relation to prefrontal cortex volumes according to some clinical and socio-demographic caractheristics, such as number of previous episodes and continuous use of medical psychotropic drugs that may induce neuroplasticity phenomena, which restore cerebral volume and possibly can lead to long-term euthymia state.

Keywords: Schizophrenia; pragmatic language, metaphor.

Rocha M et al. / Arch Clin Psychiatry. 2020;47(6):187-191

Introduction

Patients with Bipolar Disorder (BD) have the highest lifetime risk for suicidal behavior (SB) compared to other psychiatric disorders[1]. In fact, the prevalence of suicide attempt (SA) in BD I is 29,9%[2], and suicides about 13%[3]. The prevention of suicide poses some clinical challenges: SB remains difficult to predict, just as its management and treatment. The current suicide risk assessment is based on a number of socio-demographic and clinical risk factors[4], but we do not have biomarkers in order to anticipate suicidality and guide a more adequate treatment in BD and others psychiatric disorders.

In this sense, brain imaging is a promising tool for the identification of cortical and subcortical areas of the brain potentially involved in suicidality. Some neuroimaging studies have focused on the orbitofrontal cortex (OFC). In fact, the OFC mediate the individual's affect, impulse control, and recognition of reinforcing stimuli and has strong structural and functional connections to several regions including the dorsolateral prefrontal cortex (DLPFC), amygdala, and hippocampus. Besides, some authors have demonstrated an association between OFC dysfunction, decision-making impairment and SB[5]. Really, the OFC is a crucial region involved in impulsive behavior, and impulsivity has also found to

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be a nuclear and measurable feature of BD phenomenology, which can also play a role in SB[1]. Studies shows that reduction in this area is associated with a history of SA in youth with BD[6-8], but in adults the researchers are scarce and with different methotologies[9-11].

So, the purpose of this study was to assessed the volume of prefrontal cortex in euthymic BD I outpatients, with and without history of SA.

Methods

This study is part of a larger project of evaluation and treatment of patients with BD (all using lithium) followed at the research Center in Salvador-Bahia-Brazil (Mood and Anxiety Program) –CETHA-, of the Federal University of Bahia- in which data is continuously collected. Patients were recruited from this Center and were interviewed using the Structured Clinical Interview with the DSM-IV axis I (SCID-I)[12], the Hamilton Depression Rating Scale (HDRS)[13], the Young Mania Rating Scale (YMRS)[14], and the Barratt Impulsiveness Scale (BIS-11)[15]. The BIS is a self-report questionnaire composed of 30 items with Likert-type questions, rated from 1 (rarely/never) to 4 (almost always/always). Scoring yields a total score and 3 subscale scores derived by factor analysis: attention, motor and non-planning. Score varies from 30 to 120 and there is no established cut-off point[15]. The BIS differs from performance-based or cognitive measures of impulsivity as scores reflect self-rated behaviors rather than discrete cognitive processes and thus may be closer to psychiatric symptomatology[15]. The euthymia criteria were scores for both the YMRS and HDRS below 7 points, and no recurrences of affective phases for at least two months, state of recovery[13,14].

Demographic and clinical data were gathered through a questionnaire, and all assessment instruments were administered by two trained experts in psychiatry. Patients were classified as having a history of SA if they reported one or more self-injurious acts committed with intent to die.

Recruitment of 22 HC was from patients social network and they were interviewed using the same evaluation instruments. The choice of these controls as a group was to try to prevent bias associated with differences in socio-demographic data between groups. None of these subjects had a current or past Axis I DSM-IV psychiatric disorder or a first-degree relative with an Axis I psychiatric disorder.

Exclusion criteria of all subjects were: age less than 18 and more than 60 years, current serious medical conditions, history of head trauma and neurological disorders or substance abuse at any time, and serious medical problems in the preceding six months.

Structural Magnetic Resonance Imaging procedure

All MRI scans were acquired at the Image Memorial Clinic–Medicina Diagnóstica-Bahia-Brazil, using a 1.5-T Symphony Master/Class Siemens scanner (Ellagen, Germany) and conducted and interpreted in a blind manner by one research assistant (GLR), trained in neuroradiology. Structural MRI images were acquired using a sagittal T1 acquisition series (TR = 9.8 ms, TE = 3.1 ms, flip angle = 30°, NEX = 1, matrix size = 256 × 256, FOV = 24 cm, thickness = 1.0 mm), yielding 160 slices. MRI images were processed using an automated, non-biased, atlas-based Bayesian segmentation procedure, which was applied using the Freesurfer software suite to derive quantitative brain structure estimates and label cortical and subcortical tissue classes.

The Freesurfer image analysis suite (version 5.0, http://surfer.nmr.mgh.harvard.edu) surface-based processing pipeline was used to derive measures of volume. Freesurfer processing for volumetric T1-weighted images included the following: motion correction; brain extraction and removal of non-brain tissue using a hybrid watershed and surface deformation procedure; automated spatial transformation and white-matter (WM) segmentation of subcortical volumetric structures; intensity normalization, tessellation of grey-matter (GM)/WM boundaries, and automated topology correction; and surface deformation following intensity gradients to optimally place GM/WM and GM/cerebrospinal-fluid (CSF) borders where the greatest intensity shift defines the transition to the other tissue class. Image outputs from each stage of Freesurfer processing were visually inspected and edited by an experienced imaging analyst. Volume was then calculated as the product of the surface area and cortical thickness for each region. Intracranial volume was calculated by determining the sum of all volumes and CSF. To account for inter-individual differences in head size, intracranial and cerebral volumes were corrected by dividing by each subject's intracranial volume and multiplying this ratio by 1000). Left and right hemispheres were assessed for cortical structures as follows: caudal middle frontal, rostral middle frontal, frontal pole, superior frontal, lateral orbitofrontal, medial orbitofrontal, pars opercularis, pars triangularis, and pars orbitalis.

The study was approved by the local Medical Review Ethics Committee and was performed in accordance with the ethical standards of the Declaration of Helsinki. All patients had provided written informed consent prior to their inclusion in the study.

Statistical Analysis

Data were analyzed with Software Statistical Package for Social Sciences (SPSS for Windows, version 17.0). All socio-demographic variables were analyzed by a chi-squared test, Student's T-test or a univariate analysis of variance, as appropriate.

Two analysis were proceeded. The first, Analysis of Variance (ANOVA) assessed the differences in three groups (subjects with BD and SA, BD without SA, and HC), related to the following dependent variables: age of onset, type of first episode, length of illness, history of psychiatric hospitalizations, number of psychiatric hospitalizations, lifetime psychoses, and family history of suicide or SA, symptoms of impulsivity (measured by BIS scale), partial frontal volumes. The second used the T-test to assess the differences between subjects with BD and controls in terms of socio-demographic characteristics. Bonferroni method was used in the two steps to corrected multiple comparisons. Adopted statistical significant level was 0.05.

Results

Our study included 40 patients with BD type I, 19 with history, 21 without history of SA and 22 HC. There were no significant differences between suicidal and non-suicidal bipolar patients and HC with respect to age, gender and years of education ($p > 0.5$). There were also no significant differences between group of patients for age of onset, type of first episode, length of illness, history of psychiatric hospitalizations, number of psychiatric hospitalizations, lifetime psychoses, and family history of SB. All BD patients were on medication, mostly lithium. However, the suicidal group had significantly more psychiatric comorbidities, than non-suicidal ($p = 0.03$) (Table 1).

Comparing BD patients as a whole with controls, the ANOVA with post-hoc analysis (Bonferroni correction) revealed that the differences were significant in BIS total ($F = 4.58$, $p = 0.01$); BIS attentional ($F = 7.75$, $p = 0.001$), and BIS non-planning ($F = 4.44$, $p = 0.02$). The BIS motor were not significant ($F = 1.31$; $p = 0.28$). For more details, see clinical and demographic data described in a previous article published by our group[16].

We did not found any differences in all areas of the frontal cortex between suicidal and non-suicidal BD patients or BD I patients as a group compared to HC ($p > 0.05$) (Table 2).

Discussion

Neuroimaging studies that investigated patients with BD and SB are scarce in the literature and they are methodologically heterogeneous; consequently, their results are inconclusive. To our knowledge this is the first study that evaluated all areas of COF in adults BD-I outpatients in a euthymic phase. We founded no differences in GM prefrontal volumes between BD suicidal and non-suicidal attempters and BD patients groups and HC did not also statistically differ on GM prefrontal volumes, as well. At present, the relationship between the OFC and SB is still unclear. One study that evaluated HC compared to depressed BD-I, BD-II, or BD-not otherwise specified (NOS) youth patients with and without a history of SA, showed that HC and BD non-attempters had significantly greater OFC cortical thickness than BD attempters, suggesting that in youth the reduced OFC can be an important factor associated to SB. Additionally, there was a negative correlation between left lateral OFC volumes and lethality and severity of the SB, which can suggest that changes of the OFC volume can be also a marker of severity of this behavior[6].

Unlike ours, another study that assessed the sample of only adults women BD-I and BD-II with and without SB in a non euthymic phase 24 depression, 1 in mania, 10 in mixed state)showed that within-patients with an SA history, those with past psychiatric hospitalization had similar prefrontal gray matter volumes compared to those without past psychiatric hospitalization. However, within-patients without an SA history, those with past psychiatric hospitalization had increased volumes compared with those with no past psychiatric hospitalization. In this way, methodological differences can explain the different results[10].

An alternative explanation for our findings is due to the fact that most of patients of our sample were receiving lithium, what can explain, in part, our results. As we described in a previous article published by our group, in this sample, 75% of the patients (attempters and non-attempters) were using lithium alone or combined with atypical antipsychotics; 25% were receiving anticonvulsant combined or not with atypical antipsychotics. In this sense, we hypothesized that there are neuroprotective and neurotrophic effects induced by chronic use of medication which

Table 1. Demographic and clinical data of the participants

	BD I patients		Healthy controls	Statistics
	Suicidal (n=19)	Non-suicidal (n=21)	(n=22)	
Gender (n)				
male	6	5	10	x2 = 2.31, p = 0.31
female	13	16	12	
Age, mean ± SD (years)	39.8 ± 11.4	42.0 ± 8.6	37.7 ± 13.5	F = 0.75, p = 0.47
Educational level, mean ± SD (years)	12.0 ± 3.0	11.2 ± 3.7	11.2 ± 2.7	F = 0.37, p = 0.69
Age of onset, mean ± SD (years)	24.3 ± 9.0	25.3 ± 9.4	NA	t = 0.34, p = 0.73
Lenght of illness, mean ± SD (years)	15.6 ± 7.2	16.5 ± 10.7	NA	t = 0.31, p = 0.75
Hospitalizations (n)				
yes	13	18	NA	x2 = 1.71, p = 0.26
no	6	3	NA	
Number of hospitalizations, mean ± SD	6.0 ± 5.8	3.1 ± 2.8	NA	t = -1.80, p = 0.08
Type of first episode				
Depression	11	10	NA	x2 = 1.84, p = 0.39
Mania	7	11	NA	
unknown	1	0	NA	
Lifetime psychoses (n)				
yes	15	9	NA	x2 = 2.77, p = 0.96
no	4	11	NA	
Family history of suicide (n)				
yes	6	4	NA	x2 = 0.83, p = 0.47
no	13	17	NA	
Family history of attempt suicide (n)				
yes	2	4	NA	x2 = 0.56, p = 0.66
no	17	17	NA	
Psychiatric comorbidities (n)				
yes	10	4	NA	x2 = 4,51, p = 0.03*
no	9	16	NA	
BIS total score, mean ± SD	67.3 ± 14.8	58.3 ± 8.6	58.5 ± 9.0	F = 4.58, p = 0.01*
Atenttion score, mean ± SD	20.5 ± 3.9	16.6 ± 2.5	17.5 ± 3.4	F = 7.75, p = 0.001**
Motor score, mean ± SD	20.4 ± 6.0	19.5 ± 4.9	17.9 ± 4.0	F = 1.31, p = 0.28
Non-planning score, mean ± SD	26.4 ± 6.2	22.1 ± 4.9	23.1 ± 4.4	F = 4.44, p = 0.02*

* Significant at the 0.05 level (2-tailed)
**Significante at the 0.001 level (2-tailed)
NA- no applicable

Table 2. Frontal gray matter volumes among bipolar patients with and without suicide attempt and healthy controls

Regions	Hemisphere	BD I patients		HC n=21 mean (SD)	Statistics
		Suicidal n=18 mean (SD)	Non-suicidal n=18 mean (SD)		
Lateral Orbital	left	1773.177 ± 198.798	1830.184 ± 179.221	1764.656 ± 290.431	$F = 0.441$, $p = 0.646$
	right	1792.895 ± 186.368	1795.057 ± 154.810	1775.739 ± 239.982	$F = 0.056$, $p = 0.946$
Medial Orbital	left	1321.323 ± 138.146	1357.651 ± 103.390	1252.792 ± 209.123	$F = 2.181$, $p = 0.123$
	right	1282.192 ± 95.447	1240.378 ± 116.646	1198.792 ± 184.781	$F = 1.706$, $p = 0.191$
Pars Opercularis	left	1116.263 ± 164.815	1137.578 ± 186.097	1102.923 ± 209.134	$F = 0.164$, $p = 0.849$
	right	928.037 ± 189.881	1016.308 ± 237.881	876.612 ± 133.703	$F = 2.672$, $p = 0.078$
Pars Triangularis	left	917.393 ± 111.918	883.221 ± 135.215	850.608 ± 185.382	$F = 0.965$, $p = 0.388$
	right	1051.638 ± 117.252	1063.789 ± 154.113	1003.259 ± 199.853	$F = 0.764$, $p = 0.471$
Pars Orbitalis	left	432.200 ± 49.272	416.700 ± 36.288	422.319 ± 68.758	$F = 0.379$, $p = 0.686$
	right	568.452 ± 80.557	529.267 ± 59.550	533.883 ± 90.066	$F = 1.362$, $p = 0.265$
Caudal Middle	left	1672.338 ± 300.132	1607.750 ± 288.390	1557.244 ± 327.042	$F = 0.682$, $p = 0.510$
	right	1470.200 ± 238.961	1403.058 ± 228.389	1533.415 ± 366.546	$F = 0.979$, $p = 0.382$
Rostral Middle	left	3928.400 ± 466.305	4096.533 ± 286.101	3923.610 ± 561.208	$F = 0.852$, $p = 0.432$
	right	4080.483 ± 424.197	4216.198 ± 271.471	4007.973 ± 552.234	$F = 1.108$, $p = 0.338$
Superior	left	5007.972 ± 398.830	5059.074 ± 509.543	4867.605 ± 659.795	$F = 0.663$, $p = 0.519$
	right	4773.080 ± 485.354	4937.547 ± 485.795	4738.626 ± 663.231	$F = 0.681$, $p = 0.510$
Pole	left	138.186 ± 28.258	144.298 ± 12.715	133.682 ± 21.508	$F = 1.155$, $p = 0.323$
	right	192.910 ± 36.843	187.269 ± 42.376	173.420 ± 36.93	$F = 1.326$, $p = 0.274$

Corrected significant level = $p < 0.0001$
BD: bipolar disorder
HC: healthy controls

implies in longer state of euthymia and restoration of the GM in specific brain regions as consequences. Besides, a systematic review with meta-analysis showed that the global volume of gray matter was significantly higher in bipolar patients treated with lithium compared to lithium-free patients, reinforcing their likely role as a neuroprotective[17].

The positive effects of psychopharmacologic treatment on neural plasticity in BD patients was also suggested from functional and structural neuroimaging studies: for instance, in a previous paper, our group assessed this same sample of euthymic BD I patients and showed normal metabolic profile in prefrontal cortex[18] and some studies have shown an increase in gray matter volume in whole brain of BD patients treated with lithium[19], and untreated patients showed decreased left anterior cingulate volumes compared to either HC or lithium-treated patients[20].

In this context, Benedetti and colleagues evaluated BD patients with and without history of SA, with both the groups currently in depression. These authors founded an association between SA and reduced GM in several brain areas, included the DLPFC, the OFC, the anterior cingulate cortex and the superior temporal cortex; besides, they showed that long term lithium treatment was associated with increased GM volumes in the same areas where suicide was associated with decreased GM[9]. This study examined only BD patients in depression, which could lead to differences in GM prefrontal volume between attempters and non-attempters; in addition, they had no healthy group for comparison, but their findings suggest that lithium treatment may beneficially act on regional GM volumes in suicidal BD patients, increasing the volume. The properties of lithium and probably other mood stabilizers to suppress cell death, attenuate neuroinflammation, and promote angiogenesis and cellular plasticity in BD patients were discussed in a review[21-23].

Our current findings must be considered in light of the study's limitations. Our sample included a relatively small number of patients, which leads to limitations in statistical power and preclude to categorize according to frequency or lethality risk of SB; others characteristics related to SB were not explored, such as cluster B personality disorders or aggressiveness; in addition, we cannot precisely determine the time of use of lithium and others mood stabilizers along the time; it was not possible to determine the lag time between suicide attempt and neuroimaging procedure as well.

However, one of the strengths of our study is that its sample consisted of well-characterized euthymic adults BD I outpatients, with strict criteria for defining euthymia without neurologic problems or other severe current medical comorbidities, with low rates of psychiatric disorders, which may result in a homogenous sample of BD patients by minimizing the confounding effects of these variables.

In conclusion, we founded no significante differentes in prefrontal cortical volume in long-term pharmacologically treated BD I outpatients, with and without SA, compared to HC. This data suggest neurotrophic and neuroplastic protective effects of long-term treatment.

Acknowledgements

The authors would like to thank all of the individuals who agreed to be included in this study for their cooperation and resilience in completing the assessments. We also thank the professionals at Image Memorial for their technical assistance. Future studies, with larger samples and monitoring with different medications and other neuroimaging methods (such as functional neuroimaging), may elucidate this hypothesis.

Disclosures

This project has been supported in part by the Mood and Anxiety Disorders Program (CETHA), Salvador, Bahia, Brazil, and by National Council of Technology and Scientific Development (CNPq), registered as no. 480918/2007-4. CNPq had no further role in the study design; in the collection, analysis and interpretation of the data; in the writing of the report; or in the decision to submit the paper for publication.

Contributors

Dr. Marlos Vasconcelos Rocha and Dr. Fabiana Nery-Fernandes contributed equally to this research. Dr. Marlos Vasconcelos Rocha and Dr. Cássio Silveira de Jesús were responsibles for preparing the manuscript. Dr. Leonardo Baldaçara was responsible for the statistics. Dr. Andrea Parolin Jackowski and Dr. Giovanna Ladeia-Rocha were responsible for the neuroimaging procedures. Dr. Lucas de Castro Quarantini, Dr. César de Araujo Neto, , Dr. Irismar Reis de Oliveira, Dr. André Caribé, Dr. Ângela Miranda-Scippa contributed with suggestions and revision of this paper.

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