White matter volume is decreased in bipolar disorder at early and late stages

O volume da substância branca está reduzido tanto nos estágios iniciais quanto nos estágios avançados do transtorno bipolar

Juliana A. Duarte,1,2,3 Raffael Massuda,3,4 Pedro D. Goi,3 Mireia Vianna-Sulzbach,3 Rafael Colombo,3,4,5 Flavio Kapczinski,3 Clarissa S. Gama3

Abstract

Introduction: Bipolar disorder (BD) is a debilitating mood condition that affects approximately 1.3% of people worldwide, although some studies report up to 3.9% lifetime prevalence and 4-6% in adults when broad diagnostic criteria are applied.

Objective: To compare differences in total white matter (WM), corpus callosum (CC) and total gray matter (GM) volumes in patients with type I BD at early and late stages compared with controls.

Methods: Fifty-five subjects were enrolled in this study protocol. The double case-control design included 14 patients with BD at early stage; 15 patients at late stage; and their respective matched controls (14 and 12 subjects).

Results: CC and total WM volumes were significantly smaller in patients with BD at early and late stages vs. controls. There was no difference for total GM volume in the early stage group, but in patients at late stage total GM volume was significantly smaller than in controls. The total GM reduction in patients at late stage is in agreement with the neuroprogression theory of BD. The reduction of WM volumes in total WM and in the CC at early and late stages supports the possibility that an early demyelination process could occur underlying the clinical manifestation of BD.

Conclusion: Our findings may direct to the investigation of WM abnormalities in populations at high risk to develop BD, perhaps as early biomarkers before the overt syndrome.

Keywords: Bipolar disorder, magnetic resonance imaging, affective disorders, staging, biomarkers.

Introdução: O transtorno do humor bipolar (THB) é uma condição debilitante que afeta aproximadamente 1,3% das pessoas em todo o mundo, embora alguns estudos relatem uma prevalência acumulada de até 3,9% e de 4-6% em adultos quando os critérios diagnósticos mais abrangentes são aplicados.

Objetivo: Comparar as diferenças nos volumes totais de substância branca (SB), corpo caloso (CC) e volume total de substância cinzenta (SC) em pacientes com THB tipo I em estágios iniciais e tardios em comparação com controles.

Métodos: Cincuenta e cinco sujeitos foram incluídos neste protocolo de estudo. O desenho de caso com duplo controle incluiu 14 pacientes com BD em estágio inicial; 15 pacientes com THB em fase tardia; e seus respectivos controles correspondentes (14 e 12 sujeitos).

Resultados: Os volumes do CC e total de SB foram significativamente menores nos pacientes com BD nos estágios iniciais e tardios vs. controles. Não houve diferença para o volume total de SC no grupo em estágio inicial, mas em pacientes em fase tardia o volume total de SC foi significativamente menor do que nos controles. A redução do volume total de SC em pacientes em fase tardia está de acordo com a teoria da neuroprogressão do THB. A redução dos volumes de SB em SB total e no CC em fases precoces e tardias suporta a possibilidade de que um processo de desmielinização precoce poderia ocorrer subjacente à manifestação clínica de THB.

Conclusão: Nossos achados podem direcionar a investigação de anormalidades da SB em populações de alto risco para o desenvolvimento de THB, talvez como biomarcadores precoces antes da síndrome aberta.

Descritores: Transtorno humor bipolar, ressonância magnética, transtornos afetivos, estadiamento, biomarcadores.
Introduction

Bipolar disorder (BD) is a debilitating mood condition that affects approximately 1.3% of people worldwide, although some studies report up to 3.9% lifetime prevalence and 4-6% in adults when broad diagnostic criteria are applied. Recurrent episodes influence the outcome of BD by increasing a patient’s vulnerability to subsequent episodes and reducing treatment response. An episode-dependent deterioration pattern has been widely described in serum biomarkers, brain imaging and functioning.

Alterations in brain structures have been widely reported in BD, including enlargement of the third and lateral ventricles and reduction in the gray matter (GM) volumes of the orbital and medial prefrontal cortex, ventral striatum and mesotemporal cortex. White matter (WM) assessment through structural volumetric imaging has provided evidence of subtle abnormalities in patients with BD compared to healthy volunteers.

The most-studied WM sub-region in BD is the corpus callosum (CC), the largest WM tract that connects the two hemispheres of the brain. Several studies have found that the CC is smaller in patients with BD. One of them has shown a decrease in volume of the posterior CC in late stage BD, but not in early stage.

These network alterations have been associated with cognitive symptoms of BD, suggesting that WM alterations may occur as an early neuropsychological process underpinning the overt cognitive decline. In summary, it is not clear whether WM alterations appear early in the course of BD or present an episode-dependent reduction like GM.

The aim of the present study was to compare differences in total WM, CC and total GM volumes in patients with type 1 BD at early and late stages compared with healthy controls.

Methods

Fifty-five subjects were enrolled in this study protocol: 29 patients and 26 controls matched for age, gender, education and body mass index (BMI). The double case-control design included 14 patients with BD at early stage (individuals who exhibit the same status in the interepisodic period as they did before the onset of BD); 15 patients with BD at late stage (individuals who are unable to maintain personal self-care and to live autonomously); and their respective matched controls (14 and 12 subjects). Patients at early stage had to present a score <36 on the Functioning Assessment Short Test (FAST), and those at late stage a score ≥36. The definition of staging was in accordance with the BD staging model described elsewhere.

All subjects were required to be at least 18 years old and no older than 60. Written informed consent was obtained from all subjects in accordance with the Declaration of Helsinki. The local ethics committee approved the study protocol.

Inclusion criteria for patients were: a) fulfilling Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for BD I; b) meeting remission criteria defined as a score <7 on the 17-item Hamilton-Depression Scale (HAM-D) and on the Young Mania Rating Scale (YMRS), for at least one month previous to the assessment. All patients received pharmacological treatment by their psychiatrist according to clinical protocols. Patients with severe clinical illnesses detected during clinical interviews or during review of medical records were excluded.

The control group consisted of healthy volunteers who had neither current or previous history nor first-degree family history of a major psychiatric disorder, including dementia or mental retardation assessed by the non-patient version of the Structured Clinical Interview for DSM-IV (SCID).

SCID Axis I and Axis II were administered to confirm diagnosis. Sociodemographic, clinical and pharmacological data were collected via a structured interview with the patient and examination of clinical records. The 17-item HAM-D and the YMRS were administered by trained raters to assess depressive and manic symptoms, respectively.

Magnetic resonance imaging (MRI) data were obtained using a Philips Achieva 1.5 Tesla scanner (Amsterdam, the Netherlands). T1 high resolution sagittal 3D magnetization-prepared rapid gradient-echo (MPRAGE) images were acquired with NEX=1, image matrix=256×232, flip angle=8 degrees, echo time=4 ms, repetition time=8.63 ms, and voxel size 1×1×1 mm³, yielding 160 slices.

Cortical and subcortical volumetric segmentations were performed with the FreeSurfer image analysis suite version 5.1.0 (http://surfer.nmr.mgh.harvard.edu/). The process includes motion correction, removal of non-brain tissue, automated Talairach transformation, segmentation of subcortical WM and deep GM volumetric structures, intensity normalization, tessellation of the GM/WM boundary, automated topology correction and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue.
Previous studies have shown that subcortical segmentations performed with the FreeSurfer software are reliable when compared to manual segmentation. All images were processed and checked by the same researcher. Intracranial volume was regressed out from the volumes of CC, WM, and GM.

Demographic and clinical characteristics were analyzed using the chi-square, Mann-Whitney or Student’s t tests. Descriptive analyses are presented as mean (standard deviation) or median (interquartile range); p-values <0.05 were considered significant. Appropriate tests were used for parametric or nonparametric distribution.

Results

The subjects’ general characteristics are summarized in Table 1. Data of patients with BD are presented in Table 2. CC (p = 0.035 for early; p = 0.028 for late stage groups) and total WM volumes (p = 0.005 for early; p = 0.021 for late stage) were significantly smaller in patients with BD than in controls. There was no difference for total GM volume in the early stage group (p = 0.306) vs. controls. Total GM volume was significantly smaller in patients with BD at late stage compared to controls (p = 0.001). Volumetric results are shown in Figure 1.

Discussion

To our knowledge, this is the first study to examine CC, total WM and total GM volumes in patients with BD at early and late stages compared to matched controls. CC and total WM volumes were decreased in patients with BD at early and late stages; total GM volume was decreased in patients at late stage, but not at early stage, when compared to matched controls.

The hypothesis of different patterns of changes in brain morphology over the course of BD is widely supported by many authors. Illness progression or neuroprogression, a term that explains the pathological reorganization of the central nervous system (CNS) as a consequence of recurrent mood episodes and their influence on BD outcomes, has been used to explain vulnerability to subsequent episodes and changes in treatment response. The

<table>
<thead>
<tr>
<th>Table 1 - Characteristics of healthy controls and patients with BD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early stage</strong></td>
</tr>
<tr>
<td>BD (n=14)</td>
</tr>
<tr>
<td>Sex (male/female)</td>
</tr>
<tr>
<td>4/10</td>
</tr>
<tr>
<td>Age (years), mean (SD)</td>
</tr>
<tr>
<td>40.79 (14.22)</td>
</tr>
<tr>
<td>No. years at school, mean (SD)</td>
</tr>
<tr>
<td>10.29 (3.17)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
</tr>
<tr>
<td>26.80 (5.49)</td>
</tr>
<tr>
<td>FAST, median (IQR)</td>
</tr>
<tr>
<td>12 (18.25)</td>
</tr>
<tr>
<td>Marital status, n (%)</td>
</tr>
<tr>
<td>Single</td>
</tr>
<tr>
<td>Married</td>
</tr>
<tr>
<td>Divorced</td>
</tr>
<tr>
<td>Widowed</td>
</tr>
<tr>
<td>Work situation, n (%)</td>
</tr>
<tr>
<td>Employed</td>
</tr>
<tr>
<td>Unemployed</td>
</tr>
<tr>
<td>Medical benefits</td>
</tr>
<tr>
<td>Invalidity</td>
</tr>
</tbody>
</table>

BD = bipolar disorder; BMI = body mass index; IQR = interquartile range; SD = standard deviation.

p-values in bold font are statistically significant.

* Chi-square; † Student’s t test; ‡ Mann-Whitney test.
neuroprogression pattern has been widely described in serum biomarkers,\textsuperscript{5,6} functioning,\textsuperscript{9,13} cognitive performance,\textsuperscript{42,43} and brain imaging.\textsuperscript{7,8,40} The classical brain findings in BD are a result of GM reduction, including enlargement of the third and lateral ventricles and reduction in total GM volumes of the orbital and medial prefrontal cortex, ventral striatum and mesotemporal cortex.\textsuperscript{1-3} These changes also seem to be related to illness progression.\textsuperscript{40}

Conversely, a number of studies have shown that the CC may play a significant role in the pathophysiology of BD\textsuperscript{38,39} and highlight the importance of WM alterations in underpinning the clinical presentation of BD.\textsuperscript{37} The CC is the main interhemispheric commissure and is crucial for interhemispheric communication and cognitive processes.\textsuperscript{38,39} CC abnormalities may lead to altered interhemispheric communication, which could be relevant for the pathophysiology of the cognitive disturbances present in patients with BD.\textsuperscript{44-46} It is also possible that reduced CC volume is secondary to abnormalities of glial cells.\textsuperscript{47} Glia, especially oligodendrocytes and the myelin that they produce, are essential in achieving and maintaining optimal brain function.\textsuperscript{48} In humans, approximately 50% of the WM volume is composed of myelin, demonstrating that changes in volume can have serious functional repercussions.\textsuperscript{49} Myelination can increase the speed of propagation of electrical information by ~100 times. At the same time, there is a 30-fold reduction in the refractory period, increasing the number of action potentials propagated per unit time. Taken together, these changes increase connectivity and promote a 3000-fold increase in the brain’s information-processing capacity, which is essential for the maintenance of cognition.\textsuperscript{48,50} The continuum of increasing myelin vulnerability resulting from the protracted myelination that underlies disease phenotypes have been reported in BD.\textsuperscript{51}

Table 2 - Characteristics of patients with BD

<table>
<thead>
<tr>
<th></th>
<th>BD early (n=14)</th>
<th>BD late (n=15)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Illness duration (years)</td>
<td>8 (7.5)</td>
<td>18 (23.75)</td>
<td>0.017*</td>
</tr>
<tr>
<td>No. mood episodes</td>
<td>5 (4)</td>
<td>16 (26.5)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Suicide attempts</td>
<td>2 (0)</td>
<td>1 (1)</td>
<td>0.023*</td>
</tr>
<tr>
<td>No. hospitalizations</td>
<td>2 (2.5)</td>
<td>3 (4)</td>
<td>0.093*</td>
</tr>
<tr>
<td>HAM-D</td>
<td>0 (2)</td>
<td>5 (2.5)</td>
<td>0.011*</td>
</tr>
<tr>
<td>YMRS</td>
<td>0 (2)</td>
<td>1 (2.5)</td>
<td>0.572</td>
</tr>
<tr>
<td>No. patients under..., n (%)</td>
<td></td>
<td></td>
<td>0.003†</td>
</tr>
<tr>
<td>One drug</td>
<td>7 (50)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Two drugs</td>
<td>6 (42.9)</td>
<td>5 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Three drugs</td>
<td>0</td>
<td>5 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Four drugs</td>
<td>1 (7.1)</td>
<td>4 (26.67)</td>
<td></td>
</tr>
<tr>
<td>Five or more drugs</td>
<td>0</td>
<td>1 (6.67)</td>
<td></td>
</tr>
<tr>
<td>No. patients under clozapine</td>
<td>0</td>
<td>5</td>
<td>0.042†</td>
</tr>
<tr>
<td>No. patients under..., n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lithium</td>
<td>9 (64.3)</td>
<td>5 (41.7)</td>
<td></td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>6 (42.9)</td>
<td>12 (100)</td>
<td></td>
</tr>
<tr>
<td>Atypical antipsychotics</td>
<td>0</td>
<td>4 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Typical antipsychotics</td>
<td>4 (28.6)</td>
<td>2 (16.7)</td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td>0</td>
<td>4 (33.3)</td>
<td></td>
</tr>
</tbody>
</table>

Data presented as median (interquartile range), unless otherwise specified.
BD = bipolar disorder; HAM-D = 17-item Hamilton-Depression Scale; YMRS = Young Mania Rating Scale.
p-values in bold font are statistically significant.
* Mann-Whitney test; † Chi-square test.

280 – Trends Psychiatry Psychother. 2018;40(4)
Figure 1 - A) Box-plot of total corpus callosum size in patients at early and late BD and their matched controls. Median levels are indicated by horizontal lines (Mann-Whitney: control early vs. BD early, p = 0.035; control late vs. BD late, p = 0.028). B) Box-plot of total white matter volume in patients with BD and their matched controls. Median levels are indicated by horizontal lines (Mann-Whitney: control early vs. BD early, p = 0.005; control late vs. BD late, p = 0.021). C) Box-plot of total gray matter volume in patients with BD and their matched controls. Median levels are indicated by horizontal lines (Mann-Whitney: control early vs. BD early, p = 0.306; control late vs. BD late, p = 0.001). BD = bipolar disorder.
WM in general and CC in particular seem to be especially vulnerable to perceived stress\(^5\) and have been shown to be impaired by stressful events and trauma.\(^5\)\(^3\),\(^5\)\(^4\)

Reductions in CC volume have been demonstrated in both children\(^5\)\(^5\) and adults with post-traumatic stress disorder (PTSD).\(^5\)\(^6\),\(^5\)\(^7\) Although there is robust evidence of gross WM involvement in BD, the origin of these abnormalities remains unclear. Evidence suggests that neuronal metabolic disorders, inflammation and mitochondrial dysfunction are associated with demyelination and functional deterioration in BD.\(^4\)\(^1\),\(^5\)\(^8\)

Some of these changes may be mediated by decrease in the activity of protein kinase B (Akt) and increase in the activity of glycogen synthase kinase 3β (GSK-3β). Activation of GSK-3 β increases inflammation and promotes demyelination, while inactivation by phosphorylation of this protein acts in the opposite way.\(^4\)\(^8\) As a matter of fact, structural MRI studies have found abnormalities in volume, signal intensity and microstructure in patients suffering from BD.\(^1\)\(^6\),\(^5\)\(^9\),\(^6\)\(^0\)

The increasing attention devoted to WM disruption in other neuropsychiatric conditions, such as multiple sclerosis (MS), has allowed to draw an analogy considering the inflammatory processes and clinical progression of WM abnormalities. BD has a well-documented inflammatory component\(^6\)\(^1\)-\(^6\)\(^5\) that could exert deleterious effects on glia components, such as myelin,\(^4\)\(^8\),\(^5\)\(^1\),\(^6\)\(^6\),\(^6\)\(^7\) and also on WM, as mentioned before. Current findings reinforce the presence of WM abnormalities at the first episode,\(^3\)\(^7\) differently from GM findings, which show an episode-dependent deterioration pattern\(^9\)\(^0\) along with cognitive and functioning decline.\(^1\)\(^3\),\(^4\)\(^2\)

Our findings support the growing body of evidence that patients with BD have smaller total WM volume, particularly in the CC, compared to controls, in line with previous studies.\(^1\)\(^6\),\(^5\)\(^9\),\(^6\)\(^0\) A meta-analysis of MRI studies showed reduction of total intracranial and WM volumes in patients with BD at first episode, but not of GM and whole brain volumes.\(^3\)\(^7\) These meta-analytical findings are in line with our results of decreased CC and total WM volumes in patients with BD at early stage, but in contrast with others that report decrease of CC volume only in patients at late stage.\(^2\)\(^1\)

Albeit innovative, the present study has important limitations that must be pointed out. First, the use of structural MRI to assess WM may not detect subtle alterations. The 1.5-Tesla equipment may not have been able to assess those volumes compared to higher definition scanners. The heterogeneous nature of BD could also highlight non-pathological volumetric particularities. Also, the reduced number of participants in each group is a crucial limitation. Larger groups could reach more powerful results and differences among groups. For the same reason, this study was not able to investigate the characteristics of individual pharmacological treatments, which could contribute to volumetric differences. Another limitation of this study was that we could not evaluate the effect of psychotic symptoms.

In conclusion, even considering the limitations of the sample size and cross-sectional design of this study, the total GM volume reduction observed in patients at late stage is in agreement with the neuroprogression theory in BD. The reduction of WM volumes in total WM and in the CC at both early and late stages of the disease is consistent with the disconnection syndrome of frontal and subcortical regions described since the early stage of the illness.\(^3\)\(^7\) These findings on WM, added to the current evidence, support the possibility that an early demyelination process could occur underlying BD symptoms. Our findings, together with current literature, direct to the need to investigate WM abnormalities in populations at high risk to develop BD, perhaps as early biomarkers before the overt syndrome.

**Acknowledgements**

This work was supported by Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES; grants CNPq Universal 443526/2014-1 and 470326/2011-5; CNPq Produtividade em Pesquisa 304443/2014-0) and by Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS; PRONEM 11/2057-2).

**Disclosure**

Flavio Kapczinski has received grant/research support from AstraZeneca, Eli Lilly, Janssen-Cilag, Servier, CNPq, CAPES, NARSAD, and the Stanley Medical Research Institute; has been a member of the speakers’ boards of Astra-Zeneca, Eli Lilly, Janssen, and Servier; and has served as a consultant for Servier. Clarissa S. Gama has served as a paid speaker for Lundbeck and as a consultant/speaker for Roche, Pfizer, Daichii-Sankyo, and Actelion. No other conflicts of interest declared concerning the publication of this article.

**References**

and bipolar disorder within UK biobank: cross-sectional study of 72,751 participants. PLOS One. 2013;8:e75362.


White matter volume and staging in bipolar disorder - Duarte et al.


Correspondence:
Clarissa S Gama
Hospital de Clínicas de Porto Alegre
Rua Ramiro Barcelos, 2350
90035-903 - Porto Alegre, RS - Brazil
Tel.: +55 (51) 33598845
E-mail: cgama@hcpa.edu.br