Preserved white matter in unmedicated pediatric bipolar disorder

Ana Maria A. Teixeira a,b,c,*, Ana Kleinman a, Marcus Zanetti b,c, Marcel Jackowski c,d, Fábio Duran b,c, Fabrício Pereira b,c, Beny Lafer a, Geraldo F. Busatto b,c, Sheila C. Caetano a,b,c,d

a Bipolar Research Program, Department of Psychiatry, University of São Paulo School of Medicine, São Paulo, Brazil
b Laboratory of Psychiatric Neuroimaging, Department of Psychiatry, University of São Paulo School of Medicine, São Paulo, Brazil
c Center for the Support of Research in Applied Neuroscience, University of São Paulo, São Paulo, Brazil
d Child and Adolescent Psychiatry Unit (UPA), Department of Psychiatry, Federal University of São Paulo (UNIFESP), São Paulo, Brazil

HIGHLIGHTS

- No white matter abnormalities in pediatric, unmedicated bipolar disorder.
- No white matter abnormalities in young, healthy offspring.
- Disease ontology and brain development dynamics may explain differences in findings.

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ABSTRACT

White matter (WM) abnormalities have been reported in bipolar disorder (BD) patients, as well as in their non-BD relatives, both children and adults. Although it is considered an emerging vulnerability marker for BD, there are no studies investigating WM alterations in pediatric unmedicated patients and young healthy offspring. In this study, we evaluated the presence of WM alterations in 18 pediatric, non medicated BD patients, as well as in 18 healthy offspring of BD type I parents and 20 healthy controls. 3T DT-MRI data were acquired and scans were processed with tract-based spatial statistics to provide measures of fractional anisotropy and diffusivity. We found no significant differences in WM microstructure between BD patients, healthy offspring and healthy controls. Previous studies that reported WM alterations investigated older subjects, either on medication (BD patients) or with psychiatric diagnoses other than BD (unaffected offspring). Our findings highlight the importance of the understanding of disease ontology and brain development dynamics in the search for early vulnerability markers for psychiatric disorders.

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1. Introduction

Bipolar disorder (BD) affects up to 2.5% of the adult and adolescent populations [1,2], but its etiology and pathophysiology remain elusive. There is compelling evidence that the early-onset form of the disease (prior to age 18) displays significant differences compared to the late-onset presentation [3]. Considering that brain development is a dynamic, genetically predetermined and environment-dependent process, cross-sectional imaging studies of the same disease in different stages of neurodevelopment (e.g., childhood, late adolescence) may yield significantly different results. It means that not only the clinical and methodological differences among studies should be taken into account, but also the ontogenetic aspects of the disorder itself.

It is also important to consider that BD is a progressive disease [4], and that many structural alterations that have been associated to it may be chiefly a scarring effect of repeated mood episodes [5] and/or continued medication exposure [6,7]. Hence, it is of paramount importance to assess unmedicated patients early in the course of the disease. Furthermore, healthy relatives, such as healthy BD offspring (HO), can constitute an important model by putatively displaying a number of disease-associated markers without the complete disease phenotype.

White matter abnormalities detected by Diffusion Tensor Magnetic Resonance Imaging (DT-MRI) have been consistently reported both in BD patients [8,9] and in their non-BD relatives...
in adulthood [10–12]. Children and adolescents with BD also have been found to display decreased fractional anisotropy (FA), a measure of fibers coherence and organization, but findings differ across studies [13–15]. Results on young, unaffected BD relatives are even more heterogeneous [16–18]. It is important to notice that DT-MRI studies with unaffected BD relatives frequently include subjects with current or past history of other psychiatric diagnoses or subthreshold mood symptoms.

Our aim in this study was to evaluate the presence of white matter alterations in healthy children at risk, as well as in pediatric, non medicated BD patients, using DT-MRI.

2. Method

This study was undertaken in accordance with the guidance of the Ethics Committee of the University of Sao Paulo. Informed consent was obtained from parent or legal guardian, and assent was obtained from all subjects.

2.1. Participants

Healthy offspring of adult BD patients were included if they: (a) were between 6 and 17 years of age; (b) had at least one parent with BD type I diagnosis according to DSM-IV-R criteria; and (c) had no lifetime history of DSM-IV axis I diagnosis. Pediatric BD patients were recruited from the outpatient clinic of the Bipolar Disorder Research Program and included if they: (a) were between 6 and 17 years of age; (b) fulfilled DSM-IV-R criteria for BD; and (c) were not taking psychotropic medication for at least four weeks prior to the examination. Healthy controls (HC) within the same age range were recruited through advertisement and included if they had no personal or family history of any DSM-IV axis I diagnosis. Exclusion criteria for the entire sample were: (a) head trauma resulting in loss of consciousness; (b) neurological or medical disorders; (c) IQ < 70; and (c) substance use disorders.

2.2. Clinical assessment

Children and adolescents were interviewed using the Schedule for Affective Disorders and Schizophrenia for School-Age Children- Present and Lifetime Version (K-SADS-PL) [19]. All interviews were rated by trained psychologists and child psychiatrists and reviewed by board certified child psychiatrists (AK and SCC). Children and adolescents were diagnosed as BD NOS if they presented clear manic or hypomanic episodes with elation and/or grandiosity but lacked the duration needed to be classified as BD I or BD II [20]. Patients were rated using the Children Depression Rating Scale—Revised (CDRS-R) [21], the Young Mania Rating Scale (YMRS) [22] and the Clinical Global Impression Scale (CGI) [23]. Pubertal status of all participants was assessed using the Petersen Pubertal Scale [24]. Parental diagnoses were obtained using the Structured Clinical Interview for the DSM-IV (SCID-1) [25]. Intelligence scores were assessed using Wechsler Abbreviated Scale of Intelligence [26].

2.3. Neuroimaging data acquisition

Gradient echo planar MR images were acquired using a 3.0T Philips Achieva MR system (Philips Healthcare, USA) fitted with 40 mT/m highspeed gradients. Foam padding and a forehead strap were used to limit head motion, and a quadrature birdcage head coil was used for radio frequency transmission and reception. Data acquisition parameters for the DTI scan were repetition time (TR) = 6106 ms, echo time (TE) = 65 ms, field of view (FOV) = 224 x 224 mm, slice thickness = 2 mm, no gap, number of slices = 70, acquisition matrix = 112 x 112, number of diffusion gradient directions = 32, b = 0 and 1000 s/mm², number of averages = 3, and the total scan time = 24 min. The MRI protocol also included a tridimensional (3-D) T1-weighted imaging using a fast spoiled gradient-echo sequence (TR = 7 ms, TE = 3.2 ms, FOV = 240 x 240 x 180, slice thickness = 1 mm, no gap, number of averages = 1, acquisition matrix = 240 x 240). All scans were reviewed by a radiologist to ensure that no gross brain abnormalities were evident.

2.4. Statistical analysis

2.4.1. Clinical data

Statistical analyses were performed with the SPSS software, version 14 (SPSS, Inc., Chicago, IL). We adopted a 2-tailed significance level of 0.05. We tested the data distribution using the Kolmogorov–Smirnov Z test. To compare demographic and clinical characteristics among the three groups, we used analyses of variance (ANOVA) and chi-square tests.

2.4.2. DT-MRI data

Diffusion-weighted images were first aligned to the B0 image by Fourier interpolation [27]. Head motion and eddy current-induced distortion correction were performed using the “eddy current” script, and brain segmentation was carried out by the software “bet”, both implemented in the FSL toolbox [28]. Subsequently, the software “dtifit”, which is implemented in FSL, was used to compute the image tensor using the adjusted diffusion-weighted B0 images and a simple least squares fit. Group comparisons were carried out using the tract-based spatial statistics (TBSS) approach on the FSL software [29]. Voxelwise analyses of data were performed using permutation-based inference as implemented in Randomise [30] in FSL using threshold-free cluster enhancement (TFCE) [31]. Linear effects of diagnostic group on FA, MD, RD and AD were tested using general linear models with age as covariate. Five thousand permutations were performed for each contrast. Statistical maps were thresholded at P < 0.05, fully corrected for multiple comparisons (family-wise error). Region of interest (ROI) analyses were performed using probabilistic WM ROIs included in FSL comprising 11 tracts, two of which were considered a priori regions: corpus callosum and cingulum. The mean voxel intensity value was obtained for each skeletonized ROI for the three groups, and group means were compared with analyses of covariance (ANCOVA), with age as covariate.

3. Results

Sociodemographic variables are displayed in Table 1. Groups did not differ in age, gender, IQ, puberty degree or socioeconomic status.

3.1. Clinical characteristics

The BD group was comprised by children and adolescents diagnosed with BD type I (n = 8), BD type II (n = 2) and BD NOS (n = 8). At scan time, BD patients were in mania (n = 6), mixed (n = 4) or euthymia (n = 8). The mean age at BD onset (SD) was 9.5 (3.9) years old. The mean Young Mania Rating Scale (SD) was 8.7 (6.1) and the mean Children's Depression Rating Scale score (SD) was 28.9 (12.6). The mean Clinical Global Impression Scale score (SD) was 4.1 (1.1). BD patients (n = 14) had comorbidities with attention deficit hyperactivity disorder (n = 9), oppositional defiant disorder (n = 5), generalized anxiety disorder (n = 3), conduct disorder (n = 2), simple phobia (n = 2), post-traumatic stress disorder (n = 2), panic disorder (n = 1), separation anxiety disorder (n = 1), obsessive-compulsive disorder (n = 1) and Tourette (n = 1). Nine (50%) BD
patients had mood congruent psychotic symptoms. BD patients were either medication-naive \((n=10)\) or were off medication for at least 4 weeks \((n=8)\).

3.2. Neuroimaging results

TBSS results showed no significant differences in FA, MD, RD or AD indices between BD, HO, and HC, both in the whole-brain pairwise comparisons (Fig. 1) and ROI analyses. ROI indices for all white matter tracts analyzed are shown in Table 2.

4. Discussion

In this young, unmedicated sample, we did not find any significant white matter differences across diagnostic groups. The most replicated white matter finding in pediatric BD seems to be decreased FA in anterior corpus callosum \([14,32,33]\), followed by decreased FA in the anterior cingulate and cingulate gyrus \([15,16,33]\), and in the corona radiata \([33,34]\). In most previous studies, though, participants were on medication, and subjects' mean age was usually 2–3 years older compared to the present study. Only Lu et al. \([35]\) evaluated unmedicated pediatric BD, and found lower FA in the anterior limb of the internal capsule. However, their data had low spatial resolution, and they did not have any findings in larger white matter tracts, neither in children nor in adults, suggesting results could be a partial volume artifact.

TBSS results also found smaller tract volumes in HO children compared to controls, with the largest differences in the lateral/inferior longitudinal fasciculus and arcuate fasciculus. However, no statistically significant group differences were found in the uncinate fasciculus, genu of the corpus callosum, and posterior cingulate/precuneus. Our choice for scanning preferentially drug-naive subjects led to a particularly young sample of BD patients. Despite the ongoing controversy of BD diagnosis in prepubertal children, we consider that our sample may provide important information regarding the underlying neurobiology of BD. First, half of our sample, though young, was classified as BD type I, fulfilling diagnostic criteria for classic mania presentation. Children diagnosed as BD not otherwise specified (NOS) had to present clear manic or hypomanic symptoms, including elated mood. None of our subjects presented with irritable mood only. All BD patients in this sample have been followed up in our services, and there have been no changes in diagnoses.

Fig. 1. TBSS statistical maps showing no clusters of higher FA in controls compared to BD \((P<0.05)\), both in the TCFE-corrected (left) and uncorrected (right) maps. A: anterior; P: posterior.
BD and schizophrenia mean age of onset – late adolescence – is associated with a deregulation of later maturational processes in the brain, such as abnormal myelination or altered expression of neurotransmitters and their receptors [41,42]. Consequently, brain alterations would become visible as the patients become older and their brain development trajectories begin to visibly deviate from the typical course.

It is also important to consider this was an unmedicated BD sample, half of which was drug-naive. Youth with BD are prescribed antipsychotic medication more often than adults [43] and, though antipsychotics may acutely increase frontal lobe intracortical myelin volume, chronic use may exert the opposite effect [44,45]. Moreover, a recent longitudinal study with drug-naive patients with schizophrenia showed differences in FA indices only after medication: after 6 weeks of antipsychotic treatment patients showed decreased FA when compared to healthy controls and to baseline [46].

The most relevant limitation to our study is the relatively modest size of the sample. However, it should be noted that our sample is of comparable [17,35] or larger [32,47] size than those included in most DT-MRI studies that have reported white matter abnormalities in BD groups of older age and/or with a history of continuous medication exposure.

In conclusion, there is a growing body of evidence associating BD to gray and white matter abnormalities. Nevertheless, heterogeneity among studies is high and should be properly addressed. Our study offers another evidence for the hypothesis of neuroprogression in BD, suggesting that unmedicated pediatric patients do not carry observable white matter alterations, despite completing the complete disease phenotype. Similarly, white matter abnormalities are also absent in healthy, young offspring of BD parents. Future longitudinal studies are warranted to evaluate the progression of structural alterations in BD pediatric patients and to further investigate possible vulnerability markers in offspring at high-risk for BD.

References


