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Original Article
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White Matter Reductions and Basal Ganglion Asymmetries in First Manic Episode Bipolar Disorder

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WHAT IS ALREADY KNOWN ON THIS TOPIC?

- *Previous studies have shown reduced white matter volume in individuals with bipolar disorder.*
- *Hemispheric asymmetries in the brain have been linked to structural changes related to mood regulation in bipolar disorder.*
- *However, findings across studies have been inconsistent due to variables such as episode type and medication use.*

WHAT DOES THIS STUDY ADD TO THIS TOPIC?

- *This study demonstrates significant reductions in cerebral and cerebellar white matter volumes in drug-naive patients experiencing their first manic episode of bipolar I disorder.*

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ABSTRACT

Objective: In this study, the volumes and asymmetries of various brain regions of drug-naive patients with first manic episode bipolar disorder type 1 (FME-BD-1) were examined via magnetic resonance imaging (MRI) and compared with the healthy control (HC) group.

Methods: The current study included 54 patients diagnosed with FME-BD-1 and 67 age- and sex-matched HCs. Brain MRI segments of subjects were processed using the VolBrain software. The Young Mania Rating Scale (YMRS) was used to assess manic symptoms and their severity.

Results: There were 34 males (63.00%) and 20 females (37.00%) in FME-BD-1 group, 38 males (56.7%) and 29 females (43.3%) in the HC group. The percentages of total ($P = .018$), right ($P = .014$), and left cerebrum white matter (WM) ($P = .022$) of the FME-BD-1 group were significantly lower than the HC group. The percentages of total ($P = .020$), right ($P = .028$), and left cerebellum WM ($P = .022$) of the FME-BD-1 group were significantly lower than the HC group. The volumes of the total ($P = .026$) and left cerebellum WM ($P = .030$) in the FME-BD-1 group were significantly lower than the HC group. Accumbens ($P = .018$) and caudatus asymmetries ($P = .006$) were significantly different between the FME-BD-1 and HC groups. A significant negative correlation was found between total cerebrum WM and YMRS scores ($r = -0.611$, $P < .001$).

Conclusion: In conclusion, drug-naive FME-BD-1 is associated with cerebral and cerebellar volume reductions. Moreover, nucleus caudatus asymmetry and accumbens asymmetry were significantly different in FME-BD-1 compared to HCs.

Keywords: Basal ganglion, cerebellum, cerebrum, hemispheric asymmetry, white matter

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- *Notable asymmetry differences were identified in the nucleus accumbens and caudate nucleus.*
- *These structural brain changes may precede the onset of manic symptoms, offering insight into early pathophysiological markers of the disorder.*

INTRODUCTION

Bipolar disorder (BD) is a serious mental health condition marked by cyclical mood shifts, involving episodes of mania, hypomania, and depression. It is still difficult to find reliable and repeatable biomarkers that can help us better understand diagnosis, neurobiology, nosology, and the targeted medications required to improve patient outcomes in BD.[1] Neuroimaging studies have revealed important findings in elucidating the pathophysiology of BD. It has been shown that there are structural and functional brain abnormalities in BD, which are related to many factors such as disorder duration, episode type, and medication use.[2] Limited data suggest that modest white matter (WM) abnormalities in BD are associated with neurofunctional alterations. This evidence includes an increase in the number of WM hyperintensities and a decrease in whole brain WM density, which provide a local estimate of WM volume within the particular voxel.[3] The study by Pezzoli et al[4] (2018) revealed reductions in WM volume in the posterior corpus callosum extending to the cingulate cortex. Sub-regional studies of WM volume have revealed abnormalities in prefrontal WM in an adult BD population and bilateral superior temporal gyrus in pediatric BD.[5,6] On the other hand, in some studies, WMs of BD and control groups were found to be similar.[7] That is, the findings of studies comparing WMs of BD and control groups are inconsistent. Since these differences between studies were thought to be due to the limitations (episode type, drug use, etc.), studies were conducted on patients diagnosed with first episode BD. Comparing patients with first episode BD to controls, frontal and parietal WM were shown to exhibit volumetric impairments,[8] and in patients with chronic BD, these deficits were detected across the entire brain.[9] A meta-analysis of magnetic resonance imaging (MRI) studies examining brain structure in individuals with BD found a reduction in total WM volume in those experiencing their first episode of the disorder.[10] According to Rosso et al[11] (2007), first-episode BD patients had a tendency toward reduced cerebral WM volume, and patients compared to controls had a statistically significant association between cerebral WM volume and total amygdala volume. As can be seen, various studies have shown that cerebral WM is reduced in first-episode BD.

Another abnormality detected in BD patients is brain hemispheric asymmetry.[12] An essential component of the human brain's organization for a variety of cognitive activities, including executive function, language, affective processing, and social cognition, is left-right hemisphere asymmetry. A number of factors can change hemispheric asymmetry, including gyrification, functional and structural connections, behavioral associations, and anatomical gray matter (GM) and WM volumes.[13,14] The findings of studies examining hemispheric asymmetry in BD are inconsistent. In their scoping review, Moebus et al[12] (2023) demonstrated that the dorsal anterior cingulate cortex and left dorsolateral prefrontal cortex are 2 areas of the left frontal lobe that are associated with cerebral dominance during manic episodes. Caligiuri et al[15] (2004) reported the presence of a right hemisphere disturbance in BD. On the other hand, according to several studies, patients with manic episodes exhibit more activity in the right hemisphere than the left in the amygdala,[16] temporal lobes,[17] and basal ganglia.[18]

Studies examining brain volumes and hemispheric asymmetries in BD are limited, and the relationship between them has not yet been investigated. In this study, the volumes and asymmetries of some brain regions of drug-naive patients with first manic episode BD type 1 (FME-BD-1) were examined and compared with healthy control (HC) groups.

MATERIALS AND METHODS

Study Design

In this retrospective study, the cerebral and cerebellar volumes, and basal ganglia asymmetries of FME-BD-1 with an HC group were compared. Patients diagnosed with FME-BD-1 according to the text revision of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5-TR)[19] who were admitted to Adıyaman Training and Research Hospital Hospital between January 1, 2018, and October 1, 2022, were included in this study. Individuals who were similar to the FME-BD-1 group in terms of age and gender, who admitted to the hospital where the study was conducted for any reason (e.g., headache, vertigo) and had MRIs but were not diagnosed with any disease, were accepted as the HC group. In the hospital, MRI is routinely performed in the first episode of patients diagnosed with BD to exclude organic brain diseases. At the same time, the medical history, and the Young Mania Rating Scale (YMRS) score of all patients are recorded in patient files. Ethics committee approval was obtained from Adıyaman University Non-invasive Clinical Researches Ethics Committee (Protocol Number: 2022/8-4; Date: November 15, 2022).

Inclusion and Exclusion Criteria

Information about assessed individuals is routinely uploaded to the patient registration system, e-nabiz. The e-nabiz application serves as a database that provides access to comprehensive medical

histories of patients, including details on surgeries, hospital stays, laboratory results, imaging studies, allergy information, diagnoses, prescribed medications, vaccination history, cancer screening records, intensive care details, reports, and emergency documentation. The treatment processes of patients followed up for depression spectrum disorders are recorded by their physicians. Through the patient registration system, information on the duration of medication use, depression severity score, and treatment resistance status of the patients can be accessed.

The compliance of the HC group with the inclusion and exclusion criteria was checked via e-nabiz. Patients diagnosed with FME-BD-1 according to a structured clinical interview for DSM-5-TR were included in the study. Accordingly, there were no additional psychiatric disorders in the patients at the time of admission. Patients and controls had not used any medication in the last month before the current admission. Patients and controls had no history of using psychotropic agents. Patients and controls with a history of alcohol and substance use disorder were excluded. All patients presenting with manic and psychotic symptoms in the hospital were routinely screened for illegal substances and alcohol through urine toxicology analysis. None of the patients included in this study were under the influence of alcohol or illicit substances. Patients and controls with chronic organic diseases such as hypertension and diabetes mellitus were excluded. Patients and controls with mental retardation were not included in the study. All patients and controls included in this study were right-handed according to the short version of the Edinburgh Handedness Inventory.[20] Although some patients were diagnosed with FME-BD-1 according to DSM-5-TR, they were excluded from the study due to certain conditions. Three patients were excluded from the study because they had a history of chronic alcohol use, and 6 patients were excluded from the study because ethyl alcohol had been detected in the blood in the current application, although they did not have chronic alcohol use. Although 3 patients were diagnosed with FME-BD-1 according to DSM-5-TR, they were not included in the study because they did not comply with the MRI application. The flow chart is shown in Figure 1.

Clinical Procedures

All of the patients presenting with FME-BD-1 were hospitalized. Two trained clinical psychiatrists performed all clinical assessments and confirmed the BD diagnosis. The YMRS was administered to all hospitalized patients. The YMRS scale was applied taking into account the patients' condition at the time of admission. Magnetic resonance imaging (MRI) was performed immediately on hospitalized patients who were stable and compatible. In the entire patient group, the maximum duration between admission and MRI application was 8 days. Patients were conscious, cooperative, and oriented during MRI. However, all patients were sedated to varying degrees so that they could better adapt to the MRI procedure. All patients were using some psychotropic medications at the time of MRI. The patients were using medications such as valproic acid plus sodium valproate, lithium, quetiapine, olanzapine, risperidone, amisulpride, diazepam, lorazepam, and haloperidol plus biperiden during the MRI application. However, drug use status at the time of recordings was not clearly evident. There were no patients who received electroconvulsive therapy or long-acting antipsychotic injections.

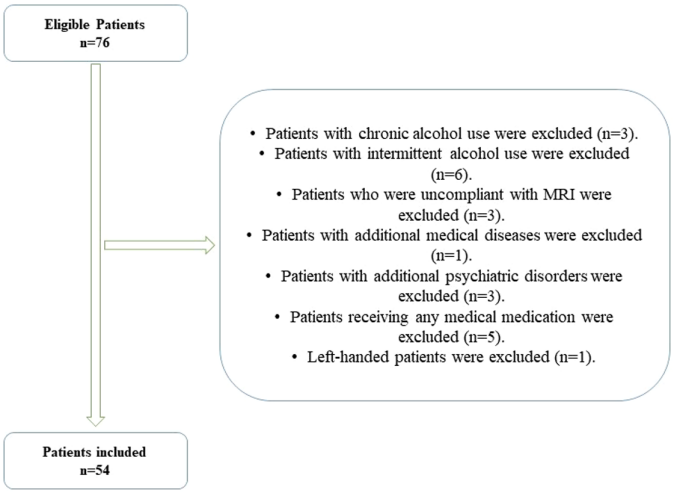

Figure 1. Flowchart of the study.

Young Mania Rating Scale

Young Mania Rating Scale (YMRS) is a scale consisting of 11 items, each of which includes 5° of severity. The fifth, sixth, eighth, and ninth items were given double weight to better distinguish patients with whom communication is difficult. Young Mania Rating Scale is administered by an experienced clinician with a 15- to 30-minute interview. Grading the severity is based on the patient's subjective opinion in the last 48 hours and the clinician's observations of the patient's behavior during the interview. Turkish validity and reliability were performed by Karadağ et al.[21]

Image Acquisition

The MRI scan was acquired from the Philips Achieva MR device (Philips Medical Systems, Best, Netherlands) with a 1.5-Tesla magnetic field strength using a head coil. [Time to repeat (TR): 1665 ms, time to echo (TE): 20 ms, FOV: 220 × 230, slice thickness: 5 mm, matrix: 292 × 214, NSA: 1, gap: 1 mm, voxel: 0.75 × 1.07 × 5, slices: 24 sections].

Volume Measurement

MRI brain segments from the participants were processed using the VolBrain (VB) software.[22] VolBrain is a pipeline dedicated to automatically analyzing MRI brain data. It takes an anonymized MRI brain volume in Neuroimaging Informatics Technology Initiative format and produces a portable document format report. VolBrain software calculates the volumes of subcortical structures, the cerebellum, brainstem, cerebral hemispheres, brain tissues, and the intracranial cavity. Volume calculation according to tissue types is made as follows: Intracranial Cavity (IC) (cm^3/%) = Brain (WM + GM (cm^3/%)) + Cerebro Spinal Fluid (cm^3/%). In other words, the percentage (%) value of any parameter given in the findings section and tables expresses the ratio of the percentage (%) of that parameter to the IC percentage (%); the volume (cm^3) value of any parameter given in the findings section and tables expresses the ratio of the volume (cm^3) value of that parameter to the IC volume (cm^3) value. T1-weighted axial brain MRI sequence was used. The asymmetry index was calculated using the [(L − R)/[(L + R)/2] × 100 formula. Brain MRI examination of the participants was carried out by 2 radiologists with 7 and 16 years of professional experience. The separation of brain segments in VB is shown in Figure 2.

Statistical Analysis

Windows SPSS 26.0 (Statistical Package for the Social Sciences Inc.) was used for the statistical analysis. Continuous variables and descriptive statistics are presented as mean ± SD, while categorical

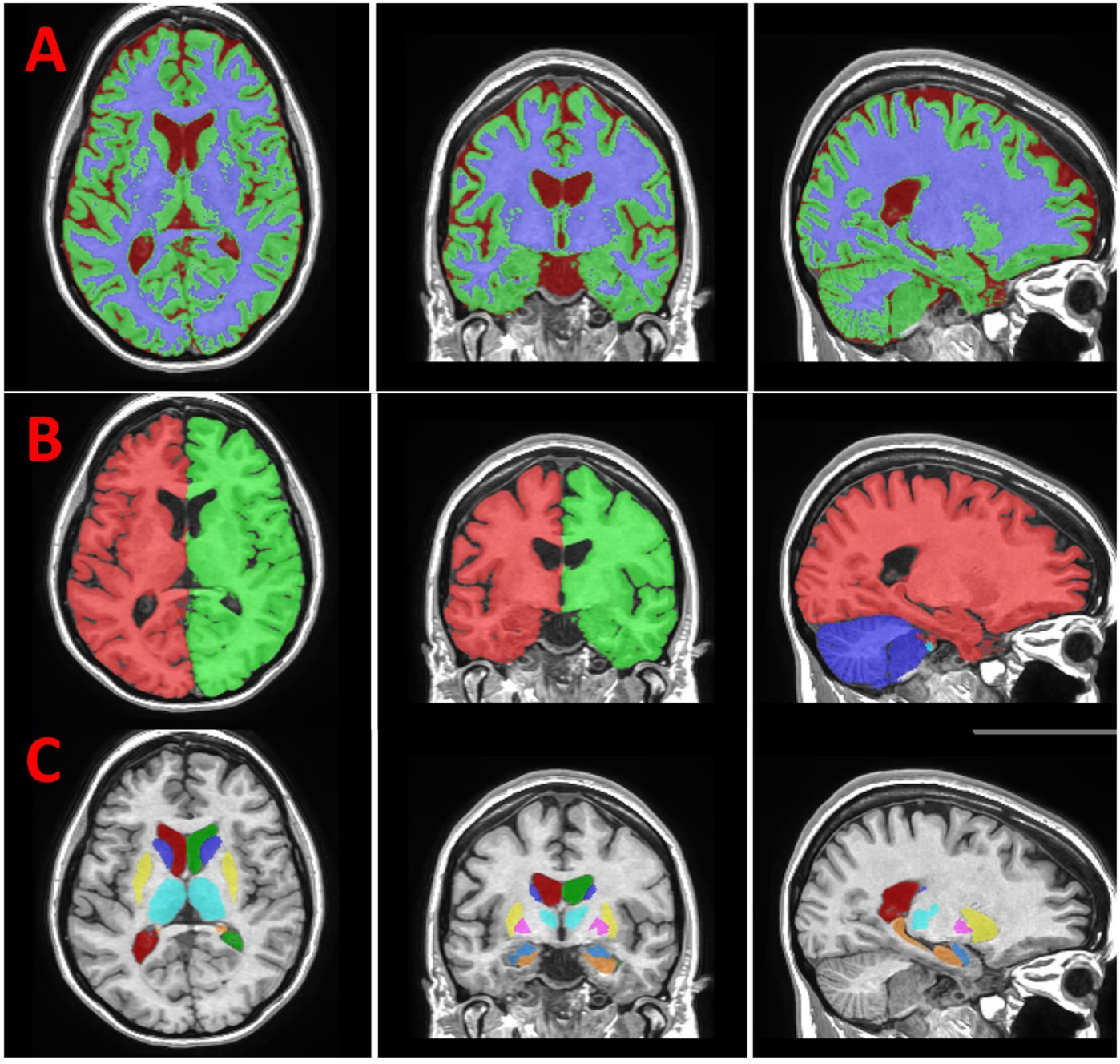

Figure 2. Illustration of brain structures (A: Tissue classification, B: Macrostructures, C: Subcortical structures).

variables are presented as frequency and percentage. The categorical data were analyzed using the chi-square test. The Kolmogorov–Smirnov test was used to determine whether a normal distribution was appropriate. Independent-samples *t*-test was used to make comparisons between 2 groups to determine significant differences between groups. Independent-samples *t*-test was used to make comparisons between 2 groups to determine significant differences between groups. ROC (Receiver Operating Characteristic) curve analysis was used to measure the diagnostic value of volumetric parameters. Pearson correlation analysis was performed. Binary logistic regression analysis was used in disorder prediction. Cohen's d was calculated as the effect size. A value of less than 0.05 (*P* value) was considered statistically significant. Bonferroni correction was applied. According to the 42 parameters compared between the 2 groups in the independent *t*-test, it was considered statistically significant if the *P* value was less than .049. The formula $P = 1-(1-0.05/\text{test count})^{\text{test count}}$ was used in the Bonferroni calculation.[23] In the power analysis, data from Rosso et al[11] (2007) were taken into account. When alpha was accepted as 0.05, beta as 0.2, and power as 80%, it was determined that 45 patients should be included in each group.

RESULTS

There were 34 males (63.00%) and 20 females (37.00%) in FME-BD-1 group, 38 males (56.7%) and 29 females (43.3%) in the HC group. The mean age was 24.28 ± 3.76 years in the FME-BD-1 group and 24.91 ± 4.18 years in the HC group. There was no significant difference

between the FME-BD-1 and HC groups in terms of age ($P = .389$) and gender ($P = .487$). The mean education level was 7.94 ± 1.48 years in the FME-BD-1 group and 9.85 ± 3.29 years in the HC group ($P < .001$). While 12 (22.2%) of the patients had a job that brought regular income, all of the HCs (100.0%) had a job that brought regular income ($P < .001$).

The time between the onset of patients' first manic symptoms and admission to the hospital was 29.46 ± 14.11 days (minimum 5 days, maximum 61 days).

Table 1 presents the IC parameter volumes for both FME-BD-1 and HC groups.

Comparisons of cerebral WM parameters between FME-BD-1 and HC groups are shown in Table 2, indicating significantly lower percentages of total ($P = .018$), right ($P = .014$), and left ($P = .022$) cerebral WM in the FME-BD-1 group.

Similarly, Table 3 presents cerebellar WM parameters, with patients showing notably reduced percentages in total ($P = .020$), right ($P = .028$), and left ($P = .022$) cerebellar WM compared to HCs. Additionally, the total ($P = .026$) and left ($P = .030$) cerebellar WM volumes were also markedly lower in FME-BD-1 than in HC.

Asymmetries in brain structures, including the basal ganglia, were assessed. Significant differences were observed between FME-BD-1 and HC in accumbens ($P = .018$) and caudate asymmetries ($P = .006$), as outlined in Table 4.

Table 5 displays correlations between various parameters and YMRS scores, adjusted for age, showing a significant negative correlation between cerebrum WM volume and YMRS scores. In patients, no significant correlation was found between the time from initial manic symptoms to hospital admission and cerebrum WM, cerebellum WM, or asymmetries in the caudate and accumbens ($P > .05$), when controlling for age.

An ROC curve analysis was conducted on 54 patients with FME-BD-1 and 67 HCs. The caudate asymmetry's area under the ROC curve (AUC) was 0.655 ($P = .003$; 95% CI: 0.557-0.753), while the total cerebrum WM percentage showed an AUC of 0.637 ($P = .010$; 95% CI: 0.534-0.740). The caudate asymmetry's optimal threshold was 2.79, with sensitivity and specificity for FME-BD-1 diagnosis at 16.7% and 94.0%, respectively. For the total cerebrum WM percentage, the optimal threshold was 31.86, yielding sensitivity and specificity of 10.4% and 95.4%.

Table 1. Comparison of the IC Parameters of the Patient and Healthy Control Groups

Parameters	FME-BD-1 (n = 54) (mean ± SD)	HC (n = 67) (mean ± SD)	*P*
Total WM tissue, cm^3	417.16 ± 63.03	437.86 ± 54.65	.054
Total GM tissue, cm^3	767.58 ± 108.66	765.25 ± 133.84	.918
Total CSF, cm^3	196.17 ± 87.25	182.22 ± 73.26	.340
IC, cm^3	1380.92 ± 116.32	1385.34 ± 136.58	.852

All the volumes are presented in absolute value (measured in cm^3) and in relative value (measured in relation to the IC volume).
CSF, cerebrospinal fluid; FME-BD-1, first manic episode bipolar disorder type 1; GM, gray matter; HC, healthy control; IC, intracranial cavity; WM, white matter.
*$P < .05$.

Table 2. Comparison of the Cerebrum Parameters of the Patient and Healthy Control Groups

Parameters	FME-BD-1 (n = 54) (mean ± SD)	HC (n = 67) (mean ± SD)	*P*	Cohen's *d*
Cerebrum total, cm^3	1033.87 ± 126.81	1048.61 ± 150.36	.566	0.10
Cerebrum total, %	74.79 ± 5.76	75.49 ± 5.31	.492	0,20
Cerebrum WM total, cm^3	375.06 ± 56.48	391.86 ± 49.31	.084	0.30
Cerebrum WM total, %	27.11 ± 3.01	28.29 ± 2.38	.018*	0.39
Cerebrum R, cm^3	517.51 ± 63.11	525.20 ± 75.04	.548	0.11
Cerebrum R, %	37.44 ± 2.84	37.81 ± 2.66	.462	0.13
Cerebrum R-WM, cm^3	188.94 ± 28.94	197.66 ± 24.55	.076	0.33
Cerebrum R-WM, %	13.65 ± 1.53	14.27 ± 1.21	.014*	0.44
Cerebrum L, cm^3	516.35 ± 63.80	523.40 ± 75.39	.584	0.10
Cerebrum L, %	37.35 ± 2.93	37.67 ± 2.66	.528	0.11
Cerebrum L-WM, cm^3	186.12 ± 27.64	194.19 ± 24.86	.094	0.30
Cerebrum L-WM, %	13.45 ± 1.48	14.02 ± 1.18	.022*	0.42
Cerebrum GM total, cm^3	658.81 ± 98.55	656.74 ± 118.63	.918	0.01
Cerebrum GM total, %	47.67 ± 5.62	47.19 ± 5.20	.622	0.09

All the volumes are presented in absolute value (measured in cm^3) and in relative value (measured in relation to the intracranial volume).
FME-BD-1, first manic episode bipolar disorder type 1; GM, gray matter; HC, healthy control; L, left; R, right; WM, white matter.
*$P < .05$.

To explore relationships between significant variables and group membership, binary logistic regression analysis was performed, examining each variable individually before constructing the model. After modeling gender alone, no significant findings were obtained

Table 3. Comparison of the Cerebellum Parameters of the Patient and Healthy Control Groups

Parameters	FME-BD-1 (n = 54) (mean ± SD)	HC (n = 67) (mean ± SD)	*P*	Cohen's *d*
Cerebellum total, cm^3	129.59 ± 14.99	132.54 ± 15.28	.290	0.20
Cerebellum total, %	9.39 ± 0.89	9.57 ± 0.63	.218	0.23
Cerebellum WM total, cm^3	28.82 ± 7.85	31.88 ± 7.15	.026*	0.40
Cerebellum WM total, %	2.08 ± 0.53	2.32 ± 0.55	.020*	0.44
Cerebellum R, cm^3	64.45 ± 7.57	66.03 ± 7.76	.262	0.28
Cerebellum R, %	4.67 ± 0.45	4.76 ± 0.32	.192	0.23
Cerebellum R-WM, cm^3	15.92 ± 4.30	17.53 ± 3.94	.064	0.39
Cerebellum R-WM, %	1.15 ± 0.29	1.27 ± 0.30	.028*	0.40
Cerebellum L, cm^3	65.14 ± 7.55	66.51 ± 7.62	.326	0.18
Cerebellum L, %	4.72 ± 0.44	4.80 ± 0.31	.260	0.28
Cerebellum L-WM, cm^3	12.90 ± 3.76	14.34 ± 3.43	.030*	0.40
Cerebellum L-WM, %	0.93 ± 0.25	1.04 ± 0.26	.022*	0.43
Cerebellum GM total, cm^3	100.77 ± 12.03	100.66 ± 16.23	.968	0.01
Cerebellum GM total, %	7.31 ± 0.76	7.25 ± 0.75	.654	0.09

Independent-samples *t*-test was used. All the volumes are presented in absolute value (measured in cm^3) and in relative value (measured in relation to the intracranial volume).
FME-BD-1, first manic episode bipolar disorder type 1; GM, gray matter; HC, healthy control; L, left; R, right; WM, white matter.
*$P < .05$.

Table 4. Comparison of the Asymmetry Parameters of the Patient and Healthy Control Groups

Parameters	FME-BD-1 (n = 54) (mean ± SD)	HC (n = 67) (mean ± SD)	*P*	Cohen's *d*
Accumbens asymmetry	−6.74 ± 32.79	−21.19 ± 33.31	.018*	0.43
Caudatus asymmetry	7.47 ± 8.90	3.04 ± 8.59	.006*	0.50
Amygdala asymmetry	2.21 ± 24.50	5.93 ± 20.17	.362	0.16
Hippocampus asymmetry	−1.30 ± 12.37	−1.61 ± 7.86	.866	0.02
Globus Pallidus asymmetry	1.43 ± 25.12	−2.29 ± 16.35	.328	0.17
Thalamus asymmetry	−0.17 ± 7.46	−0.38 ± 10.15	.900	0.02
Putamen asymmetry	−2.81 ± 6.91	−2.97 ± 9.15	.598	0.01
Lateral ventricle asymmetry	−12.17 ± 36.01	−7.25 ± 39.96	.483	0.12
Cerebrum asymmetry	0.24 ± 0.96	0.35 ± 0.90	.524	0.02
Cerebellum asymmetry	−1.07 ± 3.24	−0.75 ± 2.61	.544	0.02

Independent-samples *t*-test was used. The Asymmetry Index is calculated as the difference between right and left volumes divided by their mean (in percent).
FME-BD-1, first manic episode bipolar disorder type 1.
*$P < .05$.

and it was not included in the model (Beginning block, −2 log-likelihood = 166.342[a]; Block 1, −2 log-likelihood = 165.857[a]; Cox & Snell R^2= 0.004; Nagelkerke R^2 = 0.005; $P = .487$). After modeling age alone, no significant findings were obtained and it was not included in the model (Beginning block, −2 log-likelihood = 166.342[a]; Block 1, −2 log-likelihood = 165.585[a]; Cox & Snell R^2 = 0.006; Nagelkerke R^2 0.008; $P = .386$). After various modeling, it was seen that the relationship between the percentages of total cerebellum WM and the percentages of total cerebrum WM was higher, and the percentages of total cerebellum WM, which was found to contribute less to the model, were not included in the model. As a result, a model was created using accumbens asymmetry, caudate asymmetry, and the percentages of total cerebrum WM. According to the binary logistic regression analysis, the sensitivity of parameters (accumbens asymmetry, caudate asymmetry, and the percentages of total cerebrum WM) related to determining the participants who were involved in FME-BD-1 & HC groups was 51.9%, and the specificity was 71.6% (Beginning block, −2 log-likelihood = 166.342[a], overall $P = .001$; Block 1, −2 log-likelihood = 147.292[a]; Cox & Snell R^2 = 0.146; Nagelkerke R^2 0.195; Hosmer and Lemeshow Test $P = .183$). The accumbens asymmetry ($P = .008$, Exp(B) = 1.017, B = 0.017), caudate asymmetry ($P = .010$, Exp(B) = 1.066, B = 0.063), and the percentages of total cerebrum WM ($P = .049$, Exp(B) = 0.859, B = −0.152) contributed significantly to the model. Binary logistic regression analysis is shown in Table 6.

Table 5. Correlation of Various Parameters with YMRS Controlling for the Effect of Age

Parameters	YMRS Patient (r, *P*)
Accumbens asymmetry	−0.193, .166
Caudatus asymmetry	0.095, .499
Cerebrum WM total, cm^3	−0.611, <.001**
Cerebrum WM total, %	−0.590, <.001**
Cerebellum WM total, cm^3	−0.298, .030*
Cerebellum WM total, %	−0.184, .186

Pearson correlation analysis was used.
WM, white matter; YMR, Young Mania Rating Scale.
*$P < .05$.

Table 6. Binary Logistic Regression Analysis of FME-BD-1 and Healthy Control Groups

Independent Variables	B	Sig.	Exp (B)	95% CI for Exp (B) Lower	95% CI for Exp (B) Upper
Accumbens asymmetry	0.017	0.008*	1.017	1.004	1.030
Caudate asymmetry	0.063	0.010*	1.066	1.015	1.118
Percentages of total cerebrum WM	−0.152	0.049*	0.859	0.739	0.999
Constant	3900	0.071	49.384		

Binary logistic regression analysis was used. Model summary: In beginning block, −2 log-likelihood=166.342[a], overall $P = .001$; Block 1, −2 log-likelihood=147.292a; Cox & Snell $R^2 = 0.146$; Nagelkerke R^2 0.195; Hosmer and Lemeshow Test $P = .183$).
FME-BD-1, first manic episode bipolar disorder type 1.
*$P < .05$.

DISCUSSION

This study compares the cerebrum, cerebellum WM volume and asymmetry, and basal ganglia asymmetries of drug-naive FME-BD-1 and an HC group. It has been shown that the total, right, and left WM percentages of cerebrum and cerebellum were decreased in the FME-BD-1 group. Additionally, it has been shown that the total and left WM volume values of cerebellum were decreased in the FME-BD-1 group. Accumbens and caudatus asymmetry has been shown to be significantly impaired. It is important that drug-naive FME-BD-1 patients were examined in this study. The time between the first manic symptoms of FME-BD-1 patients and their admission to the hospital was found to be approximately 1 month. The fact that there was no relationship between this period and volumetric MRI findings suggests that WM and asymmetry changes may have occurred before manic symptoms appeared.

The first studies investigating WM volumes in BD were unsuccessful due to MRI acquisition and processing techniques and methodological approaches.[24] Research shows that episode type, treatment response characteristics, and number of episodes affect WM findings.[2] With technological developments, it has been shown that some brain structures are affected in BD.[24] Cerebral and cerebellar WM are 2 of these structures affected.[25] The distributed neuronal circuits that support sensory function, intelligence, and emotion are made possible by the cerebral WM, which has fiber channels that carry axons connecting cerebral cortical areas with one another and with subcortical structures.[26] In the study conducted by Davis et al[27] (2004) on patients diagnosed with euthymic BD type 1, it was shown that cerebral WM was decreased in the FME-BD-1 group compared to the HC group. Moore et al[24] (2001) reported that a poor response to treatment in BD was associated with increased cerebral WM abnormalities. Macoveanu et al[28] (2021), in a study comparing remitted BD patients with HCs, reported that

cognitively impaired patients had lower cerebral WM volume and that low WM volume was correlated with impaired neuropsychological test performance. Rosso et al[11] (2007) also demonstrated that the cerebral WM volumes of FME-BD patients tend to decrease compared to HCs. This finding suggests that cerebral WM changes in BD occur before the disorder presents itself. This study is different from the majority of studies in the literature in that it included adult drug-naive FME patients. According to this study, the percentage of cerebrum WM decreased significantly in the FME-BD-1 group. The volume reduction detected even in the first episode in patients diagnosed with FME-BD-1 suggests that brain cell loss and atrophy begin before the disorder is diagnosed. In the study conducted by Gao et al[29] (2024) on pediatric patients diagnosed with FME-BD, findings supporting this claim were obtained. According to Gao et al[29] (2024)'s study, compared with the pediatric BD-first episode depression and HCs, the pediatric FME-BD group had reduced GM volume in the left thalamus, bilateral hippocampus, and right amygdala. Additionally, they reported right cortico-amygdaloid transient, bilateral accessory-basal nucleus, left hippocampal tail, and right hippocampal head, and body volume reduction in the pediatric FME-BD group.

Another important finding of this study is the cerebellar WM volume differences in FME-BD-1. Numerous cognitive, linguistic, and emotional disorders have been linked to damage to the cerebellar WM.[28] In contrast to the multitude of cerebral WM studies, the cerebellar WM profile of BD is relatively understudied. This study showed that, just like cerebral WM volume, cerebellar WM volume was decreased in FME-BD-1. According to these findings, it is possible that cerebellar WM abnormalities may have occurred in patients diagnosed with BD before the FME symptoms appeared.

Another parameter affected in patients diagnosed with BD is hemispheric asymmetry. The human brain is lateralized or asymmetrical both physically and functionally.[30] Cognitive and emotional functions can be disturbed by even subtle changes in the structural asymmetries between the 2 hemispheres, such as differences in GM volume, cortical thickness, or WM integrity.[31] Convergent research on BD has revealed abnormal WM asymmetries, such as reduced WM volume in the left frontal lobes and WM that is displaced to the right in the orbital frontal. Understanding the fundamental nature of the alteration in the brain of BD may be helped by analyzing the hemispheric anatomical networks and further determining the status of the anatomical network asymmetries, which may also help to clarify the etiology of the disorder. However, the hemispheric asymmetries of anatomical networks in patients with BD remain unclear.[31] In this study, basal ganglion and limbic system elements such as accumbens, caudatus, amygdala, globus pallidus, putamen, thalamus, hippocampus, as well as lateral ventricles, cerebrum, and cerebellum asymmetries were examined. Only accumbens and caudatus asymmetries were found to be significant. According to the findings, in FME-BD-1, the right nucleus caudatus volume was found to be larger than the left, while the left nucleus accumbens volume was found to be larger than the right.

Nucleus accumbens functions in hedonic-based behavior and the reward system in humans. The interaction of the nucleus accumbens with the ventromedial prefrontal cortex has been shown to be crucial in regulating responses to reward and emotional symptoms in psychiatric disorders. It has been shown that there are abnormal nucleus accumbens functions and abnormalities in its interaction with the ventromedial frontal cortex in BD.[32] Nucleus caudatus is involved in higher neurological functions such as learning, memory, motivation, reward, and affect. Nucleus caudatus dysfunction has been reported in BD. Increased activation in the left nucleus caudatus has been reported in manic attacks. Shape and size anomalies in the nucleus caudatus have also been previously demonstrated in BD.[33]

The reductions in white matter (WM) volumes in both the cerebrum and cerebellum in patients with FME-BD-1, compared to HCs, are striking. A deeper exploration of how these reductions might be linked to specific cognitive or behavioral symptoms would provide more context. For example, discussing how abnormalities in cerebellar and cerebrum WM might affect emotional regulation, cognition, and motor control could offer greater clinical insights into the significance of these structural changes. Additionally, the significant asymmetry in basal ganglia regions, such as the accumbens and caudatus, should be interpreted in relation to the pathophysiology of manic episodes. Exploring how these brain regions, which are involved in mood regulation and reward processing, might contribute to the observed clinical symptoms of FME-BD-1 would strengthen the findings.

Regarding the limitations, while the retrospective and cross-sectional nature of the study has been addressed, it would be beneficial to more clearly emphasize the potential impact of these limitations on the generalizability of the findings. For instance, a prospective design could have provided clearer insights into the causality of the observed structural changes. Additionally, the use of psychotropic medications during MRI imaging should be briefly discussed in terms of how it might have confounded the results. Lastly, suggesting areas for future research, such as the need for longitudinal studies to track changes over time, would help position the study's findings within the broader scope of BD research.

In conclusion, drug-naive FME-BD-1 is associated with cerebral and cerebellar volume reductions. Moreover, nucleus caudatus asymmetry and accumbens asymmetry were significantly different in FME-BD-1 compared to HCs. These findings are valuable in terms of showing that structural brain abnormalities in BD may start from the early stages of the disorder. Further studies are recommended for the interpretation of the significant findings.

Availability of Data and Materials: The data that support the findings of this study are available upon request from the corresponding author.

Ethics Committee Approval: Ethical approval was obtained from the Adıyaman University Non-invasive Clinical Researches Ethics Committee, and the 1964 Declaration of Helsinki was complied with (Approval number: 2022/8-4; Date: November 15, 2022).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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