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ORIGINAL ARTICLE

Neurocognitive and neurobiological features of early-stage, unmedicated patients with bipolar disorder

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Objective: This study aimed to identify young adults who met the criteria for bipolar disorder (BD) but had not yet been diagnosed or treated. It also aimed to evaluate their neurocognitive and neurobiological changes compared to healthy controls (HC).
Methods: Individuals at high risk for BD were identified by using the Hypomania Checklist 32 items (HCL-32R). Participants were then assessed with the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) to identify previously undiagnosed and drug-naive patients (DNP) (n=27). A matched HC group (n=27) was included for comparison. All participants completed a cognitive battery assessing executive function, attention, working memory, and verbal learning. Magnetic resonance imaging (MRI) was used to assess cortical thickness. Oxidative stress markers – including thiobarbituric acid reactive substances (TBARS), nitric oxide (NO), and the antioxidant enzymes superoxide dismutase (SOD) and catalase (CAT) – were measured.
Results: The DNP group underperformed across all the tests administered but group differences were significant in the Wisconsin Card Sorting Test (WCST) and Rey Auditory Verbal Learning Test (RVALT). Among oxidative stress markers, only CAT levels were significantly higher in the DNP group. Additionally, patients exhibited significant cortical thinning in several brain regions.
Conclusion: Neurobiological alterations and neurocognitive dysfunction are present in the early-stage, unmedicated stages of BD. However, longitudinal studies are needed to better understand the progression of these changes.

Keywords: MRI; cortical thickness; oxidative stress; affective disorders

Introduction

Bipolar disorder (BD) is a common and disabling mental illness characterized by recurrent mood episodes. It is a major public health concern due to its association with increased risks of suicidality and mortality.[1] In a worldwide mental health survey involving 61,392 adults across 11 countries, the lifetime prevalence of BD-I was 0.6%, BD-II was 0.4%, and subthreshold BD was 1.4%, resulting in a total lifetime prevalence of bipolar spectrum disorder of 2.4% worldwide.[2] A major challenge in BD is the significant delay in accurate diagnosis, which is estimated to be around 10 years.[3] This delay has been linked to poorer clinical outcomes and impaired social functioning, including higher rates of annual hospitalizations and lifetime suicide attempts.[4,5] Additionally, since depression is the most common presenting polarity in BD, patients are often misdiagnosed with major depressive disorder (MDD) and treated with antidepressants, which may worsen their prognosis.[6] These findings highlight the importance of better understanding the characteristics of early stages of BD.

Some patients with BD exhibit cognitive impairments, particularly in executive functioning, attention, processing speed, and verbal memory, with medium to large effect sizes.[7,8] Neurocognitive dysfunction has been consistently reported during acute episodes – regardless of polarity[9,10] – as well as during remission,[7,11] and in both the early[12] and chronic stages of BD.[13] Furthermore, neurocognitive impairment in patients with BD has been repeatedly associated with reduced social and occupational functioning.[14,15]

In addition to cognitive dysfunction, BD has been associated with structural brain abnormalities. Recent meta-analyses have reported reduced cortical thickness in the prefrontal and precentral regions, decreased

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volume of the right superior temporal gyrus, and increased volumes of the left putamen and left posterior cingulate cortex in individuals with BD.[16,17]

Increased oxidative stress markers and lipid peroxidation have been identified as biological processes that may contribute to cognitive dysfunction and structural abnormalities in BD. Oxidative stress, which reflects an imbalance between elevated reactive oxygen species and reduced antioxidant enzyme activity, can lead to oxidative cell damage, including the peroxidation of lipids, proteins, and DNA.[18] Serum levels of reactive oxygen species, such as nitric oxide (NO), and antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), are commonly measured to assess oxidative stress.[19] Levels of thiobarbituric acid reactive substances (TBARS) are specifically used as indicators of lipid peroxidation.[20] Two meta-analyses have found evidence of increased NO levels and lipid peroxidation in BD, but no significant alterations in other antioxidant enzymes.[18,21]

Although some researchers have reported the effects of psychopharmacological treatments on cognitive function and brain structure, this issue remains unclear due to the limited number of studies and conflicting findings. To date, the therapeutic and adverse effects of lithium in BD have been extensively investigated. Neuroimaging studies suggest that lithium use in BD may normalize or increase gray matter volumes, particularly in the hippocampus, amygdala, and anterior and subgenual cingulate cortices.[22] However, while some clinical studies report that lithium improves neurocognitive function, others have found associations between lithium use and cognitive deficits, particularly in psychomotor speed. Moreover, the effects of both short- and long-term lithium treatment remain unclear.[23,24] Evidence, mostly from epilepsy studies, indicates that anticonvulsants – also used as mood stabilizers in BD – may be associated with cognitive impairments, including psychomotor slowing, memory decline, and reduced attention.[24,25] Additionally, a meta-analysis by Bora et al.[26] found that antipsychotic treatment in BD is associated with psychomotor slowing, which may also contribute to deficits in verbal fluency, attention, and executive function.

The potential effects of psychotropic medications on neurocognitive function and brain structure, along with the methodological challenges in controlling for medication use, remain major limitations in studies aiming to investigate the clinical and neurobiological characteristics of BD.

The aim of this study is to test the hypothesis that the neurocognitive and brain structural abnormalities typically reported in chronic, medicated patients are also present in early-stage, unmedicated patients, and whether these abnormalities are associated with increased oxidative stress.

Methods

Participants

The study sample consisted of early-stage, drug-naive patients (DNP) with BD (n=27) and healthy controls (HC) (n=27) matched for age, sex, and education. Participant selection followed a four-step process (Figure 1).

First, the Hypomania Checklist 32 items (HCL-32R)[27] was administered to all first-year students at Celal Bayar University (n=2,757). Of these, 1,688 screened positive, defined as a score of $\geqslant$ 14 on the HCL-32R. From this group, 1,197 individuals were successfully contacted using the information they had previously provided and agreed to participate in further assessment.

Second, all enrolled participants underwent a phone interview conducted by a psychiatrist using the Mood Disorders Module of Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I).[28] This step identified 52 individuals with a possible diagnosis of BD.

Third, these individuals were invited to the Department of Psychiatry at Hafsa Sultan Hospital, Celal Bayar University, where they completed a full SCID-CV interview conducted by a psychiatrist. A diagnosis of BD was confirmed in 30 participants. Of these, 27 met additional inclusion criteria of never having received a formal diagnosis or treatment for BD and agreed to participate in the study. The remaining 22 participants were excluded due to not meeting full diagnostic criteria according to the DSM-IV, or because of diagnoses such as Attention-Deficit/Hyperactivity Disorder (ADHD), personality disorders, or other exclusionary conditions.

Finally, a healthy control group matched for age, sex, and education was selected from participants who screened negative on the HCL-32R. These controls were also assessed using the full SCID-CV interview to confirm the absence of any personal history of psychiatric disorders and any severe psychiatric disorders in their first-degree relatives.

Additional eligibility criteria for all participants were: (i) age between 18 and 30 years; (ii) no history of brain trauma, neurological disorders, or severe medical illness; and (iii) no lifetime history of alcohol or substance abuse or dependence. Patients were excluded if they had a prior diagnosis of any other Axis I or II psychiatric disorder, any history of treatment with antipsychotics or mood stabilizers, any previous psychiatric hospitalization, or a prior diagnosis and treatment for BD.

Clinical assessment

In addition to the diagnostic interviews described above, all participants – regardless of diagnosis – were evaluated for functional outcomes using the Functioning Assessment Short Test (FAST)[29] and for psychopathology using the Structured Interview Guide for the Hamilton Depression Rating Scale – Seasonal Affective Disorder Version (SIGH-SAD)[30] and the Young Mania Rating Scale (YMRS).[31]

Cognitive assessment

All participants completed the following cognitive tasks: (i) the Wisconsin Card Sorting Test (WCST), the Stroop Color-Word Test (SCWT), and the Trail Making Test (TMT) to assess executive functions; (ii) the Continuous Performance Test (CPT) to assess sustained attention; (iii) the Digit Span subtest from the Wechsler Adult

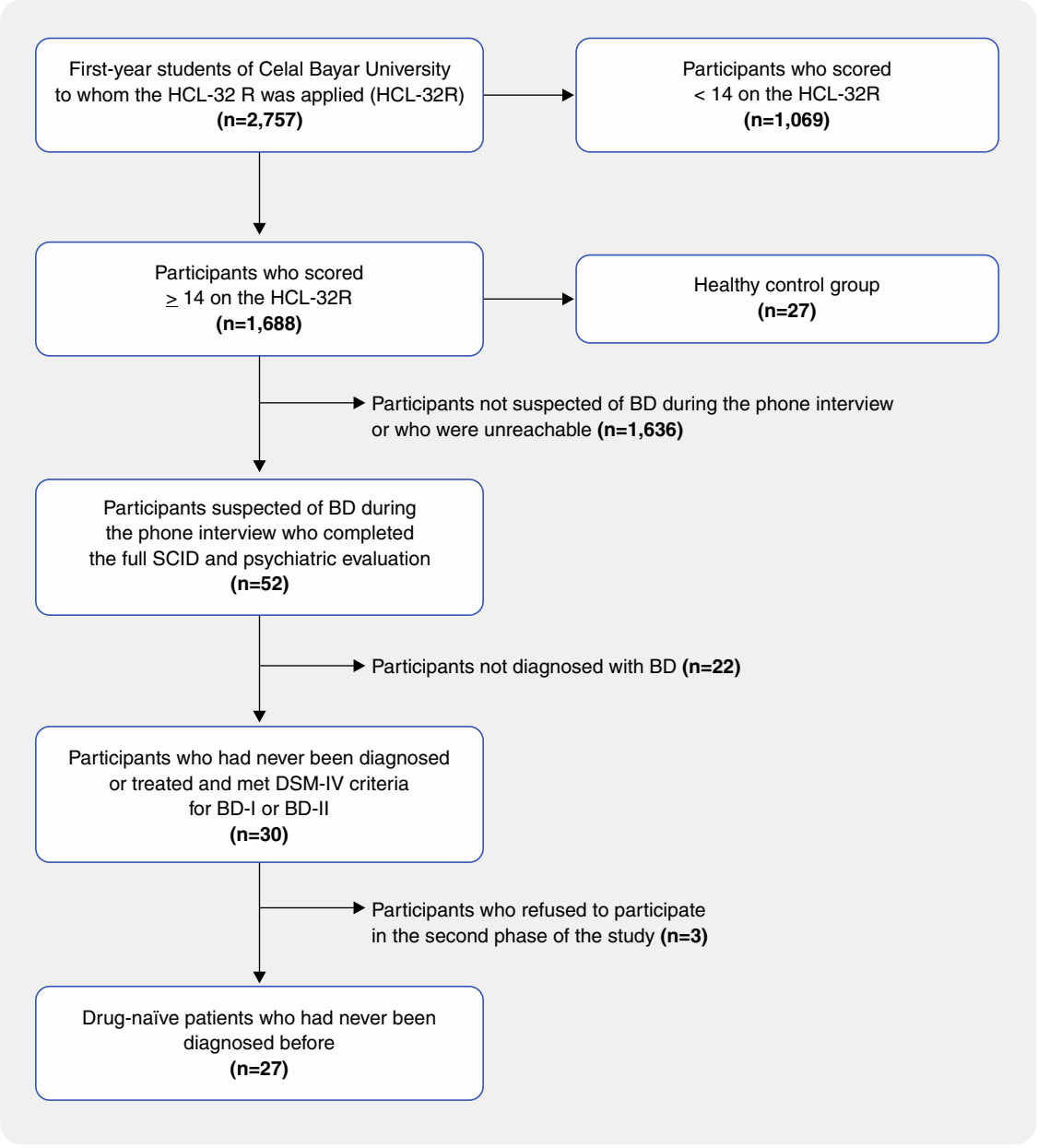


Figure 1 Participant inclusion flow chart. DNP = drug-naive patients; HC = healthy control; HCL-32R = Hypomania Checklist 32 items.

Intelligence Scale (WAIS) to evaluate working memory; (iv) the Digit Symbol Coding Test (DSCT) from the WAIS as a measure of processing speed, attention, and working memory; and (v) the Rey Auditory Verbal Learning Test (RAVLT) to assess verbal learning and memory.

The Stroop interference effect was calculated using the following formula: color word score – ([word score + color score]/2).[32]

Assessment of oxidative stress

Peripheral venous blood samples were collected in plain tubes (without anticoagulant) after overnight fasting. Samples were centrifuged at 4,000 rpm for 10 minutes at +4 °C. The separated serum was frozen and stored at -80 °C until analysis. Commercially available assay kits were used to measure SOD, CAT, NO, and TBARS. All analyses were performed in the same laboratory.

One participant from the DNP group was excluded from the oxidative stress analysis due to a spoiled sample.

Neuroimaging

Magnetic resonance imaging (MRI) image acquisition

MRI data for all participants were acquired using the same General Electric Signa HDxt 1.5 Tesla scanner at the Radiology Department of Celal Bayar University.

Images were obtained using axial 3D T1-weighted Fast Spoiled Gradient-Recalled Echo (FSPGR) sequences (TE = 7.1-17.0, field of view [FOV] = 24 cm^2, slice thickness = 1.6 mm, flip angle = 15°, read bandwidth [RBW] 10.42 kHz, NEX: 1, freq = 256, phase = 192, phase FOV = 0.85).

Image processing

All MRI scans were visually inspected for brain abnormalities and image quality. Cortical thickness and volumetric segmentation were performed using FreeSurfer v5.3.0 (http://surfer.nmr.mgh.harvard.edu/).[33-37] Each participant's T1-weighted image was first registered to Talairach space. Images were then segmented into white matter (WM) and gray matter (GM) based on local and neighboring intensity values. The cortical surface of each hemisphere was inflated to an average spherical surface to accurately delineate both the pial surface (GM) and the WM/GM boundary. The cerebral cortex was parcellated into regions according to the Desikan-Killiany atlas.

All regional measures – including cortical thickness and subcortical volumes – were extracted using FreeSurfer. Upon completion, all images were visually inspected again, and any topological inaccuracies were manually corrected.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 21.0. The normality of variable distributions was assessed using the Shapiro-Wilk test. Chi-square tests were used for categorical variables, and Student's t-tests were applied to continuous variables with normal distributions.

Differences in neurocognitive test performance, oxidative stress marker levels, and clinical variables with non-normal distributions were analyzed using Mann-Whitney U tests. The threshold for statistical significance was set at $p < 0.008$ for demographic and clinical variables, $p < 0.002$ for cognitive variables, and $p < 0.01$ for oxidative stress measures, all adjusted using Bonferroni correction for multiple comparisons.

Group differences in cortical thickness were assessed using a general linear model (GLM) implemented in the Query, Design, Estimate, Contrast (QDEC) application of FreeSurfer. Total gray matter volume was included as a covariate in the model. The significance threshold was set at $p < 0.01$, with Monte Carlo simulation (10,000 iterations) applied to provide cluster-wise correction for multiple comparisons.

Ethics statement

The study protocol was approved by the Regional Ethic Committee of Celal Bayar University, and written informed consent was obtained from all participants prior to their inclusion in the study.

Results

Demographic, clinical, and functional characteristics

The demographic and clinical characteristics of the two groups are presented in Table 1. One participant from the HC group was excluded due to poor-quality imaging data. There were no significant group differences in age, sex, or education level. Family history of BD and other psychiatric disorders was also similar between groups.

None of the DNP participants reported a family history of BD in first-degree relatives; however, one participant reported BD in a second-degree relative. Other psychiatric conditions reported in the DNP group included depressive disorder in the mothers of two participants and ADHD in the brother of one participant. In the HC

Table 1 Demographic and clinical features of the sample

	DNP (n=27)	HC (n=27)	p-value
Age, years (mean ± SD)	20.85±2.08	21.70±0.99	0.0630
Gender (%)			
Female	59.30	59.30	1.0000
Male	40.70	40.70	
Education, years (mean ± SD)	13.33±1.10	13.74±1.25	0.2100
FAST (mean ± SD)	18.44±10.97	4.74±3.66	< 0.0001
HAM-D (median)	3.00	1.00	< 0.0001
YMRS (median)	3.00	0.00	< 0.0001
BD type (%)			
BD I	55.60		
BD II	44.40		
Family history of BD in first-degree relatives (%)	0.00	0.00	
Family history of OPD in first-degree relatives (%)	11.10	7.40	0.6390

BD = bipolar disorder; DNP = drug-naive patients; FAST = Functioning Assessment Short Test; HAM-D = Hamilton Depression Rating Scale; HC = healthy controls; OPD = other psychiatric disorders; YMRS = Young Mania Rating Scale.

group, one participant's father and another's mother had been diagnosed with depressive disorder.

The DNP group showed significantly lower daily psychosocial functioning compared to the HC group across all domains of the FAST (Table 2). At the time of assessment, none of the DNP participants were experiencing a mood episode; however, only 62.9% were asymptomatic (defined as Hamilton Depression Rating Scale [HAM-D] $<$ 8 and YMRS $<$ 5). Although all participants scored below the clinical cutoff of 8 on the HAM-D, 37.03% of the DNP group showed mild manic symptoms, with YMRS scores between 5 and 8, which do not meet the threshold for a manic episode but still reflect subclinical symptoms.

None of the participants in either group reported substance use within the past year.

Cognitive task performance

The DNP group underperformed on all cognitive tasks compared to the HC group. However, group differences that survived Bonferroni correction were observed in the WCST and RAVLT (Table 3).

Patients made significantly more total errors and perseverative errors and achieved significantly fewer categories on the WCST. In the RAVLT, patients performed significantly worse across all recall conditions,

Table 2 Domain-specific psychosocial functioning in DNP and HC groups

				DNP		HC	
	z	U	p-value	Median	Mean rank	Median	Mean rank
Autonomy	-3.19	200.50	0.001	1.00	33.57	0.00	21.43
Occupational functioning	-3.31	180.00	0.001	3.00	34.33	0.00	20.67
Cognitive functioning	-3.89	142.50	0.000	4.00	35.72	2.00	19.28
Financial issues	-4.93	90.50	0.000	3.00	37.65	0.00	17.35
Interpersonal relationships	-5.36	63.00	0.000	3.00	38.67	0.00	16.33
Leisure time	-2.54	225.50	0.011	1.00	32.65	0.00	22.35

DNP = drug-naive patients; HC = healthy controls.

Table 3 Cognitive task performance in DNP and HC groups

				DNP		HC	
	z	U	p-value	Median	Mean rank	Median	Mean rank
Executive functioning							
WCST							
Total errors	-4.93	80.00	0.000	26.00	38.04	17.00	16.96
Perseverative responses	-4.31	117.00	0.000	10.16	36.67	7.81	18.33
Categories	-4.43	114.00	0.000	8.00	18.22	9.00	36.78
Stroop task							
Word score (s)	-2.39	226.00	0.017	9.64	32.63	8.58	22.37
Color Score (s)	-1.70	266.00	0.088	11.37	31.15	10.55	23.85
Color word score (s)	-2.56	216.00	0.010	22.19	33.00	17.96	22.00
Stroop interference effect[†]	-2.10	243.00	0.036	11.02	32.00	7.81	23.00
TMT-B (s)	-2.65	211.00	0.008	55.84	33.19	44.52	21.81
Working memory							
Digit Span Test							
Forward	-2.28	236.50	0.022	7.00	22.76	7.00	32.24
Backward	-2.91	203.00	0.004	5.00	21.52	5.00	33.48
Processing speed							
TMT-A (s)	-2.58	215.00	0.010	23.46	33.04	20.84	21.96
DSCT	-1.14	298.50	0.253	70.00	25.06	70.00	29.94
Sustained attention							
CPT omission error	-2.17	262.50	0.030	0.00	31.28	0.00	23.72
Verbal learning/memory							
RAVLT							
Immediate recall (total 1-5)	-3.80	145.00	0.000	50.00	19.37	60.00	35.63
Short delay recall (list 6)	-3.41	169.00	0.001	11.00	20.26	13.00	34.74
Long delay recall (list 7)	-3.71	151.50	0.000	10.00	19.61	13.00	35.39
Recognition	-2.16	244.50	0.030	13.00	23.06	14.00	31.94

CPT = Continuous Performance Test; DNP = drug-naive patients; DSCT = Digit Symbol Coding Test; HC = healthy controls; RAVLT = Rey Auditory Verbal Learning Test; TMT = Trail Making Test; TMT-A = connecting numbers in ascending order; TMT-B = alternating between numbers and letters in ascending order; WCST = Wisconsin Card Sorting Test.
[†] Interference between language and color information.

Table 4 Oxidative stress markers and lipid peroxidation levels in DNP and HC groups

				DNP†		HC	
	z	U	p-value	Median	Mean rank	Median	Mean rank
SOD (ng/mL)	-1.26	280.00	0.206	12.73	24.27	15.80	29.63
CAT (nmol/mL)	-2.98	183.00	0.003	66.08	33.46	46.43	20.78
NO (μmol/L) ± SD	-0.64	315.00	0.522	8.85	28.38	9.52	25.67
TBARS (nmol/mL)	-1.53	264.50	0.124	1.31	30.33	1.14	23.80

CAT = catalase; DNP = drug-naive patients; HC = healthy controls; NO = nitric oxide; SOD = superoxide dismutase; TBARS = thiobarbituric acid reactive substances.
† Data missing one of the patients.

but the difference in the recognition condition did not reach statistical significance.

Oxidative stress markers

None of the group differences in oxidative stress markers survived correction for multiple testing, except for CAT, which was significantly higher in the DNP group compared to the HC group (Table 4).

Brain morphometry

Cortical thickness

The DNP group exhibited significant cortical thinning in multiple regions compared to the HC group. These included the bilateral temporal lobes, superior and middle frontal gyri, superior and inferior parietal lobules, precentral, postcentral, and paracentral gyri, insula, bilateral precuneus, left orbitofrontal cortex, and the right pars triangularis (Figure 2A; Table 5).

Discussion

In the present study, psychosocial functioning, neurocognitive performance, oxidative stress, and brain structure were examined in a sample of students with previously undiagnosed and untreated BD.

Among the 1,197 respondents who screened positive on the HCL-32, we identified 30 cases of previously undiagnosed BD, yielding a point prevalence of 2.5%, assuming a similar rate among those who screened positive (n = 491) but did not participate in the subsequent assessments. This prevalence rate is remarkably close to the 2.4% reported in the World Mental Health Survey (WMH).[2]

Although the patients identified in this study could be considered high-functioning, as they were university students, their psychosocial functioning – specifically in the domains of autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships, and leisure time, as assessed by the FAST – was significantly lower than that of their peers without mental health problems. These findings are consistent with those reported in more chronic, euthymic patients with BD.[38,39] Furthermore, they confirm that these impairments are independent of psychotropic treatment, as the current sample had never received medication.[40,41] Notably, to our knowledge, this is the first study to examine psychosocial functioning in never-medicated patients with BD.

Previous studies have reported that impaired psychosocial functioning is associated with neurocognitive dysfunction and subthreshold affective symptoms.[14,15,42] Although only seven participants in the DNP group exhibited subthreshold manic symptoms, these symptoms were very mild, with a maximum YMRS score of 8, yet still higher than those reported by the HC group. This finding may suggest that a persistent vulnerability to affective morbidity is present in patients even outside of full-blown mood episodes. Such vulnerability may negatively impact their engagement in social roles and activities.

An extensive body of research has shown that many patients with BD exhibit significant cognitive impairments, regardless of mood state, particularly in executive function, attention, verbal learning, and memory.[8,11,43] In the present study, patients with BD underperformed across all cognitive tasks; however, statistically significant differences were observed in the WCST and RAVLT, which primarily assess abstraction/cognitive flexibility and verbal learning and memory, respectively. Abstraction and cognitive flexibility are typically mediated by the dorsal and ventral prefrontal cortices. Nevertheless, previous studies have demonstrated that successful performance on the WCST relies on the engagement of a widespread neural network, involving prefrontal, frontal, temporal, parietotemporal, and parieto-occipital cortical regions during various stages of the task.[44,45]

Furthermore, one study demonstrated a correlation between the recognition of familiar words and activation in the right lateral prefrontal cortex as well as between the processing of novel words and the right anterior hippocampus.[46]

The cognitive profile observed in the current sample aligns with the neuroimaging findings, which revealed cortical thinning in several regions, including the prefrontal and temporal cortices, areas critically involved in cognitive control and verbal learning and memory. Structural abnormalities in these regions, among others, have also been reported in the largest case-control study of BD to date, conducted by the Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) Consortium, which included data from 2,447 patients.[17] The present findings further support the notion that such structural brain abnormalities are an integral component of syndromal expression of BD.

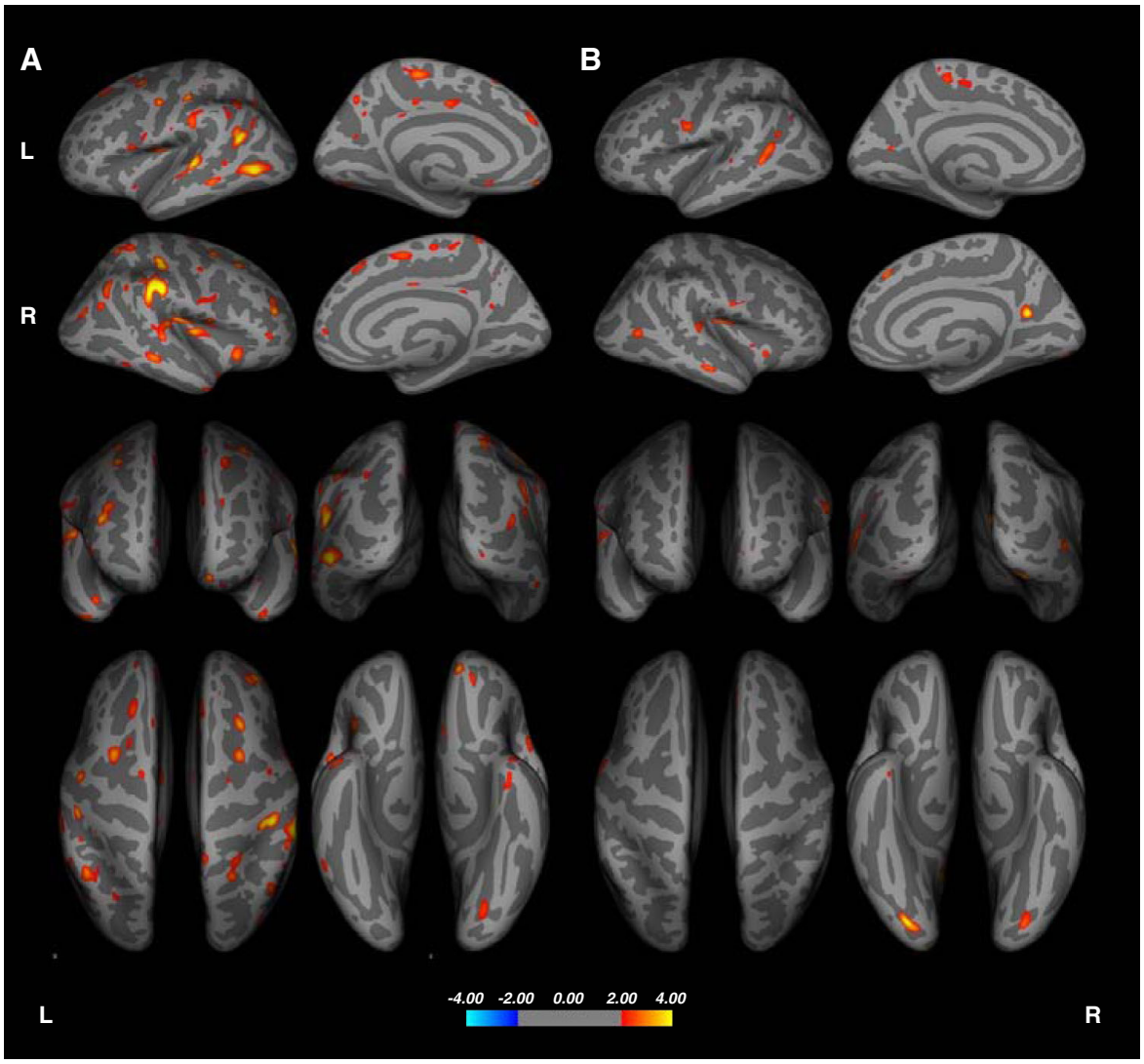


Figure 2 Cortical areas showing significant differences in healthy controls and drug-naive patients groups in A) cortical thickness and B) cortical volume, displayed on QDEC's semi-inflated cortical surfaces. Top row: L lateral and L medial; Second row: R lateral and R medial; Third row: anterior and posterior; Bottom row: superior and inferior views. The color bar indicates the significance levels of the clusters. Results were corrected for multiple comparisons using Monte Carlo simulation ($p < 0.01$, cluster-wise correction). L = left hemisphere; QDEC = Query, Design Estimate, Contrast application; R = right hemisphere.

Oxidative stress, along with associated lipid peroxidation, has been proposed as a potential mechanism underlying brain abnormalities in BD, thereby contributing to the manifestation of clinical symptoms and cognitive deficits. Two meta-analyses have reported significantly elevated levels of NO and TBARS in blood cells or serum from patients with BD, without concomitant changes in antioxidant enzymes (e.g., SOD, CAT, and GPx).[18,21]

However, our findings suggest that oxidative stress may not be present in the early stages of the disease but may instead emerge in more severe cases or as a consequence of illness progression. In contrast to the expected pattern of oxidative imbalance, patients in this study showed a significant increase in CAT levels. This is consistent with a prior study in early-stage BD, which also reported elevated CAT levels.[47] Additionally, another study found a negative correlation between CAT levels and illness duration in more chronic patients.[48]

Another possible explanation is that the oxidative stress markers used in this study are not sensitive enough to detect early alterations. For example, increases in protein carbonyl content (PCC), a marker of oxidative protein modification, have been detected in population-based samples that identified patients with less severe or early-stage presentations, similar to the current study.[49]

Moreover, elevated TBARS levels appear to be primarily observed in studies involving chronic patients or those with more severe clinical presentations. Accordingly, previous research found no case-control differences in TBARS in early-stage BD[47] or in population-based studies of BD with a milder disease course.[49] Similarly, Siwek et al.[50] reported that TBARS levels were increased

Table 5 Regional cortical thickness in DNP and HC groups

Region	Value (log p)	Talairach coordinates			Size (mm^2)
		X	Y	Z	
Superior temporal					
L	4.24	-25.7	3.8	706	328.85
R	3.32	47.2	-29.3	7.4	371.00
Middle temporal					
L	2.98	-62.3	-40.3	-9.6	102.13
R	3.05	64.6	-30.5	-9.8	139.17
Inferior temporal					
L	4.21	-45.1	-63.9	-2.1	422.63
R	2.43	52.8	-53.3	-16.8	57.68
Temporal pole					
L	2.57	-35.7	14.4	-37.4	80.89
R	2.17	31.0	3.2	-30.1	3.78
Precentral					
L	3.35	-48.7	-8.8	40.1	94.45
R	2.85	51.0	2.9	4.7	108.70
Postcentral					
L	3.56	-40.1	-9.4	16.3	145.87
R	4.22	43.0	-27.2	45.8	315.76
Paracentral					
L	3.01	-5.5	-30.9	52.9	146.51
R	2.36	7.9	-20.8	57.9	45.53
Superior frontal					
L	2.67	-20.7	24.2	46.4	122.93
R	2.66	8.7	0.7	56.4	123.43
Rostral middle frontal					
L	2.30	-17.4	49.7	26.7	26.13
R	3.67	38.3	46.1	20.6	300.94
Caudal middle frontal					
L	3.31	-27.1	0.7	47.6	129.49
R	3.52	29.4	17.0	44.2	106.06
Superior parietal					
L	2.36	-28.1	-63.8	40.0	52.56
R	2.94	24.6	-56.7	59.2	224.23
Inferior parietal					
L	4.18	-39.9	-53.0	17.1	311.34
R	2.81	44.5	-62.5	35.4	194.16
Supramarginal					
L	2.74	-60.6	-28.0	27.2	183.41
R	4.93	60.0	-28.1	36.9	819.24
Precuneus					
L	2.54	-5.8	-69.7	41.2	53.32
R	2.17	5.7	-60.0	18.7	22.46
Posterior cingulate					
L	2.72	-5.7	-7.7	40.2	80.58
R	2.63	4.5	-5.6	36.7	20.88
Isthmus cingulate					
L	2.19	-4.3	-37.3	31.4	15.25
R	2.21	4.7	-39.1	31.2	19.11
Insula					
L	2.18	-36.6	0.6	-8.9	15.67
R	3.51	34.6	-23.1	20.7	193.23
Medial orbitofrontal					
L	3.56	-5.1	53.5	-20.5	91.59
Lateral orbitofrontal					
L	2.44	16.0	43.1	-18.1	43.47
Pars opercularis					
L	2.63	-50.6	11.4	3.9	114.24
Pars triangularis					
R	2.47	44.4	37.7	0.3	58.65
Fusiform					
L	2.48	-16.0	43.1	-18.1	43.47

HC = healthy controls (n=26; one excluded due to poor image quality); DNP = drug-naive patients with bipolar disorder (n=27). $p < 0.01$. L = left hemisphere; R = right hemisphere.

only in symptomatic patients, thereby suggesting lipid peroxidation becomes more prominent as the number of mood episodes accumulates over time.

The main strength of the present study lies in the inclusion of a sample of high-functioning, early-stage, never-medicated patients with BD who were not experiencing a mood episode at the time of assessment. Consequently, the findings are free from confounding factors associated with chronicity, psychotropic medication, and acute psychopathology. Patients were carefully matched to controls in terms of academic achievement and education, as the entire sample consisted of university students. This matching strategy helps mitigate potential case-control differences that could otherwise be attributed to the effects of educational attainment. Additionally, the study adopted an epidemiological approach, rather than focusing on help-seeking or clinically referred populations. Such designs enhance the representativeness of the sample, albeit within a population of high-achieving individuals. Finally, both patients and controls underwent a comprehensive assessment, including molecular, brain structural, cognitive, and functional evaluations. This multimodal approach provides a more comprehensive understanding of the neurobiology of BD than is typically achieved in most studies. Although the sample size is relatively small, this is consistent with the generally low prevalence of BD in population-based samples and aligns with point prevalence estimates reported in the literature. The cross-sectional nature of the study does not permit conclusions about the progression of the detected abnormalities, but it provides a critical foundation for future longitudinal studies aimed at tracking the clinical trajectories of these patients and their associations with cognition, brain structure, and oxidative stress.

In summary, this study is the first to demonstrate that cognitive, functional, and brain structural alterations are already present in the early stages of BD, even among high-achieving individuals. These findings contribute valuable insights to the current understanding of the neurobiology of BD and advance the existing body of knowledge on the disorder.

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Disclosure

The authors report no conflicts of interest.

Data availability statement

The data that support this study are available from the authors upon request.

Author contributions

SO: Conceptualization, Investigation, Formal analysis, Project administration, Resources, Visualization, Writing-original draft.
FAU: Investigation, Resources, Formal analysis.
AO: Investigation, Formal analysis.
FT: Investigation, Formal analysis.
SF: Formal analysis, Supervision, Writing – review & editing.
OA: Conceptualization, Methodology, Formal analysis, Project administration, Resources, Supervision, Writing – Review & editing.
All authors have read and approved of the final version to be published.

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