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Reduced Cortical Thicknesses of Adolescents with Bipolar Disorder and Relationship with Brain-derived Neurotrophic Factor

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Abstract

Background: Cortical thickness (CT) and brain-derived neurotrophic factor (BDNF) were widely investigated in bipolar disorder (BD). Previous studies focused on the association between the volume of subcortical regions and neurotrophic factor levels.

Objective: In this study, we aimed to evaluate the association of the CT in youth with early-onset BD with BDNF levels as a potential peripheral marker of neuronal integrity.

Method: Twenty-three euthymic patients having a clinical diagnosis of BD and 17 healthy subjects as an age-matched control group with neuroimaging and blood BDNF levels were found eligible for CT measurement. A structural magnetic resonance scan (MRI) and timely blood samples were drawn.

Results: Youth with BD exhibited lower cortical thickness in caudal part of left (L) middle frontal gyrus, right (R) paracentral gyrus, triangular part of R inferior frontal gyrus, R pericalcarine region, R precentral gyrus, L precentral gyrus, R superior frontal gyrus and L superior frontal gyrus when compared to healthy controls. The effect sizes of these differences were moderate to large (d=0.67-0.98) There was a significant correlation between BDNF levels with caudal part of the R anterior cingulate gyrus (CPRACG) in adolescents with BD (r=0.49, p=0.023).

Conclusion: As a special region for mood regulation, the CT of the caudal part of the R anterior cingulate gyrus had a positive correlation with BDNF. Regarding the key role of CPRACG for affective regulation skills, our results should be replicated in future follow-up studies, investigating a predictive neuroimaging biomarker for the early-onset BD.

Keywords: Brain-derived neurotrophic factor, Cortical thickness, Early-onset bipolar disorder, Neurotrophic factors

Introduction

Early-onset bipolar disorder (BD) is a debilitating mental disorder defined with the illness-onset under the age of 18. Early-onset BD is also characterized by episodes of depression, mania, and interval periods of well-being (1). Reliable early identification of neurobiological abnormalities in BD is important to improve outcomes (2). Structural or functional disruptions of the brain could pose a state of vulnerability to BD; however, the results from morphometric imaging studies are inconsistent (3-6). Although there has been some relative agreement across studies in earlier research, neuroimaging studies of BD frequently provide inconsistent results. Increased white matter hyperintensities and ventricular enlargement were the most consistent findings from the studies conducted with patients with BD (7). Identifying robust and reliable neural biomarkers for BD is a potential strategy for better understanding the underlying neurobiology and improving patient treatment outcomes (8).

Gray matter volume (GMV) could be a useful biomarker for the early detection of BD in clinical settings. GMV is generally calculated by using two different types of measurements known as the cortical thickness (CT) and the surface area (9). Some studies have investigated CT in terms of the size and measure of cortical columns and layers in patients with early-onset BD as compared with healthy controls. In a study by Elvsåshagen and colleagues, patients with BD had thinner cortices when compared with healthy participants in some specific

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areas such as anterior cingulate cortex (ACC), prefrontal cortex (PFC) and left (L) temporal region (10). Another study found reduced local brain volume and cortical thickness among early-onset BD subjects (3). Also, the differences between bipolar-I disorder and bipolar-II disorder were found in medial orbitofrontal and superior temporal regions (3).

A recent study evaluating CT as a predictive parameter in adolescents who were at risk for BD revealed that mixed or manic mood episodes and irritability factor scores could be estimated by CT in the lower parietal lobe (11). Results reported in the Bipolar Offspring Study also indicated that higher levels of CT in the L ventrolateral prefrontal cortex could predict higher mixed/manic episode factor scores in youth (11). A neuroimaging study of early-onset BD also suggested that a decrease in the cerebellum gray matter volume of patients with early-onset BD could be an endophenotype (12).

Considering that only a few studies with relatively modest sample sizes investigated CT in patients with early-onset BD, current evidence remains inconclusive to suggest neuroimaging parameters as clinical biomarkers. Thus, CT changes in the population with early-onset BD could provide supporting evidence for the youth at-risk of developing full BD. Despite recent studies investigating early signs and symptoms of BD in the existing literature (13), the clinical need for the bipolar-specific blood biomarkers and neuroimaging signs for the early detection of BD is yet to be met. Identification of peripheral and neuroimaging biomarkers of early-onset BD may contribute to the future prediction of transformation into fully developed BD in high-risk groups (14,15).

Neurotrophins consist of a set of signaling molecules in the brain responsible for neurogenesis, synaptic strength, and synaptic plasticity (16,17). Previous studies investigated the transmission of Brain-derived neurotrophic factor (BDNF) Val66 polymorphism in patients with prepubertal BD (18). In addition to the growing evidence suggesting their possible role in the development of a list of psychiatric disorders, there are also an increasing number of studies reporting the association between disrupted neurotrophic factor activities and decreased regional brain volumes in the subjects with BD (19). In our previous reports, we found a significant positive correlation between amygdala volumes and serum BDNF levels (20). In the same study, serum BDNF levels were also correlated with the total duration of treatment (21). Conversely, hippocampal volumes were not associated with peripheral BDNF levels (21). Nevertheless, relatively few studies evaluated the effect of neurotrophic factors in the pathophysiology of BD and mainly reported inconsistent and controversial findings (22,23). In particular, it is stated that controversial results may arise from the differentiation and survival of neurons and act by modulating synaptic transmission and plasticity. Accordingly, more studies are still needed to establish the role of BDNF in early-onset BD populations.

Despite the studies investigating neuroimaging and biomarkers in early-onset BD, previous studies mainly had limitations and heterogeneity in terms of sample size, BD phenotype, psychiatric comorbidities, and biomarkers included (14). Determination of the changes in CT and the impact of BDNF may play a role as possible diagnostic and follow-up biomarkers in early-onset BD; however, the existing literature is scarce to confirm this association. The ACC is a key center integrating cognitive and affective neuronal connections, where consistent alterations in brain metabolites have been consistently reported in BD. To date, only one study has addressed the association of BDNF rs6265 on neurochemical profile in the ACC of Healthy Controls (HC) and BD subjects. In the present study, we investigated the following; i) morphometric deviations in CT of youth with BD in comparison to healthy controls and ii) relationship between serum BDNF levels and the CT of ACC as playing a key role in mood regulation. We hypothesized that the CT of ACC would be correlated with serum BDNF levels in adolescents with BD. Also, the CT measured in the early-onset BD group would be significantly thinner than that of healthy controls.

Methods

Participants

Detailed information about the participants, clinical procedures, results of blood tests, and neuroimaging procedures implemented in the current study were provided in the papers previously published (20,24,25). In brief, all subjects were consecutively recruited from the follow-up list of out- and inpatient clinics of a tertiary care hospital. Informed consent was sought from legal guardians/caregivers and written assent was obtained from the participants under 18 years of age. The Turkish version of "Kiddie and Young Adult Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version (K-SADS-PL)" was used for diagnostic assessment (26,27). Researchers also implemented the affective module of the Turkish version of "Washington University at St. Louis Kiddie and Young Adult Schedule for Affective Disorders and Schizophrenia" (WASH-U-K-SADS) (28). Exclusion criteria of the study were: i) organic brain disease (including seizures, severe head injury), ii) use of psychostimulant, antipsychotic or antidepressant medications before a full BD diagnosis was

confirmed, iii) current or history of schizophrenia and autism spectrum disorder iv), a clinical diagnosis of intellectual disability, v) any other chronic disease and vi) current substance use disorder. Comorbidities of BD group including anxiety disorders, attention deficit hyperactivity disorder, oppositional defiant disorder, and conduct disorder were endorsed in the study.

All MRI scans and blood samples were obtained when patients were in a euthymic mood state. Criteria for euthymia were defined as the total scores of the Young Mania Rating Scale (YMRS) and the total Hamilton Depression Rating Scale (HAM-D) being less than 7 during at least the previous three months.

Laboratory Procedures

All subjects underwent a blood sample collection between 09: 00 a.m. and 10: 00 a.m. after overnight fasting. BDNF (Millipore, ChemiKine, CYT306) serum levels were measured with sandwich ELISA using a commercial kit. After patients gave their blood samples, they underwent an MRI scan within 24–72 h.

MRI acquisition, preprocessing and analysis

This study investigates region of interest (ROI)-based atlas-defined differences in study sample. The vertex-based analysis is aimed to determine voxel-wise group comparison across the cortical surface, whereas the ROI-based analysis averages across all voxels within an atlas-based ROI to define differences that affect different parts of an anatomical area (ROI) across subjects. All MRI scans were acquired using a 1.5 Tesla Achieva MR scanner (Philips Medical Systems, Best, The Netherlands). Three dimensional high resolution T1 weighted coronal images (TR 25 ms; TE 6 ms; slice thickness 1 mm; FOV 230; matrix 400 ×512; flip angle 30°; NEX 1) were used for CT analysis.

Structural images were analyzed using automated procedures in the CAT12 (Computational Anatomy Toolbox; http://www.neuro.uni-jena.de/cat/) within SPM12 software (Statistical Parametric Mapping; http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) running in MATLAB R2018.b (Mathworks, Sherborn, MA, USA) to estimate CT. MR images were aligned to the MNI (Montreal Neurological Institute) standard space. These images were classified as gray matter, white matter, and cerebrospinal fluid. Images were quality checked on the CAT12 report files. It was assured that all data had an average value of B or higher for the parameters noise, resolution, bias, and weighted average, representing good image quality (http://www.neuro.uni-jena.de/cat12/CAT12-Manual.pdf).

CT was calculated based on the projection-based thickness (PBT) method for the left and right hemispheres. Tissue segmentation was used to estimate the white matter distance, then project the local maxima onto other gray matter voxels using white matter distance that describes neighbor relationships (29). The estimated mean CT values for ROIs were extracted for all the regions in the "Desikan-Killiany-Tourville" Brain Atlas (DKT40) using the CAT12 "Extract ROI-based surface values" function (30). Six (13.04%) patients record were excluded from the study due to poor image quality. CT measurements were calculated by correcting for total intracranial volume values. The extracted CT values were transferred to SPSS.

Statistical Analysis

After controlling the normal distribution of variables, independent sample t-test was used to compare CT values of both groups. The chi-square test was implemented for categorical variables. The effect size measure of significant results were calculate per Cohen's d. To test our second hypothesis, Partial correlation analyses adjusted for age at onset and socioeconomic status were preferred to investigate the relationship between serum BDNF values and the CT of ACC. In order to conduct parametric tests, serum BDNF values were converted into normal distribution by using logarithmic transformation.

Finally, we implemented posthoc analyses to reveal the effects of age, the duration of illness, and pharmacological treatments on study results. The Mann-Whitney U test was implemented to compare patient subgroups treated with mood stabilizers in posthoc tests. The serum BDNF levels and CT were compared between patient subgroups regarding the presence of lithium or valproate treatment. Pearson correlation analyses were conducted for age and the duration of the illness to test their correlation with serum BDNF levels and CT in the patient group. Alpha was set at 0.05. Trend level was defined for p values less than 0.1 level. False discovery rate correction was not implemented regarding explorative and hypothesis-generating purposes of the study. SPSS 22.0 software (IBM Corp., Armonk, NY, USA) for statistical analysis.

Results

Participants

Table 1 demonstrates the demographics and clinical characteristics of study participants. 23 (n=57.5%) adolescents with BD and 17 (n=42.5%) healthy controls were included (%52.5 female, aged between 12.0-19.0 years). The mean age at the time of the interview was 16.3 ± 1.2 years. Study groups did not

TABLE 1. Demographics and clinical characteristics of study participants

Characteristics of study participants	Patients with BD n=23	Healthy controls n=17	*Statistics*	*p*
Sex, female, n (%)	13 (56.5)	8 (47.1)	X^2=0.4	0.554
Age at the time of interview, years, mean ± SD	16.3 ± 1.4	16.2 ± 1.0	t=0.1	0.948
Socioeconomic status, n (%)			X^2=1.8	0.413
High	2 (8.7)	1 (5.9)		
Average	16 (69.6)	9 (52.9)		
Low	5 (21.7)	7 (41.2)		
Family history of psychiatric disorders, n (%)				
First-degree relative with a psychiatric disorder	11 (47.8)	-	-	-
A second-degree relative with a psychiatric disorder	13 (56.5)	-	-	-
First or second-degree relative with a psychiatric disorder	18 (78.3)	-	-	-
Illness characteristics				
Age at onset, years, mean ± SD	14.3 ± 2.1	-	-	-
Duration of BD, years, mean ± SD	2.3 ± 1.4	-	-	-
Duration of medication treatment, years, mean ± SD	2.0 ± 1.3	-	-	-
The number of mood episodes, mean ± SD	3.3 ± 2.0	-	-	-
Total YMRS score, mean ± SD [a]	3.2 ± 1.9	-	-	-
Total HAM-D score, mean ± SD [a]	2.5 ± 1.5	-	-	-
Medications, n (%)				
Antipsychotics	18 (78.3)	-	-	-
Aripiprazole	7 (30.4)	-	-	-
Risperidone	6 (26.1)	-	-	-
Quetiapine	4 (17.4)	-	-	-
Olanzapine	1 (4.3)	-	-	-
Mood stabilizers	20 (87.0)	-	-	-
Lithium	8 (34.8)	-	-	-
Valproate	11 (47.8)	-	-	-
Carbamazepine	2 (8.7)	-	-	-
Lamotrigine	2 (8.7)	-	-	-
Blood medication levels, mmol/L				
Lithium, mean ± SD	0.78 ± 0.27	-	-	-
Valproate, mean ± SD	78.6 ± 17.4	-	-	-
Blood neurotrophic factor levels				
BDNF, pg/ml, median (IQR)	1353 (1021-2797)	2227 (1205-3369)	Z=1.4 [b]	0.171

BD=bipolar disorder, BDNF=brain-derived neurotrophic factor, HAM-D=Hamilton Depression Rating Scale, IQR=interquartile range (Q1-Q3), NGF=nerve growth factor, SD=standard deviation, YMRS=Young Mania Rating Scale.
[a] At the time of interview, [b] The Mann-Whitney U test

differ regarding age, sex, and socioeconomic status. Additionally, the BD group reported presence of psychiatric disorders in their first-degree (*n*=11, % 47.8) and second-degree (*n*=13, 56.5%) relatives. The age at onset for BD was 14.3 years and the duration of BD was also 2.3 years. The total number of mood episodes ranged between 1 and 8 (mean=3.3) and the mean duration of medical treatment was two years. At the time of the interview, YMRS and HAM-D scores of all patients with BD were lower than 7 (YMRS= 3.2 ± 1.9 and HAM-D= 2.5 ± 1.5, respectively).

Medications used and neurotrophic factor levels

When MRI scanning was performed, 8 (34.8%) participants had been on lithium for 2.0 years (*range*: 0.5–4.0 years). The mean serum lithium level was 0.78 ± 0.27 (*range*:0.24–1.10 mmol/L). Eleven (47.8%) subjects were on sodium valproate (VPA) (the mean duration of 2.1 years, *range*: 0.5– 4.0) and the mean serum VPA level was: 78.6 ± 17.4 (*range*: 34.0– 97.3 mmol/L). Eighteen (78.3%) patients were also on second-generation antipsychotics (SGA). Lamotrigine (*n*=2, 8.7%) and carbamazepine (*n*=2, 8.7%) were also used in the BD group. Two (8.7%) of the subjects with BD were not on any medication when they participated in the study. Finally, there was no statistical difference for BDNF levels between the BD and control groups (p=0.171).

Evaluation of cortical thickness across various brain regions

Table 2 demonstrates cortical thickness differences between study groups across different brain regions.

TABLE 2. Measured cortical thickness of various brain regions differed between study groups for youth with BD and healthy controls.

Brain Regions	Patients with BD n=23	Healthy controls n=17	*t value*	*p*	*Cohen's d*
Cortical thickness, millimeter, mean ± SD					
The caudal part of L middle frontal gyrus	2.64 ± 0.18	2.81 ± 0.23	-2.5	0.017	0.80
The caudal part of R middle frontal gyrus	2.60 ± 0.22	2.71 ± 0.26	-1.4	0.166	-
L inferior parietal gyrus	2.60 ± 0.17	2.62 ± 0.15	-0.5	0.627	-
R inferior parietal gyrus	2.55 ± 0.16	2.64 ± 0.13	-2.0	0.056	-
L paracentral gyrus	2.30 ± 0.20	2.38 ± 0.18	-1.2	0.219	-
R paracentral gyrus	2.17 ± 0.17	2.31 ± 0.11	-2.9	0.006	0.93
Triangular part of L inferior frontal gyrus	2.83 ± 0.18	2.93 ± 0.18	-1.6	0.112	-
Triangular part of R inferior frontal gyrus	2.75 ± 0.16	2.86 ± 0.16	-2.1	0.041	0.68
L pericalcarine region	1.77 ± 0.13	1.84 ± 0.14	-1.6	0.114	-
R pericalcarine region	1.62 ± 0.10	1.70 ± 0.08	-2.7	0.009	0.88
L precentral gyrus	2.21 ± 0.13	2.30 ± 0.14	-2.2	0.032	0.71
R precentral gyrus	2.16 ± 0.11	2.25 ± 0.14	-2.3	0.024	0.75
L precuneus region	2.52 ± 0.12	2.60 ± 0.17	-1.8	0.084	-
R precuneus region	2.51 ± 0.11	2.59 ± 0.16	-2.0	0.050	-
L superior frontal gyrus	2.94 ± 0.17	3.08 ± 0.19	-2.5	0.018	0.79
R superior frontal gyrus	2.99 ± 0.19	3.15 ± 0.17	-2.6	0.012	0.85

BD=bipolar disorder,, L=left, R=right., SD= Standard Deviation

CT in the caudal part of L middle frontal gyrus revealed statistical difference between the two groups (2.64 ± 0.18 mm for BD vs. 2.81 ± 0.23 mm for healthy controls; p=0.017, d=0.80). BD group had a thinner cortical thickness in the R paracentral gyrus and triangular part of R inferior frontal gyrus than healthy controls (2.17 ± 0.17 mm vs. 2.31 ± 0.11 mm, *p*=0.006, d=0.93; 2.75 ± 0.16 mm vs. 2.86 ± 0.16 mm, *p*=0.041, d=0.68 for BD and HC, respectively). Left counterparts of these regions did not indicate difference between study groups. In addition, R pericalcarine region, L and R precentral gyrus had lower CT values in BD groups when compared to healthy controls (1.62 ± 0.10 mm vs. 1.70 ± 0.08 mm, *p*=0.009, d=0.88; 2.21 ± 0.13 mm vs. 2.30 ± 0.14 mm, *p*=0.032, d=0.71; 2.16 ± 0.11 mm vs. 2.25 ± 0.14 mm, *p*=0.024, d=0.75, for BD and HC, respectively). Additionally, CT of L and R superior frontal gyrus were lower in BD group (2.94 ± 0.17 mm vs. 3.08 ± 0.19 mm, *p*=0.018, d=0.79; 2.99 ± 0.19 mm vs. 3.15 ± 0.17 mm, *p*=0.012, d=0.85; for BD and HC, respectively). CT of rostral, and posterior parts of R and L cingulate gyri did not reach statistical significance. Only the difference in caudal and isthmus parts of R cingulate gyri between study groups were at trend level (BD=2.72 ±. 0.21 mm vs. HC=2.83 ± 0.18 mm, t=1.7, p=0.098; BD=2.47 ± 0.18 mm vs. HC=2.57 ± 0.17, t=1.7, p=0.094, respectively).

Correlations between Neurotrophic Factors Levels and Cortical Thickness

Partial correlation analyses adjusted for age at onset and socioeconomic status revealed a moderate correlation between serum BDNF levels and CT of the caudal part of the R anterior cingulate gyrus in the BD group (*r*=0.49 *p*=0.023, see Figure 1). The caudal part of the L anterior cingulate gyrus thickness was not correlated with serum BDNF levels. CT of the rostral, isthmus and posterior parts of R and L cingulate gyri also did not reveal any statistically significant correlation for serum BDNF levels. Finally, BDNF levels of healthy controls were not correlated with CT of the caudal part of the R anterior cingulate gyrus.

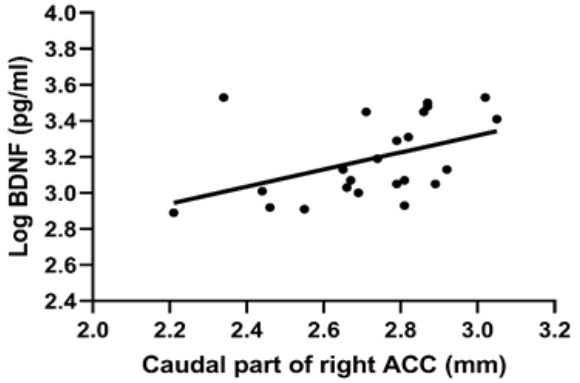

FIGURE 1. Correlation between brain-derived neurotrophic factor levels and anterior cingulate cortex thickness in youth with BD. BDNF values were transformed using logarithmic transformation. The positive correlation between both variables remained significant (r=0.49 p=0.023) after adjusted for age at onset and socioeconomic status using partial correlation. (Note ACC=anterior cingulate cortex, BDNF=brain-derived neurotrophic factor).

Post-hoc analyses for age, the duration of illness and pharmacologic treatments

In patients with BD, we did not find any correlation between the age of the participants and CT of cortical regions ($p > 0.05$). Also, The duration of BD was positively correlated with serum levels BDNF ($r=0.37$, $p=0.044$). The duration of BD was also negatively correlated with the CT of R precentral gyrus ($r= -0.52$, $p=0.011$). CT of other brain regions did not show any significant correlation with the duration of illness. Finally, we performed a subgroup analysis for the treatments used in the study. The lithium-user (n=8) and non-user (n=15) groups did not differ in terms of the serum neurotrophic factor levels and CT of involved brain regions. The valproate-treated (n=11) and comparison group (n=12) were also comparable regarding the CT of brain regions.

Discussion

Results of the present study indicate a significant association between BDNF and CT in the anterior cingulate gyrus among young patients with BD as compared to healthy subjects. In addition, reduced cortical thickness in the R paracentral gyrus, triangular part of R inferior frontal gyrus, and R pericalcarine region was found in the BD group. Second, the L counterparts of these brain regions did not differ among study groups. Thirdly, patients with early-onset BD had lower CT in their R and L superior frontal gyri and precentral gyrus. Overall, the effect size of the differences between study gruops were moderate to large. Finally, to the best of our knowledge, this is the first study to demonstrate the relationship between the CT of ACC and serum BDNF levels in early-onset BD.

As briefly mentioned in the introduction, results from previous structural imaging studies for adolescents with BD were inconsistent (3,5,6). In line with the previous reports in the patients with BD, our findings are line with cortical thinning in the R precentral gyrus involving a portion of the supplementary *motor cortex* (6*)*. Somewhat surprisingly, a recent report on structural brain anomalies in children with BD indicated that bipolar patients showed degradation in precentral gyrus in childhood, but not later in the illness course (31). Therefore, cortical thinning of the precentral gyrus could be an early manifestation of BD, which may not be apparent in the adults with BD. On the other hand, our results showed reduced CT in the triangular part of inferior frontal gyrus (also called Brodmann area 45, BA45), which plays an important role in semantic processing and cognitive control of the memory. A mega-analysis by ENIGMA consortium showed thinning in the cortex of adolescent/young adult female patients with BD, which has the greatest impact on R pars triangularis (5). Such results may indicate a possible failure of semantic activation/inhibition processes during manic phases that may continue during recovery periods. Semantic memory dysfunctions could also be attributed to some more general process dysfunctions such as inhibition and/or emotional processing (32). These deficits could lead to the development of remediation programs that enhance life quality and the degree of functioning in youth with BD.

In line with our results, previous findings indicated reduced CT in early-onset BD have already been reported in several other studies (5,33). In the previous literature, the cortical thinning in the parietal regions was reported to be correlated with a longer period of disease and treatment in the previous literature (34,35). Likewise, in our previous study, the results indicated a negative correlation between the right hippocampal volumes and the duration of the disorder (21). These structural differences in brain regions also might be related to some functional outcomes including mood regulation. While disease-related changes in young patients with BD are often viewed as evidence of abnormalities in neurodevelopment in childhood, the role of the underlying neurophysiological progression has not been sufficiently investigated. Such inquiry could be linked to the analysis of the putative functions of intracellular signaling pathways and neuroplasticity, and then to develop novel and perfected treatment modalities.

Recent studies have increasingly concentrated on possible effects of disturbances in the activities of the neurotrophic factor in BD (36). Therefore, we investigated the association between CT of the various brain regions and the serum BDNF levels, as a widely investigated neurotrophic factor. BDNF is generally distributed within critical districts in the neural pathways of affective processing in BD, such as ACC, prefrontal regions, hippocampus, and amygdala (36). Our findings indicate a relationship between the blood BDNF levels and the CT of the caudal part of the R anterior cingulate gyrus. The caudal part of the R anterior cingulate gyrus is a specific ACC sub-region integrating some distinct forms of social cognition from the various social networks, playing a key role in emotion regulation (37-39). While the exact mechanisms of the contribution of the ventral ACC (vACC) dysfunction to mood disorders are still uncertain, Anticevic et.al. suggested that alterations in connectivity between vACC and central/ dorsal medial PFC were involved in emotion regulation processes (40). In this process leading to emotion regulation problems such as bipolar disorder; the interaction of the neuroimmune system with ACC is also remarkable (41). On the

other hand, changes in the serum BDNF levels might be associated with alterations in the levels of various immune- and oxidative stress-related biomarkers (42). Interestingly, Zugman and colleagues found an inverse correlation between CT and serum BDNF values of patients with schizophrenia. In this study, the authors hypothesized that increased BDNF levels might be a resilience mechanism to prevent progressive neuronal loss (43). Yet, the association between neurotrophic signaling and ACC dysfunction is still worth exploring since both processes might be related to disease activity and neuroprogression. Additionally, these findings can also show a divergence from the expected gray matter pruning and ACC maturation during adolescence (41). This plausibility could be explored in larger samples with longitudinal and multi-modal designs.

Similar to previous reports (21), the length of the illness also was correlated with serum neurotrophic factor levels in this study. On the other hand, studies showed a decrease in BDNF in the course of the illness (44,45). A large meta-analysis also confirmed that lower BDNF levels were associated with the manic and depressive episodes, but not with euthymi (45). The severity of both episode types was also related to the alterations in BDNF, which could return the normal range after successful treatment. On the other hand, the mean duration of BD was relatively short as 2.3 years in our sample. Accordingly, it could be hypothesized that younger patients with fewer mood episodes and a shorter duration of illness did not yield major alterations in BDNF in our sample. On the other hand, the role of neurotrophins in the pathophysiology of BD remained controversial and inconsistent (22,23). Interestingly, we did not find any difference between valproate-treated and lithium-treated patients. Lithium treatment might increase serum BDNF levels in patients with acute mania.[46] Conversely, patients treated with lithium had lower BDNF values compared to those receiving other mood stabilizer medications in an early-onset BD sample (25). Considering the complex interactions among CT, mood stabilizers, the stage of illness, and neurotrophins, we could argue that posthoc subgroups comparisons and correlations analyses did not reveal any major effect of these confounding factors on our study results. Yet, larger samples including patients with early-onset BD are needed to investigate the role of illness features and neurotrophins in adjusted repeated measures models.

Limitations

Like any other study, our study has several limitations that need to be considered when interpreting the findings reported here. The first limitation is the modest sample size. There were only 23 euthymic participants with BD and 17 healthy controls, which constitutes a relatively small sample size for objective results. Second, BDNF levels were assessed in the serum samples, which cannot truly reflect their levels in the different brain regions. Third, we did not evaluate some of the possible confounding factors such as the BDNF polymorphisms and childhood traumas, since they might have potential moderating effects on brain morphometry in both groups. Fourth; the cross-sectional design of the analysis does not allow us to rule out the effects of medications on serum BDNF levels and CT. Considering the fact that BDNF level is based on peripheral blood, we should see this as a limitation, even though it seems in line with previous studies to establish a relationship with a particular brain region.

Clinical Significance

The findings are based on a small sample size of the present study indicate that adolescents with BD have reduced cortical thickness in many parts of the R brain hemisphere with moderate to large effect sizes. As a special region for mood regulation, the CT of the caudal part of the R anterior cingulate gyrus had a positive correlation with BDNF. These results may lead to generating new research questions about structural volume loss in the special brain areas involved in mood regulation as clinically relevant biomarkers. Longitudinal studies may determine the influence of BDNF on cortical thickness and examine the effects of medications in this equation.

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Statement of Ethics

The study was approved by the Ethics Committee of Dokuz Eylul University Hospital (2013-57).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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