Original Article

The Relationship between Cognition and Asymmetric Dimethyl Arginine, Symmetric Dimethyl Arginine, Nitric Oxide Levels and Total Antioxidant Capacity in Euthymic Bipolar Disorder Patients

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ABSTRACT

Objective: This study investigates the relationship between serum nitric oxide, asymmetrical dimethylarginine and symmetrical dimethylarginine levels and Total Antioxidant Capacity, and cognitive function in patients with bipolar disorder.
Method: The study included 42 bipolar patients, diagnosed and assessed according to the DSM-V criteria, and 30 healthy controls. The Sociodemographic Questionnaire was used for the collection of data, and a bivariate Pearson correlation analysis was carried out.
Results: The patient scores from a Rey Auditory Verbal Learning Test (RAVLT), Auditory Consonant Trigram (ACT), Digit Span Test (DST), Wisconsin Card Sorting Test (WCST), Trail Making-B (TMT-B) and Stroop Tests (ST) were found to be impaired in patients with BD when compared to the healthy controls. The SDMA level of the patient group was significantly higher in the control group, while the ADMA level was lower. The SDMA value was found to be positively correlated with ST-1,2,5 duration; and the NO value was positively correlated with ST-3 duration.
Conclusions: The presence of neurobiological markers may serve to predict the severity of neurocognitive deficits, and can provide information about the progress of the disease.

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Keywords: Bipolar disorder, neurocognitive impairment, total antioxidant capacity, asymmetrical dimethylarginine, symmetrical dimethylarginine

Introduction

Cognitive deficits have been reported in BD patients during both attacks and remission. Neurocognitive deficits in BD determine the progress and severity of the disorder, and repeated attacks have been associated with cognitive impairment. A long-term follow-up of patients in the euthymic period may reveal neurocognitive deterioration in such cognitive functions as functioning memory, concept change, executive function and verbal fluency [1].

In recent years, studies of free radicals, antioxidants, nitric oxide (NO) and asymmetrical dimethylarginine (ADMA) have begun to play an important role in explaining the pathophysiology of various mental disorders [2-5]. Cells are equipped with antioxidant and free radical scavenging systems that counter free radical attacks, thus protecting the cell from their corrosive effects. It has been found in patients with BD that free radical damage occurs after membrane failure [6]. NO has also been shown to have a neuroprotective function, as cytoprotective genes increase expression, and play a role in learning and memory [7]. It has been shown that ADMA inhibits the NOS enzyme, while symmetrical dimethylarginine (SDMA), as the stereoisomer of ADMA, shows no inhibition of the NOS enzyme. SDMA, arginine and ADMA have also been found to effect the entry route to the cell, and thus indirectly affect the production rate of NO, and it has been suggested that the decrease in NO levels as a result of the action of ADMA may bring about a deterioration of cerebral blood flow and cognitive function, while cognitive impairment has been associated with ADMA in patients with Alzheimer, cirrhosis and major depressive disorder. In some studies, this data has been supported by neuroimaging studies [8], with a review of literature revealing studies reporting ADMA levels to be significantly higher during manic episodes in BD patients when compared to controls, while NO levels are lower in the BD patient group, in parallel with ADMA elevation [9].

Since innumerable antioxidants can be found in plasma, serum, urine and other biological specimens, separate measurements are impractical, and are unlikely to reflect the total antioxidant status in the biosystem. Total Antioxidant Capacity (TAC) may provide more information than antioxidants measured separately in a summary of antioxidant status in biosystems, and the serum total antioxidant status may reflect the total result of many different compounds and the systemic metabolic response.

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In the present study, we hypothesize that neurocognitive functions would be worse in patients with BD than in controls during remission, and that a relationship may exist between such cognitive deficits and the ADMA, SDMA, NO and TAC levels of patients with BD. The aim of this study was to investigate this releationship in patients with BD in eutymic period. The results of this study will contribute to the investigation of the pathophysiology of cognitive deficits detected in the euthymic period of bipolar patients and new treatments to be developed in this regard.

Materials and Method

Study Groups

The study was carried out on patients with BD under long-term follow-up. All procedures were performed in accordance with the ethical standards of the institutional and/or the national research committee. Written informed consent of each participant was taken prior to the study. All patients were selected consecutively, based on the following inclusion criteria: aged 18 and above; diagnosis of BD according to the DSM-V criteria; being in remission for at least one year (all patients were using a mood stabilizer and/or an antipsychotic); a score of 7 or below on the Hamilton Depression Rating Scale (HAM-D), and/or 7 or below on the Young Mania Rating Scale (YMRS); and demonstrating sufficient physical and cognitive ability to comply with the study protocol. All of the participants were administered SCID–I, while the BD group was administered HAM-D and YMRS additionally for remission assessment. The healthy controls were recruited from the local community. The exclusion criteria for all participants were cognitive impairment or mental retardation at a level that would prevent the relevant tests from being completed; chronic alcohol or substance abuse; presence of chronic disease; and using any vitamins or medications that could affect the biochemical data. Also excluded were those diagnosed with a comorbid psychiatric disorder in the BD group, and those diagnosed with any psychiatric disorder in the healthy control group.

Procedure and Instruments

Sociodemographic Data Form

The questionnaire was designed by the researchers, and garnered such data as age, gender, education level, etc.

Hamilton Depression Rating Scale (HAM-D): The HAM-D consists of structured questions and each question is scored from 0–4. The 17-item HAM-D, the Turkish version of which was validated by Aydemir et al., is a 17-item Likert-type scale that is used to measure depressive symptoms [10].

Young Mania Rating Scale (YMRS): The YMRS comprises 11 items, each of which measures the severity of a symptom on a scale of 0–4. The validity and reliability studies of the Turkish version of the scale were conducted by Karadag et al. [11].

Neurocognitive Assessment

Rey Auditory Verbal Learning Test (**RAVLT**): This test is used to evaluate verbal episodic memory and learning, and makes use of a list of 15 separate words. Respondents are asked to repeat the words from memory after reading the list five times. For the recognition part, the respondent is asked to recognize 15 related words within a larger list (correct recognition score), and the correct distinguishing score is calculated using the formula true positive + true negative/50 [12]. A score of 1 represents an excellent result whereas 0 is the worst possible result.

Controlled Oral Word Association Test (COWAT): In this test, which is used to evaluate verbal fluency, the respondents are asked to produce as many words as possible starting with the letters K, A and S within 60 seconds [12].

Digit Span Test (DST): This test is used to evaluate verbal attention and digital processing memory (working memory), and contains "forward" and "backward" sections in which digits should be given from start-to-end or from end-to-start, respectively. The respondents are asked to repeat each digit in single steps in order, increasing by 1 each time. The "forward" part of the test evaluates verbal attention, whereas the "backward" part evaluates working memory [12].

Trail Making-B Test (TMT-B): This test is used to evaluate the frontal executive functions, attention, mental flexibility, visual pursuit and motor speed [12]. In the B section, the respondents are asked to count digits and letters such as 1-A, 2-B.

Stroop Test (ST): This test is used to evaluate frontal executive functions and attention, and involves the respondent reading the names of colors written in black ink, and then the written colors first, followed by the color of the ink [12.]

Wisconsin Card Sorting Test (WCST): This test evaluates executive functions such as cognitive flexibility, as well as problem-solving and abstraction abilities. In this part of the study, the respondents were asked to sort a series of 128 cards into three categories after being informed of a classification rule (color, number or form) [12]. A computerized version of the test was applied in the present study (WCST: CV4).

Biochemical Measurements

Blood samples were collected after 12 hours of fasting in the morning between 09:00 and 12:00. After centrifugation, serum samples were transferred into Eppendorf tubes and stored at −80 C° until assay. A NO measurement was performed of nitrite levels, in that NO reacts with oxygen and converts into nitrite and nitrate. In this method, nitrate reductase convert nitrate molecules into nitrite. The nitrite measurements were then made based on the Griess reaction.

ADMA and SDMA levels were identified based on the ELISA method. ADMA and SDMA ELISA kits work on the principles of a competitive immunoassay [13] TAC was assessed spectrophotometrically [14].

Statistical Analysis

Values were expressed as mean±standard deviation (SD) or as percentages where appropriate. The normality of the distribution of variables was evaluated with Kolmogorov-Smirnov and Shapiro-Wilk tests. Intergroup comparisons were made using a Student's t-test. To test the correlations, a bivariate Pearson correlation analysis was conducted. A P value of <0.05 was accepted as statistically significant.

Results

The study was completed with 72 test subjects (42 patients, 30 healthy controls), with a mean age of 36.1±9.6 in the patient group and 34.38±8.4 in the control group. According to descriptive statistics, the mean age of both groups was similar, and 50% of the BD group and 47% of the control group were women. The education levels of both groups were similar (Table 1).

Neurocognitive Tests

The recall and repetition scores for the first five readings of the RAVLT relate to recording and learning. When the participants test scores were compared, it was seen that the patients recalled fewer words than the controls to a statistically significant degree ($p<0.05$) when the total number of words in the 1st, 2nd, 3rd, 4th and 5th readings and between the 1st and 5th readings were taken into account in the control group.

The recall and repetition scores for the 6th and 7th readings in the RAVLT relate to immediate memory. A between-points comparison revealed that the patients recalled fewer words than the control group, to a statistically significant degree ($p<0.05$), at the 6th and 7th readings. The recognition-related scores of the RAVLT are used for the direct evaluation of late memory and learning, excluding the effect of recall on memory and learning. On the basis of these scores, the correct recall scores of the patient group were considered to be statistically significant ($p<0.05$) when compared to the control group. When compared to the control group, the number of false positives was not statistically significant ($p>0.05$) (Table 2).

The COWAT scores of the patient group were statistically lower than those in the control group ($p<0.05$). The DST scores were found to be significantly lower in patients for each and both the digit forward and back test scores compared to the control group and the patient group in the total points compared to the control group. Furthermore, the performance of the patient group in the TMT-B was significantly lower than that of the control group ($p<0.05$) (Table 3).

In the ST, the durations of the 1st, 2nd, 3rd, 4th and 5th STs of the patient group were statistically significantly higher ($p<0.05$) than those in the control group. Furthermore, the numbers of errors in the 3rd, 4th and 5th ST of the patient group were statistically significantly higher ($p<0.05$) than in the control group (Table 4).

In the WCST, the total number correct answers, errors, responses and perseverative errors; the percentage of perseverative errors, the conceptual level responses, the percent conceptual level responses, the number of complete categories and the failure to carry out the setup categories in the patient group differed significantly to the control group (Table 5).

Biochemical Parameters

The SDMA level of the patient group was significantly higher than in the control group ($p=0.007$), while the ADMA level was significantly lower ($p=0.031$). The NO level was not statistically different from the control group, although it was lower in the patient group ($p=0.554$). The TAC levels were higher in the patient group than in the control group, but not to a statistically significant degree ($p=0.650$).

Correlation between Values of Patients

The correlation between the patient values were as follows: ADMA values were positive correlated with the Rey 4, Rey Total and True Right Distinction Points, while the SDMA value was positive correlated with the ST-1,2,5 durations. The NO value was positively correlated with ST-3 duration. The TAC level was seen to be correlated with the WCST total correct score. No correlation was found between the ADMA, SDMA, NO and TAC values (Table 6).

Table 1: Sociodemographic Data

	BD (n=42)	CONTROL (n=30)
VARIABLES		
Gender		
Male	50%	53%
Female	50%	47%
Age (Mean± SD)	36,1±9,6	34,38±8,4
Marital Status		
Married	24 (57,1%)	16 (53,3%)
Single	18 (42,9%)	14 (46,7%)
Working Status		
Employed /Student	21 (50%)	22 (73,3%)
Unemployed	1 (2,4%)	3 (10%)
Retired due to the disability	1 (2,4%)	-
Retired	2 (4,8%)	2 (6,7%)
Housewife	17 (40,4%)	3 (10%)
Education status		-
Literate	1 (2,4%)	-
Primary education	17 (40,5%)	6 (20%)
High school	9 (21,4%)	5 (16,7%)
University	14 (33,3%)	11 (36,7%)
Doctorate / Master	1 (2,4%)	8 (26,7%)
Financial level rate	2075,93±1257, 22 TL	3302,33±2433,35 TL

SD:Standart Deviation

Table 2: Rey Auditory Verbal Learning Test (RAVLT) Scores

	GRUOP	N	MEAN	STD. DEVIATION	P	η2
	CONTROL	30	7,30	2,14		
REY 1	BD	42	5,52	1,37	< 0,001	0,209
	CONTROL	30	9,43	2,45		
REY 2	BD	42	7,10	1,92	< 0,001	0,227
	CONTROL	30	11,37	2,01		
REY 3	BD	42	7,95	1,92	< 0,001	0,431
	CONTROL	30	12,70	2,04		
REY 4	BD	42	8,71	2,48	< 0,001	0,427
	CONTROL	30	13,23	2,11		
REY 5	BD	42	9,55	2,29	< 0,001	0,409
	CONTROL	30	54,03	9,28		
REY TOTAL	BD	42	38,83	7,93	< 0,001	0,443
	CONTROL	30	11,93	2,36		
REY 6	BD	42	7,26	2,18	< 0,001	0,518
	CONTROL	30	12,43	3,02		
REY 7	BD	40	6,70	2,27	< 0,001	0,547
	CONTROL	30	13,93	2,02		
CORRECT RECALL	BD	41	9,56	2,63	< 0,001	0,457
	CONTROL	30	1,50	2,84		
FALSE POSITIVE	BD	41	3,07	3,87	0,018	0,049
RATIO OF REFUSING CORRECT	CONTROL	30	33,50	2,84		
	BD	42	32,00	3,85	0,025	0,045
SEPERATION RATIO OF CORRECT	CONTROL	30	0,95	0,09		
	BD	42	0,83	0,08	< 0,001	0,334

η2 : denotes eta-squared

Table 3: The Controlled Word Association Test (COWAT), Digit Span Test (DST), Trail Making Test B (TMT-B) Scores

GRUOP		N	MEAN	STD. DEVIATION	p	η2
	CONTROL	30	16,03	5,67		
LETTER "K"	BD	42	10,67	4,03	< 0,001	0,240
	CONTROL	30	10,27	4,88		
LETTER "A"	BD	42	7,40	3,93	0,009	0,098
	CONTROL	30	11,03	5,34		
LETTER "S"	BD	42	8,26	3,53	0,044	0,091
	CONTROL	30	37,33	14,40		
TOTAL	BD	42	26,26	10,37	0,001*	0,171
	CONTROL	30	6,57	1,68		
DST FORWARD	BD	42	5,33	1,32	0,003*	0,148
DST BACKWARD	CONTROL	30	5,23	1,72		
	BD	42	3,29	0,97	< 0,001	0,349
	CONTROL	30	11,80	3,19		
DST TOTAL	BD	42	8,62	1,85	< 0,001	0,289
TRAIL MAKING TEST	CONTROL	30	85,60	33,87	< 0,001	0,327
	BD	42	193,52	97,06		

*denotes statistical significance (p<0,05) η2 : denotes eta-squared

Table 4: Stroop Test (ST) Scores

	GRUOP	N	MEAN	STD. DEVIATION	p	η2
	CONTROL	30	9,67	2,77		0,129
STROOP 1 DURATION	BD	42	14,76	8,32	0,002*	
STROOP 1 NUMBER OF ERROR	CONTROL	30	0,00	-		-
	BD	42	0,00	-	1	
STROOP 1 NUMBER OF CORRECTION	CONTROL	30	0,00	-		-
	BD	42	0,00	-	1	
	CONTROL	30	10,73	5,29		0,071
STROOP 2 DURATION	BD	42	14,60	7,94	0,023*	
STROOP 2 NUMBER OF ERROR	CONTROL	30	0,03	0,18		0,014
	BD	42	0,21	0,98	0,320	
STROOP 2 NUMBER OF CORRECTION	CONTROL	30	0,03	0,18		0,007
	BD	42	0,07	0,26	0,494	
	CONTROL	30	12,37	3,31		0,306
STROOP 3 DURATION	BD	42	21,67	8,73	< 0,001	
STROOP 3 NUMBER OF ERROR	CONTROL	30	0,00	0,00		0,037
	BD	42	0,12	0,40	0,104	
STROOP 3 NUMBER OF CORRECTION	CONTROL	30	0,23	0,50		0,029
	BD	42	0,45	0,71	0,150	
	CONTROL	30	17,17	7,36		0,300
STROOP 4 DURATION	BD	42	29,76	10,94	< 0,001	
STROOP 4 NUMBER OF ERROR	CONTROL	30	0,00	0,00		0,044
	BD	42	0,24	0,73	0,077	
STROOP 4 NUMBER OF CORRECTION	CONTROL	30	0,53	1,85		0,001
	BD	42	0,67	1,63	0,748	
	CONTROL	30	27,80	9,97		0,333
STROOP 5 DURATION	BD	42	51,59	20,47	< 0,001	
STROOP 5 NUMBER OF ERROR	CONTROL	30	0,37	1,07		0,161
	BD	42	2,54	3,13	< 0,001	
STROOP 5 NUMBER OF CORRECTION	CONTROL	30	1,10	1,54		0,066
	BD	42	1,90	2,02	0,03*	

*denotes statistical significance (p<0,05)
η2 : denotes eta-squared

Table 5: Wisconsin Card Sorting Test (WCST) Scores

	GRUOP	N	MEAN	STD. DEVIATION	P	η2
TOTAL NUMBER CORRECT	CONTROL	30	110,30	22,03		
	BD	42	119,45	28,16	0,003*	0,122
TOTAL NUMBER OF ERRORS	CONTROL	30	43,23	28,54		
	BD	42	67,35	23,32	<0,001	0,182
TOTAL NUMBER OF RESPONSE	CONTROL	30	30,00	31,25		
	BD	42	50,18	32,32	0,011*	0,092
TOTAL NUMBER OF PERSEVERATİVE ERROR	CONTROL	30	36,17	20,22		
	BD	42	50,48	20,51	0,004*	0,110
PERCENT OF PERSEVERATIVE ERROR	CONTROL	30	21,17	17,18		
	BD	42	32,05	18,08	0,013*	0,087
TOTAL NUMBER OF NON-PERSEVERATİVE ERROR	CONTROL	30	17,70	13,27		
	BD	42	26,65	17,88	0,107	0,051
CONCEPTUAL LEVEL RESPONSES	CONTROL	30	54,97	21,95		
	BD	42	37,88	26,58	0,006*	0,108
PERCENT CONCEPTUAL LEVEL RESPONSES	CONTROL	30	54,07	26,37		
	BD	42	31,13	23,23	< 0,001	0,180
NUMBER OF COMPLETE CATEGORY	CONTROL	30	4,20	2,23		
	BD	42	1,95	2,09	< 0,001	0,216
FAILURE OF CARRYİNG ON SETUP	CONTROL	30	0,73	1,05		
	BD	42	1,35	1,51	0,098	0,081
	CONTROL	30	-102,87	546,00		
LEARNING TO LEARN	BD	42	-877,00	-	0,179	0,031

*denotes statistical significance (p<0,05)
η2 : denotes eta-squared

Table 6: Correlation Between Values of Patients

		Pearson Correlation Coefficients	N	p
REY 4	ADMA	0,298	42	0,011*
REY TOTAL		0,251	42	0,033*
SEPERATION RATIO OF TRUE		0,301	42	0,011*
STROOP 1 DURATION	SDMA	0,384	42	0,001*
STROOP 2 DURATION		0,390	42	0,001*
STROOP 5 DURATION		0,415	41	< 0,001
STROOP 3 DURATION	NO	0,324	42	0,038*
WCST TOTAL NUMBER CORRECT	TAC	0,310	42	0,043*

*denotes statistical significance (p<0,05)
ADMA: Asymmetrical dimethylarginine, SDMA: Symmetrical dimethyl arginine, NO: Nitric oxide,TAC: Total Antioxidant Capacity, WCST:Wisconsin Card Sorting Test

Discussion

The strength of the present study lies in its simultaneous measurement of several cognitive functions and numerous important parameters of the antioxidant system, and is also thought to be the first study of its kind based on a review of literature in the Turkish and English language to examine the relationship between impaired cognitive functions and impairments in the antioxidant system in euthymic BD patients.

An analysis of the sociodemographic data of the present study identified no difference in such parameters as age, gender and years of education, which may affect the performance in cognitive tests of the patient and control groups.

Examination of Cognitive Functions:

It was found that the euthymic BD group recalled fewer words in RAVLT and performed worse in almost all subtests than the control group. Likewise, the study established that performances in the DST (used to evaluate working memory), in COWAD (used to evaluate the linguistic function domain) and in WCST (used to evaluate abstract reasoning and conceptualization abilities) were poorer in the patient group than in the control group. A further study demonstrated that verbal memory and executive function were notably impaired in BD patients who were in a euthymic state when compared to the control group, and that this impairment was associated with previous manic attacks, hospitalizations and suicide attempts [15]. A review of literature reveals that studies evaluating the cognitive performance of euthymic BD patients recorded very similar results to those reported in the present study. That said, there are studies indicating heterogeneity in cognitive functions among BD patients, as well as some reporting similar cognitive performance results in the euthymic state and in the control group [16]. In the present study, the poorer test performances of the BD group may be associated with the low number of participants, the presence of decreased cognitive performance in different periods of the disease, or the disease becoming chronic.

ST durations were longer in all five subtests in the BD group than in the control group, and the performances of the BD group in subtests 3, 4 and 5 were poorer, with a greater number of mistakes than the control group in our study. There is currently broad consensus on the use of ST for the assessment of frontal lobe function, with studies conducted using advanced functional imaging techniques such as positron emission tomography, and those identifying activated orbitofrontal and anterior cingulate cortexes during ST in healthy subjects [17]. Neurocognitive deficits have been found to be determinants of disease course and severity in patients with BD, while recurrent attacks are associated with progressive cognitive destruction. Neurocognitive deficits and impairments in domains indicative of cognitive functions, such as working memory, concept changing, executive function and verbal fluency, were found to have continued after symptomatic recovery on the long-term follow-up of the euthymic patients, and this finding was suggested to be attributable to impairments in the frontal-subcortical circuit, supported by neuroimaging studies [18,19]. Studies in literature evaluating the attention span of BD patients mainly report attention deficit, which is consistent with the findings of the present study. The difference in the ST results of the BD and control groups in the present study may be associated with the frontal lobe functions that are believed to be impaired in BD. An association was also identified between the degree of neurocognitive impairment and the types of disease. Cognitive deficits were found to be different, and to be more severe, in patients with BD-I when compared to those with Bipolar II disorder [20]. The patients included in the present study had BD-I, which may explain the poorer performance in the cognitive tests.

Biochemical parameters

The present study identified significantly lower levels of ADMA in the BD group than in the control group, while there was no significant difference in NO levels. NO levels vary across psychiatric disorders, although it is not clear whether these variations are due to the disorder, or whether they are attributable to a compensatory mechanism, as NO has both antioxidant and pro-oxidant functions [21]. Recent studies suggests that NO is one of the key factors in the genesis of many brain-related disorders [22].

There have been further studies reporting high NO levels among BD patients experiencing manic episodes [21], contrasting other studies reporting low levels of NO [23]. Similar to our results, ADMA levels were reported to be low in the euthymic period in a recent study [24]. Additionally, high levels of ADMA have been reported during manic episodes in BD patients, while there have also been studies reporting both higher [18] and lower [21] ADMA levels in patients with depression than in control groups.

A previous study found depression to be more associated with NO levels than mania [25], while another study established that previously low NO levels increased and high ADMA levels decreased following Lithium therapy administered to BD patients experiencing a manic episode [3].

One of the reasons for the decreased ADMA levels in the BD group and the similar NO levels to those recorded in the control group may be the higher number of patients in remission for at least one year and/or using psychiatric drugs. However, in our study, the patients were not classified according to the drugs they used. There have been studies reporting increased ADMA levels due to the

weight gain and metabolic syndrome caused by antipsychotics or medication [4], while there are also studies reporting that especially lithium among the mood stabilizers decreases ADMA levels.

Low ADMA levels may increase NO levels in the BD group, although this outcome may also be related to the limited number of patients.

In the present study, significantly higher levels of SDMA were recorded in the BD patients than in the control group. In a similar vein to our study, two recent studies established higher SDMA levels in BD patients experiencing manic episodes [23], and in patients with depressive disorder [2]. The study by Arısoy et al. [25] further highlighted a positive relationship between high SDMA levels and high stress levels, which the authors associated with depression. ADMA and SDMA are considered to be markers of oxidative stress and protein catabolism, while SDMA is believed to intervene in NO synthesis by competing with L-arginine for transport through cell membranes. The function of SDMA in mood disorders is yet to be clarified, and so it would appear to merit further study, including assessments based on measurements of a larger patient group and at different stages of BD.

Considering the presence of very different antioxidants in the body, it would be logical to measure the total antioxidant capacity as an overall oxidative stress parameter in a future study [26]. In one earlier study, higher TAC levels were established in euthymic BD patients than in a control group [27]. In the present study, the TAC levels of the euthymic BD patients were higher than in the control group, although the increase was not statistically significant. Oxidative stress parameters may be affected by lifestyle and diet, as well as by antipsychotics and mood stabilizers [27], although the limited number of patients in the study may be a factor in this regard.

The present study investigated the correlations between biochemical parameters and cognitive function, and identified ADMA and SDMA as the main methylarginine derivatives. The protein arginine methyltransferase (PRMT) enzyme catalyzes methylation, resulting in the transfer of 1 or 2 methyl groups to the guanidino nitrogen of arginine in the proteins. PRMTs have been shown to regulate PRMT 2 expression in the lungs, as well as ADMA concentrations in the lungs [28]. Type 1 PRMT reactions produce ADMA, while Type 2 PRMT reactions result in SDMA. The present study found ADMA levels to be positively correlated with RAVLT scores (Rey4, Rey Total and Separation Ration of True Scores) in BD patients, and showed that increased SDMA levels decreased their performance in an ST. A previous study reported low ADMA levels to be associated with more mistakes in a continuous performance test [5]. Given the effect of hypoxia on PRMT 2 expression, increased SDMA levels and the association with decreased performance in cognitive function may be associated with increased oxidative stress.

The present study found that increasing NO levels prolonged ST-3. Previous studies have identified a positive effect of NO on learning and memory, although it has been suggested that excited amino acids stimulate NOS synthesis, which in turn leads to neural defects [29]. It is a known fact that aspartate and glutamate levels are elevated, especially during attacks, leading to the death of dendrites through an excitotoxic mechanism [30]. The decreased performance in ST that was used to evaluate cognition may have been affected by such changes.

In the present study, TAC levels were found to be correlated with the total number of correct responses in the WCST. Considering that have been studies reporting a negative correlation between TAC and symptom severity in schizophrenia patients with impaired cognition [31], and another study involving students that reported decreased TAC levels due to exam stress, as well as increased lipid peroxidation and DNA oxidation [32], it may be concluded that this finding of the present study can be attributed to the positive effect of the antioxidant system on cognitive function.

The low number of patients and controls can be considered a limitation of the present study. Furthermore, parameters such as B12, folate and diet, all of which can affect biochemical parameters, were not examined. As stated in the discussion, the age at disorder onset and the disorder course (frequency, duration, severity, etc. of attacks), which may affect the results, and the length of the existing euthymic state, were not examined in the patient group. Our study sample included patients using various and multiple drugs with potentially different effects (positive-negative) to the data garnered from literature. These limitations suggest an opportunity for further research.

Conflict of interest

There is no conflict of interest between the authors.

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