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Neurological Soft Signs, Circadian Preferences and Emotion Regulation in Bipolar Disorder and First-Degree Relatives

Bipolar Bozuklukta ve Birinci Derece Yakınlarında Silik Nörolojik Belirtiler, Sirkadiyen Tercihler ve Duygu Düzenleme

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Abstract

Introduction: This study aimed to investigate the relationships between neurological soft signs (NSS), circadian preferences, and emotional regulation difficulties in patients with bipolar disorder (BD) and their unaffected first-degree relatives (FDRs).

Materials and Methods: A total of 105 people (35 BD patients, 35 FDRs, and 35 healthy controls) enrolled in the study. They completed a sociodemographic information form, the Young Mania Rating Scale (YMRS), Hamilton Depression Rating Scale (HAM-D), Morningness-Eveningness Questionnaire (MEQ), Difficulties in Emotion Regulation Scale (DERS), and Neurological Evaluation Scale (NES).

Results: NES motor coordination, complex motor movements, other subscale and total scores were significantly higher in BD and FDRs compared to the control group. The subscales of the DERS including nonacceptance, goals, impulse, strategies, accessibility, and total DERS scores were also significantly higher in patients than the relative and control groups. A statistically positive, weak, and significant relationship emerged between the patient group's other NES sub-dimension and the DERS sub-dimensions of impulse and awareness. Meanwhile, significant relationship was found in the FDRs between NSS and the NES sub-dimensions emotional integration and complex motor movements. A significant relationship was also found between the DERS sub-dimension nonacceptance and the NSS sub-dimension complex motor movements.

Conclusion: This study discovered that NSS are associated with negative emotional regulation strategies in patients with BD during in euthymic period and FDRs. NSS and circadian preferences may be endophenotype candidates for BD.

Keywords: Bipolar disorder; neurological soft signs; circadian preferences; emotion regulation.

Özet

Amaç: Bu çalışmanın amacı bipolar bozukluğu (BB) olan hastalar ve birinci derece akrabalarında (BDA) silik nörolojik belirtiler (SNB), sirkadiyen tercihler ve duygu düzenleme güçlükleri arasındaki ilişkileri araştırmaktır.

Gereç ve Yöntem: Çalışmaya toplam 105 kişi (35 BB, 35 BDA ve 35 sağlıklı kontrol) alındı. Sosyodemografik bilgi formu, Young Mani Derecelendirme Ölçeği (YMDÖ), Hamilton Depresyon Derecelendirme Ölçeği (HAM-D), Sabahlılık Akşamlılık Ölçeği (SAÖ), Duygu Düzenleme Güçlüğü Ölçeği (DDGÖ) ve Nörolojik Değerlendirme Ölçeği (NDÖ) doldurduldu.

Bulgular: BB ve BDA'da NDÖ motor koordinasyon, karmaşık motor hareketler ve diğer alt ölçek ve toplam puanları kontrol grubuna göre anlamlı derecede yüksek saptandı. DDGÖ kabul etmeme, hedefler, dürtü, stratejiler, erişilebilirlik alt ölçek ve toplam puanları BB'de BDA ve kontrol gruplarına göre anlamlı olarak daha yüksekti. BB'de DDGÖ diğer alt ölçeği ile DDGÖ dürtü ve farkındalık alt boyutları arasında anlamlı ilişki saptandı. BDA grubunda SNB ile NDÖ alt boyutları olan duygusal bütünleşme ve karmaşık motor hareketler arasında anlamlı bir ilişki bulundu. DDGÖ kabul etmeme ile SNB karmaşık motor hareketler alt boyutları arasında da anlamlı ilişki bulundu.

Sonuç: Bu çalışmada ötimik dönemdeki BB'de ve BDA'larda SNB'nin olumsuz duygu düzenleme stratejileri ile ilişkili olduğu saptandı. SNB ve sirkadiyen tercihler BB için endofenotip adayları olabilir.

Anahtar Kelimeler: Bipolar bozukluk; silik nörolojik belirtiler; sirkadiyen tercihler; duygu düzenleme.

Introduction

Bipolar disorder (BD) is a common disorder with chronic recurrent episodes and euthymic phases in which there are no or sub-threshold symptoms (1). Psychopathological domains of the BD are risky behaviors mood swings, substance abuse, excessive spending, increased sexual desire, legal problems, and impulsivity during the periods of disease. It is important to evaluate which genetic abnormalities occur most consistently in individuals who are genetically susceptible to BD.

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Already there is substantial evidence of abnormalities arising in various neurocognitive domains in BD cases. Endophenotype is an important concept in BD and they are measurable components along the pathophysiological pathway between psychopathology and etiology (1). Accordingly, it is necessary to clinically recognize potential endophenotypes that indirectly cause symptoms or signs of the disease to help individuals determine their genetic BD load (or lack thereof) (2). The number of studies on BD endophenotypes is increasing day by day in various fields, including biochemistry, endocrinology, neurophysiology, neuroanatomy, and especially neurocognition. In this field, one of the areas that still requires attention is neurological soft signs (NSS), as research assumes that these signs are disease-specific features that do not vary according to different factors. NSS are minimal, non-localized, objectively measurable abnormalities in the cortical-subcortical junctions that indicate damage and suggest specific defect (1). The subtle deficits of NSS are in motor coordination, sensory integration, and sequencing of complex motor acts. NSS in psychiatric disorders partly indicate neurodevelopmental abnormalities as a result of genetic or non-genetic processes (3). NSS are more common in bipolar patients compared to healthy controls even in the euthymic period (4). Sensory, motor and complex neurological soft signs can be considered a part of the symptomatology of BD (1). With this in mind, if patients before the onset of BD and a healthy relative of theirs express NSS, they may have a predisposed susceptibility to the disease as in schizophrenia (5). Another important domain related to BD is biological rhythm. There is a strong relationship between mental problems, especially bipolar depression, major depression, and seasonal mood disorders, and delays or disturbances in biological rhythm (6). The most important biological rhythm is the circadian rhythm, which expresses circa (approximate) and dies (day) that change and fluctuate per an organism's physiological, biological, and behavioral processes. Chronotypes may be used to denote the strongest differences between individuals in terms of biological and behavioral rhythm timing and is divided into three categories: morning type, intermediate type, and evening type. Morning types go to bed and wake up earlier, as well as perform better in the morning hours, while evening types sleep late and prefer evening hours to perform activities. Patients with BD typically show symptoms such as waking up frequently at night, sleeping for a long time, and staying awake for a long time, even during a euthymic period as symptoms of circadian rhythm disruption and sleep problems (7). BD is characterized by intense and irregular emotional experiences due to both biological rhythm disturbances and the nature of the disease. Therefore, difficulties in emotional regulation have become more and more important in pathophysiological BD models due to mood lability and emotional regulation difficulties negatively affecting functionality (8). The clinical significance of emotional regulation difficulties is the inability of individuals to regulate and control their emotional responses in the face of stressor stimuli. Regulating and managing emotions can help restore healthy psychological and mood functionality (9). However, even in euthymic periods, patients with BD experience significant difficulties to implementing emotional regulation strategies, though it is not clear what strategies and contexts are involved in emotional regulation difficulties or what the perceived effort and success of these strategies are. It is important to define the relationship between circadian preferences, and emotional regulation because of it can help improve BD patients' quality of life and functionality. This study aims to investigate NSS, circadian preferences, and difficulties in emotional regulation in euthymic BD patients, their unaffected first-degree relatives, and healthy controls. The study also explores whether it is appropriate to evaluate them as potential endophenotype determinants by examining their relationships.

Material and Method

A total of 105 people (35 patients with BD in a euthymic period who were admitted to the Van Yuzuncu Yil University Faculty of Medicine Psychiatry clinic and diagnosed according to DSM-5 diagnostic criteria; 35 of their unaffected first-degree relatives; and 35 healthy controls) participated in this study. The patient inclusion criteria were being 18–65 years old; being in the euthymic period; having a score of 7 or less on the Hamilton Depression Rating Scale; and having a score of 5 or less on the Young Mania Rating Scale. The study's patient exclusion criteria were alcohol or substance addiction and other neurological/organic mental disorders. The study was conducted between February 1, 2019 and June 30, 2019. Neurological examination of all participants for all scale forms and neurological soft signs was performed by only one investigator to eliminate possible researcher bias. Accordingly, the 35 patients with BD, the 35 relatives, and the 35 controls completed a sociodemographic

information form, the Young Mania Rating Scale (YMRS), Hamilton Depression Rating Scale (HAM-D), Morningness-Eveningness Questionnaire (MEQ), Difficulties in Emotion Regulation Scale (DERS), and Neurological Evaluation Scale (NES).

Psychometric Instruments:

Sociodemographic data form: An information form prepared by the researchers gathered participant data such as age, gender, education level, marital status, employment status, alcohol and substance (cigarette) use, number of hospitalizations, and number of suicide attempts.

Young Mania Rating Scale (YMRS): YMRS is frequently used to evaluate manic symptoms include 11 item. YMRS was administered by a clinician to measure the severity of and changes in patient mania, evaluating specifically the 2–7 days prior (10). The Turkish validity and reliability study was conducted (11). We utilized it to exclude patients in manic episode.

Hamilton depression rating scale (HAM-D): The HAM-D is a scale that systematically records. interview-based observations. A total score is obtained by evaluating patients' depressive episode signs from the previous 7 days through 17 items measures on a 5-point scale (12). Validity and reliability studies of the HAM-D's Turkish translation and corresponding structured interview were conducted (13). We used this form to evaluate whether depressive symptoms. We included having a score of 7 or less on the Hamilton Depression Rating Scale.

Morningness - eveningness questionnaire (MEQ): Horne and Ostberg first developed the MEQ in 1976 (14). The scale classifies individuals as morning, evening, or intermediate types based on their lifestyle, sleep-wake patterns, and time of their performances of daily acivities. The MEQ is a self-report Likert-type scale consisting of 19 questions, with answers marked on a schedule. The total score obtained determines if the individual completing the MEQ is a morning, evening, or intermediate type. If the total score is 59–86, the person is considered a morning type; if the total score is 16–31, the person is considered an evening type; and if the total score is 32–58, the person is considered an intermediate type. Our study based on the Turkish validity and reliability study of the MEQ (15).

Difficulties in emotion regulation scale (DERS): The 36-question DERS was developed by Gratz and Roemer (16) to evaluate emotional regulation difficulties. Each question is measured on a 5-point Likert-type scale between 1 (never) and 5 (almost always). The scale has 6 sub-dimensions as follows: lack of awareness of emotional responses, lack of clarity of emotional responses, nonacceptance of emotional responses, limited access to effective strategies, difficulties in controlling impulsive behavior, and difficulties in engaging behavioral goals. Psychometric properties of the DERS for adults in the Turkish sample were conducted (17).

Neurological evaluation scale (NES): Buchanan and Heinrichs (18) developed the NES in 1989 to clinically evaluate NSS in patients with psychiatric disorders. In the original NES validity study, 4 subscales were proposed for the measurement tool. These include sensory integration, motor coordination, sequential motor coordination, and other neurological signs. Emotional integration consists of quenching, graphesthesia, stereognosis, right-left confusion, and auditory visual integrity tests. Motor coordination includes consecutive walking, rapid changing movements, thumb position, and finger nose tests. Complex motor movements, meanwhile, are measured with fist ring tests, fist-edge-palm tests, Ozeretski tests, and rhythm retention tests. Finally, other neurological sign tests are measured with the Romberg test, consisting of overflow movements, tremors, 5-minute memory, 10-minute memory, rhythm-holding test A, convergence, difficulty in holding gaze, glabella reflex, lip extending reflex, grasping reflex, and sucking reflex. The 14 items of the NES, as evaluated by a clinician, are evaluated separately for both halves of the body for a total of 26 items. We completed each of these tests all of our study participants.

Ethical consent: The verbal consent of all patients, their relatives, and controls was obtained prior to the study's start, and all participants received written information about the study's purpose and method. The study initiated after the approval of the Yuzuncu Yil University Faculty of Medicine Clinical Research Ethics Committee (Approval Date and Number: 19.10.2018/07) and obeyed the precepts of the Declaration of Helsinki and later amendments.

Statistical analysis: The statistical program SPSS v22.0 was used in this study. Descriptive statistics such as frequency, percentage, mean, standard deviation, and minimum and maximum values were used in the data analysis, as were parametric tests. An independent sample t test compared the means of two independent groups, while a one-way analysis of variance (one-way ANOVA) compared more than two independent groups. The Tukey HSD multi-group comparison test was used when group differences emerged in the

ANOVA tests. The Pearson correlation was also used in the correlation analyses of the scales and their sub-dimensions. All test results were evaluated at 0.05 significance.

Results

A total of 105 individuals (35 patients with BD, 35 unaffected first-degree patient relatives, and 35 healthy controls) participated in the study. The patients with BD consisted of 13 females and 22 males; the first-degree relatives were composed of 10 females and 25 males; and the healthy controls consisted of 13 females and 22 males. The mean age of the patients with BD was 32.14 ± 9.12 years, the mean age of the first-degree relatives was 34.46 ± 12.50, and the mean age of the healthy controls was 28.97 ± 7.46. The participants' sociodemographic characteristics and smoking and alcohol use did not exhibit a significant relation between the BD patient, relative, and control groups, as seen in Table 1 ($p > 0.05$). (Table 1) When the patients' first episode characteristics were evaluated, 14 experienced depression and 21 experienced mania. The mean number of patients who experienced mania was 3.63 ± 4.06; the mean number of patients who experienced hypomania was 1.5 ± 0.71; and the mean number of patients who experienced

Table 1: Comparison of participants socio-demographic characteristics.

		BD patients		**Patients' relatives**		**Controls**		**f**	**p**
Age		**32.14 ± 9.12**		**34.46 ± 12.50**		**28.97 ± 7.46**		**2.69**	**0.07**
		n	**%**	**n**	**%**	**n**	**%**	**χ^2**	**p**
Gender	Female	13	37.1	10	28.6	13	37.1	0.761	0.68
	Male	22	62.9	25	71.4	22	62.9		
Marital status	Single	24	22.9	23	21.9	26	24.8	0.62	0.73
	Married	11	10.5	12	11.4	9	8.6		
Education	Primary school	5	4.8	8	7.6	2	1.9	7.86	0.24
	Middle school	5	4.8	9	8.6	9	8.6		
	High school	3	2.9	4	3.8	2	1.9		
	College	22	21	14	13.3	22	21		
Alcohol/ Substance use	No	32	91.4	34	97.1	35	100.0	3.639	0.162
	Yes	3	8.6	1	2.9	0	0.0		
Smoking	No	19	54.3	24	68.6	24	68.6	2.062	0.357
	Yes	16	45.7	11	31.4	11	31.4		

BD: Bipolar disorder, $p \leq 0.05$ is significant

depression was 2.96 ± 2.32. As seen in Table 2, 24 patients stated that they were hospitalized, 28 of them did not attempt suicide, and all of them received treatment for their first episode. After evaluating the types of treatment they received, 27 patients received a mood stabilizer (MS) and antipsychotic; 4 received just an MS; 34 stated that they completely recovered between episodes; 28 stated they underwent no rapid cycling; and 34 stated that they experienced no legal problems.

(Table 2) This study also aimed to examine differences in the groups' emotional regulation difficulties and found that apart from DERS awareness sub-dimension score, the other NSS sub-dimension scores and total DERS score showed significant differences between groups ($p \leq 0.05$).

Table 2: Disease characteristics of bipolar patients

			min.–max.
Number of manic periods		3.63 ± 4.06	1–20
Number of hypomanic periods		1.5 ± 0.71	1–2
Number of depression periods		2.96 ± 2.32	1–10
Number of hospitalizations		2.63 ± 2.36	1–11
Number of suicide attempts		1.86 ± 1.57	1–5
Episode duration (days)		20.68 ± 16.44	5–100
		n	**%**
First episode	Depression	14	40.0
	Mania	21	60.0
Hospitalization	No	11	31.4
	Yes	24	68.6
Suicide attempt	No	28	80.0
	Yes	7	20.0
Treatment	No	0	0.0
	Yes	35	100.0
Type of treatment received	MS	4	11.4
	MS + antipsychotic	27	77.1
	No MS + other	3	8.6
	Dual MS	1	2.9
Complete recovery between episodes	No	1	2.9
	Yes	34	97.1
Rapid cycling	No	28	80.0
	Yes	7	20.0
Legal issues	No	34	97.1
	Yes	1	2.9
Rapid cycling in anamnesis	No	25	71.4
	Yes	10	28.6
Atypical depression characteristics	No	32	91.4
	Yes	3	8.6
Psychotic mania	No	19	54.3
	Yes	16	45.7
Psychotic depression	No	24	68.6
	Yes	11	31.4
Postpartum period	No	35	100.0
	Yes	0	0.0
Total		35	100.0

MS: Mood stabilizer

Table 3: Comparison of NES sub-dimension scores, DERS sub-dimension scores, and MEQ types between bipolar patients, first-degree relatives, and controls.

	BD patients		**Patient relatives**		**Controls**		**F**	**p**
NES								
Motor coordination	1.83 ± 1.4		1.34 ± 1.08		0.91 ± 0.78		5.854	0.004*
Emotional integration	2.57 ± 2.08		2.6 ± 2.09		1.8 ± 1.16		2.159	0.121
Complex motor movements	4.8 ± 2.22		4.54 ± 2.58		3.06 ± 2.25		5.581	0.005*
Other NSS	6.34 ± 3.78		5.49 ± 3.19		2.91 ± 1.93		11.847	0.000*
Total	15.54 ± 7.53		13.97 ± 7.06		8.69 ± 3.93		11.114	0.000*
DERS								
Nonacceptance	14.31 ± 5.18		12.00 ± 5.06		9.86 ± 3.00		8.947	0.000*
Goals	16.06 ± 3.53		12.89 ± 3.56		12.71 ± 3.3		10.314	0.000*
Impulse	14.49 ± 3.09		12.83 ± 3.12		10.89 ± 2.04		14.539	0.000*
Awareness	12.49 ± 4.00		12.31 ± 3.9		10.86 ± 3.01		2.089	0.129
Strategies	20.09 ± 6.80		13.4 ± 4.99		11.69 ± 3.91		23.932	0.000*
Clarity	11.23 ± 3.73		9.63 ± 3.09		7.97 ± 2.23		9.789	0.000*
Total	88.66 ± 2.23		73.06 ± 16.21		63.97 ± 10.8		20.757	0.000*
MEQ	**N**	**%**	**N**	**%**	**N**	**%**	**χ^2**	**p**
Evening type	3	8.6	1	2.9	4	11.4		
Intermediate type	23	65.7	20	57.1	18	51.4	3.540	0.472
Morning type	9	25.7	14	40.0	13	37.1		

NES: Neurological Evaluation Scale; **DERS:** Difficulties in emotion regulation scale; **MEQ:** Morningness-eveningness scale; **BD:** Bipolar disorder; one-way ANOVA, Chi-square relationship test: *p ≤ 0.05

Table 3 showed upon evaluating the differences between groups with the Tukey HSD multiple comparison test, the DERS sub-dimensions' non-acceptance (14.31 ± 5.18), goals (16.06 ± 3.53), impulse (14.49 ± 3.09), strategies (20.09 ± 6.80), and accessibility (11.23 ± 3.73) and total DERS score (88.66 ± 20.23) were significantly higher for the patients than their relatives and the controls (p ≤ 0.05). Meanwhile, no significant relationship emerged between the MEQ groups and the patients, first-degree relatives, or controls (p > 0.05) (Table 3). The total and sub-dimension NES scores were then compared between the groups, revealing motor coordination, complex motor movements, other NSS, and total NES mean scores to be higher in the patient and relative groups compared to the control group. In the patient group, the other NSS average score of those who experienced psychotic depression was higher than those who did not experience

psychotic depression, as seen in Table 4. The relationships between the DERS and NES sub-dimensions of the individuals in the BD group was evaluated with the Pearson correlation analysis. This revealed a positive and significant relationship between the NES sub-dimension other NSS, the DERS sub-dimensions impulse (r: 0.355) and awareness (r: 0.343), and the remaining

Table 4: Comparison of the bipolar patients' NES scores according to disease characteristics.

		n	NES	t/F	p
First episode[1]	Depression	14	16.71 ± 9.09	0.747	0.460
	Mania	21	14.76 ± 6.4		
Hospitalization[1]	No	11	14.55 ± 8.17	-0.525	0.603
	Yes	24	16.00 ± 7.35		
Suicide attempt[1]	No	28	15.29 ± 8.32	-0.399	0.692
	Yes	7	16.57 ± 2.88		
Type of treatment received[2]	MS	4	14.25 ± 7.14	0.210	0.889
	MS + antipsychotic	27	16.04 ± 7.97		
	No MS + other	3	12.67 ± 6.43		
	Dual MS	1	16.00		
Rapid cycling[1]	No	28	14.71 ± 6.59	-1.316	0.197
	Yes	7	18.86 ± 10.48		
Rapid cycling in anamnesis[1]	No	25	14.2 ± 6.49	-1.716	0.096
	Yes	10	18.9 ± 9.17		
Atypical depression characteristics[1]	No	32	15.66 ± 7.61	0.287	0.776
	Yes	3	14.33 ± 8.02		
Psychotic mania[1]	No	19	14.68 ± 6.98	-0.730	0.470
	Yes	16	16.56 ± 8.25		
Psychotic depression[1]	No	24	13.75 ± 6.56	-2.195	0.035*
	Yes	11	19.45 ± 8.31		

NES: Neurological Evaluation Scale, **MS:** Mood stabilizers [1]Independent sample t test; [2]one-way ANOVA; *p ≤ 0.05

DERS sub-dimensions (p ≤ 0.05; Table 5). The relationship between the DERS and NES sub-dimension values of the first-degree relatives group was also evaluated via Pearson correlation analysis, demonstrating a positive, weak, and significant relationship between total NES score (r: 0.378) and to total DERS scores (p ≤ 0.05). Additionally, there was a positive and significant relationship (p ≤ 0.05) between DERS scores and the NES sub-dimensions' emotional integration (r: 0.418) and complex motor movements (r: 0.359). A positive, weak, and significant relationship also emerged between nonacceptance, a DERS sub-dimension, and complex motor movements, an NES sub-dimension (p ≤ 0.05; Table 5).

Discussion

This study aimed to compare NSS, circadian preferences, and emotional regulation difficulties in euthymic patients diagnosed with BD, their first-degree relatives, and healthy control volunteers. The study results revealed that the mean scores for motor coordination, complex motor movements, other NSS, and total NES were significantly higher in the patient and relative groups compared to the control group. NSS was examined by dividing it into subgroups related to neuroanatomical localization. The most widely relevant group was the "other NSS" category (associated with the frontal lobe), which includes sensory integration (associated with the parietal lobe), motor coordination (associated with the frontal lobe and cerebellum), sequencing of complex motor behavior (associated with the prefrontal cortex), and primitive reflexes (19). Studies of symptomatic BD patients have identified that they expressed NSS during manic and depressive episodes, as well as had more pronounced NSS if their clinical prognosis was poor (20). Additionally, other studies have indicated that NSS are more common in patients than healthy individuals (5).

Table 5: Correlation tables.

DERS	NES	BD patients	Patients' relatives
		r	**r**
Nonacceptance	Motor coordination	-	-
	Emotional integration	-	-
	Complex motor movements	-	0.336*
	Other NSS	-	-
	Total	-	-
Goals	Motor coordination	-	-
	Emotional integration	-	-
	Complex motor movements	-	-
	Other NSS	-	-
	Total		
Impulse	Motor coordination	-	-
	Emotional integration	-	-
	Complex motor movements	-	-
	Other NSS	0.355*	-
	Total		
Awareness	Motor coordination	-	-
	Emotional integration	-	-
	Complex motor movements	-	-
	Other NSS	0.343*	-
	Total		
Strategies	Motor coordination	-	-
	Emotional integration	-	-
	Complex motor movements	-	0.410*
	Other NSS	-	-
	Total		-
Clarity	Motor coordination	-	-
	Emotional integration	-	0.378*
	Complex motor movements	-	-
	Other NSS	-	-
	Total		-
Total	Motor coordination	-	-
	Emotional integration	-	0.418*
	Complex motor movements	-	0.336*
	Other NSS	-	
	Total	-	0.378*

NES: Neurological Evaluation Scale; **DERS:** Difficulties in emotion regulation scale; **BD:** Bipolar disorder; *p < 0.05

Many studies have determined that unaffected first-degree relatives of patients with BD perform sensory integration, motor coordination, response inhibition, and ordering of complex motor tasks in all domains differently than healthy controls, suggesting NSS as potential endophenotype candidates (21). In Sharma et al.'s study (22), NSS scores among unaffected first-degree relatives of patients with BD were higher in a punching test (ordering complex motor behaviors) compared to healthy controls, as associated with NSS inheritance. The results of the current study also suggested that NSS may be trait markers of hereditable endophenotypes in BD that continue regardless of disease stage, as the patients' motor coordination, emotional integration, complex

motor movements, and other NSS sub-dimension mean scores were evaluated per their disease characteristics. Accordingly, the other NSS mean score of patients with psychotic depression was significantly higher than the mean score of patients without psychotic depression. This may indicate that the primitive reflexes classified in the other NSS sub-dimension have fronto-striatal pathway dysfunction as a predictor of poor BD prognosis. BD involves the dysregulation of emotions by definition, with research showing that the disorder advances more in the processing of emotional stimuli, such as those that take place in the amygdala, compared to healthy participants, even in remission periods (23). One study observed that patients with BD experience significant difficulties in applying emotional regulation strategies to their daily life, and their capacity to regulate emotions when instructed is greatly impaired (24). In accordance with the literature, the patients' nonacceptance, goals, impulse, strategies, accessibility, and total DERS scores were significantly higher than their unaffected relatives and the controls. This elevation suggests that in patients with BD, the brain's prefrontal cortex region, related to emotional regulation, undergoes abnormal activity also during euthymic periods (25). After evaluating the relationship between the DERS and NES sub-dimensions of the patient group, we found a statistically positive and significant relationship emerged between the other NES sub-dimension and the DERS sub-dimensions impulse and awareness. This significant relationship may indicate that even in the euthymic period, those with BD have emotional regulation difficulties and that NSS are associated with negative emotional regulation strategies. To the best of our knowledge, there is no study in the literature that investigates the relationship between NSS, emotional regulation difficulties, and chronotypes in BD. There was also a positive, weak, and significant relationship between NES scores and emotional regulation difficulties in the first-degree relative group. A positive, weak, and significant relationship emerged as well between their total DERS scores and the NES sub-dimension emotional integration; a positive and significant relationship also arose between the group's complex motor movements, the DERS sub-dimension rejection, and the NES sub-dimension complex motor movements. This shows that the patients' relatives used more incompatible emotional regulation strategies compared to the control group, and that NSS and emotional regulation difficulties are associated with the prefrontal region in the first-degree relatives of patients with BD. Most patients with BD have been shown to exhibit changes in circadian rhythm, including social life, activities, and eating and sleep-wake patterns before and during depression, or abnormalities in physiological and behavioral timekeeping during manic and euthymic episodes (26). Depressive symptoms especially are associated with the rhythmicity of daily activities, while manic symptoms are associated with changes in the rhythmicity of sleep-wake patterns (27). However, although biological rhythm disorder has been proposed as associated with early markers of and malfunctioning in BD (26,27), its relationship with mood/mood disorders is still not well understood. As expected, emotional dysregulation is not only associated with depressive symptoms, but also with chronobiological rhythm changes. Difficulties in impulse control, targeted behaviors, and access to effective regulatory strategies have been associated with chronobiological rhythm changes. Six studies on circadian typology in BD involving a total of 850 BD patients showed that the evening type was more common among the patients compared to controls as well (28). The researchers indicated that this could be a trait marker of BD, as the patients' preference for eveningness continued for a long time. Contrary to these findings, one study (119 patients) found no difference between patients with euthymic BD and controls. However, the vast majority of studies have shown impaired circadian rhythm and a preference for eveningness in patients with BD, regardless of mood (28). Research has further stated that in healthy individuals, evening types perform worse in terms of social, familial, and occupational functionality than morning types, as well as experience higher rates of distress, such as aggressive behavior, attention problems, and criminal behavior (29). Therefore, chronobiological interventions may provide preventive strategies and/or improve the treatment of mood disorders.

Study limitations: As with many others, the results obtained in this study had certain limitations. The low number of participants is one of the study's most important limitations. The small sample size and large number of variables examined reduced the statistical results' power and restricted the application of advanced statistical methods. Another limitation is the NSS's lack of validity and reliability in Turkish. Additionally, the possibility of medication that affected certain scales, especially the NES, should be considered; however, it is very difficult to find non-medicated

euthymic BD patients. One last limitation is that the interviewer was not blind to the diagnoses of the patients and controls included in the study.

Conclusions

This research sheds light on emerging evidence regarding emotional regulation difficulties, NSS, and circadian preferences patterns in BD. The study is consistent with others that demonstrate an increasing number of NSS in patients with BD. According to the results of this study, the severity and frequency of these signs in patients and their first-degree relatives are higher than in healthy individuals. Similarly, bipolar patients have more difficulties with emotional regulation, nonacceptance, goals, impulsivity, strategies, and accessibility. This study is the first to examine the relationships between NSS, emotional regulation difficulties, and circadian preferences in patients with BD and their unaffected relatives. Although the results indicate that NSS may be trait markers and potential endophenotype candidates for BD, further studies with larger samples and longer follow-up periods are needed for confirmation.

Conflict of Interest: None of the authors has any conflict of interest to declare. The final manuscript has been seen and approved by all authors. We all accept full responsibility for the design and conduct of the study, had access to the data, and controlled the decision to publish. The paper had not been published elsewhere previously.

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