

# Neuropsychological and Neurophysiological Assessment in Different Phases of Bipolar Disorder

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## ABSTRACT

**Background:** Recent studies have shown that cognitive deficits are significant and pervasive even among remitted bipolar disorder patients. The aim of the current controlled study was to investigate the relationships between cognitive performances, symptom severity, and event-related potentials with regard to different episodes in bipolar patients.

**Methods:** This study was conducted on a total of 60 patients diagnosed with bipolar disorder (20 depressive, 20 manic, and 20 in remission). The Frontal Assessment Battery and Stroop test were used for neuropsychological assessment. Event-related potentials were measured using frontal, central, and parietal EEG recordings, while Nihon-Kohden EMG-EP system was used.

**Results:** Delayed P300 latencies were observed in all phases of bipolar disorder when compared to the controls. There was a positive relationship between frontal, central P300 latencies, and Young Mania Rating Scale scores. A strong positive relationship was also observed between Young Mania Rating Scale scores and Stroop interference scores. A negative relationship was observed between Frontal Assessment Battery scores and frontal, central, and parietal N100 latencies and amplitudes in depressed patients. Consistent with these findings, there was a relationship between Hamilton Depression Rating Scale scores and N100 latencies. There was also a positive relationship between Stroop interference scores and central N200 latency, as well as frontal N200 and parietal N200 amplitudes, while a negative relationship was observed between Stroop total time scores and central N200 latency as well as parietal N200 amplitude in depressed patients.

**Conclusions:** Study findings imply that depression episodes could be associated with decision-making autonomy and memory issues, while there is also a relationship between episodes of mania, impaired inhibitory control, and issues with selective attention. Moreover, these cognitive impairments might be included in the initial phases of processing observed in N100 responses in depression, while processing impairment could be pervasive in mania that results in P300 delays.

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## INTRODUCTION

Bipolar disorder (BD) is one of the most disabling psychiatric disorders generally accompanied by lifelong social, occupational, and medical burdens.<sup>1</sup> The cumulative lifetime incidence of bipolar spectrum disorders has been reported to be approximately 6%.<sup>1</sup> Although the prognosis of BD is considered to be relatively better than schizophrenia due to the higher rates of functionality in remission phases, there is increasing data supporting the idea that cognitive impairments are prevalent and implicated in BD.<sup>2-5</sup> Cognitive impairments have been shown to be persistent in BD and have been associated with low quality of life and functional impairment.<sup>6,7</sup> Cognitive impairments have also been reported in the euthymic phases of BD in addition to manic/mixed and depression phases.<sup>4,5</sup> Similar to other psychiatric conditions

and given the fact that the underlying neurobiological mechanisms and etiopathogenetic pathways involved in BD are not yet fully understood, recent neurophysiological studies have revealed significant results associated with changes in event-related potentials (ERPs), which provide information about the neural processing of stimuli such as visual or auditory tasks in neuropsychiatric disorders. Event-related potentials are measured in terms of the EEG recorded voltage changes reflecting the processes of sensory, motor, or cognitive events.<sup>6</sup> Different domains of cognitive performance, such as attention, perception, and memory, as well as emotion regulation, can be assessed by recording ERPs.<sup>8,9</sup> Recent studies have revealed that an ERP such as P300 could be a candidate for the endophenotype of psychosis and BD.<sup>10,11</sup>

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The most prominent cognitive impairments reported to be encountered in BD patients are problems with executive functions, such as working memory, attention, and verbal and non-verbal memory.<sup>3</sup> Although 30% of BD patients have reported a normal cognitive performance range, there is also substantial evidence that cognitive deficits persist after remission.<sup>3</sup> In addition to conducting the measurement of ERPs in cognitive performance assessments, some other neurocognitive tests evaluate different domains of cognition in those with neuropsychiatric conditions. These tools have been widely used in the assessment of cognitive performance domains in BD, such as working memory, executive functions, attention, and verbal skills.<sup>12-14</sup> However, data regarding cognitive functioning in BD is still not well conceptualized. Furthermore, previous studies have yielded results on different impairments in different domains of cognitive functions with respect to the course and state of illness as well as the presence of premorbid psychiatric features.<sup>12-15</sup>

The aim of the current controlled study was to compare the results of ERPs and neurocognitive test scores and to investigate the relationship between ERPs and cognitive test performances or symptom severity in patients diagnosed with BD who were in different phases of the illness.

## METHODS

### Samples

This study was conducted with a total of 60 patients diagnosed with BD (20 depressive, 20 manic, and 20 remission-period patients) recruited from the inpatient or outpatient service facilities of a mental health and neurology training and research hospital over the course of 6 months. All patients were diagnosed in accordance with the BD criteria described in the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition Text Revision (DSM-IV-TR). A total of 20 healthy subjects who had no psychiatric disorders or perceptual dysfunctions that could interfere with communication were included in the study as the control group. All participants were between 18 and 65 years of age. Individuals with a history of head trauma accompanied by epileptic seizure or consciousness problems, severe neurological conditions including cerebrovascular events that might have impaired cognitive performance, dementia, delirium, mental retardation, perceptual impairments, substance use disorders excluding smoking and caffeine consumption, or an ongoing electroconvulsive therapy course during the study were excluded from the study. Having a comorbidity of an Axis I psychiatric diagnosis besides BD was also a criterion for exclusion. For remitted patients, having a score lower than 8 points for the Hamilton Depression

Rating Scale (HDRS) and 7 for Young Mania Rating Scale (YMRS) was obligatory.

A well-trained neurologist conducted ERP measurements in the electrophysiology laboratory of the study hospital. In this procedure, the Nihon-Kohden EMG-EP system was used. Silver electrodes were placed on the frontal (Fz), central (Cz), and parietal (Pz) scalp positions in accordance with the international 10-20 system. The reference point was considered to be the left auricular (A1) zone. Event-related potentials were recorded by utilizing an auditory oddball discrimination task. P50, N100, N200, and P300 latencies as well as amplitudes were measured using Fz, Cz, and Pz EEG recordings. Ongoing medications were maintained during the study in all patients. Written informed consent was obtained from all participants. The study protocol was approved by the local Erenköy Mental Health and Neurology Training and Research Hospital Ethics Committee for Clinical Trials (Date:02.05.2011 Number:14/3) and was conducted in accordance with the Declaration of Helsinki.

## INSTRUMENTS

### Mood Disorders Patient Registration Form (SKIP-TURK)

This is a semi-structured socio-demographic and clinical data form including 4 modules with a total of 111 items developed by Özerdem et al.<sup>16</sup> This form consists of data regarding socio-demographic variables; medical and family history; and smoking, drug and alcohol use habits and data regarding BD courses such as number and durations of episodes, age at onset, nature of episodes, childhood traumatic experiences, and treatment protocols.

### Structured Clinical Interview for DSM-IV Axis I Disorder (SCID-I)

The structured clinical interview for DSM-IV Axis I disorder (SCID-I) is a semi-structured interview comprised of 6 structured modules used to determine Axis I psychiatric disorders based on the DSM-IV criteria. This comprehensive interview was first developed by First et al.<sup>17</sup> and was designed to be conducted by a clinician or trained mental health professional. The adaption and reliability of the Turkish version of the SCID-I were completed and confirmed by Ozkurkcuoglu et al.<sup>15</sup> in 1999.

### Young Mania Rating Scale (YMRS)

The Young Mania Rating Scale (YMRS) is an 11-item clinical assessment scale used by clinicians for determining the severity of mania in BD.<sup>16</sup> This instrument is used to assess the symptoms of a patient within the last 48 hours. The Turkish reliability and validity of YMRS was confirmed by Karadag et al.<sup>17</sup>

### Hamilton Depression Rating Scale (HDRS)

The Hamilton Depression Rating Scale (HDRS) is a widely used assessment tool for both general diagnostic purposes and to determine the severity of depressive symptoms.<sup>18</sup> This scale consists of 17 items evaluating depressive symptoms. The Turkish validity and reliability of HDRS was confirmed by Akdemir et al.<sup>19</sup>

### Stroop test

The Stroop test is a very specific neurocognitive assessment tool that measures frontal cognitive performance, including the executive functions first developed by Stroop<sup>20</sup> in 1935. This test assesses the ability to inhibit cognitive interference by requesting that participants read the words or name the colors of congruent or incongruent color-words, which is referred to as the Stroop effect. Standardization for Turkish culture, reliability, and validity of the Stroop test was completed and confirmed by Karakaş et al.<sup>24</sup>

### Frontal Assessment Battery (FAB)

The Frontal Assessment Battery is a short test which measures executive functions originally designed by Dubois et al.<sup>21</sup> There are 6 subtests on the FAB that evaluate different domains of frontal functions, and they are scored between 0 and 3 with a maximum composite score of 18. Turkish validity and reliability were confirmed by Tuncay et al.<sup>26</sup>

### Statistical analysis

Statistical Package for the Social Sciences software version 15.0 (IBM Inc., Chicago, Ill, USA) was employed for the statistical analyses. Normality was determined with the Kolmogorov-Smirnov or Shapiro-Wilk test and visual tools. Chi-squared or Fisher exact tests were used to compare the categorical variables, while the Mann-Whitney *U* test was introduced to compare continuous variables between independent groups. Correlation analyses between the independent variables were measured with Pearson's correlation tests. Descriptive statistics for the data were

represented with the mean  $\pm$  standard deviation values. Continuous variables between the groups were compared by using analysis of variance, while the post hoc analysis for comparing the groups was performed using the Bonferroni test. Statistical significance was considered as  $P < .05$ .

### Ethics approval and consent to participate

Written informed consent was obtained from all participants. The study protocol was approved by the Ethical Committee of Erenköy Mental Health and Neurology Training and Research Hospital (Date: 02.05.2011 Number: 14/3) and was conducted in accordance with the Declaration of Helsinki.

## RESULTS

### Socio-demographic and clinical variables

With respect to the socio-demographic variables, there were no statistically significant differences between groups in terms of age, duration of education, and age at onset of illness ( $F=0.88$ ,  $P=.77$ ;  $F=1.54$ ,  $P=.29$ ;  $F=4.15$ ,  $P=.06$ , respectively; Table 1). The initial age of using mood-stabilizing medication was earlier in the manic group ( $F=6.52$ ,  $P=.04$ ). The number of depressive episodes was higher in the remitted group ( $F=4.91$ ,  $P=.04$ ). There was no difference between the groups in terms of the global assessment of functionality scores ( $F=0.283$ ,  $P=.908$ ; Table 1). Mean HDRS scores for the depressed group were found to be  $30.05 \pm 5.21$ , while the mean YMRS scores for the manic group were  $28.72 \pm 4.35$ .

### Comparisons of neuropsychological assessments and event-related potentials

Comparisons of the neurophysiological assessment scores between the groups are presented in Table 2. Mean FAB scores were found to be lower in the manic and depressed groups than in the remitted group and the controls ( $F=15.16$ ,  $P=.002$ ). Mean Stroop interference scores were significantly higher in the manic group, while mean Stroop total time scores were higher in all 3 of the patient groups than in the healthy controls ( $F=3.910$ ,  $P=.012$ , Table 2).

**Table 1.** Socio-demographic and Clinical Variables in Groups

	Manic Group (n=20)	Depressed Group (n=20)	Remitted Group (n=20)	Controls (n=20)	F	P
Age (years)	42.4 $\pm$ 5.4	42.7 $\pm$ 2.8	40.9 $\pm$ 3.7	39.2 $\pm$ 4.7	0.889	.773
Education duration(years)	12.6 $\pm$ 4.8	10.5 $\pm$ 2.5	12.1 $\pm$ 3.2	12.3 $\pm$ 3.8	1.543	.290
Age onset of illness(years)	24.2 $\pm$ 2.8	29.7 $\pm$ 2.0	32.5 $\pm$ 5.2		4.158	.064
Initiation age of mood stabilizer (years)	24.6 $\pm$ 3.1	35.5 $\pm$ 5.6	34.3 $\pm$ 4.5		6.527	.017
Number of manic episodes	9.4 $\pm$ 6.9	10.2 $\pm$ 5.2	11.4 $\pm$ 4.7		1.129	.290
Number of mixed episodes	3.9 $\pm$ 2.4	5.3 $\pm$ 2.1	5.5 $\pm$ 1.8		1.762	.145
Number of depressed episodes	12.8 $\pm$ 6.8	15.1 $\pm$ 2.9	20.5 $\pm$ 5.1		4.912	.042
GAF score	65.7 $\pm$ 6.5	68.1 $\pm$ 5.7	75.4 $\pm$ 9.3		0.283	.908

GAF, global assessment of functioning.

**Table 2.** Comparison of Mean Neurophysiological Assessments Scores Between Groups

Scores	Manic Group (n=20)	Depressed Group (n=20)	Remitted Group (n=20)	Controls (n=20)	F	P
FAB total	16.3±2.27	16.1±1.32	16.9±1.35	17.5±0.68	1.5164	.002
Stroop interference	1.45±0.93	1.06±0.57	1.2±0.84	0.15±0.36	2.807	.045
Stroop total time	98.2±24.9	118.4±17.9	96.3±29.7	77.2±18.4	3.910	.012

FAB, frontal assessment battery.

A comparison of the ERPs between groups showed that Fz, Cz, and Pz latencies for P50, N100, P200, and N200 were similar in all groups (Table 3). However, P300 latency was prolonged in the manic, depressed, and remitted groups when compared with the Fz, Cz, and Pz measures for the control group ( $F=24.875$ ,  $P < .001$ ;  $F=21.778$ ,  $P < .001$ ;  $F=22.757$ ,  $P < .001$ , respectively; Table 3). Additionally, Fz, Cz, and Pz amplitudes for P50, N100, P200, and P300 were similar in all groups, while the Pz amplitude for N200 was lower in the depressed group when compared with other groups ( $F=3.69$ ,  $P=.03$ ; Table 4).

In the post hoc analyses, mean Fz P300 latency was significantly higher in the 3 patient groups than in the controls ( $P < .001$ ), while mean Cz P200 latency was found to be increased in the manic patient group ( $P=.04$ ). In addition, the mean Cz P300 latency was increased in the remitted patient group ( $P < .001$ ; Table 3). Mean Pz P300 latency was higher in the remitted, depressed, and manic patient groups compared to the controls ( $P=.001$ ; Table 3).

### Correlations

When we investigated a possible relationship between neuropsychological assessment scores and ERP scores

in each group, we found that there was no relationship between FAB, Stroop, and ERP scores in manic patients.

For depressed patients, there was a strong negative relationship between FAB scores and the Fz, Cz, and Pz latencies of N100 ( $r=-0.571$ ,  $P < .001$ ;  $r=-0.500$ ,  $P=.008$ ; and  $r=-0.492$ ,  $P=.008$ , respectively). The same negative relationship was observed for FAB scores and the N100 amplitude ( $r=-0.611$ ,  $P=.006$ ;  $r=-0.783$ ,  $P < .001$ ; and  $r=-0.671$ ,  $P=.002$ , respectively). There was also a strong relationship between Stroop interference scores and the Cz N200 latency ( $r=0.680$ ,  $P=.001$ ), while a moderate positive relationship was found for the Fz N200 and Pz N200 amplitudes ( $r=0.468$ ,  $P=0.043$  and  $r=0.478$ ,  $P=.045$ , respectively). A negative relationship was observed between the Stroop total time scores and the Cz N200 latency as well as the Pz N200 amplitude ( $r=-0.462$ ,  $P=0.05$ ;  $r=-0.514$ ,  $P=.029$ , respectively).

There was a negative relationship between FAB total scores and the Fz N200 latency, while a weak positive relationship was found between FAB scores and the Cz N200 amplitude in the remitted patient group ( $r=-0.429$ ,  $P=0.054$  and  $r=0.421$ ,  $P=.054$ , respectively). A moderate positive relationship was observed between

**Table 3.** Comparison of Mean Event-Related Potentials Latencies Scores Between Groups

Latencies (ms)	Manic Group (n=20)	Depressed Group (n=20)	Remitted Group (n=20)	Controls (n=20)	F	P
P50 Fz latency	43.1±19.7	45.4±11.9	40.9±11.3	37.9±9.96	3.129	.290
N100 Fz latency	92.1±17.6	91.9±13.8	90.7±13.1	91.5±14.1	3.762	.145
P200 Fz latency	180.7±28.1	162.2±21.32	175.4±23.5	170.7±18.9	2.912	.34
N200 Fz latency	219.2±24.8	220.3±33.6	236.9±35.7	216.1±18.5	0.283	.908
P300 Fz latency	343.5±25.4	347.7±55.3	354.1±44.5	300.2±25.6	24.875	< .001
P50 Cz latency	44.5±17.8	45.3±15.2	42.5±11.8	39.9±9.3	3.121	.2
N100 Cz latency	92.2±12.7	93.6±11.0	90.7±12.8	94.3±14.2	2.762	.175
P200 Cz latency	185.1±32.9	163.4±15.5	170.4±24.4	162.5±17.6	3.912	.042
N200 Cz latency	223.3±22.6	221.2±27.8	232.6±35.8	212.4±15.2	0.583	.838
P300 Cz latency	330.6±60.2	331.8±68.4	352.3±48.3	296.1±26.11	21.778	< .001
P50 Pz latency	50.8±15.6	49.6±12.9	42.8±14.9	39.4±11.6	2.529	.190
N100 Pz latency	94.3±15.2	92.7±13.2	90.3±13.9	95.8±13.7	3.564	.145
P200 Pz latency	175.3±21.9	167.4±15.7	170.1±25.1	163.5±18.6	3.912	.072
N200 Pz latency	228.7±19.1	214.4±35.7	229.4±35.4	200.9±46.7	1.283	.628
P300 Pz latency	339.9±29.2	348.4±62.3	351.1±49.16	296.3±25.6	22.757	< .001

Fz, frontal zone; Cz, central zone; Pz, parietal zone.

**Table 4.** Comparison of Mean Event-Related Potentials Amplitudes Scores Between Groups

Amplitudes (ms)	Manic Group (n=20)	Depressed Group (n=20)	Remitted Group (n=20)	Controls (n=20)	F	P
N100 Fz amplitude	9.7±6.8	7.6±3.6	9.7±3.6	9.4±3.3	4.163	.028
P200 Fz amplitude	4.7±3.8 3	4.7±3.8	4.6±2.6	4.6±3.5	0.829	.72
N200 Fz amplitude	6.2±4.5	5.9±4.6	8.5±4.8	8.5±5.2	1.543	.290
P300 Fz amplitude	8.4±1.2	12.4±1.5	7.8±1.6	7.7±1.9	2.529	.192
N100 Cz amplitude	9.7±5.4	9.0±4.0	9.9±4.0	9.8±4.6	3.564	.145
P200 Cz amplitude	5.9±3.8	3.9±3.6	4.1±2.9	3.6±2.6	1.912	.272
N200 Cz amplitude	7.8±6.1	5.5±5.4	10.3±5.7	10.5±6.7	1.283	.628
P300 Cz amplitude	5.3±3.7	9.9±11.3	5.8±4.5	5.2±4.3	3.762	.162
N100 Pz amplitude	6.5±4.9	5.8±3.5	6.0±3.9	6.7±3.5	2.912	.342
P200 Pz amplitude	4.2±2.9	3.0±2.5	3.7±2.3	3.2±2.7	3.690	.045
N200 Pz amplitude	5.8±5.5	2.6±2.5	6.1±4.5	6.8±5.0	3.962	.033
P300 Pz amplitude	8.4±3.8	9.5±9.4	7.4±5.4	6.5±5.3	2.912	.342

Fz, frontal zone; Cz, central zone; Pz, parietal zone.

the Stroop interference scores and the Fz, Cz, and Pz N100 latencies for remitted patients ( $r=0.453$ ,  $P=.045$ ;  $r=0.464$ ,  $P=.039$ ; and  $r=0.441$ ,  $P=.052$ , respectively), while a strong positive relationship was found between Stroop total time and the Cz P50, Pz P50, N100, and N200 latencies ( $r=0.472$ ,  $P=.036$ ;  $r=0.537$ ,  $P=.015$ ;  $r=0.579$ ,  $P=.007$ ; and  $r=0.481$ ,  $P=.032$ , respectively). On the other hand, there was a strong negative relationship between Stroop total time and the Pz N200 amplitude ( $r=-0.470$ ,  $P=.036$ ).

In the healthy control group, the FAB total score was positively correlated with the Pz P300 amplitude ( $r=0.48$ ,  $P=.005$ ), and the Stroop interference scores were strongly correlated with the Fz, Cz, and Pz P300 latencies ( $r=0.538$ ,  $P=.014$ ;  $r=-0.529$ ,  $P=.016$ ; and  $r=-0.515$ ,  $P=.020$ , respectively). There was a strong positive relationship between Stroop interference and Pz N200 latency as well as amplitude ( $r=-0.507$ ,  $P=.022$  and  $r=0.529$ ,  $P=.017$ ), and a strong relationship was found between Stroop total time scores and the Fz P300 and Cz N200 amplitudes ( $r=-0.478$ ,  $P=.033$  and  $r=0.671$ ,  $P=.001$ , respectively).

In determining whether there was a relationship between the severity of mania and neuropsychological assessment and ERPs scores, we found no relationship between YMRS scores and FAB scores, while a strong positive relationship was observed between YMRS scores and Stroop interference scores ( $r=0.538$ ,  $P=.014$ ; Table 5). Furthermore, there was a moderate positive relationship between YMRS scores and the Fz P300 latency and a strong positive relationship between YMRS scores and the Cz P300 latency ( $r=0.462$ ,  $P=.04$  and  $r=0.546$ ,  $P=.013$ , respectively, Table 5). There was no relationship between HDRS scores and Stroop performance scores, while a strong negative relationship was observed between HDRS and FAB total scores ( $r=-.575$ ,  $P=.008$ ,

Table 5). A moderate positive relationship was also observed between HDRS scores and the Fz N100 latency ( $r=0.440$ ,  $P=.52$ , Table 5).

**Table 5.** Pearson's Correlation Between Psychiatric Clinical Measures and Neurophysiological Assessments Scores As Well As Event-Related Potentials

	YMRS		HDRS	
	r	P	r	P
Neurophysiological tests				
FAB total score	-0.074	.762	-0.575	.008
Stroop interference score	0.538	.014	-0.043	.856
Stroop total time	0.132	.589	0.179	.451
ERPs	YMRS		HDRS	
P50 Fz latency	-0.177	.457	-0.289	.217
N100 Fz latency	-0.202	.392	0.440	.52
P200 Fz latency	0.135	.569	0.156	.658
N200Fz latency	0.146	.552	0.133	.576
P300 Fz latency	0.462	.04	0.154	.517
P50 Cz latency	-0.102	.669	0.149	.531
N100 Cz latency	-0.208	.379	-0.139	.559
P200 Cz latency	-0.210	.373	-0.112	.648
N200 Cz latency	0.190	.435	0.259	.285
P300 Cz latency	0.546	.013	0.066	.784
P50 Pz latency	-0.369	.109	0.116	.625
N100 Pz latency	0.029	.904	0.157	.509
P200 Pz latency	0.177	.467	-0.004	.987
N200 Pz latency	0.258	.272	0.109	.657
P300 Pz latency	0.338	.145	0.120	.614

Fz, frontal zone; Cz, central zone; Pz, parietal zone; ERPs, event-related potentials; YMRS, Young Mania Rating Scale; HDRS, Hamilton Depression Rating Scale.

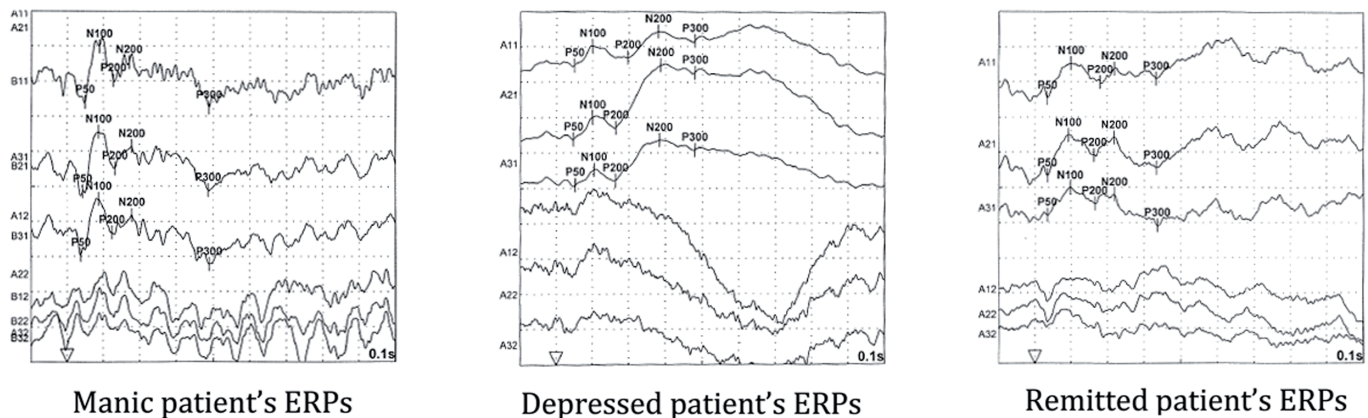


Figure 1. Event-related potential (ERP) samples comprised of one for each manic, depressed, and remitted bipolar patient.

Three ERPs samples comprised of one for each manic, depressed, and remitted bipolar patient are presented in Figure 1.

## DISCUSSION

In this study, we have investigated the cognitive functions and ERP scores along with their relationships in manic, depressed, and remitted bipolar patients, as well as healthy controls. We found a decrease in FAB scores in manic or depressed patients in relation to healthy controls and remitted patients. Furthermore, Stroop interference scores were higher in patients with manic episodes, while Stroop total time was found to be relatively low in BD patients with depressed episodes. Previous studies suggest that reduced inhibitory control, which Stroop interference reflects, is one of the core cognitive findings in cases of BD.<sup>22-24</sup> Furthermore, depression has been reported to be one of the most significant predictive factors for reduced cognitive inhibition in remitted BD patients.<sup>25</sup> However, in our study, the most decreased cognitive response inhibition was observed in patients with manic episodes.

Cognitive response inhibition has been associated with deficient ventrolateral prefrontal activation in cases of BD.<sup>26,27</sup> In our study, there was a significant relationship between mania severity and Stroop interference scores, which implies that hyper-reactivity might be correlated with the severity of manic symptoms. Although Stroop interference scores were relatively higher in depressed and remitted patients than in healthy controls, there was no relationship between depression severity and cognitive response inhibition. Previous reports have yielded a negative correlation between depression severity and Stroop task performance.<sup>25</sup> However, our results have shown that the most significant prolongation in Stroop performance was reported in the depressed group, while there was no relationship between depression severity and Stroop total time measures. Another important finding was the strong negative relationship between depression severity and executive functions, which were measured by

the FAB. This finding was consistent with previous reports demonstrating the impairment in the executive functions of those diagnosed with BD.<sup>28</sup>

Neurophysiological tests are important tools for determining cognitive performance. Event-related potentials assessment has been a widely utilized instrument in terms of determining the impaired domains of cognitive functions. Previous studies have shown that N100, P200, and N200 recordings were associated with sensory gating, recognition, discrimination, classification, behavioral inhibition, working memory, and inhibition.<sup>29</sup> While reduced P50 suppression has been linked to deficits in sensory gating, suggesting that such a presentation is an endophenotype for schizophrenia, later phases of stimuli related to sensory gating in attentive levels such as N100 and P200 have also been included in sensory gating deficits in schizophrenia and BD.<sup>30,31</sup> However, the results obtained from other studies investigating these ERPs remain inconsistent. In our study, only the Cz P200 latency was found to be delayed in mania when compared to depressed and remitted BD patients and healthy controls. This finding might imply that deficits in sensory gating could be more consistent in mania than in other phases of BD.

Another ERP, P300, is a positive waveform and is elicited in response to rare or novel target stimuli, reflecting memory context updating by amplitudes and information processing speed by latencies. Previous reports have shown that P300 might also be a promising endophenotype for schizophrenia, while numerous studies have found reduced P300 amplitudes and normal P300 latencies in BD cases.<sup>32</sup> However, some data showed delayed P300 latencies and normal P300 amplitudes in BD cases.<sup>10</sup> Our findings showed delayed P300 latencies in Fz, Cz, and Pz in all phases of BD when compared with healthy controls, which can be assumed to be demonstrative of delayed information processing in BD cases, even in remitted phases, which was previously reported by Morsel et al.<sup>32</sup>

Another significant finding in our study was a relationship between Fz and Cz P300 latencies and YMRS scores,

which could be interpreted as an information processing impairment related to mania severity. However, no relationship was observed between cognitive performance scores and ERPs in mania, and thus it can be assumed that mania could be a relatively more complicated clinical condition than depression with regards to cognitive processing. The negative relationship observed between FAB scores and the Fz, Cz, and Pz N100 latencies and amplitudes could also be considered as an interesting finding in our study considering that N100 has been reported to be intact in several studies conducted on BD while also being designated as a candidate marker distinguishing schizophrenia and BD.<sup>33</sup> This finding might contribute to investigate the involvement of N100 latencies and amplitudes in particular cognitive aspect.

Another finding with respect to depressed patients was a significant relationship between Stroop interference scores, Stroop total time scores, and N200 latencies, which might indicate that the depression phase could be connected to impaired associations in the primary auditory cortex. There are also recent studies that support an association between visual processing deficits and depression which imply perceptual deficits might be distinguished traits in depression.<sup>34</sup> Another interesting finding in the study was that the Stroop test performance scores were correlated with N200 Cz latency and Fz, Pz amplitudes. Furthermore, a relationship between FAB scores and ERPs was observed in the N100 responses of depressed patients, while it was associated with P300 responses in the healthy controls. Consistent with these findings, there was also a relationship between HDRS scores and N100 latencies. These findings might support the notion that N100-related changes might be more prominent in bipolar depressed patients when comparing healthy population. In considering the relationship between YMRS scores and Fz and Cz P300 latencies, Stroop interference scores were related to P300 responses in patients, while this relationship was observed in N200 responses in healthy controls. All of these findings imply that depressive episodes could be associated with problems with decision-making autonomy and memory issues, while mania is related to impaired inhibitory control and issues with selective attention. Moreover, these cognitive impairments might be included in the initial phases of processing observed in N100 responses in depression, while processing impairment could be pervasive in mania that results in P300 delays.

There are some limitations that should be considered when interpreting our results. Although patients were homogenous in terms of diagnosis, psychotic features which may contribute to significant differences in both cognitive abilities and ERPs might have been presented at the subthreshold level in a study population diagnosed with manic or depressed phases of BD. Another limitation was that the impact of the patient's ongoing medications

on cognitive and neurophysiological measures could not be ruled out within the context of the study.

## CONCLUSION

In conclusion, our findings suggest impairments in cognitive abilities, including sensory gating, selective attention, and information processing, are prominent and concurrent with ERP deficits in early and late phases of stimuli in all stages of BD. There might be a relationship between severity of clinical presentation and cognitive performance as well as ERPs. Although the cross-sectional design of the study yielded some significant findings, longitudinally designed comparative studies might shed even more light on the cognitive status of BD patients with even more consistent and specific findings.

**Ethics Committee Approval:** Ethics committee approval was received from the Erenköy Mental Health and Neurology Training and Research Hospital Ethics Committee for Clinical Trials (Date:02.05.2011 Number:14/3).

**Informed Consent:** Written informed consent was obtained from all participants who participated in this study.

**Peer Review:** Externally peer-reviewed.

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