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Cognitive functions in euthymic patients with bipolar disorder

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BACKGROUND: Recent studies have focused on the nature of cognitive dysfunction in bipolar patients. The purpose of the current study was to investigate cognitive performance of individuals with bipolar disorder compared to healthy control subjects during a well-established euthymic period.

METHODS: The sample consisted of 27 bipolar euthymic patients and 21 control subjects. Verbal and visual memory performance, attention, executive functions and psychosocial functions were evaluated for each participant.

RESULTS: Bipolar patients showed significant attentional deficit and executive dysfunction and also poor performance on verbal and visual memory tasks compared to the controls. Illness duration and lifetime total episode number and previous episode with psychotic features was associated with worsened performance on attention, executive and memory tasks. Psychosocial functioning was not associated with cognitive deficit.

CONCLUSIONS: The present study showed persistent cognitive impairment on inhibitory control and selective attention as well as poor performance on verbal and visual memory tests in a group of bipolar euthymic patients. The impaired neuropsychological performance was associated with duration of illness, total number of episodes per lifetime, and previous episodes with psychotic features. Attentional dysfunction seemed to be a trait abnormality for the sample studied.

Bipolar disorder is a recurrent illness with significant disability and heterogeneous outcomes.[1] The view that patients with bipolar disorder make a full recovery between episodes of illness has been widely accepted despite a lack of systematic investigation. In bipolar patients, deficits in executive function, psychomotor skills, and memory have been reported.[2,3,4,5] It has been established that deficiencies in cognitive functions may persist after clinical recovery or in remitted patients and prevent patients from attaining an optimal adaptation in their daily lives.[6-9] Recently, studies focused on the nature of cognitive dysfunction in bipolar patients by increasing body of evidence come from the studies performed on patients in the euthymic state.[3,4,10-14]

In a sample of 41 patients studied during euthymia, Ferrier et al. described poorer performance on executive function in euthymic bipolar disorder patients, regardless of outcome.[7] Further studies have confirmed the presence of cognitive impairment in euthymic patients with bipolar disorder, including reports of reduced performance on tasks verbal memory, cognitive flexibility, psychomotor speed and visuospatial ability.[3,4,10,14-16] Patient age, duration of illness, personality characteristics, treatment and the existence of psychotic symptoms were found to affect cognitive functions.[7,17-19] Recent studies have emphasized that longitudinal studies are required to elucidate the association of cognitive dysfunction with the onset and progression of bipolar disorder.[3,20,21] The purpose of the current study was to compare the cognitive performance of our own sample of patients with euthymic bipolar disorder with healthy controls. Conducting the study during a well-defined euthymic period in our sample provided for exclusion of the effect of residual mood symptoms as far as possible. We expected that the results of the present study might guide to us in future studies as a baseline definition of our group with clinical correlates.

PATIENTS AND METHODS

Twenty-seven euthymic patients (19 female, 8 male), diagnosed with bipolar disorder according to DSM-IV criteria were recruited from a patient sample routinely followed at the Mood Disorder Clinic of the

Department of Psychiatry in Pamukkale University Hospital.[22] All patients who met the inclusion criteria and gave consent enrolled to the study. The healthy controls were 21 subjects (16 female, 5 male) chosen among employees and relatives or acquaintances of the hospital staff working in clinical and administrative areas. The patients did not differ significantly from controls in age, gender and educational level (all $P>.05$). Subjects with bipolar disorder were observed in the outpatient setting for two months to ensure euthymia before the experimental procedures were administered. Subjects were included in the study if they: (1) met the diagnostic criteria for DSM IV bipolar disorder euthymic phase[22]; (euthymia was defined as having a Hamilton Depression Scale score below 7 and a Bech-Rafaelsen Mania Scale score below 6 for two consecutive monthly assessments,[23,24] just before cognitive testing, (2) had not received ECT within the last year, (3) showed no evidence of systemic or neurologic illnesses that might affect cognitive performance, (4) had no present alcohol or drug abuse or history, (5) were aged between 20-55 years, (6) had a basic educational level of at least 5 years or schooling, and (7) were able to give consent. All the subjects (patients and controls) were right-handed, according to the Turkish version of the Edinburg Handedness Inventory.[25] Comorbid psychiatric disorders (i.e. anxiety or substance abuse) were not present in the patient group at the time of testing, as assessed by the Structured Clinical Interview for DSM-IV Axis I Disorders.[26] Also, controls had no prior psychiatric history and had no first-degree relatives with affective disorder. Additional clinical information (age of onset, duration of illness, number of episodes, history of mania with psychotic features, and ongoing treatment) was recorded (Table 1). Hamilton Depression scores and Bech-Rafaelson Mania scores of the patients are also presented in Table 1.

Table 1. Demographic and clinical variables in the bipolar and control groups.

Variables	Bipolar group (n=27)	Controls (n=22)	Statistics
Female, n (%)	19 (70.4)	17 (77.3)	
Male, n (%)	8 (29.6)	5 (22.7)	$\chi^2 = 0.203$, $P>0.05$
Age (years), mean (SD)	31.81 (11.17)	34.13 (11.38)	z = -0.562, $P>0.05$*
Education (years), mean (SD)	10.00 (3.56)	10.45 (3.69)	z = -0.653, $P>0.05$
Clinical characteristics			
Age of onset (years), mean (SD)	22.59 (8.79)		
Chronicity (years), mean (SD)	9.55 (7.79)		
Total episode number, mean (SD)	5.56 (4.25)		
Previous episode with psychotic features			
Present, n (%)	11 (40.7)		
Absent, n (%)	16 (59.3)		
Treatment			
Lithium, n (%)	15 (55.6)		
Sodium valproate, n (%)	9 (34.3)		
Atypical antipsychotics, n (%)	3 (11.1)		
HRSD-17,* mean (SD)	2.55 (1.69)		
BRMAS,* mean (SD)	2.33 (2.01)		

HRSD-17: Hamilton Rating Scale for Depression, BRMAS: Bech- Rafaelsen Mania Scale *Mann Whitney U test

Each subject was evaluated with a range of cognitive tests in a fixed order: digit span, Verbal Memory Processes Test (VMPT), visual reproduction tests, Stroop Color Word Test (SCWT), Wisconsin Card Sorting Test (WCST) and delayed verbal and visual memory task. Cognitive testing lasted approximately 2 hours with a break halfway. Trained neuropsychology personnel administered all tests. All participants were tested individually. The cognitive evaluation for memory included verbal and visual tests. The verbal tests included the VMPT, an analogue of the Rey Auditory Verbal Learning test in the Turkish language, which was developed by Oktem and Tanor.[27] It uses a 15-word list that is read to the subject ten times. The VMPT provides measures of learning (i.e., registration and acquisition, acquisition being a measure of increase in registered items over trials) and short-term recall, delayed recall, and delayed recognition and intrusion. Visual memory was examined by the Visual Reproduction (VR) Test developed by Wechler and used as a subtest of the Wechsler Memory Scale. This test includes 4 different designs cards. Each design is shown for ten seconds. Following each exposure, subjects draw what they remember of the design. A delayed recall trial is given following a 30-minute delay.[28]

Executive functions and attention were assessed using the Digit span, Digit subtest (Wechsler Adult Intelligence Scale) in which the subject repeats a fixed random series of numbers of increasing length in direct order (digits forward) and in reverse order (digits backward). In addition to auditory attention and short-term retention capacity, this test assesses the ability to manipulate the information in verbal working memory. Raw scores for direct and reverse order were calculated.[28] The Stroop test (Dotrill format) was used to evaluate

selective attention, the ability of attentional set shifting and response inhibition. Two trials, one in which reading focuses on color words printed in ink of different colors, and the other requiring naming of the printed colors. For each part, both the time to complete and the number of errors were recorded.[28] WCST was used to examine persistence, strategic planning, category shifting, mental control, and organization.[29] Psychosocial functioning was assessed according to DSM-IV GAF (Global Assessment of Functioning) scale with 0-100 scores.

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version (version 10.0) on a PC. Initial data screening using the Leven test for equality of variance indicated that a number of variables had non-normal distributions and a small sample size. Therefore, statistical analyses were performed using the non-parametric Mann-Whitney U test. This method does not assume the asymptotic distribution of a test statistic, and is therefore reliable regardless of the size, distribution, sparseness, or balance of the data. The Mann-Whitney U-test is reported alongside the corrected significance level for each cognitive performance index. The difference between patients and control groups with regard to categorical variables were tested by the Chi Square test. The relationship between cognitive performance and clinical variables were examined by non-parametric correlation analysis (Spearman correlation analysis). All reported P values are two-tailed.

RESULTS

Socio-demographic variables (gender distribution, age, educational status) were not different between bipolar and control group (Table 1). For verbal memory, there were significant differences across the groups in total learning scores on the VMPT, with the bipolar group performing worse than the controls (13.55±1.8 vs. 14.68±0.77, respectively, P=0.007) (Table 2). Delayed free recall scores of patients were also significantly lower than in the control group. Bipolar patients showed more intrusion (false named words) than controls. Delayed recognition (free+cued) scores were not different between bipolar patients and controls. For visual memory, accurate recall of the figure in both short- and long-term memory scores was lower in the patients when compared to controls (P<0.05).

For attention and executive functions, the bipolar group showed poor performance on digit forward compared with controls but there were no significant differences on digit span backward in the digit span test. Color-word interference scores were found to be higher for the patients when compared to controls on the SCWT (P=0.004). There was no significant difference between patients and control groups in terms of WCST findings (P>0.05).

The lifetime total episode number showed significant correlation with poor performance on the verbal memory (delayed free recall) and visual memory task (Table 3). The color-word interference on the Stroop test was positively correlated with illness duration, and lifetime total episode number.

To investigate the influence of a previous episode with psychotic features after clinical remission we compared the cognitive test performance of patients with and without a previous episode with psychotic features and controls. To perform these analyses we preferred non-parametric variance analyses (Kruskal Wallis anal-

Table 2. Results of cognitive measures for the bipolar (n=27) and the control group (n=21).

Cognitive measures	Bipolar group Mean (SD)	Control group Mean (SD)	Z	*P*
Digit span (attention)				
Forward	5.11(0.80)	5.71 (1.10)	-1.802	0.03
Backward	4.14 (1.32)	4.52 (0.92)	-1.622	0.10
Verbal Memory Prosses Test				
learning	111.48 (22.74)	124.59 (15.20)	-2.31	0.02
delayed free recall	12.48 (2.40)	13.77 (1.30)	-2.38	0.02
delayed recognition (free+cued)	15.00 (0.0)	15.00 (0.0)	0.00	1.00
Intrusion	1.92±1.59	0.90 (1.06)	1.67	0.01
Visual Reproduction Tests				
Short-term memory	10.00 (2.84)	12.72 (1.88)	-4.04	0.0001
Long-term memory	8.62 (3.81)	12.59 (2.08)	-3.74	0.0001
Stroop Color Word Test				
Color-word interference	59.37 (31.08)	39.00 (12.81)	3.09	0.004
Spontaneous correction score	2.25 (2.31)	1.13 (1.61)	1.92	0.06
Wisconsin Card Sorting Test				
Categories achieved	3.96 (2.15)aite	4.72 (1.63)	-1.37	0.17
Number of perseverative responses	27.48 (33.91)	18.40 (16.47)	1.14	0.25
Percent perseverative errors	17.88 (20.29)	13.77 (11.01)	0.85	0.39
Percent conceptual level responses	54.88 (32.37)	59.90 (18.70)	-0.64	0.52
Failure to maintain set	0.81 (1.41)	0.90 (1.06)	-0.25	0.79

*Mann-Withney U test

Table 3. Correlations between selected clinical variables and cognitive measures in the bipolar group.

Cognitive measure	Age	Duration of illness	Lifetime total episode number
Verbal Memory Process Test			
Learning	-0.238	-0.354	-0.371
Delayed free-recall	-0.207	-0.164	-0.386*
Delayed recognition	-0.218	-0.257	-0.260
Intrusion	-0.115	-0.006	-0.077
VR (Visual Reproduction)			
Short-term memory	-0.166	-0.172	-0.592**
Long term memory	-0.236	-0.319	-0.443*
Stroop Color Word Test			
Color-word interference	0.397*	0.448**	0.410*
Spontaneous correction score	0.117	0.213	0.423*

*P<.05, **P<.01, Spearman correlation analysis

Table 4. Comparison of cognitive test performance in patients with a previous episode with psychotic features (n=11), without psychotic features (n=16) and controls (n=22).

Tests	Groups	Mean±SD	χ^{2*}	P*
Stroop Color Word Test				
Color-word interference	Psychotic	71.27±0.61		
	Non-psychotic	51.18±29.57	13.509	0.001
	Control	38.33±12.73		
Spontaneous correction	Psychotic	3.09±2.25		
	Non-psychotic	1.68±2.24	7.412	0.025
	Control	1.19±1.63		
Visual Reproduction Test				
Short-term memory	Psychotic	9.81±3.15		
	Non-psychotic	10.12±2.70	14.093	0.001
	Control	12.80±1.88		
Long-term memory	Psychotic	8.63±4.31		
	Non-psychotic	8.56±3.57	16.505	0.001
	Control	1266 ±2.10		

*Kruskal-Wallis analysis of variance

ysis of variance) due to the unequal and small sample size in each group and non-homogeneity of variance. These analyses revealed significant group differences on the SCWT and visual memory performance (Table 4). We conducted additional analyses to determine which mean was different via pairwise comparisons for these variables (Mann Whitney U test). The later analyses showed that the patients with a previous episode with psychotic features exhibited worse performance on the SCWT and visual memory performance test than controls. On the other hand, the psychotic group differed from the non-psychotic group with respect to only impaired SCWT performance. The illness duration and lifetime total episode number were not significantly different between psychotic and non-psychotic group. The rates of the patients maintaining lithium and sodium valproate treatment were not different between two groups.

To examine the influence of mood stabilizing drugs we compared the cognitive test performances of the patients receiving lithium and sodium valproate. We excluded patients receiving atypical antipsychotics because of small sample size (n=3). We found no significant differences between the cognitive performance of the patients receiving lithium and sodium valproate (P>0.05).

In the assessment of psychosocial functioning, the mean GAF score for the bipolar group was 67.66±6.201. GAF scores were negatively correlated with intrusion scores on VMPT (r=-0.532, P<0.01, Spearman correlation test). The performance on the other cognitive test was not correlated with GAF scores or with illness duration and total episode number.

DISCUSSION

The present study indicates that selective cognitive dysfunction is present in patients with bipolar disorder in the euthymic state. We found that bipolar patients performed worse than control subjects on attention, verbal learning (memory) and visual memory tasks. Our results for executive function measures presented a two-dimensional feature: impaired performance on selective attention and inhibitory control (on SCWT) and preserved performance with respect to ability to establish, maintain and change set, and cognitive flexibility (on WSCT).

The main verbal memory deficit of our study group was characterized by impairments to learning, delayed free recall, and an increase in intrusions. Recent studies have reported that euthymic patients with bipolar disorder showed cognitive deficits on a task of verbal learning and memory.[3,4,14,17,30,31] Delayed recognition scores were not different between bipolar patients and controls in our study group; this finding implied that our bipolar sample tended to show impairment to memory secondarily, in terms of an attentional deficit rather than a true memory retention (storage) or learn-

ing deficit. Bipolar patients showed a higher tendency to confabulate in verbal learning task compared with controls. In our opinion, this may be considered as an extension of attentional-executive dysfunction on SCWT, which requires an ability to inhibit a prepotent response tendency.

We also found that visual memory function was impaired in our patients both in short- and in long-term memory. As in our study, some studies have reported non-verbal memory impairment in euthymic bipolar patients.[6,16,32] As reported by Deckersbach et al euthymic bipolar patients showed impaired performance in immediate recall on the Rey-Osterreith Complex Figure Test.[32] Authors have suggested that non-verbal memory problems in these patients are mediated by poor use of non-verbal organization strategies during encoding, but these problems do not appear to reflect deficits in retention of information. Our tendency is to think in the same direction, as expected impairments of immediate visual memory possibly lead to poorer performance on delayed visual recall, and therefore the major problem appears to be the impaired immediate memory process, which is closely related to the attentional process.

Our euthymic patients also showed impairment on the digit span forward and Stroop tests than controls, but they did not differ with respect to WCST performance. The SCWT, especially owing to time pressure, is considered as more specifically focused on attentional domain, while the WCST is considered a measure of executive function, including abilities in strategic planning, organized searching and shifting cognitive set without time pressure. The WCST is more specific for assessment of executive function. Previous studies on the cognitive function of bipolar patients have included patients with different mood states ranging from an acute episode to relative remission and to euthymia.[3-8,19,31,33] Some of these studies have described poorer performance on executive function in euthymic bipolar disorder.[3,4,7,10,14,16,19] On the other hand, Rossi et al and Rubinsztein et al found no significant impairment of executive function in euthymic patients.[12,34] These discrepant findings may be explained by the differences in the samples as well as the variety of measures to assess frontal executive functions across studies. Generally, impaired executive functions have been described in older euthymic patients (39 to 52 years old), in those with a longer duration of illness (13 to 24 years) and more recurrent mood episodes (11 to 24) than our sample.[3,4,10,19,31] Our sample consisted of younger bipolar patients (mean age, 31 years) having a short duration of illness (mean, 9.5 years) and fewer episodes (mean, 5.56) than previous samples. Therefore, as a group our bipolar patients may be considered free of the deteriorative effects of long-standing illness. How can we explain the partial impairment of executive function, predominantly attentional domain, in our sample? Recent studies have suggested that attentional performance may a viable putative endophenotype or trait characteristic for bipolar disorder.[20,35] Burdick et al have studied the longitudinal stability of cognitive performance in bipolar versus schizophrenia probands.[35] They have found that many cognitive domains constantly impaired in schizophrenia and bipolar patients showed constant attentional deficit whereas improvement on executive and memory function improved over time.

We found that the lifetime total episode number, longer duration of illness and the presence of psychotic symptoms in previous episodes significantly correlated with impaired performance on memory and attentional domains. Most of previous studies have reported that patients with a greater number of episodes and longer duration of illness suffer greater cognitive decline as do bipolar patients with psychotic features.[3,12,14,19,31,36] Such associations have generally been thought of as indicating a progressive disease process. Our results have also confirmed these associations for a relatively young and less chronically ill patient sample.

Recent studies have focused more on the negative effect of cognitive dysfunction on psychosocial functioning.[3,4,14] In the present study, we have failed to find such a correlation, but we found only a limited negative effect on verbal memory tasks. The small sample size in our study, compared with others, may have contributed to the relatively well preserved cognitive functioning and reduced chronicity in our patients. Longitudinal studies may help to clarify this issue.

In conclusion, the euthymic bipolar patients in our study exhibited persistent cognitive impairment on selective attention, inhibitory control, verbal memory and learning tests, and these impairments were associated with a longer illness period, recurrent mood episodes and an episode history with psychotic features. However, some limitations of the study could affect the results. Medication effects are a methodological dilemma for euthymic patients, given that the majority of patients are medicated with various mood stabilizers, antidepressants, and antipsychotics, alone or in combination. It is clearly difficult and perhaps unethical to investigate drug-naive/medication-free patients and for this reason there are few and limited data on drug-free patients.[15,37] Even though other studies have reported that medication at the time of testing did not influence the cognitive evaluation, we cannot exclude the possibility that mood stabilizing medication could have in-

fluenced the cognitive testing in this patient group.[31,38,39] However, we found no association between mood stabilizing drugs and cognitive performance. Nevertheless our results indicating important cognitive impairment in the euthymic patients with bipolar disorder should taken with caution due to the small sample size. A longitudinal study with a larger sample size and more detailed assessment of attentional abilities could have made our results more reliable. The selective attention deficit and impaired attentional set shifting on time dependent task that may reflect trait abnormalities in bipolar disorder appear to be the most considerable results of the present study. However, this conclusion requires confirmation by further longitudinal studies.

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