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Research / Araştırma

Information Processing Abnormalities in Schizophrenia and Bipolar Disorder

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ABSTRACT

Information processing abnormalities in schizophrenia and bipolar disorder

Objective: Patients with bipolar disorder and schizophrenia exhibit abnormalities in attention, memory, working memory, verbal/visual learning and executive functions. However, many of the tests fail to detect slight changes in cognitive performance due to ceiling effect. It was aimed to determine sensitivity and specificity of the tests that measure information processing in schizophrenia and bipolar disorder in this study.

Method: Thirty four patients with schizophrenia, 35 patients with bipolar disorder according to DSM-IV and 33 healthy control subjects matched for age, education level and gender were enrolled to the study. For clinical assessments Scale for the Assessment of Positive Symptoms, Scale for the Assessment of Negative Symptoms, Hamilton Depression Rating Scale, Young Mania Rating Scale, Clinical Global Impression Scale and Abnormal Involuntary Movements Scale were used. All participants performed a battery consisting of tests measuring information processing including Adult Memory and Information Processing Battery (AMIPB), Trail Making Test (TMT) Form A and B, Digit Symbol Coding Task (DST) and Auditory and Visual Reaction Time Tests (RTT).

Results: The schizophrenia group had significantly lower performance than the healthy control group in all tests and lower performance than the bipolar disorder group in AMIPB- A and B tests, TMT A and B tests. The bipolar disorder group had lower performance than the healthy control group only in DST test. The AMIPB A and B tests were the most sensitive and specific tests in the ROC analysis.

Conclusion: Changes in cognitive function might be better monitored by the tests whose sensitivity and specificity are higher. Since psychiatric disorders are highly heterogeneous, measurement tools are important for precise measurements.

Keywords: Bipolar disorder, information processing, neuropsychological tests, schizophrenia

ÖZ

Şizofrenide ve bipolar bozuklukta bilgi işleme bozuklukları

Amaç: Şizofreni ve bipolar bozuklukta bellek, dikkat, çalışma belleği, sözel/görsel öğrenme ve yürütücü işlevler gibi birçok alanda bilişsel işlev bozuklukları görülebilmektedir. Ancak bu işlevlerin değerlendirildiği testlerde tavan etkisi nedeniyle hafif farklar ayırt edilememekte, bulgu tespit edilememektedir. Bu çalışmada şizofrenide ve bipolar bozuklukta bilgi işlemeyle ilgili değerlendirme yapan testlerin özgüllük ve duyarlılıklarının incelenmesi amaçlanmıştır.

Yöntem: Çalışmaya, yaş, eğitim durumu ve cinsiyet açısından benzer, DSM-IV ölçütlerine göre şizofreni tanısı olan 34 ve bipolar bozukluk tanısı olan 35 hasta ile 33 sağlıklı kontrol dahil edilmiştir. Klinik değerlendirme açısından Pozitif Semptomları Değerlendirme Ölçeği, Negatif Semptomları Değerlendirme Ölçeği, Hamilton Depresyon Derecelendirme Ölçeği, Young Mani Derecelendirme Ölçeği, Klinik Global İzlem Ölçeği, Anormal İstemsiz Hareketler Ölçeği kullanılmıştır. Tüm katılımcılara Yetişkin Bellek ve Bilgi İşleme Bataryası (Adult Memory and Information Processing Battery -AMIPB) Form A ve B, İz Sürme Testi (Trail Making Test- TMT) A ve B, Sayı Sembol Kodlama Testi (Digit Symbol Coding Task- DST) ve Reaksiyon Zamanı Testi (Reaction Time Test-RTT) İşitsel ve Görsel Alt-testlerinden oluşan bir batarya uygulanmıştır.

Bulgular: Şizofreni grubu tüm testlerde kontrol grubundan, yine AMIPB A ve B, TMT A ve B testlerinde bipolar bozukluk grubundan anlamlı derecede daha kötü performans sergilemiştir. Bipolar bozukluk grubuysa sadece DST'de kontrol grubuna göre anlamlı olarak daha kötü performans sergilemiştir. ROC analizinde duyarlılığı en yüksek olan testler AMIPB-A ve AMIPB-B çıkmıştır.

Sonuç: Duyarlılığı ve özgüllüğü yüksek testler bilişsel işlevlerdeki değişikliklerin daha hassas biçimde ölçülebilmesi açısından avantajlıdırlar. Psikiyatrik hastalıklar oldukça heterojen olduklarından ölçüm araçlarının daha hassas olmaları yararlı olabilir.

Anahtar kelimeler: Bipolar bozukluk, bilgi işleme, nöropsikolojik testler, şizofreni

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INTRODUCTION

The opinion that cognitive impairment constitutes core symptoms of schizophrenia and bipolar disorders have been increasingly advocated (1,2), and it was usually reported to be associated with clinical course and functioning in both disorders (1,3,4). Neuropsychological studies often provide evidence regarding impairment in cognitive areas common to both bipolar disorder and schizophrenia (5). However, many studies comparing cognitive profiles of patients with bipolar disorders and schizophrenia suggested more severe cognitive impairment in the latter (5-7). Moderate differences in cognitive domains especially in executive functions, memory and processing speed appear to differentiate patients with schizophrenia and bipolar disorders (5).

Although cognitive impairment covering many domains such as attention, working memory, verbal/visual learning, memory, and executive functions are critical for schizophrenia and bipolar disorders (7-10), it was reported that information processing had a central function involved in almost all mental activities and represented a basic cognitive skill underlying high-level cognitive functions (e.g. memory and executive functions) (11,12). Information processing is a sequenced function that starts with sensorial input and terminates with motor output (13). It can be defined as the time required to execute a cognitive activity both in motor and psychomotor manner (11).

There is substantial evidence suggesting information processing deficits to be a core feature of schizophrenia. First, a meta-analysis showed schizophrenia patients to exhibit more severe impairment of information processing domain than that of other cognitive domains (14). Second, information processing was reported to be impaired in individuals who were at higher risk for either schizophrenia (15) or psychosis (16). Third, information processing speed was found to be slowed in the unaffected relatives of schizophrenia patients (17,18). Finally, information processing deficits were reported to distinguish individuals at higher risk group for psychosis during clinical follow-up with regard to whether or not they would be diagnosed with psychosis (19). Information processing is also related with many clinical and functional conditions in schizophrenia (20,21). For instance, information processing deficits were reported to be associated with global psychosocial functioning (21,22), social skill and interpersonal conformity (23,24), daily problem-solving skills (25), and working skills (22,26). Controlling of information processing function was reported to diminish the impact of other cognitive deficits on the clinical outcome in schizophrenia (21).

Although information processing deficits have been reported to represent an endophenotype also for bipolar disorder (27), information processing could be suggested to have a key role in terms of especially understanding schizophrenia, considering all in all literature findings mentioned above and depending on associations with other cognitive areas, clinical symptoms, and functioning. There are different tests used to measure information processing speed (13) which is defined as the number of correct answers provided by the individual during the test in a specific period (28). This study aimed to evaluate whether a difference existed or not between schizophrenia and bipolar disorder in terms of information processing.

METHOD

The study included 34 outpatients with schizophrenia and 35 outpatients with bipolar disorder, diagnosed according to the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (29), and 33 healthy volunteers.

Inclusion criteria for patients were 1) being 18 to 65 years old; 2) absence of alcohol or substance abuse; 3) no history of head trauma associated with loss of consciousness; 4) absence of mental retardation, sensorial (visual or auditory) deficits or central nervous system disease (e.g. epilepsy, multiple sclerosis); 5) absence of a significant movement disorder affecting extremities or trunk; and 6) clinical remission at least for three months. Thirty-three healthy volunteers recruited to the study by snowball sampling were

confirmed to not have either prior or present psychiatric disorder by SCID-I and screened for the absence of family history, neurological disease, drug use that may affect central nervous system, and auditory and visual disorders.

Ethical approval was obtained from the local institutional ethics committee. All patients and healthy subjects gave written and oral consent. Clinical evaluations were performed via Scale for the Assessment of Positive Symptoms (SAPS) and Scale for the Assessment of Negative Symptoms (SANS) for schizophrenia patients (30,31) and via Hamilton Depression Rating Scale (HAM-D) (32) and Young Mania Rating Scale (YMRS) for patients with bipolar disorder (33). All patients underwent Clinical Global Impression Scale (34), upon which those patients ≥5 points were excluded from the study. SANS, SAPS, HAM-D, and YMRS were adapted to Turkish language with validation and reliability (35-38). Bipolar disorder patients having >5 points in YMRS or >7 points in HAM-D were not included to the study. Both patient groups underwent Abnormal Involuntary Movements Scale (AIMS), which assessed involuntary movements in seven body areas (39), and those getting <3 points were included to the study, considering the potential impact of movement disorder on motor speed (40).

Neuropsychological Assessment

All subjects were applied a battery that consisted of the tests used in the measurement of information processing speed. All participants were initially asked if they had spectacles or hearing devices and ensured to use them during the test where appropriate. Those subjects who were detected to have sleeping difficulty at the last night before the test were not included in the test. All participants were asked for avoiding the use of potentially stimulating substance or beverages like cigarette, tea, or coffee two hours before the test. The tests were performed in the morning and before the intake of morning dosages. All tests were applied in accordance with standard instructions related with the requirements of a silent room. Operating time for the test battery was detected as 45 to 60 minutes. Applied tests were as following:

Adult Memory and Information Processing Battery (AMIPB) Form A and B: AMIPB measures information processing speed by also calculating the motor speed. As suggested by Coughlan and Hollows (41), first test (Form A) includes a five-number sequence for a total of 105 rows, where the participant is asked for marking the second highest number in each sequence. Total and correctly marked items were recorded. Second test (Form B) includes two groups of number separated with a line. The difference between these two groups is a presence of a distinguishing number in one of the groups, where the participant is asked for marking the different one. Total time allowed for each test is four minutes. Adjusted score is calculated by considering motor speed and the number of total and correct answers for both tests.

Trail Making Test (TMT) A and B: TMT consists of two tests that provide information regarding visual screening, information processing speed, mental flexibility, and executive functions (42). TMT-A includes circled digits from 1 to 25, which are scattered on a paper, and the participant is asked for drawing consecutive lines between these circles in a correct order initiating from number 1. This test measures psychomotor speed. TMT-B is similar to TMT-A except that the participant is asked to switch between digits and letters (e.g. 1, A, 2, B, 3, C). It assesses executive functions, visual-spatial working memory, and strategy switch skills. Both tests are expressed and recorded in seconds.

Digit Symbol Coding Task (DST): DST is a subtest of Wechsler Intelligence Test (43). Based on the digit-symbol matching reference on the upper side of the page, the subject is asked to draw the appropriate symbol to each of the empty box under the digit sequence as quickly as possible within the assigned time. DST is a frequently used test to measure psychomotor and information processing speed (14).

Reaction Time Test (RTT) Auditory and Visual Subtests: This study used the simple auditory reaction time test including 10 auditory stimuli and

the simple visual reaction time test including 10 visual stimulus that appeared on the center of a monitor. Delivery of stimuli, records of response intervals, and reporting of mean scores were powered by a computer-assisted system. The subjects were asked for quickly pushing the space button as soon as they perceive the auditory or visual stimulus. The monitor (Samsung, model BX2231) used in this study featured a refresh rate of 75Hz, a brightness of 250cd/m^2, and a response time of 2ms. The visual stimulus was a green square of 6x10cm, which appeared on an orange background of the display. The auditory stimulus was a voice of 80dB and 1500Hz delivered by the speakers placed on each side of the computer while the participant looked at the white background of the display.

Statistical Analysis

The distribution of variables such as age, duration of education, and neuropsychological test scores were analyzed through Shapiro-Wilk test. Normally distributed variables like age was expressed as mean±standard deviation (SD), non-normally distributed variables like duration of education was expressed as median (interquartile range [IQR]), and other categorical variables like gender and employment status were expressed as number and percentages.

ANOVA was used in the case that parametric test assumptions were met in comparisons of patient groups with healthy volunteers in terms of demographic characteristics and test scores; otherwise Kruskal-Wallis was applied. Post-hoc tests of these analyses, if required, consisted of Bonferroni test and Bonferroni-corrected Mann-Whitney U test, respectively.

The differentiation power of neuropsychological tests between patient groups and healthy volunteers or schizophrenia patients and bipolar disorder patients were evaluated through ROC analysis. It provided information regarding area under the curve (AUC±standard error [SE]), 95% confidence interval (CI), cut-off point, and sensitivity and specificity values of this cut-off. Cut-off points were determined by the calculation of Youden index, ROC01 (closest point to the 0.1-point in ROC plot), MaxProdSpSe (maximization of production of sensitivity and specificity), SpEqualSe (minimizing the absolute difference between specificity and sensitivity) included in the Optimal Cutpoints pack of the R pack software. Among the cut-off points determined by these criteria, the cut-off point with the highest sensitivity was prioritized; in the presence of more than one point with equally highest sensitivity, that had a higher specificity was selected. In the presence of three different cut-off points, the cut-off point with optimal sensitivity and specificity (meeting ROC01 criteria) was preferred. An overall 5% Type-I error level was used to infer statistical significance.

Statistical analyses, calculations and graphs were composed via IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) and R pack [R Core Team (2015). R: A language and environment for statistical computing] software.

RESULTS

Among 102 participants, 34.3% constituted patients with bipolar disorder, 33.3% patients with schizophrenia, and 32.4% healthy controls. The study groups did not significantly differ in terms of gender distribution, age, and education level. Similarly, no significant difference was found between patient groups in terms of age at disease onset, duration of the disease, number of hospitalizations, and total number of episodes (Table 1). There was a statistically significant difference between the groups in terms of employment status and marital status (χ^2=21.05, p<0.001 and χ^2=21.05, p<0.001; respectively) and the percentage of employment in bipolar, schizophrenia, and healthy control group was 51.4%, 29.4%, and 84.8, respectively. Married subjects constituted 48.6%, 11.8%, and 60.6% of their respective groups.

The mean scores of all neuropsychological tests applied to all patients and comparisons between the groups are presented in Table 2. Median visual RTT scores were 0.31s (IQR=0.06) for patients with bipolar

Table 1: Comparison of the study groups by sociodemographic and clinical characteristics

	Bipolar disorder (n=35)		Schizophrenia (n=34)		Healthy control (n=33)		Total (n=102)			
	n	%	n	%	n	%	n	%	χ^2	p
Sex*										
Female	17	48.6	11	32.4	16	48.5	44	43.1	2.418	0.298
Male	18	51.4	23	67.6	17	51.5	58	56.9		
Level of education*										
Primary	9	25.7	6	17.6	10	30.3	25	24.5	10.026	0.124
Secondary	9	25.7	7	20.6	4	12.1	20	19.6		
High-school	9	25.7	19	55.9	13	39.4	41	40.2		
University and higher	8	22.9	2	5.9	6	18.2	16	15.7		
Employment status*										
Employed	18	51.4	10	29.4	28	84.8	56	54.9	21.045	<0.001
Unemployed or retired	17	48.6	24	70.6	5	15.2	46	45.1		
Marital status*										
Married	17	48.6	40	11.8	20	60.6	41	40.2	18.173	<0.001
Single or divorced	18	51.4	30	88.2	13	39.4	61	59.8		

	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD	Min	Max	F	p
Age**	34.74	8.71	19	51	38.76	10.38	18	60	36.48	9.61	23	59	36.65	9.63	18	60	1.527	0.222
	Median	**IQR**	**Min**	**Max**	**Median**	**IQR**	**Min**	**Max**	**Median**	**IQR**	**Min**	**Max**	**Median**	**IQR**	**Min**	**Max**	χ^2	**p**
Duration of education***	10	7	5	16	11	4	5	17	11	7	5	18	11	4	5	18	0.220	0.896
Age at diagnosis***	22	7	14	43	23.5	12	10	47					22	11	10	47	1.687	0.194
Duration of disease***	10	11	1	32	12.5	16	2	35					10	13	1	35	0.098	0.755
Hospitalization, n***	1	3	0	18	1.5	4	0	17					1	4	0	18	2.377	0.123
Total episodes, n***	6	5	2	18	6	11	1	35					6	6	1	35	0.115	0.734
Manic episodes, n	2	3	1	13														
Depressive episodes, n	3	5	0	11														
Young Mania Rating Scale	2	5	0	5														
Hamilton Depression Rating Scale	3	6	0	7														
Abnormal Involuntary Movements Scale	0	1	0	3	1	2	0	3					0	2	0	3		

	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD	Min	Max	F	p
Negative Symptoms Assessment Scale					33	88	2	82										
	Median	**IQR**	**Min**	**Max**	**Median**	**IQR**	**Min**	**Max**	**Median**	**IQR**	**Min**	**Max**	**Median**	**IQR**	**Min**	**Max**	χ^2	**p**
Positive Symptoms Assessment Scale					10.5	17	0	46	10.5	17								

SD: Standard deviation, IQR: interquartile range, *Chi-square test, **ANOVA, ***Kruskal Wallis test, p<0.05 was accepted as statistically significant

Table 2: Intergroup comparison of the neuropsychological test scores

	Bipolar Disorder			Schizophrenia			Healthy Control				
	n	Median	IQR	n	Median	IQR	n	Median	IQR	χ^2	p
Visual reaction time (s)*	32	0.31	0.06	32	0.34	0.18	33	0.31	0.09	7.781	0.020
Auditory reaction time (s)*	32	0.28	0.07	32	0.32	0.11	33	0.29	0.06	11.098	0.004
Trail Making Test A (s)*	35	40	22	34	41	30.5	33	30	18	14.949	0.001
Trail Making Test B (s)*	34	80.5	88	32	98	91.75	33	75	46	7.485	0.024
Digit Symbol Code Test*	35	50	34	33	43	29.5	33	65	64	23.451	<0.001
	n	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**	**F**	**p**
AMIPB-A total**	35	58.63	21.27	34	40.03	15.31	33	68.91	20.34	19.615	<0.001
AMIPB-A corrected**	35	65.14	23.95	34	43.91	17.68	33	76.24	23.20	19.095	<0.001
AMIPB-B total**	35	47.46	20.14	33	33.42	15.12	33	56.85	20.58	12.974	<0.001
AMIPB-B corrected**	35	52.14	22.93	33	36.15	17.18	33	62.42	23.31	12.684	<0.001

AMIPB: Adult Memory and Information Processing Battery, SD: Standard Deviation, IQR: Interquartile Range, *Kruskal Wallis Test, **ANOVA, p<0.05 was accepted as statistically significant

Table 3: ROC analysis of neuropsychological tests to differentiate schizophrenia and bipolar disorder groups from healthy control group

	Bipolar disorder and healthy control groups					
Tests	**AUC±SE**	**95% CI**	**Cut-off point**	**p**	**Sensitivity**	**Specificity**
Visual reaction time (s)	0.54±0.07	0.40 – 0.68	-	0.591	-	-
Auditory reaction time (s)	0.54±0.07	0.40 – 0.68	-	0.586	-	-
Trail Making Test A (s)	0.66±0.07	0.53 – 0.79	≥34.50	0.023	0.66	0.67
Trail Making Test B (s)	0.58±0.07	0.44 – 0.72	-	0.256	-	-
Digit Symbol Code Test	0.71±0.06	0.59 – 0.84	≤54.00	0.002	0.66	0.76
AMIPB-A total	0.64±0.07	0.51 – 0.77	≤60.50	0.045	0.57	0.58
AMIPB-A corrected	0.64±0.07	0.51 – 0.77	≤68.00	0.049	0.57	0.55
AMIPB-B total	0.63±0.07	0.50 – 0.76	-	0.062	-	-
AMIPB-B corrected	0.62±0.07	0.49 – 0.76	-	0.084	-	-
	Schizophrenia and healthy control groups					
Tests	**AUC±SE**	**95% CI**	**Cut-off point**	**p**	**Sensitivity**	**Specificity**
Visual reaction time (s)	0.69±0.07	0.56 – 0.82	≥0.33	0.008	0.66	0.67
Auditory reaction time (s)	0.72±0.06	0.60 – 0.84	≥0.30	0.002	0.69	0.61
Trail Making Test A (s)	0.78±0.06	0.67 – 0.89	≥5.50	<0.001	0.82	0.61
Trail Making Test B (s)	0.70±0.07	0.58 – 0.83	≥8.00	0.005	0.78	0.58
Digit Symbol Code Test	0.84±0.05	0.74 – 0.93	≤55.50	<0.001	0.79	0.73
AMIPB-A total	0.87±0.04	0.79 – 0.95	≤52.00	<0.001	0.74	0.88
AMIPB-A corrected	0.86±0.04	0.78 – 0.95	≤56.00	<0.001	0.74	0.88
AMIPB-B total	0.81±0.05	0.71 – 0.91	≤40.50	<0.001	0.67	0.82
AMIPB-B corrected	0.81±0.05	0.71 – 0.91	≤44.00	<0.001	0.67	0.82

AMIPB: Adult Memory and Information Processing Battery, AUC: Area Under the Curve, SE: Standard Error, CI: Confidence Interval, p<0.05 was accepted as statistically significant

disorder, 0.34s (IQR=0.18) for schizophrenic patients, and 0.31s (IQR=0.09) for healthy controls. Median visual RTT differed according to groups (χ^2=2.42, p=0.020), with higher values in schizophrenic patients than in healthy controls (p<0.05). The median of auditory RTT test scores was 0.28s (IQR=0.07), 0.32s (IQR=0.11), and 0.29s (IQR=0.06) for bipolar disorder, schizophrenia, and healthy controls, respectively. Median of auditory RTT were detected to be different among the groups (χ^2=11.10, p=0.004), where schizophrenia patients had significantly higher values than healthy controls and patients with bipolar disorder (p<0.05), and the latter two groups were similar with respect to the median auditory RTT (p>0.05). The median TMT-A test score was 40s (IQR=22) in the bipolar disorder group, 41s (IQR=30.5)

in the schizophrenia group, and 30s (IQR=18) in the healthy controls. TMT-A test results were found to significantly differ between the groups (χ^2=14.95, p=0.001), with higher scores in patients with schizophrenia compared with that of the control group (p<0.001). Median TMT-B test scores of bipolar disorder, schizophrenia, and control group were detected to be 80.5s (IQR=88), 98s (IQR=91.75), and 75s (IQR=46), respectively (χ^2=7.49, p=0.024), where the difference between schizophrenia and healthy control groups was statistically significant (p=0.005). Bipolar disorder, schizophrenia, and control groups had DST scores of 50s (IQR=34), 43s (IQR=29.5), and 65s (IQR=64), where the differences in median scores between bipolar disorder and control group (p=0.002) and between schizophrenia and control group (p<0.001) were statistically significant. were found to be significantly different in the median values. Total and corrected scores of AMIPB-A and AMIPB-B were provided in Table 2, which showed that all scores differed among the groups (F=19.62, p<0.001, F=19.10, p<0.001, F=12.97, p<0.001, F=12.68, p<0.001). There was statistically significant difference between schizophrenia and bipolar disorder groups and schizophrenia and healthy control groups for each of these four scores (p<0.05).

ROC analyzes of neuropsychological tests to examine the power to differentiate the patient groups from healthy controls are presented in Table 3. Total scores of visual RTT, auditory RTT, TMT-B, and AMIPB-B and corrected scores of AMIPB-B were not able distinguish bipolar disorder patients from healthy controls. TMT-A had a power of 66.1% (95% CI=0.53-07.9) to differentiate patients with bipolar disorder from healthy controls (p=0.023); where the cut-off point was 34.5 with a 65.7% sensitivity and 66.7% specificity. The power of DST to distinguish patients with bipolar disorder from healthy controls was 71% (95% CI=0.59-0.84, p=0.002) with a cut-off point of 54, where the sensitivity and the specificity was 65.7% and 75.8%, respectively. The total score of AMIPB-A had a power of 64.2% (95% CI=0.51-0.77, p=0.045) to distinguish patients with bipolar disorder from from healthy controls; the cut-off point for this test was 60.5 with a sensitivity of 57.1% and a specificity of 57.6%. The power of corrected AMIPB-A score to differentiate bipolar

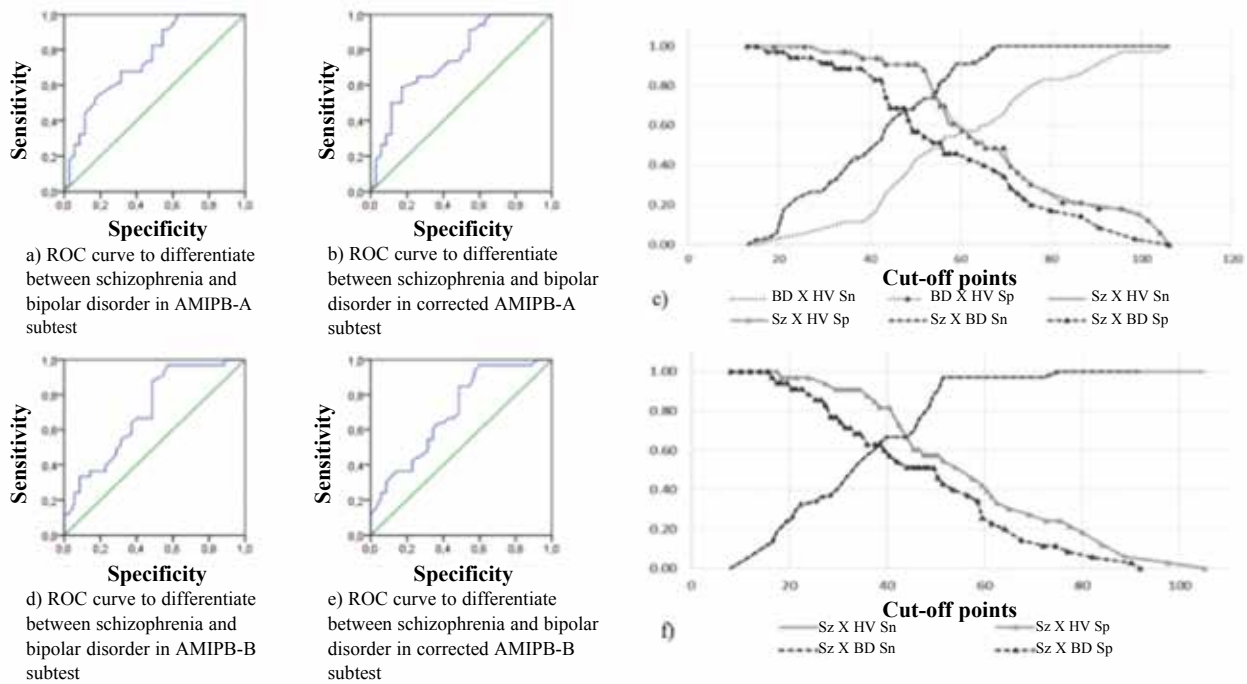


Figure 1: ROC curves of AMIPB A (a, b, c) and B (d, e, f) subtests. Values were provided in the text.
BD: Bipolar disorder, HV: Healthy volunteer, Sz: Schizophrenia, Sn: Sensitivity, Sp: Specificity

Table 4: ROC analysis of neuropsychological tests to differentiate between schizophrenia and bipolar disorder groups

Tests	AUC±SE	%95 CI	Cut-off point	p	Sensitivity	Specificity
Visual reaction time (s)	0.65±0.07	0.52 – 0.79	≥0.33	0.039	0.66	0.59
Auditory reaction time (s)	0.69±0.07	0.56 – 0.82	≥0.29	0.009	0.75	0.56
Trail Making Test A (s)	0.60±0.07	0.47 – 0.74	-	0.146	-	-
Trail Making Test B (s)	0.61±0.07	0.47 – 0.74	-	0.137	-	-
Digit Symbol Code Test	0.64±0.07	0.51 – 0.77	≤49.50	0.048	0.64	0.54
AMIPB-A total	0.75±0.06	0.64 – 0.86	≤47.50	<0.001	0.68	0.69
AMIPB-A corrected	0.76±0.06	0.64 – 0.87	≤49.50	<0.001	0.65	0.74
AMIPB-B total	0.71±0.06	0.59 – 0.83	≤49.50	0.003	0.88	0.51
AMIPB-B corrected	0.71±0.06	0.58 – 0.83	≤53.50	0.004	0.85	0.51

AMIPB: Adult Memory and Information Processing Battery, AUC: Area Under the Curve, SE: Standard Error, CI: Confidence Interval, p<0.05 was accepted as statistically significant

disorder patients from healthy individuals was 63.9% (95% CI=0.51-0.77, p=0.049), where the cut-off point was 68 with 57.1% sensitivity and 54.5% specificity (Figure 1).

All the tests assessed in this study could distinguish the schizophrenia group from healthy controls. The power of visual RTT to differentiate schizophrenia patients from healthy individuals was found to be 69.2% (95% CI=0.56-0.82, p=0.008), where the cut-off point of 0.330 could detect 65.6% of patients and 66.7% of healthy subjects. Auditory RTT had a power of 0.722 (95% CI=0.60-0.84, p=0.002) to distinguish schizophrenia patients from healthy controls with a 68.8% sensitivity and 60.6% specificity at the cut-off point of 0.295. TMT-A test was found to differentiate schizophrenia patients from healthy controls with a power of 77.7% (95% CI=0.67-0.89, p<0.001), where the cut-off point was 35.5 with a sensitivity of 82.4% and a selectivity of 60.6%. The power of TMT-B test was 70.1% (95% CI=0.58-0.83, p=0.005) to differentiate schizophrenia patients from healthy controls with a cut-off point of 78, yielding a 78.1% sensitivity and 57.6% specificity. DST had a power of 83.7% (95% CI=0.74-0.93, p<0.001) to differentiate schizophrenia patients from healthy individuals with a 55.5 cut-off point, where the sensitivity and specificity was 78.8% and 72.7%, respectively. The total AMIPB-A score had a power of 86.9% (95% CI=0.79-0.95, p<0.001) to distinguish schizophrenia patients from healthy subjects; the cut-off point for this test was 52 with a sensitivity of 73.5% and a selectivity of 87.9%. The corrected AMIPB-A score was detected to have a power of 86.2% (95% CI=0.78-0.95, p<0.001) to differentiate schizophrenia patients from healthy controls with a cut-off point of 56 for which the sensitivity and specificity was 73.5% and 87.9%, respectively. The power of total AMIPB-B score to differentiate schizophrenia patients from healthy individuals was 81.2% (95% CI=0.71-0.91, p<0.001) with a cut-off point of 40.5 where the sensitivity was 66.7% and the selectivity was 81.8%. The corrected score of AMIPB-B had a power of 81.1% (95% CI=0.71-0.91, p<0.001) to distinguish schizophrenia patients from healthy controls; the cut-off point for this parameter was 44 with a sensitivity of 66.7% and a selectivity of 81.8%.

The ability of neuropsychological tests to distinguish schizophrenia patients from the subjects with bipolar disorder is presented in Table 4. TMT-A and TMT-B tests were found to fail to differentiate patients with schizophrenia and bipolar disorder whereas visual RTT, auditory RTT, DST, AMIPB-A, and AMIPB-B tests could distinguish these two groups. The power of visual RTT was detected to be 65.0% (95% CI=0.52-0.79) to distinguish these groups at the 0.325 cut-off point where 65.6% of schizophrenic patients and 59.4% of bipolar disorder could be detected. Auditory RTT had a power of 68.9% (95% CI=0.56-0.82) to differentiate these patient groups; and 75% of schizophrenic patients and 56.2% of patients with bipolar disorder could be identified according to the 0.285 cut point. It was found that the power of DST to distinguish schizophrenia from bipolar disorder patients was

64.0% (95% CI=0.51-0.77), where 63.6% of schizophrenia patients and 54.3% of patients with bipolar disorder could be detected according to the 49.5 cut-off point. The total AMIPB-A score had a power of 75.0% (95% CI=0.64-0.86, p<0.001) to discriminate between schizophrenia (67.6%) and bipolar disorder (68.6%) patients according to the cut-off point of 47.5. The differentiation power of the corrected AMIPB-A score between patients with schizophrenia and bipolar disorder was 75.5% (95% CI=0.64-0.87, p<0.001) where the percentages of patients were 64.7% and 74.3%, respectively according to the 49.5 of cut-off point. The total score of AMIPB-B was found to have a distinguishing power of 70.8% (95% CI=0.59-0.83, p=0.003), and schizophrenic and bipolar disorder patients were distinguished by 87.9% and 51.4%, respectively according to the cut-off point of 49.5. The power of the corrected AMIPB-B score to differentiate between schizophrenia and bipolar disorder patients was 70.5% (95% CI=0.58-0.83, p=0.004), and these two groups of patients were differentiated by 84.8% and 51.4%, respectively according to the cut-off point of 53.5.

DISCUSSION

In our study, patients with schizophrenia (n=34) and bipolar disorder (n=35) who were similar in terms of age, gender, education status, duration of education, age at disease onset, duration of disease, number of hospitalizations, and total number of acute exacerbations were compared with healthy individuals (n=33) who were matched by age, gender, and level or status of education. This comparison of neuropsychological test performance evaluating the information processing showed lower performance of the schizophrenia group than that of the healthy controls in all tests, and than that of the bipolar disorder group in all test except visual RTT and DST. On the other hand, the latter group was found to perform significantly worse than the control group only in terms of DST. When the differentiating power of the applied tests was examined, it was concluded that all the tests could significantly discriminate schizophrenia patients from healthy subjects. Nevertheless, the tests other than TMT-A, DST, and AMIPB-A failed to distinguish the bipolar disorder group from the control group. The analysis of differentiating power of the tests between the patient groups yielded significant results for all tests except TMT-A and TMT-B.

In recent years, efforts to differentiate schizophrenia and bipolar disorder patients from each other and both groups from healthy populations have been increasing (44-46). Although some authors suggested schizophrenia and bipolar disorder to be assessed within a scope of a clinical spectrum (47), findings that emphasizing the difference of the two disorders were also reported (44).

Among the neurocognitive deficits, which were accepted as the core symptoms for both schizophrenia and bipolar disorder (1,2), our study investigated the power of the tests assessing the information processing, which was more prominent for schizophrenia (14) and frequently reported to be markedly associated with its clinical course (19,21), in terms of differentiating patients with schizophrenia, bipolar disorder, and healthy individuals. In the study of Van Rheenen et al. (44), information processing was reported to be one of the functions that best distinguished schizophrenia and bipolar disorder patients (besides semantic memory and close memory), consistent with our findings. The study of Ojeda et al. (21) evaluated information processing as the mediator factor in association of verbal fluency and verbal memory to overall functioning in 90 cases of chronic schizophrenia and 30 control subjects. The authors concluded that deficits in verbal fluency and memory significantly predicted the impairment in functioning, whereas the inclusion of information processing speed to the regression analysis caused a reduction in the significance, stressing that information processing played a more central role in schizophrenia. Our study suggested that all tests that evaluated information processing could distinguish schizophrenic patients from healthy individuals and that a substantial number of these tests (visual and auditory RTT, DST, and AMIPB-A and B) could

significantly distinguish these patients from the bipolar disorder group. Although information processing deficits were reported to be an endophenotype candidate for bipolar disorder (27), our study results indicate that most of the information processing tests has relatively improved sensitivity and specificity to distinguish these two groups.

Another finding of our study was the differences in the sensitivity and specificity of the tests we used to differentiate study groups. When the sensitivity of the tests to the distinguish patient groups from the healthy controls were examined, it was determined that all the tests showed higher sensitivity to distinguish the schizophrenia group from the healthy controls and that the specificity of the tests other than TMT-A and DST had higher specificity. While the difference of the sensitivity to distinguish the schizophrenia group from the control group was not significant, it was concluded that especially AMIPB-B had better performance to differentiate between patient groups than that of DST and TMT, which was often used in information processing speed studies (11,14,27,28,43). Besides, it had a relatively higher specificity to distinguish the schizophrenia group from healthy individuals. Although cognitive dysfunctions are accepted as core symptoms for psychiatric disorders (1,2) and there are many tests to measure and assess cognitive functions, no consensus on appropriate and adequate tests that can be used in clinical practice exists (48). Psychiatrist have been reported to have limited use of appropriate testing in clinical practice (49). The studies regarding information processing reported no widespread use of AMIPB, though it could be used as an alternative test to assess information processing owing to its ease and short duration of applicability in four minutes (13,50-52). The findings of our study also indicate better specificity and sensitivity of AMIPB in assessments of information processing, which may be preferred in clinical practice as well as in research.

The findings of our study should be considered within the framework of some limitations. In our study, similar groups were evaluated in terms of age, gender, and status and duration of education, yet not matched by intelligence scores. In addition, cognitive functions other than information processing were not evaluated regarding differentiating power of the study groups, as the whole battery was thought to be very extensive, prolonging the test time. Since the patients who were recruited to study were on their natural course of treatment, they were using drugs in different combinations. The effect of these drugs on the test performance was not studied in our study. As our study was cross-sectional, the inclusion criteria for remission of patients for the last three months was decided on medical records or clinical history.

In conclusion, we suggested that cognitive dysfunctions related to information processing distinguished schizophrenia patients from healthy controls better compared with that in bipolar disorder patients. The tests that measure information processing appear to distinguish schizophrenia patients also from those with bipolar disorder, implying a more important place of information processing in schizophrenia than in bipolar disorder. Apart from the tests that are frequently used in the literature, AMIPB could be recognized as a practical, easy to apply, and more sensitive and specific test to distinguish the groups.

Contribution Categories		**Author Initials**
Category 1	Concept/Design	O.D.B., M.I.A.
	Data acquisition	O.D.B., M.I.A.
	Data analysis/Interpretation	O.D.B., M.I.A., H.D.O.
Category 2	Drafting manuscript	O.D.B., M.I.A.
	Critical revision of manuscript	M.I.A., H.D.O.
Category 3	Final approval and accountability	O.D.B., M.I.A., H.D.O.
Other	Technical or material support	N/A
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