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Impairment of Executive Functions and Memory in Unaffected Siblings of Patients with Bipolar Disorder

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ÖZET:

İki uçlu bozukluk hastalarının hasta olmayan kardeşlerinde yürütücü işlev ve hafıza bozuklukları

Amaç: İki uçlu bozukluk hastalarında nörobilişsel bozukluklar muhtemel bir endofenotip adayı olarak görülmekte ve bu konuda araştırmalar gitgide artmaktadır. İki uçlu bozukluk hastalarının yakınlarında belirlenen yürüytücü işlevler ve hafızada bozuklukları bu göstergelerin genetik çalışmalarda kullanılabilecek muhtemel endofenotipler olabileceğini düşündürtmektedir. Bu çalışmada iki uçlu bozukluk tip 1 tanısı konulmuş hastaların sağlıklı olan kardeşlerine uygulanan nöropsikolojik değerlendirmeler sağlıklı kişilerden oluşan kontrol grubuyla karşılaştırılmıştır.

Yöntem: İki uçlu bozukluk tip 1 tanısı konulmuş 35 hastanın sağlıklı olan kardeşi ve 35 kişiden oluşan sağlıklı kontrol grubuna sözel akıcılık, dikkat, yürütücü işlevler ve hafıza işlevlerine yönelik testler uygulanmıştır. Uygulanan testler arasında Rey İşitsel Sözel Öğrenme Testi, Wechsler Bellek Ölçekleri görsel bellek uzamı alt testi, Stroop Testi, İz sürme testi A ve B formları, Wechsler Zeka Ölçekleri Sayı Dizileri alt testleri, kategorik akıcılık testi (Isaac SET Test) ve saat çizme testi yer almaktadır.

Bulgular: İki uçlu bozukluğu olan hastaların sağlıklı kardeşleri, kontrol grubuna göre Rey İşitsel Sözel Öğrenme Testi, Wechsler Bellek Ölçekleri görsel bellek uzamı hatırlama alt testinde, Stroop Testi, İz sürme testi A ve B formları, Wechsler Zeka Ölçekleri Sayı Dizileri düz sayı menzili testinde daha düşük bir başarı sergiledi. Basamaklı lojistik regresyon analizinde TMT-B testindeki başarı tek başına hastaların kardeşlerini sağlıklı kişilerden güçlü bir oranda ayırabiliyordu.

Sonuç: İki uçlu bozukluk hastalarının kardeşlerinde İz sürme testi-B ile ölçülen set değiştirme becerisinde önemli bir bozulma bulduk. Çalışma bulgularımıza göre set değiştirme/bilişsel esneklik iki uçlu bozuklukta bilişsel işlevler arasından bir endofenotip adayı olabilir.

Anahtar sözcükler: ikiuçlu bozukluk, endofenotip, biliş işlevleri

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ABSTRACT:

Impairment of executive functions and memory in unaffected siblings of patients with bipolar disorder

Objective: Neurocognitive impairments in bipolar patients as a possible endophenotype is a growing field of research. Impairments in executive functions and memory have been reported in relatives of patients with bipolar disorder, suggesting that they could be potential endophenotypes for genetic studies. In this study, neuropsychological performance in unaffected siblings of patients diagnosed as bipolar I disorder is compared to that of matched healthy controls.

Method: We evaluated 35 unaffected siblings of probands with bipolar I disorder and 35 healthy controls using tests of verbal fluency, attention, executive functions and memory. Rey Auditory Verbal Learning Test (RAVLT), Wechsler Memory Scale-Revised (WMS-R) visual memory test, Stroop Colour-Word Interference test (SCWIT), Trail Making Test-A and B, Wechsler Adult Intelligence Scale-Revised Digit Span test, categoric verbal fluency test (Isaac SET Test) , and clock drawing tests were performed.

Results: Unaffected siblings of patients with bipolar disorder performed poorly on the RAVLT, SCWIT, forward Digit Span Test, TMT-A and B, visual recall test. Using stepwise logictic regression TMT-B alone could highly differentiate siblings from controls.

Conclusion: We found significant impairment of set shifting task measured with TMT-B in siblings of patients with BD. Our study suggests that set shifting/cognitive flexibility could be a potential cognitive endophenotype for bipolar disorder.

Key words: bipolar disorder, endophenotype, cognitive functions

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INTRODUCTION

Bipolar disorder (BD) has a remarkably strong genetic component, supported by family, twin, adoption studies, with heritability estimated as high as 85-93% (1,2). Definition of endophenotypic features plays an important role in order to build a strategy for genetic analysis in bipolar disorder. Conventional criteria for identification of useful endophenotypes encompass that the deficits must be: (a) associated with illness; (b) heritable; (c) state-independent; it must be demonstrable in remitted patients (d) cosegregated with illness within families; and (e) also found in unaffected relatives at a higher rate than in the general population (3). With respect to these criteria, several cognitive dysfunctions have consistently been demonstrated to be state independent endophenotypes in euthymic patients (4,5), with the most significant impairment observed in verbal learning and memory, attention/processing speed, and executive functions (6,7). These cognitive deficits were also observed to be impaired in unaffected relatives of patients with bipolar disorder in comparison with the general population, although there are some contradictory results in the literature (8,9).

In this study, we aimed to evaluate unaffected siblings of patients with the diagnoses of bipolar I disorder. Based on the published literature, our hypothesis was that performance on tests of executive functions and memory would be impaired in unaffected siblings of patients with bipolar disorder compared to matched healthy controls. Our primary aim was to assess which executive function and/or memory impairments could be potential endophenotypes of bipolar disorder by examining those impairments in the healthy siblings of patients with bipolar disorder and age- and sex-matched healthy controls.

METHODS

The research was approved by the Istanbul University, Cerrahpaşa Medical Faculty Ethical Committee, and all participants provided a written informed consent. Thirty-five unaffected siblings of probands with bipolar I disorder and age and sex matched 35 healthy controls were included into the study. Healthy controls were chosen from the local community. Exclusion criteria included the presence of an Axis I disorder in participants, which was evaluated using the Structured Clinical Interview for DSM-IV Axis I Disorders (10). The presence of history of any neurological illness, head trauma, history of substance abuse, and diagnosable or self-reported visual impairment of any other cause were other exclusion criteria. Considering the possibility that subsyndromal affective symptoms may interfere with cognitive functioning among relatives, those with Hamilton Depression Scale (HAM-D) score >8 were excluded from the study (11). None of the participants were on any medication that may have an influence on cognition. All patients diagnosed as bipolar I disorder attending outpatient or inpatient unit of Cerrahpaşa Medical Facuty Department of Psychiatry between January 2011 and January 2012 were consecutively asked for consent to approach their unaffected siblings. The diagnosis of bipolar I disorder in these patients has been established according to DSM-IV criteria (12) after a detailed clinical examination by a consultant psychiatrist. Only one unaffected sibling was randomly chosen from each family.

The principal author (Deniz Uluhan Yıldırım) performed the neuropsychological assessments of each participant in a single session, in a fixed order. The neurocognitive functions were evaluated with those tests as follows:

1. Verbal learning and memory: Rey Auditory Verbal Learning Test (RAVLT) (13) is a test for verbal memory. It has two lists, A and B, with 15 words in each list. Words in list A are given at the speed of one word per second in five successive trials. The list B is interference given after five trials of list A. The test measures learning score (number of words correctly recalled in each of the five trials) and immediate and delayed recall.

2. Visual memory: Wechsler Memory Scale-Revised (WMS-R) (14) was used to assess visual memory skills.

3. Working memory: Forward and backwards digit span of the WAIS-R Digit Span (14) was used.

4. Verbal fluency: a measure of categoric (Isaac SET Test) (15) were included.

5. Response inhibition: Response inhibition refers to the suppression of actions that are inappropriate in a given context. In this study, Stroop Colour-Word Interference test (SCWIT) (16) was used to assess response inhibition deficits also cognitive flexibility. The SCWIT measures the relative speeds of reading the names of colors, naming colors, and identifying color names that are printed in another color. The last task has an interference component because it requires the subject to inhibit a reading response.

6. Psychomotor speed: Time to complete the part A of the

Trail Making Test was calculated to analyse psychomotor speed (TMT-A) (15).

7. Set shifting/cognitive flexibility: Set shifting is the mental ability to swich between different categories. To assess the impairment in the set shifting abilities Trail Making Test–Part B (TMT-B) was used (15). TMT-B measures processing speed with set shifting and selective attention.

8. Hamilton Depression Scale (11) was administered in order to assess subthreshold depressive symptoms considering the possibility that subsyndromal affective symptoms may interfere with cognitive functioning among relatives. Those with HAM-D score >8 were excluded from the study.

9. Clock drawing test: Tests executive function primarily (17).

Statistical Analysis

Averages are reported as means ± standard deviation (SD). To compare categorical variables, chi-square test was used. Normal distribution was evaluated with Kolmogorov-Smirnov test. As most cognitive variables did not follow normal distribution, Mann Whitney U test was used to examine differences between siblings of bipolar patients and normal controls.

Finally, all the cognitive domains including variables that were significant in the univariate analyses were seperately subjected to stepwise logistic regression analysis in order to identify the most significant variables in each cognitive domain, than the most significant variables were again subjected to stepwise logistic regression analysis in order to find the cognitive variables that could differentiate siblings of bipolar patients from healthy controls. Statistical analysis was carried out using Statistical Package for Social Sciences (SPSS) version 15.0 (SPSS, Inc., Chicago, IL, USA).

RESULTS

Sample Characteristics

There was not a significant difference across groups in terms of gender, age and educational attainment (Table 1).

Comparison of Cognitive Performance Across Groups

There were significant differences between siblings of bipolar patients and healthy controls in the RAVLT, Stroop test, Trail Maling A and B tests, logical memory and digit span forward tests.

In the RAVLT, a test of verbal learning and memory, significant differences between siblings and controls were detected for immediate recall, maximum learning score, delayed recall, number of error and total score (Table 1). In the Wechsler Memory Scale-Revised (WMS-R), the subscale of logical memory revealed that unaffected siblings performed worse than controls In WMS-R, the visual reproduction test performed to assess visual memory revealed no statistical difference between the two groups on copying the figure, but significant differences were demonstrated in visual recall as given in Table 1. Visual recall was found to be higher in females and younger participants ($p<0.05$); while educational level had no significant impact on visual recall in WMS-R test. Upon gender and age adjustment, visual recall was still significantly worse in siblings of patients with bipolar I disorder ($p=0.005$).

In order to assess working memory, WAIS-R Digit Span forward and backward tests were performed; siblings performed significantly poorer than controls in forwards digit span tests (Table 1). No significant difference was present between siblings and controls in performance on the categoric verbal fluency test. With respect to performance on

Table 1: Basic demographic characteristics of the groups

Characteristic		Subjects (N=70)		
		Siblings [n=35]	Controls [n=35]	Statistics
Gender				χ^2=0,52
Female,	*n (%)*	17 (49)	14 (40)	d.f.=1
Male,	*n (%)*	18 (51)	21 (60)	P=0,47
Age (year),	*median (IQR)*	35 (27-50)	31 (28-41)	U=504
			P=0,21	
Education (year),	*median (IQR)*	11 (11-11)	11 (11-11)	U=549
				P=0,38

IQR=Interquartile range, χ^2: Chi-square test

Table 2: Neuropsychological performance in siblings and controls: Tests of attention, executive functions, verbal and visual memory

Cognitive Test	Subjects (N=70)			
	Siblings [n=35]	Controls [n=35]	U	P
Trail-Making Test (TMT)				
TMT-A time taken (sec)	64.5±7.1	38.3±12.6	35	**<0.001**
TMT-A error (#)	0.5±0.8	0	420	**<0.001**
TMT-B time taken (sec)	263.4±68.1	85.7±32.4	25,500	**<0.001**
TMT-B error (#)	5.5±2.8	1.2±1.5	86	**<0.001**
Stroop Color Word Interference Test				
Stroop-1 time taken(sec)	32.6±6.1	29.8±6.2	415	**0.018**
Stroop-1 error (#)	0	0	612,500	1.0
Stroop-1 correction (#)	0.1±0.4	0.1±0.3	575,500	0.965
Stroop-2 time taken (sec)	94±23.9	78.9±17.6	377,500	**0.006**
Stroop-2 error (#)	1.3±1.9	0.4±0.8	482,500	**0.080**
Stroop-2 correction (#)	2.1±2	1.8±1.9	519,500	0.264
Stroop 2 time-Stroop 1 time (sec)	61.3±22.9	49.1±14.8	420,500	**0.024**
Rey's Auditory Verbal Learning Test				
Immediate recall	6.7±1.7	5.9±0.9	410,500	**0.013**
Learning score	113.8±15.9	116±12	484	0.130
Maximum learning score	13.8±1	14.4±1	367,500	**0.002**
Delayed recall	11.7±1.7	13±1.6	365,500	**0.003**
Error(s)	3.3±3.3	0.8±1.3	288,500	**0.001**
Total score	14.7±0.5	15.0±0	455	**<0.001**
Wechsler Memory Scale-R, Logical Memory	11.1±2.9	13.2±3.2	388,500	**0.008**
Wechsler Memory Scale-R, Visual Memory				
Visual Reproduction	10.1±2.6	10.8±2	548	0.442
Visual Reproduction Recall	1.9±0.9	2.7±0.4	309,500	**<0.001**
WAIS-R Digit Span Test				
Forwards digit span	5.1±0.9	5.5±0.8	457	**0.043**
Backwards digit span	3.6±1	3.8±0.9	591	0.777
Verbal Fluency Tests				
Categorical verbal fluency (Isaacs SET test)	36.6±2.8	37±3.1	469	0.178
Clock drawing test	3.51±0.91	3.74±0.56	563,500	0.433

Averages are reported as means±standard deviation (SD), U: Mann Whitney U test

Table 3: Model predicting group membership of subjects using TMT-B Test

	Beta	Wald Chi-square	P	Nagelkerke R Square
Trail-making test (duration)	0.1	13,860	0.001	0.899

executive functions, unaffected siblings performed significantly worse than controls on the SWCIT, a test for response inhibiton and also cognitive flexibility. In trail making tests A and B, time to complete the task was significanly longer, and the number of error was significantly higher in siblings. Time to complete the task in TMT-B test was shorted in younger participants, though not significant (p=0.109); while gender and educational level had no significant impact.

Finally, in the stepwise logistic regression analysis in order to find the most powerful cognitive variables that could differentiate siblings of bipolar patients from healthy controls we found that the duration of TMT-B test alone was an independent factor predicting group membership of subjects (p<0.001). A regression model using this variable was able to explain 89% (Nagelkerke R-square) of variance in whether participants are healthy sibligs or healthy controls. Table 3 shows the model predicting group membership of subjects using set-shifting test.

DISCUSSION

Here we found that siblings of patients with bipolar I disorder had significant impairments in verbal memory,

visual recall and executive measure assessed with TMT-B and Stroop test, working memory assessed with digit span tests and logical memory compared to the healthy controls.

In the first part of Weschler Memory Scale-R visual reproduction subscale test, short-term visual memory was assessed and the performence of siblings were found to be significantly worse than control subjects. This significance persisted after adjusment for gender and age. In most of the other studies in the literature, no difference was detected in Wechsler Memory Scale visual reproduction tests between unaffected siblings and controls (2,18,19). In parallel with our findings, Kulkarni et al. (20) reported that unaffected siblings performed poorly on the Rey's complex figure test and in another study using two CANTAB tests of visuospatial declarative memory authors found impairments in siblings of offspring of bipolar patients (18). Other studies where Rey's complex figure tests were used involving in twins (21) and offsprings (22), failed to demonstrate impairments in visual delayed recall.

In the RAVLT, a test of verbal learning and memory, siblings performed more poorly than controls on measures of maximum learning score and immediate recall and delayed recall of words. Our results are in agreement with the findings of the earlier studies of unaffected first-degree relatives of bipolar disorder relatives which showed impairments in verbal learning memory (2,20,21). Verbal memory in bipolar disorder as concluded in a meta-analysis studies and systematic review is one of the possible candidate endophenotypes (9,26) .

We found no impairment in siblings on verbal fluency tests, visual reproduction and clock drawing tests. Siblings performed poorly on WAIS-Digit Span forward tests and logical memory tests than healthy controls. In the Stroop tests we have found results that support the findings of the previous studies. Time to complete Stroop-1 and Stroop-2 tests and enterfence period was statistically significantly longer in the relatives of patients with bipolar disorder compared to healthy controls. Some of the studies analysing Stroop test failed to show impairments in SCWIT interference scores in first degree relatives (18,19,20); while three studies showed impaired performance in first-degree relatives (23-25). Bora and colleagues (8) particularly suggested that a diminished response inhibition may be associated with genetic predisposition to the disease and frontal lobe dysfunction associated with bipolar disorder. Our results support the view that impairment in response inhibition might be candidate endophenotype in bipolar disorder.

In this study, performance on TMT-A and TMT-B of unaffected relatives was significantly poorer than in healthy controls. This variable alone was found as an independent factor predicting group in siblings of patients with bipolar disease. In many previous researches, relatives had impaired performance in TMT-B or B-A impairments compared to healthy controls (23,25). Moreover, the metaanalyses by Arts et al. reported impairments mainly in TMT-B (9). It has been proposed that performance in TMT-A depends on intact functions in the area of attention, visual search, motor fuctioning and working memory; while TMT-B additionally involve executive measures and the difference in performance between part A and part B reflects an executive measure, mainly set shifting, cognitive flexibility. In this perspective, we may suggest that executive dysfunction is present in siblings of patients with bipolar I disorder, indicating a potential cognitive endophenotype for bipolar disorder.

Executive function deficits are among the most widely mentioned cognitive deficits in relatives of BD patients (10), however findings across studies are not consistent as to which executive functions are impaired. In a metaanalysis of 14 neurocognitive studies, small deficits in verbal memory and executive domains were found in the relatives of BD patients compared to healthy people (9). Recently a systematic review conducted from studies of relatives of bipolar disorder subjects found that verbal learning/memory and verbal working memory seem to be the most suitable endophenocognitypes for BD (26). In another recently conducted meta-analysis, it was demonstrated that an executive measure, impaired response inhibition might be the most prominent cognitive endophenotype of BD; however another executive measure, set shifting, also met the criteria as potential endophenotypes of BD (10). Set shifting and verbal memory impairments are also observed in relatives of patients with schizophrenia and BD, which implicates that consistent deficits in relatives of patients with schizophrenia might well be a possible cognitive endophenotype for BD (27).

In conclusion, we evaluated neurocognitive profiles of healthy relatives of patients diagnosed with bipolar I disorder, age, gender and education matched healthy contols. We found significant impairments in verbal memory, working memory, visual recall and response inhibition and

set shifting ability/cognitive flexibility in relatives compared to the controls. These deficits are consistent with the neurobiological circuits impaired in bipolar disorder: the frontotemporal and subcortical circuit. Multivariate analysis found that the duration of TMT-B test alone was an independent factor predicting group membership of subjects. A regression model using this variable was able to explain 89% of variance in whether participants are healthy sibligs or healthy controls. Our study of the unaffected siblings of bipolar disorder probands provide further evidence that an executive measure set shifting/cognitive flexibility could be a potential endophenotype marker for bipolar disorder, while other executive functions like verbal flency tests was not impaired in health relatives, thus they did not seemed to be related to genetic risk for BD.

Heterogenity of bipolar disorder could itself contribute to the difficulty of replicating findings also in relatives of patients. Our study has certain limitations. The sample size was relatively small. We did not measure the IQ of the participants, which may indicate how much the performance in cognitive tests is related to the level of IQ; though we considered educational attainment of participants as a measure of IQ. Also, a comparison of performance between bipolar disorder probands and their unaffected relatives and healthy controls might have been helpful in identifying potential neurocognitive endophenotypes much more correctly.

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