TÜBİTAK

Turkish Journal of Medical Sciences

http://journals.tubitak.gov.tr/medical/

Research Article

Turk J Med Sci
(2013) 43: 110-117
© TÜBİTAK
doi:10.3906/sag-1205-78

Neurocognitive functioning in young high-risk offspring having a parent with bipolar I disorder

Erdem DEVECİ[1,*], Erol OZAN[2], İsmet KIRPINAR[1], Meltem ORAL[2], Ali Gökhan DALOĞLU[3], Nazan AYDIN[2], Ahmet ÖZTÜRK[4]

[1]Department of Psychiatry, Faculty of Medicine, Bezmialem Vakıf University, İstanbul, Turkey
[2]Department of Psychiatry, Faculty of Medicine, Atatürk University, Erzurum, Turkey
[3]Department of Psychiatry, Palandöken State Hospital, Erzurum, Turkey
[4]Department of Psychiatry, Regional Training and Research Hospital, Erzurum, Turkey

Received: 21.05.2012 • **Accepted:** 28.06.2012 • **Published Online:** 18.01.2013 • **Printed:** 18.02.2013

Aim: To investigate attention, memory, verbal-linguistic ability, and executive functions in symptom-free young offspring having a parent with bipolar I disorder (BD_1O) in comparison with healthy controls (CO).

Materials and methods: Thirty symptom-free BD1O and 37 CO were recruited. The groups (both all participants and those ≥11 years of age) were well-matched for age, sex, IQ, and years of education. The neurocognitive battery included the Rey Auditory Verbal Learning and Memory Test, Controlled Word Association Test, Digit Span Test, Trail Making Test, Auditory Consonant Trigram Test, Wisconsin Card Sorting Test, Stroop Test, and Test of Variables of Attention.

Results: The BD_1O group demonstrated impairments in psychomotor speed, focused attention, verbal attention, phonemic verbal fluency, short-term memory, and learning functions and performed marginally worse in divided attention, information processing, and working memory. No group difference was found in sustained attention, executive functions, or alternating attention.

Conclusion: Divided attention, information processing, and working memory seem to be important in evaluating the cognitive pathology before the onset of affective psychopathology.

Key words: Bipolar I disorder, offspring, high-risk, neurocognitive functioning, endophenotype

1. Introduction

Bipolar disorder (BD) is a neurobiological disorder with a multifactorial etiology, including oligogenic and environmental influences (1). However, the identification of vulnerability genes for this disorder is complicated by the role of environmental factors, genetic heterogeneity, and the variability of the observable phenotype (2). This has prompted researchers to investigate the latent but measurable trait markers more closely linked to the responsible genes than the clinical phenotype itself, which has been conceptualized as an endophenotype (2,3). Endophenotypes are heritable biomarkers that cannot be observed by the naked eye. Gottesman and Gould's definition of an endophenotype is that it should be associated with illness, be heritable, and cosegregate with a psychiatric illness within families, yet it should be present even when the disease does not exist (i.e. state-independent) and can be found in unaffected family members at a higher rate than in the general population (4).

Investigation of the abnormalities in neurocognitive functioning has become the scope of interest within the context of endophenotype approach (1). Individuals with BD exhibit motor, perceptual, and cognitive disturbances involving predominantly right hemisphere dysfunction (5). These neurocognitive deficits are detectable during the active phase of the disorder, regardless of the episode type (6), in remission (7), and even in the first episode (8,9), and they appear to worsen as the number of episodes increases (10,11). This seems to be a cause for a continuous impairment in social and occupational functioning (12) in a large number of patients. The pursuit of identifying strategies for early and preventive interventions motivated researchers to look for these genetically transmitted abnormalities in cognition and information processing (13) in symptom-free first-degree relatives of patients

* Correspondence: erdemdeveci@gmail.com

having BD, which is conceptualized as a high-risk (HR) approach. This approach refers to a method of studying the etiology of a disorder by investigating individuals who have an increased risk for developing it (14). Recently, 2 comprehensive reviews (1,15) were published that included 23 studies investigating the neurocognitive functions in unaffected HR relatives of patients with BD. Of these studies, 18 targeted unaffected first-degree relatives who were adults. These studies showed that they performed worse than controls for memory (11,16), in executive functions (11), in executive inhibitory processes (17), and in psychomotor (attention) speed (18), as well as for immediate verbal recall and visual episodic memory (19).

In a large-scale extended pedigree study of cognitive functioning in BD held in the central valley of Costa Rica, 709 Latino individuals between the ages of 15 and 77, of which 660 were members of extended pedigrees with at least 2 siblings diagnosed as having BD, were evaluated. In that study, processing speed, working memory, and declarative (facial) memory were found to be candidate endophenotypes for BD (20).

However, studying unaffected HR relatives (parents, twins, siblings, and offspring) at adult ages may be a handicap for determining the cognitive endophenotypes, since they have mainly passed through the peak period of risk for BD with their vulnerability genes remaining unexpressed (1). In this respect, evaluating the unaffected but HR offspring of parents having BD during late childhood as well as adolescence, who on average share 50% of genes with their affected parent but are free of disease-associated factors (e.g., medication side effects, chronicity, psychiatric comorbidities, or potential neurotoxic effects of multiple episodes on limbic structures), would provide a unique opportunity to identify neurocognitive abnormalities which exist prior to the typical onset of BD. The remaining 5 reports (21–25) that were published in the 2 comprehensive reviews (1,15) were on young HR offspring of parents having BD. The first 3 of these reports, which used a limited number of tests, were published in the early 1980s when diagnostic practices according to the DSM-III were newly used to distinguish schizophrenia from BD, thus making the reported diagnoses of the affected parents doubtful. Only 2 of the studies conducted on young HR offspring mentioned in the reviews were published in the last decade. In the first study by McDonough-Ryan et al., 28 offspring (10.2 ± 2.7 years old) of BD parents were investigated with a limited neurocognitive battery, where the major cognitive domains such as verbal memory, attention, and executive functions were not evaluated (24). In the second study, Klimes-Dougan et al. investigated 43 adolescent offspring (15.1 ± 2.5 years old) of BD mothers from an affluent, high-achieving milieu, who were compared with controls (25). The deficits that they found were mainly in executive functions and attention.

The study conducted by Maziade et al. (26) was the first to provide comparative information on developmental trajectories of IQ and episodic memory impairments using the same measures across early childhood, adolescence, and young adulthood in offspring at genetic risk of major psychoses. They found the offspring performance to be lower than that of controls for IQ and episodic memory.

As discussed above, studies involving young HR offspring of parents having BD appear to be sparse and they have been conducted in different parts of the world; this calls for investigation in other regions, as well, since environmental factors have been suggested to affect the gene expression and the pathogenesis of the disorder (27). This prompted us to evaluate neurocognitive functioning in symptom-free young offspring having a parent with bipolar I disorder (BD_1O) in eastern Turkey. We assessed functioning in major cognitive domains such as attention, memory, verbal-linguistic ability, and executive functions using 8 well-validated neurocognitive tests that are commonly used in current HR studies investigating similar age groups.

2. Materials and methods

2.1. Subjects

We recruited 72 participants for evaluation at our university psychiatry clinic. Of these, 3 of the control offspring (CO) and 2 of the HR offspring who had a parent with DSM-IV-TR bipolar I disorder (BD_1O) could not complete the neurocognitive assessment due to illiteracy, inability to count, unwillingness to complete the assessments, or physical complaints such as headache and stomach ache. Thus, an analysis was carried out on 30 BD_1O and 37 CO (Table 1). The diagnosis of bipolar I disorder in parents was confirmed using the Turkish version of the Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-I). Children having a lifetime diagnosis of substance use disorder, attention deficit hyperactivity disorder, conduct disorder, mood or psychotic disorder, mental retardation (IQ < 70), serious head trauma, seizures, or any other organic mental disorder were excluded. Healthy controls were chosen from children of the parents who were referred to our outpatient clinics other than neurology and psychiatry. The parents of the healthy controls were evaluated using the SCID-I nonpatient version in order to exclude psychotic disorders and BD. Parents with any neurological diseases or those having a family history (first-degree relatives) of schizophrenia, BD, or schizoaffective disorder were also excluded. The control group consisted of 37 healthy children (CO) matched for age, sex, IQ, and years of education (Table 1). The exclusion criteria for

the study group were also applied to the control group. All subjects gave assent in conjunction with informed consent provided by a parent. The study was approved by the human research committee of our university. The prior HR group that we reported on was a group of young HR offspring having a parent with schizophrenia (28). To maximize comparability of assessments across groups, we used the same comprehensive neurocognitive battery and matched the BD_1O group for IQ as well as demographic variables, such as age, sex, and years of education, with the prior HR group.

Our intention in the present study was to evaluate young HR offspring who had not reached the period of risk for BD. For this reason, our study group consisted not only of adolescents but also offspring in late childhood. The study conducted by McDonough-Ryan et al. was a motivation for us to combine adolescents and preadolescents, because the age for their offspring at high risk for BD was 10.2 ± 2.7 years (24). Korkman et al. also evaluated 800 children in terms of neurocognitive functioning and found that neurocognitive development is rapid in the age range of 5 to 8 years and more moderate after age 9 (29). Therefore, we will discuss the results of the participants ≥11 years old, since it is suggested that age 11 is a threshold in the maturation of neurocognitive performance (30,31).

2.2. Neurocognitive evaluation and IQ assessment

We used Kent E-G-Y Test and the Porteus Maze Test for the assessment of IQ. The neurocognitive battery included the Rey Auditory Verbal Learning Test (RAVLT), Auditory Consonant Trigram Test (ACTT), Controlled Oral Word Association Test (COWAT), Digit Span Test (DST), Trail Making Test (TMT-A/B), Wisconsin Card Sorting Test (WCST), Stroop Test, and Test of Variables of Attention (TOVA) (32). The administration procedures for the neurocognitive tests used in the present study are below.

2.3. Rey Auditory Verbal Learning and Memory Test (RAVLT)

Verbal episodic memory was assessed with the RAVLT, in which subjects had to learn a series of words presented orally over 5 trials and were expected to immediately recall them after each presentation (total recall of 5 trials) or with a 20-min delay (delayed recall). They were also asked to recognize target words between distracters (recognition). The following measures were analyzed: *total learning scores* (1–5 points), the total number of correctly recalled words summed over the 5 learning trials; *delayed recall*, the number of correctly recalled words after the 20-min delay; *true positives*, the number of true answers that the subject was expected to give in the recognition section of the test; and *recognition percent correct score*, a measure calculated by the formula (true positives + true negatives) / 50, as proposed by Harris et al. (33).

2.4. Auditory Consonant Trigram Test (ACTT)

This test measures divided attention, information processing, and short-term memory. It is used for measuring working memory. The total number of recalled letters was used in evaluation.

2.5. Controlled Oral Word Association Test (COWAT)

This test is a measure of phonemic verbal fluency, in which subjects had to produce the maximum number of words with the given letters (K, A, and S, according to Turkish standardization) within 1 min for each letter (34).

2.6. Digit Span Test (DST)

This test is a subunit of the Wechsler Intelligence Scale for Children-III (35,36). It has 2 sections, digit span forward and backward. The digit span forward section measures verbal attention and the backward section measures verbal working memory. In the forward section, the subject repeats the numbers told to him/her by the rater, and in the backward section the subject repeats the numbers told to him/her backwards. The score is the sum of the correctly recalled numbers in the forward and backward sections and the total of both sections combined as well.

2.7. Trail Making Test (TMT-A/B)

This test assesses attention, mental flexibility, visual tracking, and motor abilities (32). In part A, dots numbered between 1 and 25 are combined with a continuous line and in part B, each letter is combined with a number alternatively. Part A evaluates psychomotor (attention) speed and focused attention whereas part B is the component that principally measures executive functioning (37). In this study, the times required to complete the 2 separate parts were taken into account.

2.8. Wisconsin Card Sorting Test (WCST)

Executive functions such as cognitive flexibility, as well as problem solving and abstraction abilities, were assessed with the WCST-128 cards, in which participants had to classify a series of cards into 3 categories after having found the classification rule (color, number, or forms) (38). In the present study, a computerized form of the test (WCST: CV4) was used.

2.9. Stroop Test

As one of the main tools for evaluating executive functioning, the Stroop Test assesses the ability to flexibly direct attention in the presence of a distraction (i.e. selective attention), inhibit a habitual behavioral pattern, and display unusual behavior by taking into account the individual's speed of processing in measuring resistance to interference (32).

2.10. Test of Variables of Attention (TOVA)

The TOVA is a computerized continuous performance test used for assessing sustained attention. The subjects were asked to push a button connected to a computer when they recognized the target on the monitor for an uninterrupted period of 20 min. The target is a small square appearing

in the upper part of a rectangle. The nontarget is a small square appearing in the bottom of the rectangle. A stimulus flashed on the screen every 2 s. The target is presented in 22.5% and 77.5% of the trials during the first and second halves, respectively. Data were obtained in the domains of omission error (inattention), commission error (impulsivity), response time, and variability. All the variables are recorded for each 5-min quarter and 10-min half, as well as the overall total scores for each variable. The scores are compared to the standardized norms, and the interpretation of data is reported in a printable form (39).

2.11. Test environment

Cognitive assessment was conducted in the test laboratory of our clinic. Optimal requirements for testing, such as light, silence, and the physiological necessities of the subjects, were fulfilled.

2.12. Statistical analyses

The statistics were performed with SPSS 11.0. The normality distribution of test scores was tested by Kolmogorov–Smirnov and Shapiro–Wilk tests where appropriate. The relations between test scores were tested with the Mann–Whitney U test and independent samples t-test. P-values below 0.05 were accepted as significant.

3. Results

We performed 2 separate analyses of our data. The first analysis included all the subjects. The second was performed on participants who were ≥11 years old. The results from the 2 analyses are shown together in Tables 1 and 2.

3.1. Sociodemographic features

The groups were well-matched for age, sex, IQ, and years of education to prevent these variables from skewing the outcome of the neurocognitive tests. The matching was not lost when an analysis was conducted on participants ≥11 years old only (Table 1).

3.2. Neurocognitive assessment

As seen in Table 2, the BD_1O group was significantly impaired in divided attention, information processing, and working memory (ACTT; P = 0.027) as well as psychomotor (attention) speed and focused attention (TMT-A; P = 0.034) compared to the CO. In addition, short-term memory and learning functions were impaired regardless of the recall ability (RAVLT: total learning score, P = 0.009; delayed recalling score, P = 0.005; recognition percent correct score, P = 0.020). There were no significant differences between the BD_1O and CO groups in terms of sustained attention as assessed with the TOVA; verbal attention as assessed with the DST forward; executive functions and alternating attention (set shifting) as assessed with the TMT-B, WCST, and Stroop Test; and phonemic verbal fluency as assessed with the COWAT.

Table 2 shows that when an analysis was conducted of participants ≥11 years old, the BD_1O group showed significant impairment in psychomotor (attention) speed and focused attention (TMT-A; P = 0.006), and short-term memory and learning functions regardless of the recall ability (RAVLT: total learning score, P = 0.012; delayed recalling score, P = 0.008; true positives, P = 0.039; recognition percent correct score; P = 0.004), compared to the CO group. As for divided attention, information processing, and working memory as assessed with the ACTT, the BD_1O group appeared to perform marginally worse than the CO (P = 0.069). In addition, the BD_1O group also showed significant impairment in verbal attention (DST forward score; P = 0.018) and in phonemic verbal fluency (COWAT; P = 0.025). There were no significant differences between the groups in terms of sustained attention as assessed with the TOVA or in executive functions and alternating attention as assessed with the TMT-B, WCST, and Stroop Test. While there was no difference in omission (P = 0.745) and commission (P

Table 1. Comparison of study group with healthy controls in age, sex, IQ, and years of education.

	All subjects			Subjects aged ≥ 11 years		
	BD_1O (n = 30)	CO (n = 37)	Comparison (P)	BD_1O (n = 21)	CO (n = 25)	Comparison (P)
Age	12.32 ± 2.77	12.48 ± 2.58	0.81	13.73 ± 1.95	13.93 ± 1.65	0.70
Sex (%)			0.91			0.57
Female	15 (50%)	18 (48.6%)		11 (52.4%)	11 (44%)	
Male	15 (50%)	19 (51.4%)		10 (47.6%)	14 (56%)	
IQ	99.9 ± 16.5	106.05 ± 14.07	0.10	97.81 ± 12.19	103.24 ± 12.42	0.18
Education (years)	6.3 ± 2.8	6.0 ± 2.5	0.68	7.52 ± 1.96	7.44 ± 1.50	0.93

BD_1O: High-risk offspring having a parent with bipolar I disorder. CO: Control offspring.

Table 2. Comparison of study group with healthy controls according to cognitive tests.

Neurocognitive tests	All subjects			Subjects aged ≥ 11 years		
	BD_1O (n = 30)	CO (n = 37)	Comparison (P)	BD_1O (n = 21)	CO (n = 25)	Comparison (P)
Rey Verbal Learning and Memory Test						
Total learning scores (1–5)	49.93 ± 8.80	55.51 ± 6.73	**0.009**	50.19 ± 9.26	56.56 ± 6.70	**0.012**
Delayed recalling scores (7)	10.47 ± 3.09	12.41 ± 2.69	**0.005**	10.80 ± 2.65	12.92 ± 2.36	**0.008**
True positives	13.37 ± 2.77	14.11 ± 1.66	0.090	13.19 ± 3.09	14.16 ± 1.89	**0.039**
Recognition percent correct score	0.92 ± 0.14	0.97 ± 0.04	**0.020**	0.91 ± 0.17	0.98 ± 0.04	**0.004**
Auditory Consonant Trigram Test (ACTT) total scores	38.47 ± 9.28	43.14 ± 7.63	**0.027**	40.14 ± 9.53	45.56 ± 7.64	**0.069**
Controlled Word Association Test (COWAT) total scores	21.37 ± 8.25	25.54 ± 10.20	0.075	23.57 ± 7.44	28.76 ± 10.25	**0.025**
Digit Span Test (DST)						
Forward section score	5.23 ± 1.96	6.05 ± 2.26	0.122	5.38 ± 1.80	6.88 ± 2.22	**0.018**
Backward section score	5.13 ± 2.14	5.08 ± 2.06	0.590	5.62 ± 2.16	5.68 ± 2.19	0.937
Total scores	10.37 ± 3.58	11.14 ± 3.98	0.639	11.00 ± 3.39	12.56 ± 3.99	0.195
Trail Making Test (TMT)						
Part A	52.71 ± 28.44	38.76 ± 15.83	**0.034**	46.49 ± 19.13	32.06 ± 11.25	**0.006**
Part B	166.44 ± 87.40	134.86 ± 81.98	0.113	150.71 ± 79.65	112.97 ± 63.95	0.140
Stroop Test main card reading time	37.51 ± 20.81	31.26 ± 11.67	0.377	34.26 ± 16.63	28.94 ± 11.16	0.349
Wisconsin Card Sorting Test (WCST)						
Category score	4.00 ± 1.91	4.14 ± 2.14	0.576	4.24 ± 1.89	4.44 ± 2.06	0.586
Trials to complete first category	19.60 ± 21.84	20.45 ± 27.38	0.576	18.52 ± 18.55	19.44 ± 24.52	0.374
Total correct score	60.90 ± 16.52	61.88 ± 18.72	0.825	62.66 ± 17.37	65.84 ± 17.54	0.651
Total error score	39.10 ± 16.62	38.11 ± 18.73	0.870	37.33 ± 17.54	34.16 ± 17.54	0.691
TOVA test scores						
Omission errors	10.17 ± 14.20	8.70 ± 17.68	0.780	7.19 ± 11.85	4.56 ± 5.02	0.745
Commission errors	35.77 ± 24.22	28.84 ± 17.93	0.267	31.52 ± 18.27	23.20 ± 13.07	0.120
Response time	374.18 ± 91.49	407.34 ± 90.57	0.152	334.48 ± 59.96	372.15 ± 60.77	0.041

BD_1O: High-risk offspring having a parent with bipolar I disorder. CO: Control offspring.

= 0.120) scores between the groups, the BD_1O group was faster than the controls (TOVA response time; P = 0.041) in giving responses to targets and nontargets.

4. Discussion

The BD_1O group (≥11 years old) was found to be poor in psychomotor (attention) speed, focused attention, verbal attention, and phonemic verbal fluency as well as in short-term memory and learning functions, regardless of the recall ability, in comparison with the control group. In addition, the study group appeared to perform marginally worse in divided attention, information processing, and working memory. However, there were no significant differences between the groups in terms of sustained attention, executive functions, or alternating attention. While there was no difference in omission and commission

scores between the groups, the BD_1O group was faster than the controls in giving responses to targets and nontargets.

In a metaanalysis of neuropsychological functioning in HR adult relatives, Bora et al. reported deficits in response inhibition, alternating attention (set shifting), executive function, verbal memory, and sustained attention (small to medium effect sizes) (15). However, these deficits may be components of the syndrome that are independent of the affective disorder since they have passed through the age of peak risk for BD. Therefore, studying young HR offspring has some advantages in the sense that they are exempt from the disease-associated factors seen in BD patients (1), and that the risk for developing BD remains higher than for the unaffected adult relatives, and so this would provide an opportunity to identify the neurocognitive differences present prior to the typical onset of the disorder (20). In a study that was published after the comprehensive review (1) mentioning the 5 studies investigating young offspring at high risk for BD, Maziade et al. evaluated 23 offspring (17.45 ± 4.54 years old) at extreme risk for BD due to a high family genetic loading of the affected parents. After adjusting for age, sex, and IQ, their HR offspring group showed poor performance in verbal episodic memory, executive function/problem solving, executive function/planning, letter fluency, and visual episodic memory (40). In this study, the reason why the impairments were found in a wide range of domains could be the high family genetic loading of the affected parents, since it is suggested that a dose-response relation exists between the degree of family genetic loading and cognitive impairments (41). Another reason could be that the mean age for their HR group is relatively older (17.45 years), which means that a subgroup of them might have reached the age of incidence of BD and they could be experiencing subsyndromal mood swings affecting the test performance that might result in false positive findings.

In the current study, executive functioning was measured using 3 well-validated tests: the WCST, Stroop, and TMT-B. However, the study group showed no impairment in any of these tests. Meyer et al. conducted a longitudinal prospective study on a group of HR offspring having a parent with BD, where diagnostic assessments were carried out at 5 time points (42). In the follow-up period, the impairment in executive functioning was first detected during mid-adolescence (mean age: 14.84) and the deficits in executive functioning and attention preceded a BD diagnosis in 67% of young adults. Klimes-Dougan et al. also first detected impairment in executive functioning and attention in their group at high risk for BD during mid-adolescence (mean age: 15.1) (25). Deficits in executive functioning are commonly reported in studies investigating first-degree adult relatives at high risk for BD (15). In our study, the reason for not detecting deficits in executive functioning could be that the age group we have studied was in the early adolescence stage (mean age: 13.73). Since our results reflect a certain point in time, the alterations that are suggested to appear in mid-adolescence cannot be ruled out. Giedd, by scanning the adolescent brain through structural magnetic resonance imaging, suggested that maturation of brain areas involved in executive functioning occurs after adolescence (43). Since the stabilization of neuromaturational processes is suggested to be finalized after adolescence, this might complicate the detection of probable deficits in cognitive functioning during early stages of adolescence.

Another cognitive function widely studied within the endophenocognitype concept is sustained attention (vigilance), which can be defined as the ability to focus on an activity long enough to complete a task. Studies assessing sustained attention in unaffected first-degree adult relatives of BD patients found no difference compared to controls (44–46). However, 5 studies investigating HR adolescent offspring of BD patients (21–25) found a relatively wide pattern of deficits in sustained attention. Overall, deficits in sustained attention appear to be present only in HR offspring of BD patients, but not in older relatives. We found no difference between the BD_1O and the CO groups in terms of sustained attention as assessed with a computerized continuous performance test named TOVA. A number of speculative possibilities may account for the negative results (20). First, all of these assessments are cross-sectional, which cannot exclude the impairments that may appear in the future. Second, computers have become a part of daily life and the young population is especially highly exposed to visually based computer games that reward reaction time and accurate visual discrimination. This might have led them to compensate for their slight attentional deficits when evaluated by computerized tests. Third, it is suggested that attention is one of the building blocks of IQ. Since we matched the groups for IQ in our study, this could be another reason for the nonsignificant differences between the groups.

Balanzá-Martinez et al. conducted a comprehensive review discussing multiple cognitive domains (1). In terms of psychomotor (attention) speed, 7 studies using the TMT-A found no difference between unaffected relatives and controls. As for phonemic verbal fluency, 5 out of 6 studies found no deficits between unaffected relatives and controls (16,45,47–49). As for verbal learning and memory, most of the studies found normal performances on list learning tests (18,25,48,50). Kéri et al. found that siblings of BD patients were impaired only in the delayed recall measure, with spared recognition and immediate recall. Only 2 twin studies showed a dysfunction in measures of delayed recall as well as learning (45,46). Thus, detection of deficits in our HR group in psychomotor (attention) speed with the TMT-A; phonemic verbal

fluency with the COWAT; and verbal learning and memory including immediate recall, delayed recall, and recognition abilities with the RAVLT made a contribution to this sparsely studied area. In addition, the BD_1O group appeared to perform marginally worse than the CO group in divided attention as assessed with the ACTT. There are a few studies that investigated this subdomain. Kremen et al. did not find a dysfunction in divided attention, whereas Sobczak et al. reported deficits in this subdomain in first-degree BD relatives (44,47).

Another point worth considering is the matching of groups for IQ to control this variable from skewing the outcome of the neurocognitive tests. Since general intelligence may affect the performance at each cognitive test level (1), matching for IQ might have resulted in the compensation of slight cognitive deficits. Thus, the group differences might have been minimized.

In conclusion, our findings are parallel with the reviews (51) suggesting that verbal memory/learning seem to be more useful as a cognitive endophenotype for BD as it meets all the established criteria (4). Comprehensive evaluation of neurocognitive domains through the use of sufficiently challenging tests to detect slight deficits may be beneficial for determining endophenocognitypes for the disorder and serve as a new target for early interventions. Matching the groups for age, sex, and years of education and assessing IQ and analyzing the data after adjusting for these variables also appears to be important. In addition, longitudinal studies with a larger sample size that match endophenocognitype and genotype, as well as using functional neuroimaging while administering cognitive tests, would help in determining the pathophysiology of the disorder. Brain development and its expression on cognitive functioning continue throughout childhood and adolescence. Since the age of 11 is suggested to be a threshold in the maturation of neurocognitive performance (30,31), stratifying the HR offspring and controls as preadolescents and adolescents may be the first step in the recruitment process. Furthermore, stratifying the subjects as early, middle, and late adolescents may be a practical approach in forming homogeneous groups in terms of cognitive functioning.

References

1. Balanzá-Martínez V, Rubio C, Selva-Vera G, Martinez-Aran A, Sánchez-Moreno J, Salazar-Fraile J et al. Neurocognitive endophenotypes (endophenocognitypes) from studies of relatives of bipolar disorder subjects: a systematic review. Neurosci Biobehav Rev 2008; 32: 1426–38.
2. Szatmari P, Maziade M, Zwaigenbaum L, Mérette C, Roy MA, Joober R et al. Informative phenotypes for genetic studies of psychiatric disorders. Am J Med Genet B Neuropsychiatr Genet 2007; 144B: 581–8.
3. Gottesman II, Shields J. Genetic theorizing and schizophrenia. Br J Psychiatry 1973; 122: 15–30.
4. Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry 2003; 160: 636–45.
5. Ozan E, Yıldırım S, Tatar A, Canpolat S, Yazıcı AB, Yüksel S et al. Sex- and diagnosis-related differences in nostril dominance may be associated with hemisphere dysfunction in affective disorders. Turk J Med Sci 2012; 42: 25–30.
6. Murphy FC, Sahakian BJ, Rubinsztein JS, Michael A, Rogers RD, Robbins TW et al. Emotional bias and inhibitory control processes in mania and depression. Psychol Med 1999; 29: 1307–21.
7. Rossi A, Arduini L, Daneluzzo E, Bustini M, Prosperini P, Stratta P. Cognitive function in euthymic bipolar patients, stabilized schizophrenic patients, and healthy controls. J Psychiatr Res 2000; 34: 333–9.
8. Sigurdsson E, Fombonne E, Sayal K, Checkley S. Neurodevelopmental antecedents of early-onset bipolar affective disorder. Br J Psychiatry 1999; 174: 121–7.
9. Yurgelun-Todd DA, Gruber SA, Kanayama G, Killgore WD, Baird AA, Young AD. fMRI during affect discrimination in bipolar affective disorder. Bipolar Disord 2000; 2: 237–48.
10. Martínez-Arán A, Vieta E, Colom F, Torrent C, Sánchez-Moreno J, Reinares M et al. Cognitive impairment in euthymic bipolar patients: implications for clinical and functional outcome. Bipolar Disord 2004; 6: 224–32.
11. Robinson LJ, Ferrier IN. Evolution of cognitive impairment in bipolar disorder: a systematic review of cross-sectional evidence. Bipolar Disord 2006; 8: 103–16.
12. Tabarés-Seisdedos R, Balanzá-Martínez V, Sánchez-Moreno J, Martinez-Aran A, Salazar-Fraile J, Selva-Vera G et al. Neurocognitive and clinical predictors of functional outcome in patients with schizophrenia and bipolar I disorder at one-year follow-up. J Affect Disord 2008; 109: 286–99.
13. Savitz J, Solms M, Ramesar R. Neuropsychological dysfunction in bipolar affective disorder: a critical opinion. Bipolar Disord 2005; 7: 216–35.
14. Cornblatt B, Obuchowski M. Update of high-risk research: 1987–1997. Int Rev Psychiatry 1997; 9: 437–47.
15. Bora E, Yucel M, Pantelis C. Cognitive endophenotypes of bipolar disorder: a meta-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. J Affect Disord 2009; 113: 1–20.
16. Kéri S, Kelemen O, Benedek G, Janka Z. Different trait markers for schizophrenia and bipolar disorder: a neurocognitive approach. Psychol Med 2001; 31: 915–22.
17. Zalla T, Joyce C, Szöke A, Schürhoff F, Pillon B, Komano O et al. Executive dysfunctions as potential markers of familial vulnerability to bipolar disorder and schizophrenia. Psychiatr Res 2004; 121: 207–17.
18. Antila M, Tuulio-Henriksson A, Kieseppä T, Eerola M, Partonen T, Lönnqvist J. Cognitive functioning in patients with familial bipolar I disorder and their unaffected relatives. Psychol Med 2007; 37: 679–87.

19. Arts B, Jabben N, Krabbendam L, van Os J. Meta-analyses of cognitive functioning in euthymic bipolar patients and their first-degree relatives. Psychol Med 2008; 38: 771–85.

20. Glahn DC, Almasy L, Barguil M, Hare E, Peralta JM, Kent JW Jr et al. Neurocognitive endophenotypes for bipolar disorder identified in multiplex multigenerational families. Arch Gen Psychiatry 2010; 67: 168–77.

21. Winters KC, Stone AA, Weintraub S, Neale JM. Cognitive and attentional deficits in children vulnerable to psychopathology. J Abnorm Child Psychol 1981; 9: 435–53.

22. Harvey PD, Weintraub S, Neale JM. Speech competence of children vulnerable to psychopathology. J Abnorm Child Psychol 1982; 10: 373–87.

23. Kron L, Decina P, Kestenbaum CJ, Farber S, Gargan M, Fieve R. The offspring of bipolar manic-depressives: clinical features. Adolesc Psychiatry 1982; 10: 273–91.

24. McDonough-Ryan P, DelBello M, Shear PK, Ris MD, Soutullo C, Strakowski SM. Academic and cognitive abilities in children of parents with bipolar disorder: a test of the nonverbal learning disability model. J Clin Exp Neuropsychol 2002; 24: 280–5.

25. Klimes-Dougan B, Ronsaville D, Wiggs EA, Martinez PE. Neuropsychological functioning in adolescent children of mothers with a history of bipolar or major depressive disorders. Biol Psychiatry 2006; 60: 957–65.

26. Maziade M, Rouleau N, Cellard C, Battaglia M, Paccalet T, Moreau I et al. Young offspring at genetic risk of adult psychoses: the form of the trajectory of IQ or memory may orient to the right dysfunction at the right time. PLoS ONE 2011; 6: e19153.

27. Tsuang MT, Stone WS, Faraone SV. Schizophrenia: a review of genetic studies. Harv Rev Psychiatry 1999; 7: 185–207.

28. Ozan E, Deveci E, Oral M, Karahan U, Oral E, Aydın N et al. Neurocognitive functioning in a group of offspring genetically at high-risk for schizophrenia in Eastern Turkey. Brain Res Bull 2010; 82: 218–23.

29. Korkman M, Kemp SL, Kirk U. Effects of age on neurocognitive measures of children ages 5 to 12: a cross-sectional study on 800 children from the United States. Dev Neuropsychol 2001; 20: 331–54

30. Passler MA, Isaac W, Hynd GW. Neuropsychological development of behavior attributed to frontal lobe functioning in children. Dev Neuropsychol 1985; 1: 349–70.

31. Paniak C, Miller HB, Murphy D, Patterson L, Keizer J. Canadian developmental norms for 9-14 year-olds on the Wisconsin Card Sorting Test. Can J Rehabil 1996; 9: 233–7.

32. Spreen O, Strauss E. A compendium of neuropsychological tests. Administration, norms and commentary. New York: Oxford University Press; 1991.

33. Harris ME, Ivnik RJ, Smith GE. Mayo's Older Americans Normative Studies: expanded AVLT Recognition Trial norms for ages 57 to 98. J Clin Exp Neuropsychol 2002; 24: 214–20.

34. Umaç A. Normal deneklerde frontal hasarlara duyarlı bazı testlerde performansa yaş ve eğitimin etkisi. İstanbul Üniversitesi Sosyal Bilimler Enstitüsü Psikoloji Bölümü, Yüksek Lisans Tezi, İstanbul; 1997.

35. Wechsler D. Wechsler Memory Scale-Revised. San Antonio (TX): The Psychological Corporation; 1987.

36. Lezak MD. Neuropsychological assessment. 3rd ed. New York: Oxford University Press; 1995.

37. Reitan RM, Wolfson D. The Halstead-Reitan neuropsychological test battery. Tucson (AZ): Neuropsychological Press; 1985.

38. Yalçın K, Karakaş S. Change with age of information processing meta-operations in children. Turk Psikiyatri Derg 2008; 19: 257–65.

39. Greenberg LM. T.O.V.A. interpretation manual. Minneapolis (MN): University of Minnesota; 1991.

40. Maziade M, Rouleau N, Gingras N, Boutin P, Paradis ME, Jomphe V et al. Shared neurocognitive dysfunctions in young offspring at extreme risk for schizophrenia or bipolar disorder in eastern Quebec multigenerational families. Schizophr Bull 2009; 35: 919–30.

41. Faraone SV, Seidman LJ, Kremen WS, Toomey R, Pepple JR, Tsuang MT. Neuropsychologic functioning among the nonpsychotic relatives of schizophrenic patients: the effect of genetic loading. Biol Psychiatry 2000; 48: 120–6.

42. Meyer SE, Carlson GA, Wiggs EA, Martinez PE, Ronsaville DS, Klimes-Dougan B et al. A prospective study of the association among impaired executive functioning, childhood attentional problems, and the development of bipolar disorder. Dev Psychopathol 2004; 16: 461–76.

43. Giedd JN. Structural magnetic resonance imaging of the adolescent brain. Ann NY Acad Sci 2004; 1021: 77–85.

44. Kremen WS, Faraone SV, Seidman LJ, Pepple JR, Tsuang MT. Neuropsychological risk indicators for schizophrenia: a preliminary study of female relatives of schizophrenic and bipolar probands. Psychiatr Res 1998; 79: 227–40.

45. Gourovitch ML, Torrey EF, Gold JM, Randolph C, Weinberger DR, Goldberg TE. Neuropsychological performance of monozygotic twins discordant for bipolar disorder. Biol Psychiatry 1999; 45: 639–46.

46. Kieseppä T, Tuulio-Henriksson A, Haukka J, Van Erp T, Glahn D, Cannon TD et al. Memory and verbal learning functions in twins with bipolar-I disorder, and the role of information-processing speed. Psychol Med 2005; 35: 205–15.

47. Sobczak S, Honig A, Schmitt JAJ, Riedel WJ. Pronounced cognitive deficits following an intravenous L-tryptophan challenge in first-degree relatives of bipolar patients compared to healthy controls. Neuropsychopharmacology 2003; 28: 711–9.

48. Ferrier IN, Chowdhury R, Thompson JM, Watson S, Young AH. Neurocognitive function in unaffected first-degree relatives of patients with bipolar disorder: a preliminary report. Bipolar Disord 2004; 6: 319–22.

49. McIntosh AM, Harrison LK, Forrester K, Lawrie SM, Johnstone EC. Neuropsychological impairments in people with schizophrenia or bipolar disorder and their unaffected relatives. Br J Psychiatry 2005; 186: 378–85.

50. Clark L, Sarna A, Goodwin GM. Impairment of executive function but not memory in first-degree relatives of patients with bipolar I disorder and in euthymic patients with unipolar depression. Am J Psychiatry 2005; 162: 1980–2.

51. Glahn DC, Bearden CE, Niendam TA, Escamilla MA. The feasibility of neuropsychological endophenotypes in the search for genes associated with bipolar affective disorder. Bipolar Disord 2004; 6: 171–182.