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Research report

Neurocognitive functioning in a group of offspring genetically at high-risk for schizophrenia in Eastern Turkey

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ABSTRACT

We assessed major cognitive domains in symptom-free children of patients with schizophrenia compared to the healthy children of parents with no psychopathology using neurocognitive tests. We hypothesized that, offspring at high-risk for schizophrenia would have significant impairment in major domains: attention, memory, verbal–linguistic ability and executive functions. Thirty symptom-free children (17-males, 13-females; intelligence quotient = 99.6 ± 13.6; age = 12.69 ± 2.32 and education = 5.8 ± 2.3 years) having a parent diagnosed with schizophrenia and 37 healthy children matched for gender (19-males, 18-females), IQ (106.05 ± 14.70), age (12.48 ± 2.58) and years of education (6.0 ± 2.5) were evaluated. The study group showed significant poor performance in cognitive domains, such as working memory (assessed with Auditory consonant trigram test), focused attention (Stroop test), attention speed (Trail making test), divided attention (Auditory consonant trigram test), executive functions (Wisconsin card sorting test), verbal fluency (Controlled word association test) and declarative memory (Rey verbal learning and Short-term memory test). However, no group differences were detected either on verbal attention (Digit span forward test) or sustained attention (TOVA, a continuous performance task); the latter as consistently reported to be a predictor of schizophrenia. In order to determine the cognitive endophenotype of schizophrenia, it seems more rational to conduct comprehensive evaluation of neurocognitive domains in well-matched groups via using sufficiently challenging tests to detect slight deficits. In addition, longitudinal studies with a larger sample size evaluating neurocognitive functions combined with genetic analysis may provide clues about explaining the genetic background of the disorder within the endophenocognitype concept and serve as new targets for early interventions.

1. Introduction

Schizophrenia is a neurobiological disorder, having a multifactorial etiology, including the genetic, neurodevelopmental and environmental influences [43]. In addition to well known negative and positive symptoms, deficits in neurocognitive functioning has come to be regarded as the core component of this disorder [24,43]. These deficits contribute to overall levels of dysfunction and significantly influence the functional outcome [19]. In contrast to significant improvement in positive symptoms after administering both typical [31] and atypical [23] antipsychotic medication, slight improvement in neurocognitive functions indicate that there is a relative independence between neurocognition and positive symptoms [36]. Studies emphasize that evaluating cognitive functioning in schizophrenia may shed light to the pathophysiology and treatment of this disorder.

Functional deficits in neurocognition are not only evident in frank psychosis, but also during the prodromal period of the disorder and high-risk relatives of the patients may also exhibit these deficits, which suggest that there is a genetic base. In this respect, identification of genetically transmitted abnormalities in cognition and information processing that are present even in the symptom-free biological relatives of the patients, has become the scope of interest. However, even if there is a strong support for genetic background, there are rapidly replicating evidences showing the polygenic inheritance of schizophrenia [15] which restricts the genetic studies from making firm conclusions regarding the pathophysiology of the disorder. In addition, it is difficult to find a relationship between the observable phenotype and the genetic background due to the complexity, variability and heterogeneity of clinical symptoms. It has been suggested that it may be possible to find the responsible genes that make symptom-free relatives vulnerable to schizophrenia by identifying latent trait markers [25].

Gottesman and Shields [17] suggested the concept of the endophenotype in the study of neuropsychiatric disorders to clarify classification and diagnosis as well as to foster genetic analysis.

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The concept of the endophenotype, defining the heritable phenotypes, is linked to the use of the glucose tolerance test (GTT) as an endophenotype for diabetes. Endophenotypes, such as the GTT, are heritable biomarkers that are not observed by the naked eye. Gottesman and Gould [18] definition of an endophenotype is that it should be heritable, co-segregate with a psychiatric illness, yet be present even when the disease does not exist (i.e. state independent) but can be found in non-affected family members at a higher rate than in the population. In this respect, evaluating the symptom-free but high-risk offspring of patients with schizophrenia during adolescence or late childhood, who on average share 50% of genes with their ill parents but are free of confounds associated with psychosis (e.g., they are drug-free), would provide a unique opportunity to identify the heritable phenotypes, such as neurocognitive abnormalities which exist prior to typical onset of schizophrenia [36].

The period of maximal risk for psychosis occurs during the ages of 20–30 [36]. Studying high-risk offspring during late childhood and adolescence, where the latter is a period where great neuromaturational changes occur [4,26], will help us find clues about the pathophysiology and the neurobiological differences that will be a possible predictor of the disorder. Exploring probable abnormalities in cognitive functions may serve as new targets for early interventions as well [40]. Therefore, several follow-up studies that use cognitive tests have been conducted on young relatives, usually offspring, of patients with schizophrenia in the context of high-risk approach. Sixteen of these genetic high-risk studies have been reviewed by Niemi et al. [32]. Other studies investigating teenagers and young adults at high-risk include Pittsburgh [27], Harvard [37,41], Hillside hospital [9] studies and the Colorado study [13] of children ages 6–15. Recently, Seidman et al. [36] conducted a study by combining the data of the subjects (ages 12–25) from Harvard and Hillside adolescent high-risk studies. The data on 73 high-risk schizophrenia and 84 community control subjects matched for age, gender and years of education were evaluated in this study. Using 13 tests, the researchers compared the groups on 6 domains: executive functioning/working memory, verbal memory, verbal–linguistic ability, visual–spatial ability, motor functions and sustained attention. The result of the evaluation showed that high-risk schizophrenia group had impairment in executive functioning/working memory, verbal memory, verbal–linguistic and visual–spatial abilities. The Colorado study [13] also investigated the neuropsychological functioning of high-risk children (ages 6–15) on 5 domains: working memory, visual–spatial and verbal–linguistic abilities, emotion perception and response inhibition. The result of this study manifested impairment in verbal–linguistic ability, working memory and response inhibition. However, these studies have been conducted among a group of individuals from different parts of the world and call for a replication in other regions, since environmental factors have been suggested to affect the pathogenesis of the disorder [43]. This prompted us to investigate neurocognitive functioning in symptom-free children having a parent with schizophrenia in Eastern Turkey. We founded a neuropsychological test laboratory in our department to conduct follow-up studies in high-risk groups. The neurocognitive test battery used in this study consisted of well-validated tests that were commonly used in current high-risk studies investigating similar age groups. The domains most frequently considered in detecting impairments in neurocognitive functioning are attention, memory, verbal–linguistic ability and executive functions. In addition to replicating a schizophrenia high-risk study in Eastern Turkey, we also aim to implement parallel strategies to investigate neurocognitive vulnerability to other psychopathologies such as affective disorders and personality disorders by using the same battery since there is limited data in this area.

2. Materials and methods

2.1. Subjects

Thirty children (ages 8–17; 17-males, 13-females) having a parent diagnosed with schizophrenia according to the DSM-IV-TR (American Psychiatric Association, 2000) criteria were recruited at our university psychiatry clinic. The diagnosis of schizophrenia in parents was confirmed using the Turkish version of the Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-I). The children having a lifetime diagnosis of substance use disorder, ADHD, 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 the parents who were referred to our outpatient clinics other than neurology and psychiatry. The parents of the healthy controls were evaluated via using SCID-I non-patient version in order to exclude psychotic disorders, bipolar affective disorder, etc. The parents with any neurological diseases were also excluded. The control group consisted of 37 healthy children matched for age (8–17 years), gender (19-males, 18-females) and years of education. 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.

2.2. Neurocognitive evaluation and IQ assessment

We used Kent-EGY and Porteus labyrynths tests for the assessment of IQ. The same comprehensive neurocognitive test battery was administered to both study group and controls, including the Rey auditory verbal learning test (RAVLT), Auditory consonant trigram test (ACTT), Controlled word association test (CoWAT), Digit span test (DST), Trail making test (TMT-A/B), Wisconsin card sorting test (WCST), TBAG form of Stroop test and Test of variables of attention (TOVA) [39]. Below is the explanation of the neurocognitive tests used in the present study that were summarized elsewhere [28].

2.2.1. Rey auditory verbal learning and memory test (RAVLT)

We used the Turkish version of RAVLT where the validity and reliability in Turkish was completed [1]. RAVLT assesses immediate memory span, new learning, delayed free recall and recognition for verbal items. The test was administered according to its original standards: 15 nouns (list A) were read by the examiner, followed by subjects' free recall (A1–A5), five times consecutively. After the fifth recall, the examiner read a further list (list B) of 15 new words, followed by the subjects' free recall (B). Another recall of list A (A6 and A7) was assessed immediately after and 20 min later. Recognition section of the test; with 15 words from list A intermingled with 35 words not belonging to list A, was shown to the subjects, and they were expected to identify which words belonged to the original list and which did not. The following measures were analysed; total learning scores (1–5): the total number of correctly recalled words summed over the five 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 recognition section of the test. Recognition percent correct score: this measure is calculated by the formula (true positives + true negatives)/50 proposed by Harris et al. [22].

2.2.2. Auditory consonant trigram test (ACTT)

The objective of this test is to measure short-term memory, divided attention and information processing. This test is the main tool we have used for measuring working memory. Study for validity and reliability in Turkish was completed [2]. Total number of recalled letters was used in evaluation.

2.2.3. Controlled word association test (CoWAT)

The objective of this test is to evaluate the recalling of words which begin with a given letter within a certain time interval (1 min in this study). Most frequently, F, A or S are used. In Turkish standardization K, A or S are proposed [44]. In this study total number of recalled words was assessed.

2.2.4. Digit span test (DST)

This test is a subunit of WAIS-R [29,45]. It has two sections, digits forward and digits backward. In the forward section the patient repeats the numbers told to him/her by the rater and in the backward section, the patient repeats the numbers told to him/her backwards. The score is the sum of the correct recalled numbers in forwards and backwards sections and the total of the both sections as well.

2.2.5. Trail making test (TMT-A/B)

This test assesses attention, mental flexibility, visual tracking and motor abilities [39]. 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. In this study, the durations required to complete two separate parts were taken into account.

2.2.6. Wisconsin card sorting test (WCST)

WCST measures the ability to deduce a classification principle based on ongoing feedback about the correctness of the responses and the ability to dismiss this principle when it leads to aversive behavioral consequences. Moreover, it assesses

Table 1
Comparison of study group with healthy controls in age, gender, intelligence quotient (IQ) and years of education.

	Study group (n = 30)	Controls (n = 37)	Comparison
Age	12.69 ± 2.32	12.48 ± 2.58	p = 0.725; t = 0.354
Gender (%)			p = 0.664; X^2 = 0.188
Female	13 (43.3%)	18 (48.6%)	
Male	17 (56.7%)	19 (51.4%)	
IQ	99.6 ± 13.6	106.05 ± 14.07	p = 0.169; MU = 446.0
Education (years)	5.8 ± 2.3	6.0 ± 2.5	p = 0.616; MU = 515.5

the ability to selectively attend to one part of a stimulus and to abandon the principle when receiving feedback about the incorrectness of his/her responses. In the present study, computerized form of the test was used [46].

2.2.7. TBAG form of Stroop test
The Stroop test assesses the ability to flexibly direct attention to the presence of a distraction, inhibit a habitual behavioral pattern and display non-usual behavior [39].

2.2.8. TOVA test
Test of variables of attention (TOVA) is a computerized continuous performance test. The patients were asked to push a button connected to a computer when they recognized the target on the monitor. The target means a small square appearing on the upper part of a rectangle. The non-target means a small square appearing on the bottom of the rectangle. A stimulus flashed on a screen every 2 s. The target is presented on 22.5% and 77.5% of the trials during the first and second halves, respectively. The data was obtained in the domains of the omission error, the comission error, the response time and the variability. All the variables are recorded for each 5 min quarter and 10 min halves, 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 [20].

2.3. 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.

2.4. Statistical analyses

The statistics was 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 Mann–Whitney *U* and independent samples *t*-test. The *p* value below 0.05 was accepted to flag significance.

3. Results

3.1. Socio-demographical features

We recruited 73 participants for evaluation, but 3 of the control subjects and 3 of the subjects from the study group could not complete the neurocognitive assessment due to illiteracy, inability to count, unwillingness to complete the assessments and physical complaints such as headache and stomach ache. Thus, an analysis was carried out on 30 children having a parent with schizophrenia and 37 healthy control children. The socio-demographical variables such as age, gender and education were shown in Table 1. As seen in the table, the groups were well-matched for age, gender, intelligence quotient (IQ) and years of education.

3.2. Neurocognitive assessment

Table 2 displays means and standard deviations for the 8 neurocognitive tests. As Table 2 shows, compared with controls, participants in the study group were significantly impaired in divided attention (assessed with ACTT; p = 0.015), focused attention (Stroop test main card reading time; p = 0.032), attention speed (TMT-A; p = 0.010), working memory (ACTT; p = 0.015), executive functions (WCST; p = 0.000 and p = 0.03) and verbal fluency (CoWAT

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

Neurocognitive tests	Study group n = 30	Controls n = 37	Comparison
Rey verbal learning and memory test			
Total learning scores (1–5)	51.0 ± 8.00	55.51 ± 6.73	p = 0.022; MU = 374.0
Delayed recalling scores (7)	10.40 ± 3.40	12.41 ± 2.69	p = 0.009; MU = 349.5
True positives	13.13 ± 2.60	14.11 ± 1.66	p = 0.045; MU = 408.5
Recognition percent correct score	0.92 ± 0.10	0.97 ± 0.04	p = 0.012; MU = 370.5
Auditory consonant trigram test total scores	37.87 ± 9.50	43.14 ± 7.63	p = 0.015; t = −2.506
Controlled word association test total scores	19.86 ± 9.50	25.54 ± 10.20	p = 0.024; t = −2.305
Digit span test			
Forwards section score	5.27 ± 1.70	6.05 ± 2.26	p = 0.125; t = −1.556
Backwards section score	4.50 ± 1.80	5.08 ± 2.06	p = 0.487; MU = 501.0
Total scores	9.77 ± 3.20	11.14 ± 3.98	p = 0.364; MU = 483.5
Trail making test (TMT)			
Part A	57.50 ± 23.38	38.76 ± 15.83	p = 0.010; MU = 270.0
Part B	166.61 ± 78.48	134.86 ± 81.98	p = 0.045; MU = 396.5
Stroop test main card reading time	40.58 ± 20.00	31.26 ± 11.67	p = 0.032; MU = 385.0
Wisconsin card sorting test (WCST)			
Category score	2.50 ± 2.00	4.14 ± 2.14	p = 0.003; MU = 324.0
Trials to complete 1st category	45.66 ± 39.60	20.45 ± 27.38	p = 0.000; MU = 240.5
Total correct score	52.42 ± 17.20	61.88 ± 18.72	p = 0.037; t = −2.128
Total error score	47.57 ± 17.20	38.11 ± 18.73	p = 0.037; t = 2.128
TOVA test scores			
Omission errors	17.53 ± 31.40	8.70 ± 17.68	p = 0.195; MU = 453.0
Commission errors	30.17 ± 22.10	28.84 ± 17.93	p = 0.910; MU = 546.0
Response time	433.71 ± 127.90	407.34 ± 90.57	p = 0.336; t = 0.969

total scores; $p = 0.037$). In addition, short-term memory and learning functions were impaired regardless of recall ability (RAVLT; $p = 0.022$). In the context of executive functions, all the domains, such as overcoming of a strong habitual response or resisting temptation and perseveration, planning, decision making were found to be impaired in the study group. There were no significant differences between study and control groups in terms of sustained attention as assessed with TOVA and verbal attention as assessed with digit span forward test.

4. Discussion

In the present study, as predicted, offspring at high-risk for schizophrenia demonstrated an overall difference in neurocognitive functioning compared to healthy controls. We found impairments in verbal fluency, executive functions, declarative memory, focused attention, attention speed (set shifting), divided attention and working memory. Although previous studies showed that sustained attention deficit is a robust indicator of genetic risk for schizophrenia [38], with the notable exception of some other reports [11,36], we have found no group differences on sustained attention as well as on verbal attention, which was contrary to our primary hypothesis.

Several studies that have been conducted in high-risk young relatives, often offspring, have differed in sample sizes, age groups and the tests administered. Although it is difficult to make generalizations by looking at the data on these studies [36], there is reasonably strong support for impairments in the following neurocognitive functions in relation to genetic risk for schizophrenia [8–10,13,27,32,37,41]: attention and working memory (including sustained attention and vigilance, perceptual-motor speed, short-term and working memory); concept formation and abstract reasoning; verbal fluency (including receptive language); general intelligence and declarative memory, especially verbal memory. However, investigating cognitive deficits creates a number of handicaps. It has been suggested that patients with schizophrenia appear to have general rather than specific neurocognitive impairment [5]. The isolation of one specific cognitive process seems to be complicated due to the fact that several cognitive and sensory functions are required to perform a task [13]. One of the ways to overcome this predicament is to administer several tests that are considered as belonging to a specific domain [42]. Using multiple tests enable the assessor to avoid any false findings. Depending on this information, instead of just focusing on sustained attention, we performed multiple tests to avoid overlooking probable deficits in other domains.

The basis of deficits in verbal fluency is described as the reduced ability to access semantic information storage systems with normal efficiency [16]. Neuropsychological investigations implicate that the brain areas used in this task are the frontal lobe which is important in the phonetic variant and the temporal lobe in the semantic variant. It is hypothesized that temporal lobe asymmetry plays an important role in the etiology of schizophrenia and is associated with greater verbal impairment in the risk for schizophrenia [12]. The difficulty in verbal fluency is one of the most severe impairments in patients with schizophrenia as well as their adult relatives [13]. However, verbal fluency has not been studied frequently in high-risk offspring in adolescence and late childhood. In this respect, verbal fluency deficits found in our high-risk group made a contribution to this sparsely studied area.

There has been conflicting results as to whether deficit in sustained attention, which can be defined as the ability to focus on an activity long enough to complete a task, is an indicator of genetic vulnerability to schizophrenia. This may be due to the difficulty of the tests administered and the differences in the age group studied. As summarized by Seidman et al. [36]; in the studies where difficult continuous performance tests are used [14,34], impairment in sustained attention has been found to be a determinant of developing schizophrenia. On the other hand, studies using simple continuous performance tests [3,6,21,33,35] report that, sustained attention is not impaired in high-risk offspring of patients with schizophrenia. The difference in the age group in the previous studies may be another reason for the conflicting results that are found. Michie et al. [30] suggested that assessing the sustained attention in childhood results in an unacceptable high false-positive rate (21%) when predicting which offspring at-risk for schizophrenia will develop a schizophrenia spectrum disorder. Depending on the results of several studies, it seems important to take in account both the difficulty of the tests administered and the age group studied, and their interaction while interpreting the study findings. In our study, we assessed the sustained attention using a computerized test named TOVA which is easily administered. The findings indicated that offspring at high-risk for schizophrenia had no deficit in sustained attention compared to controls. However, the subjects demonstrated poor performance when tests assessing focused attention, attention speed, divided attention, executive functions, verbal fluency and declarative memory were used in addition to the TOVA. As far as the age group is concerned; our participants consisted of children who were at least in second grade because of the test requirements.

Our results for the sustained attention assessed with TOVA, which indicated no difference between the groups, were rather unexpected. Seidman et al. [36] who also found no difference between the offspring at high-risk for schizophrenia and the control groups in terms of sustained attention have speculated the possibilities that may account for the negative results. Firstly, all of the assessments reported in these studies are cross-sectional. Since it is possible that expression of neurocognitive deficits may follow a developmental pattern in schizophrenia [13], the cross-sectional design cannot rule out the alterations that may appear in the future. Secondly, computers have become a part of daily life and children are highly exposed to visually based computer games that reward reaction time and accurate visual discrimination which may lead the children to have a well developed skill set. This may not be the case for subjects in previous high-risk studies where computerized visual attention tasks were rather unfamiliar. Therefore, these skills combined with TOVA's relatively low sensitivity in detecting slight sustained attention deficits might have resulted in the insignificant findings between the groups. Thirdly, it is suggested that attention is one of the building blocks of IQ. Since we have matched the groups for IQ in our study, this could be another reason for the insignificant findings between the groups.

On the other hand, consideration of the global measure of attentional deviance has been suggested for predictive accuracy in the context of genetic vulnerability to schizophrenia [7]. In this context, attention deviance index (ADI) which is a composite score based on response indices from several tests, has been proposed to be associated with poor adjustment and schizophrenia spectrum features in adolescence [14]. In our offspring at high-risk for schizophrenia group, poor performance findings on focused attention, attention speed, divided attention and working memory with no difference between the groups in terms of sustained attention, emphasizes the need for evaluating all the dimensions of attention through using several tests rather than focusing only on sustained attention to increase predictive accuracy.

Since several cognitive and sensory functions merge to perform a task, it is difficult to isolate one specific cognitive process [13]. This may explain why the tools that are used to assess a cognitive domain vary in their evaluation specificity. In the present study, the Auditory consonant trigram test was used as the primary assessment tool but the Digit span test backwards section, WCST and Stroop test were also beneficial in assessing working memory. Although we have found differences between groups with the Auditory consonant trigram test, WCST and Stroop test; there was no group difference with the Digit span test backwards section. The probable cause for not detecting significant impairment in the Digit span test might be that Stroop test, WCST and the Auditory consonant trigram test are literal or figurative, whereas Digit span test backwards section evaluates working memory in terms of arithmetical skills. This is another reason why using multiple tests to assess a specific cognitive function is helpful. Another point worth considering is that evaluating only the offspring at high-risk for schizophrenia may put restrictions on interpreting whether the deficits found reflect a pattern of vulnerability to schizophrenia or to non-specific psychopathology [13]. The same limitation seems also valid for our data which prompted us to investigate the offspring at high-risk for affective disorders.

5. Conclusions

In the present study, the offspring at high-risk for schizophrenia group showed significant poor performance in cognitive functions, such as working memory, focused attention, attention speed, divided attention, executive functions, declarative memory and verbal fluency. However, no group differences were detected either on verbal attention or sustained attention, the latter as consistently reported to be a predictor of schizophrenia. Instead of focusing on sustained attention in the context of genetic vulnerability to schizophrenia, it seems like a more rational approach to look at the sum of functional disturbances in dimensions of attention, which has been suggested previously within the concept of global attentional deviance. Comprehensive evaluation of neurocognitive domains through using sufficiently challenging tests to detect slight deficits with a special emphasis on dimensions of attention for the offspring at high-risk for schizophrenia may be beneficial for determining endophenocognitypes for the disorder and serve as new targets for early interventions. Also, matching the groups for age, gender, years of education and especially IQ appears to be important since IQ can interfere with cognitive performance. In addition, longitudinal studies with a larger sample size evaluating neurocognitive functions combined with genetic analysis may provide clues about explaining the genetic background of the disorder within the endophenocognitype concept and using functional neuroimaing while administering cognitive tests would help in determining the pathophysiology of the disorder.

Conflict of interest

The authors declare that they do not have any conflict of interest.

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