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Attentional and neurocognitive characteristics of high-risk offspring of parents with schizophrenia compared with DSM-IV attention deficit hyperactivity disorder children

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Abstract

Offspring of individuals with schizophrenia are at increased baseline risk for a range of early mental disorders. Studies investigating the premorbid characteristics of individuals with schizophrenia indicate that they suffer from social, behavioral, attentional and neurocognitive impairments, often resembling attention deficit hyperactivity disorder (ADHD). In this study, we compared the executive functioning and general intelligence among three groups: (i) children and adolescents with DSM-IV ADHD ($n=41$), (ii) "high-risk" (HR) offspring of parents with DSM-IV schizophrenia, and (iii) normal comparison subjects ($n=35$). Our results indicated that both HR and ADHD groups had lower Verbal IQ scores. ADHD cases had significantly lower percent correct and total errors in Wisconsin Card Sorting Test when compared with normal comparison subjects. The HR cases also had lower Performance IQ scores as well as worse abstraction–flexibility and comprehension performance. The HR group was further stratified with (HR-A) and without (HR-NA) comorbid ADHD, and HR-A subjects were significantly noted to be more impaired on most tests. The overall worse performance of HR offspring was attributable to significantly lower performance among the HR-A youth. Further, our results suggested that the most profoundly impaired HR subjects were in fact children and adolescents who also met criteria for ADHD. Future studies with broader neuropsychological test batteries are necessary to investigate the differences and similarities between ADHD and the HR-A subgroup.

Keywords

Schizophrenia; Attention deficit hyperactivity disorder; High-risk

1. Introduction

The offspring of individuals with schizophrenia are at increased risk for this disorder. In fact, the overall risk for schizophrenia among both the biological siblings and the offspring (who evidently share 50% of gene pool) is noted to be between 9% and 13% (Andreasen, 2000; Torrey and Yolken, 2000). Numerous studies have investigated the neuropsychological and behavioral profiles of children of individuals with schizophrenia

along with factors that mediate their outcome. These studies showed that the offspring of individuals with schizophrenia have lower IQ levels (e.g. Byrne et al., 1999); impairments in attention (Erlenmeyer-Kimling et al., 2000); poor memory (Erlenmeyer-Kimling et al., 2000), poor performance on tests of mathematical reasoning (Ayalon and Merom, 1985) and executive functioning (Byrne et al., 1999). It has also been suggested that some of the cognitive deficits, like lower IQ and attention problems may in fact be among factors that predict emergence of schizophrenia in their high-risk offspring (Niemi et al., 2003; Parnas et al., 1982). Attention problems seem also to be heritable (Cornblatt and Keilp, 1994). A recent study showed that ADHD was more frequent in children at high-risk for schizophrenia, and that high-risk children with ADHD had more psychotic-like clinical features when compared with high-risk children without ADHD (Keshavan et al., 2003).

Complementary evidence comes from studies that investigated the premorbid functioning of schizophrenic patients. These studies showed that the patients had suffered from low IQ, social withdrawal, and neurobehavioral problems, resembling DSM-III attention deficit hyperactivity disorder (ADHD) (Marcus, 1987). Other studies suggested that social problems (Davidson et al., 1999), attentional problems, presence of conduct disorder and substance abuse during childhood and adolescence might predict later emergence of schizophrenia (Erlenmeyer-Kimling et al., 2000; Amminger et al., 1999; Done et al., 1994).

Therefore, it seems that attention problems are prominent in prodromal phase of schizophrenia and an important predictor of future disorder in high-risk subjects. However, it is not clear whether similarities between ADHD, one of the most frequent causes of attention problems, and prototypical attention problems among HR offspring of patients with schizophrenia are merely phenomenological, or whether they have further similarities in terms of neuropsychological profiles and/or neuroimaging findings. This line of investigation therefore may yield important data about the differences and similarities of various neurodevelopmental presentations of disorders among risk groups. Moreover, comparing HR offspring with (HR-A) and without (HR-NA) attention problems with normal comparison subjects on neuropsychological tests may give additional information about the importance of attention problems observed among the HR subjects. Lack of significant neuropsychological deficits in the HR subjects without attention problems (HR-NA) may suggest that the well-known neuropsychological difficulties of the offspring of individuals with schizophrenia may be attributable to the worse performance of subjects with co-occurring attentional problems.

In this study, we compared the abstraction–flexibility, spatial organization, concept formation, executive control, and Verbal and Performance IQ scores of children and adolescents with DSM-IV ADHD, the high-risk (HR) offspring of parents with DSM-IV schizophrenia, and a comparison subjects using the Stroop Color Word Interference Test, Wisconsin Card Sorting Test (WCST), and Weschler Intelligence Scale for Children-Revised Form. The present study is novel in that we investigated the presence of ADHD and neuropsychological impairments in the HR offspring with (HR-A), and without ADHD (HR-NA) contrasted with specific ADHD and normal comparison groups. We hypothesized that both the ADHD and HR cases will have executive dysfunction, and HR cases will have lower intelligence. We further hypothesized that the HR-A subgroup would have more significant neurocognitive impairments compared to the HR-NA subgroup.

2. Method

2.1. Sample

The sample included 41 children and adolescents with ADHD (ages 7–17, mean±sd: 10.7±2.6; 31 males, 10 females), 24 HR subjects (ages 7–17, mean±sd: 11.2±2.7; 17 males,

6 females), and 35 normal comparison subjects from the community (ages 7–16, mean±sd: 11.1±2.5; 21 males, 14 females). Age and gender distribution of the groups were not significantly different. HR cases were screened for DSM-IV ADHD criteria, using the same procedure for ADHD cases. Eleven HR cases were diagnosed as also having ADHD (HR-A; mean±sd: age 10.8±2.8). Nine subjects in the HR-A subgroup met criteria for ADHD combined subtype, remaining two met criteria for ADHD inattentive subtype. The parents with schizophrenia (20 females, 1 male) were recruited among inpatients of a university psychiatry department. When a parent had more than one offspring eligible for inclusion to the study, all of the eligible children were recruited. Three such parents had two eligible children, contributing six children. This methodology was chosen in view of the reduced fertility in schizophrenia and the need for recruitment of as many HR subjects as possible; this approach was preferred as schizophrenia is a relatively rare disorder and we were not studying familial aggregation but only examining attentional and neurocognitive characteristics of the children concerned. The diagnosis of schizophrenia was established by Structural Clinical Interview (SCID-I), according to DSM-IV criteria, using all available information from the patient, the relatives, and the psychiatric records. All the SCID semi-structured interviews for axis I diagnoses were completed by trained raters (six modules, 25–60 min). The parents of ADHD subjects and normal comparison subjects were likewise screened for psychosis with SCID-I.

All the ADHD subjects were recruited from the child psychiatry outpatient clinic of the same university hospital. The DSM-IV ADHD diagnoses were made by the first author (OO), an experienced child psychiatrist, using the K-SADS-PL semi-structured interview. All the ADHD subjects included in the study met criteria for the combined disorder subtype. Almost all of the ADHD subjects and half of the HR-A cases were on methylphenidate. However, all subjects were required to be drug-free for at least 72 h prior to neuropsychological testing. This wash-out period has customarily been used in prior ADHD studies examining current neuropsychological function (e.g. Dougherty et al., 1999). None of the subjects were participating in ongoing psychotherapy. Exclusion criteria for both the HR and ADHD groups were: (i) presence of pervasive developmental disorder, and/or (ii) history of neurological disorder, or head trauma causing neurodevelopmental problems.

The normal comparison subjects were recruited from the community by local means. These subjects were also similarly screened for ADHD symptoms with the K-SADS-PL. All normal comparison subjects were also clinically screened for major depression, pervasive developmental disorders, substance abuse and psychotic disorders. Informed consent process was verbal as is customary given the literacy level of the parents. The parents could select to opt out of the study; none of the parents and their eligible high-risk children refused to participate.

2.2. Neuropsychological tests

2.2.1. Wechsler Intelligence Scale for Children-Revised Form (WISC-R)—

WISC-R consisted of 12 subtests that assessed verbal and performance abilities. Verbal subtests included Information, Similarities, Vocabulary, Comprehension and Digit Span. Performance subtests included Picture Completion, Picture Arrangement, Block Design, Object Assembly, and Digit Symbol. Verbal and Performance IQ scores are obtained from the test. The reliability and validity studies of the Turkish form of the WISC-R have been conducted (Savaşır and Şahin, 1978). While WISC-R is a relatively outdated form of the test, it is widely used, and updated forms had been translated into Turkish. Thirty-two controls, 35 ADHD and 20 HR subjects completed the WISC-R. The attrition was due to scheduling problems based on parental availability and suitable travel.

2.2.2. Stroop Color Word Interference Test (Stroop)—This test measures the ability of a subject to shift perceptual set with the changing demands, to inhibit a habitual behavior pattern and to behave in an unusual way. Deficits in these abilities result in perseveration, stereotypic behavior, and difficulty in controlling behavior. These functions are mainly frontal lobe functions. Previous studies have indicated that Stroop test also assesses information processing rate, and parallel processing of attended and non-attended stimuli, as well as attention (MacLeod, 1991). Stroop is a widely used and easily administered test that yields data readily comparable with other studies.

2.2.3. Wisconsin Cart Sorting Test (WCST)—WCST was developed by Berg (1948) and revised by Heaton et al. (1993). WCST measures abstract reasoning, building and canceling strategies, problem solving, maintaining attention, and mental flexibility abilities. These abilities are deficient in frontal lobe patients, and the deficiency in frontal lobe functions lead to perseveration. Like Stroop, WCST is one of the most widely used executive function tests. Only one HR subject was not available to take this test.

All the tests were administered by trained psychologists blind to a subject's diagnostic status. Total battery took almost 2.5 h. WISC-R and other tests were administered on separate sessions. Tests were given in a fix order in each session; WISC-R: Information, Picture Completion, Similarities, Picture Arrangement, Block Design, Comprehension, Object Assembly, and Digit Symbol; WCST was followed by Stroop.

2.3. Data analysis

The neuropsychological test scores of the groups were compared with analysis of variance (ANOVA) with diagnostic group (first normal comparison subjects, ADHD, HR) serving as the between-group factor; significant differences followed by post hoc Tukey HSD test. A second analysis with four diagnostic groups (normal comparison subjects, ADHD, HR-A and HR-NA) was also performed. Results of the second analysis commented only when different results from the first one emerged. We also transformed raw WCST categories completed, perseverative responses, and WISC-R Similarities to z scores on the basis of the scores of the control group, and averaged the z scores to obtain a composite abstraction–flexibility score, following Oie and Rund (1999). Two-tailed significance tests ($p < .05$) are reported throughout. The SPSS 10.0 statistical package was used for the analysis.

3. Results

3.1. Differences among controls, ADHD and HR subjects

Mean and standard deviations of the neuropsychological tests were summarized in Table 1. The ANOVA revealed that groups were significantly different on WISC-R Information ($F=4.75$, $df=2,84$, $p=.011$), Verbal IQ ($F=6.27$, $df=2,84$, $p=.003$), Performance IQ ($F=4.20$, $df=2,84$, $p=.018$), and summary score on abstraction–flexibility ($F=4.92$, $df=2,82$, $p=.010$). There were statistical trends for WCST total errors ($F=2.65$, $df=2,96$, $p=.076$), perseverative responses ($F=2.56$, $df=2,96$, $p=.083$) and percent correct variables ($F=2.74$, $df=2,96$, $p=.069$). Post hoc Tukey HSD revealed that both ADHD and HR groups had significantly lower WISC-R Information and Verbal IQ scores than controls. ADHD cases had worse WCST total errors, and percent correct variables than controls, however these differences were on trend level. The HR cases had significantly lower WISC-R Performance IQ score when compared with the control group.

3.2. Differences among controls, ADHD, HR-A, and HR-NA subjects

Only differences not evident in the previous section were reported here. There were additional significant group differences on WISC-R Comprehension ($F=2.71$, $df=3,81$, $p=.$

05), Picture Completion ($F=6.39$, $df=3,82$, $p=.003$), Picture Arrangement ($F=2.78$, $df=3,82$, $p=.048$), and Similarities scores ($F=3.53$, $df=3,82$, $p=.018$). HR-NA cases were not significantly worse on any of the cognitive measures than controls. Post hoc Tukey test indicated that HR-A cases had significantly lower Comprehension, Picture Completion, Picture Arrangement and Similarities scores when compared with controls, lower summary score on abstraction–flexibility than both controls and ADHD cases, and lower Performance IQ score than all of the other three groups.

4. Discussion

The results of this study indicated that compared to the normal comparison subjects the ADHD children had lower Verbal IQ scores, whereas the HR group had both lower Verbal and Performance IQ scores. This finding is consistent with previous studies showing lower IQ levels among the schizophrenia offspring (Byrne et al., 1999). A further study which compared neuropsychological profiles of ADHD cases and individuals with schizophrenia, reported that both groups had lower IQ scores than healthy controls (Oie and Rund, 1999). The HR cases also had lower WISC-R Picture Completion and Information scores, suggesting problems in visual comprehension and in obtaining knowledge, respectively (Lezak, 1997). Neither the ADHD nor the HR subjects per se had lower Block Design and Object Assembly scores, suggesting intact spatial organization capacity.

The ADHD cases had significantly lower WCST percent correct and total errors when compared with normal comparison subjects. A recent meta-analysis showed that percent correct and total errors are among the WCST variables with highest effect sizes across all studies investigating WCST performance of ADHD subjects (Romine et al., 2004). Our findings are therefore consistent with their conclusions. Raw WCST categories completed, perseverative responses and WISC-R Similarities scores were not statistically significant among the groups; however, HR subjects had significantly lower composite abstraction–flexibility score, suggesting deficits in this cognitive domain. This was consistent with a previous study that investigated the WCST performance of offspring of schizophrenia patients and found that their performance in mid-20s resemble that of schizophrenic patients (Wolf et al., 2002). The Stroop interference score was not significantly different among the groups, further suggesting that the executive control of the behavior was not impaired. However, both the ADHD and the HR groups did have lower mean WCST performance. Nevertheless, considering the small sample size the results must be interpreted with caution.

When the HR-A and HR-NA subgroups were compared separately, the results summarized in Table 1 suggest that HR-A subjects were significantly more impaired on most of the tests employed. The worse performance of HR subjects could be attributed to significantly lower performance of HR-A subjects. HR-A subjects also had more general neurocognitive problems, including abstraction–flexibility, verbal and visual comprehension when compared with ADHD subjects.

The results of the present study need to be interpreted with caution in the light of a number of important limitations. The sample size of our study was small, particularly when the multiple comparisons are taken into account. Nonetheless, the results were interesting in the light of the previous studies reporting that lower IQ and attention problems may be among the factors that predict emergence of schizophrenia among the HR offspring (Niemi et al., 2003; Parnas et al., 1982; Davidson et al., 1999), that the offspring of schizophrenia patients had neurobehavioral problems resembling ADHD (Marcus, 1987), and that the diagnosis of ADHD itself was more frequent in children at high-risk for schizophrenia. Finally, a factor which the present study did not investigate comes from further evidence that high-risk

children with ADHD had more psychotic-like clinical features when compared with high-risk children without ADHD (Keshavan et al., 2003).

Our results support and extend the previous findings in that: (i) the HR-A children with comorbid ADHD were the most impaired subgroup; (ii) the HR-A children had significantly lower performance scores on various WISC-R variables compared to ADHD subjects; and (iii) the HR-A children had more global neuropsychological deficits compared to ADHD subjects. Our results also support the notion that the HR-A offspring may have more extensive neuropsychological impairments mapping to broader brain region affected.

Supplementing these preliminary findings with studies using other methods, like neuroimaging studies, may highlight the brain regions that are affected differentially in these groups, yielding data about the similarities and differences of these neurodevelopmental conditions. However, it must be kept in mind that descriptive and “atheoretical” disorder definitions do not necessarily reflect neurobehavioral correlates. New studies using broader neuropsychological test batteries can reveal the differences and similarities between ADHD and HR-A cases. Significant differences between HR-A and HR-NA subjects may also have some practical implications. Since it seems that HR-A cases were the subjects with worst neuropsychological performance, this subgroup of cases clearly need more extensive treatment and support for these cognitive problems. Effects of cognitive mediation on these cases must also be studied.

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Table 1

Neuropsychological test scores of controls, subjects with attention deficit hyperactivity disorder (ADHD), offspring of schizophrenic patients (HR), with (HR-A) or without (HR-NA) ADHD

Test scores	Controls (n=35)	ADHD (n=41)	High-risk subjects		
			Total (n=24)	HR-NA (n=13)	HR-A (n=11)
WISC-R:					
Information ^a	10.6 (2.9)	8.7 (2.3)	8.4 (3.8)	9.7 (3.5)	8.4 (3.8)
Comprehension ^b	11.1 (3.5)	10.0 (3.5)	8.8 (3.9)	10.1 (3.4)	7.3 (4.0)
Similarities	11.6 (3.1)	9.9 (3.7)	9.5 (4.0)	11.1 (3.3)	7.7 (4.2)
Picture completion ^{c,b}	10.6 (3.1)	9.9 (3.7)	9.5 (4.0)	9.9 (3.7)	5.7 (3.6)
Picture arrangement ^b	10.5 (3.1)	10.9 (3.2)	10.9 (3.2)	9.0 (2.4)	7.1 (3.7)
Object assembly	10.5 (2.6)	11.1 (3.4)	10.2 (3.2)	11.3 (3.8)	8.7 (2.8)
Block design	11.6 (3.5)	10.7 (2.6)	10.1 (3.6)	10.7 (3.2)	9.7 (3.4)
Verbal IQ ^a	107.8 (14.7)	95.9 (13.7)	94.7 (19.8)	102.2 (12.7)	87.2 (23.2)
Performance IQ ^{d,e}	105.5 (13.9)	104.8 (14.2)	94.0 (18.6)	103.2 (13.8)	84.7 (18.8)
WCST:					
Categories completed	4.5 (1.9)	3.7 (1.9)	3.8 (1.9)	4.5 (1.8)	3.1 (1.8)
Total errors ^f	43.1 (25.0)	55.4 (22.2)	51.3 (22.9)	44.9 (24.4)	58.3 (19.9)
Perseverative responses	32.1 (24.2)	42.1 (28.3)	29.4 (15.7)	27.3 (15.3)	31.6 (16.7)
Percent correct ^f	62.8 (17.6)	54.0 (15.6)	58.3 (15.7)	63.0 (16.9)	53.2 (13.2)
Stroop interference	66.3 (39.8)	74.1 (41.3)	67.9 (30.0)	61.5 (26.9)	77.5 (34.3)

^aThe ADHD and the HR groups had worse performance than the controls, $p < .05$, post hoc Tukey HSD.

^bThe HR-A group had worse performance than the controls, $p < .05$, post hoc Tukey HSD.

^cThe HR group had worse performance than the controls and the ADHD group, $p < .05$, post hoc Tukey HSD.

^dThe HR group had worse performance than the controls, $p < .05$, post hoc Tukey HSD.

^eThe HR-A group had worse performance than the all other groups, $p < .05$, post hoc Tukey HSD.

^fThe ADHD group had worse performance than the controls, $p < .07$, post hoc Tukey HSD.