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Psychosis proneness and ADHD in young relatives of schizophrenia patients

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Abstract

Symptoms resembling the attentional deficit hyperactivity disorder (ADHD) are frequently observed in young relatives at risk for schizophrenia (HR). We examined the frequency of the ADHD syndrome and its relationship to psychosis related psychopathology and neurobehavioral abnormalities in young HR subjects ($n=29$) and healthy comparison subjects (HC; $n=30$). Thirty-one percent of HR subjects ($n=9$) had ADHD as a lifetime Axis-I diagnosis (HR-A). Compared to healthy comparison subjects, the HR-A group had impaired neurological function. The HR-A group but not the HR subjects without ADHD had higher scores on the Chapman's magical ideation and perceptual aberration scales. Thus, ADHD-like features are more prevalent in the HR population than the one described in the general population and are associated with more frequent psychosis-like clinical features. Longitudinal studies can clarify whether an "ADHD subgroup" within HR subjects predict an increased risk for future emergence of schizophrenia.

Keywords: Psychosis proneness; Young relatives; ADHD; HR subjects

1. Introduction

It is currently widely believed that schizophrenia is a neurodevelopmental disorder based on clinical, epidemiological, and neuropathological evidence (Murray and Lewis, 1987; Weinberger, 1987). However, the neurodevelopmental deviations that may predate the clinical manifestations of the illness have not been precisely characterized. One approach to study the early developmental and neurobehavioral markers of vulnerability to psychosis is to evaluate the first-degree relatives of schizophrenia patients who have an increased risk for developing the illness (Gottesman and Shields, 1982). Impaired attention is frequently seen among patients with schizophrenia and their high-risk (HR) relatives and has been considered as one of the robust markers of risk for the eventual emergence of the illness (Erlenmeyer-Kimling et al., 2000). Attention deficits have been shown to be present throughout the course of the illness in schizophrenia, are evident even before the illness starts, persist during treatment and are heritable (Cornblatt and Keilp, 1994).

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It is unclear whether the impairment in attention in the population at risk for schizophrenia is associated with the clinically diagnosed Attention Deficit Hyperactivity Disorder (ADHD). It has been shown earlier that the motor, perceptual, and attentional difficulties observed in the offspring of schizophrenia patients resemble the behavioral pattern defined as ADHD in the Diagnostic and Statistical Manual of Mental Disorders (DSM) (Marcus et al., 1987). In a retrospective study, Gomez et al. (1981) reported that 32% of the psychiatric inpatients reported symptoms similar to ADHD in their childhood. Only the psychosis subgroup of these inpatients had a significantly elevated incidence of attentional deficits. Prospective studies of children who eventually developed schizophrenia have reported an increased prevalence of attentional impairments (Cornblatt and Keilp, 1994). A high-risk study of 207 adolescent children of schizophrenic mothers showed that subjects who subsequently developed schizophrenia had a higher frequency of attentional impairments during childhood (Parnas et al., 1982). Menkes et al. (1967) followed 14 hyperkinetic children at a child outpatient psychiatric clinic and four of them were found to develop psychosis. While this (28%) high incidence could be due to biased selection of severely ill children, it does raise the question whether ADHD represents a factor for the emergence of psychotic disorders.

It is an intriguing question whether ADHD-like features in young relatives at risk for schizophrenia are associated with an increased frequency of schizophrenia-related psychopathology or ''psychosis-proneness''. Such psychosis proneness may underlie an inherited liability to schizophrenia (Lenzenweger and Moldin, 1990; Meehl, 1989). Several studies have documented the predictive value of subtle psychopathological manifestations for future emergence of psychosis. In particular, two scales, the magical ideation and perceptual aberrations (Chapman et al., 1994) have some predictive value. Some (Barnes et al., 2000; Lenzenweger et al., 1991), though not all studies (Franke et al., 1994; Laurent et al., 1999), suggest a relation between the psychometrically identified psychosis-proneness and attentional impairment. However, it is unclear whether such psychosis proneness is related to the attentional impairment in children and adolescents with a genetic predisposition to schizophrenia.

In this study, we examined the neurobehavioral parameters and psychosis proneness scores among a series of young offspring and siblings of schizophrenia patients (HR relatives) and a group of healthy comparison subjects. We hypothesized that the psychopathological features such as ADHD would be more frequent among HR relatives. We also predicted that the putative neurobehavioral indicators of vulnerability to schizophrenia (attentional measures, neurological abnormalities), as well as psychosis proneness scores will be elevated in the ADHD group as compared to the HC subjects and the HR subjects without any Axis-I psychiatric disorder.

2. Methods

This study was carried out at the Western Psychiatric Institute and Clinic (WPIC) of the University of Pittsburgh Medical Center. The study was approved by the Institutional Review Board of the University of Pittsburgh Medical Center. After a complete description of the study to the subjects, written informed consent was obtained. The parent/guardian also provided an informed consent for subjects whose age are less than 18. HR subjects were recruited by approaching parents who were patients in the Schizophrenia Services, and children and adolescents known to have a parent or sibling with schizophrenia from the Child Psychiatry Services.

2.1. Subjects

Structured clinical interviews were used; Schedule for Affective Disorder and Schizophrenia for School-Age Children (K-SADS) (Ambrosini et al., 1989) for ages 15 and below or the Structured Clinical Interview for DSM disorders (SCID) (First et al., 1995) for ages 16 and above. Interviews were conducted by trained interviewers and diagnoses were made using all the clinical and structured interview data at consensus meetings that included a senior psychiatrist. Diagnoses were made based on the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 1994). We excluded HR subjects that met any of the following criteria: (a) lifetime diagnosis of any DSM-IV psychotic disorder (since we were interested in identifying prepsychotic precursors); (b) full

scale IQ less than 70; (c) significant history of, or current, medical illness; (d) lifetime substance use disorder; (e) pregnancy or lactation; and (f) neurological disorders, epilepsy, family history of hereditary neurological disorder or head injury with loss of consciousness greater than 30 min. The HC subjects also met the above exclusion criteria and were also free of any Axis-I psychiatric disorder.

Subjects included 29 high-risk (HR) relatives (26 offspring and 3 siblings; age 9–22; 15 males and 14 females) and 30 healthy controls (age 9–22; 15.16 ± 4.69 years; 15 males and 15 females). The diagnostic breakup was as follows: no Axis-I psychopathology (HR-N) ($n=10$), those with Axis-I pathology but not ADHD (HR-NA) ($n=10$) and those with ADHD as their Axis-I diagnoses (HR-A) ($n=9$). The mean ages were 16.21 ± 2.82 years for HR-N, and 16.31 ± 3.67 years for HR-NA, and younger (12.51 ± 2.18 years) for the HR-A group. The age distribution did not significantly differ between the HC and HR groups ($F=1.84$; $df=55$; $p=0.15$). HR-N group had a male/female ratio of 4:6; the HR-NA had a male/female ratio of 4:6 and the HR-A group had a male/female ratio of 7:2. The sex distributions did not differ between the HC and the three HR groups (Chi square = 3.56; $df=3$; $p=0.31$). The IQ did not differ between the groups (HC: 111.56 ± 17.0; HR-N: 110.14 ± 13.7; HR-NA: 96.28 ± 17.32; and HR-A:106 ± 17.02; $F=1.63$; $df=43$; $p=0.20$).

The percentage of HR subjects with a DSM-IV diagnosis of ADHD was 31% ($n=9$), of whom two were of the inattentive type, one was of the hyperactive subtype, and six were of the combined subtype. The HR-A subjects had the following conditions in addition to ADHD: generalized anxiety disorder, $n=2$; oppositional defiant disorder, $n=2$; bipolar disorder, $n=1$. The diagnostic breakup among the HR-NA group was as follows: depressive disorder, $n=5$; adjustment disorder, $n=1$; separation anxiety disorder, $n=1$; opposition defiant disorder, $n=2$; and simple phobia, $n=1$.

2.2. Neurobehavioral assessments

The Continuous Performance Task (CPT)-Identical Pair version (Cornblatt et al., 1989) was selected for its ability to detect attentional impairments in the HR. CPT is frequently used to assess the severity of ADHD (Levy and Hobbes, 1997), as well as in high-risk studies of schizophrenia (Cornblatt and Keilp, 1994). Stimuli (four digit numbers or shapes) were presented on a computer screen (display time: 50 ms; interstimulus interval: 950 ms) and participants were instructed to press a button when the same stimulus appears consecutively. Scoring was completed by the computer; scores on d′ (d prime) are indicative of perceptual sensitivity (decreased signal/noise discrimination). Decreased d′ scores are indicative of attentional impairment.

The Buchanan and Heinrichs Neurological Evaluation Scale (NES) (Buchanan and Heinrichs, 1989) is a structured instrument for the assessment of neurological signs in schizophrenia and was administered to all subjects. We used a slightly modified version, with the inclusion of the palmomental reflex (Sanders et al., 1994). Total scores were computed, as well as the subscale scores (motor coordination, sensory integration, and motor sequencing) for analysis.

The HR subjects were assessed using two of the Chapman psychosis-proneness scales. The perceptual aberration and magical ideation scales (Chapman et al., 1978; Eckblad and Chapman, 1983), in particular, were chosen because they have been shown to have some predictive power for future psychosis (Chapman et al., 1994). An example of an item on the Perceptual Aberration Scale is "Parts of my body seem occasionally dead or unreal" (keyed true). An example of an item on the magical ideation scale is "Good luck charms don't work" (keyed false). These scales have been used in adolescent populations in previous studies (Obiols et al., 1999).

2.3. Data analyses

Data were checked for normality (Shapiro and Wilks W statistic) before conducting the parametric comparisons. When the distributions were nonnormal, appropriate transformations were carried out (square root transformations for the schizotypy scores). Statistical comparisons were between groups using the Analyses of Variance (ANOVA). Post-hoc comparisons were carried out, where appropriate, using the Neumann–Keuls tests. Alpha was set at $p<0.05$ (two-tailed).

3. Results

We compared the four groups for CPT (digits and shapes) d′ scores, neurological soft sign scores, and psychosis proneness scores on the Chapman scale (magical ideation and perceptual aberration). Table 1 shows the group comparisons. CPT d′ scores (digits) were significantly lower for HR subjects with ADHD as compared to the HR-N subjects. Significant group differences were seen in the NES scores; post-hoc tests revealed that the total average, motor coordination, and sensory integration subscale scores of the NES were increased in the HR-A group compared to the HR-N group. The sensory integration and motor coordination scores were also elevated in the HR-A group in comparison to the HC group. The motor sequencing was significantly higher in both the HR-A and HR-NA subjects, in contrast to the HR-N group.

Significant group differences were seen in the psychosis proneness scores. Using the post-hoc tests, the magical ideation scale scores (square root transformed) were significantly elevated in the HR-A group, compared to the HC group; the perceptual aberration scale scores were elevated in the HR-A group compared to both the HC and HR-N groups (Table 1 and Fig. 1a and b).

4. Discussion

A central feature common to ADHD and schizophrenia is the attentional dysfunction. In our study, we observed that the HR subjects with ADHD performed poorly on the CPT (digits) as compared to the HR subjects without any psychopathology. Earlier studies have shown that both high-risk offspring and schizophrenia patients have deficits in attention and poor performance on the CPT (Cornblatt and Keilp, 1994). Deficits in cognitive tasks involving the earliest phase of visual information processing by backward masking have been observed in schizophrenia (for review, see McClure, 2001), as well as ADHD (Rund et al., 1995). Both schizophrenia and ADHD children have deficits in verbal and spatial working memory (Karatekin and Asarnow, 1998b). Both disorders may be associated with diminished capacities of sensory/memory buffers and/or the availability and allocation of attentional resources.

The HR-A subjects also had more abnormal neurological soft signs compared to the HC subjects and the HR-N relatives. The motor sequencing task of the NES, which requires the mediation of the prefrontal cortex, showed significant impairment in the HR-A group as compared to the HR-N group. However, this was not specific to the HR-A group, the HR-NA

Table 1
Comparison of high-risk (HR) and healthy comparison subjects on neurobehavioral measures and psychometric indices of psychosis-proneness[a]

	HC	HR-N	HR-NA	HR-A	*F* (*df*)	*p*	Post hoc comparisons (Neumann–Keuls)
NES							
Sensory integration	0.38 (0.32)	0.31 (0.19)	0.50 (0.29)	0.71 (0.31)	3.42 (52)	0.02	HR-A > HC; HR-A>HR-N
Motor coordination	0.20 (0.29)	0.13 (0.16)	0.53 (0.53)	0.62 (0.31)	5.77 (52)	0.002	HR-A>HC; HR-A>HR-N
Motor sequencing	0.61 (0.55)	0.25 (0.31)	0.92 (0.53)	1.06 (0.65)	4.44 (52)	0.007	HR-A>HR-N HR-NA>HR-N
Total average	0.40 (0.27)	0.32 (0.13)	0.51 (0.32)	0.66 (0.27)	3.11 (52)	0.03	HR-A>HR-N
CPT							
Digits	1.21 (0.83)	1.71 (0.53)	1.32 (0.84)	0.64 (0.61)	2.93 (42)	0.04	HR-A < HR-N
Shapes	1.52 (0.85)	1.65 (0.76)	1.18 (0.92)	0.81 (0.96)	1.74 (42)	0.17	
Chapman scales							
Magical ideation	1.16 (0.82)	1.69 (0.62)	1.87 (1.20)	2.56 (1.27)	5.57 (55)	0.002	HR-A>HC
Perceptual aberration	0.73 (0.83)	0.91 (0.86)	1.62 (0.98)	2.02 (1.33)	5.47 (55)	0.002	HR-A>HC; HR-A>HR-N

[a] ANOVA. Healthy comparison subjects (HC), HR subjects with attention deficit disorder (HR-A), HR subjects with other psychopathology (HR-NA), and HR subjects with no psychopathology (HR-N).

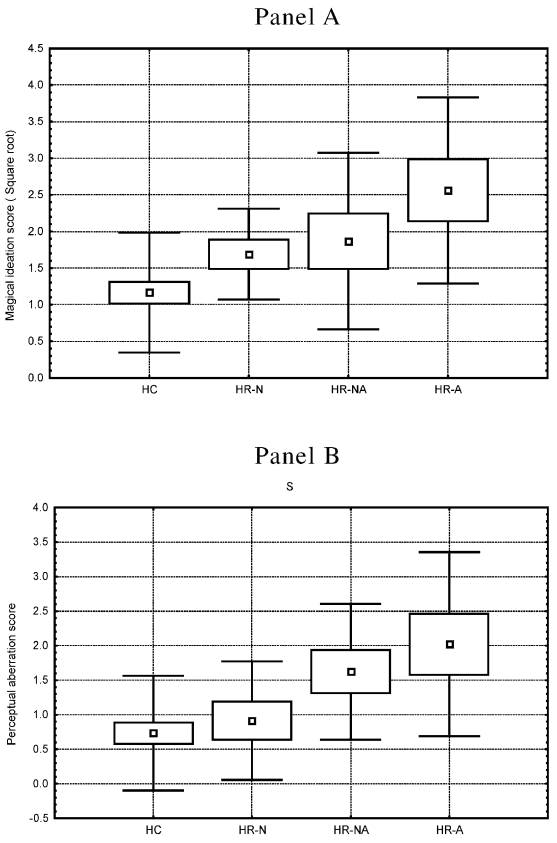

Fig. 1. Psychosis proneness scores (means, standard errors, and standard deviations) in healthy comparison subjects (HC), HR subjects with attention deficit disorder (HR-A), HR subjects with other psychopathology (HR-NA), and HR subjects with no psychopathology (HR-N). Panel A presents the magical ideation scale and Panel B presents the perceptual aberration scale scores (square root transformed).

subjects also had smaller elevations in this NES subscale. Dysfunction of the prefrontal cortex may mediate these neurological deficits (Buchanan and Heinrichs, 1989) and attentional deficits (Keilp et al., 1997); thus, these abnormalities point to a dysfunction in the prefrontal cortex in HR-A subjects similar to what is implicated in schizophrenia (Rund et al., 1999; Rund et al., 1995). In visual search tasks, both disorders (ADHD and schizophrenia) have a normal rate of parallel search but a slow rate of serial search. The impairment in the serial search in both ADHD and schizophrenia indicates that the neural connections in the frontal cortex and thalamus are inefficient (Karatekin and Asarnow, 1998a). These observations are also consistent with neuroimaging evidence implicating the prefrontal cortex in the pathophysiology of schizophrenia (Andreasen, 1999; Gilbert et al., 2000), as well as ADHD (Rubia et al., 1999). Thus, HR-A subjects may represent a subgroup of HR relatives who have neurobiological alterations similar to those observed in schizophrenia and ADHD; this suggests that they may be at an enhanced risk for developing the illness when they reach the age of risk for schizophrenia.

The observed elevations in the psychosis proneness scores among the HR-A subjects merit comment. Both psychosis-proneness or schizotypy (Chapman et al., 1994) and attentional impairments (Cornblatt and Keilp, 1994) have been considered to reflect an increased risk for the emergence of schizophrenia among the predisposed individuals. It follows, therefore, that young relatives at familial risk for schizophrenia, if they have features of both ADHD and psychosis proneness, are at a particularly heightened vulnerability to develop the illness. Prospective follow-up studies are therefore critically needed to examine this "enriched" high-risk group of prepsychotic relatives. Early identification of schizophrenia and related psychotic illnesses in such persons is likely to improve overall outcome and may even have a preventive value (Yung et al., 1998).

The possibility of some patients with schizophrenia having features similar to attentional deficit syndrome might be of therapeutic relevance. Earlier authors had argued (Bellack et al., 1987) that ADHD represents a precursor to schizophrenia in a distinct subtype of schizophrenia termed as "attention deficit disorder psychosis", which has a much varied symptomatology, anamnesis, therapeutic response (lack of/poor response to neuroleptics and favorable response to amphetamine-like drugs and tricylics), and outcome. Schizophrenia patients with history of childhood ADHD, compared to those without ADHD have more disturbances in the psychomotor development, a higher rate of soft neurological signs, emergence of childhood psychosis at a younger age, a poor response to neuroleptics, and a poorer outcome (Elman et al., 1998). Anecdotal case reports (Pine et al., 1993) of adult patients with ADHD and comorbid atypical psychosis suggest improvement following the treatment with a psychostimulant. It has been suggested earlier that stimulants may improve a unique, poorly

characterized group of chronically psychotic, neuroleptic refractory patients (Chiarello and Cole, 1987). Amphetamine has been reported to benefit cognitive function (Kirrane et al., 2000) and negative symptoms (van Kammen and Boronow, 1988) in schizophrenia and related spectrum disorders. Bellack et al. (1987) even suggested that a trial of stimulants could be used as a ''therapeutic test'' to differentiate schizophrenic syndrome and ADHD psychosis. However, the possibility that such treatment could lead to the emergence of psychosis among individuals at risk for schizophrenia should not be overlooked (Vitiello, 2001).

Our observation of a higher incidence of ADHD in the HR subjects (31%) as compared to the general population, 4–12% in primary care settings (Brown et al., 2001), raises the question of whether ADHD patients in general have a higher risk for developing psychosis in their adulthood. Literature on this issue is controversial. Anecdotal case reports suggest that some ADHD patients may eventually develop psychosis (Schmidt and Freidson, 1990), though it is unlikely if this is a common outcome of ADHD. A retrospective study (Russell et al., 1989) in schizophrenic children suggested that 40% of the subjects had a premorbid history of attentional problems and hyperactivity suggestive of ADHD. However, a prospective study of children with ADHD, who were followed up 15–21 years later, showed that 33% developed mental disorder; most of them had antisocial personality disorder and nonalcoholic substance use disorder, and none developed psychosis (Mannuzza et al., 1998). These disparities might be related to the possibility that ADHD is a heterogeneous syndrome; the risk for eventual emergence of schizophrenia may only be confined to a relatively small proportion of subjects who are at an increased familial risk for this disorder.

The strength of our study is that we examined young nonpsychotic first-degree relatives of schizophrenia patients who were studied during or prior to the age range of risk for developing schizophrenia. However, the small sample size and the lack of an ADHD comparison group are the limitations. These findings need to be confirmed with a larger sample size and using long-term prospective studies. Further studies also need to characterize the similarities and differences in the attentional impairments in relatives at risk for schizophrenia as compared to the ADHD population. If confirmed, our observations suggest the existence of a subgroup of HR individuals at an increased risk for schizophrenia, and may help detection of early vulnerability markers for schizophrenia.

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References

Ambrosini, P.J., Metz, C., Prabucki, K., 1989. Videotape reliability of the third revised edition of the K-SADS. J. Am. Acad. Child Adolesc. Psychiatry 28, 723–728.

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders, 4th edn. American Psychiatric Press, Washington, DC.

Andreasen, N.C., 1999. Understanding the causes of schizophrenia. N. Engl. J. Med. 340, 645–647.

Barnes, G.W., Rhinewine, J.P., Docherty, N.M., 2000. Perceptual aberration and schizotypy: a cautionary note. J. Neuropsychiatry Clin. Neurosci. 12, 98–99.

Bellack, L., Kay, S.R., Opler, L.A., 1987. Attention deficit disorder psychosis as a disgnostic criteria. Psychiatr. Dev. 3, 239–263.

Brown, R.T., Freeman, W.S., Perrin, J.M., Stein, M.T., Amler, R.W., Feldman, H.M., et al., 2001. Prevalence and assessment of attention deficit/hyperactivity disorder in primary care settings. Pediatrics 107, E43.

Buchanan, R.W., Heinrichs, D.W., 1989. The Neurological Evaluation Scale (NES): a structured instrument for the assessment of neurological signs in schizophrenia. Psychiatry Res. 27, 335–350.

Chapman, L.J., Chapman, J.P., Raulin, M., 1978. Body-image aberration in schizophrenia. J. Abnorm. Psychol. 87, 399–407.

Chapman, L.J., Chapman, J.P., Kwapil, T.R., Eckblad, M., Zinser, M.C., 1994. Putatively psychosis-prone subjects 10 years later. J. Abnorm. Psychol. 103, 171–183.

Chiarello, R.J., Cole, J.O., 1987. The use of psychostimulants in general psychiatry. A reconsideration. Arch. Gen. Psychiatry 44, 286–295.

Cornblatt, B., Lenzenweger, M.F., Erlenmeyer-Kimling, L., 1989.

The continuous performance test, identical pairs version: II. Contrasting attentional profiles in schizophrenic and depressed patients. Psychiatry Res. 29, 65–85.

Cornblatt, B.A., Keilp, J.G., 1994. Impaired attention, genetics, and the pathophysiology of schizophrenia. Schizophr. Bull. 20, 31–46.

Eckblad, M., Chapman, L.J., 1983. Magical ideation as an indicator of schizotypy. J. Consult. Clin. Psychol. 51, 215–225.

Elman, I., Sigler, M., Kronenberg, J., Gaoni, B., 1998. Characteristics of patients with schizophrenia successive to childhood ADHD. Isr. J. Psychiatr. Relat. Sc. 35, 280–286.

Erlenmeyer-Kimling, L., Rock, D., Roberts, S.A., Janal, M., Kestenbaum, C., Cornblatt, B., et al., 2000. Attention, memory, and motor skills as childhood predictors of schizophrenia-related psychoses: the New York high-risk project [In Process Citation] . Am. J. Psychiatry 157, 1416–1422.

First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 1995. The structured clinical interview for DSM IV and personality disorders. J. Pers. Disord. 9, 83–91.

Franke, P., Maier, W., Hardt, J., Hain, C., Cornblatt, B.A., 1994. Attentional abilities and measures of schizotypy: their variation and covariation in schizophrenic patients, their siblings, and normal control subjects. Psychiatry Res. 54, 259–272.

Gilbert, A.R., Spencer, S., Mankowski, I., Zeigler, M.R., Montrose, D.M., Rosenberg, D., et al., 2000. Thalamic volumes in first episode schizophrenic patients. Tenth Biennial Winter Workshop on Schizophrenia, vol. 41. Schizophrenia Research, Davos, Switzerland, p. 114.

Gomez, R.L., Janowsky, D., Zetin, M., Huey, L., Clopton, P.L., 1981. Adult psychiatric diagnosis and symptoms compatible with the hyperactive child syndrome: a retrospective study. J. Clin. Psychiatry 42, 389–394.

Gottesman, I.I., Shields, J., 1982. Schizophrenia: The Epigenetic Puzzle. Cambridge Univ. Press, New York.

Karatekin, C., Asarnow, R.F., 1998a. Components of visual search in childhood-onset schizophrenia and attention deficit hyperactivity disorder. J. Abnorm. Child Psychol. 26, 367–380.

Karatekin, C., Asarnow, R.F., 1998b. Working memory in childhood-onset schizophrenia and attention deficit/hyperactivity disorder. Psychiatry Res. 80, 165–176.

Keilp, J.G., Herrera, J., Stritzke, P., Cornblatt, B.A., 1997. The continuous performance test, identical pairs version (CPT-IP): III. Brain functioning during performance of numbers and shapes subtasks. Psychiatry Res. 74, 35–45.

Kirrane, R.M., Mitropoulou, V., Nunn, M., New, A.S., Harvey, P.D., Schopick, F., et al., 2000. Effects of amphetamine on visuospatial working memory performance in schizophrenia spectrum personality disorder. Neuropsychopharmacology 22, 14–18.

Laurent, A., Saoud, M., Bougerol, T., d'Amato, T., Anchisi, A.M., Biloa-Tang, M., et al., 1999. Attentional deficits in patients with schizophrenia and in their nonpsychotic first-degree relatives. Psychiatry Res. 89, 147–159.

Lenzenweger, M.F., Moldin, S.O., 1990. Discerning the latent structure of hypothetical psychosis proneness through admixture analysis. Psychiatry Res. 33, 243–257.

Lenzenweger, M.F., Cornblatt, B.A., Putnick, M., 1991. Schizotypy and sustained attention. J. Abnorm. Psychol. 100, 84–89.

Levy, F., Hobbes, G., 1997. Discrimination of attention deficit hyperactivity disorder by the continuous performance test. J. Paediatr. Child Health 33, 384–387.

Mannuzza, S., Klein, R.G., Bessler, A., Malloy, P., LaPadula, M., 1998. Adult psychiatric status of hyperactive boys grown up. Am. J. Psychiatry 155, 493–498.

Marcus, J., Hans, S.L., Nagler, S., Aurerbach, J.G., Mirsky, A.F., Aubrey, A., 1987. Review of the NIMH Israeli kibbutz-city study and the Jerusalem infant development study. Schizophr. Bull. 13, 425–438.

McClure, R.K., 2001. The visual backward masking deficit in schizophrenia. Prog. Neuropsychopharmacol. Biol. Psychiatry 25, 301–311.

Meehl, P.E., 1989. Schizotaxia revisited. Arch. Gen. Psychiatry 46, 935–944.

Menkes, M.M., Rowe, J.S., Menkes, J.H., 1967. A twenty-five year follow-up study on the hyperkinetic child with minimal brain dysfunction. Pediatrics 39, 393–399.

Murray, R.M., Lewis, S.W., 1987. Is schizophrenia a neurodevelopmental disorder? [editorial]. Br. Med. J. (Clin. Res. Ed.) 295, 681–682.

Obiols, J.E., Serrano, F., Caparros, B., Subira, S., Barrantes, N., 1999. Neurological soft signs in adolescents with poor performance on the continuous performance test: markers of liability for schizophrenia spectrum disorders? Psychiatry Res. 86, 217–228.

Parnas, J., Schulsinger, F., Schulsinger, H., Mednick, S.A., Teasdale, T.W., 1982. Behavioral precursors of schizophrenia spectrum. A prospective study. Arch. Gen. Psychiatry 39, 658–664.

Pine, D.S., Klein, R.G., Lindy, D.C., Marshall, R.D., 1993. Attention deficit hyperactivity disorder and comorbid psychosis: a review and two clinical presentations [see comments]. J. Clin. Psychiatry 54, 140–145.

Rubia, K., Overmeyer, S., Taylor, E., Brammer, M., Williams, S.C., Simmons, A., et al., 1999. Hypofrontality in attention deficit hyperactivity disorder during higher-order motor control: a study with functional MRI. Am. J. Psychiatry 156, 891–896.

Rund, R.B., Oie, M.A., Sundet, K., 1995. Backward masking deficits in adolescents with schizophrenic disorders or attention deficits hyperactivity disorder. Am. J. Psychiatry 153, 1154–1157.

Rund, B.R., Oie, M., Zeiner, P., Sundet, K., 1999. Span of apprehension in adolescents with schizophrenia or ADHD. Schizophr. Res. 40, 257–259.

Russell, A.T., Bott, L., Sammons, C., 1989. The phenomenology of schizophrenia occurring in childhood. J. Am. Acad. Child Adolesc. Psychiatry 28, 399–407.

Sanders, R.D., Keshavan, M.S., Schooler, N.R., 1994. Neurologic exam abnormalities in neuroleptic-naive, first-break schizophrenia: preliminary results. Am J. Psychiatry 151, 1231–1233.

Schmidt, K., Freidson, S., 1990. Atypical outcome in attention deficit hyperactivity disorder. J. Am. Acad. Child Adolesc. Psychiatry 29, 566–570.

van Kammen, D.P., Boronow, J.J., 1988. Dextro-amphetamine di-

minishes negative symptoms in schizophrenia. Int. Clin. Psychopharmacol. 3, 111–121.

Vitiello, B., 2001. Long-term effects of stimulant medications on the brain: possible relevance to the treatment of attention deficit hyperactivity disorder. J. Child. Adolesc. Psychopharmacol. 11, 25–34.

Weinberger, D.R., 1987. Implications of normal brain development for the pathogenesis of schizophrenia. Arch. Gen. Psychiatry 44, 660–669.

Yung, A.R., Phillips, L.J., McGorry, P.D., McFarlane, C.A., Francey, S., Harrigan, S., et al., 1998. Prediction of psychosis. A step towards indicated prevention of schizophrenia. Br. J. Psychiatry, Suppl. 172, 14–20.