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Psychopathology among offspring of parents with schizophrenia: Relationship to premorbid impairments

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Abstract

Introduction—A broad range of psychopathology, including externalizing disorders is seen in offspring at genetic risk for schizophrenia. However, it is unclear whether such psychopathology may underlie a higher predisposition to the premorbid antecedents of schizophrenia. We examined the prevalence and correlates of psychopathology in an ongoing study of offspring genetically at risk for schizophrenia.

Methods—Seventy five consenting high risk offspring (HR: offspring, age 15.68±3.27 years; male/female 34/41) and 82 matched comparison subjects (40 males and 42 females; age 15.92±3.0 years) participated in this study. Diagnoses were ascertained using structured psychiatric interviews and consensus meetings, including all available clinical information.

Results—Sixty (60%) of the HR offspring had one or more lifetime diagnosis of axis I psychiatric disorder. HR subjects with axis I psychopathology had significantly more soft neurological signs, poorer premorbid adjustment, and higher schizotypy scores as measured by Chapman psychosis proneness scales. Among those with psychopathology, HR subjects with externalizing disorders showed the most abnormal scores in schizotypy.

Discussion—A substantial proportion of HR offspring of parents with schizophrenia manifest a broad range of childhood psychiatric disorders. Psychopathology, especially externalizing disorders such as attention deficit hyperactivity disorder (ADHD) may represent a subgroup with an increased risk for schizophrenia spectrum disorders. This possibility needs to be examined by prospective follow-up studies, and would be of considerable importance to early diagnosis and intervention efforts in schizophrenia.

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Contributors

Dr. Matcheri S. Keshavan designed the study and wrote the protocol. Dr. Rajaprabhaka Rajarethinam and Dr. Debra Montrose managed the literature searches and data analysis. Dr. Vaibhav Diwadkar contributed to consensus diagnostic meetings. All authors contributed to and have approved the final manuscript.

Conflict of interest

There are no conflicts of interest.

Keywords

Schizophrenia; Genetics; Adolescents

1. Introduction

Schizophrenia is widely held to be a neurodevelopmental disorder (Murray and Lewis, 1987; Weinberger, 1987). The developmental brain abnormalities may originate during the prenatal period and continue through childhood and adolescence. The characteristic symptoms of schizophrenia, which typically emerge in the second or third decade of life, are preceded in many individuals by behavioral and psychological abnormalities dating back to early childhood. It remains unclear whether, and if so, which of these premorbid alterations may predict later emergence of schizophrenia or related psychopathology. Schizophrenia is a heritable disease and many unaffected family members have higher incidence of schizophrenia spectrum disorders and other mental illnesses. Studies of young relatives at high risk (HR), such as offspring of parents with this illness offer a valuable opportunity to characterize premorbid psychopathology in this illness.

Retrospective (Baum and Walker, 1995) and archival-observational studies (Walker et al., 1993) have identified cognitive abnormalities such as attentional and behavioral problems dating back several years before illness onset in schizophrenia. Several high-risk studies, some initiated as early as the early 1960s, have sought to characterize potential premorbid neurobehavioral markers (Cornblatt et al., 1999; Keshavan et al., 2005). These include increased frequency of cognitive and neurological abnormalities (Niemi et al., 2005; Schubert and McNeil, 2004), and premorbid adjustment deficits (Dworkin et al., 1991; Niemi et al., 2005).

Schizotypy, which refers to a set of personality characteristics and experiences related to psychosis, is one of the most frequently described premorbid psychopathological traits in persons with a genetic liability to schizophrenia. Schizotypy is elevated in children at risk for schizophrenia (Carlson and Fish, 2005) and is a sensitive and specific predictor of later development of schizophrenia spectrum disorder (Tyrka et al., 1995). Schizotypy has been found to be associated with attentional impairments in at-risk relatives, (Vollema and Postma, 2002) as well as in adult community volunteers (Bergida and Lenzenweger, 2006). Schizotypy is also associated with cortical gray matter losses in HR relatives (Diwadkar et al., 2006). It is therefore possible that attentional impairments and schizotypy might co-occur in individuals at increased genetic risk for schizophrenia.

A broad range of psychopathological manifestations emerge during adolescence and early adulthood, with a higher frequency of non-specific non-psychotic diagnoses in HR subjects including anxiety and depression (Amminger et al., 2000). In particular, a higher frequency of externalizing, or disruptive behavior disorders (attention deficit hyperactivity disorder, ADHD; conduct disorder, CD and oppositional defiant disorder, ODD) have been described (Keshavan et al., 2003b; Marcus et al., 1993; Rieder and Nichols, 1979; Ross and Compagnon, 2001; Silverton et al., 1988). These disorders have been collectively termed “externalizing” disorders and have been reported to indicate poorer outcome in subjects at risk for schizophrenia in early studies (Garnezy, 1970). Large scale population cohorts suggest that externalizing disorders in childhood may predict an increased prevalence of major psychiatric disorders including schizophrenia later in life (Robins and Price, 1991). Attention deficits have been found to be associated with features of schizophrenia spectrum disorders such as schizotypy (Gooding et al., 2006). For these reasons, it may be argued that externalizing disorders including attention deficit problems characterize a subgroup of HR

subjects with a higher propensity to manifest putative premorbid neurobehavioral alterations.

In this study being conducted since 1998, we examined the prevalence of psychopathological diagnoses (Diagnostic and Statistical Manual for Mental disorders; DSM-IV) in a series of HR offspring of parents with schizophrenia. We also examined whether HR subjects with psychopathology have elevations in quantitative indices of premorbid neurobehavioral measures (neurological signs, premorbid maladjustment, and schizotypy). We hypothesized that HR subjects with externalizing psychopathology (HR-EP) would have the most severe alterations, followed (in order of lesser severity) by those with non-externalizing psychopathology (HR-NEP), HR subjects with no psychopathology (HR-N) and healthy comparison (HC) subjects.

2. Method

2.1. Subjects

Seventy five individuals (34 males and 41 females, mean 15.68 ± 3.27 years range 9.52–21.83) with at least one parent suffering from schizophrenia or schizoaffective disorder were included in this study (high risk offspring; HR). The participants were identified at the Western Psychiatric Institute and Clinic (WPIC), Pittsburgh or related clinical sites. HR subjects were recruited by first approaching patients with schizophrenia with eligible offspring in our outpatient clinical services; we also recruited subjects via advertisements in community locations. Subjects with a DSM-IV diagnosis of a psychotic disorder (i.e. schizophrenia, schizophreniform or schizoaffective disorder) were excluded since our goal was to identify clinical characteristics of the HR subjects in the pre-psychotic phase of the illness. In addition subjects with a DSM-IV diagnosis of mental retardation, significant head injury, current substance abuse significant history of or current medical or neurological illness were also excluded. In all, 33 HR subjects were excluded prior to entry in the study because of not meeting the eligibility criteria. Eighty two age and sex matched healthy comparison (HC) subjects (40 males and 42 females; age 15.92 ± 3.8 years range 8.62–21.61) were also recruited from the same neighborhoods as the HR subjects. The HR and HC subjects did not differ in age ($t(155) = .41$; $P = .58$) or gender ($\chi^2(1) = .19$; $P = .67$). There were 21 HR and 13 HC children aged below 12 years. All experimental protocols were approved by the University of Pittsburgh Institutional Review Board. All subjects were provided written informed consent following full description of the studies. The parent or guardian also provided informed consent for subjects aged less than 18, and the subjects provided assent. The research participants were paid for their participation.

The parental diagnoses were ascertained by using Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) as well as a clinical consensus diagnosis. The raters interviewing HR and HC subjects were not blind to the parental diagnoses (this was difficult, since the assessor(s) were often involved in recruiting the participants from the clinics). The questions for the psychotic disorders are very similar between K-SADS and Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), but the K-SADS has extensive information on developmental disorders. For this reason, we used SCID-I in HR and HC participants, and we used the Behavioral disorders sections of K-SADS (Kaufman et al., 1997) as a supplement to the SCID. Life-time diagnoses were ascertained using DSM-IV criteria at consensus conference meetings attended by senior clinicians (MSK, DM). Functional status was assessed using the global assessment scale (GAS).

Schizotypy scores were obtained from the Chapman psychosis proneness scales that have shown previously to have predictive value for future psychosis (Chapman et al., 1994, 1978). The Chapman scales are true-false self-report questionnaires that measure positive

(magical ideation and perceptual aberration subscales) and negative schizotypy (social and physical anhedonia subscales). Examples of items include “The government refuses to tell us the truth about flying saucers (magical ideation)” and “Ordinary colors sometimes seem too bright to me” (perceptual aberration). We herein present only the MI and the PAS data, since we felt that many questions such as those pertaining to sexual interest and activities contained in the anhedonia subscales were not appropriate for the children who participated in this study.

Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al., 1982), using an interview with a reliable informant, typically a parent, was administered to assess psychosocial and personal functioning levels during various developmental age periods. In view of the relatively younger population, we used only the childhood subscale of PAS on which data were available in the majority of the participants. Higher scores indicate greater abnormality.

Neurological examinations were carried out by a trained rater using the Neurological evaluation scale (NES) (Heinrichs and Buchanan, 1988) modified to include the 13 most reliable items published previously by our group (Keshavan et al., 2003a). This scale yields two subscale scores: the cognitive-perceptual and Repetitive motor NES (Sanders et al., 2000).

Data analyses were carried out using Statistica software (version 6). *P* values were considered significant if $<.05$. For group comparisons, we divided the HR group into the HR-EP group with any externalizing disorder (ADHD, CD or ODD; $n=24$), those with axis I psychiatric disorder(s) other than externalizing disorders (HR-NEP; $n=21$), and those with no psychopathology (HR-N; $n=30$). We compared these groups by comparison to controls on each of the quantitative premorbid neurobehavioral indicators: childhood scores on PAS; NES (item averages for the cognitive-perceptual and repetitive motor subscales), and a composite score on schizotypy (Average of the mean item scores in the magical ideation and perceptual aberration scales). We first carried out an analysis of covariance (ANCOVA) with age as a covariate for each of the hypothesized pre morbid measures. Where significant, we conducted univariate comparisons (*t* tests) to examine pairwise differences across the four groups.

3. Results

3.1. Psychopathology in HR subjects

A total of 45 HR individuals out of 75(60%) were diagnosed with one or more DSM-IV axis I psychiatric disorder. Thirty HR subjects had a current axis I disorder and 15 were in remission at the time of entry into the study. Co-morbidity was frequent (18 of 45 HR subjects, 40%). The diagnostic breakup is presented in Table 1.

3.2. Comparison of HR subgroups and controls

The HR and HC groups did not differ in age ($df=155$; $t=.41$; $P=.68$) or gender ($\chi^2=.19$; $P=.67$). Highly significant group effects were seen, with HR subjects showing elevations across all the domains of premorbid measures. Analyses of variance suggested that the HR-EP group showed most prominent cognitive-perceptual NES abnormalities, followed by the HR-NEP and HR-N groups, by comparison to the healthy controls. The differences were not significant for the motor NES scores. Schizotypy scores were significantly higher in the HR-EP compared to the HR-NEP group (Table 2). HR-EP and HR-NEP groups did not differ in childhood premorbid impairment but were elevated compared to the HR-N and HC groups. The psychopathology groups were significantly impaired with GAS scores being lowest in the HR-EP group, and the HR-NEP group intermediate, relative to HR-N and HC subjects ($df=3, 128$; $F=54.82$; $P=.0000$).

Since Chapman scales have not been previously used in childhood populations, we reanalyzed this data using only subjects aged 15 or above. Both the magical ideation scale ($df=3, 91$; $F=5.9$; $P=.0009$) and perceptual aberration scale scores ($df=3, 91$; $F=7.47$; $P=.0002$) were significantly different across groups, being highest in the HR-EP group.

The childhood premorbid adjustment scales scores were significantly higher in all the HR subgroups (HR-EP group, $.27\pm.16$; HR-NEP $.34\pm.16$; HR-N $.17\pm.14$;) compared to healthy controls ($.09\pm.1$) ($df=3, 140$; $F=24.6$; $P=.0000$). Post-hoc pairwise t tests revealed that HR-EP and HR-NEP groups were both more abnormal compared to the HR-N group.

4. Discussion

Our findings clearly show that offspring of parents with schizophrenia have an increased frequency of a broad range of axis I psychopathology. A substantial proportion (60%) of genetically at-risk offspring had psychiatric disorders, many of them dating back to childhood, consistent with the neurodevelopmental model of this illness. Of interest is the high prevalence of neurodevelopmental, externalizing disorders as well as mood and anxiety disorders. Recent data from the Edinburgh High Risk study suggest that pre-illness, non-specific affective symptomatology may also be of considerable predictive power for later emergence of schizophrenia and related psychotic disorders. (Owens and Johnstone, 2006).

The high risk subgroups subdivided by psychopathology showed highly robust differences across all three domains of premorbid impairment (premorbid adjustment, NES and schizotypy), with the HR-EP group showing the most abnormalities, followed by the HR-NEP group for the first two domains. Previous studies have suggested a predictive value of premorbid adjustment, (Muratori et al., 2005) neurological abnormalities (Fish et al., 1965) and schizotypy (Chapman et al., 1994) for predicting schizophrenia spectrum disorders later. This suggests that cross-sectional categorical diagnoses during childhood and adolescence in young at-risk relatives may help identify subgroup(s) at enhanced high risk for eventual emergence of schizophrenia related psychopathology. HR subgroups with externalizing psychopathology appear to be particularly at risk. Accumulating literature points to the predictive value of the externalizing dimension for later psychopathology in childhood populations (Mesman and Koot, 2001; Robins and Price, 1991). Liability to externalizing psychopathology might be mediated by genetic factors that might overlap with the susceptibility to major psychiatric disorders (Krueger et al., 2002).

The association between schizotypy and externalizing disorders is of particular interest in view of the importance of the former as a potential trait measure of schizophrenia spectrum diathesis. This association is consistent with recent observations of a relationship between attentional impairment and schizotypy (Johnson et al., 2003). Schizotypal traits are highly associated with the familial diathesis for schizophrenia (Kendler and Diehl, 1993). Several studies suggest that schizotypy may have a predictive value for later schizophrenia in genetic high risk studies (Johnstone et al., 2005; Miller et al., 2002). The co-occurrence of schizotypy and attentional impairments may therefore represent a subgroup of genetic HR subjects with an increased risk for later emergence of schizophrenia spectrum disorders.

The psychopathology observed in offspring at risk for schizophrenia may not be diagnostically specific, and may also be seen in those at risk for other major psychiatric disorders. Similar to HR subjects at risk for schizophrenia, psychiatric disorders are more common in offspring at risk for alcoholism, with both externalizing and internalizing disorders being more frequent than controls (Hill et al., 1999). Offspring at risk for bipolar disorder are also more likely to have externalizing disorders such as ADHD, but mood disorders are more common in this population (Chang et al., 2000; Henin et al., 2005; Wals

et al., 2001). Offspring of depressive patients also have a similar pattern of psychopathology (Lieb et al., 2002). Additionally, children with ADHD also show elevated thought disorder scores (Caplan et al., 2001). Taken together, it appears that premorbid manifestations of attentional and behavioral pathology may cut across diagnostic boundaries; differentiation toward more specific patterns of psychopathology might evolve over time, and may be determined by variations in the neural circuitries involved (Keshavan et al., 2005).

Several methodological caveats necessitate interpretation of our findings with caution. First, given the fact that many participants were screened out of the study (including offspring of parents with severe illnesses may not have allowed their offspring to participate), it is possible that the results may not be generalizable to the high risk population as a whole. Second, the comparison subjects were screened to rule out personal or family history of mental illness and therefore do not represent general population. Third, these ratings and diagnoses could not be conducted strictly in a blind fashion (with the exception of the schizotypy scales which were self-rated) for practical reasons. Future studies ascertaining psychopathological and bio-behavioral markers of diathesis for schizophrenia need to consider blinded measurements and consider comparison samples more representative of the general population.

While studies of familial at-risk persons offer a way to potentially predict later emergence of schizophrenia, only a relatively small proportion will eventually develop the illness; therefore, use of schizophrenia narrowly diagnosed by DSM-IV as the end point for outcome prediction is not cost-effective. Rather, identifying premorbid/prodromal characteristics that may relate to the broad range of psychopathological precursors of psychosis risk, such as schizotypy, will give us a more effective “Close-in” strategy toward such efforts (McGorry et al., 2003). The approach to use presence of axis I psychopathology can therefore provide us a way of identifying an “ultra-high risk” group among genetically predisposed individuals that may eventually yield high predictive power, facilitating early diagnosis and intervention efforts.

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Table 1Diagnoses among HR offspring of schizophrenia parents ($n=75$)

<i>Externalizing disorders</i>	
Attention deficit disorder	15
Oppositional defiant disorder	8
Conduct disorder	6
<i>Non-externalizing disorders</i>	
Depression	11
PTSD	5
Bipolar disorder	2
Substance use disorder	4
Anxiety disorders	2
Phobia	2
Adjustment disorder	3
Enuresis	2
OCD	1
<i>No diagnosis</i>	30

The total numbers add up to more than 75 because of co-morbidity. 18/45 HR subjects with psychopathology had more than one diagnosis: (10 with two diagnoses; 7 with 3 diagnoses and 1 with 4 diagnoses).

Table 2
Schizotypy and neurological measures across HR subgroups divided by categorical axis I diagnoses

Schizotypy	Magical ideation		Perceptual aberration	
	Mean	SD	Mean	SD
1 HR-EP	24	0.26	0.18	0.14
2 HR-NEP	21	0.13	0.13	0.08
3 HR-N	30	0.15	0.11	0.09
4 HC	82	0.09	0.1	0.04
$d/=-3, 153;$ $F=11.1;$ $P=.0000$ $d/=-3, 153;$ $F=8.52;$ $P=.00002$ $1>2; 1>3;$ $1>4; 2>4; 3>4$ $1>2; 1>3;$ $1>4; 2>4; 3>4$				

Neurological signs	Cognitive- perceptual		Repetitive motor	
	Mean	SD	Mean	SD
1 HR-EP	24	0.65	0.5	0.59
2 HR-NEP	21	0.22	0.22	0.37
3 HR-N	30	0.3	0.42	0.39
4 HC	82	0.21	0.34	0.51
$d/=-3, 153;$ $F=8.35;$ $P=.00003$ $d/=-3, 153;$ $F=1.06; P=.37$ $1>2; 1>3; 1>4$ NS				

HR-EP: High risk subjects with externalizing psychopathology; HR-NEP: High risk subjects with non-externalizing psychopathology; HR-N: High risk subjects with no psychopathology; HC: healthy controls.