

# 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  $15.68 \pm 3.27$  years; male/female 34/41) and 82 matched comparison subjects (40 males and 42 females; age  $15.92 \pm 3.0$  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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## 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 neuro-behavioral 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  $15.68 \pm 3.27$  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

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