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Neurological abnormalities among offspring of persons with schizophrenia: Relation to premorbid psychopathology

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ABSTRACT

Background: Neurological Examination Abnormalities (NEA, often called "neurological soft signs") have been observed in early schizophrenia and may be heritable. We investigated the prevalence, and neurocognitive and psychopathological correlates of NEA among offspring of schizophrenia patients who are at increased genetic risk for this illness.
Methods: Neurological examinations were conducted on high risk (HR, $n=74$) and healthy comparison subjects (HS, $n=86$), using the Heinrichs–Buchanan scale. Cognitive–perceptual (CogPer) and repetitive motor (RepMot) subscores, and total NEA scores were computed. All HR and HS were assessed using K-SADS/SCID for diagnoses. Schizotypy was measured using the Magical Ideation and the Perceptual Aberration subscales (Chapman scale), attention using Continuous Performance Test (CPT-IP) and executive functions using the Wisconsin Card Sorting Test (WCST).
Results: CogPer ($F(1,160)=7.14$, $p=0.008$) but not RepMot NEA scores were higher in HR subjects compared to HS after controlling for age and sex. CogPer NEA scores were higher in HR subjects with axis I psychopathology compared to those without ($F(2,170)-6.41$, $p=0.002$). HR subjects had higher schizotypy scores (composite of the magical ideation and perceptual aberration scales) ($F(1,141)=23.25$, $p=0.000004$). Schizotypy scores were negatively correlated with sustained attention and executive functions. In addition, schizotypy was positively correlated with CogPer NEA scores.
Conclusions: Young relatives at increased genetic risk for schizophrenia show more frequent NEA. CogPer but not RepMot NEA scores were elevated, consistent with our prior observation of CogPer NEA being relatively specific for schizophrenia. The observed relationships between NEA, cognitive impairments, schizotypy and axis I disorders suggest that NEA may characterize a subgroup of HR offspring at an elevated risk for psychopathology.

1. Introduction

Neurological Examination Abnormalities (NEA), also called 'soft' neurological signs, are observed in a substantial portion of patients with schizophrenia. These are subtle neurological abnormalities comprising impairments in motor function and sensory integration, and persistence of primitive reflexes. NEA have been well documented in first episode antipsychotic naïve (Sanders et al., 1994; Venkatasubramanian et al., 2003), and treated subjects with schizophrenia (Chen et al., 2005), and may be more prominent in schizophrenia compared to other psychiatric disorders both among those with adult onset and

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adolescent onset (Heinrichs and Buchanan, 1988; Keshavan et al., 2003a; Woods et al., 1986; Zabala et al., 2006). NEA may also distinguish those at genetic risk for schizophrenia from those at risk for other mental disorders (Schubert and McNeil, 2004, 2005). Syndromal heterogeneity within schizophrenia may be related to NEA (Arango et al., 2000; Tosato and Dazzan, 2005). In addition, cognitive deficits are related to NEA in schizophrenia (Arango et al., 1999; Sanders et al., 2004) and among family members of subjects with schizophrenia (Hyde et al., 2007; Sanders et al., 2006). The significance of NEA is further highlighted by their association with poor premorbid function (Quitkin et al., 1976), earlier onset of the illness (Torrey, 1980), cognitive impairment (Arango et al., 1999; Flashman et al., 1996; Mohr et al., 1996), ventricular enlargement (Mohr et al., 1996) and poor long term outcome (Bombin et al., 2005; Heinrichs and Buchanan, 1988; Johnstone et al., 1990; Mohr et al., 1996; Torrey, 1980).

The etiology of NEA is uncertain although they point to abnormal neurodevelopmental trajectory with genetic underpinnings. In support of this proposition, NEA have been documented among subjects genetically at risk for developing schizophrenia (Gourion et al., 2003; Kinney et al., 1999; Schubert and McNeil, 2005; Woods et al., 1986) but who have not yet manifested the clinical symptoms of psychosis. Interestingly, in a study on a small sample of young healthy adolescents, first episode schizophrenia and non-schizophrenia patients, an inverse correlation of NEA scores with age among the healthy adolescents, a trend for inverse correlation among non-schizophrenia patients and no correlation with age among the schizophrenia patients was observed (Zabala et al., 2006). These observations suggest that NEA may be developmentally mediated, and tend to decrease in frequency as the brain matures. Such a process may be impaired among those at genetic risk for developing schizophrenia. NEA and the pathophysiology of schizophrenia may share a common genetic background that affects the neurodevelopmental trajectory. A recent preliminary study on eight multiplex multigenerational families with at least two members with schizophrenia in each family provides suggestive evidence for heritability of certain NEA (Sanders et al., 2006). The same authors observed that the heritable NEA correlated with many neurocognitive impairments that were found to be heritable in a larger set of multiplex multigenerational families (Gur et al., 2007). However, so far no specific genetic variant has been associated with NEA.

We have used an abbreviated version of the Neurological Evaluation Scale (NES) (Buchanan and Heinrichs, 1989). The abbreviated version resulted from inter-rater reliability studies (Sanders et al., 1998) and factor analyses (Keshavan et al., 2003a; Sanders et al., 2005; Sanders et al., 2000). Principal factors showed differences in relationships with diagnosis (Keshavan et al., 2003a), cognition (Sanders et al., 2004) and neuroanatomy (Keshavan et al., 2003a). We have found that cognitive-perceptual tasks are specifically impaired in schizophrenia among the psychotic disorders, are more strongly related with cognitive functioning, and are uniquely related to heteromodal cortex volume.

In this study, we examined whether the presence of NEA would identify young relatives at even higher risk for developing schizophrenia. As a first step in that direction, our goal was to examine whether NEA was associated with increased risk for axis I disorders and for schizophrenia spectrum psychopathology among offspring of schizophrenia patients. Based on prior results, we hypothesized that: (a) the NEA associated with cognitive domains will be increased among the offspring of schizophrenia patients compared to healthy controls, and (b) the cognitive NEA will be associated with increased frequency of psychopathology among offspring of schizophrenia patients. In addition, we also hypothesized that the cognitive NEA and schizotypy scores will be correlated with neuropsychological measures.

2. Methods

2.1. Subjects

A series of subjects who were deemed to be at an elevated risk for developing schizophrenia due to family history (HR, $n=74$) and matched healthy control subjects (HS, $n=86$) were recruited. The HR subjects were slightly younger (mean age, 15.09±3.62 years) than the HS (mean age 16.18±4.32 years; $t=1.73$, $p=0.086$). The gender distribution (HR, male 34, female 40; HS, male 41, female 45; $\chi^2=0.05$, $p=0.83$, NS) between the groups did not differ significantly. HR subjects were defined as those between the ages of 10 and 25 years who had at least one parent with schizophrenia, schizoaffective or schizophreniform disorder as defined in the DSM IV. HR subjects with a lifetime history of schizophrenia or schizoaffective disorder, mental retardation per DSM IV, significant current or previous head injury, medical or neurological illnesses were excluded. Subjects with current substance use disorder were excluded from the study. Healthy control subjects similar in age and gender distribution were recruited through local advertisements from the same geographical region as the HR subjects. After fully explaining the study procedures an informed consent was obtained from all subjects. For subjects below the age of 18 years we obtained consent from a parent or guardian, and informed assent from the participants. All study procedures were approved by the University of Pittsburgh Institutional Review Board.

2.2. Assessment of psychopathology

All HS and HR subjects were assessed by using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First, 1997), supplemented by the Behavioral Disorders sections of the K-SADS (Kaufman et al., 2000). Diagnoses among the parents were ascertained using the SCID-I. We ascertained the diagnoses using DSM-IV criteria at consensus conference meetings attended by senior clinicians (MSK, KMP, DM). Schizotypy was measured using the Chapman's Magical Ideation and the Perceptual Aberration scales (Chapman et al., 1978; Eckblad and Chapman, 1983). Large scale adult and adolescent studies of the Chapman scales show that these scales have robust psychometric properties and confirm their reliability and validity (Horan et al., 2008; Keshavan et al., 2003b; Lin et al., 2007). Composite schizotypy scores were calculated as an average of the Chapman's magical ideation and perceptual aberration scale scores.

2.3. Neuropsychological evaluation

Attention was evaluated using Continuous Performance Test-Identical Pair version (CPT-IP) (Cornblatt et al., 1989).