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Neurological soft signs and minor physical anomalies in patients with schizophrenia and related disorders, their first-degree biological relatives, and non-psychiatric controls

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Abstract

Background: Subtle neurological impairments and inconsequential minor anomalies of the face and limbs are manifestations of neurodevelopmental and ontogenic abnormalities that are consistently found at higher rates in individuals with schizophrenia compared to healthy controls. Limited research has been conducted on these traits among biological relatives of patients with schizophrenia. This study hypothesized that the mean NSS score and the mean MPA score would be greater in patients than controls and that first-degree relatives would have intermediate scores. Furthermore, it was hypothesized that NSS scores and MPA scores would not be correlated. This study also explored correlations between patients' NSS and MPA scores and their relatives' respective scores and sought to replicate the finding that NSS are associated with negative and disorganized symptoms of schizophrenia, whereas MPAs are not.

Methods: Patients with schizophrenia and related psychotic disorders ($n=73$), first-degree relatives ($n=44$), and non-psychiatric controls ($n=54$) were assessed. Measures included the Neurological Evaluation Scale, a structured examination for MPAs, and the Positive and Negative Syndrome Scale in patients. Analyses accounted for clustering within families.

Results: Both NSS and MPAs were greater in patients than controls, and first-degree relatives had intermediate scores. Furthermore, NSS and MPA scores were independent in all three groups. Correlations were found between patients' and their relatives' scores on one NES subscale (sensory integration) and total MPA score and several MPA regions (eyes, ears, and hands). This study replicated previous findings that in patients with schizophrenia, NSS are associated with negative, disorganized, and other domains of symptoms. Associations between MPAs and symptoms were sparse and inconsistent.

Conclusion: These findings suggest that NSS and MPAs represent two quite distinct markers of risk for schizophrenia that may stem from genetic factors, as well as from environmental/developmental influences. Future research on multivariable risk prediction models may benefit from the use of somewhat independent risk markers or endophenotypes.

Keywords: Minor physical anomalies; Neurological soft signs; Psychosis; Schizophrenia

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1. Introduction

Neurological "soft" signs (NSS)–including motor dyscoordination, difficulties with sequencing of motor tasks, the presence of primitive reflexes, and subtly impaired sensory integration–are suggestive of deficits that are not localized to a specific brain region and are not pathognomonic for a particular neurological disease. Substantial research documents higher rates of NSS in individuals with schizophrenia than in healthy controls (Boks et al., 2000; Bombin et al., 2005; Heinrichs and Buchanan, 1988) and those with other mental disorders (Boks et al., 2000; Krebs et al., 2000; Scheffer, 2004). NSS are observable in first-episode patients (Bachmann et al., 2005; Dazzan and Murray, 2002), even prior to antipsychotic administration (Chen et al., 2005; Keshavan et al., 2003; Scheffer, 2004). In fact, healthy children who later develop schizophrenia exhibit signs of neurological abnormalities, particularly motor dyscoordination, well before overt manifestations of the illness (Leask et al., 2002; Walker and Lewine, 1990). NSS are associated with more severe negative (Arango et al., 2000; Bombin et al., 2005; Chen et al., 2005; Malla et al., 1997; Prikryl et al., 2006; Yazici et al., 2002) and disorganized (Arango et al., 2000; Schroder et al., 1996) symptoms, though some have not found this correlation (Bartko et al., 1988; Braun et al., 1995).

Reports suggest that offspring of patients with schizophrenia, particularly those who develop the illness, have more NSS compared to other youth (Niemi et al., 2005; Schiffman et al., 2004; Schubert and McNeil, 2004). In accord, most (Chang and Lenzenweger, 2004; Egan et al., 2001; McCreadie et al., 2003; Niethammer et al., 2000) but not all (Tarbox and Pogue-Geile, 2006) studies report that biological relatives of patients manifest more NSS than individuals without an immediate family history. The severity of NSS appears to be graded, with patients showing the most, unaffected controls showing the fewest, and first-degree relatives falling in between (Rossi et al., 1990). This pattern suggests that the origin of NSS is at least partly genetic, and indicates that such abnormalities may be intermediate phenotypes, or endophenotypes (Cannon, 2005).

Minor physical anomalies (MPAs) are subtle signs of developmental abnormalities (Buckley, 1998; Sivkov and Akabaliev, 2004) that are assumed to represent markers of an insult during gestation while brain development simultaneously is occurring (Green et al., 1989; Lane et al., 1997; McNeil and Cantor-Graae, 2000a). MPAs are found at a higher frequency in patients with schizophrenia than in healthy individuals (Buckley et al., 2005; Dean et al., 2007; McNeil and Cantor-Graae, 2000a; see Weinberg et al., 2007 for a recent meta-analysis). In contrast to NSS, several studies report no association between MPAs and positive or negative symptoms (Lohr and Flynn, 1993; McGrath et al., 1995; Oosthuizen et al., 1998).

Research on MPAs in relatives of patients has produced mixed results. Several studies report that relatives have no MPA elevations and show frequencies similar to those in healthy controls (Gourion et al., 2003; Green et al., 1994a; Hans et al., 2005), while others report that relatives have elevated MPAs similar to patients (Gourion et al., 2004a; Ismail et al., 1998, 2000). The latter studies may suggest that the origin of MPAs is at least partly genetic, in addition to the more frequently cited potential environmental influence.

Only a few studies have assessed associations between NSS and MPAs. Most indicate that the two markers are not correlated (Gourion et al., 2003; Ismail et al., 2000; Kelly et al., 2005; Lawrie et al., 2001; O'Reilly et al., 2001), though there is one report of a positive association (Nizamie et al., 1989). In general, these findings suggest that NSS and MPAs may be distinct markers of predisposition toward schizophrenia. Because very few studies to date have assessed both markers within a sample including patients, relatives, and controls (Gourion et al., 2003, 2004b; Ismail et al., 2000), this study investigated both NSS and MPAs across these three groups. Based on the notion that both NSS and MPAs–like schizophrenia–occur as a result of genetic factors as well as environmental/developmental insult, it was hypothesized that the mean NSS score and the mean MPA score would be greater in patients than controls, and that first-degree relatives would have intermediate scores. Furthermore, it was hypothesized that NSS scores and MPA scores would not be correlated. This study also explored correlations between patients' NSS/MPA scores and their relatives' respective scores, and sought to replicate the finding that NSS are associated with negative and disorganized symptoms of schizophrenia, whereas MPAs are not.

2. Methods

2.1. Setting and sample

This study was conducted at a large, public-sector health system that serves a predominantly African American population. Patients ($n=73$) included 25 with schizophrenia, paranoid type; 22 with schizophrenia, undifferentiated type; 11 with schizoaffective disorder, depressive type; 8 with schizoaffective disorder, bipolar