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Frontal release signs among patients with schizophrenia, their first-degree biological relatives, and non-psychiatric controls

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ABSTRACT

Background: Frontal release signs (FRS) are a subset of neurological soft signs that are overrepresented among patients with schizophrenia and their unaffected relatives and may be correlated with neuropsychological functioning and chronicity of illness. This study sought to explore FRS and their associations with verbal memory and symptoms of schizophrenia in an African American sample of patients, and FRS and their associations with verbal memory and schizotypal features among first-degree relatives and non-psychiatric controls.

Method: FRS, verbal memory, schizophrenia symptoms (in patients), and schizotypal features (in relatives and controls) were assessed in 63 patients with schizophrenia and related disorders, 33 of their unaffected first-degree relatives, and 51 controls.

Results: Patients and their relatives displayed greater FRS than controls. Among relatives and controls, greater FRS were related to greater self-reported disorganized and interpersonal features of schizotypal personality disorder. FRS were not associated with patients' schizophrenia symptoms in the expected direction. In the entire sample, greater FRS were associated with poorer verbal working memory.

Conclusions: Because they are easy to assess, may be correlated with neuropsychological functioning, and appear to covary with level of genetic diathesis for schizophrenia, the study of FRS may shed light on the neurodevelopmental processes that underlie schizophrenia.

1. Introduction

For nearly a century, researchers have documented an elevated prevalence of widespread, subtle brain abnormalities among patients with schizophrenia (Arango et al., 1999; Ismail et al., 1998; Kraepelin, 1971; Mohr et al., 2003). Neurological "soft" signs (NSS) are subtle, observable signs of neurological impairment that cannot be localized to a specific brain region (Mohr et al., 2003). Patients with schizophrenia have significantly higher rates of NSS than unaffected individuals (Bombin et al., 2005; Compton et al., 2007a, Gupta et al., 1995; Heinrichs and Buchanan, 1998). These elevations in NSS exist even when controlling for the effects of antipsychotic medications (Chen et al., 2005; Gupta et al., 1995). Among patients with schizophrenia, NSS are related to greater cognitive and social impairment and more chronic course of illness (Johnstone et al., 1990; Kolakowska et al., 1985; Mohr et al., 2003).

Frontal release signs (FRS), also referred to as primitive or developmental reflexes, are a subset of NSS comprised of several motor reflexes, such as the grasp reflex. These reflexes are normally present in infancy and then typically are inhibited during the course of development, but they can be released from inhibition through neurological damage or degeneration (Schott and Rossor, 2003). FRS are uncommon among healthy adults (Jenkyn et al., 1985; Schott and Rossor, 2003), but they have been reported in 13–48% of patients with schizophrenia (Barnes et al., 1995; Boks et al., 2000; Gupta et al., 1995). Older patients with a chronic disease course and patients with earlier

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onset of schizophrenia display the highest prevalence (Biswas et al., 2007; Youssef and Waddington, 1988). NSS in general, and FRS in particular, are often found in a graded pattern with patients showing the most, controls displaying the fewest, and nonpsychotic relatives of patients falling in between patients and controls (Compton et al., 2007a; Ismail et al., 1998; Schubert and McNeil, 2004). Furthermore, in some studies, neurological abnormalities have been moderately to strongly correlated between patients and their unaffected relatives (Gourion et al., 2003; Ismail et al., 1998).

Although numerous studies document increased rates of cognitive deficits among patients with schizophrenia (Compton et al., 2006a; Neuchterlein et al., 2004), few studies have examined how FRS and cognitive impairments may be interrelated. An exception is a recent study conducted by Hyde et al. (2007). In a large Caucasian sample, they found that patients with schizophrenia displayed significantly higher FRS scores than either their unaffected siblings or healthy controls; no significant difference in FRS emerged between siblings and controls. The presence of certain FRS was related to poorer performance on neuropsychological measures among patients, such as full scale intelligence quotient (IQ), perseverative errors on the Wisconsin Card Sorting Test, and letter fluency. Because FRS are easy to assess and may be correlated with neuropsychological functioning (Hyde et al., 2007), they may be a convenient marker of the degree of neurological deficit in patients with schizophrenia.

There are numerous studies documenting the prevalence of NSS in patients with schizophrenia (Chen et al., 2005; Flyckt et al., 1999; Gupta et al., 1995; Madsen et al., 1999; Whitty et al., 2003) and several review articles discussing the association between NSS and cognitive functions (Arango et al., 1999; Mohr et al., 2003). However, there has been much less focused research attention on FRS, an interesting subset of NSS. Furthermore, although there have been numerous studies involving patients with schizophrenia and their nonpsychotic relatives (see Bombin et al., 2005), we are aware of only one study of FRS in relatives (Hyde et al., 2007). Furthermore, we are aware of no studies specifically examining FRS in other populations thought to be at high risk for schizophrenia, such as those with schizotypal personality features. Schizotypal personality disorder (SPD) is thought to reflect high genetic risk for schizophrenia, even though the full-blown phenotype of schizophrenia may never emerge (Lenzenweger, 1999). Indeed, several risk markers for schizophrenia, such as cognitive, social, and neuropsychological deficits, have been reported at elevated rates (though less prominently so) among individuals with schizotypal features (e.g., Bollini et al., 2007; Chok and Kwapil, 2005).

Therefore, the goals of the current study were to: (1) replicate the graded pattern of FRS with an African American sample of patients with schizophrenia and related disorders, their first-degree relatives (FDRs), and controls; (2) determine whether FRS are associated with symptom severity among patients and features of schizotypy among relatives and controls; (3) evaluate associations among FRS and verbal memory; and (4) assess for correlation between patients' and their own relatives' FRS. We expected that patients would display the most FRS, followed by relatives and then controls; that FRS would be continuously related to greater symptoms (among patients), greater schizotypal features (among relatives and controls), and poorer verbal memory (among patients and the entire sample); and that patients' FRS would be moderately correlated with their own relatives' FRS.

2. Materials and methods

2.1. Setting and sample

This study was conducted at a large, public-sector health system that serves a mostly low-income, African American population. A number of previous papers have been published using data from this well characterized sample, pertaining to: neurological soft signs and minor physical anomalies among patients, relatives, and controls (Compton et al., 2007a); neurological soft signs, minor physical anomalies, and schizotypy in relatives and controls (Bollini et al., 2007); an exploratory factor analysis of the Neurological Evaluation Scale (Compton et al., 2006b); verbal memory and olfactory identification ability (Compton et al., 2006a); and facial measurements in patients and controls (Compton et al., 2007b). To limit heterogeneity, the current analysis included only the African American participants (90% of the original sample). Patients with schizophrenia and related disorders ($n=63$) were recruited through the health system's outpatient and inpatient mental health programs. Some patients referred an FDR ($n=33$) to participate. Controls ($n=51$) were recruited from a medical clinic waiting room, from a food market near the health system, and through hearing of the project from other control participants.

Exclusionary criteria for all participants included: (1) inability to speak English, (2) substance dependence diagnosis not in full remission, (3) known mental retardation, and (4) history of significant head injury or neurological disease. Controls were excluded if they endorsed any personal or family history (in first- or second-degree relatives) of psychotic or mood disorders. Relatives were excluded if they endorsed a personal history of psychotic or mood disorders. Patients' diagnoses included: schizophrenia, paranoid type ($n=22$); undifferentiated type ($n=18$); disorganized type ($n=3$); catatonic type ($n=1$); schizoaffective disorder, bipolar type ($n=6$); schizoaffective disorder, depressive type ($n=11$); and psychotic disorder not otherwise specified ($n=2$).

2.2. Procedures and materials

To determine diagnoses, all participants were administered the psychotic disorders, mood disorders, and substance use disorders modules of the *Structured Clinical Interview for DSM-IV Axis I Disorders* (SCID-I) (First et al., 1997a). To measure symptom severity in patients, a doctoral-level clinical researcher administered the *Positive and Negative Syndrome Scale* (PANSS) (Kay et al., 1987). The standard three subscale scores of positive symptoms, negative symptoms, and general psychopathology were used, as well as a disorganization dimension calculated based on a previously reported factor analysis (Peralta and Cuesta, 1994).

To assess for schizotypal personality disorder (SPD) features, relatives and controls participated in the SPD module of the *Structured Clinical Interview for DSM-IV Axis II Disorders* (SCID-II) (First et al., 1997b). For this interview, nine DSM-IV