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Sexual dimorphisms and prediction of conversion in the NAPLS psychosis prodrome

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ABSTRACT

Sex differences in age at onset, symptomatology, clinical course (see Walker et al., 2002) and functional impairment (Thorup et al., 2007) are well documented in psychosis. The general pattern of findings is that males manifest an earlier onset, more severe symptoms and poorer prognosis than females. Limited studies examining individuals at clinical high-risk (CHR) suggest a similar pattern of sexual dimorphism (Holtzman et al., in review; Corcoran et al., 2011). As part of the North American Prodrome Longitudinal Study (NAPLS), the current study prospectively examined sexual dimorphisms in relationships among CHR symptoms, childhood (premorbid) academic and social functioning, baseline social and role functioning, and conversion to psychosis. Subjects included 276 (113F/163M) CHR NAPLS participants (ages 12–36.8 years). All measures/criteria were assessed at baseline except conversion status, assessed at 6-month intervals up to 30 months. Results show sex differences in baseline social and role functioning (though not in early childhood adjustment) that predate psychosis onset, with sexually dimorphic patterns in relation to prodromal symptoms. Among male (but not female) CHRs, baseline social functioning and positive prodromal symptoms predicted conversion. These findings help elucidate early course of vulnerability for, and maximally sensitive and specific etiological and prediction models of, psychosis conversion. Findings highlight the importance of considering sexually differentiated predictors of longitudinal course and outcome, in the context of emerging risk profiles. This may optimize efforts at early identification and individually tailored preventive interventions targeting different neurobiological markers/systems and/or cognitive-behavioral approaches. We speculate a contemporary, multidimensional model of psychosis risk that posits a role of sexually dimorphic, genetically linked influences that converge with a modulating role of gonadal hormones (see Walder et al., 2012) across a temporally sensitive neurodevelopmental trajectory towards conferring risk.

1. Introduction

Sex differences in age at onset, symptomatology, and clinical course are well documented in the literature on schizophrenia and other psychoses (see Walker et al., 2002; Salem and Kring, 1998; Seeman, 1982). Males tend to manifest an earlier onset, more severe negative symptoms, less severe affective symptoms, and poorer prognosis than females (see Walker et al., 2002). Among early competing theories explaining these sexually dimorphic patterns (see Castle et al., 1995) were those positing a protective role of gonadal hormones (e.g., Estrogen Hypothesis; see Häfner et al., 1991; Riecher-Rössler and Häfner, 1993; Seeman and Lang, 1990) versus subtypes of schizophrenia to which the sexes are differentially vulnerable (e.g., males more susceptible to a 'neurodevelopmental' subtype that yields a more prominent deficit syndrome) (Castle and Murray, 1991). More contemporary integrative models consider the complex interplay of these with factors such as sex differences in obstetric complications, psychosocial influences, stress sensitivity, genetic liability/familial transmission and gene expression, including a neurodevelopmental perspective.

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Although sex differences have not been studied extensively in individuals at clinical high-risk (CHR) for psychosis, limited findings suggest a similar pattern of sexual dimorphism. Although several terms have been used to refer to samples identified to be at-risk based on clinical criteria (e.g., prodromal, ultra high-risk, clinical high-risk), the present paper uses CHR to refer to all high-risk samples. One recent report from the North American Prodrome Longitudinal Study (NAPLS) showed sex differences in baseline symptom severity in a large, CHR sample; high-risk males experienced more severe negative and disorganized symptoms, whereas positive and mood symptoms were not sexually differentiated (Holtzman et al., in review). Another smaller, recent CHR study also demonstrated more negative symptoms among high-risk males than females (Corcoran et al., 2011). These findings replicate and extend earlier retrospective findings from smaller high-risk and prodromal studies (Willhite et al., 2008).

Characterization of CHR phenomenology is of high priority given that psychosis prevention strategies are limited by emphasis on late-emerging positive symptoms, which captures the period after disability is relatively well established (see Cornblatt et al., 2007, 2011). Better delineation of sexual differentiation during the prodrome holds important value towards 1) elucidating theoretical models including a dimensional perspective of psychosis-proneness (a la Meehl, 1962), 2) understanding neurobiological underpinnings of psychosis and 3) refining existing multivariate models (e.g., Cannon et al., 2008) towards predicting who is at greatest risk for psychosis and in greatest need of intervention (see Holtzman et al., in review). In turn, this may implicate sexually differentiated strategies of identifying individuals at greatest risk for psychosis and preventive intervention.

Sexual dimorphisms in functional impairment are also well documented among psychotic patients, with more impaired social (Thorup et al., 2007) and premorbid (see Walker et al., 2002) functioning, as indicated by greater premorbid academic and occupational deficits (McGlashan and Bardenstein, 1990) among males. There is, however, a dearth of prospective studies examining sex differences in role functioning in CHRs. Thus, our understanding of sex differences in the longitudinal course and predictive power of premorbid functional deficits is limited. Yet, several reports demonstrate significant social and role functioning deficits in CHR (Cornblatt et al., 2011; Corcoran et al., 2011; Woods et al., 2009). Studies show that conversion to psychosis is predicted by worse baseline functioning (Corcoran et al., 2011; Dragt et al., 2011; Yung et al., 2003; Tarbox et al., in press). Similarly, recent NAPLS studies revealed poorer childhood social functioning (Tarbox et al., in press), and baseline social (and to a lesser extent role) functioning (Cornblatt et al., 2011) predicted conversion to psychosis among CHRs. One CHR study found, despite no sex differences in symptoms or functioning, an interaction effect of recovery pattern. Women followed a progressive, sustained course of clinical improvement; whereas, among men, psychotic episode onset yielded faster and longer deterioration (Lemos-Giráldez et al., 2009). Overall, predominantly social, and to a lesser extent role, functioning deficits appear to be key conversion predictors in CHR samples.

Similar to schizophrenia patients, there is some evidence that only negative symptoms in CHRs are associated with greater social (Corcoran et al., 2011; Cornblatt et al., 2007) and role (Cornblatt et al., 2007) functioning deficits, and school failure (Cornblatt et al., 2003). One CHR study, however, showed a relationship between more severe positive symptoms and global functioning deficits (Svirskis et al., 2007), and another concluded that disorganized and general, nonspecific (but not positive or negative) symptoms are linked with more pronounced social functioning deficits (Shim et al., 2008). Inconsistencies may be attributable to heterogeneity in measures and/or sample characteristics. If study samples vary in sex ratio, and there are sex differences in the direction or strength of associations between symptoms and social/role functioning among CHRs, these may obscure the pattern of findings.

Further elucidation of sexual dimorphisms during the prodrome to psychosis, particularly among larger samples, is critical to understanding illness etiology and generating more powerful predictive models. Longitudinal studies of CHR samples, a substantial subgroup of who are 'true' prodromals, hold promise for elucidating sex differences in the antecedents and course of the prodrome to psychosis.

The current study examined sex differences in the relationships among symptoms, childhood academic and social functioning, baseline social and role functioning, and conversion to psychosis among CHR adolescents and young adults.

2. Materials and methods

2.1. Participants

Participants included the subset of 276 (113F/163M) CHR NAPLS participants (ages 12–36.8 years; $M = 18.27$, $SD = 4.64$) for whom at least partial data were available on measures of premorbid functioning (social adjustment, academic), current global functioning (social, role) assessed at baseline, and three symptom dimensions (positive, negative, disorganized) rated at baseline on the Structured Interview for Prodromal Symptoms (SIPS). The majority of the sample was Caucasian (77.2%). Exclusion criteria for NAPLS included a history of a DSM-IV-TR Axis I psychotic disorder, mental retardation (accompanied by an IQ cutoff score of 70), or neurological disorder. Participants for whom follow-up data was not available at the 6-month assessment or later, or otherwise did not have conversion follow-up data were excluded. Forty-eight females (42.5%) and 67 males (41.1%) were on psychotropic medications at baseline (data were not available for 2 females and 11 males).

2.2. Procedures

Several measures assessing premorbid childhood academic and social functioning, baseline global (social, role) functioning, baseline prodromal symptomatology, prodromal criteria, and Axis I diagnostic criteria for DSM-IV were administered to all participants at the baseline assessment. After baseline assessment, patients were assessed for conversion status at 6-month intervals up to 30 months.

2.3. Measures

2.3.1. Structured Interview for Prodromal Symptoms (SIPS; Miller et al., 2002)

The SIPS was used to assess baseline prodromal symptomatology and longitudinal conversion status. The SIPS contains an instrument, the Scale of Prodromal Symptoms (SOPS), comprised of 29 items assessing positive, negative, disorganized and general symptom severity. This study examined the three key symptom dimensions (positive, negative, disorganized) that capture the cardinal features of psychosis. For each dimension, an index of average symptom severity was derived. Index ratings reflected the average score on a seven-point scale (0–2 = non-prodromal symptoms, 3–5 = prodromal level symptom, 6 = psychotic level symptom).

2.3.2. Prodromal criteria

To identify participants who met prodromal criteria, the Criteria of Prodromal Syndromes (COPS; Miller et al., 2002) were used. Prodromal syndromes include Attenuated Positive Symptom Syndrome (APSS), Genetic Risk and Deterioration Syndrome (GRDS), and Brief Intermittent Psychotic Syndrome (BIPS). APSS is characterized by the onset or worsening of sub-psychotic symptoms within the last 12 months, occurring with a frequency of at least once per week. GRDS entails the presence of a genetic risk for psychosis, defined by having a first-degree relative diagnosed with a psychotic disorder along with a decline of at least 30% in global functioning