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Sex Differences in Symptom Presentation in the Psychosis Prodrome

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Sex Differences in Symptom Presentation in the Psychosis Prodrome

By

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B.A., Emory University, 2003

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An abstract of
A thesis submitted to the Faculty of the
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Abstract

Sex Differences in Symptom Presentation in the Psychosis Prodrome
By Carrie W. Holtzman

There are well-established sex differences in the presentation and course of schizophrenia that contribute to the heterogeneity of the disorder, but the extent to which these sex differences pre-exist the onset of psychosis is unclear. The present study examines sex differences in symptom presentation in individuals at high risk for psychosis (i.e. "prodromal") with two aims: to determine if sex differences in the prodrome mirror those seen in patients diagnosed with schizophrenia and to test whether different combinations of prodromal symptoms predict conversion to psychosis separately for males and females. The Structured Interview for Prodromal Symptoms (Miller et al., 2002) was used to assess 212 participants at baseline and a six-month follow-up, 47 of whom converted to psychosis within 24 months. Results indicated that prodromal males experienced more negative and disorganized symptoms, consistent with literature in patients diagnosed with schizophrenia. There were no sex differences in positive or mood symptoms. Prodromal symptoms predicted conversion differently for males and females. This study suggests that sex differences in symptoms presentation predate the onset of psychosis and that, accordingly, sex must be taken into account in generating accurate prediction models.

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Schizophrenia is complex, heterogeneous, and debilitating neurodevelopmental disorder that affects approximately 1% of the population (American Psychiatric Association, DSM-IV-TR, 2000). Recent research indicates that it is a syndrome that has varied etiological determinants (Tandon, Keshavan, & Nasrallah, 2008; Craddock, O'Donovan, & Owen, 2007) and that it shares genetic and other etiologic factors with psychosis, broadly defined (Post, 2010; Dutta, Greene, Addington, McKenzie, Phillips, & Murray, 2007; Tamminga & Davis, 2007). Thus, although the present paper uses the term "schizophrenia" and draws on research on patients formally diagnosed with the syndrome, it is likely that it overlaps etiologically with a spectrum of psychotic disorders.

Studies have consistently shown sex differences in many aspects of the phenomenology of the schizophrenia, including differences in incidence/prevalence, age at onset, course, premorbid functioning, and symptomatology (Leung & Chue, 2000; Taylor & Langdon, 2006; Goldstein, 1997; Salem & Kring, 1998; Bardenstein & McGlashan, 1990; Shtasel, Gur, Gallacher, Heimberg & Gur, 1992). Research on sex differences is considered important because it has the potential to shed light on etiological processes that may differ for males and females, as well as the modulating effect of sex on illness expression. Such effects may reflect psychosocial influences, biological differences between the sexes, such as hormonal influences, or a combination of both.

Although it is well established that sex is a significant contributor to the heterogeneity in the initial presentation and course of the disorder (Leung & Chue, 2000; Salem & Kring, 1998), what remains unknown is whether there are sex differences in preclinical presentation, i.e. prior to the onset of psychosis. Thus, it is not known

whether sex is linked with the early subclinical or "prodromal" antecedents to clinical onset. Because the prodromal period is increasingly viewed as the likely point of entry for preventive interventions, it is important to understand differences between males and females in the presentation of this stage.

The present study examines sex differences in the onset and course of prodromal symptoms, with two general aims. The first goal is to determine whether there are sex differences in prodromal symptoms that mirror the symptom differences that have been documented in diagnosed patients with schizophrenia and other psychoses. The second objective is to examine sex differences in prediction to conversion, in order to determine whether different constellations of prodromal symptoms are linked with conversion in males and females.

Sex Differences in the Incidence and Prevalence of Schizophrenia

Although earlier estimates of the incidence of schizophrenia suggested that rates were equal between men and women, more recent studies have found that in cases diagnosed prior to middle age, men outnumber women at a ratio of approximately 1.3:1 to 2:1 (for a review, see Aleman, Kahn, & Selten, 2003, as well as Castle, Wessely, & Murray, 1993; Iacono & Beiser, 1992; Goldstein, 1997). The magnitude of the sex difference in incidence appears to increase as the diagnostic system for identifying new cases becomes more stringent (Goldstein, 1997; Castle et al., 1993), though one study in a large community sample found the sex difference regardless of diagnostic stringency (Iacono & Beiser, 1992). After middle age, the ratio shifts in favor of higher rate of onset in women, with a male to female ratio of .5:1 (Castle et al., 1993). Overall, it appears that schizophrenia is equally prevalent in males and females, with the preponderance of

males in younger samples balanced by the greater number of females developing the disorder later in life (Leung & Chue, 2000; Bardenstein & McGlashan, 1990; Räsänen, Pakashlahti, Syvälahti, Jones, & Ishohanni, 2000; Castle et al., 1993; Tang, Gillespie, Epstein, Mao, Jiang, Cai, et al., 2007). There is a higher prevalence of schizoaffective disorder among women (Bardenstein & McGlashan, 1990), but the data are mixed regarding a sex difference in incidence (Bardenstein & McGlashan, 1990; Laursen, Munk-Olsen, Nordentoft, & Mortensen, 2007; Iacono & Beiser, 1992).

Sex Differences in Age-at-Onset

One of the most well-established findings in schizophrenia research is the presence of a sex difference in age at onset (for reviews, see Leung & Chue, 2000; Taylor & Langdon, 2006; Salem & Kring, 1998; Bardenstein & McGlashan, 1990; Angermeyer & Kuhn, 1988). Studies consistently demonstrate that males have a younger age at onset no matter the criteria used to define onset, with a single modal peak between 18-25 years. There are multiple modes for onset in females, with the first occurring in the mid-20s to early 30s, followed by another in the mid-40s to mid-50s, and another after age 65. However, recent research indicates that the presence of a family history of psychosis eliminates the sex difference in age at onset (Esterberg, Trotman, Holtzman, Compton, & Walker, 2010; Könnecke, Häfner, Maurer, Löffler, & an der Heiden, 2000; Leung & Chue, 2000; Salem & Kring, 1998), such that females with a family history have an earlier onset than females without.

Sex Differences in Course of Illness

Another consistent finding is that women with schizophrenia tend to have a less severe course of illness and a better overall prognosis (for reviews, see Leung & Chue,

2000; Bardenstein & McGlashan, 1990; Räsänen et al., 2000; Salem & Kring, 1998; Angermeyer, Kuhn, & Goldstein, 1990). Female patients tend to experience fewer relapses, fewer hospitalizations, briefer hospitalizations, more rapid symptom remission, and better response to traditional antipsychotic medications than their male counterparts (Bardenstein & McGlashan, 1990; Taylor & Langdon, 2006; Leung & Chue, 2000; Räsänen et al., 2000; Salem & Kring, 1998). A study of sex differences across multiple psychotic disorders (schizophrenia, schizoaffective, and affective with psychotic features) found that men had a more chronic course no matter what their diagnosis (Morgan, Castle, & Jablensky, 2008).

Women also tend to have better prognoses in social and occupational functioning (Leung & Chue, 2000; Räsänen et al., 2000; Bardenstein & McGlashan, 1990; Thorup, Petersen, Jeppesen, Ohlenschlæger, Christensen, Krarup, et al., 2007), are more likely to live independently (Leung & Chue, 2000; Thorup et al., 2007), and report higher quality of life than men (Shtasel et al., 1992). A review of outcome studies by Angermeyer et al. (1990) was more equivocal, with approximately half of the 102 studies included finding better outcomes in women, though it is possible that the lack of consistency is due to differences in stringency of diagnostic criteria, such that when stricter diagnostic criteria are used, the sex difference disappears (Leung & Chue, 2000).

Questions remain about the duration of the female advantage with respect to outcomes, with evidence suggesting that the sex difference in outcome diminishes over time, especially after a decade or more (Leung & Chue, 2000; Salem & Kring). Furthermore, in late-onset cases (i.e. onset after 40 years old), women show a worse

course of illness, spending more days in the hospital than their male counterparts (Riecher-Rössler, Löffler, & Munk-Jørgensen, 1997).

Sex Differences in Premorbid Functioning

The sex difference in premorbid functioning mirrors the difference in outcomes, such that women tend to have better premorbid social and occupational functioning than men (Larsen, McGlashan, Johannessen, & Vibe-Hansen, 1996; Bardenstein & McGlashan, 1990; McGlashan & Bardenstein, 1990; Andia, Zisook, Heaton, Hesselink, Jernigan, Kuck, et al., 1995). Males change schools and/or jobs more frequently and are less likely to be employed before the onset of psychosis (Larsen et al., 1996), as well as less likely to be married and/or reproduce (Morgan et al., 2008; Bardenstein & McGlashan, 1990; McGlashan & Bardenstein, 1990; Andia et al., 1995). Furthermore, males show a greater and more rapid deterioration in premorbid functioning preceding the onset of psychosis than females (Larsen et al., 1996).

Sex Differences in Suicidality

In patients diagnosed with schizophrenia, as in the general population, females tend to attempt suicide at a higher rate than males (Levine, Bakst, & Rabinowitz, 2010; Tang et al., 2007; Thorup et al., 2007; Leung & Chue, 2000), whereas males successfully complete suicide at higher rates (Limosin, Loze, Phillippe, Casadebaig, & Rouillon, 2007; Lester, 2006; Leung & Chue, 2000; Bardenstein & McGlashan, 1990). However, studies suggest that females with schizophrenia have a higher suicide mortality *ratio* than males, with the ratio calculated by comparing the suicide rate in patients of one sex to the rate in members of the same sex in the general population (Limosin et al., 2007; Leung & Chue, 2000). Furthermore, survival analyses suggest that there is no sex difference in

long-term suicide risk among patients with schizophrenia-spectrum disorders (Carlborg, Jokinen, Jönsson, Nordström, & Nordström, 2008).

Sex Differences in Symptomatology

Given the differences between males and females in the onset and course of schizophrenia, it is not surprising that there are documented sex differences in the pattern of symptom presentation. Most studies suggest that males and females do not differ in overall severity of positive symptoms (Shtasel et al., 1992; Gur, Petty, Turetsky, & Gur, 1996; Leung & Chue, 2000; Bardenstein & McGlashan, 1990; McGlashan & Bardenstein, 1990), though some studies have found higher levels in females (Tang et al., 2007; Taylor & Langdon, 2006; Thorup et al., 2007). Sampling methods might explain some of these discrepant findings. It has been suggested that samples collected in inpatient settings will likely include females presenting with a higher symptom severity than males, as the illness threshold for inpatient treatment for women is thought to be higher (Walker & Lewine, 1993). For instance, the sample in Tang et al. (2007) was comprised of 542 Chinese inpatients displaying a chronic course of the disorder, indicating that the women included might have a more severe course of illness than non-hospitalized women, and thereby possibly explaining their finding that women experienced significantly higher levels of positive symptoms.

Women do consistently show a preponderance of certain types of psychotic symptoms, however, such as auditory hallucinations (Thorup et al., 2007; Tang et al., 2007; Sharma, Dowd, & Janicak, 1999; Marneros, 1984; Rector & Seeman, 1992) and paranoia/persecutory delusions (Tang et al., 2007; Andia et al., 1995; Goldstein & Link, 1988; Räsänen et al., 2000). Conversely, there is evidence that men display more

disorganization and thought disorder (Thorup et al., 2007; Gur et al., 1996) or "illogical thinking" (Szymanski, Lieberman, Alvir, Mayerhoff, Loebel, Geisler, et al., 1995), although some investigators have not found this (Bardenstein & McGlashan; McGlashan & Bardenstein, 1990).

The most consistent sex differences in symptom presentation are that men diagnosed with schizophrenia experience higher levels of negative symptoms such as blunted/flat affect, poverty of speech, and social withdrawal, whereas women display more affective symptoms such as depression, irritability, anxiety, and dysphoria (for reviews, see Leung & Chue, 2000; Räsänen et al., 2000; Bardenstein & McGlashan, 1990; Salem & Kring, 1998; Goldstein, 1997, as well as Thorup et al., 2007). These sex differences have also been shown in general population samples in attenuated forms, with males reporting more negative-like symptoms (Maric, Krabbendam, Vollebergh, de Graaf, & van Os, 2003) and females reporting more depressive/anxious symptoms in conjunction with subclinical psychotic-like experiences (Lewandowski, Barrantes-Vidal, Nelson-Gray, Clancy, Kepley, & Kwapil, 2006).

There are some exceptions, however, such that some studies of patients diagnosed with schizophrenia reveal no sex difference in negative symptoms (Morgan et al., 2008; Tang et al., 2007; Szymanski, et al., 1995) or depressive symptoms (Shtasel et al., 1992). These results might be due to the overlap in the clinical presentation of negative and depressive symptoms (e.g. anhedonia is common to both) or the scales measuring them (Salem & Kring, 1998; Hafner, Maurer, Trendler, an der Heiden, Schmidt, & Könnecke, 2005). Sampling methods might have also contributed to these null findings. As stated above, it is likely that the women in the sample described in Tang et al. (2007) constitute

an unrepresentatively severe group, which would entail higher ratings of negative symptoms. Similarly, males and females did not differ in age-at-onset or any aspect of premorbid functioning in the sample included in Morgan et al. (2008), which suggests that their sample of women was more impaired than the general population of women diagnosed with schizophrenia (Walker & Lewine, 1993).

Theories of the Origins of Sex Differences in Schizophrenia and Other Psychoses

Among the theories of the origins of sex differences in schizophrenia, the one that has garnered the most attention and that has the largest research base is the estrogen hypothesis. It has been suggested that the different epidemiological patterns of age-at-onset for males and females reflect a possible neuroprotective effect of estrogen, in that females experience a delayed onset compared to males at a time when their estrogen levels are higher but have a second peak in onset around the age of menopause, when estrogen levels decline significantly (Riecher-Rössler, Häfner, Stumbaum, Maurer, & Schmidt, 1994; Riecher-Rössler & Häfner, 1993). More specifically, Häfner and colleagues conceive of estrogen as raising the "vulnerability threshold" for developing severe forms of schizophrenia, such that women are less likely to have an earlier onset like men (Häfner, an der Heiden, Behrens, Gattaz, Hambrecht, Löffler, et al., 1998), but that the loss of "protection" provided by estrogen around the time of menopause might explain why women outnumber men almost two to one in the incidence of late-onset cases and why post-menopausal women show a poorer course than men (Castle, 1993; Riecher-Rössler et al., 1997; Häfner et al, 1998).

Results from clinical studies also support a putative neuroprotective role of estrogen. Women diagnosed with schizophrenia have been found to have reduced serum

estradiol (the form of estrogen that is most abundant in the brain) levels compared to both healthy controls and women hospitalized for other psychiatric disorders (Huber, Borsutzsky, Schneider, & Emrich, 2004; Riecher-Rössler et al., 1994). Psychotic symptoms tend to decrease during pregnancy, a time of high estrogen levels, but then increase again in the postpartum period, when estrogen levels decline (for a review, see Häfner, Ehrenreich, Gattaz, Louza, Riecher-Rössler, and Kulkarni, 2006). There are also more hospital admissions (Huber et al., 2004; Bergemann, Parzer, Nagl, Salbach, Runnebaum, Mundt, et al., 2002) and higher levels of psychiatric symptomatology reported during low estrogen phases of the menstrual cycle (Bergemann et al., 2007; Choi, Kang, & Joe, 2001; Mahé & Dumaine, 2001; Riecher-Rössler et al., 1994). However, there is sparse evidence for a correlation between serum estradiol levels and symptom severity in cross-sectional studies (Bergemann et al., 2007; Choi et al., 2001; Huber et al., 2004 vs. Riecher-Rössler et al., 1994). This suggests that it is within-individual changes in estrogen levels that are most relevant to psychotic symptom expression.

The exact mechanism by which estrogen provides its protective effect in schizophrenia has yet to be determined. It has been shown to buffer the detrimental effects of oxidative stress and glutamatergic excitotoxicity, to regulate apoptosis, and to modulate the expression of neurotropins, such as BDNF (for reviews, see Mortimer, 2007; Meethal & Atwood, 2005; Rao & Kolsch, 2003). Estrogen also plays a role in regulating the excitability of neurons in the dopaminergic, serotonergic, γ-aminobutyric acid (GABA), cholinergic, noradrenergic, and glutamatergic systems (for reviews, see Mortimer, 2007; Meethal & Atwood, 2005; Rao & Kolsch, 2003). Studies have indicated

that estradiol reduces D_2 receptor sensitivity (for a review, see Häfner et al., 2006), but there is no evidence that estrogen acts as an "endogenous antipsychotic" during the risk period (Mortimer, 2007). Rather, it is possible that estrogen might protect against abnormal synaptic pruning throughout neurodevelopment (Mortimer, 2007).

An alternative to the estrogen hypothesis is that males and females are differentially susceptible to different forms of schizophrenia, with males being more vulnerable to an early-onset, neurodevelopmental form that resembles Kraeplin's original conceptualization of "dementia praecox" (Castle, Abel, Takei, & Murray, 1995; Murray, O'Callaghan, Castle, & Lewis, 1992). Conversely, females tend to develop a later-onset form that shows a relapsing-remitting, seasonal pattern of psychotic episodes similar to affective psychoses (Castle et al., 1995; Murray et al., 1992). Castle and colleagues (1995) argue that the estrogen hypothesis cannot explain the pattern of sex differences in pre-pubertal premorbid functioning, though it is possible that the male brain is more vulnerable to early brain insult due to the lack of protection from estrogen (Mortimer, 2007; Häfner et al., 2006). Indeed, Castle et al. grant that estrogen is likely influential, but only at "the extremes of life," i.e. neurodevelopment and post-menopause (1995). However, early subclinical, or "prodromal" signs and symptoms typically begin to appear during puberty and young adulthood, possibly in response to changing hormone levels. Research on the psychosis prodrome provides another approach to clarifying the role of sex differences in the development of psychosis.

The Psychosis Prodrome

The psychosis prodrome is defined as a period of deterioration in functioning and increasing symptoms preceding the onset of psychosis or indicating that an individual is

at significant risk for developing a psychotic disorder (Yung & McGorry, 1996). The most characteristic prodromal signs include attenuated positive and negative symptoms, "nonspecific" symptoms (e.g. anxiety and depression), social withdrawal, and impaired role functioning (Yung & McGorry, 1996). Adopting a neurodevelopmental model of schizophrenia, it might be possible to intervene in the prodromal period and thereby delay or even prevent the onset of psychosis (Cornblatt, Lencz, Smith, Correll, Auther, & Nakayama, 2003; Addington, Cadenhead, Cannon, Cornblatt, McGlashan, Perkins, et al, 2007). The first step in this process is to identify accurately and quickly who is at the most risk for developing a psychotic disorder. Studies using standardized measures of prodromal syndromes have shown that among prodromal/high-risk samples approximately 10-40% of participants go on to convert to an Axis I psychotic disorder within two years after initial assessment (Yung, Phillips, Yuen, Francey, McFarlane, Hallgren, et al., 2003; Cannon, Cadenhead, Cornblatt, Woods, Addington, Walker, et al., 2008; Ruhrmann, Schultze-Lutter, Salokangas, Heinimaa, Linszen, Dingemans, et al., 2010; Velthorst, Nieman, Becker, van de Fliert, Dingemans, Klaassen, et al., 2009). Notable among these standardized measures is the Structured Interview for Prodromal Syndromes (SIPS) which has been shown in several investigations to yield conversion rates ranging from 19-35% within 18-30 months (Cannon et al., 2008; Ruhrmann et al., 2010; Velthorst et al., 2009).

Several studies have examined differences between participants at ultra high risk (i.e. putatively prodromal) who eventually convert to psychosis (converters) and those who do not (non-converters). Because research participants are typically identified as prodromal during periods of symptom onset or exacerbation, most studies show that

prodromal symptom severity ratings decline following baseline, particularly among those who do not go on to convert to psychosis (cite). Among those who do convert, Velthorst et al. (2009) found significantly higher baseline negative symptom ratings on the SIPS, largely driven by a striking difference between the converted and non-converted groups in social anhedonia and withdrawal. Bizarre thinking, which is included in the disorganized symptom domain, also significantly differed between the converters and non-converters.

Other studies have employed multivariate predictive algorithms based on individual SIPS symptoms and other characteristics (e.g. demographic variables, substance use, family history of psychosis, etc.) to differentiate between converters and non-converters. Cannon et al. (2008) identified five uniquely predictive variables: genetic risk for schizophrenia accompanied by functional decline [GRD], unusual thought content, suspicion/paranoia, impaired social functioning, and history of substance use. Two separate three-factor models provided the most positive predictive power (74-81%, respectively) while balancing a loss of sensitivity, including GRD, unusual thought content, and either suspiciousness/paranoia or impaired social functioning. Given the relatively low sensitivity of these models (30-34%), the authors suggested that these criteria are best used with people who have already been identified as at high risk for developing a psychotic disorder to determine who will become more distressed or impaired than they already are. Similarly, Ruhrmann et al. (2010) proposed a two-step risk assessment procedure, in which patients are first identified as being at high risk for developing a psychotic disorder. To determine who amongst the high risk patients are most likely to convert, they then applied a multivariate predictive algorithm including

SIPS positive symptoms, bizarre thinking, sleep disturbance, schizotypal personality disorder, level of functioning within the past year, and years of education. These results are partially consistent with those of Cannon et al. (2008), with level of functioning and some positive symptomatology included in the models of both research groups. These studies demonstrate that combinations of individual prodromal symptoms can feasibly identify groups of patients who are at the most risk of converting to psychosis and, therefore, in the most need of targeted interventions aimed at delaying or reducing their risk.

Sex Differences in the Prodrome

Given the heterogeneity in the clinical expression of schizophrenia linked to sex differences, researchers are beginning to investigate the role of sex differences in the prodrome as a means of increasing the accuracy of detecting "true positive" cases. Amminger and colleagues hypothesized that male sex might be associated with a higher risk of conversion to non-affective psychosis in participants identified to be at ultra-high risk, but this was not confirmed in their sample of 86 participants; rather, female sex was a significant predictor of developing an affective psychotic disorder (Amminger, Leicester, Yung, Phillips, Berger, Francey, et al., 2006). There were no sex differences in symptom presentation in their sample, which might be due to the measures they used to assess negative and nonspecific symptomatology. Negative symptoms were rated with the Scale for Assessment of Negative Symptoms (Andreasen, 1982), a measure designed for use with patients diagnosed with schizophrenia. Prodromal participants are not likely to exhibit the same severity of negative symptoms as the patients for whom the measure was intended, which might lead to restriction of range in scores. The measure used to

assess depressive symptoms, the Hamilton Rating Scale for Depression (Hamilton, 1960), has been shown to correlate with positive and negative symptom scores, which suggests that it is not as "pure" a measure as the Calgary Depression Scale for Schizophrenia, for example (Addington, Addington, & Atkinson, 1996). It is possible that use of measures more tailored for this sample of participants at high risk for psychosis might have yielded significant sex differences in symptom ratings.

To date, only three studies have directly examined sex differences in symptom presentation in the prodrome. Choi et al. gathered retrospective data from the charts of 63 patients with first-episode schizophrenia and were therefore only able to glean information about symptom frequency, not severity (Choi, Chon, Kang, Jung, & Kwon, 2009). They found that males experienced more frequent negative symptoms, but that males and females did not differ in frequency of positive, depressive, or anxious symptoms.

Moukas et al. also assessed frequency of prodromal symptoms retrospectively in 73 patients hospitalized with either their first or second psychotic episode by means of an interview with patients once their psychosis had remitted, as well as corroboration from family members (Moukas, Gourzis, Beratis, & Beratis, in press). They found that more females experienced hyperacusia, magical thinking, overelaborate speech, and inappropriate affect. In contrast, bizarre behavior, aggression, vague speech, poverty of content of speech, and marked isolation were more common in males. Although this study is notably limited by its lack of systematic, empirically supported assessment of symptomatology, the findings that males have a more negative and disorganized

presentation in the prodrome (e.g. marked isolation and poverty of content of speech) corresponds to the clinical picture of schizophrenia typically seen in men.

Finally, Willhite and colleagues prospectively investigated sex differences using the SIPS/SOPS with 68 ultra-high risk individuals and found that males had higher levels of negative symptoms, consistent with the pattern seen in schizophrenia (Willhite, Niendam, Bearden, Zinberg, O'Brien, & Cannon, 2008). They did not observe any other sex differences in symptoms, though it is possible that the varied contents of the General symptom dimension on the SIPS, which includes ratings of dysphoria, motor abnormalities, sleep disturbance, and impaired stress tolerance, obscured any differences in dysphoric mood. The findings of these three studies suggest that sex differences in symptom presentation predate the onset of psychosis and, with respect to negative symptoms, mirror the differences observed in diagnosed patients with schizophrenia. Accordingly, it is possible that different patterns or combinations of symptoms will predict conversion to psychosis for males versus females.

Goals of the Present Study

As described above, a major objective of research on the prodrome is to develop clinical measures that optimize prediction of psychosis. Based on past research findings, it is plausible that there are sex difference in the symptom profiles that predict conversion to psychosis, in which case differential weighting of prodromal symptoms for males and females may be needed to optimize prediction.

The current study examines sex differences in prodromal symptom presentation and in a large, prospectively-studied sample. The study also compares participants who do and do not transition to psychosis, in order to determine whether there are sex

differences in the symptoms that predict conversion. Based on past findings, it is hypothesized that, at baseline and six-month follow-up, men will show higher levels of negative and disorganized symptoms, whereas women will show higher levels of dysphoric and anxious symptoms. No sex difference in overall positive symptom ratings is predicted. It is also hypothesized that the sample will experience a decline in the severity of symptom ratings between baseline and follow-up, although it is predicted that those who eventually convert to psychosis will have consistently higher symptom ratings than those who do not convert. Further, the present study will explore potential differences in the combination of prodromal symptoms that predicts conversion in males and females.

Method

North American Prodromal Longitudinal Study (NAPLS)

The NAPLS consortium is a collaboration among eight research sites with longstanding NIMH finding for research on the prodrome to psychosis. The sites are Emory University; Harvard University; University of Calgary; University of California, Los Angeles; University of California, San Diego; University of North Carolina, Chapel Hill; Yale University; and Zucker Hillside Hospital. Across the eight sites participating in the NAPLS consortium, data were pooled to form an aggregated dataset. The NAPLS project dataset has 888 participants who were recruited and completed a baseline assessment, including 429 prodromal subjects (including those diagnosed with schizotypal personality disorder), 174 help-seeking controls, and 195 healthy controls (for further information on this sample, see Addington et al., 2007). Follow-up assessments occurred at six-month intervals up to a maximum of 30 months after baseline

assessment at some sites. At all sites, the primary measure used to assess prodromal symptomatology was the Structured Interview for Prodromal Syndromes [SIPS] (Miller, McGlashan, Rosen, Somjee, Markovich, Stein et al., 2002).

The Current Study

Participants.

The current study focuses on a subset of 212 prodromal participants for whom data were available on all four SIPS symptom dimensions at baseline and a six-month follow-up. Demographic characteristics are presented in Table 1. Subjects ranged in age from 12-36 years (M = 18.69, SD = 4.85) at baseline. There were 86 females (40.6%), and the majority of the sample was Caucasian (80.7%). All participants were followed longitudinally and periodically assessed for up to 30 months to monitor their symptoms and collect diagnostic data on Axis 1 disorders. Among the sample included in the present study, there were 47 participants (M_{age} = 18.86 years, SD = 3.95; 42.6% female) who converted to an Axis I psychotic disorder by the 24-month follow-up assessment.

Forty-three females (50%) and 62 males (49%) were on psychotropic medications at baseline; by the six-month follow-up, the number of females on medication rose to 71 (82.5%) and the number of males rose to 87 (69%) (see Table 1). The proportion of subjects on the four main classes of medications (antidepressants, antipsychotics, anticonvulsants, and stimulants) is listed in Table 2.

In comparing the 212 in the present sample to the 217 NAPLs prodromal participants who were not included, several significant differences were observed. Those who were not included had significantly higher rates of medication with stimulants and conversion to psychosis by the six-month follow-up, though information regarding

conversion status was only available for 64 of the original 217 subjects. Those who were included in the present sample were significantly older, had more severe average positive symptom scores, greater impairment in their tolerance to normal stress, and had a higher rate of medication with SSRIs. However, there were no significant differences in the ratio of males to females, baseline average symptom scores in several domains (negative, disorganized, sleep disturbance, and dysphoric mood), and the proportion of the sample on either antipsychotic or antidepressant (other than SSRIs or tricyclics) medication.

Measures.

Structured Interview for Prodromal Symptoms (SIPS).

The SIPS (Miller et al., 2002) is comprised of 29 items assessing four symptom dimensions: *positive* (unusual thought content, suspiciousness, grandiosity, perceptual abnormalities, and disorganized communication); *negative* (social anhedonia, avolition, expression of emotion, experience of emotions and the self, ideational richness, and occupational functioning); *disorganized* (odd behavior and appearance, bizarre thinking, trouble with focus and attention, and personal hygiene), and *general* (sleep disturbance, dysphoric mood, motor abnormalities, and impaired tolerance to normal stress). In the present study, sleep disturbance, dysphoric mood, and impaired tolerance to normal stress will be examined individually so as to avoid the possibility of significant differences being obscured by the heterogeneity of the overall symptom domain. Each symptom is rated on a seven-point scale that reflects its severity, frequency, duration, and intensity (i.e. degree of conviction). Scores of 0-2 (absent, questionable, or mild) reflect normal to subprodromal symptoms; scores of 3-5 (moderate, moderately severe, or severe) signifies

prodromal level symptomatology; and a score of 6 indicates a symptom of psychotic intensity.

To identify those participants who met criteria for the prodrome, the Criteria of Prodromal Syndromes (COPS) (Miller et al., 2002) were used; these 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 subpsychotic 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, as well as a decline of at least 30% in global functioning within the last 12 months. BIPS is characterized by positive symptoms of psychotic intensity that are brief in duration, recent, and do not meet the threshold required for diagnosis of a psychotic disorder. Subjects diagnosed with schizotypal personality disorder (SPD) were also included in this sample, because SPD is genetically and developmentally linked with psychosis (Siever, Koenigsberg, & Reynolds, 2003) and is now included as a prodromal syndrome.

Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I).

The SCID-I (Spitzer, Williams, & Gibbon, 1994) is a comprehensive assessment of the symptom criteria for DSM-IV Axis I disorders (APA, 2000), which was used to identify any comorbid disorders, as well as to diagnose psychotic disorders in participants who received a score of 6 on any of the symptom scales on the SIPS.

Statistical analyses.

All analyses were performed using SPSS 17.0 (Mac). Demographic and symptom variables were examined using basic descriptive statistics to determine central tendency and variability. Student's *t*-tests were used to assess group differences in demographic characteristics and medication status. Group differences in symptom presentation at baseline and six-month follow-up were examined using repeated measures analysis of variance (ANOVA) or repeated measures analysis of covariance (ANCOVA). To determine the optimal combination of symptoms that discriminate between the participants who convert to a psychotic disorder separately by sex, a stepwise discriminant function analysis was conducted.

Results

Demographic Characteristics and Medication Status

Preliminary analyses were conducted to test potential covariates. Males and females did not differ significantly in age at baseline (see Table 1). There was also no sex difference in the proportion of subjects within racial groups [$\chi^2(4, N = 212) = 2.51, p = .64$]. As shown in Table 2, rates of treatment with stimulants, SSRIs, antipsychotics, and other antidepressants did not differ between males and females, except that a greater proportion of females were taking an SSRI at the six-month follow-up.

Analyses were also conducted to test for demographic differences between the subjects the converted and non-converted groups. As shown in Table 1, there were no significant group differences in ratio of males to females, proportion of racial groups, or in age at baseline. Pearson's χ^2 tests revealed no conversion group differences in proportions of participants treated with any medications (see Table 1).

Pearson product moment correlation *r* was used to examine correlations among symptoms and the four types of medication. In the cases of significant correlation, individual medications were included as covariates in the subsequent analysis of the associated symptom.

Longitudinal Differences in Symptom Severity by Sex and Conversion Status

Means and standard deviations of symptom ratings by sex, conversion status, and time point are displayed in Table 3. To investigate longitudinal patterns of sex differences in prodromal symptom presentation, repeated measures ANOVAs and ANCOVAs were conducted (see Table 4).

Positive Symptoms.

As shown in Table 4, there was no significant main effect for sex on mean global positive symptom scores at either baseline or follow-up. However, there was a significant Sex X Conversion status interaction, indicating that male converters had higher ratings of positive symptoms than male non-converters [$t(124) = 3.12$, $p = .03$], as illustrated in Figure 1.

At both baseline and follow-up, converters had higher ratings than non-converters. Although, as expected, the entire sample decreased in overall positive symptom severity from baseline to follow-up, the significant interaction of time and conversion status (see Table 4) indicates that converters declined less sharply in their ratings over time [$t(46) = 3.35$, $p = .002$] than non-converters [$t(164) = 17.19$, $p < .0001$]

Negative Symptoms.

As hypothesized, males had significantly higher mean negative symptom ratings than females at both baseline and follow-up (see Table 4). Converters also experienced

more severe negative symptoms than non-converters at both time points. As expected, the entire sample decreased in negative symptom severity over time, but post-hoc comparisons of the significant three-way interaction of time, sex, and conversion status demonstrates that male converters remained consistently more severe while male non-converters, female converters, and female non-converters all experienced a reduction in severity ($p < .0001$, $p = .014$, and $p < .0001$, respectively; see Figure 2).

Disorganized Symptoms.

As shown in Table 4, there was a significant main effect for sex in average disorganized symptom ratings, with males displaying more severe symptomatology at baseline and follow-up. Converters also had higher disorganized symptoms than nonconverters at both time points. There was a significant main effect for time, demonstrating that symptom ratings improved for the sample overall. No interactions were significant.

General Symptoms.

As noted, the general symptom scale of the SIPS taps a variety of symptoms, thus the individual symptom ratings were analyzed. Neither the main effects for sex or conversion status were significant in ratings of sleep disturbance. The overall sample experienced a reduction in sleep disturbance over time (see Table 4). Although there was a significant three-way interaction of time, sex, and conversion status, post-hoc analyses did not reveal any significant differences between any of the groups. It appears that, as with negative symptoms, male converters remain more stable whereas all of the other groups decline, but it is likely that there was not sufficient power to discern these differences statistically.

Analyses of dysphoric mood severity were conducted both with and without the inclusion of medications as covariates. Controlling for treatment with antipsychotics at baseline and follow-up, SSRIs at baseline, and non-SSRI antidepressants at follow-up, there was a significant interaction of sex and conversion status, such that male non-converters had lower ratings of dysphoric mood than all other groups [$F(1, 204) = 4.32$, $p = .039$]. There was a trend for a significant interaction of time and sex, such that males tended to remain more stably severe than females over time [$F = 3.03$, $p = .083$]. There was also a trend for an interaction of time and conversion status, such that converters had higher ratings in dysphoric mood than non-converters at follow-up [$F = 2.95$, $p = .088$]. As shown in Table 4, when medications were not included as covariates, the interaction of time and sex reached statistical significance (see also Figure 3).

As shown in Table 4, there was a significant interaction of sex and conversion status in ratings of impaired tolerance to normal stress, such that male converters had higher levels of impaired stress tolerance than male non-converters [$t(124) = 3.23$, $p < .01$] and female non-converters [$t(91) = 3.04$, $p < .01$]. As predicted, the entire sample decreased in symptom severity over time, though the significant interaction of time and conversion status indicates that converters maintained higher levels of impaired stress tolerance over time [$t(45) = .616$, $p = .54$], whereas the non-converters declined [$t(163) = 6.30$, $p < .0001$].

Discriminant Function Analysis

Discriminant function analysis was conducted to determine the optimal combination of prodromal symptoms that discriminate between converters and nonconverters for males and females separately. All clinical variables were entered as

independent variables using the stepwise method. Wilks' Lambda and chi-square were used to test the significance of each function that emerged from the analysis. Results indicate that for females, severity of negative symptoms best distinguished between converters and non-converters, with converters having higher scores [$\chi^2 = 3.99$, $p = .046$]; conversely, for males, a weighted combination of disorganized and positive symptoms discriminated most between converters and non-converters [$\chi^2 = 25.73$, $p < .0001$].

Standardized coefficients for the correlation between each variable and the function (i.e. the unique contribution of each variable to the discriminant function) showed that, for both sexes, the corresponding symptom ratings were positively correlated with the function. The means of each diagnostic group for the function were examined using group centroids, which showed that converters had significantly higher mean scores for the function than non-converters for both males and females.

Group classification statistics were conducted with the predicted group membership variable produced by the discriminant function analysis. This variable allows for the prediction of each individual case's conversion status based on the results of the discriminant function analysis. Of 126 males, 84.1% of cases were correctly classified as to conversion status, whereas 76.7% of 86 female cases were correctly classified. The predictive accuracy of the function could not be calculated, as no females were correctly classified as converters by the function (i.e. the female converters comprised the full 23.3% who were incorrectly classified).

Discussion

One of the main goals of prodromal research is to develop algorithms that can accurately predict psychosis. Previous literature has established that there are sex

differences in symptom presentation in patients diagnosed with schizophrenia, but there is a relative paucity of research on the role of sex in prodromal symptomatology. If sex differences occur in the prodrome, successful algorithms for predicting conversion to psychosis would likely need to be different for males and females. Therefore, it is important to determine whether there are sex differences in prodromal symptom presentation so that prediction of risk for psychosis can be optimized for males and females. The present study used the largest sample of prodromal participants to date to investigate sex differences in symptom presentation before the onset of psychosis. The results of the present study replicate and extend past research and indicate that sex differences in the prodrome to psychosis parallel those that have been observed in patients diagnosed with schizophrenia and other psychotic disorders. The discussion below summarizes the pattern of sex differences observed in each of the symptom domains.

Positive Symptoms

As predicted, men and women did not differ in ratings of overall positive symptoms, which is consistent with previous studies both in patients diagnosed with schizophrenia (Shtasel et al., 1992; Gur et al., 1996; Bardenstein & McGlashan, 1990) and prodromal subjects (Willhite et al., 2008; Choi et al., 2009). Thus, it appears that the severity of the key defining features of psychosis is similar for males and females.

It is important, however, to consider that diagnostic criteria for both the prodrome and psychosis require the presence of positive symptoms that exceed the specified severity threshold. In contrast, there is no minimal threshold for the severity of negative, disorganized, or general symptoms in the diagnostic criteria for the prodrome or for

psychosis (i e., the SIPS and DSM-IV, respectively). Accordingly, variability in the severity of positive symptoms is constrained by the diagnostic criteria for positive symptoms only. Thus, diagnostic criteria for the prodrome might obscure any naturally occurring sex differences in the positive symptom dimension of prodromal syndromes.

Among the symptoms comprising the positive dimension, however, the present study did reveal sex differences (see Table 5). Women had higher ratings for perceptual abnormalities/hallucinations, and this is consistent with previous findings that females diagnosed with schizophrenia report more hallucinations (Thorup et al., 2007; Sharma et al., 1999), as do women diagnosed with bipolar disorder (Bräunig, Sarkar, Effenberger, Schoofs, & Krüger, 2009). Related to this, it is of interest to note that Moukas et al. (in press) reported a higher frequency of hyperacusia in women who met prodromal criteria. This is similar to the item on the SIPS, "Have you been feeling more sensitive to sounds?" (Miller et al., 2002), and is also consistent with studies that suggest that the sex difference in hallucinations is most pronounced in the auditory modality (Rector & Seeman, 1992; Marneros, 1984).

There are normative sex differences in auditory perception that might be of relevance to the findings that women tend to experience more auditory hallucinations. Healthy women have been shown to have more of a perceptual bias to looming sounds, such that they perceive the sounds as closer than they really are (Neuhoff, Planisek, & Seifritz, 2009). The authors offer an evolutionary explanation of their findings, suggesting that due to the fact that females tend to be smaller, slower, and weaker than males, it is adaptive for women to experience a greater looming bias in that it would allow them to active neural systems for attention and planning earlier (Neuhoff et al.,

2009). Further, electrophysiological research has found that women tend to exihibit enhanced amplitude at the N200 component, which implies that women tend to engage in a more cognitive, top-down strategies in audiospatial processing tasks (Simon-Dack, Friesen, & Teder-Sälejärvi, 2009). The same enhanced amplitude of the N200 component was found to be positively associated with unusual experiences in a study of schizotypy in the general population (Sumich, Kumari, Gordon, Tunstall, & Brammer, 2008). In sum, the tendency for female prodromals, as well as patients with psychosis, to manifest more auditory perceptual abnormalities may reflect the moderating influence of normative sex differences in auditory perceptual processing.

Disorganized Symptoms

The present study revealed that the overall disorganized symptom domain ratings were higher in men than women, which is consistent with the literature stating that thought disorder is more common and severe in males (Thorup et al., 2007; Gur et al., 1996; Syzmanski et al., 1995). Also, within the positive symptom scale, there was a significant sex difference in disorganized communication, such that men had higher ratings. These results also converge with previous reports on prodromal and psychotic symptoms (Moukas et al., in press; Thorup et al., 2007; Gur et al., 1996). For example, Moukas et al. found that prodromal males exhibited more "vague speech," which is one of the facets that comprises the disorganized communication symptom rating. The literature on normal sex differences in expressive communication suggests that females outperform males in the quality of speech production (Hyde & Linn, 1988), and there are corresponding normative sex differences in the volume and function of areas related to language, such that the superior temporal gyrus and inferior frontal gyrus tend to be

larger and less lateralized in women (Goldstein, Seidman, Horton, Makris, Kennedy, Caviness, Jr., et al., 2001; Baxter, Saykin, Flashman, Johnson, Guerin, Babcock, et al., 2003). Here, again, these normative sex differences might be moderating the expression of disorganized symptoms.

Recent imaging studies have suggested structural and functional abnormalities language-processing areas of the brain, such as volumetric reduction in the superior temporal gyrus in patients diagnosed with schizophrenia (for reviews, see Sun, Maller, Guo, & Fitzgerald, 2009; Shenton, Dickey, Frumin, & McCarley, 2001), as well as prodromal participants (Sabb, van Erp, Hardt, Dapretto, Caplan, Cannon, et al., 2010; Crossley, Mechelli, Fusar-Poli, Broome, Matthiasson, Johns, et al., 2009), which may represent disruptions of normative sex differences in these areas (Goldstein, Seidman, O'Brien, Horton, Kennedy, Makris, et al., 2002). However, as Sun et al. (2009) note, a methodological weakness of many of these studies is an under-representation of female patients when data on sex were reported at all.

A small pilot study found that disruptions in normal sexual dimorphisms in the brain were associated with dysfunction in phonology, semantics, and grammar, especially in men (Walder, Seidman, Makris, Tsuang, Kennedy, & Goldstein, 2007). Castle and Murray suggest that males, who more frequently present with the neurodevelopmental subtype of schizophrenia, are more susceptible to developing structural abnormalities in the brain that can affect cognitive processes (Castle et al., 1995; Murray et al., 1992).

Negative symptoms

Consistent with a large body of research, negative symptoms were significantly more frequent and severe in male participants, providing further support for the stability

of this sex difference along the full schizophrenia spectrum. Studies have shown that males tend to present with more negative symptoms of varying severity in community samples (Maric et al., 2003), prodromal samples (Choi et al., 2009; Willhite et al., 2008), and patients diagnosed with schizophrenia (Leung & Chue, 2000). The higher level of negative symptoms in prodromal males is consistent with the extensive body of literature showing greater premorbid academic and occupational deficits in males with psychotic disorders (Larsen et al, 1996; Bardenstein & McGlashan, 1990; Andia et al., 1995) . The results also converge with the well-established sex difference in prognosis, with males showing poorer outcomes, social and occupational functioning, and less responsiveness to antipsychotic treatment (Leung & Chue, 2000; Morgan et al., 2008; Bardenstein & McGlashan, 1990).

Many of the symptoms that are included in the negative symptom dimension, particularly reduced emotional expression and experience, tap into affective characteristics for which there are normative sex differences. Among normal adults for example, women manifest more facial emotion than men (Lang, Greenwald, Bradley, & Hamm, 1993; Thunberg & Dimberg, 2000). Women also tend to report stronger emotional experiences, both positive and negative (for reviews, see Grossman & Wood, 1993; Plant, Hyde, Keltner, & Devine, 2000).

General Symptoms

Contrary to several studies that have found prodromal females to be more depressed, anxious, and irritable in presentation (Leung & Chue, 2000; Bardenstein & McGlashan, 1990; Morgan et al., 2008), men and women did not differ in levels of dysphoric mood in the current study. There was also no sex difference in impaired

tolerance to normal stress, which is contrary to the findings of studies in patients diagnosed with schizophrenia (Myin-Germeys & van Os, 2007; Myin-Germeys, Krabbendam, Delespaul, & van Os, 2004). However, measurement of these symptoms with the SIPS has limitations, as it was not developed with the intention of indexing mood symptoms. For example, SIPS dysphoric mood ratings are based on a composite from seven questions about general mood, depression, anxiety, irritability/anger, suicidal ideation, and homicidal ideation, providing no continuous measure of any of these specific mood symptoms. Similarly, stress tolerance is indexed by 4 questions that address subjective stress reactions. Thus the SIPS may not provide a measure of affective symptoms with sufficient discriminative power to detect sex differences.

Changes Over Time

As expected, ratings of all prodromal symptomatology improved from baseline to follow-up for both males and females, indicating that the majority of participants recruited into studies do not go on to experience more serious pathology. This has been reported in several previous studies of the course of prospectively-measured prodromal symptoms (Yung et al., 2003; Cannon et al., 2008; Yung, Stanford, Cosgrave, Killackey, Phillips, Nelson, et al., 2006; Ruhrmann et al., 2010). Although it is certainly important to better understand the protective factors that contribute either to the amelioration of symptoms or the maintenance of subsyndromal levels, these findings also highlight the need for more sensitive and specific methods for predicting who will eventually develop a psychotic disorder. That being said, those who eventually converted to psychosis achieved higher ratings of almost all prodromal symptomatology than those who did not convert. Only ratings for grandiosity did not differ between groups, though there was a

trend for the converters' ratings not to decline as much as the nonconverters between baseline and follow-up.

Predicting Conversion to Psychosis for Males and Females

The results of the discriminant function analysis provide valuable information pertaining to the development of algorithms predicting conversion to psychosis. Using symptom ratings as predictors, no females were correctly classified as converters, suggesting that prodromal symptoms alone are not sufficient to predict conversion in females. Rather, it is clear that other factors need to be taken into account to allow for successful identification of females who are at the highest risk for developing a psychotic disorder, including premorbid factors such as social and occupational/academic functioning, cognitive performance, and substance use. These are areas in which females tend to have a more benign presentation, and these are areas likely to be most affected by negative symptomatology, which explained a small, yet significant portion of the variance in determining which females would convert to psychosis. It is possible that problems in these areas would be more likely to predict conversion than prodromal symptoms alone. Further, as noted, the present study did not include a comprehensive measure of mood symptoms. It is possible that these symptoms play a greater role in prediction of conversion for females than males. Future studies should address this possibility.

Prodromal symptomatology provided more elucidation in predicting conversion for males, such that higher levels of both disorganized and positive symptoms explained nearly 20% of the variance in differentiating between those who would go on to convert to psychosis and those who would not. Further analyses need to be conducted including

factors identified as significant predictors in other studies, such as substance use or family history, as in Cannon et al. (2008), to craft more sensitive and specific models of predicition.

The Determinants of Sex Differences in Prodromal Symptoms.

There is no doubt that many of the sex differences observed in this and previous studies parallel the findings on normative sex differences in perceptual, affective and cognitive functions. Thus, for example, the heightened sensitivity to auditory stimuli may increase risk for auditory hallucinations in females, whereas their greater tendency to emotional expression and social conformity may decrease negative symptoms.

As described above, estrogen may be playing a role in these normative sex differences as well as sex differences in symptom presentation. Goldstein et al. (2002) found that the most striking sexual dimorphisms in the brain in humans occurred in homologous areas that had been determined to have higher concentration of estrogen receptors in other vertebrates. Furthermore, estrogen acts upon many neurotransmitter systems implicated in psychosis, especially dopamine, by reducing D_2 receptor sensitivity (Rao & Kolsch, 2003; Mortimer, 2007). Rao and Kolsch (2003) theorize that higher levels of estrogen might protect women from atrophy in the frontal cortex, which is correlated with negative symptomatology, by preventing cell death (Andreasen, Smith, Jacoby, Denner, & Olsen, 1982, as cited in Rao & Kolsch, 2003). It has been suggested that treatment with newer estrogen compounds, selective estrogen receptor modulators (SERMs), which act primarily in the brain without many of the undesirable side effects of estrogen exposure in other tissues, might reduce the detrimental impact of negative symptoms in patients diagnosed with and at risk for psychosis.

In conclusion, the current study demonstrates that sex differences in symptom presentation pre-date the onset of frank psychosis, highlighting the importance of taking sex into account when generating predictive algorithms for who among samples at high risk will go on to develop a psychotic disorder. Further research investigating sex differences in the chronological progression and course of symptoms throughout the prodrome has the potential to contribute significantly to the identification of sensitive and specific prediction models. In particular, future studies will benefit from more comprehensive assessment of mood symptoms that may distinguish male and female prodromals, and may be playing a greater role in prediction of conversion among females

Table 1.

Demographic Characteristics

Variable		Entire Sample (n = 212)	Converters (n = 47)	Non-Converters (n = 165)	Not Included (n = 217)
Age (Mean ± SD)		18.69 ± 4.85	18.86 ± 3.95	18.64 ± 5.09	17.01 ±4.22**
Sex (n, %)	Female	86 (40.6%)	20 (42.6%)	66 (40.0%)	76 (35.0%)
	Male	126 (59.4%)	27 (57.4%)	99 (60.0%)	141 (65.0%)
Race (n, %)	Caucasian	171 (80.7%)	38 (80.9%)	133 (80.6%)	155 (71.4%)
	African American	15 (7.1%)	4 (8.5%)	11 (6.7%)	28 (12.9%)
	Asian American	10 (4.7%)	3 (6.4%)	7 (4.2%)	14 (6.5%)
	Other	11 (5.2%)	2 (4.3%)	9 (5.5%)	19 (8.8%)
	Hispanic	25 (11.8%)	8 (17.0%)	17 (10.3%)	37 (17.1%)
Medication Status at Baseline (n, %)	Stimulants	8 (3.7%)	2 (4.3%)	6 (3.6%)	20 (9.2%)
	SSRIs	52 (24.5%)	8 (17.0%)	44 (26.7%)	36 (16.6%)
	Antipsychotics	18 (8.5%)	4 (8.5%)	14 (8.5%)	23 (10.6%)
	Other Antidepressants	27 (12.7%)	3 (6.4%)	24 (14.4%)	21 (9.7%)

** $p < .01$

Table 2.

Medication Status by Sex

Medication		Baseline	*t*	*df*	*p*	Follow-Up	*t*	*df*	*p*
Stimulants (*n*, %)	Female	1 (1.2%)	-1.65	210	.10	3 (3.5%)	-.18	210	.86
	Male	7 (5.6%)				5 (4.0%)			
SSRIs (*n*, %)	Female	25 (29.1%)	1.27	210	.21	32 (37.2%)	2.26	210	.03*
	Male	27 (21.4%)				29 (23%)			
Antipsychotics (*n*, %)	Female	5 (5.8%)	-1.15	210	.25	22 (25.6%)	-.10	210	.92
	Male	13 (10.3%)				33 (26.2%)			
Other Antidepressants (*n*, %)	Female	12 (14.0%)	.44	210	.66	14 (16.3%)	.08	210	.94
	Male	15 (11.9%)				20 (15.9%)			

Table 3.

SIPS Symptom Ratings by Sex and Conversion Status

Symptom		Baseline		Follow-Up	
		Non-Converters	Converters	Non-Converters	Converters
Unusual Thought Content	Female	3.36 (1.38)	3.95 (1.28)	1.41 (1.48)	2.75 (1.97)
(Mean ± SD)	Male	2.94 (1.40)	3.67 (1.64)	1.40 (1.48)	3.56 (2.21)
Suspiciousness	Female	2.82 (1.34)	3.40 (1.05)	1.30 (1.23)	1.80 (1.99)
(Mean ± SD)	Male	2.46 (1.44)	3.37 (1.39)	1.17 (1.28)	3.26 (1.93)
Grandiosity	Female	1.27 (1.35)	0.75 (0.97)	0.50 (0.81)	0.60 (1.05)
(Mean ± SD)	Male	1.23 (1.29)	1.48 (1.76)	0.70 (1.11)	1.15 (1.95)
Perceptual Abnormalities	Female	3.36 (1.55)	3.75 (1.29)	1.48 (1.54)	3.05 (2.26)
(Mean ± SD)	Male	2.81 (1.66)	3.22 (1.89)	1.27 (1.51)	1.85 (1.99)
Disorganized Communication (Mean ± SD)	Female	1.26 (1.28)	1.75 (1.65)	0.74 (1.03)	0.85 (1.35)
	Male	1.92 (1.48)	3.19 (1.39)	0.87 (1.23)	2.22 (1.87)
Average Positive	Female	2.42 (.80)	2.72 (0.70)	1.09 (0.78)	1.81 (1.23)
Symptoms (Mean ± SD)	Male	2.27 (.76)	2.99 (0.98)	1.09 (0.85)	2.42 (1.17)
Average Negative	Female	1.63 (1.10)	2.20 (1.11)	1.04 (1.00)	1.48 (1.37)
Symptoms (Mean ± SD)	Male	2.10 (1.18)	2.78 (1.28)	1.28 (1.15)	2.75 (1.48)
Average Disorganized	Female	1.39 (1.02)	1.81 (1.08)	0.73 (0.69)	1.28 (1.10)
Symptoms (Mean ± SD)	Male	1.58 (.85)	2.44 (0.97)	0.88 (0.84)	1.87 (1.07)
Sleep Disturbance	Female	2.20 (1.46)	2.85 (1.81)	1.38 (1.62)	1.30 (1.59)

(Mean ± SD)	Male	1.60 (1.71)	1.59 (1.60)	1.01 (1.41)	1.78 (1.87)
Dysphoric Mood	Female	3.21 (1.65)	3.55 (1.60)	1.82 (1.62)	2.20 (2.19)
(Mean ± SD)	Male	2.77 (1.84)	3.26 (1.75)	1.45 (1.73)	3.07 (1.66)
Impaired Tolerance to	Female	2.09 (1.71)	2.35 (1.66)	1.50 (1.52)	2.40 (2.06)
Normal Stress (Mean ± SD)	Male	2.06 (1.73)	3.26 (1.63)	1.09 (1.50)	2.92 (1.79)

Table 4.
Repeated Measures Analysis of Variance: Symptom Ratings by Sex and Conversion Status

Source		*df*	*F*	*p*	η^2
Between subjects					
Positive Symptoms	Sex	1	2.59	.11	.01
	Conversion	1	46.36	.00**	.18
	Sex x Conversion	1	5.07	.03*	.02
	Error	208	(.91)		
Negative Symptoms	Sex	1	13.71	.00**	.06
	Conversion	1	21.17	.00**	.09
	Sex x Conversion	1	2.72	.10	.01
	Error	208	(2.12)		
Disorganized Symptoms	Sex	1	9.56	.00**	.04
	Conversion	1	31.08	.00**	.13
	Sex x Conversion	1	3.06	.08	.01
	Error	208	(1.15)		
Sleep Disturbance	Sex	1	2.41	.12	.01
	Conversion	1	1.62	.21	.01
	Sex x Conversion	1	.00	.95	.00
	Error	207	(3.33)		
Dysphoric Mood	Sex	1	.053	.82	.00
	Conversion	1	8.39	.00**	.04
	Sex x Conversion	1	2.03	.16	.01

	Error	208	(4.25)		
Impaired Tolerance to Normal Stress[†]	Sex	1	1.43	.23	.01
	Conversion	1	21.27	.00**	.09
	Sex x Conversion	1	4.41	.04*	.02
	Error	206	(3.74)		
		Within subjects			
Positive Symptoms	Time	1	124.23	.00**	.37
	Time x Sex	1	1.79	.18	.01
	Time x Conversion	1	8.33	.00**	.04
	Time x Sex x Conversion	1	.31	.58	.00
	Error	208	(.57)		
Negative Symptoms	Time	1	34.40	.00**	.14
	Time x Sex	1	1.62	.21	.01
	Time x Conversion	1	3.39	.07	.02
	Time x Sex x Conversion	1	6.24	.01**	.03
	Error	208	(.61)		
Disorganized Symptoms	Time	1	57.70	.00**	.22
	Time x Sex	1	.06	.81	.00
	Time x Conversion	1	.63	.43	.00
	Time x Sex x Conversion	1	.00	.98	.00
	Error	208	(.48)		
Sleep Disturbance	Time	1	25.42	.00**	.11
	Time x Sex	1	7.56	.01**	.04
	Time x Conversion	1	.35	.56	.00

	Time x Sex x Conversion	1	9.04	.00**	.04
	Error	207	(1.69)		
Dysphoric Mood	Time	1	43.88	.00**	.17
	Time x Sex	1	3.78	.05*	.02
	Time x Conversion	1	3.35	.07	.02
	Time x Sex x Conversion	1	2.87	.09	.01
	Error	208	(1.83)		
Impaired Tolerance to Normal Stress	Time	1	9.70	.00*	.05
	Time x Sex	1	1.93	.17	.01
	Time x Conversion	1	3.71	.06	.02
	Time x Sex x Conversion	1	.01	.91	.00
	Error	206	(1.73)		

* $p < .05$
** $p < .01$

Table 5.
Repeated Measures Analysis of Variance: Individual Positive Symptoms by Sex and Conversion Status

Source		*df*	*F*	*p*	η^2
Between subjects					
Unusual Thought Content	Sex	1	.01	.91	.00
	Conversion	1	35.40	.00**	.15
	Sex x Conversion	1	1.387	.24	.01
	Error	208	(2.91)		
Suspiciousness	Sex	1	1.56	.21	.01
	Conversion	1	28.88	.00**	.12
	Sex x Conversion	1	6.38	.01**	.03
	Error	207	(2.56)		
Grandiosity	Sex	1	4.07	.05*	.02
	Conversion	1	.15	.70	.00
	Sex x Conversion	1	2.49	.12	.01
	Error	208	(2.26)		
Perceptual Abnormalities	Sex	1	7.65	.01**	.04
	Conversion	1	11.34	.00**	.05
	Sex x Conversion	1	1.07	.30	.01
	Error	207	(3.46)		
Disorganized Communication	Sex	1	22.44	.00**	.10
	Conversion	1	18.04	.00**	.08
	Sex x Conversion	1	7.10	.01**	.03

	Error	207	(2.56)		
		Within subjects			
Unusual Thought Content	Time	1	58.70	.00**	.22
	Time x Sex	1	5.79	.02*	.03
	Time x Conversion	1	12.09	.00**	.06
	Time x Sex x Conversion	1	1.14	.29	.01
	Error	208	(1.75)		
Suspiciousness	Time	1	65.63	.00**	.24
	Time x Sex	1	9.41	.00**	.04
	Time x Conversion	1	3.87	.05*	.02
	Time x Sex x Conversion	1	5.16	.02*	.02
	Error	208	(1.39)		
Grandiosity	Time	1	15.21	.00**	.07
	Time x Sex	1	.01	.91	.00
	Time x Conversion	1	3.22	.07	.02
	Time x Sex x Conversion	1	.84	.36	.00
	Error	208	(.94)		
Perceptual Abnormalities	Time	1	68.38	.00**	.25
	Time x Sex	1	.32	.57	.00
	Time x Conversion	1	3.72	.06	.02
	Time x Sex x Conversion	1	2.54	.11	.01
	Error	207	(1.97)		
Disorganized Communication	Time	1	46.48	.00**	.18
	Time x Sex	1	1.42	.24	.01

Time x Conversion	1	.35	.56	.00
Time x Sex x Conversion	1	.88	.35	.00
Error	207	(1.13)		

*$p < .05$
**$p < .01$

Figure 1. *Positive Symptom Severity by Sex and Conversion Status at Baseline and Follow-Up*

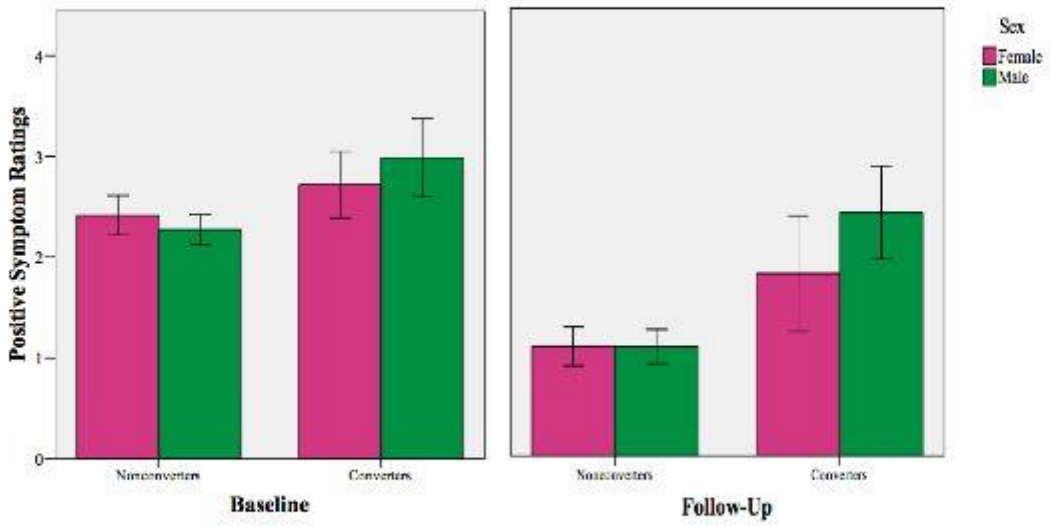


Figure 2. *Negative Symptom Severity by Sex and Conversion Status at Baseline and Follow-Up*

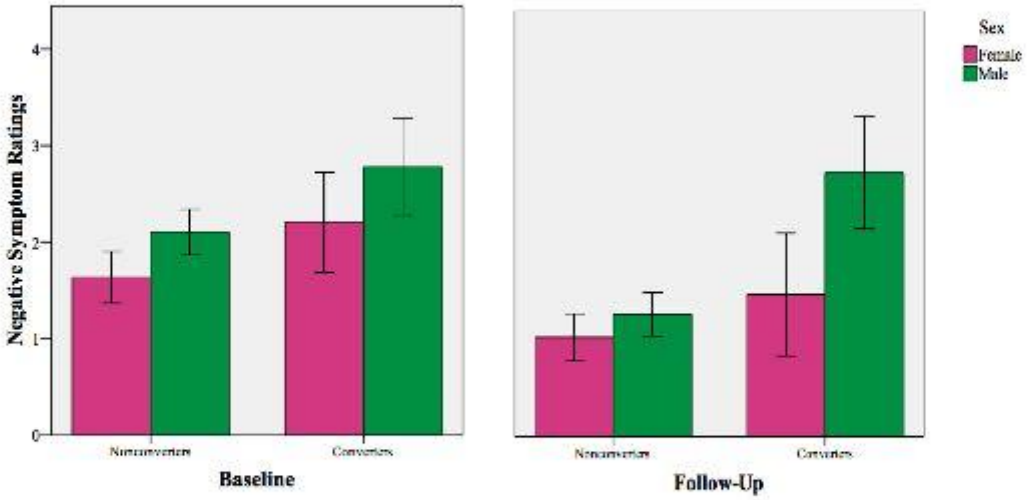
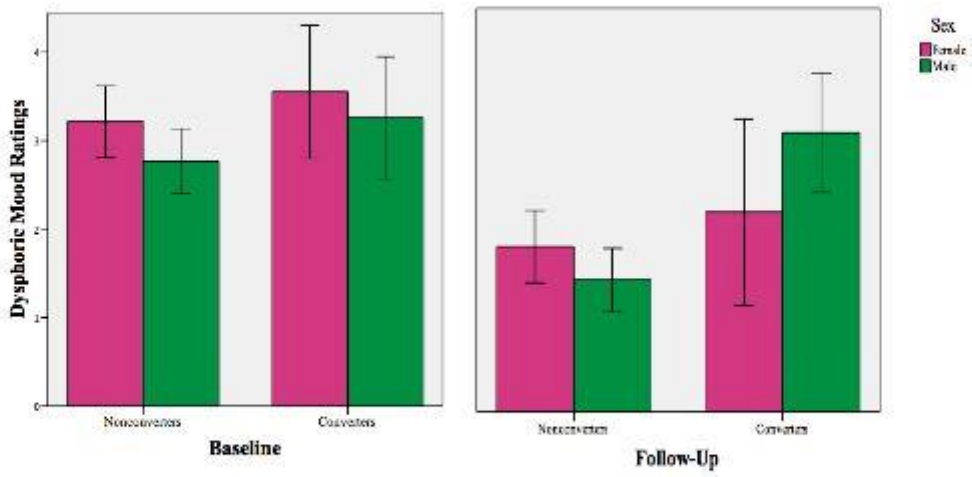


Figure 3. *Dysphoric Mood Severity by Sex and Conversion Status at Baseline and Follow-Up*



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