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Sex Differences in Stress Exposure and Reactivity in Individuals at Clinical High Risk for Psychosis

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Sex Differences in Stress Exposure and Reactivity in Individuals At Clinical High Risk for Psychosis

By

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B.A., Emory University, 2003

Advisor: Elaine F. Walker, Ph.D.

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

Sex Differences in Stress Exposure and Reactivity in Individuals
At Clinical High Risk for Psychosis
By Carrie Holtzman

Psychosocial stress is presumed to be implicated in the etiology of psychotic disorders, based on an extensive body of literature showing an association between the incidence of psychosis and exposure to multiple forms of stress, including childhood trauma, stressful life events, and minor daily stressors. In normative samples, females report greater reactivity to stress than males, and females outnumber males in the prevalence of stress-related disorders such as depression and PTSD. Previous research has demonstrated sex differences in the clinical presentation of schizophrenia and the psychosis prodrome, the period of functional decline and increasing symptoms preceding clinical illness. The present study investigated sex differences in exposure and reactivity to life event and daily stress, as well as exposure to childhood trauma, in a large sample of individuals at clinical high risk (CHR) for psychosis and controls. A stress sensitization hypothesis was also tested, by which history of childhood trauma would amplify both the psychological and biological response to later stressors; it was predicted this effect would be further moderated by sex. Females reported greater exposure to many forms of childhood trauma, as well as increased reactivity to daily stress. CHR participants endorsed greater exposure and reactivity to life event and daily stress, as well as increased exposure to all forms of childhood trauma assessed. Psychological and biological stress sensitization effects were found, but these associations were not moderated by sex. This study contributes to efforts to better understand the role of stress in the emergence of psychosis, in the hopes of further enhancing predictive models of psychosis risk.

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Schizophrenia is a complex, heterogeneous disorder that affects approximately 1% of the population (Jablensky, 1997). 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 et al., 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.

In the past decade, there has been increased interest in the period of functional decline that precedes the clinical onset of psychosis. This period, referred to as the prodrome, varies in duration from months to several years, and is increasingly thought to be the optimal time for preventive intervention (Addington et al., 2012; Addington et al., 2007; Cornblatt, Lencz, Smith, Correll, Auther, & Nakayama, 2003). Accordingly, characterizing the phenomenology of the prodrome has high priority. Indeed, future studies of preventive interventions will depend upon our ability to quickly and accurately identify who is at the greatest risk for developing a psychotic disorder. Integral to the development of sensitive and specific prediction algorithms is an understanding of the extent to which factors found to be associated with schizophrenia and other psychotic disorders impact the phenomenology and progression of the prodrome.

Psychosocial stress has long been hypothesized to be involved in the pathogenesis of schizophrenia and other psychotic disorders, and there is a large body of literature that supports an association between the experience of stress and psychosis (for reviews, see Walker, Mittal, & Tessner, 2008; Phillips, Francey, Edwards, & McMurray, 2007;

Corcoran et al., 2003). Furthermore, emerging evidence suggests that the prodrome might reflect a period of heightened stress sensitivity (Pruessner, Iyer, Faridi, Joober, & Malla, 2011; Palmier-Claus, Dunn, & Lewis, 2012). Consequently, it is of the utmost importance to gain a deeper understanding of the role of stress in the prodrome as well as other factors that might moderate the impact of stress on psychosis risk.

Studies have consistently shown robust sex differences in many aspects of the phenomenology of schizophrenia (for reviews, see Leung & Chue, 2000; Taylor & Langdon, 2006; Salem & Kring, 1998), and recent research with individuals who are at clinical high risk (CHR) for developing a psychotic disorder such as schizophrenia (i.e., individuals who are putatively prodromal) has demonstrated that some of these sex differences are apparent prior to the onset of psychosis (Holtzman et al., in review; Walder et al., 2013; Willhite et al., 2008; Choi, Chon, Kang, Jung, & Kwon, 2009). Research on sex differences 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 (e.g. hormonal influences), or and/or the interaction of these factors.

Research in normative samples has consistently demonstrated a sex difference in stress exposure and reactivity (Davis, Matthews, & Twamley, 1999; Matud, 2004; Almeida, Wethington, & Kessler, 2002), and similar sexually dimorphic patterns have been posited to underlie sex differences in the prevalence of other stress-related psychiatric disorders such as depression (Harkness et al., 2010; Kendler, Kuhn, & Prescott, 2004) and post-traumatic stress disorder (Tolin & Foa, 2006; Koenen & Widom, 2009). There is a relative dearth of studies investigating sex differences in stress

exposure and reactivity in schizophrenia, but preliminary evidence suggests that, as in normative samples, females with schizophrenia are exposed to certain types of stressors and are generally more reactive to stress than males (Fisher et al., 2009; Myin-Germeys, Krabbendam, Delespaul, & van Os, 2004).

The focus of the current study is to explore sex differences in psychosocial stress exposure and reactivity in the prodrome to psychosis, with the goal of elucidating possible etiological mechanisms that might differ for males and females.

Research in the Prodrome

The duration of the prodromal phase of psychotic disorders is highly variable, ranging from months to years, and 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). One of the primary goals of research in the pre-onset or "prodromal" period is to develop algorithms that can accurately predict psychosis so as to target early interventions for individuals who need it most (Cannon et al., 2008) with the goal of delaying or even preventing the onset of psychosis (Addington, et al., 2007). 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 et al., 2003; Cannon et al., 2008; Ruhrmann et al., 2010; Miyakoshi, Matsumoto, Ito, Ohmuro, & Matsuoka, 2009).

Recent studies have combined prodromal symptom ratings with other measures to determine whether prediction of conversion to psychosis can be enhanced beyond that achieved with the symptom ratings alone. For example, Cannon et al. (2008) showed that

positive predictive power (i.e. the proportion of true positives out of all true and false positive results) was improved substantially from 35% (SIPS symptoms alone) to 81% in a 3-factor model including symptoms, genetic risk accompanied by decline in functioning (GRD), and poor premorbid social functioning using data from the North American Prodromal Longitudinal Study (NAPLS). Thompson and colleagues (2011) attempted to replicate these findings in a sample of Australian high-risk participants and found that only unusual thought content, GRD, and low general functioning were significant predictors of conversion. The positive predictive power of the Australian model was significantly lower than the NAPLS algorithm (65.4% vs. 81%), but there were several characteristics of their sample that would likely result in the disparities between model fit, such as a higher percentage of females. The European Prediction of Psychosis Study (EPOS) group derived a prediction model that included six significant predictors, two of which overlapped somewhat with the NAPLS and Australian models—positive symptom score (of which unusual thought content is a component) and global functioning. The EPOS model provided a positive predictive power of 83.3%.

Nonetheless, although these multi-factorial predictive models achieve a higher degree of positive predictive power than prodromal symptoms alone, sensitivity (i.e. the number of true positives identified out of all positive cases and false negatives) remains relatively low, between 30-42%. Consequently, it is clear that additional factors must be taken into consideration in generating the most accurate, targeted models for identifying those at greatest risk for developing a psychotic disorder. Given the predominance of diathesis-stress models of schizophrenia (e.g. Zubin & Spring, 1977), it is possible that including measures of stress exposure and reactivity might enhance sensitivity.

Psychosocial Stress and Schizophrenia

Stressful life events. In the voluminous body of research exploring the relationship between stress and schizophrenia, the majority of studies have focused on stressful life events, i.e., significant life events or changes, especially those that are relatively independent of illness and outside of the individual's control (Phillips et al., 2007). Included among these are negative events (e g., loss of a loved one), positive events (e g., marriage) and events that can be positively or negatively valenced (e.g., moving to a new location). To date, there is no consistent evidence from cross-sectional studies that patients diagnosed with schizophrenia experience more of these stressful life events than healthy or psychiatric controls (for reviews, see Phillips et al., 2007; Walker et al., 2008). However, longitudinal designs have revealed a significant increase in the number of life events preceding psychotic relapse (for review, see Walker et al., 2008), though some studies have failed to replicate these findings (see Phillips et al., 2007).

There are several moderating factors that could explain the inconsistency of these results. First, it might be that a certain threshold in the number of stressful life events must be surpassed to result in symptom onset or exacerbation; indeed, a recent longitudinal population study found that recent negative life events increased the risk of psychotic symptom presentation, but only in the group with exposure to ten or more negative events (Lataster, Myin-Germeys, Lieb, Wittchen, & van Os, 2011). It has also been demonstrated that it is not merely the number of stressful life events that contributes to symptomatology, but rather the extent to which the patient perceives the event as stressful, undesirable, uncontrollable, and poorly handled (Horan et al., 2005; Renwick et al., 2009). Furthermore, there is evidence that patients with schizophrenia exhibit higher

levels of trait-like emotional reactivity than healthy controls, and that emotional reactivity moderates the relationship between stressful life events and increases in psychotic symptoms, such that life events led to symptom exacerbation only in those patients who were high in levels of trait reactivity and anxiety (Docherty, St.-Hilaire, Aakre, & Seghers, 2009). Taken together, these results suggest that individual differences in stress exposure and responses to stress must be taken into consideration in attempting to understand associations between stressful life events and psychosis.

Daily stress. More recently, some researchers have expanded their definition of stress to examine the impact of minor stressors, or "daily hassles" (e.g. getting stuck in traffic or running late for an appointment) on patients with psychosis. These studies have revealed that psychotic, depressive, and anxious symptoms are positively correlated with self-reported minor stressors (for review, see Phillips et al., 2007).

Findings from research using newer measurement approaches converge with these conclusions. Myin-Germeys and her research group in the Netherlands have utilized a paradigm, the Experience Sampling Method (ESM), to assess the immediate impact of stressful experiences on the mood and symptom severity of patients with psychoses (Myin-Germeys et al., 2001; 2003; 2004; 2005; Habets et al., 2012). ESM requires participants to record any stressful experiences, as well as their appraisals of and reaction to them, multiple times a day for several consecutive days. Analyses of ESM data indicated that patients and their first-degree relatives were more reactive to daily stressors than healthy controls and also report concomitant increases in negative affect and severity of psychotic symptoms (Myin-Germeys et al., 2001), which is consistent with evidence

of the moderating role of reactivity in the association between stressful life events and psychosis (Docherty et al., 2009).

Childhood trauma. Exposure to trauma in childhood, a particularly severe form of psychosocial stress, has been linked with risk for subsequent psychosis in several investigations. Varese et al. (2012) conducted a meta-analysis of research on the association between childhood trauma (CT) and psychosis. This review included 41 studies of over 79,000 individuals, encompassing case-control, prospective/quasi-prospective, and population-based cross-sectional research designs. Despite wide variability in study design and measurement of both psychosis and childhood adversity, they found a significant relationship, represented by an odds ratio (OR) of 2.78. Analyses of prospective studies revealed that individuals who had experienced childhood adversity were nearly three times more likely to exhibit psychotic symptoms than individuals with no history of adversity (OR = 2.75–2.99).

Similarly, Varese et al.'s (2012) review of retrospective studies showed that patients with psychosis were more likely to report a history of childhood adversity than controls (OR = 2.72). These associations remained significant when controlling for possible confounds such as urbanicity, gender, SES, genetic family history of mental illness, and cannabis or other drug use. Another recent meta-analysis investigating the relationship between CT and schizophrenia specifically reported similar findings, such that patients with schizophrenia reported higher rates of CT than non-psychiatric controls (OR = 3.60; Matheson, Shepherd, Pinchbeck, Laurens, & Carr, 2013).

Two previous qualitative reviews (Morgan & Fisher, 2007; Bendall, Jackson, Hulbert, & McGorry, 2008) urged caution in positing CT as a putative risk factor based

on evidence of associations between early adversity and later psychotic symptoms or diagnosis due to evidence of multiple potential confounding factors. Namely, family members of individuals with serious mental disorders are characterized by a higher rate of disorders and family discord, and thus the relation between CT and psychosis may reflect correlated family risk factors rather than a causal effect of trauma exposure. Nevertheless, Heins and colleagues (2011) found higher rates of CT in patients diagnosed with schizophrenia than in their unaffected siblings and healthy controls in a study designed to address the methodological limitations outlined by Morgan and Fisher (2007) and Bendall et al. (2008).

Several population-based studies have indicated that psychosis risk increased as a function of experiencing multiple traumas and/or types of trauma throughout childhood (Galletly, van Hooff, & McFarlane, 2011; Whitfield, Dube, Felitti, & Anda, 2005; Spauwen et al., 2006; Janssen et al., 2004; Shevlin, Houston, Dorahy, & Adamson, 2008; Saha et al., 2011). Findings regarding a "dose-dependent" relationship between CT and psychosis are not wholly consistent (e.g., Fisher et al., 2010), though there are often methodological differences between studies as to how trauma is being assessed with respect to type, severity, frequency, and duration.

There is also robust evidence to suggest that symptom severity and the course of schizophrenia are associated with a history of CT (for review, see Read et al., 2005; McCabe, Maloney, Stain, Loughland, & Carr, 2012; Heins et al., 2011; Sahin et al., 2013; Burns, Jhazbhay, Esterhuizen, & Emsley, 2011; Ramsay, Flanagan, Gantt, Broussard, & Compton, 2011; Schenkel, Spaulding, DiLillo, & Silverstein, 2005; Lysaker, Beattie, Strasburger, & Davis, 2005; Uçok & Bikmaz, 2007; Alvarez, Osés, Foguet, Solà, &

Arrufat, 2011). For example, severity and frequency of traumatic experiences has been found to be associated with severity of hallucinations and delusions (McCabe et al., 2012; Heins et al., 2011; Sahin et al, 2013; Burns et al., 2011; Schenkel et al., 2005). Furthermore, evidence indicates that presence of a trauma history is related to the severity of symptoms of depression and anxiety in patients diagnosed with non-affective psychoses (Burns et al., 2011; Schenkel et al., 2005; Lysaker et al., 2005). Research also suggests that a CT is correlated with a more severe course of illness in patients with psychosis than those who had no trauma history, as indexed by earlier age at onset of the disorder, earlier first hospitalization, and more hospital admissions (Alvarez et al., 2011; Schenkel et al., 2005).

Biological Mechanisms in the Associations Between Stress and Psychosis: The Hypothalamic-Pituitary-Adrenal (HPA) Axis

One of the primary neural systems involved in the body's stress response is the hypothalamic-pituitary-adrenal (HPA) axis. After a stressful experience, corticotrophin-releasing factor (CRF) is released from the paraventricular nucleus of the hypothalamus, which stimulates secretion of adrenocorticotrophic hormone (ACTH) from the anterior pituitary gland into the bloodstream (Jameison & Dinan, 2001). ACTH, in turn, leads to the release of glucocorticoids (GC; cortisol in primates and corticosterone in rodents) and catecholamines (adrenaline/epinephrine and noradrenaline/norepinephrine) from the adrenal glands (Lupien, Maheu, Tu, Fiocco, & Schramek, 2007). GCs bind to glucocorticoid receptors (GRs) and mineralcorticoid receptors (MRs), which mediate a negative feedback system in the hippocampus, hypothalamus, and pituitary gland that, in healthy individuals, inhibits further CRF and ACTH production in times of high cortisol

(Corcoran et al., 2003; Walker et al., 2008). As part of the feedback system, GCs cross the blood-brain barrier and they circulate from the adrenal glands to the brain, including hippocampus, hypothalamus, and pituitary gland. Accordingly, GC levels are often used to index HPA axis activity in humans and animals (Kiess et al., 1995; Kirschbaum & Hellhammer, 1989). In humans, cortisol levels are typically measured peripherally, through plasma, saliva, or urine (Levine, Zagoory-Sharon, Feldman, Lewis, & Weller, 2007).

Researchers in the field of stress biology often refer to the HPA-hippocampal system, primarily for two reasons; 1) because the hippocampus is among the brain regions that are most sensitive to the adverse effects of elevated glucocorticoids (Oitzl, Champagne, van der Veen, & de Kloet, 2010), and 2) because the hippocampus appears to play a significant role in the modulation of the HPA axis (Taliaz et al., 2011). As a result, abnormalities in hippocampal structure and function are both a consequence and a cause of HPA dysregulation, and are a focus of researchers interested in understanding the biological underpinnings of stress sensitivity.

There is strong evidence to support the involvement of HPA axis dysregulation in etiology and course of multiple psychiatric disorders, including mood disorders and psychoses (Mannie, Harmer, & Cowan, 2007; Hinkelman et al., 2009; Walker & Diforio, 1997). In a recent review, Walker and colleagues (2008) point out that there are multiple lines of research that support an association between HPA dysregulation and psychosis. First, there is strong evidence that indices of HPA axis activity (i.e., cortisol and ACTH) are elevated in some patients with psychosis. Several studies published subsequent to the review confirm these findings (Guest et al., 2011; Steen et al., 2011; Stetler & Miller,

2011). Guest and colleagues (2011) found increased levels of cortisol in a sample of 236 patients with recent-onset psychosis compared to matched controls, and Steen et al. (2011) reported elevated systemic cortisol metabolism in patients with schizophrenia compared to controls. Furthermore, results from a recent meta-analysis conclude that among patients diagnosed with depression, those with psychotic features exhibit higher levels of cortisol than those without (Stetler & Miller, 2011).

Second, the hippocampal abnormalities observed in patients diagnosed with schizophrenia and other psychotic disorders also implicate HPA axis dysfunction in the pathogenesis of the disorder. Indeed, one of the most consistent findings in neuroanatomical studies of schizophrenia patients is of reduced hippocampal volume in both first episode and chronic samples, with the hippocampus showing more profound reduction than any other brain region (Heckers & Konradi, 2010). Further, several lines of evidence converge to suggest an inverse correlation between hippocampal volume and cortisol levels (e.g., Tessner, Walker, Dhruv, Hochman, & Hamann, 2007). The number of stressful life events has been shown to be inversely correlated with gray matter volume in the hippocampus in a non-psychiatric sample (Papagni et al., 2011).

Third, neuroimaging research has revealed increases in pituitary volume in patients diagnosed with schizophrenia (for review, see Pariante, 2008; Takahashi et al., 2009). The increased volume of the pituitary is hypothesized to reflect HPA axis hyperactivity, consistent with elevations in ACTH (released by the pituitary) observed in individuals with schizophrenia (see Büschlen et al., 2011). In a study using the ESM paradigm described above, it was found that emotional reactivity to daily stress was significantly associated with pituitary volume, especially among patients with

schizophrenia as compared to their unaffected siblings and healthy controls (Habets et al., 2012).

A fourth line of investigation suggesting an association between the HPA axis and psychosis concerns the effects of psychotropic drugs on HPA function. Specifically, agents that dampen cortisol secretion reduce psychotic symptoms, whereas those that augment HPA activity increase symptom expression and psychosis risk. For instance, antipsychotic medications reduce both ACTH and cortisol secretion, in conjunction with psychotic symptoms (for review, see Walker et al., 2008). Indeed, within a sample of first-episode patients, decreases in cortisol and the cortisol/DHEAS ratio over time were directly related to the improvement in depression, negative, and psychotic symptoms (Garner et al., 2011). Conversely, drugs of abuse known to induce or exacerbate psychotic symptoms, including cannabis, amphetamines, and ketamine, increase cortisol secretion in humans (for review, see Walker et al., 2008).

Additionally, these substances have been found to act on dopaminergic transmission (Safont et al., 2011; Abi-Dargham, 2004; Kamiyama et al. 2011), which has long been linked to the etiology of psychosis (for a recent review, see Howes & Kapur, 2009). Indeed, there is substantial evidence that dopamine and glucocorticoids may act in a synergistic manner, in that glucocorticoids enhance dopamine activity, particularly in the mesolimbic region (as reviewed in Walker et al., 2008; van Winkel, Stefanis, & Myin-Germeys, 2008). There is also evidence that psychosocial stressors induce dopamine release in the striatum, with a large positive correlation between dopamine release and cortisol response to stress (Pruessner, Champagne, Meaney, & Dagher, 2004).

Psychosocial Stress in the Prodrome

Clinical researchers have just recently begun to explore the relation of stress—in its many forms—along with the progression and phenomenology of the prodrome. In samples comparing individuals at clinical high-risk (CHR) for developing an Axis I psychotic disorder to healthy controls (HC), the data are inconsistent as to whether CHR participants experience more stressful life events. One study found that adolescents who met criteria for schizotypal personality disorder (SPD), one manifestation of the clinical high-risk state (Woods et al., 2009), reported more total stressful life events than controls, as well as more independent and undesirable events (Tessner, Mittal, & Walker, 2011). Conversely, other studies comparing CHR adolescents and young adults to healthy controls have found no significant difference in number of stressful life events (DeVylder et al., 2013) or that CHR youth report fewer life events (Phillips, Edwards, McMurray, & Francey, 2012). However, in both of these studies, CHR subjects rated the events as significantly more distressing than did controls, consistent with the findings of Horan and colleagues (2005) in their sample of patients with schizophrenia. Indeed, DeVylder and colleagues found longitudinal associations between increased stress sensitivity and later positive and negative symptoms, depression, and anxiety.

With regard to daily stressors, the evidence converges to indicate that although the number of daily stressors experienced does not differ by diagnostic group, CHR individuals report them as more stressful or upsetting than controls (Tessner et al., 2011; Phillips et al., 2012). A study using the ESM paradigm found that CHR subjects were more emotionally reactive to daily stressors, and there was no significant difference between the CHR and psychosis groups in the extent to which suspiciousness increased following daily stressors (Palmier-Claus et al., 2012). Indeed, there is accumulating

support for the hypothesis that the association between stress and psychosis might be stronger in earlier phases of the illness (Corcoran et al., 2003). Pruessner and colleagues (2011) reported that high-risk participants endorsed higher levels of chronic stress than controls and patients in their first episode of psychosis, and stress was a significant predictor of both positive and depressive symptom severity only in the high-risk group.

Childhood trauma. A growing number of studies have investigated the role of trauma in the high-risk samples (Velthorst et al., 2013; Thompson et al., 2013; Sahin et al., 2013; Thompson et al., 2009; Bechdolf et al., 2010; Schürhoff et al., 2009; Holtzman et al., unpublished data). Findings indicate that prevalence rates of trauma in high-risk samples are generally consistent with studies of patients diagnosed with psychosis, though there is a high degree of variability among studies. For example, in studies reporting percentages of the sample endorsing CT, rates ranged from 15.7% (Holtzman et al., unpublished data) to a staggering 97% (Thompson et al., 2009). This stark difference is likely due to methodological issues, such as sampling bias and differences in trauma measurement. In the study by Thompson and colleagues (2009), their small sample of CHR individuals ($N = 30$) was comprised of mostly low SES, minority adolescents in New York City. The lower rates of CT reported by Holtzman et al. (unpublished data) likely result from a narrower measure of CT, in that only childhood physical or sexual abuse were assessed for in a broad, demographically diverse sample.

Despite notable methodological differences, results from studies with CHR and genetic high-risk (GHR; i.e., first-degree relatives of patients with psychosis) suggest that high-risk individuals who report a history of CT experience more severe positive symptoms (Velthorst et al., 2013; Sahin et al., 2013; Schürhoff et al., 2009; Thompson et

al., 2009; Holtzman et al., unpublished data), as well as affective symptoms (Thompson et al., 2009; Holtzman et al., unpublished data). More severe forms of CT, particularly childhood physical and sexual abuse, appear to have a particularly significant impact on later symptom severity (Velthorst et al., 2013, Sahin et al., 2013). Consistent with these findings, two studies of Australian CHR youth have found that childhood sexual abuse significantly predicts conversion to psychosis (Thompson et al., 2013; Bechdolf et al., 2010). Building off the finding that sexual abuse is associated with conversion (Bechdolf et al., 2010), Thompson and colleagues (2013) examined the impact of the severity of the abuse on conversion risk. They reported that for individuals reporting moderate sexual abuse, risk of conversion was doubled (OR= 2.1), whereas conversion risk more than quadrupled for individuals reporting severe sexual abuse (OR = 4.5). No other types of trauma independently predicted conversion to psychosis in either study.

The HPA Axis in At-Risk Samples

Research investigating HPA axis function in putatively prodromal individuals has burgeoned within recent years. Results from studies of CHR participants indicate that at-risk individuals exhibit higher cortisol levels than healthy controls (Walker et al., 2010; Sugranyes, Thompson, & Corcoran, 2012; Walker, Walder, & Reynolds, 2001; Weinstein et al., 1999). Early cross-sectional analyses from NAPLS II are consistent with these findings, in that CHR subjects had higher baseline levels of cortisol than healthy controls (Walker et al., 2013). Additionally, results indicated modest positive correlations between cortisol levels and baseline positive, negative, and disorganized symptoms, as well as dysphoric mood and stress sensitivity as indexed by the SIPS (Miller et al., 2002). Using the same measure of prodromal symptoms, Sugranyes and colleagues (2012)

reported a large correlation between cortisol levels and stress sensitivity ($r = 0.53$), which trended toward statistical significance ($p = .06$). However, no other significant associations between cortisol levels and symptom severity were identified. Corcoran et al. (2012) found significant associations between cortisol and impaired tolerance to normal stress, anxiety, and suspiciousness. These findings are partially consistent with results from an Australian prodromal clinic, which examined associations between cortisol, psychosocial stress, and clinical measures in a small sample of CHR participants ($N = 23$; Thompson et al., 2007). They found that baseline cortisol levels were associated with the severity of symptoms of depression and anxiety, but not psychotic symptoms. Further, cortisol was positively correlated with daily hassles but not stressful life events. Results from studies comparing large samples of CHR adolescents and young adults to healthy controls indicate that individuals who later converted to psychosis exhibited higher cortisol levels than non-converters and healthy controls (Walker et al., 2013; Walker et al., 2010).

Cortisol levels were also significantly associated with both positive symptom exacerbation (i.e., increase in suspiciousness) and emotional reactivity to daily stress in a cross-sectional study using the ESM paradigm in GHR participants and healthy controls (Collip et al., 2011). Consistent with reports from other high-risk samples, GHR manifested higher cortisol levels than controls, as well as greater cortisol reactivity in response to daily stress. Building off of that study, Collip and colleagues (2013a) examined whether the association between cortisol levels and ESM-measured stress reactivity is moderated by hippocampal volume in diagnosed patients, their unaffected siblings (i.e., GHR), and healthy controls. Three-way interactions between diagnostic

group, hippocampal volume, and both emotional and cortisol reactivity to daily stress were found: in both patients and their unaffected siblings, those with volumetric reductions in the left hippocampus were more reactive to daily stress as indexed by concomitant increases in negative affect and cortisol. These results provide evidence that dysregulation of the HPA axis observed in high-risk samples is associated with impaired negative feedback of the HPA axis due to decreased hippocampal volume, consistent with the findings seen in patients diagnosed with psychosis (for review see Walker et al., 2008).

There is also converging evidence of stress-induced dopamine release in the striatum of individuals at genetic (Brunelin et al., 2010) and clinical (Mizrahi et al., 2012; Soliman et al., 2008) high risk for psychosis, similar to the pattern of results seen in patients with schizophrenia (Pruessner et al., 2004). These findings suggest that stress-induced elevations of striatal dopamine release might represent a biomarker for increased risk for psychosis.

Sex Differences in Schizophrenia and the Prodrome

Studies have consistently shown sex differences in the age-at-onset, premorbid functioning, course, and symptomatology of schizophrenia. As compared with males, females diagnosed with schizophrenia have a later onset of the disorder, superior premorbid functioning as well as social and occupational functioning, a less severe course of illness, and a better prognosis (for reviews, see Leung & Chue, 2000; Salem & Kring, 1998; Bardenstein & McGlashan, 1990). With regards to symptom presentation, males experience more severe negative symptoms, whereas females report more severe affective symptoms (see Leung & Chue, 2000).

Sex differences in the early subclinical or "prodromal" antecedents to clinical onset have received comparatively little attention. Because the prodromal period is increasingly viewed as the likely point of entry for preventive interventions (Addington et al, 2007; Cornblatt et al., 2003), it is important to understand differences between males and females in this phase of the disorder. Specifically, identifying sex differences in the prodrome could contribute to refining the existing multivariate models described above (e.g. Cannon et al., 2008; Thompson et al., 2011; Ruhrmann et al., 2010) for predicting who is at greatest risk for developing a psychotic disorder and, therefore, who is in greatest need of intervention.

Regarding age-at-onset of the prodrome, the findings are mixed, with one study reporting no sex difference (Cohen, Gotowiec, & Seeman, 2000) and another reporting that males had a significantly younger onset of prodromal symptoms (Häfner, Maurer, Löffler, & Riecher-Rössler, 1993). Recent analyses indicate that CHR females exhibit superior social and role functioning (Walder et al., 2013), which converges with the evidence that females diagnosed with schizophrenia show better premorbid functioning than males (Larsen, McGlashan, Johannessen, & Vibe-Hansen, 1996; Bardenstein & McGlashan, 1990). Furthermore, several studies have found that prodromal males manifest more severe negative symptoms than females (Holtzman et al., in review; Willhite et al., 2008; Choi et al., 2009). Again, these findings are consistent with the well-replicated sex difference in negative symptoms in schizophrenia (see Leung & Chue, 2000). However, no studies have as yet extended the sex difference in affective symptoms observed in schizophrenia backward chronologically to the prodrome (Holtzman et al., in review; Willhite et al., 2008; Choi et al., 2009). This is possibly due

to lack of measures designed to assess depression specifically, such as the Calgary Depression Scale for Schizophrenia (CDSS; Addington, Addington, & Schissel, 1990).

Normative Sex Differences in Stress Exposure and Reactivity

Stressful life events. A meta-analytic review of 119 studies comprised of over 83,000 participants concluded that females endorse more stressful life events than males and also describe the events as more stressful (Davis et al., 1999). More specifically, the results indicate that the sex difference in appraisal of events as more stressful is more robust than the sex difference in stress exposure. A more recent population-based study of Spanish adults is somewhat inconsistent with the findings of Davis et al. (1999), in that there was no sex difference in number of stressful life events in the previous two-year period (Matud, 2004). However, in line with the conclusions of the meta-analysis described above, females did report that their life events were more upsetting and stressful than males. The converging evidence seems to suggest that although females might not experience significantly more stressful life events than males, they are more reactive to them. It is also possible that males have a tendency to underreport their level of subjective stress.

Daily stress. Whereas there is not a clear sex difference in frequency major life events, females tend to report more daily stressors than males (Matud, 2004; Almeida et al., 2002; Almeida & Kessler, 1998). Consistent with the data from studies of stressful life events, there is a sex difference in the perceived stressfulness of daily stressors, such that females have higher ratings of perceived stress than males (Almeida et al., 2002). One study also found that females report higher levels of chronic stress than males, which

was more strongly correlated with the number of daily stressors they experienced than the number of stressful life events they endorsed (Matud, 2004).

Childhood trauma. The results of a meta-analysis of 290 articles examining sex differences in the prevalence of trauma exposure indicate that males tend to have greater exposure to potentially traumatic events (Tolin & Foa, 2006). Females exceeded males only in sexual trauma, both in childhood and adulthood. A recent study of prospectively-followed victims of childhood trauma (as identified by court records) confirms these findings, such that females reported significantly more childhood sexual abuse (Koenen & Widom, 2009). There is no evidence to support a sex difference in rates of childhood physical abuse in the general population (Tolin & Foa, 2006; Koenen & Widom, 2009). Data are inconsistent with regards to a sex difference in childhood neglect, with a recent study finding that there was a greater prevalence of neglect among males (Koenen & Widom, 2009), yet the meta-analytic review cited above concluded that males and females did not differ in rates of neglect (Tolin & Foa, 2006).

HPA axis function. The body of research examining normative sex differences in HPA axis function is characterized by inconsistent findings. However, a recent review concluded that women tend to exhibit less HPA responsivity to stressors than males, though these findings were somewhat dependent on the type of stressor involved, menstrual status, menopausal status, and/or pregnancy (Kajantie & Phillips, 2006). These findings suggest complex interactions between the HPA and HPG axes that likely emerge over the course of adolescence. Indeed, a recent study of HPA function across the span of puberty indicated that females displayed increased baseline cortisol levels over the course of puberty as well as increased cortisol output in response to

pharmacologic challenge when compared with males (Stroud, Papadonatos, Williamson, & Dahl, 2011). Taken in concert with converging evidence that adolescence is a period of increased sensitivity to stress (for review, see Walker, Sabuwalla, & Huot, 2004: Eiland & Romeo, 2013), it seems that adolescent females might be particularly vulnerable to the deleterious effects of stress.

There is also preliminary support for a sex difference in the effects of childhood trauma on HPA axis function. DeSantis and colleagues (2011) found in a non-clinical sample that females who experienced trauma demonstrated higher response to CRH challenge than males with a trauma history (DeSantis al., 2011). Furthermore, childhood trauma was positively associated with baseline cortisol in females but negatively associated in males (DeSantis et al., 2011).

Sex Differences in Stress Exposure and Reactivity: Other Psychiatric Disorders

Sex differences in the associations of psychosocial stress exposure and risk of psychopathology in other stress-related psychiatric disorders might provide valuable insight for understanding the modulating effect of sex on the pathogenesis of schizophrenia. In major depressive disorder (MDD), in which females outnumber males almost 2:1 in lifetime prevalence (Kessler, McGonagle, Swartz, Blazer, & Nelson, 2003), it has been found that females report significantly more stressful life events prior to the onset of depression (Harkness et al., 2010) and that childhood sexual abuse predicts later MDD among women (Kendler et al., 2004; Kendler, Thornton, & Gardner, 2000).

There is also a robust sex difference in lifetime prevalence of post-traumatic stress disorder (PTSD), such that females are twice as likely to develop PTSD as males (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995). As noted above, males are more

likely to experience potentially traumatic events, with the exception of childhood sexual abuse (Tolin & Foa, 2006; Koenen & Widom, 2009). In a general population sample, childhood sexual abuse was found to be more common in women and more predictive of trauma symptoms than other forms of childhood trauma (Briere & Elliott, 2003). Taken together, these findings from stress-related psychiatric disorders other than schizophrenia indicate that sex differences in certain types of stress exposure might confer risk for psychopathology differentially for males and females.

Sex Differences in Stress Exposure and Reactivity in Schizophrenia and the Prodrome

To date, there is a relative paucity of studies investigating sex differences in psychosocial stress exposure or reactivity in schizophrenia and the putative prodrome. Evidence is converging to suggest that females diagnosed with schizophrenia or at high-risk report higher rates of some forms of CT than males (McCabe et al., 2012; Fisher et al., 2009; Thompson et al., 2013; Velthorst et al., 2013; Sahin et al., 2013). Although one study of a large sample of participants with schizophrenia reported that females reported higher rates of general childhood adversity, which included CT as well as other items like loss of a sibling or growing up in poverty (McCabe et al., 2012), Fisher and colleagues (2009) reported that females in their first episode of psychosis were more likely to report childhood physical and sexual abuse than matched control subjects. Specifically, these childhood trauma variables predicted later diagnostic group assignment (i.e., cases vs. controls) for females, but not for males. These findings held after controlling for numerous potential confounds, such as family history of mental illness.

Findings from studies with CHR participant indicate that CHR females are more likely to report childhood sexual abuse (Thompson et al., 2013; Velthorst et al., 2013; Sahin et al., 2013), which is consistent with data regarding normative sex differences in reporting of childhood sexual abuse (Tolin & Foa, 2006; Briere & Elliott, 2003). Given evidence that childhood sexual abuse is uniquely predictive of conversion to psychosis (Thompson et al., 2013; Bechdolf et al., 2013), over and above other types of trauma (Thompson et al., 2013), it is possible that the relationship between childhood trauma and later psychosis might be stronger for women.

There is also preliminary evidence that females with schizophrenia are more stress reactive. Employing the ESM paradigm in a small sample ($N = 42$) of patients diagnosed with a psychotic disorder, Myin-Germeys and colleagues (2004) found that female patients were more emotionally reactive to daily stress than males as indexed both by increases in negative affect as well as decreases in positive affect. Clearly, further research is needed to elucidate the impact of sex differences in stress exposure and reactivity in both diagnosed patients and putatively prodromal individuals in the hopes of identifying etiological mechanisms that can inform preventative interventions.

Stress Sensitization

Recently, in the field of mood disorders, the notion of "stress sensitization" has become more salient as investigators have focused on the determinants of stress reactivity in psychopathology. "Stress sensitization" refers to the augmenting effects of stress/trauma exposure on subsequent responses to stress. Several recent studies of large samples have documented this effect. For example, a recent report from a longitudinal study of a large population cohort revealed that stress exposure was associated with

increased risk of mood symptoms and appraisal of events as more stressful, but that the magnitude of these effects varied according to subjects' history of childhood trauma (McLaughlin, Conron, Koenen, & Gilman, 2010). Specifically, recent major stressors were associated with a 27.3% increase in risk of depression in the subsequent year among individuals with three traumatic childhood events, but a 14.8% increase in risk among those with no childhood trauma. These stress sensitization effects were found for depression, PTSD, and other anxiety disorders in both males and females. There were, however, sex differences in the amount of stress needed in the past year to reach the threshold for triggering such effects, with females having a lower threshold for response. Similar results of sensitization effects are reported by other investigators (Glaser, van Os, Portegijs, & Myin-Germeys, 2006; Slavich, Monroe, & Gotlib, 2011; Stroud, Davila, Hammen, & Vrshek-Schallhorn, 2011; Wichers et al., 2009). Although the neural mechanisms underlying stress sensitization are unknown, it has been suggested that alterations to the HPA axis by significant early life stress may be a factor. Specifically, it has been proposed that exposure to extreme or repeated stress/trauma can result in heightened HPA reactivity to later stressors (McLaughlin et al., 2010).

To date, the only evidence of a stress sensitization effect in patients with schizophrenia is from studies employing the ESM paradigm. For example, life events were not directly associated with perceived stressfulness of daily stressors, but patients reporting higher number of life events were more emotionally reactive to daily stress, as indexed by increases in negative affect and decreases in positive affect (Myin-Germeys et al., 2003). In a more recent study using ESM, patients with a history of CT displayed higher sensitivity to daily stress as indexed by both higher emotional and psychotic

reactivity (Lardinois et al., 2011). It has been suggested that increased stress sensitivity is an endophenotype for psychosis, constituting an "affective pathway" to illness (Myin-Germeys et al., 2007).

Potential neurobiological substrates for a sensitization effect in psychosis have been proposed (Yuii, Suzuki, & Kurachi, 2007; van Winkel et al., 2008; Collip, Myin-Germeys, & van Os, 2008). Building on research with patients with depression (Heim et al., 2000, Heim et al., 2008) it has been posited that childhood trauma leads to hyperactivity of the HPA axis in response to future stressors (Yuii et al., 2007). Further, both animal and human studies have found that the experience of significant early life stress results in stronger mesolimbic dopaminergic response to psychosocial stress (for review, see Collip et al., 2008). Given evidence cited above that these two systems interact (see Walker et al., 2008; van Winkel et al., 2008), it seems likely that the proposed sensitization effect of childhood trauma represents the synergistic effect of glucocorticoids and mesolimbic dopamine. If stress sensitization effects were identified in CHR individuals, psychosocial and medical interventions targeted at reducing stress reactivity might ultimately delay or prevent the onset of psychosis in a subset of the population. Moreover, in light of evidence that stress sensitization may be more pronounced in females at risk for mood disorders, sex differences in stress sensitization may characterize the prodrome to psychosis.

Hypotheses and Research Questions

Based on the above review, the following hypotheses and research questions will be tested:

1. Based on evidence that females report more subjective stress than males, it is hypothesized that female participants in both diagnostic groups will rate life event and daily stressors as more stressful than male participants.
2. It is hypothesized that there will be a sex difference in rates of exposure to childhood sexual abuse across diagnostic groups, with females reporting higher rates. This is based on evidence of such a sex difference in studies of both healthy and clinical samples.
3. Given evidence that females diagnosed with schizophrenia exhibit more severe affective symptomatology, it is predicted that CHR females will report higher levels of affective symptoms.
4. A significant diagnostic group difference is predicted, such that CHR participants will report significantly more childhood trauma (CT) and higher stress ratings in response to other life events and subsequent daily stressors compared to controls.
5. It is hypothesized that CT exposure will be associated with more severe positive and affective symptom severity based on research findings indicating that CT is associated with these symptom dimensions in patients diagnosed with schizophrenia, as well as evidence that childhood sexual abuse predicts conversion to psychosis.
6. Drawing on theoretical models and findings concerning stress sensitization, it is predicted that exposure to CT will be associated with 1) higher stress ratings in response to other life events and subsequent daily stressors, 2) significantly stronger positive associations between cortisol levels and stress ratings of life

event and daily stressors, and 3) significantly stronger positive associations between cortisol levels and positive and affective symptom severity.

7. Finally it is hypothesized that the stress sensitization effects described above will be moderated by sex, such that females will manifest a more pronounced stress sensitization effect of CT exposure than males.

Method

Participants

This sample includes all individuals participating in the North American Prodrome Longitudinal Study (NAPLS; Addington et al., 2012) as of October 2011 for whom baseline data were available for the PERI Life Events Scale (LES) and the Daily Stress Inventory (DSI). Of the available 540 participants, 370 had complete CT and stress data. Of this 370, 44.1% were female, and 250 met prodromal syndrome criteria (CHR; 67.6%). These participants range in age from 12-35 (M = 19.11, SD = 4.46) and are majority Caucasian (57.3%). The 370 participants who were included in this study did not differ significantly from the 170 who were excluded with regard to sex [χ^2 (1, N = 540) = 1.03, p = .311], age [t(538) = -0.54, p = .599], or race [χ^2 (1, N = 540) = 7.11, p = .262]. However, those who were excluded were more likely to endorse Latino heritage [χ^2 (1, N = 540) = 7.28, p = .007] and were less likely to report CT [χ^2 (1, N = 540) = 23.18, p < .001] than participants who were included.

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). 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. The severity ratings for dysphoric mood and impaired tolerance to normal stress will be analyzed separately as indices of affective symptomatology.

Criteria of Prodromal Syndromes. 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 (Woods et al., 2009) and is now included as a prodromal syndrome.

Psychiatric Epidemiology Research Interview Life Events Scale (PERI-LES). An abbreviated version of the PERI Life Events Scale (Dohrenwend, Askenasy, Krasnoff, & Dohrenwend, 1978) consisting of 59 items selected from the original 102 to be appropriate for age levels ranging from adolescence through early adulthood. Participants are provided with a list of major and minor stressful life events (e.g. "lost a job" or "took a vacation") and are asked to indicate whether they have experienced any of the events over the course of their lifetime. A clinician then asks follow-up questions regarding each event endorsed by the participant to determine on a scale of 1 ("no stress") to 7 ("caused me to panic") how stressful the participant felt the event was. Stressful life events are further subdivided into categories of events largely though to be independent of the individual's illness (e.g. death of a parent) as compared to those more immediately influenced by, or dependent on, illness (e.g. moving to a worse living situation).

Daily Stress Inventory (DSI). The DSI (Brantley, Waggoner, Jones, & Rappaport, 1987) is a self-report form consisting of 58 items assessing the presence of minor daily stressors or hassles (e.g. "did something you did not want to do" or "had difficulty in traffic") in the 24 hour period prior to their baseline clinical assessment. If the participant indicates he/she experienced any of the events, they were asked to indicate how stressful they found it on a scale of 1 ("occurred but was not very stressful") to 7

("caused me to panic"). The DSI has demonstrated acceptable reliability and validity (Brantley et al., 1987).

Calgary Depression Scale for Schizophrenia (CDSS). The CDSS (Addington et al., 1990) is a semi-structured interview with nine items rated on a scale from 0 to 3, with higher scores indicating greater symptom severity. This scale is designed to provide a measure of depressive symptoms separately from negative symptoms and has demonstrated reliability and validity in studies of patients diagnosed with schizophrenia (Addington et al., 1992, 1994) and in CHR individuals (Addington, Liu, & Addington, 2014).

Documentation of trauma before the age of 16. Participants were asked by an interviewer whether or not they experienced any of the following types of trauma prior to the age of 16: psychological bullying, physical bullying, emotional neglect, psychological abuse, physical abuse, and sexual abuse. Participants simply answer yes or no to each type of potentially traumatic experience. The minimum score is 0 (reflecting no endorsement of trauma), and the maximum score is 6 (reflecting endorsement of all 6 types of trauma included in the questionnaire).

Structured Clinical Interview for Axis I DSM-IV Disorders (SCID-I/P). The SCID–I/P (First, Spitzer, Gibbon, & Williams, 1998) is a comprehensive assessment of the symptom criteria for DSM-IV Axis I disorders (APA, 2000), which is used to identify any comorbid disorders.

Procedure

The study protocol was approved by Institutional Review Boards at all the participating NAPLS sites (Emory University, Harvard University, University of Calgary,

University of California Los Angeles (UCLA), University of California San Diego, University of North Carolina (UNC), Yale University, Zucker Hillside Hospital), and participants provided informed consent or assent (parental informed consent for minors).

A detailed description of study procedures has been published (Addington et al., 2012). Briefly, participants were recruited via clinician referral and through announcements on the Internet and in local periodicals and newspapers. Upon presentation to the clinic, participants received the SIPS and SCID-I/P at an initial screening interview to assess for the presence of one of the prodromal syndromes described above as well as any Axis I disorders. CHR participants were excluded if they had ever met criteria for an Axis I psychotic disorder, and control participants were excluded if they met DSM-IV criteria for an Axis I psychotic disorder, had a first-degree relative with a current or past psychotic disorder, or met prodromal criteria. General exclusions included substance dependence lasting longer than six months, presence of a neurological disorder, or Full Scale IQ < 70. Upon study entry, participants completed a baseline clinical interview, at which point the PERI-LES, DSI, CDSS, and the documentation of trauma before the age of 16 were administered, in conjunction with other questionnaires and semi-structured interviews. All interviews were conducted by trained interviewers who were clinical psychologists, psychiatrists, advanced graduate students, and other staff who all met reliability standards for the study (Addington et al., 2012)

Saliva Collection and Assay. During the course of the baseline clinical interview, participants provided three saliva samples in the research clinic, with approximately an hour in between each collection point. As reported in Walker et al.

(2013), sampling typically began around 10:00am, with a range of 9:00am-11:30am (*SD* =26 minutes). CHR and control groups did not differ in time of sampling onset (Walker et al., 2013). The cortisol values from these three saliva samples averaged to provide a more reliable measurement of baseline cortisol levels.

Prior to the baseline clinical visit, participants received instructions asking them to refrain from the intake of caffeine, alcohol, OTC medications, and dairy products both the night before and morning of their appointment. At the beginning of the appointment, the clinical interviewer ascertained the participants' adherence to these instructions. Saliva samples were collected using a passive drool method, for which participants provided 5mL of saliva. Following sample obtainment, samples were stored in a -20°C freezer. Samples were rapidly thawed and centrifuged in preparation for assay. All samples were assayed for salivary cortisol (μg/dL) using a highly sensitive enzyme immunoassay (Salimetrics, State College, Pennsylvania). The test uses approximately 25 μL of saliva (for singlet determinations), has a range of sensitivity from 0.007-1.8mg/dL, and average intra-assay and interassay coefficients of variation of less than 10% and 15% respectively. All samples were assayed in duplicate.

Data Analyses

Statistical analyses were conducted with IBM SPSS Statistics Version 21.0 (IBM Corp., Armonk, New York). Chi-square analyses and independent *t*-tests were used to compare the CHR and control groups, as well as males and females, on demographic variables and CT exposure.

Group differences in stress exposure and reactivity. To investigate group differences in exposure to life events stress, multivariate analysis of covariance

(MANCOVA) was used. As described above, some life events are considered to be relatively independent of illness status, so these events were considered separately from life events more likely to result from illness. The PERI-LES is a cumulative measure assessing exposure to major life events beginning with birth up until the baseline appointment, so the number is likely to vary given the wide age range of the sample. Moreover, many of the life events included are likely to be associated with increasing age (e.g., getting married or losing a job). Consequently, age was included in the model as a covariate. Group differences in exposure to daily stress were examined by means of univariate analysis of variance (ANOVA). Analysis of covariance (ANCOVA) was used to assess group differences in stress reactivity to life events and daily stress, with the number of events a participant endorsed as a covariate.

Group differences in symptom severity. Multiple linear regression was used to determine if group differences exist in positive and affective symptom severity, with one exception: the impact of CT, sex, and their interaction on depressive symptom severity was examined using a negative binomial regression model with log link (see Gardner, Mulvey, & Shaw, 1995). The distribution of CDSS total scores was highly positively skewed, and the negative binomial regression is the preferred analysis for the modeling of count data, particularly when there is an overrepresentation of "0" values.

Stress sensitization effects. Finally, multiple regression was used to test for a stress sensitization effect of CT on psychological and biological reactivity to life event stress, daily stress, and the severity of positive symptoms, dysphoric mood, and impaired tolerance to normal stress. The stress sensitization effect of CT on psychological and biological reactivity in the form of depressive symptom severity was tested once again

using negative binomial regression with log link. In the analyses examining sensitization of stress reactivity, sensitization was assessed by means of an interaction term of CT and exposure to either life event or daily stress. To investigate sensitization of biological stress response, an interaction of CT and exposure to life event or daily stress was tested as a predictor of mean baseline cortisol levels. Stress sensitization, as indexed by positive and affective symptom severity, was assessed by means of an interaction term of CT and mean baseline cortisol levels. To determine if sex moderates the stress sensitization effect, three-way interaction terms were created, with sex added to the interaction terms described above. Given evidence of significant effects of age and time of sampling on cortisol levels in the NAPLS 2 sample (Walker et al., 2013), these variables were included as covariates in all analyses involving cortisol. Cortisol values were centered to provide a standardized measure for analyses.

Results

Demographics and Clinical Characteristics

There were no significant sex or diagnostic group differences in age or racial/ethnic background (see Table 2). Across the entire sample, 61.6% of participants reported experiencing at least one type of trauma prior to the age of 16; however, when considering the CHR group alone, the rate increased to 74%. Nevertheless, only 2.4% of participants met criteria for PTSD on the SCID at baseline, with another 3.5% meeting a lifetime history of PTSD. All individuals determined to have either current or lifetime PTSD were in the CHR group, and there was no significant sex difference in rates of PTSD diagnosis.

Sex Differences

Sex Differences in Stress Exposure and Reactivity. As shown in Table 3, with regard to stress exposure, males and females did not differ in the total number of life events reported. Looking at specific types of life events, there was also no significant sex difference in the number of independent or dependent events. Similarly, males and females reported equivalent exposure to daily stressors. There was also no significant sex difference in reactivity to life event stress. However, as hypothesized, females exhibited higher stress reactivity to daily stress, rating daily hassles as more stressful than males, regardless of diagnostic group membership (see Table 3).

Sex Differences in Exposure to Childhood Trauma. As predicted, females across diagnostic groups reported higher rates of sexual abuse prior to the age of 16 (see Table 4). Females also endorsed higher rates of childhood physical abuse, emotional abuse, and neglect than males. Moreover, females reported greater exposure to multiple types of trauma than males [χ^2 (1, N = 370) = 19.51, p = .003].

Sex Differences in Affective Symptoms. Contrary to what was predicted, CHR males and females did not differ in their ratings of dysphoric mood [F(1,244) = 1.98, p = .161] or impaired tolerance to normal stress [F(1, 244) = 1.69, p = .195] from the SIPS. There was also no sex difference in CDSS total score [Wald χ^2 (1, N = 248) = 0.44, p = .505].

Diagnostic Group Differences: CHR vs. Controls

Diagnostic Group Differences in Stress Exposure and Reactivity. As shown in Table 5, CHR participants reported a higher number of total life events—independent as well as dependent—than controls, with small to moderate effect sizes. CHR participants also endorsed experiencing more daily stressors than controls, with a moderate-to-large

effect size (partial $\eta^2 = .11$). Further, CHR participants rated both life events and daily stressors as more stressful than controls.

Diagnostic Group Differences in Exposure to Childhood Trauma. CHR participants reported higher rates of each type of trauma than controls (see Table 6). As hypothesized and as illustrated in Figure 1, CHR participants also endorsed more exposure to multiple types of trauma than controls [χ^2 (1, $N = 370$) = 65.01, $p < .001$]. Of note, 100% of the participants who acknowledged a history of childhood sexual abuse and 90% who endorsed a history of childhood physical abuse were in the CHR group.

Childhood Trauma and Symptom Severity: Impact of Sex

Among CHR participants, the association between CT and positive symptom severity was moderated by sex as predicted (see Table 7). However, follow-up analyses indicated that the association is stronger in males than females, contrary to what was hypothesized (see Figure 2). For ratings of dysphoric mood, there was a trend for a main effect of CT. There was a significant main effect of CT in predicting ratings of impaired tolerance to normal stress. CT was also associated with depressive symptom severity [Wald χ^2 (1, $N = 248$) = 6.26, $p = .012$], but this relationship was not significantly moderated by sex [Wald χ^2 (1, $N = 248$) = 1.10, $p = .295$].

Psychological Stress Sensitization: CT and Reactivity to Life Event and Daily Stress

As hypothesized, CT moderated the relationship between exposure and reactivity to life event stress in CHR participants, such that individuals who experienced more types of CT exhibited higher reactivity to major life events (see Table 8, Figure 3). Sex also moderated this relationship, with females showing stronger reactivity to life event stress than males, but only if they experienced a high number of major life events (see Figure

4). As shown in Table 8, a similar pattern of results was found to predict reactivity to daily stress (see also Figures 5, 6).

Biological Stress Sensitization: CT and Cortisol

Table 9 indicates a lack of association between exposure to life event stress and mean baseline cortisol levels in CHR participants, regardless of sex or CT exposure. However, CT significantly moderated the association between daily stress exposure and mean baseline cortisol levels (see Table 10, Figure 7), such that the association is stronger for participants who experienced more types of CT. With regard to symptom severity, the addition of cortisol measures to the model did not predict positive symptoms above and beyond the interaction of CT and sex described above [cortisol: $\beta = -.37$, $t(181) = -0.84$, $p = .405$; cortisol x sex: $\beta = .76$, $t(181) = 1.52$, $p = .131$; CT x cortisol x sex: $\beta = -.78$, $t(181) = -1.25$, $p = .213$]. Table 11 illustrates that CT significantly moderated the relationship between baseline cortisol levels and dysphoric mood. Follow-up analyses indicated that the association was stronger for the participants who reported exposure to fewer types of trauma [$r_{lowCT}(108) = .20$, $p = .040$ vs. $r_{highCT}(71) = .04$, $p = .742$]. The direction of this interaction was counterintuitive, so the model was tested again given possible suppression effects by other predictors. When examining the interaction of CT and cortisol independently, the interaction term was no longer significant. For ratings of impaired tolerance to normal stress, there was a significant main effect of CT that was rendered non-significant when other predictors (i.e., sex, baseline cortisol levels, and interaction terms of CT, sex, and baseline cortisol) were added to the model (see Table 11). Several previous studies with CHR samples have reported correlations between baseline cortisol levels and this specific symptom rating

(Walker et al., 2013; Corcoran et al., 2012; Sugranyes et al., 2012). Notably, the study by Walker et al. (2013) used baseline data from NAPLS 2 and showed only modest correlations of cortisol with symptom severity, so the null findings in the full model of the present study likely represent suppression effects. As with positive symptoms, the inclusion of cortisol in the model of depressive symptom severity did not increase the predictive power of the model beyond the main effect of CT described above [cortisol: Wald χ^2 (1, N = 190) = 1.10, p = .294; cortisol x sex: Wald χ^2 (1, N = 190) = 0.22, p = .642; CT x cortisol x sex: Wald χ^2 (1, N = 190) = 0.44, p = .506].

Discussion

As it currently stands, there are two primary goals of research in the psychosis prodrome: 1) to gain a better understanding of the etiological mechanisms contributing to the pathogenesis of psychotic disorders, and 2) to develop predictive models that make it possible to target preventative intervention at individuals who are at highest risk. Previous literature in both patients diagnosed with schizophrenia and individuals at high risk for psychosis has implicated psychosocial stress as a likely factor in disease expression. Indeed, it has been suggested that the psychosis prodrome might be a period characterized by particular sensitivity to stress. Further, research has elucidated sex differences in many aspects of the presentation of schizophrenia, and recent studies have shown that these sex differences precede the onset of the disorder. Research with normative samples has shown sex differences in exposure and reactivity to certain forms of psychosocial stress, including types of childhood trauma, such that females report higher levels of some stressors and exhibit stronger reactivity to stress regardless of level

of exposure. As such, it is possible that women are particularly susceptible to the effects of stress in the presence of a predisposition to psychosis.

The present study used the largest sample to date of prospectively identified participants at clinical high risk for psychosis to examine sex differences in exposure and reactivity to psychosocial stress in the psychosis prodrome. Further, the present study tested a stress sensitization hypothesis, in which the experience of CT might lead to stronger psychological and biological reactivity to stress later in life, and whether this effect might be moderated by sex. Results replicate and extend past findings regarding both diagnostic group and sex differences in rates of childhood trauma and other forms of psychosocial stress, and the stress sensitization hypothesis was partially supported. The discussion below summarizes the pattern of findings, delineates limitations of the study, and identifies future directions for research in this area.

Sample Characteristics

The prevalence of exposure to CT in this sample of CHR individuals was much higher than would be expected in the general population. The current rate of 74% is nearly three times higher than a general population sample, in which 25% of individuals reported a traumatic experience by age 16 (Costello et al., 2002). The increased rate of CT in the present study is consistent with other research in high-risk samples (Velthorst et al., 2013; Thompson et al., 2009). Of note, the prevalence of posttraumatic stress disorder is much lower than the general population prevalence of approximately 8% (Kessler et al., 1995) despite the elevated rate of CT. This is likely due to the experiences and/or symptoms for which participants were recruited and included in the study (e.g. attenuated positive symptoms), which generally do not overlap with symptoms of PTSD.

Sex Differences

Consistent with studies of normative samples (Matud, 2004; Almeida et al., 2002; Almeida & Kessler, 1998), females across diagnostic groups reported higher reactivity to daily stressors than males, despite no significant difference in the number of events reported. This finding also converges with results of studies employing the Experience Sampling Method (ESM) described above in patients diagnosed with schizophrenia (Myin-Germeys et al., 2004), suggesting that sex differences in stress sensitivity precede the onset of the disorder. Collip and colleagues (2013c) extended the use of the ESM in a large general population sample of female twins and reported that the persistence of subclinical psychotic symptoms over a 14-month period was predicted by increased reactivity to daily stress. These findings lend support to the proposition that increased stress reactivity constitutes a marker of psychosis risk that might be more powerful for females, consistent with the idea of an "affective pathway" to psychosis (Myin-Germeys et al., 2007). However, a similar study needs to be conducted in a sample that includes males to determine if this is a sex-specific effect. Contrary to prediction, females in the current study did not endorse higher ratings of stress in response to major life events.

As hypothesized, females across diagnostic groups were significantly more likely than males to endorse a history of sexual abuse prior to the age of 16. The sex difference in the prevalence of childhood sexual abuse is well established in the general population (Tolin & Foa, 2009; Koenen & Widom, 2009; Briere & Elliott, 2003). Together with the findings of the present study, evidence is converging that this sex difference extends to the psychosis spectrum, including studies of both patients with schizophrenia (Fisher et al., 2009) and CHR participants (Velthorst et al., 2013; Thompson et al., 2013; Sahin et

al., 2013). This is particularly salient, as childhood sexual abuse has been found to predict conversion to psychosis in Australian CHR samples (Thompson et al., 2013; Bechdolf et al., 2010). In the present study, females were also more likely than males to report experiencing childhood physical abuse, emotional abuse, and emotional neglect, which is inconsistent with data from normative samples demonstrating no significant sex difference in nonsexual forms of abuse or neglect found. (Tolin & Foa, 2006; Briere & Elliott, 2003). Australian researchers have recently found that CHR females had higher ratings of emotional abuse (Thompson et al., 2013), but the current study appears to be the first study to find increased rates of physical abuse and neglect among females.

Evidence suggests individuals with a history of childhood sexual abuse in the general population are also more likely to experience other forms of childhood trauma, including physical abuse, neglect, and maltreatment (Pérez-Fuentes, Olfson, Villegas, Wang, & Blanco, 2013). This suggests that the heightened physical and emotional trauma in female participants compared to males within the current study may have been driven in large part by the high rate of sexual abuse among females in the CHR group. Likewise, recent studies have demonstrated that females diagnosed with schizophrenia endorsed exposure to more childhood adversity than males (McCabe et al., 2012), and CHR females endorsed higher levels of overall trauma than males (Thompson et al., 2013). It is notable that a recent study of college students indicated that self-reported stress sensitivity mediated the relationship between traumatic life events and attenuated positive symptoms, but only in females (Gibson et al., 2014). Taken together, these findings lend support to a female "preference" for the "affective pathway" to psychosis proposed by Myin-Germeys et al. (2007).

Contrary to prediction, there were no significant sex differences in affective symptoms as indexed by the "dysphoric mood" and "impaired tolerance to normal stress" items from the SIPS (Miller et al., 2002), as well as the CDSS (Addington et al., 1990). The lack of sex difference in "dysphoric mood" and "impaired tolerance to normal stress" severity is consistent with previous findings from studies examining these items on the SIPS (Holtzman et al., in review; Willhite et al., 2008). Further, research investigating sex differences in depressive symptom severity with the CDSS is inconsistent; some reports demonstrate that female patients report more severe depression (Martín-Reyes et al., 2011), others show no sex difference in depression severity (Ayesa-Arriola et al., 2014; Müller, 2007), while still others indicate that males exhibited more severe depressive symptoms (Rocca et al., 2005). It has been argued that depressive symptoms represent a core feature of the psychosis prodrome (Yung et al., 2003; Häfner, Maurer, Trendler, an der Heiden, & Schmidt, 2005; Cunningham Owens, Miller, Lawrie, & Johnstone, 2005), possibly as a reaction to increasing positive symptoms (Drake et al., 2004; Birchwood, Iqbal, & Upthegrove, 2005) and a decline in role functioning or increased withdrawal related to increasing stress sensitivity. Therefore, the lack of sex difference in affective symptoms in the present study could be due to the centrality of this clinical characteristic in this stage of the disorder, when one's insight into one's illness and functioning is still relatively intact (Cotton et al., 2012).

Diagnostic Group Differences: CHR vs. Controls

As predicted, CHR participants rated life event stressors as more stressful than controls, which is consistent with previous findings in both patients diagnosed with schizophrenia (Horan et al., 2005; Renwick et al., 2009; Docherty et al., 2009) and other

high-risk samples (Tessner et al., 2011; Phillips et al., 2012; DeVylder et al., 2013). CHR participants also endorsed a higher number of life events than controls, including events considered to be relatively independent of illness. Previous research with CHR samples is mixed with regard to whether high-risk individuals experience more stressful life events than controls; one study has found that they do (Tessner et al., 2011), one study found no significant difference between CHR and controls (DeVylder et al., 2013), and one study found that controls reported more life events than CHR (Phillips et al., 2012). The sample in the present study is the largest and most geographically and racially diverse compared to the samples of the studies listed above, so it is possible that the current findings more accurately reflect population differences in exposure to life event stressors.

Similarly, CHR participants also endorsed more daily stressors and were more reactive to them than controls. This is the first study to date to document a significant difference between CHR and controls in the number of daily stressors reported, with a moderate effect size (partial $\eta^2 = .11$) according to the Cohen's conventions for η^2 (Cohen, 1988). The finding that CHR individuals rate daily stressors as more stressful than controls is consistent with previous studies of CHR samples (Tessner et al, 2011; Phillips et al., 2012; Palmier-Claus et al., 2012). It has been suggested that the psychosis prodrome might represent a period of particular stress sensitivity (Pruessner et al., 2011; Palmier-Claus et al., 2012; Corcoran et al., 2003). Given that the age of onset for schizophrenia is typically in late adolescence to young adulthood, the stress sensitivity of the prodrome maps onto other research suggesting that adolescence is a developmental

period characterized by increased stress sensitivity as well (Walker, Sabuwalla, & Huot, 2004; Eiland & Romeo, 2013).

CHR participants reported more exposure to all six forms of CT than controls. Similar findings have been reported in an Australian CHR sample (Velthorst et al., 2013; Thompson et al., 2013). These results are consistent with the conclusions of two recent meta-analyses of case-control studies including patients diagnosed with schizophrenia, such that patients were more likely to report childhood adversity than controls (Varese et al., 2012; Matheson et al., 2013). Further, participants in the CHR group were more likely to report exposure to multiple forms of CT; in fact, all of the individuals who endorsed experiencing all six forms of trauma were in the CHR group. Results from large general population studies have suggested that experiencing multiple types of trauma predicts later psychosis in a "dose-dependent" fashion (Galletly et al., 2011; Shevlin et al., 2008). However, total trauma score on the Childhood Trauma Questionnaire (Bernstein et al., 1994) was not predictive of conversion to psychosis in a recent study of CHR individuals (Thompson et al., 2013). It is possible that the observed "dose-dependent" relationship between exposure to multiple traumas and later psychosis is mediated by other factors, such as increased sensitivity to stress.

Stress Sensitization

The present study conceptualized stress sensitization as an association between the experience of CT and later psychological reactivity to both daily and life event stress, as well as more severe positive and affective symptoms. Further, it was hypothesized that CT would result in biological stress sensitization, such that the relationship between cortisol levels and stress exposure/symptom severity would be stronger in individuals

reporting a history of CT. It was predicted that sex would significantly moderate these relationships, such that females would manifest a stronger effect of stress sensitization.

As hypothesized, CT moderated the relationship between stress exposure and reactivity for both life events and daily stress, supporting a sensitization effect of CT on the psychological response to stress. Additionally, a biological stress sensitization effect on daily stress was shown for individuals reporting greater exposure to multiple types of trauma, but no effect was found with life event stress. This is consistent with previous findings from a CHR sample (Thompson et al., 2007), in which cortisol predicted reactivity to daily stress but not life events. Moreover, these results replicate and extend previous research using the Experience Sampling Method, which demonstrated that CT amplifies emotional and psychotic reactivity to daily stress (Lardinois et al., 2011). In fact, the present study provides the first evidence of both psychological and biological stress sensitization in the psychosis spectrum observed with a procedure other than the Experience Sampling Method. This is noteworthy, as consistent findings from studies using various methodologies across different levels of measurement provides convergent validity of the effect.

Sex also significantly moderated the association between stress exposure and reactivity for both life events and daily stress. The pattern of findings indicates that, at lower levels of stress exposure, males and females do not differ with regard to the intensity of stress reactivity; however, at higher levels of life event and daily stress, females are significantly more reactive than males. It appears that the sex difference in stress reactivity to life events and daily stress among CHR participants does not become evident until the level of stress exposure has crossed some sort of threshold.

The hypothesis that sex would further moderate the sensitization effects of CT was not supported. So, although CT enhances the stress response similarly for males and females, females in this sample reported higher rates of exposure to multiple forms of trauma, as well as greater exposure to childhood sexual abuse. Consequently, it is possible that stress sensitization by CT is simply more prevalent among females, rather than exerting a stronger effect, thereby resulting in a possible female "preference" for an "affective pathway" to psychosis (Myin-Germeys et al., 2007).

As hypothesized, sex significantly moderated the relationship between CT and positive symptom severity in CHR participants, but the direction of effects was contrary to what was predicted: exposure to more types of trauma was associated with more severe positive symptoms in males but not females. As females were more likely to report exposure to multiple types of trauma, it is possible that the males who endorsed multiple traumatization manifested particularly severe positive symptoms. Given the mean age of the sample, it is also possible that stress sensitization with regard to positive symptoms is stronger in males, as late adolescence represents the modal risk period for males to experience their first psychotic episode. Further research employing more comprehensive measurement of CT is needed to determine what is driving this interaction. There was no significant association between cortisol and positive symptoms, which is not consistent with previous findings of small, yet significant, correlations between baseline cortisol levels and positive symptom severity on the SIPS (Walker et al., 2013; Sugranyes et al., 2012; Corcoran et al., 2012). Therefore, it is possible that the significant associations reported in other CHR studies reflect the impact of childhood trauma. CT also significantly predicted affective symptom severity, which is consistent with results from

studies of patients diagnosed with schizophrenia (Burns et al., 2011; Schenkel et al., 2005; Lysaker et al., 2005), but the addition of cortisol to the model did explain any additional variance in symptom severity. These findings provide evidence of a psychological, but not biological, sensitization effect with regard to symptom severity that does not differ by sex.

Strengths and Limitations

There are several notable strengths of the present study. First, the sample size is the largest of any study investigating group differences in stress exposure and reactivity in individuals at high-risk for psychosis. As a result, there was sufficient statistical power to detect small effects. As stated above, the sample of the current study is also more geographically and racially diverse than other CHR samples, which increases the extent to which findings can be presumed to represent characteristics of a psychosis risk state vs. specific geographical or cultural factors. Additionally, as noted in Walker et al. (2013), the sample of the present study is comprised of the first half of participants who completed the baseline assessment for NAPLS 2. Therefore, the other half of the sample can be used to replicate and extend the stress sensitization effects found here.

Another strength relates to the inclusion of both psychological and biological indices of the stress response. Further, the ascertainment of multiple salivary cortisol samples was advantageous, in that it allows for the derivation of a more reliable mean baseline cortisol level. Given complex interactions of cortisol and gonadal hormones (see Kajantie & Phillips, 2006), the study is limited by the lack of information regarding the menstrual status of female participants on the day they provided their saliva samples. However, data suggest that self-report of information regarding menstruation (i.e., first

day of the last period or cycle length) is unreliable (Wideman, Montgomery, Levine, Beynnon, & Shultz, 2013; Small, Manatunga, & Marcus, 2007). Indeed, Small et al. (2007) found that females who were younger, unmarried, and reported lower income were less reliable in estimating the length of their menstrual cycles; these features characterize many of the females included in the current study.

The reliance on self-report measures of CT and stressful life events is problematic due to the possibility of recall error or bias that is influenced by psychiatric symptoms (Dohrenwend, 2006). However, there is growing evidence that reports of CT by patients with schizophrenia are reliable (Fisher et al., 2011; Heins et al., 2011). Moreover, one of the advantages of prospective research in CHR samples is that the temporal distance from childhood experiences to baseline assessment is shorter than in typical retrospective designs and therefore less susceptible to the effects of illness on recall. In the present study, the mean age of participants was approximately 19 years old, and the measure of trauma inquires about exposure to events prior to the age of 16.

The primary limitation of the study is the limited measure of CT. While exposure to multiple forms of trauma is certainly one marker of the severity of childhood adversity, the documentation of trauma prior to the age of 16 provides no information regarding other factors that likely contribute to the stress sensitization effect of CT such as frequency, duration, age at first onset, and relationship to perpetrator. Many of these factors are included in the Childhood Trauma Questionnaire (CTQ; Bernstein et al., 1994), which is a 28-item self-report measure that assesses sexual, physical, and emotional abuse, as well as emotional and physical neglect. CTQ data allow for more

fine-grained analyses with regard to which aspects of trauma lead to the most deleterious outcomes.

Future Directions

The findings of the present study raise many considerations for future research. First, the present study focused only on associations at the baseline assessment, so it is of great importance to determine the impact of CT and CT-related increases in stress reactivity and symptom severity on longitudinal outcomes in CHR samples. Australian researchers have demonstrated that childhood sexual abuse is a unique predictor of conversion to psychosis (Thompson et al., 2013; Bechdolf et al., 2010), so replication should be attempted in the NAPLS 2 sample.

Further research should also investigate possible mediators and moderators of the stress sensitization effect of CT on stress reactivity and symptom severity. For example, the present study found that CT predicted affective symptom severity, and there is data to suggest that affective symptoms at least partially mediate the relationship between CT and psychosis (Bebbington et al., 2011; Freeman & Fowler, 2009). With regard to moderation, revictimization in adulthood (e.g., sexual assault) might hold significant implications for diathesis-stress models of psychosis. For instance, in a British study of the general population by Bebbington and colleagues (2011), it was found that experiencing childhood sexual abuse significantly increased an individual's risk of later psychotic symptoms (OR = 3.49), particularly if the abuse included non-consensual sexual intercourse (OR = 10.14). When revictimization in adulthood was examined as a "post-hoc moderator" on the association between childhood sexual abuse and later psychosis, they found that revictimization significantly amplified the risk (OR = 10.78),

particularly for non-consensual sexual intercourse (OR = 17.65). These results suggest that traumatization at multiple time points in the lifespan could be particularly important for psychotic outcomes, and it is important to test this hypothesis in CHR samples given findings in the general population and the greater opportunity for preventive intervention in this population. Ruling out possible confounds of the impact of CT on stress reactivity and symptom severity, such as SES or family history of mental illness, should also be a priority in future studies.

Future studies should also examine biomarkers in addition to cortisol that might underlie the stress sensitization effect of CT. For example, significant structural differences in the brain have been found as a result of CT, including reductions in the size of the corpus callosum, as well as volumetric reductions in the left hippocampus and amygdala (Teicher et al., 2003). Reduced hippocampal volume is found in both PTSD and schizophrenia (Woon & Hedges, 2008; Walker et al., 2008). Recent results from a structural imaging study indicate that childhood sexual abuse is uniquely associated—in part—with volumetric reductions in gray matter observed in patients with psychosis (Sheffield, Williams, Woodward, & Heckers, 2013). This volumetric reduction likely reflects the interaction of genetic risk factors and changes in gene expression resulting from exposure to CT. These complex interactions provide another promising field for exploration. Recent studies in general population samples have found that functional polymorphisms in the genes for *BDNF* (Alemany et al., 2011), which is associated with neuroplasticity, and *FKBP5* (Collip et al., 2013b), which modulates glucocorticoid receptor sensitivity and is associated with the feedback loop of the HPA axis, moderate the relationship between CT and later psychotic symptoms. Animal studies have also

provided evidence of increased DNA methylation of prefrontal *BDNF* (for review, see Roth et al., 2011), as well as the *NR3C1* gene (see Szyf, 2012), which codes for glucocorticoid receptors.

In conclusion, the present study found that females reported higher levels of reactivity to daily stress as well increased exposure to most forms of childhood trauma. CHR participants reported significantly higher exposure and reactivity to both life event and daily stress, as well as higher rates of endorsement of all forms of childhood trauma. Further, this study was the first to find evidence of both psychological and biological stress sensitization effects of childhood trauma on stress reactivity and symptom severity in a CHR sample. Sex did not moderate this effect as hypothesized, but rather exerted independent effects on stress reactivity. Further research is needed to elucidate the pathogenic mechanisms involved in the relationship between childhood trauma and later psychosis.

Table 1

Demographic Characteristics of Included Participants vs. Excluded Participants

Variable		Included (n = 370)	Excluded (n = 170)
Age (Mean ± SD years)		19.11 ± 4.46	18.89 ± 4.15
Sex (% male)		55.9%	60.6%
Race (n, %)	First Nations	4 (1.1%)	5 (2.9%)
	East Asian	11 (3.0%)	3 (1.8%)
	Southeast Asian	6 (1.6%)	4 (2.6%)
	South Asian	9 (2.4%)	4 (2.6%)
	Black	50 (13.5%)	29 (17.1%)
	South/Central American	18 (4.9%)	10 (5.9%)
	West/Central Asia & Middle East	3 (0.8%)	2 (1.2%)
	White	212 (57.3%)	91 (53.5%)
	Hawaiian/Pacific Islander	4 (1.1%)	0 (0.0%)
	Interracial	53 (14.3)	22 (12.9%)
Ethnicity (n, %)	Latino/a	63 (17.0%)	46 (27.1%)
Childhood Trauma Exposure (n, %)**	Any CT exposure	228 (61.6%)	67 (39.4%)

**$p < .01$