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Sex differences in morning cortisol in youth at ultra-high-risk for psychosis

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ABSTRACT

Research suggests abnormalities in hypothalamic-pituitary-adrenal (HPA) axis function play an important role in the pathophysiology of psychosis. However, there is limited research on the biological stress system in young people at ultra high risk (UHR) for psychosis. Morning cortisol levels are particularly relevant to study in this context, as these markers reflect HPA regulation. This is the first examination of sex differences in morning cortisol levels in UHR individuals. Twenty-eight UHR and 22 matched healthy control participants were assessed in respect to symptoms and had home-based collection of salivary cortisol over three time points in the morning. It was predicted that the UHR participants would exhibit lower morning cortisol levels and lower cortisol would be associated with greater symptomatology (i.e. higher positive, negative, and depressive symptoms). Additionally, sex differences in morning cortisol levels were explored based on recent evidence suggesting that sex differences may play an important role in the exacerbation of psychosis. While there were no group differences in morning salivary cortisol secretion, there was a sex by time interaction among UHR individuals, such that only UHR males exhibited flat cortisol levels across two hours after awakening, whereas UHR females had a pattern of cortisol secretion similar to healthy controls, even among medication-free individuals ($F = 6.34$, $p = 0.004$). Cortisol AUC (area under the curve) across the three time points had a trend association (medium effect size; $r = 0.34$, $p = 0.08$) with depressive, but not positive or negative, symptom severity. These results stress the importance of considering sex differences in the psychosis-risk period, as they improve understanding of pathogenic processes.

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1. Introduction

The neural diathesis-stress model for psychosis posits that early neurobiological vulnerability and psychosocial stress are important factors in the etiology and exacerbation of schizophrenia and related disorders (Walker et al., 2008). A growing body of evidence suggests that the hypothalamic-pituitary-adrenal (HPA) axis is dysfunctional in patients with schizophrenia (Belvederi Murri et al., 2012; Walder et al., 2000), yet little is known about the relationship between the HPA system and the development of psychosis. Understanding the stress systems in individuals at ultra high-risk (UHR) for developing psychosis (those deemed to meet clinical criteria for a prodromal syndrome) is integral, as the prodrome is a viable period of intervention in which considerable neuroendocrine development is still underway (Spear, 2004). Evidence suggests that HPA system impairment may be present in the prodromal stage of psychosis (Carol and Mittal, 2015; Walker et al., 2013); however, significant differences are not always observed (Cullen et al., 2014; Day et al., 2014). A better understanding of HPA system dysfunction stands to inform the etiological conceptualization of psychosis risk and refine efforts of early detection for adolescents exhibiting subthreshold psychotic-like symptoms.

The HPA axis is one of the primary biological stress systems that moderate the physiological response to psychological and physiological stressors and is sensitive to gonadal hormones (Chrousos, 2000). HPA axis function is most commonly measured through cortisol levels and cortisol secretion has a consistent circadian rhythm (Nader et al., 2010; Walker et al., 2008). The basal rhythm follows the pattern of very low levels in the late evening/early morning, fol-

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lowed by a steady rise during the few hours preceding habitual time of awakening. Superimposed on this basal rhythm is often a rapid increase in cortisol after awakening (cortisol awakening response), with increases peaking between 30 and 45 min. This awakening response resolves within 1–2 h after awakening, and then basal cortisol levels steadily decrease throughout the remainder of the day (Stalder et al., 2016). Changes to the circadian regulation of cortisol are interpreted as an indicator of a dysfunctional biological stress response system and these changes are consistently observed in patients with schizophrenia at multiple time points throughout the day (Corcoran et al., 2003; Nader et al., 2010).

Accumulating evidence suggests that basal cortisol levels during the day are elevated and the dynamic change in cortisol levels in response to awakening is blunted in patients with schizophrenia (Aas et al., 2011; Collip et al., 2011; Mondelli et al., 2010a; Pruessner et al., 2008, 2013b). Studies observed that elevated basal cortisol levels during the day are closely associated with positive symptoms in patients with schizophrenia (Collip et al., 2011; Franzen, 1971; Walder et al., 2000). Additionally, studies posit that the cortisol awakening response is lower in patients with schizophrenia when compared to controls and levels are associated with neurocognitive deficits, environmental stressors, and sex differences (Aas et al., 2011; Mondelli et al., 2010a; Pruessner et al., 2008, 2013b). Specifically, repeated studies have observed a blunted cortisol response to awakening in male but not female patients with schizophrenia (Pruessner et al., 2008, 2015). In summary, findings illustrate a paradoxical relationship between elevated basal levels and blunted awakening response in patients with schizophrenia; however, there is little understanding of this relationship in UHR individuals.

Recent investigations have observed similar basal cortisol elevations in psychosis risk populations (Carol and Mittal, 2015; Day et al., 2014; Karanikas and Garyfallos, 2014; Walker et al., 2010, 2013). Additionally, it has been shown that cortisol levels are closely tied to the illness progression in the UHR period (Walker et al., 2010, 2013); however, the relationship is nuanced, and group differences are not always observed (Cullen et al., 2014; Day et al., 2014). There is currently little understanding of morning cortisol levels and how subsequent cortisol levels change throughout the day in psychosis risk. Only one previous study has examined the cortisol awakening response in an older sample of UHR young adults (Day et al., 2014). Specifically, Day et al. (2014) reported a blunted cortisol awakening response in medication free UHR participants compared to healthy controls and no daytime group differences. Interestingly, there was no difference in the cortisol awakening response when UHR participants who were taking medication were included (Day et al., 2014). These mixed results highlight the increasing need to understand the relationship between changes in cortisol throughout the morning and the symptomatology of UHR individuals, as it stands to inform our etiological conceptualization and refine efforts of early detection for adolescents exhibiting attenuated psychosis symptoms.

In the present study, including a total of 50 adolescents (28 UHR and 22 matched healthy participants), we evaluated if morning cortisol at three different time points in UHR individuals is different compared to healthy controls and if cortisol is associated with symptomatology. Samples were collected upon waking up and 1 h and 2 h post awakening in order to gain an understanding of any abnormalities in the broader morning cortisol pattern. Collection occurred at home to allow for a naturalistic and noninvasive measurement of HPA axis functioning. At-home collection allowed us to follow-up on our previous findings of higher late morning cortisol levels in UHR youth as assessed in a lab setting (Carol and Mittal, 2015). We predicted that the UHR participants would exhibit lower morning cortisol levels when compared to matched healthy controls based on observations from previous findings in high-risk youth (Day et al., 2014). We also predicted that lower cortisol would be associated with greater symptomatology (i.e. higher positive, negative, and depressive symptoms) based on studies reporting a relationship between cortisol abnormalities and psychosis risk symptoms (Mittal and Walker, 2011; Walker et al., 2013). Additionally, in line with sex differences observed in the cortisol awakening response of patients with schizophrenia (Pruessner et al., 2008, 2013b) and recent evidence suggesting that sex differences may play an important role in the exacerbation of psychosis (Leung and Chue, 2000; Pruessner et al., 2013b; Walder et al., 2013), we conducted a secondary analysis examining sex differences in morning cortisol levels.

Table 1
Participant demographics and symptoms.

Group	Ultra High Risk	Healthy Control	*p*-value
Sex			
Male	15	11	
Female	13	11	
Total	28	22	$p = 0.802$
Age			
Mean years (SD)	18.57 (2.01)	17.05 (3.37)	$p = 0.070$
Parent Education			
Mean years (SD)	15.8 (2.00)	16 (1.89)	$p = 0.619$
SIPS Symptoms			
Positive mean (SD)	12.04 (4.96)	0.45 (1.10)	$p < 0.001$
Negative mean (SD)	9.93 (7.14)	0.23 (0.53)	$p < 0.001$
BDI			
Depression mean (SD)	19.75(12.62)	3.73(5.75)	$p < 0.001$

Note: Positive and negative symptoms reflect the total sums from domains from the Structured Interview for Prodromal Syndromes (SIPS); the Depression mean reflects the total sum form the depression domain of the Beck Depression Inventory (BDI).

2. Methods

2.1. Participants

Participants were recruited at the Adolescent Development and Preventative Treatment (ADAPT) research program and a total of 28 UHR adolescents (15 male, 13 female) and 22 control adolescents (11 males, 11 female) participated in a study (see Table 1 for demographic characteristics of this sample). Adolescent UHR and control participants (mean age = 17.9) were recruited by Craigslist, e-mail postings, newspaper ads, bus ads, and community professional referrals. Exclusion criteria included history of head injury, the presence of a neurological disorder, and lifetime substance dependence. The presence of an Axis I psychotic disorder (e.g. schizophrenia, schizoaffective disorder, schizophreniform) was an exclusion criterion for UHR participants. Other comorbid Axis I disorders were not exclusion criteria for UHR participants. Rates of current comorbid Axis I disorders in the UHR participants included 11 (39%) affective disorders, 2 (7%) PTSD, 8 (29%) other anxiety disorders, and 3 (11%) ADHD. Comorbid Axis I disorders are typical of UHR individuals and the present rates are comparable to other studies (Fusar-Poli et al., 2014). UHR individuals met criteria for a prodromal syndrome including: (a) recent onset or escalation of moderate levels of attenuated positive symptoms (a score of 3–5), and/or (b) a decline in global functioning over the last 12 months accompanying the presence of schizotypal personality disorder (SPD), and/or (c) a decline in global functioning over the last 12 months accompanying the presence of a first-degree relative with a psychotic disorder such as schizophrenia (Miller et al., 1999). Meeting for an Axis I disorder or the presence of a psychotic disorder in a first-degree relative were exclusionary criteria for controls.