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# Cortisol awakening response and diurnal cortisol among children at elevated risk for schizophrenia: Relationship to psychosocial stress and cognition

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**Summary** Abnormal hypothalamic-pituitary-adrenal (HPA) axis function, as indexed by elevated diurnal cortisol levels and/or a blunted cortisol awakening response (CAR), has been observed among patients with first episode psychosis and associated with neurocognitive deficits in this population. However, the extent to which these features precede illness onset is unclear. The current study aimed to determine whether children who are at putatively elevated risk for psychosis because they present multiple antecedents of schizophrenia (ASz), and high-risk children with a family history of illness (FHx), are characterized by abnormal cortisol levels when compared with their typically developing (TD) peers. A further aim was to investigate the extent to which cortisol levels are associated with psychosocial stress and neurocognitive function. Thirty-three ASz children, 22 FHx children, and 40 TD children were identified at age 9—12 years using a novel community-based screening procedure or as relatives of individuals with schizophrenia. All participants were antipsychotic-naive and not currently

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seeking treatment for their symptoms. At age 11—14 years, participants provided salivary cortisol samples and completed psychosocial stress measures and tests of memory and executive function. Results indicated that FHx children, but not ASz children, were characterized by a blunted CAR relative to their TD peers (effect size = −0.73, $p = 0.01$) that was not explained by psychosocial stress exposure or by distress relating to these experiences. Neither FHx nor ASz children were characterized by elevated diurnal cortisol. Among both FHx and ASz children, more pronounced HPA axis function abnormalities (i.e., higher diurnal cortisol levels and greater blunting of the CAR) were associated with poorer performance on tests of verbal memory and executive function. These findings support the notion that at least some HPA axis abnormalities described in psychosis precede illness onset, rather than being a subsequent epiphenomenon. We speculate that the blunted CAR may constitute an early (potentially genetically mediated) marker of psychosis vulnerability, whilst elevated diurnal cortisol levels may emerge only proximally to disease onset.
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## 1. Introduction

The neural diathesis-stress model of schizophrenia (Walker and Diforio, 1997; Walker et al., 2008) posits that psychosocial stress may act via the hypothalamic-pituitary-adrenal (HPA) axis (the primary system involved in coordinating the physiological response to stress) to trigger psychosis onset among individuals with an underlying vulnerability for the disorder. Abnormal HPA axis function, as indexed by elevated diurnal cortisol levels and/or a blunted cortisol awakening response (CAR), has been observed in individuals who have recently experienced their first psychotic episode (Borges et al., 2013). Additionally, elevated cortisol levels among first episode patients have been associated with reduced hippocampal volume (Mondelli et al., 2010b), and greater blunting of the CAR with more pronounced deficits in verbal memory and processing speed (Aas et al., 2011). However, the extent to which abnormal HPA axis function precedes the onset of psychosis is currently unclear. Whilst these studies suggest that the first psychotic episode is characterized by HPA axis dysfunction and that this may be associated with some of the neuroanatomical abnormalities and cognitive deficits observed in psychosis patients, it is possible that these HPA axis abnormalities may simply be a consequence of the stress associated with illness onset.

The study of individuals at elevated risk for schizophrenia provides the opportunity to directly test the assumptions of the neural diathesis-stress model (Walker and Diforio, 1997; Walker et al., 2008) and thus determine whether vulnerability for schizophrenia is associated with HPA axis dysfunction. Traditionally, high-risk approaches have focused on individuals with a family history of illness. Studies comparing young adult relatives of patients with psychosis to healthy controls have yielded inconsistent findings, perhaps due to methodological differences. A study examining salivary cortisol at random time-points throughout the day (values averaged) reported elevated cortisol among relatives (Collip et al., 2011), whilst two studies measuring fasting plasma cortisol at a single time-point did not (Brunelin et al., 2008; Yang et al., 2012). A more recent strategy focuses on youth considered at ultra high-risk (UHR) for psychosis whose clinical features (typically, attenuated psychotic symptoms) indicate that they may be in the prodromal phase of illness. Higher salivary cortisol levels (obtained at a single time-point in the morning) have been reported among UHR youth relative to healthy controls, with more pronounced effects among those who were medication-free (Sugranyes et al., 2012). Elevated cortisol levels in UHR youth were similarly observed in a study which examined salivary cortisol obtained at three time-points throughout the morning (values averaged) (Walker et al., 2013). Using a similar sampling protocol, work by Walker and colleagues also indicates that adolescents with schizotypal personality disorder (SPD), who are at greater risk for psychosis on account of their diagnosis, exhibit higher daytime salivary cortisol levels (Walker et al., 2001; Mittal et al., 2007). Thus, elevated salivary cortisol during the day has been consistently observed among youth whose clinical features designate them as being at elevated risk for psychosis. However, none of these studies obtained the multiple samples distributed throughout the day that are required for the examination of diurnal patterns of cortisol secretion (which may be a more reliable marker of HPA axis function given that cortisol levels vary substantially through the day). Furthermore, as no study of high-risk youth has yet examined the CAR, it remains unclear whether the blunted CAR observed among individuals with first episode psychosis also characterizes these youth.

Whilst studies of UHR youth suggest that HPA axis dysfunction precedes the onset of psychosis, these youth are, by definition, already sufficiently distressed as to seek treatment for their symptoms. Thus, elevations in cortisol might feasibly be due to distress relating to emerging illness, as opposed to external psychosocial stressors. Indeed, only one study of UHR youth has examined the association between psychosocial stress exposure and HPA axis dysfunction (Thompson et al., 2007). In this study, higher plasma cortisol levels obtained at a single time-point in the morning were correlated with the number of minor hassles but not with the number of major life events experienced during the past month. Studies of youth with SPD, although not typically confounded by help-seeking behaviour, are limited by the fact that these individuals already present with symptoms of sufficient severity as to meet diagnostic criteria for a schizophrenia spectrum disorder.[1]

[1] Schizotypal (personality) disorder is classified as a schizophrenia spectrum disorder in both the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013) and the International Classification of Disorders Version 10 (World Health Organization, 1992).

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