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Longitudinal Changes in Cortisol Secretion and Conversion to Psychosis in At-Risk Youth

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Abstract

Elevations in hypothalamic–pituitary–adrenal (HPA) axis activity have been implicated in the origins and exacerbation of mental disorders. Several lines of investigation suggest HPA activity, indexed by increased cortisol, is elevated in patients with schizophrenia and other psychotic disorders. This study examined the relation of cortisol levels and longitudinal changes with psychotic outcomes in at-risk adolescents. Participants were 56 adolescents who met risk criteria for psychosis, namely, schizotypal personality disorder ($n = 5$), prodromal symptom criteria based on the Structured Interview for Prodromal Symptoms ($n = 17$), or both ($n = 34$). Of these, 14 subsequently met *DSM-IV* criteria for an Axis I psychotic disorder (schizophrenia, schizoaffective disorder, or mood disorder with psychotic features). Participants were assessed at baseline and then followed longitudinally. Salivary cortisol was sampled multiple times at initial assessment, interim follow-up, and 1-year follow-up. Area under the curve (AUC) was computed from the repeated cortisol measures. The findings indicate that at-risk subjects who subsequently developed psychosis showed significantly higher cortisol at the first follow-up, a trend at the 1-year follow-up, and a significantly larger AUC when compared to those who did not convert. A similar pattern of group differences emerged from analyses excluding those who may have converted prior to the 1-year follow-up. These findings converge with previous reports on HPA activity in psychosis, as well as theoretical assumptions concerning the effects of cortisol elevations on brain systems involved in psychotic symptoms. Future research with larger samples is needed to confirm and extend these results.

Keywords

risk for psychosis; cortisol; adolescents

The role of stress in triggering the expression of biological vulnerability has become a significant focus of research. The importance of this area of investigation has been highlighted by reports on gene–environment interactions in the etiology of mental disorders, as well as advances in our understanding of the neural mechanisms involved in these interactional processes.

Within the last decade, a substantial body of literature has accumulated on hypothalamic–pituitary–adrenal (HPA) function in schizophrenia and other psychoses, and the results support four general conclusions (Walker, Mittal, & Tessner, 2008): (a) Indices of HPA activity (cortisol and adrenocorticotrophic hormone [ACTH]) are elevated in some patients with schizophrenia and other psychoses, especially in nonmedicated and first-episode

patients; (b) antipsychotic medications, particularly atypicals, significantly reduce cortisol, with more pronounced reductions in drug responders; (c) both prescription and recreational drugs that exacerbate or induce psychotic symptoms also increase HPA activity; and (d) glucocorticoid receptors appear to be down-regulated in psychotic patients, suggesting reduced negative feedback on the HPA axis. Taken together, these findings are consistent with the hypothesis that HPA activity can moderate the expression of vulnerability to psychosis.

These and other findings raise questions about the specific nature of the relation between heightened HPA and psychosis. In particular, we do not know if heightened HPA activity is the consequence of psychosis or whether it precedes the onset of psychosis and perhaps plays a role in triggering episodes. The symptoms of psychosis are subjectively stressful and may elicit activation of the HPA axis. Alternatively, as implied in diathesis–stress models, biological stress systems may play a role in triggering the expression of psychosis. Consistent with this assumption, there are a variety of potential neural mechanisms through which glucocorticoid secretion can alter neurotransmitters systems that are often implicated in the pathophysiology of psychosis, namely, dopamine, GABA, glutamate, and serotonin. In particular, the augmenting effects of elevated glucocorticoids on dopamine have been well-documented (Mittal, Dhruv, Tessner, Walder, & Walker, 2007; Walker et al., 2008). Thus, it is possible that increased HPA activity precedes the onset of psychosis.

There is now evidence that individuals at high risk for developing psychosis can be identified on the basis of subclinical signs. This “clinical” high-risk approach enhances prediction beyond that achieved with previous genetic high-risk (i.e., offspring of parents with psychotic disorders) study designs. For example, several studies using standardized procedures for assessing *prodromal* signs have demonstrated that 25% to 40% of these individuals subsequently develop a psychotic disorder (Cannon et al., 2008; Klosterkotter, Hellmich, Steinmeyer, & Schultze-Lutter, 2001; Miller et al., 2003; Olsen & Rosenbaum, 2006). The criteria used in these procedures include severity ratings for “positive” prodromal symptoms and/or the presence of schizotypal personality disorder (SPD). Recent research by our group has revealed that adolescents who meet clinical high-risk criteria show baseline elevations in salivary cortisol when compared to healthy control adolescents (Mittal et al., 2007).

The prediction of conversion to psychosis in clinical high-risk samples has now become the central focus of attention, and indicators of the biological response to stress are of particular interest. To date, only a few published reports have addressed the relation of the HPA system, or its activity, with conversion to psychosis in a high-risk or prodromal sample. In one study, a Melbourne, Australia group measured pituitary volume via magnetic resonance imaging in an ultra high-risk (UHR) group (Garner et al., 2005). Within the UHR group, a larger baseline pituitary volume was a significant predictor of future transition to psychosis. The UHR subjects who later developed psychosis ($n = 31$) had a significantly larger baseline pituitary volume compared with UHR subjects who did not develop psychosis ($n = 63$). Garner et al. (2005) suggested that the larger pituitary volume may be indicative of heightened activation of the HPA axis. However, in another report on 23 UHR subjects, this research group found no relationships of plasma cortisol with global psychopathology, psychotic symptoms, or pituitary and hippocampal volumes (Thompson, Phillips, et al., 2007).

This same group conducted another study in which they administered the dexamethasone corticotrophin releasing hormone (DEX/CRH) test to 12 participants with prodromal symptoms (M age = 19.4 years, $SD = 3.6$; range = 15–25) at baseline, and three of the 12 developed psychosis within 2 years (Thompson, Berger, et al., 2007). Due to the small

sample size, statistical analyses were not conducted, but the authors reported that participants who did not develop psychosis showed a trend toward higher plasma cortisol levels at the latter stages of the test, when compared to the three participants who did develop psychosis. However, this study is limited by the small sample size, the absence of longitudinal data on cortisol secretion, and other methodological factors.

The present study examines the developmental course of cortisol secretion in a larger sample of youth at risk for psychosis. The chief aim is to test the hypothesis that cortisol elevations precede the onset of psychotic disorders and to distinguish at-risk youth who do develop psychosis from those who do not. We focus on the adolescent/young adult period because it is characterized by a rapid increase in risk for psychosis onset, and it is likely to be a critical period for intervention (Walker, 2002).

Method

Participants

Participants were recruited from the Atlanta, Georgia area for a prospective study conducted at Emory University. Recruitment was conducted with announcements posted in health sections of local newspapers and in research newsletters circulated to all practitioners in Emory University clinics and hospitals. The announcements focused on youth with subclinical signs of risk for psychosis and described prodromal symptoms in lay terminology.

This study sample was 56 at-risk adolescents, ranging in age from 12 to 18 years, from whom data on salivary cortisol were obtained at least once during the course of the 1st year, and for whom psychiatric outcome data were also obtained. This includes all at-risk adolescents entered into the study, with the exception of one who withdrew before the baseline assessment was completed. Assent and written consent were obtained from all participants and a parent, in accordance with guidelines of the Emory University Human Subjects Review Committee.

Subjects were designated as “at-risk” if they met *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; *DSM-IV*; American Psychiatric Association, 1994) diagnostic criteria for SPD ($n = 5$), the Scale of Prodromal Symptoms (SOPS) criteria for attenuated positive symptom (APS) syndrome ($n = 17$; Miller et al., 2002), or both risk criteria ($n = 34$). The present sample included the 39 SPD participants described in the report on baseline cortisol by Mittal et al. (2007), as well as the additional 17 participants meeting criteria for APS.

Exclusion criteria at baseline were the presence of a current Axis I disorder, mental retardation, substance addiction (*DSM-IV* criteria for a substance disorder), or neurological disorder. The presence of an Axis I disorder was an exclusion criterion when the present study was initiated in 2003 in order to reduce (a) diagnostic heterogeneity and (b) the proportion of participants currently on psychotropic medications. However, it should be noted that subsequent research indicates that Axis I mood disorders often accompany prodromal symptoms in youth (Meyer et al., 2005).

Demographic characteristics by conversion status are presented in Table 1. Although priority was given to the recruitment of psychotropically naïve participants, a subgroup was on one or more psychotropics. This reflects national trends, in that there has been a significant increase in the number of children who are prescribed psychotropic medications, especially stimulants, anti-depressants, and antipsychotics (Zito et al., 2003). As shown in Table 1, this trend was apparent in the present sample such that a subgroup had been

prescribed psychotropic medication prior to initial assessment. Most of these medications had been prescribed by pediatricians, off-label, with antipsychotics primarily directed at controlling conduct problems, rather than treating psychotic symptoms. Medication status was recorded at each assessment.

Procedure

Diagnostic assessments were conducted at initial assessment and yearly follow-ups. The Structured Interview of *DSM-IV* Personality Disorders (SIDP-IV; Pfohl, Blum, & Zimmerman, 1997) was administered to diagnose Axis II disorders. Previous research has demonstrated that personality disorders, including SPD, can be reliably diagnosed in youth (Levy et al., 1999). For the present study, the standard *DSM-IV* criteria were used, and it was required that the pattern of schizotypal symptoms/signs be stable and of duration greater than 1 year.

The Structured Clinical Interview for Axis I *DSM-IV* Disorders (SCID-I/P; First, Spitzer, Gibbon, & Williams, 1998) was administered to diagnose Axis I disorders and was administered during the initial evaluation and subsequent annual follow-up assessments. The SCID-I/P was utilized to maintain consistency in the diagnostic procedure across participants and over time as they entered young adulthood through the longitudinal course of the study.

The Structured Interview for Prodromal Symptoms (SIPS; Miller et al., 2002, 2003) was administered at initial assessment and annual follow-ups to measure prodromal symptoms. This measure was designed to be appropriate for adolescents and young adults (Miller et al., 2003). The SIPS contains the SOPS, which rates the severity of relevant symptoms with the following scale: 0 = *absent*, 1 = *questionably present*, 2 = *mild*, 3 = *moderate*, 4 = *moderately severe*, 5 = *severe but not psychotic*, and 6 = *severe*. The SOPS is composed of four symptom domains that are classified as *positive* (e.g., unusual thoughts or ideas, suspiciousness, perceptual abnormalities, disorganized communication), *negative* (e.g., social isolation, avolition, decreased expression of emotion, decreased ideational richness, deteriorated role function), *disorganized* (e.g., odd behavior, bizarre thinking, trouble with focus and attention), and *general* (sleep disturbance, dysphoric mood, impaired stress tolerance, and motor disturbances). Following SIPS procedures, all subjects who were designated as prodromal received at least one rating of 3, 4, or 5 on a positive symptom and thus met the symptom severity criteria for the SOPS attenuated positive symptom (APS) syndrome. However, the onset/duration criterion (i.e., onset or 1-point worsening within past 12 months) could not be established for all participants.

Interviews were conducted by either a licensed clinical psychologist or an advanced doctoral candidate. Training of interviewers was conducted over a 2-month period; interrater reliabilities for symptoms ratings exceeded the minimum criterion of .80 (Pearson correlation), and for diagnostic status mean kappa was .85. All interviews were videotaped throughout the course of the study so that interrater reliability could be monitored. Videotapes were reviewed by a clinical psychologist and/or collaborating psychiatrist to confirm diagnostic reliability.

Finally, the Beck Depression Inventory (BDI; Beck, Steer, & Brown, 1996), a 21-item measure of depression, was administered at the baseline. Each item is rated on a scale from 0–3, reflecting severity. This measure was administered because depression is often associated with the prodrome (Myles-Worsley, Weaver, & Blailes, 2007).

Conversion to Psychosis

Of the 56 at-risk participants, two converted to an Axis I mood disorder (major depressive disorder) and 14 (25%) converted to an Axis I psychotic disorder in the 5 years since the inception of the study (initial assessment followed by four annual assessments). Of the 14 who converted to a psychotic disorder, six were diagnosed at the 1st year follow-up, five converted during the following year, and three converted in the 3rd year. Thus, 78% of conversions occurred within the first 2 years after baseline, and the mean time to onset was 19 months ($SD = 5.8$). This conversion rate and time frame is in the range reported in previous longitudinal studies of clinical high-risk samples, in particular those using the SIPS (Cannon et al., 2008; Miller et al., 2003; Olsen & Rosenbaum, 2006). Of those who were subsequently diagnosed with psychosis, nine met criteria for SPD and APS at baseline (a 26% rate of conversion for the SPD and APS group), two met criteria for APS only (a 12% rate of conversion for APS only), and three met criteria for SPD only (a 60% rate of conversion for SPD only). (Although the conversion rate was higher for those who met only SPD criteria at baseline, the total number of subjects in the SPD only group [$n = 5$] was too small to draw inferences about group differences in risk for conversion.) The Axis I psychotic disorders diagnosed in the at-risk sample were schizophrenia ($n = 4$), schizoaffective disorder ($n = 5$), bipolar I disorder with psychotic features ($n = 4$), and major depressive disorder with psychotic features ($n = 1$).

Saliva Collection and Cortisol Assay

Subjects and their parent/guardian were provided with written and verbal dietary instructions to observe the evening before and the morning of sampling. Instructions allowed a light breakfast but instructed participants to refrain from caffeine, alcohol, dairy products, and nonprescription medications, as well as brushing teeth within 30 min prior to sampling. Subjects were questioned to confirm their compliance with the instructions.

Saliva samples for cortisol assay were obtained three times, on the hour, beginning at approximately 9:00 a.m. at each of three assessments: baseline, 7- to 10-month follow-up and 12- to 14-month follow-up. Time of day for sampling was based on evidence that, when compared to afternoon and evening values, morning values are more consistent and reliable, and their variance reflects a higher proportion (60%) of trait as opposed to state variance (Kirschbaum et al., 1990). This is assumed to reflect the cumulative effects of situational factors (e.g., diet, exercise, and daily events) on variance in cortisol measured later in the day. Further, it should be noted that multiple saliva samples ($n = 3$) were obtained so an average could be derived, as this increases the reliability of the cortisol estimate (Li, Chiou, & Shen, 2007).

Saliva was stored in a -20°C freezer. In preparation for assay, samples were rapidly thawed and centrifuged at 300g for 10 min to remove coagulated protein and other insoluble material. Cortisol was assayed in duplicate 200 μL aliquots of the clear supernatant, using materials and procedures provided by Incstar Corporation (Stillwater, Minnesota). The assay was performed in tubes coated with an antiserum that shows significant cross-reactivity only with prednisone (83%), 11-deoxycortisol (6.4%), cortisone (3.6%), and corticosterone (2.3%). Standards in the range 1 to 30 ng/mL consisted of the serum standards provided with the kit materials diluted with 200 μL of phosphate-buffered saline. Protein concentrations were equalized in standards and samples by adding cortisol-free serum to the samples. The mean coefficients of variation between duplicates and between assays were less than 5%. Compared with the serum standards, the mean recovery of cortisol from saliva has been indistinguishable from 100%. Using this method, the range (central 95%) of salivary cortisol concentrations in normal adults has been determined as 1.8 to 10.1 ng/mL. A more detailed

description of methods for salivary collection and radio-immunoassay (RIA) of cortisol can be found in Mittal et al. (2007)

Data Analyses

Cortisol data were available at all three assessments for 23 nonconverted and 11 converted subjects, at the first and second assessment for 12 nonconverted and 1 converted subjects, at the first and third assessments for 7 nonconverted and 2 converted subjects. A t test revealed no differences in baseline symptoms or BDI score between those with and without data at all three assessments. However, a chi-square test revealed a sex difference, such that those with missing data at one or more follow-ups were more likely to be male than female, $\chi^2(1) = 5.30, p < .05$.

In addressing missing data, the current consensus favors multiple imputation (MI), which avoids problems inherent in mean substitution and exclusion of cases with missing data (for a comprehensive overview, see Graham, 2009). Further, MI retains the error variance lost from regression-based single imputation approaches. For the present data set, missing value analysis was first conducted using SPSS (Version 17) to examine the pattern of missing values for mean cortisol at the second and third assessments. The pattern of missing values was nonrandom, in that data were more likely to be missing for those who did not convert to psychosis versus those who did develop psychosis. This pattern likely reflects the higher rate of attrition among individuals who experience a decline in symptom severity. Thus, following Graham (2009), we conducted MI with SPSS, using fully conditional specification (Van Buuren, 2007). The results of the analyses with imputed data, described below, are presented for the pooled results, across five iterations, to derive imputed values.

Following Li et al. (2007), mean cortisol values (average of the three saliva samples from each assessment) were used to calculate the area under the curve (AUC) (Fekedulegn et al., 2007; Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003). AUC is used to derive an aggregate index based on repeated measurements over time, and it is often used in endocrinological studies because it provides a global index of hormonal exposure over time. (See Pruessner et al., 2003, for more detailed information.) Following Pruessner et al. (2003), both AUC with respect to the ground (AUC_g) and AUC with respect to increase (AUC_i) were calculated. AUC_g indexes the total area under the curve, whereas AUC_i is calculated with respect to increases from the baseline value, thereby indexing change beyond baseline over time.

We conducted t tests to compare cortisol values and AUC for the two diagnostic outcome groups, with a conservative two-tailed test criterion for p values.

Results

Analyses were first conducted to test for baseline demographic and clinical differences between those who did and did not convert to psychosis. Chi-square tests revealed no differences between the two groups in sex ratio, $\chi^2(1) = 0.98, p = .31$; ethnic distribution, $\chi^2(3) = 2.20, p = .52$; or proportion on an antipsychotic, $\chi^2(1) = 1.1, p = .31$; selective serotonin reuptake inhibitor (SSRI), $\chi^2(1) = 0.56, p = .45$; or stimulant, $\chi^2(1) = 0.98, p = .32$. As shown in Table 1, t tests showed differences in mean BDI scores by conversion status, with higher scores for those who did convert, $t(54) = 2.96, p < .01$. Also, those who converted to psychosis showed a higher level of baseline negative symptoms, as measured by the SIPS, $t(54) = 2.10, p < .05$.

Mean cortisol values, based on the imputed dataset, by conversion status are presented in Figure 1. As illustrated, the converted group showed an increase in mean cortisol levels over

time. Repeated-measures analysis of variance (ANOVA) of the three cortisol assessments revealed a significant main effect of time, $F(2, 53) = 5.70, p < .005, \eta^2 = .18$, and conversion status, $F(1, 54) = 5.92, p < .04, \eta^2 = .10$, as well as a significant interaction of Conversion Status $\times$ Time, $F(2, 53) = 3.70, p < .04, \eta^2 = .12$. This interaction was due to the absence of a conversion group difference in cortisol at baseline, $t(54) = 0.06, p = .95$, but a significant group difference at the first follow-up, $t(54) = 2.94, p < .01$, and the same trend at the 1-year follow-up, $t(54) = 2.01, p < .05$, with higher mean cortisol for the converted group. The t tests comparing the two groups revealed that the converted subjects showed significantly higher AUCg, $t(54) = 2.70, p < .01$, and AUCi, $t(54) = 2.60, p < .05$, when compared to the nonconverted participants.

Of the 14 converted subjects, six were diagnosed with a psychotic disorder at the annual follow-up. In order to restrict the sample of participants who developed psychosis to those who received a diagnosis at some point after the 1-year follow-up, analyses were conducted excluding the six subjects who were diagnosed at the first annual follow-up. Repeated measures revealed a significant main effect of conversion status, $F(1, 48) = 3.99, p < .05, \eta^2 = .12$, and a marginally significant Conversion Status $\times$ Time interaction, $F(1, 48) = 3.54, p < .05, \eta^2 = .08$. Analyses of the individual cortisol values revealed no group difference at baseline, $t(48) = 0.10, p = .91$, or 1-year follow-up, $t(48) = 0.06, p = .95$, but a significant group difference at the first follow-up, $t(48) = 3.02, p < .05$, with higher mean cortisol for the converted group. Consistent with findings for the entire sample of those who subsequently developed psychosis, t tests revealed that the converted participants showed significantly greater AUCg, $t(48) = 2.88, p < .01$, and a trend toward higher AUCi, $t(48) = 2.14, p < .05$, when compared to those without psychotic outcomes. Thus, elevations in cortisol preceded the first psychotic episode for these participants.

As noted, some participants were on psychotropic medications that can alter cortisol levels. Thus, repeated-measures analysis of covariance (ANCOVA), with medication dummy-coded, was conducted to control for the three major classes of medication reported: stimulants, antidepressants, and antipsychotics. This revealed a significant main effect of time, $F(2, 50) = 5.38, p < .05, \eta^2 = .18$; conversion status, $F(1, 51) = 5.83, p < .02, \eta^2 = .10$; and a significant Conversion Status $\times$ Time interaction, $F(2, 50) = 3.44, p < .05, \eta^2 = .12$. An ANCOVA of the individual cortisol values revealed no group difference at baseline but a significant group difference at the first follow-up, $F(1, 51) = 8.33, p < .01, \eta^2 = .14$, and a trend at 1-year follow-up, $F(1, 51) = 4.02, p = .05, \eta^2 = .07$, with higher mean cortisol for the converted group. An ANCOVA also yielded significant group differences in AUCi, $F(1, 51) = 6.74, p < .01, \eta^2 = .11$, and AUCg, $F(1, 51) = 7.18, p < .01, \eta^2 = .12$, with the converted subjects showing higher values.

Correlation coefficients were computed in order to determine whether depression was linked with heightened cortisol. The results showed no significant relations of BDI scores with cortisol as indexed by baseline and follow-up means, AUCg, or AUCi. This is consistent with previous reports that depressive symptoms are not significantly associated with cortisol secretion in adolescents, although the relation becomes apparent with maturation into adulthood (Forbes, Williamson, Ryan, & Dahl, 2004).

Discussion

We found a 25% rate of psychotic diagnoses in this sample of clinical high-risk youth within 3 years of baseline (Cannon et al., 2008; Miller et al., 2003; Olsen & Rosenbaum, 2006), consistent with the range reported in previous studies. Further, as in previous studies, the diagnostic outcomes were variable, with both affective and nonaffective psychotic diagnoses. We found a higher baseline mean BDI score in those who subsequently met

diagnostic criteria for a psychotic disorder, also consistent with recent reports that depression often precedes psychotics disorders (Miller et al., 2003). Of course, given the temporal instability of diagnoses in the psychotic and mood disorders spectrums, and the young age of the participants, it is likely that some diagnoses will change.

The present findings converge with the growing literature on HPA axis dysregulation in psychosis. Extending our previous reports of elevated cortisol secretion in at-risk youth (Mittal et al., 2007; Walker, Walder, & Reynolds, 2001), the present study revealed that those who convert to an Axis I psychotic disorder manifest a pattern of escalating cortisol secretion that distinguishes them from those who do not develop psychosis. The increase does not appear to be induced by the psychotic episode, as the subgroup who converted after 1 year showed significant elevations prior to the onset of the first episode.

These results are also consistent with reports on the relation of stress-induced striatal dopamine activity with both cortisol and the psychosis prodrome. In experimental studies using positron emission topography (PET), it has been shown that stress-induced cortisol elevations are associated with increased striatal dopamine activity in healthy participants (Oswald et al., 2005; Wand et al., 2007). More recently it has been shown that striatal dopamine activity is heightened in patients with prodromal symptoms and is correlated with severity of prodromal symptoms and neuropsychological impairment, but not with severity of depressive symptoms (Howes et al., 2009).

As noted, only one previously published study examined HPA activity in at-risk individuals who later converted to psychosis, and the focus was on post-dexamethasone suppression test (DST) cortisol levels (Thompson, Berger, et al., 2007). Although the authors deemed the sample too small for statistical analysis, the raw data revealed no trend toward elevated cortisol in those who converted. However, several methodological factors may have mitigated the detection of such a trend. Among these were the one-time measurement of cortisol, the use of blood draws that can induce cortisol elevations, the older mean age of the subjects (19 vs. 14 years for the present sample), and the small sample size. In contrast, in the present study, salivary cortisol was sampled multiple times over 1 year. Also, the younger age of the sample may have allowed us to detect a period of greater sensitivity to HPA dysregulation.

The primary question raised by the present findings is whether the longitudinal cortisol increases are causally related to psychosis conversion. Disentangling the causal mechanisms will require more fine-grained, longitudinal monitoring of both symptom progression and HPA activity in a larger samples. However, findings from several lines of investigation bear on this issue and suggest that elevated cortisol release precedes symptom exacerbation, rather than being solely a consequence of it.

To date, the only published study that entailed regular monitoring of both symptoms and cortisol secretion in psychotic patients was a longitudinal investigation of nonmedicated patients conducted by Sachar and colleagues (Sachar, Kanter, Buie, Engle, & Mehlman, 1970). They measured daily urinary cortisol over a 2- to 3-month period and found that cortisol levels were higher (250%) immediately preceding psychotic episodes when compared to periods of recovery. More recently, a case study report on a Cushing's patient with psychosis revealed that reductions in salivary cortisol concentrations were correlated with resolution of psychosis (Myhill, Sillars, Starkstein, Annus, & Yeap, 2008).

The nature of the causal relationship can also be elucidated with pharmacologic challenge studies. For example, in response to administration of m-chlorophenylpiperazine (m-CPP), a serotonin agonist, schizophrenia patients (Lindenmayer, Adityanjee, Bark, Grochowski, & Moynihan, 1997) and healthy individuals (D'Souza et al., 2006) manifest increases in both

cortisol and psychotic-spectrum symptoms, and the atypical antipsychotic olanzapine significantly blocked m-CPP-induced cortisol (Scheeper, Gespen de Wied, & Kahn, 2001). Similarly, challenge with the active ingredient in cannabis, delta-9-tetrahydrocannabinol (THC), can also activate the HPA axis and exacerbate psychotic symptoms (D'Souza et al., 2005). Further, this investigation showed that schizophrenia patients were more vulnerable than healthy participants to THC effects, although healthy individuals also showed increased cortisol, as well as subtle perceptual distortions, in response to THC.

Only a few investigations have examined the effects of glucocorticoid antagonists on psychosis, with equivocal findings. Most of this work has used mifepristone, which has a high affinity for glucocorticoid II (GRII) receptors, as well as progesterone (DeBattista & Belanoff, 2006). Several studies of patients with psychotic depression have shown that mifepristone administration reduces affective and psychotic symptoms; however, one published report on schizophrenia patients revealed no effect (Gallagher, Watson, Smith, Ferrier, & Young, 2005). However, it is important to note that mifepristone also impairs negative feedback control of the HPA axis and therefore results in a reactive increase in both cortisol and ACTH.

As noted above, it has been shown that there is a normative increase in cortisol during adolescence. Although the present 1-year window was not sufficient to detect this in the nonconverted group, increased cortisol secretion during adolescence has been demonstrated in cross-sectional (Kenny, Preyasombat, & Migeon, 1966; Kiess et al., 1995; Lupien et al., 2002) and longitudinal (Walker, 2002; Walker et al., 2001; Wajs-Kuto, De Beeck, Rومان, & Caju, 1999) studies. Thus, increased biological sensitivity to stress may accompany adolescence and contribute to the increased risk for onset of prodromal and psychotic symptoms during this period (Walker, 2002).

In summary, the present findings converge with reports on elevated stress-induced striatal dopamine in prodromal subjects (Howes et al., 2009) and are consistent with the hypothesis that HPA activity can trigger the expression of psychotic symptoms in vulnerable individuals. Adolescence/young adulthood may be a critical period for this process. Although the origins of elevated cortisol secretion in participants who converted to psychosis are not addressed in this study, it is plausible that they are a response to greater stress exposure and/or reflect genetic predispositions to HPA disturbances. Further research is needed to address these possibilities.

The main limitations of the present study were the small sample size and missing follow-up cortisol data, both of which were a consequence of the challenges entailed in recruiting and retaining at-risk subjects in a comprehensive longitudinal investigation. Further, the subgroup with conversion after the 1st year was small ($n = 8$), and we do not know if elevations in cortisol observed in the 1st year persisted or were transient spikes. Finally, missing data were more common among males than females. These inherent limitations have been the impetus behind a recently launched collaborative study among eight research sites, including ours, with experience in prodromal research (Cannon et al., 2008). By pooling data from participants across sites, it will eventually be possible to examine cortisol changes through the course of the prodrome over a 5-year period in a larger sample. Given the demonstrated effects of sustained glucocorticoid elevations on brain structure and function, this collaborative study will explore the origins of HPA elevations as well as the relation of HPA indices with brain changes during the prodrome.

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Figure 1. Mean cortisol levels, AUCg (area under the curve with respect to the ground), and AUCi (area under the curve with respect to increase) by conversion status. FU1 = Follow-up 1; FU2 = Follow-up 2. Error bars represent $\pm 2 SE$.

Table 1

Demographic and Clinical Characteristics of the At-Risk Sample

Characteristic	Nonconverted	Converted to psychotic disorder	Total
Gender, <i>n</i>			
Male	30	8	38
Female	12	6	18
Baseline age in years, <i>M (SD)</i>	14.02 (1.79)	14.36 (1.55)	
Age in years at conversion, <i>M (SD)</i>		16 (0.52)	
Ethnicity, <i>n</i>			
African American	13	3	16
Caucasian	25	11	36
Asian American	3	0	3
Other	1	0	1
Baseline medication, <i>n</i>			
Stimulant	12	4	16
SSRI	10	2	12
Antipsychotic	8	1	9
SIPS negative symptoms, <i>M (SD)</i>	9.33* (5.8)	14.36* (8.6)	
BDI, <i>M (SD)</i>	13** (7.5)	21** (8.8)	

Note. SSRI = selective serotonin reuptake inhibitor; SIPS = Structured Interview for Prodromal Syndromes; BDI = Beck Depression Inventory.

*
 $p < .05$.

**
 $p < .01$.