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Cortisol Levels and Risk for Psychosis: Initial Findings from the North American Prodrome Longitudinal Study

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Abstract

Background—Studies of biomarkers of hypothalamic-pituitary-adrenal (HPA) activity indicate that psychotic disorders are associated with elevated cortisol. This study examined cortisol levels in healthy controls and individuals who meet clinical high risk (CHR) criteria for psychosis. It was hypothesized that cortisol levels would be; a) elevated in the CHR group relative to controls, b) positively correlated with symptom severity, and c) most elevated in CHR patients who transition to psychotic level severity.

Methods—Baseline assessments were conducted at eight centers in the North American Prodrome Longitudinal Study (NAPLS). The present CHR sample included 256 individuals meeting Structured Interview for Prodromal Syndromes (SIPS) criteria, and 141 controls, all of whom underwent baseline assessment and measurement of salivary cortisol.

Results—Consistent with previous reports, there was an effect of age on cortisol, with increases through the adolescent/early adult years. Analysis of covariance (ANCOVA) showed a main effect of diagnostic group, with the CHR group showing higher cortisol. There were modest, positive correlations of cortisol with baseline symptom severity, and ANCOVA revealed higher baseline

cortisol in those who transitioned to psychotic level symptoms when compared to healthy controls and CHR subjects who remitted.

Conclusions—The present findings add to accumulating evidence of heightened cortisol secretion in CHR individuals. The findings also indicate nonspecific associations between cortisol levels and symptom severity, as well as symptom progression. The role of HPA activity in prediction of conversion to psychosis, and its relation with other biomarkers of risk, should receive attention in future research.

Keywords

psychosis; prodrome; high-risk; stress; cortisol; longitudinal

Introduction

The role of stress hormones in triggering the expression of vulnerability to mental disorder has become a significant focus of research.(1) The importance of this area of investigation has been highlighted by advances in our understanding of neurohormonal signaling, epigenetic processes, and gene–environment interactions in the etiology of mental disorders.

Within the last decade, a substantial body of literature has accumulated on hypothalamic–pituitary–adrenal (HPA) function in schizophrenia and other psychoses, and a 2008 review of the results supports five general conclusions (1): 1) Indices of HPA activity (cortisol and adrenocorticotropic hormone [ACTH]) are elevated in some patients with schizophrenia and other psychoses, especially in nonmedicated and first-episode patients; 2) antipsychotic medications typically reduce cortisol, with more pronounced reductions in drug responders; 3) drugs that augment dopamine (DA) or exacerbate/induce psychotic symptoms also increase HPA activity; 4) glucocorticoid receptors appear to be down-regulated in psychotic patients, suggesting reduced negative feedback on the HPA axis, and 5) reduced hippocampal volume, a correlate of hypercortisolemia, is among the most consistently reported brain abnormalities in psychotic patients.

Reports published subsequent to the above review have yielded similar findings (2–8). For example, research has shown elevated cortisol in first episode and recent onset psychotic patients (3–4), and increased activity of systemic cortisol metabolism in schizophrenia patients (5). Among mood disorders patients, those with psychotic symptoms manifest greater elevations in cortisol (6). Further, heightened cortisol levels (7) and more pronounced cortisol reactivity to daily stress (8) have been observed in relatives of psychotic patients. Recently, a study of first-episode psychotic patients revealed no differences from controls in cortisol, but the magnitude of the decrease in cortisol over 12 weeks was associated with the decline in severity of psychotic, negative, and mood symptoms (9). Consistent with this, cortisol levels are correlated with severity ratings of a range of symptoms in psychotic patients (10).

Because many view the prodromal phase as affording the greatest opportunities for preventive intervention, individuals who manifest clinical signs of psychosis risk (Clinical High Risk - CHR) have become the focus of research interest. Structured measures for prospective assessment of the prodrome have been developed (11–12), and individuals who meet criteria using these measures are shown to have a significantly elevated rate of conversion to psychosis; 20% to 40% of these individuals subsequently develop a psychotic disorder (11–13). Further, CHR subjects manifest brain abnormalities similar to those detected in first-episode patients; namely reduced gray matter volume and white matter abnormalities (15–18).

Indices of the biological response to stress are of particular interest during the prodromal phase, given that stress is assumed to play a role in triggering symptoms. To date, only a few published reports have explored the HPA system, or its activity, in a CHR or 'prodromal' sample (19). In one study, pituitary volume was measured via magnetic resonance imaging in a CHR group (20). The subjects who later developed psychosis had a significantly larger baseline pituitary volume compared with those who did not. The authors suggested that the larger pituitary volume may be indicative of heightened HPA activation (20). However, in another report on 18 CHR subjects, this same research group found that cortisol showed no significant relationship with global psychopathology, psychotic symptoms, or pituitary and hippocampal volumes, but was positively correlated with ratings of depression and anxiety (21). These investigators also conducted a study in which they administered the dexamethasone corticotrophin releasing hormone (DEX/CRH) test to twelve CHR subjects at baseline (22). Three of the twelve developed psychosis within 2 years. Given 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 cortisol levels at the latter stages of the test, when compared to the three participants who did develop psychosis.

Other studies with larger samples have indicated that CHR subjects do manifest higher cortisol levels (23–25). A recent report indicates that CHR youth who go on to develop a psychotic disorder show significantly higher cortisol levels in the year preceding onset (24). The study included 56 CHR youth, with 14 subsequently converting to a psychotic disorder. Multiple saliva samples were obtained to enhance cortisol estimation reliability. As in previous studies of HPA activity in adolescence, an age-related increase in cortisol secretion was also observed, suggesting that the developmental period of peak risk for prodromal onset is also characterized by greater stress sensitivity. Other research on CHR samples has shown an association between cortisol and severity of positive and nonspecific symptoms (2, 19). Finally, a novel study of CHR and psychotic patients measured stress-induced cortisol and DA release, using PET to index percent change in receptor binding between conditions (stress versus control) in the limbic, associative, and sensorimotor striatum (25). The stressor was a challenging mental arithmetic task. Compared to healthy controls, CHR and psychotic patients had more pronounced DA response in the associative and sensorimotor striatum, as well as a greater cortisol response to the stressor. Further, there was a significant association between the increases in cortisol and DA.

With increasing evidence that neurohormones play a role in neuronal function and epigenetic processes, the importance of research on HPA activity in CHR samples has become more apparent (26). To date, the research in this area has often utilized nonoptimal measurement procedures (e g., single assays without controlling for diurnal changes) and has involved small samples that vary in demographics. The present study extends this line of investigation in a larger sample of CHR individuals participating in the North American Prodrome Longitudinal Study (NAPLS). It is hypothesized that the CHR group will show significantly higher cortisol levels than healthy controls, and that cortisol levels will be positively correlated with ratings of symptom severity and with the progression of positive prodromal symptoms.

Methods and Materials

Sample

The NAPLS prospective study of prodromal syndromes is an ongoing, collaborative longitudinal project (27). The objectives are to enhance prediction of psychosis in clinically-defined high-risk individuals and shed light on the neural mechanisms subserving conversion. At the half-way mark of baseline data collection, with a sample of 540 (360

CHR and 180 controls), there is adequate power to conduct data analyses aimed at addressing key hypotheses. The second half of the baseline sample will provide the opportunity for replication analyses.

The present investigation includes those participants, of the 540 assessed at baseline, for whom dietary information and saliva for assay were obtained, and the samples were adequate for assay. These data were available for 397 participants; 256 CHR subjects (146 males, 110 females) who met prodromal syndrome criteria and 141 (76 males, 65 females) healthy controls. This subsample comprises all participants in the NAPLS project, as of the study midpoint, for whom at least one saliva sample for baseline cortisol assay was available (27). The age range of all participants was 12 to 35 years with a mean age of 19 (SD=4.2) for the CHR group and 19.1 (SD= 4.6) for the control group.

The protocol was approved by Institutional Review Boards at all NAPLS sites where data were collected (Emory University, Harvard University, University of Calgary, University of California Los Angeles (UCLA), University of California San Diego (UCSD), University of North Carolina (UNC), Yale University, and Zucker Hillside Hospital), and all participants provided informed consent or assent (and parental informed consent) for minors.

ASSESSMENT PROCEDURES AND MEASURES

Participants were screened using the Structured Interview for Prodromal Syndromes (SIPS) (11) at initial assessment and follow-ups. The SIPS contains the Scale of Prodromal Symptoms (SOPS) which rates the severity of symptoms with the following scale: 0 = *absent*, 1 = *questionably present*, 2 = *mild*, 3 = *moderate*, 4 = *moderately severe*, 5 = *severe but not psychotic*, and 6 = *very severe and psychotic*. The rated symptoms comprise four domains; *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, subjects were designated as prodromal if they met one or more of four sets of criteria; 1) *Brief Intermittent Psychotic Syndrome* (BIPS) if rated a 6 on one positive symptom in the past 3 months, *Attenuated Positive Symptom* (APS) syndrome if rated a 3, 4, or 5 on at least one positive symptom, 3) *Genetic Risk and Deterioration Syndrome* (GRDS) in a person with a first degree relative with a nonaffective psychotic disorder who shows a steep functional decline over the past year, or 4) meeting criteria for *Schizotypal Personality disorder* (SPD) at the age of 18 or under. Individuals in the CHR group can meet criteria for more than one prodromal syndrome. Among the sample of 256 CHR participants in the present study, 89% met criteria for APS, 18% met criteria for GRD, 14% met criteria for SPD, and 3% met criteria for BIPS.

The Structured Clinical Interview for Axis I *DSM–IV* Disorders (28) was administered to diagnose Axis I disorders at the initial and 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.

A detailed description of the study procedures is presented in detail elsewhere (27). In brief, CHR participants were excluded if they had ever met DSM-IV criteria for an Axis I psychotic disorder. Control participants were excluded if they met 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, neurological disorder, or Full Scale IQ <70.

Assessments were conducted by trained interviewers who met reliability standards for the project (27). Interviewers were clinical psychologists, psychiatrists, and other mental health staff. Cross-site reliability in symptom ratings was established prior to study initiation and on a yearly basis. The kappa statistic was used to compare trainee agreement with the "gold standard" diagnosis on the SOPS ratings. Within all sites, intra-class correlations for the symptom ratings exceeded .80, thus were high.

SALIVA COLLECTION AND ASSAY

Participants were provided with dietary instructions to observe the evening before and the morning of sampling. These included refraining from caffeine, alcohol, dairy products, and nonprescription medications. They were queried to confirm compliance with these instructions.

Saliva samples for cortisol assay were obtained three times during baseline assessment in the research clinic, prompted by a timer to be approximately on the hour (i e, over two hours), beginning on average about 10:00 a.m., with a range from 9:00 to 11:30 a.m. at onset of sampling (SD= 26 minutes), and no difference between the groups in time of sampling onset, $t(1,396) = 1.39$, $p=.17$). Multiple saliva samples ($n = 3$) were obtained to derive an average and increase the reliability of the cortisol estimate (29).

Saliva was stored in a −20°C freezer. In preparation for assay, samples are rapidly thawed and centrifuged. All samples are assayed for salivary cortisol (ug/dl) using a highly sensitive enzyme immunoassay (Salimetrics, State College, PA). The test uses about 25 micro liter of saliva (for singlet determinations), has a range of sensitivity from 0.007 to 1.8 mg/dl, and average intra- and interassay coefficients of variation of less than 10% and 15%. All samples are assayed in duplicate.

DATA ANALYSES

Statistical analyses were conducted with PASW statistics 18 (SPSS Inc, Chicago, Illinois) statistical software. Independent sample t-tests or chi-square tests were used to compare the CHR and control groups on demographic and clinical characteristics, and analyses of covariance (ANCOVA) was used to test group differences in cortisol. Correlational analyses were conducted to examine the relation of cortisol levels with symptom ratings.

For purposes of normalizing the distribution of age for analysis, the sample was divided into eight age groups; 12–13 year, 14–15 years, 16–17 years, 18–19 years, 20–21 years, 22–23 years, 24–25 years, and 26–35 years. The later part of the sampled age range was collapsed due to smaller numbers of subjects at each year over the age of 26 years.

Saliva was available for all 397 subjects at first sampling, but fewer had data for the second (1% missing) and third (11% missing) samples obtained on the same day. The current consensus in addressing missing data favors multiple imputation (MI), which avoids problems inherent in mean substitution and exclusion of cases with missing data (30). 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 PASW to examine the pattern of missing values for cortisol at the second and third samples, then MI was conducted with PASW, using fully conditional specification (31). The results of the analyses with imputed data are presented below. (When the analyses were conducted without imputation, the same pattern of results was obtained.)

RESULTS

Participant Characteristics

Consistent with the demographics presented in the recently published overview of the project (27), the CHR and control groups did not differ on age (t (1,396) = .19, p=.86), sex (X^2 (1) = .007, p=.973) or ethnicity (X^2 (9) = 7.1, p=.63). The demographic characteristics of the sample are shown in Table 1.

ANALYSES OF CORTISOL DATA

Analyses showed significant correlations among the 3 salivary cortisol samples; samples 1 & 2, r =.74, p<.001, samples 2 & 3, r = .76, p<.001, and samples 1 & 3, r = .62, p<.001, indicating reliability of the assay. Mean cortisol across the 3 samples was derived for each subject.

Preliminary analyses were conducted to identify correlates of cortisol for inclusion as covariates in analyses of diagnostic group differences. Because some prodromal subjects were on psychotropic and other medications when they entered the study, analyses were also conducted to examine the relation of medication with cortisol. These analyses revealed no significant relation of mean cortisol with antipsychotics (p=.53), antidepressants (p=.99), stimulants (p=.50), or mood stabilizers (p=.12) in the prodromal group, and no relation with birth control medication in the females (p=.43).

As expected, correlational analyses revealed a significant inverse relation between time of onset of saliva sampling and mean cortisol, r = −.12, p<.01. This reflects the normal diurnal decline in morning cortisol. Thus sampling time was included as a covariate in subsequent analyses. T-tests revealed no significant relation between cortisol and alcohol, dairy, or caffeine consumption, subsequent to 7 pm the night before saliva sampling. But those who reported tobacco use had higher cortisol values than nonusers (t(1, 396)=2.50, p<.05). Tobacco use was also included as a covariate in analyses.

ANCOVAs, with sampling time and tobacco use as covariates, revealed no significant differences in mean cortisol as a function of sex or ethnicity, but consistent with previous reports, there was a significant difference as a function of age group, with higher levels associated with increasing age, F(7,387)=2.70, p<.01.

Cortisol data were analyzed in a one-way (diagnostic group: CHR versus Control) ANCOVA, with age group, time at onset of saliva sampling and tobacco use as covariates. The results yielded a significant main effect for diagnostic group, F(1,392)=5.05, p<.05, with higher levels in the CHR group. (See Figure 1.)

THE RELATION OF CORTISOL WITH BASELINE SYMPTOM SEVERITY

Correlational analyses were conducted to examine the relation of cortisol with ratings of symptoms severity for the four prodromal symptom scales. Significant, modest, positive correlations with cortisol were obtained for the *positive*, r =.13, p<.01, *negative*, r =.09, p<.05, *general*, r =.11, p<.05, and *disorganized* symptom ratings, r =.11, p<.05. As described, among the *general* symptoms there are four items, including separate ratings of dysphoric mood and impaired stress tolerance. Because of the potential relevance of these individual items to cortisol levels, they were examined separately. The correlations between baseline cortisol and symptom ratings were significant for dysphoric mood r =.11, p<.05, and impaired stress tolerance, r =.12, p<.05, but not sleep disturbance, r =.08, p=.09, or motor disturbances, r =.00, p=49.

SYMPTOM PROGRESSION

At the time of this writing, follow-up assessments of CHR participants are ongoing, so the final conversion rate is not yet known. And, of those who have reached a psychotic level of severity on the SIPS, the DSM diagnosis has not yet been established for all. In the interim, in order to determine whether baseline cortisol is linked with symptom progression, preliminary analyses were conducted using data for those 136 CHR subjects in the present sample who had been followed at least 24 months without manifesting psychotic symptoms *or* had reached a psychotic level of symptom severity based on the SIPS. The exclusion of CHR subjects who were not yet followed 24 months *and* had not transitioned reduced the likelihood of including false negatives. The following categorization was used: *remission* (n=43) (all positive symptoms are rated less than 3), *symptomatic* (n=37) (one or more of positive symptoms in the previous 4 weeks were rated 3 – 5, but with no increase in last year), *prodromal progression* (n=24) (continues to meet prodromal criteria with one or more positive symptom rated 3–5 and increasing in severity), or *psychotic* (n=32) (has increased to a rating of 6 on one or more positive symptoms).

Cortisol data were analyzed in a one-way (diagnostic group; controls, remission, symptomatic, prodromal progression, or psychotic) ANCOVA, with age, time at onset of saliva sampling, and tobacco use as covariates. There was a significant main effect for diagnostic group, $F(4,346)=2.46$, $p<.05$, with posthoc groups contrasts showing that CHR subjects in the psychotic group had significantly higher baseline cortisol than those in the control ($p=.01$) and remission ($p=.03$) groups. There were no other significant group differences. (See Figure 2.)

DISCUSSION

This study examined cortisol levels in healthy controls and subjects designated as CHR for psychosis. As previously reported, there was an age-related increase in cortisol through adolescence/young adulthood, for both diagnostic groups. Also, as predicted, the CHR group showed significantly higher cortisol levels than controls, and cortisol levels were correlated with ratings of symptom severity at baseline and with the progression of prodromal syndromes.

The finding of nonspecific and modest relations between symptom severity and cortisol levels is consistent with several previous reports (8–10). The small magnitude of the correlations may partially reflect the restricted range of symptom severity ratings (0 to 5) utilized by the SIPS and similar measures for the prodromal range, with a rating of 6 being at the psychotic level of severity and rarely occurring at baseline. Also relevant to consider is that the correlations are based on cross-sectional data and may be diminished by individual differences in sensitivity to the effects of glucocorticoids on brain and behavior. Thus the relations might be more pronounced in within-subjects designs where the covariance between cortisol and symptoms is measured longitudinally.

Though preliminary, the analyses of the interim outcome data suggest that baseline cortisol is linked with the progression of the prodrome; those who transition to the level of 6 or higher on one or more of the SIPs positive symptoms showing the highest cortisol level. Of course, the CHR group has only been followed to a maximum of two years, and it has been shown that there are a substantial number of transitions to psychosis that occur beyond the second year after prodrome ascertainment. It should therefore be assumed that there are false negatives in this interim outcome measure. When the entire NAPLS CHR sample is recruited and the follow-up diagnostic assessments completed, we will conduct analyses that include specific DSM diagnostic outcomes,

The current and similar previous findings raise questions about the relation between heightened HPA activity and risk for psychosis. Is heightened cortisol the consequence of developing clinical risk symptoms *or* does it play a role in triggering or exacerbating symptoms? The symptoms of the CHR syndromes are often subjectively stressful, and it is plausible that this distress activates the HPA axis. Alternatively, as implied in diathesis–stress models, the causal relation may be in the opposite direction, such that biological stress systems trigger the expression of symptoms in some CHR individuals.

There are a variety of potential neural mechanisms through which heightened cortisol secretion might trigger or exacerbate psychotic symptoms, as well as the cognitive deficits that often accompany them (32). Animal and human research has shown that HPA activation can augment dopamine activity (33–38). In nonhuman primates, stress-induced cortisol levels are associated with higher binding of a dopamine agonist to striatal D2/D3 receptors as measured by PET (36). Similar results have been reported with CHR and normal human subjects, such that cortisol levels are correlated with amphetamine-induced DA release in the striatum (37–38). These findings suggest that HPA activity may be linked with psychosis via transient effects on DA. Consistent with this interpretation, daily, repeated measurement of cortisol and symptoms showed that first-degree relatives of psychotic patients manifested increases in psychotic experiences in conjunction with increased cortisol (8).

It is also possible that genomic mechanisms are mediating effects of HPA activity on vulnerability to psychotic symptoms via intracellular receptors (39–46). Genomic mechanisms, via nuclear receptors, can regulate gene expression and modulate brain development. There is extensive evidence from experimental animal research that steroid hormones affect brain organization during adolescence (41), and recent data indicate similar effects in humans (42, 43). Several recent studies of human subjects also show an inverse relation of baseline cortisol with cortical gray matter and hippocampal volume (44, 45). As noted above, the prodrome is associated with brain changes, including reduced gray matter volume, beyond that observed in healthy controls (15–18). Cortisol levels outside the normative range may be altering gene expression and contributing to these more pronounced volumetric declines via modulation of BDNF and other aspects of neurogenesis (47–50). Alternatively, some CHR subjects may have vulnerability genes that are being triggered by heightened cortisol. Finally, genes involved in cortisol metabolism may be among the risk genes for psychotic disorders (5).

In addition to the issue of the relation between cortisol and brain abnormalities, the complex interplay between cortisol levels and receptor characteristics is relevant. There is a dynamic relation of cortisol activity with glucocorticoid (GC) and mineralocorticoid (MR) receptors and with the genes that govern their expression (51–53). The effect of cortisol on brain and behavior would be expected to vary as a function of receptor characteristics. Thus, measurement of receptors, when combined with measures of cortisol, may yield a more complete picture of the role of the HPA axis in psychosis. To date, the few studies of receptors in psychotic disorders indicate reductions in brain GR mRNA (54–55), and MR mRNA expression (56).

The primary limitation of the present, and most other studies of CHR subjects, is the absence of control over psychotropic medications. A subgroup of the present sample was on a psychotropic medication, and the protocol did not require medication withdrawal. Although we found no relation between psychotropics and cortisol, as described above, previous longitudinal studies have revealed that atypical antipsychotics reduce cortisol levels (1, 57). If pre-baseline symptom severity was a precipitant of antipsychotic prescription in the present sample, as would be expected, the result may have been a reduction in baseline cortisol levels and symptoms for the medicated subgroup. In other words, medicated

participants may have had higher pre-baseline cortisol levels *and* symptoms that were lowered with medication, thereby attenuating the difference between the medicated and nonmedicated CHR participants. This possibility can be examined in subsequent studies of this sample, as medication changes are monitored longitudinally in conjunction with cortisol.

As noted above, this is an ongoing study and follow-ups are not complete, thus we do not know the eventual rate of psychosis or the optimal set of predictors of conversion. Nonetheless, the present sample exceeds that of most CHR studies, and the second half of the sample will provide opportunities for replication. These studies will address questions concerning the relation of cortisol with other biomarkers, symptom progression, and diagnostic outcome, as well as heterogeneity among CHR converters in these relations. With respect the latter, it is of interest to determine whether hypersecretion of cortisol characterizes an etiological subgroup.

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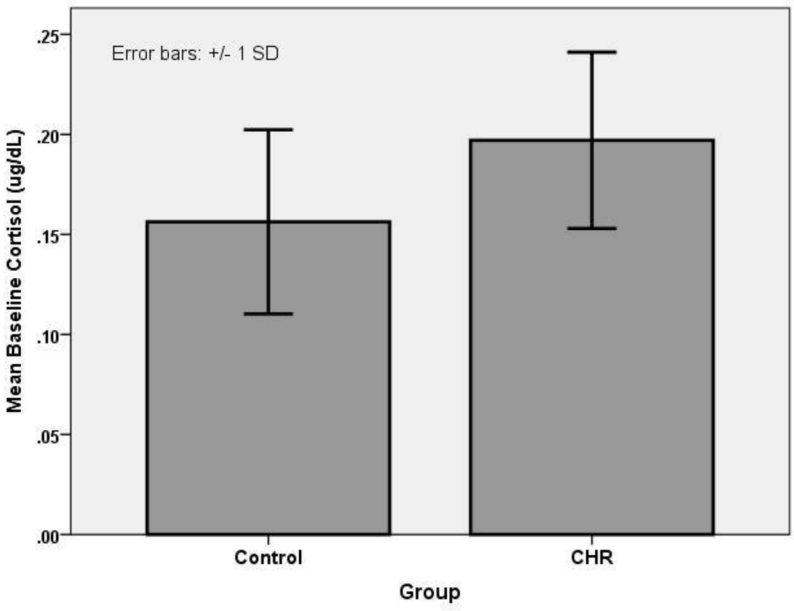

Figure 1.
Mean Cortisol Levels For CHR and Healthy Control Groups.

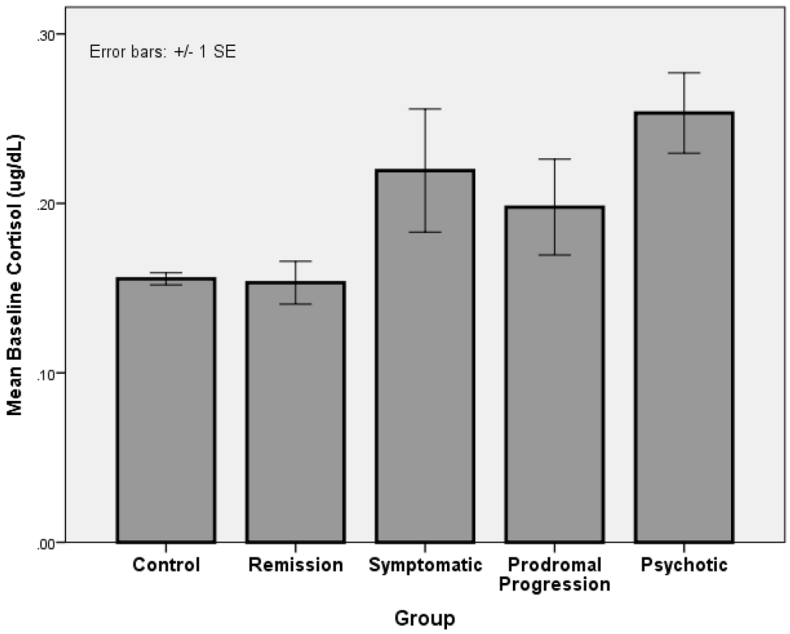

Figure 2.
Mean Cortisol Levels by Diagnostic Outcome Group

Table 1

Demographic and Clinical Characteristics

	Healthy Controls	Clinical High Risk (CHR)
Number of Participants (N=397)	141	256
Age, years (SD)	19.1 (4.6)	19 (4.2)
Sex, male/female	76/65	146/110
Education, years (SD)	12.17 (3.52)	11.72(2.64)
Current Psychotropic medication, %	0%	25%
Race/ethnicity (%)		
First Nations	2%	2%
East Asian	4%	2%
Southeast Asian	2%	2%
South Asian	2%	3%
Black	15%	14%
Central/South American	4%	6%
West/Central Asia and Middle East	1%	1%
White	58%	54%
Native Hawaiian or Pacific Islander	1%	1%
Interracial	11%	15%