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The Relations of Age and Pubertal Development with Cortisol and Daily Stress in Youth at Clinical Risk for Psychosis

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Abstract

BACKGROUND—Prodromal syndromes often begin in adolescence – a period of neurodevelopmental changes and heightened stress sensitivity. Research has shown elevated stress and cortisol in individuals at clinical high risk (CHR) for psychosis. This cross-sectional study examined relations of age and pubertal status with cortisol and self-reported stress in healthy controls (HCs) and CHR adolescents. It was hypothesized that the relations of age and pubertal stage with cortisol and stress would be more pronounced in CHR youth.

METHODS—Participants were 93 HCs and 348 CHR adolescents from the North American Prodrome Longitudinal Study (NAPLS). At baseline, measures of stress (Daily Stress Inventory – DSI), Tanner stage (TS), and salivary cortisol were obtained.

RESULTS—ANCOVA revealed increased DSI scores with age for both groups, and higher DSI scores in CHR adolescents than HCs, with a more pronounced difference for females. Contrary to prediction, with age controlled, HCs showed greater TS-related DSI increases. Analysis of cortisol showed no significant interactions, but a main effect of age and a trend toward higher cortisol in the CHR group. Correlations of cortisol with TS were higher in HC than CHR group.

CONCLUSIONS—Stress measures increased with age in HC and CHR adolescents, and DSI scores also increased with TS in HCs. The results do not support a more pronounced age or TS increase in stress measures in CHR adolescents, but instead suggest that stress indices tend to be elevated earlier in adolescence in the CHR group. Potential determinants of findings and future directions are discussed.

Keywords

Schizophrenia; psychosis; puberty; stress; cortisol; Clinical High Risk

1. Introduction

Vulnerability to psychotic disorders is assumed to be congenital (Dempster et al., 2011), but its expression appears to be triggered by environmental factors, including stressful events

(Dvir et al., 2013). It has been proposed that the adverse effects of stress exposure on vulnerable individuals are partially mediated by the consequent increase in activation of the hypothalamic pituitary-adrenal (HPA) axis and elevated cortisol secretion (Walker et al., 2008). In addition, independent of stress, there is evidence that normal neuromaturational processes augment stress and cortisol levels during adolescence, and it has been suggested that these processes increase risk for onset of the prodrome to serious mental disorders, including psychosis (Trotman et al., 2013; Walker et al., 2008). Specifically, the risk for psychosis onset rises dramatically following age 13, and increases with each year of age through adolescence (de Girolamo et al., 2012; Thorup at al., 2007). In clinical high risk (CHR) samples, the prodromal syndrome shows a similar trend, and appears to predate psychosis onset by about a year (Chung et al., 2010).

1.1 Adolescent development and stress

Research on normal adolescents has demonstrated that self-reported stress and psychiatric symptoms increase with age and pubertal stage (De Vriendt et al., 2011; Lenroot & Giedd, 2010; Oldehinkel et al., 2011; Rudolph, 2008; Sumter et al., 2010). Similarly, basal cortisol increases with both age and pubertal development in healthy adolescents (Sinclair et al., 2014; Gunnar et al., 2009; Kiess et al., 1995; Matchock et al., 2007; Netherton et al., 2004). These findings are consistent with the generalized increase in risk for onset of behavioral disorders during adolescence/young adulthood, as well as the notion that the biological systems involved in the stress response, including the HPA axis, may play a role in triggering the expression of vulnerability (Walker et al., 2008).

While activation of the HPA axis in response to stress is adaptive, prolonged cortisol elevations may compromise brain function, which can then contribute to dysregulation of the HPA axis and the emergence of psychiatric symptoms (Herbert et al., 2006; Zhu et al., 2014). Also, independent of stress exposure, the normative rise in cortisol during adolescence may increase susceptibility to psychiatric disorders in vulnerable individuals (Quevedo et al., 2009; Sontag-Padilla et al., 2012). It has been suggested that increased HPA activation following the onset of puberty may increase susceptibility for a range of psychiatric syndromes, including psychosis (Trotman et al., 2013).

In recent years, the focus of research on stress and psychotic disorders has shifted towards the prodromal phase; individuals who meet standardized criteria for the prodrome are designated as CHR, and the estimated rate of conversion to psychosis in this group ranges from 20–40% (Larson et al., 2010). Because prodromal syndromes most often arise in adolescence/young adulthood, CHR studies focus on this transitional stage (Addington & Heinssen, 2012).

To date, findings from CHR research generally parallel those from studies of psychotic patients. For example, CHR individuals report more stress than healthy controls (HCs) (Cullen et al., 2014; Pruessner et al., 2011). In a report based on the first half of the North American Prodrome Study (NAPLS-2) cohort, aged 13 to 30 years, CHR subjects reported more daily stress than HCs, and the CHR subjects who subsequently converted to psychosis reported greater stress than remitted CHR subjects, with those who remained prodromal

falling in between (Trotman et al., 2014). Also, of interest to note, there was a trend for a more pronounced relation between stress and age for the CHR group.

With regard to stress biomarkers, there is evidence that CHR subjects manifest heightened basal cortisol (Carol & Mittal, 2015; Karanikas & Garyfallos, 2015; Shah & Malla, 2015). Another recent report on the first-half cohort from NAPLS-2, again with subjects ranging from 13 to 30 years, indicated that both HCs and CHR subjects manifested an age-related increase in cortisol through this period (Walker et al., 2013). Further, heightened basal cortisol was found in CHR individuals when compared to HCs, and those CHR participants who later converted showed higher levels than those who remitted, but not those who continued to meet prodromal criteria.

While pubertal development is associated with increased stress and cortisol in healthy adolescents, the relation of pubertal stage with these variables in CHR adolescents has not yet been examined. Some have proposed that the clinical expression of the prodrome to psychosis typically arises in adolescence because it is triggered by abnormalities in the timing and/or magnitude of postpubertal neuromaturational processes (Keshavan et al., 2014; Trotman et al., 2013). It is possible that, when compared to HCs, CHR adolescents manifest a more pronounced increase and/or an earlier onset of rising stress indices with the progression of puberty, and that this contributes to risk for psychosis. The present study addresses this issue by examining the relations of age and pubertal stage with stress and cortisol levels in youth from NAPLS-2. The complete sample from this multi-site, prospective study now includes over 700 CHR and 200 HC subjects, and a measure of Tanner stage (TS) was administered to all of those under 19 years of age. Thus, there are now enough subjects in the 13 to 19 year age-range to examine TS. Based on the evidence that both stress indices and prodromal/psychotic symptoms increase through the adolescent years, and that age-related increases in stress may be greater for CHR subjects (Trotman et al., 2014), it is hypothesized that CHR youth will show a more pronounced relation of age and Tanner pubertal stage with self-reported daily stress and basal cortisol.

2. Experimental/Materials and methods

2.1 Sample

Participants were drawn from the completed cohort of 764 CHR participants and 280 HCs in NAPLS-2 (Addington & Heinssen, 2012). The present subsample includes all participants, aged 13 to 18, for whom baseline data on TS, and self-reported stress and/or salivary cortisol were obtained; 348 CHR youth and 93 HCs. (Degrees of freedom vary in the analyses, as presented below, due to missing data on one of the dependent measures for some subjects.) Approximately 50% of these adolescents were included in the previous reports on stress and cortisol in the entire first half (13–30 years) of the NAPLS-2 sample. Demographic data on the present sample are presented in Table 1.

Exclusion criteria for both groups were substance dependence, neurological disorders, serious head trauma, IQ less than 70, and meeting DSM-IV criteria for a psychotic disorder, currently or in the past. For the HCs, those with a first-degree relative with psychosis or who met prodromal criteria were excluded. Details on sample characteristics and study

procedures are presented in previous reports on NAPLS-2 (Addington & Heinssen, 2012; Walker et al., 2013).

2.2 Assessment Procedures and Measures

Sites screened participants using the Structured Interview for Prodromal Syndromes (SIPS), and diagnosed CHR participants based on the Scale of Prodromal Syndromes (SOPS) at baseline (Miller et al., 2003). The Structured Clinical Interview for DSM-IV Disorders was used to diagnose Axis I disorders (First et al., 2002).

2.3 Salivary Cortisol

Details about NAPLS-2 saliva collection and cortisol assay procedures are presented in a previous report (Walker et al., 2013). In brief, dietary instructions to be observed the evening and morning before sampling were provided. Instructions included avoidance of nonprescription medications, and foods and beverages known to affect cortisol. At baseline, three saliva samples were obtained via passive drool. Multiple samples were obtained in order to derive an average and increase the reliability of the cortisol estimate.

Saliva was stored at −20°C. Samples were assayed in duplicate for cortisol (mg/dL) using a highly sensitive enzyme immunoassay (Salimetrics, State College, Pennsylvania). The test uses about 25 mL of saliva, has a range of sensitivity from 0.007 to 1.8 mg/dL, and average intra-assay and inter-assay coefficients of variation of less than 10% and 15%.

2.4 Pubertal Stage

A self-report measure of pubertal status, the Tanner Scale (Petersen et al., 1988), was administered to NAPLS-2 subjects who were between the ages of 13 and 18. The Tanner scale is a gender-specific, one-page self-assessment that uses drawings of standard photographs illustrating breast and genital development. Tanner stages range from 1–5, with 1 indicating the beginning of puberty to 5, the most mature stage. The scale was selected because it is less invasive than examination and has good reliability and validity (Forbes et al., 2010). The scale yields two scores for males (pubic score and penis score) and for females (pubic score and breast score). The TS was designated based on the average total score on the two dimensions within gender. Because only a small number of subjects (n = 2) self-rated in TS 1 on the scale, stages 1 and 2 were combined.

2.5 Daily Stress

The Daily Stress Inventory (DSI) is a 58-item measure of stressors over the past 24 hours (Brantley et al., 1987). Items include "misplaced something", "encountered bad weather", "was interrupted during task/activity", and "had sleep disturbed." The DSI has been utilized with healthy and clinical adolescent samples, and the results support its validity and reliability with this age range (Gallaty & Zimmer-Gembeck, 2008; Tessner, Mittal, & Walker, 2011; White & Shih, 2012). Participants indicated whether the event occurred and rated each on a 7-point scale, ranging from "occurred, but was not very stressful" to "caused me to panic." Ratings of stressfulness were summed to derive a total score, and the distribution normalized with logarithmic transformation.

2.6 Data Analyses

Using the Statistical Package for the Social Sciences (SPSS), Pearson correlations were computed, followed by analyses of covariance (ANCOVAS-GLM), with age as the covariate, sex, TS, and diagnostic group (CHR versus HC) as the independent variables, and cortisol and DSI as dependent variables. Age was included as a covariate to determine the independent effects of TS. For ANCOVA of cortisol, saliva sampling time was also controlled, due to the diurnal fluctuations in secretion.

3. Results

There were no significant differences between the CHR and HC groups in age, sex ratio, or TS (See Table 1). Bivariate correlations, by group and sex, are presented in Table 2. (It is important to note that the sex groups differed in size, and consequentially in power for detecting significant relations.) For the HC group, all coefficients were positive and most statistically significant. Although all coefficients were positive for the CHR group, the magnitudes were smaller and more did not reach significance. Using r-to-Z transformation for comparing the group differences, there were three differences at p<.05, with higher correlations for the HC group (See underlined values in Table 2). The relation of TS with cortisol was higher for HCs of both sexes than for CHR subjects. Also, the relation of male TS with age was higher for HCs. As expected, for both groups, age was correlated with male and female TS, DSI scores, and cortisol. The nonsignificant correlations of DSI scores and cortisol in both groups suggest that the two are primarily indexing independent constructs.

The above correlational analyses did not test the effects of TS independent of age. The ANCOVAS of DSI scores, with age as a covariate, yielded significant main effects of age [$F(1, 392) =13.010$, p<.001, eta^2=.03] and diagnostic group [$F(1, 392) =39.02$, p<.001, eta^2=.09], and a trend toward a main effect of TS [$F(3, 392) =2.52$, p=.06, eta^2=.19]. As reported previously for the 13 to 30 year-old NAPLS-2 sample (Trotman et al., 2014), the CHR adolescents in this subsample had higher DSI scores than the HC group and, as age increased from 13 to 18, scores increased for both groups. However, these main effects were qualified by significant two-way interactions: TS X Diagnostic Group, [$F(3, 392) =2.73$, p<.05, eta2=.021], and Sex × Diagnostic Group, [$F(3, 392) =9.42$, p<.05, eta2=.023].

As illustrated in Figure 1, when controlling for age, the DSI scores for CHR subjects were elevated relative to HCs across all TSs. To further explore the significant TS × Diagnostic Group interaction, post hoc tests were conducted. In all TSs, the CHR showed significantly higher DSI scores than the HC group (TS 2, t(1, 16) = 3.30, p=.005; TS 3, t(1, 76) = 2.75, p=.00; TS 4, t(1, 153) = 2.24, p=.03, TS 5, t(1, 159) = 6.01, p=.000). Comparing TSs within group, the HC group showed a rise in DSI scores when comparing TS 2 to subsequent stages; TS 3 (t(1, 15) = 2.06, p<.05), TS 4 (t(1,28) = 3.75, p=.001) and TS 5, t(1,45) = 2.91, p=0.01, but no significant increase between stages 3, 4 and 5. In contrast, there was little change in DSI scores with TS in the CHR group; specifically, there was no significant rise beyond TS 2, although those in TS 5 reported significantly higher stress compared to those in TS 4, (t(1, 247)= 2.60, p=.01).

The significant Sex × Diagnostic Group interaction is illustrated in Figure 2, and is due to a significant difference in self-reported stress between female and males subjects in the CHR group, $t(1,347)= 4.14$, $p<.001$, but not in the HC group, $t(1,92)= .464$, $p=.64$.

ANCOVA of cortisol levels yielded a significant main effect of the covariate age, $[F(1, 295) =7.12, p<.01, eta^2=0.024]$, consistent with the positive correlations between age and cortisol reported above, and a trend for Diagnostic Group $[F(1, 295) =3.73, p=0.05, eta^2=0.012]$, with higher cortisol levels in the CHR than HC group. There were, however, no main effects for TS or sex, and no significant interactions.

4. Discussion

The present results indicate that stress and cortisol secretion increase with age in HC and CHR adolescents, and that the latter group is characterized by greater stress. But, contrary to prediction, when controlling for age, the changes in stress as a function of TS were more pronounced in HCs than in the CHR group. Further, the correlations of age and TS with stress did not differ in magnitude for the two groups. In the following, we discuss the findings separately by measure.

As mentioned, a study of the entire age-range in the first half of the NAPLS-2 cohort revealed an increase in DSI scores with age for both diagnostic groups, as well as higher DSI scores for the CHR group relative to controls (Trotman et al., 2014). These findings hold for the present subsample of adolescents. In addition, when controlling for age, TS interacted with group to account for a significant proportion of the variance in self-reported stress. This interaction reflected a rise in mean DSI scores as a function of TS in the HC group, particularly when comparing TS 2 to subsequent stages. But for the CHR group there was relatively less change across TSs. Thus, it possible that CHR participants experienced a rise in subjective stress that occured prior to, or earlier, in the course of pubertal development than is normally the case, and that this elevation is sustained through subsequent stages. Of course, this study is cross-sectional, so we do not know what the stress/cortisol levels of the older CHR subjects were in earlier stages.

Diagnostic group also moderated the relation of sex with stress. While both male and female CHR subjects reported greater stress than same-sex HC subjects, the group difference was more pronounced for females. It is well established that females report higher stress than males, apparently beginning in adolescence (Hastings et al., 1996; Hyde et al., 2008; Leadbeater et al., 1995; Matud, 2004), and there is evidence that the magnitude of the difference is greater in clinical populations (Hastings et al., 1996; Matud, 2004). It has been suggested that this is due to biological and psychological differences that increase postpubertally and heighten the tendency for females to experience and describe events as stressful. Similarly, the amplification of the sex difference in CHR adolescents in the present study may indicate that CHR females experience symptoms as more distressing than CHR males. Further research is needed to elucidate this difference.

There was no relation of cortisol with TS, independent of age, but there was an age-related increase and a trend toward a diagnostic group difference in this adolescent sample. Again,

there was no evidence of a greater relation between TS and cortisol in the CHR group; in fact, the opposite was the case when age was not controlled. Differences between age and TS in their pattern of relations with biological and psychological variables have been documented in previous studies of adolescents (Blum et al., 1997; Goddings et al., 2014), and this has been attributed to differences between the processes indexed by measures of physical changes (ie., TS indicators), versus those captured by chronological age, which more broadly indexes cumulative exposures and maturational processes that extend into early adulthood. Also, differences in measurement reliability should be considered; it is reasonable to assume that there is minimal error in the measurement of age, whereas TS reliability is influenced by multiple factors. The physical manifestations on which TS is based are "proxy" measures of underlying hormonal changes. Further, self-report is another potential source of error, and this may be greater in CHR than control youth.

Measurement error and confounds are also an issue to consider with the DSI. As with all self-report measures of stress, responses to some of the items, or their occurrence of some of the stressors, may be attributable to psychopathology. Disentangling the direction of causal effects would be facilitated by repeated-measures designs, such as the experience sampling method (ESM) used by Collip and colleagues (Collip et al., 2011), which does suggest that increases in stress precipitate increases in psychiatric symptom severity. Further, for this adolescent subsample from NAPLS-2, the cross-sectional relationship between DSI scores and cortisol did not reach significance. The ESM study, cited above, did reveal a moderate but significant positive relation between daily stress and cortisol in genetic high-risk subjects (Collip et al., 2011), and a longitudinal study using the DSI with healthy subjects revealed a positive relation with cortisol (Brantley et al., 1988). Similarly, a cross-sectional study of healthy subjects found a positive relation of daily stress with cortisol, but it varied in magnitude as a function of family environment (Hanson & Chen, 2010). Yet, in contrast, one report on first episode psychosis patients indicated an inverse relation between recent stress and cortisol (Mondelli et al., 2010), although most of the patients were on antipsychotics which is associated with cortisol suppression. Another study of CHR subjects found an inverse relation of cortisol with stress in the past year (Pruessner et al., 2013). Both of the latter two studies were cross-sectional, so it is possible that cross-sectional designs do not afford the level of statistical power for detecting relations between stress and cortisol that would be obtained with repeated-measures designs such as ESM. It is clear that further research is needed to identify the determinants of differences among studies in their findings; investigations that examine both cross-sectional and longitudinal relations in the same sample may be especially informative.

Another limitation of this study is that inclusion in a CHR group requires the presence of a prodromal syndrome which has a low incidence in pre- and early-puberty; The present sample contained only two individuals in TS 1. Obtaining more CHR subjects in TS 1 would require a larger sample than NAPLS-2, or targeted recruitment of these individuals.

4.1 Conclusions

Our findings reveal a relation between TS and stress that differs for CHR and HC subjects. HCs showed a greater rise in DSI with TS, whereas CHR youth manifest elevated DSI

scores throughout the TSs measured here, with the most pronounced elevation relative to controls in the earliest TS. This may indicate that, for CHR youth, the normative changes associated with puberty onset are more stressful, that antecedent influences (e.g., childhood stress/trauma) have amplified self-reported stress, and/or that there is an abnormality in pubertal neuromaturational processes. As noted, some previous research shows that life event stress exposure is higher in CHR subjects, and this may set the stage for a more pronounced increase in subjective stress in early adolescence. With respect to neuromaturation, research has shown brain abnormalities in CHR subjects, including reports of a reduction in hippocampal volume (Nenadic et al., 2015). The hippocampus is involved in negative feedback to the HPA axis, so this abnormality may contribute to elevated stress in CHR youth. Finally, CHR subjects may experience abnormalities in gonadal hormones that amplify stress-sensitivity through pubertal development. We hope to address these alternative possibilities in future studies.

Acknowledgments

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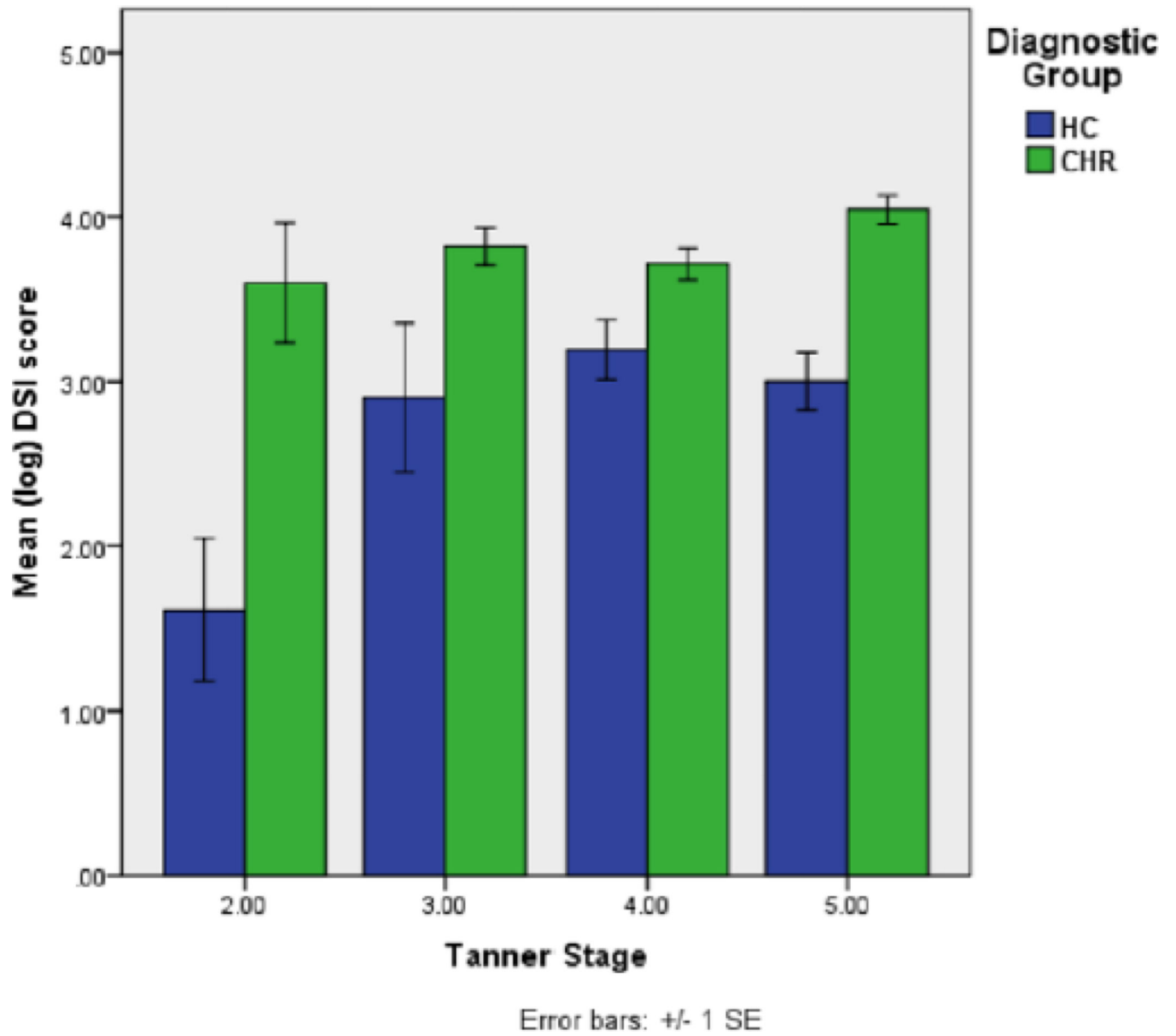
Figure 1.
Mean Daily Stress Inventory (DSI) Scores by Tanner stage in the CHR and HC Groups.
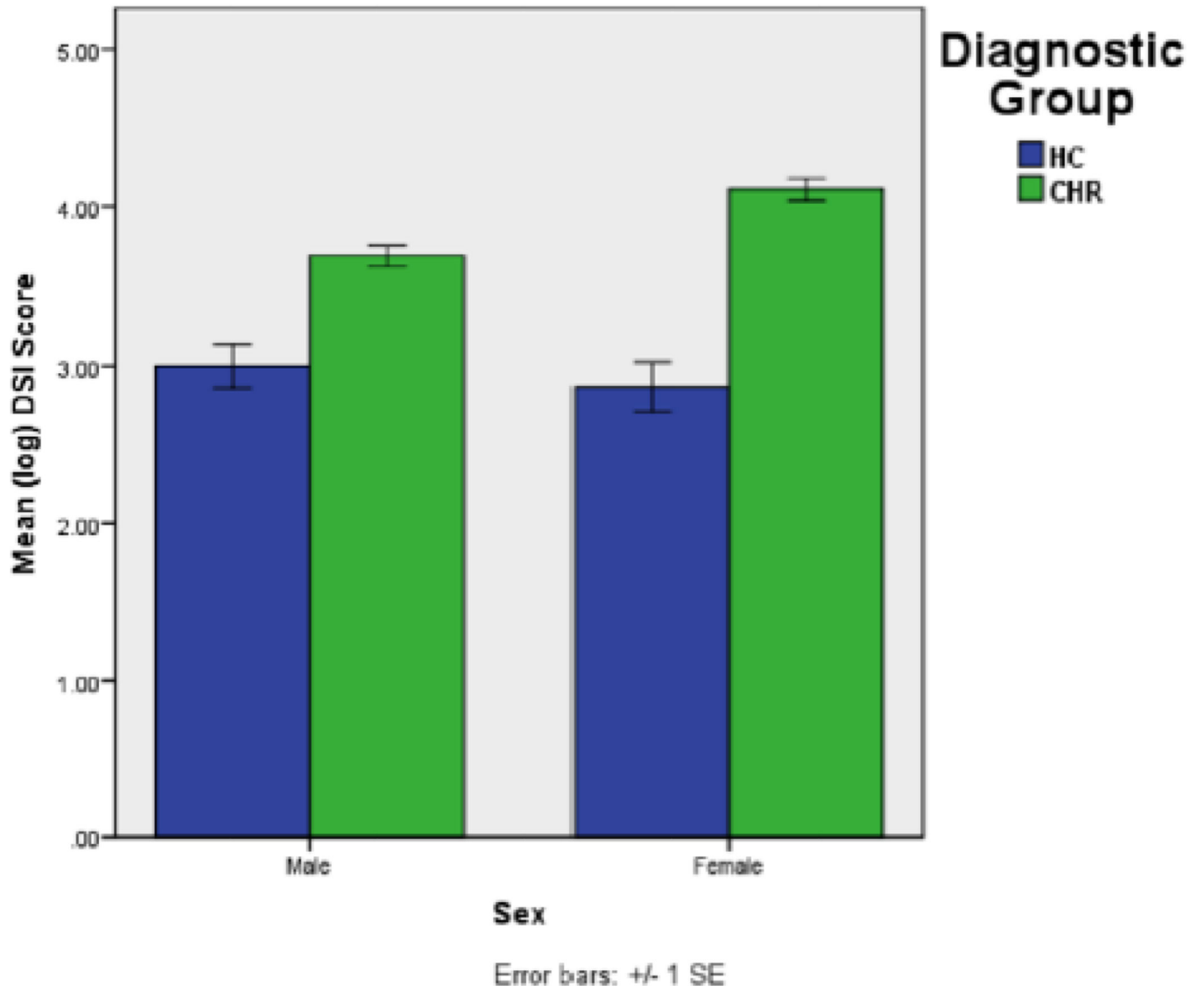
Figure 2.
Mean DSI Scores by Sex and Diagnostic Group.

Table 1

Demographic and Clinical Characteristics

	Healthy Controls N=348	CHR N=93
Baseline Age		
M (SD), n		
Males	14.93 (1.83), 60	15.78 (1.72), 196
Females	15.63 (1.81), 33	15.36 (1.61), 152
Tanner Total Male Score		
M (SD)	8.18 (1.95)	8.26 (1.64)
Tanner Total Female Score		
M (SD)	7.67 (1.88)	7.25 (1.65)

Table 2

Correlations among Measures for CHR and HC Samples.

	Pearson Correlations				
	BC	DSI	Age	TM	TF
BC	1	0.08	0.13[*]	0.07	0.01
DSI	0.14	1	0.19[*]	0.25[*]	0.09
Age	0.34[*]	0.29[*]	1	0.46[*]	0.27[*]
TM	0.31[*]	0.24[*]	0.66[*]	1	
TF	0.35[*]	0.27	0.40[*]		1

Upper righthand part of the table denotes correlations for CHR subjects; bottom lower left of the table denotes correlations for healthy controls.

Note. BC = Baseline Cortisol; DSI = Daily Stress Inventory score; TM = Tanner total Male score; TF = Tanner total Female score.

[*] Indicates correlation significant at 0.05.

Underlined values indicate significant diagnostic group differences in correlation coefficient magnitude, using r-to-Z transformation at $p < .05$.