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The Cortisol Awakening Response Predicts Subclinical Depressive Symptomatology in Mexican American Adults

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Abstract

While childhood trauma appears to be a risk factor for the onset of depression and subclinical depressive symptomatology in Mexican Americans, the specific physiological mechanisms contributing to this relationship remain to be clarified. Stress-induced dysregulation of the Hypothalamic-Pituitary-Adrenal (HPA) axis is associated with depressive symptomatology in non-Hispanics. The current study assessed the extent to which the cortisol awakening response (CAR) predicts subclinical depressive symptomatology beyond the influence of childhood trauma in a sample of 55 Mexican American males and females ages 18–38 years, without a diagnosis of clinical depression. Participants were assessed for exposure to early trauma and current depressive symptomatology. Salivary cortisol samples were collected on two consecutive days at awakening, 30, 45, and 60 minutes thereafter, and again at 3pm, 6pm and 9pm. Data were analyzed using general linear models with repeated measures at four morning time points, and again, at three afternoon and evening time points. Results indicated a significant Symptoms × Time interaction for the CAR ($p < .05$). The Symptom × Time interaction was not significant for afternoon and evening cortisol concentrations. Moreover, subclinical symptomatology was associated with attenuation of the initial rise in CAR, after controlling for the total frequency of exposure to childhood traumas. Hierarchical analyses show attenuation of the initial rise in the CAR was the best predictor of greater subclinical depressive symptomatology beyond the influence of trauma, and independent of a current diagnosis of major depression in a sample of adult Mexican Americans.

Keywords

Childhood Trauma; HPA; Cortisol; Depression; Mexican Americans; Hispanics

Introduction

Hispanic children comprise a significant percentage of children exposed to childhood trauma in the U.S. (NCANDS, 2002; NCTSN, 2005). The stress associated with childhood trauma increases the risk for depression in adulthood (Gillespie et al., 2009; Heim et al., 2008, 2009; Kendler et al., 2001), and Mexican American adults with a history of childhood

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trauma report higher rates of clinical depression and more subclinical depressive symptomatology compared to their trauma-free counterparts (Aranda et al., 2001; Martinez-Taboas & Bernal, 2000; Mennen, 2000; Zayas et al., 2002). In addition, clinical depression is more likely to go undetected, untreated, and lead to more persistent depressive symptomatology in Mexican Americans compared to their non-Hispanic counterparts (Marin et al., 2006). Thus, the identification of specific biological risk factors associated with subclinical depressive symptomatology in Mexican Americans with a history of childhood trauma is of particular importance. There is interest in the extent to which exposure to traumatic stress is associated with injury to crucial biological, stress response systems. Stress-induced dysregulation of the Hypothalamic-Pituitary-Adrenal (HPA) axis is one neurobiological pathway that may link childhood trauma to greater depressive symptomatology (Goodwin & Stein, 2004; Heim et al., 2006). Indeed, exposure to traumatic stress is associated with alterations of HPA axis functioning and greater risk for depression in non-Hispanics (Goodwin & Stein, 2004; Heim et al., 2006). The Cortisol Awakening Response (CAR) is utilized as a means to investigate stress-induced injury to the HPA Axis (Pruessner et al., 1999). Basal HPA axis activity is characterized by a distinct diurnal rhythm, with increasing cortisol secretion in the second half of the night followed by peak cortisol levels in the early morning hours. Cortisol levels steadily decline throughout the day to nadir during the first half of the night (Dallman et al.,2000; Tsigos and Chrousos, 2002). The CAR is a discrete phenomenon superimposed on the circadian rhythm characterized by a sharp increase in cortisol concentration between twenty and thirty minutes following awakening in the morning (Wilhelm et al., 2007). Changes in the CAR can yield important information regarding the relationship between altered stress responsivity and injury to the awakening portion of the cortisol circadian rhythm. The CAR is a reliable biological marker of HPA activity, dependent on a moderate genetic influence (Bartels et al., 2003; Schmidt-Reinwald et al., 1999). The sensitivity/capacity of the adrenal cortex is proposed to play a crucial role in the magnitude of the CAR (Kudielka and Kirschbaum, 2003; Pruessner et al., 1997, 1999).

Studies in non-Hispanic adults suggest that childhood trauma is associated with attenuation of the CAR (Meinlschmidt & Heim, 2005; Shea et al., 2007). Although studies in Hispanics are practically non-existent, a single study conducted in our laboratory demonstrated attenuation of the CAR in Mexican American adults with a history of childhood trauma (Mangold et al., 2010). Moreover, prospective evidence suggests that following childhood trauma there is a transition from a higher CAR in childhood to an attenuated CAR in adulthood (Trickett et al., 2010). Indeed, some studies show less decline in afternoon and evening cortisol levels coupled with attenuation of the CAR reflecting an overall flattened diurnal cortisol rhythm with a higher daily output in non-Hispanic adults with a history of trauma (Miller et al., 2007; Weissbecker et al., 2005).

The CAR is also attenuated in non-Hispanic adults with clinical (Huber et al., 2006; Oquendo et al., 2003; Peeters et al., 2004;Strickland et al., 2002; Taylor et al., 2009) and subclinical depressive symptoms independent of a formal diagnosis of major depression (Dedovic et al., 2010). This is of particular interest because attenuation of the CAR may be a biological risk factor that is a precursor to the development of clinical depression in some high risk groups (Adam et al., 2010; Dedovic et al., 2010). However, studies examining the CAR and depressive symptomatology in Mexican Americans are scarce. The single available study in distressed, adult, Hispanic caregivers suggests an association between subclinical depressive symptomatology and a flatter slope to the daytime salivary cortisol curve (Gallagher-Thompson et al., 2006).

Equally lacking, are studies designed to differentiate the extent to which the CAR compared with waking day cortisol concentrations (e.g., 12 hour AUC) predicts subclinical depressive

symptomatology in Hispanics and non-Hispanics. Cross-sectional studies of clinically depressed, non-Hispanics show elevated evening cortisol concentrations (Forbes et al., 2006; Shirtcliff & Essex, 2008; Van den Bergh & Van Calster, 2009). However, recent prospective evidence suggests an enhanced initial rise in the CAR, but not evening cortisol concentrations predicts greater risk for future episodes of major depressive disorder (Adam et al., 2010). Thus the differential effects of the CAR compared with afternoon and evening cortisol concentrations on subclinical depressive symptomatology remains to be clarified.

While studies in non-Hispanics indicate injury to the CAR may be a biological risk factor associated with both subclinical and clinical depressive symptomatology, there are few studies examining this potential risk factor in Mexican Americans. There are several likely pathways to the onset of clinical depression in which specific patterns of injury to the HPA axis are linked to the development of particular forms of depressive symptomatology in certain high-risk groups (Adam et al., 2010; Dedovic et al., 2010; Ehlert et al., 2001). In view of the fact that Mexican Americans with a history of childhood trauma are at greater risk for undetected and untreated depression, the identification of early biological risk factors independent of a formal diagnosis are of particular importance (Marin et al., 2006). Recent findings from our laboratory have shown that childhood trauma is associated with attenuation of the CAR in highly acculturated Mexican Americans without a lifetime diagnosis of major depressive disorder (Mangold et al., 2010). However, the extent to which the CAR compared with afternoon and evening cortisol concentrations predicts subclinical depressive symptomatology beyond the influence of childhood trauma remains to be clarified. Therefore, the objectives of the current investigation were to: 1) examine the association between the CAR and subclinical depressive symptomatology in Mexican Americans utilizing a carefully constructed sample monitoring system with respect to time of awakening and while carefully controlling for the known effects of childhood trauma and demographic factors previously shown to influence the CAR and; 2) distinguish to what extent the CAR compared with 12hr waking day AUC predicts subclinical symptomatology.

Materials and Methods

Participants

The current study was reviewed and approved by the University of Texas Institutional Review Board. Participants, primarily college students of Mexican descent (n=55), aged 18 to 38 years, were recruited from the San Antonio metropolitan area, through advertisements in the local community and college campuses. Complete details of the recruitment and screening procedures for the current study are reported elsewhere (Mangold et al., 2010). Participants were fully informed of study procedures and consent was obtained prior to enrollment in the study. During an initial visit to the laboratory, participants underwent a screening interview and a battery of self-report assessments designed to identify and exclude factors known to potentially affect the HPA axis, including current depression (Huber et al., 2006; Oquendo et al., 2003), use of oral contraceptives in the past 60 days (Meulenberg & Hofman, 1990; Pruessner et al., 1997,1999), current pregnancy (Meulenberg & Hofman, 1990), menstrual cycle abnormalities in the past 60 days (Bao et al., 2003, 2004; Suh et al., 1988), strenuous aerobic exercise (more than 2 hours per day for 4 or more days per week in the past 60 days (Hansen et al., 2008; Kelly et al., 2008), certain reported medical conditions, history of head trauma, use of medications, severe obesity (defined as a body mass index of > 30.0 kg/m^2) and alcohol or other drug use disorders (Hansen et al., 2008;Wand & Dobs, 1991). Additional exclusion criteria included abnormal sleeping patterns, (Lasikiewicz et al., 2008) and shift and overtime work (Clow et al., 2004; Lundberg & Hellstrom, 2002; Hanrahan et al., 2006).

Psychometric Assessments

Diagnosis of Major Depression—Participants were screened for depression using the Hamilton Depression Inventory Short Form (HDI-SF; Reynolds & Kobak, 1995) and excluded from participation based on a score of 10 or greater indicating a strong likelihood of depressive disorder (Reynolds & Kobak, 1995). Reliability for the HDI-SF for the sample was acceptable (α = .78).

Substance Abuse/Dependence—Participants were screened and excluded for current or lifetime alcohol and other drug use disorders using the World Health Organization Alcohol, Smoking and Substance Involvement Screening Test (WHO ASSIST; Humeniuk et al., 2008). Reliability for the sample was acceptable (α = .81).

Assessment of Ethnicity/Nativity—Participants were determined to be of Mexican descent if both biological parents and both maternal and paternal grandparents were of Mexican descent. Generational status was characterized as first generation (subject immigrated to U.S. as child or as an adult, with both parents born in Mexico; Second Generation (subject was born in the U.S. with at least one parent born in Mexico), Third Generation or higher (subject was born in the U.S. and at least one parent and one grandparent born in Mexico).

General Health—Subjective general health was assessed with the RAND 36-Item Health Survey (RAND-36; Stewart et al., 1988). Reliability for the RAND-36 is demonstrated for Mexican American samples (Ayuso-Mateos et al., 1999) with good reliability for the current sample (α = .85).

Childhood Trauma—Exposure to childhood trauma was assessed using the Early Trauma Inventory–Short Form (ETISR-SF; Bremner et al., 2007). The ETI-SF assesses General Trauma, Physical Punishment, Emotional Abuse and Sexual Events, and has strong psychometric properties (Bremner et al., 2007; Hyman et al., 2005) with good reliability for the current sample (α = .80).

Psychiatric Symptoms—Severity of depressive symptomatology was assessed with the Revised Symptom Checklist (SCL-90-R; Derogatis,1976, 1977; Derogatis & Cleary 1977a, 1977b). The SCL-90-R is a self-report, clinical rating scale providing global indices and scores on symptom dimensions psychological distress. The instrument is comprised of 90 items across nine symptom categories: Somatization, Obsessive-Compulsive, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobia, Paranoid Ideation, and Psychoticism. Subjects' responses to each of these items provide information on the intensity of experienced symptoms (5-point scale: not at all; a little bit; moderately; quite a bit; extremely) in the past seven days before completing the questionnaire. Each of the scales has exhibited good internal consistency (coefficient alpha from 0 .77 to 0.90) and high concurrent validity with MMPI clinical profiles (Derrogatis et al., 1976). Good psychometric properties are reported for Hispanic samples (Martinez et al., 2005) with good reliability for the depression subscale used for the current sample (α = .97).

Acculturation—The revised Acculturation Rating Scale for Mexican Americans (ARSMA-II; Cuéllar et al., 1995) was used to characterize the sample on level of acculturation by measuring subjects' orientation towards Anglo culture and Mexican culture. The ARSMA-II has strong psychometric properties with good reliability for the current sample (α = .78).

Procedure

Measurement of Waking Cortisol Concentrations—Complete details of the salivary collection procedure have been previously reported (Mangold et al., 2010). Participants were free to wake up as usual (using an alarm or spontaneously) and instructed to start sampling immediately at awakening, 30, 45 and 60 minutes thereafter, and again at 3pm, 6pm and 9pm. Participants were instructed to collected samples on two consecutive weekdays and log wake-up times along with sampling times for comparison with electronic monitoring data. Additional instructions included refraining from strenuous exercise, brushing teeth, eating or drinking, and use of alcohol, caffeine and nicotine during sampling to avoid contamination of cortisol samples (Badrick et al., 2007; Clow et al., 2004). Immediately after awakening, participants collected saliva in a salivette test tube (Sarstedt; Rommelsdorft, Germany), and remained sitting upright in bed until the second sample was obtained. They were then free to follow their normal weekday routine during the remaining sampling period. Cortisol was assessed in females during the early follicular phase of their menstrual cycle (Bao et al., 2003, 2004). We utilized electronic monitoring devices together with self-reported time of sampling to determine concordance between monitored times and self-reported times, detect deviations from the protocol, and maximize accuracy in the documentation of sample times (Jacobs et al., 2005; MEMS; Aardex; Zug, Switzerland).

Hormonal Assays—Participants stored the samples in their home freezers until they were returned to the laboratory the next day and stored at −80 C. On the day of analysis for cortisol, saliva samples were thawed at room temperature and centrifuged at 2500g for fifteen minutes at −4 C. Saliva samples were assayed for cortisol level in duplicate using a high sensitivity enzyme immunoassay kit (Diagnostic Systems Laboratories; Webster, Texas) with a mean lower sensitivity limit of 0.11 ug/dL, standard curve range from 0.1 to 10.0 ug/dL. The intra and inter-assay coefficients of variation were less than 5% at all levels of the calibrator curve. The concentration of cortisol in saliva was expressed as ug/dL. To minimize the potential effects of exposure to stressful events during the sampling period, participants who were currently students were not sampled the week prior to scheduled class examinations. In addition, participants indicating daily hassles, or exposure to stressful daily events during the sampling period (Van Eck et al., 1996), sleep disturbances (Lasikiewicz et al., 2008), and other unusual events or protocol noncompliance (teeth brushing, eating, etc), during sampling periods were excluded from the final analyses.

Statistical Analyses—The current sample includes data from 55 of 59 original participants in a previous study examining the effects of childhood trauma and acculturation on the CAR in Mexican Americans (Mangold et al., 2010). As an extension of the previous study, 55 participants consented to complete additional study phases (including completion of an assessment of depressive symptom severity and three additional cortisol sampling sessions in the afternoon and evening) designed to test a priori hypotheses to determine the extent to which the CAR compared with 12 hr waking day AUC predicts subclinical symptomatology while controlling for the effects of childhood trauma.

The primary statistical design included two General Linear Models with repeated measures at four morning time points (awakening, 30, 45, and 60minutes thereafter) and three afternoon and evening time points (3pm, 6pm and 9pm). Fixed design effects were Subclinical Depressive Symptomatology, used as a continuous, dimensional variable (SCL-90-R scores ranged from 0 to 3.38) and Time (a fixed classification factor with four levels and again with three levels). The Subclinical Symptomatology × Time interactions were the primary focus of the current study, testing the association between symptoms and initial changes in morning, afternoon and evening salivary cortisol concentrations over time. Summary cortisol statistics are presented separately for days one and two for comparison

with previous data and to demonstrate minimal between-day variability in cortisol concentrations. Inferences are based on the results of the analyses using continuous measures, but analyses were also performed by grouping depressive symptom severity scores into classes (high, moderate and low scores) to aid in the interpretation of the graphics presented.

In addition, two cortisol summary measures were calculated using salivary cortisol concentrations sampled across the morning, afternoon and evening to measure: (1) 12hr area under the curve (AUC) calculated across seven time points (Altman, 1991) and; (2) Delta calculated as the change in cortisol concentration in the period between awakening and thirty minutes thereafter. A series of four hierarchical regressions assessed the extent to which the set of demographic and health variables (general health, sex, BMI, age and household income) each of the four childhood trauma variables of interest (emotional abuse, sexual abuse, physical abuse and general traumas), and the set of two cortisol summary variables (Delta and AUC) predicted subclinical depressive symptomatology. Statistical analyses were performed using SPSS (version 11.0), and all statistical tests were two tailed. The accepted level of significance was set at an alpha level of 0.05.

Results

Demographic Characteristics

Demographic characteristics for the participant sample are presented in Table 1. Participants were first (31.0%), second (34.5%), and third generation or higher (34.5%), Mexican Americans, ranging in age from 18 to 38 (M = 21.80, SD = 5.2), and primarily undergraduate college students (26 males and 29 females). Results of chi-square tests (χ^2) showed no significant differences in the composition of the sample between males and females. Participants were healthy with mean scores on the General Health scale of the RAND-36 for the current sample (M = 80.05, SD = 16.68) in line with those previously reported for healthy, young adults (M = 77.60, SD = 20.10, Vander Zee et al., 1996). The mean score on the HDI for the sample was lower than normative means reported for college-aged participants (M = 5.16, SD = 4.48; Reynolds & Kobak, 1995; Vander Zee et al., 1996) due to exclusion criteria including a diagnosis of current and lifetime depression and HDI scores higher than 10. Participants endorsed a range of depressive symptoms with HDI scores ranging from 0 to 9.50 (M = 2.68, SD = 2.26) for the sample. Participants reported no use of psychotropic medication.

The majority of respondents reported speaking English very often or almost always (91%). However, approximately 67% reported enjoying speaking Spanish very often or almost always and nearly 38% reported enjoying Spanish language movies very often or almost always, suggesting many of the participants were bilingual. There was little intra-individual variability in the timing of cortisol sampling. Approximately ninety percent of the samples were obtained within less than 10 minutes of protocol. Calculations of the change in mean cortisol concentration from awakening to 30 min post-awakening for trial one (12.70 ± 13.8 nmol/l) and trial two (9.38 ± 15.18 nmol/l) comparable to the mean change previously reported for normals, although with greater dispersion (9.3 ± 3.1 nmol/l) (Clow et al., 2004). The correlation coefficients between days one and two for Delta were r = .42 (df = 51, p = .002; Spearman rho = .29, p = .04) and, for AUC were r = .70 (df = 51, p = .001; Spearman rho = .66, p = .001) suggesting minimal variability in cortisol responses between days one and two for the current sample. Results from analyses of day one data are presented, however, analyses using summary variables aggregated from Days 1 and 2 produced similar results.

Mean number of exposures for each subtype of trauma and composite exposures are reported in Table 2. Total trauma exposures were lower than those previously reported in a healthy non-Hispanic sample of trauma victims, without psychiatric diagnoses (Klassens et al., 2009). Males in the current sample reported more exposure to total traumas ($p < .01$), physical punishment ($p < .01$), and general traumas ($p < .05$) compared with females. There were no differences in trauma exposures among first, second and third generation groups or low, moderate and high acculturation groups.

Raw scores on the SCL-90-R for the current sample of Mexican Americans are in line with raw scores reported by Martinez et al. (2005) for a similar Hispanic college sample (Table 2). However, raw scores are much higher than those reported by Derogatis et al. (1977) for normal, non-patient samples of non-Hispanic males and females with depressive symptomatology.

The first model examining the two- factor Symptomatology × Time interaction (morning cortisol concentrations) was significant ($p = .009$) when the subclinical symptomatology scale was included as a dimensional covariate and after applying the Bonferroni adjustment. To clarify this interaction, the sample was divided into approximate thirds based on symptom severity scores. The two-factor interaction using the three symptom groups in place of the dimensional covariate was again, significant ($F(6,96) = 2.23$, $p<.05$). Contrast tests indicated the CAR significantly differed in the group with the highest symptomatology when compared with the low and moderate groups ($p = .014$) although the low and moderate symptom groups did not differ from one another ($p = .16$). The low and moderate symptom groups were therefore combined and compared to the higher symptom group. A test of the change in cortisol during the first 30 minutes in the high symptom group showed that it was significantly attenuated compared to the average change in the same time interval in the low and moderate groups combined ($F(1,52) = 5.99$, $p = .02$). Figure 1 presents cortisol concentrations for the three subclinical symptom groups at awakening, 30, 45 and 60 minutes thereafter. The second model examining the two-factor Symptomatology × Time interaction (afternoon and evening) was not significant when symptomatology was included as a dimensional covariate and again when symptom scores were grouped into three classes. Figure 1 presents cortisol concentrations for the three subclinical symptom groups at 3pm, 6pm and 9pm.

A series of hierarchical regression analyses were conducted to determine the extent to which health variables (general health, body mass index, age, sex, and household income) exposure to each of four subtypes of childhood trauma (emotional abuse, sexual abuse, general traumas, and physical punishment) and two cortisol summary variables (Delta and AUC) predict subclinical depressive symptomatology. Table 3 presents zero order correlations among the variables in the models, and shows attenuation of the CAR is associated with childhood exposure to emotional abuse and general traumas similar to previously reported findings from our laboratory (Mangold et al., 2010). In each analysis, the block of demographic/health variables were entered first, followed by the trauma variable of interest and finally, the block of two cortisol summary variables. Demographic and health variables did not predict symptomatology. However, the first three models including the block of health/demographic variables, trauma variable of interest and block of cortisol variables (Delta and AUC) significantly predicted depressive symptomatology, even after adjustments to control for experiment-wise error due to multiple tests (i.e. 4 regressions): The Holm-Bonferroni and the Benjamini-Hochberg False Discovery Rate (FDR) criteria for significance at $p<0.05$ (Benjamini and Hochberg, 1995; Holm 1979). The first three models were significant at $p < 0.05$ by unadjusted F-tests and remain significant at $p < 0.05$ using either criteria according to the step down Holm-Bonferroni or FDR methods: Emotional Abuse ($R^2_{adj.} = 0.39$, $F(8, 46) = 5.23$, $p < .001$); Sexual Abuse ($R^2_{adj.} = 0.32$, $F(8, 46) =$

4.24, $p < .001$) and; General Traumas ($R^2_{adj.} = 0.18$, $F(8, 46) = 2.49$, $p < .05$). The final model was not significant at unadjusted $p < 0.05$, although was very close to significance: Physical Punishment ($R^2_{adj.} = 0.14$, $F(8, 46) = 2.13$, $p = .05181$). Computation of standardized beta coefficients in the final models showed that increased exposure to some, but not all types of childhood trauma were significant predictors of greater subclinical depressive symptomatology: Emotional Abuse ($\beta = 0.51$; $p < .001$), Sexual Abuse ($\beta = 0.44$, $p < .001$), General Traumas ($\beta = 0.25$, $p = .08$), and Physical Punishment ($\beta = 0.14$, $p = .32$).

Of particular interest, attenuation of the initial morning rise in cortisol expressed as Delta, significantly contributed to the prediction of subclinical depressive symptomatology beyond the contribution of each type of trauma: Emotional Abuse (Delta: $\beta = -0.40$, $p < .05$); Sexual Abuse ($\beta = -0.45$, $p < .01$); General Traumas ($\beta = 0.45$, $p < .05$); and Physical Punishment ($\beta = -0.50$, $p < .01$). In two of the final models Delta, but not Physical Punishment and General Traumas, exclusively predicted subclinical depressive symptomatology. Moreover, Delta cortisol was a better predictor of subclinical depressive symptomatology compared to 12 hr AUC, and in each case when Delta was removed from the final analyses, AUC alone did not significantly predict subclinical symptomatology.

Discussion

The current study assessed the extent to which exposure to childhood trauma and injury to the CAR predict subclinical symptomatology in Mexican Americans. This is the first study to examine this relationship in Mexican Americans, and thus the first to demonstrate that attenuation of the initial rise in CAR is associated with greater subclinical depressive symptomatology in this minority group. Notably, this is also the first study to distinguish the effects of alterations in cortisol concentrations from the effects of childhood trauma on subclinical depressive symptomatology in adults, and thus the first to demonstrate that attenuation of the initial rise in CAR (delta) predicts greater subclinical depressive symptomatology beyond the contribution of trauma, even after controlling for sex, health, age, body mass index and household income. An additional novel finding demonstrates that after controlling for trauma, attenuation of the initial rise in the CAR is a better predictor of subclinical symptoms than 12 hr AUC.

Several strengths of the study increase our confidence in our findings. Our findings are not likely attributable to the known effects of antidepressant use or substance abuse on the CAR given that subjects were assessed and excluded for use of psychotropic medications, and current alcohol, nicotine and other drug use disorders which helped to minimize the potential influence of these confounds on the HPA axis (Aihara et al., 2007; Wand & Dobs, 1991). Female participants were screened and excluded for use of oral contraceptives prior to enrollment in the current study and sampled during the early follicular phase to minimize the effects of estrogen and progesterone on the HPA axis. Subjects were allowed to wake naturally and measurements were performed with strict reference to time of awakening (Federenko et al., 2004; Williams et al., 2005; Wust et al., 2000) to minimize the influence of time on measurement of the CAR (Edwards et al., 2001; Federenko et al, 2004). Further, we minimized sampling error through the use of electronic monitoring devices (Broderick et al., 2004; Kudielka et al., 2003; Mangold et al., 2010; review in Hansen et al., 2008).

Our finding that attenuation of the initial rise in CAR is associated with greater subclinical depressive symptomatology in Mexican American adults is consistent with previous findings in non-Hispanics (Ahlberg et al., 2002; Dedovic et al., 2010; Tops et al., 2008). Findings are also consistent with the majority of cross-sectional studies showing attenuation of the CAR in non-Hispanics with a formal diagnosis of major depression (Huber et al., 2006; Stetler & Miller, 2005) with a few exceptions (Bhagwagar et al., 2003; Vreeburg et

al., 2009). However, our findings are in contrast with studies showing an enhanced CAR in asymptomatic, high risk adults with a family history of major depression, and in adolescents who develop future major depressive episodes (Adam et al., 2010). The discrepancies in findings may be due to widespread variations in sampling methodologies across studies, and temporal differences in the development of the disorder. Indeed, it is proposed that subclinical depressive symptomatology is a less severe condition that may be a precursor to the onset of a formal diagnosis of major depression (Cuijpers & Smit, 2004; Shankman et al., 2009). In line with this contention, studies have shown a negative association between the CAR, length of time following the onset of trauma or chronic stress and the severity of depressive symptomatology (Chida & Steptoe, 2009; Miller et al., 2007).

Afternoon and evening cortisol concentrations were not associated with subclinical depressive symptomatology in the current sample of Mexican Americans. Our findings are similar to those of a few previous studies in clinically depressed non-Hispanic samples demonstrating minimal differences in afternoon and evening cortisol levels (Burke et al., 2005) and in a symptomatic subjects with a family history of mental illness (Hsiao et al., 2010). However, our findings are in contrast to the majority of cross-sectional studies demonstrating increased evening cortisol levels in clinically depressed non-Hispanic adults (Dahl et al., 1991). Previous studies examining the relationship between afternoon and evening cortisol concentrations and subclinical depressive symptomatology are scarce hence; our current findings are difficult to interpret. It is possible that attenuation of the CAR coupled with minimal difference in afternoon and evening cortisol concentrations is a unique neuroendocrine profile in subjects with a history of childhood trauma who develop subclinical depressive symptomatology.

Final results from hierarchical models including health, childhood trauma and summary cortisol variables accounted for up to thirty-nine percent of the variance in subclinical depressive symptomatology. The heterogeneity of depression suggests numerous possible mechanisms influence the onset of the disorder and specific alterations in HPA axis dynamics may be linked to the development of particular symptom profiles in certain high risk groups (Adam et al., 2010; Dedovic et al., 2010; Ehlert et al., 2001; Heim et al., 2000). It is plausible that specific patterns of HPA axis injury are linked to the development of a specific profile of subclinical depressive symptomatology in Mexican Americans with a history of childhood trauma.

When compared with overall waking day cortisol concentrations (12 hr AUC), attenuation of the CAR is a better predictor of greater subclinical depressive symptomatology. This is consistent with recent investigations showing that the CAR is distinct from diurnal variations in HPA axis activity, possibly reflecting a unique role related to the process of awakening (Wilhelm et al., 2007), and with prospective evidence suggesting the CAR is a better predictor of future depressive episodes when compared with other predictors (Adam et al., 2010).

There are some limitations to the current study. The study was not prospective, but retrospective in design. Therefore, we are unable to determine causal pathways between CAR and subclinical depressive symptomatology. While it is conceivable that an attenuated CAR is present prior to the development of a formal diagnosis and is a biological risk factor that may play a role in the pathophysiology of depression (Dedovic et al., 2010; Van Praag, 2004), it is also possible that injury to the CAR is merely an epiphenomenon of subclinical depressive symptomatology. Additional prospective studies utilizing larger sample sizes are necessary to address this debate.

Determination of the precise developmental mechanisms underlying the relationship between attenuation of the CAR and greater subclinical depressive symptomatology in individuals with a history of childhood trauma is beyond the scope of the current study. However, given that the HPA axis is particularly sensitive to adverse psychosocial experiences in early life during critical periods of neuronal plasticity (Halligan et al., 2004) it is possible that the CAR is a potential biological risk factor that confers risk for subclinical depressive symptomatology in individuals with a history of childhood trauma. According to the "attenuation hypothesis" exposure to childhood trauma may alter the set point of the hypothalamic CRF system leading to enhanced stress reactivity followed by down regulation of central glucocorticoid receptors over time. The hypothalamic CRF system may undergo desensitization leading to attenuated cortisol responses to stress and an attenuated CAR (Gunnar & Vazquez, 2001; Heim et al., 2008; Susman, 2006; Trickett et al., 2010). Alternatively, it is also plausible that early childhood stress or persistent chronic stress produces a blunted CAR with no antecedent HPA axis hyperactivity. This is unlikely given that adolescents with elevated morning cortisol are at greater risk for future depressive episodes (Adam et al., 2010; Halligan et al., 2007) and studies demonstrating a transition from initial childhood hypercortisolism to adult hypocortisolism following exposure to childhood trauma (Trickett et al., 2010).

Taken together, these findings show that greater subclinical depressive symptomatology is associated with attenuation of the CAR, but not 12 hr waking day AUC in Mexican American adults with a history of childhood trauma. It will be important to determine if injury to the HPA axis confers greater risk for additional hypocortisolemic syndromes in this minority group.

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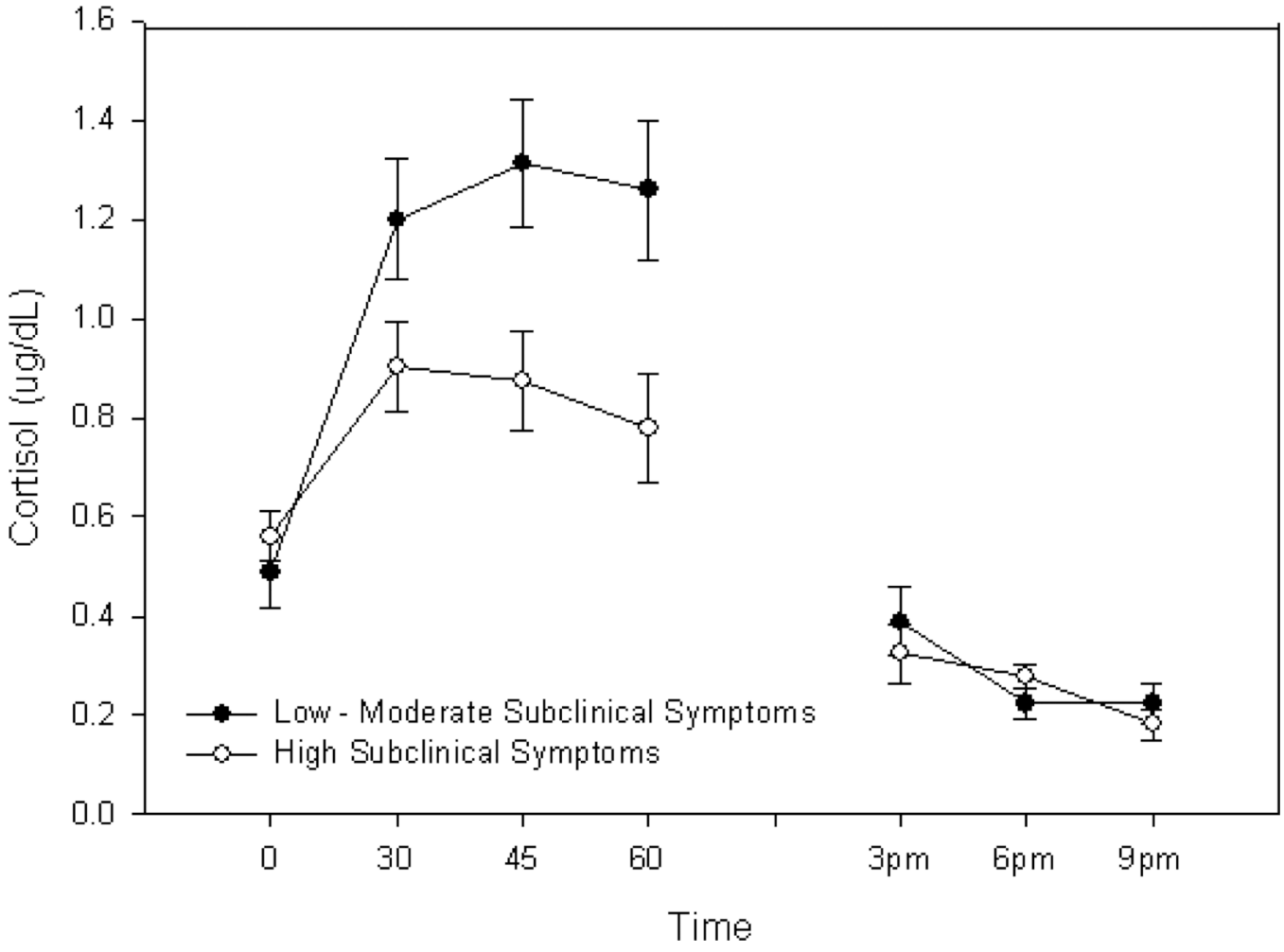

Figure 1.
Morning, Afternoon and Evening Salivary Cortisol in Mexican Americans with Subclinical Depressive Symptoms

Table 1

Sample Demographics for Mexican American Adult, Males and Females

Variable	Overall Sample	Males	Females
Gender	55(100.0%)	26(47.3%)	29(52.7%)
Age			
(Mean and SD)	21.80(5.2)	24.20(5.8)	21.00(4.7)
Body Mass Index			
(Mean and SD)	24.28(4.21)	24.20(3.8)	24.35(4.6)
Participants' Education Level			
Freshman	27(49.1%)	14(53.8%)	13(44.8%)
Sophomore	11(20.0%)	2(7.7%)	9(31.0%)
Junior	6(10.9%)	4(15.4%)	2(6.9%)
Senior	11(20.0%)	6(23.1%)	5(17.3%)
Participants' Generational Status			
First Generation*	17(31.0%)	9(34.6%)	8(27.6%)
Second Generation	19(34.5%)	9(34.6%)	10(34.5%)
Third Generation (or above)	19(34.5%)	8(30.8%)	11(37.9%)
Acculturation Level**			
High Mexican Orientation	16(29.1%)	8(30.8%)	8(27.6)
Moderate Mexican Orientation	17(30.9%)	7(26.9%)	10(34.5%)
Low Mexican Orientation	22(40.0%)	11(42.3%)	11(37.9%)
Household Income			
Below 40K	31(56.3%)	11(42.3%)	20(69.0%)
40K–80K	15(27.3%)	9(34.6%)	6(20.7%)
80K and above	9(16.4%)	6(23.1%)	3(10.3%)
Parental Occupational Status			
Executive	19(34.5%)	10(38.4%)	9(31.0%)
Administrative/Management	12(21.8%)	6(23.1%)	6(20.7%)
Clerical/Skilled Manual Labor	20(36.4%)	8(30.8%)	12(41.4%)
Semi-skilled or Unskilled Labor	4(7.3%)	2(7.7%)	2(6.9%)

*Subjects who emigrated from Mexico to the United States either as adults or as children are grouped together as 'First Generation'.

**The revised Acculturation Rating Scale for Mexican Americans (ARSMA-II; Cuéllar et al., 1995) was used to assess acculturation by measuring subjects' orientation towards Anglo culture and Mexican culture. Scores on the ARSMA-II reflect the extent to which participants endorsed Anglo relative to Mexican orientations.

Table 2

Childhood Trauma Exposures amd Psychiatric Symptomatology for Mexican-American Males and Females (Means and SD).

	Overall Sample (N=55)	Males (N=26)	Females (N=29)
Childhood Trauma Exposures†			
Total Traumas	5.33 (4.22)	7.01 (4.91)	3.83 (2.80)**
Emotional Abuse	1.15 (1.53)	1.42 (1.75)	0.90 (1.29)
Physical Punishment	1.38 (1.46)	1.96 (1.59)	0.86 (1.13)*
General Traumas	2.37 (1.76)	2.97 (1.89)	1.83 (1.47)*
Sexual Events	0.44 (0.88)	0.65 (1.02)	0.24 (0.69)
Psychiatric Symptomatology††			
Anxiety	0.54 (.52)	0.61 (.55)	0.47 (.48)
Depression	0.78 (.77)	0.89 (.83)	0.68 (.68)
Interpersonal Sensitivity	0.88 (.81)	1.04 (.85)	0.74 (.76)
Obsessive-Compulsive	1.06 (.81)	1.27 (.89)	0.88 (.70)
Paranoid Ideation	0.78 (.82)	0.86 (.81)	0.71 (.83)
Phobic Anxiety	0.23 (.38)	0.24 (.29)	0.22 (.44)
Psychoticism	0.48 (.55)	0.60 (.56)	0.37 (.54)
Somatization	0.47 (.49)	0.56 (.53)	0.39 (.44)
Hostility	0.46 (.48)	0.58 (.55)	0.36 (.38)

* $p < .05$,

** $p < .01$,

*** $p < .001$

† Early Trauma Inventory (ETISR-SF; Bremner et al., 2007); Although there were no gender differences in trauma exposure overall, males reported significantly more exposures to General Traumas [$F(1,16.9) = 5.83$, $p < .05$], Physical Punishment [$F(113.12) = 6.50$, $p < .05$], and Total Traumas [$F(1, 125.13) = 7.32$, $p < .01$] compared with females. Mean ETI-SF scores are lower than those previously reported in healthy non-Hispanic participants without psychiatric diagnoses (Klaassens et al., 2009).

†† Symptom Checklist-90-R (SCL-90-R; Derrogatis, 1977); There were no significant gender differences in symptom severity. Mean SCL-90-R scores for each symptom dimension are in line with those previously reported for Hispanic college students (Martinez et al., 2005). Published normed SCL90-R scores for Hispanics are not available.

Table 3

Zero-Order Correlation Coefficients for the Total Sample

(N=55)	1	2	3	4	5	6	7	8	9	10	11	12
1. Depressive Symptomatology	-											
2. General Health	−.19	-										
3. Body Mass Index	.17	.29*	-									
4. Gender	−.14	−.10	.02	-								
5. Age	.13	−.21	.29*	−.16	-							
6. Household Income	.06	.29*	−.28*	−.25	−.18	-						
7. Emotional Abuse	.57**	−.07	.07	−.17	.13	.18	-					
8. Sexual Abuse	.48**	−.00	.02	−.24	.23	.15	.37**	-				
9. General Traumas	.38**	.05	.03	−.33*	.17	.15	.35**	.43**	-			
10. Physical Abuse	.28*	.09	−.02	−.38**	.04	.22	.51**	.36**	.39**	-		
11. CAR (Delta)	−.35**	.14	−.08	.30*	−.38**	.15	−.28*	−.23	−.34*	−.25	-	
12. Cortisol (AUC)	−.12	.19	−.17	.20	−.23	.13	−.17	−.09	−.12	−.07	.68**	-

* $p<.05$,

** $p<.01$