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Dexamethasone-suppressed salivary cortisol and pain sensitivity in female twins

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Abstract

Objectives—Hypothalamic-pituitary-adrenal (HPA) axis dysregulation is associated with chronic pain. Studying pain sensitivity and the HPA axis could elucidate the role of stress in chronic pain development, which might be influenced by familial factors, including genes.

Methods—Associations between pain sensitivity and salivary cortisol and familial confounding in these associations were examined in 88 female, community-based twin pairs (75% monozygotic, mean age 29 years). Cortisol was assessed after 0.25 mg dexamethasone, recovery from 0.25 mg dexamethasone, and after 0.5 mg dexamethasone. Cold pressor task pain ratings were obtained at threshold and at tolerance. Conditioned pain modulation (CPM) was examined using thermal heat as the testing stimulus and hot water as the conditioning stimulus. Generalized estimating equation models were used and adjusted for baseline pain rating, age, and other relevant covariates.

Results—After controlling for baseline cortisol, greater cortisol suppression following dexamethasone administration and lower recovery cortisol levels were associated with higher pain ratings at tolerance during the cold pressor task (*B*'s = −2.42 to −17.82; *p*'s = 0.031 to < 0.001) as well as with reduced CPM (*B*'s = −0.92 to −1.68; *p*'s = 0.003 to 0.046). Interestingly, familial

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Conflicts of Interests

All authors have no conflicts of interest to declare.

confounding was evident in the cold pressor task and CPM during recovery from dexamethasone administration, but not immediately following dexamethasone administration.

Discussion—These findings contribute to understanding possible mechanisms underlying chronic pain by demonstrating that HPA axis response to negative feedback is related to pain sensitivity.

Keywords

salivary cortisol; dexamethasone; HPA axis; pain sensitivity; cold pressor; genetics

Introduction

Chronic pain conditions involve complex systems of risk factors, including biological, psychological, and social characteristics [1]. The hypothalamic-pituitary-adrenal (HPA) axis may mediate the influence of psychological stress on the development and maintenance of pain [2, 3]. People with chronic pain conditions often exhibit HPA axis dysregulation, although the evidence for specific changes is inconsistent [4–6]. HPA axis functioning can be examined by cortisol, which is produced in a cascade of hormones down the HPA axis [7]. Cortisol levels are usually higher in the morning, lower in the evening, and spike in response to acute stressors among healthy individuals [8]. Negative feedback regulation of cortisol at the level of the hypothalamus and pituitary is important for maintaining basal levels [9]. One standardized approach of assessing negative feedback is the dexamethasone suppression test (DST). Dexamethasone is a steroid (glucocorticoid) and cortisol analog that reduces the action of the pituitary gland and lowers or suppresses cortisol release [10]. The DST can be used to assess the integrity of the HPA axis system by providing a test of negative feedback, and has been used widely in research and clinical setting to understand the unique stress response profiles of people with post-traumatic stress disorder [11] and of people at risk of developing chronic pain [12, 13].

Chronic pain is typically accompanied by numerous symptoms and consequences, such as sleep deprivation and physical deconditioning, that are difficult to disentangle from HPA axis function [3]. In order to better understand the relationship between HPA axis function and chronic pain, it is important to characterize the relationship between cortisol and pain sensitivity in individuals without chronic pain as increased pain sensitivity is often a marker of chronic pain development [14]. Cortisol levels are associated with experimental pain sensitivity in healthy persons, though the direction is inconsistent [15–18]. Previously in our laboratory, we found flatter diurnal variation in cortisol rhythms were related to greater pain sensitivity during the cold pressor task (CPT) [19]. Inconsistent findings have also been reported in studies assessing pain sensitivity after the DST. For example, one investigation found that the DST reversed exercise-induced analgesia during a dental pain procedure [20]. However, another study found no effect of the DST on thermal pain sensitivity [21].

More research is needed to elucidate the relationship between HPA axis functioning and pain sensitivity, and develop more complex paradigms of pain sensitivity. To our knowledge, no study has assessed “dynamic” models of endogenous pain inhibition, namely conditioned pain modulation (CPM), in relation to cortisol levels following the DST. This is important

because a deficiency in endogenous pain inhibition more strongly predicts the development of chronic pain than do deviations in other measures of experimental pain (e.g., pain thresholds, supra-threshold pain) [22].

Genetic factors and exposure to early-life or ongoing stressors are also known to influence HPA axis function [23, 24]. Individuals also differ substantially in their experience of painful stimuli, so that genetic background and shared family environment (collectively, familial factors) have emerged as a source of individual differences in pain sensitivity and potential source of chronic pain development [25, 26]. Research has begun to identify specific sets of single-nucleotide polymorphisms that may be involved in the stress-pain relationship. One large prospective cohort study found a significant relationship between a haplotype variation at the COMT gene, basal experimental pain sensitivity, and the development of temporomandibular disorder during a 3-year follow-up period, suggesting a genetic contribution to pain sensitivity and chronic pain development [27].

The current study expands on previous investigations by assessing the relationship between HPA axis function (cortisol suppression following the DST and recovery cortisol levels) and experimental pain sensitivity, including CPM, in female twins without chronic pain. An additional contribution of the present study is to examine the role of familial confounding in this relationship. We hypothesize that 1) greater cortisol suppression following the DST and lower recovery cortisol levels will be associated with greater pain sensitivity during the CPT and reduced CPM among female twins, and 2) familial factors will account for variance in the relationship between HPA axis function and experimental pain sensitivity.

Materials and Methods

Participants

Ninety-nine female twin pairs (N=198) were recruited from the University of Washington Twin Registry, a community-based registry of twins drawn from the Washington State Department of Licensing [28, 29]. This study recruited adult female twin pairs living in the greater Seattle area from 2006 to 2010 by contacting potential participants. Twins were asked to take part in a study of psychological, behavioral, and physiological risk factors for medically unexplained pain [30]. Exclusion criteria included medical conditions that could account for the presence of pain, such as autoimmune disease or cancer, or could alter data collection, such as uncontrolled allergies or neuroendocrine conditions, heart or lung problems, and sleep disorders. Other exclusion criteria were current smoking, a positive screen for drugs of abuse, body mass index under 18.5 or over 30 kg/m^2, and pregnancy, all of which could influence the measurement of cortisol, and any physical or sensory disability that would prevent completion of study tasks. Written informed consent was obtained from all participants before they undertook any study procedures. The Institutional Review Boards of the University of Washington, the University of California, San Diego, and the University of Kentucky approved all study protocols.

Procedures

Potential participants were screened with the London Fibromyalgia Epidemiology Study Screening Questionnaire [31] before enrollment. Enrolled participants completed a seven-day protocol at home for collecting salivary cortisol, administering dexamethasone (DEX), and taking a questionnaire that assessed sociodemographic and other study measures. Within approximately two weeks of finishing these tasks, twins completed a two-day laboratory session at the University of Washington General Clinical Research Center. The session included a medical and physical examination, tasks for pain sensitivity, and other study procedures. Members of each twin pair completed the study visit at the same time but performed each of the laboratory tasks separately.

During the two-day study visit, and for two weeks beforehand, participants were asked to avoid all medications that might affect sleep, pain, the HPA axis, or the autonomic nervous system. During the same period, they were also asked not to drink more than two alcoholic drinks per week or one cup of coffee per day. Over-the-counter pain medicines (e.g., ibuprofen or acetaminophen) were permitted for administration as needed during the study visit. However, no participants reported taking these or other pain relievers during the visit. A standard urine drug screen during the visit ensured that no recreational drugs were used. Zygosity of twin pairs was examined first by using a questionnaire on childhood similarity that has demonstrated 95–98% accuracy relative to verification with biological markers [32–35]. Zygosity was then confirmed with genetic testing at the University of Washington Center for Clinical Genomics by using either the AmpFlSTR® Identifiler® Plus PCR Amplification Kit or the PowerPlex® 16 HS System, with all assays conducted according to manufacturer's instructions.

Salivary cortisol and dexamethasone

Participants collected salivary cortisol at home twice a day for seven consecutive days. The morning (AM) collection occurred within 30 minutes after waking up and the evening (PM) collection either within 30 minutes before going to bed or by 11:30 PM at the latest. Three days of baseline cortisol levels were collected at the start of the at-home protocol. Because these data were used in a previous study [19], they were not included in analyses reported here. At the end of day 3 participants took 0.25 mg DEX, so day 4 recorded cortisol levels post-0.25 mg DEX. Days 5 and 6 were recovery days. At the end of day 6 participants took 0.5 mg DEX, so day 7 recorded cortisol levels post-0.5 mg DEX. Based on the participant logs, 98% of participants received 0.25mg DEX between 8 PM and 11:30 PM, and 96% of participants received 0.5mg DEX between 8 PM and 11:30 PM. During at-home activities, research staff maintained daily contact with participants to troubleshoot problems with study procedures. Participants recorded any problems they encountered during saliva collection, as well as the times when they went to sleep and woke up.

Saliva was collected by asking participants either to chew absorbent swabs (Salimetrics, State College, PA) or to place the swabs under the tongue, and then insert them in a Salivette tube. Participants stored the tubes in home freezers and brought them on ice to Seattle for their two-day laboratory visits. After collection from participants, samples were stored in a freezer at −80°C and batch-shipped on dry ice to the University of Kentucky Center for

Clinical and Translational Science. After centrifugation, samples were assessed for cortisol concentrations with High Sensitivity Salivary Cortisol Enzyme Immunoassay Kits (Salimetrics, State College, PA) according to manufacturer's instructions. The sensitivity of this assay is < 0.003 μg/dL. Internal control samples in every assay were used to obtain inter-assay variability. A KC4 uQuant Plate Reader (BioTek Instruments, Inc., Winooski, VT) was used to analyze the samples. Cortisol values from AM and PM collections were used in analytic models.

Pain sensitivity

Cold Pressor Task—Cold water pain sensitivity was measured with the CPT, using water kept at 1–2°C in a large container with ice cubes and a pump [36]. To start, participants submerged their dominant hand and forearm in the water. To identify threshold and tolerance time points, they indicated the time when the sensation first became painful (i.e., pain threshold) and the time when it became too painful to tolerate (i.e., pain tolerance). The times from start to threshold and from start to tolerance were used as pain latency variables in the analyses. Participants also rated any general pain they were experiencing at baseline (before starting), at threshold, and at tolerance on a visual analog scale anchored at "no pain" (score of 0) and "worst pain ever" (score of 100).

Conditioned Pain Modulation—CPM was conducted as described by Granot et al. [37]. Briefly, a Thermal Sensory Analyzer (TSA) II system (Medoc, Ramat-Yishai, Israel) with a 30 × 30 mm Peltier surface stimulator strapped to the volar part of the dominant forearm served as the test stimulus, while a hot water bath (Hot Tub 14 L, Boekel Scientific, Pennsylvania, USA) maintained at 46.5 °C (± 0.1° C) served as the conditioning stimulus. Participants first completed a training phase to familiarize them with the devices. Following the training phase, participants were exposed to contact heat of 45, 46, and 47° C, each 7 seconds (s) in duration with a 1-minute inter-stimulus interval, in order to find a temperature that produced a pain rating of 6 (hereafter referred to as "Pain-6") on a verbal numerical pain scale ranging from 0 = "no pain" to 10 = "the worst pain imaginable." If one of these stimulations induced Pain-6, that temperature was subsequently used as the test stimulus temperature; if not, additional temperatures were applied until Pain-6 was attained [37].

For the CPM task, the test stimulus was applied for 30 s at Pain-6. Pain ratings were captured at 0, 10, 20, and 30 seconds, and the mean score of the last 3 pain ratings was calculated. Five minutes after delivering the test stimulus, participants were asked to place their non-dominant hand in the hot water bath (conditioning stimulus) in a still position with their fingers wide apart for 60 seconds. Participants rated the pain intensity from the hot water bath at 0, 10, 20, and 30 seconds following immersion. After the fourth pain rating for the conditioning stimulus, the test stimulus was applied again and participants were asked to shift their focus to the contact heat pain. Participants rated the pain intensity from the test stimulus at 40, 50, and 60 seconds while their non-dominant hand remained in the hot water bath.

Statistical analyses

Means and standard deviations were calculated for continuous measures (age, cortisol variables, and pain ratings), and percentages were derived for categorical variables (ethnicity, zygosity, education, marital status). The diurnal variation in cortisol was calculated by subtracting PM values from AM values and calculating the mean diurnal variation across recovery days. Generalized estimating equation (GEE) regressions were run to examine the relationships between cortisol variables and pain sensitivity variables. GEE models were used because they are suited to analyze data that are not independent, such as data on twin pairs. Overall models included each twin as an individual to examine overall cortisol-pain sensitivity relationships. All models for the CPT pain sensitivity measures included age, baseline pain intensity ratings, and pain latency as covariates. The pain latency variable included in each model corresponded to the time of the pain rating (e.g., threshold pain latency was used in the threshold pain rating model); this variable was included to control for the varying amount of time each participant spent in cold water. CPM response was calculated by subtracting the mean pain rating during the conditioning plus test stimulus trial from the mean pain rating during the test stimulus only trial. Thus, negative values are representative of pain inhibition. The CPM variables included in statistical models were CPM response and Pain-6. All models for the CPM variables included age as a covariate. Models of post-DEX cortisol values included the cortisol levels for that time point from the previous day (e.g., post-0.25 mg DEX AM models included morning cortisol levels from baseline day 3). Cortisol values from the previous day were included to examine the cortisol response (i.e., change in cortisol level) after DEX administration by controlling for baseline or typical cortisol levels for each participant at that collection time point. In this way, the models captured cortisol response to DEX while accounting for individual differences in absolute cortisol output.

For relationships with significant overall models, we estimated within-pair models that accounted for the familial factors shared by twin pairs, which might influence the relationship between cortisol and pain. The within-pair models were based on the following assumptions: members of monozygotic (MZ) twin pairs share 100% of genes, members of dizygotic (DZ) twin pairs share on average 50% of genes, and both MZ and DZ twin pairs share a common developmental and familial environment. The influence of familial factors was considered to be present if significant relationships observed in the overall models were reduced in magnitude in the within-pair models. However, if within-pair associations were not attenuated relative to the overall models, then familial factors were considered unlikely to play a role in these relationships. Within-pair models were calculated by using GEE linear regression models with the exposure or independent variable set as the individual twin's deviation from the mean cortisol value of the pair [38]. Significance was set at $alpha = 0.05$ for all analyses, which were performed by using Stata/SE 12.0 for Windows (StataCorp LP, College Station, TX, 2012).

Results

Participant Characteristics

Of the 99 twin pairs who participated in the study, 88 pairs (176 individuals) had complete data for all variables of interest and were included in the analyses. All participants were female, and 77% were MZ. The average age was 29 years (*SD* = 10); 85% were White; 52% had a Bachelor's degree or higher, and 23% were married or cohabitating. Based on the London Fibromyalgia Epidemiology Study Screening Questionnaire [31], 70% of the sample had no pain and 30% reported some pain, but none had chronic pain (i.e., pain lasting greater than 3 months). Table 1 shows means and standard deviations for cortisol variables from the seven consecutive at-home days. Consistent with expected patterns of diurnal variation, cortisol levels were higher in the morning and lower in the evening on baseline, non-DEX days. Compared to baseline and recovery days, cortisol levels after DST were substantially lower in the morning and slightly lower in the evening, on average. The overall pattern of cortisol values is consistent with the expected diurnal variation in cortisol on baseline days, and with suppression of cortisol output in response to DST. Table 2 displays the means and standard deviations of the CPT and CPM pain sensitivity variables. The average baseline pain intensity rating before the CPT was 7.8 (*SD* = 12.06) on a 0–100 scale, confirming that the sample was relatively pain-free. During the CPT, pain ratings increased as expected from baseline to threshold and to tolerance. For the CPM task, pain ratings during the second test stimulus were lower than pain ratings during the first test stimulus. The mean Pain-6 or test stimulus temperature was 46.57° C. Sixty-two percent of participants experienced pain inhibition during the CPM test whereas 7% reported no difference in pain between conditions, and 31% of participants did not exhibit pain inhibition and reported increased pain with the conditioning and test stimulus present compared to the condition with only the test stimulus.

Cortisol and CPT

Table 3 presents results of overall and within-pair GEE models to examine the association of cortisol with CPT variables. None of the cortisol variables were significantly associated with pain ratings at threshold. Greater PM cortisol suppression following the 0.25mg DST, and greater AM and PM cortisol suppression following the 0.5 DST were associated with higher pain ratings at tolerance (p's: 0.031 - <0.001). Consistent with our previous findings, lower diurnal variation of cortisol during recovery between DST administrations was also significantly associated with higher pain ratings at tolerance ($p = 0.014$). The within-pair models of significant overall associations between pain at tolerance and post-DST cortisol remained significant (p's = 0.023 - <0.001), whereas the association of pain at tolerance with recovery cortisol levels became non-significant (p's: 0.083 – 0.712).

Cortisol and CPM

Table 4 presents results of overall and within-pair GEE models to examine the association of cortisol and CPM variables. Greater Pain-6 temperatures (i.e., less pain sensitivity) was associated with higher recovery AM cortisol levels ($p = 0.01$). In regard to CPM, reduced pain inhibition was associated with lower recovery diurnal variation of cortisol ($p = 0.046$) and greater AM cortisol suppression following the 0.5mg DST ($p = 0.003$). In the within-

pair models, the association of Pain-6 and recovery AM cortisol was no longer significant (p = 0.31), nor was the relationship between CPM and recovery diurnal variations of cortisol (p = 0.27); the relationship between CPM and cortisol suppression following the 0.5mg DST remained significant (p = 0.001).

Discussion

In the present study, greater cortisol suppression following the DST for three of the four collection points, as well as lower recovery AM cortisol levels and recovery diurnal variation of cortisol, were associated with greater pain ratings at tolerance during the CPT. Lower recovery AM cortisol levels was also associated with lower temperatures required for producing moderate thermal pain (i.e., Pain-6). In regard to CPM, lower recovery diurnal variation of cortisol and greater AM cortisol suppression following the 0.5 mg DST were associated with reduced pain inhibition. Interestingly, when considering findings from both the CPT and CPM analyses, familial confounding was evident in the relationship between recovery cortisol levels and pain responses, but not in the relationship between cortisol suppression following the DST and pain responses.

The current study supports and extends our previous findings [19] on the CPT and cortisol by demonstrating associations between DST recovery and cold pain ratings at tolerance, but not at threshold. The relationship between recovery cortisol levels and pain ratings at tolerance, but not at threshold, during the CPT suggests that the stress response system might be differentially involved in various aspects of pain perception. This study also adds to the pain literature by supporting that lower cortisol levels after the DST and lower DST recovery cortisol levels are related to reduced pain inhibition. Although a prior investigation found no relationship between CPM and circulating cortisol levels obtained prior to pain testing [39], to the best of our knowledge, this is the first study to assess the relationship between CPM and cortisol levels following the DST.

The DST is one of most widely used methods to assess HPA-axis integrity. Past research has consistently noted greater cortisol suppression after the DST in trauma exposed healthy persons compared to non-exposed healthy persons [40], suggesting stress exposure is linked to enhanced negative feedback. Further, stressful life changes are associated with enhanced cortisol suppression among healthy persons [41]. The association of greater cortisol suppression following the DST with higher pain ratings and less efficient CPM could result from several different underlying processes. People with lower cortisol levels might demonstrate hyper-suppression or reduced overall output of cortisol in response to DEX; alternatively, they might experience a relatively prolonged inhibition of negative feedback. Under the second interpretation, an HPA axis with relatively normative pain sensitivity might respond to a stressor and then quickly recover to normal levels. The HPA axis response of people with higher pain sensitivity might involve a combination of hyper-suppression and slower rebound from DST. Future research with more frequent cortisol collection is needed to determine which patterns of HPA axis function are likely to be responsible for these results. Various abnormal profiles of basal cortisol output suggest that HPA axis dysregulation affects both pain sensitivity [19, 42] and the development of chronic pain [4–6]. Chronic stress might therefore lead to chronic dysregulation of the baseline

activity of the HPA axis and alter endogenous pain regulatory systems [7, 43]. Our current findings suggest that dysregulation of the response to acute stress as modeled by the DST might also be associated with alterations in endogenous pain regulatory systems.

In our analyses, the significant association between pain sensitivity and CPM with cortisol suppression following the DST was not diminished after controlling for shared familial factors, suggesting a direct association with HPA axis function. It should be noted that by including cortisol levels from matched collection times on the previous day in our analytic models, we were able to control for baseline cortisol levels. Thus, our models represent the relationship between cortisol response to feedback inhibition with pain sensitivity at tolerance and CPM while accounting for inter-individual differences in cortisol levels. A potentially direct relationship between pain and the HPA axis response to cortisol suppression is consistent with results from a prospective study in which authors found that cortisol levels after DST were stronger predictors of chronic pain development than were baseline cortisol levels [13]. Therefore, pain sensitivity and chronic pain might have a stronger and more direct association with HPA axis function after stress, which may explain why previous studies found no relationship between CPM and cortisol levels [39]. Further, findings from this and our previous study [19] suggest familial factors influence the stress-pain relationship in the baseline or recovery rhythms of the HPA axis, but not in the HPA axis response to negative feedback. The present research therefore highlights the potentially unique role of familial factors in HPA axis health, both in response to and recovery from the DST.

Findings from this study may inform research of clinical populations with chronic pain and elucidate the pathways leading to chronic pain. Physiological changes in the stress response system could provide insights into the mechanisms of chronic pain development that operate before any perpetuating factors, such as central sensitization or chronic inflammation, transform sensitivity into chronicity [44, 45]. Particularly relevant is our finding of enhanced negative feedback and reduced CPM. Less efficient CPM is associated with several chronic pain conditions, including myofascial temporomandibular joint pain [46], chronic low back pain [47], fibromyalgia [48], osteoarthritis [49], and chronic tension-type headaches [50], and also is associated with the development of chronic pain. For example, in pain-free participants undergoing a thoracotomy, Yarnitsky et al. [22] found that reduced pain inhibition was a significant, independent predictor of chronic post-operative pain. In light of these previous studies, our finding that enhanced negative feedback is related to reduced endogenous pain inhibition suggests the DST among persons without chronic pain may be a useful marker for predicting the development of chronic pain, though prospective studies are needed to confirm this hypothesis. However, the literature on DST in chronic pain conditions remains mixed [13, 51, 52], and patterns of HPA axis response in patients with chronic pain might be complicated by the influence of comorbid disorders, such as major depression [52, 53], or shared risk factors, such as early-life stressors [54]. Clearly, more work is needed in both clinical and non-clinical samples to better characterize the stress response system and elucidate the influence of risk and protective factors.

Limitations

This study has several limitations. Our sample was limited to young chronic pain-free female twin pairs, so our findings may not generalize to men, older adults, or samples with chronic pain. Future studies with twins who are discordant for chronic pain conditions are necessary to replicate our findings on associations of cortisol-pain sensitivity as well as the role of familial factors. Our saliva sampling procedure was also restricted in order to reduce participant burden, limiting our ability to perform more complex cortisol analyses such as determining overall cortisol output or cortisol awakening response. The pain sensitivity paradigms that we present involved only cold and heat pain, so results might differ in experimental testing with other modalities such as chemical or mechanical pain. Finally, our study design was cross-sectional. Prospective designs are necessary to further investigate these findings, to examine potential mediators, and to more fully understand the direction of association between pain sensitivity and HPA axis functioning under stress.

Conclusions

We found that HPA axis physiology is related to pain sensitivity and endogenous pain inhibition in response to a negative feedback paradigm and in recovery periods with familial confounding found only during recovery. These findings add to the evidence that cortisol is a useful biomarker of pain sensitivity in research studies. Future investigations should identify specific genetic and other familial influences on the stress-pain relationship. More research is needed to better understand the role of stress in the development and maintenance of chronic pain and in the biological, psychological, and social mechanisms at work in this process.

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Table 1

Means and standard deviations for cortisol variables from seven consecutive days.

***Cortisol* (μg/dL)**	**AM, *M (SD)***	**PM, *M (SD)***
Baseline 1	0.40 (0.32)	0.08 (0.15)
Baseline 2	0.39 (0.25)	0.08 (0.13)
Baseline 3	0.35 (0.23)	0.13 (0.37)
Post-0.25 mg DEX	0.20 (0.29)	0.10 (0.30)
Recovery 1	0.38 (0.29)	0.09 (0.25)
Recovery 2	0.37 (0.29)	0.14 (0.40)
Post-0.50 mg DEX	0.13 (0.28)	0.10 (0.29)

Abbreviations: AM, morning; PM, evening; DEX, dexamethasone; M, mean; SD, standard deviation.

Table 2

Means and standard deviations of pain sensitivity variables.

Cold Pressor Task	**Baseline, *M (SD)***	**Threshold, *M (SD)***	**Tolerance, *M (SD)***
Pain Latency (seconds)	–	18.30 (19.93)	65.77 (73.90)
Pain Rating (0–100)	7.80 (12.06)	43.94 (19.31)	66.93 (18.89)
Conditioned Pain Modulation	**Test stimulus, *M (SD)***	**Conditioning + test stimulus, *M (SD)***	**CPM Response, *M (SD)***
Pain Rating (0–10)	5.06 (1.86)	4.53 (1.71)	−0.50 (1.40)
Pain-6 (degrees Celsius)	46.57 (1.17)	–	–

Abbreviations: M, mean; SD, standard deviation.

Notes: Pain latency is defined as the time between the start of the cold pressor task to the time of threshold or tolerance. Cold pressor task pain ratings used a visual analog scale to rate painfulness of the cold water bath. Conditioned pain modulation pain ratings used a verbal numerical pain rating to rate painfulness of the test stimulus during the stages of the protocol. Pain-6 is the temperature of the test stimulus at which participants rate the pain as 6 on a scale from 0 to 10 as determined before the conditioned pain modulation protocol and was used for the test stimulus temperature.

Table 3

GEE models of overall and within-pair associations between cold pressor pain ratings and cortisol levels after DEX administrations and during the two-day recovery period.

Response: Pain Rating at Threshold		**Overall GEE**			**Within-pair GEE**	
Predictors: Cortisol	***B***	**(95% CI)**	***p***	***B***	**(95% CI)**	***p***
Post 0.25 DEX AM	−0.33	−10.58, 9.92	0.95			
Post 0.25 DEX PM	−0.40	−6.82, 6.01	0.90			
Recovery AM	−4.30	−11.82, 3.22	0.26			
Recovery PM	−0.60	−11.86, 10.66	0.92			
Recovery DV	−2.48	−11.74, 6.78	0.60			
Post 0.5 DEX AM	−0.73	−10.87, 9.41	0.89			
Post 0.5 DEX PM	0.83	−6.00, 7.67	0.81			
Response: Pain Rating at Tolerance		**Overall GEE**			**Within-pair GEE**	
Predictors: Cortisol	***B***	**(95% CI)**	***p***	***B***	**(95% CI)**	***p***
Post 0.25 DEX AM	−3.59	−13.35, 6.17	0.47			
Post 0.25 DEX PM	−9.85	−13.71, −5.99	<0.001	−7.67	−14.31, −1.04	0.023
Recovery AM	−8.26	−15.38, −1.14	0.023	−7.99	−17.03, 1.04	0.083
Recovery PM	4.40	−4.64, 13.43	0.34			
Recovery DV	−9.23	−16.58, −1.88	0.014	−2.42	−15.32. 10.47	0.71
Post 0.5 DEX AM	−8.62	−16.47, −.77	0.031	−7.04	−12.53, −1.55	0.012
Post 0.5 DEX PM	−9.66	−13.41, −5.90	<0.001	−17.82	−24.19, −11.45	<0.001

Abbreviations: AM, morning; *B*, change in pain rating for one unit increase in cortisol (μg/dL); CI, confidence interval; DEX, dexamethasone; GEE, generalized estimating equations; PM, evening.

Notes: All models included baseline pain, age, and pain latency as covariates. Post-DEX models also controlled for baseline cortisol levels at the time of cortisol collection.

Table 4

GEE models of overall and within-pair associations between conditioned pain modulation pain ratings and cortisol levels after DEX administrations and during the two-day recovery period.

Response: Pain-6		**Overall GEE**			**Within-pair GEE**	
Predictors: Cortisol	***B***	**(95% CI)**	***p***	***B***	**(95% CI)**	***p***
Post 0.25 DEX AM	0.65	−0.01, 1.31	0.06			
Post 0.25 DEX PM	0.09	−0.31, 0.49	0.67			
Recovery AM	0.69	0.16, 1.22	0.01	0.35	−0.33, 1.03	0.31
Recovery PM	0.59	−3.61, 4.80	0.78			
Recovery DV	0.36	−0.56, 1.29	0.44			
Post 0.5 DEX AM	0.18	−0.12, 0.47	0.24			
Post 0.5 DEX PM	0.19	−0.24, 0.61	0.38			
Response: CPM Response		**Overall GEE**			**Within-pair GEE**	
Predictors: Cortisol	***B***	**(95% CI)**	***p***	***B***	**(95% CI)**	***p***
Post 0.25 DEX AM	−0.66	−1.60, 0.28	0.17			
Post 0.25 DEX PM	−0.51	−1.01, <0.001	0.05			
Recovery AM	−0.46	−1.17, 0.24	0.20			
Recovery PM	0.76	−1.76, 3.29	0.56			
Recovery DV	−0.94	−1.87, −0.02	0.046	−1.68	−4.66, 1.29	0.27
Post 0.5 DEX AM	−0.54	−0.88, −0.19	0.003	−0.92	−1.47, −0.38	0.001
Post 0.5 DEX PM	−0.32	−0.72, 0.07	0.11			

Abbreviations: AM, morning; *B*, change in pain rating for one unit increase in cortisol (μg/dL); CI, confidence interval; DEX, dexamethasone; GEE, generalized estimating equations; PM, evening. Pain-6 is the temperature of the test stimulus at which participants rate the pain as 6 on a scale from 0 to 10 as determined before the conditioned pain modulation protocol and was used for the test stimulus temperature. CPM Response is the mean pain rating during the test stimulus only trial minus the mean pain rating during the conditioning plus test stimulus trial.

Notes: All models included age as a covariate. Post-DEX models also controlled for baseline cortisol levels at the time of cortisol collection.

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