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Cortisol Profile Mediates the Relation between Childhood Neglect and Pain and Emotional Symptoms among Patients with Fibromyalgia

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Abstract

Background—The relation between childhood trauma and chronic pain and emotional symptoms in adulthood has been well-documented, although physiological mechanisms mediating this link have not been elaborated.

Purpose—This study examined the mediating role of cortisol profile in the linkage between childhood maltreatment and pain and emotional symptoms in individuals with fibromyalgia (FM).

Methods—179 adults with FM first provided retrospective self-reports of childhood maltreatment; then attended a standardized session during which cortisol was sampled across 1.5 hours; and subsequently, completed assessments of daily pain, depressive symptoms, and anxiety. Latent growth curve modeling estimated the hypothesized mediation models.

Results—Childhood neglect predicted a flattened cortisol profile, which, in turn, predicted elevated daily pain and emotional symptoms. The cortisol profile partially mediated the neglect-symptom relation.

Conclusions—Early maltreatment may exert enduring effects on endocrine regulation that contributes to pain and emotional symptoms in adults with chronic pain.

A significant body of evidence suggests that exposure to childhood trauma is a prevalent experience that is linked with risk for adult chronic pain (1, 2). Moreover, among patients with a chronic pain condition, those with greater exposure to early maltreatment also experience more severe physical symptoms, including more extensive pain, and poorer psychological adjustment, including increased risk of depression and anxiety (3–8).

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Conflict of Interest

All the authors of the current study have no conflict of interest to disclose.

Adherence to Ethical Standards

All procedures were approved by the Institutional Review Board at Arizona State University and all the participants gave their informed consent prior to their inclusion in the study.

A number of mechanisms likely account for the links between early maltreatment and elevated pain and emotional distress among adults with chronic pain. One plausible mechanism is via enduring alterations in the hypothalamic-pituitary-adrenal (HPA) axis, an endocrine system that plays a central role in maintaining physiological homeostasis. Daytime cortisol profiles normally display a pronounced decline from early morning until bedtime, and offer one potential indicator of the functioning of the HPA axis (9); a strong negative cortisol profile is the normative pattern, and a weak, inconsistent or absent decline is indicative of HPA dysregulation (10). The HPA system is shaped during infancy and childhood by environmental factors, including maltreatment (11). Children who have been neglected and/or abused show less marked cortisol decline relative to children who have not been mistreated (12, 13), consistent with experimental data derived from nonhuman primates (14). Furthermore, the impact of early maltreatment on the HPA axis function may endure into adulthood. For example, among adopted children followed into adulthood, those who experienced early severe neglect showed flatter cortisol profiles (i.e., diminished daytime cortisol decline) in adulthood relative to adoptees who were not neglected (13). Similar patterns emerge among adults with chronic pain, where retrospective reports of physical and/or sexual maltreatment are related to diminished cortisol decline (1, 15–17). Taken together, the evidence suggests that early maltreatment exerts effects on HPA function that persists over decades.

Cortisol dysregulation has also been linked to pain and mood disturbance. Cross-sectional evidence points to flattened cortisol profiles in individuals with chronic pain and with depression relative to controls (18, 19). There are data, though, to suggest that cortisol dysregulation may precede symptoms. For example, a blunted cortisol pattern predicts subsequent risk of developing widespread pain among adults, even after adjustment for initial levels of anxiety and depressive symptoms (5), and subsequent psychological symptom severity among youth (20).

To our knowledge, no study to date has tested whether HPA dysregulation, reflected in a flattened cortisol profile, mediates the relation between childhood maltreatment and daily pain and mood disturbance among adults with chronic pain. To address this question, the current study drew on retrospective self-reports of early maltreatment, repeated assessments of salivary cortisol during a standardized laboratory visit, and subsequent daily pain and mood reports among individuals with chronic pain due to fibromyalgia (FM). FM is a condition characterized by widespread musculoskeletal pain of unknown etiology (21). Of relevance for the current study, the prevalence of depression and anxiety symptoms are elevated among patients with FM even relative to those with other chronic pain conditions (7, 22). In fact, some investigators have suggested that FM be considered an affective spectrum disorder (23). Moreover, accruing data highlight the links between the neurobiological systems underpinning affective and chronic pain symptoms (24, 25). Thus, the current study focused on the shared factor that underlies the links between psychological and pain symptoms, an approach that is both conceptually grounded and parsimonious (26). Because some evidence suggests that HPA dysregulation patterns may depend on the type of maltreatment, we tested whether neglect and abuse show distinct associations with cortisol profiles and FM pain and emotional symptoms (3, 16). We expected that childhood

maltreatment would predict flattened cortisol profiles, which, in turn, would predict higher levels of pain, depressive symptoms, and anxiety.

Method

Participants

The sample for the present study was recruited through 1) newspaper ads, 2) online postings to FM support groups, and 3) flyers placed in physician offices in the Phoenix metropolitan community in Arizona to participate in a behavioral intervention trial. To be eligible for the study, respondents were required to meet the following inclusion criteria: 1) be at least eighteen years of age, 2) be English-speaking, 3) report widespread pain lasting at least three months, 4) have at least eleven of the eighteen known tender points associated with FM, and 5) have no pending litigation related to their pain condition. One hundred ninety-five individuals completed the thermal pain induction protocol of the laboratory assessment (described below) that constituted part of the pre-intervention evaluation. Of these, 179 individuals were included in analysis; 16 individuals were excluded due to: reported use of corticosteroids ($n = 8$) or reproductive hormone medications ($n = 5$) that affect cortisol levels, loss of cortisol measures due to technical difficulties ($n = 1$), or missing data regarding childhood maltreatment ($n = 2$).

Procedure

The data for the current study were drawn from the *pre*-intervention period of a larger intervention study that assessed the efficacy of different cognitive and affective interventions in treating FM. The Institutional Review Board at Arizona State University approved all procedures employed in this study. Interested individuals were first screened by phone, and then visited at their home by a registered nurse. During the nurse visit, participants provided informed consent, then underwent a tender point exam to confirm widespread pain consistent with the American College of Rheumatology criteria for a diagnosis of FM (21). They also filled out a questionnaire packet that included measures assessing their history of physical and emotional health, including exposure to childhood trauma.

Subsequently, participants visited the laboratory for a three-hour session during which four salivary samples were collected for assessment of free cortisol levels. Laboratory sessions were scheduled to begin either in the morning or in the afternoon, based on the participants' availability. Forty-eight percent of the sessions were conducted in the morning, and 52% of the sessions were conducted in the afternoon. During the session, participants: (1) were given an overview of the laboratory session, completed questionnaires regarding their current medications, pain, and affect, and were fitted with facial EMG and EKG electrodes (30 minutes) and then provided *the first cortisol sample (T1)*; (2) participated in an emotion modulated acoustic startle probe protocol (28) during which heart rate and facial electromyographic responses were recorded (20 minutes), which was followed by a rest period (10 minutes); (3) provided *the second cortisol sample (T2)*; (4) completed thermal pain threshold and tolerance assessments (20 minutes) and then rested (10 minutes); (5) provided *the third cortisol sample (T3)*; (6) completed a thermal pain suprathreshold

assessment (20 minutes) and then rested (10 minutes); and (7) provided *the fourth, final cortisol sample (T4)*.

Participants' heat pain threshold, tolerance, and suprathreshold perceptions of pain unpleasantness were assessed through use of the Medoc TSA II Neurosensory Analyzer (Medoc Ltd, Israel), which delivered thermal stimuli via a thermode placed just above the wrist of the right arm. Prior to initiating the thermal pain induction, participants were told that they could stop the pain stimulus at any time by removing their arm from the thermode. To determine *pain threshold*, the thermode temperature increased from 38 °C to a possible maximum of 50 °C, and the participants were instructed to press a button on the response unit as soon as the sensation became painful (5 trials, 90-sec intertrial interval). To assess *pain tolerance*, participants were instructed to note the temperature at which they found the heat to be extremely uncomfortable [i.e., pain intensity rating of 8 on a scale ranging from 0 (no pain) to 10 (most intense pain imaginable); 5 trials, 90-sec intertrial interval]. Finally, to assess *suprathreshold pain perceptions*, participants rated the intensity and unpleasantness [(i.e., 0 (not at all unpleasant) to 10 (most unpleasant feeling imaginable))] of 5-sec heat pulses at temperatures that fell between the participants' threshold and tolerance levels delivered at random temperatures for a total of 10 trials (90-sec intertrial interval).

Of note, the startle probe procedure and thermal pain assessments did not involve social evaluative threat, a stimulus characteristic that most reliably predicts a cortisol stress response (29). Rather, the procedure provided participants with complete control over their experience (e.g., ability to terminate any stimuli at any time), and was conducted with minimal contact with a single experimenter.

Following participation in the laboratory assessment, participants completed a 21-day electronic daily diary that included questions regarding pain, depressive symptoms, and anxiety. Participants were compensated \$50 for the laboratory visit and \$63 for the diary; no monetary compensation was involved in the nurse visit or the health questionnaire.

Salivary Cortisol Assessment—Four salivary cortisol samples were collected during the laboratory session, as described above. The first cortisol collection for morning sessions was between 10am–12pm, and the cortisol collection for afternoon sessions was between 2–4 pm. At each assessment, participants were instructed to chew on a roll-shaped synthetic saliva collector (Sarstedt, Inc., Newton, NC) for approximately one minute. Free salivary cortisol was determined through the use of a radioimmunoassay, performed in duplicate on 100 µL of saliva (Biochemisches Labor, Unversitaet Trier, Germany). Cortisol levels were determined using a competitive solid phase time-resolved fluorescence immunoassay with fluoumeric end point detection (DELFI). The intra-assay coefficient of variation in these samples was 7.25%, which fell within the standard for accurate measurement in duplicate (< 10%). The inter-assay coefficient of variation was less than 9% reported by Biochemisches Labor, Unversitaet Trier, Germany.

Individual cortisol samples that were more than four standard deviations above or below the mean of the sample, or that were greater than 55 nmol/L were excluded from analyses, as

these values lie outside of the normal physiological range (30). From the possible 716 samples, 96.5% were retained for data analysis.

Measures

Childhood maltreatment—Childhood maltreatment was assessed via a validated self-report measure, the Childhood Trauma Questionnaire-short form (31). The questionnaire consists of 25 questions that assess five subscales (5 items each): emotional and physical neglect, emotional and physical abuse, and sexual abuse. Each item is rated on a 5-point scale from 1 (never true) to 5 (very often true). A total CTQ score was generated by summing across all items, with a range of possible scores between 25 and 125. In addition, childhood neglect scores were calculated by summing the emotional neglect and physical neglect items, and childhood abuse by summing the emotional abuse and physical abuse items. In the current study, the internal reliabilities were .94 for the total CTQ, .90 for childhood neglect, and .92 for childhood abuse.

Pain—Pain level throughout the day was assessed in a 21-day electronic daily diary by one item, “What was your overall level of pain?” on a 101-point scale where 0 indicates “no pain” and 100 indicates “pain as bad as it can be” (32). This item was rated three times a day at 11 am and 4 pm (pain rated for the past 2–3 hours), and 7 pm (pain rated for the entire day), and these ratings were averaged across all diary days.

Depression—Depressive symptoms were assessed with the use of the Hamilton Depression Inventory-short form (33). The HDI-sf is a reliable and valid 9-item questionnaire that evaluates depressive symptoms. Scores can range from 12 to 62 points, with higher scores reflecting more severe depressive symptomatology. In the current sample, the internal reliability for the HDI-sf was .88.

Anxiety—Anxiety was assessed with the use of the Mental Health Inventory – Anxiety subscale (34). This subscale consists of 9 questions regarding the experience of anxiety, with scores that can range from 9 to 54 points. In the current sample, the internal reliability of the MHI-Anxiety scale was .92.

Potential covariates—One set of covariates comprised factors specifically related to cortisol measures during the laboratory assessment, including time of day of laboratory session [0 = am, 1 = pm]; time since last consumption of food/beverage, caffeine, and tobacco; rating of current stress level [1 = none to 5 = extreme]; and pain unpleasantness rating to induced pain.

Additional covariates that might confound the relations between maltreatment, cortisol change, and symptoms included the following demographic and health characteristics: gender, age, smoker status [0 = non-smoker, 1 = smoker (19%)], and medication use (30). With regard to medication use, participant reports of current medication usage were coded into three broad categories of medications: antidepressants (54%), anxiolytics (39%), and analgesics (87%). Medications were designated without regard to dosage or last use, and coded as 0 = no use of anti-depressant, anti-anxiety, or pain medications, or 1 = used any of the three classes of medications (92%).

Data reduction and analytic strategy

Examining and Modeling the Trajectory of Cortisol Change Over Time—Before testing the mediating role of cortisol change over time in the relation between childhood maltreatment and pain and emotional symptoms, we first performed a visual examination of the trajectory of cortisol change over time. Generating empirical growth plots is a routine procedure in latent growth curve (LGC) modeling, allowing researchers to identify appropriate functional forms to model the trajectory of change over time (35). We then statistically modeled the nature of the trajectory (linear vs. quadratic) of the cortisol change over time by comparing the unconditional linear model with the unconditional quadratic LGC models. These unconditional models excluded the influences of the predictors.

Estimation of the Unconditional Linear LGC Model of Cortisol Change Over Time—The unconditional linear LGC model included two latent variables – a latent intercept and a latent linear slope – to characterize the intraindividual change in cortisol across individuals. (a) The latent intercept was regressed on the four manifested repeated measures of cortisol with factor loadings of one across all the measures. This parameter captured the constant level of cortisol over time across individuals. (b) The latent linear slope was also regressed on the same four manifested repeated measures of cortisol. It was centered at the first measure (T1) with a factor loading of zero. The rest of the loadings were specified to reflect the proportion of time elapsed of each of the given repeated measures relative to the T1. In the current study above, as noted, each measure of cortisol was separated by the same time interval (30 minutes), thus the loadings of the second (T2), third (T3), and fourth (T4) measures were 1, 2, and 3, respectively. This parameter captured the average linear change of cortisol level over time across individuals.

Estimation of the Unconditional Quadratic LGC Model of Cortisol Change Over Time—Compared to the linear model, the unconditional quadratic LGC model included one additional latent variable, the latent quadratic slope, allowing us to model the average curvilinear nature of the intraindividual change of cortisol over time across individuals. The latent quadratic slope was also regressed on the four manifested repeated measures of cortisol. The factor loadings were the square of the loadings specified in the latent linear slope. In other words, the loadings from the first to the fourth measures were 0, 1, 4, and 9, respectively. Finally, the likelihood ratio test for model selection was employed to compare the relative fit of the linear and quadratic models (36), and selected the best fitting model for subsequent analyses.

Modeling Cortisol Change Over Time as a Mediator of the Trauma – Symptom Relation—After determining the better-fitting model (i.e., linear vs quadratic) of cortisol change, the latent components of the better-fitting model served as the intervening variables (i.e., intercept, slope), mediating the relation between childhood maltreatment and pain and emotional symptoms. In our hypothesized mediation model, a latent variable, pain and emotional symptoms, defined by three measured indicators – pain, depression, and anxiety – was modeled as the outcome. Use of a latent factor representing emotional and physical symptoms as the outcome is based on evidence of their shared biological and psychological

underpinnings (24). Separate models were conducted with overall childhood maltreatment, childhood neglect, or childhood abuse serving as the predictor in three mediation models.

Specifications of Mediation Model—The hypothesized mediation model was estimated by *Mplus* 6 (37) using maximum likelihood estimation. This estimation routine was robust to missing data allowing us to retain all the cases even when they had missing values in the mediators and outcomes (37). Figure 1a shows one of the hypothesized mediation models in which childhood neglect is the predictor, as an example for illustration. In this model, the hypothesized paths are: (1) a_{ls} , FM patients who report higher levels of childhood neglect will show a smaller degree of decline of cortisol levels over time (latent linear slope); (2) b_{ls} , the flatter the cortisol linear slopes, the higher the levels of pain and emotional symptoms after controlling for the influence of childhood neglect; and (3) $a_{ls}b_{ls}$, the relation between childhood maltreatment and pain and emotional symptoms will be mediated by cortisol profile.

Estimation of Mediated Effect—The mediated effect, $a_{ls}b_{ls}$, is the product of a_{ls} and b_{ls} and is asymmetrically distributed. The skewness of the distribution of the mediated effect varies according to the correlation between the a_{ls} and b_{ls} paths. To obtain unbiased inferential statistics of the mediated path, *RMediation* was employed. *RMediation* takes the correlation between the a_{ls} and b_{ls} paths into consideration in producing the asymmetric confidence interval for the evaluation of the significance of the mediated effect (38, 39). In addition to the three hypothesized focal paths delineated above, the associations between experience of childhood neglect with the cortisol intercept (a_i) and quadratic slope (a_q), the associations between the cortisol intercept (b_i) and quadratic slope (b_q) and the pain and emotional symptoms, and the direct association between childhood neglect and pain and emotional symptoms were also estimated to obtain unbiased hypothesized a_{ls} and b_{ls} paths.

Results

Sample demographics

The 179 individuals included in the current study were on average 51.83 years of age ($SD = 10.33$; range 20–72). Most of the participants were female (89%), married or living with a romantic partner (56%), Caucasian (79%), attended at least 1–3 years of college (70%), and had an annual household income greater than \$30,000 (59%). Half of the sample was employed (50%).

Variable descriptives, intraclass correlations, and intercorrelations

Table 1 reports the means, standard deviations, skewness, kurtosis, and intercorrelations among the variables in our hypothesized model. The skewness and kurtosis of the raw cortisol variables were high; thus, the raw scores were subsequently log-transformed. For the log-transformed cortisol variables, skewness and kurtosis ranged from $-.22$ to $-.40$ and $.85$ to 2.18 , respectively, resulting in normal distributions for modeling LGC. The intraclass correlation ($ICC = .76$) was high, as expected among the cortisol repeated measures. The intercorrelation matrix highlights the significant positive relations between the different types of childhood maltreatment and the constructs of pain and emotional symptoms.

Visual examination of cortisol trajectory and model fitting of unconditional latent growth curve models

Visual inspection of the trajectory of log-transformed cortisol change over time for each participant showed (1) a gradual decline of cortisol over time, and (2) both linear and curvilinear patterns. The likelihood ratio test was employed to compare the relative fit of two nested models – unconditional *linear* and *quadratic* LGC models. The -2 log-likelihood (-2LL) of the linear model was 1106.382, whereas the -2LL of the quadratic model was 1079.334. Comparing the linear and the quadratic models, $\chi^2 = 27.048$ for $df = 4$, the fit of the quadratic model was significantly better than the linear model. Thus, the latent intercept, and linear and quadratic slopes were used in the subsequent mediation models.

Mediation models with three latent intervening variables – intercept, and linear and quadratic slopes

We estimated the mediation models in which pain and emotional symptoms were the outcome variable; the latent intercept, and linear and quadratic slopes of cortisol change were the mediators; and each of the different types of childhood maltreatment (separate models) was the predictor. The findings of these models showed that there was not enough variance to reach model convergence. Thus, in the next step, the quadratic slope, which was not hypothesized, was dropped as an intervening variable in the following mediation analyses.

Mediation models with two latent intervening variables – intercept and linear slope

This step tested our three hypothesized models by estimating the mediating effects of cortisol change (i.e., intercept, linear slope) in the relation between different types of childhood maltreatment and pain and emotional symptoms. Covariates that might relate to cortisol measures during the laboratory assessment were tested, but they were all nonsignificant. Thus, they were not included in the final model. Among all the remaining covariates that might affect the final mediation models, only age and smoking status were significant. Thus, all the estimates reported below have been adjusted by including these two covariates in the models.

Childhood neglect

The data showed a relatively good fit when childhood neglect was modeled as the predictor in the mediation model with root mean square error of approximation (RMSEA) = .058 and comparative fit index (CFI) = .978. The findings of the mediation analysis with childhood neglect as a predictor were consistent with our hypotheses (Figure 1b): (1) Self-report ratings of higher levels of childhood neglect were significantly associated with a smaller degree of decline in cortisol levels over time (flatter slopes) ($a_1 = .078$, $SE = .037$, $p < .05$). (2) The flatter slopes were significantly associated with higher levels of physical and emotional symptoms controlling for childhood neglect ($b_1 = .270$, $SE = .093$, $p < .005$). (3) The mediated effect of flatter slopes on the relation between childhood neglect and pain and emotional symptoms was significant, indicated by the asymmetric confidence interval [.001, .05] with $-.013$ as the correlation between a_1 and b_1 paths. Since the direct path (c' path) between childhood neglect and symptoms was still significant, the neglect-symptom

relation was partially mediated by cortisol change over time. Figure 2a shows the relation between childhood neglect and cortisol change over time. In the mediation model, childhood neglect was modeled as a continuous variable. In this figure, a median split of childhood neglect scores was used to create high and low neglect groups simply to illustrate the association between neglect and cortisol change over time. This figure shows that individuals who experienced higher versus lower levels of childhood neglect show a flatter slope of cortisol change over time. In Figure 2b, a median split of physical and emotional symptoms was used to create groups with high and low symptom levels, again, simply to illustrate the association between cortisol change over time and levels of physical and emotional symptoms.

Childhood abuse

The mediation analysis with childhood abuse as a predictor also showed a relatively good model fit with RMSEA = .064 and CFI = .974. However, it did not show a significant mediated effect: (1) Self-report ratings of childhood abuse had no association with linear rate of change of cortisol ($a_1 = .041$, $SE = .036$, $p > .05$). (2) The flatter cortisol slopes were significantly associated with higher levels of physical and emotional symptoms controlling for childhood abuse ($b_1 = .275$, $SE = .092$, $p < .005$). (3) However, the mediated effect of cortisol change over time on the relation between childhood abuse and pain and emotional symptoms was not significant. We also tested a mediation model in which childhood abuse consisted of physical, emotional, and sexual abuse subscales. The mediated effect of cortisol change over time in this model was also not significant.

Overall experience of childhood maltreatment

The mediation model with overall experience of childhood maltreatment as a predictor also showed a relatively good model fit, with RMSEA = .063 and comparative fit index (CFI) = .975. Similar to overall childhood abuse, it did not show any significant mediated effect: (1) Self-report ratings of overall childhood maltreatment had no association with linear rate of change of cortisol ($a_1 = .044$, $SE = .037$, $p > .05$). (2) Although the flatter cortisol slopes were significantly associated with higher levels of physical and emotional symptoms controlling for overall experience of childhood maltreatment ($b_1 = .284$, $SE = .091$, $p < .005$). (3) The mediated effect of cortisol change over time on the relation between overall experience of childhood maltreatment and pain and emotional symptoms was not significant.

In sum, these findings suggest that childhood neglect is related to cortisol change over time, which, in turn, predicts pain and emotional symptoms in FM. To verify that cortisol change rather than symptom reports functioned as the mediator (i.e., to test the directionality of this hypothesized mediation model), we also tested a model in which childhood neglect predicted physical and emotional symptoms, which, in turn, predicted cortisol change over time. The mediated effect in this model was not significant.

Discussion

Previous studies have documented a robust association between the experience of childhood adversity, and not only HPA dysregulation, but also chronic pain and symptoms of affective distress (1, 3). The current findings suggest that expression of the HPA axis, reflected in a flattened daytime cortisol profile, is a mediator of the relation between early maltreatment and clinical pain and distress in individuals with FM. In particular, the experience of childhood emotional and physical neglect, but not overall maltreatment or abuse, predicted a flattened cortisol profile across a 1.5 hour laboratory period, which, in turn, was associated with subsequent elevations in daily pain, depression, and anxiety symptoms. Cortisol rhythm only partially mediated the trauma-symptom relation, indicating that other mediators not identified here are relevant to this association. Nevertheless, the model held when statistically adjusting for age and smoking status. The association between maltreatment due to neglect and a flattened cortisol profile is consistent with experimental data derived from primate models of early adversity; infants deprived of versus exposed to maternal care and affection exhibit a blunted cortisol decline (40). To our knowledge, ours is the first study to test the mediational chain of experience of childhood maltreatment, cortisol profile, and pain and emotional symptoms in adults with FM.

Of note, although models that included either childhood abuse or overall childhood maltreatment as the predictor did not yield a significant mediated effect of cortisol change over time on symptom outcomes, the directions of the *a* and *b* paths in these models were consistent with those in the model that included childhood neglect. Because types of childhood maltreatment tend to co-occur, it can be difficult to determine which aspects are more toxic. In the current sample, neglect and abuse shared 64% of their variance, and including both factors in the mediated model rendered the maltreatment-cortisol association nonsignificant. Thus, it is possible that it is not neglect per se, but also some aspects of maltreatment shared between neglect and abuse that predicted a flattened cortisol profile.

Alternatively, it is plausible that neglect and abuse exert distinct effects on the HPA axis and physical and psychological health. In fact, the literature regarding the effects of social isolation suggests that social rejection, ostracism, and social neglect may have stronger associations with pain and mood symptoms than abuse (41, 42). One plausible explanation for the current findings is that the social disengagement that characterizes neglect provides limited opportunity for children to learn how to effectively process and cope with emotional information. In contrast, the social dynamic that characterizes abuse is one of dysfunctional engagement, a dynamic which may still allow children to learn strategies to manage their emotional experiences. Consistent with this possibility, neglect yields more severe effects than abuse on cognitive and social function among children (43). In a similar vein, a recent study of young to middle-aged adults reported that early life exposure to neglect showed a stronger association with emotional processing impairment than did early exposure to abuse (44). Another possible account for the distinct patterns evident for neglect and abuse focuses on the timing of maltreatment. The first two years of life are a critical developmental period, such that exposure to maltreatment during this period increases risk for developing long-term detrimental consequences that are resistant to the beneficial influence of interventions and/or exposure to positive experiences later in life (45). Thus, to the extent that exposure to

neglect occurs earlier in life than exposure to abuse, its more detrimental effects may be accounted for by the timing rather than the nature of the maltreatment. Only replication of the current pattern of findings in a study that incorporates detailed assessment of 1) the type and relative timing of early maltreatment, and 2) social and emotional processing capacities of pain patients can establish the unique contributions of neglect and abuse to HPA profile and symptoms, and plausible mechanisms by which those types of maltreatment exert their effects.

Not only did maltreatment predict cortisol declines, but also cortisol declines predicted clinical symptoms. The current findings documenting an association between cortisol profile and clinical symptoms build on earlier prospective work showing that cortisol rhythms predict clinical pain and affective disturbance (15, 20). Because the current data are correlational, however, alternative explanations of the findings are possible. A flattened daytime HPA profile may exacerbate symptoms, symptoms may provoke the HPA profile, and/or a third factor may drive both the HPA profile and clinical symptoms. We probed the possibility of an alternative model by examining a mediated model that specified symptoms as a mediator of the neglect-cortisol profile relation, and found that the mediated path was not significant. Thus, the current data are in line with a model suggesting that a flattened daytime cortisol profile serves as a mediator. Moreover, there are plausible mechanisms whereby disrupted cortisol regulation may impact pain and affective symptoms. For example, the HPA axis is integrated with serotonergic and noradrenergic neurotransmission (46, 47), both of which influence pain and affective symptoms (48), and are targets of pharmacologic interventions (49). At present, these mechanisms remain intriguing but speculative.

Although the current findings suggest that diminished cortisol decline mediates the relation between childhood trauma (particularly neglect) and clinical pain and emotional distress in adulthood, their interpretation is constrained by some important methodological limitations. First, childhood maltreatment was assessed via a retrospective self-report measure, which may introduce error due to biased recall of earlier experiences. Some previous work has observed a significant relation between childhood maltreatment and pain in retrospective self-report studies, but not in prospective studies that focused on cases of abuse that were documented through public records (50, 51). However, other prospective studies have found evidence to support the maltreatment-pain relation (52, 53). As Tietjen (2010) pointed out, both retrospective and prospective studies have their unique pitfalls (54). Retrospective reports are affected by the passage of time and suppression of traumatic experience, which may cause underreporting, whereas current emotional distress may cause over reporting of childhood maltreatment. Thus, the relation between childhood maltreatment and adult health is optimally assessed with a multi-method approach, such as use of self-reports, reports by family relatives, and public records.

A second issue is the limited nature of our cortisol assessment. The cortisol profile was assessed during a very abbreviated time frame, during a 1.5 hour period of a laboratory visit. Typically, links between early trauma and a maladaptive cortisol profile have been documented in studies where cortisol assessments occurred over a period that spanned the majority of waking hours (15, 16). Thus, our assessment of flattened cortisol profiles

represented a much more abbreviated slice of the participant's day and our findings, therefore, are not directly comparable to those of other studies.

On a related note, we cannot rule out the possibility that cortisol declines were affected by the startle probe, and particularly, the pain induction that occurred during the laboratory visit, and therefore represent "reactivity" to some extent. Although cortisol declined during the session, the final cortisol sample was collected only 10 minutes following the pain induction; thus, we may not have captured peak cortisol levels, which typically occur between 20 and 30 minutes after stressor onset (29). On the other hand, findings from laboratory studies that have assessed salivary cortisol over periods ranging from 20–60 minutes post-pain induction suggest that significant increases in cortisol are not elicited by heat pain (55, 56) or ischemic pain (55), but are elicited by cold pressor pain (55, 57; *cf.* 58). Thus, the lack of a cortisol stress response following thermal pain in the current study is not likely due to the timing of the assessments, but rather to the modality of the pain stimulus. Nevertheless, we cannot rule out the possibility that the magnitude of the decline across the 1.5 hours was influenced by exposure to the laboratory tasks, and reflects more than a diminished daytime cortisol decline.

Assessing participants more frequently and over a more extended period of time over the course of a day would permit a more rigorous evaluation of the relation between early maltreatment and cortisol trajectory. Nevertheless, the fact that the link between early maltreatment and a flattened cortisol profile emerged even under constrained conditions suggests that the abbreviated estimate of cortisol profiles captures a meaningful aspect of HPA function.

Third, the sample was comprised of individuals with FM, a pain condition associated with a high prevalence of childhood maltreatment and comorbid depression and anxiety (7, 27). Thus, the findings may not generalize to healthy individuals or to those with other chronic pain conditions. It is worth noting that depression and anxiety commonly co-occur not just with FM but also with other chronic pain conditions, pointing to the possibility that they are driven by overlapping genetic vulnerabilities and pathophysiological processes (24). Finally, the majority of our patients were taking medication to manage their symptoms. We excluded individuals who were on medications likely to influence the HPA axis, and statistically adjusted for use of other classes of medications likely to influence cortisol or symptom reports. An optimal test of the links between maltreatment, cortisol profile and symptoms would involve a sample of medication-free individuals. However, such a sample would not resemble the population of individuals with FM.

The current study also has several notable strengths. First, our analyses were based on a large sample of FM patients, including men, and it was similar to other samples of FM patients in terms of rates of childhood maltreatment, and depressive and anxiety symptoms (16). Thus, the findings are likely to generalize to the broader population of individuals with FM. Second, the predictor, mediator, and outcome were temporally ordered. Retrospective self-reports of childhood maltreatment were assessed weeks before cortisol was sampled, and pain, depression and anxiety were assessed weeks after the laboratory assessment. Nevertheless, additional work that includes several waves of assessment of cortisol profiles

and clinical symptoms over years rather than weeks or months would build on the current findings. Third, standardization of both the environment in which cortisol was assessed and the temporal spacing of cortisol assessments in the laboratory visit increase the internal validity of the findings. Finally, our mediation model included three common co-morbid symptoms of FM (24). Understanding their associations with childhood maltreatment and cortisol profile may inform current approaches to treatment of FM.

For many individuals with chronic pain, the detrimental effects of childhood maltreatment endure well into adulthood. Our investigation tested the role of disrupted cortisol regulation as a mediator of the relation between early maltreatment and clinical pain and distress. The findings underscore the potential importance of attending to specific characteristics of childhood maltreatment to clarify the clinical significance of HPA profile in FM. Additional research evaluating the impact not only of the type of maltreatment, but also its timing and duration, has the potential to improve interventions to limit the negative effects and improve functioning and quality of life among adults with FM pain and distress.

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Figure 1.

Figure 1a. The hypothesized mediation model of cortisol change over time on the relation between childhood trauma and pain and emotional symptoms. a_i is the estimate for the trauma-cortisol intercept relation. a_{ls} is the estimate for the trauma-cortisol linear slope relation. a_q is the estimate for the trauma-cortisol quadratic slope relation. b_i is the estimate for the cortisol intercept-symptom relation. b_{ls} is the estimate for cortisol linear slope-symptom relation. b_q is the estimate for cortisol quadratic slope-symptom relation. c' is the coefficient for the direct effect of trauma on symptoms.

Figure 1b. The mediating effect of cortisol change over time on the relation between childhood neglect and pain and emotional symptoms. Standardized parameter estimates and standard errors (in parentheses) are reported, with significant parameters bolded. a_i is the estimate for the neglect-cortisol intercept relation. a_{ls} is the estimate for the neglect-cortisol linear slope relation. b_i is the estimate for the cortisol intercept-symptom relation. b_{ls} is the estimate for cortisol linear slope-symptom relation. c' is the coefficient for the direct effect of neglect on symptoms. $*p < .05$, $**p < .01$, and $***p < .005$.

Figure 2.

Figure 2a. The relation between log-transformed cortisol level and time in the laboratory session by high and low neglect groups based on a median split of childhood neglect scores.

Figure 2b. The relation between log-transformed cortisol level and time in the laboratory session by high and low symptom levels based on a median split of physical and emotional symptoms.

Table 1
Means, Standard Deviations, and Correlations Among Variables in the Hypothesized Model

Variable	M	SD	Skewness	Kurtosis	1	2	3	4	5	6	7	8	9	10
1. CTQ - Total	47.61	19.33	0.76	-0.41	1									
2. CTQ - Neglect	19.15	8.19	0.67	-0.54	0.89	1								
3. CTQ - Abuse	19.75	9.49	1.00	0.08	0.94	0.80	1							
4. T1 Cortisol	2.91	3.04	4.36	24.95	0.01	-0.05	0.00	1						
5. T2 Cortisol	2.73	2.91	3.99	23.43	0.00	-0.01	-0.01	0.72	1					
6. T3 Cortisol	2.33	2.68	4.32	25.69	0.06	0.04	0.06	0.73	0.87	1				
7. T4 Cortisol	2.13	2.64	4.48	25.55	0.05	0.07	0.04	0.67	0.83	0.92	1			
8. Pain	49.84	17.44	-0.27	-0.51	0.19	0.10	0.21	-0.07	0.03	0.04	0.04	1		
9. Depression	11.75	5.88	0.44	-0.42	0.28	0.21	0.29	-0.15	0.03	-0.03	0.01	0.34	1	
10. Anxiety	3.25	1.10	0.16	-0.93	0.27	0.25	0.24	-0.13	0.04	-0.04	0.00	0.33	0.67	1

Note. The means, standard deviations, skewness, and kurtosis of cortisol were calculated based on the raw scores.

The intercorrelations of cortisol were calculated based on the log-transformed scores.