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FMR1 Premutation Carrier Mothers’ Daily Negative Affect and Cortisol: Probing the Impacts of Stress Exposure, Coping Style, and CGG Repeats

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Abstract:	Fragile X Syndrome (FXS) is the most prevalent inherited single gene cause of intellectual disability and autism. Many studies have provided evidence that children and adults with FXS display high rates of behavior problems, a significant source of stress for their mothers. Protective factors, such as coping, may reduce the effect of stress exposure. The present study utilized a daily diary methodology to investigate the effects of stress exposure, coping style, and CGG repeat length on premutation carrier mothers’ (n=104) negative affect and cortisol secretion. We also investigated whether coping style moderated the effects of daily behavior problems on daily stress responses for these mothers, and whether mothers with varying numbers of CGG repeats differed in the extent to which their coping style impacted daily outcomes. Results indicated that high levels of problem-focused coping buffered the effects of daily behavior problems on mothers’ negative affect and cortisol secretion. Additionally, there was a significant interaction between CGG repeat group and coping in predicting mothers’ negative affect, with mothers who had mid-range CGG repeats significantly less likely to benefit from coping than those who had fewer repeats.

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Key words: fragile X syndrome; premutation; behavior problems; coping; daily diary; negative affect; cortisol

Abstract

This study utilized a daily diary methodology to investigate negative affect and cortisol secretion of mothers of adolescents and adults with fragile X syndrome (n=104). We investigated whether coping style moderated the effects of child behavior problems on daily stress responses for these mothers, and whether mothers with varying numbers of CGG repeats differed in the extent to which their coping style impacted daily outcomes. Results indicated that high levels of problem-focused coping buffered the effects of behavior problems on mothers' negative affect and cortisol secretion. There was a significant interaction between CGG repeat group and coping in predicting negative affect; mothers with mid-range CGG repeats were less likely to benefit from coping than those who had fewer repeats.

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Introduction

Fragile X Syndrome (FXS) is the most prevalent inherited single gene cause of intellectual disability and autism, and is associated with a wide range of behavioral, neurological, psychiatric, and medical conditions (Hagerman et al., 2009). This neurodevelopmental disorder is caused by a large expansion of 200 or more repeats in the CGG sequence in the 5' untranslated region of the fragile X messenger ribonucleoprotein 1 (*FMR1*) gene located on the X chromosome (Garber et al., 2008). In contrast, 30 CGG repeats is the modal number in the larger population and is not associated with health conditions.

Current estimates indicate that approximately 1 in 150 to 1 in 209 women are carriers of the *FMR1* premutation, defined genetically as 55-200 CGG repeats (Seltzer et al., 2012; Tassone et al., 2012), and are at risk of giving birth to a child with FXS. The *FMR1* premutation itself may additionally lead to psychiatric, reproductive, motor, and other health conditions (Hagerman et al., 2018; Wheeler et al., 2017). Of particular relevance to the present study is the elevated risk of psychiatric conditions experienced by premutation carrier women, who have been found to have elevated symptoms of depression and anxiety (Gossett et al., 2016; Kenna et al., 2013). This psychiatric phenotype is increasingly referred to as FXAND (Fragile X-Associated Neuropsychiatric Disorder; Hagerman et al., 2018).

Heterogeneity within the *FMR1* Premutation Range

Not all women who are premutation carriers are at equal risk for health and mental health problems, and some of this heterogeneity has been shown to be associated with CGG repeat number. Many past studies have divided the CGG distribution within the premutation range into low, mid-range, and high levels although the boundaries of these categories have varied across studies. Notably, as Loesch et al. (2015, pp.176-177) pointed out, the "midsize range may vary according to the dependent variable being studied, the size and composition of the sample and the statistical model applied." For example, Klusek and colleagues (2018) defined the mid-range as 70-110 repeats and in a subsequent study (Klusek et al, 2020) the mid-range was defined as 80-100 repeats. Roberts et al. (2016) defined the mid-range as 75-95 repeats, and Allen et al. (2007) defined the mid-range as 80-96. Despite these differences in the quantitative definition of the mid-range of the CGG distribution, *FMR1* premutation carrier women with mid-range CGG repeats in these studies were found to have greater vulnerability even though the cut points varied from study to study. Specifically, women with mid-range repeats experienced an earlier age of menopause (Allen et al., 2007; Mailick et al., 2014; Spath et al., 2011), more symptoms of depression and anxiety (Loesch et al., 2015; Roberts et al., 2016), poorer sleep quality (Dembo et al., 2023), greater linguistic disfluency (Klusek et al., 2018), and greater executive functioning deficits (Klusek et al., 2020), than those with a smaller or larger number of CGG repeats within the premutation range.

In a prior study that partially overlapped with the current study's sample, mothers of children and adults with FXS who had mid-range CGG repeats were less likely to derive a health benefit from positive resources than those who have fewer or a greater number of repeats. Specifically, the health of premutation carrier mothers with mid-range CGG repeats benefited less from positive emotional support than those with lower or higher numbers of repeats within the premutation range (BLINDED). Examples of positive emotional support included someone listening to your problems, receiving advice, or receiving comfort. This finding in part motivated the current research, as little is known about how other protective factors, such as coping style, may have direct and/or buffering impacts on outcomes for these mothers, or if the impact of coping might differ based on CGG repeat number within the premutation range.

Impacts of Stress on Premutation Carrier Mothers

Many studies have provided evidence that children and adults with FXS display high rates of behavior problems and related symptoms, and that higher levels of behavior problems are associated with higher levels of stress for their premutation carrier mothers (Bailey et al., 2008; Kau et al., 2004; Usher et al., 2020). Research has shown that some premutation carriers, particularly those who have mid-range CGG repeats, have atypical patterns of stress reactivity. Such women have been shown to display both elevated psychological distress and low or flattened cortisol patterns in response to major adverse life events, such as death of friends and family, health problems in family members, and financial difficulties (Hong et al., 2021; Seltzer et al., 2012). Acutely stressful situations have been shown in past research to be associated with elevated cortisol (Miller et al., 2007). In contrast, flattened cortisol patterns have been observed in response to chronic stress, for example in individuals suffering from depression, fibromyalgia, and other chronic health conditions (Pruessner et al., 1999; Yehuda, 2000), individuals who experienced high levels of early life adversity (Schwartz et al., 2023), as well as in mothers of children diagnosed with autism (Seltzer et al., 2010) and serious mental illness (Barker et al., 2012). Low levels or blunted patterns of cortisol secretion have been interpreted in these studies to indicate poorer physiological functioning. Less well-understood, however, are whether protective strategies such as coping can reduce the negative effects of stress exposure on cortisol, and whether the impact of these strategies differs by *FMR1* CGG repeats.

Coping Style

Coping has long been studied in the general population as a way in which individuals regulate their emotional reactions to stressful situations (e.g., Folkman et al., 2004; Pearlin et al., 1990). One prominent conceptualization classifies coping strategies into the categories of *problem-focused* and *emotion-focused* coping (Folkman & Lazarus, 1980). Problem-focused coping involves cognitive strategies and solutions that target the problem or stressor. Examples include generating a list of solutions or deciding on a plan of action. Emotion-focused coping involves strategies aimed at reducing cognitive distress to allow the individual to disengage from or escape the stressor. Examples include avoidance, distraction, or wishful thinking (Connor-Smith & Flachsbart, 2007; Folkman & Lazarus, 1980).

Past research has found that parents of children with developmental disabilities have better psychological well-being when they utilize problem-focused coping strategies that aim to solve or directly address the stressor (Piazza et al., 2014; Smith et al., 2008; Woodman & Hauser-Cram, 2013). Problem-focused coping may have a protective (i.e., buffering) effect for these parents in the presence of stressors such as problematic child behavior. In one study of mothers of autistic individuals, Smith and colleagues (2008) not only found evidence of direct effects of problem-focused coping on maternal well-being (lower levels of depressive symptoms) but also evidence of buffering effects (lower levels of anger), particularly for mothers of adolescents. In contrast emotion-focused coping has been shown to have deleterious effects on mothers' well-being. In a study of mothers of individuals with intellectual disability (Kim et al., 2003), emotion-focused coping strategies were associated with an increase in depression over the three-year study period. A similar negative effect of emotion-focused coping was reported in the Smith et al. (2008) cited above, and in a population-based study of parents of adult children with developmental disabilities (Piazza et al., 2014).

However, very little is known about the coping style of mothers of children with FXS. In an early study, Abbeduto et al. (2004) compared mothers of children with FXS (n = 22) with mothers of children with other developmental disabilities along several dimensions including coping style. However, in that study, variation associated with the CGG repeat number of premutation carrier mothers was not examined. To the best of our knowledge, no subsequent study of coping by premutation carrier mothers has focused on the potential buffering effect of their coping style or whether the effects of coping varied across the premutation CGG repeat range.

The Present Study

Given the paucity of past research on coping in premutation carrier mothers of children with FXS, the present study investigated the effects of daily exposure to their child's behavior problems. [Note that in this study, the individuals with FXS ranged from 12 to 43 years of age and therefore we do not imply young age when we use the term "children".] We examined whether variation in coping style and in CGG repeat number within the premutation range was associated with the mother's daily stress response (as measured by daily negative affect and daily cortisol). A novel feature of the present research was that each day's behavior problems were evaluated relative to that child's average number of behavior problems over the daily diary period, yielding categorization of each day as a "worse" or "better" day with respect to daily behavior problems for that particular child.

The measurement of coping and the daily diary study were conducted at the first wave of data collection in this longitudinal study (2008-2009). Mothers' general coping style was measured first, and then two weeks later, mothers participated in an eight-day telephone diary study (Almeida et al., 2009). At the end of each day, the mother reported the daily behavior problems manifested by their child with FXS, and rated her own feelings of negative affect on that day. In addition, on days 2, 3, 4, and 5, saliva samples were collected from the mother and used to assay cortisol secretion.

The overall goal of present research was to understand the associations between the behavior problems of children with FXS, and their mothers' coping style, *FMR1* CGG repeat numbers within the premutation range, and stress responses. To do so, here we focused on daily behavior problems and investigated whether the daily behavior problems of the children with FXS and mothers' coping style had independent, direct effects on mothers' daily stress responses (negative affect and cortisol). We also investigated whether coping style buffered the effects of daily behavior problems on daily stress responses for these mothers, and whether mothers with varying numbers of CGG repeats differed in the extent to which their coping style predicted their daily negative affect and daily cortisol. We explored whether the buffering effects of coping on behavior problems would be different for mothers with varying numbers of CGG repeats. These research questions build on our prior findings on coping in a cohort of mothers of adolescents and adults with autism (BLINDED) and in the general population (BLINDED) as well as the prior literature on the effects of CGG repeat number on maternal mental health.

Materials and Methods

Participants and Procedures

Participants were drawn from an ongoing, longitudinal study of 147 mothers of adolescents and adults with the full mutation of FXS (BLINDED) from 35 U.S. states and one Canadian province, almost all of whom were premutation carriers. To qualify for the larger study, mothers had to be the biological parent of an adolescent or adult with FXS (12 years or older) and had to live with their son or daughter with FXS or have at least weekly contact with them. Documentation that the son or daughter had the full mutation of FXS (in genetic or medical records) was required for study participation. Within families of multiple children with FXS age 12 years or older, mothers were asked to report on the child with FXS who lived at home with the mother (if only one child with FXS lived at home) or identify the child most severely affected by FXS (if more than one child with FXS lived at home), who was designated as the target child.

The present study focused on 104 premutation carrier mothers whose son or daughter with FXS lived at home and who participated in the daily diary study. The requirement that the son or daughter co-resided with the mother during the daily diary period ensured that the mother was exposed on a daily basis to behavior problems that the child might exhibit. Premutation carrier status was based on mothers' CGG repeat length as quantified by medical records and/or molecular assays conducted by the Rush University Medical Center Molecular Diagnostics Laboratory under the direction of Elizabeth Berry-Kravis, MD, PhD. DNA was isolated from buccal samples using standard methods. *FMR1* genotyping to determine CGG repeat length was conducted with the Asuragen AmplideX® Kit (Chen et al., 2010; Grasso et al., 2014). For the present sample, CGG repeat length ranged from 67 to 138 repeats (mean = 94.7).

Demographic characteristics are presented in Table 1. Age of these mothers at enrollment into the study ranged from 36 to 70 years and was significantly correlated with their son's or daughter's age ($r=.78$, $p <.001$). Approximately three-quarters were employed at least part-time, the majority were married, over half had completed a bachelor's degree or higher and the median household income was $80,000-89,999 with a range from $10,000-$19,999 to $160,000 or higher. Over 94% were non-Hispanic White. Over 80% of the adolescents and adults with FXS were male and met criteria for an intellectual disability. Individuals with FXS ranged from 12 to 43 years of age at the start of the study. Over two-thirds were enrolled in school (67.3%) and almost all of the remainder were engaged in various settings (e.g., vocational training, working in the community, volunteering).

Measures

Categorization of Mid-Range CGG Repeat Length

For this analysis, mothers were divided into three CGG repeat groups – low, mid-range, and high. The low group (67-90 CGGs) included 49% of the present sample. The mid-range group (91-105 CGGs) included 31.7% of the sample. The high group (106-138 CGGs) included 19.2% of the sample. As noted earlier, the boundaries of low, mid-range, and high CGG repeats within the premutation range have varied across past studies based on the dependent variable being studied, the size and composition of the sample, and the statistical model being applied. For the present study, in preliminary analyses we probed four definitions of the mid-range (three categorical definitions (86-105 CGGs, 91-110 CGGs, and 91-105 CGGs) and one based on a continuous analysis of CGG repeat numbers), to investigate the interaction of coping and CGG repeats in the prediction of negative affect and cortisol. Notably, all four approaches yielded similar patterns, and we selected the best definition overall. For example, when mid-range repeats of 86-105 were used to estimate the interaction effect of problem-focused coping (PFC) and CGG repeat in predicting negative affect, this categorical definition yielded a *p* value of 0.069. When mid-range repeats of 91-105 were used, the *p* value was 0.011. When 91-110 repeats were used, the *p* value was 0.018. When CGGs were modeled continuously, interaction of PFC and CGG repeat yielded a *p* value of 0.067. We selected the mid-range definition of 91-105 repeats for the present study not only because of the slightly higher *p* value but also because it increased the sample size in the high CGG group.

Coping Style

After enrollment in the study, and prior to participating in the daily diary portion of the study, mothers participated in an interview and completed a self-administered questionnaire. As part of the questionnaire, mothers rated their coping style using the Coping Orientations to Problems Experienced (COPE) scale (Carver et al., 1989). Notably, the COPE reflected a mother's general approach to coping (here referred to as *coping style*), not how she coped with a specific situation or at a specific time. The present study analyzed both problem-focused and emotion-focused coping styles. PFC included four subscales (4 items in each of the subscales), with each item rated on a 4-point scale, from 0 = *I usually do not do this at all* to 3 = *I usually do this a lot*. Ratings were summed (possible range = 3 to 48). The subscales were positive reinterpretation and growth, active coping, planning, and suppression of competing activities. Examples of items were "I try to come up with a strategy about what to do" (planning); "I take additional action to try to get rid of the problem" (active coping). Cronbach's alpha for PFC in the present sample was 0.92. Emotion-focused coping (EFC) also included four sub-scales (mental disengagement, behavioral disengagement, focus on and venting emotion, and denial), with items measured on the same 4-point scale and summed (possible range = 3 to 48). Examples of EFC items included "I get upset and let my emotions out" (focus on venting and emotions); "I give up the attempt to get what I want" (behavioral disengagement). Cronbach's alpha for EFC in the present sample was 0.76.

Levels of coping. In the statistical analyses presented below, the effects of coping style are analyzed continuously. However, to illustrate interaction effects in the figures, these effects are shown at three estimated points – at the mean of the coping distribution (for PFC, a score of 30; for EFC, a score of 13), at one standard deviation above the mean (scores of 39 and 18, respectively), and at one standard deviation below the mean (scores of 21 and 7, respectively).

We also note that the mean and median for PFC and EFC are equal, with plus or minus one standard deviation covering about 60% for PFC and 75% of EFC.

Measures Collected During the Daily Diary Study

The daily diary study included two components. One included reports of mother's daily negative affect and child behavior problems on eight consecutive days. The other component was a collection of saliva samples to measure cortisol four times a day on Days 2-5. This paradigm was adapted from the widely-used MIDUS methodology (Almeida, 2009).

Daily Behavior Problems

Two weeks after completing the questionnaire, mothers participated in the eight-day diary study described above, in which they reported "yes" or "no" to whether their child with FXS manifested each of the following behavior problems that day: unusual or repetitive behaviors, uncooperative behavior, withdrawn or inattentive behavior, socially offensive behavior, disruptive behavior, hurtful to self, hurtful to others, and destructive to property. A count of these behavior problems for each day provided the daily total score of behavior problems. Although the focus of the present paper was on behavior problems measured over the course of eight days, we note that the association of daily behavior problems and the level of chronic behavior problems manifested during the previous six months was significant ($p < .001$), reflecting the chronic nature of behavior problems in the FXS population.

Calculating Daily Deviation Scores of Behavior Problems. The *daily deviation score* of behavior problems was calculated for each child. As noted above, the deviation score reflected the difference between the number of behavior problems on a given day and the eight-day average number of behavior problems of that child during the diary study (i.e., day minus average). A "better" day was defined as one with fewer than average numbers of behavior problems for that child, while a “worse” day was defined as one with a greater than average numbers of behavior problems for that child. In the present study, the key analytic measure of behavior problems was the daily deviation score, with the average number of behavior problems across the diary study included as a covariate in the multilevel models.

Outcome Variables: Daily Negative Affect and Daily Cortisol

In the present study, we investigate two indicators of stress responses, namely daily negative affect and daily cortisol patterns. Both are conceptually and empirically distinct from global mental health measures, such as depression and anxiety.

Daily Negative Affect. Daily negative affect was measured across eight days, resulting 796 daily observations. Mothers’ daily negative affect was measured using the negative affect items included in the Positive and Negative Affect Schedule (PANAS; Watson et al., 1988). At the end of each of the eight days in the diary study, mothers indicated how frequently they felt five emotional mood states (“afraid”, “jittery”, “irritable”, “ashamed”, and “upset”) over the past 24 hours, each measured on a 5-point scale from 1 = *none of the time* to 5 = *all of the time.* The measure of *negative affect* used in the present study reflects the sum of the 5 items. Across the days of the diary study, Cronbach’s alpha averaged .76.

Daily Cortisol. On Days 2 through 5 of the diary study, mothers collected saliva samples four times throughout the day (morning awakening, 30 minutes after awakening, at midday, and at bedtime) for a total of 373 observations. Saliva was collected using Sarstedt salivette collection devices. Numbered and color-coded salivettes, a detailed instruction sheet, and a prepaid courier envelope were included in a collection kit that was mailed to the participant. Collection procedures were also reviewed over the telephone. Mothers were instructed to record the time they provided each sample; to collect their first sample before eating, drinking, or brushing their teeth; not to consume any caffeinated products before taking their subsequent samples; and to store all samples in the refrigerator. Those who had a temperature of >102 °F were instructed to forgo collecting a sample. The exact time participants collected each saliva sample was obtained from telephone interviews on collection days and on a paper-and-pencil log. Saliva samples were sent in courier packages to our research office and stored in an ultracold freezer at −60 °C. For analysis, the salivettes were thawed and centrifuged at 3000 rpm for 5 min. Cortisol concentrations were quantified with chemiluminescence immunoassay (IBL; Hamburg, Germany), with intra-assay coefficient variations below 5% (Polk et al., 2005).

The measure of cortisol used in this study was *total AUC* (Area Under the Curve) reflecting total cortisol output over the course of the day. Figure 1 illustrates the average daily cortisol levels by collection times. Using the log-transformed values of cortisol levels at each of the four times of cortisol measurement, AUC was calculated with respect to ground, or AUC_g, by employing the trapezodal formula (Pruessner et al., 2003). This measure captures the within-person mean level of cortisol activity across the day averaged across the four days. This approach has been employed to measure total day cortisol in prior research using the MIDUS daily diary data (Karlamangla et al., 2019). Cortisol AUC_g differs from other cortisol parameters such as the cortisol awakening response or its daily decline. We focus on total cortisol across the day for the present study because a mother's exposure to her son or daughter's behavior problems could occur at any point throughout the day, from awakening until the time she goes to bed, and the mother's negative affect was assessed at the end of the day.

Definition of a Buffering Effect. For this research, buffering was conceptualized as stable levels of the maternal outcome variables on a "worse" day as compared with a "better" day with respect to their son or daughter's behavior problems. That is, coping style was considered a buffer when, on a day with a higher number of behavior problems relative to the child's own average (a worse day), maternal negative affect or cortisol remained at the same level as when behavior problems were low relative to the child's average (a better day). See Cohen and Wills (1985) for comprehensive research review of the multiple forms a buffering effect can take, including stability across high and low stress exposure.

Covariates

Four covariates were included in the multilevel models: mothers' age (in years), mothers' marital status (1 = *married* or 0 = *not married*), mothers' educational attainment (1 = bachelor's degree or more or 0 = less than bachelor's degree), and the average number of daily behavior problems exhibited by the child with FXS across the 8 days of the diary period.

Results

Analytic Plan

The present research utilized two-level hierarchical linear modeling to account for the nested data structure, with days (level 1) nested within an individual (level 2). Parallel multilevel models were conducted to estimate the effects of coping and daily deviation behavior problems score on the outcome variables (daily negative affect and daily cortisol AUC_g). For each, we examined the cross-level interactions between maternal CGG and coping style (level 2) and her child's deviation behavior problem score (level 1) on the two outcomes. Significant interaction effects were graphed and simple slopes were tested. In the interactions involving CGG repeats, the sample was divided into three CGG groups as described above (low, mid-range, and high), with the omitted category being the mid-range CGG group (91-105 repeats). This group was selected to be the omitted category because past research (reviewed above) has shown women with repeats in this range to be the most vulnerable to poor health and mental health and to the negative effects of stress.

Preliminary ANOVA analyses indicated that there were no differences in PFC or EFC by CGG group. In further preliminary analyses, we tested the effects of the three-way interaction between behavior problems, CGG repeat group, and coping in predicting the outcome variables to determine whether the moderating effects of coping on behavior problems would be different for mothers with varying numbers of CGG repeats. This interaction effect was not significant in any of the models, and for this reason we do not include the results of the three-way interaction in Tables 3-6 below. Therefore, in each table, we present two models: Model 1 tests the main effects of deviation behavior problems, coping style, and CGG repeat group on maternal daily negative affect and daily cortisol AUC_g, in addition to the covariates. Model 2 additionally tests the interactions between deviation behavior problems and coping style and the interaction between CGG repeat group and coping style.

All analyses were conducted using Stata version 18.0. Throughout the analyses, the level of statistical significance was set at less than 0.05.

Descriptive Findings

Table 2 presents the frequencies of daily behavior problems during the diary period. As shown in Table 2, nearly all mothers (90.4%) experienced at least one day during the diary study when their child manifested at least one behavior problem, and behavior problems were experienced on half of the days (4.4 days on average). The most frequently experienced behavior problems were unusual or repetitive behaviors and uncooperative behaviors (69.2% and 65.4% of mothers experienced at least one day with these behavior problems, respectively). Notably, even more disturbing behavior problems, such as disruptive behavior and behavior that is hurtful to others, property, or self, were experienced by between 15% and nearly 40% by mothers during the diary period. The data presented in Table 2 confirms the high prevalence and heterogeneity of child behavior problems experienced by mothers in the present study.

Figure 2 present a histogram of the difference between daily behavior problems and the 8-day average of behavior problems for the sample. As shown in Figure 2, on most days, there was no difference between the number of behavior problems to which a mother was exposed on any single day and the average number of behavior problems across the daily study days (i.e., most days were typical days), although there was a wide range as indicated by deviation scores: -4.3 (a "better" day than average) to +4.1 (a "worse" day). The correlation between the average number of behavior problems during the eight days and the deviation behavior problem score was 0.58 ($p < .001$).

Multilevel Models: Problem-Focused Coping Style and Daily Negative Affect

Table 3 presents the results of multilevel models examining the effects of daily deviation score of behavior problems on the mother's daily negative affect, as moderated PFC style and CGG repeat category. As shown in Model 1, the deviation score of behavior problems significantly predicted maternal daily negative affect ($p<.01$), such that the greater the deviation above the average, the higher the negative affect, net of the average number of behavior problems manifested by the child. However, neither problem-focused coping style nor CGG repeat group were associated as main effects with daily negative affect.

In Model 2, the interaction effects were brought into the analysis. The interaction between PFC style and the deviation score of behavior problems was significant ($p = 0.036$) and is illustrated in Figure 3, which contrasted a "better" versus a "worse" day of behavior problems with respect to mothers' daily negative affect. The non-significant simple slope for mothers who endorsed a high level of PFC style indicated that these mothers were able to maintain stable levels of daily negative affect on a worse day as on a better day with respect to her child's behavior problems. Thus, high levels of PFC buffered the effects of a worse than average day with respect to mothers' negative affect. However, there was no evidence of buffering for mothers who endorsed a low or medium level of PFC.

Model 2 also reports the interaction between CGG repeat group and PFC style. The CGG x PFC interactions show that the effect of PFC on negative affect varied by the CGG groups. Specifically, mothers who were in the mid-range CGG repeat group (91-105 CGGs, which was the omitted category in the statistical analysis) differed significantly in the association between PFC and negative affect from those in the low repeat group (67-90 CGGs; $p < 0.05$), but there was no significant difference between those in the mid-range and those with higher numbers of CGGs within the premutation range. Figure 4 illustrates the significant contrast from this interaction, comparing the mid-range and the low CGG groups. The simple slopes indicate that for mothers in the low CGG group (who were genetically closer to the normal end of the premutation range), higher levels of PFC style were significantly associated with lower daily negative affect ($p < 0.05$). In contrast, for mothers in the mid-range CGG group, there was no association between level of PFC style and daily negative affect. These results suggest that for mothers with lower numbers of CGG repeats, there was a protective effect of PFC but for mothers with mid-range CGGs, there was no protective effect.

Multilevel Models: Emotion-Focused Coping Style and Daily Negative Affect

Table 4 presents the results of multilevel models focused on the effects of EFC style on mothers' daily negative affect. The models were structured in the same way as the PFC analysis reported above. As shown in Model 1 of Table 4, similar to the PFC analysis, the deviation behavior problem score was directly associated with daily negative affect ($p < 0.01$). However, whereas in the PFC analysis, there was no main effect of coping on daily negative affect, here the main effect of EFC style was a significant predictor of daily negative affect (higher levels of EFC predicted greater daily negative affect; $p < 0.001$). Finally, CGG repeat group was not significantly associated with daily negative affect in Model 1.

As shown in Model 2, the interaction effect of EFC and behavior problems was not significant, indicating that EFC did not buffer the effects of a worse versus a better day with respect to mothers' daily negative affect, nor was there a differential effect of EFC style across the CGG repeat groups.

Multilevel Models: Problem-Focused Coping Style and Daily Cortisol AUC_g

Table 5 focuses on the outcome of daily cortisol AUC_g. Note that this analysis was based on one fewer participant ($n = 103$), as this participant did not provide saliva samples. This analysis was also based on fewer days than in the negative affect analyses (359 vs 787 days), as saliva samples were collected only on days 2, 3, 4, and 5 of the 8-day diary study. However, the multilevel models are structured similarly to the analyses presented above.

As shown in Model 1 of Table 5, there were no significant main effects of the deviation behavior problems score, PFC style, or CGG repeat group on cortisol AUC_g. However, as shown in Model 2, there was a significant interaction between PFC style and the deviation behavior problems score in predicting daily cortisol AUC_g ($p < 0.001$). This interaction effect is illustrated in Figure 5. The non-significant simple slopes for mothers who endorsed high or medium levels of PFC style suggested that they were able to maintain stable levels of daily cortisol secretion, regardless of whether a given day was worse or better than their child's average level of behavior problems, suggesting a buffering effect of PFC on cortisol. However, mothers with low levels of

PFC had significantly lower levels of total cortisol secretion on worse days than on better days ($p < 0.001$). Finally, there was no interaction between CGG repeat group and PFC in predicting cortisol AUC_g.

Multilevel Models: Emotion-Focused Coping Style and Daily Cortisol AUC_g

The multilevel models shown in Table 6 are distinct from the previous analyses in that none of the effects reached statistical significance.

Covariates

Among the covariates, maternal marital status was significantly associated with negative affect in all models, with married mothers having lower levels of negative affect than those not currently married (all p's < 0.01). Mothers' age was a significant covariate in the emotion-focused coping model, with younger mothers having higher levels of negative affect ($p < .05$). The eight-day average number of behavior problems exhibited by the child with FXS was a significant predictor of negative affect (p's < 0.01), with a greater average number of behavior problems predicting higher negative affect in the mother. However, none of the covariates predicted cortisol AUC_g. Finally, college degree attainment was not a significant predictor in any of the models.

Discussion

The present study analyzed daily diary data from a sample of 104 premutation carrier mothers of adolescents and adults with FXS to examine the effects of exposure to child behavior problems, coping style, and CGG repeat length on maternal stress responses. Prior research has documented the significant impact of child behavior problems on the global well-being of parents of children with disabilities, generally measured over periods of months or longer (e.g., Miodrag, & Hodapp, 2010). In contrast, the present study used daily data to reveal day-to-day associations between the daily behavior problems of adolescents and adults with FXS and the daily psychological and physiological distress of their mothers (measured respectively by variations in daily affect and cortisol). On days marked by above average behavior problems, mothers reported higher levels of negative affect. Importantly, the present study also found interaction effects of coping style by behavior problems in the prediction of both psychological and physiological outcomes. High levels of PFC buffered the effects of a "worse" than average day of child behavior problems, such that mothers nevertheless maintained stable levels of negative affect and cortisol even on these stressful days. These findings align with prior research on parental coping styles which has found that PFC serves as a buffer for global parent well-being and caregiver burden (Piazza et al., 2014; Smith et al., 2008; Woodman & Hauser-Cram, 2013); indeed, in the current research, the effectiveness of coping extended to daily physiological regulation as well as psychological well-being. Thus, the current research built on prior studies showing how positive resources (e.g., emotional support and PFC) can serve as protective factors for mothers exposed to high levels of daily stress.

Findings from the present study also offer insights into how specific forms of coping have differential effects on daily stress responses. Although higher levels of PFC were associated with *lower* levels of daily negative affect, EFC style directly predicted *higher* negative affect. These findings align with a prior study by Kim and colleagues (2003) that found that mothers of adults with disabilities who increased their PFC reported lower feelings of burden and better relationships with their children three years later, while those who increased their use of EFC over the same period had increased burden and worse relationships with their children. Although more research is needed on long-term coping effects within families affected by FXS, our findings suggest that EFC style, in contrast with a PFC style, may have detrimental effects for emotional health for *FMR1* premutation carrier mothers. Further, future research will need to examine potential bidirectional effects of affect and coping.

We also observed a significant interaction between CGG repeat length and coping style in predicting mothers' daily negative affect. PFC was associated with lower levels of negative affect only for mothers in the low CGG repeat category, suggesting a protective effect of coping in that genetic subgroup. In contrast, for mothers in the mid-range CGG group, there was no association between the level of PFC style and daily negative affect, suggesting that for these mothers, coping did not facilitate emotional regulation. This finding builds upon the results of multiple other studies that revealed the vulnerability of mothers with mid-range CGG repeats (e.g., Dembo et al., 2018; Klusek et al., 2018; Klusek et al., 2020; Loesch et al., 2015; Roberts et al., 2016; Seltzer et al., 2012).

Prior research points to potential molecular mechanisms for this curvilinear association. Compared to the normal population, premutation carriers are known to have elevated levels of mRNA, which may be toxic (Berry-Kravis & Hall, 2011; Hoem et al., 2011). Additionally, they make longer polyglutamine and other RAN translation products based on the impact of the long CGG repeat in the RNA at the ribosome, which are also potentially toxic (Zhang et al., 2022). Based on these explanations, premutation carriers with lower numbers of CGG repeats within the premutation range have lower levels of toxic mRNA and less and shorter polyglutamine peptides, and thus may have phenotypic patterns more similar to women with normal numbers of CGG repeats. As the CGG repeat expands into the mid-range, toxic mRNA and polyglutamine may increase and result in greater phenotypic vulnerability with respect to a range of health and mental health outcomes, as has been reported in many prior studies. However, as the number of CGG repeats increases further and approaches 200 repeats, the *FMR1* gene becomes fully methylated and begins to shut down, resulting in less toxic mRNA and thus loss of RAN translation. Hence, the toxic mRNA and/or RAN translation hypotheses may be possible explanations for the elevated vulnerability in premutation carriers with mid-range CGG repeats. Although not measured in the current study, elevated mRNA containing CGG repeat expansions and/or RAN translation might be an underlying mechanism for the curvilinear effects that we observed.

Patterns of association with covariates also offer insights into coping with daily behavior problems for premutation carrier mothers. Particularly important was our finding regarding marital status, which was associated with daily negative affect. This is consistent with prior research showing that being married is related to better psychological well-being in the general population (Hsu & Barrett, 2020; Lansford et al., 2024). In addition to the effect of marital status, the covariates of age and behavior problems were significant predictors of negative affect, with younger mothers and mothers of children with a higher average number of behavior problems having greater levels of daily negative affect. None of the covariates were associated with cortisol, similar to prior studies of premutation carriers (Seltzer et al., 2012; Hartley et al., 2012). This may be due to the fact that there were half the number of days models for cortisol than for daily negative affect. Future research is needed to understand potential demographic and contextual factors effecting cortisol expression in this population.

Several important clinical implications emerge from the present study. Taken together, the findings underscore the need for interventions and treatments to reduce the behavior problems of individuals with FXS across the life course, which will benefit both generations within the family. Although the level of daily behavior problems displayed by the adolescents and adults with FXS was concerningly high, with significant consequences for mothers, our prior research has shown that behavior problems decrease as individuals with FXS move through adulthood (BLINDED). Probing specific types of behavior problems and their association with age will be an important direction for future research and clinical interventions. Further, as coping style did not serve as a buffer for some premutation carrier mothers (i.e., those with mid-range repeats), interventions to directly address child behavior problems are critical (e.g., functional communication training; Hall et al., 2022). Findings also point to the importance of interventions to support mothers in using problem-focused and avoiding emotion-focused coping (see Ho & Liang, 2021 for a coping intervention that has been found to reduce emotion-focused coping among parents of children with a range of disabilities). In addition to supporting *FMR1* premutation carrier mothers in utilizing problem-focused versus emotion-focused coping, future interventions could provide training in how to increase awareness of stress such as mindfulness (e.g., Neece, 2014).

Findings from the present study must be considered in context of various limitations. The sample was relatively homogenous with respect to demographic characteristics, reducing the generalizability of the findings. Future research on more representative samples is needed to examine child behavior, stress responses, and coping in other contexts. These mothers experienced a high degree of child-related stressors and subsequent psychological and physiological responses; these relationships might be even more pronounced in groups with additional life stressors. Future research should probe for potential confounders and moderators of these associations (e.g., stressful life events, neighborhood factors, other child characteristics such as intelligence quotient). Also, in the present study, coping styles reflected mothers' general coping strategies, not the specific coping cognitions or behaviors they used on a given day. It will be valuable for future research to examine mothers' coping on a daily basis to understand potential variation in coping across days and differences in impacts on emotion regulation. Additional limitations were the relatively small number of mothers who had CGG repeats at the upper end of the premutation range (i.e., between 105 and 200), and the absence of more in-depth measures of child behavior problems (e.g., intensity or duration of episodes). Furthermore, the count measure of behavior problems did not differentially weigh behaviors that were more disturbing (e.g., self-injurious behaviors) versus less disturbing (e.g., unusual or repetitive behaviors). Juxtaposed against these limitations are a number of strengths of the present research, including the utilization of both self-report and biomarker data for understanding the daily well-being of mothers, inclusion of CGG repeats to probe for potential genetic subgroups of mothers at risk, wide range of ages of mothers and their children, and determination that PFC has protective effects for sustaining the well-being of these premutation carrier mothers.

In conclusion, behavior problems are a frequent source of stress exposure for mothers of adolescents and adults with FXS. In this research, mothers' coping style was shown to buffer the negative effects of behavior problems with respect to negative affect and cortisol secretion across the day. In addition, the impact of behavior problems on mothers' well-being was found to be in part a function of genetic variation in *FMR1*, with mothers who had mid-range CGG repeats significantly more likely to experience negative affect than those who had fewer repeats. The results of this study also revealed the importance of a person- and family-centered understanding of the impact of daily behavior problems, with different effects of a "worse" than a "better" day and rippling effects on their premutation carrier mothers.

Table 1. Descriptive Statistics of Study Variables (N = 104).

Variables	% or mean (s.d.) [min, max]
Maternal age	49.7 (7.1) [36, 70]
Maternal employment status (working = 1)	76.9%
Maternal marital status (married = 1)	88 (84.6%)
Maternal educational attainment (college degree = 1)	61 (58.7%)
Household income[b]	9.0 (3.3) [2, 14]
Maternal race (non-Hispanic White = 1)	94.2%
CGG repeat length	94.7 (16.0) [67, 138]
	CGG 67 - 90: 51 (49.0%)
	CGG 91 - 105: 33 (31.7%)
	CGG 106 - 138: 20 (19.2%)
Target child age	19.8 (6.6) [12, 43]
Target child sex (male = 1)	85.6%
Target child with intellectual disability (yes = 1)	83.7%
Target child enrolled in school	67.3%
8-day average number of daily behavior problems:	1.3 (1.3) [0.0, 7.3]
Problem Focused Coping	30.1 (9.0) [13, 47]
Emotion Focused Coping	12.8 (5.7) [3, 27]
Deviation from the 8-day average number of behavior problems (787 days)	0.0 (0.9) [-4.3, 4.1]
Daily negative affect (796 days)	6.4 (2.0) [5, 20]
Daily cortisol: AUCg (373 days)	28.1 (7.4) [4.2, 67.1]

Note: AUCg: Area Under the Curve. a. Means, standard deviations (in parentheses), and ranges (in brackets) are reported unless the variable is marked with (%). b. Household income was measured on an ordinal scale: (1) $1 - $9999, (2) $10,000 - $19,999, (3) $20,000 - $29,999, (4) $30,000 - $39,999, (5) $40,000 - $49,999, (6) $50,000 - $59,999, (7) $60,000 - $69,999, (8) $70,000 - $79,999, (9) $80,000 - $89,999, (10) $90,000 - $99,999, (11) $100,000 - $119,999, (12) $120,000 - $139,999, (13) $140,000 - $159,999, (14) $160,000 + .

Table 2. Prevalence of Behavior Problems During the 8-Day Diary Study.

	Percent of mothers with at least one day with at least one behavior problem	Average number of days with at least 1 behavior problem out of 8 days (SD) [min, max]
Behavior problems		
Any behavior problem	*90.4%*	*4.4 (2.7) [0, 8]*
Unusual or repetitive behavior	69.2%	2.9 (2.9) [0, 8]
Uncooperative behavior	65.4%	2.0 (2.2) [0, 8]
Withdrawn or inattentive behavior	49.0%	1.4 (2.1) [0, 8]
Socially offensive behavior	40.4%	1.1 (1.8) [0, 8]
Disruptive behavior	39.4%	1.0 (1.8) [0, 8]
Hurtful to others	18.3%	0.4 (1.1) [0, 8]
Destructive to property	17.3%	0.4 (1.1) [0, 8]
Hurtful to self	15.4%	0.5 (1.5) [0, 8]

Table 3. Multilevel Models: Predicting **Daily Negative Affect** by Daily Behavior Problems, **Problem-Focused Coping** and CGG Repeat Length Category (n = 104, with 787 days).

	Model 1	Model 2
Fixed Effect		
Maternal age	-0.03 (0.02)	-0.03 (0.02)
Maternal marital status (married=1)	-1.41 (0.35)***	-1.43 (0.35)***
Maternal education (college degree or more = 1)	-0.15 (0.26)	-0.06 (0.26)
8-day average number of daily behavior problems:	0.32 (0.10)**	0.30 (0.10)**
Deviation from the 8-day average number of behavior problems (Deviation BP)	0.20 (0.06)**	0.21 (0.06)***
Problem Focused Coping (PFC)	-0.02 (0.01)	0.01 (0.02)
CGG Repeat Group		
(middle PM (91- 105) as reference group)		
low PM (< 91)	0.00 (0.29)	-0.03 (0.28)
high PM (> 105)	-0.11 (0.36)	-0.15 (0.35)
Deviation BP x PFC	--	-0.013 (0.006)*
CGG Repeat Group x PFC	--	
low PM (< 91) x PFC		-0.06 (0.03)*
high PM (> 105) x PFC		-0.02 (0.04)
Constant	7.30 (0.41)***	7.31 (0.40)***
Random Effects[a]		
Var. (Intercept)	1.24 [0.88, 1.74]	1.18 [0.84, 1.67]
Var. (Level-1 residual)	2.35 [2.11, 2.61]	2.33 [2.10, 2.59]

Notes.
Regression coefficients are presented with standard errors in parenthesis.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$
Deviation BP: Deviation score of Behavior Problems from the 8-day average.
PFC: Problem Focused Coping.
a. Estimated variances (Var.) of random parts of the mixed models are reported with 95% confidence intervals in brackets.

Table 4. Multilevel Models: Predicting **Daily Negative Affect** by Daily Behavior Problems, **Emotion-Focused Coping** and CGG Repeat Length Category (n = 104, with 787 days).

	Model 1	Model 2
Fixed Effect		
Maternal age	-0.03 (0.02)*	-0.03 (0.02)*
Maternal marital status (married=1)	-0.98 (0.32)**	-0.98 (0.32)**
Maternal education (college degree or more = 1)	-0.14 (0.23)	-0.06 (0.26)
8-day average number of daily behavior problems:	0.26 (0.09)**	0.24 (0.09)**
Deviation from the 8-day average number of behavior problems (Deviation BP)	0.20 (0.06)**	0.19 (0.06)**
Emotion Focused Coping (EFC)	0.10 (0.02)***	0.09 (0.04)**
CGG Repeat Group		
(middle PM (91- 105) as reference group)		
low PM (< 91)	-0.00 (0.26)	-0.02 (0.26)
high PM (> 105)	-0.13 (0.33)	-0.15 (0.31)
EFC x Deviation BP	--	0.01 (0.01)
CGG Repeat Group x EFC	--	
low PM (< 91) x EFC		0.01 (0.05)
high PM (> 105) x EFC		0.00 (0.06)
Constant	7.02 (0.38)***	6.98 (0.37)***
Random Effects[a]		
Var. (Intercept)	0.97 [0.67, 1.39]	0.97 [0.68, 1.39]
Var. (Level-1 residual)	2.35 [2.11, 2.61]	2.34 [2.11, 2.61]

Notes.
Regression coefficients are presented with standard errors in parenthesis.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$
Deviation BP: Deviation score of Behavior Problems from the 8-day average.
EFC: Emotion Focused Coping.
a. Estimated variances (Var.) of random parts of the mixed models are reported with 95% confidence intervals in brackets.

Table 5. Multilevel Models: Predicting **Cortisol AUC** by Daily Behavior Problems, **Problem-Focused Coping** and CGG Repeat Length Category (n = 103, with 359 days).

	Model 1	Model 2
Fixed Effect		
Maternal age	0.05 (0.09)	0.04 (0.08)
Maternal marital status (married=1)	-0.33 (1.66)	-0.57 (1.63)
Maternal education (college degree or more = 1)	-1.96 (1.22)	-2.05 (1.21)
8-day average number of daily behavior problems:	0.42 (0.47)	0.41 (0.47)
Deviation from the 8-day average number of behavior problems (Deviation BP)	-0.42 (0.32)	-0.51 (0.32)
Problem Focused Coping (PFC)	0.09 (0.07)	-0.02 (0.11)
CGG Repeat Group		
(middle PM (91- 105) as reference group)		
low PM (< 91)	1.14 (1.37)	1.41 (1.34)
high PM (> 105)	1.29 (1.70)	1.53 (1.67)
Deviation BP x PFC	--	0.13 (0.04)***
CGG Repeat Group x PFC	--	
low PM (< 91)) x PFC		0.22 (0.14)
high PM (> 105) x PFC		0.08 (0.19)
Constant	28.3 (1.95)***	28.3 (1.91)***
Random Effects[a]		
Var. (Intercept)	27.4 [19.1, 39.3]	26.1 [18.2, 37.5]
Var. (Level-1 residual)	24.1 [20.2, 28.7]	23.1 [19.4, 27.6]

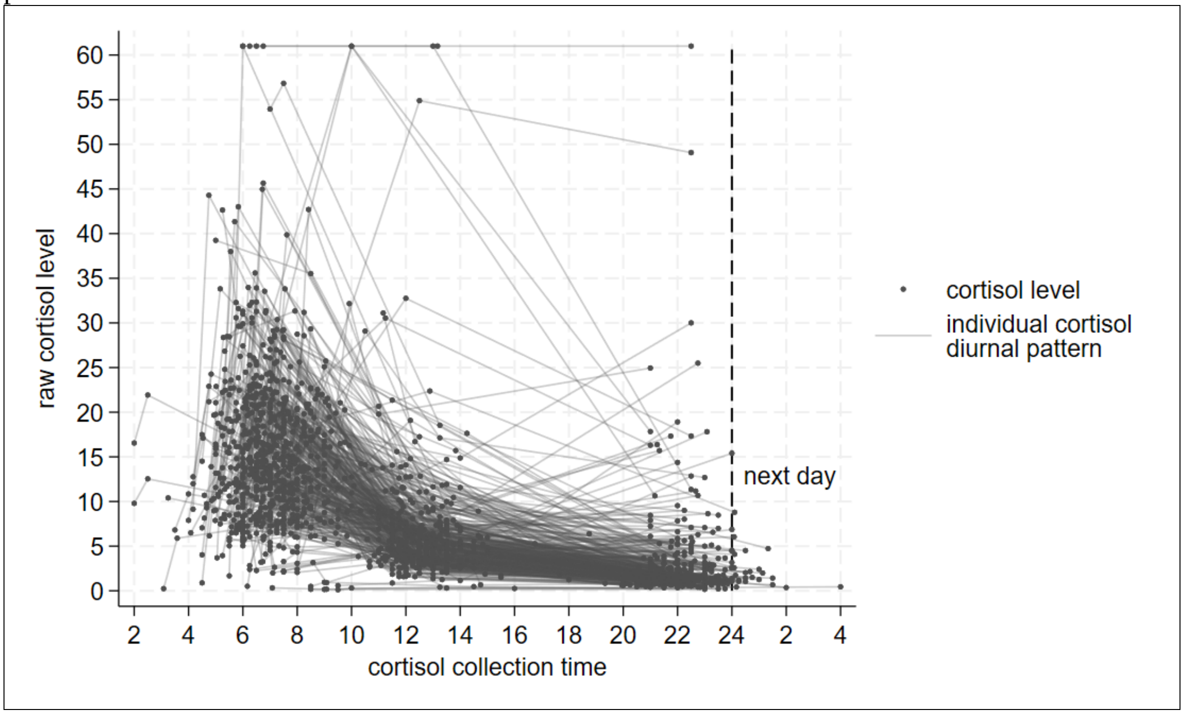
Notes.
Regression coefficients are presented with standard errors in parenthesis.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$
Deviation BP: Deviation score of Behavior Problems from the 8-day average.
PFC: Problem Focused Coping.
a. Estimated variances (Var.) of random parts of the mixed models are reported with 95% confidence intervals in brackets.

Table 6. Multilevel Models: Predicting **Cortisol AUC** by Daily Behavior Problems, **Emotion-Focused Coping** and CGG Repeat Length Category (n = 103, with 359 days).

	Model 1	Model 2
Fixed Effect		
Maternal age	0.07 (0.09)	0.07 (0.09)
Maternal marital status (married=1)	-0.33 (1.68)	-0.36 (1.67)
Maternal education (college degree or more = 1)	-1.96 (1.22)	-1.94 (1.20)
8-day average number of daily behavior problems:	0.44 (0.47)	0.44 (0.47)
Deviation from the 8-day average number of behavior problems (Deviation BP)	-0.42 (0.32)	-0.27 (0.34)
Emotion Focused Coping (EFC)	0.11 (0.10)	-0.01 (0.18)
CGG Repeat Group		
(middle PM (91- 105) as reference group)		
low PM (< 91)	1.24 (1.37)	1.24 (1.35)
high PM (> 105)	1.50 (1.70)	1.57 (1.68)
EFC x Deviation BP	--	-0.09 (0.05)
CGG Repeat Group x EFC	--	
low PM (< 91) x EFC		0.11 (0.24)
high PM (> 105) x EFC		0.27 (0.28)
Constant	28.2 (1.96)***	28.2 (1.96)***
Random Effects[a]		
Var. (Intercept)	27.4 [19.1, 39.4]	26.6 [18.4, 38.4]
Var. (Level-1 residual)	24.1 [20.3, 28.8]	24.0 [20.2, 28.7]

Notes.
Regression coefficients are presented with standard errors in parenthesis.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ Deviation BP: Deviation score of Behavior Problems from the 8-day average.
EFC: Emotion Focused Coping.
a. Estimated variances (Var.) of random parts of the mixed models are reported with 95% confidence intervals in brackets.

Figure 1. Observed and estimated diurnal cortisol levels.
A. Observed individual cortisol levels at each collection time and individual diurnal cortisol patterns.



B. Estimated average cortisol levels by collection times

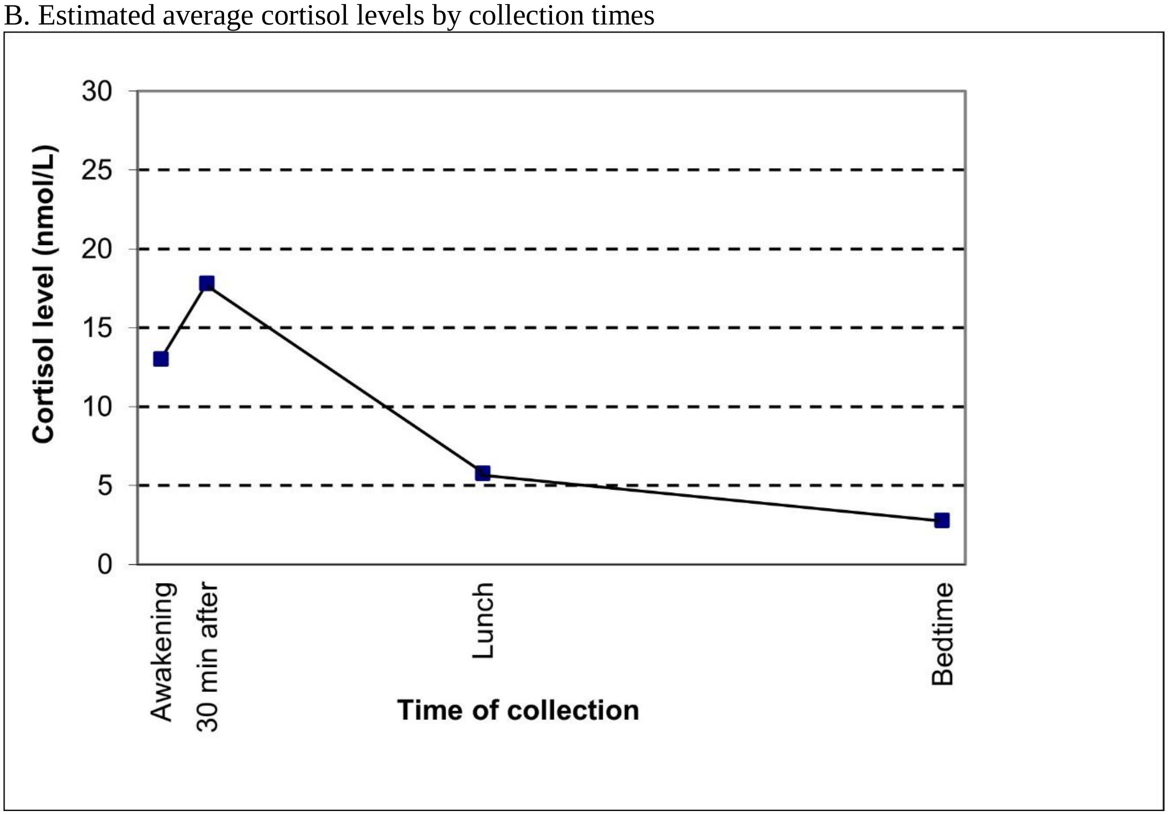


Figure 2. Histogram: The daily behavior problems deviation from the 8-day average.

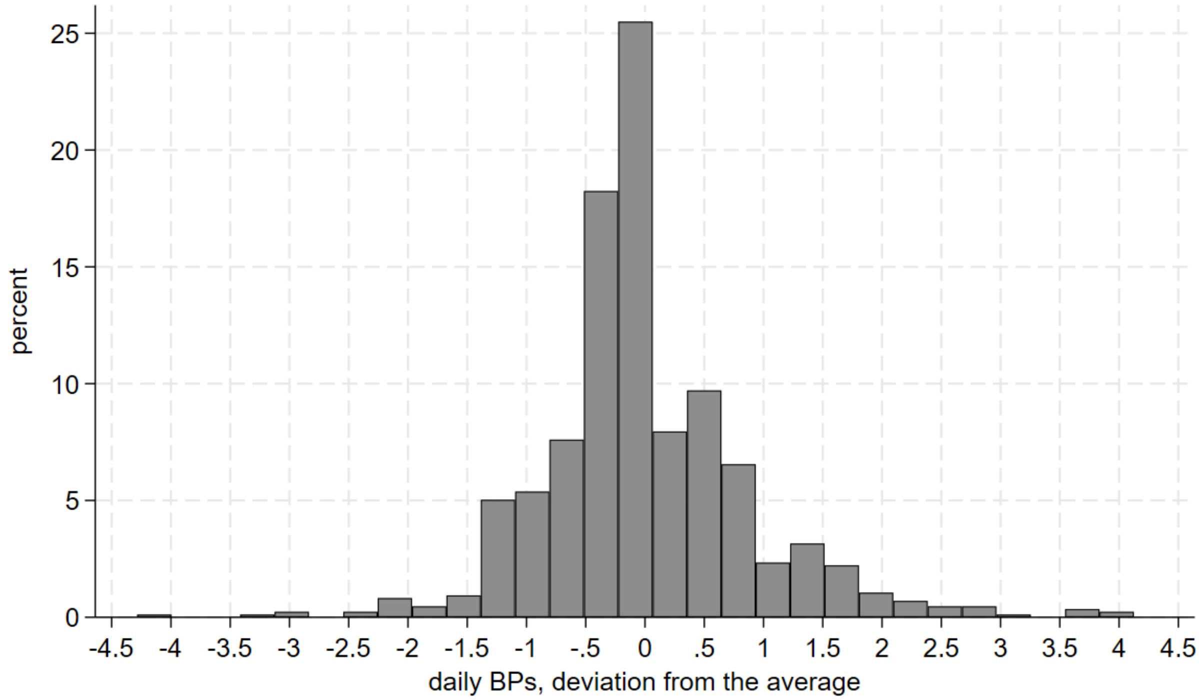
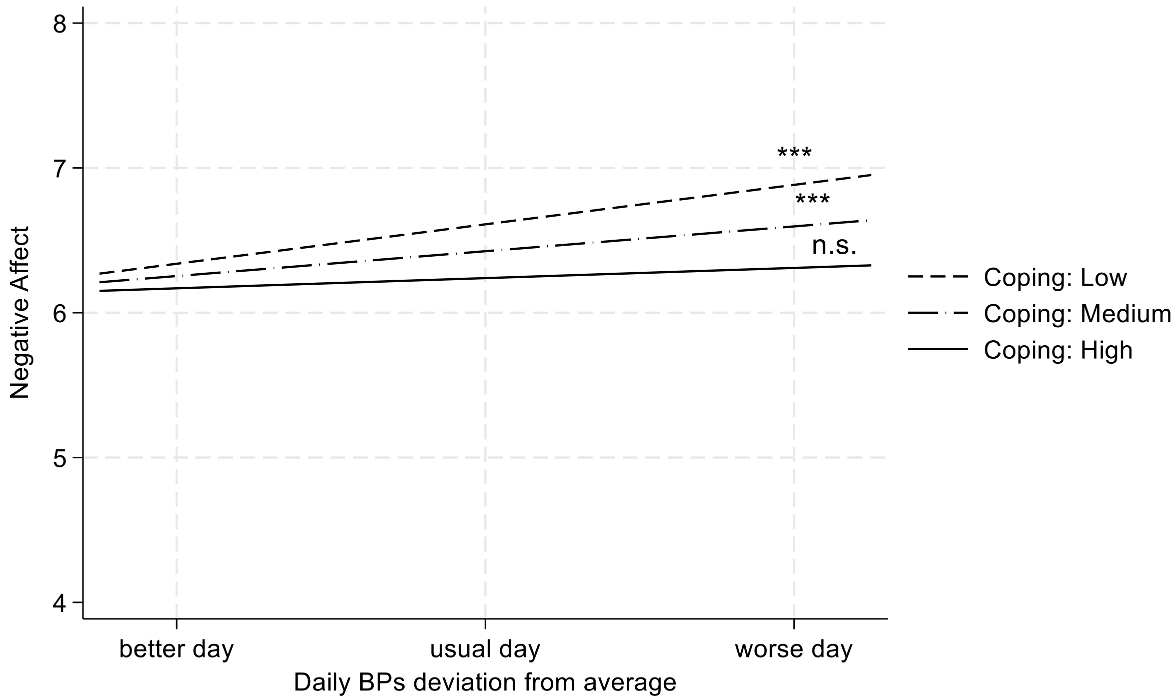


Figure 3. Interaction between problem-focused coping and the deviation score of behavior problems on negative
affect.



Note: As noted above, although we show three levels of coping here for illustrative purposes, it was modeled continuously in the statistical analysis shown in Table 3.

Figure 4 Interaction between problem-focused coping and the CGG repeat groups.

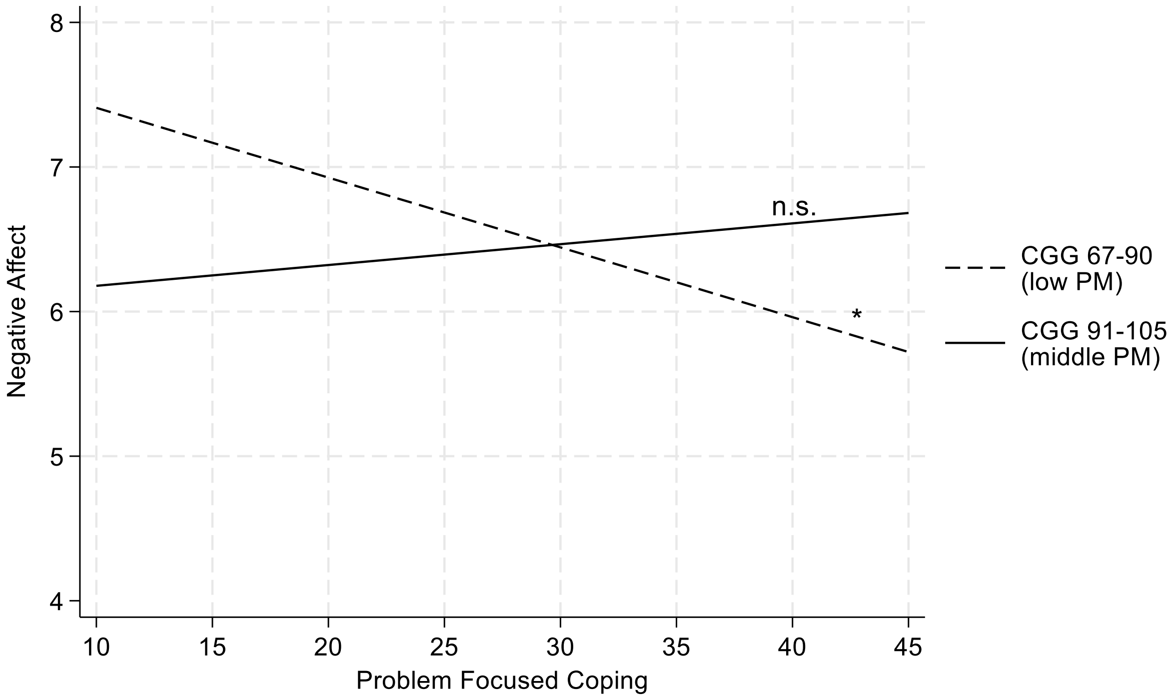
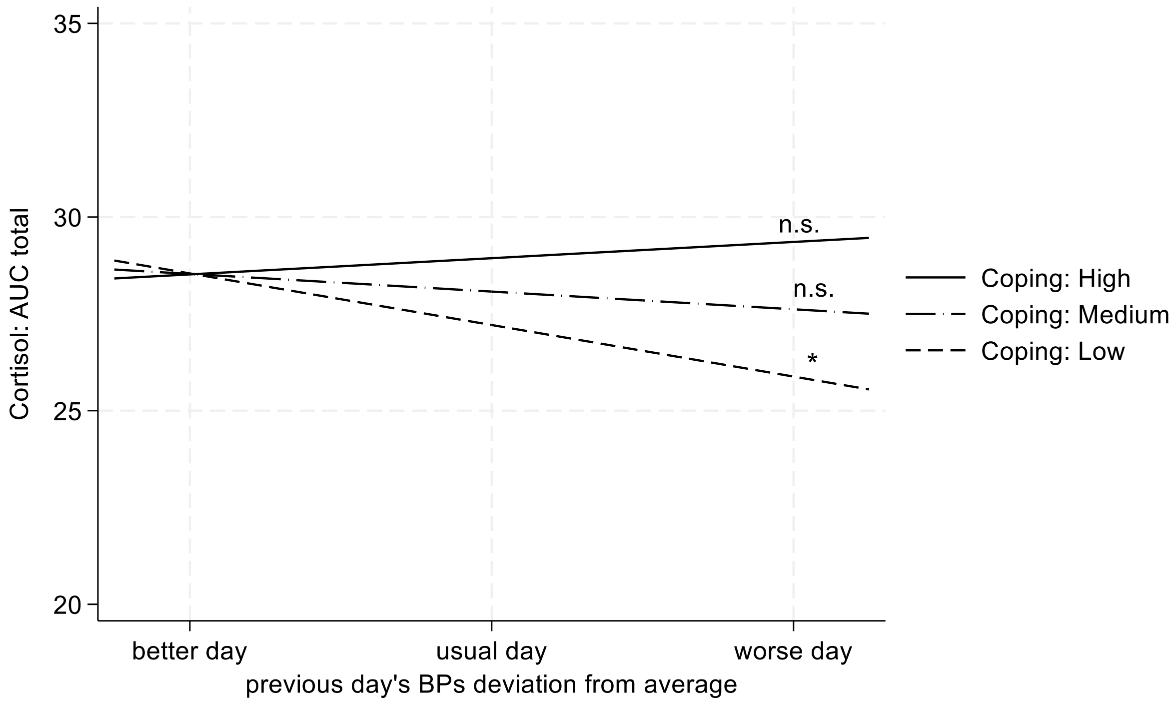


Figure 5. Interaction between problem-focused coping and the deviation score of behavior problems on cortisol AUC.



Note: As noted above, although we show three levels of coping here for illustrative purposes, it was modeled continuously in the statistical analysis shown in Table 5.

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