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COMT Moderates the Relation of Daily Maladaptive Coping and Pain in Fibromyalgia

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Abstract

Forty-five women with fibromyalgia (FM) engaged in a 30-day electronic diary assessment, recording daily ratings of pain and two forms of maladaptive coping: pain catastrophizing and pain attention. Participants were genotyped for the val158met single nucleotide polymorphism (rs4680) in the catechol-O-methyltransferase (COMT) gene. COMT genotype moderated the daily relations of both maladaptive coping processes and pain. FM women with the homozygous met/met genotype evidenced more pain on days when pain catastrophizing was elevated relative to heterozygous and homozygous val158 carriers. FM women with the homozygous met/met genotype evidenced more pain on days when pain attention was elevated relative to those with the homozygous val/val genotype. Evidence is presented to suggest that these are independent effects. The findings provide multi-measure and multi-method support for genetic moderation of a maladaptive coping and pain process, which has been previously characterized in a sample of post-operative shoulder pain patients. Further, the findings advance our understanding of the role of COMT in FM, suggesting that genetic variation in the val158met polymorphism may affect FM pain through pathways of pain-related cognition.

Chronic pain presents homeostatic challenges to an individual's affective regulatory system [46,13] and psychiatric health [26,28]. Patients use a variety of strategies to cope with chronic pain and although many have been shown to reduce pain, some coping processes are maladaptive. Maladaptive coping processes, such as attention to pain and pain catastrophizing, promote heightened pain and functional disability in a variety of chronic pain groups [20,30]. The harmful effects of maladaptive coping may be especially potent for patients with fibromyalgia (FM), a chronic pain disorder characterized by widespread musculoskeletal pain, as well as a reduced capacity for emotional resilience in the face of elevated pain [46]. Past research, however, has suggested that there is meaningful inter- and intra-individual variability in FM patients' psychosocial response to pain [47], as well as in pain reports themselves. A growing body of research has turned to genetics to help explain

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some of the variance in FM pain and its psychosocial concomitants [38,21,24,13]. The purpose of the present investigation was to determine if genetic variation in the catechol-O-methyltransferase (*COMT*) gene moderated the relations between maladaptive coping and pain in a sample of FM patients.

The *COMT* gene is thought to be involved in central pain processing via its direct regulation of dopaminergic pathways, which result in compensatory changes in opioidergic processing in response to pain [48,8,43]. The $val^{158}met$ single nucleotide polymorphism (SNP; rs4680) has been the most commonly analyzed variant in *COMT* in the context of pain research. However, its role in FM is as yet unclear, as no large-scale association study (e.g., N > 1000) has been reported, and its association with complex process-oriented phenotypes in chronic pain populations is only beginning to be elucidated [e.g., 13]. *COMT*'s role in the relation of maladaptive coping to chronic pain was examined by George et al. [16], who found that a diplotype in *COMT*, which was constructed with SNPs in high linkage disequilibrium with the $val^{158}met$ SNP, moderated the relation of trait-level pain catastrophizing and post-operative shoulder pain. High catastrophizers who carried the diplotype conferring low COMT enzymatic activity (as is also conferred by the met^{158} allele) reported greater pain post-operation. Despite those important findings, it has yet to be shown whether genetic moderation of the relation between maladaptive coping and pain extends to processes that occur in the flow of daily life. Such a naturalistic phenotypic measurement strategy is an important complement to trait-level analyses when there is within-person variation in the phenotype. Indeed, daily within-person relations between pain catastrophizing and pain intensity have been identified in a sample of rheumatoid arthritis patients [18].

Using a 30-day electronic diary assessment paradigm, we hypothesized that homozygous met^{158} carriers would report greater pain on days when cognitive-oriented maladaptive coping processes were more strongly endorsed. Through the use of a naturalistic phenotyping strategy, we sought to advance prior work by examining the daily contingencies of this chronic pain phenotype, and provide further clarification of the role of *COMT* in FM.

Method

Participants

The data that were analyzed for the current study were collected as part of a larger project (R01 AR46034) designed to identify factors related to adaptation to pain and stress in FM. The larger study included female participants with FM, osteoarthritis, or a dual diagnosis of both FM and osteoarthritis. For the current study, only participants with a diagnosis of FM, but not osteoarthritis, were analyzed. This decision was made in an effort to optimize the specification of the phenotype. Selection of FM-only participants minimizes the potential for separate disease processes to confound the analysis of genetic influences in FM. Further, we have previously characterized *COMT* moderation of positive affective reactivity to pain in this sample [13]. As we seek to develop salient phenotypes for FM, an important step is to consistently test hypotheses in well-characterized samples [see: 12]. Moreover, to test hypotheses regarding genetic association with complex process-oriented phenotypes, such as maladaptive coping with daily pain, it is essential to minimize the potential for phenotype contamination [3]. Limiting the sample to FM-only participants achieves those aims in our study.

Participants in the current study were 46 women between the ages of 38 and 72 with a physician-confirmed diagnosis of FM. One participant was excluded from analyses because she had fewer than 10 valid diary days for the variables of interest in this study, resulting in

a final sample of 45. Participants were recruited in the Phoenix, AZ metropolitan area from physician's offices, advertisements, senior citizen groups, and mailings to members of the Arthritis Foundation. Included in the study were participants who had no diagnosed autoimmune or arthritic disorders, a pain rating above 20 on a 0-100 scale, and who were not involved in litigation regarding their condition. All participants reported their diagnosis to research staff and subsequently signed a HIPAA release form. Research staff then contacted each participant's physician, who sent a written confirmation of the participant's FM diagnosis and disconfirmed diagnoses of other autoimmune and arthritic disorders.[1] Consent and study procedures on all participants were approved by the Institutional Review Board at the authors' institutions.

Procedure

After being screened into the study, participants were visited by a clinician for a tender point exam. The tender point exam was conducted by trained research personnel supervised by licensed rheumatologists in a method consistent with medical standards. The clinician used a dolorimeter to apply 4 kg of pressure to each of 18 musculoskeletal regions identified as part of the American College of Rheumatology 1990 criteria [42] as tender points, and to three control points, that can aid in FM diagnosis. The results of the tender point exam were used primarily to identify outliers whose reported pain may have differed from expectations based on physician diagnosis. As detailed in a previous publication from our group [13], ten of the 45 FM patients in our study endorsed fewer than 11 tender points, which has been recognized as a diagnostic cut-off by the American College of Rheumatology 1990 criteria [42]. A more recent investigation of FM diagnostic criteria by the American College of Rheumatology cautions that tender point assessment is an incomplete and imperfect proxy for FM [41]. Some investigators have recommended moving away from tender point palpation and toward a more comprehensive assessment of patient well-being for FM diagnosis [5]. We therefore chose to use the physician's diagnosis to identify patients in the study, and did not find enough outlying evidence from our tender point exams to exclude any of the 45 participants from the study. However, we took two conservative measures to determine if tender point endorsement in our sample biased the results of the present study. First, we excluded the ten participants who endorsed fewer than 11 tender points and re-ran the primary analyses. In all instances, results that we report to be significant with the full sample remained significant with the restricted sample. Second, in all primary analyses, we tested raw tender point endorsement as a covariate. Raw tender point endorsement was not a significant covariate in any analysis, and did not alter the magnitude or direction of any of the reported effects. Therefore, we are confident that the physician's confirmed diagnosis of FM provided an adequate characterization of our sample.

After the clinician visit, participants were trained in our laboratory by a research assistant to use a laptop computer to complete daily diaries each night for 30 days. Participants were encouraged to call our laboratory staff immediately if a problem occurred with the laptop. A built-in date-checking software program prevented data entry on days other than the correct day. After completing the 30-day diary, participants were visited by a clinician, and buccal cells were collected via a cheek swab method that followed published procedures [40]. Participants were compensated $90 for completion of the diary. The overall rate of diary completion for the main outcome measures was 93.3% (1260/1350 days), with participants completing an average of 28 days (range: 15-30).

[1]The confirmed and disconfirmed diagnoses provided by participants' physicians were not independently verified by other physicians. We did not provide participants' physicians with a standardized definition of fibromyalgia or other autoimmune disorders to make their diagnoses. Therefore, we relied on physicians' diagnostic discretion in rendering diagnostic status.

Genotyping

Genomic DNA was purified from buccal cheek swab samples by the University of Connecticut Health Center GCRC Core Lab. DNA samples were placed in 96-well plates and genotyped using PCR based TaqMan 5'-nuclease allelic discrimination assay methods in the GCRC Core Lab. All 45 samples from the current study were accurately genotyped on first assay. Fifteen percent of genotypes (N=7) were randomly repeated to monitor reproducibility, and no discrepancies were found. The primer and probes used to genotype the *COMT val*^{158}*met* polymorphism (rs4680) were (CCCAGCGGATGGTGGAT and AACGGGTCAGGCATGCA), and (Vic-TCCTTCAcGCCAGCGA-MGB and Fam-TCCTTCAtGCCAGCGA-MGB).

Measures

Soft Tissue Pain (STP)—The daily diary included a body diagram that depicted the major quadrants of the body [1], with instructions for participants to rate their soft tissue pain in 15 specific areas including parts of their neck, shoulders, chest, upper and lower arms, upper and lower legs, back, and buttocks. Ratings were made on a scale of 0-3, where zero (0) = "No pain" and three (3) = "Severe pain." Sum scores were computed from the 15 items to create an overall score of soft tissue pain. A preliminary unconditional model indicated that 79.3% of the variance in STP was accounted for by between-person factors, while 20.7% was accounted for by within-person factors.

Numerical Rating Scale (NRS)—Daily NRS pain was measured in the diary with the standard instruction for a numerical rating scale [19], "Please choose a number between 0 and 100 that best describes the average level of pain you have experienced today due to your Fibromyalgia." A zero (0) would mean 'no pain' and a one hundred (100) would mean 'pain as bad as it can be.' A preliminary unconditional model indicated that 51.6% of the variance in STP was accounted for by between-person factors, while 48.4% was accounted for by within-person factors.

Pain Catastrophizing—Pain catastrophizing was measured as part of the Coping Strategies Questionnaire [31]. The measure was an average of two items rated on a scale of 1-5 with 5 representing "Strongly Agree" and 1 representing "Strongly Disagree." The two items read, "I worry about whether my pain will ever end," and, "I felt my pain so bad I couldn't stand it anymore." Test-retest reliability across days was .81.

Pain Attention—Pain attention was measured with the Pain Vigilance and Awareness Questionnaire [25]. The measure was an average of three items rated on a scale of 1-5 with 5 representing "Strongly Agree" and 1 representing "Strongly Disagree." The three items read, "I was quick to notice changes in the intensity of my pain"; "I was quick to notice changes in the location of my pain"; and, "I noticed my pain when I was busy with activities." Test-retest reliability across days was .81.

Data Analysis

The primary models in this study were designed to assess main effects of daily maladaptive coping on daily pain and interaction effects in which that relation was moderated by *COMT*. The decision to model pain as the criterion and maladaptive coping as the predictor was based upon prior theoretical models that conceptualize pain perception as a neurobiological process that can be modulated by cognitive and affective input [37,15,36]. The daily measurement paradigm results in dependencies between these variables such that the causal ordering of variables chosen as predictors and criteria is often ambiguous. We chose to elaborate upon a specific chronic pain phenotype identified by George et al. [16], and

therefore made a decision *a priori* to model maladaptive coping variables as predictors and pain variables as criteria.

Repeated daily measurements resulted in a hierarchical nested data structure, with up to 30 observations nested within each person. Given such a data structure, multilevel modeling, executed using SAS PROC MIXED [22], was an appropriate data analytic tool. Predictor variables in the current study were centered within-person [27,9]. For each observation, the participant's mean across diary days was subtracted from the daily score, yielding an index of within-person *daily change*. Within-person centered variables are denoted in this manuscript by the Greek letter Δ. Centering in this fashion allows for the interpretation of the intercept based on the individual's mean on the independent variable of interest. As an example, if pain is the outcome and catastrophizing is the predictor, our centering decisions allow for an interpretation of the intercept as the average value for pain when individuals are at their mean level of catastrophizing.

Both Level 1 (within-person) and Level 2 (between-person) variables, as well as cross-level interactions (Level 1 x Level 2), were modeled as predictors. We highlight the basic equations used in the present study, involving daily pain as the criterion:

$$\text{Level 1: } y_{ij}(\text{Daily Pain}) = \beta_{0j} + \beta_{1j}(\Delta\text{Catastrophizing}) + r_{ij} \quad (1)$$

There are *i* observations of pain for *j* individuals. β_{0j} yields an estimate of the average level of pain at the individual's mean level of catastrophizing. β_{1j} is the coefficient for the daily influence of catastrophizing on pain and r_{ij} is the within-person error component. At Level 2, individual differences in the average level of pain are probed, along with cross-level interactions. The Level 2 intercept is specified as follows:

$$\text{Level 2: } \beta_{0j} = \gamma_{00} + \gamma_{01}(\text{Average Catastrophizing}) + \gamma_{02}(COMT) \quad (2)$$

where the equation for β_{0j} predicts each person's Level 1 intercept from the grand mean, the mean level of catastrophizing, and the individual's *COMT* genotype. The Level 2 slopes are specified as follows:

$$\text{Level 2: } \beta_1 = \gamma_{10} + \gamma_{11}(COMT) \quad (3)$$

The second Level 2 equation models a cross-level interaction, whereby between-person differences in *COMT* genotype (Level 2) moderate the relation of within-person changes in catastrophizing (Level 1) and the outcome, daily pain. In all models, a first-order autoregressive variance-covariance matrix was chosen to model the within-person variance on the dependent variables. Additionally, because our study sample included women who were pre-, peri-, and post-menopausal, we covaried age in all analyses. Significance was determined at $p < .05$.

Main effect models in which maladaptive coping variables predicted pain included the predictor as a random slope parameter. Allowing the slopes to vary randomly in main effect models permitted a test of whether variance remained to be explained in the criterion beyond that which was accounted for by the predictor. Thus, modeling random slopes in the Level 1 main effect models allowed for an evaluation of our decision to examine genetic moderation in the hypothesized cross-level interaction models. The cross-level gene X coping models lack a random slope component (but retain a random intercept component) because we

expected that the effect sizes would be relatively small. In such cases, power to model random effects is limited.

A large Northern European sample [35] with 3,140 participants yielded the following *val*^{158}*met* genotype frequencies: [26% (*val/val*), 50% (*val/met*), 24% (*met/met*)]. We used these estimates as points of comparison for our genotype frequencies. Because the heterozygous *val/met* genotype produces functional changes in COMT enzymatic activity intermediate to those of the two homozygous genotypes, gene effects were expected to be largest for individuals with homozygous genotypes.

Population stratification, which occurs when a sample consists of individuals from several different subgroups in which mating over time has been non-random, is a potential threat to internal validity in genetic association studies [4]. Ethnocentric mating is the cardinal example of a behavior that can lead to population stratification. Vargas-Alarcon et al. [38] reported differences between Mexican and Spanish FM samples in the frequency of *met*^{158}, and other ethnic differences have been reported elsewhere [23]. To address the potential threat of population stratification, ethnic differences were probed on the primary outcome variable (e.g., pain), and all analyses were re-run excluding non-Caucasian participants to test the generalizability of the results for Caucasian-only participants.

Results

Participant Characteristics

Participants mean age was 53 (SD=7.82); 67.5% had completed some college, with 25% holding post-graduate degrees, and 75.7% reported earning over $30,000 per year, with 41.5% earning over $70,000 per year (demographic data was missing on six participants). Our sample was of a higher socioeconomic status than the general FM population [29]. Ethnicity data were only available for 41/45 participants. Of that group, 38 participants reported Caucasian ethnicity, two participants reported African-American ethnicity, and one participant reported Hispanic ethnicity. Descriptives for characteristic FM symtpoms, including tender points, pain, fatigue, and interpersonal stress are included in Table 1.

The observed genotype frequencies were in Hardy-Weinberg equilibrium. The following genotype frequencies were observed for the *val*^{158}*met* polymorphism: *val/val*=12 (26.1%), *val/met*=24 (52.2%), *met/met*=10 (21.7). Genotype frequencies resembled general population estimates in a northern European sample [35].

Descriptives for the main study variables, stratified by genotype, can be found in Table 2. Correlations among the study variables can be found in Table 3. Pain attention was more strongly endorsed than pain catastrophizing, $t(44) = -10.70$, $p < .001$. Moderate correlations were evidenced between the two pain variables (r = .63) and the two maladaptive coping variables (r = .41).

Gene X Coping Multilevel Models

Pain Catastrophizing—Our first model specified daily soft tissue pain as the criterion and pain catastrophizing as the predictor. A significant main effect was observed, such that on days when pain catastrophizing was elevated, STP was also elevated, $\beta = .20$ (SE = .02), $F(1, 1223) = 78.31$, $p < .0001$. A similar main effect was observed when NRS pain was the criterion, $\beta = 10.07$ (SE = 1.19), $F(1, 1222) = 70.97$, $p < .0001$. Pain catastrophizing was modeled as a random effect in the initial models to confirm our decision to examine individual differences at Level 2. Indeed, covariance parameters for both models indicated that there was random between-person variance in the slope of pain catastrophizing and pain (STP: $\delta_{\beta 1} = .01$, $p < .01$; NRS: $\delta_{\beta 1} = 37.40$, $p < .01$).

COMT was entered as a Level 2 moderator of the relation of pain catastrophizing with STP. Due to power concerns, random slopes were not modeled. A significant interaction emerged, $F(2, 1221) = 9.57$, $p < .0001$, such that *met/met* carriers experienced more pain on days when pain catastrophizing was elevated than either *val/val* ($\beta = -.15$, $p < .0001$) or *val/met* ($\beta = -.08$, $p < .01$) carriers. The interaction was also significant when NRS pain was the criterion, $F(2, 1220) = 5.23$, $p < .01$. Age was not a significant covariate and did not alter the direction or significance of the main or interaction effects, and therefore was not retained in the final model. These effects are presented graphically in Figures 1a and 1b, with separate lines for each *COMT* level traversing an X-axis that was artificially dichotomized to represent the top and bottom thirds of pain catastrophizing responses. The multilevel statistics for this model are presented in Table 4.

The amount of variance explained by the interaction effect can be assessed by computing an intraclass correlation coefficient (ICC) from the variance components, which amounts to an estimate of the amount of explainable variance accounted for by a particular model. For STP, the amount of residual variance in an unconditional model decreased by 22% when pain catastrophizing was entered into the equation. When the *COMT* X pain catastrophizing interaction was entered, the residual variance decreased by another 6%, indicating that the *COMT* X pain catastrophizing interaction explained 6% of the explainable variance in STP, over and above that which was accounted for by pain catastrophizing alone. Pain catastrophizing explained 22% of the variance in NRS pain, but the *COMT* X pain catastrophizing interaction only explained an additional 2% of variance.

Pain Attention—A significant main effect was observed for pain attention on STP, $\beta = .19$ (SE = .02), $F(1, 1406) = 67.81$, $p < .0001$, such that on days when pain attention was elevated, STP was also elevated. This effect was also observed for NRS pain, $\beta = 10.29$ (SE = 1.44), $F(1, 1405) = 50.97$, $p < .0001$. Again, covariance parameters in the Level 1 models indicated that a significant amount of random between-person variance was left to be explained at Level 2 (STP: $\delta_{\beta 1} = .02$, $p < .01$; NRS: $\delta_{\beta 1} = 70.24$, $p < .001$), supporting a decision to model *COMT* as an interaction term.

The *COMT* moderation models were again designed to examine fixed effects. A significant interaction was observed with STP as the criterion, $F(2, 1217) = 7.83$, $p < .001$, indicating that *met/met* carriers experienced more pain on days when pain attention was elevated than *val/val* ($\beta = -.17$, $p < .0001$) carriers. The contrast with *val/met* participants was not significant ($\beta = -.04$, $p = .38$). Age again was not a significant covariate and did not alter the direction or significance of the main or interaction effects, and therefore was not retained in the final model. The effect is displayed graphically in Figure 2, with *COMT* groups contrasted at the top and bottom thirds of pain attention responses. The multilevel statistics for this model are presented in Table 4. Pain attention explained 12% of the variance in STP, and the *COMT* X pain attention interaction explained 1% of additional variance.

The overall interaction effect was only observed as a trend for NRS pain, $F(2, 1216) = 2.45$, $p = .09$, but the individual contrast between *met/met* and *val/val* carriers was significant ($\beta = -5.52$, $p < .05$).

To establish independence of the *COMT* X pain catastrophizing and *COMT* X pain attention fixed effects, we ran an omnibus model separately for each pain outcome that included all main effect and interaction terms. In the prediction of STP, both the *COMT* X pain catastrophizing ($p < .001$) and the *COMT* X pain attention ($p < .01$) interactions remained significant when simultaneously entered. In the prediction of NRS pain, the *COMT* X pain catastrophizing interaction was significant ($p < .01$), and the *COMT* X pain attention interaction again failed reach significance ($p = .25$) when both interaction terms were

simultaneously entered. Together, these tests suggest that the *COMT* X pain catastrophizing and *COMT* X pain attention interactions were independently associated with pain.

Lagged Analyses

The structure of our data allowed for a test of the temporal ordering of the effects reported above. Each of the interactions was analyzed in a lagged framework to determine if maladaptive coping on one day affected pain outcomes on the next day, and if those relations were moderated by *COMT*. Neither pain catastrophizing ($p = .67$) nor pain attention ($p = .22$) evidenced carry-over effects to next day pain outcomes. Further, no interactions emerged when *COMT* was included as a moderator. Therefore, we cannot offer conclusions regarding the directionality of the maladaptive coping/pain relations.

Tests for Population Stratification

Caucasians (N = 38) were significantly different from non-Caucasians (N = 3) in soft tissue pain (Caucasians: M = .94, SD = .53; non-Caucasians: M = 2.04, SD = 1.19), t (39) = 3.15, $p < .01$, and NRS pain (Caucasians: M = 56.29, SD = 15.42; non-Caucasians: M = 75.74, SD = 24.29), t(39) = 2.03, $p < .05$. Based on these findings, the primary analyses were re-run with a sample restricted to Caucasians only. Largely, the results were consistent with those reported above with the full sample. For the analyses in which soft tissue pain was the outcome, results remained significant at $p < .001$. For the *COMT* X pain catastrophizing interaction on NRS pain, the finding fell out of significance ($p = .21$), but the direction of the effect remained the same. The trend for an interaction of COMT x pain attention on NRS pain became non-significant ($p = .70$).

Discussion

At present, there is a need to develop and enrich the phenotypic characterization of chronic pain disorders. The current study addressed that aim by examining a putative chronic pain phenotype among FM patients in a naturalistic setting: the relation between daily maladaptive coping and daily pain. The data presented herein provide further validation for an effect originally reported by George et al. [16], whereby variation in *COMT* moderated the relation of pain catastrophizing and pain following shoulder surgery. Our study found that the relations between the daily maladaptive coping processes of pain catastrophizing and pain attention and daily pain in FM patients were moderated by variation in *COMT*.

We utilized a daily process design [e.g., 2] to simultaneously examine the within-person and between-person differences in the maladaptive coping/pain relation. The repeated-measures design yields a phenotypic measurement with greater reliability than can be captured in a single-occasion measure [10,11]. For many chronic pain conditions, including FM, pain is variable and each day brings new challenges to one's coping resources. Therefore, modeling the time-variant relation of maladaptive coping and pain may more closely approximate the phenotype as it occurs in the flow of daily life.

The interaction effect of *COMT* and maladaptive coping on pain was found when either pain catastrophizing or pain attention was the predictor, and when either STP or NRS pain was the criterion. Pain catastrophizing and pain attention measure two similar, but distinct, aspects of cognitive coping with pain. Discriminant validity between the two constructs was evidenced by their moderate (but not exceedingly large) correlation of .41. Additionally, both interaction effects significantly predicted STP when entered simultaneously in the same model. Whereas pain attention primarily reflects the cognitive activity of attending to ongoing pain, pain catastrophizing evokes more of a fear-avoidance emotive response that activates brain regions that regulate both cognitive and emotional processing, such as the

anterior cingulate cortex [17]. A recent study supports this view by demonstrating that the affective component of pain processing, separate from cognitive attention to pain, results in distinct activation in the anterior cingulate cortex [39].

The current findings expand our knowledge of the role of *COMT* in FM. Although some studies have reported genetic association between the frequency of the met^{158} allele of the $val^{158}met$ polymorphism and incidence of FM in basic case-control designs [e.g., 14,38], other studies have failed to find association [34]. One problem with basic case-control association designs is that little to no information is provided regarding the complex process-oriented mechanisms that account for the association between the gene and the downstream distal disease-based phenotype. The relation between maladaptive coping and pain, as measured in the current study, is an intermediate phenotype that provides potentially useful information about the complex naturalistic processes that characterize the daily experience of FM.

The finding that *COMT* moderates the relation between daily maladaptive coping and daily pain in FM follows a recent report from our group that *COMT* moderated the daily positive affective reactivity to pain in the FM sample [13]. By extending our naturalistic phenotyping approach to a different phenotype with different clinical implications—maladaptive coping with pain—the role of *COMT* in FM has been further elucidated. Thus, it is now apparent that *COMT*'s involvement in FM is not directly characterized by its association with pain. Rather, by coupling the findings from the current investigation with those reported by Finan et al. [13], we can conclude that *COMT* may best be characterized as a moderator of pain coping and pain affect processes.

The *COMT* $val^{158}met$ polymorphism has been an attractive variant in pain research for several reasons. First, it alters the theromstability of the COMT enzyme, producing changes in tonic dopamine levels as a result of lower COMT activity [32,43]. Second, it is in high linkage disequilibrium with several other SNPs that, through haplotype analysis, have been associated with variation in pain sensitivity [8]. Third, homozygous met^{158} subjects exhibit enhanced cognitive capacity in working memory and attention tasks, while displaying poor emotion regulation during emotionally evocative situations, relative to val^{158} carriers [for a review, see: 33]. The so-called 'worrier-warrior' hypothesis [33] that people with the met^{158} allele enjoy greater attention-related abilities at the expense of emotional resilience is intriguing in the context of chronic pain research, and aligns with the findings presented in this article. Prior evidence that the met^{158} allele is associated with reduced mu-opioid receptor activation, which in turn results in enhanced negative emotional reactivity in the context of both pain and affective stressors [49,48], supports our finding that *COMT* moderates the relation of pain catastrophizing and pain, a pathway characterized by heightened emotionality (i.e., fear of pain). Further, that line of work provides a rationale for the relative independence of the pain catastrophizing and pain attention effects in the current study. Whereas the altered dopaminergic activity fostered by the met^{158} allele may influence pain catastrophizing via its connections to the opioidergic system in the limbic regions, its effect on pain attention may be mediated by its influence over dopaminergic-prefrontal cortical pathways [45].

The dynamic physiological mechanisms that may account for the moderating effects of the *COMT* genotype on daily catastrophizing-pain relations remain to be elaborated. COMT gene transcription is thought to be affected by estradiol, a female sex hormone that is produced in varying amounts throughout the menstrual cycle [44]. Our sample included women in age ranges associated with pre-, peri-, and post-menopausal status. However, controlling for age (and thus menopausal status) did not alter the pattern of our findings. Nevertheless, at least among women of reproductive age, some of the *COMT* interaction

effects reported may be due to daily fluctuations in estradiol levels. This is an empirical question, and one that could be addressed through future work that experimentally controls estradiol levels across a menstrual cycle.

We have purposely avoided interpreting our findings as a replication of those presented by George et al. [16]. Our studies differed in several key respects including the pain catastrophizing measure used, the methods of measurement employed, the pain population sampled, and the *COMT* variant selected for analysis. Notably, we used the *val*^{158}*met* SNP while George et al. used a diplotype composed of two SNP's in high linkage disequilibrium with *val*^{158}*met*. Diatchenko et al. [8] have argued that a haplotypic analytic framework may be preferable to a single variant analysis of *COMT*'s association with pain outcomes. We agree with this viewpoint as a general premise for approaching genetic association analyses and, thus, believe that our study was limited in that respect. However, a counter argument could be made that because our findings were so similar to those of George et al., despite the difference in genetic variation assessed, our understanding of the role of *COMT* in chronic pain processes was broadened by the examination of the *val*^{158}*met* SNP.

This study may be limited by the threat of population stratification. Although the results of the primary analyses run with a sample restricted to Caucasians were consistent with the results from the analyses with the full sample, we cannot rule out the possibility that the *COMT* X coping interactions could vary by population substructures. Our sample size was further limited by a lack of ethnicity data on four participants. Thus, we are unable to determine if our null findings were due to a loss of power, or to population stratification. This uncertainty warrants future inquiry with a larger and more diverse sample to fully explicate the potential role of population substructures on the pain coping processes examined herein.

The temporal ordering of the daily relations between maladaptive coping and pain could not be established in this study, as the null hypothesis was confirmed for all of the lagged analyses. One reason for this could be that the measures were completed roughly 24 hours apart from one another, thereby introducing the potential influence of other variance not accounted for in our models.

Another limitation of this work is that the amount of variance explained by the gene X coping interactions was small. Historically, *COMT* association effects tend to be small. Therefore, it came as no surprise that the addition of the *COMT* X coping interaction term to the multilevel models explained only 1-6% of explainable variance in the overall model. It is difficult, then, to extrapolate clinical implications from the findings presented here. However, as others have noted in daily process studies [see: 6,7], the relatively small effects of ongoing cognitive and emotional processes on physical or behavioral outcomes are likely to derive more clinical meaning as they accrue over time.

In summary, our results indicate that genetic variation in *COMT* moderates the daily relation of maladaptive coping and pain among FM patients. These findings extend prior work and venture into new territory, expanding knowledge on the role of *COMT* in FM. In so doing, they provide support for the hypothesis that *COMT* may affect pain processes in FM through its role in the neural regulation of pain-related cognition.

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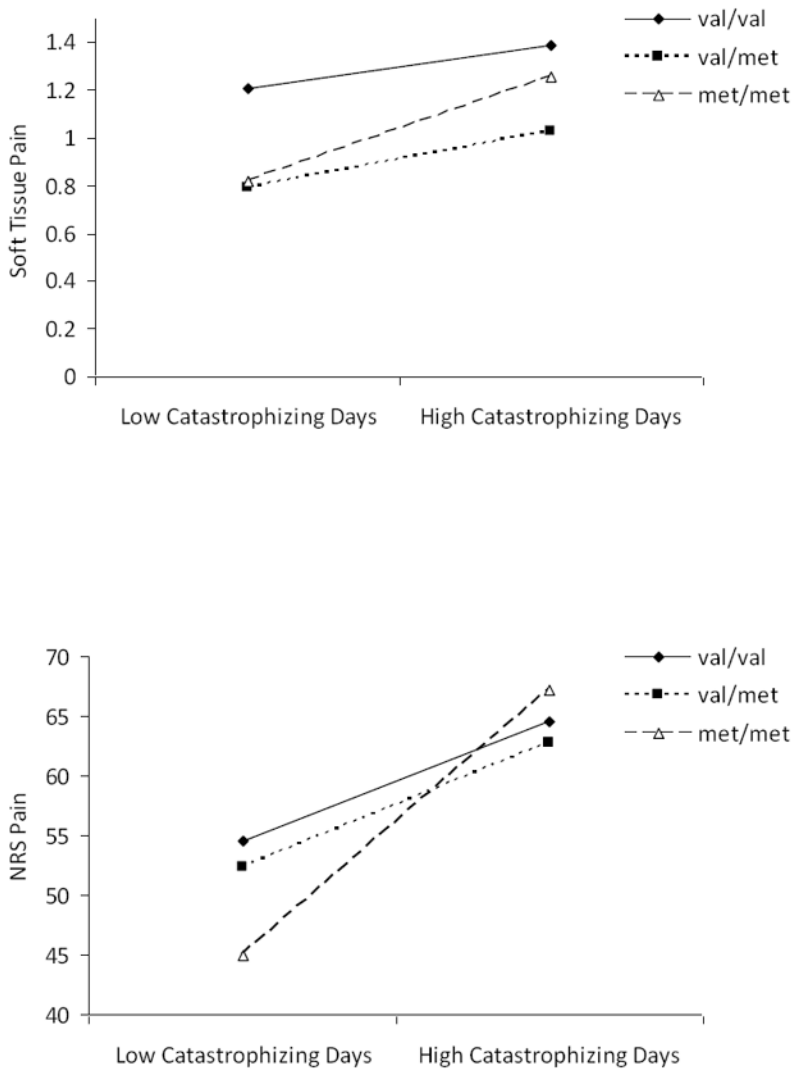

Figure 1.

a. COMT Moderation of the Relation of Pain Catastrophizing and Soft Tissue Pain

b. COMT Moderation of the Relation of Pain Catastrophizing and NRS Pain

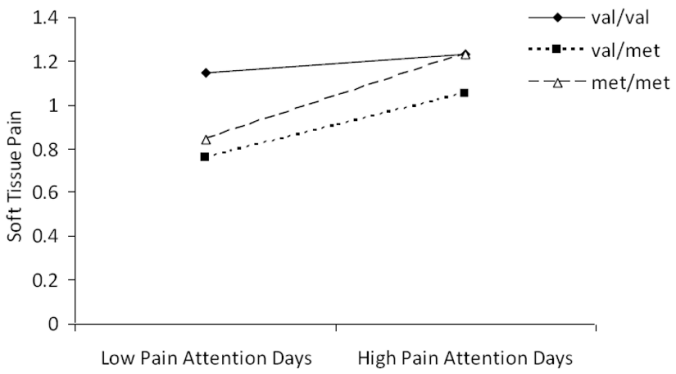

Figure 2.
COMT Moderation of the Relation of Pain Attention and Soft Tissue Pain

Table 1

Descriptive Statistics for Common Fibromyalgia Symptoms and Diagnostic Indicators.

	FM Patients (N = 45) M (SD)
Tender Points (# endorsed)	13.78 (3.87)
Average Daily NRS Pain (0-100)	51.78 (24.91)
Average Daily NRS Fatigue (0-100)	51.33 (26.40)
Average Daily Interpersonal Stress (1-4)	1.51 (0.29)

Note. Means (and standard deviations) of common FM symptoms are provided in the right column. Tender points were assessed according to American College of Rheumatology criteria [41]. Average daily numeric rating scale [NRS; 19] pain and fatigue scores were assessed in the diary on a 0-100 scale. Average daily interpersonal stress was assessed in the diary on a 1-4 Likert scale as part of an abridged version of the Inventory of Small Life Events [46].

Table 2

Means and Standard Deviations of Study Variables by COMT Group (N = 45)

	COMT		
Study Variables	***val/val (N = 12)***	***val/met (N = 24)***	***met/met (N = 10)***
Soft Tissue Pain	1.16 (0.94)	0.91 (0.66)	1.10 (0.49)
Numeric Rating Scale Pain	55.11 (26.96)	56.89 (23.65)	55.75 (20.73)
Pain Catastrophizing	2.14 (1.10)	2.19 (1.03)	2.11 (.92)
Pain Attention	3.37 (0.96)	3.47 (.86)	3.60 (.74)

Note. Means (and standard deviations) are provided for study variables separately for each genotype. The scores for each variable were averaged across each participant's range of diary days.

Table 3

Correlations Between Study Variables

	Soft Tissue Pain	Numeric Rating Scale Pain	Pain Catastrophizing	Pain Attention
Soft Tissue Pain	-	.64	.56	.27
Numeric Rating Scale Pain	-	-	.58	.54
Pain Catastrophizing	-	-	-	.41
Pain Attention	-	-	-	-

Note. Correlations are between-person, based on the average of each variable across each participant's range of diary days. N = 45.

Table 4

COMT Moderation of the Relation of Daily Maladaptive Coping and Daily Soft Tissue Pain

Random Effects					
Covariance Parameter Estimates	**Subject**	**β**	***SE***	***Z***	***p***
Pain Catastrophizing Intercept	ID	.41	.92	4.53	<.0001
Pain Catastrophizing Residual		.08	.004	21.44	<.0001
Pain Attention Intercept	ID	.41	.09	4.51	<.0001
Pain Attention Residual		.10	.005	20.34	<.0001

Fixed Effects					
Predictor Variables	**β**	***SE***	***df***	***t***	***p***
Level 1					
Δ Pain Catastrophizing	.28	.02	1221	11.89	<.0001
Δ Pain Attention	.25	.04	1217	6.25	<.0001
Level 2					
COMT (*val/val* vs. *met/met*)	.08	.29	42	.27	.79
COMT (*val/met* vs. *met/met*)	-.19	.25	42	-.73	.47
Level 1 X Level 2					
Δ Pain Catastrophzing X *COMT* (*val/val* vs. *met/met*)	-.16	.04	1221	-4.37	<.0001
ΔPain Catastrophizing X *COMT* (*val/met* vs. *met/met*)	-.08	.03	1221	-2.71	<.01
Δ Pain Attention X *COMT* (*val/val* vs. met/*met*)	-.17	.05	1217	-3.37	<.001
ΔPain Attention X *COMT* (*val/met* vs. *met/met*)	-.04	.04	1217	-.88	.38

Note. The results of the multilevel analyses of the cross-level interactions of *COMT* genotype and daily pain catastrophizing (Δ Pain Catastrophizing) and COMT and daily pain attention (Δ Pain Attention) on daily soft tissue pain among FM patients are presented. The effects presented for each Level 2 and cross-level effect are separated according to contrast with the target group, *met/met* individuals.

met/met= individuals homozygous for the met allele; *val/met* = individuals with a heterozygous genotype; *val/val* = individuals homozygous for the *val* allele.

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