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Biopsychosocial Influence on Exercise-induced Delayed Onset Muscle Soreness at the Shoulder: Pain Catastrophizing and Catechol-O-Methyltransferase (*COMT*) Diplotype Predict Pain Ratings

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Abstract

Objective—The experience of pain is believed to be influenced by psychological and genetic factors. A previous study suggested pain catastrophizing and catechol-O-methyltransferase (*COMT*) genotype influenced clinical pain ratings for patients seeking operative treatment of shoulder pain. This study investigated whether these same psychological and genetic factors predicted responses to induced shoulder pain.

Methods—Participants (n=63) completed self-report questionnaires and had *COMT* genotype determined before performing a standardized fatigue protocol to induce delayed onset muscle soreness. Then, shoulder pain ratings, self-report of upper-extremity disability ratings, and muscle torque production were reassessed 24, 48, and 72 hours later.

Results—This cohort consisted of 35 women and 28 men, with a mean age of 20.9 years (SD=1.7). The frequency of *COMT* diplotypes was 42 with “high *COMT* enzyme activity” (low pain sensitivity group) and 21 with “low *COMT* enzyme activity” (average pain sensitivity/high pain sensitivity group). A hierarchical regression model indicated that an interaction between pain catastrophizing and *COMT* diplotype was the strongest unique predictor of 72-hour pain ratings. The same interaction was not predictive of self-report of disability or muscle torque production at 72 hours. The pain catastrophizing × *COMT* diplotype interaction indicated that participants with high pain catastrophizing and low *COMT* enzyme activity (average pain sensitivity/high pain sensitivity group) were more likely (relative risk=3.5, *P*=0.025) to have elevated pain intensity ratings (40/100 or higher).

Discussion—These findings from an experimental model converge with those from a surgical cohort and provide additional evidence that the presence of elevated pain catastrophizing and *COMT* diplotype indicative of low *COMT* enzyme activity have the potential to increase the risk of developing chronic pain syndromes.

Keywords

biopsychosocial model; chronic pain; catastrophizing; *COMT* genotype; shoulder pain; delayed onset muscle soreness

The experience of pain varies considerably among individuals. Social, cultural, environmental, psychologic, and genetic factors are all believed to contribute to this variability. A model for the development of idiopathic pain conditions that takes into consideration these sources of variability was recently proposed.¹ In this model, it is suggested that high levels of psychologic distress and pain amplification (ie, genetic predisposition for biologic or physiologic processes) are the primary factors contributing to the development of idiopathic pain conditions.¹

Few studies to date have reported specific instances of psychologic distress and genotype influencing pain perception. That is, it has not been established if psychologic and genetic risk factors increase the probability of developing chronic pain conditions as hypothesized in the model. We previously investigated² whether psychologic factors consistent with the Fear-Avoidance Model of Musculoskeletal Pain (FAM)³ and variations in the catechol-O-methyltransferase (*COMT*) gene were predictive of pain ratings for patients seeking shoulder surgery. The FAM was selected as our psychologic model because elevated levels of pain-related fear and pain catastrophizing are hypothesized to be associated with risk of developing chronic musculoskeletal pain conditions.³ Furthermore, data supporting FAM have been reported for patients with low back,^{4,5} knee,^{6,7} cervical,^{8,9} and shoulder pain.¹⁰ The *COMT* gene was selected as our genetic risk factor because it has been identified as 1 of the 20 high priority pain candidate genes.¹¹ *COMT* is an enzyme involved in pain modulation both directly and indirectly, via effects on endogenous μ -opioid function.¹² Polymorphisms in the *COMT* gene that result in reduced *COMT* enzyme production lead to chronic overactivity of the μ -opioid system, decreasing its ability to modulate nociceptive input. Supporting this assertion are studies that have demonstrated that *COMT* gene polymorphisms have an effect on μ -opioid receptor binding potential and activation,¹³ *COMT* enzyme activity, and experimental pain sensitivity.^{14,15}

Theoretically, elevated pain-related fear and pain catastrophizing and low levels of *COMT* enzyme could interact to increase the risk of experiencing chronic pain due to a compound risk of elevated pain sensitivity from both psychologic and genetic factors. Our previous study² reported that patients with both elevated levels of pain catastrophizing and a *COMT* gene variation associated with low enzyme activity had higher preoperative and postoperative shoulder pain ratings. Patients with both psychologic and genetic risk factors were 6.8 times more likely to have elevated shoulder pain 3 months after the surgery in comparison with those without both risk factors.² These findings provided preliminary support for the validity of an interaction between psychologic and genetic factors and general support for the proposed model of idiopathic pain development.¹ However, these findings were preliminary and additional evidence of this particular interaction is warranted given the lack of replication often noted for genetic association studies.¹⁶

Therefore, the purpose of the present study was to further investigate whether pain catastrophizing and *COMT* genotype have the potential to influence pain reports. In the current study, we used an experimental model of pain by inducing delayed onset muscle soreness (DOMS) at the shoulder. An experimental model of pain was selected for this follow-up study

because it provided more control over the mechanism of injury, in comparison with the previous investigation involving clinical pain. The shoulder was selected because it matched the anatomic location of our previous study and we have prior experience inducing DOMS to the shoulder.¹⁰ Our a priori hypothesis was that participants with higher levels of pain catastrophizing and genetic predisposition to low COMT enzyme would have the highest pain and disability ratings after induction of DOMS at the shoulder. We further hypothesized that there would be no differences in muscle torque production, providing an indication that similar amounts of muscle injury were experienced on the basis of psychologic and genetic status.

MATERIALS AND METHODS

Participants

The University's institutional review board for human participants approved this study and all participants provided informed consent before participating in this study. Participants were recruited from undergraduate and graduate courses at the University and received \$75.00 compensation for their research participation. Exclusion criteria for the study were any one of the following: previous history of or currently experiencing neck or shoulder pain, sensory or motor impairment of the shoulder, regular or recent participation in high or low intensity upper-extremity weight training, and currently or regularly taking pain medication.

Self-report Measures

Key psychologic factors in the current FAM include pain-related fear and pain catastrophizing³ and participants completed the following self-report questionnaires to assess these components. We reported total scores of these questionnaires for the purposes of this study.

The Fear of Pain Questionnaire (FPQ-III) measured fear of pain. The FPQ-III is a 30-item, 5-point rating scale that measures fear about specific situations that would normally produce pain.¹⁷ The FPQ-III is a commonly used and well-validated instrument that is appropriate for use in nonclinical and clinical populations.^{17–19}

The Pain Catastrophizing Scale (PCS) measured pain catastrophizing. The PCS is a 13-item, 5-point rating scale that assesses the degree of catastrophic cognitions a patient experiences while in pain.²⁰ The PCS is commonly used in pain studies and psychometric studies suggest acceptable levels of reliability and validity for the PCS, both at the item and total scale levels.^{20,21} Factor analysis suggests a hierarchical factor structure, with 3 individual subscales of the PCS (rumination, magnification, and pessimism) contributing to an overall factor of pain catastrophizing.^{20,21}

Genetic Samples

Participant DNA was extracted from buccal swabs using the Gentra PureGene system (Minneapolis, MN). Genotyping was performed by 2 authors (B.K.S. and D.M.H.) using methods that have been previously reported in more detail.² Briefly, 2 single nucleotide polymorphisms (SNPs) in the *COMT* gene were chosen, rs4633 and rs4818, because these allow us to create the *COMT* haplotypes of interest. The selected SNPs were genotyped using polymerase chain reaction amplification of the regions containing the SNPs, followed by restriction digestion and gel electrophoresis to distinguish the alleles.² The MIT Primer3 program (frodo.wi.mit.edu/cgi-bin/primer3/primer3_www.cgi) was used to design polymerase chain reaction primers for the genotyping assays.

On the basis of previously published linkage disequilibrium and pain-related data, haplotypes and diplotypes were inferred from the resulting genotypes at the 2 loci.¹⁴ The previously

reported *COMT* haplotypes are LPS (low pain sensitivity), APS (average pain sensitivity), and HPS (high pain sensitivity). Hardy-Weinberg equilibrium was analyzed using standard χ^2 analysis for each SNP, and the resulting *P* values were not significant ($P>0.05$), suggesting that these loci were in equilibrium in the population. The genetic data were then prepared for statistical analysis by dichotomizing the participants into those with (1) high *COMT* activity and predicted to have low pain sensitivity (LPS group) and (2) low *COMT* activity and predicted to have high pain sensitivity (APS/HPS group).

Shoulder Fatigue Procedure

The specific procedure used in this study was based on previous studies that induced muscle fatigue with isokinetic equipment.^{22–25} In the present study, shoulder fatigue was induced using a Kin-Com (Chattanooga, TN) isokinetic dynamometer. Research personnel performing the fatigue protocol were blinded to psychologic and genetic profile of the participants.

One familiarity trial was run to get the participants accustomed to apparatus and the testing procedures. Participants were placed in a seated position, with shoulder straps applied to support the torso as per manufacturer's recommendations. Specifically, the shoulder was at 60 degrees abduction, 30 degrees cross flexion, and neutral rotation. The dominant shoulder was placed in the scapular plane because this position has been associated with high test-retest reliability and is believed to have decreased impingement of the greater tuberosity under the acromion.^{26,27} Maximum voluntary isometric contraction (MVIC) was determined by having the participants perform 5 repetitions of isometric shoulder external rotation. For the instructional set, participants were asked to perform the contractions with maximal effort and were given verbal encouragement during the contractions. The MVIC was calculated by averaging peak torque recorded during the middle 3 repetitions. After MVIC was calculated, participants completed eccentric/concentric external rotation repetitions to induce muscle fatigue. The first set of repetitions was completed at 100 degrees/s to familiarize the participants with the testing apparatus. Then, the speed was lowered to 60 degrees/second for 3 sets of 10 repetitions that constituted the fatigue protocol. Participants performed repetitions until their peak force was <50% of the initial MVIC, as previous research has indicated this is a consistent indicator of muscle fatigue.^{22–25} Additional sets of repetitions were added as needed if participants did not reach 50% of the initial MVIC after the third set.

This procedure mimics our previous study that successfully generated DOMS in the shoulder.¹⁰ Induction of upper-extremity DOMS has the potential to mimic clinical conditions because the duration of pain lasts for several days and results in increased pain intensity, loss of range of motion, inflammatory responses, altered proprioception, and use of self-care behaviors.^{10, 22,23,25,28–30}

Outcome Measures

All research personnel collecting outcome data were blinded to the psychologic and genetic profile of the participants. All outcome measures were collected before and 24, 48, and 72 hours after completion of the muscle fatigue protocol. The primary outcome measure was pain intensity and secondary outcome measures included evoked pressure pain, muscle torque production, and self-report of upper-extremity disability.

A visual analog scale (VAS) was used to measure pain intensity. The VAS is a valid measure of pain intensity as a prior study demonstrated its ratio scale properties.³¹ The specific VAS used for this study was a 10-cm line with the left side described by “no pain at all” and the right side described by “worst pain ever experienced.” Pain intensity was assessed in all participants before any other procedures were performed. Participants were seated comfortably

with their arm at the side and instructed to make a single pen mark through the line that indicated the amount of shoulder pain they were currently experiencing.

Evoked pressure pain was assessed with a Fischer algometer (Pain Diagnostics and Thermography Inc, Great Neck, NY). Acceptable reliability of pressure algometry for shoulder pain assessment has been previously reported.³² Research personnel used the algometer to apply 4 kg/cm² of force at a steady pace to the rotator cuff tendon insertion inferior to the acromion process. Once the pressure reached 4 kg/cm², the data collector would say “now” and the participant would make a pen slash on a VAS line indicating how much pain the pressure was causing.

MVIC was used to assess muscle torque. MVIC was determined in the same manner as previously described in the shoulder fatigue protocol section. This measure was selected because measuring torque is one of the most reliable indirect methods of measuring muscle damage associated with DOMS.³³ Descriptively, postfatigue MVIC was expressed in raw units and as a percentage of the baseline MVIC to account for individual differences related to body mass or sex.²² In regression analysis, percentage of baseline MVIC was used as the dependent variable.

The Disability of Arm, Shoulder, and Hand (DASH) Questionnaire measured self-report of upper-extremity disability. The DASH Questionnaire contains 30-items, ranging from 1 (no difficulty) to 5 (unable) and has been validated as an outcome measure.³⁴

Data Analysis

Descriptive statistics were generated for demographic, self-report, and genetic data. *COMT* genotype frequency for our sample was compared with previously reported frequencies for healthy volunteers¹⁴ and those seeking shoulder surgery² by χ^2 analysis. Two preliminary analyses were then performed using data collected 24 hours after the fatigue protocol as these parameters matched our previous study.¹⁰

The first preliminary analysis was to verify that the fatigue protocol induced DOMS. This was accomplished by using paired *t* tests to compare change scores in the primary and secondary outcome measures. The second preliminary analysis was performed to confirm that pain catastrophizing should be included in the primary analysis. Fear of pain and pain catastrophizing were entered into a simultaneous regression model with pain intensity as the dependent variable. The a priori criterion for consideration in the subsequent regression model was the psychologic variable that uniquely contributed to 24-hour pain ratings. This analysis was necessary because a previous study from George et al¹⁰ suggested fear of pain was a stronger predictor of 24-hour DOMS pain intensity, but this finding has not been replicated.

The primary analysis involved the prediction of pain intensity ratings at the final assessment (72 h after the fatigue protocol). We selected this time as our primary outcome because we were interested in predictors of continued elevated pain for this particular research question, not predictors of peak pain. Therefore, assessment was at 72 hours because it was beyond expected normal peak ratings for response to DOMS (ie, 24 to 48 h).³⁵ The primary analysis involved a hierarchical regression model with sex entered first to account for any variance in pain intensity ratings due to sex differences. Second, pain catastrophizing and *COMT* diplotype were entered. Third, the interaction between pain catastrophizing and *COMT* diplotype was entered into the regression model.

As appropriate, post-hoc analysis of the interaction involved creation of 3 risk factor groups on the basis of psychologic and genetic status. One group consisted of no psychologic or genetic risk factors, 1 group consisted of 1 psychologic or genetic risk factor, and 1 group consisted

of both psychologic and genetic risk factors. Three risk factor groups were created because our prior study suggested no differences in pain ratings for patients with 1 psychologic or genetic risk factor.² First, separate intraclass correlation coefficient (3,1) models with absolute agreement were calculated from the individual MVIC trials to report reliability of generating muscle torque across the different risk factor groups. Then, analysis of variance models were used to report differences in these risk factor groups for pain intensity. Finally, χ^2 analysis and relative risk estimate identified if having both psychologic and genetic risk factors was associated with greater frequency of 40/100 pain intensity ratings at 72 hours. This pain rating threshold was selected because it corresponds with a threshold for treatment satisfaction³⁶ and the same pain rating threshold was used in a prior study involving patients seeking surgical treatment for shoulder pain.² The rationale for this analysis was to provide a magnitude estimate for prediction of elevated pain rating that would give an indication of the relative strength of the predictors and allow for comparison across other studies. The secondary measures of evoked pain ratings, muscle torque production, and self-report of disability were invested in a similar manner using analysis of variance models. All analyses were performed with SPSS for Windows, Version 13.0 (SPSS Inc, Chicago, IL) and a type I error rate of 0.05.

RESULTS

There were no adverse events reported and descriptive statistics for this sample (n=63) are summarized in Table 1. There were no statistical differences ($P>0.05$) in *COMT* allele and haplotype frequencies for this sample, in comparison with samples of healthy volunteers¹⁴ and those seeking shoulder surgery.² *COMT* diplotypes (the combination of both of a participant's haplotypes) were used to represent the overall *COMT* genotype for each participant. For example, LPS/HPS represented someone with both LPS and HPS haplotypes. Diplotypes were then further combined into 2 groups (Table 1); those with at least 1 LPS haplotype (LPS/LPS, APS/LPS, and HPS/LPS) and inferred high *COMT* activity and those without LPS haplotype (APS/HPS, APS/APS, and HPS/HPS) and inferred low *COMT* activity. This decision was made because our sample size was not conducive to analyzing *COMT* haplotypes independently. Furthermore, previous work has indicated that having at least 1 LPS haplotype was protective of the development of temporomandibular pain¹⁴ and elevated postoperative shoulder pain.²

There were no sex differences in *COMT* diplotype frequencies, fear of pain, or pain catastrophizing scores ($P_s > 0.05$ for sex comparisons). The paired *t* tests indicated that the fatigue protocol successfully induced DOMS in our sample as the outcome measures of pain and disability were significantly increased from baseline to 24, 48, and 72 hours later (Table 2). Fear of pain and pain catastrophizing were correlated ($r=0.637$) and together explained 15% of the variance in pain intensity ratings 24 hours after the fatigue protocol with low variance inflation factor (Table 3). However, only pain catastrophizing contributed unique variance; therefore, pain catastrophizing was confirmed as the appropriate FAM-specific variable for the primary analysis.

The first step (sex) of the hierarchical regression model explained 2.0% of the variance in pain intensity ratings 72 hours after the fatigue protocol. The second step (pain catastrophizing and *COMT* diplotype main effects) explained an additional 10.0% of the variance ($P<0.041$ for the change). Pain catastrophizing ($\beta = 0.32$, $P=0.012$) was the only unique predictor at this stage of the analysis. The third step (pain catastrophizing $\times$ *COMT* diplotype) explained an additional 8.1% variance ($P=0.019$ for the change). In the final model, the pain catastrophizing $\times$ *COMT* diplotype interaction term ($\beta=0.60$, $P=0.019$) was the strongest unique contributor to induced shoulder pain intensity ratings (Table 4). This regression model was repeated with only the white participants to investigate the potential of a racial confound. There were no

substantive changes in the regression model when this was carried out. Therefore, all participants were included in the final regression model reported in Table 4.

The reliability assessment indicated no systematic differences across risk factor groups for the MVIC procedure at each assessment (Table 5). Post-hoc analysis of the interaction investigated differences in primary and secondary outcome measures from the 72-hour assessment. The PCS was dichotomized into high and low scores on the basis of a median split of the sample scores at the 70th percentile. This criterion was selected on the basis of guidelines from a disability prevention program that establish similar percentile ratings as “at risk” for patients seeking treatment of musculoskeletal pain.³⁷

Three risk factor groups were then formed for analysis purposes. One group had neither psychologic nor *COMT* diplotype risk factors (LPS and low PCS scores, $n=24$), 1 group had either psychologic or *COMT* diplotype risk factor (LPS or low PCS scores, $n=29$), and 1 group had both psychologic and *COMT* diplotype risk factors (APS/HPS and high PCS scores, $n=10$). Patients having both risk factors (mean pain intensity=33.8, $SD=24.2$) had significantly higher ratings ($P<0.05$) in comparison with those with only one (mean pain intensity=16.8, $SD=19.2$) or no risk factors (mean pain intensity=17.7, $SD=18.6$). There were no other significant differences among the groups for pain intensity ratings (Fig. 1). χ^2 analysis indicated that 11.5% of participants with 1 or fewer risk factors reported 40/100 or greater pain intensity, in comparison with 40% of participants with 2 risk factors ($P=0.025$). This corresponded to a relative risk ratio of 3.5 for having both psychologic and genetic risk factors and reporting elevated shoulder pain 72 hours after the fatigue protocol.

For the secondary outcome measures, there were differences for evoked pressure pain that followed a pattern that would be predicted by risk factor group assignment (Fig. 2). Patients having both risk factors (mean pressure pain=23.6, $SD=21.1$) had significantly higher ratings ($P=0.012$) in comparison with those with no risk factors (mean pressure pain=7.9, $SD=10.1$). Patients having both risk factors (mean pressure pain=23.6, $SD=21.1$) also had higher ratings than those with 1 risk factor (mean pressure pain=12.3, $SD=18.2$), but the comparison was not statistically significant ($P=0.060$). There were no differences in the 3 risk factors groups for muscle torque production and self-report of upper-extremity disability ($P>0.05$).

DISCUSSION

Shoulder pain is a commonly experienced and potentially disabling form of musculoskeletal pain.^{38–42} Despite this, prognostic factors for persistent shoulder pain are generally underreported in the literature.⁴³ This current study considered the role that psychologic and genetic factors play in the development of chronic shoulder pain, following a proposed model.¹ As hypothesized, our findings suggest that an interaction between pain catastrophizing and *COMT* genotype has the potential to be predictive of pain reports after induced shoulder pain. Interestingly, this finding parallels what we had previously reported for a group of participants seeking surgical treatment of shoulder pain.²

General psychologic stress has been associated with shoulder pain,^{44,45} but few investigations have supported the role of variables that are specific to FAM.⁴⁶ We previously reported that fear of pain uniquely predicted 24-hour outcomes after induced shoulder pain, but not pain catastrophizing.¹⁰ In the current study, we report that pain catastrophizing uniquely predicted 24-hour outcomes after induced shoulder pain, but not fear of pain. The same fatigue protocol was used for both studies, but we used different measures of pain catastrophizing. The first study used the Coping Strategies Questionnaire, whereas the current study used the PCS. Therefore, the discrepancy in findings could be attributed to the difference in pain catastrophizing measures and it seems the PCS could potentially be the more appropriate

measure. We suggest consideration of both pain-related fear and pain catastrophizing measures in future studies, as both are theoretically consistent with the FAM and have demonstrated their ability to predict induced shoulder pain outcomes.

The influence of *COMT* genotype for clinically relevant phenotypes has been questioned in the literature due to a null association reported in a postoperative pain model.⁴⁷ We considered *COMT* genotype in this study because of its high-priority candidate rating¹¹ and its previous influence on pain perception for healthy participants,^{13–15} and also those seeking surgical treatment for shoulder pain.² We did not detect a main effect for *COMT* genotype in the current study, however, our primary hypothesis did not involve testing main effects of *COMT* genotype. We were most interested in investigating whether an interaction between pain catastrophizing and *COMT* diplotype had the potential to influence reports of induced shoulder pain.

The observed interaction was such that higher pain ratings were observed for participants with both psychologic and genetic risk factors. Participants that endorsed cognitions consistent with pain catastrophizing and had a genetic predisposition to low *COMT* enzyme activity had significantly higher pain intensity and pressure pain ratings when compared with groups with 1 or no risk factors. Interestingly, our data did not support a protective effect of having no psychologic or genetic risk factor for elevated pain sensitivity. That is, participants with low PCS scores and high *COMT* activity did not necessarily have lower pain ratings in comparison with those with low PCS scores or high *COMT* activity. We verified these findings by investigating muscle torque. There was no difference in either reliability or percentage of baseline MVIC by psychologic and genetic risk factor group. This finding suggests each risk factor group had experienced similar effort during the fatigue procedure and similar effects on muscle performance following the fatigue protocol. This is an encouraging finding because differences in MVIC could have potentially confounded our results for measures of pain perception. We also verified these findings by ensuring that *COMT* genotype was not associated with PCS scores, and found no difference in PCS scores ($t=0.368$, $P=0.714$) in LPS versus APS/HPS groups.

Although we did detect an interaction between psychologic and genetic factors in this study, the total amount of variance explained was approximately 20%, which could suggest limited clinical utility of these findings. However, there are several additional points to consider whether an interaction between pain catastrophizing and *COMT* diplotype has potential for clinical relevance. The first point to consider is the model of pain induction used in this study. Shoulder pain induced from DOMS is not a perfect model of clinical pain conditions, but it does share more characteristics of clinical pain syndromes when compared with other methods of inducing pain that have been used in previous genetic studies.^{14,15,48,49} Increased pain intensity, loss of range of motion, inflammatory responses, altered proprioception, and the use of self-care behaviors are characteristics of clinical pain conditions and these have also been associated with upper-extremity DOMS.^{10,22,23,25,28–30} Furthermore, the symptoms of DOMS last for several days,³⁵ which is another shared characteristic with clinical pain syndromes, in contrast to other methods of inducing pain used in previous genetic studies.

The second point is that support for the clinical relevance of these findings can be found by comparing these results to those from our previous study.² Patients with high baseline PCS scores and low *COMT* enzyme activity (APS/HPS group) were 6.8 times more likely to have elevated postoperative shoulder pain ratings, in comparison with other groups.² Because replication of genetic association studies are rare,¹⁶ the current study was completed to investigate the same interaction in a more controlled setting (ie, participants experiencing induced shoulder pain through a fatigue protocol). Interestingly, pain catastrophizing and *COMT* genotype were also predictive of the development of induced shoulder pain reports.

Participants with high baseline PCS scores and low COMT activity were 3.5 times more likely to report elevated pain ratings 72 hours after performing the fatigue protocol.

Therefore, the clinical relevance of the current study is not reflected in the total amount of variance explained by the regression model, but in the replication of predictive factors across experimental and clinical pain models. Collectively, these studies suggest that the interaction of pain catastrophizing and *COMT* diplotype could play a meaningful role in the development of chronic pain syndromes as has been proposed in a recent model.¹ It is encouraging that convergent results have been demonstrated for the selected psychologic and genetic factors, especially as the studies used different samples and methodologies. However, future study in this area is required to further confirm the validity and clinical utility of these particular psychologic and genetic risk factors.

These results provide support for a biopsychosocial influence on shoulder pain, but there are also several limitations that need to be considered when interpreting these results.^{11,16} The primary limitation is our relatively small sample size for the number of participants with 2 risk factors (n=10) and for the overall sample (n=63). A small sample size was purposely used because the current study had a very specific purpose of determining whether previously reported psychologic and genetic risk factors replicated in a more controlled setting. When reviewing the sample size, it should be noted that the number of participants with 2 risk factors in the current study was comparable with the clinical sample.² Furthermore, our sample size provided enough statistical power to address our primary and secondary outcome measures. However, the sample size did limit our regression models by not being able to investigate full models. For example, even though we did not find any obvious sex differences in the psychologic and genetic factors we studied, we were not able to consider interactions with sex. Furthermore, our sample was predominantly white, which is generally considered a strength in genetic studies.¹⁶ However, the homogeneity of our sample meant we could not consider interactions with race in this analysis. Future researchers wishing to consider factors related to sex, race, and individual *COMT* haplotypes (as opposed to the grouping system we used) while attempting to replicate this interaction should recruit sample sizes of greater than 100, given the allele frequencies and the occurrence of elevated shoulder pain observed in this study.¹¹

The focus on *COMT* diplotypes was necessary in this study because we were attempting to replicate the results of a previous study. We did not measure the commonly reported *COMT* SNP involving val/met substitution at codon 158 (rs 4680) because the *COMT* haplotypes used in this study have a stronger association with enzyme activity.¹⁴ Furthermore, the val/met SNP has such strong linkage disequilibrium with the other SNPs that its genotype can be inferred extremely accurately. The direct influence *COMT* genotype has on metabolic processes has been the topic of several other studies.^{13,50,51} We did not directly measure *COMT* enzyme activity in these participants, which could be considered a limitation associated with this current study.

Another limitation of this study is that the psychologic and genetic interaction of interest was not predictive of disability ratings. This finding was contrary to our hypothesis, but 1 potential reason could be because the fatigue protocol did not induce high enough levels of upper-extremity disability for the predictive model to be valid. Support for this contention can be found from clinical studies that report higher DASH scores for those seeking treatment, in comparison with this sample.^{52,53} Therefore, it would not be appropriate to conclude that this interaction affects disability ratings of the upper extremity, as our data only indicated a relationship for reports of pain intensity. We recruited healthy participants and did not attempt to age or sex match this sample with what we would be expected from “typical” clinical pain cohorts or our previously reported surgical cohort.² Our rationale for this sampling method was that we did not hypothesize that age or sex would affect the interaction, and this hypothesis

is supported by the fact that these results were similar to our clinical cohort. However, it should be noted that this sample may not be directly comparable with most clinical pain cohorts because of the young age of the participants.

There are some limitations of the fatigue protocol and associated pain assessment that should also be considered when interpreting these results. First, we did not record perceived effort from participants during the trial or record the actual number of repetitions performed. We only monitored when participants failed to reach 50% of the baseline MVIC. Therefore, it is possible that the risk groups performed different amount of work to reach the 50% MVIC criterion. Second, we had participants rate their resting pain and evoked pressure pain to the tendon insertion, as opposed to shoulder pain during a standard activity. Future studies using a DOMS pain model should consider obtaining ratings of perceived effort, recording total amount of work performed to reach the MVIC criterion and implementing a standard shoulder activity during pain assessment.

This study investigated a specific psychologic and genetic interaction for its influence on induced shoulder pain. Given that the experience of musculoskeletal pain is likely influenced by multiple genetic and psychologic factors, this focused approach could be considered a limitation of our model as a whole. Future studies should include larger sample sizes and consider a wider range of pain candidate genes beyond *COMT*¹¹ and additional psychologic factors beyond pain catastrophizing. Future studies could also investigate this predictive model in other musculoskeletal pain conditions (ie, low back pain) because these risk factors are likely to have a broad influence on pain perception that is not specific to the shoulder.

CONCLUSIONS

Multiple factors are hypothesized to influence pain perception, and a recent model suggests psychologic and genetic factors have the potential to influence development of chronic pain syndromes.¹ This study was the first we are aware of to investigate a specific interaction between psychologic and genetic factors for their influence on exercise-induced shoulder pain. Findings from this study suggest that high pain catastrophizing and *COMT* diplotype were predictive of elevated induced shoulder pain ratings after performing a standard fatigue protocol. These results from a more controlled setting converge with our recent report suggesting that the same factors were predictive of postsurgical shoulder pain.² Collectively, these studies suggest the presence of elevated pain catastrophizing and *COMT* diplotype indicative of low *COMT* enzyme activity have the potential to increase the risk of developing chronic pain syndromes.

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FIGURE 1.

Interaction of pain catastrophizing and *COMT* diplotype on pain intensity ratings 72 hours after induced shoulder pain. APS/HPS indicates low *COMT* activity; error bars, 1 standard error; high PCS, high pain catastrophizing scores from PCS; low PCS, low pain catastrophizing scores from PCS; LPS, high *COMT* activity. APS indicates average pain sensitivity; *COMT*, catechol-O-methyltransferase; HPS, high pain sensitivity; PCS, Pain Catastrophizing Scale.

COMT Diplotype and Pain Catastrophizing Status

FIGURE 2.

Interaction of pain catastrophizing and *COMT* diplotype on evoked pressure pain ratings 72 hours after induced shoulder pain. APS/HPS indicates low *COMT* activity; error bars, 1 standard error; high PCS, high pain catastrophizing scores from PCS; low PCS, low pain catastrophizing scores from PCS; LPS, high *COMT* activity. APS indicates average pain sensitivity; *COMT*, catechol-O-methyltransferase; HPS, high pain sensitivity; PCS, Pain Catastrophizing Scale.

TABLE 1

Descriptive Statistics for Induced Shoulder Pain Cohort (n = 63)

Variable	Values	% or SD
Sex (no. females, %)	35	55.5%
Age	20.9	1.7
Hand dominance (no. right handed, %)	62	98.4%
Race		
No. white, %	60	95.2%
No. African American, %	3	4.8%
Fear of Pain Questionnaire	77.9	21.0
Pain Catastrophizing Scale	14.5	8.8
High COMT activity (LPS group)	42	66.7%
No. LPS/LPS, %	6	9.5%
No. LPS/APS, %	28	44.4%
No. HPS/LPS, %	8	12.7%
Low COMT activity (APS/HPS group)	21	33.3%
No. APS, %	12	19.0%
No. HPS/APS, %	8	12.7%
No. HPS/HPS, %	1	1.6%

All values are means and SDs, unless otherwise indicated.

APS indicates average pain sensitivity; COMT, catechol-O-methyltransferase; HPS, high pain sensitivity; LPS, low pain sensitivity.

TABLE 2

Effect of Fatigue Protocol on Primary and Secondary Outcome Measures

Variable	Prefatigue	24 Hours	48 Hours	72 Hours
Pain intensity (VAS rating)	2.1 (3.3)	27.2 (19.5) [*]	23.9 (20.1) [*]	19.9 (20.5) [*]
<i>Effect size vs. baseline</i>	<i>N/A</i>	<i>2.2</i>	<i>1.9</i>	<i>1.5</i>
Evoked pressure pain (VAS rating)	10.4 (13.0)	18.4 (17.8) [*]	16.4 (17.9) [*]	12.4 (16.6)
<i>Effect size vs. baseline</i>	<i>N/A</i>	<i>0.5</i>	<i>0.4</i>	<i>0.1</i>
Muscle torque (% of initial MVIC) [†]	100%	76%	78%	79%
(N/m)	23.7 (10.4)	18.1 (8.9) [*]	18.1 (9.7) [*]	18.9 (10.1) [*]
<i>Effect size vs. baseline</i>	<i>N/A</i>	<i>0.6</i>	<i>0.6</i>	<i>0.5</i>
Upper-extremity disability (DASH score)	3.3 (3.8)	16.5 (13.5) [*]	16.9 (14.2) [*]	13.8 (14.7) [*]
<i>Effect size vs. baseline</i>	<i>N/A</i>	<i>1.5</i>	<i>1.5</i>	<i>1.1</i>

^{*} Indicates statistically significant difference ($P < 0.01$) in comparison with baseline value.

[†] Lack of variability in baseline values limit statistical comparison and calculation of effect size.

Effect sizes (in italics) calculated by mean difference from baseline divided by pooled SD.

DASH indicates Disability of Arm, Shoulder, and Hand; MVIC, maximum voluntary isometric contraction; N/A, not available; VAS, visual analog scale.

TABLE 3
 Fear-avoidance Specific Variables Influence on Induced Shoulder Pain Intensity
 at 24 h

Overall Model				
R-square = 0.152				
Adjusted R-square = 0.123				
$F_{2,60} = 5.37$				
$P = 0.007$				
Variables	B	Standard β	<i>P</i>	VIF
Fear of pain	0.08	0.09	0.580	1.7
Pain catastrophizing	0.72	0.33	0.038	1.7

Fear of pain measured with Fear of Pain Questionnaire.

Pain catastrophizing measure with Pain Catastrophizing Scale.

Bold font indicates variable was selected for use in subsequent regression model for investigating genetic influence.

VIF indicates variance inflation factor.

TABLE 4
Evidence for Biopsychosocial Influence on Induced Shoulder Pain Intensity at 72 h

Final Model			
R-square = 0.203			
Adjusted R-square = 0.147			
$F_{4,57} = 3.63$			
$P = 0.01$			
Variables	B	Standard β	P
Sex	- 4.45	- 0.11	0.366
Pain catastrophizing	0.15	0.07	0.680
COMT diplotype	- 19.88	- 0.46	0.041
Pain catastrophizing $\times$ COMT diplotype	1.31	0.60	0.019

Individual main effects of pain catastrophizing and COMT diplotype were not considered in subsequent analyses because of significant interaction term.

Sex was coded (men = 1, women = 0).

COMT diplotype was coded (APS/HPS = 1, LPS = 0).

APS indicates average pain sensitivity; COMT, catechol-O-methyltransferase; HPS, high pain sensitivity; LPS, low pain sensitivity.

TABLE 5

Reliability of Individual MVIC Trials by Risk Factor Group Assignment

	LPS and Low PCS	LPS or Low PCS	APS/HPS and High PCS
Baseline (prefatigue)	0.965 (0.928–0.984)	0.971 (0.944–0.986)	0.988 (0.967–0.997)
Baseline (postfatigue)	0.934 (0.871–0.969)	0.945 (0.901–0.972)	0.984 (0.955–0.996)
24 h	0.950 (0.861–0.980)	0.962 (0.928–0.981)	0.971 (0.856–0.993)
48 h	0.974 (0.946–0.988)	0.955 (0.915–0.978)	0.981 (0.933–0.995)
72 h	0.968 (0.938–0.985)	0.945 (0.901–0.972)	0.987 (0.963–0.996)

All values reported are for ICC (3, 1) model with absolute agreement and 95% CI.

APS indicates average pain sensitivity; CI, confidence interval; HPS, high pain sensitivity; LPS, low pain sensitivity; MVIC, maximum voluntary isometric contraction; PCS, Pain Catastrophizing Scale.