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Evidence for a biopsychosocial influence on shoulder pain: Pain catastrophizing and catechol-*O*-methyltransferase (COMT) diplotype predict clinical pain ratings

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Abstract

The experience of pain is believed to be influenced by social, cultural, environmental, psychological, and genetic factors. Despite this assertion, few studies have included clinically relevant pain phenotypes when investigating interactions among these variables. This study investigated whether psychological variables specific to fear-avoidance models and catechol-*O*-methyltransferase (COMT) genotype influenced pain ratings for a cohort of patients receiving operative treatment of shoulder pain. Patients ($n = 58$) completed questionnaires and had COMT genotype determined pre-operatively. Then, shoulder pain ratings were collected 3–5 months post-operatively. This cohort consisted of 24 females and 34 males, with mean age of 50.3 (SD = 15.0) and pre-operative pain rating of 4.5/10 (SD = 1.8). The frequency of COMT diplotypes was 34 with “high COMT activity” (LPS group) and 24 with “low COMT activity” (APS/HPS group). Preliminary analysis indicated that of all the fear-avoidance variables considered (fear of pain, kinesiophobia, pain catastrophizing, and anxiety), only pain catastrophizing was a unique contributor to clinical pain ratings. A hierarchical regression model indicated that an interaction between pain catastrophizing and COMT diplotype contributed additional variance in pre-operative pain ratings. The pain catastrophizing $\times$ COMT diplotype interaction demonstrated predictive validity as patients with high pain catastrophizing and low COMT activity (APS/HPS group) were more likely (RR = 6.8, 95% CI = 2.8–16.7) to have post-operative pain ratings of 4.0/10 or higher. Our findings suggest that an interaction between pain catastrophizing and COMT diplotype has the potential to influence pain ratings in patients seeking operative treatment of their shoulder pain.

Keywords

Biopsychosocial model; Catechol-*O*-methyltransferase (COMT); Pain catastrophizing; Diplotypes; Single nucleotide polymorphism; Chronic pain; Prognosis; Shoulder surgery

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1. Introduction

The experience of musculoskeletal pain varies considerably among individuals. Social, cultural, environmental, psychological, and genetic factors are all believed to contribute to this variability. Shoulder pain represents a commonly occurring musculoskeletal disorder, with 1 year prevalence estimates ranging from 5% to 47% (van der Heijden, 1999; Kuijpers et al., 2004) and point prevalence estimates ranging from 14% to 21% (Urwin et al., 1998; Picavet and Schouten, 2003). Outcomes from new shoulder pain episodes vary, with 30–50% of individuals reporting limitations in activities of daily living (Croft et al., 1996) and only 60% of individuals reporting full recovery in 1 year (van der Windt et al., 1996). Early and accurate identification of poor outcome from shoulder pain is currently not possible because valid prognostic factors have not been reported in the literature (Kuijpers et al., 2004).

The influence of psychological factors on pain perception and the development of chronic musculoskeletal pain has been previously reported (Linton, 2000; Pincus et al., 2002). Recently, studies of musculoskeletal pain have focused on fear-avoidance models, with data supporting the validity of these models for patients with low back (Fritz et al., 2001; Staerkle et al., 2004), knee (Granot and Ferber, 2005; Kvist et al., 2005), and cervical pain (George et al., 2001; Nederhand et al., 2004). Fear-avoidance models have ambiguous support for patients with shoulder pain. One study involving induced muscle pain offered support for the model (George et al., 2007), while other studies involving general practice patients reported weak associations of fear-avoidance specific variables and shoulder outcomes (Kuijpers et al., 2006; van der Windt et al., 2007).

Recent studies have suggested that genetic factors also influence pain perception. Candidate pain genes have been identified and one gene with a high priority score is the catechol-*O*-methyltransferase (COMT) gene, in which polymorphisms affect COMT enzyme activity (Belfer et al., 2004). COMT is an enzyme with wide-ranging biological functions and as a result could potentially be involved in a number of pathophysiological processes (Zhu, 2002). One of its functions is metabolizing catecholamines involved in pain modulation both directly and indirectly, via effects on endogenous μ -opioid function. It has been suggested that polymorphisms resulting in reduced COMT enzyme production lead to chronic over-activity of the μ -opioid system, decreasing its ability to modulate nociceptive input. This assertion was confirmed in healthy volunteers as μ -opioid receptor binding potential and activation were predictably associated with a COMT gene single nucleotide polymorphism (SNP) at codon 158 (Zubieta et al., 2003) and experimental pain sensitivity was associated with COMT haplotypes (Diatchenko et al., 2005, 2006). In contrast, other studies have found no association with COMT genotype and pain sensitivity in healthy volunteers (Kim et al., 2004) or weak associations in a post-surgical pain model (Kim et al., 2006).

Despite the assertion that pain perception and the subsequent development of chronic pain conditions are influenced by multiple variables, few studies have included clinically relevant pain phenotypes when investigating specific interactions involving these variables. Therefore, our purpose was to investigate whether psychological variables specific to fear-avoidance models and COMT genotype influence clinical pain ratings for a cohort of patients receiving operative treatment of shoulder pain. Our *a priori* hypothesis was that a statistical interaction would exist, such that patients with higher levels of psychological distress and a COMT genetic predisposition to heightened pain sensitivity would have the highest clinical pain ratings.

2. Methods

2.1. Subjects

This study was a prospective cohort of consecutive patients seeking treatment of shoulder disorders at the University of Florida's Orthopaedics Sports Medicine Institute (OSMI) in Gainesville, FL. Subjects were recruited for 15 consecutive months with the goal of recruiting a cohort of patients with discrete shoulder pain that was primarily managed with arthroscopic surgery.

The following were the inclusion criteria for this study: (a) between 18 and 85 years of age, (b) complaints of pain limited to anterior, lateral, or posterior shoulder, (c) documented or suspected rotator cuff tendinopathy (evidence from clinical examination or imaging studies) including small (<1 cm), medium (1–3 cm), and large (3–5 cm) tears, (d) documented or suspected adhesive capsulitis (evidence from clinical examination or imaging studies), (e) documented or suspected SLAP lesion (evidence from clinical examination or imaging studies), and (f) scheduled for arthroscopic procedure.

The following were the exclusion criteria for this study: (a) current complaints of pain lasting greater than the past 3 months involving neck, elbow, hand, low back, hip, knee, or ankle, (b) massive or complete rotator cuff tear (>5 cm), (c) documented shoulder OA or RA, (d) prior shoulder surgery within the past year or currently complaining of pain from prior shoulder surgery, (e) current shoulder fracture, tumor, or infection, (f) previously diagnosed chronic pain disorder (including, but not limited to IBS, fibromyalgia, TMD, CLBP, etc.), (g) current psychiatric management, and (h) current gastrointestinal or renal illness.

Three of the authors (T.W.W., M.W.M., and W.H.G.) evaluated patients for study eligibility during routine clinical visits to the OSMI. As appropriate, patients provided informed consent for study participation following guidelines set forth by the University of Florida's Institutional Review Board for Human Subjects. Patients had arthroscopic shoulder surgery performed by two of the authors who were board-certified orthopaedic surgeons (T.W.W. and M.W.M.). Post-operative management was under the supervision of these authors, with standard recommendations for pain management, rehabilitation, and return to activity.

The general post-operative regimen for pain included the use of inter-scalene regional anesthetics immediately and narcotic medication in decreasing quantities until patients were 6 weeks post-operative. After 6 weeks patients' pain was controlled with non-narcotic pain medication. Rehabilitation started immediately post-operatively with use of pain relieving modalities and passive range of motion of the shoulder joint. This part of rehabilitation lasted for 2–6 weeks depending on the pathology and was advanced to an active range of motion program for an additional 6 weeks. After that period, a strengthening program was initiated with release to full activities occurring at 3–4.5 months depending on the procedure performed and the patient's prior activity level. Compliance to post-operative management recommendations was not measured as part of this study.

2.2. Measures

Patients completed demographic information, self-report questionnaires, and genetic samples pre-operatively (range: 1–4 days before surgery date). The post-operative assessment included clinical shoulder pain ratings (range: 3–5 months following the date of surgery). All measures were collected by two of the authors (S.Z.G. and W.H.G.), or by research assistants under their direct supervision.

2.2.1. Demographic information—Sex, age, sex, self-report of race, medication status, work-status, marital status, and involved upper extremity were collected from each patient.

2.2.2. Self-report questionnaires—We investigated several fear-avoidance specific psychological variables (fear of pain, kinesiophobia, pain catastrophizing, and anxiety) because of their relevance in other musculoskeletal conditions and their hypothesized influence on shoulder pain (Kuijpers et al., 2004). These psychological factors were assessed with previously validated self-report questionnaires commonly used in pain research. Fear of pain was assessed with the Fear of Pain Questionnaire (FPQ-III) (McNeil and Rainwater, 1998; Osman et al., 2002; Albaret et al., 2004), kinesiophobia was assessed with the shortened version of the Tampa Scale of Kinesiophobia (TSK-11) (Goubert et al., 2004; Roelofs et al., 2004; Woby et al., 2005), pain catastrophizing was assessed with the Pain Catastrophizing Scale (PCS) (Sullivan et al., 1995; Van Damme et al., 2002; D'Eon et al., 2004). Trait anxiety was assessed with the State-Trait Anxiety Index (STAI) (Spielberger et al., 1983). All questionnaires were reported as total scores for the purposes of this study.

Clinical shoulder pain ratings were assessed with the Brief Pain Inventory (BPI), which includes a numerical rating scale (NRS) for pain intensity (Cleeland and Ryan, 1994; Cleeland et al., 1996; Tan et al., 2004). Subjects used the BPI to rate their shoulder pain intensity over three conditions, the present pain intensity, the worst pain intensity over the past 24 h, and the best pain intensity over the past 24 h. These three ratings were summed and divided by three (arithmetic mean) because that methodology was most consistent with the purposes of this study (Jensen et al., 1996, 1999).

2.2.3. Genetic samples—Subject DNA was extracted from buccal swabs using the Gentra PureGene system (Minneapolis, MN). The focus of the genetic analysis was on the COMT gene because it is a commonly investigated pain candidate gene, with recent studies suggesting a meaningful influence on human pain perception (Zubieta et al., 2003; Diatchenko et al., 2005, 2006). Furthermore, its role in modulating nociceptive input was theoretically complementary to the psychological factors we were studying.

Genotyping was performed by two authors (B.K.S. and D.M.H.) as follows. Two SNPs in the COMT gene were chosen, rs4633 and rs4818, because they allowed us to create the COMT haplotypes of interest. The selected SNPs were genotyped using PCR amplification of the regions containing the SNPs, followed by restriction digestion and gel electrophoresis to distinguish the alleles. The MIT Primer3 program (frodo.wi.mit.edu/cgi-bin/primer3/primer3_www.cgi) was used to design PCR primers for the genotyping assays.

For rs4633, the PCR primers were COMTrs4633 5': 5'-TATCGGCTGGAACGAGTTCAT and COMTrs4633-3': 5'-CTTCTGCTCGCAGTAGGTGTC. Standard PCR conditions were used, with annealing temperature of 61 °C. The 341 bp PCR product was digested with restriction enzyme BsaAI (New England Biolabs), yielding two fragments of sizes 79 and 82 bp for the C allele. For rs4818, the PCR primers were COMTrs4818-5': 5'-CAACCCTGCACAGGCAAGAT and COMTrs4818-3': 5'-GCCCTTTTCCAGGTCTGACA. Standard PCR conditions were used, with an annealing temperature of 61 °C. The 296 bp PCR product was digested with BclI, yielding two fragments of sizes 116 and 145 bp for the G allele. These products were resolved by electrophoresis on ethidium-bromide-stained 8% native polyacrylamide gels.

Based on previously published linkage disequilibrium and pain-related data (Diatchenko et al., 2005), haplotypes and diplotypes were inferred from the resulting genotypes at the two loci. 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 chi-square analysis for each SNP in this group, 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 subjects 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). This decision was made because our sample size was not conducive to analyzing all COMT haplotypes independently and previous work has indicated that high COMT activity (LPS group) was protective of the development of a clinical pain syndrome, temporomandibular pain (Diatchenko et al., 2005).

2.2.4. Data analysis—Descriptive statistics were generated for demographic, self-report, and genetic data. Differences in pre-operative clinical pain reports by pain medication status were investigated by independent *t*-test. COMT genotype frequency for our clinical sample was compared to previously reported frequencies for healthy volunteers (Diatchenko et al., 2005) by chi-square analysis. Fear of pain, kinesiophobia, pain catastrophizing, and anxiety were entered into a simultaneous regression model with pre-operative clinical pain rating as the dependent variable. The *a priori* criterion for consideration in the subsequent regression model was any fear-avoidance variable that uniquely contributed to pre-operative clinical pain ratings.

The primary analysis involved a multivariate, hierarchical regression model to predict pre-operative clinical pain ratings. Sex and age were first entered into the model to account for any variance in pain ratings attributed to these factors. Second, the appropriate psychological and COMT diplotype were entered. Last, the interaction between the psychological variable(s) and COMT diplotype was entered into the regression model. Post-hoc analysis of statistically significant interactions was investigated by ANOVA models, as appropriate.

The validity of the psychological $\times$ COMT interaction term for predicting post-operative clinical pain ratings was then investigated using a 2×2 ANOVA. Relative risk rates were calculated for identifying patients that reported greater than 4.0/10 post-operative pain ratings, based on having the psychology $\times$ COMT interaction compared to not having it. A 4.0/10 pain rating cut-off was selected based on our previous clinical experiences with this particular population and data suggesting that this pain intensity rating exceeds a patient determined threshold for what constitutes “successful” treatment (Robinson et al., 2005).

Descriptive statistics and general linear model analyses were performed with SPSS for Windows, Version 13.0 (SPSS Inc., Chicago, IL). Relative risk estimates were generated with Confidence Interval Analysis 2.0.0 (Trevor Bryant, University of Southampton). All analyses were performed with a type I error rate of 0.05.

3. Results

Over the 15 month recruitment period, 59 eligible patients gave informed consent for study participation. One patient was removed from the analysis due to having an extremely rare COMT genotype that was not conducive to categorization in the previously described COMT haplotypes (Diatchenko et al., 2005, 2006). Descriptive statistics for the remaining cohort ($n = 58$) is summarized in Table 1. The distribution of pre-operative testing was 4 days for 30/58 (51.7%), 3 days for 1/58 (1.7%), 2 days for 14/58 (24.2%), and 1 day for 13/58 subjects (22.4%). There were no statistical differences in psychological questionnaires or pre-operative pain intensity ratings based on day of testing ($p > 0.05$). There were no statistical differences ($p > 0.05$) in preoperative clinical pain ratings for patients taking pain medication for their shoulder. Also, there were no statistical differences ($p > 0.05$) in COMT frequencies for this sample, in comparison to a previously reported sample (Diatchenko et al., 2005). Only pain catastrophizing made a unique contribution to pre-operative clinical pain ratings (Table 2). Therefore, pain catastrophizing was used in the subsequent regression analysis.

The first step (age and sex) of the hierarchical regression model explained 13.5% of the variance in pre-operative clinical pain ratings. The second step (pain catastrophizing and COMT diplotype main effects) explained an additional 32.9% of the variance ($p < 0.001$ for the change). Pain catastrophizing (beta = 0.53, $p < 0.001$) and COMT diplotype (beta = 0.26, $p = 0.032$) factors were both unique predictors at this stage. The third step (pain catastrophizing $\times$ COMT diplotype) explained an additional 4.6% variance ($p = 0.033$ for the change). In the final model, sex (beta = -0.25, $p = 0.026$), pain catastrophizing (beta = 0.35, $p = 0.008$), and the pain catastrophizing $\times$ COMT diplotype interaction term (beta = 0.41, $p = 0.033$) were the only unique contributors to pre-operative clinical pain ratings. This regression model was repeated on only the Caucasian patients ($n = 51$), to investigate the potential of an ethnic confound for our sample. There were no substantive changes in the regression model (data not reported) when this was done. All subjects ($n = 58$) were included in the final regression model for pre-operative clinical pain ratings in Table 3.

Post-hoc analysis of the interaction was performed by a 2×2 ANOVA to report on the magnitude of differences in pre-operative pain ratings by the pain catastrophizing $\times$ COMT diplotype interaction (Fig. 1a). For the post-hoc analyses, the PCS was dichotomized into high and low scores (70th percentile) based on guidelines from a disability prevention program (Sullivan et al., 2006). Patients having high PCS scores and low COMT activity (APS/HPS group) had significantly higher pre-operative pain ratings ($n = 8$, mean = 6.7, SD = 0.95) in comparison to the high PCS and high COMT activity (LPS group) pain ratings ($n = 10$, mean = 4.6, SD = 1.4), the low PCS and low COMT activity (APS/HPS group) pain ratings ($n = 16$, mean = 4.0, SD = 1.4), or the low PCS and high COMT activity (LPS group) pain ratings ($n = 24$, mean = 3.9, SD = 1.7). There were no other significant differences among these groups.

Forty-seven out of 58 (81.0%) subjects were re-evaluated for clinical pain ratings during the follow-up period. The distribution of post-operative assessment was 3 months for 20/47 (42.5%), 4 months for 14/47 (29.8%), and 5 months for 14/58 (27.7%). There was no statistical difference in post-operative pain intensity ratings based on month of testing ($p > 0.05$). Subjects that completed the study did not differ ($p > 0.05$) from those lost to follow-up on age, sex, pre-operative clinical pain ratings, or COMT diplotype. Average clinical pain intensity decreased from mean pre-operative rating of 4.4/10 to mean post-operative rating of 2.6/10 ($p < 0.001$). The previously described pain catastrophizing $\times$ COMT diplotype interaction was a significant predictor of post-operative pain ratings (Fig. 1b). As with the pre-operative interaction, subject with high PCS scores and low COMT activity (APS/HPS group) had significantly higher post-operative pain ratings ($n = 6$, mean = 5.1, SD = 2.2), in comparison to the high PCS and high COMT activity (LPS group) pain ratings ($n = 8$, mean = 2.5, SD = 1.9), the low PCS and low COMT activity (APS/HPS group) pain ratings ($n = 13$, mean = 2.2, SD = 1.6), or the low PCS and high COMT activity (LPS group) pain ratings ($n = 20$, mean = 2.1, SD = 2.0). There were no other significant differences among these groups. The relative risk of rating post-operative shoulder pain of greater than 4.0 was 6.8 (95% 2.8–16.7) for those patients having high pre-operative PCS scores and low COMT activity (APS/HPS group), in comparison to all other groups.

4. Discussion

Prognostic factors for shoulder pain are generally under-reported in the literature (Kuijpers et al., 2004). This current study considered the role that psychological and genetic factors play in the development of chronic post-operative shoulder pain. General psychological stress has been previously associated with shoulder pain (Badcock et al., 2002; Kuijpers et al., 2006), but few investigations to date have considered specific psychological models. We selected a fear-avoidance model because of its relevance in other musculoskeletal pain conditions, and our data suggest that pain catastrophizing was a unique contributor to clinical shoulder pain ratings

for this cohort. Pain catastrophizing is considered a maladaptive cognitive coping style comprised of magnification, rumination, and helplessness components (Sullivan et al., 2001). Pain catastrophizing's influence on pain perception and clinical outcomes has been well documented for other clinical samples (Keefe et al., 1989, 2000; Sullivan et al., 1998, 2002; Picavet et al., 2002), but not for patients with shoulder pain seeking treatment from a general practitioner (van der Windt et al., 2007). Therefore, it can be considered a somewhat novel finding that pain catastrophizing had a positive association with pain intensity in this cohort of patients seeking operative treatment of their shoulder pain. We selected the COMT gene because of its high priority candidate rating (Belfer et al., 2004) and its previous influence on pain perception for healthy subjects (Zubieta et al., 2003; Diatchenko et al., 2005, 2006). The influence of COMT genotype for clinically relevant phenotypes has been questioned in the literature (Kim et al., 2006), but our data suggested that COMT diplotype had an influence on pain ratings, at least when determined by LPS and APS/HPS groups.

Our primary hypothesis did not involve testing main effects, however. We were most interested in investigating the potential of an interaction between these pain-related psychological and genetic factors. Biopsychosocial models have been proposed for musculoskeletal pain, yet few have investigated the extent to which specific genetic and psychological factors may interact to influence pain perception. Our findings provided preliminary support for a biopsychosocial model involving catastrophizing and COMT diplotypes. The observed interaction is partially what would be expected from a combination of these factors. One would predict higher pain ratings among patients that frequently endorse cognitions consistent with pain catastrophizing (i.e. those with high PCS scores) and have a decreased ability to modulate pain through endogenous pain inhibitory systems (i.e. those with low COMT activity).

Indeed, patients with high PCS scores and low COMT activity (APS/HPS group) had significantly higher pre- and post-operative clinical shoulder pain ratings when compared to the other three groups. Interestingly, our data did not support the presence of the other part of this interaction. That is, patients with low PCS scores and high COMT activity (LPS group) did not have lower pain ratings in comparison to the high PCS scores and high COMT activity (LPS group) or the low PCS and low COMT activity (APS/HPS group) pain ratings. Therefore, it appears that having both "protective" factors (low PCS scores and/or high COMT activity) did not favorably alter the probability of reporting lower post-operative shoulder pain ratings. We verified this finding by ensuring that COMT genotype was not associated with PCS scores, and found no difference in PCS scores ($t = 0.211$, $p = 0.834$) in LPS vs. APS/HPS groups.

The interaction between pain catastrophizing and COMT diplotype seems to have potential for clinical relevance when the probability of having persistent pain following shoulder surgery is considered. At the post-operative assessment, patients with high baseline PCS scores and low COMT activity (APS/HPS group) were 6.8 times more likely to have pain ratings of 4.0/10 or greater, in comparison to other groups. This information could potentially add to clinical decision making by improving the accuracy of prognosis for outcomes following arthroscopic shoulder surgery. This information would appear to be especially relevant if pain relief was a primary reason for the patient seeking operative treatment of his/her shoulder.

These results provide promising support for this biopsychosocial model, but there are also several limitations that need to be considered when interpreting these results (Belfer et al., 2004; Max, 2004). The primary limitation is our relatively small sample size. We had enough statistical power to address our primary outcome measure of clinical pain ratings, but the small sample size limited our regression models by not being able to investigate full models. For example, we were not able to consider additional interactions with sex or age, and could not consider individual COMT haplotypes in our analysis. Future studies attempting to replicate

this interaction should consider sample sizes of greater than 100, given the allele frequencies and the occurrence of persistent shoulder pain observed in this study (Belfer et al., 2004).

Another limitation of this study was that this was an ethnically diverse sample, which is not ideal for genetic association studies (Max, 2004). The regression analysis was similar whether we included only Caucasian patients or the entire sample, so we included all patient data in this manuscript. With a larger and more diverse sample, future studies could consider separate models for different ethnicities or include ethnicity as a variable in regression models to account for potential confounding due to ethnic differences in COMT polymorphisms and/or expression of pain (Max, 2004). We focused only on the COMT gene because of its previously mentioned associations with experimental pain sensitivity and development of facial pain. This could be considered a limitation as other high priority pain candidate genes have been identified (Belfer et al., 2004) and pain perception is likely to be influenced by variations in multiple genes.

In this study, we used haplotypes because they are directly related to COMT enzyme activity and are genetically more informative than individual SNPs. We did not measure the commonly reported COMT SNP involving val/met substitution at codon 158 (rs4680) because it has such strong linkage disequilibrium with the other SNPs that its genotype can be inferred extremely accurately. Since recent work suggests differing influence on experimental pain sensitivity for the COMT val/met substitution at codon 158 and the diplotypes included in this study (Diatchenko et al., 2006), future study will include this SNP to detect any rare recombinant haplotypes for independent analysis of the val/met SNP.

Another limitation is that although patients followed a standard post-operative management plan, we did not systematically track the post-operative course for each patient. Therefore, there could have been variation with regard to compliance of pain management and rehabilitation following arthroscopic surgery. These untracked factors could have potentially contributed to the prediction of clinical pain ratings in this study. Finally, the direct influence COMT genotype has on metabolic processes has been the topic of several other studies (Zubieta et al., 2003; Nackley et al., 2006a, b). We did not directly measure COMT enzyme activity in these subjects, which could be considered a limitation associated with this current study.

This study is one of the first we are aware of that investigated a specific psychological and genetic interaction for its influence on operative shoulder pain. Since replication of gene association studies is rare (Max, 2004), future study is necessary to validate this interaction in a larger cohort of patients. Future study in larger sample sizes should consider a wider range of pain candidate genes, beyond COMT. Methodology in future studies should include standard pain stimuli to determine if this model is applicable to experimental pain sensitivity, as well as clinical pain reports. This predictive model could also be investigated in other pain conditions because its factors (pain catastrophizing and COMT genotype) are likely to have a broad influence on pain perception that would not be specific to the anatomical region of the shoulder. It is a viable hypothesis that pain catastrophizing and COMT genotype may influence pain perception in other musculoskeletal pain conditions receiving operative care. Another viable hypothesis is that other psychological factors could interact with different pain candidate genes to influence pain perception in musculoskeletal pain conditions.

In summary, multiple factors are hypothesized to influence pain perception, but few studies have considered specific models in clinically relevant phenotypes. Our results suggest that high pain catastrophizing and a low COMT activity were associated with higher pre-operative pain ratings, and an increased chance of experiencing persistent pain following arthroscopic shoulder surgery. Currently, psychological factors, like pain catastrophizing, are utilized for risk screening in some settings (Sullivan et al., 2006). With the human genome completed, clinical settings will soon have routine access to patient genotypes associated with pain

perception. If predictive models involving psychological and genetic factors are validated, screening for development of chronic pain may be enhanced, resulting in early application of preventative treatment strategies.

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Fig. 1.

(a) Interaction of pain catastrophizing and COMT diplotype: pre-operative shoulder pain ratings. (b) Interaction of pain catastrophizing and COMT diplotype: post-operative shoulder pain ratings. Figure key: Error bars, two standard error; LPS, high COMT activity; APS/HPS, low COMT activity; low PCS, low pain catastrophizing scores from Pain Catastrophizing Scale; high PCS, high pain catastrophizing scores from Pain Catastrophizing Scale.

Table 1Descriptive statistics for operative shoulder pain cohort (*n* = 58)

Variable	Values	% or SD
Sex (# females, %)	24	41.4%
Age	50.3	15.0
Race		
(# Caucasian, %)	51	89.5
(# African American, %)	4	7.0
(# Not specified, %)	2	3.5
Taking pain medication for shoulder (# yes, %)	24	41.4%
Work related shoulder injury ^a (# yes, %)	8	13.8%
Marital status ^a (# married, %)	31	63.3%
Involved upper extremity (# right, %)	37	63.8%
Fear of pain questionnaire	71.0	21.4
Tampa scale of kinesiophobia ^b	25.1	6.4
Pain catastrophizing scale	13.6	9.6
State-Trait Anxiety Inventory	36.8	11.7
Average pre-operative pain rating (0–10 NRS)	4.5	1.8
Low COMT activity (LPS group)	34	58.6%
(#LPS/LPS, %)	11	19.0%
(#LPS/APS, %)	19	32.8%
(#HPS/LPS, %)	4	6.8%
High COMT activity (APS/HPS group)	24	41.4%
(#APS, %)	19	32.8%
(#HPS/APS, %)	5	8.6%
Completed post-operative follow-up (#, %)	47	81.0%
Average post-operative pain rating (0–10 NRS)	2.6	2.1

All values are means and standard deviations, unless otherwise indicated.

^aNine subjects did not respond to this category.

^bEleven-item version of the TSK was used in this study.

Table 2

Fear-avoidance specific variables, influence on shoulder pain

<i>Overall model</i>			
R-Square = 0.276			
Adjusted R-Square = 0.221			
$F_{4,53} = 5.05$			
$p = 0.002$			
Variables	<i>B</i>	Std. beta	<i>p</i> -value
Fear of pain	0.01	0.08	0.584
Kinesiophobia	−0.04	−0.15	0.329
Pain catastrophizing	0.10	0.53	0.001
Anxiety	0.01	0.07	0.646

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

Table 3

Evidence for biopsychosocial influence on pre-operative clinical pain ratings

<i>Final model</i>			
R-Square = 0.510			
Adjusted R-Square = 0.462			
$F_{5,51} = 10.62$			
$p < 0.001$			
Variables	B	Std. Beta	<i>p</i> -value
Age	0.02	0.21	0.053
Sex	−0.86	−0.25	0.026
Pain catastrophizing	0.06	0.35	0.008
COMT diplotype	−0.23	−0.07	0.712
Pain catastrophizing × COMT diplotype	0.08	0.41	0.033

Bold font indicates variable was statistically significant predictor in final model.

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

Sex was coded (males = 1, females = 0).

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