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INVESTIGATING THE INTERACTION BETWEEN SELF-REPORTED MEASURES OF PAIN AND COMT AND BDNF POLYMORPHISMS IN THE SETTING OF CHRONIC LOW BACK PAIN

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BACKGROUND

Low back pain is the leading cause of disability worldwide and is the second most common reason for health care visits. Chronic low back pain (CLBP) is defined by the NIH Task Force on Research Standards for Chronic Low Back Pain as pain occurring for at least 3 to 6 months and for over half the days in the past 6 months.(1)

Catechol-o-methyltransferase (COMT) and brain-derived neurotrophic factor (BDNF) are neurotrophic factors, with COMT functioning in catecholamine degradation and BDNF up-regulating excitatory signaling via ascending pathways.(2) Single nucleotide polymorphisms (SNPs) of COMT and BDNF have been shown to affect pain outcomes. Literature demonstrates that the variants with the greatest influence over pain are the COMT Val158Met (rs4860) and BDNF Val66Met (rs6265) polymorphisms.(3, 4)

Studies on COMT and BDNF SNPs have shown that their relationships to pain outcomes may not be linear due to potential interactions with cognitive responses to pain, such as pain catastrophizing and pain self-efficacy.(4-6) In addition, pain catastrophizing and low pain self-efficacy have been shown to independently contribute to the onset and maintenance of pain intensity. The concepts of pain catastrophizing and pain self-efficacy may be measured using validated research instruments, such as the Pain Catastrophizing Scale (PCS) and the Pain Self Efficacy Questionnaire (PSEQ).(7-8)

Literature has shown that COMT and BDNF SNPs and pain catastrophizing and pain self-efficacy may predict pain outcomes through some interaction of their independent effects.(9,10) A study by George and colleagues established an interaction between COMT variant Val158Met and pain catastrophizing as a strong predictor of shoulder pain.(11) Furthermore, BDNF Val66Met polymorphisms were associated with decreased and altered cognitive function in pain settings, such as females with menstrual pain, indicating a relationship with cognitive-affective assessments of pain.(12-14) This study will investigate how psychological aspects of pain, including pain catastrophizing and pain self-efficacy, may mediate the effects of COMT and BDNF variants on pain intensity as measured with a numerical rating scale (NRS) using a mediation model of analysis (Figure 1).

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METHODS

This cross-sectional study included 423 subjects with CLBP within the Pain Registry for Epidemiological, Clinical, and Interventional Studies and Innovation (PRECISION) at the University of North Texas Health Science Center.(15) During the initial visit, subjects provided biological samples for analysis and completed psychological measures of pain, including the PCS and PSEQ. DNA was extracted from saliva using Omega HDQ extraction Chemistry and quantified using the Qubit BR DNA Quantification Kit. rs4680 and rs6265 were mined from the genome-wide data, and SNPs were verified for quality based on internal controls and clustering efficiency.

Descriptive statistics were used to summarize subject characteristics. One-way analysis of variance was then performed using rs4680 and rs6265 genotypes (GG, AG, AA) as independent variables and the PCS, PSEQ, and NRS scores as dependent variables. Fisher's LSD post-hoc test was used to further assess any results that demonstrated statistical significance ($p<.05$). Subsequently, multiple mediation models were used to determine if pain catastrophizing or pain self-efficacy mediated the effects of either COMT rs4680 or BDNF rs6265 on pain intensity. These mediation analyses were performed using the PROCESS V3.2 macro and 5,000 bootstrap samples. All analyses were performed with the SPSS Statistical Software package.

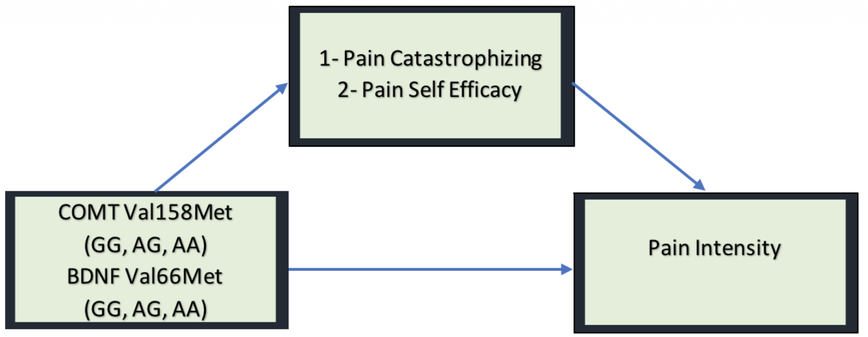

Figure 1 Mediation Model for Pain Intensity

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Results

The sociodemographic characteristics of subjects are presented in Table 1. Overall, the mean pain intensity was 6.06 (SD, 1.98). Mean levels of pain catastrophizing and pain self-efficacy were 18.57 (SD, 14.16) and 34.76 (SD, 15.25), respectively.

Table 1 Cohort Sociodemographic Characteristics Overall

Demographic variable	Total subjects N=423
Age, mean (SD) years	53 ±10.6
Sex, N (%)	
Male	137 (32%)
Female	286 (68%)
Race, N (%)	
Hispanic, N (%)	57 (13.4%)
Black or African American	122 (29%)
Native American Indian/Alaskan/Hawaiian or other Pacific Islander	7 (1.7%)
Asian	5 (1%)
Caucasian	286 (67.6%)
Native Pacific Islander	3 (0.7%)
Education, N (%)	
High school diploma or below	111 (26%)
Some college/Post HS	178 (42%)
Bachelor or Master's Degree	122 (29%)
Doc or Prof degree	12 (3%)

Subjects with the COMT rs4680 AA genotype reported significantly greater pain intensity (mean, 6.36; 95% CI, 5.97-6.74) than patients with the AG genotype (5.79; 95% CI, 5.51-6.06) (p=0.03). However, there was no significant difference in pain intensity across the BDNF rs6265 genotypes (p=0.40) (Figure 2).

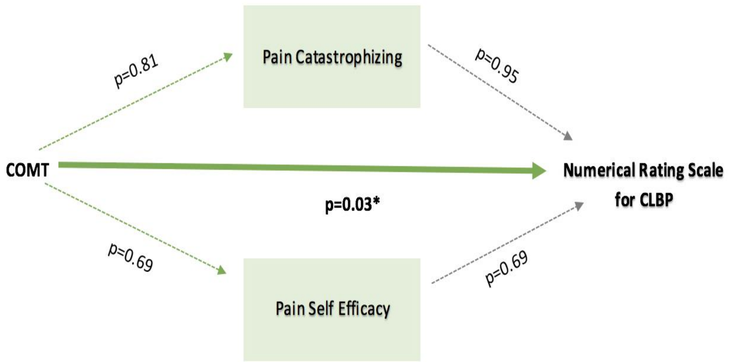

Figure 3 Mediating Effects of COMT, Pain Catastrophizing, and Pain Self-Efficacy. Green boxes indicate mediating variables, pain catastrophizing and pain self-efficacy. The dotted green lines (if indicated) are nonsignificant (p>.05). Bold lines (if indicated) are significant (p<.05)

Pain catastrophizing (p=0.81) and pain self-efficacy (0.69) did not vary significantly across COMT rs4680 genotypes. Similarly, pain catastrophizing (p=0.67) and pain self-efficacy (0.85) did not vary significantly across BDNF rs6265 genotypes. Mediation analysis indicated that neither pain catastrophizing nor pain self-efficacy were significant mediators of the effect of COMT rs4680 (Figure 3) or BDNF rs6265 (Figure 4) on pain intensity.

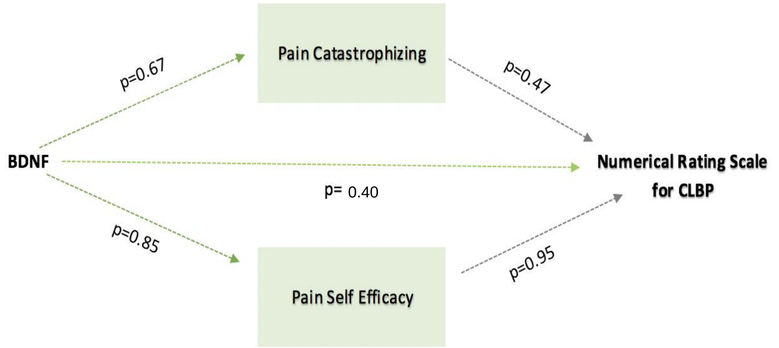

Figure 4 Mediating Effects of BDNF, Pain Catastrophizing, and Pain Self-Efficacy. Green boxes indicate mediating variables, pain catastrophizing and pain self-efficacy. The dotted green lines (if indicated) are nonsignificant (p>.05). Bold lines (if indicated) are significant (p<.05)

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DISCUSSION

Results indicate that pain intensity in rs4680 AG heterozygotes is statistically lower than in AA homozygotes, the Met/Met genotype. Despite literature, there was not a strong association between the rs4680 (COMT) and PCS, nor was a mediating effect of pain catastrophizing observed. Furthermore, rs4680 genotypes did not show an association with pain self-efficacy.

Our results support the null hypothesis that is no relationship between BDNF SNPs and cognitive measures relating to pain and pain intensity. A possible explanation may be that in the setting of chronic low back pain, the interaction between cognitive functions and SNPs may not be pronounced compared to conditions such as dysmenorrhea or shoulder pain.[11,12]

Another possible explanation for our results is that the race, gender and ethnic population distribution in previous literature that supported the hypothesis of a mediation effect did not match the representation of the subjects in our study, who came from the Dallas Fort Worth area and were mostly of female Caucasian background (Table 1). Regardless, the AA genotype of rs4680 (COMT) could be a significant predictor of pain intensity in the setting of CLBP.

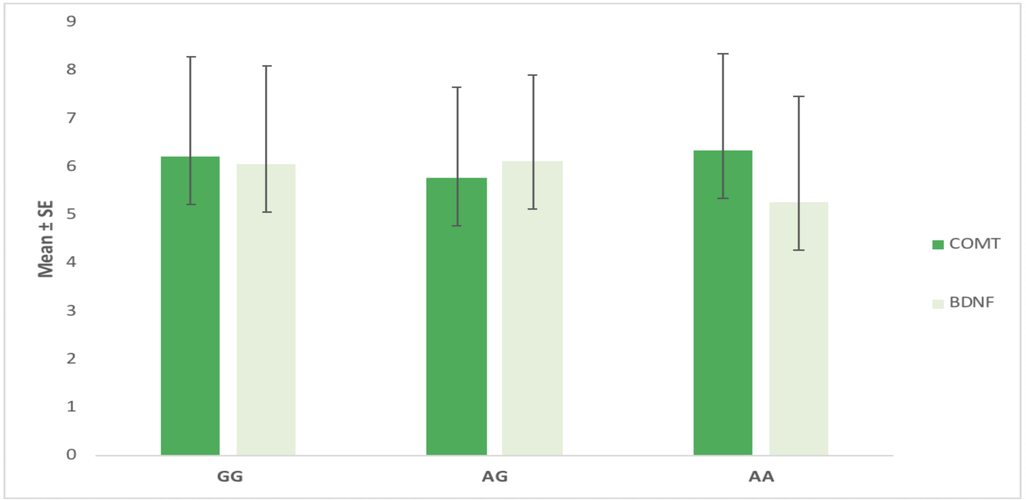

Figure 2 Mean expression of COMT and BDNF genotypes with standard deviation. COMT genotypes are denoted in dark green boxes. BDNF genotypes are denoted by light green boxes.

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