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Sex moderates the effects of positive and negative affect on clinical pain in patients with knee osteoarthritis☆

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HIGHLIGHTS

- In adults with knee osteoarthritis, sex moderates relationship of pain and affect.
- Men reported higher stable positive affect and lower central sensitization to pain.
- Women showed no relationship between stable positive affect and pain.
- Men showed stronger relationship between stable negative affect and pain.
- Men may be more sensitive to sex-specific effects of affect on pain.

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ABSTRACT

Background and aims: Sex differences in clinical pain severity and response to experimental pain are commonly reported, with women generally showing greater vulnerability. Affect, including state (a single rating) and stable (average daily ratings over two weeks) positive affect and negative affect has also been found to impact pain sensitivity and severity, and research suggests that affect may modulate pain differentially as a function of sex. The current study aimed to examine sex as a moderator of the relationships between affect and pain-related outcomes among participants with knee osteoarthritis (KOA).
Methods: One hundred and seventy-nine participants (59 men) with KOA completed electronic diaries assessing clinical pain, positive affect, and negative affect. A subset of participants ($n = 120$) underwent quantitative sensory testing, from which a single index of central sensitization to pain was derived. We used multiple regression models to test for the interactive effects of sex and affect (positive versus negative and stable versus state) on pain-related outcomes. We used mixed effects models to test for the moderating effects of sex on the relationships between state affect and pain over time.
Results: Sex differences in affect and pain were identified, with men reporting significantly higher stable positive affect and lower central sensitization to pain indexed by quantitative sensory testing, as well as marginally lower KOA-specific clinical pain compared to women. Moreover, there was an interaction between stable positive affect and sex on KOA-specific clinical pain and average daily non-specific pain ratings. Post hoc analyses revealed that men showed trends towards an inverse relationship between stable positive affect and pain outcomes, while women showed no relationship between positive affect and pain. There was also a significant interaction between sex and stable negative affect and sex on KOA-specific pain such that men showed a significantly stronger positive relationship between stable negative affect and KOA-specific pain than women. Sex did not interact with state affect on pain outcomes.
Conclusions: Findings suggest that men may be particularly sensitive to the effects of stable positive affect and negative affect on clinical pain. Future work with larger samples is needed in order to identify potential mechanisms driving the sex-specific effects of affect on pain.
Implications: The current study provides novel data that suggesting that the association of positive affect, negative affect, and pain are different in men versus women with KOA. Further understanding of the difference in affective expression between men and women may lead to the development of novel therapeutic interventions and help to identify additional modifiable factors in the prevention and management of pain.

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1. Introduction

Research suggests that women are more vulnerable to pain than men [1,2]. Women with chronic pain report more severe pain [3–5] and disability [3,5–8], and greater sensitivity to laboratory pain [9,1,10,11]. Women have an increased risk of chronic pain disorders, including osteoarthritis [3,12–15]. However, other studies have evidenced increased clinical pain severity among men [16], or shown no sex differences in laboratory pain sensitivity [17] nor clinical pain severity [18,19]. These inconsistencies suggest other factors, including psychological factors, may influence pain differentially across sexes.

One promising and modifiable factor is affective experience, including positive and negative affect. Research indicates that positive and negative affects are psychometrically distinct [6,20–22] and independently impact pain outcomes. Negative affect is associated with enhanced pain and disability [21,23–26]. Positive affect improves resilience in managing chronic pain [27,28]. Furthermore, positive affect may mitigate the detrimental effects of negative affect on pain [20,29–31]. The temporal stability of affect (stable vs. state) may also influence the experience of pain [17]. Stable (i.e., trait-like) measures of affect reflect mood over time versus state measures, which reflect transient changes. Both stable and state positive affects are associated with reduced pain [20]. Our lab has demonstrated that stable negative affect is a better predictor of clinical compared with stable positive affect; however, state positive affect is a better predictor of knee-specific and experimental pain than state negative affect [32]. Thus elucidating distinguishable roles of both affective valence and stability is warranted in pain research [33].

Further evidence suggests that sex differences in affective expression [34] may contribute to sex discrepancies in the pain experience. Women have an increased risk of depressive and anxiety disorders [35–37], which augment negative affect in pain [3,24]. Women may be more emotionally expressive [38], however, men react more to positive stimuli [39]. Rhudy and Williams [24] suggest that women may be more vulnerable to the pain-enhancing effects of negative affect [19,40,41]; while men may be protected by pain-reducing effects of positive affect [42]. However, this model [24] was based largely on healthy participants. In osteoarthritis, positive affect may serve as a resilience factor in women [30]; however, men were not included as a comparison group. While studies of individuals with osteoarthritis show sex differences in the experience of pain [43,44], how affect may modulate clinical pain as a function of sex in individuals with osteoarthritis remains unclear.

This study is a secondary analysis on a subset of individuals with knee osteoarthritis (KOA) and extends previous findings from our group [32]. The primary aim of this study was to investigate the relationships between positive and negative affect and pain-related outcomes (i.e., daily clinical pain, KOA-specific pain, pain catastrophizing, and central sensitization) as a function of sex in adults with KOA. We evaluated the effects of positive and negative affect in two separate ways: state (i.e., affect ratings collected at a single time point) vs. stable (i.e., average affect ratings over a two week period). We hypothesize that men with KOA will show stronger inverse relationships between both state and stable positive affect and pain, while women will show stronger positive relationship between both state and stable negative affect and pain.

2. Materials and methods

2.1. Participants

One hundred and seventy-nine participants (59 men) were recruited as a part of a larger study designed to evaluate the role of sleep on pain modulation in older adults with and without KOA [45]. In order to qualify for inclusion in the study, participants had to meet the American College of Rheumatology criteria for KOA as diagnosed by a board-certified rheumatologist, needed radiographic evidence of KOA with a Kellgren-Lawrence grade $\geq$1 for at least one knee, and report typical pain ratings of $\geq$2 out of 10 at least 4 days per week for 6 months or more before entering the study. Participants were excluded if they had serious comorbid medical conditions that would affect sleep or pain, or were diagnosed with severe or unstable psychiatric illness, cognitive impairments/dementia, or current substance use disorders (or a positive urine toxicology screen). Participants agreed to discontinue any analgesic and sedative medications for 24 h prior to laboratory pain testing. Due to the larger sleep-related aims of the project, we over-sampled for patients reporting insomnia and conducted at-home polysomnographic (PSG) studies on all participants to test for sleep apnea. The majority of the sample (n = 143; 79.9%) met diagnostic criteria for insomnia disorder. Results from the at-home PSG studies also revealed a broad range of sleep apnea severity (Apnea-Hypopnea Index (AHI) range = 0–46.75; Mean AHI = 8.82; SD = 9.53; 17.9% of participants had AHI > 15). Please see past publications stemming from this data set [32,45] for more details on sample selection. The study was approved by the Johns Hopkins School of Medicine Institutional Review Board.

2.2. Procedures

After obtaining informed consent, participants completed questionnaires, the Structured Interview for Sleep Disorders (SIS-D [46]), and bilateral knee X-rays to confirm study eligibility. They were trained to complete daily measures of pain and affect using a personal digital assistant (Palm Pilot). Participants were instructed to complete diaries in the evening before bed every day for two weeks. Diaries were completed for 1992 (85.8%) of 2322 possible days. We compared those who completed <15% of diary entries with those who completed >15% and did not see differences in terms of baseline pain measures. Participants returned after two weeks for a second baseline visit, during which they returned the Palm Pilot and completed quantitative sensory testing (QST) measures of pain. A subset of participants provided baseline laboratory ratings of positive affect and negative affect immediately prior to QST (n = 120). These baseline laboratory studies were added later as a part of an ancillary study of inflammatory response to pain, and will be presented in the current study as measures of state affect (referred to as "lab affect" hereafter in order to differentiate these ratings from the individual daily ratings of state affect collected from daily Palm Pilot diaries) in analyses that include QST assessments as the outcome variable. In summary, the analyses examining state ("lab") positive affect and negative affect assessed immediately prior to QST included only this subsample of 120 people, while all other analyses included the larger sample of 179. Participants in this subsample did not differ from the full participant sample in terms of age, race, sex, or clinical pain.

2.3. Measures

2.3.1. Insomnia symptom measure

2.3.1.1. Insomnia Severity Index (ISI; [47]). The ISI is a 7-item self-report questionnaire used to measure insomnia symptom severity based on DSM-IV criteria. ISI scores were examined as a potential covariate in the current study.

2.3.2. Positive affect and negative affect

2.3.2.1. Daily diary measures of positive and negative affect. Before going to bed each night, patients completed several affect ratings reflecting how they felt on average over the course of the day