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Emotional modulation of pain and spinal nociception in fibromyalgia

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ABSTRACT

Fibromyalgia (FM) is characterized by widespread pain, as well as affective disturbance (eg, depression). Given that emotional processes are known to modulate pain, a disruption of emotion and emotional modulation of pain and nociception may contribute to FM. The present study used a well-validated affective picture-viewing paradigm to study emotional processing and emotional modulation of pain and spinal nociception. Participants were 18 individuals with FM, 18 individuals with rheumatoid arthritis (RA), and 19 healthy pain-free controls (HC). Mutilation, neutral, and erotic pictures were presented in 4 blocks; 2 blocks assessed only physiological-emotional reactions (ie, pleasure/arousal ratings, corrugator electromyography, startle modulation, skin conductance) in the absence of pain, and 2 blocks assessed emotional reactivity and emotional modulation of pain and the nociceptive flexion reflex (NFR, a physiological measure of spinal nociception) evoked by suprathreshold electric stimulations over the sural nerve. In general, mutilation pictures elicited displeasure, corrugator activity, subjective arousal, and sympathetic activation, whereas erotic pictures elicited pleasure, subjective arousal, and sympathetic activation. However, FM was associated with deficits in appetitive activation (eg, reduced pleasure/arousal to erotica). Moreover, emotional modulation of pain was observed in HC and RA, but not FM, even though all 3 groups evidenced modulation of NFR. Additionally, NFR thresholds were not lower in the FM group, indicating a lack of spinal sensitization. Together, these results suggest that FM is associated with a disruption of supraspinal processes associated with positive affect and emotional modulation of pain, but not brain-to-spinal cord circuitry that modulates spinal nociceptive processes.

1. Introduction

Fibromyalgia (FM) is characterized by widespread pain and hyperalgesia, which is believed to be a result of abnormal central nervous system processing of nociception [32,41,55,77]. For example, in experimental pain studies, noxious stimuli elicit greater pain in FM than healthy pain-free controls (HC) [6,35,42,51,71,74], and imaging studies have found that FM patients have greater cortical and subcortical activation during noxious stimulation than HC [15,28]. Further, 2 studies have shown that lower stimulus intensities evoke the nociceptive flexion reflex (NFR; a spinally mediated reflex activated by Aδ fiber activation that is used as an index of spinal nociception) in FM than HC [4,19].

It is still unclear what drives central sensitization, but animal studies suggest that it can be promoted by descending modulation from supraspinal structures (eg, amygdala, periaqueductal gray [PAG], rostral ventromedial medulla) [26,49,54,57,79]. Consistent with this, several investigations have noted a relationship between abnormalities in descending modulation and clinical pain syndromes, including FM [36,41,76].

One supraspinal process that modulates pain is emotion [44,56,66,70,82]. Moreover, emotions also modulate the NFR [60,67–69], such that positive emotions inhibit pain/NFR, and negative emotions enhance pain/NFR. Because the NFR is a spinal reflex, these observations provide evidence that brain-to-spinal cord circuitry is engaged by emotional processes – a circuit likely to involve the amygdala, insula, PAG, and rostral ventromedial medulla [2,49,70]. Given how reliably emotion modulates pain and NFR in HC [45,60,67–70], emotion-induction procedures can be used to study the emotion-pain relationship, but also the integrity of modulatory mechanisms. Due to the fact that FM patients are prone to affective disturbance (eg, anxiety, depression) and maladaptive cognitive-emotional coping, emotional processes may play a particularly important role in promoting pain in this group [3,14,27,72,75].

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The present study used a well-validated picture-viewing paradigm to study emotional modulation of pain and NFR in FM [60,67–69]. Rheumatoid arthritis (RA) patients were included to control for history of chronic pain that could otherwise explain differences between FM and HC. Group differences in emotional processing of pictures were also studied in the absence of pain testing. Specifically, indices of emotional valence (ie, pleasure/valence ratings, corrugator electromyogram [EMG], startle) and arousal (ie, arousal ratings, skin conductance) were measured to comprehensively assess physiological-emotional reactivity to pictures [17,39,53]. The inclusion of startle was important because it is: 1) a nonvoluntary reflex (like NFR); 2) inhibited by positive emotions and enhanced by negative emotions (like pain/NFR); and 3) modulated by a descending circuit that includes the amygdala and PAG (like pain/NFR) [37,39].

It was predicted that, compared to RA and HC, FM will be associated with disrupted emotional processing [5,87] and disrupted emotional modulation of pain and NFR. An ancillary goal was to replicate prior observations that NFR threshold is lower in FM, suggesting tonic spinal sensitization.

2. Materials and methods

2.1. General overview of procedures

This study used affective picture-viewing to evoke emotional reactions in FM, RA, and HC participants (Fig. 1). Pictures were split up into 4 Blocks, with 2 Blocks assessing emotional processing in the absence of pain (which included the presentation of loud, abrupt noises to elicit startle) and 2 Blocks assessing emotional modulation of pain and NFR. The first Block always assessed emotional processing in the absence of pain (prior to any exposure to painful shocks), because the startle reflex can become sensitized by shock exposure [29]. Emotional reactions to pictures were assessed from startle eyeblink modulation (ie, magnitude of orbicularis oculi EMG), corrugator EMG (ie, frowning muscle), skin conductance (measure of sympathetic activation), and subjective ratings of valence (pleasure) and arousal. Ratings of the noises were made following each abrupt noise (ie, startle probe) to keep procedures the same, given that pain ratings were made during pain/NFR Blocks. Next, NFR threshold was assessed in order to determine the electric stimulation intensity to use during pain/NFR Blocks (ie, stimulation intensity = 120% NFR threshold) and to assess group differences in spinal sensitization. The next 3 Blocks alternated between modulation of pain/NFR, startle, and then pain/NFR. Corrugator EMG, skin conductance, valence ratings, and arousal ratings were also collected during emotional modulation of pain/NFR Blocks to assess reactivity to pictures in the presence of pain. All procedures were approved by the ethics review board at The University of Tulsa.

2.2. Participants

Participants were recruited from the community using fliers, radio/newspaper advertisements, and e-mail announcements. Patients were also recruited from outpatient clinics, rheumatologist referrals, and FM/arthritis support groups. Mailed advertisements also targeted rheumatologists in the local area. Participants were excluded for: age <18 years; history of cardiac disorders, circulatory problems, or uncontrolled diabetes; body mass index of 35 or above (due to potential difficulties obtaining an NFR in individuals with high adiposity); use of antidepressant, anxiolytic, or high blood pressure medications (except as noted below); and/or recent psychological trauma. HCs were also excluded for any history of chronic pain or neurological/neuromuscular disorders. FM participants were excluded if they had symptoms of a chronic pain condition unrelated to FM, including arthritis, sciatica, or injury (eg, motor vehicle accident). RA patients were excluded for chronic pain conditions other than RA. FM and RA patients were required to have a formal diagnosis by a physician to be considered for the study, which was verified by medical chart review. Further, FM participants were examined by laboratory personnel (trained by a rheumatologist) and were included only if they met the 1990 American College of Rheumatology criteria of 11 out of 18 tender-points (assessed by digital algometer) and widespread pain for over 3 months [85]. Participants were asked to abstain from narcotic analgesics for 2 weeks prior to the experiment and non-narcotic analgesics (eg, nonsteroidal antiinflammatory drugs, acetaminophen) for 24 hours prior to the experiment. Low-dose muscle relaxants and tricyclic antidepressants for the treatment of sleep problems were permitted [73]. Ultimately, recruitment of FM and RA patients who were not on any medications (eg, analgesics, antidepressants, antihypertensives) proved difficult; thus, a few participants (4 FM, 4 RA) were allowed to participate as long as they were stabilized on their medications for at least 4 weeks and had not taken break-through or as-needed pain medications before the testing session (24 hours for over-the-counter medications, 2 weeks for narcotic meds). Analyses were conducted with and without these individuals to determine whether medications confounded the results. Participants who completed the study received a $100 honorarium.

Effect-size estimates for nociceptive outcomes based on our prior research were large and the range was f = .43-.56. A power analysis with 2 within-subject degrees of freedom (3 picture contents), 2 between-group degrees of freedom (3 groups), $\alpha = .05$, power = .80, and the lowest effect size (f = .43) suggested 19 per group. For the present study, a total of 55 participants were recruited (HC = 19 [15 females], RA = 18 [15 females], FM = 18 [16 females]). Participant characteristics by group are presented in Table 1. All participants provided verbal and written informed consent. All participants were informed that they could withdraw from the study at any time.

2.3. Apparatus, stimulus parameters, and physiological signals

Stimulus presentation, self-report ratings, and physiological data collection were controlled by a PC with dual monitor capacity, A/D board (PCI-6036E; National Instruments, Austin, TX, USA), and LabVIEW software (National Instruments). One computer monitor was used by the experimenter to monitor physiological signals, and a second monitor was used by the participant to complete electronic questionnaires and to make ratings of electric stimuli. Testing was completed in a sound-attenuated and electrically shielded testing chamber. Participants were monitored from an adjacent control room via a video camera connected to a flat panel television. Participants wore sound-attenuating headphones (TDH-49, Telephonics, Farmingdale, NY, USA) that allowed them to hear the experimenter's instructions and they could speak to the experimenter via the microphone on the video camera. The headphones were also used to present startle probe stimuli.

Acoustic startle noise bursts to assess startle were delivered by a Coulbourn Instruments audio signal generator (Part number A12-33, Whitehall, PA, USA) and amplified by a 250 W amplifier (MPA-250A, Radio Shack, Fort Worth, TX, USA) to 105 dB. Startle probes had a near-instantaneous rise time and were 50 ms in duration. Electric stimuli to assess pain/NFR were generated by a Digitimer stimulator (DS5; Hertfordshire, England) and delivered using a bipolar surface-stimulating electrode (Nicolet, Madison, WI, USA; 30-mm interelectrode distance) attached to the left leg over the retromalleolar pathway of the sural nerve. A computer controlled

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