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# Emotional modulation of pain and spinal nociception in persons with major depressive disorder (MDD)

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## Abstract

Major depressive disorder (MDD) is associated with risk for chronic pain, but the mechanisms contributing to the MDD and pain relationship are unclear. To examine whether disrupted emotional modulation of pain might contribute, this study assessed emotional processing and emotional modulation of pain in healthy controls and unmedicated persons with MDD (14 MDD, 14 controls). Emotionally-charged pictures (erotica, neutral, mutilation) were presented in four blocks. Two blocks assessed physiological-emotional reactions (pleasure/arousal ratings, corrugator EMG, startle modulation, skin conductance) in the absence of pain and two blocks assessed emotional modulation of pain and the nociceptive flexion reflex (NFR, a physiological measure of spinal nociception) evoked by suprathreshold electric stimulations. Results indicated pictures generally evoked the intended emotional responses; erotic pictures elicited pleasure, subjective arousal, and smaller startle magnitudes, whereas mutilation pictures elicited displeasure, corrugator EMG activation, and subjective/physiological arousal. However, emotional processing was partially disrupted in MDD as evidenced by a blunted pleasure response to erotica and a failure to modulate startle according to a valence linear trend. Furthermore, emotional modulation of pain was observed in controls, but not MDD, even though there were no group differences in NFR threshold or emotional modulation of NFR. Together, these results suggest supraspinal processes associated with emotion processing and emotional modulation of pain may be disrupted in MDD, but brain-to-spinal cord processes that modulate spinal nociception are intact. Thus, emotional modulation of pain deficits may be a phenotypic marker for future pain risk in MDD.

### Keywords

major depressive disorder; pain modulation; RIII reflex; affective processing; psychophysiology; supraspinal processing

## 1.0 Introduction

Major depressive disorder (MDD) is associated with increased risk for chronic pain[3,17,45]. Given that supraspinal regions involved with emotional processing are interconnected with those involved with pain and pain modulation[59,77,86], one factor that



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might increase pain risk in MDD is a disruption of these supraspinal processes and thus emotional modulation of pain.

In healthy participants, pain and nociception (like startle) are emotionally modulated according to a linear trend that covaries with picture valence[62,69,71,73]. Specifically, pain outcomes evoked during pleasant, neutral, and unpleasant pictures show the following pattern: pleasant<neutral<unpleasant (but like startle[11,13,22,23] comparisons with neutral are not always significant[eg, 68,71,72]). We originally hypothesized that "healthy" emotional modulation would involve augmented pleasure-induced pain inhibition and attenuated displeasure-induced pain facilitation[70]. However, this was revised after we observed that persons with fibromyalgia[FM; 63] and insomnia (a chronic pain risk factor) [21] failed to show the valence linear trend (ie, pleasant=neutral=unpleasant). We now believe it is adaptive to be able to down- *and* up-regulate pain according to a linear trend in order to respond flexibly to the environment[84]. Sometimes it is helpful to dampen pain (eg, during consummation, procreation), whereas other times it is helpful to enhance pain (eg, improving pain detection, promoting recuperation)[9,29,44,84]. Interestingly, the FM and insomnia groups both showed the valence linear trend modulation of the nociceptive flexion reflex (NFR, a measure of spinal nociception), suggesting that the disruption occurs at the supraspinal level where pain is perceived rather than the spinal level. Thus, a failure to show the linear valence modulation of pain may be a phenotype for pain risk.

At least four lines of evidence suggest emotional modulation of pain should be disrupted in MDD: 1) affective disturbance is an essential feature of MDD[2] and is often present in chronic pain[3,45], 2) MDD is associated with abnormalities in the emotion-pain circuitry (eg, anterior cingulate cortex, amygdala, insula)[25,36,79], 3) emotional responsivity to affective stimuli is disrupted in MDD[16], including a failure to show a linear valence modulation of startle[1,22,23], and 4) pain-free individuals with MDD have abnormal responses to experimental pain[5-7,24,78]. Thus, when taken together, problems with the emotion-pain circuitry (and emotional modulation of pain) may confer pain risk in MDD.

To our knowledge, only one study has examined emotional modulation of pain in MDD[80]. That study found that sad mood enhanced pain similarly in MDD and controls. However, the MDD patients were medicated which might have reversed any disruption of emotional modulation. Furthermore, it is unclear whether pain was modulated according to a valence linear trend because pleasant mood was not also induced.

The present study examined whether emotional modulation of pain/NFR is disrupted in unmedicated participants with MDD (Goal 1). Given findings from FM and insomnia, we predicted unmedicated MDD participants would have disrupted pain modulation, but it was unclear whether NFR modulation would also be disrupted. Two ancillary goals were also addressed: 1) whether NFR threshold (a measure of spinal nociceptive sensitivity[76]) differs in MDD, and 2) whether abnormalities in emotional reactivity in MDD could be replicated[1,16,22,23].

## 2.0 Materials and Methods

### 2.1 Brief Overview of Procedures

This study presented emotionally-charged pictures to examine emotional processing and emotional modulation of pain/NFR in unmedicated MDD and healthy controls (HC). Pictures were divided into 4 Blocks, with 2 Blocks assessing emotional processing and startle modulation in the absence of pain and 2 Blocks assessing emotional modulation of pain and NFR. Block 1 always assessed emotional processing and startle modulation (without painful stimuli), because the startle reflex may be influenced by shock

exposure[37]. Emotional reactions to pictures were assessed from several physiological-emotional measures of valence/pleasure (valence ratings, corrugator EMG, startle modulation) and arousal (arousal ratings, skin conductance response [SCR]). Furthermore, ratings of the startle-evoking noises were made to keep procedures the same between emotion processing Blocks and pain/NFR modulation Blocks (given that pain ratings were made during pain/NFR Blocks). 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 nociceptive sensitivity. Blocks 2, 3, and 4 were pain/NFR, emotion processing, and pain/NFR, respectively.

### 2.2 Participants

Healthy participants with and without MDD were recruited from the local community using fliers, radio/newspaper advertisements, and email announcements. A brief phone screening was conducted with all potential participants to establish whether they met inclusion criteria; however, a more thorough evaluation was conducted at the beginning of the experimental session. Participants were excluded for factors that might confound pain testing including: history of cardiovascular or neurological disorders; Raynaud's disease; hypertension; uncontrolled diabetes; kidney disorders; current or history of chronic pain; having more than mild pain unrelated to a chronic pain condition (ie, pain ≥20 out of 100 on visual analog scale); current use of narcotic (last 2 weeks) and non-narcotic (last 24 hours) analgesics, antidepressants (last 3 weeks, or fluoxetine in last 8 weeks), or anxiolytics (24 hours); recent psychological trauma; current Axis I pathology other than MDD as defined by the DSM-IV-TR[2] (with the exception that participants in the MDD group were allowed to have a current anxiety disorder given the high degree of comorbidity between these disorders); body mass index (BMI) of 35 or greater (because high adiposity makes it difficult to record EMG for NFR); and age below 18 years. Current MDD was assessed from the Structured Clinical Interview for the DSM IV[28] by trained clinical psychology graduate students. Fourteen participants met current MDD and 14 participants who were free of current or past psychopathology served as controls. Of the 14 participants with MDD, 4 indicated they had too many depressive episodes to accurately recall. The mean number of episodes for the remaining 10 participants was $M$=2.6 ($SD$=1.96; 4 reported it was their first episode). Only 2 MDD participants had a current anxiety diagnosis (1 posttraumatic stress disorder [PTSD], 1 panic with agoraphobia) and conclusions were the same if these individuals were excluded. No other current Axis I diagnoses were met in the MDD group, but 7 met criteria for past substance dependence, 4 for past alcohol dependence, 3 for past anxiety not otherwise specified, 2 for past PTSD, 3 for past panic disorder with agoraphobia, and 2 for past dysthymia. Three MDD participants reported current mild pain (ratings of 3, 12, and 14 out of 100) unrelated to a chronic pain condition. See Table 1 for demographic data by group. Participants were provided a detailed description of the study and gave informed consent prior to any data collection. In addition, participants were told both verbally and in writing that they could withdraw from participating in the study at any time. Participants were provided a $100 honorarium upon completion of the experiment.

### 2.3 Apparatus, Electrode Application, and Signal Acquisition

LabVIEW software (National Instruments, Austin, TX) and a computer with a dual monitor capacity and A/D board (PCI-6036E; National Instruments) controlled all stimuli, questionnaire presentation, and physiological data collection. An experimenter monitored physiological signals and experimental progression in an adjacent control room and the participant was observed via a flat panel television that was connected to a video camera in the experimental room. The participant used the second computer monitor to complete electronic questionnaires, make pain ratings, and view pictures. The experimental room was electrically-shielded and sound-attenuated. The participant wore sound attenuating

headphones (TDH-49, Telephonics, Farmingdale, New York) which allowed the experimenter to communicate with the participant, and the participant was able to communicate with the experimenter using a microphone that was connected to the video camera. The headphones were also used to present startle probe stimuli (ie, white noise bursts).

Acoustic startle noise bursts to assess the startle response were delivered by a Coulbourn Instruments audio signal generator (Part number A12-33, Whitehall, PA) and amplified by a 250 W amplifier (MPA-250A, Radio Shack, Fort Worth, TX) to 105 dBA. Startle probes were 50 ms in duration with near instantaneous rise time. A Digitimer stimulator (DS5; Hertfordshire, England) and bipolar stimulating electrode (Nicolet, 019-401400, Madison, WI) were used to deliver noxious electrocutaneous stimulations to the left ankle over the retromalleolar pathway of the sural nerve. Electric stimuli were used to evoke pain and NFR. A computer controlled the timing and intensity of the electric stimulations, and the maximum stimulation intensity was set at 50 mA to ensure safety. Each electric stimulus was a train of five 1 ms square wave pulses delivered at 250 Hz.

All physiological signals were sampled at 1000 Hz and amplified/filtered using a Grass Technologies (West Warwick, RI) Model 15LT amplifier with AC (15A54) and DC (15A12) modules. Skin conductance response (SCR) was measured using an adaptor (Grass, Model SCA1) for the 15A12 amplifier and electrodes filled with isotonic paste (EC33, Grass Instruments). Resting blood pressure was recorded using a Critikon Dinamap PRO 100 Monitor (Tampa, FL) four times at 3-min intervals before experimental testing began. A mechanical physical scale with attached height rod (Detecto, Webb City, MO) was used to assess weight and height in order to calculate BMI.

To apply all surface electromyography (EMG) and stimulating electrodes, the skin was first cleaned with alcohol and exfoliated using Nuprep gel (Weaver and Company, Aurora, CO) until impedances below 5kΩ were achieved (≤2kΩ for stimulating electrode). All recording electrodes were Ag-AgCl electrodes. Conductive gel (EC60; Grass Technologies) was placed in the center of the electrode and the electrode was applied to the skin using self-adhesive collars. NFR was assessed by attaching two electrodes over the biceps femoris muscle of the left leg 10 cm superior to the popliteal fossa, with a ground electrode placed over the lateral epicondyle of the left femur. The raw biceps femoris signal was amplified (x10,000), bandpass filtered (10 Hz - 300 Hz) online, and rectified. Corrugator EMG was measured by two miniature Ag/AgCl electrodes filled with conductive gel (EC60, Grass Technologies) attached over the left corrugator supercilii muscle. Corrugator EMG was amplified (x20,000), bandpass filtered (30 Hz - 1000 Hz) online, and rectified. Startle eyeblink magnitude was measured by two miniature Ag/AgCl electrodes filled with conductive gel (EC60, Grass Technologies) attached over the left orbicularis oculi muscle. Orbicularis oculi EMG was amplified (x20,000), bandpass filtered (10 Hz -1000 Hz) online, and rectified. Two electrodes filled with isotonic paste (EC33, Grass Technologies) were attached to the volar surface of the index and middle fingers of the non-dominant hand of each participant to measure SCR.

### 2.4 Questionnaires

**2.4.1 Background variables—**A custom-built questionnaire designed to obtain demographic information and health problems was administered. Questions regarding health problems asked specifically about exclusionary criteria (eg, chronic pain, medication use).

**2.4.2 Structured Clinical Interview for DSM-IV Axis I Disorders, Non-Patient Version (SCID-I/NP)—**This structured interview was designed to diagnose current and lifetime psychiatric diagnoses as defined by the DSM-IV-TR[2] and is considered the “gold

standard" of diagnostic instruments. The SCID-I/NP is for use in studies in which the subjects are not identified as psychiatric patients (eg, community). The SCID-I/NP contains modules to assess mood episodes, psychotic disorders, mood disorders, substance use disorders, anxiety disorders, somatoform disorders, eating disorders, and adjustment disorder[28]. This instrument was used to diagnose MDD and to exclude for other current Axis I psychopathology. It was also used to exclude for current or lifetime Axis I psychopathology in HC participants.

**2.4.3 Health Survey - Short Form (SF-36)—**The general health scale from the Short-Form Health Survey (SF-36) was used to measure quality of life. This is a 5-item reliable (Cronbach's = .78) and valid scale that ranges from 0 to 100 and measures the person's general perception of their health[52,85]. Higher scores reflect the belief that one's health is excellent.

**2.4.4 Center for Epidemiological Studies Depression Scale (CES-D)—**Severity of depressive symptoms was assessed using the CES-D[58]. The CES-D is a 20-item self-report questionnaire that asked participants to indicate how often they have felt or behaved in a certain way in the past week, ranging from 0 (rarely or none of the time) to 3 (most or all of the time). Items were summed to achieve a total score that could range from 0 to 60, with higher scores indicating greater symptomatology. The internal consistency for the CES-D total score was s =.91, suggesting this is a reliable measure.

**2.4.5 Emotion ratings—**Self-reported valence and arousal ratings to pictures were assessed using the Self-Assessment Manikin (SAM)[15]. The SAM is a two item questionnaire that yields ratings between 1 and 9 for the dimensions of valence (pleasure) and arousal. Higher scores indicate greater pleasure or arousal, respectively. After each picture was presented, an electronic version of the SAM[71] was used to make ratings with instructions for participants to "rate your emotional reaction to the picture."

**2.3.6 Subjective pain ratings—**To assess pain intensity in response to electric pain stimuli, participants used a computer-presented numerical rating scale (NRS) that ranged from 0 (no sensation) to 100 (maximum tolerable). Although these anchors are different from those used on other visual analogue scales, scales using these anchors have been used in numerous prior studies [eg, 8,26,30,32,33,65,71,81]. Participants used a computer mouse to slide an indicator along the scale to make ratings. A mouse button press was used to submit the rating and return the scale to zero before the next rating.

**2.4.7 Noise ratings—**To keep procedures identical between emotion processing Blocks and pain/NFR Blocks, participants were asked to rate their reactions to the acoustic startle stimuli using a computer-presented NRS that was constructed to parallel the pain NRS. The noise NRS ranged from 0 (no noise) to 100 (maximum tolerable). Participants used a computer mouse to slide an indicator along the scale to make ratings. A mouse button press was used to submit the rating and return the scale to zero before the next rating.

### 2.5 Determination of Stimulation Intensity: Nociceptive Flexion Reflex (NFR) Threshold Assessment

The suprathreshold stimulation intensity used during emotional picture viewing was set to 120% NFR threshold. NFR threshold procedures were the same as those used previously[63]. NFR threshold was assessed using 3 ascending-descending staircases of electric stimuli. The first ascending staircase started at 0 mA and increased in 2 mA steps until an NFR was detected. NFR was defined as a mean rectified biceps femoris EMG response in the 90-150 ms post-stimulus interval that exceeded the mean rectified biceps

femoris EMG activity during the 60 ms pre-stimulus baseline interval by at least 1 standard deviation[63]. This criterion was chosen because it increased sensitivity for detecting an NFR which reduced the burden on the participants, but also retained adequate specificity[31,64]. After an NFR was obtained, the current was decreased in 1 mA steps until an NFR was no longer detected. The second and third ascending-descending staircases used 1 mA steps. The interval between electric stimulations varied randomly between 8-12 s to reduce predictability and reflex habituation. The average stimulus intensity of the last two peaks and troughs were used to define NFR threshold. NFR threshold was increased by 20% to generate the suprathreshold stimulation intensity that was used during picture-viewing (120% NFR threshold). This intensity minimizes ceiling and floor effects[19].

## 2.6 Emotion-Induction

**2.6.1 Picture stimuli—**Several studies have demonstrated that emotion elicited by picture-viewing reliably modulates pain and nociception[20,43,53,71], with the most robust modulation occurring during mutilation and erotic picture contents[62]. In the present study, 72 digital pictures were selected from the International Affective Picture System[47]. The pictures were delivered in 4 blocks of 18 pictures with each block containing 6 mutilation, 6 neutral, and 6 erotic. Two Blocks (Blocks 1 & 3) were used to assess emotional reactivity in the absence of pain and two Blocks (Blocks 2 & 4) were used to assess emotional modulation of pain and NFR. Normative ratings of valence and arousal were used to ensure pictures evoked similar emotional responses across all 4 blocks.[1] Picture order within each block was randomized with the limitation that not more than two pictures of similar content were shown consecutively.

**2.6.2 Emotional reactions to pictures—**Emotional experience can be assessed from two dimensions: valence and arousal[10,11]. Valence refers to the unpleasantness or pleasantness of the emotion and usually indicates whether defensive or appetitive motivation is experienced, respectively. By contrast, arousal refers to the emotional activation or intensity. To assess participants' physiological-emotional reactions to pictures, five measures were employed. Three covary with emotional valence (valence ratings, corrugator EMG, startle modulation) and two covary with emotional arousal (arousal ratings, SCR). However, it is important to note that although measures of valence correlate with each other and measures of arousal correlate with each other, they can diverge[11,49]. For example, subjective measures (valence, arousal) and facial expressions (corrugator EMG) are under voluntary control and are therefore more susceptible to bias, whereas sympathetic arousal (SCR) and startle modulation are reflexes and less likely to be influenced by bias. Moreover, different measures are mediated by different supraspinal structures[51,56,87] For example, measures of subjective emotional experience are correlated with activity in the hippocampus and orbitofrontal cortex, whereas startle modulation is mediated by the amygdala and PAG[35,48,87]. Thus, these five measures provide unique indices of valence and arousal to comprehensively assess emotional experience.

Self-reported valence and arousal were assessed by the SAM, as previously noted. The corrugator muscle controls the eyebrow and pulls it down into a frown during unpleasant

[1]Image numbers by Block were: Block 1 – mutilation (3010, 3030, 3069, 3102, 9253, 9405; $_{\text{Valence}}$= 1.76, $M_{\text{Arousal}}$=6.52), neutral (7002, 7035, 7041, 7050, 7090, 7150; $M_{\text{Valence}}$= 4.96, $M_{\text{Arousal}}$=2.73), and erotica (4599, 4607, 4609, 4659, 4669, 4687; $M_{\text{Valence}}$= 6.76, $M_{\text{Arousal}}$=6.19); Block 2 - mutilation (3015, 3060, 3061, 3068, 3071, 3130; $M_{\text{Valence}}$= 1.82, $M_{\text{Arousal}}$=6.48), neutral (7009, 7020, 7038, 7080, 7170, 7950; $M_{\text{Valence}}$= 5.01, $M_{\text{Arousal}}$=2.67), and erotica (4611, 4650, 4660, 4672, 4676, 4695; $M_{\text{Valence}}$= 6.77, $M_{\text{Arousal}}$=6.21); Block 3 - mutilation (3000, 3053, 3062, 3101, 3120, 3150; $M_{\text{Valence}}$= 1.75, $M_{\text{Arousal}}$=6.50), neutral (6150, 7004, 7006, 7034, 7100, 7705; $M_{\text{Valence}}$= 4.99, $M_{\text{Arousal}}$=2.69), and erotica (4608, 4624, 4658, 4689, 4690, 4800; $M_{\text{Valence}}$= 6.78, $M_{\text{Arousal}}$=6.22); Block 4 – mutilation (3051, 3064, 3080, 3100, 3110, 3140; $M_{\text{Valence}}$= 1.74, $M_{\text{Arousal}}$=6.47), neutral (7000, 7175, 7211, 7217, 7233, 7235; $M_{\text{Valence}}$= 4.93, $M_{\text{Arousal}}$=2.73), and erotica (4623, 4643, 4652, 4666, 4670, 4694; $M_{\text{Valence}}$= 6.78, $M_{\text{Arousal}}$=6.22).

experiences; therefore, corrugator activity is inversely related to subjective reports of pleasure[11,49]. The startle response is a reflexive response to an abrupt, unexpected stimulus that helps an organism protect itself from a potential threat[38]. In humans, startle is quantified from the eyeblink response (via orbicularis oculi EMG) that occurs 21-120 milliseconds after an abrupt noise stimulus. Startle magnitude follows a valence linear trend (unpleasant > neutral > pleasant)[38,46]; therefore, startle inversely correlates with subjective reports of pleasure (valence). Given that startle is a reflex mediated by a simple neurocircuit[48], it is less likely to be influenced by voluntary control. Sweat glands on the palms of the hands are controlled exclusively by the sympathetic nervous system. When sweat is released, it increases skin conductivity; thus skin conductance response (SCR) is a measure of sympathetic activation and correlates with subjective reports of arousal[11,49]. All 5 emotional reactions were collected during all blocks, including pain/NFR Blocks. But, because emotional reactivity did not appreciably differ between pain and non-pain Blocks, data from pain/NFR Blocks are not reported to reduce redundancy.

### 2.7 Procedure

All procedures were fully approved by the University of Tulsa Institutional Review Board and were administered in a single testing session. Upon arrival to the testing session, informed consent was obtained followed by a comprehensive assessment of inclusion criteria. Afterwards, height and weight were assessed and then the SCID-I/NP was administered. Participants were then taught to use the pain NRS and the SAM, instrumented for physiological recording, administered background questionnaires (SF-36, CES-D), and then asked to sit quietly for 5-mins to acclimate to the testing environment.

In Blocks 1 and 3, emotional reactivity to pictures was assessed in the absence of pain testing. Each picture was shown for 6 s and inter-picture intervals varied randomly from 12-22 s. In each Block, startle probes were delivered during 9 pictures (3 per content). Probes were also delivered during 4 randomly determined inter-picture intervals to minimize the predictability of their delivery. Therefore, a total of 13 probes were delivered during each Block (26 total). Each probe was delivered 3 to 5 s after picture onset and 11 to 21 s after inter-picture interval onset in order to reduce predictability. The 3-5 s post picture onset interval was chosen because this produces the greatest linear valence modulation of startle[12,14,18]. After the offset of each picture (regardless of whether a startle probe was delivered), participants rated their emotional response on the SAM. A noise NRS was presented after each startle probe. If the probe occurred during a picture, the rating was made after picture offset. If the probe occurred during an interval, the noise NRS was presented immediately after the probe. To ensure that a picture or probe was not delivered during a rating period, the computer automatically paused the experiment during rating periods until the participant submitted their ratings.

In Blocks 2 and 4, emotional modulation of pain and NFR was assessed. These procedures were identical to those used in Blocks 1 and 3, except that electric stimulations set at 120% NFR threshold were delivered during pictures instead of startle probes, and pain NRSs were administered rather than noise NRSs. Between Blocks 2 and 3, there was a 5-min mandatory break during which participants were asked to sit quietly and relax. Optional 5-min breaks were offered between other Blocks. After completion of the testing day, participants were provided their honorarium.

### 2.8 Preliminary Data Screening/Scoring

All physiological signals were scored offline and a trained experimenter visually inspected the waveforms for errors. Corrugator responding was calculated by subtracting the mean rectified EMG (in V) in the 1 s prior to picture onset from the mean rectified EMG during

the 6 s of picture presentation. SCR was calculated by subtracting the mean skin conductance (in S) in the 1 s prior to picture onset from the peak skin conductance that occurred in the 2-6 s interval after picture onset. Eyeblink magnitude was scored by subtracting the mean EMG of the 60 ms prior to startle probe onset from the peak rectified and integrated (8 ms time constant) EMG response in the 21-120 ms following startle-probe onset. NFR magnitude was calculated as a *d*-score. To calculate the *d*-score, four summary statistics must be obtained first: 1) mean rectified EMG during 90-150 ms post-stimulus interval, 2) *SD* of rectified EMG during 90-150 ms post-stimulus interval, 3) mean rectified EMG during 60 ms prestimulus interval, and 4) *SD* of rectified EMG during 60 ms prestimulus interval. *d* = [mean of poststimulus interval - mean of prestimulus interval] / [average of two SDs]). Research has shown that calculating NFR magnitude from a *d*-score produces a stronger correlation with pain ratings than other methods of scoring NFR magnitude and improves the distributional qualities of the NFR (ie, distribution is normal in shape)[66,67].

### 2.9 Data Analysis

To determine whether there were group differences in participant characteristics, *t*-tests and chi-square analyses were used. All other analyses were conducted using the MIXED procedure in SPSS 17.0 to increase power and include cases with missing data[41]. The results from the linear mixed models are interpreted as if 2(Group: HC vs. MDD) x 3(Picture Content: mutilation, neutral, erotica) ANOVAs were conducted. Data were kept in "long form" so that the SPSS 17.0 MIXED procedure could be used to conduct mixed effects modeling of the data. For example, each Block contained 18 pictures and electric stimulations/startle probes were delivered during 9 pictures in each Block; therefore, each participant contributed 36 responses (2 Blocks x 18 pictures = 36) for analysis of emotional reactivity to pictures (ie., valence ratings, arousal ratings, corrugator EMG, SCR) and 18 responses (2 Blocks x 9 stims or probes = 18) for analysis of reactions to stimulations/probes (ie, startle reflexes, noise ratings, pain ratings, NFRs). Keeping the data in long form increases denominator degrees of freedom (*dfs*) for within-subject effects, thus greatly increasing power [41].

Subject ID was used as the grouping variable to designate the Level 2 units (ie, to account for non-independence of observations given that each participant contributed multiple rows of data). Level 1 units were responses to pictures (valence ratings, arousal ratings, corrugator EMG, SCR) or stimulations/probes (pain, NFR, startle, noise ratings). The variance-covariance structure of the repeated measures within each Block was modeled using an autocorrelation matrix (AR1). All models included a random intercept to allow outcomes to vary across individuals (Level 2 units). The SPSS MIXED procedure uses Satterthwaite estimation for the denominator *dfs* which produces non-integer values that vary from analysis to analysis (even if the number of observations is the same across analyses).

Dependent variables for emotional reactivity in the absence of pain were valence ratings, corrugator EMG, startle magnitude, arousal ratings, SCR, and noise intensity ratings. Dependent variables assessed during emotional modulation of pain/NFR were pain ratings and NFR magnitude. Independent variables were Group (HC, MDD) and Picture Content (Mutilation, Neutral, Erotica). In addition, a continuous predictor called "Order" was entered that coded for the order in which stimulations, probes, or pictures occurred (eg, stims 1 - 9 in each Block). This variable controlled for any habituation or sensitization effects within a Block that are unrelated to emotional modulation. Controlling for order improves statistical power and improves the validity of the statistical models by removing potential habituation/ sensitization confounding[60]. Significant *F*-tests were followed up using Fisher's LSD tests. In the event of a significant interaction, the simple effect of Picture Content was examined

because this provides insight into the primary effect of interest (ie, emotional modulation effects). However, if the Picture Content simple effect tests did not adequately describe the interaction, the simple effect of Group was also examined. In the analyses of startle, noise ratings, pain ratings, and NFR, linear and quadratic trends were examined to determine whether linear valence modulation was present. Significance was set at $p < .05$ (two-tailed).

## 3.0 Results

### 3.1 Demographic and Background Information

Three participants did not complete all procedures (2 MDD, 1 HC). One MDD participant quit during NFR threshold testing and another quit after Block 2 because they could not tolerate the painful stimulations. The HC quit after Block 1 because he/she found the mutilation pictures too disturbing. Therefore, partial data were available for 14 HC and 14 MDD to assess emotional reactivity in the absence of pain, 13 HC and 13 MDD for NFR threshold, and 13 HC and 13 MDD to assess emotional modulation of pain/NFR.

Table 1 presents group comparisons on demographic and background information. There were no significant group differences in age, sex, employment status, body mass index, blood pressure, or general perception of health. As expected, MDD participants reported more severe depressive symptoms than HC. There was also a significant group difference in years of education, with MDD having fewer years of education than HC.

### 3.2 NFR Threshold

NFR threshold did not differ by group (Table 1). Thus, groups did not differ in spinal nociceptive sensitivity.

### 3.3 Emotional Reactions to Pictures

Figure 1 depicts means, SEMs, and significant mean contrasts for subjective and physiological variables. Main effects are depicted by the “All” group.

**3.3.1 Valence ratings—**The main effect of Picture Content was significant, $F(2,804.70) = 745.67$, $p<.001$, indicating that mutilation pictures decreased pleasure, whereas erotic pictures increased pleasure, relative to neutral (all $p$s $< .05$). But, this effect was qualified by the significant Group X Picture Content interaction, $F(2,803.85) = 11.76$, $p<.001$. Initially, the Picture Content simple effects were examined, but these found that both groups had a similar pattern of means. Specifically, erotica led to the highest valence ratings, neutral was intermediate, and mutilation led to the lowest ratings (all $p$s $< .01$). Given that this did not explain the interaction well, the simple effects of Group were also examined. These indicated that valence ratings of erotica were lower for MDD relative to HC ($p < .05$), but groups did not differ in their ratings of neutral or mutilation pictures ($p$s $> .05$). The main effect of Group [$F(1, 28.03) = 1.34$, $p=.26$] was non-significant.

**3.3.2 Corrugator EMG—**The main effect of Picture Content was significant, $F(2,346.71) = 9.17$, $p<.001$, indicating that mutilation pictures evoked greater corrugator activity than neutral and erotic pictures ($p$s $< .05$), but neutral and erotica did not differ from one another ($p > .05$). The main effect of Group [$F(1, 26.74) < 1$, $p=.60$] and the Group X Picture Content interaction [$F(2, 347.11) = 1.85$, $p=.16$] were non-significant. Therefore, groups did not differ in corrugator reactivity.

**3.3.3 Startle magnitude—**The main effect of Picture Content was significant, $F(2,380.27) = 4.11$, $p=.02$, indicating that startle reflexes were inhibited during erotica relative to mutilation and neutral ($p$s $< .05$). But, this effect was qualified by a significant

Group X Picture Content interaction, $F(2,381.97) = 4.26$, $p=.02$. The interaction suggested mutilation facilitated startle reflexes relative to neutral and erotica in HC ($ps < .05$). By contrast, erotica inhibited startle reflexes relative to neutral in MDD ($p < .05$), but there was no significant difference between mutilation and erotica or mutilation and neutral ($ps < .05$). Consistent with this, the linear trend [$F(1, 384.30) = 7.59$, $p=.006$] and the Group X Quadratic Trend interaction [$F(1, 378.13) = 7.32$, $p=.007$] were significant, but not the Group X Linear Trend interaction [$F(1,386.77) = 1.31$, $p=.25$] or the quadratic trend [$F(1,377.19) < 1$, $p=46$]. The main effect of Group [$F(1, 27.92) < 1$, $p=.94$] was non-significant. Taken together, these results indicate startle modulation followed a valence linear trend in the HC group, but followed a quadratic trend (inverse U) in the MDD group.

**3.3.4 Arousal ratings—**The main effect of Picture Content was significant, $F(2,756.30) = 176.41$, $p<.001$, indicating that erotic and mutilation pictures were more arousing than neutral pictures ($ps < .05$), but were not different from one another ($p > .05$). There was also a significant Group X Picture Content interaction, $F(2,755.26) = 3.47$, $p=.03$. Initially, the simple effects of Picture Content were examined. These indicated that mutilation and erotica were more arousing than neutral ($ps < .05$), but mutilation and erotica were not different from one another ($p > .05$). This was true for both groups. Given that this did not describe the interaction well, the simple effects of Group were also examined, but none of these were significant ($ps > .05$). Furthermore, the main effect of Group [$F(1, 28.14) < 1$, $p=.48$] was non-significant. Thus, there were group differences in arousal ratings.

**3.3.5 Skin Conductance Response (SCR)—**The main effect of Picture Content was significant, $F(2,350.44) = 2.95$, $p=.05$. Mutilation pictures evoked greater SCR than neutral pictures ($p < .05$), but no other comparison was significant ($ps > .05$). The main effect of Group [$F(1, 25.26) < 1$, $p=.60$] and the Group X Picture Content interaction [$F(2,350.59) = 0.54$, $p=.58$] were both non-significant. Thus, groups did not differ in sympathetic activation.

**3.3.6 Noise ratings—**The main effect of Picture Content was significant, $F(2,319.66) = 11.89$, $p<.001$, indicating that erotica inhibited noise ratings relative to neutral and mutilation ($ps < .05$), but neutral and mutilation did not differ ($p > .05$). This effect was qualified by a significant Group X Picture Content interaction, $F(2,320.96) = 5.15$, $p=.006$, indicating that, relative to neutral, noise ratings were inhibited during erotica and facilitated during mutilation in HC (all $ps < .05$). By contrast, erotica inhibited noise ratings relative to neutral in MDD ($p < .05$), but there were no significant differences between mutilation and erotica or mutilation and neutral ($ps > .05$). Consistent with this, the linear trend [$F(1, 321.61) = 20.18$, $p<.001$] and the Group X Linear Trend interaction [$F(1,323.81) = 8.31$, $p=.004$] were significant. There was also a marginal quadratic trend [$F(1,317.91) = 3.23$, $p=.07$, but the Group X Quadratic Trend interaction [$F(1, 318.29) = 2.15$, $p=.14$] was non-significant. The main effect of Group [$F(1, 27.79) < 1$, $p=.55$] was non-significant. Taken together, these results indicate modulation of noise ratings corresponded to a valence linear trend in the HC group, but followed a quadratic trend (inverse U) in the MDD group.

### 3.4 Emotional Modulation of Pain and NFR outcomes

Figure 2 depicts means, SEMs, and significant mean contrasts for pain and NFR modulation outcomes. Main effects are depicted by the “All” group. Because groups did not differ on NFR threshold, any group differences noted in emotional modulation of pain/NFR cannot be attributed to group differences in suprathreshold stimulus intensity.

**3.4.1 Pain ratings—**The main effect of Picture Content was significant, $F(2,323.67) = 17.76$, $p<.001$, indicating that mutilation pictures facilitated pain and erotic pictures

inhibited pain, relative to neutral (all *p*s < .05). But, this was qualified by a significant Group X Picture Content interaction, $F(2,322.00) = 5.82$, $p=.003$, indicating mutilation led to facilitation of pain ratings relative to neutral and erotica for HC (*p*s < .05). By contrast, pain ratings did not differ by picture content in the MDD group indicating a lack of emotional modulation of pain (all *p*s > .05). Consistent with this, the linear trend was significant [$F(1, 318.39) = 34.54$, $p<.001$] and the Group X Linear Trend interaction was significant [$F(1,316.48) = 8.95$, $p=.003$], but not the quadratic trend [$F(1,329.34) = 1.12$, $p=.29$] or the Group X Quadratic Trend interaction [$F(1, 327.71) = 2.79$, $p=.10$]. The main effect of Group [$F(1, 26.01) < 1$, $p=.87$] was non-significant. Together, these results suggest a valence linear trend explains the modulation of pain in the HC group, but not the MDD group.

**3.4.2 Nociceptive Flexion Reflex (NFR)—**The main effect of Picture Content was significant, $F(2,321.46) = 11.87$, $p<.001$, indicating mutilation enhanced NFR magnitudes relative to neutral and erotica (*p*s < .05). However, the main effect of Group [$F(1,24.14) = 1.56$, $p=.22$] and the Group X Picture Content interaction [$F(2,319.62) = 0.02$, $p=.98$] were both non-significant. The linear trend was significant [$F(1, 310.83) = 23.12$, $p<.001$], but not the Group X Linear Trend interaction [$F(1,309.45) < 1$, $p=.89$], the quadratic trend [$F(1,332.91) < 1$, $p=.41$] or the Group X Quadratic Trend interaction [$F(1, 330.31) < 1$, $p=.87$]. Therefore, the valence linear trend modulation of NFR was present in both groups.

## 4.0 Discussion

### 4.1 Emotion Processing

According to most emotion outcomes, pictures evoked emotional reactivity in both groups that is consistent with prior studies of healthy individuals[11]. Erotic pictures evoked pleasure, subjective arousal, and smaller startle magnitudes, whereas mutilation pictures evoked displeasure, corrugator EMG activation, subjective arousal, and sympathetic activation (SCR). Thus, pictures had the intended effect of manipulating emotion. Nonetheless, there were two group differences that suggested emotion processing was disrupted in MDD[16].

First, erotic pictures evoked less pleasure in MDD participants than HC. This finding has been noted by prior studies[16] and is indicative of anhedonia (blunted appetitive responding), a cardinal feature of MDD[2]. Interestingly, group differences in response to erotica were not noted on any physiological outcome (corrugator, SCR, startle). This divergence between subjective and physiological emotion outcomes is important because it can help identify which aspects of emotional processing are disrupted in MDD. For example, some supraspinal regions are associated with the conscious emotional evaluation of stimuli (eg, hippocampus, orbitofrontal cortex), whereas others are associated with non-conscious detection and processing of stimuli (eg, amygdala)[48,87]. Therefore, disrupted hippocampus and/or orbitofrontal responsivity may have mediated the blunted appetitive responding. Additionally, deficits in fronto-striatal anatomy and/or function might contribute because these have been linked to anhedonia[39,40,42,83].

Second, startle modulation was disrupted in MDD and showed a quadratic trend (Fig 1). This is consistent with several studies that failed to find linear valence modulation of startle in MDD, even when significant deficits in subjective reactions to pictures is not observed[eg, 1,22,23]. Thus, it appears that the pathophysiology of MDD does not affect all emotion response systems equally.

Interestingly, the present study also found a quadratic trend for noise intensity ratings in MDD. As we have noted[63], ratings of noises are modulated in HC according to a valence linear trend. These parallels between startle and noise ratings suggest they may be mediated

by a common circuit. Currently, nothing is known about the circuit that modulates noise ratings, but startle modulation involves the amygdala and periaqueductal gray (PAG)[48,51] which are also involved in pain modulation[27,74,86]. Thus, dysfunction in these structures could cause a disturbance in startle modulation (without substantial changes in subjective emotion[87]), but also perhaps pain modulation [54].

It is important to note that aberrant emotional reactivity to pictures is neither necessary nor sufficient to have disrupted emotional modulation of pain. For example, we have shown that men and women differ in their subjective responses to pictures, but show similar pain/NFR modulation[61]. Further, persons with insomnia show only minor differences in emotional reactions (ie, small valence rating differences), but do not emotionally modulate pain[21]. These observations likely reflect that the neural structures that mediate emotional reactivity and emotional modulation of pain/NFR are not completely overlapping (but are both activated by picture-viewing). Thus, it is important to comprehensively assess emotional reactivity and pain outcomes because they assess distinct, but related, processes and thus provide unique information about emotion/pain processing.

### 4.2 Emotional Modulation of Pain/NFR

As expected, linear valence modulation of pain was noted in HC, but not in MDD. By contrast, linear valence modulation of NFR was present in both groups. Together, this suggests MDD is associated with disrupted emotional modulation of pain, but intact circuitry that modulates spinal nociception. Indeed, emotion modulates pain and spinal nociception via two different modulatory mechanisms[72,74]. This idea was first suggested by Rhudy and colleagues[72] when they observed that emotional modulation of pain and NFR could diverge. Roy et al[74] subsequently identified these two circuits by examining which supraspinal structures correlated with the valence linear trend in pain and NFR. They found that NFR modulation correlated with the dorsolateral prefrontal cortex, parahippocampal gyrus, thalamus, amygdala, and brainstem nuclei, whereas pain modulation correlated with the orbitofrontal cortex, subgenual anterior cingulate cortex (sgACC), cuneus, and insula. Given evidence that abnormalities in the sgACC and orbitofrontal cortex and their connections to limbic structures (eg, amygdala, striatum) play an important role in the pathophysiology of MDD[57], the present study suggests they may also play an important role in MDD-related risk for pain by disrupting the capacity to regulate pain in response to environmental demands.

Interestingly, these findings in MDD are similar to what we recently observed in individuals with FM[63] and primary insomnia[21]. FM was associated with reduced pleasure and arousal in response to erotica and a quadratic modulation of startle. Insomnia was associated with reduced pleasure to erotica, but intact linear valence modulation of startle. But in both groups, emotional modulation of pain was absent, whereas emotional modulation of NFR was intact. Given these similarities between FM, insomnia, and MDD, it is possible that they share a common pathophysiology that does not influence emotional reactivity the same across all disorders. One possibility is that depressive symptoms could explain the similarities between MDD and FM; however, it is not clear if this could explain the similarities with insomnia. By contrast, a disruption of the monoamine systems could potentially explain the linkages between affective disturbance, sleep problems, and chronic pain[4]; therefore, this is an area worth following up on.

Importantly, the pathophysiological mechanism might not be common to all pain disorders, because emotional modulation of pain was not disrupted in patients with chronic lower back pain (NFR modulation was not tested)[34]. Future studies should examine whether disorders comorbid with FM, insomnia, and MDD (eg, vulvodynia, irritable bowel syndrome) show

similar disruptions in emotional modulation of pain to help determine whether a lack of linear valence modulation of pain is a shared phenotype for pain risk.

One study found pain inhibition (as measured by diffuse noxious inhibitory controls, DNIC) was intact in MDD and HC, but deficient in FM[55]. This might suggest different pathophysiology in MDD and FM; however, all MDD participants in their study were on medications known to influence pain modulation (eg, antidepressants)[4,27]. Therefore, it is possible that their failure to find pain modulation deficits in MDD was due to medications reversing the deficits. Alternatively, given that emotional modulation and DNIC are mediated by different neurocircuits[50,74,82], pain risk in MDD may specifically stem from deficits in supraspinal structures associated with emotional modulation of pain, not DNIC.

### 4.3 Spinal Nociceptive Sensitivity

The current study measured NFR in two ways. NFR magnitude was used to examine within-subject changes in spinal nociception that covaried with picture-viewing. Additionally, NFR threshold was measured to determine the suprathreshold stimulation intensity used during picture-viewing. Spinal nociception is under constant, tonic, descending modulation from supraspinal centers[76]; therefore, NFR threshold can be used to assess individual differences in tonic modulation (spinal sensitivity) that might contribute to pain risk[75]. Groups did not differ in NFR thresholds; therefore, when considered together with the emotional modulation of NFR data, persons with MDD appear to be able to normally regulate spinal nociceptive processing.

### 4.4 Study Limitations

This study had several strengths: stringent inclusion/exclusion criteria for MDD, well-validated methodology for assessing emotion processing and emotional modulation of pain/NFR, assessment of reactions to pleasant and unpleasant stimuli, assessment of physiological (NFR) and perceptual pain outcomes, and statistically powerful analyses. Nonetheless, two limitations should be mentioned.

First, use of strict inclusion/exclusion criteria for MDD can also be a limitation. To reduce confounds, MDD participants were excluded for chronic pain conditions, comorbid psychiatric problems, and medications used to control pain (eg, analgesics) and treat depression (eg, antidepressants). These strict inclusion/exclusion criteria improved the internal validity of the study and are consistent with criteria used in other pain research on MDD[7,78], but may have reduced external validity (generalizability). Second, the present study had small sample sizes which reduced statistical power and increased chances of Type II error. To counteract this problem we used within-subject emotion manipulations and picture contents known to produce the most robust modulation of pain/NFR[62]. Furthermore, our powerful statistical approach[41] increased our denominator degrees of freedom 12-fold for within-subject effects (ie, Picture Content main effect, Group x Picture Content interaction) for emotional reactions and 6-fold for pain/NFR. This is similar to having a sample size of 168 participants per group for emotional reactions and 84 participants per group for pain/NFR to detect within-subject effects using traditional ANOVAs. As a result, we were able to detect several effects, including many that are consistent with prior studies. Nonetheless, future research is needed to replicate these results in a larger, more diverse sample.

### 4.5 Summary

The present study found that MDD was associated with a failure to emotionally modulate pain and abnormalities in emotional reactivity (abnormal startle modulation, reduced pleasure to erotica). The deficit in emotional modulation of pain was not due to a

dysfunction of brain-to-spinal cord circuitry that modulates spinal nociception, because there were no group differences in NFR threshold or emotional modulation of NFR. Given that MDD is associated with increased risk for pain, and similar deficits in emotional modulation of pain have been noted in FM and insomnia [21,63], a failure to emotionally modulate pain according to a valence linear trend might be a phenotypic marker for chronic pain risk stemming from disrupted supraspinal circuitry (eg, sgACC, orbitofrontal cortex, connections to amygdala).

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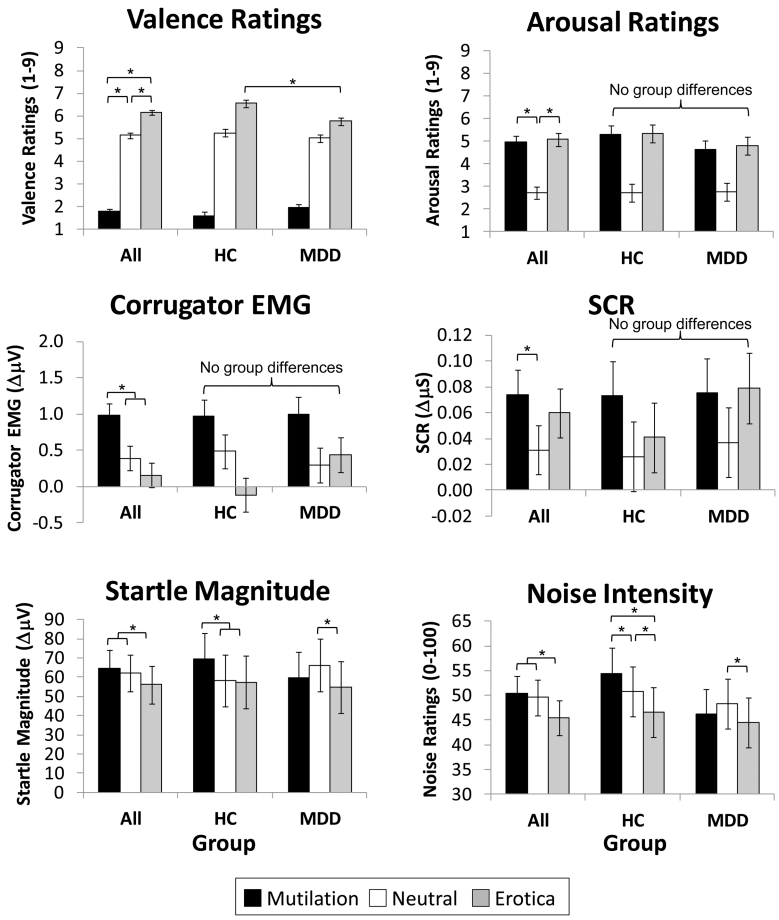


**Figure 1.**

Emotional valence (valence ratings, corrugator EMG, startle) and arousal (arousal ratings, skin conductance response [SCR]) reactions to pictures in the absence of pain testing. Emotional modulation of noise ratings is depicted in the bottom right graph. HC=healthy controls, MDD= participants with major depressive disorder. *$p$<.05

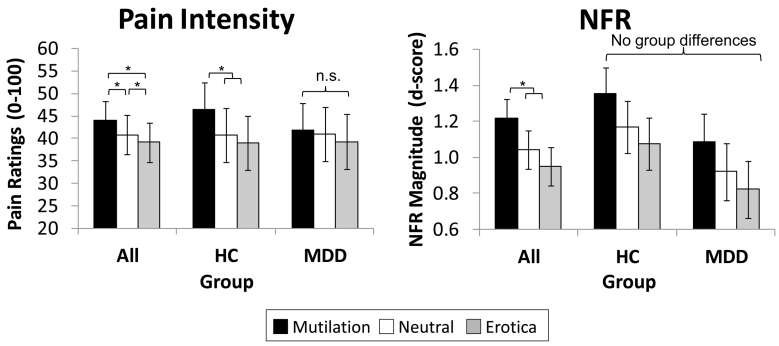


**Figure 2.**

Emotional modulation of pain (left graph) and nociceptive flexion reflex (NFR; right graph) in healthy controls (HC) and participants with major depressive disorder (MDD). *$p$<.05. Emotional modulation of pain was evident in HC, but not MDD. By contrast, both groups demonstrated emotional modulation of spinal nociception (NFR).

## Table 1

### Participant Characteristics by Group

| | HC (*n*=14) | | MDD (*n*=14) | | | | Effect Size |
|---|---|---|---|---|---|---|---|
| **Characteristics (units)** | ***M* or *n*** | ***SD* or %** | ***M* or *n*** | ***SD* or %** | **$\chi^2$/*t*-test** | ***p*-value** | ***Cohen's d*** |
| Age (years) | 37.00 | 13.45 | 35.07 | 12.09 | 0.40 | .69 | 0.15 |
| Sex (% Female) | 7 | 50% | 6 | 43% | 0.14 | >.99 | |
| Race (% Caucasian) | 13 | 100% | 10 | 71% | 2.39 | .12 | |
| Marital Status (% Married) | 7 | 50% | 2 | 14% | 2.62 | .11 | |
| Employed (% full or part-time) | 10 | 77% | 7 | 54% | 0.68 | .41 | |
| Years of Education | 15.50 | 2.18 | 13.31 | 3.25 | 2.07 | .049 | 0.79 |
| Body Mass Index (kg/m$^2$) | 25.78 | 3.93 | 23.94 | 3.26 | 1.35 | .19 | 0.51 |
| Systolic Blood Pressure (mmHg) | 117.82 | 14.60 | 113.68 | 9.23 | 0.90 | .38 | 0.34 |
| Diastolic Blood Pressure (mmHg) | 74.25 | 10.79 | 71.79 | 8.73 | 0.66 | .51 | 0.25 |
| General Health Perception, SF-36 (0-100) | 80.71 | 12.54 | 73.21 | 20.06 | 1.19 | .25 | 0.45 |
| Depression, CES-D (0-60) | 5.64 | 6.06 | 35.43 | 11.06 | 8.84 | <.001 | 3.34 |
| Nociceptive Flexion Reflex (NFR) Threshold[#] | 16.51 | 13.48 | 15.99 | 13.27 | .10 | .92 | 0.04 |

Note:

[#]For NFR threshold there were only 13 participants per group. HC= healthy, pain-free, psychopathology-free controls. MDD = healthy, pain-free, participants with major depressive disorder.