Stress-induced analgesia: an evaluation of effects on temporal summation of pain and the role of endogenous opioid mechanisms

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Abstract

Introduction: Acute stress reduces responses to static evoked pain stimuli (stress-induced analgesia [SIA]). Whether SIA inhibits temporal summation of pain, a dynamic evoked pain measure indexing central sensitization, has been little studied and mechanisms were not evaluated.

Objectives: We tested whether acute laboratory stressors reduce temporal summation and whether endogenous opioid (EO) mechanisms contributed.

Methods: Participants were 72 healthy individuals who attended 2 laboratory sessions, receiving either oral naltrexone (50 mg; opioid antagonist) or placebo (randomized, counterbalanced order). In each session, participants underwent a temporal summation protocol with evoked heat pain stimuli, once after extended rest and once after experiencing 2 acute stressors (public speaking and mental arithmetic challenge). Reduced temporal summation in the stress/pain relative to rest/pain condition indexed SIA.

Results: Analyses in the placebo condition indicated significant SIA on initial pain ratings but not temporal summation slope (index of central sensitization). This SIA effect was moderated by stress reactivity, with SIA only observed in high stress responders. Analyses comparing SIA across the drug conditions did not reveal any evidence of stress-related EO inhibition of temporal summation outcomes. Moderation analyses revealed that high, but not low, stress responders exhibited paradoxical analgesic effects of naltrexone on initial pain ratings but not temporal summation slopes. Independent of stress effects, significant EO inhibition of temporal summation slopes was observed, but only in females.

Conclusions: Results suggest that acute stress may reduce initial ratings in temporal summation protocols via nonopioid mechanisms but does not alter the temporal summation slope commonly used to index central sensitization.

Keywords: Stress, Stress-induced analgesia, Endogenous opioid, Naltrexone, Temporal summation, Central sensitization

1. Introduction

Acute stress is associated with decreased pain responsiveness6,17,47 (stress-induced analgesia [SIA]). Human SIA studies have historically focused on effects of acute stress on static evoked pain measures, such as pain threshold and tolerance.2,9,16,24,25,36,51–53 Such measures are nonspecific, broadly indexing overall pain sensitivity. In contrast, dynamic evoked pain measures capture specific pain modulatory processes. For example, temporal summation of pain protocols that elicit increases in perceived pain intensity during rapid application of the same brief stimulus at 2- to 3-sec intervals index central sensitization.15 A few studies using temporal summation protocols have begun addressing the question of whether SIA inhibits temporal summation. In 2 studies of individuals without chronic pain, laboratory stress protocols (public speaking and cognitive tasks) were shown to reduce temporal summation, although only in Anglo-American participants in one study,14,19 in contrast, a more recent study reported no effect of an acute laboratory social stressor on temporal summation.32

To the extent that SIA inhibits expression of central sensitization, mechanisms underlying those effects remain untested. In animals, it is well-accepted that SIA has an endogenous opioid (EO) component.17,36 Human studies, although not entirely consistent, also suggest a likely EO component to SIA. Studies using laboratory stressors have reported that pharmacological opioid blockade reduces or eliminates SIA.2,9,16,24,25,36,51–53
Such findings have also been extended to acute naturalistic stress (eg, parachute jumping).24,36 All these studies have focused solely on static evoked pain measures. Whether opioid-mediated SIA effects inhibit central sensitization (indexed by temporal summation) is unknown.

The limited human work evaluating whether EO activity inhibits temporal summation in the absence of acute stress has been negative; temporal summation under resting conditions was unaltered by opioid blockade in 2 studies.21,38 However, 2 animal studies suggest possible EO inhibition of temporal summation.20,56 In the current work, we sought to test whether SIA in response to acute laboratory stressors altered temporal summation and whether these effects were EO-mediated. We hypothesized that under placebo, temporal summation would be significantly lower in the stress than the no-stress condition. Moreover, we hypothesized that opioid blockade would eliminate the SIA in the placebo condition. Because age and sex both may moderate temporal summation,10,41,42 we evaluated whether SIA effects on temporal summation were moderated by these factors. A multilevel modelling approach was used to permit quantitative evaluation of SIA effects on temporal summation itself (slope of pain ratings across temporal summation stimuli) vs on initial pain ratings in the temporal summation series (intercept).

2. Methods

2.1. Participants

This was a secondary analysis from a larger study focusing on opioid regulation of the stress response. Results from this project regarding opioid-mediated SIA effects on static measures of cold-pressor pain responsiveness have previously been reported.5 Potential participants (n = 88) were recruited from the community through print and online advertisements using procedures described previously.5 Participants meeting the following criteria were invited for on-site screening: weight within ±30% of ideal body weight; regular sleep cycle; and consuming ≤2 drinks/day of alcohol. Participants were excluded based on chronic medical conditions (eg, cardiac disease or hypertension), major psychiatric disorders (eg, psychotic, bipolar, depression, anxiety, or substance use), opiate dependence, or pregnancy. The final sample analyzed consisted of 72 participants because of missing or insufficient temporal summation data (ie, <2 ratings) for one or more experimental conditions in 16 participants. All procedures were approved by the Institutional Review Board, and all participants provided written informed consent.

2.2. Procedures

2.2.1. Stres sor condition

We used a stress protocol previously used effectively to induce significant physiological, biological, and psychological changes indicative of a stress response.1 The stressors included public speaking and mental arithmetic challenges. The public speaking challenge involved preparing (4 minutes) and delivering a 4-minute speech while being videotaped as described in previous studies.3,4,50 The scenarios differed in the 2 sessions but with similar demands. The mental arithmetic challenge also lasted for 8 minutes and required participants to add the digits of a 3-digit number then add the sum to the original number continuously. If a response was incorrect, the participant was interrupted and instructed to return to the last correct response (ie, a mild form of harassment). Order of stress condition vs the comparison rest condition (seated rest while watching nature films for 16 minutes) was randomly determined, but fixed for each participant across drug conditions.

2.2.2. Drug condition

Naltrexone (50 mg oral) or placebo was consumed by participants after a baseline rest period. Drug condition was double-blinded and counterbalanced, and drug order was randomly determined. Drug administration was followed by a 60-minute absorption period to allow for peak absorption of naltrexone.

2.3. Measures

Demographic information (ie, age, gender, body mass index, race/ethnicity, education, and marital status) was collected via self-report during on-site screening.

2.3.1. Temporal summation of pain

A standardized oscillating heat pain stimulation protocol (Medoc TSA 2001, Minneapolis, MN) was used to determine temporal summation, similar to our previous work.43,44 A sequence of 10 heat pulses, 0.5 seconds in duration, with a 35°C base temperature, an intertrial interval of 2.5 seconds, and 50°C target stimulus intensity was applied to the left volar forearm. Participants were asked to provide verbal numeric pain ratings (0 = “no pain” to 100 = “most pain possible”) immediately after the peak of each pulse. Participants completed the temporal summation protocol 4 times across 2 separate laboratory sessions (placebo, naltrexone): placebo/rest; placebo/stress; naltrexone/rest; naltrexone/stress. Drug sessions were conducted on separate days with a minimum of 72 hours between sessions. Experimenters terminated the temporal summation protocol immediately after any pain ratings of 100/100. Early termination occurred for: n = 18 placebo/rest, n = 15 placebo/stress, n = 16 naltrexone/rest, and n = 14 naltrexone/stress.

2.3.2. Distress

Subjective distress (ie, anxiety, irritability, impatience, restless-ness) was assessed through a modified version of the Subjective States Questionnaire.28 Items ranged from 0 (“not at all”) to 8 (“very strong”), with the overall distress score (also on a 0–8 scale) reflecting the item mean. Stress reactivity was operationalized as change in distress ratings from baseline to the end of the stress (or rest) period in each condition.

2.4. Data analytic plan

Temporal summation outcomes were examined as a continuous measure with multilevel models specified using hierarchical linear models (HLM v.8).49 Missing temporal summation data were handled using maximum-likelihood estimation. Analyses consisted of a within-person (level 1) submodel describing how pain ratings changed across the temporal summation protocol by stressor and drug condition and a between-person (level 2) submodel describing how these changes varied across participants.44 To evaluate whether SIA altered temporal summation, a multilevel model tested the influence of stress condition on temporal summation slopes in the placebo condition. Next, age and gender were tested as moderators of SIA effects on temporal summation responses in this model. To evaluate whether any SIA effects on temporal summation were EO mediated, a multilevel model was then used to examine the main and interactive effects
of stressor and drug conditions on initial pain ratings in the temporal summation protocol (intercept) and temporal summation slopes. Age and gender were next tested as moderators of SIA and drug effects on temporal summation responses. Finally, we evaluated whether stress reactivity (ie, change in distress ratings from baseline to the stressors) moderated SIA and drug effects on initial pain ratings (intercept) and temporal summation slopes (ie, a dose response for stress). As an example, we specified the model below:

**Level 1 model:**

\[ \text{Pain}_{t} = \pi_0 + \pi_1 \text{Session Order}_{t} + \pi_2 \text{Pulse}_{t} + \pi_3 \text{Stress}_{t} + \pi_4 \text{Drug}_{t} + \pi_5 \text{Drug} \times \text{Pulse}_{t} + e \]

**Level 2 model:**

\[ \pi_0 = \beta_{00} + \beta_{01} \text{Distress} + \gamma_{0} \]
\[ \pi_1 = \beta_{10} + \beta_{11} \text{Distress} \]
\[ \pi_2 = \beta_{20} \]
\[ \pi_3 = \beta_{30} + \beta_{31} \text{Distress} \]
\[ \pi_4 = \beta_{40} + \beta_{41} \text{Distress} \]
\[ \pi_5 = \beta_{50} + \beta_{51} \text{Distress} \]
\[ \pi_6 = \beta_{60} + \beta_{61} \text{Distress} \]

In this equation, Pain\(_{t}\) indicates the numerical pain rating (0–100) at pulse \(t\) for person \(i\), Session Order\(_{t}\) denotes the effects of repetitive application of the stimuli across stress conditions and drug sessions (sessions 1–4), Pulse denotes the temporal summation task pulse number (1–10), Stress denotes the main effect of stressor condition (0 = rest; 1 = stress task), and the Stress × Pulse interaction captures potential stressor effects on temporal summation slopes. Drug denotes the main effect of drug condition (0 = placebo; 1 = drug), the Drug × Pulse interaction captures potential drug effects on temporal summation slopes, and Distress denotes stress reactivity (positive values reflect increases in distress from baseline to stress task). Of primary interest for stress reactivity analyses were the interactions of distress with stressor condition (\(\beta_{31}\)) and drug (\(\beta_{51}\)) condition, which focused on initial pain ratings in the temporal summation protocol (intercepts), and the distress × stress × pulse (\(\beta_{41}\)) and distress × drug × pulse (\(\beta_{61}\)) interactions, which focused on temporal summation slopes (index of central sensitization). The possibility that assigned rest/stress condition order or drug condition order might have confounded primary results was considered; preliminary analyses indicated that neither of these order variables significantly influenced temporal summation outcomes (\(P > 0.30\)).

To account for multiple testing (ie, stress condition, drug condition, and stress reactivity each examined as moderators of initial pain ratings and temporal summation slopes), we used the Benjamini–Hochberg false discovery rate correction to control for the rate of type I errors by adjusting the \(P\)-value based on the number of significant results in a family of tests.\(^{11} \) Significant interactions were probed, simple slopes were calculated using the online calculator of Preacher et al.,\(^{37} \) and interaction patterns are presented graphically for higher (ie, +1 SD) and lower (−1 SD) values of continuous moderators.

### 3. Results

#### 3.1. Sample characteristics and manipulation checks

Sample characteristics are described in **Table 1**. Participants were predominantly young and male, Anglo-American, and had a healthy body weight. As a manipulation check, the stressors were associated with significant increases in self-reported distress (on a 0–8 scale) in both the placebo (mean change = 1.8, SD = 3.7; \(t[71] = 4.10, P < 0.001; \text{Cohen } d = 0.48\)) and the naltrexone (mean change = 2.2, SD = 4.6; \(t[70] = 4.11, P < 0.001; \text{Cohen } d = 0.49\)) conditions. Significant mean changes from initial to maximal pain ratings during the temporal summation protocol, consistent with temporal summation of pain,\(^{8} \) were observed for the placebo/rest (mean change = 16.8, SD = 14.1; \(t[71] = 10.15, P < 0.001; \text{Cohen } d = 1.20\)), placebo/stress (mean change = 16.8, SD = 14.9; \(t[71] = 9.59, P < 0.001; \text{Cohen } d = 1.13\)), naltrexone/rest (mean change = 17.1, SD = 14.1; \(t[71] = 10.29, P < 0.001; \text{Cohen } d = 1.21\)), and naltrexone/stress (mean change = 19.1, SD = 14.9; \(t[71] = 10.91, P < 0.001; \text{Cohen } d = 1.29\)) conditions. Together, these manipulation checks confirm that the stressors elicited increased self-reported distress as expected and the quantitative sensory testing protocol elicited increased pain ratings across stimuli consistent with temporal summation of pain.

#### 3.2. Stressor condition effects on temporal summation of pain

Pain ratings across the temporal summation protocol for rest and stress conditions during the placebo session are presented in **Figure 1**. Analyses revealed that under placebo, the stress manipulation was associated with significant changes in intercepts among participants (\(b = -3.43, \text{SE} = 0.89, t[1230] = 3.86, P < 0.001\)), such that initial pain ratings in the temporal summation stimulus series were lower in the stress than rest condition. This is consistent with an SIA effect. Stressor condition was not, however, associated with temporal summation slopes

| Table 1 |
|---|
| Descriptive characteristics. |
| Mean (SD) or n (%) |
| **Sociodemographic** |
| Age (y) | 20.8 (2.7) |
| Gender | |
| Female | 25 (35%) |
| Male | 47 (65%) |
| Race/ethnicity | |
| White | 61 (85%) |
| African American | 3 (4%) |
| Asian | 5 (7%) |
| Hispanic | 1 (1%) |
| Other | 2 (3%) |
| Marital status | |
| Single | 66 (92%) |
| Married | 4 (1%) |
| Missing | 5 (7%) |
| Education (y) | 14.4 (2.4) |
| Body mass index (kg/m²) | 24.6 (3.9) |
| **Stress reactivity** |
| Distress at rest (placebo) | 4.1 (3.4) |
| Distress during stress (placebo) | 5.9 (4.2) |
| Distress at rest (naltrexone) | 4.1 (3.2) |
| Distress during stress (naltrexone) | 6.4 (5.2) |
| **Temporal summation** |
| Placebo, rest condition | |
| Initial pain rating | 64.6 (19.0) |
| Maximal pain minus first pain rating | 16.8 (4.1) |
| Placebo, stress condition | |
| Initial pain rating | 62.1 (19.6) |
| Maximal pain minus first pain rating | 16.8 (4.1) |
| Naltrexone, rest condition | |
| Initial pain rating | 63.5 (17.7) |
| Maximal pain minus first pain rating | 17.1 (14.1) |
| Naltrexone, stress condition | |
| Initial pain rating | 59.2 (18.9) |
| Maximal pain minus first pain rating | 19.1 (14.9) |
Neither gender nor age moderated stressor effects on intercepts or temporal summation slopes among participants in the placebo condition (Ps > 0.08). However, the age × pulse interaction \( (b = -0.19, SE = 0.05, t[1,227] = 3.90, P < 0.001) \) revealed increased temporal summation slopes \( b \) (ie, greater central sensitization) in relatively younger as compared with relatively older participants.

Stress reactivity (ie, changes in distress from baseline to the end of the stressors) moderated associations between stress condition and initial pain ratings \( (b = -2.52, SE = 0.88, t[1,227] = 2.86, P = 0.004) \). Simple slope analysis revealed significantly lower initial pain ratings in the stress than the rest condition among participants with higher stress reactivity \( (b = -5.92, SE = 1.24, t[1,227] = 4.78, P < 0.001) \); in contrast, initial pain ratings did not differ between stress and rest conditions for participants with lower stress reactivity \( (b = -0.89, SE = 1.25, t[1,227] = 0.71, P = 0.48) \) \( \) (Fig. 2). Stress reactivity did not moderate associations between stress condition and temporal summation slopes \( (b = 0.11, SE = 0.17, t[1,227] = 0.63, P = 0.53) \).

### 3.3. Main and interactive effects of drug and stressor condition on temporal summation of pain

Naltrexone administration was associated with changes in initial pain ratings (intercept) during the temporal summation protocol \( (b = -1.37, SE = 0.70, t[2,533] = 1.97, P < 0.05) \), such that initial pain ratings were lower under opioid blockade than placebo. Drug condition was not, however, associated with temporal summation slopes \( (b = 0.13, SE = 0.14, t[2,533] = 0.94, P = 0.35) \). The main effect of stressor on initial pain ratings described above remained significant in this drug effect model \( (b = -3.35, SE = 0.70, t[2,533] = 4.81, P < 0.001) \), indicating an SIA effect on initial pain ratings independent of opioid blockade status. In addition, a significant main effect of session order \( (b = 0.36, SE = 0.18, t[2,533] = 2.04, P = 0.04) \) revealed increasing initial pain ratings in the temporal summation protocol with each successive exposure to the protocol \( (2 \) trials per session across 2 lab sessions [placebo/naltrexone]). Stressor and drug condition did not interact to predict initial pain ratings \( (b = 0.06, SE = 1.39, t[2,531] = 0.04, P = 0.97) \) or temporal summation slopes \( (b = 0.01, SE = 0.27, t[2,531] = 0.05, P = 0.96) \). Hence, subsequent moderator analyses excluded this 3-way interaction and focused on the drug \( \times \) pulse and stress \( \times \) pulse interactions.

There was a significant gender \( \times \) drug \( \times \) pulse interaction on temporal summation slopes \( (b = -0.65, SE = 0.28, t[2,526] = 2.30, P = 0.02) \). Simple slope analysis revealed increased temporal summation slopes for women in the naltrexone \( (b = 2.04, SE = 0.20, t[2,528] = 10.36, P < 0.001) \) compared with placebo condition \( (b = 1.49, SE = 0.20, t[2,528] = 7.45, P < 0.001) \), indicating EO inhibition of temporal summation in women, independent of stress effects. In contrast, minimal difference in slopes was observed for men in the naltrexone \( (b = 0.97, SE = 0.14, t[2,528] = 6.79, P < 0.001) \) compared with placebo conditions \( (b = 1.07, SE = 0.14, t[2,528] = 7.53, P < 0.001) \) \( \) (Fig. 3).

Age did not significantly moderate stressor or drug condition effects on temporal summation slopes \( (Ps > 0.83) \). However, the age \( \times \) drug interaction was significant for initial pain ratings \( (b = -0.59, SE = 0.27, t[2,528] = 2.20, P = 0.028) \). Simple slope analysis revealed more significant naltrexone-related decreases in initial pain ratings for relatively older \( (b = -12.65, SE = 6.17, t[2,528] = 2.05, P = 0.04) \) than relatively younger participants \( (b = -9.48, SE = 4.74, t[2,528] = 2.00, P < 0.05) \). In addition, the age \( \times \) pulse interaction was significant \( (b = -0.10, SE = 0.05, t[2,528] = 2.28, P = 0.023) \); as for the placebo condition, increased temporal summation slopes were noted in relatively younger participants.

Stress reactivity moderated associations between drug condition and initial pain ratings \( (b = -2.84, SE = 0.79, t[2,528] = 3.62, P < 0.001) \), with significantly lower initial pain ratings in the naltrexone than the placebo condition among participants with higher stress reactivity \( (b = -4.40, SE = 1.08, t[2,528] = 4.07, P < 0.001) \). In contrast, initial pain ratings did not differ significantly between drug conditions for participants with lower stress reactivity \( (b = 1.28, SE = 1.01, t[2,528] = 1.27, P = 0.20) \) \( \) (Fig. 4). Stress reactivity did not moderate the association between drug condition and temporal summation slopes \( (b = 0.03, SE = 0.15, t[2,528] = 0.19, P = 0.85) \).
between SIA effects on initial pain ratings in the temporal summation protocol (intercept) and the temporal summation slope that is the marker for central sensitization. In the current study, a significant SIA effect was observed when EO systems were intact (placebo condition), although this effect was noted only for initial pain ratings in the temporal summation series. Findings that a greater “stress dose” was associated with greater SIA on this measure supports the stress-specific effects of this finding. Stress-induced analgesia effects on initial pain ratings in the temporal summation protocol are consistent with prior work indicating SIA effects on static evoked pain stimuli. In contrast, there was no SIA effect on temporal summation slope under placebo in the current work, arguing against the hypothesis that SIA specifically inhibits expression of central sensitization.

The current findings have methodological implications for studies using temporal summation protocols. There are several alternative methods for quantifying temporal summation, with one being the slope of the pain ratings across temporal summation trials and another being simple difference scores (eg, pain ratings for the maximal minus the first temporal summation trial). Although our primary temporal summation analyses adopted the slope method, we also reported values obtained with the latter method to facilitate comparison across studies. Mean changes from initial to maximal pain ratings in the present study (≥16 point pain increase across conditions) were greater than those reported in other studies of healthy adults (eg, 10 point pain increase). Temporal summation results using various methods available are generally highly intercorrelated. The current findings indicate that elevated stress can significantly reduce the first rating in a temporal summation series, an effect potentially exaggerating the apparent magnitude of temporal summation if based on simple difference scores. Thus, temporal summation values based on difference scores may be more susceptible to confounding by recent stress exposure than slope-based temporal summation measures, which the current work indicates are not significantly influenced by stress effects.

Whether EO mechanisms contribute to SIA effects on temporal summation has not previously been explored. In the overall sample, naltrexone vs placebo condition did not alter SIA effects on initial pain ratings or slope in the temporal summation protocol. To the extent that initial pain ratings in the temporal summation protocol might be considered a static evoked pain measure, absence of opioid blockade effects on these initial ratings in the current work stand in contrast to significant opioid blockade effects (ie, endogenous opioid-mediated inhibition) on static evoked pain responses to a cold-pressor pain stimulus reported previously in the current sample. It is possible that the relatively extended nature of the cold-pressor stimulus relative to the brief thermal stimuli in the current protocol could have affected on these differing patterns of findings regarding opioid inhibition. Overall, in the current study, there was no evidence of EO mechanisms contributing to the effects of acute stress on temporal summation outcomes. However, irrespective of stress effects, other findings supported possible EO inhibition of temporal summation slope (ie, central sensitization), at least in females. Specifically, in females but not males, opioid blockade with naltrexone significantly increased temporal summation slope across stimuli relative to the placebo condition (ie, disinhibition of central sensitization), a finding independent of any stress effects. This effect could simply represent regression to the mean over temporal summation trials in females when administered naltrexone, although the within-subject nature of the comparisons might argue against this. Nonetheless, this finding suggestive of EO inhibition of temporal summation stands in contrast to negative results of the 2 previous opioid blockade studies evaluating this issue. Differences between the current findings and these latter 2 studies may be because of the fact that both prior studies were conducted in small samples.
consisting largely of individuals with diverse chronic pain conditions rather than healthy individuals as in the current work.

Sex-specific opioidergic inhibition of temporal summation might be expected, given previous work suggesting sex differences in EO systems.18,46,46,56 The current results build on a previous study using positron emission tomography imaging in healthy individuals, which reported that greater temporal summation was associated with lower basal opioid receptor density (presumably reflecting less EO inhibition) in pain-relevant motor areas of the brain.55 In contrast to the current work, these latter findings were observed in an all-male sample. Although sex-specificity of the current findings requires replication because of the modest sample size of female participants, further investigation seems warranted regarding possible EO inhibition of central sensitization. If confirmed, these results raise the possibility that interventions for chronic pain that can enhance EO tone (eg, aerobic exercise training17) could potentially have beneficial effects on central sensitization in women.

Examination of opioid blockade effects also revealed an intriguing finding of potential mechanistic relevance to SIA. In individuals responding to the acute stressors with a greater stress response, a notable paradoxical analgesia was observed on initial temporal summation ratings when EOs were blocked by naltrexone. Although the source of this effect cannot be directly tested in the current work, we speculate that it may reflect activation of nonopioid SIA mechanisms. Endogenous opioids serve to inhibit physiological stress responses.30,31 In the present study, opioid blockade with naltrexone may have exaggerated the paradoxical analgesia noted with naltrexone, which reflected observed. Moreover, carryover effects would not explain the paradoxical naltrexone analgesia that was observed argues against ceiling effects substantially confounding our results. Findings of significant naltrexone-induced increases in temporal summation slope in females (independent of stress effects) are also inconsistent with ceiling effects being a significant confound.

In summary, the current results indicate that acute psychosocial stress elicited SIA that reduced initial pain ratings in the temporal summation protocol but did not influence the temporal summation slope. This latter finding argues against SIA specifically inhibiting expression of central sensitization. There was no evidence that EO mechanisms contributed to observed SIA effects on initial pain ratings. However, EO function did appear to inhibit central sensitization (temporal summation slopes) independent of stress effects, although only in females.

Disclosures
The authors have no conflict of interest to declare.

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