Age does not affect sex effect of conditioned pain modulation of pressure and thermal pain across 2 conditioning stimuli

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Abstract
Introduction: Conditioned pain modulation (CPM) is a laboratory test resulting in pain inhibition through activation of descending inhibitory mechanisms. Older adults consistently demonstrate reduced CPM compared with younger samples; however, studies of sex differences in younger cohorts have shown mixed results.

Objectives: This study tested for sex differences in CPM within samples of younger and older adults.

Methods: Participants were 67 younger adults (mean age = 25.4 years) and 50 older adults (66.4 years). Study conditioning paradigms were the cold-pressor test and contact heat pain administered in separate sessions. Pressure pain threshold and ramping suprathreshold heat were the test stimuli across three time points after presentation of the conditioning stimuli (CS).

Results: Significant inhibition was observed during both testing sessions. The hypothesis for sex differences across both age cohorts was supported only for ΔPPTh. However, sex differences did not reach significance for either paradigm using ascending suprathreshold heat as the test stimuli. The overall trend was that younger males experienced the strongest CPM and older females the weakest. From a methodological perspective, duration differences were seen in CPM, with inhibition decaying more quickly for PPTh than for suprathreshold heat pain. Furthermore, there were no differences in inhibition induced by cold-pressor test and contact heat pain as CS.

Conclusion: Sex differences were similar across both age cohorts with males experiencing greater inhibition than females. Cross-sectional associations were also demonstrated between CPM inhibition and measures of recent pain, further supporting CPM as an experimental model with clinical utility.

Keywords: Sex differences, Aging, Conditioned pain modulation, Conditioning stimulus, Test stimulus, CPM duration

1. Introduction
The experience of pain is a dynamic balance of excitatory and inhibitory endogenous modulatory mechanisms. Studies of pain processing systems frequently use laboratory protocols that engage pain inhibition. The phenomenon of diffuse noxious inhibitory controls is established in animal models and implicates the existence of an endogenous pain modulation system. The basic principle is “pain-inhibition-by-pain” where pain in a local area is inhibited by a second pain administered heterotopically. The term “conditioned pain modulation” (CPM) is used to refer to this phenomenon in humans and the resulting pain inhibition is thought to be a consequence of the activation of descending inhibitory mechanisms.

A number of studies have shown that deficits in CPM are associated with a range of pain disorders, suggesting that a shift in balance between pain facilitation and pain inhibition is either antecedent to or the result of prolonged pain. Six studies have reported reduced pain inhibition associated with older age using protocols consistent with CPM. A larger number of studies have examined sex differences in CPM, typically in samples of healthy younger adults, but with mixed findings. A recent review concluded that about 40% of the publication have found males showing greater CPM than females. Few studies have compared the magnitude of sex differences across age cohorts.

This study tested the hypothesis that sex differences will be observed within samples of both younger and older adults using 2 well-validated laboratory pain modalities, the cold-pressor test (CPT) and contact heat pain (CHP) as conditioning stimuli (CS), in separate
sessions. After consensus recommendations,2 test stimuli (TS) have been used: an ascending thermal stimulus to pain at 40 (0–100) and pressure pain threshold (PPTh). An innovative aspect of the current methodology allowed testing the duration of CPM through 30 minutes across 4 combinations of stimuli and comparisons across 4 age–sex subgroups. We hypothesize that CPM would be significant at 3 and 15 minutes after presentation of the CS but not at 30 minutes. We also examined differences between the CPT and CHP to the foot, providing sensory input at the same spinal level and ascending–descending long tract activity. It was also hypothesized that significant associations between CPM and measures of recent pain will occur while adjusting for age and sex as a test of clinical relevance.

2. Materials and methods

2.1. Participants

Participants were 67 younger adults (age: mean = 25.4, SD = 6.8, range: 19–49 years; 36 females and 31 males) and 50 older adults (age: mean = 66.4, SD = 5.9, range: 56–77 years; 26 females and 24 males) and were balanced on race and ethnicity.

Interested individuals reviewed and signed an informed consent form. Eligibility was determined after completion of a health history questionnaire and interview. Study exclusion criteria included a Mini Mental Status score below 23,6 current use of narcotics or chronic use of analgesics, uncontrolled hypertension, systemic disease that restricts normal daily activities, neurological problems with significant changes in somatosensory perception, or serious psychiatric conditions. Recruits who received a grade 4 on the Graded Chronic Pain Scale (GCPS) (high disability–severely limiting) were excluded. The sampling strategy was to increase external validity by recruiting and study procedures.

2.2. Orientation and training session

Participants watched a video that described the study, the testing protocols, and rating pain in the 0 to 100 pain scale. Multiple training trials were administered using the study stimuli and sites while participants practiced using the pain rating system.

2.3. Testing sessions

This report used data collected during 2 sessions where only CPM testing was performed that occurred within the same calendar week with at least one washout day. No participants dropped out between CPM sessions; however, 5 participants discontinued after the orientation session. To start each session, participants relaxed in a comfortable chair for several minutes, and were shown the video presentation seen during the orientation session.

Conditioned pain modulation was assessed using a within-session design with the order of the 2 CS sessions counter-balanced across participants. Two trials of PPTTh followed by one trial of ascending contact heat stimuli to a pain rating of 40 (0–100 scale) were the study TS and were administered at baseline followed by administration of the conditioning stimulus (CS) assigned to that session. The CS consisted of the CPT or CHP, which were administered in 4 × 45-second trials with approximately 60 seconds between trials. Forty-five-second trials were used to ensure a robust inhibitory response among responders, reduce the potential for participants to withdraw early, and avoid vasovagal syncope. Participants were told that they may withdraw at any time by lifting their foot; however, none discontinued any trial. Subjects made a verbal rating of pain intensity on a 0 to 100 scale at 40 seconds during each CS trial that was averaged. The Situational Pain Catastrophizing Scale was administered verbally during the later breaks between CS trials. Post-CS trials of the TS occurred at 3, 15, and 30 minutes after the termination of the last CS trial (Fig. 1).

2.3.1. Pressure pain threshold

A handheld Medoc Digital Pressure Algometer with a 10-mm diameter tip was used for the mechanical procedures. To assess PPTTh, increasing pressure was applied centrally over the extensor/superior muscle group on the nondominant dorsal forearm at a rate of 0.25 kg per second. The participant was instructed to press a button when he or she first felt pain, at which time the device recorded the pressure in kilograms.

2.3.2. Ascending suprathreshold heat pain (Pain40)

The thermal stimulus was delivered to the midpoint of the nondominant ventral forearm with a computer-controlled Medoc Pathway Thermal Sensory Analyzer (Ramat Yishai, Israel) using a 16 × 16-mm thermode. Pain was measured with an electronic visual analogue scale and a low-friction sliding potentiometer of 100-mm travel with the position of the slider electronically converted into a pain rating between 0 and 100. For the Pain40 measure, heat stimulus was applied in an ascending intensity (0.25°C per second) beginning at 43°C until a pain rating of 40 is achieved. The dependent variable was the temperature recorded at Pain40.

2.3.3. Cold-pressor test

Participants immersed their dominant foot to the ankle into a water bath cooled by a Neslab refrigerated water circulator (Neslab, Portsmouth, NH). Water was continuously recirculated to prevent local warming and was maintained at a constant temperature. The water level was set at a height of 7 cm to keep the simulated area consistent. The temperature used for the first trial (8°C for males and 10°C for females) was adjusted on subsequent trials as needed to target pain ratings between 40 and 60.

2.3.4. Contact heat pain

Thermal stimuli were delivered using the Medoc Pathway and the 16 × 16-mm thermode. The thermode was placed and held with moderate pressure on the bottom of the dominant foot immediately above the heel within the L4, L5 dermatome. The

| Baseline | Conditioning stimuli | 3-min post-CS | 15-min post-CS | 30-min post-CS |
|----------|----------------------|---------------|----------------|----------------|
| PPTTh Pain40 | CP or CHP 4 × 45-sec | PPTTh Pain40 | PPTTh Pain40 | PPTTh Pain40 |

Key: CS = final trial of the conditioning stimulus, PPTTh = pressure pain threshold, Pain40 = temperature where a pain rating of 40 is reached, CP = cold pressor task, CHP = contact heat pain.

Figure 1. Timeline showing session progression.
temperature used for the first trial (47°C for males and 46°C for females) was adjusted on subsequent trials as needed to target pain ratings between 40 and 60.

2.4. Self-report measures

The Situational Pain Catastrophizing Scale (S-PCS) is a 6-item adaptation of the Pain Catastrophizing Scale that assesses situation specific catastrophizing.2 This instrument asks about negative thoughts associated with the experimental pain just experienced. The Short-Form Health Survey-36 is a health survey that measures physical and psychological health.37,38 We adapted the time frame to the past 3 months. This study used the SF-36 Bodily Pain Scale in which a higher score indicates less bodily pain. The study primary dependent variable was the bodily pain score of the SF-36, the GCPS pain intensity and pain disability scores, pain duration, and the number of pain sites reported. In addition, the GCPS allows for the calculation of a chronic pain grade with 5 hierarchical categories: grades 0 (no pain) to 4 (high disability-severely limiting).

2.5. Statistical methods

SPSS version 23 was used for statistical analysis. Descriptive statistics were calculated for the study variables. Paired-samples t-tests were used to determine whether significant CPM occurred for each age-sex subgroup at each time point by comparing the baseline with the post-CS values. The study primary dependent variables, ΔPPTθ and ΔPain40, were calculated as the difference between the baseline and the post-CS values at each time point so that greater CPM is represented by a negative number.41 Interclass correlations or Pearson correlations were calculated within and across sessions for baseline PPTθ and Pain40 and within and across sessions for ΔPPTθ and ΔPain40.

Age and sex differences for each of the outcome variables (ΔPPTθ and ΔPain40) were tested using 4-way repeated-mesures analyses of variance (ANOVA). S-PCS scores were entered as covariates. PARADIGM (CPT, CHP) and TIME (3, 15, and 30 minutes) were within-subject factors and AGE and SEX were between-subjects factors. For ease of presentation, nonsignificant effects are not described with the exception of the AGE × SEX interaction, which tested one of the study hypotheses. The Greenhouse–Geisser degrees of freedom adjustment was used when the assumption of sphericity was violated.41 A critical value of $P = 0.05$ was used as the cut point for interpretation of omnibus ANOVA effects. Next, correlations and multiple linear regression were used to test for associations between overall CPM and recent bodily pain. Conditioned pain modulation indices were created by averaging CPM across the 3 time points and creating CPT-ΔPain40 index, CHP-ΔPain40 index, CPT-ΔPPTθ index, and CHP-ΔPPTθ index. In step 1, age, sex, and the S-PCS were entered to adjust for differences. In step 2, the bodily pain score of the SF-36, the GCPS pain intensity and pain disability scores, pain days, and the number of pain sites were tested using the F to change statistic increase in $R^2$.

3. Results

Mean and SD for the self-reported pain measures by age and sex are presented in Table 1. There were no differences across age group ($P = 0.452$) or sex ($P = 0.631$) in assignment to GCPS classifications31 (overall frequencies: 0-no pain = 40%, 1-low intensity = 36%, 2-high intensity = 15%, 3-moderately limiting = 9%). Mean and SD for the temperature and pain ratings for the CPT and CHP by age and sex are presented in Table 2. For the CPT, age ($P = 0.09$) and sex differences ($P = 0.06$) in the temperature approached significance. For the CHP, the mean temperature for the younger adults was lower than that for the older group ($P = 0.044$). No age or sex differences were seen for the pain intensity during the CS for either CPM session.

Interclass correlations between baseline values for both PPTθ ($r = 0.80$) and Pain40 ($r = 0.72$) were significant at $P < 0.001$, suggesting good reliability for the study TS.4 Correlations between baseline TS within-session (PPTθ − Pain40) were $r = 0.40$ and $r = 0.43$ for CPT and CHP, respectively.

Mean and SD for ΔPPTθ and ΔPain40 at each time point are presented in Tables 3 and 4 by age and sex. The results of paired-samples t-tests between baseline and post-CS values are also presented in Tables 3 and 4 for each subgroup at each time point. ΔPPTθ and ΔPain40 were not associated with the CS testing temperatures or the pain experienced during administration of the CPT or CHP ($P > 0.05$). However, the S-PCS was significantly correlated with ΔPPTθ during the CPT and ΔPain40 for both the CPT and CHP and was used as a covariate in testing the study hypotheses. Correlations between the CPM experienced during CPT and CHP trials for ΔPPTθ and ΔPain40 are presented in Table 5.

3.1. Age and sex differences in conditioned pain modulation using analysis of variance

For ΔPPTθ, the TIME $F(1,1643,111) = 17.625, P < 0.001$, AGE $F(1,111) = 5.623, P = 0.041$, and SEX $F(1,111) = 5.459, P = 0.044$ effects were significant. The AGE × SEX interaction was not significant. Conditioned pain modulation decreased from 3
Table 2

Mean and SD for the temperature and pain ratings by age and sex for both the CPT and CHP models.

|                | Cold-pressor test paradigm | Contact heat pain paradigm |
|----------------|---------------------------|---------------------------|
|                | Temperature | Pain rating | Temperature | Pain rating |
| Younger        | 9.7°C (2.6)* | 56.5 (15.2) | 46.3°C (1.4) | 47.9 (8.8) |
| Older          | 8.6°C (2.8)* | 55.7 (16.0) | 47.0°C (1.4) | 48.2 (9.6) |
| Males          | 8.4°C (2.7)† | 55.7 (14.5) | 46.8°C (1.5) | 48.2 (9.9) |
| Females        | 9.6°C (2.7)† | 57.5 (17.3) | 46.4°C (1.4) | 47.7 (8.3) |
| Total sample   | 9.2°C (2.7)† | 56.1 (16.3) | 46.6°C (1.4) | 48.0 (9.1) |

* Approached significance, *P* = 0.09.
† Significantly different, *P* = 0.06.
‡ Significantly different, *P* = 0.04.
CPT, cold-pressor test.

Each time point indicate that at 3 minutes, the younger group (mean = -0.08, 95% CI = -1.16 to -0.80) differed from the older group (-0.39, 95% CI = -0.60 to -0.18). At 15 minutes, the younger group (-0.80, 95% CI = -0.99 to -0.62) differed from the older group (-0.33, 95% CI = -0.54 to -0.11). At 30 minutes, the younger group (-0.38, 95% CI = -0.61 to -0.15) did not differ from the older group (-0.15, 95% CI = -0.40 to 0.10).

3.1.2. Contact heat pain for \( \Delta \text{Pain40} \)

The 3-way ANOVA (TIME × AGE × SEX) for the CHP paradigm resulted in significant effects for TIME [F(1, 879, 208, 540) = 5.320, *P* = 0.007] and AGE [F(1, 111) = 12.108, *P* = 0.001]. The main effect of SEX approached significance [F(1, 111) = 2.987, *P* = 0.077]. The AGE × SEX interaction was not significant. Figure 4 presents mean and SE across time and for each age group. Pairwise comparisons at each time point indicated that CPM was greater at the 3-minute (mean = -0.62, 95% CI = -0.76 to -0.48) and 15-minute time points (-0.70, 95% CI = -0.87 to -0.51) compared with the 30-minute time point (-0.27, 95% CI = -0.44 to -0.10). Conditioned pain modulation at 3 minutes and 15 minutes were not significantly different (*P* = 0.09). When collapsed across time, younger adults experienced greater inhibition (-0.80, 95% CI = -0.98 to -0.63) when compared with the older group (-0.34, 95% CI = -0.54 to 0.14).

3.2. Conditioned pain modulation and recent pain

Correlations between the CPM indices and the self-reported measures of recent pain are presented in Table 6. For the CPT-\( \Delta \text{PPT} \), the addition of the pain variables resulted in an increase in \( R^2 \) of 0.12 [\( \Delta F(5,108) = 4.179, *P* = 0.002 \)] with the GCPS disability score significant (*P* = 0.014). For the CHP-\( \Delta \text{PPT} \), the addition of the pain variables resulted in an increase in \( R^2 \) of 0.15 [\( \Delta F(5,108) = 4.648, *P* = 0.001 \)] with the GCPS number of painful sites significant (*P* = 0.006). For the CPT-\( \Delta \text{Pain40} \) the addition of the pain variables resulted in an increase in \( R^2 \) of 0.12 [\( \Delta F(5,108) = 3.741, *P* = 0.006 \)] with the GCPS disability score significant (0.006). For the CHP-\( \Delta \text{Pain40} \), the addition of the pain variables resulted in an increase in \( R^2 \) of 0.15 [\( \Delta F(5,108) = 5.046, *P* < 0.001 \)] with the GCPS disability score significant (*P* = 0.001).

Table 3

Unadjusted mean and SD for \( \Delta \text{PPT} \) for each time point by age and sex groupings.

|                | Cold-pressor test paradigm | Contact heat pain paradigm |
|----------------|---------------------------|---------------------------|
|                | 3-minute, mean (SD) | 15-minute, mean (SD) | 30-minute, mean (SD) | 3-minute, mean (SD) | 15-minute, mean (SD) | 30-minute, mean (SD) |
| Younger males  | -0.71 (0.69)* | -0.37 (0.57)* | -0.09 (0.49) | -0.67 (0.69)* | 0.47 (0.63)* | -0.14 (0.63) |
| Younger females| -0.35 (0.54)* | -0.16 (0.46) | 0.03 (0.45) | -0.26 (0.61)* | -0.11 (0.64) | -0.04 (0.68) |
| Older males    | -0.27 (0.53)* | -0.19 (0.43) | -0.01 (0.63) | -0.23 (0.52) | -0.12 (0.64) | -0.03 (0.58) |
| Older females  | -0.21 (0.64) | 0.03 (0.56) | 0.20 (0.79) | -0.25 (0.73) | -0.01 (0.61) | 0.16 (0.64) |
| Younger group  | -0.51 (0.63)* | -0.20 (0.53)* | -0.03 (0.47) | -0.45 (0.68)* | -0.23 (0.64)* | -0.08 (0.65) |
| Older group    | -0.24 (0.58)* | -0.08 (0.55) | 0.11 (0.73) | -0.24 (0.63)* | -0.06 (0.62) | 0.07 (0.61) |
| Males          | -0.52 (0.65)* | -0.29 (0.52)* | -0.06 (0.56) | -0.48 (0.65)* | -0.26 (0.64)* | -0.09 (0.61) |
| Females        | -0.29 (0.58)* | -0.02 (0.49) | 0.12 (0.62) | -0.26 (0.66)* | -0.07 (0.63) | 0.04 (0.67) |
| Total sample   | -0.40 (0.62)* | -0.15 (0.59)* | 0.04 (0.59) | -0.36 (0.66)* | -0.16 (0.64)* | -0.02 (0.64) |

These values are the difference in kg for the pressure at which pain threshold was achieved at baseline minus the pain threshold at each reference time point. Therefore, a smaller negative number represents a larger CPM effect. The Levene test was not significant comparing across the Age × Sex subgroups at each time point indicating that the assumption of homoscedasticity was not violated.

* Significant difference between baseline and post-CS values at *P* < 0.01 for that group and time interval using the paired-sample *t*-test and indicates a significant CPM effect.

CPM, conditioned pain modulation; PPT, pain pressure threshold.
4. Discussion

The study hypothesis for sex differences in both age cohorts was only supported for ΔPPTh as the sex effect was significant in the absence of an age by sex interaction. However, sex differences did not reach significance for either paradigm using ascending suprathreshold heat as the TS. A new finding was that younger males experienced the strongest CPM and older females the weakest, with an age effect larger than the sex effect. Earlier studies have not examined data across age–sex subgroups. The data also revealed duration differences with inhibition of PPTh decaying more quickly than pain induced by ascending suprathreshold heat. In addition, cross-sectional associations were demonstrated between measures of CPM and recent pain.

4.1. Methodological considerations

A 2013 consensus meeting called for greater standardization of procedures for performing CPM. Recommendations included the addition of a second test stimulus and second CPM conditioning protocol to permit comparisons. Avoiding concurrent administration of CS and TS was recommended because sequential test protocols represent a cleaner measure of CPM. Furthermore, the use of contralateral sites on the upper limb and lower limb was suggested. This study followed these recommendations. The rationale for different initial temperatures between males and females is the well-documented sensitivity differences. Conditioned pain modulation is based on the "pain-inhibition-by-pain" principle and our target is to standardize the level of pain of the CS and not the stimulus intensity. This also eliminated to possibility of only mild CS-related pain in less sensitive males because several studies have shown that CS-related pain of >20 is needed for consistent CPM.

Reliability of CPM is dependent on the reliability of the TS used. Performing 2 CPM sessions allowed for the calculation of reliability coefficients for the study TS by comparing the baseline values across both sessions. Interclass correlations across sessions for PPTh (r = 0.80) and Pain40 (r = 0.72) were within the range considered good reliability. Reaction time was minimized because slow ramping speeds were used for both stimuli. Correlations between baseline levels for PPTh and Pain40 (within-session) were only moderate (shared variance of approximately 16%). However, this is consistent with studies showing pressure threshold and heat pain load on different components after factor analysis.

Cold-pressor test has demonstrated better reliability and produces a stronger CPM effect when compared with other modalities. This study found that both CPT and CHP results in robust inhibition that was similar in magnitude. However, differences in the time course and magnitude in circulating substance P, β-endorphin, and several cytokines after CPT compared with CHP have been demonstrated, suggesting differing mechanisms, at least peripherally. Studies have examined whether pain level or stimulus intensity drives CPM with mixed findings. The current study adjusted the pain level of the CS and not the stimulus intensity. This also eliminated to possibility of only mild CS-related pain in less sensitive males because several studies have shown that CS-related pain of >20 is needed for consistent CPM.

Table 4

Unadjusted mean and SD for ΔPain40 for each time point by age and sex groupings.

|                      | Cold-pressor paradigm | Contact heat pain paradigm |
|----------------------|-----------------------|---------------------------|
|                      | 3-minute, mean (SD)   | 15-minute, mean (SD)      | 30-minute, mean (SD)   |
|                      |                       |                           |                           |
| Younger males (n = 31) | −1.05 (0.89)*        | −0.92 (0.81)*             | −0.67 (0.97)*            |
| Younger females (n = 26) | −0.94 (0.89)*        | −0.70 (0.91)*             | −0.19 (0.99)             |
| Older males (n = 24)   | −0.40 (0.79)*        | −0.42 (0.79)*             | −0.16 (0.98)             |
| Older females (n = 26) | −0.34 (0.79)*        | −0.20 (0.85)*             | −0.13 (0.82)             |
| Younger group (n = 67) | −0.99 (0.89)*        | −0.81 (0.87)*             | −0.39 (0.94)*            |
| Older group (n = 50)   | −0.37 (0.76)*        | −0.31 (0.74)*             | −0.15 (0.89)             |
| Males (n = 55)         | −0.77 (0.81)*        | −0.68 (0.76)*             | −0.42 (0.90)             |
| Females (n = 62)       | −0.69 (0.85)*        | −0.49 (0.87)*             | −0.16 (0.84)             |
| Total sample (n = 117) | −0.73 (0.83)*        | −0.59 (0.82)*             | −0.30 (0.90)             |

These values are the difference in °C for the temperature at which a pain rating of 40 (0–100 scale) was achieved at baseline minus the temperature for Pa in40 at each referenced time point. Therefore, a smaller negative number represents a larger CPM effect. The Levene test was not significant comparing across the Age × Sex subgroups at each time point indicating that the assumption of homoscedasticity was not violated.

Table 5

Correlations within and across sessions at each time point for test stimuli.

|                      | 3-minute | 15-minute | 30-minute |
|----------------------|----------|-----------|-----------|
| ΔPPTh (CPT, CHP)     | 0.61***  | 0.40***   | 0.30**    |
| ΔPain40 (CPT, CHP)   | 0.53***  | 0.41***   | 0.16      |
| CPT (ΔPPTh, ΔPain40) | 0.36***  | 0.29**    | 0.20*     |
| CHP (ΔPPTh, ΔPain40) | 0.39***  | 0.24*     | 0.19*     |

Each correlation represents the association between the magnitude of CPM at each time point within and across CS paradigms. This allows for examination of repeatability of CPM using different TS within a session or the same TS across different CS.

*P < 0.05, **P < 0.01, ***P < 0.001.

CPT, cold-pressor test; CHP, conditioned pain modulation; CPT, cold-pressor test; PPTh, pressure pain threshold; TS, test stimuli.
is possible that standardization of the pain experienced attenuated
the associations that others have reported.

A systematic review has assessed the reliability of CPM protocols
and found considerable variability within and across methodological
parameters.16 Of the studies reviewed, intrasession reliability ranged
from good to excellent and intersession reliability from poor to
excellent. Kennedy encouraged future studies to report repeatability
for CS and TS when feasible.16 Although this study administered 2
standardized TS across both testing sessions, our experimental
design examined the effects of CPT and CHP in separate sessions.
Nevertheless, the magnitude of the inhibitory effect observed,
particularly at 3 minutes (ΔPTh, r = 0.61 and ΔPain40, r = 0.53),
was similar (eg, repeatable), despite session differences in the CS. At
15 minutes, possible individual differences in the duration of the CPM
effect resulted in a less consistent pattern, which dropped further as
might be expected by 30 minutes. The magnitude of CPM across
paradigms was similar for each time point.

The current findings support the use of short time delays after
CS administration. Yamitsky et al. suggest TS be administered
twice, with at least a 10-minute interstimulus interval.42 Lewis
found a measure of PTh was reduced at 1, 5, and 10 minutes
but not 15 minutes after either CPT or ischemic pain as CS.21 The
current study found similar duration of inhibition for PTh, which
was shorter compared to inhibition of ascending suprathreshold
heat, with none of the age–sex subgroupings experiencing
inhibition at 30 minutes with PTh.

The advantages of ascending suprathreshold pain vs a pain
threshold measure have been debated.17,30 Threshold involves
a decision regarding the change from nonnoxious to noxious,
whereas the suprathreshold pain measures require interpretation
and may evoke different cognitive and emotional responses.24,34,35
Different stimulus modalities may also activate peripheral nerve fibers
(A vs C) in a dissimilar manner, thereby stimulating different
nociceptive pathways that have varying influences on central nervous
system activity.14 Furthermore, the longer stronger pain signal
associated with Pain40 vs threshold may also elicit differences in
central processing. This finding supports CPM as a broad measure of
inhibition, suggesting that common and unique mechanisms may be
engaged across time and by differing methodologies.23,24 This is
supported by correlations within CPM paradigms (ΔPTh with
ΔPain40) that were moderate or small for CPT (r = 0.36–0.20) and
CHP (0.39–0.19) at the same time points. Consequently, it seems
that the selection of TS modality/endpoint has a stronger effect on
CPM than a choice between CPT and CHP as CS.

4.2. Age and sex differences in conditioned pain modulation

As hypothesized, this study supports the existing literature that
older adults exhibit diminished descending inhibition. Such age

Figure 2. Adjusted mean and SE for ΔPTh across time (A) and by age and by
sex (B) across time collapsed across CPM paradigms. The TIME (P < 0.001),
AGE (P = 0.041), and SEX (P = 0.044) main effects were significant.
Conditioned pain modulation decreased significantly from the 3-minute (mean
= −0.37) to 15-minute (−0.15) time points and was not significant at the 30-
minute time point (0.11). Overall, younger adults experiencing significantly
greater inhibition (−0.26) compared to the older group (0.06) and males (−0.26)
exhibited significantly greater CPM than females (−0.08), CPM,
conditioned pain modulation; PTh, pressure pain threshold.

Figure 3. Adjusted mean and SE for ΔPain40 for the cold-pressor test
paradigm for each age group across time. The TIME (P = 0.004), AGE (P = 0.001),
and TIME × AGE (P = 0.048) effects were significant. At 3 minutes, the
younger group (mean = −0.98) differed from the older group (mean = −0.39).
At 15 minutes, the younger group (−0.80) differed from the older group
(mean = −0.33). At 30 minutes, the younger group (−0.36) and the older
group (−0.13) were not significantly different.

Figure 4. Adjusted mean and SE for ΔPain40 for the contact heat pain
paradigm across time and for each age group. The TIME (P = 0.007) and AGE
(P = 0.001) main effects were significant. Conditioned pain modulation was
greater at the 3-minute (mean = −0.62) and 15-minute time points (−0.70)
compared to the 30-minute time point (−0.27). Conditioned pain modulation
at the 3-minute and 15-minute time points was not significantly different.
Collapsed across time, younger adults experienced greater inhibition (mean =
−0.83) compared with the older group (−0.34). CPM, conditioned pain
modulation.
threshold measures and our effect sizes fell in that direction. Differences were more consistent for mechanical pressure. Pain40 (CPT and CHP, respectively). Hermans reported that sex differences were more consistent for mechanical pressure thresholds as TS.

Individual-level variable | Cold-pressor test paradigm | Contact heat pain paradigm |
|-------------------------|---------------------------|--------------------------|
|                         | CPT-ΔPain40 | CPT-ΔPPTh | CHP-ΔPPTh | CHP-ΔPain40 |
| CS-related variables  | 0.29** | 0.20 | 0.12 | 0.22* |
| Pain variables | | | | |
| SF-36 bodily pain | −0.33*** | −0.30*** | −0.34*** | 0.34*** |
| GCPS duration | 0.24* | 0.30*** | 0.16 | 0.21* |
| GCPS painful sites | 0.29** | 0.36*** | 0.49*** | 0.27** |
| GCPS intensity | 0.28** | 0.34*** | 0.30*** | 0.30*** |
| GCPS disability | 0.33*** | 0.33*** | 0.24* | 0.35*** |

*P < 0.05, **P < 0.01, ***P < 0.001.

Table 6. Correlations between individual variables within a domain with zero-order correlations at P < 0.05 with the CPM indices.

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References
[1] Arendt-Nielsen L, Stuka KA, Nie HL. Experimental muscle pain impairs descending inhibition. PAIN 2008;140:465–71.
[2] Campbell CM, Quartana PJ, Buenaver LF, Haythornthwaite JA, Edwards RR. Changes in situation-specific pain catastrophizing precede changes in pain report during capsaicin pain: a cross-tagged panel analysis among healthy, pain-free participants. J Pain 2010;11:876–84.
[3] Cardoso JS, Riley JL III, Glover T, Sibille KT, Bartley EJ, Goodin BR, Bulls HW, Herbert M, Addison AS, Staud R, Redden DT, Bradley LA, Fillingim...
RB, Cruz-Almeida Y. Experimental pain phenotyping in community-dwelling individuals with knee osteoarthritis. PAIN 2016;157:2104–14.

[4] Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale, NJ: Lawrence Erlbaum Associates; 1988.

[5] Cruz-Almeida Y, Aigbue M, Sorenson HL, Tighe P, Wallet SM, Riley JL III. Age differences in cytokine expression under conditions of heat using experimental pain models. Exp Gerontol 2015;72:150–6.

[6] Edwards RR, Fillingim RB, Ness TJ. Age-related differences in endogenous pain modulation: a comparison of diffuse noxious inhibitory controls in healthy older and younger adults. PAIN 2003;101:155–65.

[7] Fillingim RB, King CD, Ribeiro-Dasilva MC, Rahim-Williams B, Riley JL III. Sex, gender, and pain: a review of recent clinical and experimental findings. J Pain 2000;10:447–85.

[8] Folstein M, Folstein S, McCugh P. Mini-mental state examination—a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1983;12:381–4.

[9] Granot M, Weissman-Fogel I, Crispel Y, Pud D, Granovsky Y, Sprecher E, Granovsky Y, Hansson P, Lautenbacher S, Marchand S, Wilder-Smith O. A psychophysical study of endogenous analgesia: the role of the conditioning pain in the induction and magnitude of conditioned pain modulation. Eur J Pain 2011;15:491–7.

[10] Willer JC, Roby A, Le Bars D. Psychophysical and electrophysiological approaches to the pain-relieving effects of heterotopic nociceptive stimuli. Brain 1984;107:1095–112.

[11] Yarnitsky D, Arendt-Nielsen L, Bouhassira D, Edwards RR, Fillingim RB, Granot M, Hansson P, Lautenbacher S, Marchand S, Wilder-Smith O. Recommendations on terminology and practice of psychophysical DNIC approaches to the pain-relieving effects of heterotopic nociceptive stimuli. Eur J Pain 2010;14:339.

[12] Yarnitsky D, Bouhassira D, Drewes AM, Fillingim RB, Granot M, Hansson P, Landau R, Marchand S, Matre D, Nilsen KB, Stubhaug A, Treede RD, Wilder-Smith OH. Recommendations on practice of conditioned pain modulation (CPM) testing. Eur J Pain 2015;19:805–6.

[13] Yarnitsky D. Conditioned pain modulation (the diffuse noxious inhibitory control-like effect): its relevance for acute and chronic pain states. Curr Opin Anaesthesiol 2010;23:611–5.