Systemic Exercise-Induced Hypoalgesia Following Isometric Exercise Reduces Conditioned Pain Modulation

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**Title:** Systemic exercise-induced hypoalgesia following isometric exercise reduces conditioned pain modulation

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**Running title:** Exercise and conditioned pain modulation

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ABSTRACT

Objective: Physically active individuals show greater conditioned pain modulation (CPM) compared to less active subjects. Understanding the effects of acute exercise on CPM may allow for a more targeted use of exercise in the management of pain. This study investigated the effects of acute isometric exercise on CPM. In addition, the between and within sessions reliability of CPM was investigated. Design: Experimental, randomized crossover study. Setting: Laboratory at Marquette University. Subjects: Thirty healthy adults (19.3±1.5 years; 15 males). Methods: Subjects underwent CPM testing before and after isometric exercise (knee extension, 30% maximum voluntary contraction for 3 minutes) and quiet rest in 2 separate experimental sessions. Pressure pain thresholds (PPTs) at the quadriceps and upper trapezius muscles were assessed before, during, and after ice water immersions. Results: PPTs increased during ice water immersion (i.e., CPM), and quadriceps PPT increased after exercise (p<0.05). CPM decreased similarly following exercise and quiet rest (p>0.05). CPM within session reliability was fair to good (ICC: 0.43-0.70) and the between sessions reliability was poor (ICC: 0.20-0.35). Due to the variability in the systemic EIH response, participants were divided into systemic EIH responders (n=9) and non-responders (n=21). EIH responders experienced attenuated CPM following exercise, whereas the non-responders showed no significant change (p=0.03).

Conclusions: Isometric exercise decreased CPM in individuals that reported systemic EIH suggesting activation of shared mechanisms between CPM and systemic EIH responses. These results may improve the understanding of increased pain after exercise in patients with chronic pain, and potentially attenuated CPM.

Keywords: Exercise; CPM; pain; hypoalgesia; pressure pain; reliability
**Introduction**

Conditioned pain modulation (CPM) and exercise-induced hypoalgesia (EIH) have similar manifestations in humans including systemic hypoalgesia in pain-free individuals (1-3), interaction with the opioid systems (4-7), and impaired responses in patients with chronic pain (8,9). Furthermore, CPM, which is often described as ‘pain inhibits pain,’ may contribute to EIH (2). Specifically, exercise may act as a painful conditioning stimulus, thereby, activating descending inhibitory pathways resulting in systemic hypoalgesia (10,11). This is supported in young healthy adults in which greater hypoalgesia was observed following painful aerobic or isometric exercise compared to non-painful exercise (12,13). Moreover, CPM has been shown to predict EIH in young and old healthy individuals (2) as well as in patients with chronic musculoskeletal pain (8). In individuals with knee osteoarthritis (OA), those with normal CPM responses experienced EIH, whereas individuals with abnormal CPM did not experience EIH (9).

Physical activity level and body composition may contribute to both EIH and CPM. For instance, physically active individuals show a greater CPM response compared to their less active counterparts (2,14,15), and EIH is less in adolescents with greater sedentary bouts (16). In relation to body composition, CPM efficiency was related to lean mass in adolescents (16), and adolescents with higher total body lean mass experience greater EIH (16). Thus, similar contributing factors, such as physical activity and body composition, influence how people respond to potentially noxious stimulus (i.e., exercise or a conditioning stimulus).

Acute isometric exercise has been shown to reduce central pain facilitatory mechanisms (i.e. temporal summation of pain) (10,17); however to our knowledge, no study has investigated the
effect of acute isometric exercise on central pain inhibitory mechanisms (i.e. CPM). Previous research has shown that stimulation of the motor cortex, via transcranial direct current stimulation, enhances CPM in healthy men (18). Accordingly, activation of the motor cortex occurs with exercise and may enhance the CPM response.

Initially, CPM was used to quantify efficiency of descending pain inhibition in healthy and clinical populations (19). This technique has progressed to predict non-pharmacological treatment responses (2,3,8) and identify how treatments impact endogenous pain modulation. Therefore, repetitive CPM testing is frequently done within and between sessions. The reliability of CPM depends on the parameters of stimulation, study methodology, and study population (20). Research is ongoing to identify if CPM reliability is consistent across these parameters.

The primary aim of this study was to investigate both the local (quadriceps) and systemic (upper trapezius) effects of lower extremity isometric exercise on the CPM response in young healthy individuals. Moreover, the experimental design allowed for investigation of the between and within session reliability of CPM. Because physical activity and anthropometrics may influence CPM and EIH, these measures were also included. It was hypothesized that 1) isometric exercise would enhance the CPM response in young healthy individuals and 2) CPM would have fair to good between and within session reliability.

Methods

Subjects
Thirty young healthy and pain-free men and women (mean age, 19.3 ±1.5 yr; 15 females) completed the study. Individuals were excluded from the study if they presented with the following: 1) acute or chronic pain, 2) mental health disorder, 3) history of traumatic injury or neurological disorder, 4) inability to tolerate ice water (e.g. Reynaud’s disease or cold urticaria), 5) or contraindication to exercise. Screening done via the phone eliminated two potential participants. On the days of testing, participants were asked to refrain from exercise. The protocol was approved by the Institutional Review Board at Marquette University.

**Experimental Design**

Participants completed one familiarization session and two randomized and counterbalanced experimental sessions (isometric exercise or quiet rest) that were separated by one week. During the familiarization session, subjects signed a written informed consent, completed body composition testing (dual-energy X-ray absorptiometry [DXA] scan), and were familiarized to the experimental procedures and the pressure pain device. Because the performance of maximal voluntary isometric contractions (MVIC) may influence pain perception in young adults (13,21), MVIC force was determined at the end of the familiarization session. Specifically, three MVICs were performed with the right knee extensor muscles with 1 minute rest between contractions. Participants were given verbal encouragement to achieve maximal force. The highest value was used to calculate the submaximal (30% MVIC) target force in the exercise session.
During the experimental sessions (Fig. 1), conditioned pain modulation (CPM) was assessed before and after isometric exercise or quiet rest. In both sessions, 20 minutes of quiet rest separated the first CPM assessment and initiation of exercise or quiet rest as previous studies have shown that the conditioning effects of pain return to baseline within 15 minutes (19). Participants also completed the pain catastrophizing scale (PCS) (22) and international physical activity questionnaire (IPAQ) (23), during the quiet rest in the first and second experimental sessions, respectively. These measures were collected to assess their potential influence on CPM and EIH.

**Conditioned Pain Modulation**

Pressure pain thresholds (PPT) were measured at the right upper trapezius and right quadriceps muscles (test stimuli) before, during (after 20 seconds), and after submersion of the left foot in a noxious ice water (0°C ± 1°C) bath (conditioning stimulus). Participants were instructed to keep their foot in the ice water bath until the PPTs were completed at which point they removed their foot from the ice water bath. During foot submersion, foot pain intensity was measured at 20 seconds using a 0-10 numerical rating scale (NRS) with the following anchors: 0= “no pain” and 10= “worst pain” (24) followed by PPT measurements. Immediately after foot removal from the ice water bath, peak pain intensity was measured.

**Exercise**

Participants performed a submaximal (30% MVIC) isometric contraction of the right knee extensor muscles that was held for 3 minutes while seated upright on the edge of a plinth table.
The hips and knees were positioned at 90° while the right foot was unsupported and aligned with the plinth table’s metal leg. A hand held dynamometer (Commander Echo Muscle Testing Dynamometer, JTech Medical, USA) was stabilized using Velcro® straps to the leg of the plinth and around the participant’s leg (above the malleolus). Two stabilizing straps were placed over the thighs; one distal to the hip joint and the other proximal to the knee joint. Subjects were instructed to fold their arms across their chest and to extend their knee while pushing against the Velcro® strap attached to the dynamometer. During the performance of the submaximal isometric contraction, participants were instructed to match the target force as displayed on the wireless portable monitor (Commander Echo Console, JTech Medical, USA) while receiving verbal encouragement to maintain the force. All participants maintained the force for the entire 3 minutes. Participants were asked to rate their perceived exertion using a 0-10 scale with the following anchors: 0= “nothing at all” and 10= “very very strong” and pain intensity in the leg in relation to the muscle contraction using the NRS at the beginning of the contraction, midway (1.5 min), and at the end of the contraction (3 min).

**Pressure Pain Thresholds**

During each experimental session, PPTs were measured a total of 7 times at the quadriceps and upper trapezius muscles with a handheld algometer (Algomed, Medoc Ltd); three times with each of the two CPM protocols (before, during, and after ice), and one immediately before quiet rest or exercise (20 minutes after the 1st CPM protocol) (Fig. 1). For the PPTs, a 1-cm² rubber tip was used with a ramp protocol at a rate of 50 kPa/sec. Subjects were instructed to
press a timing device when the pressure first changed to pain, which was electronically recorded in kilopascals. To minimize exposure time to ice water, two PPT trials were recorded at each site with a 10 second inter-stimulus interval and the two trials were averaged at each measurement site for further analysis. At the beginning of each experimental session, the order for the sites (upper trapezius and quadriceps) was randomized and counterbalanced and kept consistent throughout the session. PPTs were recorded with the participant seated upright in a chair with their knees and hips at 90°. The sites were located and marked as follows: the quadriceps muscle site was located midway between the anterior superior iliac spine and the patella while the upper trapezius muscle site was located midway between the C7 spinous process and the lateral tip of the acromion (25).

**Body Composition**

Body composition was measured using a total body scanner (Lunar iDXA, GE Healthcare, Madison, WI). Scan analyses were performed using enCore™ software (version 14.10, GE Healthcare) to obtain the following outcome measures: body mass index (BMI), total body fat (%), android fat (%), gynoid fat (%), android/gynoid (A/G) ratio, leg fat (%), leg lean (lbs), and visceral fat mass (lbs).

**Statistical Analysis**
Data were analyzed using the IBM Statistical Package for Social Sciences (SPSS version 23, Chicago, IL) and reported as mean ± SD in the text and tables and mean ± SEM in the figures. Normality was checked using the Kolmogorov-Smirnov test. Outliers were tested with the Grubbs test and removed when significant.

**Conditioned Pain Modulation at Baseline**

A repeated measures ANOVA (session [exercise and quiet rest] x site [quadriceps and upper trapezius] x time [before, during and after ice]) was performed to determine if PPTs increased at the upper trapezius and quadriceps muscle during and/or after the baseline ice water bath performed in the two experimental sessions. In addition, a repeated measures ANOVA was done comparing the relative change in CPM at baseline between session (quiet rest and exercise) at each site (upper trapezius and quadriceps). Relative change was calculated while the foot was submerged in ice water: CPM\text{during ice} = \frac{([\text{PPT during ice} – \text{PPT pre ice}])}{\text{PPT pre ice}}

and immediately following removal of the foot from ice water: CPM\text{after ice} = \frac{([\text{PPT after ice} – \text{PPT pre ice}])}{\text{PPT pre ice}}. This analysis was repeated with sex as a between subject factor to examine sex differences in CPM at baseline. To identify potential differences in peak pain intensity of the ice water bath and the total time of foot submersion in the ice during CPM protocols, paired t-tests or the Wilcoxon signed rank test for non-normally distributed data were done as appropriate.

**Exercise-Induced Hypoalgesia**

To identify potential changes in PPT following quiet rest and exercise (i.e., EIH), a repeated measures ANOVA was performed (session [exercise and quiet rest] x site [quadriceps and upper
This analysis was repeated with sex as a between subject factor to identify potential sex differences.

**Conditioned Pain Modulation after exercise and quiet rest**

To investigate the effect of exercise on the CPM response, relative change in CPM following quiet rest and exercise was analyzed using a repeated measures ANOVA (session [exercise and quiet rest] x site [quadriceps and upper trapezius] x time [CPM performed pre and post exercise or quiet rest]). Because there was considerable variability in systemic but not local EIH, EIH responders and non-responders at the upper trapezius muscle were categorized based on the PPT minimum detectable change (42.7 kPa) in a healthy pain-free population with a non-pharmacological intervention (26). Subjects who had an increase in PPT greater than 42.7 kPa at the upper trapezius muscle after exercise compared to pre-exercise were placed in the EIH responders group (n= 9). Changes in CPM at the upper trapezius following quiet rest and exercise were analyzed using repeated measures ANOVA with EIH response (responders and non-responders) as a between-subject factor (time x session x EIH response). When a significant effect was found, *post hoc* analyses were done using paired t-tests. Independent t tests or the Mann-Whitney U tests for non-normally distributed data were performed between the groups (EIH responders or non-responders) to identify potential differences in characteristics.

**Within and between session reliability of CPM**

To examine the reliability of CPM between sessions, repeated measures ANOVA were done comparing the relative change in CPM at baseline at each site. Within the quiet rest session, relative change in CPM was compared using a repeated measures ANOVA (time [pre and post
Intraclass correlations (ICC’s) on the bases of absolute agreement were computed for relative change in CPM during ice between sessions (pre-session 1 and session 2) and within the quiet rest session for each site with 95% confidence interval (CI).

**Correlations**

To determine potential factors that influenced CPM and or EIH, Pearson correlations or Spearman correlations for non-normally distributed data were calculated to determine associations between the relative changes in CPM and EIH, body composition measures, pain catastrophizing (PCS), and self-reported physical activity (IPAQ). In addition, Spearman correlations were performed between the relative changes in CPM or EIH and the pain intensity induced by the ice or exercise, respectively. Because the absolute change in CPM was not normally distributed, all the analyses were performed using the relative change in CPM. For statistical significance, a $P$ value ≤ 0.05 was used initially (i.e. for RM ANOVA); however a more rigorous alpha level was selected ($p ≤ 0.01$) to minimize type I and II errors with multiple group comparisons (i.e. post hoc analyses) and multiple correlations (27,28).

**Results**

**Participant characteristics**

A summary of the subject characteristics is found in Table 1. According to Body Mass Index (BMI) classification, 8 participants (26%) were overweight and 22 participants (73%) were normal weight. The individuals self-reported physical activity levels were categorized as either
moderate or vigorous; no participants reported low physical activity level. The majority of pain catastrophizing scores were considered normal as well; four participants had a score over 30. The following variables were non-normally distributed and therefore nonparametric tests were used: PCS scores, physical activity scores, pain intensity scores during ice water submersion, duration of ice water bath submersion, A/G ratio, and visceral fat mass (lbs). One outlier was identified and removed from the variable CPM after ice at the quadriceps muscle.

**Conditioned Pain Modulation at Baseline**

Subjects completed all the CPM protocols except two subjects who removed their foot from ice water before completing the test. These subjects, however kept their foot in the ice water for at least 20 seconds and completed all PPT assessments. The analyses of CPM were done with and without these subjects, which did not affect the results. Subjects reported moderate-to-severe peak pain intensity (NRS= 6.6 ± 1.8) during submersion of foot in the ice water bath. Peak pain intensity during foot submersion in ice decreased significantly between sessions (session 1: 7.0 ± 1.0; session 2: 6.4 ± 1.7; p = 0.01) but was similar within sessions (p > 0.05). The average duration for submersion of the foot in ice water was 99.7 ± 24.5 seconds. This was dependent on PPT duration for each subject and was similar across all CPM protocols (p > 0.05).

Results of the analysis for baseline CPM demonstrated a site x time interaction (F(2,28) = 3.526, p < 0.05, ηp²= 0.201). *Post hoc* analysis showed that while the foot was submerged in the ice water bath (CPM during ice), there was an increase in PPTs at the quadriceps muscle and upper trapezius (p < 0.001), which signifies CPM (Fig. 2). The majority of subjects reported CPM during ice (28/30). Immediately following removal of the foot from the ice water bath (CPM after ice), PPTs
were not significantly different from baseline at the quadriceps and upper trapezius muscles (p > 0.05). In addition, PPTs were higher at the quadriceps muscle compared with the upper trapezius muscle (p < 0.001; Fig. 2); however, CPM_{during ice} had similar relative change between the two sites (p > 0.05; Fig. 3). No other interactions were found (p > 0.05). When analyses were repeated with sex as a between subject factor, no main effects of sex or interactions were found (p > 0.05). Pain intensity at 20 seconds, peak pain intensity during ice water bath, and duration of ice water bath submersion were not related to the relative change in CPM in all protocols at both sites (p > 0.05).

**Exercise-Induced Hypoalgesia**

During exercise, subjects reported no pain (NRS= 0.0 ± 0.3) at the beginning of the isometric contraction, minimal pain (NRS= 2.2 ± 1.9) at the midpoint, and moderate pain (NRS= 3.8 ± 2.5) at the end. Likewise, subjects reported ‘very weak’ exertion (RPE= 1.6 ± 1.5) at the beginning of the isometric contraction, ‘somewhat strong’ exertion (RPE= 4.1 ± 1.5) at the midpoint, and ‘strong’ exertion (RPE= 5.5 ± 2.1) at the end.

For PPTs, there was a session x site x time interaction (F(1,29) = 13.203, p = 0.001, ηₚ²= 0.313). Post hoc analyses showed PPTs increased following exercise at the quadriceps muscle (mean 15 ± 19% change; p < 0.001) and were unchanged following quiet rest (p > 0.05; Fig. 2). At the upper trapezius muscle, no significant differences in PPTs were found (mean 2 ± 14 % change; p > 0.05) following exercise or quiet rest. Due to differences in the EIH response at the upper trapezius muscle, participants were divided into systemic EIH responders (n=9) and non-
responders (n=21). The average change in PPTs at the upper trapezius muscle following exercise for EIH responders was 20 ± 9 % compared to -5 ± 8 % in the non-responders. When analyses were repeated with sex as a between subject factor, no main effects of sex or interactions were found (p > 0.05). Neither RPE nor pain intensity at all time points during the exercise were related to EIH at either site (p > 0.05).

Conditioned Pain Modulation after exercise and quiet rest

Following quiet rest and exercise, CPM_{during ice} decreased at the quadriceps and upper trapezius muscles (F(1,29) = 13.069, p= 0.001, \eta^2_p = 0.311); this decrease was similar for the quiet rest and exercise sessions (time x session: p > 0.05, \eta^2_p = 0.052) and between sites (session x site x time: p > 0.05, \eta^2_p = 0.037; Fig. 3). At the quadriceps muscle, CPM_{during ice} decreased following exercise (32% to 19%) and quiet rest (35% to 26%). Similarly, CPM_{during ice} decreased at the upper trapezius following exercise (40% to 23%) and quiet rest (37% to 32%).

The CPM response was different following exercise compared to quiet rest in systemic EIH responders and non-responders (time x session x EIH response; p = 0.03, \eta^2_p = 0.154). Post hoc analyses showed that the EIH responders had a significant decrease in the CPM response following exercise (52% to 8%; p = 0.01) without any change following quiet rest (27% to 22%; p > 0.05; Fig. 4). The EIH non-responders did not have a significant change in their CPM response following exercise (34% to 29%) or quiet rest (40% to 36%; p > 0.05).
Within and between session reliability of CPM

Results from the ANOVA showed no significant main effects or interactions within or between sessions; relative change in baseline CPM was similar between the first and second session, and the CPM responses was similar within the quiet rest session ($p > 0.05$). ICC results are shown in table 2. There was a fair to good within session reliability for CPM during the quiet rest and poor reliability when comparing relative change in CPM at baseline between the two sessions.

Correlations

Self-reported physical activity (IPAQ MET-min/week and IPAQ total walking MET-min/week) was moderately correlated with EIH at the quadriceps muscle, however, this relationship did not reach statistical significance when correcting for multiple correlations ($r = 0.43$, $p = 0.02$ and $r = 0.38$, $p = 0.04$, respectively). Similarly, CPM during ice at the quadriceps after exercise was moderately related to A/G ratio ($r = 0.432$, $p = 0.02$) but failed to reach statistical significance after adjusting for multiple correlations. No other relations were found for pain catastrophizing, physical activity, or body composition with CPM or EIH ($p > 0.05$).

Discussion

The novel finding of the study was that individuals who reported systemic EIH had a significant decrease in CPM following exercise only, whereas those individuals that had no systemic EIH had no change in CPM following exercise or quiet rest. Thus, activation of descending inhibitory
pathways was less following sustained isometric contractions for those individuals with systemic EIH indicating the possibility of shared mechanisms with CPM. Moreover, this study demonstrated that the decrease in CPM response after exercise and quiet rest was comparable and the within session reliability of the CPM protocol used was fair to good. The reliability of CPM between sessions was poor.

**Conditioned Pain Modulation**

In the current study CPM occurred only when the testing and conditioning stimuli were performed at the same time, which is in agreement with previous studies (1,8,29-31), but not in line with other studies (19,32) or recent recommendations for CPM testing that favors measuring the test stimulus sequential to the conditioning stimulus (33). The discrepancy in these results could possibly be explained by the location of the conditioning stimulus, as the location in the previous studies (32,34) was the hand while the present study used the foot. The representation of the hand in the brain is larger than the foot, which may have yielded more central activation and a longer lasting effect compared to the current study (35). The results of Vaegter and colleagues (1) support this hypothesis where a higher CPM magnitude was observed during cold pressor test on the hand compared to the foot.

To our knowledge, this is the first study to report reliability of CPM with foot submersion in a conditioning ice water bath. Despite acceptable within session reliability (fair to good), CPM decreased following quiet rest. This decrease reflects the mean change in CPM magnitude as a group, whereas ICCs represent the differentiability of the measure between subjects. Thus
following quiet rest, CPM decreased but the rank of subjects between others was relatively the same yielding an acceptable ICC value.

One approach to attenuate potential changes in CPM magnitude following quiet rest is to increase the duration of the washout period. Valencia et al. (36) found that a repeated assessment of CPM with a washout period of 2 minutes was not adequate, since CPM magnitude decreased significantly in the second CPM trial even with good to excellent reliability. Previous studies have been equivocal in relation to the washout period with ranges from 2-60 minutes (20). The reliability in these studies was between fair and excellent (34,36,37) but not all studies examined the difference in CPM magnitude following the washout period. Therefore, future studies with repeated CPM assessments should consider a longer washout period.

In the current study the between session reliability was poor; despite similar magnitude between the two sessions. A recent study by Imai et al. (39) tested the reliability of CPM using different test and conditioning stimuli and concluded that the best between session reliability was measuring PPTs during hand submersion in ice water (0-4°C) (ICC = 0.49). One potential reason for the poor between session reliability in the current study could be the low temperature (i.e. high intensity) of the conditioning stimulus. Olesen et al. (40) observed poor reliability (ICC = 0.10) when using a conditioning cold water immersion of the hand at 2°C for 3 minutes in patients with chronic pain. The authors reported that not all patients tolerated the conditioning stimulus, which may have impacted the reliability and was similar to our study where two people did not tolerate the ice water bath. Furthermore, a systematic review of the CPM reliability suggested temperatures between 8°C and 12°C of the cold conditioning water
for improving repeatability (20). Thus, these results demonstrate that reliability may be less when applying a stronger conditioning stimulus (ice water) to a larger surface area (foot vs. hand).

The comparable decrease in CPM following exercise and quiet rest suggests that the modulatory effects of pain are not restored following the first CPM exposure, despite PPTs returning to baseline following the washout period. Thus, using a static pain assessment (PPTs) as a restorative marker for a dynamic process (CPM) may not be appropriate. Alternatively, the influence of expectations of a painful response has been shown to affect the CPM magnitude (38) where a higher expectation of the noxious conditioning stimulus results in a lower CPM magnitude. While not measured in this study, it is possible that participants in the current study had a higher expectation for the conditioning stimulus in the second CPM testing that resulted in a lower CPM magnitude.

**Exercise-Induced Hypoalgesia**

In the current study, EIH occurred locally at the exercising muscle (quadriceps muscle) and not systemically (upper trapezius muscle). The local effects are in line with previous research showing greater EIH effects at the exercising muscle compared to contralateral or distal sites (1,11). However, several studies have demonstrated systemic hypoalgesia after isometric exercise (36, 37). One explanation for the lack of systemic hypoalgesia is that baseline CPM testing negatively impacted systemic EIH potentially due to their shared manifestations. It is possible that CPM is a contributing mechanism to systemic EIH. Since CPM was initiated earlier
in the session and not enough washout period was provided to restore CPM, systemic EIH was not observed. Not all our data supports this explanation as there were no correlations observed between CPM and EIH. Previous research has demonstrated an association between CPM and EIH across the lifespan (2, 3, 41). This relation is more consistent when EIH is measured systemically and following exhaustive exercise. However, similar to the current study, Vaegter et al. (1) showed no correlation between CPM and EIH after low intensity isometric exercise held for 3 minutes. The relation between CPM and EIH is likely dependent on both the exercise dose and testing site for EIH.

To our knowledge this is the first study to investigate the effect of isometric exercise on CPM. Because stimulation to the motor cortex enhances CPM we expected that CPM would be enhanced following exercise. Contrary to our hypothesis, CPM decreased following exercise only in those individuals who had systemic EIH. This is potentially related to 1) a ceiling effect for PPTs and the exercise-induced increase in PPT attenuated the subsequent testing stimulus (42); or 2) systemic hypoalgesia that occurs following exercise is due to CPM. Arendt-Nielsen et al. (43) found that two concurrent painful conditioning stimuli (muscle pain and cold presser pain) had a decreased effect than either stimulus alone. Because the exercise protocol in this study was painful, the increase in PPTs at the upper trapezius muscle following exercise may actually be a CPM protocol with exercise acting as the conditioning stimulus and PPT the testing stimulus. EIH responders experienced a 20% increase in PPTs following exercise and an additional 8% increase following the ice conditioning stimulus, which is comparable to what they have experienced with the conditioning stimulus alone in the quiet rest session (27%). The non-responders had only local hypoalgesia (i.e., quadriceps muscle) following exercise; the lack
of hypoalgesia systemically (i.e. upper trapezius muscle) suggests that local exercise effects do not influence CPM due to different mechanisms. Previous reports have shown that CPM magnitude is influenced by the intensity of conditioning stimulus but not by the pain reported during the conditioning stimulus (44). Likewise in this study, pain reported during exercise or ice water bath did not influence EIH nor CPM. If exercise produces hypoalgesia via activation of the CPM response, then increasing the exercise intensity (i.e. the conditioning stimulus) should produce greater hypoalgesia.

Emerging evidence has shown that body composition and physical activity may influence EIH and CPM (2,14-16). This is contrary to the current study in that body composition and self-reported physical activity were not correlated with EIH or CPM. This is similar to a recent study by Black et al. (45) that showed no relation between EIH and physical activity assessed via accelerometer. These results may be due to the homogenous sample in the current study as most individuals reported moderate to vigorous physical activity levels and normal to slightly overweight BMI levels. Likewise, the weakly correlated pain catastrophizing scores with neither CPM nor EIH may be due to relatively normal catastrophizing scores (e.g. only 4 individuals above 30) observed in this sample.

Several potential limitations should be taken into consideration. First, a small number of individuals had a systemic EIH response (n=9) possibly due to the low intensity and short duration of the isometric exercise thereby limiting the generalizability of the results. Future studies should verify these results following an exercise duration that is known to produce systemic effects (e.g. isometric exercise until task failure or aerobic exercise). In addition, the between sessions reliability of CPM was poor. However, this should have minimal effects with
our results since we are comparing changes in CPM within session. Finally, the results in the present study are generalizable to young healthy adults only. It is unclear whether individuals with chronic pain would yield similar results.

Despite these limitations, several clinical implications can be drawn from this study. Our results suggest that the systemic effects of exercise activates descending inhibitory pathways making it a good clinical modality in the management of pain. Thus, in individuals with impaired CPM, the systemic effects of exercise maybe more variable in producing pain relieving effects. The local effects, however do not appear to be mediated by CPM and could be an alternative clinical tool in those conditions with impaired CPM. Finally, our results show the potential benefits in assessing CPM to help guide clinical decision making. With repeated assessments an appropriate length of time (e.g. greater than 23 minutes) is necessary for the restoration of CPM. Additional research that includes individuals with chronic pain is essential including whether this relation between systemic EIH and CPM occurs with exercise training. Understanding these effects in patients will allow for a more targeted use of exercise in the management of pain.

**Conclusion**

Individuals that experienced EIH systemically had an attenuated CPM response compared with those individuals that only experienced local EIH. The results raise the possibility that there are shared mechanisms between CPM and systemic EIH. In addition, CPM decreased following
exercise and quiet rest, which may be due to an insufficient washout period while the within session reliability was fair to good and the between sessions reliability was poor.

**Conflict of interest:** the authors have no conflict of interest

**References**


**Figure Legends**

**Fig. 1.** Study design of the experimental sessions. “↑” = PPTs at the quadriceps and upper trapezius muscle. Abbreviations: PPT, pressure pain threshold; CPM, conditioned pain modulation; EX, exercise; QR, quiet rest.
**Fig.2.** Pressure pain thresholds (kPa) at the quadriceps muscle and the upper trapezius muscle during the exercise session and the quiet rest session. Significantly different compared to pre exercise (*) and significantly different compared to pre exercise (#). Data is presented as mean ± SEM. Abbreviations: EX, exercise; QR, quiet rest.

**Fig.3.** Relative change in CPM at the quadriceps muscle and the upper trapezius muscle before and after exercise or quiet rest. Significantly different compared to pre exercise or quiet rest (*). Data is presented as mean ± SEM. Abbreviations: CPM, conditioned pain modulation.

**Fig.4.** Relative change in CPM at the upper trapezius muscle before and after exercise or quiet rest for EIH systemic responders and non-responders. Significantly different compared to pre exercise (*). Data is presented as mean ± SEM. Abbreviations: CPM, conditioned pain modulation.
Table 1
Participant characteristics

<table>
<thead>
<tr>
<th></th>
<th>All Participants n= 30</th>
<th>Systemic EIH Responders n= 9 (30%)</th>
<th>Systemic EIH non-responders n= 21 (70%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>19.3 ± 1.5</td>
<td>19.7 ± 1.3</td>
<td>19.8 ± 1.6</td>
<td>0.803</td>
</tr>
<tr>
<td>Females (%)</td>
<td>n= 15 (50%)</td>
<td>n= 4 (44%)</td>
<td>n= 11 (52%)</td>
<td>0.695</td>
</tr>
<tr>
<td><strong>Exercise</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVC</td>
<td>368.5 ± 107.9</td>
<td>399.2 ± 143.1</td>
<td>355.4 ± 90</td>
<td>0.414</td>
</tr>
<tr>
<td>Peak pain</td>
<td>3.8 ± 2.5</td>
<td>3.4 ± 2.1</td>
<td>4.0 ± 2.6</td>
<td>0.571</td>
</tr>
<tr>
<td>Peak RPE</td>
<td>5.5 ± 2.1</td>
<td>4.7 ± 2.3</td>
<td>5.8 ± 1.9</td>
<td>0.242</td>
</tr>
<tr>
<td><strong>Weight status and body composition</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>23.0 ± 3.1</td>
<td>22.2 ± 3.2</td>
<td>23.3 ± 3.0</td>
<td>0.230</td>
</tr>
<tr>
<td>Total body fat (%)</td>
<td>24.3 ± 6.8</td>
<td>23.1 ± 7.2</td>
<td>24.8 ± 6.8</td>
<td>0.554</td>
</tr>
<tr>
<td>Android fat (%)</td>
<td>22.8 ± 8.4</td>
<td>22.0 ± 7.9</td>
<td>23.2 ± 8.7</td>
<td>0.733</td>
</tr>
<tr>
<td>Gynoid fat (%)</td>
<td>26.5 ± 8.6</td>
<td>25.0 ± 9.6</td>
<td>27.2 ± 8.4</td>
<td>0.533</td>
</tr>
<tr>
<td>Android/gynoid (A/G)</td>
<td>0.86 ± 0.2</td>
<td>0.89 ± 0.13</td>
<td>0.85 ± 0.22</td>
<td>0.213</td>
</tr>
<tr>
<td>ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leg fat (%)</td>
<td>25.6 ± 8.2</td>
<td>24.2 ± 8.7</td>
<td>26.1 ± 8.1</td>
<td>0.573</td>
</tr>
<tr>
<td>Leg lean (lbs)</td>
<td>19.2 ± 4.5</td>
<td>19.3 ± 4.8</td>
<td>19.1 ± 4.5</td>
<td>0.906</td>
</tr>
<tr>
<td>Visceral fat mass (lbs)</td>
<td>0.35 ± 0.38</td>
<td>0.30 ± 0.25</td>
<td>0.37 ± 0.42</td>
<td>0.982</td>
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<tr>
<td><strong>Physical Activity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activity Type</td>
<td>IPAQ (minutes/week)</td>
<td>MET (minutes/week)</td>
<td>p-value</td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>---------------------</td>
<td>-------------------</td>
<td>--------</td>
<td></td>
</tr>
<tr>
<td>Total walking</td>
<td>1495.1 ± 1011.0</td>
<td>1827.8 ± 853.9</td>
<td>0.245</td>
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</tr>
<tr>
<td>Moderate</td>
<td>674.6 ± 1506.7</td>
<td>550.0 ± 867.5</td>
<td>0.772</td>
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</tr>
<tr>
<td>Vigorous</td>
<td>1900.0 ± 1665.0</td>
<td>1680.0 ± 1570.3</td>
<td>0.617</td>
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<tr>
<td>MET</td>
<td>4069.7 ± 2963.8</td>
<td>4057.8 ± 3033.4</td>
<td>0.989</td>
<td></td>
</tr>
<tr>
<td>Sitting</td>
<td>2991.0 ± 1124.1</td>
<td>2503.3 ± 959.8</td>
<td>0.122</td>
<td></td>
</tr>
</tbody>
</table>

**Pain catastrophizing**

<table>
<thead>
<tr>
<th>Scale Type</th>
<th>PCS (mean ± SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>18.1 ± 10.1</td>
<td>0.699</td>
</tr>
<tr>
<td>Helplessness</td>
<td>6.6 ± 5.0</td>
<td>0.792</td>
</tr>
<tr>
<td>Magnification</td>
<td>4.1 ± 2.7</td>
<td>0.345</td>
</tr>
<tr>
<td>Rumination</td>
<td>7.3 ± 4.1</td>
<td>0.554</td>
</tr>
</tbody>
</table>

BMI, body mass index; IPAQ, International Physical Activity Questionnaire; PCS, Pain Catastrophizing Scale; yr, year; RPE, rate of perceived exertion. There were no significant differences between systemic EIH responders and non-responders.
### Table 2
Reliability values (ICCs) and percent change for CPM within and between sessions

<table>
<thead>
<tr>
<th></th>
<th>Percent change</th>
<th>ICCs (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Within quiet rest session</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPM Quad trial 1</td>
<td>35.4%</td>
<td>0.707 (0.395-0.859)</td>
</tr>
<tr>
<td>CPM Quad trial 2</td>
<td>26.5%</td>
<td></td>
</tr>
<tr>
<td>CPM Upper trap trial 1</td>
<td>36.7%</td>
<td>0.433 (-0.190-0.730)</td>
</tr>
<tr>
<td>CPM upper trap trial 2</td>
<td>31.9%</td>
<td></td>
</tr>
<tr>
<td><strong>Between sessions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPM Quad session 1</td>
<td>33.4%</td>
<td>0.208 (-0.715-0.628)</td>
</tr>
<tr>
<td>CPM Quad session 2</td>
<td>34.2%</td>
<td></td>
</tr>
<tr>
<td>CPM Upper trap session 1</td>
<td>38.6%</td>
<td>0.350 (-0.401-0.694)</td>
</tr>
<tr>
<td>CPM upper trap session 2</td>
<td>38.1%</td>
<td></td>
</tr>
</tbody>
</table>

ICC, intraclass correlation coefficient; CPM, conditioned pain modulation; CI, confidence interval
Pressure Pain Threshold (kPa)

- Exercise Quad
- Quiet Rest Quad
- Exercise Upper trap
- Quiet Rest Upper trap

Time Points:
- Pre Ice
- During Ice
- After Ice
- Pre EX/QR
- Post Ex/QR
- During Ice
- After Ice

Significance:
- * indicates significance
- # indicates trend