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Lean Mass Predicts Conditioned Pain Modulation in Adolescents Across Weight Status

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Conflicts of interest:

None declared.

Abstract

Background

There is a wide continuum of conditioned pain modulation (CPM) in adults with older adults experiencing an attenuated CPM response compared with younger adults. Less is known for adolescents and the role of anthropometrics.

Methods

Fifty-six adolescents (15.1 ± 1.8 years; 32 normal weight and 24 overweight/obese; 27 boys) completed in a CPM session that included anthropometric testing. Pressure pain thresholds were measured at the nailbed and deltoid muscle (test stimuli) with the foot submerged in a cool or ice water bath (conditioning stimulus). Weight status, body composition (Dual-energy X-ray absorptiometry scan), physical activity levels and clinical pain were also evaluated.

Results

The CPM response in adolescents was similar across sites (nailbed vs. deltoid), weight status (normal vs. overweight/obese) and sex. CPM measured at the deltoid muscle was positively associated with left arm lean mass but not fat mass; lean mass of the arm uniquely predicted 10% of the CPM magnitude. CPM measured at the nailbed was positively correlated with physical activity levels.

Conclusions

These results suggest that lean mass and physical activity levels may contribute to endogenous pain inhibition in adolescents across weight status.

What's already known about this topic?

- Conditioned pain modulation (CPM) exists in adolescents with a developmental progression that is similar between boys and girls
- CPM is similar between normal weight and obese adults when tested at a site with little excess subcutaneous fat

What does this study add?

- Normal weight and overweight/obese adolescents experience equivalent CPM responses
- Lean mass uniquely predicts CPM efficiency
- Increasing lean mass and physical activity levels may contribute to endogenous pain inhibition in adolescents across weight status

1 Introduction

Conditioned pain modulation (CPM) is a measure of endogenous pain inhibition and may identify those at risk for developing chronic pain (Yarnitsky et al., **2008**; Staud, **2012**). Adults demonstrate a wide range of variability in the CPM response with older adults experiencing an attenuated CPM response compared with younger adults (Edwards et al., **2003**; Lariviere et al., **2007**; Lemley et al., **2015**). Less is known regarding the CPM response for children and adolescents.

Marchand and colleagues showed that children (7–11 years) born preterm with numerous painful procedures did not exhibit CPM, whereas children born full-term and preterm with minimal painful exposures demonstrated a CPM response (Goffaux et al., **2008**). Recently the child's age was shown to impact the CPM response (Tsao et al., **2013**). Younger healthy children (8–11 years) exhibited less CPM than adolescents (12–17 years); no sex differences were observed (Tsao et al., **2013**). These paediatric findings suggest a developmental progression in the CPM response (Tsao et al., **2013**).

An overlooked issue is the influence of weight status on CPM as nearly one-third of US youth are overweight/obese (Ogden et al., **2014**). Obese children tend to have increased pain reports (Hainsworth et al., **2012**). This suggests that overweight/obese youth may have less efficient CPM compared with normal weight peers because CPM is less effective in chronic pain conditions (Staud, **2012**). The influence of a child's weight status on CPM has never been studied.

To our knowledge, only one adult study has investigated the influence of anthropometrics on conditioned pain modulation. Price and colleagues have shown that subcutaneous fat effects pain sensitivity in adults (Price et al., **2013**); obese adults are less sensitive to painful and non-painful stimuli in areas with excess subcutaneous fat compared with normal weight adults. No CPM differences were reported at a test site of minimal subcutaneous fat (i.e. forehead) (Price et al., **2013**).

Physical inactivity, a major cause of the obesity epidemic, is implicated as a factor for increased pain (Ladabaum et al., **2014**). Increasing physical activity is an important component of rehabilitation, especially for managing pain, due to the potential to impact endogenous pain modulation. Younger and older healthy adults that report higher levels of physical activity exhibit greater CPM (Naugle and Riley, **2014**; Lemley et al., **2015**). Whether this relation occurs in adolescents across weight status is not known.

The purpose of this study was to investigate the impact of weight status and body composition (lean vs. fat mass) on the CPM response in adolescents using test sites with varying subcutaneous fat (deltoid muscle vs. nailbed). We hypothesize that adolescents across weight status and body composition will experience CPM at both sites with less CPM response in adolescents of higher weight status and poor body composition. Because physical activity levels have been shown to influence CPM and weight status (Ladabaum et al., **2014**; Naugle and Riley, **2014**; Lemley et al., **2015**), we assessed physical activity participation. We hypothesize that adolescents with higher physical activity levels will exhibit greater CPM efficiency.

2 Methods

2.1 Subjects

A prior sample size was determined via G power ($\alpha = 0.05$, repeated ANOVA Critical $F = 2.798$, Actual Power = 0.9548, $N = 52$) (Faul et al., **2007**, **2009**). Sixty-two adolescents [15.1 ± 1.8 years (12.0–17.9 years); 29 boys] were recruited from a Midwestern US metropolitan area (Milwaukee, WI) through advertisements. Adolescents were enrolled as part of a larger research study investigating the association between weight status and physical fitness in adolescents. All adolescent subjects were screened via a phone conversation with respective parent/legal guardian about the study components and exclusionary criteria: (1) body mass index below the 10th percentile for age and gender; (2) inability to report pain threshold (i.e. tissue trauma or neurological condition that would affect sensory perception); (3) inability to tolerate ice water submersion (e.g. Raynaud's Disease or cold urticaria); (4) American College of Sports Medicine (ACSM) exercise testing contraindications; (5) non-English speaking participants; (6) cognitive delays; (7) pregnancy; (8) claustrophobia; and/or (9) history of mental health disorder. The protocol was approved by the Institutional Review Board at Marquette University.

2.2 Sessions

Adolescents participated in three experimental sessions with approximately 1 week between sessions. At the start of the first session, adolescents completed informed assent while the parent/legal guardian completed informed consent. During this session, resting vitals, weight status, pain assessment [McGill pain questionnaire (MPQ)], Tanner staging, and physical activity levels were obtained from the adolescent. Pressure pain thresholds were also measured before and after 20 min of quiet rest. During the second or third session, adolescents completed the CPM protocol and body composition testing [Dual-energy X-ray absorptiometry (DXA) scan]. See **3.6** for specific details.

2.3 Weight status and body composition

A calibrated stadiometer and standing scale were used to measure height and weight, respectively. From the height and weight measurements, body mass index (BMI) was calculated and plotted for percentile and Z-score to account for growth based on age and sex, as recommended by Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO). Based on BMI Z-score, subjects were categorized as normal weight ($n = 32$) or overweight/obese ($n = 24$) (Preedy, **2012**).

At the start of the CPM session, a DXA scan was performed using the Lunar GE Prodigy (GE Healthcare, Madison, WI, USA) bone densitometer. Prior to each scan, a quality assurance and calibration protocol were completed. All adolescents refrained from food/drink for 1–2 h prior to the DXA, and female adolescents were given a pregnancy test. Scans were analysed using the Lunar GE Prodigy paediatric software to quantify total body lean body mass (lb), total body fat mass (lb) and total body fat percentage (%). Total body fat percentage was calculated as fat mass/total mass $\times 100$, whereas total mass was the sum of lean mass, fat mass and bone mass (Kelly et al., **2009**). Total body fat Z-scores for age and sex were determined using the online Baylor College of Medicine Body Composition Laboratory Paediatric Body Composition Reference Charts (Kelly et al., **2009**). Because pressure pain thresholds (PPT) were done at the left deltoid muscle, DXA measurements of the left upper extremity were included in analyses [i.e. left arm lean mass (lb), fat mass (lb) and total mass (lb)].

2.4 Tanner staging

Each adolescent completed a Tanner Staging questionnaire to determine sexual maturation level (Marshall and Tanner, **1969, 1970**). This has been validated via self-report for adolescents (Schlossberger et al., **1992**). Stage 1 is indicative of prepubertal level; Stages 2–4 are peripubertal; and Stage 5 is mature stage.

2.5 Physical activity

Self-reported physical activity was quantified using the physical activity questionnaire-Elementary School & High School Versions (PAQ). The PAQ is a reliable and valid instrument which provides a general measure of physical activity for youth in grades 4–12 (Crocker et al., **1997**; Thompson et al., **2003**). The PAQ activity score is derived from nine items each scored on a 5-point scale. A score of 1 indicates low physical activity, whereas a score of 5 indicates high physical activity. Cut-off points of <2.9 for boys and <2.7 for girls were used to identify those adolescents at risk for future health complications (Voss et al., **2013**).

2.6 Experimental pain and CPM protocols

PPTs were measured during the first experimental session (pre/post 20-min quiet rest) and in the CPM protocol with a battery-operated algometer (Algomed) using a 1 cm² probe at a rate of 50 kPa/s at two sites: left 4th digit nailbed and left middle deltoid muscle (Birnie et al., **2014**). Adolescents were instructed to press the Patient Response Unit when he/she first felt pain (i.e. PPT) (Hogeweg et al., **1996**). During quiet rest, three trials were completed at each site with a 10-s inter-stimulus interval; the three trials were averaged at each measurement site. During the CPM protocol, one trial was done at each site to limit exposure of the foot submerged in the ice water bath.

For the CPM protocol, PPTs (test stimulus) at the nailbed and deltoid muscle were measured while the right foot was submerged in a cool water bath [76–78 °F (24–25 °C) distraction control] and repeated with submersion in an ice water bath [34–36 °F (1–2 °C); noxious conditioning stimulus] (Fig. 1) (Dailey et al., **2013**; Liebano et al., **2013**; Lemley et al., **2015**). The neutral cool water bath was used to control for potential distraction associated with water immersion (Moont et al., **2010**). Twenty minutes separated the cool and ice water baths, which is the same duration as quiet rest, to control for any potential analgesic effect that distraction may have on the CPM response.

Figure 1. Conditioned pain modulation protocol. PPTs (testing stimulus) were measured at the nailbed and deltoid while the foot was submerged in cool water (distraction control). After 20 min of quiet rest, PPTs were measured at the nailbed and deltoid while the foot was submerged in ice water (conditioning stimulus). PPT, pressure pain threshold.

2.7 Statistical analysis

Data were analysed using Statistical Package for the Social Sciences (SPSS, version 21, IBM, Chicago, IL, USA). Data were checked for normality using the Shapiro–Wilk test and visually inspected using histograms. When data were not normally distributed, the data were transformed and parametric statistics were completed; in addition, non-parametric comparison statistics were utilized as appropriate. Mean $\pm$ standard deviations were used in tables and mean $\pm$ standard errors in figures. An initial alpha level of $p \leq 0.05$ was used for all analyses; however, a more rigorous alpha level was selected ($p \leq 0.01$) to minimize type I and II errors with multiple group comparisons (Garamszegi, **2006**; Avin and Law, **2011**).

Independent *t*-tests or Mann–Whitney tests were completed between weight (normal weight vs. overweight/obese) and sex (male vs. female) groups to identify potential differences for the subjects regarding demographics, weight, body composition, physical activity and clinical pain reports.

To compare changes in PPTs following quiet rest and with the CPM protocol, a repeated measures ANOVA [trial $\times$ session (control vs. CPM)] was done. Weight status (normal weight vs. overweight/obese), sex (male vs. female) and physical activity levels (PAQ cut-offs: ‘at risk’ vs. ‘not at risk’) were used as separate between subject factors for the CPM protocol using a repeated measures ANOVA [trial (cool water and ice water) $\times$ site (nailbed vs. deltoid muscle)] was done. Partial eta squared is reported for each ANOVA with the ranges for partial eta squared as follows: small <0.01 , medium <0.06 and large <0.14 (Richardson, **2011**). Foot pain ratings in the water baths and baseline pain (PPTs) were analysed with independent *t*-tests or Mann–Whitney tests to determine differences by weight status (normal weight vs. overweight/obese) and sex (male vs. female).

Associations with the magnitude of CPM at each site (deltoid and nailbed) was done for continuous variables (e.g. BMI Z-score, body composition, pain during conditioning stimulus and physical activity) using Pearson correlations. CPM (kPa) was calculated as follows: $\text{PPT}_{\text{ice water}} - \text{PPT}_{\text{cool water}}$.

Due to the interaction between lean mass at the CPM deltoid but not the nailbed, hierarchical regression analysis was done to identify significant predictors of the CPM response. Candidate variables were identified using Pearson correlations, which were then entered into hierarchical regression analysis. The dependent variable was $\text{CPM}_{\text{Deltoid}}$. Left arm lean mass (lb) was entered as a predictor variable in step one. Because baseline pain ($\text{PPT}_{\text{Deltoid}}$ in control condition) can influence CPM, baseline pain ($\text{PPT}_{\text{Deltoid}}$) was entered to control for potential confounding effects in step two (Lemley et al., **2015**).

3 Results

3.1 Subjects

Of the 62 adolescents who participated in this study, 56 adolescents (12.0–17.5 years, 27 boys) completed the CPM protocol (Table 1). Six adolescents did not complete the CPM protocol due to the following reasons: three adolescents were unable to tolerate the ice water bath; one had a positive pregnancy test; one dropped out of the study; and one adolescent's data were missing due to software malfunction.

Table 1. Descriptives for adolescent subjects

	All adolescents <i>n</i> = 56	Normal weight <i>n</i> = 32	Overweight/Obese <i>n</i> = 24	boys <i>n</i> = 27	girls <i>n</i> = 29
Demographics					
Age (years)	15.1 ± 1.8	16.0 ± 1.8	14.5 ± 1.7a	15.0 ± 2.0	15.2 ± 1.6
Sex (male)	27	17	10	27	
Tanner stage I	0	0	0	0	0
Tanner stage II	3	1	2	3	0
Tanner stage III	8	4	4	0	8
Tanner stage IV	24	15	9	12	12
Tanner stage V	21	12	9	12	9
Weight status					
BMI (kg/m ²)	25.4 ± 6.7	21.3 ± 1.8	30.9 ± 7.0c	24.6 ± 5.6	26.1 ± 7.7
BMI Z-score	1.0 ± 0.9	0.30 ± 0.44	1.89 ± 0.51c	0.97 ± 0.88	0.99 ± 0.97
Body composition					
Total body					
Body fat (%)	28.4 ± 13.0	19.9 ± 8.9	39.8 ± 7.7c	21.4 ± 12.5	34.9 ± 9.8c
Body fat Z-score (Age and sex)	0.25 ± 1.44	-0.77 ± 1.00	1.60 ± 0.46c	-0.24 ± 1.56	0.70 ± 1.16a
Lean mass (lb)	102.4 ± 24.3	100.9 ± 22.8	104.4 ± 26.5	113.9 ± 27.5	91.7 ± 14.5b
Fat mass (lb)	47.6 ± 32.4	26.5 ± 12.2	75.6 ± 29.6c	36.6 ± 30.8	57.7 ± 31.0b
Left arm					
Lean mass (lb)	6.0 ± 1.9	6.0 ± 2.0	6.0 ± 1.9	7.1 ± 2.1	4.9 ± 1.0c
Fat mass (lb)	2.2 ± 1.8	1.1 ± 0.5	3.7 ± 1.7c	1.7 ± 1.6	2.8 ± 1.8b
Total mass (lb)	8.6 ± 2.8	7.4 ± 1.9	10.2 ± 2.9c	9.2 ± 2.9	8.0 ± 2.5
Physical activity					
PAQ score	2.6 ± 0.6	2.7 ± 0.6	2.5 ± 0.7	2.8 ± 0.6	2.4 ± 0.6b
Clinical pain					
MPQ (Total)	3.64 ± 5.70	4.47 ± 6.29	2.54 ± 4.70	3.30 ± 3.90	3.97 ± 7.03

BMI, body mass index; MPQ, McGill pain questionnaire; PAQ, physical activity questionnaire.

^a *p* ≤ 0.05.

^b *p* ≤ 0.01.

^c *p* ≤ 0.0001.

As a group, adolescents reported none to minimal levels of clinical pain (MPQ Total Score: 3.64 ± 5.7) (Table 1). Self-reported physical activity, however, was at risk for adverse metabolic health for the adolescents (Voss et al., **2013**). Based on the BMI Z-score, 32 adolescents were normal weight, and 24 adolescents were overweight/obese (Table 1). Total and left arm body composition differed by weight status except for lean mass, which was similar between weight groups. No differences existed in self-reported physical activity (PAQ scores) or current clinical pain between the weight groups.

With regard to sex differences, boys ($n = 27$) and girls ($n = 29$) had similar BMI Z-scores but significant differences in total and left arm body composition (Table 1). Boys reported higher participation in physical activity (PAQ scores) than girls. Both sexes would be considered at risk for adverse metabolic health based on the self-reported physical activity levels (Voss et al., 2013). Clinical pain was similar between the sexes.

3.2 Experimental pain following quiet rest and CPM

The change in pain thresholds differed between sessions (trial $\times$ session:

$F_{(1,55)} = 4.30$, $p = 0.04$, $\eta_p^2 = 0.07$). Following quiet rest, there was no change in PPTs ($p > 0.05$), but increased within the CPM session. PPTs were greater while the foot was in the ice water bath than the cool water bath (i.e. CPM, trial: $F_{(1,55)} = 54.75$, $p < 0.0001$, $\eta_p^2 = 0.50$). This response was similar between the nailbed and deltoid muscle (trial $\times$ site: $F_{(1,55)} = 2.47$, $p = 0.12$, $\eta_p^2 = 0.04$; Fig. 2 and Table 2).

Figure 2. Conditioned pain modulation. PPTs increased significantly from the cool water (control condition) to ice water (experimental condition) at the nailbed and deltoid muscle ($p < 0.0001$) with no significant differences between sites ($p > 0.05$). PPT, pressure pain threshold.

Table 2. Conditioned pain modulation by weight status and sex

CPM by weight status	Adolescents $n = 56$	Normal weight $n = 32$	Overweight/Obese $n = 24$	boys $n = 27$	girls $n = 29$
PPT nailbed cool water (kPa)	451.9 $\pm$ 211.8	453.6 $\pm$ 201.0	449.6 $\pm$ 229.7	468.8 $\pm$ 228.0	436.1 $\pm$ 198.2
PPT nailbed ice water (kPa)	528.2 $\pm$ 230.7	549.1 $\pm$ 235.2	500.4 $\pm$ 226.5	549.4 $\pm$ 246.4	508.5 $\pm$ 217.6
PPT deltoid cool water (kPa)	375.1 $\pm$ 258.5	374.9 $\pm$ 277.9	375.4 $\pm$ 236.1	409.1 $\pm$ 302.1	343.5 $\pm$ 210.7
PPT deltoid ice water (kPa)	466.5 $\pm$ 293.2	457.7 $\pm$ 310.6	478.1 $\pm$ 274.5	534.5 $\pm$ 349.9	403.2 $\pm$ 215.8
Absolute CPM nailbed (kPa)	76.3 $\pm$ 99.5	95.5 $\pm$ 88.5	50.8 $\pm$ 109.2	80.6 $\pm$ 94.9	72.4 $\pm$ 105.1a
Relative CPM nailbed (%)	21.8 $\pm$ 28.2	22.5 $\pm$ 20.9	20.8 $\pm$ 36.3	24.1 $\pm$ 32.2	19.7 $\pm$ 24.4
Absolute CPM deltoid (kPa)	91.4 $\pm$ 122.4	82.8 $\pm$ 128.6	102.8 $\pm$ 115.2	125.4 $\pm$ 140.3	59.7 $\pm$ 94.8a
Relative CPM deltoid (%)	33.8 $\pm$ 44.7	28.3 $\pm$ 44.4	41.1 $\pm$ 45.0	40.3 $\pm$ 47.1	27.8 $\pm$ 42.2

Foot pain 20 s cool water	0.2 ± 0.7	0.3 ± 0.8	0.0 ± 0.2	0.4 ± 0.9	0.1 ± 0.2
Peak foot pain cool water	0.3 ± 0.8	0.4 ± 1.0	0.1 ± 0.4	0.4 ± 0.9	0.2 ± 0.7
Foot pain 20 s ice water	5.6 ± 2.5	5.6 ± 1.8	5.6 ± 3.2	5.9 ± 2.4	5.3 ± 2.6
Peak foot pain ice water	7.0 ± 2.5	7.3 ± 2.0	6.7 ± 3.0	7.0 ± 2.4	7.0 ± 2.6

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

^a $p \leq 0.05$.

^b $p \leq 0.01$.

^c $p \leq 0.0001$.

3.3 Sex differences

Baseline experimental pain (PPTs while foot was in cool water) did not differ by sex (boys vs. girls) at either the nailbed ($p = 0.76$) or deltoid muscle ($p = 0.33$). CPM was also similar between boys and girls (trial $\times$ sex: $F_{(1,54)} = 1.09$, $p = 0.30$, $\eta_p^2 = 0.02$) at both sites (trial $\times$ site $\times$ sex: $F_{(1,54)} = 0.48$, $p = 0.49$, $\eta_p^2 = 0.01$).

3.4 Weight status and body composition

Baseline experimental pain (PPTs while foot was in cool water) was similar between the normal weight and overweight/obese adolescents at the nailbed ($p = 0.56$) and deltoid muscle ($p = 0.65$). The CPM response was also similar between the two weight groups (trial $\times$ weight status: $F_{(1,54)} = 0.31$, $p = 0.58$, $\eta_p^2 = 0.01$) at both sites (trial $\times$ site $\times$ weight status: $F_{(1,54)} = 2.42$, $p = 0.13$, $\eta_p^2 = 0.04$).

In relation to total body composition (body fat Z-score, lean mass, and fat mass), there were no correlations with CPM_{Nailbed} or CPM_{Deltoid}. Specific to the left arm body composition (lean mass, fat mass and total mass), CPM_{Deltoid} was positively associated with left arm lean mass (Fig. 3 and Table 3); adolescents with greater left arm lean mass report greater CPM at the deltoid muscle than those with less lean mass of the arm.

Figure 3. Conditioned pain modulation relation with left arm lean mass and fat mass. Conditioned pain modulation at the left deltoid is significantly correlated with left arm lean mass (A, $r = 0.34$, $p = 0.01$) but not fat mass (B, $p > 0.05$).

Table 3. Correlations with CPM

	CPM nailbed	CPM deltoid
Body fat Z-score	$r = 0.24$	$r = 0.02$
Total body fat mass (lb)	$r = -0.20$	$r = -0.04$
Total body lean mass (lb)	$r = -0.04$	$r = 0.29^a$
Left arm fat mass (lb)	$r = -0.16$	$r = -0.04$
Left arm lean mass (lb)	$r = -0.01$	$r = 0.34^b$
Left arm total mass (lb)	$r = -0.09$	$r = 0.24$
Peak pain (Foot in ice water)	$r = 0.07$	$r = -0.02$
PAQ score	$r = 0.34^b$	$r = 0.19$

PAQ, physical activity score; CPM, conditioned pain modulation.

^a $p \leq 0.05$.

^b $p \leq 0.01$.

3.5 Physical activity

Self-reported physical activity levels (PAQ scores) were positively correlated with CPM_{Nailbed} but not CPM_{Deltoid} (Table 3). Based on the PAQ cut-off scores, adolescents at risk for future health complications had similar CPM responses compared with adolescents not at risk (trial $\times$ PAQ: $F_{(1,54)} = 0.63$, $p = 0.43$, $\eta_p^2 = 0.01$).

3.6 Hierarchical regression analysis

Hierarchical regression analysis was used to assess the ability of lean mass of the arm (model 1) to predict the CPM response at the deltoid muscle after controlling for baseline pain (model 2) (Lemley et al., 2015). Preliminary analyses determined violation of normality with left arm lean mass and baseline pain, thus the data were log transformed. In model 1, left arm lean mass was identified as a significant predictor of CPM_{Deltoid} ($F_{(1,54)} = 6.84$, $p = 0.01$) accounting for 10% of the change in CPM_{Deltoid}. In model 2, the total variance explained by left arm lean mass and baseline pain was 9% ($F_{(2,53)} = 3.68$, $p = 0.03$) but did not significantly differ from model 1 (Table 4). Adolescents with greater lean mass of the arm demonstrated greater CPM magnitude at the deltoid muscle testing site.

Table 4. Hierarchical regression analysis

		Model 1				Model 2			
DV	IV	<i>B</i>	<i>SE B</i>	β	<i>p</i> value	<i>B</i>	<i>SE B</i>	β	<i>p</i> value
CPM at left deltoid muscle	Left arm lean mass (lb)	303.401	116.055	0.335	0.01	344.887	128.621	0.381	0.01
	Baseline pain (PPT deltoid in cool water)					-50.633	66.502	-0.108	0.45
	R^2 /Adjusted R^2		0.112/0.096				0.122/0.089		
	F for change in R^2		6.835		0.01		0.58		0.45
	F for model		6.835		0.01		3.681		0.03

CPM, conditioned pain modulation; DV, dependent variable; IV, independent variable; PPT, pressure pain threshold.

4 Discussion

Adolescents experienced CPM in a similar manner between test sites and weight groups. While body fat had no effect on the CPM response, arm lean mass was related to CPM magnitude at the deltoid muscle but not the nailbed. Arm lean mass uniquely predicted 10% of the variance in the CPM response. This may explain why CPM efficiency was similar between the two weight groups. Overweight/obese adolescents had higher body fat compared with normal weight adolescents, but both groups had similar lean mass.

Our data demonstrating the adolescent CPM response are similar in methodology to other paediatric studies (Goffaux et al., **2008**; Evans et al., **2013a,b**; Tsao et al., **2013**; Williams et al., **2013**). Previous studies all used a cold water bath with hand submersion as the conditioning stimulus, comparable to our study except with foot submersion. The previous testing stimuli included pressure pain ratings at the nailbed (Evans et al., **2013b**; Tsao et al., **2013**), heat pain ratings at the calf and forearm (Goffaux et al., **2008**), and heat pain threshold at the forearm (Williams et al., **2013**). Our study was the first in paediatric literature using pressure pain thresholds (nailbed and deltoid) as the testing stimulus. Despite these slight methodology differences, all studies elicited CPM.

To our knowledge, this study is the first to assess body composition on the CPM response in children or adults. Price and colleagues examined the influence of body weight (Price et al., **2013**) by measuring heating pain ratings on the forehead (testing stimulus) before and after hand submersion in a cold water bath (conditioning stimulus) in obese and non-obese adults. As with our results, the CPM response was similar between the weight groups. Interestingly, despite similar CPM responses between the deltoid muscle and nailbed, lean mass was not related to the CPM response at the nailbed site which has minimal lean mass.

In contrast to the CPM results, Price has shown that pain sensitivity is less at sites with excess subcutaneous fat (abdomen) in obese adults compared with non-obese adults (Price et al., **2013**). In this adolescent population, pain sensitivity (baseline PPTs in cool water) was similar between weight groups at sites that varied in adiposity (nailbed and deltoid). The potential difference between this study and Price et al. may be related to the larger potential for adiposity for the abdomen (central) than the deltoid (proximal muscle) (Lee et al., **2013**).

Local factors (mechanical or chemical) were suggested to be responsible for the change in pain sensitivity that occurred in the obese adults (Price et al., **2013**). Our results showing the relation between lean mass and the CPM response at the deltoid would further suggest that peripheral mechanisms were involved in endogenous pain modulation. One explanation for the link between CPM and lean mass is the opioid system. CPM is partially mediated by the release of endogenous opioids (King et al., **2013**), and opioid peptides are released from the muscle (Evans and Smith, **2004**; Denning et al., **2008**; Lesniak and Lipkowski, **2011**). Consequently, greater activation of the opioid system would occur with increased lean mass explaining the association between CPM and lean mass at the deltoid muscle but not the nailbed.

During puberty, lean mass increases (Guo et al., **1998**) and habitual physical activity independently influences this growth (Baxter-Jones et al., **2008**). On the other end of the age spectrum, lean mass decreases in older adults (Roubenoff and Hughes, **2000**; Goodpaster et al., **2006**). Similarly, CPM has

been shown to have a developmental improvement from younger children to older children (Tsao et al., **2013**), decreased responses in middle-aged adults (Lariviere et al., **2007**; van Wijk and Veldhuijzen, **2010**) and an attenuation in older adults (Edwards et al., **2003**; Lemley et al., **2015**). Therefore, it could be postulated that the link between CPM efficiency across the lifespan may be related to changes in lean mass. Future studies investigating rehabilitation interventions to increase lean mass are necessary to determine if the CPM magnitude is affected by resistance training.

We originally hypothesized that overweight/obese adolescents would experience less CPM than normal weight adolescents due to the increased probability of clinical pain. Previous literature has shown that adults and children with chronic pain have reduced endogenous pain inhibition (van Wijk and Veldhuijzen, **2010**; Yarnitsky, **2010**; Staud, **2012**; Williams et al., **2013**). Our adolescent population reported minimal clinical pain and suggests that increased weight status does not preclude adolescents from reporting normal pain reports and endogenous pain inhibition.

In addition to lean mass, self-reported physical activity levels were related to the CPM response at the nailbed but not deltoid. Previously, we demonstrated a similar association in young and older adults using a pressure testing stimulus applied to the finger (Lemley et al., **2015**). Naugle and Riley showed higher vigorous and total physical activity was related to the CPM magnitude using a thermal testing stimulus on the palm (Naugle and Riley, **2014**). When comparing inactive and active adults, similar CPM responses exist using a pressure testing stimulus applied to the leg and arm (Vaegter et al., **2014**). Whether the positive relation between physical activity and CPM is specific to testing sites with minimal subcutaneous lean mass (i.e. nailbed, finger, palm) is not known.

Physical activity levels parallel cardiovascular health; adolescents with lower physical activity are considered to be at risk for future health complications. The average physical activity levels of our adolescent population fall within the at risk range (Voss et al., **2013**). Our results demonstrate that participating in physical activity may also lead to improved pain modulation. Furthermore, despite boys having greater physical activity participation and more lean mass, boys and girls had comparable CPM efficiency. The lack of sex differences in the CPM response is similar to other paediatric studies (Evans et al., **2013b**; Tsao et al., **2013**) and highlights that while lean mass and physical activity are related to endogenous pain modulation, a multitude of factors are involved.

While this study lays the foundation for the role of body composition in CPM efficiency, limitations exist. First, overweight and obese adolescents were combined into one group. To further define the impact of anthropometrics on CPM, the categories should be expanded to include adolescents across more distinct weight groups (overweight through class III obesity). Second, one PPT was obtained at each site (nailbed and deltoid muscle) during each condition (cool or ice water) in order to limit the total exposure time of the foot to the ice, which is not as valid as measuring 2–3 PPTs and then averaging the results. Third, the conditioning stimulus (ice water) was always applied following the testing stimulus and not randomized to avoid the confounding issue of analgesic effects that may occur with the conditioning stimulus. This could potentially result in an ordering or habituation effect. Finally, lean mass predicted the CPM magnitude as measured with absolute changes in PPTs. Our preliminary data analysis did not show any correlation with relative change in PPTs. Therefore, interpretation of our finding should be done with careful consideration given that different analyses may produce

equivocal results. Future studies should be done to identify the most appropriate analyses in assessing CPM.

5 Conclusion

Our results show that overweight/obese and normal weight girls and boys from a community-based sample have similar CPM responses. In this adolescent population, lean mass predicted the CPM response. Activities that increase lean mass may be an avenue to enhance endogenous pain inhibition in adolescents. Whether this relation between lean mass and CPM remains in patient or adult populations is not known.

Author contributions

S.S. and M.H.B. are designated authors for this manuscript due to substantial contributions towards research design, data acquisition and data analysis/interpretation. The manuscript was drafted by S.S. and revised for important intellectual content by M.H.B. Final approval of the manuscript was completed by both S.S. and M.H.B.

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