Does Intensive Interdisciplinary Pain Treatment (IIPT) Enhance Endogenous Pain Modulation in Youth With Chronic Pain Syndromes?

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Objectives: This study aimed to investigate whether endogenous pain modulation (EPM) improves after intensive interdisciplinary pain treatment (IIPT) and its relationship with clinical outcomes in youth with chronic pain syndromes. EPM is a physiological process in the nervous system that inhibits pain perception. EPM is often impaired in youth with chronic pain syndromes and is a potential mechanism by which IIPT interventions act.

Methods: EPM was measured using offset analgesia (OA) in 27 youth with primary and secondary chronic pain syndromes before and after IIPT. Test-retest reliability was measured in a subset of participants (n = 12) within 5 days of IIPT admission to examine whether the observed change was meaningful and beyond the limits of error.

Results: On average, OA response improved by 12.4% between admission and discharge (95% CI: 3.0, 21.8%), even after controlling for covariates using a mixed effects multivariable repeated measures ANOVA ($P = 0.009$). OA responses demonstrated excellent test-retest reliability, intraclass correlation coefficient = 0.919 (95% CI: 0.718, 0.977), and minimum detectable change (MDC_{95}) of the OA response was 13%. Participants also demonstrated an improved ability to adapt to a constant noxious heat stimulus ($P = 0.044$) that moderately correlated with improvements in self-reported pain intensity and sensitivity to stimuli ($P < 0.05$).

Discussion: Overall, 52% of participants demonstrated meaningful improvements (ie, change greater than the MDC_{95}) in EPM after IIPT participation. The contributions of specific IIPT interventions (eg, exercise, desensitization, cognitive-behavioral therapy) to improvements in EPM need further exploration.

Key Words: intensive interdisciplinary pain treatment, chronic pain, offset analgesia, endogenous pain modulation, pediatrics

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Pediatric chronic pain syndromes occur in an estimated 20% of youth[1] and 5% to 8% of these children experience severe pain-related disability[2] associated with poorer quality of life, increased health care utilization, and emotional and financial burden.[3–6] Central sensitization is an overarching mechanism of pediatric and adult chronic pain syndromes[7] defined as an imbalance of pain signal traffic in the central nervous system where excessive facilitation, deficient inhibition (ie, endogenous pain modulation), or both leads to pain amplification and chronicity.

Pain alerts the body of potential or actual harm and its perception is modulated by biological, psychological, and social factors.[8,9] Thus, biopsychosocial and intensive interdisciplinary pain treatment (IIPT) approaches are most effective for treating pain and related disability in youth with chronic pain.[10–12] The physiological mechanism(s) by which complex IIPT interventions reduce pain and restore function are yet to be determined. One mechanism postulated is that interventions designed to enhance self-management of pain (eg, exercise, re-engaging in valued activities, learning to manage emotions and beliefs related to pain, and pain neuroscience education) may restore the balance between facilitatory and inhibitory interactions in the central nervous system and improve clinical outcomes.[13,14]

Endogenous pain modulation (EPM) is a process that inhibits pain perception and involves several mechanisms distributed throughout the brain and spinal cord.[13,15] Offset analgesia (OA) is one measure of EPM characterized by a disproportionately large decrease in pain (ie, analgesia) in response to a small decrease (ie, offset) in a noxious stimulus.[16] OA responses are reduced in adult and pediatric chronic pain syndromes, suggestive of impaired EPM.[17,18] Several adult studies attempted to elucidate the impact of opioid and nonopioid therapies on OA response and showed no effect,[19–24] but the mechanism of a multifaceted intensive nonpharmacologic intervention, such as IIPT, has not been explored. Our previous cross-sectional study demonstrated that most youth with chronic pain admitted to IIPT have impaired OA at baseline, and OA response < 63% distinguished patients from healthy controls with 60% specificity and 78% sensitivity.[18] Because youth demonstrate improved pain and disability after IIPT,[10,25] the next logical question is to investigate whether IIPT exerts its effect, in part, by improving EPM in these youth.

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This preliminary study aimed to examine whether EPM improves after IIPT in youth with chronic pain syndromes. Specifically, we aimed to (1) evaluate the stability of the OA testing paradigm in youth with chronic pain, (2) evaluate the magnitude of change in OA and constant test responses before and after IIPT, and (3) explore relationships between improvements in EPM and clinical outcomes of pain and disability. Disability is a multidimensional construct defined by the International Classification of Functioning, Disability, and Health (ICF),[26] and outcome measures were selected to encompass body structures and functions (eg, central sensitization, pain, baseline sensitivity), activities (eg, walking, climbing stairs, exercise tolerance), and participation (eg, going to school, playing sports) in addition to personal and environmental factors (eg, fear of pain, anxiety, depression) that may contribute to disability.[27] Overall, we hypothesized that OA responses would demonstrate adequate test-retest reliability in youth with chronic pain and that IIPT improves responses on the OA and constant tests.

MATERIALS AND METHODS

Enrollment, Inclusion, and Exclusion Criteria

This longitudinal cohort study examined responses to the OA test at 2 time points: (1) within 5 days of IIPT admission and (2) within 1 week of IIPT discharge. To examine test-retest reliability, a subset of participants (n = 12) repeated the OA test within 5 days of the baseline visit with a minimum 24-hour interval between tests. The first 12 participants who consented to the additional test-retest reliability visit were included in this arm of the study on a first come first serve basis. The 5-day window for completion of baseline and test-retest study visits (ie, the first week of admission) was selected both to allow participants adequate time for informed consent and to best capture the individual's responses before the onset of treatment effects and is consistent with prior reliability studies using quantitative sensory testing that range between 1 and 14 days.[28–30] Between October 2022 and October 2023, we recruited 43 youth with primary and secondary chronic pain syndromes[31,32] ages 10 to 17 years admitted to the Mayo Family Pediatric Pain Rehabilitation Center at Boston Children's Hospital, Boston, Massachusetts, United States (Fig. 1). Participants received a $20 Amazon gift card for completing each study visit. The study was approved by Boston Children's Hospital's institutional review board (IRB) and registered with the National Institutes of Health (clinicaltrials.gov; NCT5491499). Written informed consent and assent were obtained from one caregiver and the participant, respectively. Data for participant characteristics and clinical outcomes were obtained and merged with OA data using an IRB-approved data registry in the same clinic for which caregiver consent and participant assent were obtained separately. Participants and caregivers were not involved in the study design, analysis, or interpretation.

Eligibility criteria included: (1) age 10 to 17 years, (2) first test completed within 5 days of admission, (3) established diagnosis of primary or secondary chronic pain,[31,32] and (4) stable use of medications for at least one week before the first study visit. Exclusion criteria were: (1) presence of pain or allodynia in either upper extremity that would limit QST tolerance or use of the computerized visual analog scale; (2) a history of central nervous system, heart, kidney, liver, and respiratory system diseases, functional movement, or seizure disorders because they differ in mechanisms and could impede reliable QST testing interactions, or severe psychiatric disorders (eg, bipolar, psychosis); (3) reported current consumption of alcohol, cannabis, or tobacco products; (4) inability to read English or follow testing instructions; (5) intolerance to the thermal test stimulus; or (6) no pain reported at maximum test stimulus (48°C). The presence or absence of allodynia was assessed by patient report after stroking the skin with a handheld soft brush swept at a rate of approximately 3 to 5 cm/sec.[33]

Thermal Testing

A preset computer-controlled temperature paradigm was programmed to deliver each stimulus using the Medoc TSA-2001 device (Medoc Ltd. Advanced Medical Systems, Ramat Yishai, Israel). The thermal sensory analyzer operates by a microcomputer-driven 3 cm×3 cm (9 cm^2) Peltier contact thermode. The entire thermode-stimulating surface was in contact with the skin on the volar surface of the nondominant forearm and secured by a Velcro band without stretch. All tests were performed in a quiet 20 to 23° C room with the participant comfortably seated. The testing site was exposed to ambient temperature for 10 to 15 minutes before testing and divided into 4 zones. Participants were not permitted to view the computer screen and were unaware of the type of test being performed and expected response patterns during testing. Before testing, participants completed a training session with 2, 5-second heat stimuli (42°C and 43°C) administered 30 seconds apart to familiarize themselves with the thermal stimulus and confirm their understanding of eVAS use. Testing began with identification of the individualized test temperature (ITT), followed by 3 heat pain tests (offset analgesia, control, and constant) performed in a randomized order. Each heat pain test was repeated 3 times at 1- to 2-minute intervals. Between tests, the probe was moved between 4 zones on the forearm alternating between the medial and lateral antebrachial cutaneous nerve distributions (T1 and C5 dermatomes, respectively) to prevent sensitization of the skin as follows: (1) distal lateral forearm, (2) distal medial forearm, (3) proximal lateral forearm, and (4) proximal medial forearm. The baseline temperature for each test was set to 32°C. For OA, control and constant tests, ascending and descending temperature rates were 1.5°C/s and 6°C/s, respectively. A single examiner (JS), who was not blinded, conducted all tests.

Assessment of Pain Intensity During Thermal Testing

During all tests, participants rated heat pain intensity continuously in real time using a linear electronic visual analog scale (eVAS). Participants used their dominant hand to operate a knob on a horizontal sliding eVAS scale (0 to 100 mm) with the following 2 anchors: the left defined as "no heat pain sensation" (0 mm) and the right as "most intense heat pain sensation imaginable" (100 mm). Participants were instructed to move the knob on the scale in proportion to perceived heat pain intensity and not temperature intensity during testing.

Determination of the Individualized Test Temperature (ITT)

Calibration of test temperatures remains controversial,[34] and was performed in this study to: (1) determine if individual pain sensitivity changed between

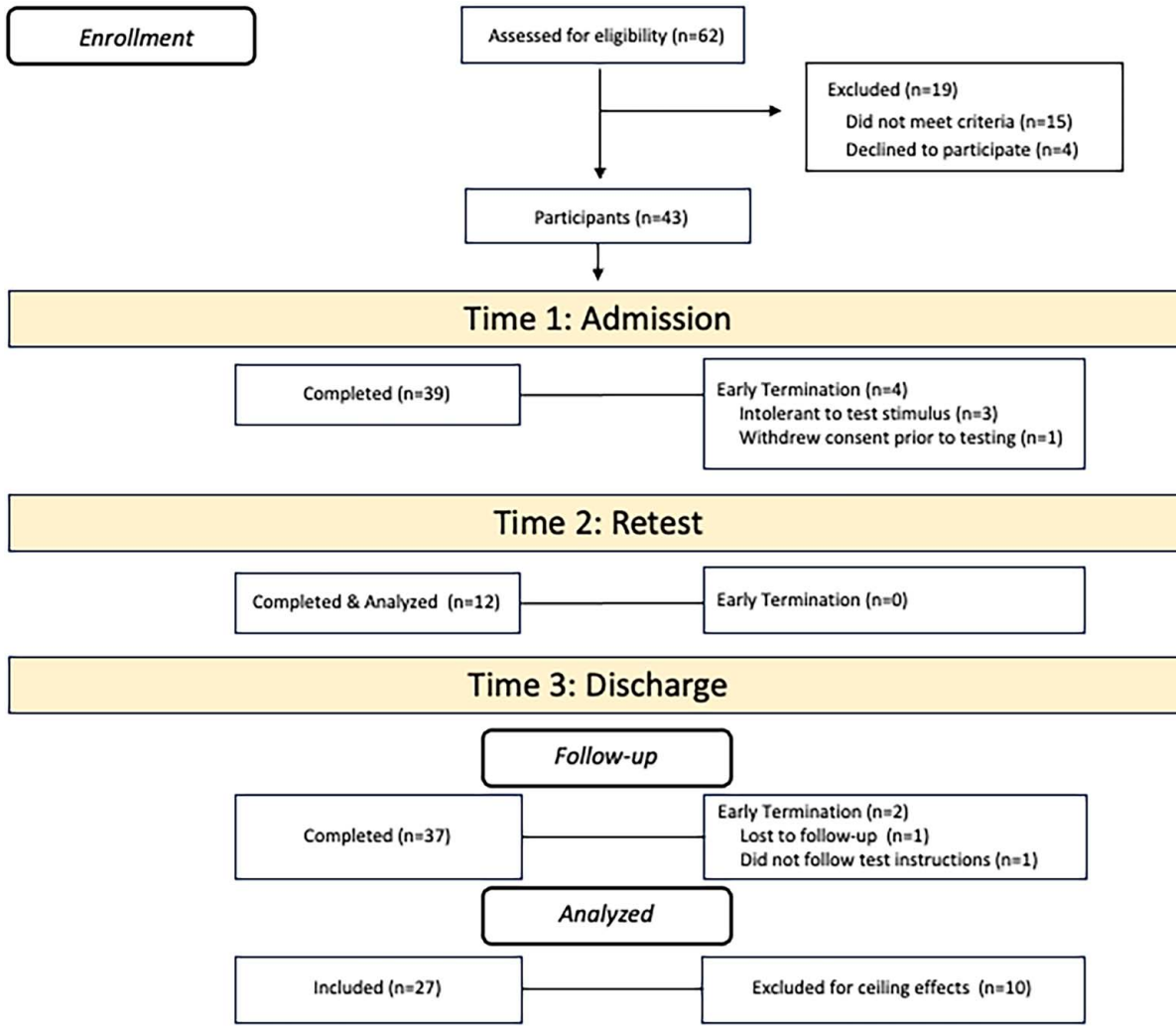

FIGURE 1. CONSORT flow diagram of study enrollment.

admission and discharge testing; (2) improve the generalizability of the results; and (3) limit exposure to unnecessarily intolerable stimuli that would be objectionable to youth, caregivers, and ethical review boards. To determine ITT, the first temperature stimulus ramped from baseline (32°C) to 46°C (the 75th percentile heat pain detection threshold for children ages 7 to 17 y)[35] and was held for 5 seconds. Then, the temperature returned to baseline (32°C) for 30 seconds; this process was repeated twice such that the participant was exposed to the 46°C temperature 3 times. If an eVAS of 75/100 mm was not consistently reported on all 3 trials, this paradigm was repeated at 48°C. The lowest temperature that consistently evoked an eVAS $\geq$75/100 mm was used as the first temperature (T1) in all tests (Fig. 2). ITT testing was repeated before each study visit for the reasons noted above.

Offset Analgesia Test

We used the same paradigm as in our previous study, except for increasing the ITT threshold to 75/100 mm, as described above.[18] The first temperature (T1) is set to the ITT (46°C or 48°C) and held for 5 seconds, followed by a second temperature (T2) 1°C higher for 5 seconds, and then returns to a third temperature (T3) that is equal to T1 for 20 seconds before returning to baseline (32°C) (Fig. 2). OA responses are calculated as a percentage of perceived pain reduction following the 1°C noxious thermal stimulus offset. A larger OA response (ie, greater pain reduction) reflects a greater ability to actuate pain modulation. A video explaining the OA test and its interpretation is included in Supplemental Digital Content 1, http://links.lww.com/CJP/B235.

Control Test

For control tests, T1 and T2 temperatures are identical to those used in the OA test, but T3 is set at the non-noxious baseline temperature (32°C) (Fig. 2). The control test serves as a physiological discriminative stimulus to examine participants' pain perception in the presence versus absence of a noxious heat stimulus.

Constant Test

For constant tests, the ITT (T1) is applied and held for 30 seconds before returning to baseline (32°C) (Fig. 2). The constant test compares the magnitude of adaptation or summation occurring during constant and OA tests. Failure

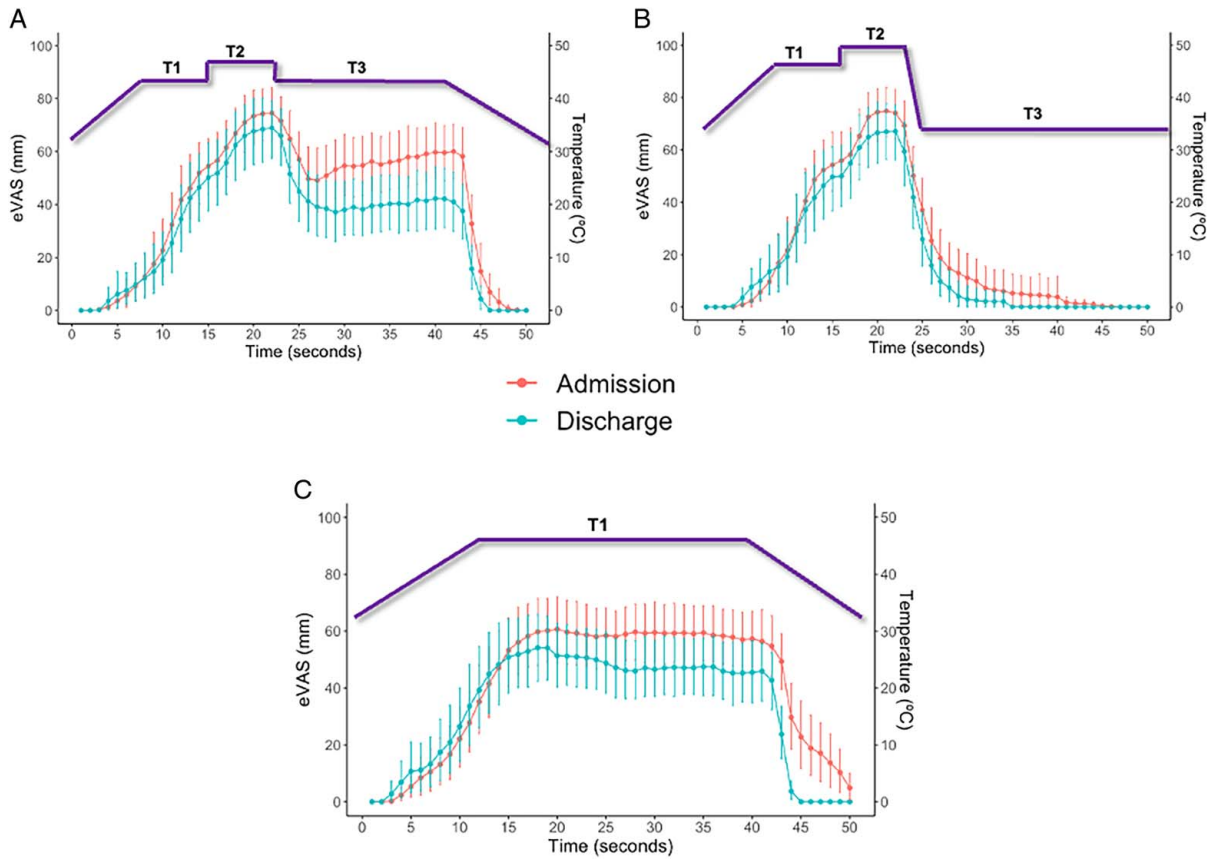

FIGURE 2. Thermal electronic visual analog scores (eVAS) for 27 participants with chronic pain at intensive interdisciplinary pain treatment admission versus discharge: (A) the offset analgesia test, (B) the control test, and (C) and constant test. Data represents the mean ± SD for eVAS rating. The continuous purple line above each diagram represents the pattern of each thermal test when the individualized test temperature (ITT) is set to 48°C. For each test, T1 = ITT.

to adapt may result from weakened descending pain inhibition, contributing to pain chronicity.[36]

Intensive Interdisciplinary Pain Treatment (IIPT)

IIPT programs offer a rigorous biopsychosocial approach in outpatient or inpatient rehabilitation settings.[10,27] These programs involve coordinated interventions of at least 3 disciplines working together in an integrated way in the same facility, and typically include physicians, nurses, psychologists, physical therapists, and occupational therapists. The program in this study treats youth ages 8 to 18 years with chronic pain and associated disability using a day-hospital rehabilitation model further described in Supplementary Digital Content 2, http://links.lww.com/CJP/B236.[37] Patients and families receive 40 hours per week of individual, group, and family therapies with goals of improving functioning, resuming developmentally appropriate daily activities, and optimizing patient and family self-management of pain. Essential treatment components include cognitive-behavioral therapy, medication management, desensitization, and exercise. Treatment length of stay is individualized and typically lasts 4 to 6 weeks.

Clinical Outcomes of Pain and Disability

Pain Intensity

Current pain at rest was assessed using the self-report numeric rating scale (NRS), with 0 indicating "no pain" and 10 indicating "worst pain you can imagine." The NRS is a valid and reliable measure of pain intensity in youth as young as age 7.[27]

Sensory Sensitivities

The Highly Sensitive Child (HSC) scale is a 12-item inventory assessing children's sensitivity to environmental stimuli (eg, "I notice when small things have changed in my environment").[38] The measure was developed as a variant of the Highly Sensitive Person scale.[39] Participants rated their agreement to the 12 items on a 7-point Likert scale ranging from 1 = *Not at all* to 7 = *Extremely*. Items were averaged to calculate a total score and 3 subscale scores: Ease of Excitation (EOE), Aesthetic Sensitivity (AES), and Low Sensory Threshold (LST).

Fear of Pain

The Fear of Pain Questionnaire, Child Report (FOPQ) is a 24-item self-report questionnaire used to assess pain-related fears and behavioral avoidance. Each item is rated on a 5-point Likert-type scale (0 = *"strongly disagree"* to 4 = *"strongly agree"*). The FOPQ demonstrates strong internal consistency and construct validity.[25] The total FOPQ score was used in this study; higher scores represent greater fear of pain and avoidance behaviors.

Pain Interference, Anxiety, and Depressive Symptoms

Symptoms of depression and anxiety, and pain interference with daily activities were assessed with the Patient Reported Outcomes Measurement Information System (PROMIS) Pediatric Short Form v3.0—Depressive Symptoms 8a, PROMIS Pediatric Short Form v2.0—Anxiety 8a,[40] and PROMIS Pediatric Pain Interference Short Form 8a, v2.0.[40] Participants rated how often each statement applies to them in the past 7 days using a 5-point Likert scale ranging from 0 (never) to 4 (almost always). Item scores are summed and converted to T-scores, with higher T-scores reflecting higher levels of pain interference or depressive and anxiety symptoms.

Cardiovascular Endurance

The Fitkids Treadmill Test (FTT) is a reliable and valid measure of submaximal cardiovascular endurance and was recently normed in a Dutch sample of healthy children ages 6 to 18.[7,8] Time to exhaustion (TTE) on the FTT provides an objective, norm-referenced marker of cardiovascular endurance in youth and is defined as the total time completed on the test, excluding the warm-up and cool-down phases. Our prior research demonstrates the feasibility and clinical utility of the FTT in youth with chronic pain.[41] All youth capable of safely walking on a treadmill at admission completed the FTT (n = 25).

Functional Disability

The Functional Disability Inventory (FDI)[20] is a valid and reliable self-report measure in children ages 8 to 18, consisting of 15 items looking at the perception of physical and psychosocial functioning in the past 2 weeks. Total scores range from 0 to 60, with higher scores indicating greater disability. Functional disability levels are defined as: no/minimal disability (0 to 12), moderate (13 to 29), and severe (≥ 30).[21]

Data and Statistical Analyses

Data were analyzed using IBM SPSS Statistics (version 29.0, IBM Corporation, Armonk, NY) unless otherwise specified and all reported *P* values are 2-tailed. Descriptive statistics were used to evaluate participant characteristics. OA and control test responses are expressed as a percent reduction in pain at the stimulus offset (T3) relative to the peak (Fig. 2). First, the magnitude of pain reduction (ΔVAS) after the offset is calculated by subtracting the nadir VAS within 10 seconds of the stimulus offset (T3) from the peak VAS during T2: $\Delta VAS = VAS_{peak} - VAS_{nadir}$. Then, the percent reduction is calculated by dividing the magnitude by the peak: OA/control test response (%) $= \Delta VAS/VAS_{peak} \times 100$.[42,43] Each test is repeated 3 times, and the final response is calculated as a mean of each trial. To assess stimulus adaptation during the constant test, area under the curve (AUC) is determined using the trapezoidal rule, and greater AUC indicates more pain amplification and reduced adaptation to heat pain over time (Fig. 2). AUC analyses were completed in RStudio (version 3.6.2, Vienna, Austria) using the "metrumrg" package.[44,45] Improvements in OA response and AUC on the constant test between admission and discharge were evaluated using mixed-effects multivariable repeated measures ANOVAs in Stata (version 18, StataCorp LLC, College Station, TX) adjusting for the following covariates: age, sex, body-mass index, admission pain intensity, duration of chronic pain, and chronic pain diagnosis. Changes in responses on the offset analgesia, constant, and control tests were evaluated using paired *t* tests. Participants with an OA response $\geq 95\%$ at admission were included in reliability analyses and excluded from longitudinal analyses of intervention effects due to the influence of ceiling effects on longitudinal models.[46] Test-retest reliability was determined using the intraclass correlation coefficient (ICC 2,1) and ICC ≥ 0.75 was deemed adequate. To evaluate how improvements in endogenous pain modulation related to improvements on clinical outcomes, change scores were calculated for all variables by subtracting admission and discharge scores; then, bivariate Spearman and Pearson correlations were analyzed for nonparametric and parametric variables, respectively. Only participants with complete data were included in each analysis. To determine if the amount of change observed between admission and discharge was clinically meaningful and beyond the threshold of random error, standard error of measurement (SEM), and minimum detectable change (MDC_{95}) values for OA percent response and AUC during the constant tests were calculated using the formulae below,[47] where Δresponse represents the difference between either OA percent response or AUC at the test and retest visits.

$$SEM = SD_{(\Delta response)} \times \sqrt{(1\text{–}ICC)}$$

$$MDC_{95} = SEM \times 1.96 \times \sqrt{2}$$

Power Analyses

For longitudinal analyses, *a priori* power calculations indicated that 34 participants provided 80% power to detect a 10% improvement in OA response magnitude using a paired *t* test, assuming a SD of 20%[42,48] (standardized effect size: 10/20 = 0.50) with a 2-tailed alpha level of 0.05 (G*Power, version 3.1.9.6, Dusseldorf, Germany).[49] Forty-three participants were recruited allowing for a 20% dropout rate. For evaluating test-retest reliability, *a priori* power analysis indicated that 12 participants would provide 90% power to detect an ICC $\geq$ 0.75 for measuring the repeatability of OA percent response (RStudio, version 3.6.2, Vienna, Austria).[45,50] A sample size of 26 provides 80% power for detecting moderate to large relationships (effect sizes of 0.5 or greater) between improvements in endogenous pain modulation and clinical outcomes of pain and disability.

RESULTS

Participant Characteristics

Participant characteristics of the 27 youth included in longitudinal analyses are presented in Table 1. Baseline characteristics (age, sex, diagnosis, pain intensity, disability outcomes) for youth who were excluded from the analysis did not differ from the 27 youth included in longitudinal analyses ($P > 0.05$), except for race. Both participants who identified as Black were excluded due to ceiling effects at baseline. Participants included in longitudinal analyses were all White and the majority were female. Chronic headache was the most common primary pain symptom. On average, participants reported moderate pain at admission of greater than 2 years' duration and were admitted to the IIPT program for 5.6 ± 0.9 (mean ± SD) weeks. The ITT for 19 (70%) participants was 48°C at admission, and pain intensity ratings at the ITT did not significantly differ between

TABLE 1. Participant Characteristics

Characteristic			
Age, y		14.4 ± 2.1	
Sex, M/F		7/20	
BMI, kg/cm^2		25.1 ± 9.1	
Race, n (%)			
White		27 (100)	
Pain Diagnosis, n (%)			
Musculoskeletal		4 (14.8)	
Headaches		14 (51.9)	
Abdominal		2 (7.4)	
CRPS		1 (3.7)	
Widespread		6 (22.2)	
Pain duration (mo)		32.8 ± 34.7	
Length of stay (wk)		5.6 ± 0.9	
Characteristic	Admission	Discharge	*P*-value mean difference (95% CI)
Pain Intensity (NRS)*	**6 (3-7)**	**5 (3-7)**	0.051
ITT (°C), n (%)			
46°C	8 (29.6)	7 (25.9)	
48°C	19 (70.4)	20 (74.1)	
ITT VAS, mm	63.4 ± 27.9	54.7 ± 31.7	0.068 8.7 (−0.7, 18.1)
OA test response, %	47.9 ± 23	60.3 ± 26.8	**0.015** **12.4 (2.6, 22.3)**
Control test response, %	95.6 ± 12.7	99.8 ± 0.7	0.091 4.2 (−9.2, 0.7)
Constant test AUC, mm×s	1878 ± 821	1627 ± 894	0.055 250 (−534, 506)
Highly sensitive child*			
Ease of excitation	4.2 (3.4, 5.5)	4.4 (3, 5)	0.767
Low sensory threshold	4.3 (2.5, 5.1)	3.3 (2.7, 5)	0.704
Aesthetic sensitivity	5 (3.9, 5.8)	4.75 (3.8, 5.8)	0.618
Total	4.6 (3.6, 5.4)	4 (3.3, 4.8)	0.527
PROMIS pain interference T-score	71.7 ± 4 (severe)	65.4 ± 5 (severe)	**< 0.001** **6.3 (4.1, 8.4)**
Fitkids treadmill test (min)	8.5 ± 2.5	10.1 ± 2.3	**< 0.001** **1.5 (1.0, 2.0)**
Functional disability inventory*	27 (18.5, 34.3) (moderate)	11 (5, 19) (no/minimal)	**< 0.001**
PROMIS anxiety T-score	54.0 ± 12.5 (normal)	51.8 ± 11.2 (normal)	0.268 2.2 (−1.8, 6.2)
PROMIS depressive symptoms T-score	55.0 ± 10.8 (Mild)	53.4 ± 10.5 (normal)	0.341 1.6 (−1.8, 5.1)
Fear of pain questionnaire*	47 (26, 57.5) (moderate)	29 (10.8, 41.8) (low)	**< 0.001**

Significant *P* values (< 0.05) are bolded.

Data presented as mean ± SD and *P* values result from paired *t* tests. For continuous outcomes, the mean difference and associated 95% CI are presented alongside the *P*-value as well as established clinical scoring interpretations. An *denotes median (interquartile range) and *P*-values result from Wilcoxon signed-rank tests.

AUC indicates area under the curve; BMI, body-mass index;CRPS, complex regional pain syndrome; ITT, individualized test temperature; NRS, numeric rating scale; OA, offset analgesia; VAS, visual analog scale.

admission and discharge. All participants selected the same ITT during admission and retest visits; only one participant selected a different ITT between admission and discharge, shifting from 46°C at admission to 48°C at discharge.

Test-retest Reliability

The offset analgesia and adaptation tests demonstrated excellent test-retest reliability in this sample. On average, the retest visit occurred within 1.8 ± 0.8 days (mean ± SD) of the first study visit. Reported pain intensity (NRS) did not significantly differ between visits ($P = 0.19$); median (IQR) at admission was 6 (2 to 6.75) compared with 6.5 (2.25 to 7) at the retest visit. For the 12 participants who completed a retest visit, the mean ± SD OA response was 59.6% ± 32.8% at admission and 66.4% ± 26.3% at retest (n = 12). The ICC of the OA test was 0.919 (95% CI: 0.718, 0.977). For the constant test, mean ± SD for AUC was 1641 ± 9881 mm*s at admission and 1473 ± 9855 mm*s at retest (n = 12). The ICC of the constant test was 0.969 (95% CI: 0.892-0.991). Of these 12 participants, 3 were excluded from longitudinal analyses for the following reasons: OA response > 95% at admission (n = 2) and lost to follow-up (n = 1).

Treatment Effects

Offset Analgesia

For the 27 participants included in longitudinal analyses, OA response improved from 47.9% ± 23% (mean ± SD) at admission to 60.3% ± 26.8% at discharge. A paired *t* test showed a statistically significant improvement in OA response after IIPT ($P = 0.015$), suggesting improved EPM.

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The effect of IIPT remained statistically significant when controlling for the 7 covariates using mixed-effects multivariable repeated measures ANOVA ($P = 0.009$) (Table 2). Longer length of stay in the IIPT program was also associated with greater improvement in OA response in the model ($P = 0.045$). On average, OA response improved by 12.4% between admission and discharge (95% CI: 3.0, 21.8%). SEM and MDC_{95} for OA response were 4.8% and 13%, respectively. Of the 27 participants, 14 (52%) showed a > 13% improvement (MDC_{95}) in OA response between admission and discharge, and one participant showed a > 13% decline in OA response. All other participants improved or declined within the MDC_{95} value. Group OA responses at admission and discharge are presented in Figure 2.

Constant Test

On average, adaptation during the constant test stimulus improved significantly between admission and discharge (Fig. 2), reflecting reduced sensitivity and improved adaptation to the noxious thermal stimulus. Constant test AUC mean ± SD was 1878 ± 821 mm*s at admission compared with 1627 ± 894 mm*s at discharge. Paired samples *t* test results showed marginally significant improvement in AUC after IIPT ($P = 0.05$). The effect of IIPT was statistically significant when controlling for the 7 covariates using a mixed-effects multivariable repeated measures ANOVA ($P = 0.044$) (Table 2). On average, AUC during the constant test improved by 251 mm*s between admission and discharge (95% CI: 7, 495 mm*s).

Control Test

At both admission and discharge, participants reported near-complete reductions in pain in response to large changes in temperature to non-noxious levels at the stimulus offset during control tests (Fig. 2). On average, participants reported no significant differences in mean ± SD percent pain reductions of 95.6% ± 12.7% at admission compared with 99.8% ± 0.7% at discharge ($P = 0.091$).

Relationships Between Endogenous Pain Modulation and Clinical Outcomes

OA responses were not associated with any clinical outcomes of pain or disability ($P > 0.05$). Improved adaptation during the constant stimulus (lower AUC) was moderately and positively correlated with improvements in pain intensity ($r_s = 0.451$; $P = 0.018$), HSC total score ($r_s = 0.445$; $P = 0.023$), and the HSC aesthetic sensitivity subscale ($r_s = 0.390$; $P = 0.049$). Improvements in adaptation during the constant test were also moderately, positively associated with improvements in OA response ($r = 0.413$; $P = 0.032$). Correlation statistics are displayed in Table 3.

DISCUSSION

To the authors' knowledge, this is the first study to evaluate improvements in EPM after IIPT in youth with chronic pain syndromes. Findings from this preliminary study suggest that most youth with chronic pain syndromes demonstrate improvement in EPM after participation in IIPT, even after adjusting for covariates. This study is also the first to demonstrate excellent test-retest reliability of OA responses in a pediatric clinical sample. While these findings point to potential biobehavioral mechanisms by which IIPT may enhance central pain inhibition and reduce disability, the clinical relevance and mechanisms of these findings still need to be determined.

Relationships Between Thermal Tests and Clinical Outcomes of Pain and Disability

Relationships between psychophysical tests and physical and emotional functioning remain elusive, especially in youth. This study found that improvements in endogenous pain modulation during the constant test between admission and discharge (lower AUC) were associated with reduced pain intensity (NRS) and lower self-reported sensitivities on the HSC. These combined improvements suggest reduced nervous system sensitivity to noxious and non-noxious sensory stimuli after IIPT. In contrast, no relationships between OA response and clinical outcomes of pain and associated disability were observed. Because improvements in adaptation were modestly correlated with improvements

TABLE 2. Results of Mixed-effects Multivariable Repeated Measures Analyses of Variance

	OA response (%)			Habituation (AUC, mm*s)		
Variable	**Coefficient**	**95% CI**	***P***	**Coefficient**	**95% CI**	***P***
IIPT	12.4	3.0, 21.8	0.009*	−251	−495, −7	0.044*
Length of stay	9.3	0.2, 18.4	0.045*	−34.3	−397, 328	0.853
Age	−0.3	−4.6, 3.9	0.879	−37.4	−207, 132	0.666
Sex	6.4	−19.3, 32.2	0.626	−77	−1103, 949	0.883
Body-mass index	0.6	−0.4, 1.6	0.252	−33	−73.3, 7.8	0.114
Pain chronicity	−0.1	−0.4, 0.2	0.509	1.8	−9.7, 13.2	0.764
Admission pain intensity	−2.7	−7.6, 2.3	0.289	92.6	−105, 290	0.358
Pain Diagnosis						
Widespread	15.3	−22.3, 52.9	0.425	−501	−2000, 997	0.512
Headache	15.2	−18.7, 49.1	0.380	62.4	−1288, 1413	0.928
CRPS	25.5	−29.2, 80.1	0.361	−1189	−3365, 988	0.284
Musculoskeletal	2	−39.7, 43.6	0.927	455	−1204, 2114	0.591
Constant	−10.3	−106.7, 86	0.833	2941	−897, 6778	0.133

*An asterisk (*) denotes significant contributors to the predictive model.

Coefficients, 95% CI, and *P* values are presented for improvements in offset analgesia (OA) response and habituation response between admission and discharge (IIPT) adjusting for the additional 7 covariates. The reference diagnosis is abdominal pain.

IIPT indicates intensive interdisciplinary pain treatment.

TABLE 3. Relationships Between Improvements in Endogenous Pain Modulation and Clinical Outcomes

	OA test % response		Constant test AUC	
	r_s	*P*	r_s	*P*
Pain intensity	−0.174	0.384	**0.451**	**0.018**
Sensory sensitivity				
Aesthetic sensitivity	0.093	0.652	**0.390**	**0.049**
Ease of excitation	−0.069	0.738	0.347	0.070
Low sensory threshold	0.086	0.678	0.376	0.058
Total score	0.072	0.726	**0.445**	**0.023**
Pain interference*	−0.043	0.841	0.011	0.960
Cardiovascular endurance*	−0.127	0.544	0.070	0.727
Functional disability	−0.083	0.687	0.150	0.465
Anxiety symptoms*	−0.048	0.823	−0.178	0.406
Depressive symptoms*	0.311	0.139	0.271	0.201
Fear of pain	−0.069	0.749	−0.126	0.559
Constant AUC*	**0.413**	**0.032**	–	–

Significant correlations are in bold.
*Denotes Pearson correlation reported.
OA indicates offset analgesia; AUC, area under the curve.

in pain intensity and general sensory sensitivity, improvements on the constant test may be indicative of enhanced central pain inhibition after IIPT. This is clinically relevant, as recent studies found that lower general sensory sensitivity on the HSC was associated with better quality of life among adolescents with chronic pain.[51] Our study results provide initial evidence that general sensory sensitivity may improve alongside pain sensitivity after IIPT. This may be especially important for improving quality of life and pain and sensory sensitivity among neurodivergent youth who experience chronic pain at higher rates than the general population.[52]

The sparse relationships observed between thermal testing and clinical outcomes in this study are not surprising. Several adult studies also failed to identify relationships between quantitative sensory testing and clinical outcomes of physical and psychological functioning.[53,54] Chronic pain is a related but distinct syndrome from anxiety and depression and research consistently demonstrates that youth can improve functioning in the presence of pain without reporting changes in their emotional experience.[10,55] The neural mechanisms involved in EPM and mood may not overlap in all patients. In healthy adults, OA activates endogenous pain modulatory centers (eg, anterior insula, dorsal lateral prefrontal cortex, intraparietal sulcus, inferior parietal lobule).[15] These brain regions may not fully overlap with brain regions associated with elevated anxiety, depressive symptoms, or pain-related fear. In youth with complex regional pain syndrome higher pain-related fear is primarily associated with increased functional connectivity between the left amygdala and several brain regions that minimally overlap with OA mechanisms.[56] In one pediatric chronic headache study, alterations in functional connectivity were predominantly observed in the cerebellum, which plays a key role in endogenous pain modulation,[57] and were not correlated with clinical outcomes of physical or psychological functioning.[58] There remains a lot to learn about the intersectionality of EPM and clinical outcomes and future studies should continue to explore these relationships in larger, and more diverse samples.

Clinical Implications for Improvements in Endogenous Pain Modulation

IIPT programs emphasize teaching patients and caregivers to self-manage and cope with pain through cognitive restructuring, behavioral activation, graded exercise, and activity pacing to help youth return to valued, age-appropriate activities, such as school, sports, and social activities. The interventions are complex, involving several disciplines simultaneously coordinating multimodal treatments that likely interact, making it challenging to identify the key components and mechanisms driving observed improvements in pain and disability.[12,27] Pain-focused psychotherapy (incorporating acceptance and commitment and cognitive and behavioral strategies) is one component commonly delivered in IIPT that may contribute to observed improvements given its influence on pain modulation centers in the brain.[13] This is thought to be directly related to patients experiencing increased confidence engaging in valued activities in their everyday life and independently managing pain that arises during those activities.[12,27] Music therapy and recreational therapies also support youth in learning to shift attention away from pain, which may in turn support improvements in pain processing. A recent adult study found that distraction with preferred music attenuated OA responses, improved heat and pressure pain thresholds, and did not affect conditioned pain modulation and temporal summation of pain, suggesting that attention to a noxious stimulus may differentially impact pain facilitation and inhibitory pathways.[59]

Exercise is believed to modulate pain via exercise-induced hypoalgesia,[14] which can be measured, in part, using offset analgesia and quantitative sensory tests not included in this preliminary study. Studies evaluating the influence of exercise interventions on OA are scant in adults and none have been reported in youth. Two studies examined the impact of a single session of isometric and isotonic resistance exercise on endogenous pain modulation using OA and found no effect.[23,60] In this study, we did not find a relationship between thermal tests and cardiovascular endurance. There remains a need to examine the short- and long-term effects of aerobic and resistive exercise programs on both facilitatory and inhibitory mechanisms of pain processing using a diverse battery of quantitative sensory tests, especially in children and adolescents with and without chronic pain.

While the majority of participants demonstrated impaired OA at IIPT admission, 10 participants (27%) showed robust OA responses ($\geq$95%), which is consistent with previous studies of OA in adults and youth with chronic pain.[17,18] Because OA measures only one distinct pathway of EPM that variably correlates with different psychophysical tests of facilitatory and inhibitory pain modulation,[61,62] it is plausible that youth with robust OA responses would have impairments in different pain modulatory pathways not administered in this study, such as mechanical or heat temporal summation of pain and conditioned pain modulation. Given the diverse pathophysiologic and psychosocial basis of various chronic pain disorders, an expanded battery of reliable and valid psychophysical testing of complex facilitation and inhibition pathways may help elucidate the mechanisms driving

individual pain syndromes and recovery responses after rehabilitation interventions.

Nine (33%) participants showed unchanged or worse OA responses after IIPT. This is not entirely unexpected considering that most youth do not experience pain relief until months or years after IIPT discharge. A study of pain recovery trajectories in youth admitted to IIPT found that only one-third of youth reported clinically significant improvements in self-reported pain intensity at IIPT discharge compared with two-thirds at 1-year follow-up.[25] Another study demonstrated that the majority of youth report ongoing pain relief up to 5 years after IIPT.[63] Our study also observed that a longer length of stay in the IIPT program was associated with greater OA response. On the basis of these findings, measurable improvements in descending pain modulation may require more time to detect, and longer follow-up intervals in future studies will better characterize the stability and trajectories of endogenous pain modulation after IIPT participation.

Study Limitations and Future Directions

This study has limitations to consider. First, the sample is small and lacks diversity; all participants were White, and most were female. The diagnoses were heterogeneous, and we cannot determine if outcomes differed based on diagnosis, sex, or race. Sex was included as a biological variable and how gender diversity impacts pain sensitivity still needs to be explored. Furthermore, we are unable to characterize how EPM may vary by pain location or diagnosis. Similar to other IIPT programs, the majority of youth in our sample had chronic headaches of varying subtypes and pathophysiology.[27] One adult migraine study found impaired OA in the trigeminal region during pain-free intervals but not at external sites, such as the forearm.[64,65] Other adult studies report both cephalic and extra-cephalic allodynia in adults with migraine. All youth in this study were experiencing chronic pain during testing, had varying chronic headache diagnoses, and were pediatric, which may explain the observed differences. Further exploration of EPM responses by chronic pain diagnosis and location is important to conduct in future research, as it will inform mechanisms and treatment targets.

The lack of association between OA and clinical outcomes may be due, in part, to limitations in sample size. More extensive clinical trials may overcome these limitations. There was no control group in this study receiving standard multidisciplinary care; thus, we cannot determine if IIPT improves EPM differently than treatment as usual. However, prior research on youth with chronic pain admitted to IIPT revealed that the IIPT group outperformed a multidisciplinary control group in recovery from pain and related disability.[11] Finally, the IIPT treatment approach is individualized to address each patient's unique precipitating, perpetuating, and protective factors. OA represents only one marker of treatment response and thus should be interpreted within the constraints of this study design.

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