Self-reported Physical Activity Predicts Pain Inhibitory and Facilitatory Function

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ABSTRACT

NAUGLE, K. M., and J. L. RILEY. Self-reported Physical Activity Predicts Pain Inhibitory and Facilitatory Function. *Med. Sci. Sports Exerc.*, Vol. 46, No. 3, pp. 622–629, 2014. Considerable evidence suggests regular physical activity can reduce chronic pain symptoms. The dysfunction of endogenous facilitatory and inhibitory systems has been implicated in multiple chronic pain conditions. However, few studies have investigated the relationship between levels of physical activity and descending pain modulatory function. **Purpose**: The purpose of this study was to determine whether self-reported levels of physical activity in healthy adults predicted 1) pain sensitivity to heat and cold stimuli, 2) pain facilitatory function as tested by temporal summation (TS) of pain, and 3) pain inhibitory function as tested by conditioned pain modulation (CPM) and offset analgesia. **Methods**: Forty-eight healthy adults (age range = 18–76 yr) completed the International Physical Activity Questionnaire (IPAQ) and the following pain tests: heat pain thresholds, heat pain suprathresholds, cold pressor pain, TS of heat pain, CPM, and offset analgesia. The IPAQ measured levels of walking, moderate, vigorous, and total physical activity over the past 7 d. Hierarchical linear regressions were conducted to determine the relationship between each pain test and self-reported levels of physical activity while controlling for age, sex, and psychological variables. **Results**: Self-reported total and vigorous physical activity predicted TS and CPM ($P < 0.05$). Individuals who self-reported more vigorous and total physical activity exhibited reduced TS of pain and greater CPM. The IPAQ measures did not predict any of the other pain measures. **Conclusions**: These results suggest that healthy older and younger adults who self-report greater levels of vigorous and total physical activity exhibit enhanced descending pain modulatory function. Improved descending pain modulation may be a mechanism through which exercise reduces or prevents chronic pain symptoms. **Key Words:** VIGOROUS, PAIN MODULATION, TEMPORAL SUMMATION, CONDITIONED PAIN MODULATION, EXERCISE

The prevalence estimates of chronic pain among adults in the United States may be as high as 40%, affecting approximately 100 million adults (15). Pain increases physical disability (32), reduces quality of life, and is costly to both the individual experiencing pain and the nation (15). Alarmingly, a recent study reported that the national cost of pain exceeds the cost of the nation's priority health conditions (e.g., cardiovascular disease, neoplasms, endocrine, and nutritional and metabolic diseases), with costs ranging from $560 to $635 billion annually (15). Clearly, a need exists for effective methods to prevent and treat chronic pain.

A rapidly growing body of evidence suggests that exercise may be a viable means to aid in the prevention of chronic pain and reduce ongoing pain symptoms in chronic pain populations. Indeed, data from observational studies (23), randomized controlled trials (RCT) (19), and laboratory studies suggest a relationship between levels of physical activity (PA) and chronic pain (12,26). For example, RCT demonstrate that systematic aerobic exercise reduces pain symptoms and improves physical function in multiple chronic widespread (19) and regional pain conditions (17). In addition, recent laboratory studies have showed that subjective and objective measures of PA are negatively related to suprathreshold pain sensitivity of painful heat stimuli in FMS patients (13,26).

A few studies have examined the relationship between pain sensitivity and PA in healthy adults. Most recently, Ellingson et al. (12) found that greater vigorous PA (VPA) as measured by accelerometers was significantly related to reduced pain intensity and unpleasantness ratings to noxious thermal stimuli in healthy, younger women. Similarly, Adrzejewski et al. (3) revealed that pressure pain thresholds at a variety of skeletal muscles sites were higher in younger adults who reported engaging in VPA compared with those who reported participation in only moderate PA (MPA). Anshel and Russel (4) demonstrated that an aerobic training intervention increased pressure pain tolerance compared with a control group with no exercise training. Although these studies suggest a link between PA and pain sensitivity, it is not known whether levels of PA are related to the functionality of pain modulatory processes. Importantly, several studies have shown that regular physical exercise exerts

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beneficial effects on several biological mediators (e.g., serotonin, endogenous opioids) of pain inhibition and facilitation (1,14,34).

Pain is modulated by complex endogenous systems that both facilitate and inhibit pain. Alterations in the function of these systems have been implicated in multiple chronic pain conditions (24) and in older adults (31). Several sophisticated tests of pain modulatory mechanisms exist in the pain literature. The dysfunction of pain facilitation has often been assessed by the method of temporal summation (TS). This procedure consists of the administration of short-duration repeated noxious stimuli of a constant intensity and measuring the consequent increase in pain as an indirect method of evaluating sensitization of the central nervous system (11). Endogenous pain inhibition has typically been assessed by a "pain inhibits pain" model termed conditioned pain modulation (CPM) or a model called offset analgesia (offset). CPM is the central inhibition of pain in a local area by a second pain that can be experienced anywhere in the body (38). Offset is an inhibitory temporal sharpening mechanism characterized by a pronounced reduction in perceived pain intensity evoked by slight decreases in noxious temperatures compared with those of equal magnitude increases (16). To date, no studies have investigated whether individuals who are more physically active exhibit enhanced descending pain modulatory function using the tests of TS of pain, CPM, or offset analgesia.

The purpose of this study was threefold. We sought to determine whether self-reported levels of PA in healthy adults predicted 1) pain sensitivity to heat and cold stimuli, 2) pain facilitatory function as tested by TS of pain, and 3) pain inhibitory function as tested by CPM and offset analgesia. We hypothesized that participants who reported relatively greater levels of PA would exhibit less pain sensitivity to thermal stimuli, reduced TS of pain, and greater inhibition of pain via CPM and offset analgesia.

METHODS

Participants

Participants were 48 healthy adults ranging in age from 18 to 76 yr (males = 24, age = 39.28 ± 21.55 yr; females = 24, age = 45.64 ± 21.06 yr; mean ± SD). The racial composition of the sample included 27 Caucasians, 8 Asians, 6 Hispanics, 2 African Americans, and 2 other. Participants were recruited through posted advertisements in the local community. Individuals meeting any of the following criteria were excluded from the study: 1) inability to reliably rate pain, 2) current use of narcotics or any tobacco products and chronic use of analgesics, 3) serious systemic disease (e.g., diabetes and thyroid problems, 4) uncontrolled hypertension, 5) cardiovascular or pulmonary disease, 6) neurological problems with significant changes in somatosensory and pain perception at the intended stimulation sites, 7) serious psychiatric conditions (e.g., schizophrenia and bipolar disorder), and 8) chronic pain or any ongoing pain problem (headaches, injury-related pain, etc.). In addition, participants were instructed to refrain from use of coffee or any pain medications before the experimental sessions.

Orientation and Training Session

The orientation and training session lasted approximately 2 h and occurred on a separate day than the experimental sessions. All participants were provided information about the experimental procedures and reviewed and signed an informed consent form approved by the institutional review board before participation in the study. To determine eligibility, participants completed a health history questionnaire, supplemented by interview and blood pressure measurements. No participants were excluded after the orientation and training session. Participants also completed a battery of psychological questionnaires (including the Short-Form Health Survey [SF-36], the State-Trait Anxiety Inventory–Trait Version [STAI-T], the Pain Catastrophizing Scale [PCS], and the Pain Attitudes Questionnaire–Revised [PAQ-R]) and a questionnaire measuring PA behaviors over the past 7 d. Participants then completed a training session that 1) allowed them to become accustomed to the stimulus levels and laboratory setting and 2) determined individualized temperatures of the stimuli for the TS and offset protocols such that participants would experience moderate pain.

Assessment of PA

The International Physical Activity Questionnaire–Long Form (IPAQ) is a subjective measure of PA that asks subjects to recall the amount of time doing PA during the past 7 d (10). VPA, MPA, and walking are assessed across a comprehensive set of domains, including transport-related physical, work-related PA, domestic and gardening activities, and leisure time PA. Guidelines provided by www.ipaq.ki.se/ipaq.htm were used for data processing and scoring of the questionnaire. Each activity was assigned a MET score, which is based on the intensity of that activity. These MET scores were derived from the IPAQ reliability study (9) and Ainsworth et al. (2). The MET scores are then multiplied by the reported number of minutes per week spent performing that activity, which produces an activity score of MET-minute per week. Scores were calculated for VPA, MPA, walking (W), and total PA. The test has shown acceptable concurrent and construct validity and test-retest reliability (0.66–0.89) (9).

Psychophysical Pain Testing

The psychophysical pain tests listed below were conducted on four separate days. The heat pain threshold (HPT) and suprathreshold tests were conducted during the first session (i.e., training session), with the threshold test always conducted first. The TS of heat pain test was conducted on two separate days. The CPM test was conducted on the same day as one of the TS tests, with the CPM test always administered at least 10 min after the TS test. The offset analgesia test was

administered on a separate day. The CPM, TS, and offset test days were conducted in random order. In the offset analgesia test, stimuli were delivered with a 30 × 30-mm thermode (Medoc Pathway Neurosensory Analyzer; Medoc, Ltd, Ramat Yishai, Israel) placed and held by the experimenter during testing. All the other heat-based tests were administered by activation of a solenoid that brought a 23 × 23-mm Peltier device thermode into skin contact through a square hole. For each psychophysical test, pain was rated with a 0–100 electronic visual analog scale (eVAS), with "0" indicating no pain and "100" indicating intolerable pain.

Heat pain thresholds. HPT was assessed with thermal stimuli delivered to the left forearm. The thermode temperature increased from a baseline of 32°C with a rise rate of $0.5°C \cdot s^{-1}$. Participants were instructed to say "pain" when they felt the transition from heat to the sensation of heat pain. When participants said "pain," the temperature of the thermode was recorded. Two trials were performed. The HPT was defined as the temperature recording for the second trial.

Heat pain suprathreshold. Using a ramp-and-hold paradigm, heat pain suprathreshold (HPS) levels were determined with thermal stimuli delivered to the right forearm. Up to seven trials were administered, with the thermode temperature set at 42°C for the first trial and increasing by 1°C across trials until a pain rating of 50 was reached or exceeded on a scale 0–100. Each trial lasted 8 s, and the intertrial interval was 20 s. Participants rated the pain immediately after each trial. The temperature which first produced pain ratings equal to or exceeding 50°C (T50) was used for data for analysis.

Cold pressor Pain. A refrigerated water circulator (Neslab, Portsmouth, NH) cooled a 10 × 18-inch insulated water bath. Water was maintained at a constant temperature (10°C for men and 12°C for women) and continuously recirculated to prevent local warming around the foot. Participants immersed their right foot to the ankle in the water. The water bath manipulation included 3 × 45-s immersion trials. Participants rated their pain every 15 s on a 0–100 scale. Intertrial intervals lasted 15 s. The nine pain rating values were averaged to obtain one cold pressor pain (CPP) value per participant. This test served as the conditioning stimulus during the CPM test. Given that we wanted to have a conditioning stimulus that induced similar levels of pain in men and women, two different temperatures were used during the cold pressor test (10°C for men and 12°C for women). Generally, men show less pain sensitivity to cold water baths (as demonstrated by our pain rating data reported in Table 2); thus, we gave men a slightly lower test temperature.

TS of heat pain. Brief repetitive thermal stimuli were administered to assess TS of pain. On two separate days, a series of 10 heat pulses (<1.5 s) was delivered to the left forearm. For all series, the baseline temperature was 38°C, and the target temperature was the individualized temperature determined during the training session (46°C–52°C). The short thermal contact stimuli were separated by intervals of 2.5 s. Participants were instructed to rate the intensity of the pain experienced after each pulse (i.e., second pain) with a 0–100 scale. For each trial, TS was calculated by subtracting the pain rating after the first pulse from the highest pain rating. This score captures the maximum amount of TS across the 10 pulses. The two trials were averaged to produce one TS score for each participant.

Conditioned pain modulation. CPM is an experimental model of endogenous pain inhibition and refers to the inhibition of pain in a local area by a second pain experienced anywhere in body. CPM was tested with two 150-s trials in which the experimental thermal stimulus was brought into contact with the thenar eminence of the left palm. Ten minutes separated the two trials with a 3-min conditioning stimulus applied to the right foot just before the second trial. The conditioning stimulus consisted of placing the foot in a cold water bath, as described in the CPP section. A paradigm of response dependent stimulation (REDSTIM) was used for the 150-s heat trials (36). During these trials, participants continuously rated pain intensity with the right hand by adjusting an eVAS, ranging from 0 to 100. At the beginning of the trial, the thermode temperature gradually increased from 35°C until pain ratings reached or exceeded a set point of 20 on the 1–100 scale. Then, the thermode temperature reversed direction until the ratings were equal or less than the set point. Alternating series of ascending and descending steps in thermode temperature continued for 150 s, with the computer programmed to maintain the average eVAS rating near the set point of 20. The REDSTIM paradigm and set point of 20 was chosen because 1) it allows the experience of mild to moderate levels of pain during continuous stimulation with no risk of intolerable pain, 2) most stimuli using REDSTIM are painful with participants blinded to stimulus magnitude and 3) it is free of participant–experimenter interactions. The presence of CPM was indicated by an increase from trial 1 to trial 2 (CPM session) in the average thermode temperature needed to maintain an average eVAS rating of 20. Thus, each participant's CPM score was calculated by subtracting the average thermode temperature of trial 1 (pre cold-water bath) from the average thermode temperature from trial 2 (post–cold water bath). A positive change score indicates the presence of CPM.

Offset analgesia. Offset is another experimental model of endogenous pain inhibition and refers to a pronounced reduction in pain intensity evoked by slight decreases in noxious temperatures compared those of equal magnitude increases. Thermal stimuli were delivered by a Peltier-based thermode (23 × 23 mm) in three 30-s trials to the right forearm. For each trial, a three temperature stimulus train (e.g., 47°C [15 s], 48°C [5 s], and 47°C [10 s]) was used to test for offset analgesia (16). Once in contact with the skin, the thermode was ramped from a neutral temperature to the participant's testing temperature for 15 s (T1). Although past offset research has commonly used a duration of 5 s for T1, we chose 15 s to allow perceived pain to stabilize and provide a more valid comparison with the last phase of the

temperature train. Then the thermode was heated an additional 1°C for 5 s for a manipulation phase (T2) and then cooled back to the subjects testing temperature for 10 s for the inhibition or offset phase (T3). During each trial, participants rated pain intensity continuously using an eVAS (range = 0–100). For each trial, we quantified the magnitude of offset analgesia as calculated by prior studies (31). The maximum eVAS rating during T2 and the minimum eVAS rating from the end of T2 until the end of T3 were extracted from the real-time eVAS ratings. The magnitude of offset analgesia was calculated as the difference between the maximum pain rating during T2 and the minimum pain rating during T3, corrected for the value of the peak eVAS during T2. Thus, 100% would be the highest score possible representing high inhibition, whereas 0% represents the lowest score and no inhibition/offset.

Psychological Questionnaires

State-Trait Anxiety Inventory–Trait Version. The STAI (33) has extensive normative data and is a frequently used measure of anxiety in pain studies. The trait subscale consists of 20 items that evaluate how respondents feel in general.

Pain catastrophizing scale. The PCS (35) consists of 13 items rated on a 5-point Likert scale. The PCS asks the respondents to reflect upon past painful experiences and to rate the degree to which they experienced negative thoughts or feelings about pain. The PCS measures three dimensions of catastrophizing: rumination, helplessness, and magnification.

Pain Attitudes Questionnaire–Revised. The PAQ is a 24-item questionnaire designed to assess stoicism and cautiousness relevant to pain perception in adults (40). The five PAQ subscales (stoic fortitude, stoic concealment, stoic superiority, cautious self-doubt, and cautious reluctance) show good internal consistency and retest reliability.

Short-Form Health Survey-36. The SF-36 is a health survey that yields eight scale scores (physical functioning, role limitations due to physical problems, bodily pain, vitality, general health perceptions, social functioning, role limitations due to emotional problems, and mental health) (37). The SF-36 is commonly used in studies of pain, sensitive to changes in pain following treatment, and associated with laboratory pain testing (5).

Data Analysis

Descriptive statistics were calculated for age; IPAQ total and subscale scores; psychological questionnaire scores; thermode test temperature for the HPT, HPS, TS, CPM, and offset tests; and pain ratings during the CPP test that served as the conditioning stimulus during the CPM test. Shapiro–Wilk's test of normality indicated that the IPAQ data were not normally distributed; thus, Mann–Whitney *U*-tests were conducted to determine whether the IPAQ scores differed by sex. Independent *t*-tests were conducted to determine whether the other variables differed by sex. Furthermore, bivariate correlations were conducted to determine associations between age, PA levels (MPA, VPA, walking, and total PA), and thermode test temperatures. Pairwise *t*-tests were also conducted to determine whether participants exhibited significant TS of heat pain (first pulse vs max pulse rating), CPM (average temperature for trial 1 vs average temperature for trial 2), and offset analgesia (change in pain rating from T1 to T2 vs change in pain rating from T2 to T3).

We conducted spearman bivariate correlations between the pain scores and the IPAQ measures (MPA, VPA, walking, and total PA). In addition, hierarchical linear regressions were performed to determine the relationship between the self-reported level of PA and each pain score while controlling for factors known to influence experimental pain testing. To control for potential confounds related to demographic variables, sex and age were always entered into the first block. For regressions on offset magnitude and TS, thermode temperature was added into the second block. For regressions on CPM score, the change in average pain rating from trial 1 to trial 2 and average pain rating of the cold water bath were added into block 2. Psychological variables (i.e., PAQ-R, PCS, and STAI-T) were entered into the third block. The PA score was always entered into the last block for each regression (block 3 for HPT, HPS, and CPP and block 4 for TS, CPM, and offset). Separate regressions were conducted with MPA, VPA, walking, and total PA as the final predictor variable. Two participants did not report any pain during the conditioning stimulus and were therefore excluded from the CPM analyses.

RESULTS

Participant characteristics are presented in Table 1. No significant differences existed between males and females on age, PA on the IPAQ subscales and total scores, and on the psychological variables. Average score and thermode temperature for the psychophysical tests are presented in Table 2. No sex differences were found for these variables. Importantly, the CPP data indicated that the cold water bath (conditioning stimulus during CPM) was perceived as moderately painful for men and women. Bivariate correlations revealed a positive association between age and 1) self-reported levels of walking ($P = 0.020$, $r = 0.346$) and 2) TS thermode temperature ($P = 0.003$, $r = 0.422$). No significant correlations were found between IPAQ scores and thermode temperature for the TS, CPM, or offset tests ($P > 0.05$).

Pairwise *t*-tests indicated that TS of pain occurred for trials 1 and 2 ($P < 0.001$), with the max pulse pain rating (mean ± SD = 51.54 ± 17.51) significantly greater than pain rating for pulse 1 (12.24 ± 13.06). Significant CPM was also found ($P = 0.014$), with the average temperature for trial 1 (45.43°C ± 2.63°C) less than the average temperature for trial 2 (46.00°C ± 2.52°C). Furthermore, participants demonstrated significant offset analgesia ($P < 0.001$). Specifically, participants showed a disproportionate decrease in pain intensity ratings (37.46 ± 18.26) after a 1°C decrease in temperature compared with those of equal magnitude increases (22.30 ± 9.63).

TABLE 1. Participant descriptive characteristics.

	Males	Females	P
Age, yr	39.28 ± 21.55	45.64 ± 21.06	0.342
Walking, MET·min·wk^{-1}	1350.87 ± 1064.87	1558.92 ± 1301.37	0.648
MPA, MET·min·wk^{-1}	1958.75 ± 1635.67	2264.20 ± 1955.37	0.945
VPA, MET·min·wk^{-1}	2202.00 ± 2327.22	1761.60 ± 2477.63	0.273
Total PA, MET·min·wk^{-1}	5476.62 ± 3396.34	5584.72 ± 4062.96	0.946
SF-36–Physical Health ± 0–100)	84.09 ± 16.79	87.60 ± 10.56	0.387
SF-36–Mental Health (0–100)	82.08 ± 15.82	81.08 ± 14.75	0.853
PAQ-R	76.05 ± 15.56	70.76 ± 10.10	0.169
PCS	11.09 ± 9.32	10.46 ± 6.90	0.790
STAI-T	30.05 ± 9.18	30.80 ± 8.04	0.764

Data are presented as mean ± SD. VPA, vigorous physical activity; PA, physical activity; SF-36, Short Form Healthy Survey; PAQ-R, Pain Attitudes Questionnaire–Revised; PCS, Pain Catastrophizing Scale; STAI-T, State Trait Anxiety Inventory–Trait version.

Bivariate correlations. As displayed in Table 3, HPT, HPS, CPP, CPM, and offset analgesia were not significantly correlated with any of the IPAQ measures. Max TS was negatively correlated with VPA, indicating that greater TS was associated with lower self-reported levels of VPA.

Hierarchical regressions. Hierarchical regressions revealed that after controlling for sex, age, thermode temperature, and psychological variables, self-reported VPA predicted TS of pain (Table 4), accounting for 13.4% of the variance. Total PA score was also a significant predictor of TS (Table 4), accounting for 10.7% of the variance. This finding may have been driven by the VPA component of the total score. Individuals who self-reported more total and VPA exhibited less TS of pain. MPA ($\beta = -0.225$, $P = 0.197$) and walking ($\beta = -0.013$, $P = 0.937$) were not significant predictors of TS of pain.

After controlling for sex, age, change in pain rating from trial 1 to trial 2, CPP score, and psychological variables, VPA also predicted CPM, accounting for 14.3% of the variance (Table 5). In a separate model, total PA score predicted CPM, accounting for 14.6 % of the variance (Table 5). Individuals who reported greater vigorous and total PA exhibited greater CPM. MPA ($\beta = 0.290$, $P = 0.113$) and walking ($\beta = 0.127$, $P = 0.479$) were not significant predictors of CPM. The IPAQ measures were not significant predictors of HPT, HPS, CPP, or magnitude of offset analgesia ($P > 0.05$).

DISCUSSION

This study provides preliminary evidence, suggesting that the level of vigorous and total PA is related to the functioning of descending pain modulatory systems. Specifically, three key findings emerged from the data: 1) no relationship was found between the level of PA and the measures of noxious heat and cold sensitivity, 2) the level of total and VPA predicted pain facilitatory function as measured by TS, and 3) the level of total and VPA predicted pain inhibitory function as measured by CPM. As indicated by the R^2 values, the effects of PA on CPM and TS were medium (7), even after accounting for age, sex, and psychological status of participants. In line with prior work (12), our results emphasize the importance of considering PA behaviors when examining experimental models of pain between different populations of people (e.g., young vs old, chronic pain vs healthy control), particularly given that many chronic pain conditions are characterized by deconditioning and sedentary behavior (20).

Contrary to our first hypothesis, self-reported PA did not predict pain sensitivity to noxious heat and cold stimuli. This result is in contrast to several studies showing a relationship between VPA and pain sensitivity measures (3,4,12). Specifically, prior work has shown that greater VPA in younger adults is associated with lower pain unpleasantness and intensity ratings in response to noxious thermal stimuli applied to the palm (12) and greater pressure pain thresholds at several different muscle sites (3). Several methodological differences may explain the discrepancies between the current study and prior work. For example, the study of Ellingson et al. examined young women, whereas the current study examined men and women who spanned a broad age range. Indeed, the relationship between PA and pain sensitivity may depend on a combination of factors including sample characteristics (old vs young), the pain induction technique (i.e., pressure vs heat vs cold), the site of bodily application (i.e., palm vs forearm), the dimension

TABLE 2. Average scores and thermode temperature for psychophysical tests.

	Males	Females	P
HPT, °C	43.67 ± 4.01	44.27 ± 3.22	0.570
HPS, °C	50.22 ± 1.76	50.08 ± 1.73	0.771
CPP, pain rating	53.64 ± 27.51	51.72 ± 29.03	0.821
TS score	39.79 ± 14.51	40.33 ± 18.18	0.911
Average TS thermode temperature, °C	50.76 ± 1.87	50.39 ± 1.96	0.505
CPM score, change in °C	0.36 ± 1.62	0.73 ± 1.51	0.403
Average CPM thermode temperature T1, °C	45.48 ± 2.72	45.38 ± 2.59	0.899
Average CPM thermode temperature T2, °C	45.84 ± 2.84	46.13 ± 2.27	0.703
Offset analgesia magnitude, %	69.20 ± 24.75	75.53 ± 25.44	0.379
Average offset thermode temperature, °C	46.88 ± 1.24	46.75 ± 1.53	0.748

Data are presented as mean ± SD. TS, temporal summation; CPM, conditioned pain modulation; T1, trial 1; T2, trial 2; CPP, cold pressor pain.

TABLE 3. Bivariate correlation matrix between PA levels and experimental pain measures.

	1	2	3	4	5	6	7	8	9	10
1. Walking	1.00									
2. Mod PA	0.28	1.00								
3. Vig PA	0.13	0.18*	1.00							
4. Total PA	0.55**	0.68**	0.69**	1.00						
5. HPT	−0.08	0.04	−0.13	−0.09	1.00					
6. HPS	0.19	0.04	0.03	0.03	0.51**	1.00				
7. CPP	−0.27	−0.23	−0.13	−0.24	−0.30*	−0.47**	1.00			
8. TS	0.13	0.02	−0.44**	−0.24	0.11	0.38**	−0.20	1.00		
9. CPM	0.04	0.07	0.15	0.16	−0.22	−0.26	0.22	−0.27*	1.00	
10. Offset	−0.03	−0.07	0.06	−0.05	−0.05	0.04	−0.19	0.17	0.26	1.00

*$P < 0.05$, **$P < 0.001$.

PA, physical activity; Mod, moderate; Vig, vigorous; HPT, heat pain threshold; HPS, heat pain suprathreshold; CPP, cold pressor pain; TS, temporal summation; CPM, conditioned pain modulation; Offset, offset analgesia.

of pain being measured (i.e., pain unpleasantness vs pain intensity), and the method used to measure and categorize levels of PA (i.e., subjective vs objective measures, continuous vs categorical levels of PA).

Endogenous pain modulatory systems have the capacity to amplify or diminish the perception of noxious stimuli. Furthermore, the dysfunction of these systems has been implicated in multiple chronic pain conditions and is predictive of acute and chronic postoperative pain (39). Prior work in chronic pain patients has shown that time spent in low to MPA is associated with pain modulation during cognitive tasks (13). In line with this finding, the current study provides evidence suggesting that PA behaviors also influence the functional capacity of endogenous facilitatory and inhibitory systems in healthy adults. As hypothesized, individuals who reported relatively greater VPA demonstrated enhanced pain inhibition during the CPM paradigm and less TS of second pain, after controlling for potential confounding variables. Total PA level also predicted CPM and TS; however, these findings may have been driven by the VPA component of the score. Notably, CPM and PA were not significantly correlated when this relationship was examined with bivariate correlations. The discrepancy between the CPM and PA correlation (i.e., CPM and PA not significantly correlated) and the regression results was potentially caused by the fact that our sample was characterized by high variability in several factors known to influence CPM (e.g., age, sex, psychological factors, intensity of conditioning stimulus). Thus, the relationship between CPM and PA was likely not revealed until these sources of variation were controlled for. Interestingly, PA behaviors did not predict pain inhibition in the offset analgesia paradigm. Given that different neuroanatomical pathways underlie CPM and offset analgesia (25,28), different relationships between these two inhibitory processes and PA behaviors are biologically plausible.

Several different mechanisms exist by which regular exercise could beneficially affect endogenous pain inhibitory and facilitatory processes. Potential mechanisms likely involve alterations in the primary excitatory and inhibitory neurotransmitters of the central nervous system (CNS), increased endogenous opioids, and the preservation of brain structures important to the functioning of these pain modulatory systems. Glutamate and GABA are the primary excitatory and inhibitory neurotransmitters in the CNS, and a spinal and supraspinal imbalance of these neurotransmitters

TABLE 4. Summary of hierarchical regression analyses for TS with vigorous and total PA as predictors ($N = 48$).

Step Variables	R	ΔR^2	Standardized β	P value for β	Model P
VPA					
1. Age	0.125	0.016	−0.104	0.495	0.003
Sex			0.055	0.406	
2. Thermode Temp	0.540	0.276	0.504	0.004	
3. STAI-T	0.552	0.013	0.071	0.615	
PCS			0.070	0.657	
PAQ-R			0.140	0.420	
4. VPA	0.662	0.134	−0.384	0.007	
Total PA					
1. Age	0.125	0.016	−0.104	0.495	0.006
Sex			0.055	0.406	
2. Thermode Temp	0.540	0.276	0.504	0.004	
3. STAI-T	0.552	0.013	0.071	0.615	
PCS			0.070	0.657	
PAQ-R			0.140	0.420	
4. Total PA	0.642	0.107	−0.366	0.016	

PA, physical activity; Temp, temperature; PCS, Pain Catastrophizing Scale; PAQ-R, Pain Attitudes Questionnaire–Revised; STAI-T, State Trait Anxiety Inventory–Trait version.

TABLE 5. Summary of hierarchical regression analyses for CPM with vigorous and total PA as predictors ($N = 46$).

Step Variables	R	ΔR^2	Standardized β	P Value for β	Model P
VPA					
1. Age	0.284	0.081	0.006	0.924	0.007
Sex			0.305	0.015	
2. Δ pain rating	0.416	0.093	0.172	0.262	
CPP rating			0.237	0.098	
3. STAI-T	0.544	0.122	0.071	0.082	
PCS			0.070	0.072	
PAQ-R			0.140	0.854	
4. VPA	0.662	0.143	0.318	0.006	
Total PA					
1. Age	0.284	0.081	−0.120	0.416	0.006
Sex			0.348	0.017	
2. Δ pain rating	0.416	0.093	0.219	0.117	
CPP rating			0.303	0.031	
3. STAI-T	0.544	0.122	0.202	0.161	
PCS			0.254	0.083	
PAQ-R			−0.013	0.931	
4. VPA	0.665	0.146	0.431	0.005	

PA, physical activity; Temp, temperature; CPP, cold pressor pain.

(i.e., enhanced excitatory glutamatergic signaling and reduced inhibitory GABAergic signaling) likely play a key role in the development and maintenance of central sensitization (14). Furthermore, a greater activity of glutamic acid decarboxylase, the rate-limiting enzyme in the conversion of glutamate to GABA, is associated with decreased glutamatergic signaling paralleled by attenuated pain responses (14). Importantly, animal studies have found that regular exercise increases the expression of GABA in the forebrain and enhances the activity of glutamic acid decarboxylase (18). Hence, regular vigorous exercise may help to maintain the balance of excitatory and inhibitory transmission in the ascending and descending pain pathways, thereby impeding the processes that lead to central sensitization (i.e., increased TS of pain).

A mechanism whereby regular exercise may influence CPM is by increasing the availability of serotonin and endogenous opioids in the central nervous system. Animal models and human studies suggest that the CPM is greatly dependent on the integrity of endogenous opioid (21) and descending bulbospinal serotonergic systems (6). Most recently, King et al. (21) found that the administration of an opioid antagonist blocked the inhibition of focal heat pain of the palm during cold water immersion of the foot. Animal studies show that regular physical exercise increases endogenous opioid content in the central nervous system (e.g., cerebrospinal fluid and brainstem; 34) and the availability of serotonin in the brain (1).

Finally, although TS pain and CPM strongly depend on spinal cord mechanisms, the pain modulation observed under these paradigms also involves cortical factors (9,27). Along these lines, prior work has associated CPM capacity with cognitive factors (29), such as expectations of pain. A substantial amount of evidence indicates that aerobic fitness training improves cognition and leads to more efficient brain function (22). Furthermore, regular exercise enhances and maintains the structural preservation (i.e., increased brain volume and gray matter) of several of the brain areas involved with CPM and TS including the prefrontal corex, ACC, and posterior insula (8,30). However, whether structural differences in brain morphology account for differences in pain modulatory capacity has not yet been determined. Nonetheless, the proposed mechanisms are clearly speculative, and additional research is needed to explore the biological mechanisms through which exercise may improve pain modulation and chronic pain.

Limitations and future directions. Several limitations of this study need to be acknowledged. First, PA was assessed by a questionnaire rather than by objective methods. Subjective measures of PA can result in underestimation and overestimation of the amount of PA reported, as answers depend on subject's memory. Thus, the current results need to be substantiated with objective measures of PA. Second, the cross-sectional nature of the study renders it possible that dysfunctional pain modulation leads to reduced participation in VPA. Future research is warranted to verify the causal relationship between increased PA and enhanced descending pain modulatory control. Specifically, RCT are needed to determine whether exercise training improves descending pain modulatory control and whether this enhanced pain modulation translates to reduced clinical pain. In addition, longitudinal studies are needed to investigate whether increased PA can have a protective effect and prevent the decline of descending pain modulatory capacity. Third, the sample of participants in the current study consisted of healthy adults. Therefore, generalization to individuals with chronic pain conditions is limited. Fourth, most of the psychophysical pain tests administered in the current study used moderately painful stimuli. Thus, these results may not generalize to more intense painful stimuli. Fifth, PA was assessed only for the last 7 d, which may not have been representative of overall PA habits for each participant.

In conclusion, extensive evidence has shown that PA beneficially influences chronic pain symptoms in older adults and those with chronic pain conditions. We provide evidence that PA is related to endogenous pain modulatory function, a potential mechanism underlying multiple pain conditions. Indeed, PA may have a protective effect against the decline in pain modulatory capacity seen in older adults and those with chronic pain. Future studies should continue to clarify the beneficial effects of PA on chronic pain and the mechanisms underlying this effect.

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