Published in final edited form as:
Med Sci Sports Exerc. 2014 March ; 46(3): 622–629. doi:10.1249/MSS.0b013e3182a69cf1.

Self-reported Physical Activity Predicts Pain Inhibitory and Facilitatory Function

Kelly M. Naugle and **Joseph L. Riley 3rd**
Pain Research and Intervention Center of Excellence, University of Florida, Gainsville, FL

Abstract

Considerable evidence suggests regular physical activity can reduce chronic pain symptoms. 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—This study's purpose 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 of pain (TS), and 3) pain inhibitory function as tested by conditioned pain modulation (CPM) and offset analgesia.

Methods—Forty-eight healthy adults (age range 18–76) completed the International Physical Activity Questionnaire (IPAQ) and the following pain tests: heat pain thresholds (HPT), heat pain suprathresholds, cold pressor pain (CPP), temporal summation of heat pain, conditioned pain modulation, and offset analgesia. The IPAQ measured levels of walking, moderate, vigorous and total physical activity over the past seven days. 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's <.05). Individuals who self-reported more vigorous and total physical activity exhibited reduced temporal summation of pain and greater CPM. The IPAQ measures did not predict any of the other pain measures.

Conclusion—Thus, 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.

Keywords

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

Corresponding Author: Kelly M. Naugle, College of Dentistry, University of Florida, 1329 SW 16th Street, Rm 5180, Gainesville, FL 32608, Phone: 352-273-5975, Fax: 352-273-5985, knaugle@dental.ufl.edu.

Conflict of Interest
There are not actual or potential conflicts of interest for any of the authors.
The results of the present study do not constitute endorsement by ACSM.

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, 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 (19), and laboratory studies suggest a relationship between levels of physical activity and chronic pain (12, 26). For example, RCTs demonstrate that systematic aerobic exercise reduces pain symptoms and improves physical function in multiple chronic widespread (19) and regional pain conditions (17). Additionally, recent laboratory studies have showed that subjective and objective measures of physical activity 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 physical activity in healthy adults. Most recently, Ellingson and colleagues found that greater vigorous physical activity as measured by accelerometers was significantly related to reduced pain intensity and unpleasantness ratings to noxious thermal stimuli in healthy, younger women (12). Similarly, Adrzejewski et al. revealed that pressure pain thresholds at a variety of skeletal muscles sites were higher in younger adults who reported engaging in vigorous physical activity compared to those who reported participation in only moderate physical activity (3). Anshel and Russel demonstrated that an aerobic training intervention increased pressure pain tolerance compared to a control group with no exercise training (4). While these studies suggest a link between physical activity and pain sensitivity, it is not known whether levels of physical activity are related to the functionality of pain modulatory processes. Importantly, several studies have shown that regular physical exercise exerts 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. Dysfunction of pain facilitation has often been assessed by the method of temporal summation. 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 to 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 temporal summation of pain, CPM, or offset analgesia.

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

to thermal stimuli, reduced temporal summation of pain, and greater inhibition of pain via CPM and offset analgesia.

Methods

Participants

Participants were forty-eight healthy adults ranging in age from 18 to 76 (males=24, age=39.28 years ±21.55; females=24, age=45.64 years ±21.06). 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, 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.). Additionally, participants were instructed to refrain from use of coffee or any pain medications prior to the experimental sessions.

Orientation and Training Session

The orientation and training session lasted approximately 2 hours 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 prior to participation in the study. To determine eligibility, participants completed a health history questionnaire, supplemented by interview and blood pressure measurements. No participants were excluded following the orientation and training session. Participants also completed a battery of psychological questionnaires (including the Short-Form Health Survey, State-Trait Anxiety Scale- Trait version, Pain Catastrophizing Scale, and Pain Attitudes Questionnaire-Revised) and a questionnaire measuring physical activity behaviors over the past 7 days. Participants then completed a training session which 1) allowed them to become accustomed to the stimulus levels and laboratory setting and 2) determined individualized temperatures of the stimuli for the temporal summation and offset protocols such that participants would experience moderate pain.

Assessment of Physical Activity

The International Physical Activity Questionnaire – Long Form (IPAQ) is a subjective measure of physical activity that asks subjects to recall the amount of time doing physical activity during the past 7 days (10). Vigorous physical activity, moderate physical activity, and walking are assessed across a comprehensive set of domains including: transport-related physical, work-related physical activity, domestic and gardening activities, and leisure time physical activity. Guidelines provided by www.ipaq.ki.se/ipaq.htm were used for data processing and scoring of the questionnaire. Each activity was assigned a metabolic equivalent score (MET), 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 METs-minute/week. Scores were calculated for vigorous activity (VPA), moderate activity (MPA), walking (W), and Total activity (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 4 separate days. The Heat pain threshold and suprathreshold tests were conducted during the first session (i.e., training session), with the threshold test always conducted first. The temporal summation (TS) of heat pain test was conducted on two separate days. The CPM test was conducted on the same day as one of the temporal summation tests, with the CPM test always administered at least 10 minutes 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 × 30mm 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 × 23mm peltier device thermode into skin contact through a square hole. For each psychophysical test, pain was rated with a 0–100 electronic visual analogue scale (eVAS), with “0” indicating no pain and “100” indicating intolerable pain.

Heat Pain Thresholds (HPT)—Heat pain threshold 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/s. 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 (HPS)—Using a ramp-and-hold paradigm, heat pain suprathreshold 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 inter-trial-interval was 20 s. Participants rated the pain immediately following 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 (CPP)—A refrigerated water circulator (Neslab, Portsmouth, NH) cooled a 10″ × 18″ insulated water bath. Water was maintained at a constant temperature (10°C for men; 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 second immersion trials. Participants rated their pain every 15 s on a 0 to 100 scale. Inter-trial-intervals lasted 15 s. The nine pain rating values were averaged to obtain one 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; 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.

Temporal Summation of Heat Pain (TS)—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 following the first pulse from the highest pain rating. This score captures the

maximum amount of temporal summation across the 10 pulses. The two trials were averaged to produce one TS score for each participant.

Conditioned Pain Modulation (CPM)—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 minute conditioning stimulus applied to the right foot just prior to 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 electronic visual analogue scale (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 setpoint of 20 on the 1–100 scale. Then, the thermode temperature reversed direction until the ratings were equal or less than the setpoint. 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 setpoint 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 (23mm × 23mm) in three 30s trials to the right forearm. For each trial, a three temperature stimulus train (e.g., 47°C [15 s], 48°C [5 s], 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). While 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 (STAI-T)—The STAI (33) has extensive normative data and is a frequently used measure of anxiety in pain studies. The Trait-Anxiety subscale consists of 20 items that evaluate how respondents feel in general.

Pain Catastrophizing Scale (PCS)—The Pain Catastrophizing Scale (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 catastophizing: rumination, helplessness, and magnification.

Pain Attitudes Questionnaire-Revised (PAQ-R)—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, Cautious-Reluctance) show good internal consistency and retest reliability.

Short-Form Health Survey-36 (SF-36)—The SF-36 is a health survey that yields 8-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, is sensitive to changes in pain following treatment, and is associated with laboratory pain testing (5).

Data Analysis

Descriptive statistics were calculated for age, the IPAQ total and subscale scores, the psychological questionnaire scores, thermode test temperature for the HPT, HPS, TS, CPM, and offset tests, and the 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 if 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, physical activity levels (MPA, VPA, walking and total PA), and thermode test temperatures. Pair-wise t-tests were also conducted to determine whether participants exhibited significant temporal summation of heat pain (first pulse v. 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 v. change in pain rating from T2 to T3).

We conducted spearman bivariate correlations between the pain scores and IPAQ measures (MPA, VPA, walking and total PA). Additionally, hierarchical linear regressions were performed to determine the relationship between self-reported level of physical activity 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., PAQR, PCS, and STAI-T) were entered into the third block. The physical activity score was always entered into the last block for each regression (block 3 for HPT, HPS, CPP and block 4 for TS, CPM, 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, physical activity 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=.020, r=.346) and 2) TS thermode temperature (p=.003, r=.422). No significant correlations were found between IPAQ scores and thermode temperature for the TS, CPM, or offset tests (p's > 0.05).

Pair-wise t-tests indicated that temporal summation of pain occurred for trial 1 and 2 (p <. 001), with the max pulse pain rating (M=51.54 ±17.51) significantly greater than pain rating for pulse 1(M=12.24 ±13.06). Significant CPM was also found (p=.014), with the average temperature for trial 1 (M=45.43 ±2.63 C°) less than the average temperature for trial 2 (M=46.00 ±2.52 C°). Furthermore, participants demonstrated significant offset analgesia (p<.001). Specifically, participants showed a disproportionate decrease in pain intensity ratings (M=37.46 ±18.26) following a 1 C° decrease in temperature compared to those of equal magnitude increases (M=22.30 ±9.63).

Bivariate Correlations

As displayed in Table 3, heat pain threshold, heat pain suprathreshold, cold pressor pain, CPM, and offset analgesia were not significantly correlated with any of the IPAQ measures. Max temporal summation was negatively correlated with vigorous physical activity, indicating that greater temporal summation was associated with lower self-reported levels of vigorous physical activity.

Hierarchical Regressions

Hierarchical regressions revealed that after controlling for sex, age, thermode temperature, and psychological variables, self-reported vigorous physical activity predicted temporal summation of pain (Table 4a), accounting for 13.4% of the variance. Total physical activity score was also a significant predictor of TS (Table 4b); accounting for 10.7% of the variance. This finding may have been driven by the vigorous physical activity component of the total score. Individuals who self-reported more total and vigorous physical activity exhibited less temporal summation of pain. Moderate physical activity (βeta= −.225, p=. 197) and walking (βeta= −.013, p=.937) were not significant predictors of temporal summation of pain.

After controlling for sex, age, change in pain rating from trial 1 to trial 2, cold pressor pain score, and psychological variables, vigorous physical activity also predicted CPM, accounting for 14.3% of the variance (Table 5a). In a separate model, total physical activity score predicted CPM, accounting for 14.6 % of the variance (Table 5b). Individuals who reported greater vigorous and total physical activity exhibited greater CPM. Moderate physical activity (βeta= .290, p=.113) and walking (βeta= .127, p=.479) were not significant predictors of CPM. The IPAQ measures were not significant predictors of heat pain threshold, heat pain suprathreshold, cold pressor pain, or magnitude of offset analgesia (p's > .05).

Discussion

This study provides preliminary evidence suggesting that level of vigorous and total physical activity is related to the functioning of descending pain modulatory systems. Specifically, three key findings emerged from the data: 1) no relationship was found between level of physical activity and the measures of noxious heat and cold sensitivity, 2) level of total and vigorous physical activity predicted pain facilitatory function as measured by temporal summation, and 3) level of total and vigorous physical activity predicted pain inhibitory function as measured by CPM. As indicated by the R^2 values, the effects of physical activity on CPM and temporal summation were medium in size (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 physical activity behaviors when examining experimental models of pain between different populations of people (e.g., young vs. old; chronic pain v. healthy control), particularly given that many chronic pain conditions are characterized by deconditioning and sedentary behavior (20).

Contrary to our first hypothesis, self-reported physical activity did not predict pain sensitivity to noxious heat and cold stimuli. This result is in contrast to several studies showing a relationship between vigorous physical activity and pain sensitivity measures (3, 4, 12). Specifically, prior work has shown that greater vigorous physical activity 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). A number of methodological differences may explain the discrepancies between the current study and prior work. For example, Ellingson et al.'s study examined young women, while 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), dimension of pain being measured (i.e., pain unpleasantness v. pain intensity), and the method used to measure and categorize levels of physical activity (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, 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 moderate physical activity is associated with pain modulation during cognitive tasks (13). In line with this finding, the current study provides evidence suggesting that physical activity behaviors also influence the functional capacity of endogenous facilitatory and inhibitory systems in healthy adults. As hypothesized, individuals who reported relatively greater vigorous physical activity demonstrated enhanced pain inhibition during the CPM paradigm and less temporal summation of second pain, after controlling for potential confounding variables. Total physical activity level also predicted CPM and TS; however, these findings may have been driven by the vigorous physical activity component of the score. Notably, CPM and physical activity were not significantly correlated when this relationship was examined with bivariate correlations. The discrepancy between the CPM and physical activity correlation (i.e., CPM and physical activity not significantly correlated) and 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 physical activity was likely not revealed until these sources of variation were controlled for. Interestingly, physical activity behaviors did not predict pain inhibition in the offset analgesia paradigm. Given that different neuroanatomical pathways underlie CPM and offset

analgesia (25), different relationships between these two inhibitory processes and physical activity behaviors are biologically plausible.

Several different mechanisms exist by which regular exercise could beneficially impact endogenous pain inhibitory and facilitory 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 (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, greater activity of glutamic acid decarboxylase (GAD), 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 GAD (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 temporal summation 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 and colleagues 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 (21). 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 cortex, 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, physical activity was assessed by a questionnaire rather than by objective methods. Subjective measures of physical activity can result in under- and overestimation of the amount of physical activity reported, as answers depend on subject’s memory. Thus, the current results need to be substantiated with objective measures of physical activity. Secondly, the cross-sectional nature of the study renders it possible that dysfunctional pain modulation leads to reduced participation in vigorous physical activity. Future research is warranted to verify the causal relationship between increased physical activity and enhanced descending pain modulatory

control. Specifically, RCT's are needed to determine whether exercise training improves descending pain modulatory control and whether this enhanced pain modulation translates to reduced clinical pain. Additionally, longitudinal studies are needed to investigate whether increased physical activity 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, the majority 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, physical activity was assessed only "over the last 7 days", which may not have been representative of overall physical activity habits for each participant.

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

Acknowledgments

Funding: This research was supported by NIH Grant T32 T32NS045551-06.

References

1. aan het Rot M, Collins KA, Fitterling HL. Physical exercise and depression. Mt Sinai J Med. 2009; 76(2):204–214. [PubMed: 19306383]
2. Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exerc. 2000; 32(9S):S498–504. [PubMed: 10993420]
3. Andrzejewski W, Kassolik K, Brzozowski M, Cymer K. The influence of age and physical activity on the pressure sensitivity of soft tissues of the musculoskeletal system. Journal of Bodywork and Movement Therapies. 2010; 14(4):382–390. [PubMed: 20850046]
4. Anshel MH, Russell KG. Effect of aerobic and strength training on pain tolerance, pain appraisal and mood of unfit males as a function of pain location. J Sports Sci. 1994; 12(6):535–547. [PubMed: 7853450]
5. Bergman S, Jacobsson LT, Herrstrom P, Petersson IF. Health status as measured by SF-36 reflects changes and predicts outcome in chronic musculoskeletal pain: a 3-year follow up study in the general population. Pain. 2004; 108(1–2):115–123. [PubMed: 15109514]
6. Chitour D, Dickenson AH, Le Bars D. Pharmacological evidence for the involvement of serotonergic mechanisms in diffuse noxious inhibitory controls (DNIC). Brain Res. 1982; 236(2): 329–337. [PubMed: 6978166]
7. Cohen, J. Statistical Power Analysis for the Behavioral Sciences. 2. Hillsdale (NJ): Lawrence Erlbaum Associates; 1988. p. 590
8. Colcombe SJ, Erickson KI, Scalf PE, et al. Aerobic exercise training increases brain volume in aging humans. J Gerontol A Biol Sci Med Sci. 2006; 61(11):1166–1170. [PubMed: 17167157]
9. Craggs JG, Staud R, Robinson ME, Perlstein WM, Price DD. Effective connectivity among brain regions associated with slow temporal summation of C-fiber-evoked pain in fibromyalgia patients and healthy controls. J Pain. 2012; 13(4):390–400. [PubMed: 22480771]
10. Craig CL, Marshall AL, Sjöström M, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc. 2003; 35(8):1381–1395. [PubMed: 12900694]
11. Edwards RR, Fillingim RB. Effects of age on temporal summation and habituation of thermal pain. J Pain. 2001; 2(6):307–317. [PubMed: 14622810]

12. Ellingson LD, Colbert LH, Cook DB. Physical activity is related to pain sensitivity in healthy women. Med Sci Sports Exerc. 2012; 44(7):1401–1406. [PubMed: 22217571]
13. Ellingson LD, Shields MR, Stegner AJ, Cook DB. Physical activity, sustained sedentary behavior, and pain modulation in women with fibromyalgia. J Pain. 2012; 13(2):195–206. [PubMed: 22245361]
14. Fitzgerald CT, Carter LP. Possible role for glutamic acid decarboxylase in fibromyalgia symptoms: a conceptual model for chronic pain. Med Hypotheses. 2011; 77(3):409–415. [PubMed: 21684692]
15. Gaskin DJ, Richard P. The economic costs of pain in the United States. J Pain. 2012; 13(8):715–724. [PubMed: 22607834]
16. Grill JD, Coghill RC. Transient analgesia evoked by noxious stimulus offset. J Neurophysiol. 2002; 87(4):2205–2208. [PubMed: 11929939]
17. Henchoz Y, So A. Exercise and nonspecific low back pain: a literature review. Joint Bone Spine. 2008; 75(5):533–539. [PubMed: 18801686]
18. Hill LE, Droste SK, Nutt DJ, Linthorst AC, Reul JM. Voluntary exercise alters GABA(A) receptor subunit and glutamic acid decarboxylase-67 gene expression in the rat forebrain. J Psychopharmacol. 2010; 24(5):745–756. [PubMed: 18801833]
19. Huser W, Klose P, Langhorst J, et al. Efficacy of different types of aerobic exercise in fibromyalgia syndrome: a systematic review and meta-analysis of randomised controlled trials. Arthritis Res Ther. 2010; 12(3):R79. [PubMed: 20459730]
20. Kadetoff D, Kosek E. The effects of static muscular contraction on blood pressure, heart rate, pain ratings and pressure pain thresholds in healthy individuals and patients with fibromyalgia. Eur J Pain. 2007; 11(1):39–47. [PubMed: 16480906]
21. King CD, Goodin B, Kindler LL, et al. Reduction of conditioned pain modulation in humans by naltrexone: an exploratory study of the effects of pain catastrophizing. J Behav Med. 2012 Epub ahead of print.
22. Kramer AF, Erickson KI, Colcombe SJ. Exercise, cognition, and the aging brain. J Appl Physiol. 2006; 101(4):1237–1242. [PubMed: 16778001]
23. Landmark T, Romundstad P, Borchgrevink PC, Kaasa S, Dale O. Associations between recreational exercise and chronic pain in the general population: evidence from the HUNT 3 study. Pain. 2011; 152(10):2241–2247. [PubMed: 21601986]
24. Lewis GN, Rice DA, McNair PJ. Conditioned pain modulation in populations with chronic pain: a systematic review and meta-analysis. J Pain. 2012; 13(10):936–944. [PubMed: 22981090]
25. Martucci KT, Eisenach JC, Tong C, Coghill RC. Opioid-independent mechanisms supporting offset analgesia and temporal sharpening of nociceptive information. Pain. 2012; 153(6):1232–1243. [PubMed: 22503222]
26. McLoughlin MJ, Stegner AJ, Cook DB. The relationship between physical activity and brain responses to pain in fibromyalgia. J Pain. 2011; 12(6):640–651. [PubMed: 21330218]
27. Moont R, Crispel Y, Lev R, Pud D, Yarnitsky D. Temporal changes in cortical activation during conditioned pain modulation (CPM), a LORETA study. Pain. 2011; 152(7):1469–1477. [PubMed: 21339052]
28. Niesters M, Hoitsma E, Sarton E, Aarts L, Dahan A. Offset analgesia in neuropathic pain patients and effect of treatment with morphine and ketamine. Anesthesiology. 2011; 115(5):1063–1071. [PubMed: 21878810]
29. Nir RR, Yarnitsky D, Honigman L, Granot M. Cognitive manipulation targeted at decreasing the conditioning pain perception reduces the efficacy of conditioned pain modulation. Pain. 2012; 153(1):170–176. [PubMed: 22119318]
30. Peters J, Dauvermann M, Mette C, et al. Voxel-based morphometry reveals an association between aerobic capacity and grey matter density in the right anterior insula. Neuroscience. 2009; 163(4):1102–1108. [PubMed: 19628025]
31. Riley JL, King CD, Wong F, Fillingim RB, Mauderli AP. Lack of endogenous modulation and reduced decay of prolonged heat pain in older adults. Pain. 2010; 150(1):153–160. [PubMed: 20546997]

32. Scudds RJ, McD Robertson J. Empirical evidence of the association between the presence of musculoskeletal pain and physical disability in community-dwelling senior citizens. Pain. 1998; 75(2–3):229–235. [PubMed: 9583758]
33. Spielberger, CD.; Gorsuch, RL.; Lushene, RE. Manual for the State-Trait Anxiety Inventory. Palo Alto: Consulting Psychologists Press; 1972.
34. Stagg NJ, Mata HP, Ibrahim MM, et al. Regular exercise reverses sensory hypersensitivity in a rat neuropathic pain model: role of endogenous opioids. Anesthesiology. 2011; 114(4):940–948. [PubMed: 21386701]
35. Sullivan MJL, Bishop SR, Pivik J. The Pain Catastrophizing Scale: development and validation. Psychol Assess. 1995; 7:524–532.
36. Vierck CJ, Riley JL, Wong F, King CD, Mauderli AP. Psychophysical demonstration of bidirectional pain modulation (sensitization and desensitization) by ascending or descending progressions of thermal stimulus intensity. Brain Res. 2010; 1347:58–64. [PubMed: 20537988]
37. Ware, JE.; Kosinski, M.; Dewey, JE. How to Score Version Two of the SF-36 Health Survey. Lincoln, RI: QualityMetric, Incorporated; 2000. p. 231
38. Willer JC, Roby A, Le Bars D. Psychophysical and electrophysiological approaches to the pain-relieving effects of heterotopic nociceptive stimuli. Brain. 1984; 107 (Pt 4):1095–1112. [PubMed: 6509310]
39. Yarnitsky D, Crispel Y, Eisenberg E, et al. Prediction of chronic post-operative pain: pre-operative DNIC testing identifies patients at risk. Pain. 2008; 138(1):22–28. [PubMed: 18079062]
40. Yong HH, Gibson SJ, Horne DJ, Helme RD. Development of a pain attitudes questionnaire to assess stoicism and cautiousness for possible age differences. J Gerontol B Psychol Sci Soc Sci. 2001; 56(5):279–284.

Table 1

Participant descriptive characteristics

	Males *Mean* (*SD*)	Females *Mean* (*SD*)	p-value
Age, years	39.28 (21.55)	45.64 (21.06)	.342
Walking, met-min/week	1350.87 (1064.87)	1558.92 (1301.37)	.648
Moderate PA, met-min/week	1958.75 (1635.67)	2264.20 (1955.37)	.945
Vigorous PA, met-min/week	2202.00 (2327.22)	1761.60 (2477.63)	.273
Total PA, met-min/week	5476.62 (3396.34)	5584.72 (4062.96)	.946
SF36 – Physical Health (0–100)	84.09 (16.79)	87.60 (10.56)	.387
SF36 – Mental Health(0–100)	82.08 (15.82)	81.08 (14.75)	.853
PAQR	76.05 (15.56)	70.76 (10.10)	.169
PCS	11.09 (9.32)	10.46 (6.90)	.790
STAI- Trait Version	30.05 (9.18)	30.80 (8.04)	.764

Note: VPA=Vigorous Physical Activity; PA=physical activity; SF36=Short Form Healthy Survey; PAQR=Pain attitudes Questionnaire-Revised; PCS=Pain Catastrophizing Scale; STAI=State Trait Anxiety Inventory.

Table 2

Average scores and thermode temperature for psychophysical tests

	Males Mean (SD)	Females Mean (SD)	p-value
Heat pain thresholds, C°	43.67 (4.01)	44.27 (3.22)	.570
Heat pain suprathresholds, C°	50.22 (1.76)	50.08 (1.73)	.771
CPP, pain rating	53.64 (27.51)	51.72 (29.03)	.821
Temporal summation score	39.79 (14.51)	40.33 (18.18)	.911
Ave. TS thermode temp, C°	50.76 (1.87)	50.39 (1.96)	.505
CPM score, change in C°	0.36 (1.62)	0.73 (1.51)	.403
Ave. CPM thermode temp T1, C°	45.48 (2.72)	45.38 (2.59)	.899
Ave. CPM thermode temp T2, C°	45.84 (2.84)	46.13 (2.27)	.703
Offset analgesia magnitude, %	69.20 (24.75)	75.53 (25.44)	.379
Ave. offset thermode temperature, C°	46.88 (1.24)	46.75 (1.53)	.748

Note: TS=temporal summation; temp=temperature; Ave=average; CPM=conditioned pain modulation; T1=trial 1; T2=trial 2; CPP=Cold pressor pain.

Table 3

Bivariate correlation matrix between physical activity levels and experimental pain measures

	1	2	3	4	5	6	7	8	9	10
1. Walking	1.00									
2. Mod PA	.28	1.00								
3. Vig PA	.13	.18*	1.00							
4. Total PA	.55**	.68**	.69**	1.00						
5. HPT	−.08	.04	−.13	−.09	1.00					
6. HPS	.19	.04	.03	.03	.51**	1.00				
7. CPP	−.27	−.23	−.13	−.24	−.30*	−.47**	1.00			
8. TS	.13	.02	−.44**	−.24	.11	.38**	−.20	1.00		
9. CPM	.04	.07	.15	.16	−.22	−.26	.22	−.27*	1.00	
10. Offset	−.03	−.07	.06	−.05	−.05	.04	−.19	.17	.26	1.00

Note:

*=p<.05;

**=p<.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.

Med Sci Sports Exerc. Author manuscript; available in PMC 2015 March 01.

Table 4

Summary of Hierarchical Regression Analyses for Temporal Summation with vigorous and total physical activity as predictors (N=48)

Table 4A. Vigorous PA

Step Variables	R	ΔR^2	Standardized β	P value for β	Model P-value
1. Age	.125	.016	−.104	.495	.003
Sex			.055	.406	
2. Thermode Temp	.540	.276	.504	.004	
3. STAI-T	.552	.013	.071	.615	
PCS			.070	.657	
PAQR			.140	.420	
4. Vigorous PA	.662	.134	−.384	.007	

Table 4B. Total PA

Step Variables	R	ΔR^2	Standardized β	P value for β	Model P-value
1. Age	.125	.016	−.104	.495	.006
Sex			.055	.406	
2. Thermode Temp	.540	.276	.504	.004	
3. STAI-T	.552	.013	.071	.615	
PCS			.070	.657	
PAQR			.140	.420	
4. Total PA	.642	.107	−.366	.016	

Note: PA=physical activity; Temp=Temperature; PCS=Pain Catastrophizing Scale; PAQR=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 physical activity as predictors (N=46)

Table 5A. Vigorous PA

Step Variables	R	ΔR^2	Standardized β	P value for β	Model P-value
1. Age	.284	.081	.006	.924	.007
Sex			.305	.015	
2. Δ pain rating	.416	.093	.172	.262	
CPP rating			.237	.098	
3. STAI-T	.544	.122	.071	.082	
PCS			.070	.072	
PAQR			.140	.854	
4. Vigorous PA	.662	.143	.318	.006	

Table 5B. Total PA

Step Variables	R	ΔR^2	Standardized β	P value for β	Model P-value
1. Age	.284	.081	−.120	.416	.006
Sex			.348	.017	
2. Δ pain rating	.416	.093	.219	.117	
CPP rating			.303	.031	
3. STAI-T	.544	.122	.202	.161	
PCS			.254	.083	
PAQR			−.013	.931	
4. Vigorous PA	.665	.146	.431	.005	

Note: PA=physical activity; Temp=Temperature; CPP=Cold pressor pain.