Physical Activity to Prevent the Age-Related Decline of Endogenous Pain Modulation

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NAUGLE, K.M., K.E. NAUGLE, M. TEEGARDIN, and A.S. KALETH. Physical activity to prevent the age-related decline of endogenous pain modulation. *Exerc. Sport Sci. Rev.*, Vol. 51, No. 4, pp. 169–175, 2023. *As humans age, the capacity of the central nervous system to endogenously modulate pain significantly deteriorates, thereby increasing the risk for the development of chronic pain. Older adults are the least physically active cohort of all age groups. We hypothesize that a sedentary lifestyle and decreased physical activity may contribute to the decline of endogenous pain modulation associated with aging.* **Key Words:** older adults, pain modulation, physical activity, conditioned pain modulation, temporal summation, exercise-induced hypoalgesia

KEY POINTS

- The prevalence of chronic pain rises across the age span.
- One mechanism predisposing older adults to increased risk of chronic pain is an age-related decline in the capacity of the central nervous system (CNS) to endogenously modulate pain.
- Older adults who do more moderate to vigorous physical activity (MVPA) per week exhibit less pain facilitation by the CNS and have a greater capacity for exercise-induced hypoalgesia.
- Older adults who are less sedentary and do more light physical activity per week exhibit greater endogenous pain inhibitory capacity.
- We propose that maintaining an active lifestyle can prevent or slow the decline in endogenous pain modulation with aging.

INTRODUCTION

Epidemiological data indicates that the prevalence of chronic pain rises across the age span until the seventh decade of life (1), with estimates reaching as high as 60% to 75% among community-dwelling older adults in the United States (2). Older adults also report more severe pain and pain at more body locations relative to younger persons (3,4). Chronic pain can have a detrimental effect on the quality of life in older adults (4) because it increases the risk for physical disability (5), depression (4), and sleep disturbance (5). Older adults are the fastest growing segment of the U.S. population, with people aged older than 65 yr expected to increase by almost 70% by the year 2060 (6). As the number of older adults continues to increase, the number of people with chronic pain will likely rise. Given the burden of chronic pain in the elderly, this demographic is in need of evidenced-based and cost-effective prevention modalities for chronic pain.

One mechanism predisposing older adults to increased risk of chronic pain is an age-related decline in the capacity of the central nervous system (CNS) to endogenously modulate pain. In humans, sophisticated and dynamic quantitative sensory tests (QSTs) are used to noninvasively assess endogenous pain modulatory function (7). Older compared with younger adults are characterized by unbalanced and dysregulated pain modulation as evidenced by increased pain facilitation and decreased pain inhibition on these QSTs (8). Determining modifiable and behavioral factors contributing to this dysregulated pattern of pain modulation in older adults is crucial to the development of strategies to prevent persistent pain in older people. This review explores the novel hypothesis that a sedentary lifestyle and decreased levels of physical activity contribute to dysregulated pain modulation associated with aging. Importantly, older adults are the least physically active cohort of all age groups (9). This review highlights studies that have investigated the relation of endogenous pain modulation to physical activity behavior, with emphasis on studies in older adults. These studies suggest that different types of physical activity behavior may differentially impact endogenous pain inhibitory and facilitatory processes in older adults. This review also discusses the potential mechanisms through which physical activity behavior may improve or deteriorate pain modulatory function, and future research directions.

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DECLINE OF ENDOGENOUS PAIN MODULATION WITH AGING

The experience of pain is regulated by complex peripheral and central endogenous systems that both facilitate and inhibit pain. In the pain field, dynamic QSTs have been extensively studied and validated to measure various pain modulatory mechanisms in humans. Temporal summation (TS) of pain is the most common test used to measure endogenous facilitation of pain by the CNS. As shown in Figure 1a, the TS test consists of delivering repetitive noxious stimuli of a constant intensity and then assessing the amount of pain facilitation across the stimuli as an indicator of sensitization of the CNS (10). In contrast, endogenous pain inhibition is most commonly evaluated by a "pain inhibits pain" model called conditioned pain modulation (CPM). In the CPM test, a noxious stimulus applied to one body part (conditioning stimulus) inhibits pain perception of another painful stimulus (test stimulus) applied to a distant body part (11) (Fig. 1b). CPM is considered the behavioral correlate to diffuse noxious inhibitory controls in animals, a pain inhibitory mechanism involving the spinal-bulbo-spinal loop (11). Another well-studied pain inhibitory mechanism is exercise-induced hypoalgesia (EIH), which is characterized by decreased pain sensitivity and perception to noxious stimulation immediately after an acute bout of exercise (12) (Fig. 1b). Animal and human data indicate the mechanisms of EIH involve the CNS but are separate mechanisms than those regulating pain inhibition through CPM (13). Generally, the extant evidence suggests that enhanced pain facilitation and poor pain inhibitory capacity on the aforementioned tests increase the susceptibility for persistent and intense pain. Indeed, reduced CPM and greater TS are characteristic of many chronic pain conditions common in older adults, such as osteoarthritis, low back pain, and fibromyalgia (7). In addition, studies show that dysfunctional pain modulation is associated with reports of increased pain intensity (14) and predicts the transition from acute to chronic pain after injury (15) and surgery (16). Consequently, dysregulated pain modulation is considered a key risk factor for the development and maintenance of persistent pain.

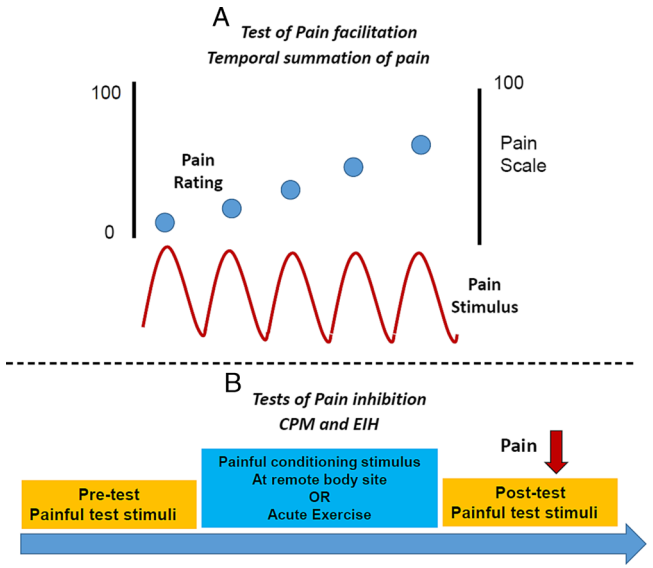

Figure 1. A. Test of pain facilitation: temporal summation (TS) of pain. This test consists of delivering repetitive noxious stimuli of a constant intensity (represented by red lines), usually with an interstimulus interval of 3 s or less. Participants then rate the intensity of the pain (represented by blue circles) for each noxious stimulation or for the first and last stimulation. TS is considered the degree of pain increase (*i.e.*, facilitation) across the stimuli. B. Tests of pain inhibition: conditioned pain modulation (CPM) and EIH. The CPM and exercise-induced hypoalgesia (EIH) protocols consist of delivering a painful test stimulus to one part of the body part (*e.g.*, pressure pain thresholds to the left arm) on two separate occasions (pretest and posttest represented by yellow boxes). For CPM, a painful conditioning stimulus (*e.g.*, cold water immersion of right hand) is applied to a distant body part either immediately before or during the posttest stimulus (represented by blue box). Pain inhibition during CPM is evaluated as the change in pain perception or sensitivity from the pretest to the posttest. EIH is similar except the conditioning stimulus is replaced by an acute bout of exercise.

Strong evidence indicates an age-related decline in the capacity of the CNS to endogenously modulate pain (8), as indicated by the tests of TS, CPM, and EIH. Our laboratory conducted a metaanalysis on studies that compared TS and CPM in healthy, acute and chronic pain-free younger, middle-aged, and older adults (8). Evaluation of the 19 studies indicated that older and middle-aged adults relative to younger adults exhibit enhanced TS and deficient CPM. In many studies, older adults exhibited no pain inhibition or even pain facilitation during the CPM protocol. Overall, the metaanalytic review concluded that the decline in pain modulatory function likely begins in middle age (~≥45 yr). In a separate study, we also showed that older adults experience diminished EIH compared with younger adults after aerobic and isometric exercise (17). Thus, the collective research indicates that aging is associated with a reduced capacity to activate multiple pain inhibitory mechanisms coupled with enhanced pain facilitation by the CNS, which likely increases the risk for intense and persistent pain.

RELATION OF PHYSICAL ACTIVITY LEVELS TO PAIN MODULATION IN OLDER ADULTS

A growing body of evidence has begun to link physical activity behavior to endogenous pain modulatory function, with generally more effective pain modulation observed in more active individuals. This body of research has been conducted in a variety of populations (*i.e.*, young, old, chronic pain patients, injured adults, athletes), with a variety of research designs (*i.e.*, cross-sectional, prospective, experimental), and using various methods to measure physical activity. First, this review focuses on studies that directly relate to our novel hypothesis linking physical activity behavior to the dysregulated pain modulation associated with aging. Reduced physical activity facilitates the aging process and physiological decline (18) and hence, could play a key role in the decline of endogenous pain inhibitory and facilitatory systems observed in older adults.

A decade ago, Naugle and Riley (19) conducted the first study to investigate whether individuals who are more physically active exhibit reduced pain facilitation on the TS test and greater inhibition of pain on the CPM test. In this study, healthy adults without chronic pain or ongoing pain problems (aged 18–76 yr) completed several QSTs including heat pain thresholds, heat pain suprathreshold test, cold pain test, TS of heat pain, offset analgesia, and CPM. Physical activity over the past 7 d was measured with the International Physical Activity Questionnaire – Long Form (IPAQ). The IPAQ includes vigorous physical activity, moderate physical activity, and walking subscales, as well as a total physical activity score. Hierarchical regressions indicated that vigorous physical activity and total physical activity predicted both TS of pain and CPM, even after controlling for age, sex, and

psychological variables (Table). Specifically, adults who self-reported relatively more vigorous physical activity demonstrated less TS of pain and greater pain inhibition during the CPM test. The relation between total physical activity and pain modulation was likely driven by the vigorous physical activity component of the score. Self-reported physical activity did not predict pain sensitivity to noxious cold and heat stimuli or offset analgesia. This study provided some of the first preliminary evidence of a relationship between physical activity levels and the functioning of the endogenous pain modulatory systems.

This initial study had several limitations including the use of only a 7-d recall of physical activity, the use of subjective versus objective measures of physical activity, and a mixed sample of older and younger adults. Therefore, Naugle *et al.* (20) conducted a follow-up study to determine whether objective measures of physical activity predicted pain modulation on the TS and CPM tests in a sample of healthy, older adults without chronic pain or ongoing pain problems. Participants, ranging in age from 60 to 77 yr, wore an accelerometer on the hip for 7 d to measure the amount of time each participant spent in daily sedentary, light, and moderate to vigorous physical activity (MVPA). Two key results emerged from these data. First, and similar to the previous study, MVPA predicted pain facilitation on the TS test, even after controlling for sex, body mass index (BMI), and psychological factors (Table). Older adults who performed more MVPA per day exhibited less pain facilitation on three different tests of TS of heat pain (*i.e.*, 44°C, 46°C, 48°C). The second key finding was that sedentary time and light physical activity, rather than MVPA, predicted pain inhibitory function on the CPM test. Older adults who performed more light physical activity and were less sedentary each day exhibited greater pain inhibition. Sedentary time accounted for more than 25% of the variance in CPM (Table). Overall, this study provided the first objective evidence that physical activity behavior is related to the functioning of pain modulatory systems in older adults.

Our laboratory also conducted a study to examine whether physical activity behavior influences the magnitude of exercise-induced hypoalgesia after an acute bout of isometric exercise in older adults without chronic pain or ongoing pain problems (21). Weekly physical activity levels were measured with accelerometers worn on the hip. The EIH protocol consisted of testing for changes in heat and pressure pain sensitivity after a 3-min isometric handgrip held at 25% of maximum voluntary contraction. Across the whole sample, older adults did not experience a reduction in pain sensitivity after the bout of isometric exercise. However, older adults who performed more MVPA per week exhibited greater EIH. Time spent in weekly sedentary behavior and light physical activity were not related to the magnitude of EIH. These findings highlight the potential benefits of MVPA in maintaining EIH capabilities with age. Collectively, the evidence suggests that different types of physical activity behavior may differentially impact endogenous pain inhibitory and facilitatory processes in older adults.

One limitation of the aforementioned studies is their cross-sectional design, which prevents the determination of causal relationships. For example, it is possible that greater pain reduction after exercise facilitates more MVPA in older adults rather than a greater level of MVPA enhancing EIH capabilities. Although some bidirectionality in this relationship could exist, we hypothesize that physical activity behavior helps shape the pain modulatory profile of older individuals, thereby reducing (increased physical activity) or enhancing the risk (increased sedentary time) for developing chronic pain. Compelling indirect support for the directionality of this hypothesis comes from large prospective epidemiological studies showing a protective effect of regular physical activity for the development of chronic pain in older adults (22,23). Next, we briefly review the research examining physical activity behavior and pain modulatory function in other populations because this body of research is also critical for a comprehensive understanding of the complex relationship between these two variables.

RELATION OF PHYSICAL ACTIVITY LEVELS TO PAIN MODULATION IN OTHER POPULATIONS

Healthy Younger Adults

Most studies investigating the influence of physical activity on pain modulation in healthy younger and middle-aged adults have involved comparing active with less active groups. Several studies have observed an enhanced CPM response in endurance athletes (*e.g.*, triathletes, runners), but not strength athletes, compared with active controls (24–27). In contrast, Peterson *et al.* (28) found that endogenous pain inhibitory function was similar between endurance-trained athletes and active controls for both CPM and isometric EIH. Interestingly, aerobic EIH was attenuated in the endurance-trained athletes compared with active controls after 30 min of running. The authors attributed this unexpected finding to the superior fitness levels of the runners, which consequently lead to less discomfort during the running exercise compared with the controls. In young, healthy

TABLE. Summary of significant results from studies evaluating the relation between regular physical activity behavior and pain modulation in chronic pain-free older adults.

Study	Dependent Variable	Predictor Variable	Control Variables	R^2 for Predictor	β for Predictor	β *P*
Naugle (20)[a]	TS – individualized temperature	Self-reported vigorous PA on IPAQ	Age, sex, thermode Temp, STAI, PCS	13.4%	−0.384	0.007
Naugle (20)[a]	CPM	Self-reported vigorous PA on IPAQ	Age, sex, CS pain rating, STAI, PCS	14.3%	0.318	0.006
Naugle (21)	TS at 44°C	MVPA (acc)	Sex, BMI, STAI, PCS	11.5%	−0.366	0.013
Naugle (21)	TS at 46°C	MVPA (acc)	Sex, BMI, STAI, PCS	16.1%	−0.433	0.005
Naugle (21)	TS at 48°C	MVPA (acc)	Sex, BMI, STAI, PCS	10.0%	−0.337	0.024
Naugle (21)	CPM	LPA (acc)	Sex, BMI, STAI, PCS, acc wear time	20.1%	−0.495	0.001
Naugle (21)	CPM	Sedentary time (acc)	Sex, BMI, STAI, PCS, acc wear time	25.5%	1.266	<0.001
Ohlman (22)	EIH	MVPA (acc)	Age, PPT pretest	11.0%	0.334	0.019

[a]Study included a mixed sample of healthy younger and older adults.

acc indicates accelerometer; CS, conditioning stimulus; LPA, light physical activity; MVPA, moderate-to-vigorous physical activity; PA, physical activity; PCS, pain catastrophizing scale; PPT, pressure pain threshold; STAI, State Trait Anxiety Inventory.

nonathlete adults, Umeda *et al.* (29) found greater CPM in individuals reporting more than 150 min of moderate physical activity per week compared with those reporting less than 60 min·wk^{-1}. In another study with nonathletes and a larger sample size, Shiro and colleagues (30) showed the relation between physical activity and CPM may differ between sexes because MVPA was associated with enhanced CPM in women but not men. Overall, the data support a relation between aerobic-type MVPA and CPM in younger adults, which contrasts with the CPM-light physical activity relation in older adults. Perhaps, a greater intensity threshold of activity is needed for a physical activity-CPM relation to emerge in younger adults. It is also important to note that much of the younger adult research did not assess light physical activity and sedentary behavior, and the methods of physical activity assessment varied greatly.

Few studies have investigated the relation of physical activity with TS and EIH in healthy younger adults. As previously mentioned, Naugle and Riley (19) revealed that self-reported MVPA predicted TS in a sample of younger and older adults. In contrast, Awali and colleagues (31) revealed that TS of pain administered on the arm was associated with lean mass of that arm but not associated with physical activity variables measured with an accelerometer. In addition, Assa *et al.* (24) found no differences in TS between endurance athletes, strength athletes, and active controls. Thus, the evidence for a relation between TS and physical activity in younger adults is limited and unclear. Regarding EIH, Umeda *et al.* (32) demonstrated that race differences in EIH were partially explained by differences in lifestyle physical activity. In contrast, Black and colleagues found no differences in isometric EIH in young adult women based on whether participants reported meeting the American College of Sports Medicine's (ACSM) guidelines for aerobic and resistance exercise (33). These lack of differences could be because the insufficiently active group in this study still completed at least 13 min of vigorous activity per day. Furthermore, the authors point out that the influence of physical activity on pain modulatory processes may be greater in older compared with younger healthy adults, given the decline of physical activity and pain modulatory function with age. As previously mentioned, the aging and pain modulation literature suggests middle age (>45 yr) is the period in which pain modulation begins to decline (8). The lack of significant pain modulation dysfunction in younger adults could explain the mixed and apparent attenuated relationship of physical activity with pain modulation in younger adults.

Clinical Populations

Compared with research in healthy adults, research investigating the influence of regular physical activity on pain modulation in clinical populations is sparse but includes longitudinal designs. For example, a recent study by Holm *et al.* examined the effects of 12 wk of neuromuscular exercise with and without resistance training on TS and CPM in people with symptomatic knee osteoarthritis (KOA) (34). Despite improvements in pain sensitization (as measured by pressure pain thresholds and tolerance) in the group performing combined exercise therapy, neither group displayed changes in CPM or TS. In another study with a smaller sample size (and no control group), Hansen *et al.* (35) found that neuromuscular exercise alone performed twice weekly for 6 wk did not induce changes in EIH or TS, despite improvement in self-reported pain in individuals with symptomatic KOA. The lack of changes in pain modulation outcomes in these studies is not surprising given that the younger adult data suggest that the type of physical activity (*i.e.*, aerobic vs strength) is important for a significant relation between pain modulation and physical activity. However, Kroll *et al.* (36) found reductions in the severity of migraines after 3 months of aerobic exercise training but no changes in TS. Taken together, these interventional studies found no effects of regular exercise on TS, CPM, or EIH. As such, the pain relief obtained from exercise was not explained by improvements in endogenous pain modulation. However, these studies had substantial heterogeneity in the methodology and exercise modalities used, small sample sizes, and limited exercise program durations (6–12 wk), making it difficult to draw any meaningful conclusions on whether regular physical activity can alter the ability to endogenously modulate pain. Furthermore, a study examining acute exercise in fibromyalgia demonstrated that experimental pain responses to exercise can be extremely variable (37). Thus, it is possible that exercise may improve pain modulation in some but not all individuals.

To our knowledge, only one prospective observational study has examined physical activity behavior and pain modulation. Naugle *et al.* examined whether physical activity behavior in the first month after a mild traumatic brain injury (TBI) predicts pain modulation capacity in individuals with mild TBI. Importantly, greater self-reported volumes of walking and moderate intensity physical activity performed during the first 2 wk after the injury predicted greater pain inhibitory capacity on the CPM test at 1 month postinjury. Related, higher levels of sedentary behavior (*i.e.*, sitting) cross-sectionally predicted reduced pain inhibition on the CPM test at 1 month postinjury (38). This study provided the first evidence that physical activity behavior can predict future pain inhibitory function. In a cross-sectional study, Ellingson and colleagues (39) found that patients with fibromyalgia who had relatively higher levels of sedentary time were less able to modulate pain during distraction. Furthermore, sustained sedentary behavior had a negative relationship with brain responses in areas involved in pain modulation. Although a different test than CPM was used to assess pain inhibitory function, these results support the notion that sedentary behavior is related to worse CNS modulation of pain. Overall, the studies in clinical populations support a relation between light to moderate activity and sedentary behavior with pain inhibition, but it remains unclear whether regular exercise can alter TS, CPM, or EIH in those experiencing chronic pain.

POTENTIAL MECHANISMS LINKING PHYSICAL ACTIVITY AND PAIN MODULATION IN OLDER ADULTS

A multitude of mechanisms exist through which regular physical activity, particularly MVPA, could prevent and reduce pain. Much, but not all, of this mechanistic knowledge has been obtained through animal models. Lesnak and Sluka (40) recently published an excellent review of the preclinical evidence for the peripheral and central mechanisms underlying the beneficial effects of regular physical activity on pain prevention and chronic pain alleviation. In the current review, we focus specifically on those mechanisms through which physical activity behavior could prevent an age-related decline in endogenous pain modulation. Indeed, regular physical activity is known to reduce many pathophysiological changes associated with aging,

including several that could underlie dysregulated pain modulation in older adults.

Aging is characterized by a decline in proper physiological function partly due to an accumulation of oxidative stress (*i.e.*, imbalance between reactive oxidative species and antioxidants in the body) (41). Age-associated oxidative stress facilitates the production of proinflammatory molecules and a consequent state of chronic inflammation in the elderly (42). Peripheral proinflammatory cytokines sensitize peripheral nociceptors and induce spinal release of cytokines (43). Central proinflammatory cytokines induce sensitization of spinal dorsal horn neurons (44), a key mechanism underlying TS of pain (10). Regular MVPA participation prevents or reduces the age-related decreases in antioxidant defenses, thereby reducing levels of oxidative stress in older adults (45). Furthermore, multiple studies have documented an antiinflammatory effect of regular aerobic exercise in older adults (46). Therefore, the antiinflammatory and antioxidant effects of MVPA could theoretically impede the processes that facilitate central sensitization (*i.e.*, elevated TS of pain) in older adults. However, additional studies are needed to test this mechanistic hypothesis.

Researchers have also speculated that changes in body composition could underlie the age-related decline in pain modulation. Generally, lean mass decreases and fat mass increases into older adulthood (47). Greater fat mass contributes to systemic inflammation in older adults (48). Furthermore, decreased lean mass has been related to increased TS in adults (31). However, research on the relationship of body composition with CPM and EIH is mixed (49,50), with null finding in adults. Importantly, increased MVPA and total physical activity is associated with increased lean mass and decreased fat mass (51). Thus, future research should investigate whether differences in body composition mediate the relationship between TS and MVPA in older adults.

We found that regular MVPA also was associated with an enhanced ability to inhibit pain after acute exercise in older adults (21). Although not the only potential mechanism, a widely studied mechanism of EIH involves the activation of the endogenous opioid system during exercise. Animal studies demonstrate that moderate intensity exercise decreases pain sensitivity in rodents via exercise-induced release of central and peripheral beta-endorphins, an endogenous opioid neuropeptide involved in pain inhibition (40). Furthermore, a recent study comparing individuals with fibromyalgia and healthy controls revealed, by genetic association, that opioid and serotonergic mechanisms interactively regulate pain inhibition after acute isometric exercise (52). Animal studies also indicate that opioid peptide and receptor levels decrease in the brain with aging (53), which could contribute to the diminished EIH observed in older adults. Importantly, endogenous opioid content in the brain is elevated after regular aerobic exercise in rodents (54). Although clearly speculative, regular MVPA could potentially slow the age-related decrease in opioid peptides and receptors in the CNS, and therefore help adults maintain EIH capabilities with age. Notably, several human EIH studies have demonstrated that an opioid antagonist does not alter EIH after isometric exercise. Thus, researchers have also proposed nonopioid mechanisms for EIH, such as involvement of the endocannabinoid system (55,56). For example, Koltyn *et al.* (55) discovered a significant increase in circulating endocannabinoid concentrations (*e.g.*, 2-AG) after isometric exercise during an EIH protocol. Accumulating preclinical and clinical research suggests the endocannabinoid system plays a role in pain modulation (56). Furthermore, animal studies indicate endocannabinoids, such as 2-AG, decline in the brain with age (57). However, limited research has assessed the effects of regular physical activity on endocannabinoid levels, with mixed results (58,59).

Research investigating the influence of light physical activity and sedentary behavior on pathophysiological pain mechanisms is more limited. One possible mechanism linking light physical activity and more efficacious CPM involves enhanced serotonin neurotransmission in the CNS after regular light intensity physical activity. The descending bulbospinal serotonergic pathways are critical to the integrity of the brain circuitry regulating pain inhibition during CPM (60), and serotonin levels generally decline with age (61). Importantly, preclinical evidence indicates that regular light intensity exercise decreases pain-like behaviors in mice by increasing the expression of serotonin receptors and the availability of serotonin in the brain stem (62). As such, regular light physical activity could help maintain the functioning of the serotonergic pathways that are integral to CPM in older adults. Another potential mechanism involves the detrimental effects of sedentary behavior on brain function. In older adults, greater sedentary time has been associated with reduced cerebral blood flow in multiple brain regions (63), poorer outcomes on measures of brain plasticity (64), and white matter brain atrophy (65). Specific to the pain field, Ellingson and colleagues (39) revealed that sedentary behavior in adults with fibromyalgia was

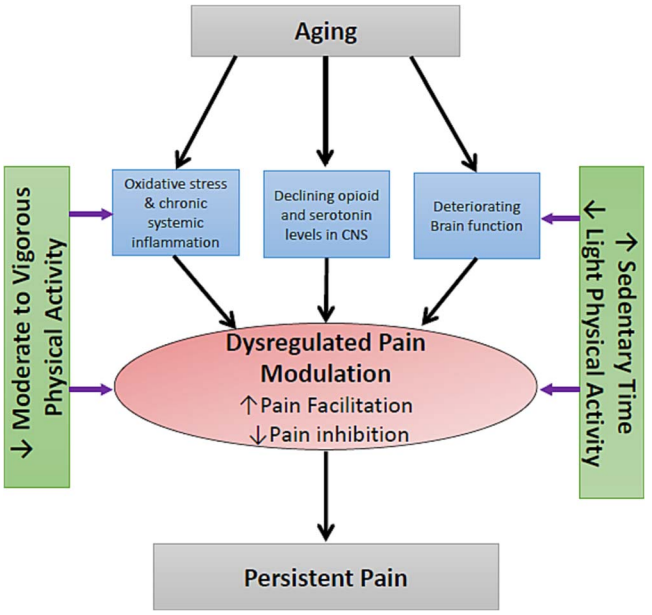

Figure 2. The conceptual model representing our novel hypothesis that a sedentary lifestyle and decreased levels of physical activity contribute to dysregulated pain modulation associated with aging. We hypothesize that reduced physical activity facilitates many pathophysiological changes associated with aging that results in dysregulated pain modulation in the central nervous system (CNS). Reduced moderate-to-vigorous physical activity (MVPA) in older adults is predictive of greater endogenous facilitation of pain by the CNS and a reduced capability to inhibit pain after acute exercise. In addition, greater sedentary behavior and reduced light physical activity are associated with deficient pain inhibitory capacity in older individuals. This dysregulated pain modulatory profile of older adults increases risk for intense and persistent pain. Thus, we propose that an active lifestyle can prevent or slow the decline of endogenous pain modulation with aging, thereby decreasing risk for chronic pain.

linked to reduced pain modulation during a cognitive task and altered brain responses in the prefrontal and cingulate cortices during the task. Altered responsiveness in these brain regions have been associated with individual differences in the capacity to inhibit pain during the CPM test in chronic pain patients and healthy adults (66). Overall, these mechanistic hypotheses are speculative and need additional support from animal and human studies.

CONCLUSIONS

The capacity of the CNS to modulate pain substantially declines with age, placing older adults at an increased risk for chronic pain. Figure 2 provides a conceptual model representing our hypothesis that a sedentary lifestyle and decreased levels of physical activity contribute to dysregulated pain modulation (*i.e.*, increased pain facilitation, decreased pain inhibition) associated with aging. Older adults are the most sedentary cohort in the United States, with up to 80% of waking hours spent being sedentary. In addition, most older adults in the United States do not participate in the minimum physical activity recommendations put forth by the ACSM (67). In support of our hypothesis, we have shown that older adults who do more MVPA per week exhibit less pain facilitation by the CNS and have a greater capacity for EIH. Furthermore, our data indicate that older adults who are less sedentary and do more light physical activity per week exhibit greater endogenous pain inhibitory capacity. Regular physical activity combats many of the pathophysiological mechanisms associated with aging and dysregulated pain modulation. Thus, we propose that maintaining an active lifestyle can prevent or slow the decline in endogenous pain modulation with aging, thereby reducing the risk for chronic pain.

More research is needed to confirm our overall hypothesis because several research questions remain. Specifically, future studies are needed to determine whether the relation between physical activity and pain modulation in older adults differs depending on the presence of chronic pain or demographic factors (*e.g.*, sex, race). Indeed, a larger study in younger adults revealed this relation may differ as a function of sex (30), with CPM associated with physical activity in women but not men. In addition, longitudinal investigations are warranted to determine whether regular physical activity works better as a preventative strategy in older adults (*i.e.*, to prevent the decline of endogenous pain modulation) or as a means to "normalize" pain modulatory function that is already "deficient." Finally, our evidence suggests different intensities of physical activity behavior may differentially impact endogenous pain facilitatory and pain inhibitory processes in older adults. Thus, future studies should investigate whether the effectiveness of physical activity interventions to reduce and prevent pain in older adults could be optimized by coupling the dysfunctional pain modulation pattern observed in older adults with the type of physical activity performed.

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References

1. Helme RD, Gibson SJ. The epidemiology of pain in elderly people. *Clin. Geriatr. Med.* 2001; 17(3):417–31.
2. Tsang A, Von Korff M, Lee S, et al. Common chronic pain conditions in developed and developing countries: gender and age differences and comorbidity with depression-anxiety disorders. *J. Pain.* 2008; 9(10):883–91.
3. Frolund F, Frolund C. Pain in general practice. Pain as a cause of patient-doctor contact. *Scand. J. Prim. Health Care.* 1986; 4(2):97–100.
4. Rustoen T, Wahl AK, Hanestad BR, Lerdal A, Paul S, Miaskowski C. Age and the experience of chronic pain: differences in health and quality of life among younger, middle-aged, and older adults. *Clin. J. Pain.* 2005; 21(6):513–23.
5. Hopman-Rock M, Odding E, Hofman A, Kraaimaat FW, Bijlsma JW. Physical and psychosocial disability in elderly subjects in relation to pain in the hip and/or knee. *J. Rheumatol.* 1996; 23(6):1037–44.
6. United States Census Bureau. *Projected Age Groups and Sex Composition of the Population: Main Projections Series for the United States, 2017–2060.* Washington, DC: U.S. Census Bureau, Population Division. p. . Available from: https://www.census.gov/data/tables/2017/demo/popproj/2017-summary-tables.html. Accessed January 5, 2023.
7. Staud R. Abnormal endogenous pain modulation is a shared characteristic of many chronic pain conditions. *Expert Rev. Neurother.* 2012; 12(5):577–85.
8. Hackett J, Naugle KE, Naugle KM. The decline of endogenous pain modulation with aging: a meta-analysis of temporal summation and conditioned pain modulation. *J. Pain.* 2020; 21(5–6):514–28.
9. Matthews CE, Chen KY, Freedson PS, et al. Amount of time spent in sedentary behaviors in the United States, 2003–2004. *Am. J. Epidemiol.* 2008; 167(7):875–81.
10. Price DD, Dubner R. Mechanisms of first and second pain in the peripheral and central nervous systems. *J. Invest. Dermatol.* 1977; 69(1):167–71.
11. Yarnitsky D. Conditioned pain modulation (the diffuse noxious inhibitory control-like effect): its relevance for acute and chronic pain states. *Curr. Opin. Anaesthesiol.* 2010; 23(5):611–5.
12. Naugle KM, Fillingim RB, Riley JL 3rd. A meta-analytic review of the hypoalgesic effects of exercise. *J. Pain.* 2012; 13(12):1139–50.
13. Ellingson LD, Koltyn KF, Kim JS, Cook DB. Does exercise induce hypoalgesia through conditioned pain modulation? *Psychophysiology.* 2014; 51(3):267–76.
14. Edwards RR, Ness TJ, Weigent DA, Fillingim RB. Individual differences in diffuse noxious inhibitory controls (DNIC): association with clinical variables. *Pain.* 2003; 106(3):427–37.
15. Naugle KM, Carey C, Evans E, Saxe J, Overman R, White FA. The role of deficient pain modulatory systems in the development of persistent post-traumatic headaches following mild traumatic brain injury: an exploratory longitudinal study. *J. Headache Pain.* 2020; 21(1):138.
16. 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):22–8.
17. Naugle KM, Naugle KE, Riley JL 3rd. Reduced modulation of pain in older adults after isometric and aerobic exercise. *J. Pain.* 2016; 17(6):719–28.
18. Moreno-Agostino D, Daskalopoulou C, Wu YT, et al. The impact of physical activity on healthy ageing trajectories: evidence from eight cohort studies. *Int. J. Behav. Nutr. Phys. Act.* 2020; 17(1):92.
19. Naugle KM, Riley JL 3rd. Self-reported physical activity predicts pain inhibitory and facilitatory function. *Med. Sci. Sports Exerc.* 2014; 46(3):622–9.
20. Naugle KM, Ohlman T, Naugle KE, Riley ZA, Keith NR. Physical activity behavior predicts endogenous pain modulation in older adults. *Pain.* 2017; 158(3):383–90.
21. Ohlman T, Miller L, Naugle KE, Naugle KM. Physical activity levels predict exercise-induced hypoalgesia in older adults. *Med. Sci. Sports Exerc.* 2018; 50(10):2101–9.
22. Bruce B, Fries JF, Lubeck DP. Aerobic exercise and its impact on musculoskeletal pain in older adults: a 14 year prospective, longitudinal study. *Arthritis Res. Ther.* 2005; 7(6):R1263–70.
23. Hartvigsen J, Christensen K. Active lifestyle protects against incident low back pain in seniors: a population-based 2-year prospective study of 1387 Danish twins aged 70–100 years. *Spine (Phila Pa 1976).* 2007; 32(1):76–81.
24. Assa T, Geva N, Zarkh Y, Defrin R. The type of sport matters: pain perception of endurance athletes versus strength athletes. *Eur. J. Pain.* 2019; 23(4): 686–96.
25. Flood A, Waddington G, Thompson K, Cathcart S. Increased conditioned pain modulation in athletes. *J. Sports Sci.* 2017; 35(11):1066–72.
26. Geva N, Defrin R. Enhanced pain modulation among triathletes: a possible explanation for their exceptional capabilities. *Pain.* 2013; 154(11):2317–23.
27. Umeda M, Okifuji A. Comparable conditioned pain modulation and augmented blood pressure responses to cold pressor test among resistance exercisers compared to healthy controls. *Biol. Psychol.* 2020; 153:107889.

28. Peterson JA, Schubert DJ, Campbell J, Bemben MG, Black CD. Endogenous pain inhibitory function: endurance-trained athletes vs active controls. *Pain Med.* 2019; 20(9):1822–30.
29. Umeda M, Lee W, Marino CA, Hilliard SC. Influence of moderate intensity physical activity levels and gender on conditioned pain modulation. *J. Sports Sci.* 2016; 34(5):467–76.
30. Shiro Y, Ikemoto T, Terasawa Y, et al. Physical activity may be associated with conditioned pain modulation in women but not men among healthy individuals. *Pain Res. Manag.* 2017; 2017:9059140.
31. Awali A, Alsouhibani AM, Hoeger Bement M. Lean mass mediates the relation between temporal summation of pain and sex in young healthy adults. *Biol. Sex Differ.* 2018; 9(1):42.
32. Umeda M, Kempka LE, Greenlee BT, Weatherby AC. A smaller magnitude of exercise-induced hypoalgesia in African Americans compared to non-Hispanic whites: a potential influence of physical activity. *Biol. Psychol.* 2016; 113:46–51.
33. Black CD, Huber JK, Ellingson LD, et al. Exercise-induced hypoalgesia is not influenced by physical activity type and amount. *Med. Sci. Sports Exerc.* 2017; 49(5):975–82.
34. Holm PM, Petersen KK, Wernbom M, Schroder HM, Arendt-Nielsen L, Skou ST. Strength training in addition to neuromuscular exercise and education in individuals with knee osteoarthritis-the effects on pain and sensitization. *Eur. J. Pain.* 2021; 25(9):1898–911.
35. Hansen S, Vaegter HB, Petersen KK. Pretreatment exercise-induced hypoalgesia is associated with change in pain and function after standardized exercise therapy in painful knee osteoarthritis. *Clin. J. Pain.* 2020; 36(1):16–24.
36. Kroll LS, Sjodahl Hammarlund C, Gard G, Jensen RH, Bendtsen L. Has aerobic exercise effect on pain perception in persons with migraine and coexisting tension-type headache and neck pain? A randomized, controlled, clinical trial. *Eur. J. Pain.* 2018; 22:1399–408.
37. Hoeger Bement MK, Weyer A, Hartley S, Drewek B, Harkins AL, Hunter SK. Pain perception after isometric exercise in women with fibromyalgia. *Arch. Phys. Med. Rehabil.* 2011; 92(1):89–95.
38. Naugle KM, Corrona S, Smith JA, Nguyen T, Saxe J, White FA. Physical activity behavior in the first month after mild traumatic brain injury is associated with physiological and psychological risk factors for chronic pain. *Pain Rep.* 2021; 6(4):e969.
39. 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.
40. Lesnak JB, Sluka KA. Mechanism of exercise-induced analgesia: what we can learn from physically active animals. *Pain Rep.* 2020; 5(5):e850.
41. Wang CH, Wu SB, Wu YT, Wei YH. Oxidative stress response elicited by mitochondrial dysfunction: implication in the pathophysiology of aging. *Exp. Biol. Med. (Maywood).* 2013; 238(5):450–60.
42. Sarkar D, Fisher PB. Molecular mechanisms of aging-associated inflammation. *Cancer Lett.* 2006; 236(1):13–23.
43. Sommer C, Kress M. Recent findings on how proinflammatory cytokines cause pain: peripheral mechanisms in inflammatory and neuropathic hyperalgesia. *Neurosci. Lett.* 2004; 361(1–3):184–7.
44. Kawasaki Y, Zhang L, Cheng JK, Ji RR. Cytokine mechanisms of central sensitization: distinct and overlapping role of interleukin-1beta, interleukin-6, and tumor necrosis factor-alpha in regulating synaptic and neuronal activity in the superficial spinal cord. *J. Neurosci.* 2008; 28(20):5189–94.
45. Radak Z, Chung HY, Goto S. Exercise and hormesis: oxidative stress-related adaptation for successful aging. *Biogerontology.* 2005; 6(1):71–5.
46. Woods JA, Wilund KR, Martin SA, Kistler BM. Exercise, inflammation and aging. *Aging Dis.* 2012; 3(1):130–40.
47. He X, Li Z, Tang X, et al. Age- and sex-related differences in body composition in healthy subjects aged 18 to 82 years. *Medicine (Baltimore).* 2018; 97(25):e11152.
48. Berg AH, Scherer PE. Adipose tissue, inflammation, and cardiovascular disease. *Circ. Res.* 2005; 96(9):939–49.
49. Peterson JA, Lohman C, Larson RD, Bemben MG, Black CD. Body composition does not influence conditioned pain modulation and exercise-induced hyperalgesia in healthy males and females. *Eur. J. Pain.* 2022; 26(8):1800–10.
50. Stolzman S, Hoeger Bement M. Lean mass predicts conditioned pain modulation in adolescents across weight status. *Eur. J. Pain.* 2016; 20(6):967–76.
51. Galmes-Panades AM, Konieczna J, Varela-Mato V, et al. Targeting body composition in an older population: do changes in movement behaviours matter? Longitudinal analyses in the PREDIMED-Plus trial. *BMC Med.* 2021; 19(1):3.
52. Tour J, Lofgren M, Mannerkorpi K, et al. Gene-to-gene interactions regulate endogenous pain modulation in fibromyalgia patients and healthy controls-antagonistic effects between opioid and serotonin-related genes. *Pain.* 2017; 158(7):1194–203.
53. Morley JE, Flood JF, Silver AJ. Opioid peptides and aging. *Ann. N. Y. Acad. Sci.* 1990; 579:123–32.
54. Hoffmann P, Terenius L, Thoren P. Cerebrospinal fluid immunoreactive beta-endorphin concentration is increased by voluntary exercise in the spontaneously hypertensive rat. *Regul. Pept.* 1990; 28(2):233–9.
55. Crombie KM, Brellenthin AG, Hillard CJ, Koltyn KF. Endocannabinoid and opioid system interactions in exercise-induced hypoalgesia. *Pain Med.* 2018; 19(1):118–23.
56. Koltyn KF, Brellenthin AG, Cook DB, Sehgal N, Hillard C. Mechanisms of exercise-induced hypoalgesia. *J. Pain.* 2014; 15(12):1294–304.
57. Piyanova A, Lomazzo E, Bindila L, et al. Age-related changes in the endocannabinoid system in the mouse hippocampus. *Mech. Ageing Dev.* 2015; 150:55–64.
58. Fernandez-Aranda F, Sauchelli S, Pastor A, et al. Moderate-vigorous physical activity across body mass index in females: moderating effect of endocannabinoids and temperament. *PloS One.* 2014; 9(8):e104534.
59. Gasperi V, Ceci R, Tantimonaco M, et al. The fatty acid amide hydrolase in lymphocytes from sedentary and active subjects. *Med. Sci. Sports Exerc.* 2014; 46(1):24–32.
60. 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):329–37.
61. Meltzer CC, Smith G, DeKosky ST, et al. Serotonin in aging, late-life depression, and Alzheimer's disease: the emerging role of functional imaging. *Neuropsychopharmacology.* 1998; 18(6):407–30.
62. Bobinski F, Ferreira TAA, Cordova MM, et al. Role of brainstem serotonin in analgesia produced by low-intensity exercise on neuropathic pain after sciatic nerve injury in mice. *Pain.* 2015; 156(12):2595–606.
63. Zlatar ZZ, Hays CC, Mestre Z, et al. Dose-dependent association of accelerometer-measured physical activity and sedentary time with brain perfusion in aging. *Exp. Gerontol.* 2019; 125:110679.
64. Engeroff T, Fuzeki E, Vogt L, et al. Is objectively assessed sedentary behavior, physical activity and cardiorespiratory fitness linked to brain plasticity outcomes in old age? *Neuroscience.* 2018; 388:384–92.
65. Arnardottir NY, Koster A, Domelen DRV, et al. Association of change in brain structure to objectively measured physical activity and sedentary behavior in older adults: Age, Gene/Environment Susceptibility-Reykjavik Study. *Behav Brain Res.* 2016; 296:118–24.
66. Youssef AM, Macefield VG, Henderson LA. Cortical influences on brainstem circuitry responsible for conditioned pain modulation in humans. *Hum. Brain Mapp.* 2016; 37(7):2630–44.
67. Evenson KR, Buchner DM, Morland KB. Objective measurement of physical activity and sedentary behavior among US adults aged 60 years or older. *Prev. Chronic Dis.* 2012; 9:E26.