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PHYSICAL ACTIVITY AND ENDOGENOUS PAIN MODULATION IN OLDER PEOPLE: A SCOPING REVIEW

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List of abbreviations

CPM = Conditioned Pain Modulation

CS = Conditioning Stimulus

CPT = Cold Pressure Test

D = Duration

EIH = Exercise-Induced Hypoalgesia

EPM = Endogenous Pain Modulation

GLA:D® = Good Life with osteoArthritis in Denmark

M. Quad. Femoris = Musculus Quadriceps Femoris

MJL = Medial Joint Line

MVC = Maximal Voluntary Contraction

N/A = Not Applicable

NEMEX-EDU = Neuromuscular exercise and education

OA = OsteoArthritis

PA = Physical Activity

PPT = Pressure Pain Threshold

PTT = Pain Tolerance Threshold

RCT = Randomized Controlled Trial

ST+NEMEX-EDU = Neuromuscular exercise, education, and strength training

T = Timing

TKR = Total Knee Replacement

TIDieR = Template for Intervention Description and Replication

TS = Test Stimulus

VO2max = Maximal Oxygen consumption

Résumé

Objectif: Cette revue de la littérature visait à fournir un aperçu de l'influence de l'activité physique (AP) sur la modulation endogène de la douleur (MED), évaluée à l'aide de la Conditioned Pain Modulation (CPM), chez les personnes âgées souffrant de douleur.

Introduction: La douleur est un problème fréquent chez les personnes âgées et l'AP est l'un des traitements les plus fréquemment utilisés pour la gestion de la douleur. Un mécanisme possible sous-tendant les effets positifs de l'AP sur la douleur pourrait être lié à son influence sur la CPM. L'étude a cartographié (i) les types d'AP utilisés pour étudier son effet sur la MED ; (ii) les protocoles d'intervention étudiant l'AP et la MED, mesurées à l'aide de CPM ; et (iii) les lacunes de connaissances.

Méthodes: Les critères d'inclusion ont pris en compte des études portant sur des personnes de 60 ans ou plus, utilisant CPM pour examiner l'effet sur la MED. Cette revue de la portée a été réalisée selon la méthodologie de la JBI. Plusieurs bases de données ont été consultées : MEDLINE (Ovid), CINAHL (EBSCOhost), Embase, Cochrane Library, Web of Science, JBI Evidence Synthesis, PsycINFO et PEDro. Les études incluses couvrent la période de l'année 2000 à 2023.

Résultats: La recherche dans les bases de données a produit 938 articles, auxquels ont été ajoutés 135 articles par des méthodes de recherche alternatives. Six articles ont été identifiés, et les résultats ont été présentés de manière narrative, en ajoutant des tableaux et des figures.

Conclusion: Les études ont montré que différentes formes d'AP peuvent avoir un effet hypoalgésique chez les personnes âgées, mais toutes n'ont pas montré un effet positif sur la MED. Il est nécessaire d'adapter le protocole de CPM en fonction de la personne âgée, et de créer des recommandations spécifiques pour l'AP, notamment en ce qui concerne la personnalisation des programmes d'exercices pour améliorer l'adhérence et les résultats souhaités.

Abstract

Objective: This scoping review aimed to provide a systematic overview of the existing literature on physical activity (PA) and endogenous pain modulation (EPM), assessed using conditioned pain modulation (CPM), with a specific focus on older people with pain.

Introduction: Pain is a common issue in older adults and PA is one of the most frequently used treatments for pain management and relief. A possible mechanism underlying the positive effects of PA on pain may be related to its influence on EPM. The study mapped (i) types of PA used to study its effect on EPM in older people; (ii) intervention protocols investigating PA and EPM, measured using CPM, in older people experiencing pain; and (iii) knowledge gaps requiring further research or interventions adapted to older people with pain.

Methods: The inclusion criteria considered studies of people aged 60 years or older, using CPM to examine the effect of PA on EPM. This review was conducted following the JBI methodology for scoping reviews. Multiple databases were searched; MEDLINE (Ovid), CINAHL (EBSCOhost), Embase, Cochrane Library, Web of Science, JBI Evidence Synthesis, PsycINFO, and PEDro. The studies were included from the year 2000 onwards.

Results: The database search yielded 938 articles, and 135 articles were added using alternative search methods. Six articles were identified, and the results have been presented narratively, by using tables and figures to support the text.

Conclusion: All six studies showed that different forms of PA can have a hypoalgesic effect in older adults, but not all showed a positive effect on EPM. There is a need to adapt and uniformize the CPM protocol in function of the older adult and future research should aim to create more specific recommendations for PA, especially regarding the personalization of exercise programs to enhance adherence to exercise programs and desired outcomes.

Introduction

Experiencing pain and suffering tends to heighten vulnerability, particularly in the context of older adults. Aging is also commonly linked to delayed healing and diminished recovery from acute injury or illness, potentially elevating the risk of developing persistent pain issues (1). Collectively, they create a dual state of jeopardy for this demographic. Given that the number of older adults is increasing each year, predictions indicate that by 2050, 30% of the European population will be aged 65 years or older (3). This is concerning because the prevalence of chronic pain already exceeds 50% in community-dwelling older adults and 80% in nursing home residents (2). This impacts the individual's health and quality of life, and impacts society due to the associated large costs (2-4). In older adults, such impact precipitates social isolation that can lead to increased symptoms such as depression and heightened cognitive impairment (2, 3). Additionally, addressing pain promptly, even before it becomes chronic, is crucial for maintaining overall well-being and preventing potential long-term consequences (5).

To prevent pain going to chronic pain, pain management strategies can be either pharmacological or non-pharmacological, or it can involve multimodal, interdisciplinary treatment (6). Due to the potential side effects of polypharmacy and addiction, non-pharmacological treatments are preferable (7). Physical activity (PA) has been considered of great importance in improving pain and physical function (8). In a study conducted by Geneen and colleagues (2017) (9), exercise was associated with a decrease in pain severity among individuals with chronic pain. However, the evidence supporting this connection was somewhat constrained. The limitations of this evidence may be attributed to a large variety of interventions studied, encompassing mobility, strength, endurance, and more. Additionally, the heterogeneity across studies in terms of samples, methodologies, and analyses contributes to the overall weakness of the evidence. The 2020 WHO Guidelines on Physical Activity (10) state that for older adults, it is recommended that as part of their weekly PA, older adults should do varied multicomponent physical activities at moderate or greater intensity on 3 or more days a week to enhance functional capacity and prevent falls. To safely perform and augment the benefits of PA, Bull and colleagues (2020) (10) stated that it is important to adapt PA to an individual's current activity level, health status, and physical functioning level. Unfortunately, the mode of exercise, in terms of type, frequency, duration, and intensity to manage and reduce pain has not been clearly addressed for this population. Although PA seems to have an important role in terms of pain reduction and general health, knowledge of the underlying mechanisms as well as adapted protocols for exercise prescription and PA are lacking.

A possibility of the positive impact of PA on pain may be attributed to its influence on endogenous pain modulation (EPM) (11, 12). EPM encompasses a range of mechanisms by which the central nervous system regulates the perception of pain (13). The concept was initially studied on rats, which demonstrated that introducing new pain in a distant area could inhibit ongoing pain (14). It revealed changes in the activity of convergent dorsal horn neurons through a spino-bulbo-spinal loop, illustrating the intricate interactions within the central nervous system that modulate pain signals, which (14). This showcased the concept of EPM by showing that the modulation of pain signals can occur through complex interactions within the central nervous system. This pain inhibitor–pain mechanism is a fundamental aspect of the human body's pain modulation system (15). Notably, it aligns closely with the descending pain inhibitory pathway, a nervous system network responsible for diminishing the intensity of pain signals as they travel from their source to the brain (16). Activation of the descending pain inhibitory pathway suggests an easing of pain signals, resulting in a natural relief effect (16). Both the descending and ascending pain inhibitory pathways are distinct mechanisms contributing to pain signal modulation, collectively forming components of the broader EPM concept (13, 17). A deeper understanding of the dynamics of the descending pain inhibitory pathway in humans and its connection to EPM can be gained through conditioned pain modulation (CPM), a psychosocial experimental measure (16).

CPM measures the net effect of the descending pain pathway by applying a secondary painful stimulus (conditioning stimulus or CS) after an initial painful stimulus (test stimulus or TS) (13). The pain intensity is measured after exposure to a painful TS, whereas in most cases, the pain intensity is reduced after exposure to CS. In this case, the application of CS has facilitated the descending inhibitory pathway. However, in people with chronic pain and older adults, CS may provoke an augmented pain intensity, meaning that the descending inhibitory pathway is inhibited (11, 16, 18). This showcases that EPM may be compromised in these populations, possibly explaining the high prevalence of chronic pain in older adults (12). Fortunately, it seems that engaging in regular vigorous is associated with improved CPM (11). Reasons for this positive effect may be that the balance of excitatory and inhibitory transmission in the ascending and descending pain pathways is adjusted, alterations in neurotransmitters of the central nervous system, increased endogenous opioids, and preservation of brain structures that are critical to the functioning of EPM (11, 19).

The reduction of pain that occurs during or following exercise is also called Exercise Induced Hypoalgesia (EIH). In a recent study of Zi Han et al. (2023) (20), moderate- and low-intensity running showed significant EIH effects and increased CPM responses in healthy females. Naugle and colleagues (2017) (11), observed that more regular activity was associated with a larger CPM than in more sedentary people. Similarly, isometric exercises have also shown positive effects on pain responses (21). However, Coombes et al. (2016) (22) observed that isometric exercise above, but not below, an individual's pain threshold increased pain responses to exercise in people with lateral epicondylalgia. This raises questions about the types of PA that should be used, their frequency, duration, and intensity to positively influence CPM in this demographic.

Scope of the review

Pain among older individuals is a widespread issue, and while PA holds promise as a treatment with minimal side effects, there remains a lack of clarity on its optimal adaptation for older adults dealing with pain. Despite its potential, the intricate relationship between PA and EPM, assessed through CPM, is not thoroughly understood in the context of older populations.

This scoping review aimed to delve into the existing evidence concerning the effectiveness of PA on EPM, particularly when assessed using CPM, with a nuanced focus on older individuals experiencing pain. By synthesizing current knowledge, we sought to identify gaps, challenges, and potential opportunities for tailoring PA interventions and CPM protocols to meet the unique needs of older adults facing pain.

Review questions

Specifically, the review questions were:

- What types of PA are used to study its effect on EPM in older people?

- What intervention protocols are used to investigate PA and EPM, measured using CPM, in older people experiencing pain?

- Are there knowledge gaps requiring further research or interventions adapted to older people with pain?

Methodology

The objectives, approach to searching, inclusion criteria and methods of analysis for this review were specified in advance and documented in a published protocol (23).

Inclusion criteria

Participants

This scoping review considered all individuals aged 60 years or older with both acute and chronic pain. The World Health Organization (WHO) indicates that common health conditions are associated with aging, as well as the emergence of several complex health states corresponding to the targeted population of this scoping review (24).

Concept

The overarching concept of interest in this scoping review was PA as an intervention because it may relieve pain and seems to have a positive influence on EPM (25). PA can be defined as 'people moving, acting, and performing within culturally specific spaces and contexts, and influenced by a unique array of interests, emotions, ideas, instructions, and relationships' (26). The review included PA interventions as planned, structured, and repetitive bodily movements with the objective of improving or maintaining physical fitness (27). Therefore, the review included studies that used 1) PA and 2) CPM to assess the (in)efficacy of EPM in older people with pain. All types of PA were analyzed in terms of frequency, duration, intensity, and/or mode of PA that was completed.

Context

Studies in all types of care settings were eligible (acute care, inpatient rehabilitation, outpatient rehabilitation, and chronic care) in any country.

Although the term CPM was not introduced before 2010, studies were included from the year 2000 onward (28). Before 2010, other terms, such as DNIC, counterirritation, and heterotopic noxious counter stimulation, were used. To ensure relevance regarding current practice, studies were limited to the years 2000 and onwards.

Type of sources

This scoping review considered quantitative and mixed methods study designs for inclusion.

Methods

The proposed scoping review was conducted in accordance with the JBI methodology for scoping reviews (29) and in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) (30).

Search strategy

The search strategy aimed to locate both published and unpublished studies. A three-step search strategy was utilized in this review. An initial limited search of MEDLINE (Ovid) and CINAHL (EBSCO) was undertaken followed by an analysis of the text words contained in the title and abstract, and of the index terms used to describe article. A second search using all identified keywords and index terms (Appendix I) was undertaken across all included databases. Third, the reference list of all identified reports and articles was searched for additional studies. For the scoping review itself, the following databases were included; MEDLINE (Ovid), CINAHL (EBSCO), Embase (Elsevier), Cochrane Library (Wiley), Web of Science (Clarivate), Joanna Briggs Institute EBP Database (Ovid), APA PsycINFO and PEDro (perdo.org.au). The main search was reviewed by an experienced librarian and peer-reviewed by another librarian to ensure that the employed strategies identified all relevant studies available. The search of unpublished studies and conference proceedings were performed to reveal additional gray literature unpublished studies. These included OpenGrey, ProQuest Dissertations and Theses, DART Europe E-theses Portal, WHO International Clinical Trials Registry Platform, ClinicalTrials.gov, and BASE (Bielefeld Academic Search Engine).
The Initial keywords were: Elderly OR Old people OR Older people OR Old patient OR Older patient OR Pain AND Physical activity OR Exercise OR Physical therapy OR Training OR Movement AND Pain modulation OR Hypoalgesia OR Modulation of pain OR Conditioned Pain Modulation OR Hyperalgesia OR Nociception. The search strategy used for the other databases are provided in Appendix I.

Studies published in any language were included. Any potential sources other than English were initially translated through Google translate, and, if deemed to meet the inclusion criteria, the full text was professionally translated.

Study/source of evidence selection

Following the search, all identified citations were collated and uploaded to a citation management system (Endnote 20 [Clarivate Analytics, PA, USA]), and duplicates were removed. Titles and abstracts were screened by two independent reviewers (DV and NK) to assess the inclusion and exclusion criteria using the web-based citation management system Rayyan (Qatar Computing Research Institute, Doha, Qatar) (31). A pilot test with a random sample of 25 titles from relevant sources was conducted by two reviewers (DV and NK) and the team only started screening when a

75% (or greater) agreement was achieved (32). Potentially relevant papers were retrieved in full. The full text of the selected citations was assessed in detail against the inclusion criteria by two independent reviewers. Reasons for the exclusion of sources of evidence in the full text that did not meet the inclusion criteria were recorded and reported in the scoping review. Any disagreements between the reviewers at each stage of the selection process were resolved through discussion and decision involving third reviewer (EO). The results of the search and study inclusion process are reported in full, presented in the Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for scoping review (PRISMA-ScR) flow diagram (Fig 1) (32).

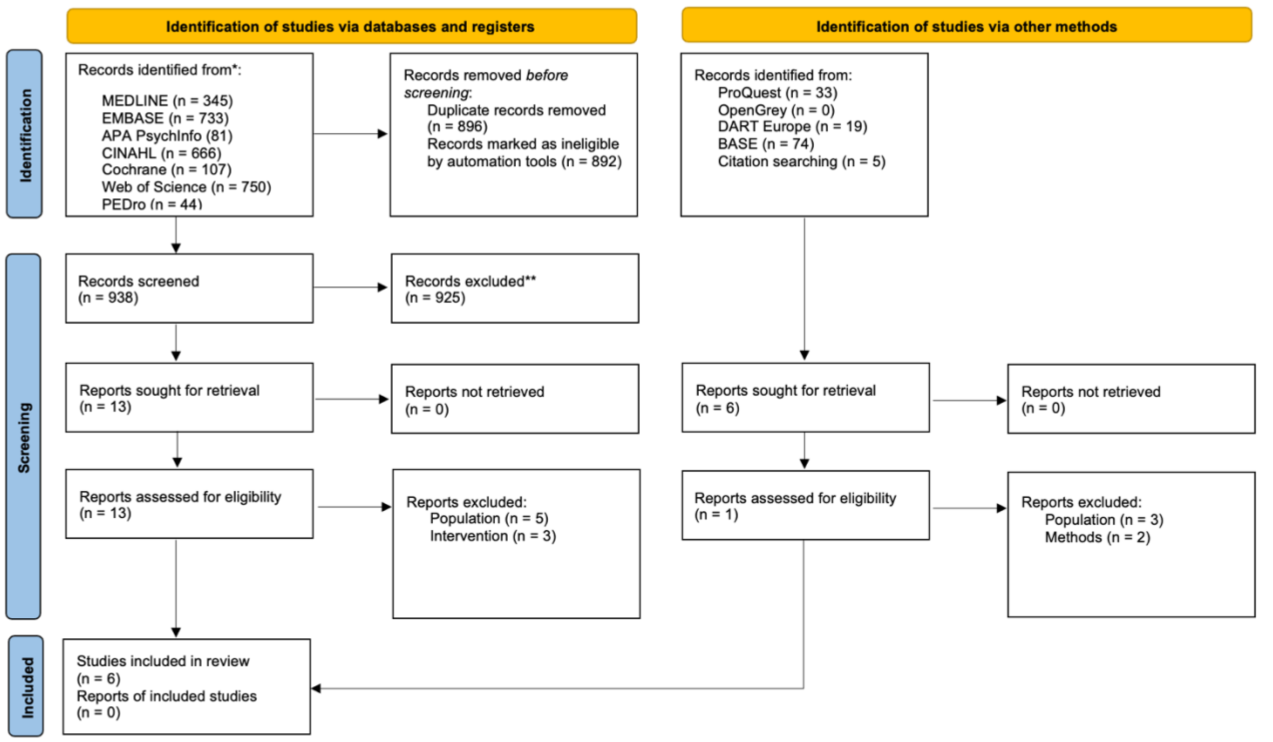
Data extraction

Data was extracted from papers included in the scoping review by two independent reviewers using a data extraction tool developed by the reviewers based on JBI template source of evidence details characteristics and results extraction instrument.

Key information of the selected studies was recorded in a charting table, as recommended by the JBI methodology for scoping reviews (Table 1) (33). The draft extraction tool was tested beforehand to determine its feasibility. The draft data extraction tool was slightly modified compared to the published protocol (23); specifications the CPM protocol were added (TS, Application sites, CS, timing between TS and CS, CPM effect and analysis of CPM) to enhance the understanding of the variations in CPM protocols (Appendix II).

Results

The search process initially identified a total of 2,726 studies. After the removal of duplicate records and the application of automated eligibility assessment tools, 938 studies remained for further consideration. Subsequently, titles and abstracts were reviewed, applying the predetermined inclusion criteria, leading to the identification of thirteen full-text articles for more detailed evaluation. Among these articles, only five ultimately met the inclusion criteria, mainly due to differences in the study population and intervention approaches leading to the exclusion of the others. To enhance the search efforts, alternative search methods were employed, resulting in an additional 135 results. Within this supplementary set of findings, one article was identified as aligning with our predefined selection criteria. Consequently, our data extraction process proceeded with a total of six articles deemed suitable for inclusion in our analysis (Fig.1 Flowchart of study selection and inclusion process).



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Figure 1: Flowchart of study selection and inclusion process.

The study characteristics of the six articles, including author, year of publication, type of evidence, total sample size, age (mean +SD), pain characteristics, exclusion criteria, and the aim of the study, were succinctly summarized in Table 1 for reference and comprehensive overview.

Study characteristics of the included studies

Author, year, type of evidence	Total sample size	Age (mean +SD)	Pain characteristics	Exclusion criteria	Aim of the study
Holm, 2021, Denmark, RCT	Group NEMEX-EDU: 42 Group ST+NEMEX-EDU: 35	Group NEMEX-EDU: 66,4(±9,3) Group ST+NEMEX-EDU: 63.2(±10.7)	Symptomatic and radiographic knee OA	- Ineligible for knee replacement surgery. - Less than "mild" symptoms (score >75 in 0–100) on KOOS-ADL questionnaire. - Morphine usage for pain other than knee joint pain. - Previous ipsilateral knee arthroplasty. - Rheumatoid arthritis. - Inability to comply with the protocol. - Inadequacy in written and spoken Danish.	To investigate the effects of strength training in addition to neuromuscular exercise and education on experimental measures of pain sensitization.
Fingleton, 2017, quasi-experimental	Group with knee pain: 40 Group pain-free controls: 20	Group knee OA abnormal CPM 64,05(±11,04) Group knee OA normal CPM: 63,29(±9,02) Controls: 62,00(±7,90)	-Diagnosis of knee OA according to American College of Rheumatology classification and pain >3/10 on a numerical rating scale. -Pain due to knee OA was the participants' main pain.	- Rheumatologic disease such as rheumatoid arthritis, fibromyalgia, or ankylosing spondylitis. - A neurologic disorder such as Parkinson's disease, shingles, multiple sclerosis, or stroke. - Cognitive impairment. - Current use of antidepressant or anticonvulsant medication. - Knee OA group participants were excluded if they had undergone a TKR and had <90 degrees knee flexion.	To investigate whether knee OA patients with abnormal CPM exhibit dysfunctional EIH, measured by changes in PPTs in response to aerobic and isometric exercise compared with those with normal CPM and pain-free controls.
Vaegter, 2017, pilot study	Total: 14	65,2 (±5,8)	The study included individuals with knee OA who were scheduled to undergo TKR surgery.	None of the included patients had neurological, psychiatric, cardiovascular diseases, or other chronic pain conditions.	To investigate whether the effect of CPT and different exercises on PPT and PTT assessed preoperatively in patients with knee OA were associated with pain relief 6 months after TKR. A secondary aim was to investigate the effect of TKR on clinical pain, pain sensitivity, CPM, and EIH responses.
O'Leary, 2018, cohort	Total: 134 Responders: 45 Non-responders: 89	Total: 64,2 (± 9,3) Responders: 65 (± 7.8) Non-responders: 63.6 (±10.1)	-Participants with moderate/severe symptomatic knee OA (referred for physiotherapy treatment by a hospital consultant or clinical specialist physiotherapist). -Knee pain intensity of at least 4/10 on a verbal rating scale. -Self-reported knee pain as the primary musculoskeletal complaint.	- Knee joint injection or recent physiotherapy treatment within the past 3 months. - Systemic inflammatory disease. - Cognitive impairment affecting cooperation with testing. - Self-reported knee symptoms rated as mild. - Leg pain referred from the lumbar spine. - Presence of possible or definite neuropathic pain. - Use of centrally acting medications such as antidepressants or anticonvulsants.	To prospectively investigate the association between features of pain sensitization and clinical outcome (non-response) after guideline-based physiotherapy in people with knee OA.
Lemley, 2015, quasi-experimental	Group young: 20 Group old: 19	10 older men: 71.4 (± 4.7) 9 older women: 72.7 (± 4.6)	N/A	- Acute or chronic pain. - Were using analgesics or psychotropic medications. - Scored less than 25 out of 30 on the Mini-Mental Status Examination. - Had risk factors that could interfere with the exercise session or ice water bath immersion. - Were unable to tolerate the ice water bath.	To determine whether there are age-related differences in CPM using a noxious pressure TS and whether there was a predictive relation between CPM and EIH using a painful exercise protocol.

Naugle, 2017, cross-sectional	Total: 51	31 women: 67.2 (± 5.0) 20 men: 67.7 (± 5.3)	N/A		- The use of narcotics or tobacco products, chronic pain conditions, cognitive impairment that would interfere with understanding of the study procedures. - Systemic diseases that restricted normal daily activities, uncontrolled hypertension, cardiovascular, metabolic, or pulmonary disease, neurological disease, serious psychiatric conditions (e.g. schizophrenia and bipolar disorder). - Chronic pain or any ongoing pain problem (headaches, injury-related pain, etc.).	The purpose of this study was 2-fold; to determine whether objective measures of physical activity in healthy older adults predicted (1) pain facilitatory function as tested by TS of pain, and (2) pain inhibitory function as tested by CPM.

Table 1: Presentation of the characteristics of the included studies.

RCT=Randomized Controlled Trial, OA=OsteoArthritis, N/A=Not Applicable, CPM=Conditioned Pain Modulation, NEMEX-EDU=Neuromuscular exercise and education, ST+NEMEX-EDU=Neuromuscular exercise, education and strength training, CPT=Cold Pressure Test, PPT=Pressure Pain Threshold, PTT=Pain Tolerance Threshold, EIH=Exercise-Induced Hypoalgesia, TKR=Total Knee Replacement, TS=Test Stimulus

Review question 1: What types of physical activity were used to study its effect on endogenous pain modulation in older people?

To assess the influence of PA on EPM in older adults, it is essential to provide a thorough description of the intervention. This study adheres to the Template for Intervention Description and Replication (TIDieR) framework outlined in BMJ (2014) (34) to provide a comprehensive account of the specific physical activities employed in the research (Table 2).

Some studies provided more detailed insights and a clearer view of the intervention itself. For instance, the study of Holm et al. (35) offered a comprehensive view of exploring the effectiveness of two intervention 12-week programs derived from the Good Life with osteoArthritis in Denmark (GLA:D®) program. More specifically, two intervention types were used, neuromuscular exercise and education alone (NEMEX-EDU) and strength training in addition to neuromuscular exercise and education (ST+NEMEX-EDU). The exercises focused on core stability, postural orientation, functional exercises, and leg muscle strength with a clear description of the session and its progression. The study of Holm et al. (35) and O'leary et al. (36) were the only ones that used an exercise program. However, the latter used physiotherapy as an intervention to measure the clinical outcome of pain sensitization after guideline-based physiotherapy in people with knee OA (OsteoArthritis), without giving a detailed description of the physiotherapy sessions.

On the contrary, the studies of Fingleton et al. (37), Vaegter et al. (38), and Lemley et al. (39), used acute bouts of PA to assess the EIH response after exercise. The studies of Fingleton et al. (37) and Vaegter et al. (38) used both an aerobic and isometric exercise protocol, whereas the study of Lemley et al. (39) only used an isometric exercise protocol. The aerobic exercise for both studies consisted of a bicycling exercise, however the protocol differed. In the study of Fingleton et al. (37) the aerobic exercise protocol consisted of the "Aerobic Power Index" test while sitting on a cycle ergometer. The participants started pedaling at a low workload and gradually increased the workload every minute until they reached a submaximal level defined as 75% of the age-predicted maximum heart rate. The test was based on the study of Wallman et al. 2003 (40). In the study of Vaegter et al. (38), the bicycling exercise included a warm-up and a main program based on age-related target heart rates corresponding to 50% and 75% of their estimated maximal oxygen consumption. Among the three studies that executed isometric exercises, a lot of differences were found. Their application sites, their submaximal values (10%, 30%, 25%), their duration (5 min, 90 sec, until task failure), their timing, the measurements taken for Maximal Voluntary Contraction (MVC) (two to three attempts), and possible modifications when the pain exceeded a certain pain score, differed for all three studies.

Lastly, in the study of Naugle et al. (11), no specific activities were imposed, but participants were equipped with an accelerometer to measure PA behavior and assess whether this predicted pain inhibitory function on CPM. A PA diary was also provided by the participants, helping them document daily start and end times, along with any periods they removed from the accelerometer, noting the duration and reason.

Overall, these studies investigated PA's impact on EPM in older individuals, employing diverse interventions, ranging from structured exercise programs targeting knee OA to short-term activities like cycling and isometric exercises to assess EIH.

A comprehensive interpretation of the specific physical activities

Author, year	Brief name, why	What	Who provided, how, where	When and how much	Tailoring	Modifications	How well
Holm, 2021	Non-surgical treatment for knee OA in Denmark. Exploration the effectiveness of two intervention programs derived from the GLA:D® program.	NEMEX-EDU and ST+NEMEX-EDU with the focus on the affected leg	Sessions led by certified physiotherapists. Group-based. At the exercise facilities in the Departments of Physiotherapy and Occupational Therapy at Næstved and Slagelse Hospitals.	Both groups had 10 specific exercises, 2-3 sets of 10-15 repetitions with three difficulty levels with rest corresponding to one set. ST+NEMEX-EDU: consisted of an additional component of strength training with specific activation of M. Quad. Femoris.	Both programs were done during a 12 week-period, twice a week, with 60 min/session.	N/A	78% in the ST+NEMEX-EDU group and 93% in the NEMEX-EDU group completed the 12-week follow-up. All the reasons were considered unrelated to treatment allocation.
Fingleton, 2017	Aerobic and isometric exercise protocol to assess and compare the EIH response between people with knee OA with normal and abnormal CPM response and pain-free controls.	The aerobic exercise protocol consisted of the "Aerobic Power Index" test while sitting on a cycle ergometer. The participants started pedaling at a low workload and gradually increased the workload every minute until they reached a submaximal level defined as 75% of the age-predicted maximum heart rate. For the isometric exercise, participants were then instructed to hold an isometric knee extension contraction until exhaustion, up to a maximum of 5 minutes, while a weight corresponding to 10% of their MVC was placed in an adjustable ankle weight cuff.	N/A	The protocol commenced pedaling at a rate of 25 Watts for one min. This workload was increased by 25 W for every subsequent min, with the test terminating at the end of the min during which target heart rate was reached. The test took between 4 and 10 minutes. For the isometric protocol, participants were instructed to hold an isometric knee extension contraction until exhaustion. The isometric protocol took place first, and 15 min afterwards the aerobic exercise.	If pain at the knee joint exceeded 3/10, during the isometric exercise protocol, the participant was instructed to decrease the angle of knee extension. If pain persisted, the weight of the ankle cuff resistance was decreased by up to 20%.	N/A	2 participants did not complete the exercise protocol due to pain >3/10.
Vaegter, 2017	Aerobic and isometric exercise protocol to assess and compare the EIH response before and after TKR.	The aerobic protocol consisted of a bicycling exercise with a main program based on age-related target heart rates corresponding to 50% and 75% of VO2max. For the isometric muscle contractions: participants performed a sustained 90-second isometric muscle contraction of the dominant M. Quad. Femoris at a submaximal intensity corresponding to 30% MVC.	N/A	The protocol was executed before and 6 months after TKR. The bicycling exercise took 15 minutes in total, resistance was increased until 75% VO2max intensity was reached, and participants continued at this resistance for 10 minutes. For the isometric protocol, participants were required to match the target force displayed on the monitor of the force transducer. Participants	For the bicycling exercise they used heart rate monitoring and estimated VO2max percentages based on age.	N/A	1 participant did not attend follow-up 6 months after TKR due to personal issues.

				were verbally encouraged to sustain the force throughout the 90-second duration.			
O'Leary, 2018	Physiotherapy as an intervention to measure the clinical outcome of pain sensitization after guideline-based physiotherapy in people with knee OA.	The intervention was individualized and prescribed at the discretion of the treating physiotherapist, and not strictly standardized. Based on clinical practice guidelines, the physiotherapists received updates on recommended non-pharmacological treatments for knee OA through workshops led by the principal investigator.	Treatment delivered by physiotherapists, N/A	4 to 6 individual treatment sessions with a combination of group and individual sessions. No other information was given.	N/A	N/A	57 participants were lost to follow-up
Lemley, 2015	Isometric exercise protocol to evaluate whether CPM could predict pain relief after exercise.	Participants underwent an isometric contraction of the left elbow flexor muscles. The contraction was submaximal, with participants exerting 25% of their MVC. During the contraction, participants were required to match the target force displayed on a monitor until task failure.	N/A	3 sessions, separated by one week.	N/A	N/A	N/A
Naugle, 2017	Participants were equipped with an accelerometer to measure physical activity behavior and whether this predicted pain inhibitory function on the CPM.	The accelerometers captured step counts, body positions, and activity counts, with measurements recorded at 1-minute intervals. Moments of nonwear time were identified as periods of consecutive zero counts lasting 60 minutes. To be considered valid, a day's data required the accelerometer to be worn for over 10 hours. A physical activity diary was also provided to participants, helping them document daily start and end times, along with any periods they removed the accelerometer, noting the duration and reason.	N/A	The participants wore the accelerometer and held a physical activity diary for one week.	N/A	N/A	N/A

Table 2: Evaluation of the structure used to describe the interventions using the Template for Intervention Description and Replication (TIDieR). RCT=Randomized Controlled Trial, OA=OsteoArthritis, TKR=Total Knee Replacement, N/A=Not Applicable, CPM=Conditioned Pain Modulation, NEMEX-EDU=Neuromuscular exercise and education, ST+NEMEX-EDU=Neuromuscular exercise, education, and strength training, M. Quad. Femoris=Musculus Quadriceps Femoris, EIH=Exercise-Induced Hypoalgesia, GLA:D®=Good Life with osteoArthritis in Denmark, MVC=Maximal Voluntary Contraction, VO2max=Maximal oxygen consumption

Review question 2: What intervention protocols were used to investigate physical activity and endogenous pain modulation measured with CPM in older people suffering from pain?

This section delves into the heterogeneity of research methodologies employed in investigating PA and its impact on EPM, specifically measured through CPM. As outlined in Table 3, a detailed breakdown of TS, CS, their temporal alignment, and the methodology for calculating the CPM effect is provided.

The evaluation of TS and CS, their application sites, as well as their temporal sequence, exhibited considerable heterogeneity across the analyzed studies. Within the domain of TS, two predominant test stimuli emerged; Pressure Pain Threshold (PPT) and continuous heat tests being administered across diverse anatomical application sites (Fig. 2). Notably, multiple anatomical sites were utilized for TS, and three studies specifically targeted regions within the affected knee area. Conversely, for CS, a solitary study deviated from the inclusion of the Cold Pressure Test (CPT) as a CS, instead employing a cuff algometer on the contralateral lower leg (Fig. 2). Furthermore, in the case of CPT, the choice of body parts subjected to cold water immersion varied among the studies, with some immersing hands and others immersing feet.

Regarding the sequencing of TS and CS, a notable divergence in methodologies emerged, characterized by a significant variance across the studies. This disparity encompassed an even distribution between the utilization of sequential and parallel sequences, with one study adopting a hybrid approach that incorporated both parallel and sequential elements. Furthermore, it is noteworthy that a substantial majority of the studies, five out of six to be precise, employed the Numeric Rating Scale as the standardized metric for pain assessment. However, the timing of inquiry and pain intensity rating during CS administration exhibited, marked variation.

Presentation of the test- and conditioning stimuli, and their application site across the included studies

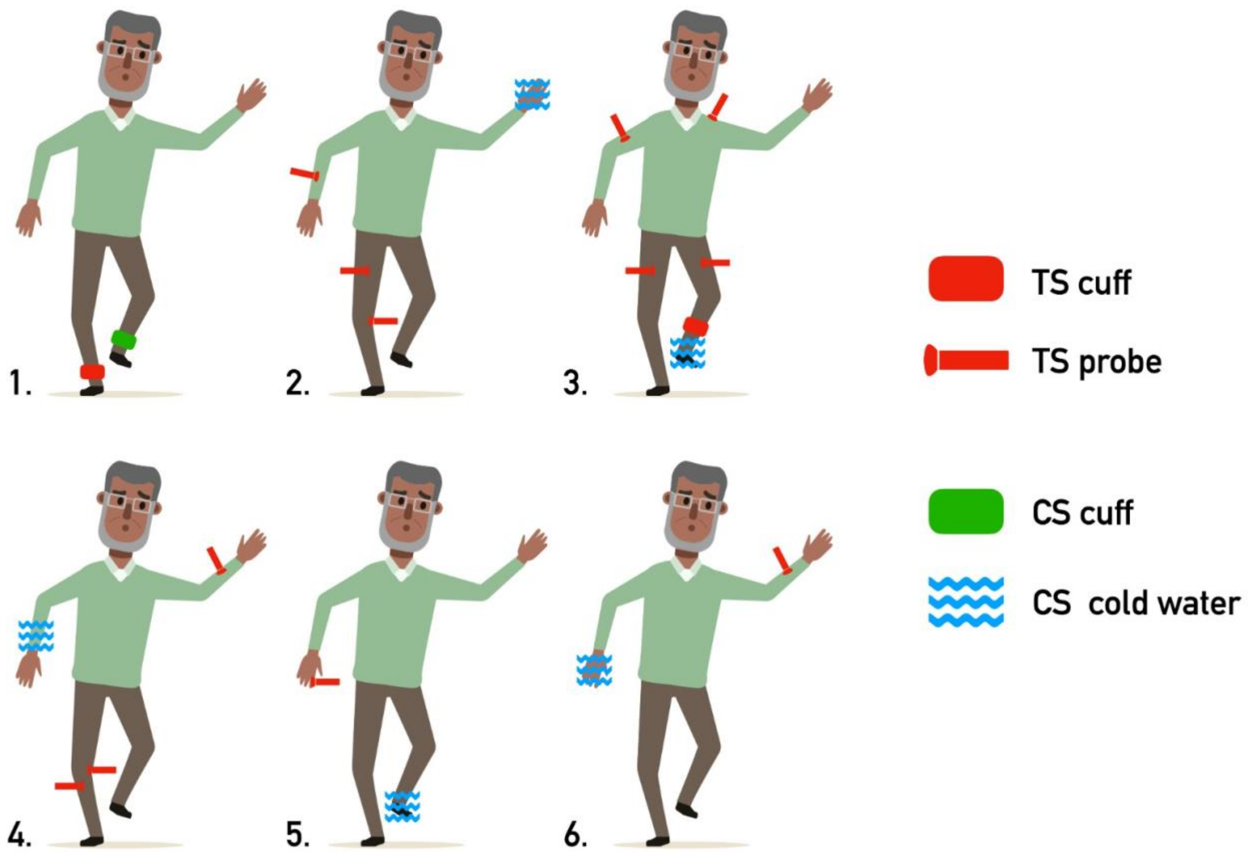


Figure 2: Experimental procedure and application sites for CPM used in each study.

Right site: Index or non-affected site / Left site: Non-index or affected site. 1. Holm et al. (2021), 2. Fingleton et al. (2017), 3. Vaegter et al. (2017), 4. O'Leary et al. (2018), 5. Lemley et al. (2015), 6. Naugle et al. (2017). CPM= Conditioned Pain Modulation, TS=Test stimulus, CS=Conditioning stimulus.

Overview of the testing paradigms of Conditioned Pain Modulation

Author, Year	TS	CS	Sequence of TS and CS, timing	Pain scale	CPM effect
Holm, 2021	Application sites: Index lower leg Type: Computer-controlled cuff algometer Rate of pressure: 1kPa/s.	Computer-controlled cuff algometer on the opposite lower leg. A constant pressure stimulus was applied at 70% of the recorded PTT for that leg.	Parallel. Both cuffs were inflated. Participants were instructed to only focus on the TS on the index leg and to disregard the CS when rating pain for the knee OA leg.	VAS	= The difference in pressure (kPa) when subtracting the conditioned PPT by the previously recorded PPT without the CS on the knee OA leg.
Fingleton, 2017	Application sites: - MJL of the index knee: 3 cm medial to the midpoint on the medial edge of the patella. - M. Quad. Femoris: midway between the groin and the apex of the patella on the index knee. - Forearm: volar surface of the forearm, specifically 5 cm distal to the lateral epicondyle. Type: Handheld pressure algometer with 2 cm² probe Rate of pressure: 30 kPa/s	Immersion of the participant's contralateral hand in cold water. T: 4°C (41°F). D: a maximum of 60 seconds. Attention: If the pain became intolerable during the test, participants were allowed to remove their hand before the completion of the trial.	Sequential. After the hand was withdrawn from the cold water, the PPTs at the specific sites were immediately reassessed.	NRS: Participants used the NRS to continuously rate the pain intensity while their contralateral hand was immersed in the water bath.	= The difference between the pre-CPT and post-CPT measurements of the PPT scores (average of PPTs measured at different sites) were examined to determine the participants' CPM response.
Vaegter, 2017	Application sites: - Affected lower leg: cuff PPT sites: - M. Quad. Femoris of the affected leg: in the middle and 20 cm proximal to the base of patella. – M. Quad. Femoris of the non-affected leg. - M. Biceps Brachii: in the middle of the dominant 10 cm proximal to the cubital fossa. - M. Trapezius: nondominant site, 10cm from the acromion in direct line with the neck. Type: Computer-controlled cuff algometer Handheld pressure algometer with 1 cm² probe. Rate of pressure: Cuff: N/A, PPT: 30 kPa/s	Immersion of the foot of the non-affected site (5cm above the ankle joint for 2 minutes) in a container filled with circulating ice water. T: 1 to 2° C. D: 2 min.	Parallel and sequential. PPT was assessed before, during, immediately after and 15 min after CPT.	NRS: Just before removing the foot from the ice water the participant was instructed to rate the pain intensity caused by the cold water.	= Calculated as percentage change (i.e. 100 x after/before) in manual and cuff algometry parameters during or immediately after CPT and exercises with manual algometry averaged between the 4 assessment sites.
O'Leary, 2018	Application sites: - The knee joint line: 3 cm medial or lateral to edge of the patella depending on the site of greatest pain. - 5 cm distal to the ipsilateral tibial tuberosity. - The volar aspect of the contralateral forearm, distal to the lateral epicondyle. Type: Electronic digital algometer with 2 cm² probe size of 1 with Rate of pressure: 30 kPa/s	Immersion of the arm contralateral up to the elbow to the one used for PPT testing. T: 4°C. D: 60 seconds.	Sequential. PPT values were measured immediately before and after immersion.	NRS, timing N/A.	= Calculated by subtracting the mean PPT value before cold immersion from the mean PPT value after cold immersion, following consensus recommendations on CPM testing.
Lemley, 2015	Application sites: The dorsum of the right index finger + immersion of the foot in a neutral water bath. Type: Custom-made pressure pain device. Rate of pressure: weighted Lucite edge (8 x 1.5 mm) equivalent to a 1.5-kg mass	Immersion of the foot contralateral to the site used for PPT in a cold water bath. T: 2°C ± 1°C D: 80 sec.	Parallel. 30 min between TS and CS. 20 sec in the water bath, subsequently, PPT with the foot still in the water.	NRS: after 20 sec of foot immersion participants rated the pain.	= Calculated by subtracting the average pain rating of the second pressure pain test from the average pain rating of the first pressure pain test (i.e., preexercise average - postexercise average or neutral water average - ice water average, respectively).

Naugle, 2017	Application sites: Left ventral forearm: for PPT and continuous heat. Type: Clinical grade pressure algometer with 1 cm² probe Rate of pressure: 30 kPa/s	Immersion of the right hand up to the wrist in a cold-water bath. T: 10°C. D: 3x 45-sec with 15-second rest periods in between.	Sequential. 7 min between pre-pain assessments and the initiation of CS. The PPT and continuous heat pain test stimuli were administered consecutively before and after the conditioning stimulus. The intertrial interval for the heat pain test was 1 minute.	NRS: Cold pain intensity was rated by participants every 15 seconds.	= Calculation of a percent change score for each TS (CPM-PPT and CPM-Heat) with the following formula: ([postCPM trial score - preCPM trial score]/pre CPM trial score) x 100.

Table 3: Test paradigm of CPM.

RCT= Randomized Controlled Trial, T=timing, D=duration, MJL=medial joint line, M. Quad. Femoris= Musculus Quadriceps Femoris, PTT= Pain Tolerance Threshold, OA= OsteoArthritis, CPT=Cold Pressure Test, NRS=Numeric Rating Scale, PPT=Pressure Pain Threshold, CPM=Conditioned pain modulation, TS=Test stimulus, CS=Conditioning stimulus, VAS=Visual analogue scale, N/A=Not applicable

Lastly, the calculation of the CPM effect was not consistently derived. The considerable disparity in methodological approaches employed in this calculation reflected the multifaceted nature of CPM assessments within the selected studies.

The evaluation of intervention protocols for investigating PA's impact on EPM in older individuals suffering from pain revealed significant heterogeneity in methodologies. This included variations in the choice of TS, CS, their application sites, temporal alignment, and the calculation of the CPM effect, emphasizing the complexity and diversity of approaches in the analyzed studies.

Review question 3: Are there knowledge gaps requiring further research or design of interventions adapted to older people with pain?

The selected studies presented some limitations, offering insights into certain knowledge gaps requiring further research and interventions.

The study of Holm et al. (35) used a study sample tailored for the primary randomized controlled trial (41), prompting a cautious interpretation of these findings due to their exploratory nature. Secondly, uncertainties regarding the cuff algometer's reliability and potential measurement error in assessing PPT and Pain Tolerance Threshold (PTT) suggest possible learning effects, further complicating the interpretation. The absence of established benchmarks for minimal detectable change and minimal important difference in pain sensitization evaluated via cuff pressure algometry impedes the determination of clinical relevance concerning observed differences in PPT and PTT between the exercise modes. For future research, it was suggested that there is a necessity to clarify how experimental pain, correlates or interacts with clinical pain. Understanding this relationship is crucial to determine how various forms of exercise impact both types of pain. By investigating how different exercise modes influence these pain outcomes, researchers can unravel the connections between experimental pain responses and the real-life pain experiences of individuals undergoing these exercises. Moreover, there is a need for a better understanding of the long-term effects of exercise interventions, particularly prolonged exposure to high-intensity strength training (35).

The study of Fingleton et al. (37) subdivided people with knee OA in two groups, with normal CPM and abnormal CPM. However, the testing was carried out by an unblinded assessor and replication is required using independent, blinded assessment to corroborate their findings. As the intensity and duration of exercise was not the same for all participants, it is also possible that a dose-response effect could have influenced results. Also, the current PA levels of participants were not measured and might be another limitation. Future studies would benefit from controlling for participant activity levels, as emerging evidence suggests that it may impact on efficiency of pain modulation.

The pilot study of Vaegter et al. (38) has limitations due to its small sample size, impacting its statistical reliability and increasing the possibility of false-positive findings. Therefore, caution is needed in interpreting the results, particularly regarding the comparison of pain responses before and after surgery. Larger studies are necessary to validate these findings. Additionally, the study's design might have influenced the results, as the order of assessments could have affected the outcomes, and the absence of a healthy control group limits comparisons with individuals without health issues. The way the study measured and set the intensity and duration of aerobic exercise might have affected the results, and the use of opioid painkillers before assessments might have influenced the pain responses observed. These factors need further exploration in studies involving a broader range of patients.

The treatment in the study of O'leary et al. (36) was personalized by physiotherapists however, few specifications were given. The substantial proportion of individuals who opted not to participate may have led to selection bias. Additionally, this study may have been underpowered for the regression analysis that was executed. The multitude of variables related to outcome events could have led to overfitting the model. Moreover, the absence of an untreated OA control group complicates understanding whether patient characteristics influenced treatment response or were inherent to disease progression independent of therapy. This highlights the need for further research to evaluate pain treatments tailored to specific subsets within the diverse knee OA population.

The study of Lemley et al. (39) had a limited sample size which hindered the identification of characteristics distinguishing older adults experiencing hypoalgesia from those with hyperalgesia during CPM testing. A key difference in protocols was the pressure pain device parameters; earlier studies used a 1.0-kg mass and 2-minute test duration, while the current study opted for a 1.5-kg mass for 1 minute to shorten the ice water bath duration. Future experiments using a lighter weight are recommended to prevent pain saturation, clarifying whether older adults exhibit attenuated EIH after painful isometric exercise. This understanding of the CPM and EIH relationship could inform clinical practices for exercise as a pain management tool, pinpointing individuals who would benefit the most.

The cross-sectional design of the study of Naugle et al. (11) leaves open the possibility that altered pain regulation influences reduced PA and increased sedentary behavior. Longitudinal research is essential to confirm the cause-and-effect relationship between activity levels and pain modulation, requiring intervention studies manipulating both exercise and sedentary behaviors to unravel their distinct and combined impact on pain modulation. Additionally, the study primarily involved healthy, active, and Caucasian older adults, possibly limiting the extension of findings to diverse ethnic backgrounds or those with chronic pain. The brief assessment of PA over a 7-day period might not fully represent participants' overall activity patterns. Lastly, considering the study's power analysis, a larger sample size might have made certain predictive models statistically significant, encouraging further exploration into tailoring PA interventions to counter dysfunctional pain modulation in older adults.

The reviewed studies highlight crucial limitations and knowledge gaps in understanding the effect of PA on EPM among older individuals. This emphasizes the need for larger, and more longitudinal studies, as well as adapted PA interventions and CPM protocols to properly measure its influence on EPM.

Discussion

This study exclusively focused on older adults, exploring the relationship between PA and EPM, evaluated through CPM. Only six articles met the inclusion criteria, underscoring the limited research on this subject and its promising stage of exploration.

All selected studies have demonstrated that PA can positively affect pain sensitivity or have a hypoalgesic effect, although not all the studies showed a positive effect on EPM. Various forms of PA have proven effective, ranging from acute bouts of aerobic (37, 38) and isometric exercises (37-39), to longer-term strength exercises (35, 36) and more active lifestyles (11). However, this positive effect can be limited or absent if participants exhibit preliminary disturbed CPM responses (11, 37-39). Moreover, a more active lifestyle has been demonstrated to positively influence CPM (11), as also observed in healthy adult populations (11, 42, 43). These findings highlight that PA can have positive effects on EPM. Additionally, CPM could be used to assess the anticipated positive effects of PA on EPM.

Various CPM protocols were utilized to measure EPM; most of them found a CPM effect (11, 37-39) while others did not (35, 36). Consistent with earlier research, there is a lack of uniformity across modalities, making it challenging to draw conclusions across studies. Some individuals are more sensitive to noxious heat, others to ischemia, and others to heat temporal summation (44). This has also been confirmed in the study of Law et al. (45) that included different population types. Their study revealed that the inconsistencies and variations in the relationships between PA and CPM, using different test modalities, were not surprising (45). Already in 2014, Yarnitsky et al. (46) pleaded for standardized CPM protocols. Despite these recommendations, CPT was the only commonly used variable for CPM, employed in five out of six studies. Consequently, the task of defining normative data for CPM effects and determining optimal protocols for demonstrating EPM in older adults remains elusive (28, 47, 48). To create optimal protocols for this population to effectively measure EPM, multiple variables of aging should be considered. Firstly, aging is often associated with decreased pain tolerance, which might influence an individual's ability to undergo CPM protocols, potentially affecting their effectiveness (53). Secondly, age-related changes in sensory perception, such as diminished proprioception or alterations in nerve function, could further influence pain signal processing and responses to CPM stimuli (54). Moreover, the aging process is associated with chronic low-grade systemic inflammation and heightened oxidative stress, recognized factors known to sensitize both the peripheral and central nervous systems, ultimately contributing to decreased pain tolerance (55). These factors show that the actual recommendations for CPM might not be adapted for older adults. This advocates for creating a CPM protocol tailored to this population to effectively measure the outcomes of PA on EPM.

The complexity of creating PA recommendations is outlined in the study of Lemley et. al (39), noting that while older adults generally exhibit lower responses of EPM to PA compared to younger counterparts, some individuals experience equally effective pain modulation outcomes. The association found between CPM and EIH in both young and older adults is of significant note, revealing that individuals with a greater capacity to activate descending inhibitory pathways experience more substantial EIH, independent of age (39). Conversely, Fingleton's study (37) adds an extra layer of complexity by identifying a subgroup of knee OA patients exhibiting worsened pain sensitivity following exercise. This revelation questions the suitability of exercise interventions for this specific subgroup and emphasizes the necessity of tailoring interventions to individuals' unique pain modulation profiles. Although causality is not established, these findings underscore the variability in pain responses following exercise and suggest that an aberrant descending inhibition system may contribute to the observed diminished pain relief or even pain exacerbation. However, the intricate interplay between age and these relationships calls for a deeper exploration of the nuances. Also, Wewege et al. 2021 (49), stated in their review that there is insufficient evidence to support any mode of exercise causing EIH to experimental pain in people with chronic musculoskeletal pain because of mostly small, very low-quality studies with an unclear risk of bias. This could suggest that a normal or disturbed CPM may be important when deciding the appropriateness of exercise interventions for older adults and may allow for a more individualized and graded approach to exercise in individuals with inefficient EPM. There is a need for research that determines the participants' pain modulation profile, using CPM, and adapt PA accordingly. A longitudinal study examining the long-term effects of various exercise modalities on EPM, using an adapted CPM protocol among older adults with diverse pain profiles would be a logical next step. One of the challenges that might arise from this study could be managing confounding factors, such as medication use, comorbidities, and lifestyle variations.

Our scoping review unveiled a diverse range of PA types, encompassing strength-based exercises and aerobic activities. This makes sense, as both types, strength-based and aerobic exercise are part of the current PA guidelines for older adults. These guidelines advocate moderate to vigorous aerobic exercises, muscle strengthening, and flexibility exercises (50, 51). The results of Naugle et al. (11), are in line with the recommendations of PA. They found that moderate to vigorous PA predicted pain inhibitory function as measured by CPM better than light PA and sedentary behavior. These forms of PA are as such recommended not only for cardiovascular health, but also to benefit pain reduction (52). However, compared to younger adults, older adults more often experience significant declines in function. The challenge arises in adapting the current PA guidelines to individual needs. The struggle older adults face in engaging in sufficient aerobic training due to declines in function and neuromuscular capacity highlights a critical barrier to conventional exercise recommendations (53). Notably, while both aerobic and strength training hold benefits, the evidence leans towards the effectiveness of strength-based resistance training for muscle strength and hypertrophy in older adults (53). Exercise for older adults, specifically resistance training, counteracts declines in muscle strength and mass, and is positively associated with cardiorespiratory capacity (54). Therefore, when prescribing exercise programs to older adults, it seems advised to first address neuromuscular capacity through strength-based exercises before engaging in aerobic exercise modalities (53). One crucial aspect of resistance training programs revolves around the interplay between intensity, the weight lifted during exercises, and the duration. Among the studies reviewed, a variety of intensities of MVC and duration were utilized. Two meta-analyses on this subject indicated that during a training program, progressively increasing loads to 70 and 80% of 1RM showed greater muscle strength gains than keeping light (i.e., <50% of 1RM) and moderate intensities (i.e., < 70% of 1RM) (55, 56). However, Sylva and colleagues (2014) (57) showed in their meta-analysis that strength training causes strength gains in elderly individuals, provided the training duration is sufficiently long, regardless of the combination of other training variables. In clinical practice, aerobic and strength training are both present, and although beneficial, aerobic training is not as effective as strength-based resistance training for increasing muscle strength and hypertrophy (58). This underscores the need for more extensive research focusing on the use of both aerobic and strength-based exercises to better understand their impact on EPM in older adults.

Strength training thus needs an individual approach where progression depends on individual responses. As shown in previous research, older adults exhibit greater inter-individual differences in training responses, with possible responders, non-responders and even adverse responders (59). This corresponds with our results, where in Fingleton's study (34), a subgroup of knee OA patients exhibited worsened pain sensitivity following exercise. Even though these differences exist, research and clinical experience indicate that resistance training is safe for older adults in general, from healthy, to pre-frail, to individuals with multiple chronic diseases (59, 60). Possible adverse responses might be due to the lack of individually adapted exercise programs, which is confirmed by the study of Pickering et al. (2019) (61). They suggested that it is unlikely that global non-responders to exercise exist and that there is a need to create more nuanced, efficacious, and individually-focused exercise to overcome non-responsiveness (61). While strength training and aerobic exercise are clearly advised for older people, there is still a scarcity of truly individualized programs and guidelines on how to individualize exercise programs to obtain better results. Research is needed to craft personalized exercise frameworks considering medical history, functional abilities, and preferences.

As shown in the TIDier template (Table 2), only in the study of Holm et al. (35) was the intervention modified during the course of the study, and only a few studies were adapted to the participants' needs. In the study of Holm et al. (35) three levels of difficulty in the neuromuscular program were offered to meet the needs of the participant at the beginning of the intervention. For the strength training exercises, if the participants had a set completion (volitional failure) outside this range, the load was adjusted accordingly. If the participant was unable to perform the requested number of repetitions, the load was immediately decreased for the following set. Also, the isometric protocol of Fingleton et al. (37) specified that if pain at the knee joint exceeded 3/10, the participant was instructed to decrease the angle of knee extension. In the protocol of Fingleton et al. (37) and Vaegter et al. (38) the bicycling exercise was adapted based on age estimated percentages. Indeed, O'Leary et al. (36) also mentioned that the treatment was individualized. However, no further specifications were given. Although these adaptations were made to individualize the intervention, it does not fully consider the heterogeneity of this population concerning health, physical function, work, leisure activities, psychological attributes, social environment, and ethnic background (11, 62). While some studies attempted to personalize interventions, the overall adherence to these tailored programs among participants was limited. This raises a crucial concern, the lack of intervention modification throughout the studies and the minimal adaptation to participants' needs could potentially limit the adherence and the effectiveness of PA on EPM. Further research should propose a larger spectrum of exercise and modalities, where participants, depending on their preferences, choose their activities and modalities, which should create more adherence and larger effectiveness.

The limited number of articles, small sample sizes, and the different methodologies warrant caution in generalizing our findings. Additionally, the study population of the included studies might be a limitation. The mean age varied between 63.2 (±10.7) and 71.4 (± 4.7), which covers only a small range of older adults and might not be representative of the older population in general.

To our knowledge, this is the first scoping review to summarize available evidence on the influence of PA on EPM in older adults using CPM. These findings provide substantial information to raise questions about whether the PA and protocols for CPM, that are currently used for older adults, are sufficiently adapted to show differences in EPM.

Conclusion and perspectives

The studies reviewed collectively reveal the positive impact of PA on pain sensitivity, though not always on EPM. They showcase diverse forms of exercise, from acute bouts of aerobic and isometric exercises to longer-term strength training and active lifestyles, all yielding favorable effects on pain sensitivity. However, these benefits might be constrained in individuals with disturbed CPM responses. Intriguingly, an active lifestyle appears to enhance CPM, echoing findings seen in healthy adult populations. Various CPM protocols were used to measure EPM, where most of them, but not all, found a CPM effect. There is a need to adapt and standardize the CPM protocol for older adults to facilitate result comparison and demonstrate the effectiveness of interventions. Additionally, future research should aim to create more specific recommendations for PA, especially concerning the personalization of exercise programs to enhance adherence to exercise programs and achieve desired outcomes. Comprehensive studies are needed to harmonize both the characterization of older adults based on their pain profiles and the subsequent design of tailored PA programs. Embracing this holistic methodology could pave the way for a paradigm shift in geriatric healthcare, providing tailored interventions that optimize not only physical function but also pain management for an enhanced quality of life. Overall, these findings collectively emphasize the potential of PA in improving EPM, highlighting the role of CPM as a predictive marker and evaluation tool.

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Annexes

I. Search strategies

MEDLINE (Ovid)
Search conducted on #14 #12, 2022#

Search	Query	Records retrieved
#1	("pain modulat*" or "endogenous analges*" or "modulation of pain" or "endogenous pain modulat*" or "pain mechanism*" or (pain adj3 modulation)).ti,ab.	6943
#2	exp Physical Therapy Modalities/ or exp Exercise/ or ("physical activit*" or exercis* or "physical therap*" or train* or movement).ti,ab. or (physical adj3 therap*).ti,ab. or (physical adj3 activit*).ti,ab.	1481659
#3	exp Aged/ or exp geriatrics/ or geriatric nursing/ or geriatric assessment/ or homes for the aged/ or health services for the aged/ or (elderly or "old people" or "older people" or "old" or "old patient*" or "older patient*" or "older adult*" or geriatric* or gerontolog* or "aged care" or "geriatric nursing").ti,ab. or exp Chronic Pain/ or exp back pain/ or (chronic adj3 pain).ti,ab.	4657359
#4	1 and 2 and 3	345
No limits		345

Embase (Elsevier)
Search conducted on #19 #12, 2022#

Search	Query	Records retrieved
#1	'geriatrics'/exp OR 'geriatric nursing'/exp OR 'geriatric assessment'/exp OR 'home for the aged'/exp OR 'chronic pain'/exp OR 'aged'/exp OR (Elderly OR "old people" OR "older people" OR "old" OR "old patient*" OR "older patient*" OR "chronic pain"):ab,ti,kw	5,310,941
#2	('physical activity'/exp OR 'exercise'/exp OR ("physical activit*" OR exercis* OR "physical therapy" OR train* OR movement):ab,ti,kw)	2139392
#3	('pain modulation'/exp OR ("pain modulat*" OR hypoalgesi* OR "hypo algesi*" OR hyperalgesi* OR “hyper algesi*” OR "modulation of pain"):ab,ti,kw)	28389
#4	#1 AND #2 AND #3	733
No filters		733

APA PsycInfo (Ovid)
Search conducted on #19 #12, 2022#

Search		Records retrieved
#1	exp Aged/ or exp geriatrics/ or geriatric nursing/ or geriatric assessment/ or homes for the aged/ or health services for the aged/ or (elderly or "old people" or "older people" or "old" or "old patient*" or "older patient*" or "older adult*" or geriatric* or gerontolog* or "aged care" or "geriatric nursing").ti,ab. or exp Chronic Pain/ or exp back pain/ or (chronic adj3 pain).ti,ab.	390984

#2	exp Physical Therapy Modalities/ or exp Exercise/ or ("physical activit*" or exercis* or "physical therap*" or train* or movement).ti,ab. or (physical adj3 therap*).ti,ab. or (physical adj3 activit*).ti,ab.	549328
#3	("pain modulat*" or "endogenous analges*" or "modulation of pain" or "endogenous pain modulat*" or "pain mechanism*" or (pain adj3 modulation)).ti,ab.	2471
#4	1 and 2 and 3	81
No filters		

CINAHL Complete (EBSCO)
Search conducted on #19 #12, 2022#

Search	Query	Records retrieved
#1	((MH "Aged+" OR MH "Chronic Pain" OR MH "geriatrics" OR MH "geriatric nursing" OR MH "geriatric assessment" OR MH "homes for the aged") OR TI(Elderly OR "old people" OR "older people" OR "older patient*" OR "chronic pain") OR AB(Elderly OR "old people" OR "older people" OR "older patient*" OR "chronic pain"))	4,725,666
#2	((MH "Physical Activity" OR MH "Exertion+" OR MH "Exercise+") OR TI("physical activit*" OR exercis* OR "physical therapy" OR train* OR movement*) OR AB("physical activit*" OR exercis* OR "physical therapy" OR train* OR movement*))	2,013,733
#3	((TI("pain modulat*" OR hypoalgesi* OR "hypo algesi*" OR "modulation of pain" OR hyperalgesi* OR nocicept*) OR AB("pain modulat*" OR hypoalgesi* OR "hypo algesi*" OR "modulation of pain" OR hyperalgesi* OR nocicept*))	13,923
#4	S1 AND S2 AND S3	666
No limits		666

Cochrane (Wiley)
Search conducted on #14 #12, 2022#

Search	Query	Records retrieved
#1	(elder* OR geriatric* OR (older NEXT people*) OR (Chronic NEAR/3 pain) OR (persistent NEAR/3 pain) OR aged OR (older NEXT patient*) OR senior* OR older NEXT adult* OR (older NEXT person*)):ti,ab,kw	617522
#2	("physical activity" OR exercis* OR train* OR mouvement):ti,ab,kw	230456
#3	("pain modulat*" OR hypoalgesi* OR hyperalgesi* OR "modulat* of pain"):ti,ab,kw	2247
#4	#1 AND #2 AND #3	107
No limits		107

Web of Science (Clarivate)
Search conducted on #19 #12, 2022#

Search	Query	Records retrieved
#1	elder* OR geriatric* OR "older people*" OR aged OR "older patient*" OR "older person*" OR senior* OR "older adult*" OR (chronic NEAR/3 pain) or (persistent NEAR/3 pain)	11,620,426
#2	"physical activity" OR exercis* OR train* OR mouvement	33921664

#3	"PAIN MODULAT*" OR HYPOALGESI* OR HYPERALGESI* OR "MODULAT* OF PAIN"	39390
#4	#3 AND #2 AND #1	750
NO LIMITS		750

PEDRO
SEARCH CONDUCTED ON #15 #12, 2022#

ABSTRACT & TITLE	PAIN MODULATION
THERAPY	
PROBLEM	
BODY PART	
SUBDISCIPLINE	/
TOPIC	CHRONIC PAIN
METHOD	
AUTHOR/ASSOCIATION	
TITLE ONLY	
SOURCE	
PUBLISHED SINCE	
NEW RECORDS ADDED SINCE	
SCORE OF AT LEAST	
RETURN	46
WHEN SEARCHING	MATCH ALL SEARCH TERMS (AND)
RECORDS RETRIEVED	44

JBI SYNTHESIS
CONDITIONED PAIN MODULATION: NO PROTOCOLS OR REVIEWS HAVE BEEN DONE ON THE MATTER.

SEARCH FOR GREY LITERATURE

PROQUEST
SEARCH CONDUCTED ON #2 #2, 2023#

SEARCH	QUERY	RECORDS RETRIEVED
#1	NOFT(ELDER* OR GERIATRIC* OR "OLDER PEOPLE*" OR AGED OR "OLDER PATIENT*" OR "OLDER PERSON*" OR SENIOR* OR "OLDER ADULT*" OR (CHRONIC NEAR/3 PAIN OR PERSISTENT NEAR/3 PAIN))	134510
#2	NOFT("PHYSICAL ACTIVITY" OR EXERCIS* OR TRAIN* OR MOVEMENT)	4880518
#3	NOFT("PAIN MODULAT*" OR HYPOALGESI* OR HYPERALGESI* OR "MODULAT* OF PAIN")	32421
#4	1 AND 2 AND 3	1241
LIMITS FOR #1,#2, #3, #4: DISSERTATION, THESIS		33

FINGELTON AND LEMLEY MASTER DISSERTATIONS: EXCLUSION, ALREADY INCLUDED

OPENGREY
SEARCH CONDUCTED ON #2 #2, 2023#

SEARCH	QUERY	RECORDS RETRIEVED

#1	ELDER* OR GERIATRIC* OR "OLDER PEOPLE*" OR AGED OR "OLDER PATIENT*" OR "OLDER PERSON*" OR SENIOR* OR "OLDER ADULT*" OR "CHRONIC PAIN"	2709
#2	"PHYSICAL ACTIVITY" OR EXERCIS* OR TRAIN* OR MOVEMENT	2856
#3	"PAIN MODULAT*" OR HYPOALGESI* OR HYPERALGESI* OR "MODULAT* OF PAIN"	7
#4	#3 AND #2 AND #1	0
NO LIMITS		

DART EUROPE E-THESES PORTAL
SEARCH CONDUCTED ON #2 #2, 2023#

SEARCH	QUERY	RECORDS RETRIEVED
#1	ELDER* OR GERIATRIC* OR "OLDER PEOPLE*" OR AGED OR "OLDER PATIENT*" OR "OLDER PERSON*" OR SENIOR* OR "OLDER ADULT*" OR "CHRONIC PAIN"	28
#2	"PHYSICAL ACTIVITY" OR EXERCIS* OR TRAIN* OR MOVEMENT	61536
#3	"PAIN MODULAT*" OR HYPOALGESI* OR HYPERALGESI* OR "MODULAT* OF PAIN"	254
#4	#3 AND #2 AND #1	19
NO LIMITS		

WHO INTERNATIONAL CLINICAL TRIALS REGISTRY PLATFORM
SEARCH CONDUCTED ON #2 #2, 2023#

SEARCH	QUERY	RECORDS RETRIEVED
#1	ELDER* OR GERIATRIC* OR "OLDER PEOPLE*" OR AGED OR "OLDER PATIENT*" OR "OLDER PERSON*" OR SENIOR* OR "OLDER ADULT*" OR "CHRONIC PAIN"	24123
#2	"PHYSICAL ACTIVITY" OR EXERCIS* OR TRAIN* OR MOVEMENT	25399
#3	"PAIN MODULAT*" OR HYPOALGESI* OR HYPERALGESI* OR "MODULAT* OF PAIN"	358
#4	#3 AND #2 AND #1	0
NO LIMITS		

CLINICALTRIALS.GOV
SEARCH CONDUCTED ON #2 #2, 2023#

SEARCH	QUERY	RECORDS RETRIEVED
#1	"PAIN MODULAION*" OR "MODULATION OF PAIN"	2
LIMITS FOR #1: COMPLETED, AVAILABLE, OLDER ADULT (65+), WITH RESULTS		

NO RELEVANT STUDIES

BASE

SEARCH CONDUCTED ON #2 #2, 2023#

SEARCH	QUERY	RECORDS RETRIEVED
#1	ELDER* OR GERIATRIC* OR "OLDER PEOPLE*" OR AGED OR "OLDER PATIENT*" OR "OLDER PERSON*" OR SENIOR* OR "OLDER ADULT*" OR "CHRONIC PAIN"	2 902 182
#2	"PHYSICAL ACTIVITY" OR EXERCIS* OR TRAIN* OR MOVEMENT	7 019 390
#3	"PAIN MODULAT*" OR HYPOALGESI* OR HYPERALGESI* OR "MODULAT* OF PAIN"	23 251
#4	#3 AND #2 AND #1	74
LIMITS FOR #1,#2, #3, #4: SUBJECT		

CITATION SEARCHING (BACKWARD AND FORWARD)

NO NEW ARTICLES FOUND.

II. Data extraction form

1. General information

Author/s	Title of source (full title)	Country	Type of evidence source	Aim of the article	Population (age, gender)	Total sample size

2. Inclusion and exclusion criteria / types of PA

Inclusion criteria	Exclusion criteria	Type of PA	Duration and intensities of PA

3. Details about the CPM protocol

CPM protocol					CPM effect	Analysis of CPM data
Test stimulus	Application sites	Conditioning stimulus	Timing between TS and CS	Parrallel/sequential protocol		

4. Key findings and knowledge gaps

Key findings related to PA and CPM	Limitations of the study	Knowledge gaps related to intervention and CPM protocol	Overall	Aim of CPM in the study