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The Relation of Peripheral and Central Sensitization to Muscle Co-contraction: The MOST Study

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Abstract

Objective: To examine the relation of pain sensitization to altered motor activity in knee OA as assessed by hamstrings muscle co-contraction during maximal effort knee extension.

Design: Medial, lateral, and overall hamstring co-contraction was assessed in the Multicenter Osteoarthritis (MOST) Study cohort using electromyography during isokinetic knee extension at 60°/second. Mechanical temporal summation of pain (TS) was assessed at the right wrist and pressure pain thresholds (PPT) were assessed at the patellae; PPTs were categorized into sex-specific tertiles. Muscle co-contraction was categorized into age- and sex-specific tertiles. We evaluated the relation of measures of sensitization to muscle co-contraction using a generalized logistic regression model.

Results: 1633 participants were included: mean age and BMI was 67.3 ± 7.7 years and 30.3 ± 5.6 kg/m^2, respectively; 58% were female. Presence of TS was associated with higher overall (OR 1.3, 95% CI (1.0–1.8)), medial (1.4 (1.0–1.9), and lateral (1.3 (1.0, 1.9)) hamstring co-contraction.

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AUTHOR CONTRIBUTIONS

All authors were fully involved in: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, and (3) final approval of the version to be submitted. Dr. Stefanik takes responsibility for the integrity of the work as a whole, from inception to the submitted article.

COMPETING INTERESTS

None

The lowest PPT tertile (greater sensitivity) was associated with higher overall (1.5 (1.0, 2.3)) and medial (1.5 (1.0, 2.3)) hamstring co-contraction compared with those in the highest PPT tertile.

Conclusion: Greater pain sensitization, as assessed by presence of TS at the wrist and low patellar PPT, was associated with greater overall and medial hamstring co-contraction during knee extension. This provides support to the possibility that peripheral and/or central nervous system alterations may not only affect pain sensitivity, but also motor function.

Keywords

Knee osteoarthritis; sensitization; muscle; co-contraction

INTRODUCTION

Knee osteoarthritis (OA) is a chronic condition affecting ~12% of older adults in the United States[1] and a leading cause of disability[2]. Knee pain is the most common clinical manifestation that leads individuals with OA to seek medical care and is recognized to be an important contributor to poor functioning in OA. While it is well-accepted that pain affects motor function in knee OA[3], the specific mechanism(s) by which this occurs is not fully understood. One well-recognized interaction between pain and motor response is the nociceptive withdrawal reflex. This spinal somatic reflex arc demonstrates one pathway in which sensory afferent input results in a stereotypical, rapid efferent motor output. Beyond such reflexes, several conflicting theories propose a range of motor responses to painful conditions ranging from reduced (motor inhibition), increased (spasm), or some combination of altered muscle force production[4–8]. While these theories argue for varying motor adaptations, they each agree that altered movement coordination in response to pain may play a protective role or provide shortterm relief, but with potential for long-term deleterious consequences (e.g., increased mechanical loading on other (initially) non-painful tissues, decreased function, disuse, etc.)[6, 9, 10].

Patients with painful knee OA are often noted to have altered gait in an attempt to off-load the affected joint. Further, a form of altered motor patterns that has been observed using a variety of methodologies in patients with knee OA is the co-contraction of antagonistic hamstring muscles during quadriceps agonist activity[11–14]. This co-contraction may represent another motor function alteration influenced by sensory input, but is not inconsistent with the Pain Adaptation Theory, which suggests pain will result in agonist muscle inhibition and antagonist muscle facilitation[6]. hile co-contraction may attempt to reduce joint instability, it may have adverse consequences as it can also increase compressive joint loading, which consequently may decrease cartilage volume[12].

In recent years, much attention has been given to increasing our understanding of the neurobiology of the pain experience across a range of conditions including knee OA. Animal studies demonstrate that inflammation and/or mechanical tissue injury, both of which are part of the knee OA disease process, can lead to alterations in nervous system processing of nociceptive input resulting in heightened central and peripheral pain sensitivity (i.e., sensitization)[15–18]. Additionally, greater sensitization is present among persons with painful knee OA compared with pain-free, healthy controls[19, 20], and is associated with pain severity

in those with knee OA[21]. However, whether measures of pain sensitization and altered motor responses are related is unknown.

There is evidence that motor responses are altered with increasing pain in this population[22]. However, to date there are no published studies investigating the relation of altered pain processing to motor responses in individuals with knee OA. As altered central pain processing and motor responses have both been demonstrated with knee OA, it is certainly possible that alterations in the nervous system affecting both ascending and descending afferent pathways, leading to heightened pain sensitivity, could also have adverse motor effects through influences on the efferent pathways. We therefore examined whether measures of pain sensitization, i.e., temporal summation of pain and pressure pain thresholds, are associated with altered motor activity in knee OA as assessed by muscle co-contraction during an isokinetic knee extension task.

METHODS

Study Participants

The Multicenter Osteoarthritis (MOST) Study is a NIH-funded longitudinal, prospective, observational study of 3,026 older adults, aged 50–79 years, who have or are at risk of knee OA. Subjects were recruited from two communities in the US: Birmingham, Alabama, and Iowa City, Iowa. Full details of study population have been previously published[23]. All participants provided informed consent and ethical approval was provided by the institutional review boards at participating sites and complied with the Helsinki Declaration. The current study uses data from the 60-month study visit where measures of pain sensitivity and electromyography (EMG) of the quadriceps and hamstrings during knee strength assessment were assessed for the first time. Specific details on the strength and EMG[24] and pain sensitivity[21, 25] measurement protocols have been published elsewhere and are briefly summarized below.

Assessment of Pain Sensitivity

We assessed two measures of pain sensitivity: 1) *Mechanical Temporal Summation*, an augmented pain response to repetitive mechanical noxious stimuli, is a measure thought to reflect central pain processing[19–21]. Temporal summation was assessed by first applying a 60g monofilament to the skin over the right wrist four times. Participants then reported their pain using a 0–10 numeric rating scale (NRS). Then the 60g monofilament was applied repeatedly at 1 Hertz for 30 seconds, after which the participants again reported their peak pain (NRS). Temporal summation was considered to be present if the participant reported an increased pain level at the end of the 30-second trial compared with the pain level after the initial stimulation[19–21]. 2) *Pressure Pain Threshold (PPT)* is a measure of mechanical pain sensitivity that may involve peripheral and central mechanisms. PPTs were assessed with a pressure algometer (Wagner, 1cm^2 tip) applied at a rate of 0.5 kg/second on the patella until participants indicated that the pressure sensation first changed to slight pain[26]. The average of 3 trials was used to calculate the PPT. Lower PPT values reflect greater pain sensitivity.

Surface EMG Procedures

Surface EMG (Bagnoli, Delsys, Boston, MA) of the medial and lateral quadriceps and hamstrings were assessed during maximal isokinetic knee strength testing (Cybex 350 Dynamometer, CSMi, Stoughton, MA). Four repetitions of alternating knee flexion and extension maximum voluntary contractions (MVCs) were performed at 60°/second, after a brief warm-up of three 50% effort repetitions on the right limb. However, in those with a right total knee replacement, then the left limb was tested. If participants reported pain during the testing, they were then asked if the pain limited their ability to maximally push or pull. If the pain limited this ability, their trials were removed from the current analysis (7% of participants tested).

Signals were collected at 1000 Hz and filtered using an anti-aliasing 20 – 450 Hz bandpass filter (Delsys). All data were collected and later post-processed using a 200 ms root mean square (RMS) window using custom LabView programs (NI, Austin, TX). The average EMG amplitude (volts) for medial and lateral hamstring calculated across the duration of each knee extensor contraction, adjusting for baseline noise $\left(\sqrt{active\ EMG^2 - baseline\ EMG^2}\right)$[27–29]. These amplitudes were then standardized to the corresponding peak amplitudes measured for each muscle, during the knee flexion MVCs. Thus, the co-contraction for medial and lateral hamstring was quantified separately using this relative activation (% max EMG) for each repetition during the extension MVCs (i.e. when the quadriceps were maximally active). This approach is consistent with previously reported methodology[28–31]. The median of the four strength repetitions were extracted for each muscle. In addition to evaluating medial and lateral hamstring muscles separately, a combined hamstring co-contraction estimate was computed as a measure of overall hamstring co-contraction behavior (using the root mean square, $\left(\sqrt{\left(LH^2 + MH^2\right)/2}\right)$)[30–32]. The inter- and intra- rater ICCs for the assessment of co-activation ratios ranged from 0.87–0.95.

Statistical Analysis

Based on the methods described above for the assessment of temporal summation, we dichotomized temporal summation into a binary variable (i.e., presence or absence). PPTs were categorized into sex-specific tertiles because of known gender differences[33]. Because muscle co-contraction was not normally distributed and there is no widely acceptable cut-point to define abnormal muscle co-contraction, we categorized medial, lateral, and overall co-contraction into age- and sex-specific tertiles. The relation of pain sensitivity (exposures) to medial, lateral, and overall hamstring co-contraction (outcomes) was assessed using a generalized ordered logistic regression model, comparing the highest two co-contraction tertiles to the lowest (referent group). Separate models were used with temporal summation and PPTs as the primary exposure of interest for each outcome. These analyses were done among all subjects, then repeated among those with radiographic knee OA (Kellgren-Lawrence grade ≥ 2) because relationships between pain sensitivity and motor responses may be more apparent in those with knee OA. All analyses were adjusted for age, sex, BMI (continuous), presence of depressive symptoms (Center for Epidemiologic Studies Depression Scale[34] ≥16), clinic site, presence (Kellgren-Lawrence grade ≥ 2) of radiographic OA (only in analyses including all subjects) as potential confounders. Pain

severity was not adjusted for in these analyses because we were interested in understanding if sensitization and muscle co-contraction co-exist or are associated regardless of potential mechanism, and also because pain may be in the causal pathway. Thus, adjusting for pain severity would result in bias by conditioning on an intermediate in the causal pathway. All analyses were performed using SAS Version 9.4 (Cary, North Carolina).

RESULTS

Of the 2330 participants who attended the 60-month study visit in person, 1633 participants had all necessary measures necessary for these analyses. The mean age and BMI of the participants included was 67.3 ± 7.7 years and 30.3 ± 5.6 kg/m^2, respectively; 58% were female and 37% with tibiofemoral OA (KL grade ≥ 2) (Table 1). Temporal summation was present in 40% of participants. The median (IQR) for PPT was 4.9 (3.6–6.6) kg/cm^2, and for overall hamstring co-contraction was 10.1% (5.7–15.1).

Individuals with temporal summation had 30% greater odds of being in the highest rather than the lowest tertile of exhibiting both overall and lateral hamstring co-contraction compared with individuals without temporal summation, and 40% greater odds for medial co-contraction. (Table 2). Similarly, individuals with low PPT (lowest tertile, greater pressure pain sensitivity) exhibited greater 50% greater odds of being in the highest rather than the lowest tertile of overall and medial hamstring co-contraction compared with those in the highest tertile PPT (Table 2). The association with lateral hamstring co-contraction was of similar magnitude, but did not reach statistical significance.

Similar results were noted when the cohort was limited to only those with radiographic knee OA (Table 3), but several associations were no longer statistically significant. Only temporal summation of pain demonstrated a statistically significant increased odds of being in the highest tertile of overall hamstring co-contraction. There was no higher likelihood of having greater co-contraction in those with lower compared with higher PPT among those with knee OA.

DISCUSSION

This is the first study to demonstrate that greater pain sensitivity, assessed with either mechanical temporal summation of pain or PPTs, was associated with greater overall and medial hamstring co-contraction during maximal knee extension in a cohort of individuals with, or at risk for, knee OA. This relationship was not limited to those with radiographic knee OA, but was present even in those without clear signs of OA. We were not able to examine possible mechanisms for this association, but since functional limitation is a common consequence of chronic pain, these results suggest that pain sensitivity and motor function may be both influenced by shared central mechanisms. This knowledge may be useful for the development of treatment strategies targeting both physical impairments and chronic pain.

Motor responses to nociception may be reduced, increased, or some combination of altered muscle force production[4–6]. These altered motor responses may initially occur to play a protective role, but may ultimately increase mechanical loading on other (initially) non-

painful tissues or decrease function[6, 9]. Despite early evidence for motor responses to be augmented with pain, and its use as an indirect measure of sensory amplification[35], we remain relatively naïve on the associations between pain sensitivity and motor function. Co-contraction of opposing muscles is one motor control strategy that is assessed in an effort to better understand this aspect of motor function.

Some muscle co-contraction around the knee joint during walking is normal in healthy adults and can provide joint stability and stiffness that is purposeful[36]. However, elevated levels or greater durations of co-contraction during ambulation in those with knee OA may contribute to structural disease progression[11–13]. Elevated co-contraction is thought to be a protective response to increase the stability of a potentially unstable joint[13] or may be a protective response to pain with greater lateral co-contraction proposed to counter knee adduction moments[37]. However, these heightened co-contraction strategies may be detrimental to the joint by increasing loading leading to progression of disease and pain severity[11–13]. Additionally, increased muscle co-contraction may increase fatigue which may adversely affect global function and/or pain. Thus, while heightened co-contraction may initially serve a protective role, it may ultimately be mal-adaptive.

Individuals with worsening knee OA are likely to develop more functional limitations over time[38]. The current study demonstrates that presence of temporal summation and lower PPTs (i.e., greater pain sensitivity) were related to increased overall and medial hamstring co-contraction; muscle co-contraction has in turn been demonstrated to be associated with worsening knee OA[12] and decreased function[39]. Accordingly, treatments targeting pain sensitization may directly or indirectly influence co-contraction in those with knee OA, thereby preventing loss of function. We have shown that measures of sensitization can be improved with weight loss, potentially by decreasing mechanical and inflammatory causes of sensitization[40]. Further, increased physical activity is associated, albeit inconsistently, with reduced pain sensitivity measures in healthy adults[41–43]. Indeed, animal models support the many pathways in which physical activity has beneficial effects on reducing inflammatory processes, macrophage differentiation, and intramuscular protein transcription ultimately influencing mitochondrial and metabolic gene expression[44, 45]. As most individuals with knee OA are advised to exercise for weight management and/or as part of their rehabilitation; exercise may also effect change through improving sensitization, which in turn may influence motor control strategies. In fact, there is high-quality evidence in patients with knee OA supporting exercise to reduce pain and moderate-quality evidence for improved function, supporting this proposed relationship[46].

Other sensory systems are affected in patients with knee OA, consistent with our results suggesting more widespread influences throughout the central nervous system. Altered lower extremity proprioception and vibratory sensation are related to knee OA severity, knee pain, and knee joint loading[47–49]. Additionally, Rosland et al. reported a correlation between the distribution and magnitude of plantar forces, a measure of the biomechanical response to motor control strategies, and select pain sensitivity measures: PPTs about the knee, but not temporal summation or conditioned pain modulation[50]. These findings, along with the findings from our study, offer preliminary evidence that knee OA can produce alterations in

multiple sensory and motor system pathways that may be influenced by shared central modulatory inputs.

We recognize limitations to our study. Co-contraction was assessed during a seated maximal strength evaluation, as opposed to during a functional task, such as ambulation. Both approaches have been previously reported in multiple knee populations[13, 30, 31, 51, 52] each with their own merit and drawbacks. Also, we did not specifically characterize these measures in individuals with knee OA. About one-third of our participants had radiographic knee OA resulting in limited precision of our results, though similar magnitudes of effect were noted when limiting the analyses to those individuals. It remains unclear whether our findings are applicable to older adults generally and not necessarily unique to knee OA. We also recognize that the co-contraction assessed during an isokinetic knee extension task may be the result of an early learning effect. However, we are confident that the co-co-contraction we have assessed is not primarily due to a learning effect as isokinetic knee extension tasks are commonly assessed OA populations. Participants also had practice trials to get accustomed to the procedure before data was collected. Lastly, we assessed two forms of pain sensitivity, PPTs at the knee and mechanical temporal summation at the wrist. Thus, our results may not reflect all forms of pain sensitivity.

In summary, our study supports the premise that peripheral and central nervous system alterations may not only affect pain sensitivity, but also motor function in the form of muscle co-contraction. While it remains unclear whether hamstring co-contraction serves an adaptive (e.g., facilitate joint stability) or mal-adaptive (e.g., increase destructive joint loading forces) role in knee OA, the associations observed between pain sensitivity and co-contraction provide additional insights into the complexity and inter-dependence of the sensory and motor systems. Future investigations may further illuminate whether effective pain treatments can similarly alter pain sensitivity and muscle co-contraction.

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REFERENCES

1. Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, Gabriel S, Hirsch R, Hochberg MC, Hunder GG, Jordan JM, Katz JN, Kremers HM, and Wolfe F. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States: Part II. Arthritis Rheum. 2008; 58(1):26–35. [PubMed: 18163497]
2. Guccione AA, Felson DT, Anderson JJ, Anthony JM, Zhang Y, Wilson PW, Kelly-Hayes M, Wolf PA Kreger BE, and Kannel WB. The effects of specific medical conditions on the functional limitations of elders in the Framingham Study. Am J Public Health. 1994; 84(3):351–8. [PubMed: 8129049]
3. Brandt KD. Neuromuscular aspects of osteoarthritis: a perspective. Novartis Found Symp. 2004; 260:49–58; discussion 58–63, 100–4, 277–9. [PubMed: 15283443]

4. Henriksen M, Rosager S, Aaboe J, Graven-Nielsen T, and Bliddal H. Experimental knee pain reduces muscle strength. J Pain. 2011; 12(4):460–7. [PubMed: 21146464]
5. Hodges PW, Tsao H, and Sims K. Gain of postural responses increases in response to real and anticipated pain. Exp Brain Res. 2015; 233(9):2745–52. [PubMed: 26105752]
6. Lund JP, Donga R, Widmer CG, and Stohler CS. The pain-adaptation model: a discussion of the relationship between chronic musculoskeletal pain and motor activity. Can J Physiol Pharmacol. 1991; 69(5):683–94. [PubMed: 1863921]
7. Merkle SL, Sluka KA, and LA Frey-Law. The interaction between pain and movement. J Hand Ther. 2018.
8. Chimenti RL, Frey-Law LA, and Sluka KA. A Mechanism-Based Approach to Physical Therapist Management of Pain. Phys Ther. 2018; 98(5):302–314. [PubMed: 29669091]
9. Hodges PW and Tucker K. Moving differently in pain: a new theory to explain the adaptation to pain. Pain. 2011; 152(3 Suppl):S90–8. [PubMed: 21087823]
10. Sluka KA and International Association for the Study of Pain, Mechanisms and management of pain for the physical therapist. Second edition ed. 2016, Philadelphia: Wolters Kluwer xii, 448 pages.
11. Childs JD, Sparto PJ, Fitzgerald GK, Bizzini M, and Irrgang JJ. Alterations in lower extremity movement and muscle activation patterns in individuals with knee osteoarthritis. Clin Biomech (Bristol, Avon). 2004; 19(1):44–9.
12. Hodges PW, van den Hoorn W, Wrigley TV, Hinman RS, Bowles KA, Cicuttini F, Wang Y, and Bennell K. Increased duration of co-contraction of medial knee muscles is associated with greater progression of knee osteoarthritis. Man Ther. 2016; 21:151–8. [PubMed: 26254263]
13. Lewek MD, Rudolph KS, and Snyder-Mackler L. Control of frontal plane knee laxity during gait in patients with medial compartment knee osteoarthritis. Osteoarthritis Cartilage. 2004; 12(9):745–51. [PubMed: 15325641]
14. Baker M, Stanish W, and Rutherford D. Walking challenges in moderate knee osteoarthritis: A biomechanical and neuromuscular response to medial walkway surface translations. Hum Mov Sci. 2019; 68:102542. [PubMed: 31710922]
15. Grigg P, Schaible HG, and RF Schmidt. Mechanical sensitivity of group III and IV afferents from posterior articular nerve in normal and inflamed cat knee. J Neurophysiol. 1986; 55(4):635–43. [PubMed: 3701397]
16. Schaible HG and Schmidt RF. Effects of an experimental arthritis on the sensory properties of fine articular afferent units. J Neurophysiol. 1985; 54(5):1109–22. [PubMed: 4078610]
17. Schaible HG and Schmidt RF. Time course of mechanosensitivity changes in articular afferents during a developing experimental arthritis. J Neurophysiol. 1988; 60(6):2180–95. [PubMed: 3236065]
18. Sharif Naeini R, Cahill CM, Ribeiro-da-Silva A, Menard HA, and Henry JL. Remodelling of spinal nociceptive mechanisms in an animal model of monoarthritis. Eur J Neurosci. 2005; 22(8):2005–15. [PubMed: 16262639]
19. Arendt-Nielsen L, Nie H, Laursen MB, Laursen BS, Madeleine P, Simonsen OH, and Graven-Nielsen T. Sensitization in patients with painful knee osteoarthritis. Pain. 2010; 149(3):573–81. [PubMed: 20418016]
20. Finan PH, Buenaver LF, Bounds SC, Hussain S, Park RJ, Haque UJ, Campbell CM, Haythornthwaite JA, Edwards RR, and Smith MT. Discordance between pain and radiographic severity in knee osteoarthritis: findings from quantitative sensory testing of central sensitization. Arthritis Rheum. 2013; 65(2):363–72. [PubMed: 22961435]
21. Neogi T, Frey-Law L, Scholz J, Niu J, Arendt-Nielsen L, Woolf C, Nevitt M, Bradley L, Felson DT, and S Multicenter Osteoarthritis. Sensitivity and sensitisation in relation to pain severity in knee osteoarthritis: trait or state? Ann Rheum Dis. 2015; 74(4):682–8. [PubMed: 24351516]
22. Astephen Wilson JL, Deluzio KJ, Dunbar MJ, Caldwell GE, and Hubley-Kozey CL. The association between knee joint biomechanics and neuromuscular control and moderate knee osteoarthritis radiographic and pain severity. Osteoarthritis Cartilage. 2011; 19(2):186–93. [PubMed: 21074628]

23. Felson DT, Niu J, Guermazi A, Roemer F, Aliabadi P, Clancy M, Torner J, Lewis CE, and Nevitt MC. Correlation of the development of knee pain with enlarging bone marrow lesions on magnetic resonance imaging. Arthritis Rheum. 2007; 56(9):2986–92. [PubMed: 17763427]
24. Segal NA, Nevitt MC, Welborn RD, Nguyen US, Niu J, Lewis CE, Felson DT, Frey-Law L, and MI Group. The association between antagonist hamstring coactivation and episodes of knee joint shifting and buckling. Osteoarthritis Cartilage. 2015; 23(7):1112–21. [PubMed: 25765501]
25. Neogi T, Guermazi A, Roemer F, Nevitt MC, Scholz J, Arendt-Nielsen L, Woolf C, Niu J, Bradley LA, Quinn E, and Law LF. Association of Joint Inflammation With Pain Sensitization in Knee Osteoarthritis: The Multicenter Osteoarthritis Study. Arthritis Rheumatol. 2016; 68(3):654–61. [PubMed: 26554395]
26. Wylde V, Palmer S, Learmonth ID, and Dieppe P. Test-retest reliability of Quantitative Sensory Testing in knee osteoarthritis and healthy participants. Osteoarthritis Cartilage. 2011; 19(6):655–8. [PubMed: 21329759]
27. Law LF, Krishnan C, and Avin K. Modeling nonlinear errors in surface electromyography due to baseline noise: a new methodology. J Biomech. 2011; 44(1):202–5. [PubMed: 20869716]
28. Kellis E Quantification of quadriceps and hamstring antagonist activity. Sports Med. 1998; 25(1):37–62. [PubMed: 9458526]
29. Baratta R, Solomonow M, Zhou BH, Letson D, Chuinard R, and D'Ambrosia R. Muscular coactivation. The role of the antagonist musculature in maintaining knee stability. Am J Sports Med. 1988; 16(2):113–22. [PubMed: 3377094]
30. Biscarini A, Benvenuti P, Botti FM, Brunetti A, Brunetti O, and Pettorossi VE. Voluntary enhanced co-contraction of hamstring muscles during open kinetic chain leg extension exercise: its potential unloading effect on the anterior cruciate ligament. Am J Sports Med. 2014; 42(9):2103–12. [PubMed: 24918112]
31. Krishnan C, Allen EJ, and Williams GN. Effect of knee position on quadriceps muscle force steadiness and activation strategies. Muscle Nerve. 2011; 43(4):563–73. [PubMed: 21404288]
32. Farfan FD, Politti JC, and Felice CJ. Evaluation of EMG processing techniques using Information Theory. Biomed Eng Online. 2010; 9:72. [PubMed: 21073705]
33. Racine M, Tousignant-Laflamme Y, Kloda LA, Dion D, Dupuis G, and Choiniere M. A systematic literature review of 10 years of research on sex/gender and experimental pain perception - part 1: are there really differences between women and men? Pain. 2012; 153(3):602–18. [PubMed: 22192712]
34. Radloff LS. The CES-D Scale: A self-report depression scale for research in the general population. Applied Psychological Measurment. 1977; 1(3):385–401.
35. Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. Nature. 1983; 306(5944):686–8. [PubMed: 6656869]
36. Jones M, Stanish W, and Rutherford D. Co-activation is not altered in the contralateral limb of individuals with moderate knee osteoarthritis compared to healthy controls. Clin Biomech (Bristol, Avon). 2018; 59:71–77.
37. Heiden TL, Lloyd DG, and Ackland TR. Knee joint kinematics, kinetics and muscle co-contraction in knee osteoarthritis patient gait. Clin Biomech (Bristol, Avon). 2009; 24(10):833–41.
38. White DK, Zhang Y, Niu J, Keysor JJ, Nevitt MC, Lewis CE, Torner JC, and Neogi T. Do worsening knee radiographs mean greater chances of severe functional limitation? Arthritis Care Res (Hoboken). 2010; 62(10):1433–9. [PubMed: 20506398]
39. Lo J, Lo OY, Olson EA, Habtemariam D, Iloputaife I, Gagnon MM, Manor B, and Lipsitz LA. Functional implications of muscle co-contraction during gait in advanced age. Gait Posture. 2017; 53:110–114. [PubMed: 28129590]
40. Stefanik JJ, Felson DT, Apovian CM, Niu J, Margaret Clancy M, LaValley MP, and Neogi T. Changes in Pain Sensitization After Bariatric Surgery. Arthritis Care Res (Hoboken). 2018; 70(10):1525–1528. [PubMed: 29316386]
41. Ellingson LD, Colbert LH, and Cook DB. Physical activity is related to pain sensitivity in healthy women. Med Sci Sports Exerc. 2012; 44(7):1401–6. [PubMed: 22217571]
42. Naugle KM and Riley JL 3rd. Self-reported physical activity predicts pain inhibitory and facilitatory function. Med Sci Sports Exerc. 2014; 46(3):622–9. [PubMed: 23899890]

43. Geva N and Defrin R. Enhanced pain modulation among triathletes: a possible explanation for their exceptional capabilities. Pain. 2013; 154(11):2317–23. [PubMed: 23806655]
44. Handschin C and Spiegelman BM. The role of exercise and PGC1alpha in inflammation and chronic disease. Nature. 2008; 454(7203):463–9. [PubMed: 18650917]
45. Leung A, Gregory NS, Allen LA, and Sluka KA. Regular physical activity prevents chronic pain by altering resident muscle macrophage phenotype and increasing interleukin-10 in mice. Pain. 2016; 157(1):70–9. [PubMed: 26230740]
46. Fransen M, McConnell S, Harmer AR, Van der Esch M, Simic M, and Bennell KL. Exercise for osteoarthritis of the knee. Cochrane Database Syst Rev. 2015; 1:CD004376. [PubMed: 25569281]
47. Shakoor N, Agrawal A, and Block JA. Reduced lower extremity vibratory perception in osteoarthritis of the knee. Arthritis Rheum. 2008; 59(1):117–21. [PubMed: 18163397]
48. Shakoor N, Lee KJ, Fogg LF, Wimmer MA, Foucher KC, Mikolaitis RA, and Block JA. The relationship of vibratory perception to dynamic joint loading, radiographic severity, and pain in knee osteoarthritis. Arthritis Rheum. 2012; 64(1):181–6. [PubMed: 21898358]
49. Thorlund JB, Shakoor N, Ageberg E, Sandal LF, Block JA, and Roos EM. Vibratory perception threshold in young and middle-aged patients at high risk of knee osteoarthritis compared to controls. Arthritis Care Res (Hoboken). 2012; 64(1):144–8. [PubMed: 21905255]
50. Rosland T, Gregersen LS, Eskehave TN, Kersting UG, and Arendt-Nielsen L. Pain sensitization and degenerative changes are associated with aberrant plantar loading in patients with painful knee osteoarthritis. Scand J Rheumatol. 2015; 44(1):61–9. [PubMed: 25296895]
51. LaBella C Patellofemoral pain syndrome: evaluation and treatment. Prim Care. 2004; 31(4):977–1003. [PubMed: 15544830]
52. Song H, Dai X, Li J, and Zhu S. Hamstring Co-Contraction in the Early Stage of Rehabilitation After Anterior Cruciate Ligament Reconstruction: A Longitudinal Study. Am J Phys Med Rehabil. 2018; 97(9):666–672. [PubMed: 29613884]

Table 1.

Participant Characteristics (n=1633)

Mean Age, years (SD)	67.3 (7.7)
Female, %	58
Mean BMI, kg/m^2 (SD)	30.3 (5.6)
Tibiofemoral OA in either knee, %	37
Prevalence of wrist temporal summation, %	40
Median Patella PPT, kg/cm^2 (IQR)	4.9 (3.6–6.6)
Median hamstring co-contraction, % (IQR)	10.1 (5.7–15.1)

Table 2.

Relation of measures of pain sensitivity to hamstring co-contraction in all participants (n=1633)

Sensitization Measure (Exposure)	Crude and Adjusted OR (95% CI) for Hamstring Muscle Co-contraction (Outcome): Highest third vs Lowest third					
	Overall Hamstring		Medial Hamstring		Lateral Hamstring	
	Crude	Adjusted	Crude	Adjusted	Crude	Adjusted
Temporal Summation	**1.3 (1.0–1.7)**	**1.3 (1.0–1.8)**	**1.3 (1.0–1.8)**	**1.4 (1.0–1.9)**	**1.7 (1.3, 2.3)**	1.3 (1.0–1.9)
PPT (kg/cm^2):						
Lowest Third	**1.4 (1.0–2.0)**	**1.5 (1.0–2.3)**	1.2 (0.9–1.8)	**1.5 (1.0–2.3)**	**1.5 (1.2–2.0)**	1.4 (0.9–2.2)
Middle Third	0.9 (0.7–1.4)	0.9 (0.6–1.4)	1.2 (0.8–1.7)	1.1 (0.7–1.7)	0.9 (0.6–1.4)	1.0 (0.7–1.6)
Highest Third	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
p for linear trend		p=0.04		p=0.01		p=0.06

*Adjusted for age, sex, BMI, depressive symptoms, clinic site, radiographic OA

**Measures of central sensitization were not significantly associated with middle vs lowest third of hamstring co-contraction

Table 3.

Relation of measures of pain sensitivity to hamstring co-contraction among participants with KL grade ≥ 2 (n=512)

Sensitization Measure (Exposure)	Crude and Adjusted* OR (95% CI) for Hamstring Muscle Co-contraction (Outcome): Highest third vs Lowest third					
	Overall Hamstring		Medial Hamstring		Lateral Hamstring	
	Crude	Adjusted	Crude	Adjusted	Crude	Adjusted
Temporal Summation	**1.7 (1.1–2.6)**	**1.8 (1.1–3.0)**	0.6 (0.4, 1.0)	1.1 (0.7–1.9)	**1.9 (1.2–3.0)**	1.5 (0.9–2.6)
PPT (kg/cm^2):						
Lowest Third	1.3 (0.7–2.3)	1.2 (0.6–2.3)	1.3 (0.7–2.4)	1.4 (0.7–2.7)	1.5 (0.8–3.0)	1.5 (0.7–3.0)
Middle Third	0.8 (0.4–1.5)	0.8 (0.4–1.5)	1.2 (0.6–2.2)	1.1 (0.5–2.1)	0.9 (0.5–1.8)	1.0 (0.5–2.0)
Highest Third	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
p for linear trend		p=0.9		p=0.2		p=0.2

*Adjusted for age, sex, BMI, depressive symptoms, clinic site

**Measures of central sensitization were not significantly associated with middle vs lowest third of hamstring co-contraction