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Original article

Associations between joint pathologies and central sensitization in persons with hand osteoarthritis: results from the Nor-Hand study

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Abstract

Objective. Pain sensitization is associated with pain severity in persons with hand OA. What contributes to pain sensitization is unclear. This study explores whether hand OA pathologies and symptom duration are related to central sensitization.

Method. Participants with hand OA in the Nor-Hand study underwent bilateral hand radiography and US examination. Central sensitization was assessed with pressure pain thresholds (PPT) at remote sites (wrist, trapezius and tibialis anterior muscles) and temporal summation. We examined whether hand OA pathologies, independent of each other, including structural severity (Kellgren–Lawrence sum score, presence of erosive hand OA), inflammatory severity (greyscale synovitis and power Doppler activity sum scores) and symptom duration, were related to central sensitization, adjusting for age, sex, BMI, comorbidities and OA-severity of knee/hip.

Results. In 291 participants (88% women, median age 61 years, interquartile range 57–66 years) Kellgren–Lawrence, greyscale synovitis and power Doppler activity sum scores were not associated with lower PPTs at remote sites. Persons with erosive hand OA had lower PPTs at the wrist (adjusted beta −0.75, 95% CI −1.32, −0.19) and tibialis anterior (adjusted beta −0.82, 95% CI −1.54, −0.09) and had greater temporal summation (adjusted beta 0.56, 95% CI 0.12, 1.01) compared with persons with non-erosive disease. No associations were found for symptom duration.

Conclusions. A person's overall amount of structural or inflammatory hand OA pathologies was not associated with central sensitization. Although persons with erosive hand OA showed greater signs of central sensitization, the small differences suggest that central sensitization is mainly explained by factors other than joint pathologies.

Key words: hand osteoarthritis, arthritis, inflammation, pain mechanisms, pain sensitization, central nervous system sensitization, central sensitization, quantitative sensory testing

CLINICAL SCIENCE

Rheumatology key messages

- Central sensitization indicated by higher widespread pain sensitivityand temporal summation was not more common in persons with severe radiographic or inflammatory hand OA.
- The theory of peripheral OA disease as driver of central sensitization could not be translated in a clinical setting.
- Persons with erosive hand OA showed greater signs of central sensitization, but the clinical relevance of these results were uncertain and need to be followed-up in prospective studies.

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Introduction

Pain is a major concern for patients with symptomatic hand OA that significantly reduces health-related quality of life [1]. Symptomatic pain treatment can be challenging, and no disease-modifying drugs exist. Although previous research has found both structural and inflammatory features to associate with pain in the same joint, these features fail to fully explain the overall hand pain experience in hand OA [2, 3].

Recent clinical studies have reported pain sensitization to be a clinically relevant contributor to hip and knee OA pain [4]. The role of pain sensitization in hand OA is less studied. A few small-scale studies have demonstrated that peripheral and central sensitization are more common in hand OA patients than in healthy individuals [5–7]. The authors of this report have previously reported data from the Nor-Hand study where the prevalence of central sensitization was 40% and peripheral and central sensitization was associated with greater hand pain severity [8], suggesting a likely clinical relevance of sensitization also in persons with hand OA. Pain sensitization involves mechanisms responsible for facilitated responsiveness of peripheral and central nociceptors to painful stimuli and to previously non-painful stimuli, causing increased pain sensitivity and pain perception [9, 10]. In arthritic diseases like hand OA, chronic joint pathologies, both mechanical and inflammatory, are believed to cause peripheral sensitization with primary hyperalgesia and allodynia, and possibly over time also central sensitization with widespread hyperalgesia and allodynia [8]. Experimental models of OA in animals report that both mechanical stimuli and inflammation induce peripheral sensitization as well as neuroinflammation in the CNS, which is associated with central sensitization [11]. The translation of this theory was recently illustrated in a brief report using data from the Nor-Hand study [12]. These analyses showed that the severity of structural OA pathology and inflammatory severity in finger joints, independent of each other and of pain, were related to peripheral sensitization. Whether hand joint pathologies are related to clinical assessment of central sensitization like widespread hypersensitivity and temporal summation (TS) has not yet been explored.

New OA-pain therapeutics and pain management may be developed to target sensitization. Therapeutic trials targeting OA-related pathology, including inflammation and sensitization, are ongoing [13]. Along this line, identifying patients' phenotypes will enable more individualized treatment strategies [14]. To achieve these goals, we need greater understanding of the causes and mechanisms behind pain sensitization in individuals with hand OA. Hence, the current study explores the relationship of structural and inflammatory hand OA pathologies, as well as symptom duration, to central sensitization assessed by quantitative sensory testing (QST).

Methods

Design, setting and study population

The Nor-Hand study is a Norwegian hospital-based hand OA cohort that includes 300 men and women aged 40–70 years with hand OA, defined as at least one IP or thumb base joint with OA on clinical and/or US examination. The main exclusion criteria were diagnoses of systemic inflammatory rheumatic diseases or hemochromatosis. A full description of the study protocol and study population has been published previously [8, 15].

The Nor-Hand study complies with the declaration of Helsinki and the protocol was approved by the Norwegian Regional Committee for Medical Health Research Ethics (Ref. no. 2014/2057). All participants gave written informed consent before participating in the study.

QST of peripheral and central sensitization

Two medical students performed the QST examinations. They were trained prior to the data collection and had printed protocols available to ensure that identical procedures and instructions were given to all participants. Pressure pain detection threshold (PPT) was tested with a hand-held algometer (Force One FXPI25, Wagner Instruments, Greenwich, Connecticut, United States, 1 cm^2 rubber tip) at the wrist (dorsal aspects of the left radioulnar joint) and two other remote sites (mid-portions of the trapezius and tibialis anterior muscles). Each location was tested by applying the algometer in perpendicular position against the skin with a rate of 0.5 kg/s. The participant was instructed to indicate when the pressure first started to feel painful, and the value (kg/cm^2) was recorded. The test was performed three times at each site, with an interval of 30 s, and the average value was used in analyses. Low PPT values indicate greater sensitivity to pain, i.e. pain sensitization. PPT tested at a distant or remote non-diseased site away from the affected joint (i.e. the leg) is considered to be a measure of widespread sensitivity and to reflect central pain sensitization. The selection of test sites was based on previous studies of knee OA [16–18].

Temporal summation (TS) is the augmented nociceptive response to repetitive stimuli, which is a physiological phenomenon, but which can be maladaptively increased and is then considered a marker of central sensitization. TS of pain was assessed with a train of 10 stimuli at the dorsal side of the left wrist using a punctate probe (MRC Systems GmbH The PinPrick, Heidelberg, Germany, set with seven weighted probes; 8, 16, 32, 64, 128, 256 and 512 nM) at a rate of 1 Hz. The probe used to assess TS was determined by testing each probe sequentially in order of increasing weight to identify the probe that first yielded pain on a numerical rating scale (NRS; 0–10 where 0 is no pain and 10 is worst pain imaginable) of 4 or more with a single touch of the wrist. If none of the probes reached a pain rating of 4, the 512 nM (highest weight) probe was used. For the TS assessment the participants had their hands

resting flat on a table with eyes closed during the test. A repetition of 10 stimuli was applied at a rate of 1 Hz, and the participants were instructed to rate their NRS pain on the first, fifth and tenth tap. TS was calculated by subtracting the NRS rating of the first tap from the peak NRS rating of the fifth or tenth tap. We also defined TS to be present if the pain increased more than the smallest detectable change during the test. The smallest detectable change was calculated from a test–retest of nine participants and represents the TS value that is larger than what can be attributed to random variation or measurement error, previously calculated and described to be $\geq$2 in the Nor-Hand baseline data [8].

Inter-reader reliability of QST results between the two medical students was calculated for nine participants and found to range from poor to good (intraclass correlation coefficients, two-way mixed effects model, average measure; PPT at wrist 0.14, PPT at trapezius 0.41, PPT at tibialis anterior 0.60, TS 0.72 and kappa; presence of TS *vs* no TS 0.36). The results have been published previously [8].

Pathological features on radiographs and US examination

Bilateral hand radiographs with posteroanterior view were obtained prior or after the study visit with QST, with a mean number of days from the study visit of 46 (S.D. 43) days. Bilateral hand joints including the DIP, PIP including the first IP, MCP, first CMC (CMC1) and scaphotrapeziotrapezoidal joints were scored by an experienced reader (I.K.H.) according to a modified Kellgren–Lawrence scale (grade 0–4) [19]. The DIP and PIP joints were also scored according to the Verbuggen–Veys anatomical phase score [19, 20]. As an overall score for structural hand OA severity, we calculated the Kellgren–Lawrence sum score of all hand joints (scale 0–128). Persons with at least one DIP or PIP joint in the erosive or remodelled phases on the Verbuggen–Veys scale were defined as having erosive hand OA [20]. The reader re-assessed 20 radiographs after a mean (S.D.) of 16 (4) days, with excellent reliability (weighted kappa values of 0.92 for Kellgren–Lawrence and 0.93 for Verbuggen–Veys).

A trained medical student performed US examinations of both hands on the same day as the QST by use of a Logic S8 US machine (General Electric Healthcare, United States) with a linear 6–15 Mz probe and a preset for optimal greyscale synovitis and power Doppler (pulse repetition frequency 0.6 kHz and frequency 7.7 MHz). Initial scorings were done in consensus with an experienced ultrasonographer (A.M.). The examination was carried out with the participant's hands resting on a small table. The ultrasonographer scored the dorsal side (sliding from side to side) of the bilateral DIP, PIP, MCP and CMC1 joints with longitudinal projection. An additional transverse scanning was carried out when presence of pathology was uncertain. Greyscale synovitis and power Doppler signals were scored on semi-quantitative 0–3 scales [21]. As overall scores for the severity of inflammation, we calculated greyscale synovitis and power Doppler activity sum scores of all joints (0–90), respectively. A subset of 10 participants was examined by both the medical student and the expert (A.M.) with good inter-reader reliability (prevalence and bias adjusted kappa values for ordinal scales of 0.82 for greyscale synovitis and 0.87 for power Doppler activity).

Using the same settings, on a Logic E9 US machine (General Electric Healthcare, United States), another medical student examined bilateral hips and knees with the participant resting in supine position on an examination bed with the hips and knees extended and the feet in neutral position. The hip was evaluated in a longitudinal scan along the femoral neck. Osteophytes, defined as a definite irregularity of the bone cortex located at the femoral head and/or neck, were scored on 0–3 scales [22]. The knees were evaluated for osteophytes at the medial and lateral bone margins of the tibiofemoral joint (scored 0–3 in each compartment; 0 = no, 1 = small, 2 = medium, 3 = large osteophytes) scanned longitudinally. Inter-reader reliability between the student and an experienced ultrasonographer (H.B.H.) of a subset of 10 participants was moderate for hip and knee combined (weighted kappa 0.57).

Symptom duration

The participants responded to a questionnaire including the question 'Which year did you first notice hand OA symptoms?' Symptom duration was calculated as year of baseline examination minus recalled first year of hand OA symptoms.

Covariates

We recorded age and sex and calculated BMI based on measured height and weight (kg/m^2). The severity of hip and knee OA was defined as the sum of the osteophyte grades on US examination in each hip and highest graded osteophyte in each of the knees (total knee/hip OA scale 0–12). To assess the burden of comorbidities we used the Self-Administered Comorbidity Questionnaire (scale 0–45) [23]. Finally, we gathered data of regular use (yes/no) of NSAIDs through questionnaires.

Statistical analyses

We used regression analyses to examine whether joint pathologies and symptom duration as explanatory variables were associated with QST results as outcome variables. For continuous outcome variables (PPTs and TS) we used linear regression and for the dichotomized outcome (presence of TS) we used logistic regression. Explanatory variables were studied categorically based on group tertiles (Kellgren–Lawrence sum score, greyscale synovitis sum score, power Doppler activity sum score and symptom duration) or predefined categories (presence of erosive hand OA). We also examined the linear associations of continuous explanatory variables (Kellgren–Lawrence sum score, greyscale synovitis sum score, power Doppler activity sum score and symptom duration) per 1 S.D. increase. All analyses were adjusted

for age, sex, BMI, total hip/knee OA and comorbidities. Hip/knee OA represents a possible confounding bias as those with comorbid hip/knee OA are more likely to have hand OA, and hip/knee OA also might be a contributor to central sensitization. To evaluate the independent role of hand OA pathology on sensitization we adjusted for hip/knee OA. In addition, the analyses of structural severity were adjusted for inflammation (greyscale synovitis sum score) and vice versa, and the analyses of symptom duration were adjusted for both Kellgren–Lawrence sum score and greyscale synovitis sum score. Sensitivity analyses of inflammatory features including adjustment for use of NSAIDs, and interaction analyses of all covariates were also performed. Missing Kellgren–Lawrence scores due to trapeziectomy or arthrodesis were replaced with grade 4 (11 joints), while missing scores due to amputation (17 joints) and joint outside the X-ray image (1 joint) were replaced with the mean of available scores. Missing greyscale synovitis and power Doppler activity scores were replaced with the mean of available scores (trapeziectomy 5 joints, amputation 16 joints, unknown reason 5 joints). We used Stata software (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC) and *P*-values of <0.05 were considered statistically significant.

Results

Characteristics of the study population

In total, 291 of 300 participants were eligible for analyses. Nine participants did not complete the QST due to a technical error of the equipment. Because of missing data ($n=22$), the analyses on symptom duration included 269 participants.

Characteristics of the study population are shown in Table 1. The majority of the study population were women (88%) and fulfilled the ACR criteria for hand OA (93%). The participants had a wide range in symptom severity, symptom duration, structural OA severity and synovitis. PPT values were higher at tibialis anterior (mean 5.5 kg/cm^2, S.D. 2.6) than at the wrist (mean 4.4 kg/cm^2, S.D. 2.0) and trapezius (mean 4.4 kg/cm^2, S.D. 2.0). Presence of TS was observed in 42% ($n=122$) of the study population, while median TS was 1 (interquartile range 0–2) and ranged from 0 to 7.

Associations between structural and inflammatory hand OA features and remote PPTs

Participants with erosive hand OA had lower PPT at the wrist and the tibialis anterior muscle but not at the trapezius muscle (Table 2) compared with those with non-erosive hand OA. Kellgren–Lawrence, greyscale synovitis and power Doppler activity sum scores were not associated with PPT at the radioulnar joint, the trapezius or tibialis anterior muscles (Table 2).

Associations between structural and inflammatory hand OA features and TS

Persons with erosive disease had slightly greater TS than those without (Table 3). Presence of TS was not more common in persons with erosive (44%) *vs* non-erosive (42%) hand OA. Persons in the most extreme tertiles with regards to Kellgren–Lawrence, greyscale synovitis and power Doppler sum scores had higher odds of having presence of TS compared with those in the lowest tertiles, but the results were not statistically significant (Table 3).

Table 1 Demographics and clinical characteristics, $n=291$

Characteristics	Value
Sex, women, *n* (%)	257 (88)
Age, years, median (IQR)	61 (57–66)
BMI, kg/m^2, mean (S.D.)	26.4 (4.8)
Fulfil ACR criteria for hand OA, *n* (%)	271 (93)
NRS hand pain[a] (0–10), mean (S.D.)	3.8 (2.3)
Radiographic severity (number of joints with KL $\geq$2) (0–32), median (IQR)	9 (4–14)
KL hand sum score (0–128), median (IQR)	28 (16–43)
Erosive OA, presence of erosive OA in at least one DIP/PIP joint, *n* (%)	102 (35)
GS synovitis sum score (0–90), median (IQR)	3 (1–7)
Power Doppler activity sum score (0–90), median (IQR)	1 (0–4)
GS synovitis joint count (0–30), median (IQR)	1 (0–2)
Power Doppler activity joint count (0–30), median (IQR)	1 (0–3)
Symptom duration[b], years, median (IQR)	6 (3–13)
Comorbidity index (0–45), mean (S.D.)	9 (4)
Knee and hip OA severity (0–12), median (IQR)	2 (1–4)

[a]$N=290$ (due to one participant missing the NRS hand pain question), [b]$N=269$. IQR: interquartile range; NRS: numerical rating scale; PPT: pressure pain threshold; KL: Kellgren–Lawrence grading; GS: greyscale.

Table 2 Associations of joint pathology and symptom duration with pressure pain thresholds

	PPT wrist		PPT trapezius		PPT tibialis anterior	
	Mean (s.d.)	Adjusted beta (95% CI)	Mean (s.d.)	Adjusted beta (95% CI)	Mean (s.d.)	Adjusted beta (95% CI)
KL sum score[a]						
0–20 ($n = 98$)	4.4 (2.1)	Ref.	4.3 (2.1)	Ref.	5.7 (2.6)	Ref.
21–37 ($n = 99$)	4.5 (2.2)	−0.01 (−0.59, 0.58)	4.4 (2.1)	0.03 (−0.56, 0.62)	5.5 (2.7)	−0.28 (−1.02, 0.47)
>37 ($n = 94$)	4.4 (1.8)	−0.18 (−0.92, 0.57)	4.3 (1.9)	−0.15 (−0.87, 0.57)	5.4 (2.4)	−0.53 (−1.44, 0.38)
Continuous		−0.24 (−0.54, 0.06)		0.02 (−0.29, 0.33)		−0.24 (−0.62, 0.15)
Erosive phenotype[a]						
No ($n = 189$)	4.6 (2.1)	Ref.	4.4 (2.1)	Ref.	5.7 (2.7)	Ref.
Yes ($n = 102$)	4.2 (1.8)	**−0.75 (−1.32, −0.19)**	4.3 (1.9)	−0.38 (−0.86, 0.29)	5.2 (2.2)	**−0.82 (−1.54, −0.09)**
GS sum score[b]						
0–2 ($n = 119$)	4.3 (2.0)	Ref.	4.3 (2.2)	Ref.	5.5 (2.8)	Ref.
3–7 ($n = 89$)	4.6 (2.1)	0.21 (−0.35, 0.76)	4.6 (2.1)	0.24 (−0.31, 0.80)	5.6 (2.6)	−0.04 (−0.74, 0.66)
>7 ($n = 83$)	4.5 (1.9)	0.27 (−0.38, 0.93)	4.2 (1.7)	−0.22 (−0.88, 0.44)	5.5 (2.3)	0.13 (−0.70, 0.97)
Continuous		0.15 (−0.18, 0.43)		−0.12 (−0.40, 0.16)		0.12 (−0.23, 0.48)
Power Doppler sum score[b]						
0 ($n = 108$)	4.2 (1.8)	Ref.	4.3 (2.1)	Ref.	5.4 (2.6)	Ref.
1–3 ($n = 109$)	4.6 (2.3)	0.33 (−0.20, 0.86)	4.5 (2.2)	−0.01 (−0.54, 0.52)	5.7 (2.7)	0.16 (−0.51, 0.83)
>3 ($n = 74$)	4.5 (2.0)	0.27 (−0.38, 0.91)	4.3 (1.7)	−0.24 (−0.89, 0.41)	5.5 (2.4)	0.06 (−0.76, 0.88)
Continuous		0.07 (−0.20, 0.33)		−0.18 (−0.45, 0.08)		0.11 (−0.22, 0.44)
Symptom duration[c]						
0–4 ($n = 109$)	4.5 (2.1)	Ref.	4.5 (2.0)	Ref.	4.5 (2.0)	Ref.
5–10 ($n = 74$)	4.4 (2.0)	−0.14 (−0.72, 0.43)	4.5 (2.3)	0.07 (−0.52, 0.66)	4.5 (2.3)	−0.04 (−0.79, 0.71)
>10 ($n = 86$)	4.4 (1.8)	−0.11 (−0.72, 0.50)	4.1 (1.9)	−0.39 (−1.01, 0.23)	4.1 (1.9)	−0.20 (−0.98, 0.59)
Continuous		0.01 (−0.25, 0.28)		−0.14 (−0.41, 0.13)		0.08 (−0.26, 0.43)

Explanatory variables are reported as group tertile categories and as continuous values. Continuous values are reported per s.d. increase. All analyses are adjusted for age, sex, BMI, comorbidities and generalized OA (knee and hip OA severity). Additional adjustment of: [a]GS sum score, [b]KL sum score and [c]both.
Results with P-value <0.05 are shown in bold. PPT: pressure pain threshold; KL: Kellgren–Lawrence grading; GS: greyscale.

TABLE 3 Associations of joint pathology and symptom duration with temporal summation

	Presence of TS		Change in TS	
	N (%)	Adjusted OR (95% CI)	Mean (S.D.)	Adjusted beta (95% CI)
KL sum score[a]				
0–20 ($n=98$)	41 (42)	Ref.	1.6 (1.6)	Ref.
21–37 ($n=99$)	42 (42)	1.19 (0.63, 2.22)	1.5 (1.7)	0.07 (−0.39, 0.53)
>37 ($n=94$)	39 (41)	1.24 (0.57, 2.69)	1.6 (1.6)	0.27 (−0.29, 0.83)
Continuous		1.08 (0.76, 1.50)		0.23 (−0.02, 0.47)
Erosive phenotype[a]				
No ($n=189$)	77 (41)	Ref.	1.5 (1.5)	Ref.
Yes ($n=102$)	45 (44)	1.51 (0.81, 2.80)	1.7 (1.8)	**0.56 (0.12, 1.01)**
GS sum score[b]				
0–2 ($n=119$)	45 (38)	Ref.	1.4 (1.7)	Ref.
3–7 ($n=89$)	40 (45)	1.71 (0.93, 3.15)	1.7 (1.6)	0.32 (−0.11, 0.75)
>6 ($n=83$)	37 (45)	1.84 (0.90, 3.77)	1.7 (1.6)	0.21 (−0.30, 0.72)
Continuous		1.07 (0.80, 1.44)		−0.06 (−0.28, 0.17)
Power Doppler sum score[b]				
0 ($n=108$)	49 (45)	Ref.	1.6 (1.8)	Ref.
1–3 ($n=109$)	39 (36)	0.75 (0.42, 1.33)	1.5 (1.6)	−0.06 (−0.47, 0.35)
>3 ($n=74$)	34 (46)	1.24 (0.62, 2.47)	1.7 (1.5)	0.04 (−0.46, 0.54)
Continuous		0.99 (0.75, 1.31)		−0.06 (−0.27, 0.15)
Symptom duration[c]				
0–4 ($n=109$)	46 (42)	Ref.	1.5 (1.7)	Ref.
5–10 ($n=74$)	29 (39)	0.86 (0.45, 1.63)	1.8 (1.7)	0.02 (−0.44, 0.48)
>10 ($n=86$)	41 (48)	1.29 (0.66, 2.51)	1.4 (1.3)	0.18 (−0.31, 0.67)
Continuous		1.11 (0.83, 1.49)		0.07 (−0.14, 0.28)

Explanatory variables are reported as group tertile categories and as continuous values. Continuous values are reported per S.D. increase. All analyses are adjusted for age, sex, BMI, comorbidities and generalized OA (knee and hip OA severity). Additional adjustment of: [a]GS sum score, [b]KL sum score and [c]both. Results with *P*-value <0.05 are shown in bold. TS: temporal summation; OR: odds ratio; KL: Kellgren Lawrence grading; GS: greyscale.

Sensitivity analyses including adjustment for regular use of NSAIDs did not alter any results.

We found no consistent interactions with age, BMI, sex, comorbidities or total hip/knee OA. Further, there were no significant interactions between inflammation and structural pathology when included in the same models.

Association between symptom duration and QST

One-third (86/269, 32%) of participants reported symptom duration of >10 years. There were no associations between symptom duration and PPT of any of the test sites (Table 3). Those with symptom duration in the highest tertile (>10 years) had only slightly higher prevalence of TS than those in the lowest tertile (48% *vs* 42%) and the association was not statistically significant (Table 3).

Discussion

This study explored the relation of the total amount of structural and inflammatory OA features in the hands to QST measures of central pain sensitization. We found no associations between the sum of radiographic pathologies or US-detected inflammation in the hands, and PPTs at remote sites or TS. The subgroup with the erosive hand OA subtype had lower remote PPTs and greater TS, indicating more central sensitization.

Several mediators in the OA joint have been identified as causes of peripheral sensitization, such as nerve growth factor, which sensitizes peripheral nociceptors following joint tissue damage and inflammation [24, 25]. Lower PPT at DIP and PIP joints in hand OA patients, indicating higher pain sensitivity, is associated with higher Kellgren–Lawrence grade [5]. We have previously shown that inflammatory hand OA severity is also associated with local PPT [12], supporting the translational evidence from basic to clinical science that peripheral pathology drives peripheral sensitization [11].

Less is known about peripheral drivers of central sensitization, but preclinical experiments illustrate a possible link between OA joint pathology and central sensitization [26–28]. In humans, activation of brain areas related to central pain sensitization has been found in hand OA patients and not healthy controls during painful hand exercises during functional MRI [6]. Previous clinical studies using QST, none of which has focused on hand

OA, show conflicting results. A longitudinal knee OA study found that knee effusion was associated with decrease in PPT at the wrist (i.e. increased sensitivity at a remote site) and incident TS, while another study showed no association between tissue damage, i.e. radiographic OA and bone marrow lesions, and remote PPTs or TS [16, 29]. No differences in remote PPT values or TS were found between persons with different levels of finger joint pathology sum scores in our study. Interestingly, we found an association between erosive hand OA and central sensitization, where those with erosive hand OA showed greater TS and lower PPT at distant sites. However, the clinical relevance of this finding seems minimal. Persons with erosive hand OA had 0.5 points greater TS, which is below the smallest detectable change of 2 or more, which represent the smallest TS that is greater than the random variation or measurement error. Further, using our results from previous published analyses [8], this TS value corresponds to only 0.10 points higher NRS hand pain. Similarly, 0.75kg/cm^2 lower PPT at the wrist corresponds to only 0.15 points higher NRS hand pain. Despite doubtful clinical relevance, our results may suggest that erosive hand OA is a subtype that is more susceptible to central sensitization.

Our results do not rule out that hand OA pathology could drive spinal and supraspinal mechanisms of sensitization that influence hand pain severity. Yet, in clinical settings where QST is the most feasible measures of central sensitization available, the lack of association with measures of widespread sensitivity and TS indicates that factors other than the joint disease itself seem important and need to be investigated to understand the role of central sensitization on chronic hand OA pain. Genetics and epigenetics might cause individual predisposition to pain sensitization [30, 31]. Comorbidities and generalized OA might be more important for central sensitization for some individuals, while psychological and social factors and different coping skills might contribute to the enhanced expression of the pain experience that may or may not be related to pain sensitization for others [30, 32].

The mechanisms and time-related factors underlying the transition from acute to chronic pain is not understood. Beside a weak trend, no association between symptom duration and central sensitization was found in the present study. Previous knee OA studies have shown conflicting results [16, 33]. In patients with established RA (>10 years disease duration), localized PPT tested at the thumb nail was significantly lower than in those with shorter disease duration [34]. Theoretically, disease severity of OA might drive peripheral and central sensitization at an earlier time in the disease course, while joint pathologies may be less relevant at later stages when neuroplasticity may be lost, and sensitization may be maintained by other factors. Although our study suggests no relationship, prospective studies are needed to draw conclusions.

The strength of our study is the large study population, the broad examination of joint pathologies and the extensive QST assessment, making it possible to evaluate central pain mechanisms. Also, we were able to adjust for important confounders, such as other comorbidities and knee/hip OA, which may also contribute to central sensitization [35].

The main limitation of this study is the cross-sectional design and lack of healthy controls. Longitudinal studies examining whether joint pathologies predict worsening or incident central sensitization are needed to investigate if there is a causal pathway. Our study does not indicate whether targeting e.g. joint inflammation, may or may not reduce or prevent pain sensitization. Second, inter-reader reliabilities of the QST were not optimal. Calculations were based on only nine participants, making the results sensitive to few discordant measurements. Others have achieved excellent reliability of PPT and TS of the forearm using the same equipment and method as in our study [36]. The majority of the examinations were conducted by one of the examiners ($n = 214$). Another important limitation is the self-reported onset year of hand OA symptoms, which is prone to recall bias. Finally, the US examinations provide only a snapshot of the current inflammation, which cannot inform us about the total burden of joint inflammation during the course of the disease. Inflammation early in the disease course might have been important for the development of central sensitization, even though the cross-sectional analyses are negative.

Our study could not demonstrate any clinically relevant associations between radiographic OA severity or US-detected inflammation and remote PPTs or TS. This implies that while hand OA joint pathologies seem to drive peripheral sensitization, they appear to contribute less to central sensitization. Erosive hand OA was associated with central sensitization in our study, and whether this subtype has greater risk of central sensitization should be investigated in longitudinal studies.

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Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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