Pain sensitization in hand osteoarthritis

Doctoral thesis by

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2021

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Oslo, Norway

University of Oslo

Faculty of Medicine

Oslo, Norway

Series of dissertations submitted to the
Faculty of Medicine, University of Oslo

ISBN 978-82-8377-928-8

Cover: Hanne Baadsgaard Utigard.
Photo cover: Nicolas Tourrenc/Diakonhjemmet sykehus.
Print production: Reprosentralen, University of Oslo.

Content

Acknowledgements

At elementary school I wrote an assignment about Dr. Hansen's discovery of the Mycobacterium Leprae and drew a detailed granuloma from my father's histopathology book. This is my earliest memory of feeling enthusiastic about medicine and research and it inspired my choice of carrier path. Today I am so grateful for having had the opportunity to complete a three-year PhD-project and a doctoral thesis. It is a true privilege. I want to express my gratitude to all who has made this possible and supported me in this work.

I thank the Diakonhjemmet Hospital and especially the Division of Rheumatology and Research for hosting this project and including me with such warmth. I also thank the Faculty of Medicine at the University of Oslo, for not only providing me my medical degree but also the PhD-programme.

The Nor-Hand study and the opportunity for me to write this thesis would not have happened without my main supervisor and the master brain behind it all, Ida K. Haugen. Ida, very early in our work I realized that this was going to be a rewarding and educational time, and I am grateful for the trust you have put in me and how you have challenged and taught me to work independently.

Tuhina Neogi – my co-supervisor and Professor at Boston University Schools of Medicine, thank you for the invaluable feedback on manuscripts and for responding thoroughly and patiently to long emails with questions about quantitative sensory testing. Your involvement has inspired me to continue to explore the relevance pain sensitization in osteoarthritis.

My second co-supervisor, Professor Hilde Berner Hammer. Thank you for being my pain-research mentor and always being encouraging and pragmatic. I am also forever grateful for introducing and teaching me to examine joints with ultrasound.

Professor Tore K. Kvien – former head-of-department and my co-supervisor who responded positively to my email four years ago inquiring about a PhD-position. Thank you for the groundwork you have built at the department, and for your lessons and guidance in trying to write consistent, systematic and to the point.

Professor Till Uhlig – my co-supervisor. Thank you for your kind support and for always being enthusiastic and interested in me and my work.

Karen Magnusson and Alexander Mathiessen – You are among the smartest persons I know, and I am grateful and proud to have co-authored papers with you.

Øystein Maugesten, Elisabeth Mulrooney and Marthe Glørsen, my Nor-Hand PhD-colleagues, it has been invaluable to share the PhD-roller coaster-life with you.
Thank you for being so kind, collaborative and fun!

I would like to thank the head of the division and of the research unit, Kjetil Bergsmark and Espen Haavardsholm, both of you made me feel included at the department since day one.
I appreciate my workplace and your leadership a lot.

Statisticians Joe Sexton and Øivind Skare – Thank you for always taking time to help and guide me in the matrix of STATA.

I would also like to sincerely thank all my colleagues in the research-Villa: former and current PhD-students, senior researchers, and coordinators. Thank you all for being so inspiring, down to earth, and making our department such a good place to work.

Gratitude is also extended to all those who made the Nor-Hand study possible: Coordinators, Barbara Slatkowski-Christensen, the medical students who performed the ultrasound and quantitative sensory testing examinations (Nicolai Ravn Aarskog, Caroline M. Fjellstad, Julie Bergh and Malin Eijsink) and, especially, to all the study participants.

I would like to thank my supportive and enthusiastic friends. You have helped me to keep an eye open for the bigger picture both in research and life during these last years. Thank you, Mamma, Pappa, Rasmus and Sebastian, for all your love and faith in me and for always being there when I need you. I love the combination of ambitiousness and *joie de vivre* you have thought me. And finally, thank you Axel and Georg, for reminding me of positive thoughts when I sometimes forget them myself – I love you.

Oslo, November 8th, 2021

Pernille Steen Pettersen

Funding

This PhD-project was funded by grants from the South-Eastern Norway Regional Health Authority. Institutional support was provided by the administration at Diakonhjemmet Hospital. The data collection of the Nor-Hand study was supported by grants from Jan A. Pahle's foundation, Simon Fougner Hartmanns Family foundation and Trygve Gythfeldt´s research foundation.

Abbreviations

ACR: American College of Rheumatology

AUSCAN: The Australian/Canadian Osteoarthritis Hand Index

BMI: Body mass index

CCP: Cyclic citrullinated protein

CI: Confidence interval

CMC-1: first carpometacarpal

DFNS: German Research Network on Neuropathic Pain

DIP: distal interphalangeal

IASP: International Association for the Study of Pain

ICC: Intraclass correlations coefficient

MCP: metacarpophalangeal

MRI: Magnetic Resonance Imaging

NGF: Nerve growth factor

NRS: Numeric rating scale

NSAID: Nonsteroidal anti-inflammatory drug

OA: Osteoarthritis

OARSI: Osteoarthritis Research Society International

PASS: Patient acceptable symptom state

PIP: proximal interphalangeal

PPT: Pressure pain threshold

QST: Quantitative sensory testing

SD: Standard deviation

STT: scaphotrapeziotrapezoidal

TNF: Tumor necrosis factor

TS: Temporal summation

List of papers

Paper I

Peripheral and Central Sensitization of Pain in Individuals with Hand Osteoarthritis and Associations with Self-Reported Pain Severity

Pernille Steen Pettersen, Tuhina Neogi, Karin Magnusson, Hilde Berner Hammer, Till Uhlig, Tore Kristian Kvien, Ida Kristin Haugen.
Arthritis Rheumatol. 2019;71(7):1070-7. https://doi.org/10.1002/art.40850

Paper II

Associations of radiographic and ultrasound-detected features in hand osteoarthritis and local pressure pain thresholds

Pernille Steen Pettersen, Tuhina Neogi, Karin Magnusson, Hilde Berner Hammer, Till Uhlig, Tore Kristian Kvien, Ida Kristin Haugen.
Arthritis Rheumatol. 2020;72(6):966-71 https://doi.org/10.1002/art.41199

Paper III

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

Pernille Steen Pettersen, Tuhina Neogi, Karin Magnusson, Alexander Mathiessen, Hilde Berner Hammer, Till Uhlig, Tore Kristian Kvien, Ida Kristin Haugen.
Submitted to Rheumatology (Oxford) March 2021

Edit September 24, 2021: Paper published in Rheumatology (Oxford)
https://doi.org/10.1093/rheumatology/keab708

Abstract

Pain sensitization, i.e. increased pain sensitivity, is believed contribute to chronic pain in many diseases, including osteoarthritis (OA). Hand OA is a serious, painful, and disabling disease. This doctoral thesis aimed to examine the relevance of peripheral and central pain sensitization in persons with hand OA.

Pain sensitization by pressure pain algometry and temporal summation was tested cross-sectionally in a large cohort and their relationships with pain severity as well as structural and inflammatory OA changes were analysed. Almost 300 participants were included, making it the largest study on the subject so far.

The results showed that central sensitization was common, and that peripheral and central sensitization was associated with higher hand pain intensity, independent of psychosocial factors and radiographic OA. The degree of structural and inflammatory changes in a finger joint was associated with pressure pain threshold of the same finger joint as a measure of peripheral and possibly also central sensitization in multilevel analyses. These results were not statistically significant in nonpainful joints alone. The overall amount of hand joint pathologies in a person with hand OA was not related to central sensitization except for presence of erosive hand OA. Disease duration was not associated with central sensitization.

The cross-sectional study design limited the ability to draw conclusions about causality. Prospective studies are needed to better understand the risk factors for pain sensitization and the causal association between pain sensitization and hand pain. Further, reliability-testing of pain algometry and temporal summation showed variable results and efforts should be made to enhance the reliability of these tests in future studies.

The papers of this thesis confirm the clinical relevance of pain sensitization in hand OA. The results lay a groundwork for further exploration of how pain sensitization may be targeted to reduce chronic pain from hand OA.

Sammendrag

Betydningen av overfølsomhet for smerte ved leddsykdommen håndartrose

Personer med håndartrose, kan ha plagsomme smerter uavhengig av om de har milde eller alvorlige forandringer på røntgen av hendene. En av forklaringene er smertesensitivering – mekanismer i nervesystemet som fører til økt følsomhet for smerte.

I avhandlingen *«Pain sensitization in hand osteoarthritis»* har Pernille Steen Pettersen og medarbeidere brukt kliniske smerteføIsomhetstester for å undersøke sensitivering i det det perifere og sentrale nervesystemet hos personer med håndartrose. Med nesten 300 studiedeltagere er dette per i dag den største studien i verden på dette feltet.

De fant de at rundt 40% av personer med håndartrose har økt smerteoverfølsomhet og at det å være sensitivert er forbundet med mer smerter.

Følsomheten for trykksmerte på fingerledd var forbundet med grad av selvrapporterte håndsmerter. Følsomheten for trykksmerte andre steder på kroppen som ikke er rammet av artrose var også forbundet med grad av håndsmerter. Disse funnene var tilstede uavhengig av andre faktorer, som kjønn, depresjon, angst og alvorlighetsgrad av artrose.

Jo høyere grad av leddforandring eller leddbetennelse som fantes i et ledd, jo høyere var sensitiviteten for trykksmerte i det samme leddet. Dette bekrefter tidligere funn og understøtter teorien om at perifer smertesensitivering forårsakes av artrose.

Når man så på den totale alvorlighetsgraden av leddforandringer og leddbetennelse i hendene til deltagerne var det ingen sammenheng med smerteføIsomhet på steder på kroppen som ikke var rammet av artrose. Det tyder på at andre faktorer enn artrose er viktige forklaringer på sentral sensitivering.

Avhandlingen viser at perifer og sentral sensitivering forklarer en del av smerteopplevelsen hos personer med håndartrose. Dette er viktig å vite når man skal kartlegge artrosesmerte og velge behandling. De underliggende årsakene er fortatt uavklart, men resultatene danner viktig grunnlag for videre forskning på medikamenter og behandlingsmetoder som kan redusere smerter.

1. Introduction

Osteoarthritis (OA) is the most common chronic joint disease worldwide and a leading cause of disability(1). While all joints of the body may be affected, the hand is one of the most frequent sites. By the age of 85, about every second woman and one in four men, is estimated to have had symptomatic hand OA during their lifetime, and almost all will have signs of OA on radiographs(2, 3). Hand OA is characterized by bone enlargements, deformities and inflammation of finger joints, and varying and intermittent symptoms of pain, stiffness and reduced motion and strength of the hands(4).

The dominant OA symptom that drives people to seek health care is pain. Pain significantly reduces health-related quality of life for OA patients, and is for hand OA comparable to the burden of pain in patients with rheumatoid arthritis(5, 6). Despite decades of research, there are no therapies available for OA that may reverse, stop, or halt the disease, and no symptom relieving options with acceptable effectiveness. This has made the search for a better understanding of the underlying mechanisms of OA pain a research priority.

Chronic pain does not follow the same rules as acute pain and the acknowledgement of this is incorporated in modern pain research. Chronic pain is more complex and heterogeneous, and it is argued that chronic pain should be considered a disease entity of its own(7). During the last two decades OA pain research has become a research field in its own, where rheumatology and pain medicine meet and share necessary knowledge. In hand OA, and OA in general, structural abnormalities and inflammation contribute to pain but the overall relationship between structural damage/inflammation and pain severity is weak(8).

Neuroplastic changes in the peripheral and central nervous system, i.e., pain sensitization, is found to contribute in the development of maladaptive chronic pain in OA(9). Already, evidence of pain sensitization as a possible direct or indirect treatment target is emerging. However, the majority of studies on pain sensitization are of persons with knee and hip OA. There is a gap of knowledge of pain sensitization and its relevance in hand OA, which is crucially needed for hand OA to be included in the modernization and improvement of OA pain therapy.

2. Background

2.1 Hand osteoarthritis

OA is a common joint disease characterized by pain and disability which can affect all joints of the body. Although hand OA is the most prevalent subtype with substantial symptomatic burden, it received little attention compared to knee and hip OA until about 20 years ago(10). It's involvement of several joints at the same time make hand OA more complex and difficult to study. Today, increasing knowledge about clinical burden, subtypes, disease course and treatment is available.

2.1.1 Definitions and classifications

The Osteoarthritis Research Society International (OARSI) defines OA as "a disorder involving movable joints characterized by cell stress and extracellular matrix degradation initiated by micro and macro-injury that activates maladaptive repair responses including pro-inflammatory pathways of innate immunity. The disease manifests first as a molecular derangement (abnormal joint tissue metabolism) followed by anatomic, and/or physiologic derangements (characterized by cartilage degradation, bone remodelling, osteophyte formation, joint inflammation and loss of normal joint function), that can culminate in illness"(11).

There is no uniform definition of hand OA. It can be defined based on the presence of typical radiographic findings alone, referred to as radiographic hand OA, or as a combination of typical symptoms and clinical and/or radiographic findings (symptomatic OA). The ACR classification criteria of hand OA include a combination of symptoms (pain, aching or stiffness on most days of the prior month) and typical clinical findings (hard tissue enlargement and deformity) including criteria of distribution and number of hand joints that are affected (Textbox 1)(12). These criteria are ment to define persons with hand OA in clinical studies, including observational studies as well as clinical trials. The criteria are, however, hampered by not being able to classify early disease and not differing between different hand OA subtypes (e.g., thumb base and interphalangeal OA). The criteria require clinical examination data, which is not available in large observational studies and is often associated with poor reliability. New classification criteria for hand OA overall, thumb base OA and interphalangeal OA are currently being developed by a EULAR task force(13).

Various other independent definitions of symptomatic hand OA are also used in literature(14). They have in common a criterion of typical radiographic OA which might be of a single radiographic feature, i.e., osteophyte or of a minimum grade of 2 ("definite OA") of the Kellgren Lawrence grading system for hand OA, of one or several hand joints.

Textbox 1. ACR criteria for classification of hand OA.

Hand pain, aching or stiffness for most days of the prior month
+
Three of the following

- Hard tissue enlargement of 2 or more of 10 selected joints
- Hard tissue enlargement of 2 or more DIP joints
- Fewer than 3 swollen MCP joints
- Deformity of at least 1 of 10 selected joints

*Selected joints: bilateral DIP 2nd and 3rd, PIP 2nd and 3rd and CMC-1.

The hands can be the only joint group affected by OA or it can be one of several joint groups affected in person. This is often referred to as generalized OA, but there are no standard definition(15). OA of several joint groups of the body, e.g., both hands, knees and hips are of interest as the clinical burden of generalized OA disease can be greater and because it suggests a possible systemic aetiology for a subgroup of patients(4, 16).

2.1.2 Clinical features and diagnosis

A joint comprises of not only the articular cartilage surfaces, but also the bone beneath, synovium, ligaments, tendons, and muscles. OA is considered a disease of the whole joint and symptoms and presentations from any of the structures may be attributed to OA.

Hand OA usually involve approximately symmetrical distribution of joints, either in rows or rays, and symptoms are therefore often bilateral. Characteristically, hand OA affect the distal interphalangeal joints (DIP), the thumb base with the first carpometacarpal (CMC-1) and scaphotrapeziotrapezoidal (STT) joint, the proximal interphalangeal joints (PIP, including the first interphalangeal joint) and the metacarpophalangeal (MCP) joints, with decreasing prevalence (Figure 1)(4). The symptoms are intermittent and may affect just one or a few joints at the time(4).

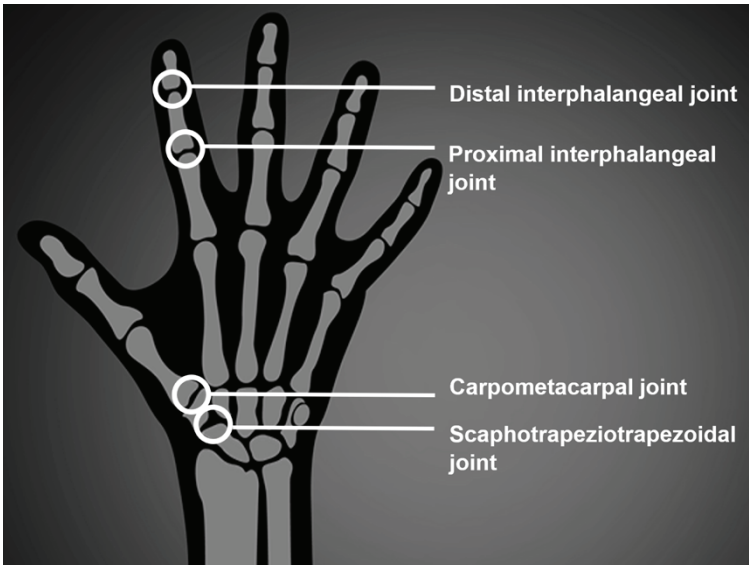

Figure 1. Anatomy of the hand. *Figure made by Anne-Therese Tveter, Diakonhjemmet Hospital.*

Symptoms

The main symptom of hand OA is pain, which is ranging from mild to severe. Hand OA pain fluctuates during the day, worsens on usage, especially repetitive and heavy activity, and there might be resting pain and even night pain(17, 18). Pain characteristics of hand OA are heterogeneous, but common descriptions of pain are dull, aching, sore, inhibiting, radiant, pricking and burning(19). Many of these descriptors are similar to features of neuropathic pain, which also is common in knee OA. A systematic review of knee OA pain found that about 23% report neuropathic-like pain(20). We use our hands almost for everything we do during a day and the limiting consequence of hand pain may for some cause negative emotions: “I can’t do fun things”(21). Persons with hand OA have reduced health-related quality of life compared to controls and have similar levels of health-related quality of life, pain, and disability as patients with rheumatoid arthritis(5, 6, 22).

Other symptoms are stiffness and impaired function. Stiffness is usually in the morning (<30minutes) or after a period of inactivity (a few minutes)(18). Restricted function is caused by reduced range of motion and reduced grip strength and patients might complain about difficulties in handling small objects, writing and twisting the hands(23). In addition, persons with hand OA may report that they feel uncomfortable by the appearance of their hands(24).

Diagnosis

Hand OA can be diagnosed based on a history of symptoms, risk factors and typical findings on physical examination alone. The European League Against Rheumatism (EULAR) elaborate on the evidence-based recommendation for diagnosis of hand OA in their paper from 2009(4). Imaging, such as radiographs or ultrasound, and supplementary tests can be used in the case of uncertainty, to verity the diagnosis and exclude differential diagnoses such as rheumatoid arthritis, psoriatic arthritis, gout, and hemochromatosis. On physical examination of the hands, findings include bony enlargement, deformities, soft tissue swelling, erythema, tenderness, and limited motion. An evaluation of subtype should be made as they may require different treatment and follow-up.

Clinical features of nodal, thumb base and erosive OA

Heberden's and Bouchard's nodes are firm swellings on the dorsal or lateral aspects of the PIP and DIP joints, respectively (Figure 2). These nodes are often associated with underlying structural OA abnormalities like osteophytes and when they are, they are the hallmark of *nodal OA*(4). Nodes most frequently occurs at the index and middle finger(12). In addition to nodes, lateral deviation towards the middle finger and restricted motion of the PIP and DIP joints are common.

OA of the CMC-1 joint with or without STT OA comprises the *thumb base* OA subtype, although nodal OA is often coexisting(25). On examination one can find deformity by radial subluxation of the metacarpal base and abduction of the thumb which gives a squaring formation of the joint (Figure 2). Grip and pinch strength is reduced compared to healthy individuals(26).

If a patient presents with severe symptoms either with subacute onset of pain and inflammation in several joints and/or in the presence of many nodes, they may have *erosive* hand OA(27). Erosive hand OA is a subtype that is defined radiographically by subchondral erosion, cortical destruction, and subsequent reparative changes, and therefore not possible to diagnose by certainty by clinical examination alone(4). Erosive hand OA of the DIP and PIP joints is seen three times as common in women than men(3). Erosive joints and persons with erosive OA have more severe pain, stiffness, disability, tenderness, and radiographic findings compared to non-erosive joints and persons with non-erosive OA(3, 27-30). It is not decided if erosive OA is a separate disease entity or a severe stage of OA. The clinical burden of

erosive hand OA may be attributed to the greater disease severity itself. Also, persons with erosive hand OA have more inflammation, and experience more frequently progression of inflammation and structural changes, independent of inflammation and structural severity, and it is therefore suggested to represent an inflammatory phenotype, possibly with a distinct pathophysiology(31, 32).

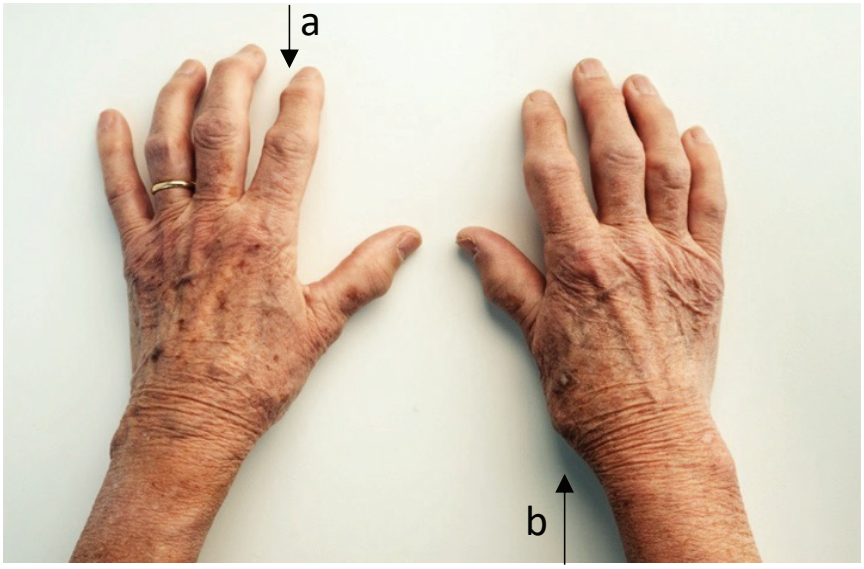

Figure 2. Typical hand OA features of PIP, DIP and the thumb base joints. a) Heberdens's nodes at the second DIP, b) Subluxation of the right CMC-1 joint. *Photo by Nicolas Tourrenc.*

2.1.3 Imaging

Conventional radiographs

Conventional radiography is considered the "gold standard" imaging modality of structural hand OA, both as a diagnostic tool and as outcome measure of structural damage in clinical trials(4, 33). It provides two-dimensional pictures of bony OA changes such as deformities, osteophytes, joint space narrowing, erosions, subchondral cysts, and sclerosis. It has the advantages of being inexpensive, fast, and easily accessible. Conventional radiographs may not visualize soft tissues, including cartilage which is evaluated indirectly by joint space narrowing. The radiation exposure for a hand radiography is minimal (0.001 millisievert, which corresponds to only 3 hours of natural background radiation).

Several scoring methods exists, where the most used are Kellgren Lawrence grading, Verbruggen-Veys anatomical phase score, Kallman grading system and the OARSI atlas(34-38).

Ultrasound

Ultrasound examinations provide the opportunity to visualize multiple anatomical and pathological features of a joint from multiple angles, including cartilage, joint capsule, joint space narrowing, osteophytes, erosions, synovial hypertrophy, effusion, and increased vascularization of synovitis, without exposing the patient to radiation. For an experienced operator, multiple joints may be evaluated within reasonable time. A disadvantage of ultrasound examination is its dependency on an experienced operator and thus sufficient training is mandatory.

Ultrasound is useful for research purposes, especially for evaluation of joint inflammation where the primary alternative is MRI which is expensive and demands time consuming interpretation of images. Scoring systems and atlases with illustration images of pathologic features have been developed for hand OA(39-42). Joint inflammation may be evaluated on grey-scale imaging of the size of synovial hypertrophy and of effusion, and by power Doppler signal for vascularization within the area of synovial hypertrophy. The first scoring system, by Keen *et al*. in 2007, recommended to consider synovial hypertrophy and effusion together as grey-scale synovitis(39). The detection of synovitis by ultrasound correlates well with MRI and is more sensitive than clinical examination(43, 44). Also, the sensitivity of structural abnormalities in hand OA, including osteophytes and erosions has been found to be good compared to conventional radiographs(45). Ultrasound images are not recommended by OARSI as a primary outcome measures in clinical trials of hand OA, but its scientific use is anticipated to increase as prospective research strengthen its validity(33).

Other imaging techniques

Other imaging modalities with a potential role in research are MRI, computer tomography and optical imaging. MRI is the only modality that can visualize bone marrow lesions and is generally more sensitive than radiography for structural features and as sensitive as ultrasound of inflammation(45). Bone marrow lesions are of interest because they, in OA, represent vascularization, remodelling and fibrosis in the bone which may be an important feature for pain(45, 46). Computer tomography is limited to visualization of bone abnormalities but may be useful as a “gold standard” for validation of several MRI features. Optical imaging represents a potential alternative for assessment of joint inflammation, but preliminary results in hand OA suggest that the value of the examination is questionable(47, 48).

2.1.4 Epidemiology

Hand OA is a highly prevalent disease. The probability of developing symptomatic hand OA during a lifetime is about 40%, considerable higher for women (50%) than for men (25%)(2). Prevalence estimates of hand OA in adults vary depending on hand OA definition and populations that are being studied. Symptomatic hand OA is less common than radiographic. In a US population the age-standardized prevalence of radiographic hand OA was 44% of women and 38% of men, while the age-standardized prevalence of symptomatic hand OA was 14% of women and 7% of men(3). In a Chinese population the prevalence of symptomatic hand OA was considerable lower (6% of women and 3% of men)(49). Recent results from a community-based study from USA found that both radiographic and symptomatic hand OA was more than twice as common in white than African American participants(50). Although hand OA may occur as a symptomatic disease in relatively young persons, the prevalence increases with age and at the age of 80 one can find radiographic hand OA in close to 100% of men and women(3).

2.1.5 Aetiology and pathogenesis

Aetiology

OA used to be considered as a disease of cartilage degradation but is now viewed as a disease of the whole joint also involving bone, synovial membrane, and periarticular tissue(51). It is not a passive disease, but the result of an ongoing dynamic imbalance between repair and destruction of join tissues with associated inflammation. And finally, OA is a heterogeneous disease with multifactorial origin where biomechanical, systemic, genetic, and environmental factors contribute.

Risk factors for hand OA are, in addition to female sex, age and race, considered to include also menopausal status, obesity, high bone mineral density, mechanical forces through occupational or other hand related activities, history of injury and family history(52).

Pathogenesis

The diarthrodial joint, like finger-, knee- and hip joints, consists of two bones covered by cartilage tissue and encapsuled by the synovium. The cartilage is a specialized articular cartilage made of a single cell type, the chondrocyte, and of extracellular matrix with water, collagens (mainly type II collagen), proteoglycans and other proteins. Healthy cartilage is

avascular and has no nerves. The chondrocytes secure a dynamic homeostatic environment of the matrix, with repairing and regenerating processes, needed for the joint to function. In early OA this balance of anabolic and catabolic processes is impaired such that the chondrocytes are in an overly active metabolic state. As the disease progresses there is gradual depletion of proteoglycans and erosion of the collagen. The changes of the composition and structure of cartilage lead to surface fibrillations, fissures with exfoliation of cartilage and gradually exposure of the bone beneath. Also, there are reparative processes of calcification and new bone formation. The change of the cartilage weakens its ability to withstand physical forces causing a vicious cycle of cartilage damage. Part of the disease process are also: upregulation of genes of proteins that are associated with catabolic and inflammatory responses, chondrocyte production and secretion of pro-inflammatory products like cytokines and chondrocyte death(51).

Periarticular bone is also important in OA pathogenesis. It can be divided into subchondral bone (cortical bone), the subchondral trabecular bone and the joint margins. Osteoclast and osteoblast cells, together with local hormones and soluble mediators, resorb bone and mediate formation of new bone as a response to mechanical stimuli. The OA abnormalities reflect alterations of this repair and remodeling process. The cortical bone increases in volume and thickness while the trabecular bone changes its architecture and bone mass and there is formation of subchondral cysts and of osteophytes at the joint margins(51). Bone marrow lesions are formed(53). Subchondral cysts are hypothesized to be a consequence of these changes, because they seem to develop at sites with bone marrow lesions(54). Finally, angiogenesis with vascular invasion in meniscus, osteophytes and subchondral bone has been demonstrated(55).

A synovial membrane and the synovial fluid make up the synovium. The membrane allows transfer of important molecules in and out of the joint, and the synovial fluid consist of lubricant factors and nutrients. Low-grade inflammation has increasingly been recognized as part of OA pathogenesis(56). Inflammation of the synovium, synovitis, is assumed to be secondary to cartilage breakdown. The pro-inflammatory factors generated by the chondrocytes and cartilage degradation act on the synovium and stimulate proliferation and further production of pro-inflammatory factors. Synovitis act as feedback on the cartilage to further (de)regulate their function, introducing another vicious circle of pathogenesis. In addition to hyperplasia of the synovium, synovitis is characterized by infiltration of T- and B-lymphocytes and there has been detected cytokines and chemokines (such as IL-1, IL-6, IL-8,

IL-15, and tumor necrosis factor (TNF)) in synovial fluid(51). The findings of immune system activation with associated pain have led to the hope of finding targets for disease-modifying drugs(57).

2.1.6 Management

There is no known cure for OA. Evidence-based recommendations of management for hand OA are therefore confined to symptomatic pharmacological and non-pharmacological treatment aimed at reducing pain and physical disability (Figure 3)(58). A main principle is that treatment should be individualized and tailored with a multidisciplinary approach where disease characteristics, comorbidities, comedication and the patients' own preferences are considered.

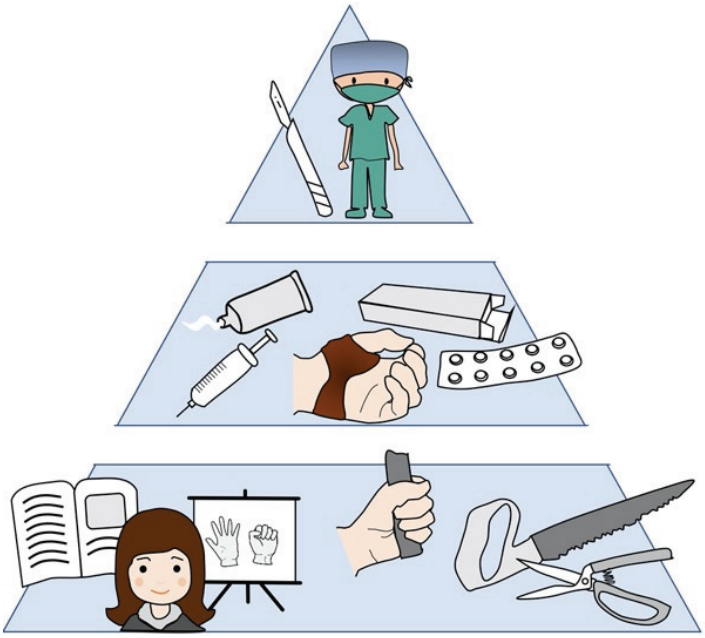

Figure 3. Available treatment options for hand OA. *Education with information on hand OA and advise on self-management, use of supportive devices and exercise are the first-line options that should be considered first for all patients. If further treatment is needed, orthosis for thumb base OA, intra-articular injections of glucocorticoids for painful interphalangeal OA and topical or oral analgesics may be considered. Surgery, including trapeziectomy for thumb base OA and arthrodesis or arthroplasty of interphalangeal OA, should be considered when conservative treatment fails to relieve severe symptoms. Figure made by Anne-Therese Tveter, Diakonhjemmet Hospital.*

Effectiveness of various treatment strategies in hand OA are seldom better than mild to moderate. For example, hand exercises may reduce pain and stiffness in hand OA patients, but a recent Cochrane systematic review found only evidence for a small to moderate beneficial effect with questionable clinical importance(59). Of pharmacological options, topical NSAIDs are the first choice, and despite multiple trials proving pain relief, effect is considered small(58). Other options such as surgery, patient education on joint protection and use of supportive splints may be beneficial for some, but not for all(60). The heterogeneity of OA disease and the complexity of pain may explain variation in treatment response. Defining phenotypes of OA based on aetiology, structural characteristics, pain mechanisms, trajectories etc. may possibly allow established and future therapies to be targeted for subgroups of patients with better effects(61).

2.2 Pain

The word pain derives from the Latin word *poena*, meaning penalty. Pain is a primitive motivator for our survival just like hunger, thirst, and reproductive drive. It prevents damage by alerting, making us withdraw or move more carefully, and it is important in teaching us what is safe and not safe to do in life.

2.2.1 Definitions and terminology

The international association for the study of pain (IASP) define pain as “an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage”(62). The term *experience* acknowledges pain as a subjective phenomenon where the bodily sensory component ultimately is uniquely colored by personality and environmental influences. It also calls for a biopsychosocial approach from health care professionals when the aim is to understand and treat pain. The physiological response to tissue damage, i.e., the sense of pain, is called nociception. A stimulus that causes nociception is called a noxious stimulus.

Acute and chronic pain

Pain can be classified as acute or chronic pain. Acute pain is the expected response to an injury, a disease process, abnormal function of internal organs or surgery. When pain persists even after the tissue has healed or longer than expected, it is defined as chronic pain(63). This

definition is somewhat unsuited for chronic pain caused by OA where we do not expect the damaged joint tissue to ever heal. In 2011, chronic pain and specific chronic pain diagnoses were for the first time systematically included in the International Classification for Diseases. In the International Classification for Diseases-11 chronic pain is defined as "pain that persists or recurs for longer than three months" and divide chronic pain in six subcategories: primary, cancer related, traumatic/postsurgical, secondary musculoskeletal, secondary visceral, neuropathic and headache/orofacial pain(64). It allows the combination of a disease specific diagnosis with a chronic pain diagnose, e.g., combining the diagnosis of OA of the hand with "Chronic secondary musculoskeletal pain associated with structural changes".

Chronic pain has a huge impact on global health. Musculoskeletal diseases, including chronic low back pain, neck pain, OA and rheumatoid arthritis were ranked as the first and biggest contributors to global disability in 2019 by the Global Burden of Disease Study(65). The prevalence of chronic pain in the general population varies due to various definitions being used. A meta-analysis from 2017 estimated a prevalence of 33% from 80 studies of worldwide populations, ranging from 9% in Singapore to 64% in the US(66).

Nociceptive, neuropathic and nociplastic pain

Another classification of pain is of its underlying pathophysiologic mechanisms where the taxonomy developed by IASP divide pain into three types: nociceptive, neuropathic and nociplastic (Textbox 2) (67). Nociceptive pain is defined as "pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors". "Pain caused by a lesion or disease of the somatosensory nervous system", for example diabetic neuropathy, post-herpetic neuralgia or central pain caused by multiple sclerosis, is termed neuropathic pain. Neuropathic pain is a clinical description, but it demands either verified nerve damage or fulfillment of established diagnostic criteria of neurological conditions. The third descriptor is named nociplastic pain: "pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain".

Nociplastic pain was added in 2018 by the IASP Terminology Task Force to encompass the many patients with chronic pain that have clinical and psychophysical signs of changed nociceptive function but do not fulfill the criteria for nociceptive or neuropathic pain(68). Nociplastic pain should not be interpreted or misclassified as idiopathic pain or pain of

unknown origin, as nociplastic pain requires a demonstrable altered nociception by either neurography, functional magnetic resonance imaging (MRI) or quantitative sensory testing (QST). Examples of conditions where nociplastic pain is considered the main pain mechanism is fibromyalgia, complex regional pain syndrome and irritable bowel syndrome(69-71). A patient may have a combination of nociplastic and nociceptive and/or neuropathic pain. The term is suggested to be a useful clinical descriptor of the results from psychophysical tests like QST, in other words as a nominator for pain that is believed to be caused by pain sensitization. Although the terminology in pain research probably always will be a subject of dispute, nociplastic pain is already being used extensively in literature as a search in scientific databases like PubMed will reveal.

Textbox 2. IASP Mechanistic classification of pain

Nociceptive	**Neuropathic**	**Nociplastic**
Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors.	Pain caused by a lesion or disease of the somatosensory nervous system.	Pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain.

2.2.2 Neurophysiology

The nociceptive system consists of peripheral and central sensory afferent nerves, nociceptors. The cell bodies of the nociceptors are in the dorsal root ganglia. Nociceptors are thinly myelinated (rapid conductive) Aδ or unmyelinated (slow conductive) C fibers with free nerve endings. The neurophysiological process of pain consists of transduction, transmission, modulation, and perception.

At the terminals of the peripheral nociceptors, noxious stimuli are transduced into electrical activity by specific receptors or ion-channels that are sensitive to mechanical, thermal or chemical stimuli. Most nociceptive terminals are polymodal, meaning that they respond to several types of noxious stimuli. For example, TRPV1, also known as the capsaicin and vanilloid receptor, is activated both by noxious heat and the noxious chemical compound from chilipeppers, capsaicin. Voltage gated sodium channels are essential for transduction of

stimuli as they regulate excitability(72). $Na_v1.7$, $Na_v1.8$ and $Na_v1.9$ are selectively expressed at peripheral nociceptors(73).

Action potentials are conducted to the dorsal horn of the spinal cord and, through synapses and interneurons, further transmitted via the spinothalamic and spinoparabrachial pathways to the brain. Several areas of the brain are involved and activated including the thalamus, the somatosensory cortex, the ventral medial nucleus of hippocampus and the central nucleus of amygdala (which are involved in the affective component of pain)(74).

Ascending nociceptive signals are modulated by inhibition and facilitation at the spinal level by descending tracts originating in the brainstem nuclei of the periaqueductal grey and nucleus raphe magnus. Finally, nociceptive signaling is integrated to a subjective perception of pain.

2.2.3 Pain sensitization

Nociceptors normally have high thresholds for activation and is only activated by noxious stimuli. If the body is exposed to intense noxious stimuli or repeated noxious stimuli the nociceptive system responds with a state of heightened sensitivity. For example, after a burn injury, light touch at the site of injury may feel painful or there may be pain from the area around the injury. When the damage is healed the hypersensitivity gradually resolves. This is the physiological protective and plastic function of pain sensitization. However, central pain sensitization mechanisms may be maladaptive and become persistent and is believed to be a contributing factor developing and maintaining chronic pain(75).

Peripheral sensitization

Peripheral sensitization is defined by IASP as “Increased responsiveness and reduced threshold of nociceptive neurons in the periphery to the stimulation of their receptive fields”(67). It is caused by the release of inflammatory chemical mediators (often called “inflammatory soup”) as a response to injury, inflammation, or disease related tissue damage(74). The inflammatory soup, including chemicals such as histamines, serotonin, bradykinin, prostaglandins, nerve growth factor (NGF) and interleukins, stimulate and sensitize the nociceptive terminals by reducing the activation thresholds of receptors and making them more susceptible to respond to both noxious and non-noxious stimuli. The clinical result of peripheral sensitization is primary hyperalgesia (exaggerated pain from pain

stimuli at the site of injury) and primary allodynia (pain from normally non-noxious stimuli, like light touch, at the site of injury).

Central sensitization

IASP define central sensitization as "Increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input"(67). Central sensitization involves both spinal and supraspinal neurons and may be described as a generalized hyperexcitable state. It causes hypersensitivity by increasing spontaneous activity in central neurons, reducing activation thresholds of central nociceptors, amplifying input from peripheral nociceptors, and expanding of the receptive field(76-78). The clinical result of hypersensitivity due to central sensitization is secondary hyperalgesia, secondary allodynia, a larger area of receptive field for a pain stimulus and higher pain intensity and duration. Widespread hyperalgesia is also a nominator for the clinical consequence of central sensitization.

Impaired descending pain modulation

Reduced ability of the descending pain modulation to control pain is another central neuroplastic mechanism. It is often considered as a separate phenomenon to central sensitization, although it contributes to the net clinical consequence of central sensitization. The clinical consequence is widespread hyperalgesia(79).

Measuring pain sensitization

One approach that is increasingly being used in OA pain research is QST. QST evaluate sensory mechanisms by evoking controlled noxious and non-noxious stimuli in a systematic manner at different sites of the body, while the person being examined expresses what they sense. Different stimuli modalities may be used, including mechanical pressure and punctuate stimuli, hot and cold thermal, electric, and chemical stimuli(80). QST examinations that specifically examine peripheral and central sensitization, and impaired descending pain modulation have been developed(79).

In literature questionnaires are also frequently used as a measure of central sensitization. Examples of questionnaires design to identify patients that have symptoms that may be related to central sensitization are the Central Sensitization Inventory and the Pain Sensitivity Questionnaire(81, 82). A validated Norwegian version is available of the Pain Sensitivity

Questionnaire(83). Also, the painDETECT questionnaire, developed to identify neuropathic pain in persons with back pain, has been associated with signs of central sensitization and is sometimes used as an indicator(84, 85).

Functional MRI makes it possible to detect activated brain regions by measuring signals of increased blood flow(86). By combining functional MRI with evoked pain, painful activities and/or pain reports of persons being examined, indications of central sensitization may be inferred by visualizing activity in brain areas associated with chronic pain.

2.3 Osteoarthritis pain

As the aetiology of OA is not fully understood and a cure still is unavailable, OA pain itself has naturally become a research field of interest. OA is the most common cause of chronic joint pain and was ranked as the 15th largest contributor to global disability in 2019(65). OA pain is the main cause of reduced function and quality of life and the primary reason to seek help from the health care system(87).

Traditionally, OA pain was considered nociceptive and related to local tissue damage. However, its chronicity, variation in character and response to therapy as well as the discordance between radiographic and symptomatic prevalence has recognized OA pain pathophysiology to be much more complex(8, 88). Structural factors, joint inflammation, peripheral and central sensitization, neuronal changes, and contextual factors contribute to OA pain.

2.3.1 Nociceptive pain

Stimulation of mechano- and chemosensitive receptors by structural changes and tissue inflammation may cause nociceptive pain in OA joints. All tissues of the joint, except the healthy articular cartilage, is highly innervated by sensory afferent fibres and about 80% of these are nociceptors(55). However, the exact mechanisms by which OA causes pain are not clear. A structure-symptom discordance of weak associations between radiographic and symptomatic OA has questioned the role of structural alterations on pain experience(89-91). However, methodological limitations and the challenge of accounting for psychological and environmental factors may have concealed the true contribution of joint pathologies on pain(8). Indeed, more recent studies using MRI, which is more detailed and sensitive, have

revealed several distinct features, notably of inflammation, to be of importance for OA pain experience(92).

A 2015 systematic review of Barr *et al*. of associations between bony OA imaging features by MRI with pain found that bone marrow lesions and osteophytes of knee OA, and bone marrow lesions and cysts of hip OA, were associated with pain severity(93). An earlier systematic review of knee OA from 2011 included MRI features of synovitis and found synovitis (both synovial thickening and effusion) to associate with knee pain(94). These findings were shortly after supported by a large high-quality study by Baker *et al*. that found synovitis to strongly associate with knee pain severity(95). Regarding structural features on conventional radiographs, in 2009 Neogi *et al*. used a method of matched knees with and without pain within the same participants to account for person-related confounding and demonstrated a clear and strong dose-dependent relationship of definite and severe structural OA severity and knee pain(96). Finally, it is worth mentioning the effect of joint replacement in knee and hip OA, where about 80% are pain free after surgery(97).

Barr *et al*. concluded in their review that MRI detected bone marrow lesions, osteophytes and cysts were not associated with pain in hand OA(93). They referred to the association of sum scores of features across bilateral hand joints with overall hand pain severity. Similarly, sum scores of MRI- and ultrasound-detected synovitis are only weakly or not associated to hand pain(98-101). However, when examining the associations between pathologic features of a hand joint and presence of pain in the same joint, there are strong associations. Radiographic severity of Kellgren Lawrence grade, ultrasound-detected synovitis and power Doppler activity and MRI-detected bone marrow lesions and synovitis have repeatedly been shown to be associated with joint tenderness(57, 90, 98, 100, 101). In these studies, joint tenderness was examined as absent/present or by the Doyle index (grade 0-3, evaluated by the assessor by observing the reaction of the participant when pressing on the joint) which may reflect different aspects of pain than self-reported measures. Interestingly, recent results from the Nor-Hand study by Maugesten *et al*. and by Fjellstad *et al*., found strong dose-response associations of increasing MRI- and ultrasound-defined synovitis and power Doppler activity with presence of self-reported pain at joint level(101, 102).

2.3.2 Nociplastic pain

About 20 years of research have determined that peripheral and central sensitization contribute to OA pain. Evidence of this is derived from preclinical and clinical research. Pain sensitization is suggested to contribute to pain especially in individuals where there are seemingly discrepancies between severity of joint pathology and pain severity, i.e., partly nociplastic pain. Attention has been predominantly on knee OA and to a lesser extent hip OA, while research on this subject in hand OA has been minimal.

Peripheral and central sensitization: Preclinical

Experiments of evoked pain, behavioural observations, electrophysiology and neurobiological imaging techniques in animal models of OA have repeatedly demonstrated that peripheral nociceptors become sensitized to mechanical stimuli during the course of the OA disease(103). These experiments have also suggested that peripheral sensitization occurs by recruitment of new neurons, "silent nociceptors" that become sensitized to mechanical stimuli(55). Another interesting recent finding of peripheral nociception is that blocking/silencing of neurons that express the voltage-gated sodium channel $Na_v1.8$, reversed peripheral sensitization in early but not late stages of OA(104). This both confirms that this channel is a potential treatment target for pain sensitization and raises the question of a "window of opportunity" for preventing pain sensitization.

Animal model experiments have also found that OA seem to drive and maintain central sensitization at the level of dorsal horn neurons(105). For example, activation of resting microglial cells (microgliosis) in the area of spinal dorsal horn is associated with the onset of pain sensitization in a surgical OA model of mice, suggesting that targeting microgliosis may prevent pain sensitization(106).

Peripheral and central sensitization: Clinical

Clinical research has found clear signs of peripheral and central sensitization by QST in knee and hip OA and confirmed that it contributes to OA pain as systematically reviewed by Soukas *et al*. (2011), Lluch *et at*. (2014) and Fingleton *et al*. (2015) and narratively reviewed by Hassan and Walsh (2014) and Arendt-Nielsen (2017)(9, 77, 107-109). Meta-analyses repeatedly find that persons with OA have lower pain thresholds at the affected joint and lower widespread pain thresholds than persons without OA(108, 109). Local and widespread

pain thresholds and facilitated pain responses are associated with pain severity in knee and hip OA(110-114). Finally, peripheral and central sensitization is associated with development/persistent pain even after joint replacement surgery, further indicating that pain sensitization is of importance for OA pain(114, 115).

Research on pain sensitization in hand OA is limited. A handful of small-sized studies found persons with hand OA to be more sensitized by QST than healthy controls but have not found associations with pain(116, 117). A study using functional MRI found evidence of central sensitization to mechanical stimuli in hand OA patients and not in healthy controls(118). These suggests similar relevance of pain sensitization in hand OA as of other joints, but this needs to be confirmed in larger studies.

Mediators of pain sensitization

Mediators of pain sensitization are of great interest as they represent possibly modifiable treatment targets of analgesic drugs.

NGF is found to play an important mediating role in peripheral sensitization in OA pain. NGF binds to its tropomyosin-related kinase A (TrkA) and p75 neurotrophin receptor, which lead to peripheral sensitization of the TRPV1 receptor (Figur 4)(119). Levels of NGF have been found to be increased in synovial fluid of human OA joints, and synovial expression of NGF is associated with pain(55). Clinical trials of antibodies that block NGF have successfully achieved OA pain reduction, which validate the clinical relevance of peripheral sensitization on OA pain(120).

As previously described in section 2.2.5 about OA pathogenesis, many cytokines and chemokines have been detected in OA joints. In addition to their potential role in inducing nociceptive pain through promotion of inflammation of the synovium, they may also cause sensitization of joint nociceptor. For example, injection of TNF-α and Il-6 into knee joints of rats caused peripheral sensitization of C-fibers(121, 122).

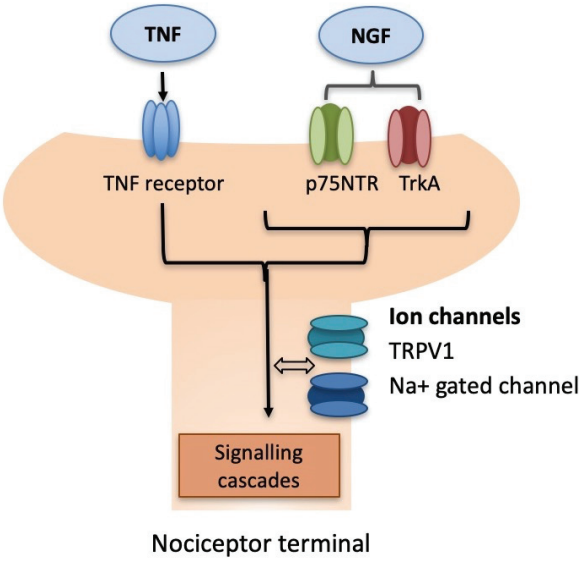

Figure 4. Nociceptor terminal. *Figure made by I.K Haugen, Diakonhjemmet Hospital.*

What causes pain sensitization in clinical OA?

Although preclinical research demonstrates direct link between OA and pain sensitization, the translational evidence for this is not clear. In knee OA, only synovitis, and not bone marrow lesions or structural OA, has so far been found to associate with peripheral and central sensitization(110, 113, 123). Further research of possible OA-related drivers of pain sensitization is needed.

The association between OA disease and central sensitization is possibly a combination of 1) a causal consequence of structural and low-grade inflammatory pathogenesis and 2) an a priori susceptibility or state of central sensitization determined by biologic, genetic, psychological, and environmental factors. Further, the relation between OA pathology and pain sensitization may be complicated by a time-dependent transition from neuroplasticity to chronic manifestations where peripheral input from joints may no longer be important.

2.3.3 Neuropathic pain

Remodelling of the innervation of OA joints is suggested to be a part of the OA disease pathogenesis and may contribute to pain. There is evidence of decreased innervation of the synovium, ectopic sprouting of sensory and sympathetic nerves in synovium and periosteum (possibly mediated by NGF) and of vascular penetration with accompanying nerve growth in

meniscus, osteophytes and subchondral bone(55). Interestingly, in both humans and experimental OA there has been observed neovascularization into cartilage (which under normal circumstances is nonvascular), which has led to the hypothesis that potential sensory nerves in the vascular channels may be a source of peripheral sensitization and pain(124). Finally, there is emerging evidence of sensory nerve damage in the joint, in dorsal root ganglia and in the spinal cord as part of the OA disease development(55, 125). Although this theory needs further investigation, it suggests that there might be a neuropathic component to OA pain, and that the neuropathic-like pain OA patients describe may actually be of partly neuropathic origin(20, 126).

2.3.4 Contextual aspects

IASP defines pain within the biopsychosocial model. This aspect is also important for OA pain. A multitude of factors are found to influence OA pain: biological factors such as obesity, diabetes mellitus, comorbidities and the gut-microbiome, psychological factors such as fatigue, anxiety, depression and pain catastrophizing and social and environmental factors such as level of education and weather (meteoropathi)(127-133), Various genetic variants have also been associated with OA pain, pain severity and pain sensitivity as summarized by Eitner *et al(105)*.

For hand OA specifically, little evidence is reported in literature. Diabetes mellitus, female sex, poor mental health, and lower education is found to influence pain(134). Recently presented preliminary results from the Nor-Hand study found strong associations between lower education, sleep disturbances, pain catastrophizing and anxiety/depression and hand pain in persons with hand OA(135).

3. General aim and research questions

3.1 General aim

The general aim of the thesis was to increase our knowledge of peripheral and central pain sensitization in hand OA by exploring pressure pain thresholds (PPT) and temporal summation (TS) in a large study population, and their relations to hand pain severity and of radiographic and ultrasound-detected joint pathologies.

3.2 Specific research questions

- What is the inter-rater reliability of manual algometry PPT and mechanical TS testing in persons with hand OA (paper I)?

- What is the prevalence and level of peripheral and central pain sensitization in persons with hand OA (paper I)?

- Are peripheral and central sensitization related to more severe hand pain (paper I)?

- Is the severity of structural and inflammatory features associated with peripheral and central sensitization (paper II and III)?

- Do severity of structural and inflammatory features of a joint affect peripheral sensitization regardless of concomitant joint pain (paper II)?

- Are persons with longer disease duration more likely to show signs of central sensitization (paper III)?

4. Materials and methods

4.1 Study design

All papers in this thesis are based on cross-sectional observational data from the baseline examinations of the Nor-Hand study. The Nor-Hand study is a cohort of persons with hand OA where one of the primary aims is to gain better understanding of pain and pain mechanisms(136).

Paper I and III explore the relationship of pain sensitization to hand pain and the relationship of joint pathology to pain sensitization in persons, while paper II examines the relation of joint pathologies and PPT at the same joint. In paper I we also report results from a test-retest of QST of nine participants.

4.2 Study population

The majority of the participants were recruited from the outpatient clinic at the Division of Rheumatology and Research at Diakonhjemmet Hospital, previously Department of Rheumatology. A few participants were also recruited from the "OA-school", a self-management day-course where patients are referred from either a rheumatologist or their primary physician and a few by convenience as they contacted the study coordinator directly and asked to participate. All participants were between 40 and 70 years of age and had hand OA diagnosed by an experienced rheumatologist on clinical and/or ultrasound examination as at least one finger joint with bony pathology and no signs of inflammatory arthritis (full description of inclusion/exclusion criteria in Textbox 3). The study sample size of 300 subjects was based on experience from previous studies and was not based on power calculations. In total 431 persons underwent screening of whom 311 were included and examined. After baseline examinations 11 subjects were excluded due to newly diagnosed inflammatory arthritis disease, psoriasis, withdrawal of consent and complete missing data, leaving 300 participants in the Nor-Hand study population (Figure 6).

Nine participants were not examined with QST because of a technical equipment error at a study visit. These were excluded from all papers. Paper II excluded an additional 6 participants due to incomplete data of PPT of interphalangeal joints, e.g., missing PPT at nonpainful joint or unclear which finger joint that had been examined and therefore impossible to match with corresponding radiographic and inflammatory score. In paper I, we

also excluded nine participants to whom we had failed to distribute the Hospital Anxiety and Depression Scale (HADS) questionnaire. Thus, for the primary analyses in paper I-III, we included 282, 285 and 291 participants, respectively (Figure 6).

Textbox 3. Inclusion and exclusion criteria for subjects in the Nor-Hand study.

Inclusion criteria

- Age between 40 and 70 years at screening
- Proven hand osteoarthritis by clinical examination and/or ultrasound
  Clinical examination criteria: Heberden/Bouchards nodes and/or bony enlargement, squaring and/or deformity of the thumb base and no clinical signs of inflammatory arthritis (eg, soft tissue swelling of two or less metacarpophalangeal (MCP) joints, and no soft tissue swelling of the wrist).
  Ultrasound criteria: Osteophytes in the interphalangeal joints and/or the thumb base, and no signs of inflammatory arthritis (e.g., synovitis with power Doppler activity in two or less MCP joints and no synovitis with power Doppler activity in the wrist).
- Capable of understanding and signing an informed consent form
- Provided a written informed consent to participate in the study

Exclusion criteria

- Diagnosis of inflammatory arthritic disease, for example, seropositive or seronegative rheumatoid arthritis, psoriatic arthritis, reactive arthritis, spondyloarthritis or arthritis related to connective tissue disorders (self-reported or from the medical chart)
- Diagnosis of psoriasis (self-reported, from the medical chart or presence of skin lesions suspect of psoriasis)
- Erythrocyte sedimentation rate >40 mm/hour and/or C reactive protein >20 mg/L, without a known ongoing infection
- Anti-cyclic citrullinated protein and/or rheumatoid factor positivity
- Ferritin >200 µg/L for women and >300 µg/L for men and s-iron/s-total iron binding capacity above 50% to rule out haemochromatosis
- Major comorbidities (eg, severe malignancies, severe diabetes mellitus, severe infections, uncontrollable hypertension, severe cardiovascular disease or severe respiratory disease)
- Mental or psychiatric disorders, alcohol or drug abuse, language difficulties or other factors that make compliance to the study protocol difficult.

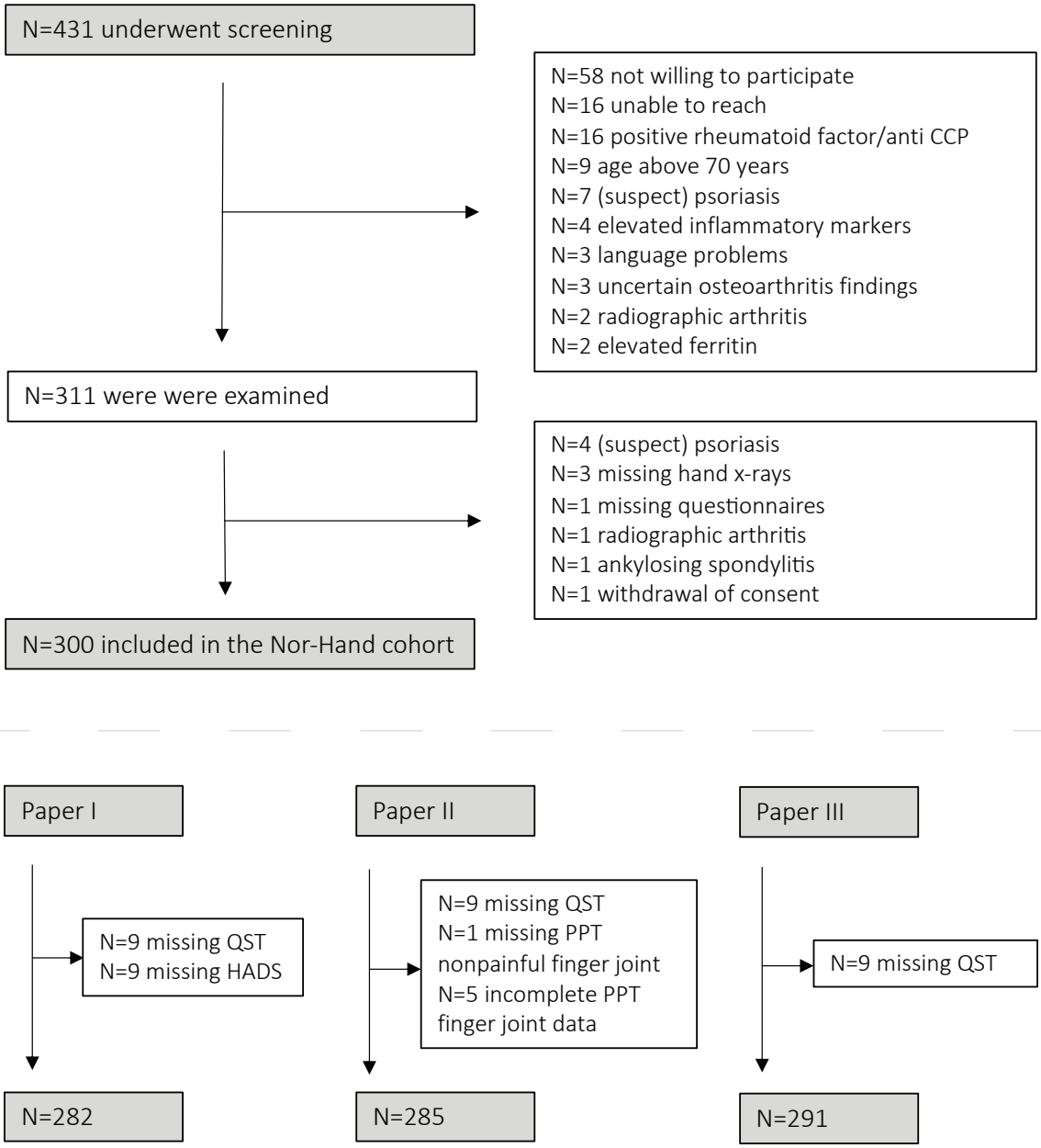

Figure 6. Flowchart of the participants in the Nor-Hand study and in each of the papers. *CCP cyclic citrullinated protein; HADS The Hospital Anxiety and Depression Scale; PPT pressure pain threshold; QST quantitative sensory testing.*

4.3 Data collection

Clinical examinations, including QSTs, were conducted at 42 dedicated study visits that were scheduled between April 2016 to November 2017. Four to ten participants attended each study visit slot. The participants received questionnaires electronically prior to the study visits and were instructed to respond within 14 days before or after the study visit. However, 81/300 (27%) responded earlier or later than instructed. Twenty-nine subjects were accommodated for their preference to fill out paper-versions, which they completed during the study visit. Conventional radiographs were taken prior or after the study visit, with a mean number of days from the study visit of 46 (standard deviation (SD) 43) days.

Self-reported pain, QST and scores from radiographs and ultrasound-examinations comprise the main variables in the papers of this thesis, while demographics and background variables described below, including analgesics and psychosocial factors, represent potential confounders. Table 1 gives an overview of the variables used in the different papers.

4.3.1 Demographics and self-reported measures

Age: Birthdate from the medical chart was used to calculate age at baseline.

Body mass index (BMI): We measured height without shoes and weight barefoot with light clothes. We calculated BMI as kg/m^2.

Education: We asked, "What is your highest completed education?" and the options were 1) 7 years of elementary school or less, 2) 9 years of elementary and secondary school, 3) Complete 10 years of elementary and secondary school, 4) One or two years of high school, 5) Complete 3 years of high school, 6) University or college for 4 years or less, 7) University or college for more than 4 years.

Comorbidities: We used the Self-Administered Comorbidity Questionnaire to assess comorbidities and the burden of comorbidities(137). The questionnaire lists 12 conditions (heart disease, hypertension, lung disease, diabetes, gastric ulcer or abdominal disease, renal disease, liver disease, haematological condition, cancer, depression, osteoarthritis, back pain) and includes three lines where the participant can fill out extra conditions, e.g. fibromyalgia. They tick three "yes/no"-boxes for each condition, 1) Do you have this condition, 2) Do you receive treatment for this and 3) Does this condition affect your activity level. Each "Yes"

gives one point on a total scale from 0-45. The form was filled out together with a medical student at the study visit, ensuring that the list of medications and comorbidities matched.

The use of analgesics/nonsteroidal anti-inflammatory drugs (NSAIDs): At the study visit the participants brought their list of medications or recorded all medications they were using on a daily basis and on demand in a form. A medical student checked the list together with the participant to ensure that it was complete and matched the comorbidities. Dichotomized data of regular use of NSAIDs, acetaminophen, opioids and opioid-like drugs were extracted manually by P. Steen Pettersen.

Sleep disturbances: One question in questionnaire was about sleep disturbances. The participants were instructed to pick one of the following statements; "I have…" 1) no troubles sleeping, 2) slight sleep problems, like troubles falling asleep or awaking during the night, 3) moderate sleep problems, my sleep is disturbed or I feel I don't get enough sleep, 4) big sleeping problems, I have to use sleeping medications often or routinely or I wake up during the nigh and/or too early in the morning, 5) serious sleep disturbances with a feeling of not getting enough sleep or serious sleep disturbances where sleep is almost impossible despite use of hypnotics. This question is taken from the 15-D instrument of health-related quality of life where each of the 15 dimensions (mental function, vision, eating etc.) being measured can be used as single measures or as combined profiles(138). It was previously used in the Oslo RA Register and was therefore chosen for the Nor-Hand study(139).

Depression and anxiety: As a measure of level of depressive symptoms and anxiety the HADS was used (scale 0-42)(140). It consists of seven items for anxiety and seven items for depression, each scored on a four-point scale from 0 (not present) to 3 (considerable). This is a commonly used tool to measure depression and anxiety with a cut-off for clinical disease of ≥ 8 points for each subcategory(141). The Norwegian version is validated for adults and elderly in both hospital settings and the general population(141, 142).

Pain catastrophizing: Catastrophizing is defined as "an exaggerated negative mental set brought to bear during actual or anticipated painful experience" and is related to higher pain intensity(143). The Pain Catastrophizing Scale (PCS) comprises three dimensions: rumination (4 items), magnification (3 items), helplessness (6 items). Each item asks the participant to what degree (0, not at all – 4, all the time) they agree with a feeling or thought when they reflect on their pain, e.g. "It's awful and I feel that it overwhelms me". A sum score of the 13

items give a total scale of 0-52 where higher score indicates greater tendency of catastrophizing(144).

NRS hand pain: The participants responded to the question "How much pain in your hands did you experience during the past 24 hours?" by ticking one of 11 boxes marked 0 to 10. The NRS is one of the most widely used measures of pain, it is validated against other measures of hand pain and is sensitive to change(145). It is the recommended main outcome measure for pain in clinical trials of hand OA(33). The Patient Acceptable Symptom State (PASS), i.e., the threshold score for clinically relevant hand pain, is 4(146). The minimal clinical important difference of change on an NRS scale of pain for chronic musculoskeletal pain, including hand OA, has been found to be one point or a reduction of 15%(147).

The Australian Canadian hand OA Index (AUSCAN) pain subscale: The Nor-Hand study obtained admission to use the copyrighted AUSCAN questionnaire(17). The Norwegian version is validated and has acceptable performance as a disease specific measure for hand OA(148). It consists of three parts: pain, function and stiffness. We used the pain subscale which include five questions about hand pain during the past 48 hours, one about resting pain and four about pain during different hand activities. The response is level of agreement of a five-point Likert scale from no to extreme pain (total scale 0-20). At least three of the five items had to be assigned by the participant for the subscale to be calculated. We obtained the subscale score by calculating the mean of the available scores and multiplying with five to account for missing values. The AUSCAN is frequently used in studies of hand OA and has good reliability, validity and responsiveness(145, 149). PASS for AUSCAN pain is 8 points (equivalent to 4 points on the NRS) and minimal clinical important improvement is 1.6 points(150).

Symptom duration: The response to the question "What year did you first experience symptoms of your hand OA?" was used to calculate symptom duration in number of years until baseline.

4.3.2 Quantitative sensory testing

In the Nor-Hand study a QST protocol was developed in cooperation with Professor T. Neogi to suit the study setting, hand OA disease and research questions, complementing methods used in other OA studies. The protocol included testing of local and remote pain detection

thresholds to mechanical pressure and pain facilitation from repetitive mechanical punctuate probes.

The examinations were conducted by two trained medical students who had a written protocol available to ensure identical examination of all participants throughout the baseline period. The participants were instructed to talk as little as possible during the examination and were told that they could stop further examination at any point if they wanted. The tests were conducted in the order below.

Temporal summation (Image 1): TS is a phenomenon where repeated application of a noxious stimulus with the same intensity at a uniform frequency causes an increase in intensity of pain experience experienced at the end of the train(151). The mechanism behind this phenomenon occurs in the dorsal horn of the spinal cord when repeated presynaptic inputs from the peripheral afferent neurons summates due to the frequency and cause increased response in the postsynaptic neurons (Figure 7). Some increase in pain is physiological, reflecting central addition of nociceptive input(152), while an augmented response is seen in patients with chronic pain and considered a feature of hypersensitivity and central sensitization (Figure 7) (153). TS can be measured with QST of different modalities, including mechanical stimuli at the skin.

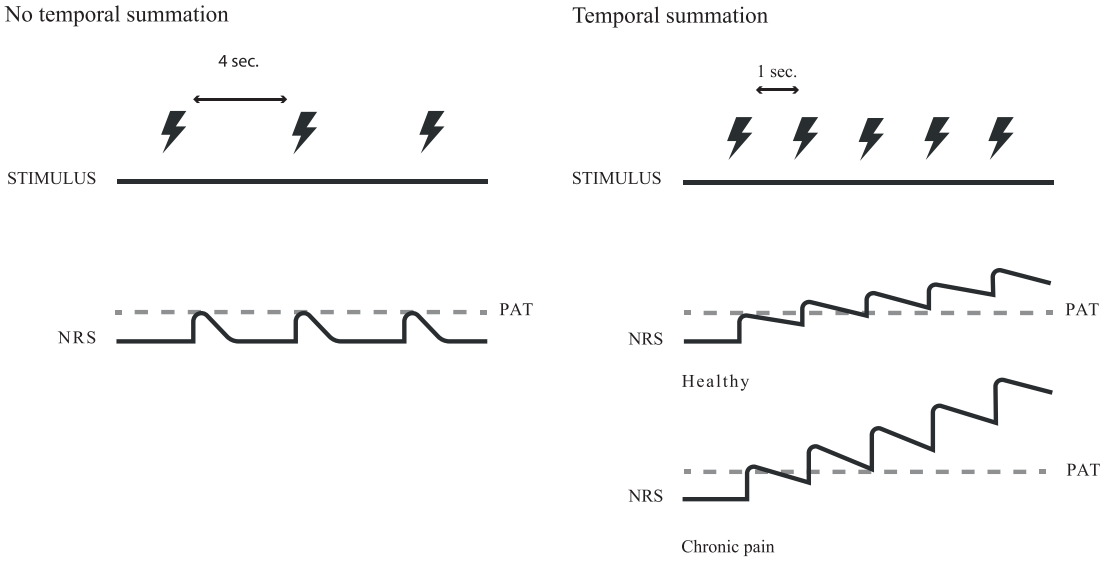

Figure 7. Temporal summation. NRS: *Numeric rating scale of pain. PAT: Pain activation threshold.*

We used a set of seven punctuate probes with fixed intensities that exerted forces of 8, 16, 32, 64, 128, 256 and 512 Newton metre which were used to tap the skin on the dorsum of the left radioulnar joint (Image 1). Participants had their eyes closed during the examination and their arm resting on a table. To identify the probe to be used for the train of stimuli, each probe in the set is tapped once in their numerical order with the participant instructed to vocally rate the pain intensity experienced on an 0-10 NRS scale where 0 is no pain and 10 worst pain imaginable. The probe that first evokes a pain rating of 4 or more is then tapped 10 times with a pace of one tap per second at the same location. The participant was instructed to vocally rate the NRS-pain of the first, fifth and tenth tap. The *summation* of pain, i.e., the change in NRS-pain during the examination, was calculated by subtracting the first pain rating from the peak pain rating of the fifth or tenth tap. This method is established in pain research and has been used in rheumatic arthritis patients as well as in knee OA patients(113, 154-156).

Pressure pain threshold: PPT refers to the point at which the applied pressure first feels like slight pain, i.e., the detection threshold for pain stimuli from pressure. Lowered *local* PPT at the site of disease is thought to reflect peripheral and/or central sensitization and lowered *remote* PPTs at sites not affected by pathology is considered to represent widespread hypersensitivity and central sensitization(153). Other QST modalities can be used similarly, e.g., detection threshold for thermal stimuli, but PPT has demonstrated good test-retest reliability and sensitivity for testing pain sensitization in OA patients(108, 157).

We tested pressure pain detection threshold using a handheld algometer (FPIX25, 1cm^2 flat rubber probe). Locally we tested two interphalangeal joints of each participant: the joint reported to be the most painful joint on a daily basis and a nonpainful joint (Figure 3). The algometer was placed in perpendicular position to the dorsal side over the joint. The pressure of the algometer was then increased at 0.5 kg per second guided by a metronome, while the participant rested his/her hands on a table (Image 2). The participants were instructed to say stop when the pressure first changes to feeling slight painful. The examination was repeated three times with the algometer placed at slightly different positions over the same joint with a pause of 30 seconds between the measurements. The mean value of the three tests was calculated as the PPT. The procedure was then repeated at three sites: the dorsum of the left distal radioulnar joint and over mid-portions of the trapezius and tibialis anterior muscle (right/left according to how the subject is positioned relative to the examiner) (Figure 8). The latter was assessed while the participant was resting in supine position on an examination bench.

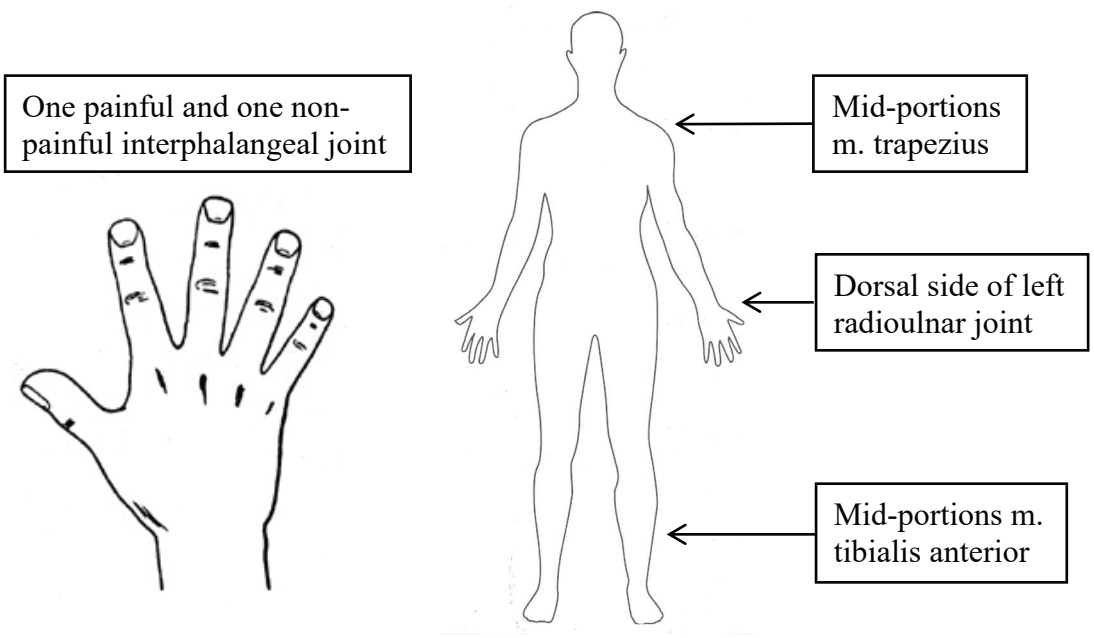

Figure 8. Test sites of pressure pain thresholds. *Selection of interphalangeal joints: The most painful in daily life and a random selection of the nonpainful joints. If none of the joints were reported to be painful the joint with the most severe clinical OA was chosen (swelling and/or bony enlargements) was chosen to represent the painful joint. If all joints were painful, the joint with the least pain and no OA or the least clinically severe OA was chosen to represent the nonpainful joint.*

Reliability: Nine participants were examined by both medical students at the same study visit to calculate inter-tester reliability.

In the result and discussion part of this thesis we refer to the results of the QSTs as peripheral (local PPTs) and central (local and remote PPTs and TS) sensitization. Although the test modalities are measures of sensitization, they are psychophysical and not electrophysical, and we acknowledge that they may also represent heightened sensitivity.

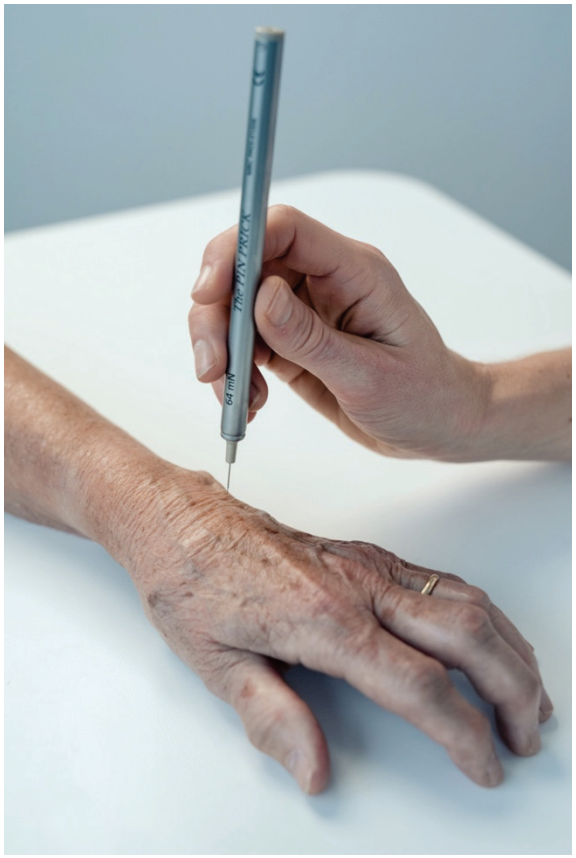

Image 1. Testing temporal summation. *Photo by Nicolas Tourrenc.*

Image 2. Testing pressure pain threshold. *Photo by Nicolas Tourrenc.*

4.3.3 Conventional radiography

Frontal images of both hands with posterior-anterior view were obtained. The participants were sitting with their hands on the detector with their palms facing up (source to image-receptor distance: 115 cm, exposure: 46 kilovoltage peak and 2 milliampere-seconds). They were instructed to have a slight ulnar deviation of the wrist ensuring a straight longitudinal axis through radius and the index finger.

Two validated scoring systems were used to evaluate structural pathology of the joints of the hands: a modified version of the Kellgren-Lawrence scale (including bilateral DIP 2-5, PIP 1-5, MCP 1-5, CMC-1 and STT) and the Verbruggen-Veys anatomical phase score (bilateral PIP 1-5 and DIP 2-5). A trained reader, I.K. Haugen, performed the readings. The Kellgren Lawrence scale is a well-known scoring system that grades OA on a semi-quantitative scale from 0-4 (of which grade ≥ 2 represents definite OA) and is based on the presence/severity of osteophytes/ossicles, narrowing of the joint space, sclerosis of the subchondral bone, pseudocystic areas, and altered shape of bone ends(14, 34).

The Verbruggen-Veys anatomical phase scoring system identifies an assumed radiographic evolution of finger joint pathology and enables classification into progressive phases(35). The phases evolve from normal to stationary phase (small ossification centres, osteophytes at joint margins and discrete narrowing of the joint space) to the joint space narrowing phase (destruction of joint and disappearance of articular cartilage) to the erosive phase (erosion of the subchondral plate and pseudoenlargement of joint space) and to the final remodelling phase (formation of new irregular sclerotic subchondral plates and huge osteophytes). Joints in the erosive and remodelling phases are defined as erosive OA. For this thesis we classified individuals with erosive OA in at least one DIP/PIP-joint as having erosive hand OA(158).

Radiographs of 20 random participants were re-read by the same reader after approximately two weeks (mean (SD) of 16 (4) days). Intra-reader reliability was excellent for both Kellgren Lawrence grade 0-4 (weighted kappa 0.92) and erosive hand OA (kappa 0.98).

4.3.4 Ultrasound examinations

Ultrasound examinations were performed of bilateral hands, hips and knees by two medical students who received training by experienced ultrasonographers: H. Berner Hammer and A. Mathiessen. For the hands we used a General Electric Logic S8 ultrasound machine with a linear 6-15 Mega Hertz probe and a preset for optimal imaging of synovitis by grey-scale ultrasound and power Doppler sonography (pulse repetition frequency 0.6 kiloHertz, frequency 7.7 MegaHertz). For the lower extremities a General Electric Logic E9 machine, with same settings, was used. Initial scorings were done in consensus with A. Mathiessen.

All joints of the hands were scanned longitudinally at the dorsal side from ulnar to radial side. The participant had his/her hand resting at a table, supined to the sagittal plane for the CMC-1 and STT joints and with palms facing down for the rest. An additional transverse scanning was done if the examiner was uncertain of the presence of a pathological feature. A scoring system for ultrasonographic features of hand OA made by a group of experts was used to score grey scale synovitis (a combined score of based on thickened synovium and/or effusion) and power Doppler activity signals (presence of vascularization) on a semiquantitative scale from 0-3(39).

The hips and knees were examined with the participant lying in supine position on an examination bench with their legs extended and their feet in neutral position. The anterior aspects of the femoral head and neck was scanned longitudinally and osteophytes, defined as

definite irregularity of the bone cortex located at the femoral head and/or neck, were scored on a semiquantitative 0-3 scale(159). The knees were scanned longitudinally by moving the transducer from the anterior to the posterior part of the medial and lateral joint space. Osteophytes at the medial and lateral bone margins of the tibiofemoral joint were evaluated (scored 0-3 in each compartment, 0=no, 1=small, 2=medium, 3=large osteophytes)(160).

A subset of ten participants were examined by both the medical students and the experienced ultrasonographer (A. Mathiessen) with good inter-reader reliability for the examinations of the hands (prevalence and bias adjusted kappa values for ordinal scales of 0.82 for grey scale synovitis 0-3 scale and 0.87 for power Doppler activity 0-3 scale) and moderate for osteophyte 0-3 scale evaluation of the hips and knees (weighted kappa 0.57).

4.4 Statistical analyses

Statistical analyses for paper I-III were conducted by P. Steen Pettersen using STATA statistical software (College Station, TX, USA) version 14.0 (paper I) and version 15.0 (paper II and III). Statistical advice throughout the work on the papers was provided by statisticians Øivind Skare (PhD) and Joseph Sexton (PhD). P-values less than 0.05 were considered statistically significant.

4.4.1 Missing data

Overall, there were few missing data. For the PCS and HADS questionnaires to be valid the majority of items within all dimensions had to be assigned by the participant to obtain the sum scores. To obtain the sum scores of PCS and HADS, respectively, we calculated the mean of available scores within each dimension and multiplied it with the number of items (to correct for missing values) before summing the sub scores. One participant responded to too few items of the PCS questionnaire for the sum score to be calculated. To calculate sum scores of Kellgren Lawrence scale grades (0-128) of the total amount of structural pathology of the hands, missing scores due to trapeziectomy or arthrodesis were replaced with grade 4 (11 joints) based on the assumption that surgery was undertaken due to severe OA, 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. To calculate sum scores (0-90) of the total amount of grey scale synovitis and power Doppler activity of the hands, missing scores were replaced with

the mean of available scores (trapeziectomy 5 joints, amputation 16 joints, unknown reason 5 joints), respectively.

In *paper I,* missing data of the confounders sleep (n=1), PCS (n=1) and education (n=1) were given the mean of available scores of the rest of the population (simple imputation). We chose not to impute on exposure or outcome measures which excluded one participant from analyses of NRS hand pain, one participant from analyses of PPT at the nonpainful finger joint and both from the analysis of NRS hand pain across PPT of nonpainful joint. In *paper II* there were no missing data. In *paper III* analyses of symptom duration excluded 22 participants with missing data of year of symptom onset (participants had not filled out the question in the questionnaire for unknown reason n=21, symptom duration of 100 years discovered in data washing and therefore erased n=1).

4.4.2 Descriptive statistics

Continuous and normally distributed data were presented as mean values with standard deviations (SD) while variables with non-normal distribution evaluated by histograms were presented as median with interquartile range (25^{th} percentile – 75^{th} percentile). Range was presented when appropriate. Ordinal or dichotomized data were presented as proportions (%).

4.4.3 Selection of covariates

We built analytic models with theoretical causal modelling with directed acyclic graphs to define exposure and outcome variables (i.e., independent and dependent variables) and to identify possible confounders (Table 1). In all papers we adjusted for age, sex and BMI as well as use of analgesics or NSAIDs where appropriate. All papers also include adjustment of OA disease severity, either as a sum score or joint level score. Paper I also include adjustment of factors that may influence both pain sensitization and pain, including sleep disturbances, sociodemographic (education) and psychological factors (pain catastrophizing, anxiety and depression). Finally, paper III also included adjustment for factors related to generalized OA and general disease status.

Table 1. Overview of variables used in paper I-III. *Cross-sectional models of exposure variables (green), outcome variables (blue) and confounders (red).*

	Paper I	Paper II	Paper III
Numeric rating scale hand pain last 24 hours	O		
AUSCAN pain subscale	O		
Local pressure pain threshold	E	O	
Remote pressure pain threshold	E		O
Temporal summation	E		O
Kellgren Lawrence scale	C	E C	E C
Verbruggen Veys anatomical phase score		E	E
Grey scale synovitis		E C	E C
Power Doppler activity		E	E
Symptom duration			E
Age, sex, body mass index	C	C	C
Analgesics/NSAIDs	C	C	C
Comorbidities			C
Hip/kne OA			C
Education	C		
The Hospital Anxiety and Depression Scale	C		
Pain Catastrophizing Scale	C		
Sleep disturbances	C		

AUSCAN The Australian/Canadian Osteoarthritis Hand Index; NSAID Nonsteroidal anti-inflammatory drug; OA Osteoarthritis.

4.4.4 Regression analyses

Relationships between exposure and outcome variables were inspected with boxplots and scatterplots. Before conducting regression analyses, assumptions were evaluated by considering independence of observations and checking interactions (considered significant if p-value greater that 0.10), normal distribution of the residuals and heteroskedasticity. In *paper I,* linear univariable and multivariable regression analyses were used to evaluate crude and adjusted associations. In *paper III* linear and logistic multivariate regression analyses were used to evaluate adjusted associations. In *paper II* multilevel (linear mixed model) regression was used to evaluate associations between joint pathologies and PPT at joint level. Due to suspicion of heteroskedasticity robust analyses were conducted, but non-robust analyses were kept as the results remained identical. We stratified the main analyses in paper II on painful and nonpainful joints, resulting effectively in regular linear multivariable analyses at person level due to only two joint per person.

4.4.5 Reliability

Reliability of QST: Intraclass correlation coefficients, kappa and weighted kappa was used to estimate reliability of continuous (continuous PPTs and change in TS) and ordinal (PPT tertiles and TS) variables.

Smallest detectable change of TS: We used the reliability testing to calculate the smallest detectable change of TS to obtain a cut off value to dichotomize participants as having TS or not. The smallest detectable change estimates the smallest statistically significant change between two dependent measures which is larger than the measurement error. First, we calculated the change in TS for both repetitions of the nine participants by subtracting the first NRS score from the peak NRS score of the fifth or tenth score. We then calculated the difference between the change in TS of the first and second repetition for each participant. Finally, we calculated the mean and SD of the TS differences and used the SD in the formula for the smallest detectable change: $\pm 1.96 \times SD/(\sqrt{2}x\sqrt{k})$ $(where\ k = number\ of\ repetiotions = 1)$. The method was obtained from K. Bruynesteyn *et al.'s* report on the matter of scoring radiographic progression of joint damage in rheumatology(161).

4.5 Ethics

The study complies with the principles of the Declaration of Helsinki and was approved by the Regional Committee for Medical and Health Research Ethics (Ref. no: 2014/2057). The participants gave written informed consent before inclusion and were informed that they could withdraw from participation at any time without reporting any reason. Collected personal information and data were de-identified with identification-numbers and is stored securely.

5. Summary of results

5.1 Paper I

Peripheral and central sensitization of pain in individuals with hand osteoarthritis and associations with self-reported pain severity

Pain sensitization, i.e., increased pain sensitivity to pain due to neuroplastic changes in nervous system pain processing, contributes to knee and hip OA pain. The objective of this paper was to investigate and describe local and remote PPTs and TS of a large sample of persons with hand OA and to explore whether these indications of peripheral and/or central sensitization were related to greater hand pain severity independent of several important confounders.

In the Nor-Hand study, manual pressure pain algometry was tested at a painful and at a nonpainful interphalangeal finger joint, at the wrist and at the mid-portions of the trapezius and tibialis anterior muscle. Mechanical TS was tested at the wrist with a punctuate probe. Hand pain severity was assessed with NRS of hand pain during the last 24 hours (0-10) and the AUSCAN pain subscale (0-20). Linear analyses were adjusted for demographics, psychosocial factors and radiographic severity. Inter-rater reliability of PPT and TS testing was calculated for nine participants.

This cross-sectional study found that 42% of the 282 included participants had TS. PPTs were lowest at the painful interphalangeal joint and highest at the trapezius. The one-third of the individuals of the study sample with the lowest PPTs in their finger joints, wrist and trapezium experienced higher NRS hand pain than those with the highest PPT values (painful finger joint: unstandardized beta coefficient (beta)=0.7 (95% confidence interval (CI) 0.1 to 1.3), nonpainful finger joint: beta=0.9 (95% CI 0.3 to 1,5), wrist: beta=0.8 (95% CI 0.2 to 1.3) and trapezium: beta=0.6 (95% CI 0.0 to 1.2). The participants with TS reported higher NRS hand pain compared to those without (beta=0.6, 95% CI 0.2 to 1.1). No statistically significant associations were found between measures of pain sensitization and AUSCAN pain. Inter-rater reliability of PPT and TS testing ranged from poor to good.

This paper is the first to describe TS as well as the independent contribution of peripheral and central pain sensitization on hand pain in a hand OA population. We found that central sensitization was common and that pain sensitization was related to higher self-reported hand pain severity, independent of both demographic and psychosocial factors and radiographic

severity. Although our results need to be confirmed in other hand OA studies and with longitudinal data, they indicate that pain sensitization is a clinically relevant pain mechanism in hand OA that may represent a therapeutic target.

5.2 Paper II

Associations between radiographic and ultrasound-detected features in hand osteoarthritis and local pressure pain thresholds

Paper I highlighted the clinical relevance of pain sensitization in hand OA. Basic research has demonstrated that OA pathology, including inflammation, can induce and uphold peripheral sensitization. The aim of paper II was to translate this theory to a clinical setting by examining the relation of structural and inflammatory finger joint pathologies to PPTs of the same joints, as well as investigating the role of pain on these associations.

We tested manual algometry PPTs at one painful and one nonpainful interphalangeal joint of each participant. The association of radiographic severity (Kellegren Lawrence grade 0-4 and presence of erosive OA) and ultrasound-detected inflammatory severity (grey scale synovitis grade 0-3 and presence of power Doppler activity) to PPTs were analyzed with mixed-effects multilevel analyses to examine joint level associations independent of within-person related factors.

In total 570 joints from 285 Nor-Hand study participants were included. PPTs decreased with increasing severity of all pathological features; structural OA of minimal, moderate and severe degree (unstandardized beta coefficient (beta)=-1.4, 95% CI -1.9 to -0.9); erosive OA (beta=-0.7, 95% CI -1.1 to -0.2); synovitis of moderate and severe degree (beta=-1.2, 95% CI -1.8 to -0.6) and power Doppler activity (beta=-0.9, 95% CI -1.2 to -0.5), compared to those without such features (adjusted for age, sex, BMI and Kellgren-Lawrence grade/grey scale synovitis grade in analyses of inflammatory and structural features respectively).

Regression analyses stratified on joint pain showed similar results for the painful joints as in the main analyses. For the nonpainful joints we saw a trend of decreasing PPT with severities of all pathological features compared to those without the feature, but none reached statistical significance.

In conclusion, both structural and inflammatory pathologies were independently associated with higher local pain sensitivity. This suggests that nociception from chronic OA pathology as well as inflammation drive sensitization in persons with hand OA. Both prevention of structural progression and treatment of inflammation may be potential targets for pain management.

5.3 Paper III

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

Paper II indicated that structural and inflammatory pathologies contribute to local hypersensitivity, most likely through peripheral sensitization. However, OA pathology is also postulated to cause central sensitization through activation of spinal microglia. Whether the development of central sensitization is related to disease duration is unknown. The objective of this paper was to explore whether the sum of finger and thumb base joint pathologies in persons with hand OA was associated with central sensitization, as well as whether those with longer symptom duration were more likely to have central sensitization.

Structural pathology was evaluated on radiographs and inflammatory features by ultrasound examination. Symptom duration was recorded by participants recalling their first year with hand symptoms. Central sensitization was assessed with remote PPT of the wrist and the trapezius and tibialis anterior muscle, and mechanical TS. We also collected information about comorbidities and hip and/or knee OA as potential confounders.

We found that the sum scores of Kellgren Lawrence grades, grey scale synovitis or power Doppler activity were not statistically significantly associated with PPTs or TS. The participants with the erosive OA phenotype (35% of the study population) had lower PPTs at the wrist (unstandardized beta coefficient (beta)=-0.75, 95% CI -1.32 to -0.19) and trapezium (beta=-0.82, 96% CI -1.54 to -0.09), and they had greater TS (beta=0.56, 95% CI 0.12 to 1.1) than those without erosive hand OA. Symptom duration was not associated with PPTs or TS.

In conclusion, the total amount of structural or inflammatory features of hand OA was not associated with central sensitization. Having an erosive hand OA phenotype was associated with higher widespread sensitivity and TS, but these results have unclear clinical relevance. We did not find any relation between duration of symptomatic hand OA and central sensitization. Our study was not designed to rule out peripheral joint pathology as contributors to central sensitization, but the negative results in a clinical setting indicate that other factors are more important. Exploring how individual factors contribute to and modulate central pain sensitization is needed to further understand hand OA pain.

6. Discussion

6.1 Methodological aspects

This section will discuss the possible biases and limitations of the design, conduct and analyses of the three papers, as well as their strengths.

6.1.1 Study design

The Nor-Hand study is an epidemiological study with observational design aimed at exploring prevalence and etiological associations of joint pathologies, different biomarkers, including pain sensitization, and self-reported measures. All three papers include cross-sectional data, based on information gathered at the baseline examination of the Nor-Hand study. The cross-sectional design suited the aim to explore prevalence and level of pain sensitization in a large population of patients but had the disadvantage that we could not analyze pain sensitization as a risk or causal factor for pain, nor were we able to make conclusions about the effect of pathology over time on pain sensitization. However, since the results of this thesis implicate a possible clinical relevance of pain sensitization in hand OA, the QST protocol is repeated in the follow-up examinations, and we plan to examine longitudinal association.

6.1.2 Study population

The method of how a study population is selected will have consequences for how well the results can be applied to the general population, i.e., external validity. The Nor-Hand study include men and women between 40-70 years who were recruited from secondary care in a hospital setting. Hand OA is uncommon in persons younger than 40 years, but common above 70 years(3). Since follow-up examinations were planned after 4 and 8 years, this age limit was chosen to minimize the risk of loss-to-follow-up. The hospital-based recruitment of the cohort made by experienced rheumatologists made it feasible to include such a large population. However, the age limit and hospital setting weaken the generalizability of the results to the general population. Also, the majority of the participants were women who may cause a bias in the results and make the results less representative for men. It also makes us unable to explore stratified analyses of men and women separately, which is a limitation.

There is a likely selection bias of the Nor-Hand population of persons that are more willing to participate in research. Recruitment was not systematic and allowed convenience sampling from the outpatient clinic, the OA school and of a few persons who contacted the study

coordinator directly. Additionally, 58 of the 431 screened participants were not included because of unwillingness (Figure 1).

The main inclusion criterion was proven hand OA by a rheumatologist on clinical examination or ultrasound examination and, in contrast to the ACR hand OA criteria, pain, aching or stiffness was not required. The advantage of this is the opportunity to include persons with early or low-degree hand OA which increases the external validity. As an illustration, the structural severity ranges from osteophytes in two joints detected on ultrasound examination (n=1) to >20 joints with definite OA (8% of the study population in paper I). Yet, it limits the possibility to compare results with other study populations based on the ACR hand OA criteria. After inclusion we saw that as many as 93% fulfil these criteria and none did not fulfil the criteria due to lack of hand pain.

All papers exclude 9 participants due to missing QST (equipment error at one study visit), and paper I exclude additional 9 participants because of missing the HADS variable (failure of distributing the questionnaire). If the reason for missing this information had been *not random*, e.g., unwillingness to undergo QST or unwillingness to respond to the questionnaire this would have introduced a bias of the results. However, as both of these variables may be considered *missing of completely at random*, omitting these participants is likely not introducing selection bias(162).

6.1.3 Self-reported measures

A strength of the Nor-Hand study is the comprehensive data collection. The hospital-based design with centered data collection made it possible to conduct specialized QST and ultrasound examinations which would have been a challenge in a community-based setting. Another advantage of the broad data collection which included questionnaires about psychological factors including sleep disturbances, is the possibility to take into account how these factors influence pain and pain sensitization.

The main outcome measure in paper I was the NRS of hand pain last 24 hours. This is the most prevalent measure used to describe chronic rheumatic pain and the current recommended main outcome measure of pain in clinical trials of hand OA(33, 163). NRS is also the recommended assessment of pain intensity in pain research in general, with good compliance and applicability across conditions(164). Pain diaries are increasingly being used to study pain severity and may often represent a good alternative outcome measure for OA

pain which is fluctuating. Pain sensitization may also fluctuate, and we considered pain during the last 24 hours from the examinations to be a feasible outcome measure. However, a pain diary over, of for example, a three-month period, encompassing the study visit, would have been a more valid measure of persistent pain and it would have been interesting to examine how such a variable would have influenced our results.

In addition, we used the AUSCAN pain subscale for assessment of hand OA. AUSCAN is specifically developed for hand OA pain and captures pain related to hand activities. We could have included several measures of pain in paper I to further explore if pain sensitization is related more to specific hand pain characteristics. From knee OA studies OA pain has been described with neuropathic-like qualities, e.g., tingling, radiating or electric shock-like pain, which again is associated with central sensitization(165, 166). We have collected data about neuropathic-like pain through the painDETECT and the McGill pain questionnaire(84, 167, 168), but these are the content of a separate work in progress by our research group. Another aspect we considered to investigate was the relation of pain sensitization to the acknowledged persistent or intermittent type of OA pain though the ICOAP questionnaire of constant and intermittent knee/hip OA(169). However, in a recent validation study of the ICOAP questionnaire in hand OA we found a large overlap between the two types of pain and could not recommend its use in hand OA(170).

Although we had retrospective information about symptom duration from questionnaires, this information is subject to large uncertainty due to recall bias which is a common bias in cross-sectional studies(171).

The intake or application of analgesic medications is included as a confounder in all papers, based on the assumption that analgesics may reduce both pain sensitization and self-reported pain. We were able to adjust for regular use of various analgesics in paper I and for regular use of NSAIDs in sensitivity analyses in paper II and III, but there may be residual confounding bias from those who use analgesics intermittingly. Alternatively, we could have modelled use of analgesics as a consequence of pain and/or as an intermediate on the pathway from pain sensitization to pain and left if out of the analysis completely. Finally, a preferable approach would have been to have instructed the participants to refrain from taking analgesics on the day of QST examination, or at least collect information about intake on that day which is currently done at the follow-up examinations.

6.1.4 Quantitative sensory testing

Pain sensitization mechanisms are complex: the exact neuronal responses and signals cannot technically be measured in humans. Therefore, there are no gold standards, and from a biological point of view it is not possible to classify someone as sensitized or not. Both peripheral and central pain sensitization are neurophysiological alterations of pain processing mechanisms that are best considered as a spectrum. Consequently, it is not possible to define sensitivity and specificity of the QST tests. In specialized clinical practice where QST are part of the diagnostics (e.g., assessing neuropathic pain or small fiber neuropathies) reference values are utilized from large samples of healthy individuals, for example from the German Research Network on Neuropathic Pain (DFNS)(80, 172). Our test protocol was tailored for elucidating pain sensitization in a specific sample of patients (here for persons with hand OA) and used only manual equipment and verbal responses from the participants. In the case of reference values, they must be obtained from testing controls using the same test procedures on the same locations which we did not do in our study.

There are several issues that can be discussed regarding the QSTs. TS was only tested once per participant. Since the testing method is manual and the testing relies on the ability of the participant to orally report their NRS pain three times during the test, there might be a within-person variance in the test result, which makes the test less presice. This issue could have been minimized if we had performed the test two or three times and calculated mean ratings like what we did with the PPT testing. The DFNS protocol of neuropathic pain repeats the TS test five times(80), while several protocols testing TS in OA patients only conduct one TS test (110, 111, 115). This limitation may be ameliorated to some degree in the analyses that are based on the dichotomized TS variable based on the smallest detectable change.

Test site for TS of the left radioulnar joint was chosen because it had been previously used in knee OA studies by Professor Tuhina Neogi. The location for TS testing varies, as it is frequently tested both at the location of the disease and at a control site. Rolke *et al.* found in their test of the DFNS' protocol using similar method as in our study, that TS did not depend on body site(154) and another study found moderate correlations of TS at different sites(113). This would mean that a test site can be chosen pragmatically. However, in pain conditions with primary hyperalgesia at the site of pain it is advised to test TS at a reasonable distance from the painful body part. In knee OA studies the wrist is a reasonable site to test, but in retrospect we have discussed that a different site for TS testing should have been chosen. In

our study, the possibility of hyperalgesia at the dorsal side of the wrist in a person with inflammatory CMC OA, may have introduced a bias with overestimation of TS.

The digital algometer displays the PPT in kgf which is equal to kilogram per square centimeter since the algometer rubber probe is approximately 1cm^2. The SI unit for pressure force is pascal and this is also the most widely used unit to report PPT values. Conversion from kg/cm2 to kilo Pascal by multiplying the values with 98,0665 would have facilitated comparison with other studies in the literature.

PPT was tested at two finger joints only. In knee OA each knee is either painful or not, while in hand OA painfulness can be either defined on a person level or at the individual joint level. The selection of two joints was pragmatic and chosen both to suit the research objectives and to be feasible within the timeframe of the examination. The alternative would have been to test all hand joints or a pre-defined selection of the same hand joints in all participants. Sofat *et al.* and Wajed *et al.* tested all joints of the bilateral hands, including the CMC-1 in their studies and conducted analyses based on mean values across joint groups(117, 173). With this method we could have increased the strength of our analyses considerably, especially in paper II with joint level analyses, but at the cost of participant and tester burden.

A methodological weakness regarding the PPT protocol is the definition of painful and nonpainful joints. Most of the joints are selected by the examiner asking for the most painful interphalangeal joint on a daily basis and then randomly selecting one of the nonpainful joints. However, in the case where none/all joints are equally painful/nonpainful the protocol allows joint pathology as part of the inclusion criterium for the painful/nonpainful joint (Figure 3). When a set of variables that predispose selection into an exposure variable are also related to the outcome it can cause confounding(174). This is relevant for the secondary analyses in paper II where the objective was to compare findings from analyses of painful versus nonpainful joints. There is no available overview of when these exceptions were made, but we do not expect that they were made very often.

6.1.5 Conventional radiographs and ultrasound examinations

The radiographs were taken some time apart from when the QSTs were performed, up to 90 days after. This could mean that some of the data from the radiographs show more or less severe pathology than what was present at the time of QST, yet it is unlikely that substantial

structural alterations are evident within 3 months. Ultrasound examinations were all performed on the same day as QST, which is important due to fluctuations in synovitis.

All finger joints and the thumb base joints were scored according to a modified version of the Kellgren Lawrence scale. The original Kellgren Lawrence system from 1957 has been criticized for placing too much emphasis on osteophytes compared to joint space narrowing(175). The original version that often is referred to in research, includes only example images of Kellgren Lawrence grade 0-4 but no descriptions. According to a later published description of the grading system a joint with joint space narrowing cannot be defined as OA (Kellgren Lawrence grade 2 or more) unless there is a definite osteophyte, and it is unclear how joints with possible or mild joint space narrowing should be classify (176). This suggests that despite good intra- and inter-reader reliability of readers within a study, there might be some disagreement between readers across studies. The modified version allows the reader to classify joints with questionable joint space narrowing without osteophytes as doubtful OA (Kellgren Lawrence grade 1) and definite joint space narrowing without osteophytes as mild OA, especially if other findings such as sclerosis is present (Kellgren Lawrence grade 2)(3). Thus, our study could be more sensitive than others in the definition of Kellgren Lawrence grade 1-2. This should be kept in mind when interpreting the results, especially of paper II.

In paper III the exposure variable (independent variable) is hand OA severity at person level and structural OA is reported in tertiles of Kellgren Lawrence sum score across both hands. We considered to define hand OA severity based on joint counts of joints with Kellgren Lawrence grade of 2 or more, but decided to use the sum score in order not to lose information and to avoid misclassification. In paper II we found dose dependent associations between the severity of radiographic OA by the Kellgren Lawrence scale and PPTs in the same joint. The Kellgren Lawrence is a global scale of structural alterations and does not discriminate independent features. We did conduct analyses based on single features such as osteophytes and joint space narrowing, as these had been scores according to the OARSI atlas but did not include these results due to the confinement of a brief report(37, 38). This may be of interest to examine further, especially on longitudinal data where it is interesting to see if changes in any specific radiographic individual features associate with changes in PPT.

The DIP and PIP joints on the radiographs were also scored according to the Verbruggen Veys anatomical phase score which classify joints in five different phases that correspond to

the radiographic evolution of erosive hand OA(35). In paper II, DIP and PIP joints were defined as erosive if they were either in the erosive (erosions and destruction of the subchondral plate and complete loss of joint space) or remodeling (remodeling of a new subchondral plate and pseudo enlargement of the joint space) phase, while in paper III a participant with at least one DIP or PIP joint in the erosive or remodeling phase was defined as having the erosive hand OA phenotype. There is no standardized definition of erosive hand OA, either in a single joint or as a phenotype. This is partly because it is unknown whether erosive OA is a unique disease or a subtype of hand OA. A review of the various definitions used in literature found that the majority of researchers use individual radiographic definitions of erosive hand OA and the threshold for number of DIP/PIP joints with these features varied from ≥ 1 to ≥3 joints(177). Until a consensus on a definition is reached it may be an advantage to use well described scoring methods with accompanying examples images or atlas, like the Verbruggen Veys scoring method, which make reproducibility easier. An alternative method could have been to use the OARSI atlas' to define DIP and PIP joint as erosive(38). A limitation of that approach is that this atlas includes few images of erosive joints.

We used ultrasound examinations both as a tool to define hand OA in the inclusion criteria and to score inflammatory pathology. Ultrasound is not recommended as a diagnostic tool in OA. In clinical practice, especially in primary care, OA is a clinical diagnosis. The EULAR recommendations for diagnosis of hand OA state that other imaging modalities than conventional radiographs seldom are indicated for diagnosis(4). However, more recent hand OA studies have found ultrasound to be more sensitive than radiographs in detecting osteophytes, and ultrasound findings are associated with pain(42, 98, 178). In a EULAR recommendation of the use of imaging in OA from 2017 the use of ultrasound might be considered to exclude differential diagnoses and in cases of atypical OA presentation(179).

MRI is the gold standard for assessing synovitis in OA(180). MRIs were taken in the Nor-Hand study, but images were available for less than half of the interphalangeal joints that were tested with PPT as only the dominant hand of the participants were obtained and thus, we did not include MRI.

6.2 Discussion of the main results

6.2.1 Reliability

The reliability of a test refers to the agreement between repeated assessments of the same test by the same or other persons. In our reliability exercise between the two medical students who performed the QSTs, we found varying reliability with intraclass correlation coefficient (ICC) values between 0.40 (fair) and 0.61 (good) for most PPTs and 0.72 (good) for TS. However, the reliability for PPT of the wrist (ICC 0.14) was poor(181).

The poor ICC for PPT at the wrist in our study is an indication of low agreement between the students, which may have introduced a systematic bias of the results. The two medical students received training prior to the initiation of the study visits, and the reliability exercise was conducted during the period of study visits. They had written protocols available to ensure identical procedures between them. Inter-tester reliability depends highly on the testers ability to perform the QST in a standardized way. It is apparent that this kind of manual testing demands high-quality training and preferably some experience and training over time.

Our reliability results are overall weaker than other studies using QST in OA patients. A systematic review by A.K. Soukas *et al*. found three studies which reported excellent reliability (ICC >0.75) of PPT testing in knee OA(108). Neogi *et al.* found excellent 14-day test-retest reliability of PPT (ICC 0.85-0.90) for the knee and wrist, and adequate reliability of TS in the Multicenter Osteoarthritis Study of knee OA (kappa 0.61)(113). A recent French study reported excellent reliability of both PPT (ICC 0.83-0.93) and TS (0.73-0.91) of the wrist in healthy individuals, using almost identical PPT and TS procedures as we used(182). These studies demonstrate that good reliability is achievable of QST testing, however they all test intra-rater reliability, i.e., the test-retest agreement of one examiner. Few studies report on inter-rater reliability of QST. One recent study tested inter-tester reliability of PPT and TS of 20 healthy persons at the same day and found varying results similar to ours; ICC of PPT varied from 0.60-0.92 and TS (ratio of first and peak NRS) varied from -0.03 to 0.82(183). This illustrates perhaps a general weakness of the QST tests and their dependence on the examinator.

A pilot exercise of inter-reliability between the students, as well as between themselves, could possibly have improved their training and ensured better reliability during the study. A more automatic testing method could also possibly have improved the test reliability in a research

setting with inexperienced research assistants. The tests are psychophysical which mean that they are also dependent on the participants ability to stay concentrated, to understand the instructions correctly and in the same way, and to cooperate with the examiner during testing. In the Nor-Hand study all examinations were conducted at the same study visit, which took place in the afternoon. The participants rotated through stations with different examinations and for some participants these tests were consequently performed quite late in the afternoon. This may have affected their concentration and influenced reliability. Finally, a larger sample for the reliability exercise than 9 persons would have increased the strength of the analyses and may possibly have improved the reliability results. Nevertheless, the results regarding PPT at the wrist should be interpreted with caution.

We also used the reliability data to calculate the smallest detectable change in TS to be able to dichotomize persons as having TS or not. The literature state that facilitated TS is pathological and a sign of central sensitization, but we also know that the mechanism of TS can be demonstrated in healthy individuals (Figure 2). We discussed how we better could separate "normal" TS from pathological TS. Due to the psychophysical nature of the test we were concerned how the small measurement error could cause misclassification when dichotomizing TS(184). By calculating the smallest detectable change, we intended to minimize the risk of misclassification and increase the positive predictive value and specificity for defining someone as having central sensitization. The smallest detectable change of TS was 1.28, which made us set the cut off at two points or more. Our method had not been used before which excluded the comparison with other findings. We might have underestimated the prevalence and consequently biased the results of further analyses, which is why we combined analyses of dichotomized TS with TS.

6.2.2 Prevalence and level of peripheral and central sensitization

Paper I is the first report of TS testing in persons with hand OA. As many as 42% had presence of TS and the median TS of NRS pain was 1 point on the NRS. PPT was lower at the painful than the nonpainful interphalangeal joint.

Central pain sensitization has for some time been recognized as an important pain mechanism in OA and assessment of central sensitization is considered as a useful prognostic factor as well as a tool for mechanistic pain phenotyping(185). Yet, most of published research on this topic focuses on knee OA. Of the 41 identified studies of QST in OA patients by Soukas *et al.* from 2012, only two studies, both from the same research group (Farrell *et al.),* examined

patients with hand OA, while 28 were of knee OA and 5 of hip OA(108, 186, 187). Since 2012, the research group of Sofat *et al*. has published two papers investigating different aspects of peripheral and central sensitization with QST in hand OA patients(117, 173). None of these studies examined pain facilitation of repetitive stimuli or pain thresholds at remote sites, hence they cannot discuss central sensitization without the possible influence of peripheral sensitization. The relevance of central pain mechanisms in hand OA was demonstrated in a fMRI study where hand OA patients showed more brain activity in areas known to implicate central sensitization, during painful hand activities, compared to controls(118). Also, pregabalin was found superior to placebo in reducing hand OA pain(173). Since pregabalin is partly working centrally, the reduction of hand OA pain suggests a central component of pain.

The Nor-Hand study is the first study to test TS of individuals with hand OA, and paper I of this thesis is the first to report the prevalence of TS. These results would have been considerably strengthened by comparison to TS of matched healthy controls. Also, a control sample would have provided the opportunity to create reference values for the QST results. Although we state that TS is common, the design does not allow us to report whether it is more common than in a general population. Yet, because it is common to report TS dichotomized as present or not in studies of painful conditions, we chose to include this result(123).

TS of pain is commonly reported as the ratio of the pain of repetitive stimuli to pain of a single stimulus(80). This corresponds to the "change in TS" that we calculated, similar to the methods that were used in a knee OA study from 2010 by Arendt-Nielsen *et al.*(111). They found significantly greater TS of pain in patients compared to controls after testing TS both at the knee and at tibialis anterior, where tibialis anterior is the most comparable to our site at the wrist. Interpreting their figure that illustrates change in pain at tibialis anterior, TS is about 1 on a 0-10 VAS. Another knee OA study that used change in TS scores reported pre-and post-prosthetic knee surgery change of TS between 0.75 and 2 point on their VAS 0-10(115). In the absence of a control group, we used the smallest detectable change to dichotomize TS and calculated the prevalence. The prevalence in our study was the same as the prevalence seen in persons with knee OA(113). Hence, both the magnitude and prevalence of TS in our study of persons with hand OA seem to be similar to that of knee OA patients. Through research on the role of central sensitization on conditions with chronic pain it has been noted a variability in the severity of central sensitization between conditions. For example, among

patients with fibromyalgia central sensitization is more common and of greater severity than for OA, while for shoulder pain and lower limb tendinopathies central sensitization occur, but less often(185).

Without a control group it is difficult to discuss whether the PPT values of different locations are decreased, i.e., hyperalgesia. However, hyperalgesia and lower mechanical pain thresholds at finger and thumb joints as well as at remote sites in hand OA patients compared to controls has been observed earlier(116, 117, 186, 188). Wajed *et al.* used a manual pressure algometer to test PPT at all finger joints and the thumb in 13 hand OA patients recruited from a rheumatology department and reported a mean PPT value of 23 (SD 11.9) Newtons across all joints. This corresponds to 2.4 (SD 1.2) kg/cm^2, which is lower than the mean PPT of the painful interphalangeal joints in our study (3.9, SD 1.9 kg/cm^2). There are differences between our studies that limit the value of a comparison. For example, their participants had likely more severe OA as suggested by higher hand pain (mean VAS 59.3 on a 0-100 scale) than our population (mean NRS 3.7 on a 0-10 scale). Finally, similar to other studies of PPTs the values vary greatly between individuals as shown by the wide SDs. However, the difference in characteristics between patients demonstrating high or low pain sensitization are of more importance than the absolute value.

6.2.3 Pain sensitization and hand pain

In paper I we found that peripheral and central sensitization contributed to pain in persons with hand OA, also when accounting for radiographic severity, demographics, co-morbidities, analgesics, and psychological factors. Pain sensitization reflected by lower local and remote PPTs and presence of TS was associated with higher NRS hand pain while associations with activity-related hand pain measured with the AUSCAN subscale did not reach statistical significance. Previous studies have indicated similar results but our is the largest to date, the first that include TS and the first to illuminate the potential role of pain sensitization independent of several confounders.

Although previous studies have examined the relationship between QST measures of peripheral and central sensitization and pain severity in hand OA, none have found statistically significant associations(116, 117, 173, 188). We found associations of PPTs at painful and nonpainful interphalangeal joints, the wrist and trapezium, and of presence of TS and TS to NRS, but not AUSCAn pain. Chiarotto *et al*. did not find correlations between PPTs at the thumb (n=32) or at distant and remote locations (n=16) with NRS pain in patients

with CMC-1 OA, while Wajed and Sofat *et al*. did not find correlations of finger and thumb PPTs to either NRS or AUSCAN pain in their studies with rather small patient numbers (n=13 and 43)(116, 117, 173, 188). Wajed and Sofat present scatterplots of their raw data of PPT values across pain severity, which give the impression of a linear association but with large between-persons variances. It is possible that larger study samples would have increased power in their studies and that there are confounders that are unaccounted for. Indeed, the association with AUCSAN pain was borderline significant with p-value of 0.06 in the study by Sofat *et al*.(173).

Pain or a specific level of pain severity was not an inclusion criterion in our study. Several hand OA studies recruit only patients with NRS hand pain ≥4, which is also the proposed minimum pain level recommended for inclusion in clinical trials of hand OA(33). Yet, in our study about half of the participants had hand pain above this level. We consider our wide range of pain severity as a strength. Since more than 90% fulfilled the ACR hand OA criteria, we would have needed an extra inclusion criterion of NRS hand pain ≥ 4 to achieve a higher mean hand pain in our study. This would have reduced the external validity of the cohort significantly. Also, although we found that the association of pain sensitization with pain severity was statistically significant only for those with PPTs in the lowest tertiles and not the middle tertile compared to the highest, we found that decreasing local and remote PPTs and TS on continuous scales was associated with increasing pain suggesting a role for pain sensitization also in those with milder pain.

We do not know why the analyses with AUSCAN pain did not reach statistical significance, but it raises some interesting questions. Is pain sensitization associated with certain types of pain more than others? OA pain is commonly described in terms of intermittent and/or constant pain and as resting and/or activity-dependent pain. Attention has also been shed at a subgroup of patients who describe their pain with neuropathic-like terms, and it has been suggested to be a clinical sign of central sensitization and as a sign of a neuropathic component to pain sensitization(165, 189). In the Nor-Hand study 30-46% of the study sample report neuropathic-like pain characteristics like pricking and burning, and neuropathic-like pain is associated with pain sensitization(19, 190). A possible explanation for our divergent results (i.e., associations between pain sensitization and NRS pain and not for AUSCAN pain) could be that pain from joint movement predominantly is nociceptive pain from mechanical stimuli, while pain caused by pain sensitization, i.e., nociplastic pain, is

experienced as less activity dependent. Indeed, in our sensitivity analyses local PPTs were associated with the single AUSCAN pain question about resting pain. On the other hand, the opposite has been suggested for knee OA, where activity dependent pain has been linked to central sensitization(191). Another explanation could simply be that those with the most severe pain use their hands less actively and consequently do not experience activity-dependent pain as often. Nevertheless, the relation of pain sensitization to different pain characteristics in hand OA patients is clinically relevant and warrants further exploration.

Pain is complex and as stated by IASP's definition of pain, it is both sensory and emotional. Through the work on this thesis, we have sought to explore pain sensitization as a distinct independent pain mechanism and included therefore a broad set of possible confounders. The definition of a confounder is a factor that is causally associated with both the independent and dependent variable and therefore can produce untruthful results that can be attributed to the confounder and not the independent variable. As an example, physical activity is associated with pain and somatosensory function and our positive results could be explained by level of physical activity in the study sample. Except for age, other hand OA studies of pain sensitization have not adjusted for confounding variables. We adjusted for age, sex and BMI in all analyses because these variables have previously been shown to explain individual variance in pain and pain sensitization(192, 193). Lower level of education, as a proxy for socioeconomic status, greater pain catastrophizing, anxiety, and depression, and reduced sleep quality, are related to increased OA pain severity(131, 132). At the same time these factors may influence central sensitization directly or indirectly through their effect on central pain processing, which there are some indications for in literature(194). Thus, we included these variables in our analyses. Regarding physical activity, the causal pathway between physical activity and pain can be argued to go in both directions. As we did not have a reliable variable of physical activity, we chose not include it. Also, in our preparations there was a pragmatic balancing of sufficient but not unnecessary adjustments or overadjustment.

We adjusted for Kellgren Lawrence sum score to account for the effect of OA severity on both pain sensitization and pain. To keep as much information as possible in the radiographic variable we chose the sum score of Kellgren Lawrence grade across all finger and thumb joints. However, in the preparation of the paper we repeated all analyses using number of joints with definite OA in the adjusted model and observed that the results did not change. In paper III we used the sum score again, as an independent variable, but also here we repeated the analyses using joint counts and found similar results.

Analgesic medications are another important confounder as it may influence both pain reporting on the questionnaires and QST results. For this reason, we included adjustment of regular use of analgesics. The lack of information about in facto use of analgesics on the study visit day, including intermittent usage, leaves some residual confounding that may have underestimated our results. The observed results might have been stronger. On the other hand, there were not any statistically significant interactions between QST results and regular use of analgesics in the analyses on either NRS or AUSCAN pain.

A limitation of non-community based studies is that they only include symptomatic patients, and thus persons with structural asymptomatic OA are not included, because they do not fulfill the inclusion criteria. The association between pain sensitization and pain experience could therefore be explained by person-related factors that are the same factors that explain why they have symptomatic OA in the first place. This selection bias is not possible to rule out completely.

6.2.4 Joint pathologies and peripheral and central sensitization

OA pain experience is often weakly related to the amount of joint damage which is not what one would expect if OA pain was nociceptive from mechanical stimuli. Since OA pain is also influenced by pain sensitization it raises the question of whether OA pathology might induce and maintain pain sensitization. And if this is the case, which pathological features? In paper II, we found that both structural and inflammatory disease severity was associated with pain sensitization in the same joint in persons with hand OA, but we were not able to distinguish if these associations reflect peripheral or central sensitization or one of these more than the other. In paper III we found that the total amount of disease pathology did not associate with measures considered to reflect central sensitization.

A clear dose-response relation between decreasing PPTs at interphalangeal joints with increasing Kellgren Lawrence grade has been demonstrated earlier and this observation is now strengthened by our replication of similar findings in paper II(117). The local PPTs reflect peripheral sensitization because of its proximity to pathology but they also encompass central sensitization as altered central pain processing necessarily also will affect the hands. Our findings are in line with theories from animal studies, where both peripheral and central sensitization is associated with structural joint damage(106, 195). However, the same association was not seen in persons with knee OA where the PPT at the patella did not vary across joints with different levels of Kellgren Lawrence grades at all(113). This study

included more than 4000 knees of persons with or at risk of knee OA where about one-third were nonpainful. A potential reason for the discrepancy between the results from the knee OA study and our results is the influence of pain in our study that might have biased our results, and this is discussed in the next section. Alternatively, methodological differences, like selection of study population, statistical method, choice of covariates or sensitivity of PPT test site (at bony surface of patella versus directly at dorsal side of interphalangeal joints) are potential causes for different findings. Another potential explanation is fundamental differences of knee and hand OA pain mechanisms. Finally, neither our study nor the two other studies mentioned are longitudinal. Preferably a longitudinal study of patients with early-stage disease should explore the relationship between joint pathology and pain sensitization.

On the other hand, our finding of a dose dependent relationship between inflammatory severity and pain sensitization in paper II, is in line with findings in knee OA. Knee OA inflammation, assessed as synovitis and effusion by MRI was associated with peripheral and central sensitization cross-sectionally but did also predict peripheral and central sensitization over a two-year period(123). Ultrasound examination of synovitis may be less sensitive than MRI, yet we saw the same relation of inflammation, independent of structural severity. These are interesting results as they support results from basic science that indicate that joint synovitis mediate pain sensitization at both peripheral and central level. Animal studies have demonstrated that hyperactivation of macrophages is associated with increased nociceptive excitability and activation of microglia in dorsal horn neurons as a response to OA related joint synovitis(196).

In paper III we examined if larger amounts of hand OA pathology in both hands increased the likelihood of central sensitization. We explored this through signs of widespread hypersensitivity and facilitated pain signaling, however, the results mainly were negative. Interestingly, having the erosive hand OA phenotype was statistically significantly associated with lower remote PPT and TS. We can speculate whether this result reflects an association with more inflammation and structural changes over a longer period, since erosive hand OA is characterized by a more aggressive inflammation and structural damage(32). Erosive hand OA is a more painful phenotype and pain sensitization may represent an important pain mechanism for these patients.

The different findings of paper II, where we found strong dose-dependent associations between pathological features and local PPTs, and paper III, where there were no associations of pathological features to remote PPTs and TS, may be explained by several reasons. First, they may indicate that peripheral, but not central sensitization, is directly related to hand OA pathology and that other factors are more important for the clinical outcome of central sensitization, i.e., widespread hypersensitivity. Second, the associations at joint level in paper II may well represent central sensitization, but these mechanisms might be impossible to disentangle from the complexity of central sensitization at person level. For example, central sensitization in a person may be the result of other diseases with chronic pain or OA of other joints, although we adjusted for co-morbidities and generalized OA to account for this. And finally, there may segmental central sensitization that were not exhibited at the distant sites tested.

6.2.5 The influence of pain on the associations between joint pathology and pain sensitization

In paper I we found that pain sensitization was associated with pain independent of structural severity of OA disease. The strength of the associations was weakened in the model adjusted for Kellgren Lawrence sum score, demographics, BMI, psychological factors and analgesics as compared with the crude model, but we did jot not evaluate the effect of structural disease alone as several covariates were included. In paper II, we found associations of moderate to severe structural and inflammatory joint pathology to pain sensitization in the painful interphalangeal joints. In nonpainful joints, the mean PPT value was lower, with a clear dose dependent pattern with increasing severity of all pathological features, but none of the fully adjusted analyses reached statistical significance.

The lack of statistically significant associations between OA pathology and PPT values in the nonpainful joints in paper II may be explained by the low prevalence of joints with moderate and severe pathology among the nonpainful joints, hampering our precision. As mentioned earlier, when the selection of painful and nonpainful joints were made, the protocol allowed selection based on clinical OA severity if needed. If all interphalangeal joints were painful the least painful with no clinical OA was chosen to represent the nonpainful joint, while if none of the joints were painful the joint with most severe clinical OA was chosen to represent the painful joint. This might have underestimated strength of associations in nonpainful joints and likewise overestimated the strength of associations in painful joints.

Yet, since the results in paper II were clearly weakened in stratified analyses of nonpainful joints alone it suggests, indirectly, that pain has an independent role. All analyses in this thesis are cross-sectional. It is unclear whether it is pain sensitization that drives pain or whether pain sensitization is a consequence of pain, or if the association is bidirectional. After all, both structural and inflammatory joint features on radiographs, MRI and ultrasound are strongly associated with joint tenderness on palpation(90, 98, 100). Therefore, the associations of joint pathology with pain sensitization we see in paper II may partly reflect an association with synovitis- or osteophyte-induced pain that is mediated through nociception rather than pain sensitization.

6.2.6 Symptom duration and central sensitization

The *persistent* nociceptive input from chronic/progressive joint pathology is often described as the theory behind OA pathology as a possible cause of central sensitization(103, 197). We hypothesized therefore that longer disease duration was associated with greater central sensitization and examined this in paper III. We did not find any associations between symptom duration and TS or PPT of remote sites, i.e., central sensitization.

In agreement with our study, Neogi *et al*. did not find any associations of pain sensitization (local and remote PPTs and TS at the wrist and patella) to disease duration (defined from first study visit with radiographic knee OA) in the Multicenter Osteoarthritis Study(113). In another study, Arendt-Nielsen *et al.* tested pain sensitization (local PPT and TS at the knee) in 217 knee OA patients and an association with self-recalled symptom duration(198). However, they used correlation analyses without adjustment for confounders. PPT decrease with increasing age and their results might be the result of lower PPTs in older patients with longer symptom duration(199, 200). Another possible explanation is that there is a relationship between disease duration and peripheral sensitization but not central sensitization. The analyses by Arendt-Nielsen *et al.* include measures of the knee only, i.e., they may reflect predominantly peripheral sensitization. Yet, local PPTs in our cohort were not associated with symptom duration (results omitted from paper III in the version that is currently under review).

In paper III we discussed that the lack of associations might be that other factors dominate in the later stages of the disease course when chronic pain is established. Interestingly, in paper II we saw a trend (mostly statistically nonsignificant) of lower PPTs in the nonpainful joints with more structural changes and more signs of inflammation. We could speculate whether

pain sensitization develops before symptoms, and whether this is true for peripheral more than central sensitization as associations with OA pathology seemed absent in paper III. If this is the case it can be a potential window of opportunity to prevent the development of central sensitization. On the other hand, the lack of associations with symptom duration may indicate that central sensitization is not the consequence of OA disease but rather an individual characteristic, as was suggested in the knee OA study with negative findings(113).

Another interesting study that indirectly can inform us about pain sensitization in the disease course of OA is the study by Carlesso *et al.* on pain susceptibility phenotypes in knee OA(201). They found increased risk of developing persistent knee pain after 2 years in a group of persons characterized with a high degree of pain sensitization compared with a group with very little pain sensitization. Hence, pain sensitization may predate symptom severity, either as a step in the transition to chronic pain or as a underlying risk factor for chronic OA pain.

We were aware that our study was far from optimal to address this objective of temporal relationships. The cross-sectional design as well as recalled symptom duration as a proxy for disease duration have clear limitations. While the absence of associations does not exclude OA pathologies as important for central sensitization, disease duration is probably is not a contributing factor of importance.

7. Conclusion and future perspectives

7.1 Answers to research questions

- Inter-rater reliability of PPT and TS testing varied from poor to good. (Paper I)

- The prevalence of central sensitization by TS was about 40%. Peripheral and central sensitization by PPTs was higher at painful than nonpainful finger joints. Pain sensitization by PPTs showed a wide variation at all test sites. (Paper I)

- Peripheral and central sensitization were associated with higher NRS hand pain independent of several important confounders. Pain sensitization was not associated with activity-related hand pain. (Paper I)

- The severities of structural radiographic and ultrasound-detected inflammatory pathologies were associated with PPTs at the same finger joint as a measure of peripheral and possibly also central sensitization (Paper II). The total amount of structural or inflammatory hand OA pathology in a person was not associated with central sensitization (Paper III). Persons with the erosive hand OA phenotype were more likely to have central sensitization (Paper III).

- The associations between joint pathologies and pain sensitization were numerically stronger in painful than nonpainful joints (Paper II).

- We found no association of longer disease duration and central sensitization (Paper III).

7.2 Clinical implications and future perspectives

The results of this thesis have increased our understanding of pain mechanisms in persons with hand OA. It has implications for clinicians who seek to understand and explain pain for patients with painful hand OA. They may communicate that not only hard tissue enlargement, deformities and low-grade inflammation contribute to their pain experience, but also nociplastic pain mechanisms, independent of psychological and contextual factors. From the perspective of the patients, the relevance of peripheral and central sensitization provides evidence-based support for the burden of pain also in the absence of severe structural or inflammatory features.

For the future, quality training and calibration of examiners should be prioritized when using QST to assess pain sensitization. PPT testing of the wrist as a remote test site may be avoided for hand OA because of its low reliability, proximity to the finger joints and possible influence by peripheral sensitization. Also, analgesics on the day of QST testing should be controlled. Finally, observational prospective studies are needed to explore causal relationships and further clinical implications. Pain sensitization is associated with pain severity, but it is unknown whether it predicts worsening of hand OA pain. Joint pathology of a joint is associated with peripheral and possibly central sensitization, but future studies should explore whether OA pathologies predict incident or worsening of pain sensitization. Of special interest would be to investigate if pain sensitization in nonpainful joints with pathology predict development of pain at a later stage.

Pain sensitization is already considered important for persons with hip and knee OA as well as for persons with other rheumatic conditions, such as fibromyalgia and rheumatic arthritis. Our results add hand OA to the list and put further research of the clinical relevance of pain sensitization in hand OA on the agenda. This is important to take advantage of potential novel analgesic therapeutic options where I) treatments target pain sensitization mechanisms directly, such as anti-NGF antibodies and duloxetine, II) pain sensitization may be indirectly targeted through disease-modifying agents, such as anti-inflammatory rheumatic drugs or III) pain sensitization is reflected in mechanistic pain phenotypes aimed at predicting treatment effects or used as stratification tools to provide individualized management with improved therapeutic effectiveness.

8. Errata

Errata paper I. Published in Arthritis & Rheumatology November issue:

“In the article by Steen Pettersen et al in the July 2019 issue of *Arthritis & Rheumatology* (Peripheral and Central Sensitization of Pain in Individuals With Hand Osteoarthritis and Associations With Self-Reported Pain Severity [pages 1070–1077]), a minus sign was inadvertently inserted at the proof stage for the upper 95% confidence value in two instances where the value was not a negative number. The first full paragraph in the right column of page 1073 should have read as follows: "When repeating the analyses using PPTs at the finger joints as a continuous variable, we found significant inverse associations with NRS pain scores (adjusted β = −0.2 [95% CI −0.3, −0.1] for both the painful and nonpainful finger joints), but not with AUSCAN pain scores (adjusted β = −0.2 [95% CI −0.4, 0.1] for the painful finger joint and −0.1 [95% CI −0.3, 0.1] for the nonpainful finger joint).”

Errata list

Doctoral candidate: Pernille Steen Pettersen

Title of the thesis: Pain sensitization in hand osteoarthritis

Abbreviations for different types of formal corrections:

Cor – Correction of language

Cpltf – Change of page layout or text format

Page/Line	**Original text**	**(Type of correction) Corrected text**
18/26	"…criteria are however hampered…"	(Cpltf) "…criteria are, however, hampered…"
18/29	"…is not also available…"	(Cor) "…is not available…"
19/2	"…litterature."	(Cor) "…literature."
23/16	"…correlate…"	(Cor) "…correlates…"
28/15	"…a US…"	(Cor) "…the US…"
34/23	"…surgical OA…"	(Cor) "…a surgical OA…"
43/8	"…by PSP."	(Cpltf) "…by P. Steen Pettersen."
46/11	"…research as has…"	(Cor) "…research and has…"
53/7	"In *paper II*…"	(Cor) "In *paper III*…"
53/8	"In *paper III*…"	(Cor) "In *paper II*…"
61/28	"Finally, preferable…"	(Cpltf) "Finally, a preferable…"
66/19	"A recent French…"	(Cor) "A recent French study…"
66/29	",as well as between them,"	(Cor) ",as well as between themselves,"
68/27	"TA"	(Cor) "TS"
72/4	"…including on intermittent…"	(Cor) "…including intermittent…"
73/23	"In paper III where we…"	(Cor) "In paper III we…"
74/13	"There are known sex-differences in pain, QST results and there also is emerging evidence from animal models of OA of differences between the genders regarding nociception."	(Work-in-progress comment erased) "-"
Reference 1	"…1990–2016…"	…"1990-2016…"

9. References

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10. Papers I-III

II

Arthritis & Rheumatology
Vol. 72, No. 6, June 2020, pp 966–971
DOI 10.1002/art.41199

American College of Rheumatology
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BRIEF REPORT

Associations Between Radiographic and Ultrasound-Detected Features in Hand Osteoarthritis and Local Pressure Pain Thresholds

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Objective. Pain sensitization contributes to the complex osteoarthritis (OA) pain experience. The relationship between imaging features of hand OA and clinically assessed pain sensitization is largely unexplored. This study was undertaken to examine the association of structural and inflammatory features of hand OA with local pressure pain thresholds (PPTs) in the Nor-Hand study.

Methods. The cross-sectional relationship of severity of structural radiographic features of hand OA (measured according to the Kellgren/Lawrence scale [grade 0–4] and the absence or presence of erosive joint disease) as well as ultrasound-detected hand joint inflammation (assessed by gray-scale synovitis [grade 0–3] and the absence or presence of power Doppler activity) to the PPTs of 2 finger joints was examined by multilevel regression analyses adjusted for age, sex, and body mass index, using beta values with 95% confidence intervals (95% CIs).

Results. A total of 570 joints in 285 participants included in the Nor-Hand study were assessed. Greater structural and inflammatory severity was associated with lower PPTs, with adjusted beta values of –0.5 (95% CI –0.6, –0.4) per Kellgren/Lawrence grade increase, –1.4 (95% CI –1.8, –0.9) for erosive versus non-erosive joints, –0.7 (95% CI –0.9, –0.6) per gray-scale synovitis grade increase, and –1.5 (95% CI –1.8, –1.1) for joints with power Doppler activity on ultrasound versus those without.

Conclusion. Greater severity of structural pathologic features and hand joint inflammation was associated with lower PPTs in the finger joints of patients with hand OA, indicating pain sensitization. Our results indicate that pain sensitization might be driven by structural and inflammatory pathology in hand OA.

INTRODUCTION

Pain is the main symptom experienced by patients with hand osteoarthritis (OA) and represents a major health care challenge (1). About 14% of women and 7% of men between the ages of 40 and 84 years are estimated to have symptomatic hand OA (2). Although OA is one of the most prevalent chronic pain conditions worldwide, treatment options remain focused on symptom relief, and both traditional analgesics and nonpharmacologic strategies have limited effect on pain or problematic side effects. The lack of effective analgesics may be due to our poor understanding of the determinants of OA-related pain. Increased knowledge of the mechanisms causing OA pain is therefore needed to develop new and better strategies for pain management and prevention.

A peripheral nociceptive input is traditionally believed to cause OA pain, and both structural and inflammatory changes in finger

Previously published in abstract form: Steen Pettersen P, Neogi T, Magnusson K, Hammer HB, Kvien TK, Uhlig T, et al. Severity of structural and inflammatory features are associated with pain thresholds in hand osteoarthritis [abstract]. Osteoarthritis Cartilage 2019;27:25–6; and Steen Pettersen P, Neogi T, Magnusson K, Hammer HB, Uhlig T, Kvien T. Severity of structural and inflammatory features are associated with lower pressure pain thresholds in hand osteoarthritis [abstract]. Ann Rheum Dis 2019; 78:496.

Supported by the South-Eastern Norway Regional Health Authority, Pahles Foundation, Simon Fougner Hartmanns Family Foundation, and Trygve Gythfeldt Research Foundation. Dr. Neogi's work was supported by the NIH (grants K24-AR-070892 and R01-AR-062506).

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No potential conflicts of interest relevant to this article were reported.

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Submitted for publication October 3, 2019; accepted in revised form December 31, 2019.

joints are associated with pain (3–5). However, by which mechanisms joint pathologies mediate pain is unclear. Alterations in the peripheral and central sensory nervous system, called peripheral and central sensitization, allow pain signaling to be facilitated and cause an increased pain experience. These mechanisms may be induced by injury from, for example, mechanical pressure or inflammatory cytokines, and have been proposed as an explanation as to why OA pain becomes chronic and persistent for a subgroup of patients. Clinically assessed signs of pain sensitization, using quantitative sensory testing methods, have been found to be related to the presence and severity of pain in knee and hand OA (6,7). Pain sensitization is acknowledged as a clinically important treatment target. Yet, whether there are certain pathologic features that cause sensitization, and whether these are potential targets for the prevention or treatment of OA pain, is largely unknown.

OA-related tissue damage and inflammation has been associated with peripheral sensitization to mechanical stimuli in animal studies (8). The excitation threshold for local nociceptors and the transmission of pain signals is lowered and causes increased sensitivity to painful stimuli (hyperalgesia) and painful sensation from normally nonpainful stimuli (allodynia), consequently aggravating OA pain. Pain sensitization is difficult to investigate in humans because of the complexity of the many factors that influence pain perception. Sensory testing of the mechanical pressure pain threshold (PPT) on skin in close proximity to an affected joint is considered to reflect mechanisms of peripheral and/or central sensitization (9). Magnetic resonance imaging (MRI)–detected inflammation in knee OA, but not severity of radiograhic features, is associated with the development and worsening of local pressure pain sensitivity in the knee (10). In contrast, a study on hand OA found that greater structural damage was associated with greater local sensitivity to mechanical pressure pain stimuli (11). However, the study sample was small (n = 13), and no data on inflammation were reported. Inflammation in hand OA is an important symptom and might precede damage of cartilage and bone as an inducer of sensitization.

More knowledge about the mechanisms by which pain sensitization occurs in OA is needed, especially for hand OA wherein the role of inflammation in the pathogenesis of pain sensitization is unknown. Hence, this study was undertaken to explore the cross-sectional association of structural radiographic features and ultrasound-detected inflammatory features with local PPTs in the finger joints of patients with hand OA in a large study from Norway and, additionally, to examine whether the observed associations were different between joints with pain and those without.

PATIENTS AND METHODS

Study design and population. We used baseline data from the Nor-Hand study, which included 300 individuals with hand OA. Detailed inclusion and exclusion criteria have been previously published (12). Participants received oral and written information and provided their written informed consent to participate. The Norwegian Regional Committee for Medical and Health Research Ethics approved the study (reference no. 2014/2057).

Pressure pain threshold of painful and nonpainful finger joints. We tested PPTs in each participant at the following sites in the hand: 2 joints among the distal interphalangeal (DIP) joints 2–5 and proximal interphalangeal (PIP) joints 1–5, the joint a patient reported to be "the most painful in daily life," and a nonpainful joint. If none of the joints were reported to be painful, the joint with the most severe clinical OA (swelling and/or bony enlargements) was chosen for assessment. If none of the joints were pain free, the joint with the least pain and either no OA or the least clinically severe OA was chosen. A handheld algometer (FPIX 25; 1 cm^2 flat rubber probe) was applied in a perpendicular direction on the dorsal aspect of the joint with increasing pressure (0.5 kg/second). The participants were instructed to say "stop" when the pressure first changed to slight pain. The average value (kg/cm^2) from 3 tests on each joint was recorded

Table 1. Demographic and clinical characteristics of the 285 study participants at the person level and joint level*

Demographic variables	
Age, median (IQR) years	61 (57–66)
Female sex	251 (88)
Fulfillment of ACR hand OA criteria	268 (94)
Body mass index, mean ± SD kg/m^2	26 ± 5
Symptom duration, median (IQR) years	6 (3–13)
Numeric rating scale of hand pain in the last 24 hours, mean ± SD (0–10)	3.8 ± 2.3
Regular use of analgesics	
Acetaminophen	11 (4)
Oral or topical nonsteroidal antiinflammatory drugs	35 (12)
Opioids or opioid-like drugs	5 (2)
Antiepileptics, TCAs, and/or SNRIs	15 (5)
Kellgren/Lawrence sum score, median (IQR) (0–128)†	28 (16–43)
Erosive OA‡	101 (35)
Ultrasound gray-scale synovitis sum score, median (IQR) (0–90)†	3 (1–7)
Number of joints with power Doppler activity grades 1–3 on ultrasound, median (IQR) (0–30)†	1 (0–3)
Finger joints assessed (n = 570)§	
Joints with Kellgren/Lawrence grade ≥2	290 (51)
Joints with erosive joint disease	63 (11)
Joints with gray-scale synovitis grades 1–3 on ultrasound	147 (26)
Joints with power Doppler activity grades 1–3 OA on ultrasound	98 (17)

* Except where indicated otherwise, values are the number (%). IQR = interquartile range; ACR = American College of Rheumatology; OA = osteoarthritis; TCAs = tricyclic antidepressants; SNRIs = serotonin and norepinephrine reuptake inhibitors.
† Includes the bilateral distal and proximal interphalangeal, metacarpophalangeal, first carpometacarpal, and scaphotrapeziotrapezoidal joints.
‡ Defined as a participant having disease activity in the Verbuggen/Veys erosive or remodeling phases present in at least 1 interphalangeal joint.
§ Two joints (the joint reported to be most painful by a participant as well as a nonpainful joint among distal interphalangeal joints 2–5 and proximal interphalangeal joints 1–5) were assessed in each participant.

(12). In a subset of 9 participants, test–retest reliability of PPT was found to be moderate to good (intraclass correlation coefficient 0.52–0.61).

Hand radiographs. Radiographs of the bilateral posteroanterior hand joints were obtained for all participants. One experienced reader (IKH) scored all hand joints for OA severity on a 0–4 scale using a modified Kellgren/Lawrence (K/L) scale (2) and scored the DIP/PIP joints using the Verbruggen/Veys (V/V) anatomical phase scoring system (13). Joints in the erosive or remodeling phases were defined as erosive (14). DIP/PIP joints on 20 radiographs were reassessed for intrareader reliability, which was excellent (κ with linear weighting = 0.92 for K/L grades 0–4; κ = 0.98 for the absence/presence of erosions in a yes/no format).

Ultrasound. On the same day as PPT testing, a trained medical student (Nicolai Ravn Aarskog, Diakonhjemmet Hospital, Oslo, Norway) performed the ultrasound examinations using a Logic S8 ultrasound machine with a linear 6–15 MHz probe and a preset for optimal imaging of gray-scale synovitis and power Doppler (PD) activity (pulse repetition frequency 0.6 kHz, frequency 7.7 MHz) (General Electric). Initial scorings were done in consensus with an experienced ultrasonographer (Alexander Mathiessen, MD, PhD, Diakonhjemmet Hospital, Oslo, Norway).

The hand examination was performed with the participant's hands resting in a flat position. All hand joints were scanned dorsally with longitudinal projection from the radial to the ulnar side of each joint. An additional transverse scan was performed when the presence of pathologic features of OA was uncertain. Gray-scale synovitis and PD activity were scored on 0–3 scales (15). Due to the low frequency of grade 2–3 PD activity, we dichotomized this variable (grade 0 versus grades 1–3). Interreader reliability of the assessments of the DIP/PIP joints in 10 participants between the medical student (Nicolai Ravn Aarskog) and the ultrasonographer (Alexander Mathiessen) was good, determined by prevalence and bias–adjusted kappa values for categorical variables with linear weighting (κ = 0.80 for gray-scale synovitis grades 0–3 and κ = 0.79 for the absence/presence of PD activity).

Statistical analysis. Our study sample includes the assessment of 2 joints per participant. The PPTs of 2 joints in 1 person are likely to correlate. To account for this within-person effect, mixed model regression analyses were performed. The association between each structural and inflammatory imaging feature (independent variables) and PPT (dependent variable) was examined with adjustment for age, sex, and body mass index, using beta values with 95% confidence intervals (95% CIs). To explore whether inflammation is a confounder in the associations between radiographic OA and PPTs and whether radiographic severity is a confounder in the associations between inflammatory features and PPTs, we repeated the analyses, with adjustment for gray-scale synovitis and K/L grade, respectively. We also explored whether additional adjustment for nonsteroidal antiinflammatory drugs (NSAIDs) altered the associations between inflammation and PPT. Finally, to explore how pain influences these associations, we performed separate analyses for the painful joints and

Table 2. Associations between OA characteristics (structural radiographic features and ultrasound-detected inflammation) and PPTs in the same finger joints among 570 total joints assessed*

	No. (%)	PPT, mean ± SD kg/cm^2	Adjusted β (95% CI)	Adjustment for Kellgren/Lawrence OA grade or synovitis grade, β (95% CI)†
Kellgren/Lawrence				
Grade 0	187 (33)	4.9 ± 2.1	Referent	Referent
Grade 1	93 (16)	4.7 ± 2.0	−0.3 (−0.6, 0.1)	−0.1 (−0.5, 0.2)
Grade 2	137 (24)	4.7 ± 2.1	−0.5 (−0.9, −0.2)	−0.4 (−0.7, 0.0)
Grade 3	79 (14)	3.5 ± 1.6	−1.6 (−2.0, −1.1)	−1.2 (−1.7, −0.7)
Grade 4	74 (13)	2.9 ± 1.3	−2.0 (−2.4, −1.6)	−1.4 (−1.9, −0.9)
Erosive OA disease				
No	507 (89)	4.6 ± 2.1	Referent	Referent
Yes	63 (11)	2.9 ± 1.2	−1.4 (−1.8, −0.9)	−0.7 (−1.1, −0.2)
Gray-scale synovitis on ultrasound				
Grade 0	423 (74)	4.7 ± 2.1	Referent	Referent
Grade 1	72 (13)	3.9 ± 1.9	−0.9 (−1.3, −0.5)	−0.3 (−0.7, 0.1)
Grade 2	48 (8)	3.3 ± 1.2	−1.4 (−1.9, −1.0)	−0.9 (−1.4, −0.4)
Grade 3	27 (5)	2.5 ± 1.5	−2.0 (−2.6, −1.4)	−1.2 (−1.8, −0.6)
Power Doppler activity grades 1–3 on ultrasound				
No	472 (82)	4.7 ± 2.1	Referent	Referent
Yes	98 (17)	3.1 ± 1.4	−1.5 (−1.8, −1.1)	−0.9 (−1.2, −0.5)

* Mixed-effects multilevel regression analysis of 2 joints (units) per person (cluster). All analyses were adjusted for age, sex, and body mass index. PPT = pressure pain threshold; 95% CI = 95% confidence interval.
† Analyses of Kellgren/Lawrence grade of radiographic osteoarthritis (OA) severity and erosive OA were adjusted for gray-scale synovitis. Analyses of gray-scale synovitis and power Doppler activity were adjusted for Kellgren/Lawrence OA grade.

the nonpainful joints. Analyses were performed using Stata software version 15.

RESULTS

Quantitative sensory testing data were missing for 15 of the 300 individuals in the cohort due to equipment error (n = 9), incomplete examination (n = 1), and incomplete information on assessed joints (n = 5). Hence, 570 joints from 285 participants were examined in analyses (Table 1).

Radiographic OA features and PPT. As a continuous variable, a higher grade on the K/L scale was statistically significantly associated with lower PPT values (β = –0.5 [95% CI –0.6, –0.4]). Joints with possible, definite, or severe OA observed on radiographs (K/L grades 2, 3, or 4, respectively), but not joints with doubtful radiographic OA (K/L grade 1), had significantly lower PPTs than joints with no radiographic OA (K/L grade 0) (Table 2). Similarly, the PPT values were significantly lower in erosive versus non-erosive joints (Table 2). Additional adjustment for gray-scale ultrasound synovitis led to small reductions in the strength of the estimates, but the associations observed between OA severity on radiographs and PPT remained statistically significant (Table 2).

Ultrasound-detected inflammation and PPT. Greater severity of gray-scale synovitis (indicated by higher synovitis grades) was associated with lower PPT values (β = –0.7 [95% CI –0.9, –0.6]). Joints assessed as having synovitis grade 1, 2, and 3 had statistically significantly lower PPTs than joints without synovitis (gray-scale synovitis grade 0), even after additional adjustment for K/L grade (Table 2). Similar associations were found for PD activity (Table 2). Additional adjustment for regular use of NSAIDs did not alter the results (data not shown).

Sensitivity analyses. In separate analyses of the painful finger joints (n = 285), the strength of the associations remained similar to the main analyses (Table 3).

In the nonpainful joints (n = 285), similar trends were observed between lower PPTs and increasing K/L grade as a continuous variable (adjusted β = –0.3 [95% CI –0.5, –0.1]), presence of erosions (adjusted β = –1.2 [95% CI –2.6, 0.2]), increasing gray-scale synovitis grade as a continuous variable (adjusted β = –0.6 [95% CI –1.3, 0.0]), and presence of PD activity grades 1–3 (adjusted β = –1.0 [95% CI –2.1, 0.2]). Pathologic features were less frequently present in these nonpainful joints (Table 3), and fewer associations reached statistical significance.

DISCUSSION

In our study, both structural and inflammatory hand OA features, independent of each other, were associated with lower PPT at finger joints and may represent possible drivers of pain sensitization. We also demonstrated that the relationship between more severe joint disease and greater local pain sensitivity was similar in joints with pain and those without.

Previous hand OA studies have shown that structural features and inflammatory severity observed on radiographs, MRI, and ultrasound are strongly associated with joint tenderness on palpation (3–5). Our results are the first to support these findings with a semiobjective quantitative measure of pain sensitization. While the Doyle Index evaluates the *presence* of pain elicited by pressure or passive joint movement on a 0–3 scale (16), PPT determines the exact *threshold* at which increasing pressure first feels slightly painful. PPT testing, a recognized measure of pain sensitivity in pain research, is more standardized and nuanced with a scale value and could be more sensitive to change than joint tenderness, though we acknowledge that the potential added clinical value of PPT needs further exploration.

Our results are consistent with a small study of 13 patients with hand OA, in whom significant correlations between K/L grade and PPT at the same IP joint were found (11). Other studies have explored the associations between knee OA pathology and local pain sensitivity. MRI-detected synovitis was associated with lower PPT at the patella and predicted a significant reduction in PPT after 2 years (10). In contrast to the strong association we observed between radiographic features of OA and PPT values, several studies on knee OA have not been able to demonstrate such an association between radiographic knee OA and PPT after adjustment for potential confounders and pain severity (10). While the differences in our results between the painful and nonpainful joints should be interpreted with caution due to potential issues of precision, the stronger associations observed with painful joints may indicate an important role for pain symptoms themselves beyond radiographic abnormalities, similar to prior findings observed at the knee.

By using the PPT testing method, we demonstrated for the first time that even in joints without self-reported pain, radiographic structural severity and ultrasound-detected inflammatory severity were associated with local pain sensitivity. These new and important findings may indicate that pain sensitization is an early feature in the pathogenesis of pain. Future longitudinal studies are needed to explore whether a low PPT in pain-free joints predicts the development of self-reported pain.

A limitation of our study is its cross-sectional design. However, the observed dose-dependent associations and the unlikeliness that pain sensitivity causes joint disease supports a true relationship. Further, the study population assessed in this study has a wide range of disease severity, which makes it possible to present dose-response data that otherwise could have been difficult to uncover. This study was confined to explore primarily peripheral sensitization via joint level associations. Local PPT was only tested in 2 finger joints per participant, which was a pragmatic choice. DIP/PIP joints are the joints with the highest prevalence of OA, and we considered the selection of the most

Table 3. Association between PPT values and severity levels of structural radiographic features/inflammatory characteristics of OA in 285 painful finger joints and 285 nonpainful finger joints*

	No. of patients	PPT, mean ± SD kg/cm^2	Adjusted β (95% CI)	Adjustment for Kellgren/Lawrence OA grade or synovitis grade, β (95% CI)†
Painful finger joints				
Kellgren/Lawrence				
Grade 0	63	4.5 ± 1.9	Referent	Referent
Grade 1	41	4.3 ± 1.8	−0.3 (−1.1, 0.4)	−0.3 (−1.0, 0.4)
Grade 2	62	4.6 ± 2.2	0.0 (−0.7, 0.7)	0.0 (−0.7, 0.7)
Grade 3	55	3.2 ± 1.6	−1.4 (−2.1, −0.7)	−1.2 (−1.9, −0.5)
Grade 4	64	2.8 ± 1.2	−1.9 (−2.5, −1.2)	−1.6 (−0.4, −0.9)
Continuous scales (grades 0–4)			−0.5 (−0.6, −0.3)	−0.4 (−0.6, −0.2)
Erosive OA disease				
No	231	4.1 ± 2.0	Referent	Referent
Yes	54	2.8 ± 1.2	−1.3 (−1.9, −0.7)	−1.0 (−0.6, −0.2)
Gray-scale synovitis on ultrasound				
Grade 0	159	4.3 ± 2.0	Referent	Referent
Grade 1	57	3.8 ± 2.0	−0.5 (−1.1, 0.1)	0.0 (−0.5, 0.6)
Grade 2	43	3.3 ± 1.2	−1.0 (−1.6, −0.3)	−0.3 (−0.9, 0.4)
Grade 3	26	2.5 ± 1.5	−1.8 (−2.6, −1.0)	−1.1 (−1.9, −0.3)
Continuous scales (grades 0–3)			−0.6 (−0.8, −0.3)	−0.3 (−0.5, −0.0)
Power Doppler activity grades 1–3 on ultrasound				
No	201	4.2 ± 2.0	Referent	Referent
Yes	84	3.0 ± 1.3	−1.3 (−1.8, −0.8)	−0.8 (−1.3, −0.3)
Nonpainful finger joints				
Kellgren/Lawrence				
Grade 0	124	5.1 ± 2.3	Referent	Referent
Grade 1	52	5.0 ± 2.1	−0.1 (−0.7, 0.6)	−0.0 (−0.7, 0.6)
Grade 2	75	4.8 ± 2.0	−0.3 (−0.9, 0.4)	−1.2 (−0.8, 0.4)
Grade 3	24	4.2 ± 1.6	−1.0 (−1.9, −0.1)	−0.9 (−1.9, 0.0)
Grade 4	10	3.6 ± 1.3	−1.4 (−2.7, −0.0)	−1.3 (−2.8, 0.1)
Continuous scales (grades 0–4)			−0.3 (−0.5, −0.1)	−0.2 (−0.5, −0.0)
Erosive OA disease				
No	271	5.0 ± 2.1	Referent	Referent
Yes	9	3.6 ± 1.4	−1.2 (−2.6, 0.2)	−1.1 (−2.5, 0.3)
Gray-scale synovitis on ultrasound				
Grade 0	264	5.0 ± 2.1	Referent	Referent
Grade 1	15	4.3 ± 1.4	−0.7 (−1.8, 0.4)	−0.1 (−1.3, 1.1)
Grade 2	5	3.4 ± 1.2	−1.4 (−3.3, 0.4)	−1.3 (−3.2, 0.6)
Grade 3	1	3.7 ± 0	−1.1 (−5.2, 2.9)	−1.1 (−5.2, 3.0)
Continuous scales (grades 0–3)			−0.6 (−1.3, −0.0)	−0.4 (−1.1, 0.2)
Power Doppler activity grades 1–3 on ultrasound				
No	271	5.0 ± 2.1	Referent	Referent
Yes	14	3.9 ± 1.4	−1.0 (−2.1, 0.2)	−0.5 (−1.7, 0.7)

* Data were examined by linear regression analysis. All analyses were adjusted for age, sex, and body mass index. See Table 2 for definitions.
† Analyses of Kellgren/Lawrence grade of radiogrpahic OA severity and erosive OA were adjusted for gray-scale synovitis. Analyses of gray-scale synovitis and power Doppler activity were adjusted for Kellgren/Lawrence OA grade.

symptomatic joint and an asymptomatic joint to be sufficient to represent the local mechanisms we examined. Still, it is important to acknowledge that a PPT assessed adjacent to a site of pathologic changes in an individual could also be considered a component of the individual's overall central pain sensitization. Although the results of our study imply that preventing structural changes and treating inflammation might have clinical consequences, the relationship between structural changes/inflammation and central sensitization is still unknown. A study investigating the relationship between OA joint pathologic changes in the hand and PPTs at distant sites with no evident disease, or utilizing other quantitative sensory testing modalities of central sensitization (e.g., temporal summation), might help in making a clear distinction between peripheral sensitization and central sensitization.

Our results have potential implications for future research and therapeutic approaches. Pain sensitization is a potential treatment target both indirectly and directly. Indirectly, disease-modifying drugs that target structural and inflammatory disease activity could alter

pain sensitization and consequently pain. Directly, mechanisms by which pain sensitization occurs are potential treatment targets themselves. Studies performed in recent years have revealed several promising targets that are mediators of pain sensitization (e.g., nerve growth factor, tropomyosin-related kinase receptor A, and ion channels [1]). So far, only one clinical trial of disease or symptom–modifying drugs in hand OA has included characterization of pain sensitization (17). Future clinical trials could benefit from including quantitative sensory testing of pain sensitization as a predictor of treatment efficacy, as a stratification tool to evaluate subgroup effects, or as an inclusion criterion to select the right pain phenotype for the intervention in question.

In summary, this is the first study to demonstrate an independent association of structural and inflammatory hand OA features with lower local PPTs, indicating pain sensitization. The associations were similar in joints with pain and those without. These results complement preclinical evidence that pain sensitization, especially peripheral, might be driven by structural and inflammatory features. Future research should investigate the role of pain sensitization as a potential target for hand OA pain management or prevention.

ACKNOWLEDGMENTS

We would like to thank the study participants in the Nor-Hand study. A thank you is also extended to the project coordinators, Elisabeth Mulrooney and Janicke Magnus, as well as Nicolai Ravn Aarskog for performing ultrasound examinations.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Steen Pettersen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Steen Pettersen, Neogi, Hammer, Uhlig Kvien, Haugen.

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III

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

Journal:	*Rheumatology*
Manuscript ID	Draft
Manuscript Type:	Original Article
Date Submitted by the Author:	n/a
Complete List of Authors:	Steen Pettersen, Pernille; Diakonhjemmet Hospital, Division of Rheumatology and Research Neogi, Tuhina; Boston University School of Medicine, Clinical Epidemiology Research &Training Unit Magnusson, Karin; Lund University Faculty of Medicine, Department of Clinical Sciences Lund, Orthopaedics, Clinical Epidemiology Unit; Norwegian Institute of Public Health, Cluster for Health Services Research Mathiessen, Alexander; Diakonhjemmet Hospital, Division of Rheumatology and Research Hammer, Hilde; Diakonhjemmet Sykehus AS, Division of Rheumatology and Research; University of Oslo, Faculty of Medicine Uhlig, Till; Diakonhjemmet Hospital, Division of Rheumatology and Research; Diakonhjemmet Hospital, National Advisory Unit on Rehabilitation in Rheumatology Kvien, Tore; Diakonhjemmet Hospital, Division of Rheumatology and Research Haugen, Ida K; Diakonhjemmet Hospital, Division of Rheumatology and Research
Keywords Please select a minimum FIVE keywords from the list provided. These keywords will be used to select reviewers for this manuscript. The keywords in the main text of your paper do not need to match these words.:	Osteoarthritis < RHEUMATIC DISEASES, Hand < REGIONAL RHEUMATISM, Nervous < TISSUES, Cartilage < TISSUES, Bone < TISSUES, Synovium < BASIC & CLINICAL SCIENCES, Radiology < DIAGNOSTIC METHODS, Ultrasonography < DIAGNOSTIC METHODS, Pain assessment and management < THERAPIES

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 osteoarthritis (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 ultrasound examination. Central sensitization was assessed with pressure pain thresholds (PPT) at remote sites (wrist, trapezius and tibialis anterior muscles) and temporal summation (TS). 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, body mass index, comorbidities and OA-severity of knee/hip.

Results In 291 participants (88% women, median age 61, IQR 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 TS (adjusted beta 0.56, 95%CI 0.12, 1.01) compared to 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 does not appear to drive 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 other factors than joint pathologies.

Keywords: Hand osteoarthritis, arthritis, inflammation, pain mechanisms, pain sensitization, central nervous system sensitization, central sensitization, quantitative sensory testing.

Key messages

- Widespread hypersensitivity and temporal summation are 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.

Introduction

Pain is a major concern for patients with symptomatic hand osteoarthritis (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 central nervous system which is associated with central sensitization(11). The translation of this theory was recently

illustrated in a brief report using data 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 relation between structural and inflammatory hand OA pathologies as well as symptom duration to central sensitization assessed by quantitative sensory testing (QST).

Method

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 interphalangeal or thumb base joint with OA on clinical and/or ultrasound 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 received oral and written information about the study and provided written consent to participate.

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 (Wagner FXPI25, 1cm^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 rate of 0.5kg/second. 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 seconds, 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 hypersensitivity 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 ten stimuli at the dorsal side of the left wrist using a punctate probe (MRC Systems GmbH The PinPrick, set with seven weighted probes; 8, 16, 32, 64, 128, 256 and 512nM) at a rate of 1Hz. 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 512nM (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 ten stimuli were applied at a rate of 1Hz, and the participants were instructed to rate their NRS pain on the 1st, 5th and 10th tap. TS was calculated by subtracting the NRS rating of the 1st tap from the peak NRS rating of the 5th or 10th tap. We also defined TS to be present if the pain increased more than the smallest detectable change (SDC) during the test. The SDC was calculated from a test-retest of 9 participant 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 were 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 ultrasound examination

Bilateral hand radiographs with posteroanterior view were obtained and scored by an experienced reader (IKH). Bilateral hand joints including the distal interphalangeal (DIP), proximal interphalangeal (PIP) including the first interphalangeal, metacarpophalangeal (MCP), first carpometacarpal (CMC1) and scaphotrapeziotrapezoidal joints were scored 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(s) 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 mean (standard deviation, SD) 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 ultrasound examinations of both hands the same day as the QST by use of a General Electric Logic S8 ultrasound machine with a linear 6-15Mz probe and a pre-set 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 (AM). 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

ten participants were examined by both the medical student and the expert (AM) 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 General Electric Logic E9 ultrasound machine, 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 (HBH) 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 body mass index based on measured height and weight (BMI; kg/m^2). The severity of hip and knee OA was defined as the sum of the

osteophyte-grades on ultrasound 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 non-steroidal anti-inflammatory drugs (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 increase in one standard deviation (SD). 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 of 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 grey scale 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 SE 14.0 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 5.5kg/cm^2, SD 2.6) than at the wrist (mean 4.4kg/cm^2, SD 2.0) and trapezius (mean 4.4kg/cm^2, SD 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 to 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

Although 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%) versus 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 to those in the lowest tertiles, but the results were not statistically significant (Table 3).

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%) reported symptom duration of more than 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% versus 42%) and the associations were 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 could not find any relevant associations between the sum of radiographic pathologies or ultrasound-detected inflammation in the hands, and PPTs at remote sites or TS. Hence, other factors than hand OA joint pathologies appear to drive central pain sensitization.

Several mediators in the OA joint have been identified as causes of peripheral sensitization, such as nerve growth factor (NGF), which sensitizes peripheral nociceptors following joint tissue damage and inflammation(24, 25). PPT at DIP and PIP joints in hand OA patients are lower the higher the KL grade(5). We have previously shown that also inflammatory hand OA severity is associated with local PPT(12), supporting the translational evidence from basic to clinical science that peripheral pathology drives peripheral sensitization(26).

Less is known about peripheral drivers of central sensitization, but animal experiments illustrate a possible link between OA joint pathology and central sensitization(27-29). 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 magnetic resonance imaging(6). Previous clinical studies using QST, where none have 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, 30). 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 SDC 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 0.1 points higher NRS hand pain, which is not considered clinically relevant. Hence, although the results are borderline statistically significant, the clinical relevance is doubtful.

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 QSTs is the most feasible measures of central sensitization available, the lack of association with measures of widespread sensitivity and temporal summation indicates that other factors 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(31, 32). Co-morbidities 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(31, 33).

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, 34). In patients with established rheumatoid arthritis (more than 10 years disease duration), localized PPT tested at the thumb nail was significantly lower than in those with shorter disease duration(35). 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(36).

The main limitation of this study is the cross-sectional design and lack of healthy controls, making us unable to conclude about causal relationships. Second, inter-reader reliabilities of the QSTs were not optimal. Calculations were based on only 9 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(37). 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 ultrasound 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 ultrasound-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. Mechanisms contributing to central sensitization may therefore be distinct from those contributing to peripheral sensitization in OA.

Funding This work was supported by funds from the South-East Norway Regional Health Authority; Jan A. Pahle's foundation; Simon Fougner Hartmanns Family foundation; Trygve Gythfeldt´s research foundation and National Institute of Health [K24 AR070892 to TN, R01 AR062506 to TN].

Conflicts of interest The authors declare no conflicts of interest.

Acknowledgements The authors would like to thank the study participants in the Nor-Hand study. A thank you is also extended to the project coordinators Elisabeth Mulrooney and

Janicke Magnus, and to the medical students who performed the quantitative sensory testing and ultrasound examinations of the hands and lower extremities.

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

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Table 1. Demographics and clinical characteristics, n=291

Characteristics	Value
Sex, n (%) women	257 (88)
Age, years, median (IQR)	61 (57-66)
BMI, mean (SD) kg/m2	26.4 (4.8)
Fulfil ACR criteria for hand OA, n (%)	271 (93)
NRS hand pain[a], mean (SD) [0-10]	3.8 (2.3)
Radiographic severity (number of joints with KL ≥ 2), median (IQR) [0-32]	9 (4-14)
KL hand sum score, median (IQR) [0-128]	28 (16-43)
Erosive OA, presence of erosive OA in at least one DIP/PIP joint, n (%)	102 (35)
GS synovitis sum score, median (IQR) [0-90]	3 (1-7)
PD activity sum score, median (IQR) [0-90]	1 (0-4)
GS synovitis joint count, median (IQR) [0-30]	1 (0-2)
PD activity joint count, median (IQR [0-30]	1 (0-3)
Symptom duration[b], median (IQR) years	6 (3-13)
Comorbidity index, mean (SD) [0-45]	9 (4)
Knee and hip OA severity, median (IQR) [0-12]	2 (1, 4)

BMI; body mass index, ACR; American College of Rheumatology, NRS; numerical rating scale, PPT; pressure pain threshold, KL; Kellgren Lawrence grading, OA; osteoarthritis, GS; grey Scale, PD; Power Doppler.

[a]N=290, [b]N=269.

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

	PPT radioulnar joint		PPT trapezius		PPT tibialis anterior	
	Mean (SD)	Adjusted beta (95% CI)	Mean (SD)	Adjusted beta (95% CI)	Mean (SD)	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)
>6 (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)
PD 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)

PPT; pressure pain threshold, KL; Kellgren Lawrence grading, GS; grey Scale, PD; Power Doppler. Explanatory variables are reported as group tertile categories and as continuous values. Continuous values are reported as increase per SD. 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.

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Table 3. Associations of joint pathology and symptom duration with temporal summation

	Presence of TS		Change in TS	
	N (%)	Adjusted OR (95% CI)	Mean (SD)	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)
PD 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)

TS; temporal summation, KL; Kellgren Lawrence grading, GS; grey Scale, PD; Power Doppler. Explanatory variables are reported as group tertile categories and as continuous values. Continuous values are reported as increase per SD. 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.