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"Effect of neuroscience education on subjects with chronic knee pain related to osteoarthritis: a randomized controlled trial"

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Que el presente trabajo, titulado: "**Effect of neuroscience education on subjects with chronic knee pain related to osteoarthritis: a randomized controlled trial**", ha sido realizado bajo su dirección en el *Departament de Fisioteràpia de la Universitat de València,* por D. Enrique Juan Lluch Girbés, para optar al grado de Doctor. Habiéndose concluido, y reuniendo a su juicio las condiciones de originalidad y rigor científico necesarias, autorizan su presentación a fin de que pueda ser defendido ante el tribunal correspondiente.

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RESUMEN

INTRODUCCIÓN GENERAL

La osteoartritis (OA) es la causa principal de dolor, discapacidad y pérdida de calidad de vida en las personas mayores que afecta a más del 80% de la población a partir de los 55 años de edad [1, 2]. Si bien la presentación clínica de OA es muy variable, el dolor es el principal síntoma y los niveles elevados de dolor se asocian a niveles mucho más bajos en la función física, la autoeficacia y la calidad de vida [3, 4]. La OA es una enfermedad que se caracteriza inicialmente por la degeneración del cartílago, a menudo precedido por cambios en el hueso subyacente. Es el resultado de una inadecuada regeneración de daños producidos en la articulación por las tensiones relacionadas con factores biomecánicos, bioquímicos y genéticos [5]. Algunos estudios han demostrado, sin embargo, que, además de la continuada destrucción articular, la producción y remodelación de tejido nuevo se evidencia por el aumento de la síntesis de proteínas por los condrocitos, especialmente en las primeras etapas de OA [6]. Aunque la artrosis se ha considerado tradicionalmente una patología de la población anciana, puede también afectar a personas jóvenes [7]. En concreto, la presencia de obesidad y una historia de lesión traumática en la rodilla (p.e.j. rotura del ligamento cruzado anterior o lesión meniscal) son factores de riego clave que favorecen el desarrollo de artrosis en la rodilla [8]. Por otro lado, la presencia de deformidades estructurales en la cadera (p.e.j. deformidad tipo CAM o tipo PINCER), pueden favorecer la progresión hacia una artrosis de cadera [8]. Las articulaciones que soportan peso, como la cadera y la rodilla, y las articulaciones periféricas menores, incluidas las manos, son las más afectadas por la artrosis [9].

Históricamente, la artrosis se ha considerado un problema estructural secundario a una lesión degenerativa del cartílago articular [10]. Sin embargo, puesto que el cartílago es un tejido avascular y aneural, el cartílago articular dañado no puede generar dolor directamente [11]. Hay estudios que han demostrado cómo la presencia de inflamación en estructuras no cartilaginosas como la membrana sinovial o lesiones en la médula ósea, pueden contribuir al dolor crónico de la artrosis [12-15]. De hecho, la hipertrofia y derrames de la membrana sinovial y las anomalías en el hueso subcondral se han asociado al dolor crónico de la artrosis de rodilla en estudios de cohorte de gran tamaño [16]. Aedmás, se ha constatado una liberación de diferentes mediadores pro-inflamatorios en la articulación afectada por artrosis, como el factor de crecimiento nervioso o el óxido nítrico [6], que podrían contribuir un al dolor de la artrosis. Del mismo modo, la literatura científica muestra como la expresión de determinados factores de crecimiento, en particular el factor de crecimiento endotelial vascular (VEGF *vascular endothelial growth factor*) y el factor de crecimiento derivado de las plaquetas (PDGF *platelet derived growth factor*), pueden inducir una neovascularización en la articulación afectada por artrosis [14]. La angiogénesis osteocondral se ha relacionado con el dolor crónico de la artrosis [17]. Sobre la base de todos estos hallazgos, resulta incuestionable la presencia de un fenómeno local de inflamación de los tejidos blandos en la artrosis, lo que contribuye a la gravedad y frecuencia de dolor en dicha patología [6, 18].

La discordancia que se observa a menudo entre la gravedad del dolor reportada por los pacientes con artrosis y el grado de patología articular (evaluada según los criterios de clasificación radiológica de Kellgren-Lawrence) [19], en particular durante las etapas crónicas de la artrosis, ha cuestionado la idea de que el dolor de la artrosis sea meramente secundario a un daño estructural de la articulación [10]. La alteración del

procesamiento del dolor a nivel del sistema nervioso central (sensibilización central) ha cobrado importancia en los últimos años como un factor que puede contribuir al dolor de la artrosis [5, 7, 10, 20-23]. Si bien se ha considerado durante mucho tiempo que el dolor asociado a la artrosis tiene una naturaleza puramente nociceptiva, la creciente evidencia científica indica que la sensibilización central parece desempeñar un papel muy importante en el dolor experimentado por un subgrupo de pacientes con artrosis en la rodilla [20-33]. Sin embargo, en el momento de iniciar la presente Tesis Doctoral, no se disponía de una revisión sistemática de la literatura en cuanto al papel de la sensibilización central en personas con artrosis de rodilla.

Los mecanismos fisiopatológicos subyacentes a la sensibilización central son complejos y numerosos, pero el efecto neto es una amplificación de las señales nerviosas dentro del sistema nervioso central que provoca una hipersensibilidad al dolor [34, 35]. La sensibilización central es un concepto amplio que refleja no sólo una amplificación del dolor a nivel de la médula espinal (fenómeno de wind up), sino también una mayor actividad de las vías nociceptivas de facilitación descendente [36, 37], la pérdida de mecanismos anti-nociceptivos descendentes [38, 39], la hiperactividad en la neuromatriz del dolor [40], y la potenciación a largo plazo de las sinapsis neuronales en el córtex cingulado anterior [41]. Por lo tanto, el término sensibilización central implica cambios en el procesamiento del dolor que ocurren a diferentes niveles del sistema nervioso central. Actualmente, sin embargo, no existe un término universalmente aceptado para el fenómeno de la sensibilización central y su uso en la literatura científica aún es controvertido [42-44]. Además, la sensibilización central no es una única entidad o fenómeno que puede existir o no existir, estar presente o ausente, sino que se produce a lo largo de un continuo. De hecho, un estudio reciente demostró que

aunque la hipersensibilidad central generalizada o sensibilización central es prevalente, no está presente en todos los pacientes con dolor crónico [45]. Aunque generalmente la sensibilidad al dolor es más acusada en ciertas condiciones de dolor crónico, igualmente es un continuo en estas condiciones [46]. En algunos pacientes, la sensibilización central puede ser la característica principal del trastorno doloroso (por ejemplo, en la fibromialgia). Sin embargo, en otros cuadros clínicos de doloro como la artrosis de rodilla, no todos los pacientes tienen sensibilización central, sino tal sólo un subgrupo. Se ha estimado que alrededor del 30% de los sujetos con artrosis de rodilla tienen sensibilización central como parte de su cuadro clínico [47, 48].

A pesar de los conocimientos cada vez más amplios sobre la importancia de los mecanismos de centrales en el dolor de la artrosis de rodilla, la evaluación sistemática de la sensibilización central aún no se ha incorporado en la práctica clínica. Esto podría deberse en parte al hecho de que la investigación de la sensibilización central se ha realizado fundamentalmente en el ámbito del laboratorio, donde los equipos y los protocolos utilizados para identificar la sensibilización central (por ejemplo, análisis cuantitativo sensorial [49, 50], reflejo nociceptivo de retirada [51], técnicas de neuroimagen [52, 53]) son relativamente sofisticados, requieren una gran inversión de tiempo, tienen un elevado coste y no son adecuados para el entorno clínico.

La clasificación de los pacientes con artrosis de rodilla en función de los mecanismos de dolor dominante, incluyendo aquellos pacientes con dolor por sensibilización central "como mecanismo dominante", está generando cada vez más interés en la literatura tal como demuestra el creciente número de propuestas de clasificación publicadas en los últimos años [54-56]. La ausencia de este tipo de clasificaciones por subgrupos en

ensayos clínicos previos podría explicar la escasa eficacia observada con la mayoría de de los tratamientos disponibles para la artrosis de rodilla. [57]. Así pues, caracterizar o fenotipar el dolor en la artrosis de rodilla se ha convertido en una prioridad básica, no sólo para comprender mejor la experiencia del dolor de cada paciente, sino también para enfocar mejor el tratamiento de forma individual [58]. La identificación temprana del dolor por sensibilización central en personas con artrosis de rodilla es fundamental ya que su presencia puede predecir la obtención de peores resultados con Fisioterapia [59] o cirugía [60,61].

Identificar la sensibilización central en un paciente con artrosis de rodilla supone un reto a nivel clínico, ya que actualmente no existe una definición de consenso internacional ni un conjunto de criterios clínicos válidos para el diagnóstico de la sensibiliación central [34,43,44]. Algunos autores han propuesto que la información derivada del diagnóstico médico, la anamnesis, la exploración física y la respuesta al tratamiento, puede ser útil para identificar la sensibilización central en la práctica clínica [62]. Recientemente, se han publicado criterios clínicos de clasificación para ayudar a los fisioterapeutas a distinguir y diagnosticar el mecanismo dominante del dolor incluida la sensibilización central en sujetos con trastornos musculoesqueléticos crónicos [63]. Dado que como hemos mencionado anteriormente, las pruebas utilizadas para identificar la sensibilización central son básicamente tests de laboratorio no accesibles en el ámbito clínico, se requieren protocolos más cortos y equipos menos costosos que permitan la identificación clínica de los mecanismos del dolor incluyendo la sensibilización central en pacientes con dolor por artrosis de rodilla [64].

A pesar de que hay cada vez más publicaciones que subrayan la importancia de la sensibilización central en la artrosis de rodilla, los tratamientos de rehabilitación que se utilizan para esta patología no suelen considerar las posibles alteraciones en el procesamiento central del dolor relacionados con el dolor en la artrosis de rodilla. De hecho, las estrategias convencionales de rehabilitación para la artrosis de rodilla se centran en gran parte en los mecanismos de entrada (p.e.j. reducir la inflamación articular) y mecanismos de salida (p.e.j. mejorar la fuerza muscular, control motor, propiocepción) asociados a la enfermedad [65]. Por lo general, las estrategias de tratamiento que se dirigen a las estructuras locales son poco eficaces en pacientes cuyo cuadro clínico está caracterizado por un mecanismo dominante de sensibilización central [66,67]. De hecho, la presencia de sensibilización central en un paciente con artrosis de rodilla puede implicar una mayor complejidad del cuadro clínico y menos posibilidades de lograr resultados positivos con las intervenciones de fisioterapia convencionales [59]. Por lo tanto, un enfoque dirigido mayormente a desensibilizar el sistema nervioso central parece estar más justificado para el tratamiento de la sensibilización central en la artrosis de rodilla [29]. Se han publicado en los últimos años varias guías de práctica clínica informando de las opciones disponibles para el tratamiento de la sensibilización central en pacientes con dolor crónico de diversa etiología [65, 68-70]. Éstas abarcan entre otras intervenciones como la educación en neurociencia del dolor, las terapias cognitivo-conductuales, la imaginería motora graduada, la discriminación sensorial, la terapia manual o la terapia con ejercicios [65,68-70]. La aplicación de programas de tratamiento fisioterápico que combinasen el abordaje de la lesión estructural periférica en la rodilla a la vez que los cambios neuroplásticos derivados de la sensibilización central en áreas distribuidas del sistema nervioso, podrían ayudar a mejorar los resultados obtenidos en pacientes con artrosis de

rodilla con un mecanimo central dominante [29, 65]. Sin embargo, la combinación de tratamientos dirigidos al sistema nervioso central con tratamientos tradicionales dirigidos a la articulación de la rodilla, es un enfoque prometedor para la artrosis de rodilla que a día de hoy todavía no se ha investigado. Se argumenta, que debido a la compleja naturaleza multidimensional del dolor en la artrosis de rodilla y los efectos moderados que ejerce la Fisioterapia de forma aislada en dicha patología, la combinación de tratamientos dirigidos tanto a la rodilla como al sistema nervioso central podrían reforzarse mutuamente mejorando así los resultados obtenidos en estos pcientes [29,58,65].

OBJETIVOS

El primer objetivo de la presente Tesis Doctoral fue revisar la evidencia disponible en la literatura científica relacionada con la presencia o ausencia de sensibilización central en pacientes con artrosis, incluyendo personas con artrosis de rodilla, y las opciones disponibles para el tratamiento de la sensibilización central en dicha patología. En segundo lugar, se buscó evaluar si diferentes medidas de sensibilización central en pacientes con artrosis de rodilla guardaban alguna correlación con el área del dolor y los síntomas clínicos del paciente (grado de dolor de rodilla, discapacidad y variables de índole psicosocial) registrados durante la evaluación subjetiva. En tercer lugar, se investigó el efecto antes y después de la cirujía de un programa de Fisioterapia combinada dirigida al sistema nervioso central (educación en neurociencia del dolor) y a la rodilla (terapia manual de la rodilla) en sujetos con artrosis de rodilla que estaban esperando a ser operados. Esta Tesis Doctoral se divide en tres partes, cada una de ellas dirigida a uno de estos tres objetivos.

La siguiente pregunta de investigación se abordó en la primera parte:

- *¿Cuál es el papel que desempeña la sensibilización central en las personas con artrosis, incluidas aquellas con artrosis de rodilla y cuáles son las opciones disponibles para el tratamiento?*

Para examinar esta pregunta de investigación se realizó una revisión narrativa y una revisión sistemática de la literatura relacionada con la presencia de sensibilización central en la artrosis y las opciones actuales para el tratamiento de la sensibilización central específicamente en pacientes con artrosis. Los resultados de dicha investigación se presentan en el capítulo 1, que comprende 2 artículos publicados.

La siguiente pregunta de investigación se abordó en la segunda parte:

- *¿Están asociadas las medidas de sensibilización central con el área de dolor y los síntomas clínicos en sujetos con artrosis de rodilla?*

El capítulo 2 presenta un estudio experimental que analiza si el área de dolor de los pacientes con artrosis de rodilla recogida mediante mapas o dibujos de dolor se relaciona con diferentes medidas de sensibilización central y los síntomas clínicos referidos por estos pacientes durante el examen subjetivo.

La siguiente pregunta de investigación se abordó en la tercera parte:

- *¿Resulta eficaz para las personas con artrosis de rodilla un programa de Fisioterapia que combina la terapia manual dirigida a la rodilla con la educación en neurociencia del dolor dirigida al sistema nervioso central?*

El capítulo 3 incluye dos estudios para tratan de responder a esta pregunta. El primer estudio presenta los fundamentos teóricos para la aplicación simultánea de un programa de Fisioterapia que combina la terapia manual y la educación en neurociencia del dolor

en pacientes con artrosis de rodilla. En el segundo estudio se presentan los resultados de un ensayo clínico aleatorizado que evalúa los efectos de un programa de tratamiento fisioterápico preoperatorio que combina la educación en neurociencia del dolor con la movilización de la articulación de la rodilla en sujetos con artrosis de rodilla.

Capítulo 1. ¿Cuál es el papel que desempeña la sensibilización central en las personas con artrosis, incluidas aquellas con artrosis de rodilla y cuáles son las opciones disponibles para el tratamiento?

Contenido:

Evidence for central sensitization in patients with osteoarthritis pain: a systematic literature review

Lluch E, Torres R, Nijs J, Van Oosterwijck J.

Eur J Pain. 2014;18(10):1367-75.

Pain treatment for patients with osteoarthritis and central sensitization

Lluch Girbés E, Nijs J, Torres-Cueco R, López Cubas C.

Phys Ther. 2013;93(6):842-51.

Evidence for central sensitization in patients with osteoarthritis pain: a systematic literature review

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RESUMEN

Introducción y objetivos: La sensibilización central se sugiere que juega un papel importante en el dolor crónico que experimentan los pacientes con artrosis. Se llevó a cao una revisión sistemática siguiendo la guía PRISMA para evaluar la evidencia existente en la literatura relacionada con la presencia de sensibilización central en pacientes con artrosis.

Bases de datos y tratamiento de los datos: Se realizó una búsqueda bibliográfica en las bases de datos Pubmed y Web of Science con el objetivo de identificar los artículos más relevantes utilizando palabras claves predeterminadas relacionadas con la artrosis y sensibilización central. Se incluyeron artículos a texto completo que habían investigado la sensibilización central en sujetos adultos con artrosis. La calidad metodológica de todos los artículos fue evaluada por dos investigadores de forma independiente.

Resultados: De los 40 artículos que fueron elegidos inicialmente para la evaluación de la calidad metodológica, 36 consiguieron una puntuación suficiente y fueron discutidos en esta revisión. La mayoría de los estudios fueron estudios de casos-controles y dirigidos a la articulación de la rodilla. Se encontraron distintos parámetros subjetivos y objetivos considerados manifestaciones clínicas de sensibilización central en los pacientes con artrosis de rodilla. Dichos parámetros se han encontrado previamente en otras poblaciones con dolor crónico como sujetos con latigazo cervical o artritis reumatoide. En general, los resultados de esta revisión sugieren que aunque mecanismos periféricos están envueltos en el dolor de la artrosis, la sensibilización central juega un papel importante en un subgrupo de pacientes dentro de esta población.

Conclusiones: Aunque la mayoría de la literatura pone de manifiesto la presencia de sensibilización central en el dolor crónico de la artrosis, la identificación clínica y el tratamiento de la sensibilización central en la artrosis todavía está en su infancia. Futuros estudios con buena calidad metodológica son necesarios en este sentido.

Palabras clave: osteoarthritis, pain, central sensitization, neuroscience education, exercise therapy, graded activity.

Pain treatment for patients with osteoarthritis and central sensitization

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RESUMEN

La artrosis es una de las patologías más frecuentes, discapacitantes y costosas de la sociedad moderna. Uno de los principales objetivos del tratamiento de la artrosis es el control del dolor y la mejora de la capacidad funcional del paciente. La causa exacta de la artrosis todavía se desconoce a día de hoy. Además de los cambios que se producen a nivel de las estructuras articulares, parece ser que se produce una alteración en el procesamiento del dolor a nivel del sistema nervioso o sensibilización central que puede estar envuelto en el dolor que refieren los pacientes con artrosis. Este último punto alerta de la necesidad de utilizar un abordaje más amplio en el tratamiento de los pacientes con artrosis de rodilla que incluya estrategias de desensibilización del sistema nervioso. Sin embargo, la literatura científica evaluada en esta revisión narrativa ofrece poca información relativa al tratamiento de la sensibilización central en pacientes con artrosis. Intervenciones como la terapia cognitiva-conductual y la educación en neurociencia potentialmente van dirigidas a la sensibilización cognitiva-emocional (facilitación descendente), mientras que los medicamentos de acción central como la duloxetina o la terapia por ejercicios son capaces de mejorar los mecanismos de analgesia endógena o inhibitorios descendentes del dolor. Futuros estudios deberían valorar la eficacia de estas nuevas estrategias de ratamiento en pacientes con artrosis.

Palabras clave: osteoarthritis, pain, central sensitization, neuroscience education, exercise therapy, graded activity.

Capítulo 2. ¿Están asociadas las medidas de sensibilización central con el área de dolor y los síntomas clínicos en sujetos con artrosis de rodilla?

Contenido:

Expanded distribution of pain as a sign of central sensitization in individuals with symptomatic knee osteoarthritis

Lluch E, Dueñas L, Barbero M, Falla D, Baert I, Meeus M, Sánchez-Frutos J, Aguilella L, Nijs J.

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Expanded distribution of pain as a sign of central sensitization in individuals with symptomatic knee osteoarthritis

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RESUMEN

Introducción: La expansion del área del dolor hcaia areas difusas o extensas se considera uno de los signos de sensibilización central. La relación entre los síntomas clínicos referidos por los pacientes con artrosis de rodilla y la sensibilización central ha sido poco investigada en la literatura científica.

Objectivo: Examinar si el área de dolor dibujada por los pacientes con artrosis de artrosis se relaciona con medidas de sensibilización central y con distintos síntomas clínicos recogidos durante el examen subjetivo incluyendo el grado de dolor de rodilla, discapacidad y variables de índole psicosocial.

Diseño: Estudio transversal observacional.

Métodos: Se estudiaron 53 sujetos con artrosis de rodilla que estaban en lista de espera para operarse de una prótesis de rodilla. Todos los sujetos completaron un mapa del dolor utilizando un dispositivo digital novedoso y diferentes cuestionarios relacionados con el dolor y discapacidad de rodilla y factores de índole psicosocial. Además, se realizó un análisis cuantitativo sensorial a todos los sujetos que incluía el cálculo de los umbrales de dolor a la presión, la sumación temporal al dolor y la analgesia condicionada. Se generaron mapas de frecuencia del dolor de forma separada para los hombres y mujeres que formaban parte de la muestra de estudio. Se calculó el coeficiente de correlación de Spearman para ver posibles correlaciones entre el área del dolor y el análisis cuantitativo sensorial y los síntomas clínicos de los pacientes.

Resultados: Los mapas de frecuencia del dolor mostraron áreas de dolor más extensas especialmente en las mujeres. La presencia de áreas de dolor extendidas se asoció a una mayor severidad de dolor en la rodilla (r_s= .325, P < 0.05) y rigidez (r_s=.341, P < 0.05), menor umbral de dolor a la presión en la rodilla (r_s=-.306, P < 0.05) y el epicóndilo (r_s=-.308, P < 0.05) y puntuaciones más elevadas en el cuestionario Central Sensitization

Inventory (r_s=.456, P < 0.01). No se encontró una correlación significativa entre el área del dolor y el resto de síntomas clínicos y medidas de sensibilización central.

Limitationes: Debido al diseño de este estudio, no se pueden extraer conclusiones firmes sobre la capacidad predictiva de los mapas de dolor a la hora de determinar la presencia de sensibilización central. Se necesitan mayor investigación para determinar la fiabilidad y la validez de los mapas de dolor en los pacientes con artrosis de rodilla.

Conclusiones: La extension del área del dolor hacia zonas difusas o extendidas se correlacionó con algunas medidas de sensibilización central en sujetos con artrosis de rodilla. Los mapas de dolor pueden ser una herramienta útil para identificar de forma precoz la presencia de sensibilización central en sujetos con artrosis de rodilla, pero se necesita mayor investigación en este sentido.

Palabras clave: Knee osteoarthritis, chronic pain, pain location, central nervous system sensitization.

Capítulo 3. ¿Resulta eficaz para las personas con artrosis de rodilla un programa de Fisioterapia que combina la terapia manual dirigida a la rodilla con la educación en neurociencia del dolor dirigida al sistema nervioso central?

Contenido:

Balancing “hands-on” with “hands-off “ physical therapy interventions for the treatment of central sensitization pain in osteoarthritis

Lluch Girbés E, Meeus M, Baert I, Nijs J.

Man Ther. 2015;20(2):349-52.

Preoperative pain neuroscience education combined with knee joint mobilization for knee osteoarthritis: a randomized controlled trial

Lluch E, Dueñas L, Falla D, Baert I, Meeus M, Sánchez-Frutos J, Nijs J.

Under review

Balancing "hands-on" with "hands-off " physical therapy interventions for the treatment of central sensitization pain in osteoarthritis

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RESUMEN

La forma tradicional de entender la artrosis de rodilla como un problema meramente relacionado con los tejidos articulares se ha puesto en tela de juicio, en vista de la evidencia que apoya un papel de la sensibilización central en un subgrupo de pacientes afectos de esta patologia. Este hecho puede conducir de forma errónea a los fisioterapeutas a concluir que las intervencions manuales no tienen cabida en el tratamiento de la artrosis de rodilla y que solo deben de aplicarse técnicas de tratamiento "*hands off*". El objetivo de este articulo es animar a los clínicos a encontrar el equilibrio entre técnicas manuales y técnicas "*hands off*" durante el tratamiento de los pacientes con artrosis de rodilla cuyo clínico doloroso esté dominado por la sensibilización central. Se presentan los fundamentos teóricos para la aplicación simultánea de un programa de Fisioterapia que combina la terapia manual y la educación en neurociencia del dolor en pacientes con artrosis de rodilla, así como los problemas que se puede encontrar el fisioterapeuta en la práctica clínica cuando trate de aplicar esta estrategia combinada de tratamiento. Futuros estudios deberían explorar los efectos terapeúticos de estas estrategias de tratamiento combinadas para valorar si los resultados son superiores a los tratamientos actuales empleados para la artrosis de rodilla.

Preoperative pain neuroscience education combined with knee joint mobilization for knee osteoarthritis: a randomized controlled trial

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RESUMEN

Objectivos: Comparar los efectos sobre la sensibilzaición central de un tratamiento aplicado en la fase pre-operatoria que combina educación en neurociencia del dolor con terapia manual de la rodilla con un tratamiento que combina educación basada en un modelo biomédico con terapia manual de la rodilla, en pacientes con artrosis de rodilla. Secundariamente, los efectos de los dos programas de tratamiento en el dolor de rodilla, discapacidad y variables psicosociales también serán investigados.

Métodos: Cuarenta y cuatro sujetos con artrosis de rodilla que estaban esperando a ser operados de una prótesis de rodilla fueron aleatoriamente asignados a recibir 4 sesiones de educación en neurociencia del dolor con terapia manual de la rodilla o educación basada en un modelo biomédico con terapia manual de la rodilla antes de la cirujía. Todos los sujetos completaron diferentes cuestionarios y se les realizó un análisis cuantitativo sensorial que incluía el cálculo de los umbrales de dolor a la presión, la sumación temporal al dolor y la analgesia condicionada. Todas estas variables se midieron al inicio, después de las 4 sesiones de tratamiento, al mes (antes de la cirujía) y a los 3 meses después de la cirujía.

Resultados: Se encontraron diferentes estadística y clínicamente significativas en el tiempo después de los dos ratamientos para el dolor y discapacidad de la rodilla y para algunas de las medidas evaluadas de sensibilización central (hiperlagesia generalizada, cuestionario Central Sensitization Inventory), sin diferencias significativas entre grupos. Otros indicadores de sensibilización central (analgesia condicionada, sumación temporal del dolor) no cambiaron con ningún tratamiento o incluso los cambios observados no fueron en la dirección prevista. Los sujetos que recibieron educación en neurociencia del dolor con terapia manual de la rodilla mostraron una mayor mejoría en las variables de índole psicosocial (catastrofismo, kinesiofobia) en relación al grupo que

recibió educación basada en un modelo biomédico con terapia manual de la rodilla, en las mediciones de tanto antes como después de la cirujía.

Conclusiones: La aplicación de un programa pre-operatorio de educación en neurociencia del dolor junto con terapia manual dirigida a la rodilla no produce ningún efecto beneficioso adicional en el dolor, discapacidad y medidas de sensibilización central en comparación con el mismo tratamiento de terapia manual pero combinado con educación basada en un modelo biomédico. Sólo se obtuvieron efectos superiores en el grupo que recibió educación en neurociencia del dolor junto con terapia manual de la rodilla en las variables psicosociales relacionadas con el catastrofismo y la kinesiofobia.

Palabras clave: Knee osteoarthritis, central sensitization syndromes, physical therapy, education

CONCLUSIONES

Las conclusiones generales de esta tesis doctoral son las siguientes:

1. La evidencia científica actual indica que la sensibilización central juega un papel importante en un subgrupo de pacientes con artrosis, incluyendo la artrosis de rodilla. Sin embargo, es necesario desarrollar estrategias de valoración que permitan identificar de forma fiable y sistemática a aquellos pacientes con artrosis cuyo mecanismo dominante del dolor sea la sensibilización central.

2. El tratamiento fisioterápico de los pacientes con artrosis de rodilla requiere de un enfoque biopsicosocial, dónde se determinen en qué medida los factores periféricos y centrales contribuyen al dolor en cada paciente, con el fin de poder establecer las estrategias de tratamiento más adecuadas. Los fisioterapeutas están bien posicionados para ofrecer una intervención individualizada en estos pacientes porque son conocedores de la necesidad de un abordaje biopsicosocial.

3. El área de dolor que refieren los pacientes con artrosis de rodilla se relaciona con algunas medidas de sensibilización central. Los clínicos deben estar atentos ante aquellos pacientes con artrosis de rodilla que presenten áreas extendidas de dolor, ya que esto puede ser un indicador de la presencia de mecanismos alterados de procesamiento central de la información nociceptiva. Los mapas de dolor son una herramienta fácil y económica que puede ayudar a identificar de forma precoz la presencia de sensibilización central en pacientes con artrosis de rodilla.

4. Se anima a los fisioterapeutas a buscar un equilibrio entre las intervenciones manuales y las no manuales en pacientes con artrosis de rodilla cuyo mecanismo de dolor dominante es la sensibilización central. A la luz de la evidencia existente sobre el papel clave que puede jugar la sensibilización central en un subgrupo de pacientes con artrosis de rodilla, es fundamental que los fisioterapeutas reconsideren el uso de las intervenciones manuales empleadas para la artrosis de rodilla y enfaticen el uso de intervenciones no manuales con el objetivo de mejorar el dolor, la autoeficacia y las cogniciones y conductas ante el dolor de los pacientes.

5. Se han desarrollado bases científicas sólidas y directrices prácticas para la aplicación de un enfoque combinado de terapia manual y educación en neurociencia del dolor en pacientes con artrosis de rodilla y sensibilización central como mecanismo dominante del dolor.

6. Una intervención pre-operatoria de Fisioterapia dirigido a pacientes con artrosis de rodilla que combina la educación en neurociencia del dolor junto con terapia manual dirigida a la rodilla no produjo ningún beneficio adicional en cuanto a dolor de rodilla, discapacidad o medidas de sensibilización central frente a un tratamiento combinado de educación biomédica y terapia manual de rodilla. Sólo se observaron mayores efectos con la educación en neurociencia del dolor y terapia manual de rodilla en las variables psicosociales relacionadas con el catastrofismo y la kinesiofobia.

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CHAPTER 1

CHAPTER 1
Introduction

Partially based on:

Criteria for the classification of central sensitization pain in patients with knee osteoarthritis in clinical practice.

Lluch E, Nijs J, Courtney C, Rebbeck T, Wylde V, Baert I, Wideman T, Howells N, Skou ST. Submitted.

GENERAL INTRODUCTION

OSTEOARTHRITIS

Osteoarthritis (OA) is the main cause of pain, disability and loss of quality of life in the elderly affecting over 80% of the population beyond the age of 55 [1, 2]. Although the clinical presentation of OA can be very variable, pain is the primary symptom in OA and high levels of pain are associated with much lower levels of physical function, self-efficacy, and quality of life [3, 4]. OA is a disease characterized initially by cartilage degeneration, often preceding changes in the underlying bone. It is the consequence of a failed regeneration of damage to the joint due to stresses from biomechanical, biochemical and the influence of genetic factors [5]. Some studies have shown however that, besides ongoing joint destruction, new tissue production and remodeling occurs evidenced by increased protein synthesis by chondrocytes, especially in the early stages of OA [6]. OA affects at least 50% of people >65 years of age, but also occurs in younger individuals following joint injury [7]. The weight-bearing joints such as the hip and knee and smaller peripheral joints, including the hands, are the most commonly affected by OA [8]. Significant disability and healthcare costs are derived from OA, especially when affecting the elderly population.

Historically, OA has been considered a primary disorder of the cartilage. However, since cartilage is an avascular and aneural tissue, damaged articular cartilage is not capable of directly generating nociception, and hence a pain experience [9]. Studies using ultrasound and MRI have demonstrated how the presence of inflammation in non-cartilaginous structures such as synovial membrane and bone marrow are important factors contributing to chronic pain in OA [10-13]. In fact, synovial hypertrophy,

synovial effusions, and abnormalities in the subchondral bone have been associated with chronic knee OA pain in large cohort studies [14]. Different pro-inflammatory mediators may be released into the OA joint with damage such as nerve growth factor, nitric oxide and prostanoids [6], each of which can have a role in OA pain. In addition, studies indicate that expression of grown factors, in particular vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF), can induce neovascularization in the OA joint [12]. Osteocondral angiogenesis, in turn, has been linked to chronic OA pain [15]. Based on all this findings, the presence of a phenomenon of local soft tissue inflammation in OA is unquestionable, contributing to the severity and frequency of OA pain [6, 16].

Discordance between pain severity reported by patients and the degree of articular pathology (assessed by the Kellgren-Lawrence radiologic classification criteria) [17], in particular during the chronic stages of OA, have raised the issue of centrally-mediated mechanisms contributing to pain in OA [5, 7, 18-21]. In fact, it is estimated that up to 40% of individuals with severe radiological damage have no pain, and many individuals with severe OA pain have normal radiographs [22, 23]. Dieppe [24] indicated that only half of patients with radiographic OA have pain, and that there is a weak correlation of pain severity to radiographic features. Hence radiography seems to be an imprecise guide to predict the likelihood that pain or disability will be present with OA, and its use in isolation has been discarded when assessing patients with OA pain [17]. However, other studies have demonstrated a positive correlation between OA pain severity and radiological changes [25, 26]. Poor correlation between pain intensity and peripheral joint damage seems to be only found on a population level [17] but, within individuals,

pain severity may be strongly associated with radiographic damage [26], especially if one uses more sensitive imaging techniques like MRI instead of conventional radiography [13,14,27,28]. Using these techniques, synovitis of the joint and bone marrow lesions seem to demonstrate a robust correlation with symptoms in people with knee OA [28-30].

Above all, taking together the overall results of the above studies, other mechanisms of pain that are not joint specific (i.e., altered central nociceptive processing mechanisms) seem to play a role in the variability in pain severity observed across individuals with OA. While pain associated with OA has long been considered purely nociceptive in nature, mounting scientific evidence indicates that pain in OA can be centrally-mediated as well [18-21, 31-40]. More specifically, altered central nociceptive processing [i.e., central sensitization (CS)] seems to play a key role in a subset of people with knee OA pain [18-21, 31-40]. However, at the time of initiating this PhD, a systematic review of the literature addressing the role of CS in people with knee OA was not available.

CENTRAL SENSITIZATION AND KNEE OSTEOARTHRITIS PAIN

Persistent nociceptive input from knee OA is deemed to be responsible of inducing not only peripheral sensitization (increased responsiveness to stimuli in nociceptive afferent neurons), but also CS [36, 41]. Pathophysiological mechanisms underlying CS are complex and numerous, but the net effect is an amplification of neural signaling within the central nervous system (CNS) than elicits pain hypersensitivity [41, 42]. CS is a broad concept reflecting not only spinal cord sensitization, but also enhanced activity of nociceptive descending facilitation pathways [43, 44], loss of descending anti-nociceptive mechanisms [45, 46], overactivity in the pain neuromatrix [47], and long-

term potentiation of neuronal synapsis in the anterior cingulate cortex [48]. Therefore, the term CS involves several changes in central nociceptive processing occurring at different levels of the central nervous system. Currently, however a universally accepted term for the phenomenon described as CS is not available and its use in the scientific literature is still under debate [49-51]. In addition, CS is not a yes/no or present/absent single entity or phenomenon but it occurs over a continuum. In fact, a recent study demonstrated that although prevalent, generalized central hypersensitivity or CS is not present in every patient affected by chronic pain [52]. While generally higher in certain chronic pain conditions, pain sensitivity is also along a continuum in these conditions [53]. In some patient populations, CS may be the characteristic feature of the disorder (e.g., fibromyalgia). In others, such in knee OA, not all patients have CS, but only a sub-group. It has been estimated that around 30% of subjects with knee OA have CS contributing to their clinical picture [40, 54, 55].

Altered CNS pain processing or CS does not exclusively affect knee OA [18-21, 31-40], but has been demonstrated in other chronic musculoskeletal pain conditions (i.e., fibromyalgia [56-58], chronic low back pain [59], reumathoid arthritis [60], chronic fatigue syndrome [61], chronic whiplash associate disorders [62], chronic pelvic pain [63] and shoulder pain [64]). Many of these conditions have been grouped together under the unifying term of central sensitivity syndromes, to make reference to the shared mechanism of CS underlying these chronic conditions [65, 66].

Regarding knee OA pain, it has been suggested that, the more chronic the pain becomes, the more this pain is related to neuroplastic changes in the nervous system than to an inflammatory condition of the joint [67]. Ivanivicius and colleagues [67] showed in a rat model of OA how the maximum efficacy of non-steroid anti-inflammatory drugs (NSAIDs) over time reached its peak at 14 days post-injury. Beyond this time, the effects of NSAIDs became minimal, and other (centrally acting) drugs like amitriptyline and gabapentin become more efficacious [67]. This seems to support the theory that joint pathology is responsible of the initial trigger for knee OA pain, but subsequent (chronic) pain is mostly mediated by neuronal plasticity (CS). The role of peripheral nociceptive input (i.e., OA joint damage) on the development and maintenance of CS has been supported by several studies, where removal of the inciting pain stimulus (i.e., prosthetic substitution) led to normalization of central pain processing [37, 68]. On the other hand, persistent pain following joint replacement of the damaged joint is not uncommon and has also been linked to CS [69]. This may be explained because once the CNS is sensitized, either no or minimal tissue damage is necessary to perceive pain and CS can persist in time despite the lack of new painful stimuli from the periphery [41].

RECOGNIZING CENTRAL SENSITIZATION IN PATIENTS WITH KNEE OSTEOARTHRITIS

Despite growing awareness of the important contribution of central pain mechanisms to knee OA pain, routine evaluation of CS is yet to be incorporated into clinical practice. This is likely due in part to the historical laboratory-based focus of CS research, where the equipment and protocols used to identify features of CS (e.g. quantitative sensory testing (QST) [70, 71], nociceptive reflex testing [72], brain neuroimaging techniques

[73, 74]) are relatively sophisticated, time-consuming, expensive and not well-suited for clinical settings.

The development of patient profiles to subgroup individuals with knee OA in terms of pain mechanisms, including those with “dominant” CS pain, is gaining attention in research as reflected by the increasing number of pain phenotyping proposals which have been published in recent years [75-77]. The lack of subgrouping in previous clinical trials has been proposed as an explanation for the modest efficacy of available treatments for KOA. [78]. In line with this, "phenotyping" or characterizing knee OA pain has become a research priority, not only to better understand the patients’ pain experience, but also to better target pain therapies to individual patients [79]. The biomedical model (i.e. pain is a reliable “informant” of what is happening at the peripheral tissue level) fall short in explaining chronic musculoskeletal pain, including knee OA pain [80]. Hence, a focus shift from a tissue disease (i.e. joint damage) towards identifying and targeting underlying pain mechanisms in knee OA is recommended [78, 81]. As knee OA results from a complex interaction between structural changes, physical impairments and psychological factors, three domains (knee pathology, psychological distress and pain neurophysiology) should be considered to understand pain phenotypes in knee OA [77, 79].

Early identification of dominant CS pain in people with knee OA is crucial as the presence of pain sensitization may predict poorer outcomes following physiotherapy treatment [82] or surgery [32, 35, 69, 83, 84]. For instance, a less favorable outcome after operation was observed for patients with knee OA with a high pre-operative score for pain at rest and a low pain threshold to an electrical stimulus, both features

interpreted as reflecting a CS mechanism [69]. Similarly, pre-operative widespread pain sensitization measured using pressure algometry [83] or the pre-surgical presence of an enhanced temporal summation of pain which is a hallmark sign of CS [84], have been associated with chronic pain after total knee replacement.

Technically, CS is a neuronal response that can only be measured in animals [41, 50, 51]. All of the QST protocols that have been developed in the scientific literature are indirect analog measures of CS that are believed to be analogs of these animal assessments [i.e. wind up phenomenon]. To be honest, we don't have widely accepted terminology for humans to reflect what we believe to be centrally-mediated facilitated pain responses [49-51]. Therefore, classifying a patient with knee OA as having a dominant CS pain is challenging clinically since there is currently neither an international consensus definition nor a set of valid clinical criteria for the diagnosis of CS [41, 49-51]. The diagnosis of CS in patients with chronic musculoskeletal pain, including those with knee OA, is thus not straightforward and clinicians are forced to rely on symptoms and signs suggestive of CS pain in this regard. Some authors have proposed that information derived from the medical diagnosis, subjective assessment, physical examination and treatment response, can be useful to clinically identify CS [85]. Recently, clinical classification criteria have been published that can assist clinicians to differentiate and diagnose the dominant pain mechanism in people with chronic musculoskeletal disorders [86]. Clinicians are advised to screen their patients for 3 major classification criteria, and use them to complete a classification algorithm for each patient [86]. The first and obligatory criterion for dominant CS pain entails disproportionate pain, implying that the severity of pain and related reported or perceived disability are disproportionate to the nature and extent of injury or pathology.

The two remaining criteria are 1) the presence of diffuse pain distribution, allodynia and hyperalgesia and 2) hypersensitivity of senses unrelated to the musculoskeletal system such as high sensitivity for noise, heat or cold or bright light (defined as a score of at least 40 out of 100 on the Central Sensitization Inventory (CSI) [87]. However, the suitability of this clinical algorithm for the knee OA pain population is unknown.

QST is a semi-subjective method suggested to be in detection of altered central nociceptive processing [70, 71, 88]. However, laboratory QST is not clinically pragmatic and test modalities and protocols are heterogeneous, which makes it difficult for the clinician to determine which is the best QST measure for diagnosing CS [88]. Shorter and less expensive protocols and equipments that permit clinical identification of pain mechanisms including CS in patients with knee OA pain are thus needed [88].
What follows is a summary of clinical criteria derived from subjective assessment and physical examination that may aid clinicians in identifying a dominance of CS pain in patients with knee OA. These clinical criteria have been developed here by using the current understanding of CS within the context of knee OA pain. Importantly, these criteria should not be viewed as unique signs indicating CS, but they should rather be integrated into the clinical reasoning process, since they indicate a possible contribution of central pain mechanisms to knee OA, which can affect the appropiate treatment approach for the individual. It should be therefore made clear that the criteria proposed are not necessarily CS, but appears to be consistent with CS. They are not intended to replace the laboratory-based investigation of CS, but rather to bridge the gap between research findings and clinical practice by translating the clinical and laboratory-based studies of CS in knee OA into a broader and more clinically-relevant perspective. In addition, the psychometric properties (i.e. inter- and intra-examiner reliability,

sensitivity, specificity) of the criteria proposed for identifying CS in knee OA, either when used alone or in combination, should be the subject of future research. Clinical criteria for the recognition of a dominance of CS pain in patients with knee OA will be structured into two categories for a better overview: criteria derived from the subjective assessment and criteria extracted from the physical examination.

The subjective assessment

Pain intensity and its association with structural joint changes and duration of pain

Individuals with knee OA presenting with altered central processing of pain are significantly more likely to report moderate to severe levels of pain [31, 33, 75, 89, 90]. Therefore, a moderate to severe intensity of self-reported knee pain (e.g. pain on a visual analogue scale >5/10 [91]) can be a first indicator of CS in knee OA. However, this finding in isolation is insufficient as moderate to severe intensity of self- reported knee pain defined as >5/10 likely encompasses many cases with and without CS. Additionally, studies reporting an association between higher levels of pain and more pain sensitization are not clear and consistent as to whether pain intensity is related for instance to the “worst pain", "usual pain", "current pain" or “pain with movement”.

Unlike severity of pain, the presence of more severe structural changes in the knee joint on imaging is not associated with CS [31, 75, 89]. An inconsistent correlation between the degree of structural damage and pain and disability [17, 34] could be an indicator of CS in people with knee OA, albeit the discrepancy between structural and clinical findings is well known in OA in general [17]. Indeed CS is especially apparent among patients with knee OA with high levels of pain but low levels of imaging structural damage [34, 75]. Therefore, if clinicians find insufficient evidence of injury or

pathology at the knee both at imaging findings and clinical examination that is likely to contribute to the self-reported pain and disability, it should raise suspicion about the presence of altered central pain mechanisms [86].

Regarding the duration of symptoms, there is controversy in the literature, with some studies reporting an association between a long history of symptoms and CS [75] while others do not [89]. It is assumed that the lack of association between CS and disease duration may indicate that some individuals are predisposed to CS irrespective of the duration of knee OA [89].

Pain distribution

Several methods and instruments have been used to record the patient's pain location and to classify the pattern of knee OA pain. The most common method is asking people to draw the area where they feel pain on a body chart [92, 94]. Amongst people with knee OA, the medial knee region is the most frequently reported pain location [93, 94] though generalized or diffuse knee pain is also commonly reported [92, 94, 95].

In relation to knee OA, several studies have specifically investigated the association between central pain mechanisms and a widespread distribution of symptom location [95-97]. They concluded that a widespread, non-anatomical distribution of pain seems to be a strong indicator of altered central nociceptive processing [95-97]. Accordingly, aggravation and expansion of existing symptoms to sites around and remote to the knee joint may be a clinical sign of CS. Occurrence of contralateral symptoms, commonly reported by people with knee OA, should not be therefore automatically attributed by

clinicians to altered weight bearing or biomechanics due to compensation, as mirror symptoms may also been explained through spinal and supraspinal mechanisms [98].

To capture and objectify the presence of widespread pain clinicians can calculate the total number of bodily pain sites in a region divided body chart [38, 77] or ask the patient to complete a pain drawing (e.g. in a digital tablet) and subsequently compute the total area of pain (e.g. total number of pixels inside the digital chart) [99]. When looking for a widespread distribution of pain, one should be cautious and bear in mind other explanations for an expanded distribution of pain outside the knee, such as chronic multisite joint pain which is frequent in patients with knee OA [100]. Indeed joint pain spreading to areas other than the knee joint is considered a valid indicator of joint-pain comorbidity in knee OA [101].

In summary, clinicians should obtain the area of pain of their patients with knee OA using pain drawings and if possible quantify that area, as the presence of extended areas of pain may be an indicator of CS. However, although there have been attempts to define widespread pain which serves as an indicatior of CS (e.g. Widespread Pain Index score) [102] there is no validated cutoff score for inferring whether pain is widespread or not [103].

Behaviour of knee pain

Knee OA is commonly associated with pain-at-rest (or stimulus-independent pain) and pain-on-movement (mainly during weight-bearing activities) resulting in difficulties with walking and climbing stairs [92]. In the context of knee OA, pain-on-movement is often more severe than pain-at-rest in the early stages of the disease and has an earlier

onset in the disease course [104, 105]. There is a growing recognition of the importance of distinguishing between these two types of pain due to different mechanistic pathways and clinical implications [105, 106].

Pain on-movement has been linked to CS in people with knee OA [107]. In particular, increased sensitivity to physical activity (measured by evaluating changes in patient self-reported pain over the course of a 6-minute walk test) is associated with psychophysical indices of CS such as temporal summation of pain [107]. In addition, dysfunctional exercise induced hypoalgesia/analgesia is present in different chronic pain populations where CS is a key characteristic [108]. One could argue therefore that the same would be applicable to the subgroup of patients with knee OA where CS is dominant. Previous studies reported normal exercise induced analgesia in patients with knee OA following lower [109] and upper body exercises [110]. However, in these studies no attempt was made to classify the patients in terms of pain mechanisms. Rather pressure pain thresholds instead of self-reported pain [107] were used to quantify sensitivity to physical activity. Clinicians may therefore look for a disproportionate self-reported increase in knee pain after physical activity tests or activity-based interventions to infer the possible presence of altered central nociceptive processing mechanisms.

Asking about easing and aggravating factors for knee OA pain may also be helpful to distinguish between those individuals with either a more dominant nociceptive or CS pain. A clear, proportionate mechanical/anatomical nature to aggravating and easing factors was associated with nociceptive pain in people with low back (± leg) pain [111]. In that same population, a lack of clear proportionate mechanical nature to aggravating and easing factors was considered a predictor sign of CS pain [112]. Therefore a

"*disproportionate, non-mechanical, unpredictable pattern of pain provocation in response to multiple/non-specific aggravating/easing factors*" [112] may indicate the presence of CS pain in people with knee OA.

Presence of neuropathic-like symptoms

A growing level of evidence suggests that knee OA pain has a neuropathic component in some individuals [113, 114] previously approximated to be 30% [115]. Presence of neuropathic-like symptoms in people with knee OA has been associated with CS [54, 55, 116]. It is well established that patients with chronic joint injury may present with signs and symptoms typically associated with neuropathic injury (especially with progression to chronic stages), due to changes in nociceptive processing [70, 117]. Clinical presentation of neuropathic pain in knee OA may include the use of pain descriptors such as burning, pins and needles, sensitivity to heat and/or cold, numbness or spontaneous electric-shock like pain to describe the pain associated with OA [54, 55, 116, 118]. Evidence for neuropathic pain components has also been provided in knee OA animal models besides humans [67], but the exact molecular mechanisms contributing to neuropathic-like pain in knee OA remain unclear. Because many of the joint structures are richly innervated, it has been hypothesized that local damage to these and other joint structures could cause damage to the peripheral nerves [119, 120]. Indeed animal models of knee OA have shown that sensory nerve fibers innervating the knee are significantly damaged with destruction of subchondral bone junction, and induce neuropathic pain [67]. Valdes et al. [120] established a cross-sectional association between previous history of knee surgery (arthroscopy, ligament repair or meniscectomy), and "possible" neuropathic pain (assessed with the PainDetect questionnaire), in people with knee OA. It was suggested that some of the

neuropathic-like symptoms observed in people with knee OA may result from nerve damage as a consequence of previous surgery [120]. Finally, positive treatment outcome after administration of intravenous lignocaine, a sodium channel blocker and neuronal membrane stabilizer commonly used for neuropathic pain, was reported by Duarte et al [114] in a group of knee OA patients.

Identification of neuropathic pain in subjects with musculoskeletal pain including knee OA pain has been done through QST [70, 71, 121] and questionnaire-based assessments [54, 55, 73, 116, 120, 122, 123]. Findings from both tools of assessment have demonstrated significant overlap in subjects with joint pain, demonstrating that the same underlying concept (neuropathic pain) is being assessed [124]. Patient-report questionnaires have been developed to help identify neuropathic-like symptoms in general population such as the (modified) painDETECT [(m)PD-Q], the Leeds assessment of neuropathic symptoms and signs (LANSS), Douleur Neuropathique en 4 questions (DN4), ID pain or Neuropathic Pain Questionnaire (NPQ) [125]. Of those, some of them have been used specifically in people with knee OA pain. For instance, the mPD-Q has demonstrated face and content validity for identifying neuropathic-like symptoms in people with knee OA [55]. In that study conducted by Hochman and colleagues, approximately one quarter of the total sample had symptoms of neuropathic pain (mPD-Q score ≥19/38). Moreover, higher mPD-Q scores were significantly and independently associated with high pain intensity, high OA severity and long OA duration [55]. Recently, the same group of researchers has further validated the mPD-Q, analyzing the relationship between mPD-Q scores and signs of CS obtained with QST [116]. It was found that 45% of a sample of symptomatic knee OA had findings consistent with CS (≥1 sign of CS**)** and people with higher scores on mPD-Q (>12.0)

were more likely to have QST signs of CS [116]. Another study by Ohtori et al [122] aimed at examining neuropathic pain in patients with knee OA using the PDQ. In addition, the relationship between neuropathic pain, pain intensity (using VAS and WOMAC pain subscale), and stage of OA through the Kellgren-Lawrence system was also evaluated. A total of 5.4% of subjects resulted to have "likely" and 15.2% "possibly" neuropathic pain, according to the painDETECT score. The painDETECT score was significantly correlated with higher severity of pain and increased stage of OA, although in this latter case only a tendency for positive correlation was determined [122]. Valdes et al [120] also reported a percentage of 34% of a sample of subjects with knee OA as having "possible" neuropathic pain, using the PD-Q. Neuropathic symptoms were strongly associated to worse quality of life and higher pain intensity.

Although the PainDETECT and modified PainDETECT questionnaires have been used to screen neuropathic-like symptoms in people with knee OA, they may also function as measures of characteristics that indicate augmented central nociceptive processing [123]. Like the original PainDETECT, the modified PainDETECT is comprised of nine items but with some modifications adapted to people with knee OA, such as framing of questions to ask about symptoms 'in or around' the worst knee, over a specific time frame. Therefore, this modified version of the PainDETECT seems more suitable for patients with knee OA.

Presence of centrally-mediated symptoms

Comorbid presence of some symptoms commonly associated with CS during subjective assessment, such as widespread pain, fatigue, sleep disturbance or cognitive difficulties, has been interpreted as a reflection of alteration of central pain processing in subgroups

of patients with knee OA [39, 40]. Murphy et al. [39] measured pain severity and presence of (centrally- mediated) symptoms suggesting CS in a sample of patients with knee OA. A 27% of the variance in pain severity reported by the patients was explained by age, radiographic severity, and centrally-mediated symptoms. Interestingly, after entering age and radiographic severity as variables, centrally-mediated symptoms explained an additional 10% of the variance in pain [39].

Two questionnaires have been developed for assessment of pain sensitivity and screening of CS, the Pain Sensitivity Questionnaire (PSQ) [126, 127] and the CSI [87, 128]. These self-rating measures have been proposed as useful alternatives to objective experimental pain testing (which requires more time and equipment resources and is painful for the tested subject), for determining pain hypersensitivity. Reliability and validity of both questionnaires have been demonstrated [87, 126, 127]. The CSI is a self-reported screening instrument that helps to identify key symptoms associated with CS [87, 128]. The CSI evaluates hypersensitivity of senses unrelated to the musculoskeletal system such as noise, heat or cold or bright light. People with knee OA scoring more that 40 (out of 100) before surgery, considered the cuttoff value to affirm that key symptoms associated to CS are present, reported higher pain intensity, lower satisfaction and increased analgesic requirements in the early phase after total knee replacement surgery [130]. Recently, the following CSI severity levels have been established: subclinical = 0 to 29; mild = 30 to 39; moderate = 40 to 49; severe = 50 to 59; and extreme = 60 to 100 [131]. The concurrent validity of the CSI severity levels was then confirmed in a separate chronic pain patient sample (58% with a central sensitivity syndromes diagnosis and 42% without). Compared to the non-central

sensitivity syndromes patient subsample, the score distribution of the central sensitivity syndromes patient subsample was skewed toward the higher severity ranges. In addition, patients scoring in the extreme CSI severity level were more likely to report previous diagnoses of fibromyalgia, chronic fatigue syndrome, temporomandibular joint disorder, tension/migraine headaches, and anxiety or panic attacks ($P < 0.01$). CSI severity levels were also associated with patient-reported depressive symptoms, perceived disability, sleep disturbance, and pain intensity ($P \leq 0.02$) [131]. All the above mentioned studies highlight the value of the CSI to identify CS and predict poorer outcomes after surgery in people with knee OA.

Responsiveness to previous treatment

It has been argued that an inconsistent, unpredictable or unsuccessful response to local, nociception-targeted treatments or a strong exacerbation of symptoms severity post-treatment may aid in recognition of CS in patients with chronic musculoskeletal pain [85]. There is evidence that the presence of CS is a prognostic factor for poor outcomes in response to locally-applied physical therapy interventions in some chronic pain conditions such as lateral epicondylalgia [132] or whiplash associated disorders [133]. Although it is conceivable that the presence of CS might also affect physical therapy treatment outcomes negatively in people with knee OA, this hypothesis is not yet proven [82]. An inability to endogenously modulate nociception (dysfunctional endogenous analgesia) may explain the disproportionate increase in pain often observed in people with knee OA after locally applied interventions (e.g. knee joint mobilization) [134].

Less responsiveness to analgesic and non-steroidal anti-inflamatory pain medications together with better outcomes with administration of centrally acting drugs (i.e. duloxetine), is another criteria that can further consolidate the role of CS in knee OA pain [135]. Therefore physiotherapists should routinely ask about medications and responsiveness to them.

Persistent post-surgical pain occurs in approximately 20% of patients with knee OA after total knee replacement [136] and it has been linked to the presence of CS [32, 83]. An unfavorable symptom outcome after surgery should thus alert physiotherapists to the potential presence of CS amongst other factors [32, 83]. Therefore, assessment of persistent post-surgical pain in a consistent and standardized way by mean for instance of a core outcome set [137] is considered essential for recognizing the presence of CS. Furthermore, the relatively high proportion of patients with persistent pain after total knee replacement highlights the importance of diagnosing (central) pain mechanisms before patients undergo surgery and revision surgery [32].

The physical examination

Response to clinical tests

Several types of information obtained from the physical examination can be of value in recognizing dominance of CS in individuals with knee OA pain [85]. In particular, an inconsistent or confusing response to clinical tests applied to the knee joint during the physical examination (i.e. the majority of assessment techniques provoke symptoms), may be suggestive of the presence of CS. This clinical finding has not yet been investigated, but might be plausible based on our current understanding of the

mechanism and clinical expression of CS, where a nonpainful mechanical stimulus can be interpreted as nociceptive [70].

Widespread mechanical hyperalgesia and allodynia

Research has shown evidence in support of generalized or widespread hypersensitivity to mechanical stimuli in people with knee OA as compared to healthy controls [33, 30, 71]. In particular, a systematic review and meta-analysis conducted by Suokas et al [71] addressing the use of QST in pain characterization in OA has concluded that pressure pain thresholds demonstrate a good ability to differentiate between people with OA and healthy controls. The majority of studies included in that systematic review examined pressure pain, while few studies applied electrical and/or thermal stimuli. People with OA had lower PPTs both at the affected joint and in remote sites compared to controls which was interpreted as a sign of peripheral and CS, respectively [71].

Widespread mechanical hyperalgesia is a well-recognized clinical manifestation of CS [5, 70, 71]. Hyper-responsiveness to mechanical stimuli includes exaggerated responses to pressure and touch. To apply this to clinical practice with patients with knee OA, lower pressure pain thresholds as assessed by a pressure algometer at sites around (localized pain sensitization) and remote to the knee (widespread pain sensitization) may imply hyperexcitability of central nociceptive pathways. However, as normative data or valid cuttoff values for diagnosing CS are currently lacking for knee OA, interpretation of pressure pain thresholds within an individual is challenging. Normative values are available for healthy subjects [138] which could potentially serve as a comparator when assessing patients with knee OA.

In the absence of a pressure algometer, physiotherapists can also use manual palpation (examiner's thumb) to evaluate widespread mechanical hypersensitivity. A moderate correlation between manual pressure and pressure algometry was found in people with chronic neck pain [139], albeit the suitability of this finding to patients with knee OA is unknown. Diffuse non-anatomical tenderness on manual palpation is a clinical criterion that was shown to be predictive of CS pain in patients with low back (±leg) pain [112] and chronic neck pain [139]. An expansion of receptive fields, which is characteristic of CS [70], may lead to the patient experiencing increased tenderness to palpation well outside of the painful knee joint. A novel alternative to pressure algometry is a spring clamp, as used in a previous study in patients with low-back pain. By placing the spring clamp on the thumbnail for 10 seconds and asking the patients to assess pain intensity, O'Neill et al. were able to assess the pain response of the patients [140].

The presence of mechanical (tactile) allodynia (pain due to a stimulus that would not normally provoke pain) is associated with with knee OA [54] and is considered a hallmark sign of CS [70]. Heightened sensitivity to cutaneous light touch can be assessed in the clinical setting using both static or dynamic stimuli by gently touching or brushing/stroking the skin with a cotton wisp, a cotton wool tip or a brush.

Widespread thermal hyperalgesia

Besides widespread mechanical hyperalgesia, greater pain sensititivity to heat and cold stimuli at remote sites from the knee are considered clinical indicators of deficient central processing of nociception in knee OA [141]. Hypersensitivity to heat or cold

stimuli is normally demonstrated in laboratory conditions by using a computer-controlled thermotester. However, clinical tests for thermal sensitivity have been developed in other chronic pain populations (e.g. chronic neck pain) with good correlations with quantitative measures [139, 142]

When clinically testing thermal sensitivity, the cold or hot item is placed on the skin for some seconds (e.g. 10 seconds [142) and it should be perceived as cold or hot respectively, but should not elicit pain. If it does trigger pain, then hypersensitivity to cold or heat is established and the individual can be asked to rate the pain experienced during the test on an numerical rating scale [139, 142]. Maxwell and Sterling suggested that pain>5/10 on a numeric rating scale after 10s of ice application should alert clinicians to the presence of cold hyperalgesia in whiplash thus aiding in prognosis and treatment decisions [142].

Hypoesthesia and reduced vibration sense

Hypoesthesia (increased perception threshold) to tactile and vibration stimuli has been found in people with knee OA pain, at both local and remote sites from the knee [54, 143]. Clinical finding of tactile hypoesthesia adjacent to the injured knee joint has been considered a clinical indicator of CS [70, 144]. When mapping the region of altered sensation, the pattern of sensory deficit in individuals with knee OA does not follow a nerve root or peripheral nerve distribution [70, 144], thus enabling differentiation of sensory changes secondary to nerve injury. For assessing tactile hypoesthesia, the mechanical detection threshold is calculated using calibrated and standardized von Frey utilizing a series of ascending and descending stimulus intensities [121]. As an

alternative, the clinician can use a cotton wool or cotton tipped applicator. Typically, assessment is initiated in the area of most pain and the distribution of hypoesthesia is determined by repetitively stimulating the skin, moving outward in a wheel spoke pattern.

Like altered mechanical detection threshold, reduced vibration sense may be indicative of CS in people with knee OA [70, 144]. In particular, a reduced vibration detection threshold has been demonstrated in people with knee OA at different sites of the lower extremity [145]. Vibration detection threshold is measured using a biothesiometer or vibrometer, although neither tool is commonly used in a clinical setting. As an alternative, the clinician can use a Rydell Seiffer graded tuning fork placed against different bony sites of the lower extremity [145] (i.e. first metatarsophalangeal joint, medial and lateral malleolus, medial and lateral femoral condyle). The tuning fork can be placed there and record time until the vibration can no longer be perceived by the subject. The presence of any pain with the vibration stimuli can also be recorded. A painful response with testing (vibration allodynia) has been reported as reflecting central nociceptive changes [70, 144].

A summary of clinically-relevant criteria usable during the subjective assessment and physical examination to identify the presence of a dominant CS pain in patients with knee OA has been presented. Future studies are urgently needed to empirically test validation and metrics of these criteria including cut-offs and diagnostic accuracy (i.e. sensitivity, specificity) before it can be confidently adopted in clinical practice. Unfortunately, most of our understanding of these measures from research is based on

correlational and regression type analyses. To move this field forward into the clinical application, the ability to identify true and false positives/negatives regarding CS pain is highly important. Meanwhile, this set of clinical criteria derived from subjective assessment and physical examination can facilitate the acknowledgment and recognition of CS in clinical practice by physiotherapists. As previously mentioned, clinicians should be attentive for patients with signs of CS as they might be at risk for unfavourable outcome after locally-applied interventions to the knee. A broader therapeutic approach aiming to desensitize the central nervous system, in contrast to therapeutic modalities that are only directed to structural knee joint pathology, might be more beneficial for these patients.

TREATING OPTIONS FOR CENTRAL SENSITIZATION IN PATIENTS WITH KNEE OSTEOARTHRITIS

Historically, knee OA pain has been considered a nociceptive pain related to the degree of structural damage to the affected joint, that is, pain is considered a reliable "informant" of what is happening at the peripheral tissue level. This means that greater joint degeneration would be associated with greater pain and the diagnosis of knee OA relied heavily on radiographic evidence of osteoarthtitic changes in the joint, with the rationale that joint degeneration was the primary contributor to the experience pain. This traditional view of knee OA merely reflects the biomedical model so commonly rooted among healthcare professionals dealing with knee OA pain [80].

Fortunately, this traditional view is changing and nowadays the pain experience in knee OA is considered a black box, where pain appears to be influenced by several factors including pathological changes occurring at a peripheral level, the influence of psychosocial factors and changes in pain processing occurring within the peripheral and central nervous system. However, the precise contribution of each factor to an individual pain experience is very difficult to determine [79]. This change in the view of

knee OA pain as a complex biopsychosocial phenomenon has prompted a paradigm shift in the treatment of knee OA pain. In particular, the treatment strategies for knee OA have been broadened to include not only physiotherapy interventions addressed to the knee, as further emphasized and studied in the present thesis, but also to the psychosocial factors or to changes in CNS sensitivity [36].

Despite the increase in publications emphasizing the importance of CS in knee OA pain, current interventions for rehabilitation of knee OA don't usually address altered central pain processing or CS mechanisms associated with knee OA pain. In fact, conventional rehabilitation strategies for knee OA are in large part directed toward input mechanisms (i.e., joint inflammation) and output mechanisms (i.e., muscle strength, motor control, propioception) associated with the disease [146]. Many guidelines and recommendations for the management of knee OA have been published and updated by various professional organizations such as the ACR [147], EULAR [148] or OARSI [149]. All these set of recommendations and guidelines are based on results from existing clinical trials, which vary greatly in methodological rigour and quality, and they also include expert opinion to varying degrees. Overall all of them strongly support the efficacy of non-surgical treatments for knee OA pain despite recent data suggesting that other than exercise the role of physical therapies in the treatment of knee OA is questionable [150, 151]. Interestingly, if we have a look at what patients with knee OA actually use for treatment, the results of the study by Hinman and colleagues [152] is overwhelming: in contrast to the evidence-based guidelines, the use of non-surgical interventions is low among people with knee OA despite. Also striking is the fact that none of the evidence-based recommendations gives substantial consideration to which pain mechanism might be modulated by treatment. For this reason, it seems interesting

to investigate new avenues for treating central pain processing mechanisms in people with knee OA pain.

Treatment strategies that aim at targeting local structures are typically of little value in patients with predominant CS pain [153, 154]. In fact, the presence of CS in a patient with knee OA may entail greater complexity of the clinical picture and less possibilities of achieving positive results with conventional physiotherapy interventions [82], although this needs to be further investigated. Hence a more "central" approach targeting brain and top-down mechanisms seems warranted for treating CS in patients with knee OA [36]. Several reviews have been published about options for treating CS in patients with chronic pain of different etiologies [146, 155-157]. Physiotherapists have at their disposal several tools to address neurophysiological changes across different areas of the peripheral and central nervous systems characteristic of CS pain in people with knee OA pain. They include top-down cognitive-based interventions (e.g., pain neuroscience education, cognitive-behavioral therapies such as pain coping skills training, acceptance-based interventions such as acceptance commitment therapy, mindfulness therapies, graded motor imagery, repetitive Transcranial Magnetic Stimulation; transcranial Direct Current Stimulation) and bottom-up physical interventions (e.g., motor learning, peripheral sensory stimulation, manual therapy, exercise therapy) [146, 155-157]. Comprehensive treatment approaches addressing peripheral structural injury (i.e., the knee joint) as well as neurophysiological changes occurring at distributed areas of the nervous system may help to improve outcomes in patients with knee OA with a predominant CS pain [36, 146]. However, combination of treatments targeting CNS function with traditional treatments directed towards functioning of the knee is a promising approach that has to

be further tested. It is argued that due to the complex multidimensional nature of knee OA pain and the moderate effects that physiotherapy treatments have in isolation in knee OA, combination of treatments addressing both the knee and the CNS may bolster each other thus further improving outcomes [36, 79, 146].

OUTLINE OF THE DISSERTATION

The primary aim of the present dissertation was to investigate the existing evidence from the literature related to the presence or absence of central sensitization in patients with osteoarthritis including people with knee OA and the current options for treating central pain processing mechanisms in this population. Secondly, it was aimed at evaluating whether measures of central sensitization are associated with the area of pain and clinical symptoms (including the level of knee pain, disability and psychosocial variables) recorded during the subjective assessment in subjects with knee osteoarthritis. Thirdly, the effect of a combined intervention addressing the central nervous system (pain neuroscience education) and the knee (knee joint mobilization) in subjects with knee OA was investigated. This thesis consists of three parts each targeting one of these aims.

The following research question will be addressed in the first part:

- *What is the role central sensitization plays in people with osteoarthritis including those with knee OA and which options do we have for treatment?*

  To examine this research question, a narrative and systematic review of the literature related to the presence of central sensitization in osteoarthritis pain and current options for treatment of central sensitization specifically in osteoarthritis patients was performed. The results are presented in **chapter 2**, comprising of 2 published papers.

The following research question will be addressed in the second part:

- *Are measures of central sensitization associated with the area of pain and clinical symptoms in subjects with knee osteoarthritis?*

  Chapter 3 presents an experimental study which evaluated whether the area of pain assessed using pain drawings relates to correlates of central sensitization and clinical symptoms in people with knee OA.

The following research question will be addressed in the third part:

- *Is a combined intervention of manual therapy addressing the knee and pain neuroscience education targeted to the central nervous system effective for people with knee osteoarthritis?*

  Chapter 4 includes two studies in order to answer this question. The first manuscript presents the theoretical rationale for simultaneous application of manual therapy and pain neuroscience education in people with knee osteoarthritis. The second manuscript reports the results of a randomized controlled trial assessing the effects of a pre-operative treatment combining pain neuroscience education with knee joint mobilization in subjects with knee osteoarthritis.

The final parts of the thesis include a general discussion of the study results and a general conclusion.

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CHAPTER 2

CHAPTER 2

What is the role central sensitization plays in people with osteoarthritis including those with knee osteoarthritis and which options do we have for treatment?

Content:

Evidence for central sensitization in patients with osteoarthritis pain: a systematic literature review

Lluch E, Torres R, Nijs J, Van Oosterwijck J.

Eur J Pain. 2014;18(10):1367-75.

Pain treatment for patients with osteoarthritis and central sensitization

Lluch Girbés E, Nijs J, Torres-Cueco R, López Cubas C.

Phys Ther. 2013;93(6):842-51.

EVIDENCE FOR CENTRAL SENSITIZATION IN PATIENTS WITH OSTEOARTHRITIS PAIN: A SYSTEMATIC LITERATURE REVIEW

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ABSTRACT

Background and objective: Hyperexcitability of the central nervous system has been suggested to play an important role in the chronic pain experienced by patients with osteoarthritis. A systematic review following PRISMA guidelines was performed to evaluate the existing evidence from the literature related to the presence of central sensitization in patients with osteoarthritis.

Databases and data treatment: Electronic databases Pubmed and Web of Science were searched to identify relevant articles using predefined keywords regarding central sensitization and osteoarthritis. Full text clinical reports addressing studies of central sensitization in human adults with chronic complaints due to osteoarthritis were included and screened for methodological quality by two independent reviewers.

Results: From the 40 articles which were initially eligible for methodological quality assessment, 36 articles achieved sufficient scores and therefore were discussed. The majority of these studies were case-control studies and addressed OA of the knee joint. Different subjective and objective parameters considered manifestations of CS, which have been previously reported in other chronic pain conditions such as whiplash or rheumatoid arthritis, were established in subjects with OA pain. Overall results suggest that, although peripheral mechanisms are involved in OA pain, hypersensitivity of the central nervous system plays a significant role in a subgroup of subjects within this population.

Conclusions: Although the majority of the literature provides evidence for the presence of CS in chronic OA pain, clinical identification and treatment of CS in OA is still in its infancy, and future studies with good methodological quality are necessary.

Key words: osteoarthritis, pain, central sensitization, neuroscience education, exercise therapy, graded activity.

INTRODUCTION

Osteoarthritis (OA) is one of the most frequent, disabling and costly pathologies affecting modern society. Subjects with OA pain often suffer from chronic pain leading to important disabilities and associated costs for the public health system (Jinks et al., 2007). During the last years, a growing body of research suggesting central sensitization (CS)in OA has been developed (Lluch Girbés et al., 2013). According to Woolf (2011), CS is "operationally defined as an amplification of neural signaling within the central nervous system that elicits pain hypersensitivity". CS is a broad concept reflecting not only spinal cord sensitization, but also enhanced activity of pain descending facilitation pathways (Staud et al. 2007, Meeus & Nijs 2007), loss of descending anti-nociceptive mechanisms (Meeus et al., 2008), overactivity in the pain neuromatrix (Seifert et al., 2009) and long-term potentiation of neuronal synapsis in the anterior cingulate cortex (Zhuo, 2007). Wind-up, activation of collateral synapses, apoptosis of gABAergic inhibitory interneurons, sprouting of Aß fibers in lamina II or glial activation, are also important functional changes observed in the central nervous system with CS (Woolf, 2011).

Changes which have been associated with central sensitization (CS) in OA patients include extended and remote areas of hyperalgesia from the affected joint (O'Driscoll and Jayson, 1974; Kosek and Ordeberg, 2000a; Bajaj et al., 2001; Imamura et al., 2008; Arendt-Nielsen et al., 2010), a loss of descending pain inhibitory mechanisms (Kosek and Ordeberg, 2000a; Arendt-Nielsen et al., 2010; Graven-Nielsen et al., 2012), and an increase of temporal summation (TS) (Arendt-Nielsen et al., 2010) and spatial summation (SS) (Graven-Nielsen et al., 2012). All these changes are recognized indicators of the presence of CS (Graven-Nielsen et al., 2012). Moreover, positive

effects of centrally acting drugs (Chappell et al., 2009), use of neuropathic pain descriptors (Hochman et al., 2010, 2011), presence of symptoms suggesting CS (i.e. widespread pain, fatigue, sleep disturbance and cognitive difficulties) in subgroups of patients with OA (Murphy et al., 2011b), and results from several functional brain neuroimaging studies (Kulkarni et al., 2007; Gwilym et al., 2009; Parks et al., 2011), support the role of CS in chronic OA pain.

Currently, however, it remains unclear whether sufficient evidence is available in favor of CS in chronic pain related to OA. Although narrative reviews regarding CS in OA exist (Lluch Girbés et al., 2013), there are no studies that systematically reviewed the literature regarding CS in chronic OA pain. Recent systematic reviews have demonstrated that CS plays a role in other chronic pain conditions like whiplash (Van Oosterwijck et al., 2013), and rheumatoid arthritis (Meeus et al., 2012). If CS is dominating the clinical picture of patients with chronic OA pain, then treatment programs should be adapted accordingly (Lluch Girbés et al., 2013). Hence, the aim of this study was to systematically review and evaluate the existing evidence from the literature, in order to establish if there are enough arguments to support the role of CS in chronic pain related to OA.

LITERATURE SEARCH METHODS

Search strategy

To identify relevant articles concerning central pain processing in patients with OA, a systematic search of the literature using the PRISMA guidelines (Liberati et al., 2009) was performed in databases Pubmed (http://www.ncbi.nlm.nih.gov/sites/entrez) and Web of Science (http://apps.isiknowledge.com), in January 2013. The results for every

database and combination of keywords and MeSH terms used in the search strategy are represented in Supplementary Table 1. In addition, reference lists from relevant articles were checked to obtain as complete information as possible.

Table 1. Total of hits for every keyword combination that was used at the Pubmed and Web of Science search databases.

Entry Terms		**Pubmed**	**Web of Science**
Osteoarthritis (MeSH)	AND Central Nervous System Sensitization (MeSH)	13	11
	AND sensitization	65	99
	AND central sensitivity	66	47
	AND central hyperexcitability	3	6
	AND central sensitization	36	61
	AND pain modulation	51	70
	AND neural inhibition (MeSH)	5	6
	AND hyperalgesia (MeSH)	87	154
	AND nociception (MeSH)	54	85
	AND pain threshold (MeSH)	171	212
	AND algometry	7	15
	AND hypersensitivity (MeSH) AND pain (MeSH)	57	42
Total hits		615	808

Study selection

Initially, all titles and abstracts of the retrieved articles were screened to identify relevant papers related to CS in OA using predefined inclusion criteria. In case of uncertainty regarding appropriateness of the paper after reading title and abstract, the full version of the text was retrieved and checked for fulfillment of inclusion criteria. To be included in the review, an article had to meet all the following criteria: (1) to be

reported in a peer-review academic journal; (2) the author(s) studied the phenomenon of CS in human adults (18 years or older) with chronic pain due to OA; (3) the article was a full-text original research report, and not an abstract, letter, editorial or review; and (4) the study was presented in English. No limitation regarding year of publication was used and all clinical study designs were eligible.

Although review articles were not eligible for inclusion, their reference lists were screened to collect relevant articles which were not initially retrieved by the systematic search. The full text version of all the articles that met the inclusion criteria were retrieved and methodological quality assessment and data extraction was performed.

Quality assessment

To evaluate the methodological quality of the full text papers we used a checklist of 18 criteria, which was composed and used previously by Van Oosterwijck et al. (2013) (see Table 2). We chose to use these criteria as they have proven to generate reliable risk of bias scores for papers reporting studies examining the presence of central sensitization in chronic pain patients (Van Oosterwijck et al., 2013). Indeed, the intertester reliability of the risk of bias scores was high, reflected by the 96% (416 out of 432 items) agreement in scoring between the two researchers conducting the systematic review (Van Oosterwijck et al., 2013). The quality criteria were developed by selecting criteria, of relevance to the research question of the literature review, from established risk of bias scoring lists. This is important as the present study addresses a similar research question (i.e. examining whether central sensitization is present in a specific chronic pain population) in a different patient population (chronic whiplash associated disorders versus osteoarthritis).

Two independent and blinded researchers (ELL and RT), scored the studies and assessed whether each of the evaluation criteria was fulfilled. After rating the selected articles, they compared the results and, in the case of disagreement, the article was screened a second time and the point of difference was discussed. Both reviewers could argue and convince the other to obtain a consensus. When consensus could not be reached, a third researcher (JN) was called upon to make the final decision. Besides evaluating the overall quality, articles were categorized according to purpose (etiology, prevalence, incidence, prevention, treatment, case report, diagnosis), and study design (prospective, clinical trial, hypothetical, cohort, case-control, cross-sectional).

Only those criteria that were applicable for the study design were taken into consideration. One point was given in case a study met with the related criterion, no point in case it did not fulfill the criterion. A total score was calculated as the sum of all the evaluation criteria that was fulfilled and then transformed into a percentage. For example, if only 14 out of the 18 criteria were applicable, and 7 of the 14 criteria were fulfilled, this resulted in a score of 7/14 or 50%. Papers that did not reach the minimum threshold of 40% on methodological quality scoring were not considered in this review. Finally, the results were analyzed and the existing evidence regarding CS in OA summarized.

RESULTS

Search strategy

The selection process of the articles is represented in Figure 1. The initial search resulted in 1423 hits. After removal of duplicates, 737 articles remained. Four additional references were retrieved from the reference lists of papers selected. Titles, abstracts and full text papers, if necessary, were then screened for inclusion criteria fulfillment.

After screening, 697 studies were excluded and 40 articles were initially eligible for methodological quality assessment as presented in Table 2.

Figure 1. Flowchart study selection

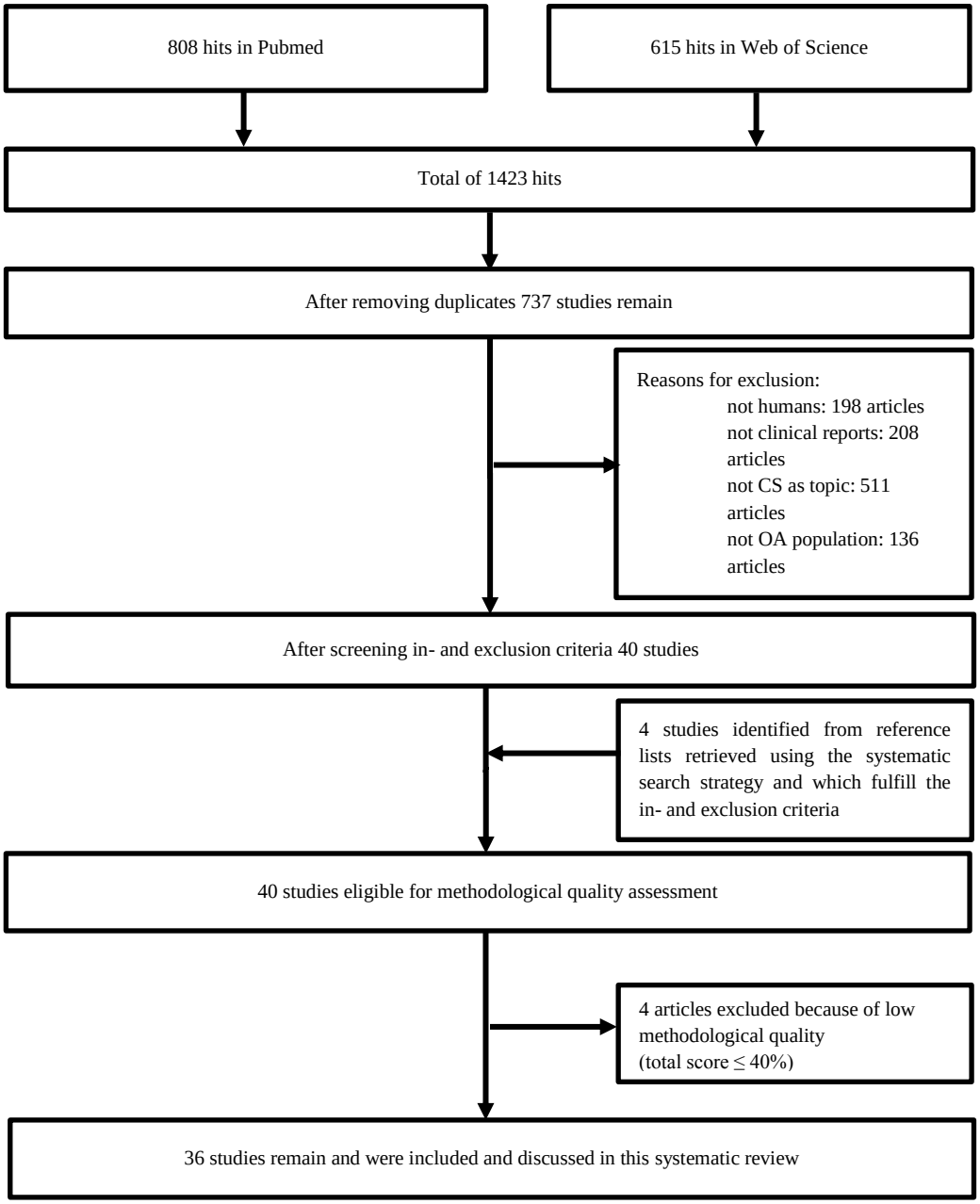

Table 2. Evaluation scores on methodological quality

Criteria methodological quality	Criterion 1	Criterion 2	Criterion 3	Criterion 4	Criterion 5	Criterion 6	Criterion 7	Criterion 8	Criterion 9	Criterion 10	Criterion 11	Criterion 12	Criterion 13	Criterion 14	Criterion 15	Criterion 16	Criterion 17	Criterion 18	Total score	%
Abou-Raya et al 2012	1	1	1	1	1	1	1	0	1	1	1	0	1	1	1	1	1	0	15/18	83.3
Arendt-Nielsen et al 2010	0	1	1	-	1	1	1	1	-	0	-	-	-	-	1	1	-	0	8/11	72.7
Bajaj et al 2001	0	1	1	0	1	0	1	1	-	0	-	-	-	1	1	1	-	1	9/13	69.2
Chapell et al 2009	1	1	1	1	1	0	1	1	1	1	1	0	1	1	1	1	1	-	15/17	88.2
Courtney et al 2009	0	1	1	-	1	0	1	-	-	0	-	-	-	1	1	1	-	-	7/10	70
Courtney et al 2010	0	1	1	-	1	1	1	-	1	0	0	0	-	1	1	1	-	0	9/14	64.2
Emery et al 2006	0	0	1	-	-	1	1	0	-	0	-	-	0	-	1	1	-	0	5/11	45.4
Farrell et al 2000a	0	1	1	-	1	0	1	-	-	0	-	-	-	-	1	1	-	0	6/10	60
Farrell et al 2000b	0	1	0	-	1	0	1	-	1	0	-	0	0	-	1	1	-	-	6/12	50
Finan et al 2013	0	1	1	-	1	0	1	-	-	0	-	-	-	-	1	1	-	-	6/9	66.6
France et al 2004	0	1	1	-	1	0	1	-	-	0	-	-	-	-	1	1	-	-	6/9	66.6
Gerecz-Simon et al 1989	0	1	0	-	1	0	0	0	-	0	-	-	0	-	1	1	-	0	4/12	33.3
Goodin et al 2012	0	1	1	-	-	1	1	-	-	-	-	-	0	-	1	1	-	-	6/8	75
Graven-Nielsen et al 2012	0	1	1	-	1	0	1	-	-	0	-	-	-	-	1	1	-	1	7/10	70
Gwilym et al 2009	0	0	1	-	1	1	0	-	-	0	-	-	1	-	1	1	-	-	6/10	60
Gwilyn et al 2010	0	0	1	-	1	0	0	0	-	-	-	-	-	-	1	1	-	1	5/10	50
Hendiani et al 2003	0	1	1	-	1	0	1	-	-	0	-	-	1	-	1	1	-	-	7/10	70
Hochman et al 2010	0	1	1	-	1	0	0	-	-	1	-	0	1	-	1	1	-	-	7/11	63.6
Hochman et al 2011	0	1	1	-	-	1	-	-	-	0	-	-	1	-	1	1	-	-	6/8	75
Howard et al 2012	0	1	1	-	1	1	1	-	-	-	-	0	1	-	1	1	-	1	9/11	81.8
Imamura et al 2008	0	1	1	-	1	1	0	0	-	0	-	-	0	-	1	1	-	-	6/11	54.5
Kavchak et al 2012	0	1	1	-	1	0	1	-	1	0	-	0	-	-	1	1	-	-	7/11	63.6
Kosek et al. 2000a	0	1	0	-	1	0	0	-	-	0	-	-	-	-	1	1	-	1	5/10	50

Table 2 (continued)

Criteria methodological quality	Criterion 1	Criterion 2	Criterion 3	Criterion 4	Criterion 5	Criterion 6	Criterion 7	Criterion 8	Criterion 9	Criterion 10	Criterion 11	Criterion 12	Criterion 13	Criterion 14	Criterion 15	Criterion 16	Criterion 17	Criterion 18	Total score	%
Kosek et al 2000b	0	1	0	-	1	0	0	-	-	0	-	-	0	-	1	1	-	1	5/11	45.4
Kulkarni et al 2007	0	1	1	-	-	0	1	-	-	-	-	-	-	-	1	1	-	-	5/7	71.4
Lee et al 2011	0	1	1	-	1	0	1	-	-	0	0	-	0	-	1	1	-	-	6/11	54.5
Lundbland et al 2008	1	0	0	-	-	1	1	-	-	0	-	-	0	-	1	1	-	1	6/10	60
Lundborg et al 2010	0	0	1	-	1	0	1	-	-	-	-	-	-	-	1	1	-	-	5/9	62.5
Moss et al 2007	0	1	1	1	-	1	1	0	1	1	0	1	1	1	1	1	-	0	12/16	75
Murphy et al 2011a	0	1	1	-	1	0	0	-	-	-	-	-	1	-	1	1	-	1	7/10	70
Murphy et al 2011b	0	1	1	-	-	0	0	-	-	-	-	-	1	-	1	1	-	0	5/9	55.5
O'Driscoll et al 1974	0	1	0	-	1	1	0	0	-	0	-	-	0	-	0	1	-	1	5/12	41.6
Parks et al 2011	0	1	1	-	0	0	1	-	-	1	-	0	0	1	1	1	-	1	8/13	61.5
Quante et al 2008	0	1	1	-	-	0	0	-	-	-	-	-	-	-	1	1	-	-	4/7	57.1
Vance et al 2012	0	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0	0	14/18	77.7
Westermann et al 2011	0	0	1	-	1	0	0	-	-	0	-	-	0	-	1	1	-	0	4/11	36.3
Wilder-Smith et al 2001	0	0	1	1	1	0	1	1	1	0	0	0	1	1	1	1	0	1	11/18	61.1
Wood et al 2007	0	1	1	-	1	0	-	-	-	1	-	0	1	-	1	1	-	0	7/11	63.6
Wylde et al 2011	0	-	0	-	0	0	0	-	-	-	-	-	1	-	1	1	-	-	3/8	37.5
Wylde et al 2012	0	0	1	-	1	0	0	-	-	0	-	-	0	-	1	1	-	0	4/12	33.3

0: criterion not fulfilled; 1: criterion fulfilled; –: criterion not applicable; papers with red shaded percentage scores were excluded from the review because scores were < 40%.

Criterion 1: The sample size was sufficient and justified (using a priori or post hoc analysis)
Criterion 2: Diagnostic criteria described?
Criterion 3: Inclusion and exclusion criteria clearly described?
Criterion 4: Randomised allocation with description of the randomization procedure?
Criterion 5: Groups were comparable at baseline (regarding demographic data)?
Criterion 6: Valid and reliable outcome measures used? -AND- Validity and reliability of every outcome measure described?
Criterion 7: Co-interventions avoided or accounted for?
Criterion 8: Wash-out period before data collection started?
Criterion 9: Blinding of all subjects?
Criterion 10: Blinding of all assessors who measured at least one key outcome?
Criterion 11: Blinding of all therapists who administered the therapy?
Criterion 12: Effectivity of the blinding procedure evaluated?
Criterion 13: Drop-outs and reason for drop-out mentioned?
Criterion 14: Treatment of both the experimental and the control group clearly described?
Criterion 15: Statistical procedure described?
Criterion 16: Outcome measures clearly described?
Criterion 17: Intention-to-treat analysis?
Criterion 18: Follow-up?

Methodological quality assessment

There was 96,5% agreement (695 of the 720 items) between the two researchers on scoring the selected papers on methodological quality. After a second review, the reviewers reached a consensus in all except for 4 items. Final decision on these 4 items was resolved by a third researcher.

Table 2 provides the details regarding fulfillment of the methodological quality criteria for each analyzed study. In only 3 out of the 40 studies the sample size was sufficient and justified for (criterion 1). Eight out of the 40 studies did not describe the diagnostic criteria for OA, while 7 research papers did not clearly describe inclusion and exclusion criteria used for patient's selection (criteria 2 and 3). Groups were comparable at baseline regarding demographic data in 29 studies (criterion 5). The validity and reliability of the outcome measures used was only described in 13 out of the 40 studies (criterion 6). Co-interventions were taken into account in 24 studies (criterion 7), whereas only 5 out of the total studies selected included a washout period before starting the study (criterion 8). Subjects were blinded in 8 studies, assessor(s) in 7 studies, and therapist who administered the therapy in 3 studies, although these criteria were not always applicable. Although 3 studies performed a double-blinded design (i.e. subjects and therapists), only 2 studies examined and reported whether the blinding procedure was effective (criterion 12). Eleven studies included a follow-up period (criterion 18).

To be further considered in this review, articles were required to have a score of ≥40% on methodological quality. If this score was not achieved, the study was rejected because of poor methodological quality. Four studies (Gerecz-Simon et al., 1989;

Westermann et al., 2011; Wylde et al., 2011, 2012) were excluded for this reason. In conclusion, 36 studies with sufficient methodological quality were considered, and the characteristics and findings of these studies are discussed below.

Study characteristics

Of the 36 selected studies, most were categorized as case-control (n=19) or cross-sectional studies (n=12). Five research papers were randomized controlled trials. Twenty-two out of the 36 studies investigated the etiology of OA, 5 were treatment-focused and 5 were classified as mixed etiology-treatment. Only 2 studies were classified as prevalence studies, and 2 more as diagnosis studies (Table 3).

OA of the knee joint was examined in 24 studies, while 5 focused their interest on the hip, 3 on the 1st carpo-metacarpal (CMC) joint, and 3 examined both hip and knee OA. One study recruited subjects with OA in the lower extremities.

Table 3. Characteristics of included studies.

Article	Purpose	Design	Sample characteristics	Joint studied	Criteria for OA diagnosis	Inclusion/exclusion criteria	Assessment regarding CS	Time of follow-up assessments	Results regarding CS	Limitations of the study
Abou-Raya et al.2012	Treatment	RCT	288 subjects with knee OA receiving two different treatments during 16 weeks: 144 receiving duloxetine 144 receiving placebo	Knee	ACR and radiographic criteria	**Inclusion**: OA with knee pain [>4 on the 24-h VAS using mean of daily ratings from week preceding randomization], for >14 days/month during three consecutive months preceding enrolment. **Exclusion**: morbid obesity (BMI greater than 32 kg/m2), joint inflammatory diseases and or crystal-induced arthropathies, any other concomitant disease (such as neuropsychiatric disease including cognitive impairment, Alzheimer's disease, Parkinson's disease, cerebrovascular disease, cardiovascular disease, liver and renal disease), or use of other antidepressants that could interfere with the evaluation of the intervention	**Primary outcome measures:** Percentage of patients with a clinical response according to the Osteoarthritis Research Society International 2004 criteria at the end of 16 weeks (pain or physical function score decreased by 50% or more and at least 20 mm on the VAS) **Secondary outcome measures:** WOMAC Use of OA rescue medication (NSAID and paracetamol) Modified version of the Katz activity of daily living scale Geriatric Depression Scale Incidence and type	2 assessments: at baseline and at 16 weeks	Significant reduction at 16 weeks on pain (VAS, WOMAC), function (WOMAC), NSAID and paracetamol use and depression (GDS) in the duloxetine group compared with the placebo group	Possible selection bias from sample selected (more women than men; relatively young patients (68 years);mean BMI of 27.6) Only 16 week of treatment) with results not generalizable to a longer duration of treatment: lack of follow-up after 16 week

							of adverse events with treatment			
Arendt-Nielsen et al. 2010	Etiology	Case-control	48 subjects with different degrees of knee OA and 24 healthy controls Patients were in turn divided into two age- and sex-matched groups: those with strong/severe pain (VAS≥6) and those with mild/moderate pain (VAS < 6)	Knee	ACR criteria	**Inclusion**: knee OA diagnosed with ACR criteria **Exclusion**: use of medication 24h before the experiment, pain problems or sensory dysfunctions (e.g. nerve damage), or mentally impaired	PPTs at different sites (peripatellar region, tibialis anterior and extensor carpi radialis longus muscles); spreading sensitization; temporal summation to repeated pressure pain stimulation; pain responses and referred pain areas after intramuscular hypertonic saline; and pressure pain modulation by heterotopic DNIC	1 assessment, no follow-up	No correlation found between radiological findings and experimental or clinical pain parameters Significant negative relationships between the degree of local (knee) sensitization and spreading (leg, arm) sensitization and the patients' clinical pain intensity (VAS) (more pain, more sensitization/less PPT) Enhanced temporal summation of pain and impaired DNIC in OA subjects compared to controls	Not specified
Bajaj et al. 2001	Etiology	Case-control	14 subjects with OA in the lower extremities and 14 healthy controls	10 OA subjects (10/14) had pain in the knee joint and 8 (8/14) also had pain in the thigh, leg or foot	ACR criteria	**Inclusion for experimental group**: OA in the lower extremities **Inclusion for control group**: absence of pain areas at the time of enrolment	Muscle hyperalgesia: VAS and assessment of pain areas before and immediately, 2, 5, 10 and 20 min after intramuscular infusion of 0.5 ml hypertonic saline (6%) into the tibialis anterior muscle and then every 10 min, until experimentally	1 assessment, no follow-up	Significant higher local pain duration and intensity, larger pain areas and increased referred and radiating pain intensity after intramuscular infusion in the OA subjects compared with controls	The chronic OA and healthy controls included subjects both with and without a past history of trauma

							induced pain disappeared			
Chapell et al. 2009	Treatment	RCT	231 OA subjects receiving two different treatments during 13 weeks: 120 receiving placebo 111 receiving duloxetine (60–120 mg/day)	Knee	ACR criteria	**Inclusion**: pain for ≥14 days of each month for 3 months before study entry, with a mean score ≥4 on the 24-h VAS **Exclusion**: BMI>40 kg/m2, confounding painful condition that would interfere with assessment of the index joint, inflammatory arthritis or an autoimmune disorder, invasive therapies to the knee in the past 3 months, knee arthroscopy within the past year, joint replacement at anytime, prior synovial fluid analysis indicative of a diagnosis other than OA, to be non-ambulatory, use of crutches or a walker, psychiatric disorders including major depressive disorder (as identified using the Mini International Neuropsychiatric Interview), previous exposure to duloxetine, pregnant or breastfeeding women, history of substance abuse or dependence, positive	**Primary outcome measure** Weekly mean 24-h pain scores **Secondary outcome measures** Patients' perceived improvement WOMAC Weekly mean of the 24-h worst pain score Several secondary outcome measures (quality of life, safety and tolerability of duloxetine, etc.)	5 visits*: Visit 1: week -1 Visit 2: week 0 Visit 3: week 4 Visit 4: week 7 Visit 5: week 13 *A 2-week taper phase was added to minimize discontinuation emergent adverse events	Duloxetine group demonstrated statistically significant pain reduction compared with placebo on the primary efficacy measure of the weekly mean 24-h average pain score Duloxetine group also demonstrated superiority over placebo on most secondary efficacy measures	Not specified

						urine drug screen for any substance of abuse, existence of any serious medical or psychiatric condition that could compromise participation in the study, history of recurrent seizures, uncontrolled narrow-angle glaucoma, acute liver injury or severe cirrhosis, known hypersensitivity to duloxetine or any of the inactive ingredients, or frequent or severe allergic reactions to multiple medications				
Courtney et al. 2009	Etiology	Case-control	20 subjects with OA of the tibio-femoral joint and 20 healthy control subjects	Knee	Radiographic criteria	**Inclusion**: OA of the tibio-femoral joint **Exclusion**: previous total knee arthroplasty in either knee, history of any diagnosed neurological or rheumatoid condition, history of ligamentous deficiency, or BMI>30	NFR threshold VAS: previous week pain	1 assessment, no follow-up	NFR threshold was significantly diminished in OA subjects versus controls, as evidenced by a reduced current amplitude and latency of reflex responses (tibialis anterior responses) at NFR threshold Increased excitability of NFRs was evident in subjects with chronic knee OA, even in the absence of pain at the time of testing	Despite use of a specific protocol of increasing current intensity to determine NFR threshold, the detection of threshold during experimental testing was initially performed visually using tibialis anterior EMG activity EMG activity was not normalized between subject groups using electrophysiological assessments

										(maximal M wave), and accurate comparison of EMG amplitudes was not performed
Courtney et al. 2010	Etiology-treatment	Case-control	10 subjects with OA of the tibio-femoral joint and 10 healthy control subjects	Knee	Radiographic criteria	**Inclusion**: OA of the tibio-femoral joint **Exclusion**: previous total knee arthroplasty in either knee, history of any diagnosed neurological or rheumatoid condition, history of ligamentous deficiency, or BMI>30	NFR threshold at baseline and after three conditions: joint compression, joint mobilization and sham intervention. VAS: present pain level *Sham and mobilization interventions were not performed on control subjects in light of previous research which has demonstrated little modulation when the intervention was applied to a healthy pain-free peripheral joint	1 assessment, no follow-up	NFR threshold was significantly diminished at baseline in OA group versus the control group After applying joint compression NFR responses markedly augmented, mostly in OA subjects, whereas joint mobilization (but not sham intervention) reduced NFR excitability in OA group	Influence of the order of experimental intervention (first joint compression; then joint mobilization) on the results

Emery et al. 2006	Etiology-treatment	Cross-sectional	62 subjects with knee OA	Knee	Radiographic criteria	**Inclusion**: radiographic evidence of OA affecting one or both knees, complaints of knee pain persisting for 6 months or longer, and postmenopausal status for women **Exclusion**: known organic disease that significantly affect function (e.g., chronic obstructive pulmonary disease) or preclude safe Participation, rheumatic disorders other than OA, evidence of cognitive impairment as indicated by a score of less than 24 on a mini-mental status exam, current use of a selective serotonin reuptake inhibitor, BMI ≥35, or lack of NFR response during the initial NFR procedure	NFR threshold Questionnaires/self-reported measures evaluating pain and state anxiety (McGill Pain Questionnaire, State-Trait Anxiety Inventory, Daily Coping Inventory, Pain Catastrophizing Scale)	2 assessments, before and after a 45-minute coping skills training session	Increased NFR thresholds and decreased pain ratings following coping skills training for both men and women Women reported more significant reductions in anxiety following coping skills training intervention compared to men Women and men did not differ significantly in terms of the effects of intervention on NFR threshold or pain ratings	Inclusion of only two NFR assessments, scheduled before and after the intervention Lack of a no-treatment control condition Small sample size
Farrell et al. 2000a	Etiology	Case-control	80 subjects divided in 3 groups: 1) Subjects with ACR clinical criteria for OA of the hands and symptoms related to OA of the 1st CMC. These, in turn, were divided	1st CMC joint	ACR criteria	**Exclusion**: use of medication which was likely to influence pain perception, or history or signs of any disorder of sensation	Thermal and mechanical detection and pain thresholds over the forearm and the 1st CMC joint Intensity ratings for 3 types of pain: continuous pain, incident pain and	1 assessment, no follow-up	Lower thermal and mechanical pain thresholds were found over the thumb relative to the forearm in groups with persistent pain (CP, MP and CMP groups). Persistent pain was therefore associated with	Great risk of spurious findings accompanying stepwise regression techniques used in this study

			in 4 groups presenting with: - Continuous and incident pain (CP) (n=10) -Movement and incident pain (MP) (n=10) -Continuous, movement and incident pain (CMP) (n=18) -Incident pain (IP) (n=12) 2) Subjects with features of OA of the 1st CMC but not pain in the hand in the last month (no pain group, NP group) (n=15) 3) Pain-free age subjects without OA of the hand (no OA group, NOA group) (n=15)				movement pain		local hyperalgesia at the thumb IP, NP and NOA groups didn't exhibit regional differences in sensitivity to thermal and mechanical stimuli. Incident pain was therefore not associated with local hyperalgesia. Increased ratings of continuous pain were associated with lower thermal and mechanical pain thresholds Variance in movement pain ratings was predicted by mechanical forearm pain thresholds	

Farrell et al. 2000b	Etiology	Cross-sectional	24 women with OA of the hands distributed in two groups: 1) 12 women with movement-related pain in at least one 1st CMC joint (movement pain group, MP group) 2)12 women with no pain in either hand (no pain group, NP group)	1st CMC joint	ACR criteria	**Inclusion for the movement pain group**: presence of symptoms (pain, stiffness) or signs (nodes, deformity, restricted or aberrant movement) associated with the 1st CMC joint	Two experiments were conducted: **First experiment**: Mechanical and thermal pain threshold over the skin of the thumb measured 3 times: pre-movement pain provocation, post-movement pain provocation and 30 minutes post-movement pain provocation *Movement pain provocation was achieved with resisted active movement of the thumb **Second experiment:** Mechanical and thermal pain threshold over the skin of the thumb after movement pain provocation with blockade of Aβ fibers	1 assessment, no follow-up	Decrease in mechanical pain thresholds (not thermal) over the 1st CMC joint and increase in thermal pain thresholds at distant sites (i.e. the contralateral thumb) in the MP group after resisted thumb movement The increased mechanical sensitivity after resisted active movement of the thumb was alleviated by Aβ fiber blockade in the MP group The NP group didn't show any changes in sensitivity to either thermal or mechanical stimuli after resisted movement	Not specified
Finan et al. 2013	Etiology	Cross-sectional	113 subjects with knee OA divided in 4 groups: low pain/low knee OA grade (n=24), high pain/high knee OA grade (n=32), low pain/high knee OA grade (n =27),	Knee	ACR criteria	**Inclusion**: ACR criteria for knee OA, score of at least 1 on the Kellgren/Lawrence scale in one or both knees, knee pain scored >2 on a 10-point scale on a near-daily basis (>4	WOMAC Kellgren/Lawrence scale (OA grade) PPT at local (i.e. insertion point of quadriceps of the affected knee) and remote unaffected	1 assessment, no follow-up	After adjusting for differences on psychosocial measures, as well as age, sex, and race, significantly heightened pain sensitivity across measures distal to the affected knee	Analyses were performed on a secondary data set: the majority of participants were recruited for the presence of comorbid insomnia

			and high pain/low knee OA grade (n=30)			days/week) for at least 6 months prior to entering the study **Exclusion**: serious medical illnesses (i.e. congestive heart failure, history of cerebrovascular accidents, cancer, or other chronic pain or rheumatic disorders), joint replacement, severe or unstable psychopathology, cognitive impairment/dementia, current substance abuse disorder, or positive findings on toxicology screening	anatomic sites (i.e. trapezius muscle bilaterally) Repeated phasic suprathreshold mechanical and thermal pain Tonic suprathreshold pain (cold pressor test) CPM Anxiety (State-Trait Anxiety Inventory) Depression (Center for Epidemiologic Studies Depression Scale) Daily Coping Inventory Pittsburgh Sleep Quality Index: sleep disturbance		was found in the high pain/low knee OA grade group, while the low pain/high knee OA grade group was less pain-sensitive* *The results suggested that central sensitization in knee OA was especially apparent among subjects with reports of high levels of clinical pain in the absence of moderate-to-severe radiographic evidence of pathologic changes of knee OA	Small sample size
France et al. 2004	Etiology	Cross-sectional	74 post-menopausal women and 58 age-matched men both with OA of the knee	Knee	Radiographic criteria	**Inclusion**: radiographic evidence of OA affecting one or both knees, complaints of knee pain persisting for 6 months or longer, and postmenopausal status for women (to provide age matching, men were recruited if they were between 50 and 75 years of age)	NFR Electrocutaneous pain threshold and tolerance at knee Daily Coping Inventory: problem and emotion-focused pain coping strategies Pain Catastrophizing Scale	1 assessment, no follow-up	Women were more likely than men to report using emotion-focused pain strategies and emotion-focused coping was associated with more arthritic pain and lower electrocutaneous pain tolerance Catastrophizing	Lack of control in women over the different forms of hormonal replacement therapy, doses of estrogen and progestin, continuous or cyclic protocols, or length of exposure to the medications.

						Exclusion: known organic disease that significantly affect function (e.g. chronic obstructive pulmonary disease), affect reflex testing or preclude safe participation, rheumatic disorders other than OA, or cognitive impairment as indicated by a score of less than 24 on a mini-mental status exam	Mc-Gill Pain Questionnaire: overall pain ratings for the experimental laboratory session Arthritis Impact Measurement Scales		was associated with greater arthritis pain and lower pain threshold and tolerance levels Catastrophizing was not related to NFR threshold No significant group differences in arthritis pain, electrocutaneous pain threshold or tolerance, or NFR threshold were observed between men, post-menopausal women receiving hormone replacement therapy, and post-menopausal women not receiving hormone replacement therapy	Potential differences as a function of natural or surgical menopause were not examined Unable to record NFR thresholds in a large proportion of the sample
Goodin et al. 2012	Etiology	Cross-sectional	140 older, community-dwelling adults with symptomatic knee OA	Knee	ACR criteria	**Inclusion**: 45-85 years of age, unilateral or bilateral symptomatic knee OA based upon ACR criteria, and availability to complete the 2-session protocol **Exclusion**: prosthetic knee replacement or other clinically significant surgery to the affected knee, uncontrolled	Temporal summation of heat pain Measures of dispositional optimism and pain catastrophizing (Life Orientation Test-Revised and Coping Strategies Questionnaire) Center for Epidemiological Studies Depression	1 assessment, no follow-up	Greater dispositional optimism was found to be associated with less pain catastrophizing and less temporal summation of heat pain Pain catastrophizing significantly mediated the association	Cross-sectional nature of the current study allows for the possibility that the associations among dispositional optimism, pain catastrophizing, and temporal summation of heat pain may be bidirectional or co-occurring

						hypertension, heart failure, or history of acute myocardial infarction, peripheral neuropathy, systemic rheumatic disorders including rheumatoid arthritis, systemic lupus erythematosus, and fibromyalgia, chronic daily opioid use, cognitive impairment (Mini-Mental Status Exam [MMSE] score), excessive anxiety regarding protocol procedures (eg, refusal to complete controlled noxious stimulation procedures), or hospitalization within the preceding year for psychiatric illness	Scale WOMAC		between dispositional optimism and temporal summation of heat pain	Pain catastrophizing was assessed according to the ‘‘standard’’ means of measurement (i.e. recall of catastrophizing in daily life), rather than the ‘‘situation-specific’’ means of measurement (i.e, catastrophizing measured during or directly after the administration of noxious stimulation) Possible bias due to sample selectivity Lack of matching the characteristics of the experimenters (e.g, sex, ethnicity/race) that facilitated the QST sessions to those of the participants Possible report biases of temporal summation procedure due to subjectivity of

										self-reported pain
Graven-Nielsen et al. 2012	Etiology	Case-control	48 subjects with knee OA either unilaterally or bilaterally and 21 healthy control subjects *20 out of 48 patients with OA were scheduled for and further evaluated 5–28 weeks following surgery	Knee	ACR criteria	**Inclusion**: severe pain for >3 months and pain score of ≥4 on VAS **Exclusion**: pain problems or sensory dysfunctions (e.g. nerve damage) or mental impairment	PPT over several local sites in the knee (i.e. in the peripatellar region) and control/remote sites (forearm and lower leg) Cuff PPTs at the lower leg Spatial summation of pressure-pain CPM	1 assessment (pre-surgery), no follow-up 2 assessments at baseline and follow-up at 5–28 weeks following surgery, on a subgroup of 20 OA patients who underwent knee replacement surgery	Reduced PPTs at the knee and at control/remote sites (forearm and lower leg), reduced Cuff PPTs and enhanced spatial and temporal summation of pain in OA subjects as compared with control subjects Loss of CPM in OA patients Reduction in the widespread mechanical hyperesthesia, normalization of spatial summation ratios and restoration of CPM in the subgroup of 20 OA subjects who underwent knee joint replacement	Lack of reassessment of the healthy controls or the OA subjects who didn't undergo surgery
Gwilym et al. 2009	Etiology	Case-control	20 subjects with hip OA and 20 controls	Hip	Not specified	**Inclusion**: hip pain secondary to primary OA of the hip **Exclusion**: any previous form of orthopedic surgery, presence of other chronic pain conditions, diabetes, and neurologic or psychiatric disorders, or exclusion criteria	Punctate stimulus detection threshold, punctate hyperalgesia, cold perception thresholds, and cold pain threshold levels in area of referred pain fMRI: 12 patients and 12 controls underwent fMRI while their areas of	1 assessment, no follow-up	OA subjects showed significantly lower threshold perception to punctate stimuli and hyperalgesia to the noxious punctate stimulus in their areas of referred pain, compared to controls	There were differences in medication use by the various groups of patients (controls versus patients, high PainDETECT versus low PainDETECT scores) Although both

						for magnetic resonance experimentation	referred pain were stimulated using cold stimuli (12°C) and punctate stimuli (256 mN). The remaining 8 of 20 patients underwent punctate stimulation only due to equipment failure during the research period Beck Depression Inventory Pain Catastrophizing Scale Tampa Scale of Kinesiophobia State Anxiety Index and Trait Anxiety Index PainDETECT		Greater activation in the brainstem (i.e. periaqueductal grey matter) of OA subjects in response to punctate stimulation of their referred pain areas compared with controls. The magnitude of this activation positively correlated with the extent of neuropathic pain-like elements to the patient's pain, as indicated by the PainDETECT score	the patients and controls were excluded from the study if they were taking neuroleptic medications, there were predictable differences in the uptake of other categories of medications between patients and controls
Gwilyn et al. 2010	Etiology	Case-control	16 subjects with hip OA and 16 controls	Hip	Not specified	**Inclusion for patients**: unilateral right-sided hip pain of sufficient magnitude to warrant total hip arthroplasty **Inclusion for controls**: free of chronic pain conditions and not regularly use of analgesic medications or alternative therapies for pain **Exclusion**: chronic neurologic or	MRI: voxel-based morphometry Oxford Hip Score PainDETECT Hospital Anxiety and Depression Score	2 assessments: 4 weeks prior to hip arthroplasty and 9 months after the surgery	Significant decreased in brain gray matter volume (i.e.thalamus) in subjects with painful hip OA compared to controls at baseline Reversal of reduced thalamic gray matter volume in OA subjects after surgery to normal levels seen in controls, which	Inherent limitations of voxel-based morphometry analysis Cross-sectional study design

						psychiatric conditions, regular medications (other than those for cardiovascular conditions), epilepsy, diabetes or lack of fulfillment criteria for safe MRI scanning			was accompanied with a decrease on pain and increased function	
Hendiani et al. 2003	Etiology	Case-control	27 subjects with RA, 28 with knee OA and 27 controls	Knee	ACR criteria	**Inclusion**: history of arthritis, either RA or OA, according to ACR diagnostic criteria **Exclusion**: arthritic condition other than RA or OA, confounding acute or chronic comorbid condition, including fibromyalgia, gout, diabetes mellitus, history of cerebral vascular accident, or peripheral neuropathy, cancer survivors treated with chemotherapeutic protocols for cancer, history of trauma to lower extremities, hips or back, including prior surgery or arthroscopy, reported or documented use of recreational drugs within a year of the study, or RA or OA reported disease duration of less than 3 months	VAS: pain intensity at the time of testing Cutaneous joint temperature Joint circumference Cold allodynia (alcohol swab application), cutaneous mechanical thresholds and cutaneous pain threshold (allodynia), at the cutaneous field overlying the knee joint	1 assessment, no follow-up	Simultaneous cutaneous hypoesthesia (increased cutaneous mechanical thresholds) and mechanical allodynia (decreased thresholds for cutaneous mechanical pain) adjacent to the involved joint was observed both in RA and OA subjects* *These paradoxical responses were interpreted as the result of activation of a descending inhibitory system. All patients and controls reported non-painful, intact cold sensation to alcohol swab application	Limited sample size Surface temperature only measured in the lateral inferior quadrant

									Mechanical allodynia and increased joint surface temperature and circumference in RA patients (but not OA) were correlated	
Hochman et al. 2010	Prevalence	Cross-sectional	80 subjects with knee OA	Knee	Radiographic criteria	**Inclusion**: English-speaking adults ages ≥40 years with knee OA (confirmed on radiographs), with aching, discomfort, pain and/or stiffness in or around a knee on most days of at least one month during the past year **Exclusion**: not specified	Analysis of transcripts for unprompted use of pain descriptors that suggested neuropathic pain (items from validated neuropathic pain symptom-based questionnaires were used to guide the analysis) Duration of knee symptoms WOMAC NRS	1 assessment, no follow-up	34% of knee OA subjects used pain quality descriptions suggestive of neuropathic pain Those who used neuropathic pain descriptors were younger and, although not statistically different, more likely to be women, with higher pain intensity and OA severity and longer OA duration, than those who did not use neuropathic pain descriptors	Qualitative assessment of the OA pain experience Lack of information on comorbid medical or neurologic conditions contributing to neuropathic pain symptoms (although people with other chronic pain conditions were excluded) Small sample size
Hochman et al. 2011	Prevalence	Cross-sectional	171 subjects with knee OA	Knee	Joint examination and radiographic criteria	**Inclusion**: discomfort in at least one non-replaced knee on most days (≥15) over the past month **Exclusion**: self-reported physician diagnosed inflammatory arthritis, bilateral	Modified painDETECT WOMAC Von Korff Chronic Pain Grade pain intensity subscale Centre for Epidemiologic Studies Depression	1 assessment, no follow-up	28% of the 171 subjects who completed the Modified painDETECT (19% after excluding participants with self-reported neurological conditions), had neuropathic pain	Insufficient power (limited sample size) to evaluate, conclusively, the independent effects of postulated correlates of neuropathic pain symptoms

						knee surgery, or factors that could interfered with questionnaire self-completion (e.g. reduced cognition)	Scale Pain Catastrophizing Scale		symptoms (Modified painDETECT score ≥19 in either knee) Excluding participants with self-reported neurological conditions, OA pain intensity, number of painful joints, and the presence of concomitant back or hip pain referred to the upper leg had high discriminative validity for distinguishing those with and without neuropathic pain range symptoms	Participants had lower scores for psychological factors that have been associated with the presence and severity of neuropathic pain. Underestimation of the prevalence of neuropathic pain symptoms in the cohort could then have occurred. Only older adults with longstanding OA included in the sample
Howard et al. 2012	Etiology	Case-control	16 subjects with 1st CMC joint OA and 17 controls	1st CMC joint	ACR criteria	**Inclusion**: 1st CMC joint OA **Exclusion**: claustrophobia, image artifacts, development of pain in other body sites, or use of analgesic medication other than the stable drug regimen required	Pulsed continuous arterial spin labeling NRS	2 assessments distributed in 2 identical sessions, separated by a minimum of 7 days and a maximum of 21 days	Subjects with 1st CMC joint OA showed increases in regional cerebral blood flow in a distributed network, including the somatosensory, insula, and cingulate cortices, thalamus, and midbrain/pontine tegmentum, compared to controls* Variability in	Not specified

									regional cerebral blood flow measures in subjects with 1st CMC joint OA pain was related to changes in their perceived ongoing pain; regional cerebral blood flow measures were stable between sessions in controls *The observed pattern of regional cerebral blood flow changes observed in OA subjects suggests dysregulation of systems that include evaluation of threat to the body from ongoing pain and the ability of the brain to modulate pain via descending modulatory mechanisms	
Imamura et al. 2008	Etiology	Case-control	62 female scheduled for a total knee replacement and 22 female controls	Knee	ACR criteria and radiographic criteria	**Inclusion for patients**: pain score ≥ 4 on a VAS during the week preceding the clinical evaluation **Inclusion for controls**: lack of pain reported in the lower back or in the lower extremities for the previous year	PPT measurements at subcutaneous, myotomal, and sclerotomal structures* -Subcutaneous: PPT during the pinch and roll maneuver at the L1, L2, L3, L4, L5, S1, and S2 dermatome levels	1 assessment, no follow-up	Knee OA subjects had significantly lower PPT versus controls throughout sites of assessment at the dermatomal, myotomal, and sclerotomal structures Even when OA was unilateral,	Lack of PPT measurement over other areas (i.e. thoracic and cervical innervated areas) Lack of evaluation of sensitization changes in central structures such as cortical

						Exclusion: clinical manifestations of OA in other joints, clinical diagnosis of associated fibromyalgia, neurologic condition such as stroke or Parkinson's disease, any systemic inflammatory disease, or impossibility to come to the hospital for evaluations	-Myotomal: PPT at the vastus medialis, adductor longus, rectus femoris, vastus lateralis, tibialis anterior, peroneus longus, iliacus, quadratus lumborum, and popliteus muscles at classically described painful areas -Sclerotomal: PPT at the L1–L2, L2–L3, L3–L4, L4–L5 supraspinous ligaments, over the L5–S1 and S1–S2 sacral areas, pes anserinus bursae, and at the patellar tendon *Except for supraspinous ligaments and the L5–S1 and S1–S2 sacral areas (6 sites), all measurements were done bilaterally VAS WOMAC Short-Form 36		both extremities were equally affected in terms of hiperalgesia Lower PPT values were correlated with higher pain intensity (VAS), higher disability scores (WOMAC) and poorer quality of life (Short-Form 36)	brain areas
Kavchak et al. 2012	Etiology	Case-control	16 subjects with knee OA and 16 controls	Knee	Radiographic criteria	**Inclusion**: Knee OA confirmed radiographically **Exclusion**: previous	Mechanical detection threshold, allodynia, vibration perception threshold local at	1 assessment, no follow-up	Concurrent findings of local allodynia and hypoesthesia ,and local and	Significant BMI differences between patients and controls

						total knee arthroplasty in either knee, history of any diagnosed neurological conditions including depression or a chronic pain syndrome, rheumatoid condition or history of knee joint trauma, or ligamentous deficiency	affected knee PPT local at affected knee and distally on the medial aspect of the lower limb Pain intensity ratings (VAS) and subjective reports of instability/buckling, at rest and while performing a step-up task		widespread hiperalgesia, in subjects with knee OA Significant differences in local but not widespread hyperalgesia between subjects with OA having severe versus mild radiographic changes A moderate correlation between greater self-reported instability and increased vibratory hypoesthesia at the knee was demonstrated in OA subjects	Possible contribution of muscle weakness to the subjective report of instability Lack of direct proprioception assessment
Kosek et al. 2000a	Etiology-treatment	Case-control	14 subjects with hip OA and 14 controls	Hip	Radiographic criteria	**Inclusion**: radiological OA and severe pain for more than one year, candidate for surgery, healthy apart from their OA, and no pain contralateral to the affected side **Exclusion**: not specified	VAS at the site of maximal pain on the affected side and the homologous contralateral site QST at the maximal pain site and the homologous contralateral site: -PPT -Perception threshold to light-touch -Perception	1 assessment (pre-surgery), no follow-up 2 assessments (pre-surgery and 10 months after surgery on average), in 12 subjects with hip OA and 12 controls	Before surgery, subjects with hip OA demonstrated lower PPT (only on the maximally painful side, and increased sensitivity to innocuous warmth, cold pain and a strong tendency toward increased heat pain sensitivity (all bilateral), compared to controls	Presence of a sensory deficit prior to pain relief was not assessed

							thresholds to innocuous cold -Perception thresholds to innocuous warmth -Heat pain threshold -Cold pain threshold		Following surgery sensitivity to light touch increased and PPT decreased on the affected side in subjects with hip OA, compared to their initial values Following surgery, neither statistically significant differences, nor trends towards statistically significant differences, in the sensitivity to any somato-sensory modality were found between patients and controls* *This finding indicated that the sensory aberrations were reversible after surgery and had been maintained by nociceptive inflow from the affected Hip	
Kosek et al. 2000b	Etiology-treatment	Case-control	15 subjects with hip OA and 15 controls	Hip	Radiographic criteria	**Inclusion**: radiological OA and severe pain for more than 1 year and waiting for surgery **Exclusion**: not specified	Perception thresholds to light touch PPT Perception thresholds to non-painful and painful warmth and cold	1 assessment (pre-surgery), no follow-up 2 assessments (pre-surgery and 6±14 months after surgery), in 13 subjects with hip OA and 13 controls	Before surgery, no statistically significant increase in PPTs was seen during the tourniquet test in subjects with hip OA, as opposed to healthy controls*	Not specified

							*All these measures were assessed before, during and 45 min following the tourniquet test		*This finding was interpreted as a sign of DNIC dysfunction Normal modulation of PPTs in subjects with hip OA was seen during the tourniquet test in a pain-free state after surgery: dysfunction of DNIC was therefore maintained by ongoing nociceptive activity	
Kulkarni et al. 2007	Etiology	Cross-sectional	12 subjects with knee OA	Knee	ACR criteria	**Inclusion**: knee OA following ACR criteria **Exclusion**: any psychiatric condition or other medical condition, or to have received opiates or antidepressants for at least 1 year prior to the study	Positron emission tomography of the brain in 3 different pain states: arthritic knee pain, experimental knee pain, and pain-free	1 assessment, no follow-up	Both pain conditions (arthritis and experimental) activated the pain matrix, but arthritic pain was associated with increased activity in the medial pain system of the brain, including most of the cingulate cortex, the thalamus, and the amygdale* *All these areas are involved in the processing of fear, emotions, aversive conditioning and motivational responses	Small sample size

Lee et al. 2011	Etiology	Case-control	26 subjects with knee OA and 33 controls	Knee	Clinical OA diagnosis (radiographs were not required to confirm/reject OA diagnosis)	**Inclusion for patients**: clinically diagnosed with knee OA (documented by a physician in the medical record), pain attributed to knee OA (documented in the medical record) **Inclusion for controls**: lack of a diagnosis of OA and a history of joint pain **Exclusion**: current mood or anxiety disorder, current infection, current pregnancy, history of autoimmune disorders, cardiovascular disease, peripheral neuropathy, Raynaud's syndrome, or peripheral vascular disease, recent history of substance abuse or to use of opioids, antidepressants, or corticosteroids	PPT bilaterally at the trapezius muscle, the 1st metacarpophalangeal joint, and the quadriceps muscle Heat pain thresholds and suprathreshold heat pain ratings Cold pain ratings and cold pain tolerance Serum levels of pro-inflammatory cytokines: C-reactive protein, IL-6, IL-1β and TNF-α *Cytokine levels were taken at baseline and at 4 points in time: immediately after testing and 15, 30 and 60 minutes after testing	1 assessment, no follow-up	Subjects with knee OA had lower PPT and higher suprathreshold heat pain ratings across multiple body sites than controls Among subjects with knee OA heightened pain sensitivity (i.e. low PPTs and high suprathreshold heat pain ratings), was associated with elevated C-reactive protein and IL-6 levels during the course of the study, respectively	Not radiographic criteria for OA diagnosis Small sample size Cross-sectional design
Lundbland et al. 2008	Etiology-treatment	Case-control	69 subjects with knee OA and 24 controls	Knee	Not specified	**Inclusion**: knee OA **Exclusion**: clinical history of drug abuse or use of opioid drugs before surgery	VAS (pain at rest and with movement) Matched pain (i.e. pain corresponding to the knee pain with movement) and sensory and pain threshold, all taken with the aid of the Pain Matcher, which is	2 assessments*: pre-surgery and at 18 months after surgery *No measurements with the Pain Matcher were made at follow-up	Before surgery, subjects with knee OA exhibited a significantly higher sensation threshold and lower pain threshold compared to controls Subjects with knee OA who reported	Not specified

							an electrical stimulation device.		a high pre-operative score for knee pain at rest (VAS) and low pre-operative pain threshold (Pain Matcher) were at increased risk of persistent pain after total knee replacement* *These latter finding was interpreted as a reflection of a central sensitization mechanism	
Lundborg et al. 2010	Etiology	Case-control	20 subjects with hip or knee OA and 20 controls	Knee/Hip	Not specified	**Inclusion**: age above 18 years and a history of at least six months of moderate to severe pain (VAS>5) **Exclusion**: acute illness, malignancy and/or current immune modulating therapy such as chemotherapy or corticosteroids	VAS Short Form-36 Intrathecally and blood concentrations of GDNF, IL-1β, TNF-α, IL-6, IL-10 and IL-8	1 assessment: no follow-up	Subjects with OA presented increased levels in the central nervous system of GDNF, but decreased in peripheral blood IL-8 was uniformly higher in OA patients, both peripherally and centrally, compared to controls Pain level in subjects with OA was associated with high and low levels of GDNF intrathecally and in blood, respectively	Small sample size

Moss et al. 2007	Treatment	RCT	38 subjects with knee OA	Knee	ACR criteria	**Inclusion**: mild to moderate pain from knee OA, knee OA following ACR classification and able to walk short distances, with or without an aid **Exclusion**: recent lower limb surgery, co-existing inflammatory or neurological conditions, altered sensation around their knee, or cognitive difficulties	PPT at local (i.e. most tender point on the medial aspect of the affected knee) and remote site (i.e. medial ipsilateral heel) Timed "Up & Go" test WOMAC	2 assessments: at baseline and following intervention* *3 interventions were applied to each subject in random order over three sessions: -Knee joint mobilization -Manual contact intervention -No-contact intervention	Significantly greater increase in PPT at knee and remote sites was observed following knee joint mobilization, compared to manual contact and no-contact interventions Knee joint mobilization reduced 'up and go' time significantly more than manual contact and no-contact interventions	Possible ceiling effect of treatment due to low baseline values in pain
Murphy et al. 2011a	Etiology	Cross-sectional	55 women with knee OA	Knee	Radiographic criteria	**Inclusion**: radiographic evidence of knee or hip OA(Kellgren/ Lawrence score ≥2), joint pain for at least 3 months in duration, and mild to moderate joint pain on the WOMAC pain scale **Exclusion**: non ambulatory patients, medical conditions other than OA that interfered with activity performance or caused pain and fatigue, joint replacement or surgery of the knee	OA radiographic severity (Kellgren/Lawrence grade, minimum joint space width) Age Pain severity over a 5-day home monitoring period Composite measure representing centrally-mediated symptoms* * It included fatigue severity, sleep efficiency	Repeated assessments of pain severity and centrally mediated symptoms during a 5-day home monitoring period	27% of the variance in pain severity was explained by age, radiographic severity, and centrally mediated symptoms Centrally-mediated symptoms explained an additional 10% of the variance in pain severity after the other 2 variables (age and radiographic severity), were entered	Highly selected sample which could have led to an underestimation of the association between centrally-mediated symptoms and pain severity Cross-sectional study design Small sample size and all subjects women Lack of QST

						or hip in the previous 6 months, inadequate cognition (by Mini-Mental State Examination or 6-Item Screener), inability to operate a wrist-worn accelerometer to measure sleep efficiency, or current non-pharmacologic treatment for OA (e.g. rehabilitation, injections)	and depressive symptoms			
Murphy et al. 2011b	Diagnosis	Cross-sectional	129 community living older adults with knee and hip OA	Knee/Hip	ACR criteria	**Inclusion**: pain in a joint with OA on the WOMAC scale of ≥ 4 with at least two of the five items on the scale rated as moderate pain or more, fatigue symptoms at least a moderate amount of the time (that is, three to four of the past seven days), adequate cognition, and able to see, hear and operate the accelerometer used for pain reporting in the study **Exclusion**: other medical conditions that are capable of causing fatigue (acute illnesses or exacerbations of chronic illnesses, including common viral or bacterial infections, autoimmune	Pain severity over a 5-day home monitoring period Center of Epidemiologic Studies Depression Scale Brief Fatigue Inventory Self-reported Illness burden* Pittsburgh Sleep Quality Index *It reflected the self-reported symptom load experienced by an individual and was calculated as the sum of 41 possible different somatic symptoms	1 assessment*: no follow-up *A hierarchical agglomerative cluster analysis was conducted	Three statistically differentiated subgroups/clusters of patients were characterized by differing symptom presentations, which may potentially be due to different pain mechanisms One group (36% of the sample) had the highest ratings on both pain and fatigue, the worst ratings on depressive symptoms and sleep and the highest illness burden, supporting a potential central nervous system contribution to symptoms	Unknown structural severity of knee and hip OA Results only applicable to people with symptomatic knee or hip OA

						diseases, fibromyalgia, chronic fatigue syndrome, and any uncontrolled illness), current treatment for cancer or treatment received for cancer in the previous 12 months, reported doctor-diagnosed obstructive sleep apnea, untreated anemia or thyroid disorders per blood work, or to be non-ambulatory				
O'Driscoll et al. 1974	Etiology	Case-control	21 subjects with hip OA awaiting total hip replacement, 12 subjects with hip OA but with insufficient symptoms to merit surgery, 22 subjects with hip OA after successful total hip replacement, and 21 controls	Hip	Radiographic criteria	**Inclusion**: radiographic changes in the joints of grades III or IV measured by reference to the Atlas of Standard Radiographs of Arthritis (Council for International Organizations of Medical Sciences, 1963) **Exclusion**: not specified	PPT at the centre of the forehead	2 assessment, before and after surgery	PPT at the centre of the forehead was significantly lower in subjects who required surgery than in controls. After successful surgery, the PPT rose to normal levels In subjects with few or no symptoms from their OA hips the PPT was high	Not specified
Parks et al. 2011	Etiology	Case-control	14 subjects with knee OA and 9 controls	Knee	ACR criteria	**Inclusion**: ACR criteria for OA, no history of other pain conditions, and OA pain for a duration longer than 3 months with a pain magnitude of at least 30/100 on VAS **Exclusion**: not	Ratings of spontaneous and evoked pain with application of mechanical painful pressure stimuli Brain activity with fMRI for spontaneous and stimulus-evoked	1 assessment, no follow-up for brain activity for spontaneous and stimulus-evoked pain 3 assessments for effect of treatment with COX2 selective inhibitor	Brain activity for pressure-evoked pain was minimally different between subjects with knee OA and healthy subjects and between knees with more or less pain among	Not specified

						specified	pain (i.e. pressure-evoked pain) Clinical characteristics of OA pain with Mc-Gill Pain Questionnaire and WOMAC Brain activity changes modulated by treatment with a COX2 selective inhibitor (COX2i, valdecoxib)	on brain activity: -Session 1: prior to the start of drug -Session 2: 24 hours after start of drug -Session 3: 2 weeks after continued use of drug	subjects with OA Brain activity associated with spontaneous pain in subjects with knee OA had a brain representation (prefrontal-limbic regions including the amygdala and nucleus accumbens), similar to that seen for spontaneous pain in other clinical chronic pain conditions (i.e. chronic low back pain)* * The latter engaging brain regions are involved in emotional assessment of the self so it was concluded that OA pain it's more of an emotional state Treatment with a COX2 selective inhibitor in subjects with knee OA decreased spontaneous pain for the worse knee and clinical characteristics of OA, which correlated positively with prefrontal-limbic brain activity	

Quante et al. 2008	Etiology	Cross-sectional	12 subjects with knee OA	Knee	Radiographic criteria	**Inclusion**: unilateral OA of the knee, radiological grade IV OA based on X-ray, pain for a minimum of 6 months limiting walking distance, presence of pain phases at rest, scheduled for an intraarticular infiltration, and instantaneous relief from OA pain obtained by a comfortable, slightly flexed knee position **Exclusion**: any previous spine surgery, any surgery or diseases of the peripheral and central nervous system, infectious, inflammatory or neoplastic diseases, epidural injections within one week prior to investigation, bilateral OA, or pain from other causes (i.e. migraine, neuropathy, etc)	DNIC function* *It was assessed by provoking OA pain by a slightly hyperextended joint position (counterirritation stimulus) while applying short electrical pain stimuli at the fingertip (middle finger) contralateral to the OA side DNIC effect on evoked brain activity with EEG and MEG	1 assessment, no follow-up	Dysfunction in DNIC Although the patients did not report a reduction of electrical pain perception, the cingulate gyrus showed a decrease of activation during provoked OA pain, while activity in the secondary somatosensory cortex didn't change	Small sample size
Vance et al. 2012	Treatment	RCT	75 subjects with knee OA	Knee	Radiographic criteria	**Inclusion**: diagnosis of medial compartment knee OA (radiographically and symptomatically diagnosed by an orthopedic surgeon), 18 to 95 years of age, able to ambulate to mailbox and back,	Cutaneous mechanical pain threshold PPT at knee and tibialis anterior bilaterally Heat pain threshold Heat temporal	1 assessment*, no follow-up Outcome measurements were obtained before and during a single TENS treatment. Participants were randomly assigned	Compared with placebo TENS, HF-TENS and LF-TENS increased PPT at the affected knee HF-TENS also increased PPT over the tibialis anterior muscle of	Only a single TENS treatment Possible influence of caffeine on the results

						stable medication schedule for 3 weeks before testing, and pain rating >3 during weight bearing on a verbal rating scale **Exclusion**: Lateral compartment knee OA, loss of sensation, uncontrolled diabetes mellitus or hypertension, dementia or cognitive Impairment, neurological disorder, permanent lower-extremity sensory loss, earlier TENS use, knee surgery in last 6 months, or knee injection in last 4 weeks	summation Timed "Up & Go" Test	to receive high-frequency(HF) TENS (100 Hz) (n=25), low frequency (LF) TENS (4 Hz) (n=25), or placebo TENS (n=25)	the affected knee There was no effect with any application of TENS on the cutaneous mechanical pain threshold, heat pain threshold, or heat temporal summation Pain at rest and during the Timed "Up & Go" Test was significantly reduced by HF-TENS, LF-TENS, and placebo TENS	
Wilder-Smith et al. 2001	Treatment	RCT	60 hip/knee OA subjects awaiting hip or knee replacement surgery randomized in two groups (30 receiving tramadol and 30 receiving dihydrocodeine) and 30 controls, with pain controlled by NSAID's alone* *Data were not evaluated in 1 and 2 subjects of the dihydrocodeine and tramadol	Hip/Knee	Not described	**Inclusion**: mean pain score of 3 or more during normal activity on a verbal rating scale of 0=none to 4=unbearable, in a 1 week run-in period despite current NSAID medication **Exclusion**: clinically relevant cardiopulmonary, hepatic, renal and mental compromise, known allergies against the study drugs, or drug abuse	Electrical 1st sensation and pain tolerance thresholds in the dermatome of the OA joint and mid-clavicle* Suprathreshold pain stimulation at affected OA joint and mid-clavicle* *Both measured on the 4th treatment day	2 assessments: during the run-in period before the start of study drug dosing and at the end of the 1st month of the treatment	In the treatment groups pain tolerance thresholds were lower before treatment and increased to values similar to controls during treatment. This antinociceptive effect was more pronounced with tramadol and mid-clavicularly and was significant after 1 month's treatment A significant inverse correlation	The potency estimation of the slow-release formulations may have been slightly biased by the availability of only fixed dose of each drug

			group, respectively						between baseline pain intensity and sensation and pain thresholds over the clavicle was found demonstrating a relationship between greater pain and generalized sensory sensitization	
Wood et al. 2007	Diagnosis	Cross-sectional	697 subjects divided in two groups: no symptomatic radiographic knee OA (n= 497) and symptomatic knee OA (n= 230)* *Symptomatic radiographic OA of the knee was defined as symptoms on most days in the previous month and definite osteophyte in index knee with current pain intensity of ≥ 2 on a NRS	Knee	Radiographic criteria	**Inclusion**: OA of the knee with some pain in the last year **Exclusion**: red flags' (recent trauma likely to be associated with significant tissue damage: acute, hot, swollen joint), not experienced knee pain within the 6 months prior to clinic attendance, pre-existing diagnosis of inflammatory arthropathy in the medical records, total knee replacement in their most affected knee, or incomplete X-ray data	Knee pain locations coded on a body chart Socio-demographic, radiographic and clinical features (WOMAC, Chronic Pain Grade, Hospital Anxiety and Depression scale)	1 assessment, no follow-up	Generalized knee pain and medial knee pain were the most common patterns among all the subjects Medial knee pain and generalized knee pain with distal radiation occurred more frequently in those with symptomatic knee OA Individuals with generalized knee pain with radiation had more persistent and severe pain, anxiety levels, and a relatively high proportion had moderate or severe radiographic disease* *This results were considered consistent with central sensitization	Heterogeneous sample Misclassification probability: definition of symptomatic knee OA didn't preclude other concomitant causes of knee pain Reliability of pain location data was not formally investigated

ACR: American College of Rheumatology; BMI: Body Mass Index; CMC: Carpo-metacarpal; CPM: Conditioned Pain Modulation; DNIC: Diffuse Noxious Inhibitory Control; EEG: electroencephalogram; fMRI: functional Magnetic Resonance Imaging; GDNF: Glial cell line-derived neurotrophic factor; MCP: Metacarpophalangeal; MEG: magnetoencephalogram; NFR: Nociceptive Flexion Reflex; NRS: Numerical Rating Scale; OA: Osteoarthritis; PPT: Pressure Pain Threshold; QST: Quantitative Sensory testing; RA: Rheumatoid Arthritis; VAS: Visual Analogue Scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Evidence for Central Sensitization in OA

Besides listing the search results and characteristics of included studies, the aim of this systematic review was to summarize the present knowledge on CS in OA. In the following section, the results of this review will be structured according to the different aspects of sensitization which have been identified in patients with OA.

Clinical manifestations of CS in OA

Three studies inferred CS based on neuropathic pain descriptors of symptoms (Gwilym et al., 2009; Hochman et al., 2010, 2011). Hochman et al. (2010) qualitatively assessed the OA pain experienced by 80 subjects with knee OA. A small subgroup of patients (i.e. 34% from the total), who used neuropathic pain descriptors was identified. Those who used neuropathic pain descriptors were mainly young women with high pain intensity, high OA severity and long OA duration. In a later study, a similar percentage of patients reporting neuropathic pain symptoms (i.e. 28% from a total of 171 subjects with knee OA) was found (Hochman et al., 2011). Gwilym et al. (2009) determined that the magnitude of activation in the periaqueductal grey matter of subjects with hip OA after punctuate stimulation of their referred pain areas was correlated with the extent of neuropathic pain symptoms.

Based on the location of the symptoms (Wood et al., 2007) and a positive correlation between OA pain severity and centrally-mediated symptoms (Murphy et al., 2011a, 2011b), some studies indicated a potential contribution of the central nervous system in subjects with OA. Wood et al. (2007) found that subjects with knee OA reporting generalized knee pain with radiation had more persistent and severe pain, and higher anxiety levels. Murphy et al. (2011a) measured pain severity and centrally mediated symptoms in women with knee OA. Age, radiographic severity, and centrally mediated symptoms explained 27% of the variance in pain severity reported by the patients. After

entering age and radiographic severity as variables, centrally-mediated symptoms explained an additional 10% of the variance in pain.

Arendt-Nielsen et al. (2010) showed how the degree of local (i.e. knee) and spreading (i.e. leg, arm) sensitization correlated with pain severity. However, no correlation was found between radiological findings and experimental or clinical pain parameters. Accordingly, Lundblad et al. (2008) demonstrated that elimination of the nociceptive input from the damaged joint (i.e. prosthetic substitution) was not always followed by a complete resolution of symptoms. Interestingly, subjects who reported a high pre-operative score for knee pain and low pre-operative pain thresholds were at increased risk of persistent pain after surgery.

Quantitative Sensory Testing results in OA

Seventeen studies in total performed quantitative sensory testing (QST) analysis as part of their outcome measures (O'Driscoll and Jayson, 1974; Farrell et al., 2000a, 2000b; Kosek and Ordeberg, 2000b; Wilder-Smith et al., 2001; Hendiani et al., 2003; France et al., 2004; Moss et al., 2007; Imamura et al., 2008; Lundblad et al., 2008; Gwilym et al., 2009; Arendt-Nielsen et al., 2010; Lee et al., 2011; Graven-Nielsen et al., 2012; Kavchak et al., 2012; Vance et al., 2012; Finan et al., 2013). Different QST modalities were used for evaluating sensory and pain perception, with the mechanical stimulus being the most common form of external stimulation used (14/17 studies) (Farrell et al., 2000a, 2000b; Kosek and Ordeberg, 2000b; Hendiani et al., 2003; Moss et al., 2007; Imamura et al., 2008; Gwilym et al., 2009; Arendt-Nielsen et al., 2010; Lee et al., 2011; Graven-Nielsen et al., 2012; Kavchak et al., 2012; Vance et al., 2012; Finan et al., 2013). Most of the studies performed QST at local (i.e. on or in close proximity to the

joint affected by OA), and distant sites (i.e. remote from the affected joint) (Kosek and Ordeberg, 2000b; Hendiani et al., 2003; France et al., 2004; Moss et al., 2007; Imamura et al., 2008; Arendt-Nielsen et al., 2010; Graven-Nielsen et al., 2012; Kavchak et al., 2012; Vance et al., 2012; Finan et al., 2013).

Several studies reported more local and widespread hyperalgesia in subjects with OA compared to controls (Farrell et al., 2000a, Kosek and Ordeberg, 2000b; Imamura et al., 2008; Arendt-Nielsen et al., 2010; Lee et al., 2011; Graven-Nielsen et al., 2012; Kavchak et al., 2012). In addition, a higher degree of general sensitization was related to higher levels of pain perception (Farrell et al., 2000a; Wilder-Smith et al., 2001; Imamura et al., 2008; Arendt-Nielsen et al., 2010; Finan et al., 2013), disability and poorer quality of life (Imamura et al., 2008), poor prognosis after joint replacement (Lundblad et al., 2008), less radiographic evidence of OA (Finan et al., 2013), and high serum concentration of pro-inflammatory cytokines (Lee et al., 2011). Improvements of widespread hyperalgesia were reported after surgery (O'Driscoll and Jayson, 1974; Kosek and Ordeberg, 2000b, Graven-Nielsen et al., 2012), mobilization of the affected joint (Moss et al., 2007), TENS application (Vance et al., 2012), and medication (Wilder-Smith et al., 2001).

Allodynia both locally (Hendiani et al., 2003; Kavchak et al., 2012) and extensively (Kosek et al., 2000b), was shown to be present in OA subjects as compared to controls. Hypoesthesia was also higher in patients with OA (Hendiani et al., 2003; Gwilym et al., 2009; Kavchak et al., 2012), but only at the affected joint.

Induced Referred pain in OA

Only one study examined the phenomenon of evoked referred pain in subjects with OA (Bajaj et al., 2001). Compared with controls, subjects with OA showed significant higher local pain duration and intensity, larger pain areas, and increased referred and radiating pain intensities after intramuscular hypertonic saline infusion.

Altered Spinal Reflexes in OA

Three studies used the Nociceptive Flexion Reflex (NFR) to investigate possible disturbances in nociceptive processes (Emery et al., 2006; Courtney et al., 2009, 2010). Increased excitability of NFR was found in subjects with chronic knee OA compared to controls (Courtney et al., 2009). In a later study, NFR responses markedly augmented after applying joint compression, whereas joint mobilization (but not sham intervention) reduced NFR excitability (Courtney et al., 2010). Emery et al. (2006) showed an increase in NFR thresholds and decrease on pain ratings following a 45-minute coping skills treatment session.

Enhanced Temporal or Spatial Summation of pain in OA

Two case-control studies reported enhanced TS in subjects with knee OA compared to healthy controls (Graven-Nielsen et al., 2012; Goodin et al., 2013). Goodin et al. (2013) assessed the relation of TS of heat pain with clinical measures like dispositional optimism, pain catastrophizing and depression. A greater dispositional optimism was found to be associated with less pain catastrophizing and less TS of heat pain.

The only study which showed enhanced SS of pressure-pain in subjects with knee OA was conducted by Graven-Nielsen et al. (2012). It is worth emphasizing that they found restoration of SS ratios following knee joint replacement surgery.

Dysfunctional endogenous nociceptive inhibition in OA

Descending modulation of pain has been evaluated through the conditioned pain modulation (CPM) paradigm which assesses the efficiency of descending pain inhibitory mechanisms. Five studies provided evidence for impaired CPM in subjects with OA (Kosek and Ordeberg, 2000a; Quante et al., 2008; Arendt-Nielsen et al., 2010; Graven-Nielsen et al., 2012). In addition, Kosek et al. (2000a) and Graven-Nielsen et al. (2012) demonstrated restoration of impaired CPM after surgery. Ischemic compression of the arm with a tourniquet cuff was used as conditioning stimuli in all (Kosek and Ordeberg, 2000a; Arendt-Nielsen et al., 2010; Graven-Nielsen et al., 2012), except for one study (Quante et al., 2008). Experimental stimuli (dependent variable) consisted of pressure pain (Arendt-Nielsen et al., 2010; Graven-Nielsen et al., 2012), electrical induced pain (Quante et al., 2008), or a combination of thermal and pressure pain (Kosek and Ordeberg, 2000a).

Dysfunctional opioid and non-opioid mechanisms of pain control in OA

In order to further unravel the role of CS in patients with OA, two randomized controlled trials evaluated the efficacy of centrally acting drugs (Chappell et al., 2009; Abou-Raya et al., 2012). Abou-Raya et al. (2012) and Chappell et al. (2009) found a significant reduction on pain after duloxetine administration compared to placebo supporting a role of CS in OA.

Altered Cytokine and Neuropeptide concentrations in OA

One study highlighted the relationship between central pain processing and the inflammatory response in OA by identifying associations between psychophysical pain measures (i.e. QST) and proinflammatory cytokine levels (Lee et al., 2011). Low PPTs

taken at remote sites from the affected joint and high suprathreshold heat pain ratings were associated with elevate C-reactive protein and IL-6 serum levels (Lee et al., 2011).

Intrathecal and blood concentrations of Glial cell line-derived neurotrophic factor (GDNF), IL-1B, TNFα, IL-6, IL-10 and IL-8 were compared between subjects with OA and controls by Lundborg et al. (2010). Subjects with OA presented higher central nervous system levels of GDNF and IL-8 than controls and pain level was associated with high levels of GDNF (Lundborg et al., 2010).

Neuroimaging

Five studies reported alterations in brain function in subjects with chronic OA pain (Kulkarni et al., 2007; Quante et al., 2008; Gwilym et al., 2009; Parks et al., 2011; Howard et al., 2012). Gwilyn et al. (2009) observed greater activation in periaqueductal grey matter in OA subjects in response to punctate stimulation of their referred pain areas. In another study, brain activity associated with spontaneous OA pain had a brain representation consisting of the prefrontal-limbic region, which is a brain region known to be involved in emotional self-assessment (Parks et al., 2011). Areas involved in the processing of fear, emotions, aversive conditioning and motivational responses (i.e. medial pain system of the brain), showed increased activity with positron emission tomography (Kulkarni et al., 2007). Quante et al. (2008) observed a decreased activation of the cingulated gyrus during provoked OA pain. Lastly, another study paid attention to patterns of regional cerebral blood flow changes in subjects with 1st CMC joint OA (Howard et al., 2012). An increase in regional cerebral blood flow in brain areas related to evaluation of threat to the body from ongoing pain and descending modulatory mechanisms was observed.

Only one study conducted by Gwilyn et al. (2010) revealed changes in brain structure in subjects with hip OA. A significant decrease in gray matter volume (i.e. thalamus) was observed, which was reversible after surgery and was accompanied with improvements on pain and function. Although not detected within our search strategy, a recent study by Baliki et al (2011) reported specific changes in the cortical gray matter in subjects with knee OA using MRI. Brain reorganization in OA patients was unique to this condition, enabling to differentiate their "brain signature" from others (chronic back pain, complex regional pain syndrome) with high accuracy.

Psychosocial influences in OA

Three studies considered psychosocial factors related to OA pain (France et al., 2004; Emery et al., 2006; Goodin et al., 2013). Emery et al (2006) observed more reduction in anxiety levels in women with knee OA compared to men, immediately after a coping skills training intervention, accompanied by an increase of the NFR threshold and a decrease of pain ratings.

Catastrophizing and emotional-focused coping strategies were associated with higher pain and lower pain threshold and tolerance levels locally, but not with NFR (France et al., 2004). Goodin et al. (2013) showed how greater dispositional optimism was associated with less catastrophizing and less TS of heat pain.

DISCUSSION AND CONCLUSIONS

The goal of this paper was to review and evaluate the existing scientific literature regarding the role of CS in chronic OA pain. Different assessment methodologies were utilized for evaluating the phenomenon of CS, aiming to understand the different changes in pain sensibility observed in this population. Overall results from our systematic review seem to support a key role of CS in chronic pain related to OA.

The term CS is not really "yes" or "no" but it occurs at different degrees over a continuum, from a little to a lot. For instance, in some patient populations, CS may be the characteristic feature of the disorder (e.g. fibromyalgia). In others, such in OA, not all patients have CS, but only a sub-group. Although peripheral mechanisms in OA pain are undeniable, our review disclosed a subgroup of subjects (around 30% of OA patients), with CS contributing to their clinical picture (Hochman et al., 2010, 2011; Murphy et al., 2011b). This was corroborated by means of different subjective (i.e. persistent pain complaints, presence of centrally mediated symptoms, neuropathic pain descriptors), and objective parameters (i.e. widespread hyperalgesia and allodynia, enlarged radiation of pain, altered spinal reflexes, abnormal spatial and temporal summation, impaired descending inhibition, enhanced descending facilitation, and brain changes). It should be acknowledged that some of these findings (i.e. enhanced temporal summation or reduced pain inhibition based on QST), provide direct evidence of CS in OA (Arendt-Nielsen and Graven-Nielsen, 2011). However, other findings (i.e. neuropathic pain descriptors, presence of symptoms such as sleep disturbance), are frequently seen but not exclusively in patients with CS so they only offer indirect evidence of hypersensitivity of the central nervous system in OA. Similar findings characteristic of CS have been previously reported in other chronic pain conditions such as whiplash (Van Oosterwijck et al., 2013) or rheumatoid arthritis (Meeus et al., 2012), suggesting these conditions are bound by the similar mechanism of altered central pain processing.

Modulation of central hyperexcitability occurred after implementation of different locally treatment modalities like manual therapy (Moss et al., 2007; Courtney et al.,

2010), TENS (Vance et al., 2012), joint replacement surgery (O'Driscoll and Jayson, 1974; Kosek and Ordeberg, 2000b; Graven-Nielsen et al., 2012), or medication (Wilder-Smith et al., 2001). This is in line with the acknowledged modulation of CS by peripheral nociceptive input observed in other chronic pain populations (Staud, 2010). Apart from one study (Emery et al., 2006), interventions specifically addressing descending facilitatory (e.g. cognitive-behavioral therapy), or descending inhibitory mechanisms (e.g. exercise therapy), were not identified in the OA literature. More research should examine the effect of treatment modalities and their influence on outcome measures related to CS in OA.

Supraspinal descending facilitatory influences are able to modulate central hypersensibility and influence the results of QST (Zusman, 2002). Only Goodin et al. (2013) assessed the impact psychosocial factors could have on psychophysical measures of CS. More research is warranted to examine the precise influence of psychological factors on the processing of sensory input in patients with OA, and hence to study cognitive-emotional sensitization in these patients (Brosschot, 2002).

Clinical and laboratory methods employed for diagnosing potential involvement of CS in musculoskeletal pain conditions are diverse (i.e. QST, brain imaging techniques, efficacy of centrally acting drugs). All of them assessed the same underlying biological concept (CS), but in its different manifestations related to the different aspects of sensitization (Graven-Nielsen and Arendt-Nielsen, 2010). For instance, widespread hyperalgesia, which is a manifestation of CS, can be assessed quantitatively in a standardized way using sensory tests, such as pressure algometry. The majority of the studies of the current review identified pain hypersensitivity within laboratory

conditions, using costly and unattainable equipment for clinicians. Therefore, evidence-based clinical strategies to more readily and systematically identify CS in OA pain are needed (Lluch Girbés et al., 2013).

Although the quality criteria used for assessing the risk of bias of the selected studies has proven to generate reliable data (Van Oosterwijck et al., 2013) and has been used previously to examine the presence of central sensitization in another chronic pain population (Van Oosterwijck et al., 2013), some issues remain. For instance, a wash-out period could be considered a strength or a weakness: having patients wash-out could itself induce CS, depending on what medications they are using. On the other hand, enrolling only those patients who are able and willing to discontinue medication use can bias the study toward patients with less severe symptoms who are less likely to show CS. These are important considerations for future research in this area.

Based on the methodological issues identified in the existing studies, future study designs should use a sufficient and justified sample size and report validity and reliability of outcome measures used. Prevention of bias by including a wash-out period before starting data collection is warranted. Finally, description of the blinding procedure is recommended, and a follow-up period should be included to evaluate the role of central alterations on the long-term.

Some limitations need to be acknowledged in this review. First, the screening of the literature databases and selection of studies was carried out by only one assessor, which implies that some relevant studies may have been excluded. Still, the methodological screening of the selected studies was conducted by two blinded researchers. Studies

assessing the phenomenon of CS in animal models were excluded, based on the observation that animal models do not closely mirror the human condition (Arendt-Nielsen et al., 2007). Finally, the majority of the selected studies addressed OA of the knee joint. Hence, care must be taken to extrapolate the results of this review to all OA patients.

In conclusion, the majority of the literature reviewed suggests that the CNS becomes hypersensitized in subjects with chronic OA pain, and that the phenomenon of CS plays a crucial role in the pain complaints reported by these patients. However, both clinical identification and treatment of CS in OA is still in its infancy, and more human research with a good methodological quality is warranted.

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PAIN TREATMENT FOR PATIENTS WITH OSTEOARTHRITIS AND CENTRAL SENSITIZATION

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ABSTRACT

Osteoarthritis is one of the most frequent, disabling and costly pathologies of modern society. One of the main aims of osteoarthritis management is pain control and functional ability improvement. The exact cause of osteoarthritis pain remains unclear. In addition to the pathological changes in articular structures, changes in central pain processing or central sensitization appear to be involved in osteoarthritis pain. The latter calls for a broader approach to the management of patients with osteoarthritis. Yet the scientific literature offers few information addressing the treatment of central sensitization specifically in osteoarthritis patients. Interventions like cognitive-behavioral therapy and neuroscience education potentially target cognitive-emotional sensitization (and descending facilitation), while centrally acting drugs and exercise therapy can improve endogenous analgesia (descending inhibition) in patients with osteoarthritis. Future studies should assess these new treatment avenues.

Key words: osteoarthritis, pain, central sensitization, neuroscience education, exercise therapy, graded activity.

INTRODUCTION

Osteoarthritis (OA) is one of the most common rheumatologic conditions in our society[1,2], which affects over 80% of the population beyond the age of 55[3]. Two of the most commonly affected joints are the knees and the hips, sharing a predominantly load-bearing function[4]. Individuals with OA often suffer from chronic pain, which causes a great deal of disabilities and significant healthcare costs[5]. Unfortunately, at present, both the causes of the pain as well as the most effective treatment have not yet been established[6,7].

Historically, OA pain has been considered a nociceptive pain related to the degree of structural damage to the affected joint. Since the cartilage, under normal physiological conditions, is an avascular and aneural tissue, the issue of whether pain could come from other joint structures was raised. Thus, OA pain has been attributed to deformation of the periarticular tissues[8] and the subchondral bone[9], increased intraosseous pressure[10], synovial inflammation[11] or injuries to the bone marrow[12]. OA pain has also been described as a chronic inflammatory response[13], partly caused by an up-regulation of Na+ channels[14] and local production of nitric oxide (NO), associated with the degeneration of the joint cartilage[15].

Recently, OA has been considered as a hypertrophic arthritis[6] in order to differentiate it from the atrophic arthritis typical of rheumatoid arthritis. This is due to the fact that, apart from cell death of chondrocytes and loss of joint cartilage, the production of new tissue has been observed in OA, including fibrocartilage. Hence, in an attempt of the cartilage to regenerate, an increase in protein synthesis by the chondrocytes has become

evident, especially in the initial stages[16]. Moreover, the osteochondral angiogenesis derived from expression of growth factors (e.g. vascular endothelial growth factor and platelet-derived growth factor) has been proposed as a factor that could facilitate the chronicity of pain in OA[17,18]. Furthermore, literature has described cases of patients suffering from OA with satisfactory results after treating myofascial trigger points, which indicates that musculoskeletal tissues may also play a part in the pain related to OA[19].

Since OA is an incurable pathology, therapeutic objectives usually focus on maximizing patient´s function and quality of life, while keeping pain under control and minimizing the adverse effects derived from the use of medication[6,20,21]. Non-steroidal anti-inflammatory drugs (NSAIDs) can be beneficial in initial stages but in time they become inefficient, being the administration of other medication such as amitriptyline or gabapentin more advisable[22]. This phenomenon might be related to the fact that chronic pain in OA is more related to neuroplastic changes in the nervous system than to an inflammatory condition of the joint[22]. Those who do not respond well to conservative treatment usually end up with a prosthetic restoration of the affected joint[20,21]. However, surgery does not always imply a complete resolution of symptoms[23].

OSTEOARTHRITIS PAIN

The understanding of pain in OA, its modulation and treatment is central to physical therapists practice as they usually manage patients affected by this disease. Although pain is a very common complaint in OA, there is scarce knowledge on the etiology,

mechanisms and treatment of OA pain by healthcare professionals[24]. General trend is for healthcare professionals to consider OA pain as a reliable "informant" of what is happening at peripheral tissue level. Thus, greater joint degeneration is used to be associated with greater pain. Nevertheless, there are different arguments that make it difficult to explain OA using exclusively a "peripheral model" of pain. It has been proven, for instance, that radiological changes identified in OA patients are not always consistent with pain[25-28], although there are studies that do prove this correlation[29,30]. The great inter-individual variability on pain severity and the unclear relationship between pain and structural damage have raised the issue of the existence of other mechanisms responsible for the pain in OA. At present, peripheral sensitization and, especially, central sensitization, have been proposed as two of the mechanisms underlying pain in OA[24,31,32], as in other chronic musculoskeletal pain conditions[33,34]. Indeed, there's a growing body of research involving pain mechanisms in OA being central pain mechanism an issue discussed in several reviews during the last years [6,24,31,32,34,35].

Mechanisms involved in central sensitization have been shown across several chronic conditions, which have been recently grouped together under the term central sensitivity syndromes (CSS)[36,37]. This novel unifying concept is now emerging as a single common set of central nervous system (CNS) processes[38] and has been proposed to include chronic painful conditions that are based on central sensitization as fibromyalgia, irritable bowel syndrome or temporomandibular disorder. For the moment, OA pain has not been included on such list because the role of central sensitization in OA is still in his infancy. Yet here we advocate that increasing evidence supports the inclusion of OA

in the group of CSS. The hallmark of these 'centrally driven' pain conditions is a diffuse hyperalgesic state identifiable using experimental sensory testing (i.e. Quantitative sensory testing[39]) and corroborated by functional neuroimaging[40]. The characteristic symptoms of these central pain conditions include multifocal pain, fatigue, insomnia, memory difficulties and a higher rate of co-morbid mood disorders[36].

CSS is an important new concept that also embraces the biopsychosocial model of disease. In this sense, OA pain experience is multidimensional fitting well with the biopsychosocial model, which reflects the influence of biological (i.e. structural changes), psychological (i.e. mood and coping), and social factors (i.e.social support) in the individual symptoms and suffering. Several psychosocial variables (i.e. catastrophizing, high level of depression, cognition about pain, etc.) have been suggested as influencing OA pain and disability[41]. Psychosocial interventions as cognitive behavioral therapy (CBT) or activity pacing may decrease OA pain and disability[42-45]and studies addressing the effects of combined physical and physocological approaches in OA pain are being conducted[46,47].

OSTEOARTHRITIS AND CENTRAL SENSITIZATION

In last decades, great progress has been made in the knowledge of pain. Nowadays, it is clear that the majority of chronic musculoskeletal pain conditions are characterized by an alteration in pain processing by the CNS[34]. More specifically, sensitivity of central neurons to inputs coming from the unimodal and polimodal receptors increase, which results in a physiopathological condition called central sensitization, characterized by a general or extended hypersensitivity. Central sensitization is defined as "*an increased response of CNS neurons which inform of pain when faced with inputs coming from low*

threshold mechanoreceptors"[48]. However, central sensitization not only refers to spinal cord sensitization or amplification of the afferent impulses coming from the periphery. It also includes an alteration of sensory processing in the brain[49], loss of descending anti-nociceptive mechanisms[50], enhanced facilitatory pain mechanisms, increased temporal summation or wind-up[51] and long-term potentiation of neuronal synapsis in the anterior cingulate cortex[52]. Pathophysiological mechanisms underlying central sensitization are complex and numerous, but the net effect is an amplification of neural signaling within the CNS than elicits pain hypersensitivity[34.]

Central sensitization is present in different chronic musculoskeletal conditions such as whiplash trauma[53], chronic low back pain[54], fibromyalgia[55] or, more recently, in OA[6,24,31,32,35] which concerns us here. One of the factors that favor the development of central sensitization in OA is the massive and repetitive nociceptive input coming from peripheral joint nociceptors arriving to dorsal horn neurons in the spinal cord. Therefore, intense and continued nociceptive input proceeding from an OA joint may cause central sensitization, as shown in different studies[56-58]. Presence of central sensitization entails greater complexity of the clinical picture[59] and less possibilities of achieving positive results with physical therapy treatment[60.]

Patients with OA quite often present referred pain and changes in skin sensitivity in remote areas with respect to the affected joint. There are various theories on referred pain, but they all include a higher centers misinterpretation of the peripheral origin of

nociception[61.] Referred pain is a phenomenon attributed to central sensitization so its presence in OA is highly indicative of changes in pain processing in the CNS.

Another phenomenon associated with central sensitization is secondary hyperalgesia. While primary hyperalgesia or peripheral sensitization involves an increased sensitivity of peripheral nociceptors in response to tissue damage, secondary hyperalgesia correspond to increased sensitivity of dorsal horn neurons, located in the spinal segments corresponding to the primary nociceptive source. Peripheral sensitization is a local phenomenon, while secondary hyperalgesia is a central process of the nervous system. Regarding OA, different studies have shown an increase in nociceptive transmission in dorsal horn neurons, typical of secondary hyperalgesia[62,63]. Im et al[7] provided key in vivo evidence that OA pain is caused by central sensitization through communication between peripheral OA nociceptors and the central sensory system. They observed that structural changes in components of the peripheral knee joint correlated with alterations in the central compartments (dorsal root ganglia and the spinal cord) and symptomatic pain assessed by behavioral hyperalgesia.

Apart from referred pain and secondary hyperalgesia, there is further evidence in scientific literature that shows how pain in OA can be modulated through mechanisms related to the CNS. It has been found, for instance, that OA not only causes a decrease in pain thresholds in the affected joint, but also far from it in remote and over extended areas[64,65]. Loss of descending pain inhibitory mechanisms[64,66], increase of temporal summation (increase of painful response to repetitive stimulation)[66] as well as the presence of extended areas of hyperalgesia in patients with OA[66,67,68], further support

the role of central sensitization in OA pain. Moreover, it is important to remember that patients with chronic musculoskeletal pain conditions usually present generalized hyperalgesia in deep tissues and an increased response to experimental painful stimulation[69,70].

Recent evidence of the role central sensitization plays in OA pain comes from a study by Arendt-Nielsen et al[71] who conducted a protocol of pain assessment in subjects with knee OA. Widespread hyperesthesia, enhanced spatial summation and loss of conditioned pain modulation (CPM) were observed which imply sensitized central pain mechanisms in these patients. Moreover, all these measurements were normalized following joint replacement which implies that these central pain processes were maintained by peripheral input.

Various animal studies have shown the contribution of the spinal glial cells to central sensitization associated with OA[72]. Glial cells are crucial in the onset and maintenance of central sensitization, especially in relation to neuropathic pain. Activated glial cells (microglia and astrocytes) in the spinal cord can contribute to central sensitization by producing pro-inflammatory cytokines, complement factors and cyclo-oxygenase (COX) type 1 and 2 inside the CNS. Their participation in OA pain indicates that mechanisms underlying neuropathic and osteoarthritis pain might be similar[22.] Still, these animal observations require confirmation in human studies.

One of the characteristics of central sensitization is that, once installed, it can persist in time despite the lack of new painful stimuli from the periphery. In clinical practice, it is not uncommon to find patients with OA who show symptoms even after prosthetic substitution. It has been noted that patients suffering from OA with a high degree of pain and low pain thresholds before surgery run a greater risk of continued pain after getting a prosthetic knee, which has been interpreted as an accurate reflection of central sensitization[23].

The effect of certain centrally acting drugs like duloxetine on OA pain[73,74] and the result of various studies carried out with functional Magnetic Resonance Imaging (fMRI) have further consolidated the role of central sensitization in this pathology. Duloxetine is a serotonin and norepinephrine reuptake inhibitor drug activating descending noradrenergic descending pathways together with serotonergic pathways[75]. fMRI is a valid test that identifies how and where the pain is processed in the brain and how this process varies for different patients[76,77]. Studies using fMRI have shown an increased activity of the periaqueductal gray in patients with OA, in comparison with healthy subjects[78]. This has been interpreted as increased activity of descending facilitatory pain mechanisms (a mechanism with the same net effect as decreased descending analgesia). Pain of knee OA is processed in areas related with emotions and fears[79] and activates pain areas of the prefrontal limbic region[80], which is also typical of other chronic musculoskeletal conditions such as low back pain[81.] These areas are involved in the emotional evaluation of one´s surroundings[82,] thus confirming that chronic pain is an emotional state. This view applies to OA pain, as already noted by Kulkarni et al[79]. Table 1 summarizes the currently available evidence regarding central sensitization in OA pain.

With regard to central sensitization in patients with OA pain, there is still much to discover. Notably, we need to determine which contributing genetic and environmental factors increase the risk of developing central sensitization, precisely what triggers and maintains this phenomenon and what is the responsible factor of its persistence in some individuals[34]. However, identifying the contribution of central sensitization to many painful clinical conditions, "inexplicable" until some time ago, has marked an important shift in clinicians' thinking model and has favored the development of new therapeutic strategies[83].

Table 1. Summary of current evidence regarding central sensitization in osteoarthritis pain. fMRI (functional Magnetic Resonance Imaging).

	Year of publication	Experimental model	Joint under study	Evidence of central sensitization
O´Driscoll et al[65]	1974	Human	Hip	Extended and remoted areas of hyperalgesia from affected joint.
Neugebauer et al[57]	1993	Animal	Knee	Dorsal horn sensitization (secondary hyperalgesia)
Kosek et al[64]	2000	Human	Hip	Extended and remoted areas of hyperalgesia from affected joint Loss of descending pain inhibitory mechanisms
Bajaj et al[67]	2001	Human	Lower extremitity	Extended and remoted areas of hyperalgesia from affected joint
Sharif et al[63]	2005	Animal	Ankle	Dorsal horn sensitization (secondary hyperalgesia)
Ivanivicius et al[22]	2007	Animal	Knee	Contribution of spinal glial cells to pain
Kulkarni et al[79]	2007	Human	Knee	fMRI
Martindale et al[56]	2007	Animal	Knee	Dorsal horn sensitization (secondary hyperalgesia)
Pinto et al[62]	2007	Animal	Ankle	Dorsal horn sensitization (secondary hyperalgesia)
Imamura et al[68]	2008	Human	Knee	Extended and remoted areas of hyperalgesia from affected joint
Lundbland et al[23]	2008	Human	Knee	Persistence of pain after prosthetic substitution
Chappell et al[73]	2009	Human	Knee	Positive effects of centrally acting drugs
Gwilym et al[78]	2009	Human	Hip	fMRI
Arendt-Nielsen et al[66]	2010	Human	Knee	Extended and remoted areas of hyperalgesia from affected joint Loss of descending pain inhibitory mechanisms
Im et al[7]	2010	Animal	Knee	Communication between peripheral OA nociceptors and the central sensory system
Hochman et al[97]	2010	Human	Knee	Neuropathic pain descriptors of symptoms

Abou-Raya et al[74]	2011	Human	Knee	Positive effects of centrally acting drugs
Parks et al[80]	2011	Human	Knee	fMRI
Murphy et al[85]	2011	Human	Knee/Hip	Identification of subgroup of patients with symptoms suggesting central sensitization
Murphy et al[86]	2011	Human	Knee	Identification of subgroup of patients with symptoms suggesting central sensitization
Sagar et al[72]	2011	Animal	Ankle	Contribution of spinal glial cells to pain
Hochman et al[98]	2011	Human	Knee	Neuropathic pain descriptors of symptoms
Arendt-Nielsen et al[71]	2012	Human	Knee	Widespread hyperesthesia, enhanced spatial summation and loss of conditioned pain modulation

IDENTIFICATION OF CENTRAL SENSITIZATION IN PATIENTS WITH OSTEOARTHRITIS

For some physical therapists, central sensitization is a theoretical concept, difficult to apply in daily clinical practice. Some have even come to believe that it is a phenomenon that can rarely occur in their patients, which contradicts reality. Unfortunately, there is currently neither an international consensus definition nor a set of valid clinical criteria for the diagnosis of central sensitization. In other words, the diagnosis of central sensitization in patients with chronic musculoskeletal pain cannot be given directly and clinicians should rely on symptoms and signs suggestive of central sensitization pain.

A recent study has shown how physical therapists can use information obtained from the medical diagnosis, patient´s medical record, physical examination and treatment response, in order to clinically identify central sensitization in patients with musculoskeletal pain[84]. Not all OA patients are characterized by central sensitization thus probably constituting a subgroup within this pathology[85]. Murphy et al[85] identified, in a heterogeneous sample of patients suffering from hip and knee OA, a small subgroup (36%) with symptoms suggesting central sensitization (widespread pain, fatigue, sleep disturbance and cognitive difficulties). However, no attempt was made to see if those symptoms were manifestations of OA or other comorbid conditions such as fibromyalgia. In a recent study Murphy et al[86] showed how 27% of the variance in pain severity in women with knee OA was explained by age, radiographic severity, and centrally-mediated symptoms. Centrally-mediated symptoms explained an additional 10% of the variance in pain severity after the other 2 variables were entered. Both radiographic severity and centrally-mediated symptoms were independently and significantly associated with pain severity. In addition to more severe radiographic features, women with higher centrally-mediated symptoms had greater pain severity.

Although studies by Murphy et colleagues have provided some evidence that patients with greater central pain contributions can be identified in routine clinical practice, the implications of this involvement in OA are just starting to be realized and larger longitudinal studies are needed. Evidence-based strategies are still needed to more readily and systematically identify these patients. Guidelines for the recognition of CS in patients with musculoskeletal pain like OA have been presented[84], and are currently being updated and upgraded towards the first international diagnostic criteria for CS in patients with musculoskeletal pain. Development of these diagnostic criteria should represent an improvement in the field and constitute an important step toward facilitating the acknowledgement and recognition of CS as a disease.

There are some classification systems based on pain mechanisms described in scientific literature[87-91]. In them, a classification of the patient´s pain is attempted according to the neurophysiological mechanism responsible for the generation or maintenance of pain[90-93]. Therefore, starting with a set of signs and symptoms, patients are classified in three groups: nociceptive pain, peripheral neuropathic pain and pain due to central sensitization. This, in theory, allows us to establish the most adequate treatment strategy and improve outcomes[87]. One of the advantages of such classifications is that they offer a better explanation of variations observed in the nature and severity of many clinical presentations of musculoskeletal pain disorders like OA, where pain can be present without pathology, pathology without pain or persistent pain despite resolution of pathology. Reliability and discriminating validity of these classification systems have been documented recently in relation to lower back and lower limb pain[94-96]. However, whether or not these results can be extrapolated to a population with OA is unknown.

Central sensitization has also been inferred from OA in humans in terms of neuropathic pain descriptors of symptoms. Hochman et al. recently identified in a sample of subjects with chronic pain due to knee OA, a small subgroup who used subjective descriptors of pain suggesting neuropathic pain[97]. The neuropathic pain subgroup mainly comprised of young women with greater pain intensity and severity, and longer duration of pain[97]. Using specific questionnaires also allowed identification of a neuropathic pain component in patients with OA[98].

In order to understand exactly the role central sensitization plays in patients with OA, it could prove useful to evaluate the response to interventions specifically addressing alterations in central pain processing. Moreover, OA patients having clear signs and symptoms of central sensitization (.i.e. a patient with hip OA with widespread pain, hypersensitivity to bright light and intolerance to stress) can be treated differently. Once the physical therapist concludes that central sensitization rather than the local joint destruction dominates the clinical picture of the patient with OA, then the treatment focus should be reset on the CNS (i.e. diminishing the hypersensitivity of the CNS). Apart from pharmacological treatments mentioned above (i.e. centrally-acting drugs), other treatments addressing cognitive-emotional sensitization such as CBT or neuroscience education should be taken into consideration[99]. However, until now, these types of interventions have been underestimated in patients with OA[100]. Finally, education can be combined with graded exercise therapy/graded activity and stress management to design a comprehensive rehabilitation program targeting central sensitization in patients with OA. These interventions will be explained below.

NEUROSCIENCE EDUCATION: A FUTURE TOOL IN OSTEOARTHRITIS?

Traditional rehabilitation treatments for OA are typically directed to the periphery (i.e. joint and surrounding structures) through interventions such as joint injections, joint protection, analgesic medication, manual therapy, exercise or TENS. Techniques used to manage pain as manual therapy[101,102], exercise or Transcutaneous Electrical Nerve Stimulation[103] can potentially target central sensitization by modulating pain and desensitizing the CNS[35,99], although its effects on central sensitization are unclear .Moreover, therapeutic strategies addressing symptom experience that accompanies OA pain (i.e. sleep disturbance, depression, fatigue) as CBT or CBT-guided and activity pacing, could also act on central factors contributing to pain in OA.

One recently intervention used to desensitize CNS is Neuroscience Education (NE). NE is an educational intervention aiming to reduce pain and disability, by explaining patient the biological processes underlying their pain condition. Its use is recommended in central sensitization conditions, where the patient presents mal-adaptive cognitions, behavior or coping strategies in response to pain[104]. In contrast to educational programs commonly used in rehabilitation that apply pathoanatomical and biomechanical models to explain the pain (focusing on the tissues and tissue damage), NE describes how the nervous system interprets information coming from the tissues through peripheral sensitization, central sensitization, synaptic activity and cortical processing. Conventional biomedical models not only have a limited efficiency in decreasing pain and disability[105,106], but they can also prove counterproductive since they increase patient´s fear, anxiety and stress, which can also increase the pain[107-109].

From a clinical perspective, it is a challenge to put into practice scientific knowledge related to central sensitization and chronic pain. Clinical guides are now available that provide information for explaining central sensitization, describing how to perfom a NE session/s with patients suffering from chronic musculoskeletal pain[104]. A systematic review of the effect of NE on pain, disability and stress in patients with chronic musculoskeletal pain has recently been published[110]. In this review it was concluded that there is convincing evidence that NE has positive effects on pain, disability, catastrophizing and physical performance in patients with chronic musculoskeletal pain. Moreover, structure, content and evidence of treatment with NE for different chronic conditions are detailed elsewhere[104,110]. Nonetheless, one of the limitations of this review is that evidence only exists for very specific pathologies such as chronic low back pain, chronic fatigue syndrome, fibromyalgia or chronic whiplash trauma. It remains to be established whether these findings can be extrapolated to other musculoskeletal pain conditions like OA. Hence, future studies should specifically evaluate efficacy of interventions addressing psychosocial aspects in OA like NE as has already been done with CBT or activity pacing. Moreover, one of the challenges clinicians are faced with is to find the perfect balance, for each OA patient, between interventions directed at musculoskeletal tissues and "*hands off*" approaches[111].

It should be emphasized that NE is not a treatment, but rather a strategy targeting cognitive barriers for behavioral change and hence effective physical therapy. NE aims at reconceptualizing chronic pain in way that pain is no longer regarded as threatening (i.e. the patient should understand that pain in case of central sensitization no longer reflect tissue damage, but rather reflects 'noise' in the sensory system). This opens the

avenue for a time contingent approach to exercise therapy and activity management, which will be explained below.

EXERCISE THERAPY AND GRADED ACTIVITY

Exercise is frequently encountered as a central component of the treatment of OA pain. Although the clinical benefits of exercise therapy in OA are well established (i.e. evidence based)[112], it is currently unclear whether exercise therapy has positive effects on the processes involved in central sensitization. From a theoretical perspective, exercise has the potential to 'treat' the process of central sensitization: exercise activates brain-orchestrated endogenous analgesia [reviewed in[113]]. From a clinical perspective, clinicians are advocated to use a time-contingent approach when exercises patients with OA and central sensitization. This implies that the patient does not cease exercise bouts once (local) pain severity increases. Instead, the patient complies with the predetermined exercise modalities (including exercise duration, cfr. *time*-contingent) and interprets pain increases as non-threatening. Such a time-contingent approach is unlikely to be effective unless the patient applies this time-contingent approach in daily life as well. Indeed, graded activity is a behavioral therapy applying such a time-contingent approach into the daily life of patients with OA. Physical activity increases are effective for treating pain in OA patients with overweight[114] and graded activity therapy is effective for patients with OA in general[115,116]. Moreover, graded activity results in better exercise adherence and more physical activity than usual care in patients with hip or knee OA, both in the short- and long term[117].

CONCLUSION

OA is a frequent chronic musculoskeletal pathology that usually causes great disability and significant healthcare costs. Even though patients with OA present structural anomalies, the severity of these changes is not always proportional with the degree of pain or disability. A significant proportion of these patients with OA show signs of central sensitization, with pain modulation and processing altered at the CNS level. Substantial scientific evidence indicates a role for central sensitization in OA pain, yet it is necessary to develop strategies to allow reliable and systematic recognition of patients with OA whose pain has a central sensitization component. Central sensitization management is an area of great interest at least in the subgroup of patients with OA pain having central sensitization. Interventions like CBT and NE potentially target cognitive-emotional sensitization (and descending facilitation), while centrally acting drugs and exercise therapy can improve endogenous analgesia (descending inhibition) in patients with OA. However, to date, evidence both on identification and treatment of central sensitization in osteoarthritis is still scarce and more human research is needed. Optimum treatment for people with OA pain requires a multidisciplinary approach and determination of how peripheral and central factors are contributing to pain in each patient, to enable individualization of treatment strategies. Physical therapists are in a good position to deliver an individualized intervention because they are cognizant of the need for a biopsychosocial approach to management. In addition, they can perform systematic assessment and choose to utilize a more peripheral or central based therapy.

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CHAPTER 3

CHAPTER 3

Are measures of central sensitization associated with the area of pain and clinical symptoms in subjects with knee osteoarthritis?

Content:

Expanded distribution of pain as a sign of central sensitization in individuals with symptomatic knee osteoarthritis

Lluch E, Dueñas L, Barbero M, Falla D, Baert I, Meeus M, Sánchez-Frutos J, Aguilella L, Nijs J. Phys Ther. 2016;96(8):1196-207

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EXPANDED DISTRIBUTION OF PAIN AS A SIGN OF CENTRAL SENSITIZATION IN INDIVIDUALS WITH SYMPTOMATIC KNEE OSTEOARTHRITIS

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ABSTRACT

Background: Expanded distribution of pain is considered a sign of central sensitization (CS). The relationship between recording of symptoms and CS in people with knee osteoarthritis (OA) has been poorly investigated.

Objective: To examine whether the area of pain assessed using pain drawings relates to CS and clinical symptoms in people with knee OA.

Design: Cross-sectional study.

Methods: Fifty-three subjects with knee OA scheduled to undergo primary total knee arthroplasty were studied. All participants completed pain drawings using a novel digital device, self-administration questionnaires and were assessed by quantitative sensory testing. Pain frequency maps were generated separately for women and men. Spearman's correlation coefficients were computed to reveal possible correlations between the area of pain and quantitative sensory testing and clinical symptoms.

Results: Pain frequency maps revealed enlarged areas of pain, especially in women. Enlarged areas of pain were associated with higher knee pain severity (r_s= .325, P < 0.05) and stiffness (r_s=.341, P < 0.05), lower pressure pain thresholds at the knee (r_s=-.306, P < 0.05) and epicondyle (r_s=-.308, P < 0.05) and higher scores with the Central Sensitization Inventory (r_s=.456, P < 0.01). No significant associations were observed between the area of pain and the remaining clinical symptoms and measures of CS.

Limitations: Firm conclusions about the predictive role of pain drawings cannot be drawn. Further evaluation of the reliability and validity of pain area extracted from pain drawings in people with knee OA is required.

Conclusion: Expanded distribution of pain was correlated with some measures of CS in individuals with knee OA. Pain drawings may constitute an easy way for the early identification of CS in people with knee OA, but further research is required.

Key words: Knee osteoarthritis, chronic pain, pain location, central nervous system sensitization.

INTRODUCTION

There is compelling evidence that central sensitization (CS) is present in a subgroup of people with knee osteoarthritis (OA) pain, especially in those with more advanced knee OA, and may be associated with knee OA symptom severity.[1,2] According to Woolf, CS is "*operationally defined as an amplification of neural signaling within the central nervous system that elicits pain hypersensitivity*".[3] CS is a broad concept encompassing numerous and complex pathophysiological mechanisms such as spinal cord sensitization, impaired functioning of brain-orchestrated descending anti-nociceptive (inhibitory) mechanisms, (over)activation of descending pain facilitatory pathways, increased temporal summation (TS) or wind-up and alteration of sensory processing in the brain.[3]

If present in people with knee OA pain, CS may mediate treatment responses. For instance, the presence of pre-operative CS [e.g. widespread pain sensitization, enhanced TS of pain] was associated with poor outcomes after total knee replacement.[4,5] Therefore, it may be important for clinicians to identify CS in people with knee OA pain. In such patients, a broader therapeutic approach aiming to desensitize the central nervous system seems warranted.[6]

Several methods for assessing CS in people with knee OA pain are available. However, they are typically performed within laboratory conditions including brain imaging techniques,[7,8] psychophysical testing with various stimuli [e.g. quantitative sensory testing (QST)[9,10]] and cerebral metabolism studies.[11] Currently, there is a lack of established criteria for the clinical diagnosis of CS in knee OA.[12] Laboratory-based measures like the nociceptive flexor reflex[13] or laser-evoked potentials provide more

objective evidence for hyperexcitability of central nervous system neurons, but no single measurement can be regarded as gold standard for establishing CS in knee OA. The lack of gold standard may be due to the complexity and diversity of the underlying mechanisms.

Recently, a set of criteria to assist clinicians on the classification of CS pain have been published,[14] but the suitability of this classification algorithm to the OA knee pain population is unknown. One criterion included for the classification of CS pain is diffuse pain distribution (i.e. large pain areas with a neuroanatomically illogical distribution) as identified from the clinical history and/or a body chart.[14] Expanded distribution of pain is a well-recognized sign of CS[12,15,16] and, in this regard, pain drawings might be useful to identify extended areas of pain distribution in people with knee OA.

Pain drawings have been used to obtain a graphic representation of pain distribution and location in people with knee OA pain.[17-23] In pain drawing, the patient or clinician indicates the location of pain by shading the painful area.[24] Several methods and instruments have been described to record the pain location and classify the pattern of knee OA pain, and the most common method is asking people to draw where they feel pain on a body chart.[17,19,20] Based on studies investigating pain drawings in individuals with knee OA pain, the medial knee region seems to be the most frequently reported pain location amongst people with knee OA pain,[19,20,25,26] though generalized or diffuse

knee pain is also commonly reported.[17,19] However, the location of pain is heterogeneous with no single pattern of pain location being pathognomonic for knee

OA.[19] This might be due to the multiple sources of pain (e.g. ligaments stretch, subchondral bone damage, bone marrow lesions) in knee OA.[20]

Recently, the presence of widespread pain as recorded on pain drawings, was most frequently reported by a subgroup of individuals with high levels of (in particular bilateral) knee OA pain and low level of structural damage on radiography (e.g. grade I and II on the Kellgren-Lawrence grading system for OA).[27] Enlarged areas of pain in this subgroup was attributed to a variety of etiological factors, including abnormal central pain processing mechanisms. Wood and colleagues found that subjects with knee OA reporting enlarged areas of pain had more persistent and severe pain and higher anxiety levels, which was also interpreted as reflecting altered central pain processing mechanisms.[19] However, it must be emphasized that in the above mentioned studies CS was only hypothesized as the explanation of the study findings, and no attempts were made to directly measure CS.

To our knowledge, only the two above mentioned studies[19, 27] related central pain mechanisms to individuals' recording of symptom location and distribution in people with knee OA pain. If CS was the dominant pain mechanism in an individual with knee OA pain, this should be reflected in more extended areas of pain mapped in pain drawings as compared to people with a lesser degree of pain sensitization.[22]

Therefore the primary aim of this study was to examine whether the area of pain assessed using pain drawings relates to direct (QST) and indirect (self-reported questionnaires, neuropathic pain) measures of CS in people with different degrees of chronic knee OA pain. As opposed to quantitative pain assessment tools which provide direct evidence of CS in chronic joint pain,[9,10,12] indirect measures of CS (e.g. self-

report questionnaires designed to determine presence of neuropathic pain) only offer indirect evidence of hypersensitivity of the central nervous system in people with knee OA pain.[1,14,28] As a secondary aim, the association between the area of pain and clinical symptoms (including the level of knee pain, disability and psychosocial variables) was also investigated. Psychosocial factors (e.g. cognitions and beliefs about pain), may explain some of the variation in pain reporting among individuals with knee OA.[29] For instance, catastrophic thinking and poor coping strategies in people with knee OA pain can predict the presence of more pain after total knee replacement surgery.[4]

METHODS

Subjects

A convenience sample of fifty-three subjects with chronic knee OA pain of more than 3 months duration who were scheduled to undergo primary total knee arthroplasty participated in the study. Subjects with knee OA affecting the tibiofemoral and patellofemoral compartments were included. These subjects participated in a randomized controlled trial investigating the effects of pain neuroscience education on pain and function in subjects with chronic knee OA pain (Clinical Trials database NCT02246088). Baseline data from the entire cohort were used for this study. All participants were recruited from the Orthopedic Surgery Service of the Hospital Universitario de La Ribera (Alzira, Spain) between January 2014 and February 2015.

All participants underwent weight bearing, fixed flexion posteroanterior and lateral X-rays of their affected knee. Radiographic disease severity of both the tibiofemoral (Kellgren–Lawrence 0–4 grading scale[30]) and patellofemoral (Ahlbäck 0-5 grading scale[31]) compartments was evaluated for each participant. Knee OA was diagnosed by a

surgeon according to the American College of Rheumatology classification,[32] including the regular experience of knee pain, plus either osteophytes on radiography or a combination of morning stiffness, crepitus and age 50 years or above. These criteria were found to be 89% sensitive and 88% specific for diagnosing knee OA.[32]

Subjects were excluded from study participation if they had previously undergone knee joint replacement surgery of the affected joint or any other lower limb surgery within the past six months, had co-existing inflammatory, metabolic, neurological or severe medical conditions hindering the ability of the patient to participate in the study or cognitive disturbances that could influence completion of the pain drawings.

This study was approved by the Ethics Committee of the Hospital Universitario de La Ribera (Alzira, Spain) and conducted in accordance with the Declaration of Helsinki. Before study participation, all the subjects carefully read an information leaflet and signed informed consent forms.

Procedure

Demographic information including age, sex, body mass index and pain duration were collected by self-report. Participants additionally completed a 11-point numeric rating scale to quantify their current pain intensity and were asked to complete a pain drawing to illustrate their area of pain.

Subjects then completed the following self-administration questionnaires in a standardized order: the Western Ontario and McMaster Universities Arthritis Index (WOMAC) scale, Pain Catastrophizing Scale (PCS), Central Sensitization Inventory (CSI), painDETECT (PD-Q), Tampa Scale for Kinesiophobia (TSK), Pain Vigilance

and Awareness Questionnaire (PVAQ) and the Chronic Pain Acceptance Questionnaire (CPAQ).

Afterwards, a standardized physical examination including physical performance tests was performed on each participant. Finally, all subjects were assessed by QST to examine pressure pain thresholds (PPT), TS and conditioned pain modulation (CPM). All QST was carried out by the same researcher in one individual session in the laboratories of the Hospital Universitario de La Ribera (Alzira, Spain). The participants were requested not to take analgesic medication 24h before the experiment. At the time of examination, the assessor was blinded to the questionnaire data including analysis of the scores obtained with pain drawings. Statistical analysis of the pain drawings data was performed by a researcher who was blinded from the QST data.

Measurements

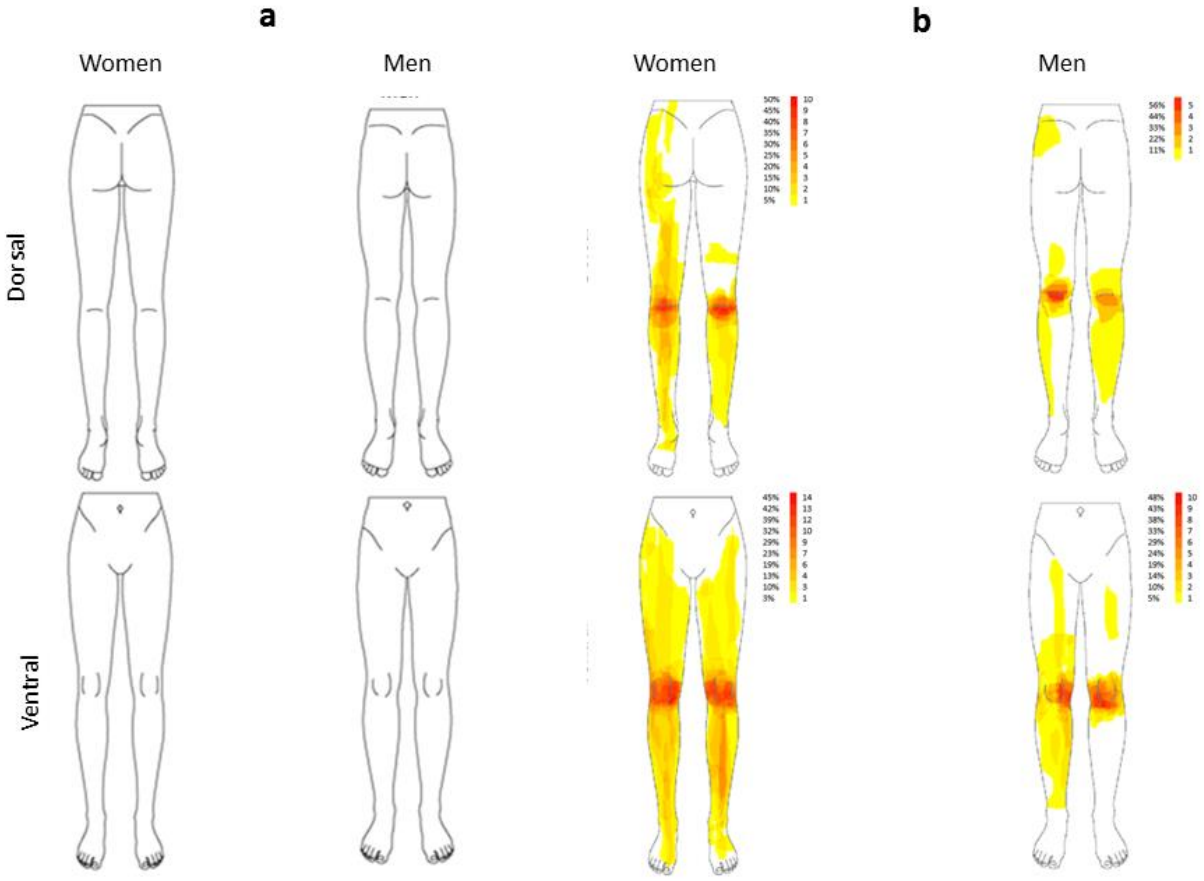
Area of pain

A novel method for obtaining and quantifying the area of pain using a digital tablet was used.[33] Test-retest reliability of this method for acquisition of pain drawings was recently demonstrated in people with chronic neck and low back pain.[33] Pain drawings were completed on a digital tablet (iPad 2, Apple Computer, Cupertino, CA, USA) using a stylus pen for digital tablets (CS100B, Wacom, Vancouver, WA, USA) and a commercially available sketching software (SketchBook Pro). Depending on the gender of the subject, a male or female body chart with different views of the knee region (frontal, dorsal) was chosen and opened in the sketching software (Figure 1A). The type, size and colour of the pen stroke were standardized across all participants.

An operator, who trained with the device in clinical practice one month prior to the start of the study, gave each subject a standardized verbal explanation on what the pain drawing was and how to complete it using the digital tablet. The pain drawing was presented to participants as a tool where they should illustrate precisely where they had felt pain during the previous week. The assessor highlighted the importance of fully illustrating all pain sites. After a demonstration and brief training to familiarize the subjects with the device, they were asked to complete their pain drawings. Participants were instructed as follows: '*Please shade the areas where you felt your usual pain during the last week on this body chart and try to be as precise as possible*'. They were instructed to colour every part of the body where they perceived pain in the previous week, independently from the type and the severity of pain. Before saving and storing the pain drawing, participants were asked if the pain drawing corresponded to their real pain distribution. If not, they were given the possibility to correct the drawing using the "eraser" tool.

A custom software was used to compute the total area of pain for each subject, and to generate two pain frequency maps (i.e. frontal and dorsal body chart) separately for men and women.[33] The area of pain was expressed as the total number of pixels coloured inside the frontal and dorsal body chart perimeter. Thus the area of pain extracted from the dorsal view and frontal view were combined to generate a single value of area of pain. Pain frequency maps were obtained by superimposing the pain drawings from all subjects to illustrate the most frequently reported location of pain across the entire sample. This was done for women and men separately. A colour grid was used to indicate the percentage of individuals that reported pain in that specific area.

Figure 1. a) Example of the available templates; b) Pain frequency maps generated separately for men and women by superimposing the pain drawings of all individuals with knee OA pain. The colour grid indicates both the number and the percentage of individuals that reported pain in that specific area. Dark red represents the most



Temporal summation of pain and Conditioned pain modulation (CPM)

For measuring excitability of nociceptive pathways and efficacy of endogenous pain inhibition, the TS and CPM paradigms were used. TS and CPM are established ways of measuring excitability of nociceptive pathways and pain inhibition, respectively.[35,36]

First, PPTs were measured at the peripatellar region and the ipsilateral extensor carpi radialis longus as described above. Second, TS was provoked by means of 10 consecutive pulses at previously determined PPT at each location. TS started 2 min after PPT measurement. For each pulse, pressure was gradually increased at a rate of 2 kg/s to the determined PPT and maintained for 1 s before being released (1 s interstimulus interval). Pain intensity of the first, fifth, and tenth pulse was rated on a numerical rating scale (0: no pain to 10: worst possible pain). Afterwards, a rest period of 5 min was given.

Third, CPM was induced by combining the TS procedure namely the test stimulus and an inflated occlusion cuff around the subject's arm, contralateral to the side of the affected knee, to a painful intensity (conditioning stimulus). The occlusion cuff was inflated at a rate of 20 mm Hg/s until 'the first sensation of pain' and maintained for 30 s. Afterwards, pain intensity, as a result of cuff inflation, was rated on a numerical rating scale. Next, cuff inflation was increased or decreased until the pain intensity was rated as 3/10. The length of time to reach 3/10 pain was recorded. TS assessment was then repeated during maintenance of the cuff inflation.[37]

The details and data supporting the test-retest reliability and validity of the protocol for examining TS and CPM are described elsewhere.[37]

Indirect measures of CS

Central Sensitization Inventory (CSI)

The Central Sensitization Inventory is a self-report screening instrument to help identify people with central sensitivity syndromes for which CS may be a common etiology.[38]

The part A of the CSI assesses symptoms common to CS and comprises of 25 items each ranged on a 5-point scale with the end points (0) "never" and (4) "always" (range: 0-100). It has high reliability and validity[38] and a cutoff score of 40 out of 100 was able to distinguish between individuals diagnosed with central sensitivity syndromes and a non-patient comparison sample (sensitivity = 81%, specificity = 75%).[39] The Spanish version of the CSI was used in this study.

Neuropathic pain

The Spanish version of the PainDETECT questionnaire (PD-Q) was used to facilitate the identification of neuropathic pain related to knee OA.[40] Although developed as a screening questionnaire for neuropathic pain, the PD-Q may also function as a measure of characteristics that indicate augmented central pain processing in people with knee OA pain.[41]

The PD-Q is a self-administered questionnaire comprised of 9 items: seven evaluating pain quality, one pain pattern and one pain radiation, which all contribute to an aggregate score (range: -1 to 38). Sensitivity, specificity, and positive predictive values for neuropathic pain symptoms in people with back pain using the cut-off score of 19 were 85%, 80%, and 83%, respectively.[42] The relationship between PD-Q scores and signs of central sensitization in people with hip OA has been previously demonstrated.[43]

Clinical symptoms

Self-reported knee pain

Participants were asked to indicate the intensity of their pain in the last week on a numeric rating pain scale ranging from 0 (no pain) to 10 (worst pain imaginable). The patient-reported numeric rating scale has demonstrated good construct validity and

moderate to large responsiveness [(standardized response mean and effect size ranging from 0.6 (hip OA) to 0.9 (knee OA)], for evaluating functional disability in people with hip and knee osteoarthritis.[44]

Physical performance tests

Range of motion measurement for both active knee flexion and extension and the Timed Up and Go test were performed in each participant. These objective measures were selected on the basis of their ability to reflect functional mobility impairments.

High intra- and intertester reliability and criterion validity of goniometry to measure range of motion has been documented for knee flexion and extension in subjects with knee restrictions of different etiologies.[45] The Timed Up and Go test is a reliable test with adequate minimum detectable change for clinical use in individuals with doubtful to moderate (grade 1-3) knee OA.[46,47] Intra-rater and inter-rater reliability of the Timed Up and Go test were 0.97 (95% confidence interval [CI], 0.95 - 0.98) and 0.96 (95% confidence interval [CI], 0.94 - 0.97), respectively. Its minimum detectable change, based on measurements performed by a single rater and between raters, was 1.10 and 1.14 seconds, respectively.[47]

Western Ontario and McMaster Universities (WOMAC) knee osteoarthritis index

The Spanish version of the self-administered Western Ontario and McMaster Universities (WOMAC) knee osteoarthritis was used.[48] The WOMAC comprises of five items for pain (score range 0–20), two for stiffness (score range 0–8), and 17 for functional limitation (score range 0–68). Total WOMAC score and scores from the pain, stiffness and functional subscales were considered. Higher scores on the

WOMAC indicate worse pain, stiffness, and functional limitations. The test-retest reliability (intraclass correlation coefficients range: 0.66 to 0.81), internal consistency (Cronbach's alpha range: 0.81 to 0.93), convergent validity (Pearson's coefficients range: -0.52 to -0.63) and responsiveness (standardized response mean range: 0.8 to 1.5) of the Spanish version of the WOMAC has been demonstrated in people with hip and knee OA.[48]

Pain Catastrophizing Scale (PCS)

The Pain Catastrophizing Scale (PCS) is a valid and reliable instrument to measure pain catastrophizing in older adults with knee OA.[49,50] It comprises of 13 items each ranged on a 5-point scale with the end points (0) "not at all" and (4) "all the time" (range: 0-52). Higher scores indicate a higher degree of pain catastrophizing. The Spanish version of the PCS showed appropriate internal consistency (Cronbach's alpha=0.79), test-retest reliability (intraclass correlation coefficient=0.84) and sensitivity to change (effect size<or=2) in patients with fibromyalgia.[51]

Tampa Scale of Kinesiophobia (TSK)

The Spanish version of the TSK-11 was used.[52] The TSK-11 is an 11-item questionnaire assessing fear of movement or fear of (re)injury during movement and eliminates psychometrically poor items from the original version of the TSK,[53] thus creating a shorter questionnaire with comparable internal consistency. It is comprised of 11 items each ranged on a 4-point scale with the end points (1) "totally agree" and (4) "totally disagree" (range: 11-44). The TSK-11 has a 2-factor structure: activity avoidance and harm, and has demonstrated acceptable internal consistency and validity (convergent and predictive) in both subjects with acute (Cronbach's alpha= 0.79) and chronic

musculoskeletal pain (Cronbach's alpha= 0.79).[52] Higher scores indicate more fear-avoidance behavior.

Pain Vigilance and Awareness Questionnaire (PVAQ)

The Spanish version of the Pain Vigilance and Awareness Questionnaire (PVAQ) was used to evaluate participants' preoccupation with or attention to pain associated with pain-related fear and perceived pain severity.[54] The PVAQ comprises of nine items each rated on a scale from 0 (never) to 5 (always) (range: 0-45). Higher scores indicate a higher degree of pain vigilance and awareness. Psychometric properties of the PVAQ were previously reported in people with chronic back pain[54] and fibromyalgia[55,56] showing good internal consistency,[55,56] reliability[54,55] and validity.[54,55] A cutoff score of 24.5 out of 45 was able to identify fibromyalgia women with worse daily functioning with a sensitivity of .71 and a specificity of .75.[55]

Chronic Pain Acceptance Questionnaire (CPAQ)

The Chronic Pain Acceptance Questionnaire (CPAQ) is the questionnaire most often used to measure pain acceptance in chronic pain populations.[57] It comprises of 20 items each rated on a scale from 0 (never true) to 6 (always true) (range: 0-120) and it has a two-factor structure: activities engagement and pain willingness. The total score results from the sum of these two factors with higher scores indicating a higher degree of chronic pain acceptance. The Spanish version of the CPAQ, which is reliable (intraclass correlation coefficient=0.83) and has valid construct validity (Cronbach's alpha: 0.83) for people with fibromyalgia, was used in this study.[57]

Statistical analysis

Distribution of the data was tested with the Shapiro-Wilk test and non-normally distributed data were identified. Descriptive statistics were used to describe the baseline characteristics of the individuals with knee OA pain. A Mann-Whitney U test was run to determine if there were differences in baseline clinical variables between males and females. Pain frequency maps were generated by superimposing the scores obtained with pain drawings considering men and women separately. TS was calculated as the difference percentage between the 10^{th} and the 1^{st} pain rating score before occlusion using the formula: ((TS10th-TS1st)/TS1st)*100.[58] The outcome measure for CPM was calculated as the difference between the 10th pain rating score before occlusion and the 10th during occlusion.[37] Spearman's correlation coefficients were computed to reveal possible correlations: (1) between the area of pain and direct measures of CS (i.e. PPT knee, PPT epicondyle, knee TS, epicondyle TS, knee CPM, epicondyle CPM), (2) between the area of pain and indirect measures of CS (i.e. CSI and PD-Q) and (3) between the area of pain and clinical symptoms (i.e. VAS, WOMAC, WOMAC pain subscale, WOMAC stiffness subscale, WOMAC functional limitation scale, PCS, TSK, PVAQ, CPAQ). Statistical analyses were performed using SPSS 22 (SPSS INc, Chicago, IL, USA). The significance level was set at $P < 0.05$.

RESULTS

Fifty-three individuals with knee OA (34 woman and 19 men) were enrolled in the study. Subjects' demographic data are reported in Table 1 and clinical characteristics and measurements of CS are detailed in Table 2. Mean and median scores for the area of pain, ROM for active knee flexion, Timed Up and Go test, WOMAC and WOMAC pain and functional limitation subscale, PCS, CPAQ, TSK, CSI, PD-Q and PPT at the knee were significantly different between males and females ($p<0.05$). Seven out of the

fifty-three subjects (13.2%) had scores that correspond to likely neuropathic pain (≥19 on the PD-Q).

Table 1. Subjects demographic characteristics are reported. *P-values refer to potential differences between male and females.

Baseline demographic characteristics of OA patients	All subjects (n=53) Mean (SD) Median (IQR)	Female (n=34) Mean (SD) Median (IQR)	Male (n=19) Mean (SD) Median (IQR)	P- value*
Age (years)	70.2 (7.4) 72 (11.5)	71.2 (7.8) 73 (11.2)	68.5 (6.3) 70 (7)	.130
BMI (Kg/m^2)	29.9 (3.9) 30 (5.5)	30.4 (4.2) 30 (6.2)	28.9 (3.1) 28 (5)	.183
Area of pain (number of pixels)	12766 (13494) 8272 (12190)	15012 (14327) 10314 (12382)	8747 (11096) 5816 (7083)	.017
Pain duration (years)	7.5 (6) 5 (10)	6.7 (5.7) 4 (10.3)	9.1 (6.3) 6 (11)	.127
Kellgren–Lawrence grade (tibiofemoral joint) grade 0 n (%)	0 (0)	0 (0)	0 (0)	.115
Kellgren–Lawrence grade (tibiofemoral joint) grade 1 n (%)	0 (0)	0 (0)	0 (0)	
Kellgren–Lawrence grade (tibiofemoral joint) grade 2 n (%)	15 (28.3)	7 (20.5)	8 (42.1)	
Kellgren–Lawrence grade (tibiofemoral joint) grade 3 n (%)	22 (41.5)	11 (32.3)	11 (57.8)	
Kellgren–Lawrence grade (tibiofemoral joint) grade 4 n (%)	16 (30.1)	8 (23.5)	8 (42.1)	
Ahlbäck grade (patellofemoral joint) grade 1 n (%)	3	2	1	.231
Ahlbäck grade (patellofemoral joint) grade 2 n (%)	19	10	19	
Ahlbäck grade (patellofemoral joint) grade 3 n (%)	30	15	15	
Ahlbäck grade (patellofemoral joint) grade 4 n (%)	1	0	1	
Ahlbäck grade (patellofemoral joint) grade 5 n (%)	0	0	0	

BMI, Body Mass Index.

Table 2. Baseline clinical measurements are reported. *P-values refer to potential differences between male and females.

Baseline measurements of OA patients	**All subjects (n=53)** Mean (SD) Median (IQR)	**Female (n=34)** Mean (SD) Median (IQR)	**Male (n=19)** Mean (SD) Median (IQR)	**P- value***
NRPS (0-10)	5.92 (17) 5.9 (22.5)	6.19 (17.2) 6.05 (27.3)	5.44 (15.8) 5.8 (20)	.217
ROM active knee flexion (degree)	115.5 (11.4) 115.5 (10)	113.9 (9.8) 115 (8.7)	118.3 (13.5) 118.5 (9.2)	.047
ROM active knee extension (degree)	-2.41 (6.3) -2 (7.9)	-3.2 (6.7) -2.6 (7.96)	-0.9 (5.4) -1.6 (5.3)	.30
Timed Up and Go test (seconds)	11.4 (5.7) 9.8 (5)	13.4 (6.2) 11.8 (5.5)	7.9 (1.6) 7.7 (2.6)	.000
WOMAC (0-96)	49.4 (16.5) 49 (25)	54.1 (16.1) 56 (24.5)	40.9 (13.9) 38 (20)	.006
WOMAC pain subscale (0-20)	9.53 (3.31) 10 (5)	10.6 (3.1) 10 (4)	7.6 (2.9) 7 (3)	.001
WOMAC stiffness subscale (0-8)	3.79 (2.11) 3 (3)	4.1 (2.3) 4 (3.8)	3.2 (1.7) 3 (2)	.119
WOMAC functional limitation scale (0-68)	36.09 (12.66) 36 (19)	39.4 (12.5) 42.5 (19.8)	30.1 (10.7) 29 (17)	.010
PCS (0-52)	23.77 (12.51) 25 (17)	27.2(11.7) 26 (15.5)	17.7 (11.8) 20 (19)	.012
PVAQ (0-45)	28.66 (6.95) 28 (9)	28.6 (7.5) 28 (10.8)	28.8 (6) 29 (6.5)	.773
CPAQ (0-120)	52.83 (18.26) 52 (28)	48.5 (17.2) 47.5 (27.8)	60.6 (18) 64 (23)	.022
TSK (11-44)	33.68 (5.98) 34 (9)	35.1 (5.6) 35 (7.8)	31.2 (5.9) 32 (8)	.029
CSI (0-100)	36.21 (15.62) 37 (23)	40.1 (16.6) 42 (22.5)	29.2 (10.8) 30 (19.5)	.014
PD-Q (-1-38)	12.25 (6.3) 11 (8)	13.6 (6.6) 12 (9)	9.8 (5.1) 10 (8.5)	.041
PPT knee (Kg/cm^2)	4.82 (2.62) 4 (3.15)	4 (1.6) 3.8 (2.5)	6.2 (3.4) 6.1 (4.9)	.018
PPT epicondyle (Kg/cm^2)	4.03 (1.72) 3.7 (2)	3.7 (1.5) 3.6 (1.3)	4.6 (2) 4.4 (2.4)	0.55
Knee TS (%)	40.44 (23.11) 43.75 (23.08)	40.53 (24.16) 42.46 (21.32)	40.28 (21.76) 44.44 (25.71)	.853
Epicondyle TS (%)	43.39 (21.46) 50 (32.14)	3 (1.7) 3 (2)	43.19 (17.79) 50 (29.56)	.978
Knee CPM (Kg/cm^2)	-0.44 (1.66) 0 (2)	-0.6 (1.6) -1 (1.5)	-0.1 (1.8) 0.50 (1.5)	.054
Epicondyle CPM (Kg/cm^2)	-0.43 (1.76) 0 (3)	-0.7 (1.7) -1 (2)	0 (1.8) 0 (2)	.200

CPAQ, Chronic Pain Acceptance Questionnaire; CPM, Conditioned pain Modulation; CSI, Central Sensitization Inventory; NRPS, Numeric Rating Pain Scale; PCS, Pain Catastrophizing Scale; PD-Q, PainDETECT Questionnaire; PPT, Pressure Pain Threshold; PVAQ, Pain Vigilance and Awareness Questionnaire; ROM, Range of Motion; TS, Temporal Summation; TSK, Tampa Scale of Kinesiophobia; WOMAC, Western Ontario and McMaster Universities knee osteoarthritis index.

The area of pain was 12766 ± 13494 pixels across the entire group of subjects whereas it was 15012 ± 14327 and 8747 ± 11096 pixels for women and men, respectively. Pain frequency maps for the individuals with knee OA are illustrated in Figure 1B and correlations between the area of pain and measures of CS and clinical symptoms are reported in Table 3.

Table 3. Spearman's correlation coefficients between the area of pain (total pain area extracted from the dorsal and ventral body views) computed using pain drawings, and measures of CS and clinical symptoms for the entire cohort of individuals with knee OA pain (n=53). *Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.001 level (2-tailed).

		Correlation with pain area r_s
Direct measures of CS	PPT knee (Kg/cm^2)	-.306*
	PPT epicondyle (Kg/cm^2)	-.308*
	Knee TS (%)	-.0183
	Epicondyle TS (%)	-.087
	Knee CPM (Kg/cm^2)	-.066
	Epicondyle CPM (Kg/cm^2)	-.040
Indirect measures of CS	CSI	.456**
	PD-Q	.266
Clinical symptoms	NRPS (0-10)	.221
	WOMAC	.259
	WOMAC pain subscale	.325*
	WOMAC stiffness subscale	.341*
	WOMAC functional limitation scale	.183
	PCS	.145
	PVAQ	.100
	CPAQ	-.195
	TSK	-.195

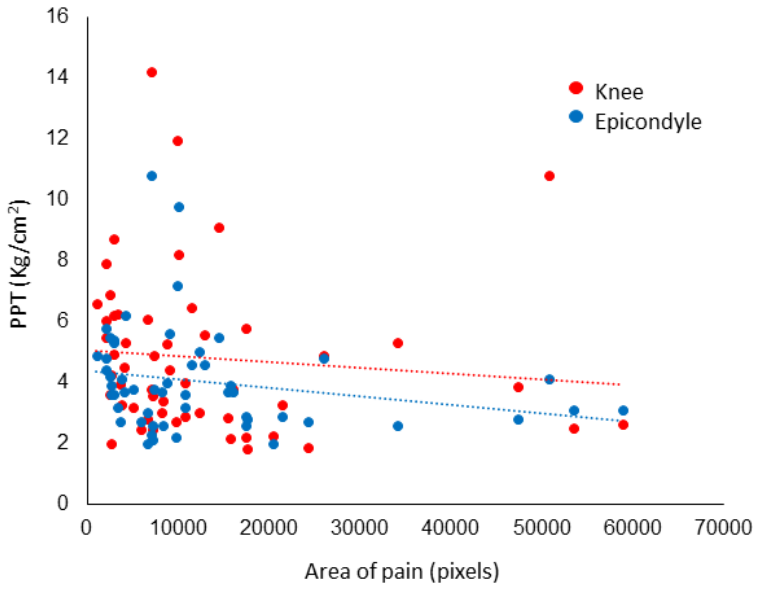
CPAQ, Chronic Pain Acceptance Questionnaire; CPM, Conditioned pain Modulation; CSI, Central Sensitization Inventory; NRPS, Numeric Rating Pain Scale; PCS, Pain Catastrophizing Scale; PD-Q, PainDETECT Questionnaire; PPT, Pressure Pain Threshold; PVAQ, Pain Vigilance and Awareness Questionnaire; TS, Temporal Summation; TSK, Tampa Scale of Kinesiophobia; WOMAC, Western Ontario and McMaster Universities knee osteoarthritis index.

Area of pain and direct and indirect measures of CS

Significant correlations were identified between the area of pain and PPT at the knee (r_s= -.306, P < 0.05) and epicondyle (r_s= -.308, P < 0.05) signifying lower PPT at both sites in individuals with larger pain areas. Figure 2 visualizes the relationship between the area of pain and the PPT for both knee and epicondyle. No significant associations

were observed between the area of pain and TS (r_s= -.0183 knee, -.087 epicondyle) or the area of pain and CPM (r_s= -.066 knee, -.040 epicondyle). A significant correlation was identified between the area of pain and the CSI score (r_s=.456, P < 0.01); subjects with higher scores on the CSI showed larger areas of pain.

Figure 2. The two scatter plots illustrating the relationship between the area of pain and the PPT for both knee and epicondyle.



Area of pain and clinical symptoms

Higher scores on the pain (r_s=.325, P < 0.05) and stiffness (r_s=.341, P < 0.05) subscale of the WOMAC were significantly associated with larger pain areas.

DISCUSSION

Several methods for illustrating the area of pain in people with chronic knee OA pain have been used. We explored, for the first time, the utility of a novel digital device using two-dimensional body charts for acquisition and analysis of the scores obtained with pain drawings[33] in a sample of individuals with chronic knee OA pain. Through a digital tablet using a user-friendly digital device, participants reported their pattern of pain on a body chart. Other systems such as the photographic knee pain map have shown good validity and reliability for people with regional knee pain to identify its location.[20]

Area of pain and direct and indirect measures of CS

The results of this study showed a significant positive correlation between the area of pain and some direct and indirect measures of CS. On the one hand, a more expanded distribution of pain was correlated with a lower PPT at a remote site from the knee (i.e. epicondyle). Increased pain sensitivity distantly from the knee may reflect widespread hyperalgesia thus providing evidence of CS in people with knee OA.[9,10,12] On the other hand, we found that a greater expansion of symptoms was associated with a higher degree of subjective CS pain descriptors as assessed with the CSI questionnaire. The CSI was recently shown to be a useful and a valid instrument for screening people with central sensitivity syndromes.[59] In addition, individuals with knee OA pain with preoperative high levels of comorbid centrally mediated symptoms measured by the CSI showed severe pain, increased analgesic requirements and were at higher risk of persistent pain after total knee arthroplasty in the early postoperative period.[60]

Previous studies have established associations between the scores obtained with pain drawings and central pain mechanisms, although in non-OA populations. For instance, a significant correlation between non-organic pain drawings and higher scores with the Waddell's non-organic physical signs was found in people with chronic low back pain.[61] Waddell's signs include physical signs or symptoms that are inconsistent with pathology and are suggestive of the presence of symptom magnification or pain behavior.[62] Nonorganic pain drawings were defined as those with poorly defined pain patterns, bizarre or non-anatomical pain areas.[61] In addition, nonorganic pain drawings were associated with maladaptive psychosocial factors (i.e. high levels of catastrophizing, anxiety and depression) in people with chronic neck-shoulder and lower-back/lower limb pain[63] and chronic low back pain.[64] However, maladaptive psychosocial factors including magnified symptom behavior as assessed with the Waddell's scale provide no direct evidence for CS. In fact, psychosocial factors were not included as essential criteria for classification of CS pain as they are also prevalent in nociceptive and neuropathic pain.[14]

Based on results of the PD-Q, 13.2% of our sample had scores that correspond to likely neuropathic pain (≥19). These results are comparable to those reported by Valdes and colleagues[65], where 14.8% of people with knee OA pain had likely neuropathic pain, and superior to the percentage obtained by Ohtori et al.[66] (e.g. 5.4%). Some studies have inferred CS based on neuropathic-like descriptors of symptoms.[67,68] Contrary to what may have been expected, we did not find an association between the presence of a more expanded distribution of pain and self-reported neuropathic pain scores. This lack of association may be either due to the small number of participants with likely neuropathic pain or to the fact that we used the PD-Q and not the *modified* version of

this questionnaire (*m*PD-Q) recently recommended for the OA pain population.[67] Like the original PD-Q, the *m*PD-Q is comprised of nine items but with some modifications adapted to people with OA, such as framing of questions to ask about symptoms 'in or around' the worst knee, over a specific time frame. Also, the presence of more extended areas of pain in people with knee OA may reflect non-neuropathic CS rather than neuropathic pain, making the lack of association between the scores obtained from the pain drawings and the PD-Q plausible.

No significant associations were observed between the area of pain and TS or the area of pain and CPM. Pain associated with knee OA is recognized as a complex phenomenon encompassing several mechanisms such as CS.[69,70] The quantification of CS is in turn multidimensional by including several objective QST techniques such as pain and tolerance thresholds, spatial summation, TS or CPM.[9,10,12] These QST techniques assess the same underlying biological concept (CS), but in its different manifestations related to the different aspects of sensitization. This could justify why the areas of pain as assessed with pain drawings were correlated with some (PPT) but no other pain biomarkers of CS such as TS and CPM.

Area of pain and clinical symptoms

A significant positive correlation between knee pain severity and stiffness and the area of pain reported by subjects was observed. Although the area of pain, pain intensity and stiffness are variables assessing different constructs, it could be expected that people with knee OA with more diffuse or more extended areas of pain would report higher pain intensity and stiffness scores. As seen in the pain frequency maps, the most common pattern of pain reported by our sample was anterior knee pain, in particular

medial knee and peripatellar pain, which is in accordance with previous research.[19,20,25,26] Interestingly, besides local knee symptoms, many participants also perceived enlarged and distant pain areas as can be seen in Figure 1B. This expansion of pain to larger areas may reflect the presence of CS in these individuals.[12] Although using an experimental pain design, Bajaj and colleagues also showed significantly larger referred pain areas after intramuscular hypertonic saline infusion in subjects with knee OA, when compared with controls.[71] Referred pain is a phenomenon attributed to CS.[12,15] In addition, enlarged areas of pain were observed in individuals with knee OA pain, in particular in those with more persistent and severe symptoms.[19]

In our study, enlarged areas of pain were especially noticeable in women. This finding is consistent with previous research where the most sensitized-groups of subjects with knee OA pain contained more women than men.[72,73] In addition, a recent study[74] looking at the moderator effect of sex in centrally-mediated changes in people with knee OA pain, found a greater number of pain sites reported by women relative to men ($p=.001$).

Psychosocial variables were unrelated to the area of pain in our study. This lack of correlation is in accordance with previous research done in non-OA pain populations, where no correlation between the area of pain and the individual psychological state was demonstrated.[75] Indeed, a systematic review on pain drawings did not support the assumption that unusual or extensive pain drawings indicate disturbed psychological state.[24]

In this study, there are some methodological issues that should be considered. We didn't collect information on the reliability or stability of pain location over time in our

sample. Reliability was assumed based on previous studies using this method for pain drawings analysis in other chronic pain populations (e.g. chronic low back and neck pain).[33] Expanded distribution of pain (e.g. referred pain) may be more commonly observed in those populations as compared to individuals with knee OA pain, although no comparative data exist in that regard. Our assumption may thus have influenced the results of this study. Future research is therefore warranted to evaluate the clinimetric properties of pain drawings in people with knee OA pain.

In addition, as positive and negative predictive values of pain drawings were not calculated and the study design was cross-sectional, firm conclusions about the predictive role of pain drawings on knee OA pain cannot be drawn. Future studies could for instance explore the possible association between the scores obtained with pain drawings and outcome measures after treatment (i.e. surgery), to determine the real clinical utility of pain drawings for people with knee OA pain. In this regard, Skou and colleagues found that subjects with pain after re-total knee arthroplasty demonstrated significantly more pain sites using a region-divided body chart when compared to participants without pain.[22]

Screening for the presence of concurrent comorbidities (e.g. hip joint or lumbar spine pathology, fibromyalgia) was not performed in this study. However, these comorbid conditions could have influenced the patterns of pain described by participants. For instance, referred pain from the lumbar spine may have contributed to the posterior areas of symptoms especially noted in female.

Despite the associations between direct and indirect measures of CS and the area of pain, it must be noted that most associations were not statistically significant. Only two

(i.e. PPT and CSI) of the six measures of CS were significantly associated with an expanded distribution of pain. In addition, even though positive associations were observed, the strength of those associations was low as reflected by the small amount of the variance of CS (i.e. 9%) explained by the areas of pain.

Examining TS directly before measurement of CPM is a challenge, as the TS measurement could potentially have an effect on the results of CPM testing. However, we performed the measurement of CPM five minutes after the TS procedure following the protocol described by others.[37] TS is short-lasting; the effects last for no more than a couple of seconds-to-minutes after stimulus application.[3] Therefore, a 5 minute wash-out period in between procedures was deemed appropriate to preclude a carry-over effect.

In conclusion, this study has shown that the area of pain reported by individuals with knee OA pain is associated with some measures of CS. Given the significant role CS plays in a subgroup of people with knee OA pain and that CS can mediate treatment responses (i.e. after surgery[76,77]), classification of people with knee OA pain in terms of pain mechanisms is a research priority.[6,23,78] However, since costly and unattainable laboratory equipment is usually necessary for diagnosis, identification of CS is clinically challenging. In this regard, pain drawings may constitute an easy and cheap way for the early identification of CS in people with knee OA pain. Clinicians should be attentive for individuals showing extended areas of pain as this may be an indicator of CS. However, further evaluation of the reliability and validity of pain area reported on pain drawings in this population is required before its use can be advocated in clinical practice.

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CHAPTER 4

CHAPTER 4

Is a combined intervention of manual therapy addressing the knee and pain neuroscience education targeted to the central nervous system effective for people with knee osteoarthritis?

Content:

Balancing “hands-on” with “hands-off “ physical therapy interventions for the treatment of central sensitization pain in osteoarthritis

Lluch Girbés E, Meeus M, Baert I, Nijs J. Man Ther. 2015;20(2):349-52.

Preoperative pain neuroscience education combined with knee joint mobilization for knee osteoarthritis: a randomized controlled trial

Lluch E, Dueñas L, Falla D, Baert I, Meeus M, Sánchez-Frutos J, Nijs J. Submitted

BALANCING "HANDS-ON" WITH "HANDS-OFF " PHYSICAL THERAPY INTERVENTIONS FOR THE TREATMENT OF CENTRAL SENSITIZATION PAIN IN OSTEOARTHRITIS

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ABSTRACT

Traditional understanding of osteoarthritis-related pain has recently been challenged in light of evidence supporting a key role of central sensitization in a subgroup of this population. This fact may erroneously lead musculoskeletal therapists to conclude that hands-on interventions have no place in OA management, and that hands-off interventions must be applied exclusively. The aim of this paper is to encourage clinicians in finding an equilibrium between hands-on and hands-off interventions in patients with osteoarthritis-related pain dominated by central sensitization. The theoretical rationale for simultaneous application of manual therapy and pain neuroscience education is presented. Practical problems when combining these interventions are also addressed. Future studies should explore the combined effects of these treatment strategies to examine whether they increase therapeutic outcomes against current approaches for chronic osteoarthritis-related pain.

INTRODUCTION

Osteoarthritis (OA) is the main cause of pain, disability and loss of quality of life in the elderly (Ma et al., 2014). Traditional management for OA mainly involves a combination of pharmacological and non-pharmacological interventions, such as physical therapy (Hochberg et al., 2012). As a consequence of their training and education, the majority of musculoskeletal therapists are educated in the biomedical model of pain (Nijs et al., 2013). This traditional model of pain assumes that there is a direct link between the amount of local tissue damage (i.e. structural joint degeneration) and the pain experienced by the patient (Haldeman, 1990).

According to this biomedical model, addressing the underlying pathology should result in a reduction or (complete) resolution of symptoms and subsequent recovery of normal function. However, chronic OA-related pain does not always adhere to this biomedical model of pain. It is common to observe a discordance between the degree of structural joint damage and the amount of symptoms experienced by the patient (Bedson and Croft, 2008; Baert et al., 2013, 2014). In addition, local application of different modalities of treatment, including prosthetic substitution, is not always followed by an amelioration or complete resolution of symptoms (Skou et al., 2013a, 2013b).

Recent evidence has established that central sensitization (CS) is the dominant pain mechanism in a subgroup of patients with chronic OA-related pain (Lluch et al., 2014). Recognition of subsets of OA patients with different pain mechanisms, including those with CS, has been suggested in order to tailor applied interventions and thus improve outcomes (Malfait and Schnitzer, 2013). Hence, in those OA patients with CS as their dominant pain mechanism, a broader therapeutic approach aiming to desensitize the

central nervous system (CNS) should be adapted (Nijs et al., 2011a; Lluch Girbés et al., 2013).

The question arises which CNS "desensitizing" strategies are available and how they can be applied when treating patients with chronic OA-related pain. These issues will be further discussed below and practical guidelines provided.

Targeting the brain without ignoring the joints for treating central sensitization pain in patients with osteoarthritis

In light of evidence regarding the role CS plays in a subgroup of patients with chronic OA-related pain (Lluch et al., 2014), musculoskeletal therapists might "swing the pendulum" too much away from the biomedical model of pain (Jull and Moore, 2012). Likewise, as psychosocial factors are of importance in OA (Somers et al., 2009), chronic OA-related pain might be envisioned as a merely psychosocial issue. One would then erroneously assume that management advocated for this subgroup of OA patients with CS as their dominant pain mechanism should radically be turned into psychosocial aspects and "hands-off" interventions, with little or no regard to biological features. However, CS in OA seems to be driven by ongoing peripheral joint pathology (Graven-Nielsen et al., 2012), which stresses the importance of reducing peripheral nociceptive input by means of locally applied interventions such as manual therapy (Moss et al., 2007; Courtney et al., 2010) or surgery (Aranda-Villalobos et al., 2013).

Therefore, the authors propose not to completely abandon the "hands-on" approach for patients with chronic OA-related pain and CS, but to find an equilibrium between hands-on treatments and other interventions addressing CS (Jull and Moore, 2012).

Musculoskeletal therapists are probably in the best position to deliver such an individualized and combined approach to patients with chronic OA-related pain (Bennell et al., 2012; Hunt et al., 2013), because they are cognizant of both locally-applied physical and non-physical centrally-oriented interventions (Louw et al., 2011; Nijs et al., 2011b).

In order to inform clinicians about new avenues on combining different treatment strategies for chronic OA-related pain management, an example of the theoretical rationale for *simultaneous* application of an approach aiming to desensitize the CNS [here represented by pain neuroscience education (PNE) (Louw et al., 2011; Nijs et al., 2011b)] and a local intervention (here represented by manual therapy), will be presented.

Combining pain neuroscience education with manual therapy in patients with chronic OA pain and CS as their dominant pain mechanism

Patient education is recommended by most of the current evidence-based guidelines for management of OA (Larmer et al., 2014). However, education by healthcare professionals is usually focused on biomedical information. This kind of education not only has shown limited efficacy in decreasing pain and disability (McDonald et al., 2004; Louw et al., 2013), but also can induce fear, reinforce the patient's belief on a patho-anatomical source of pain and consequently result in more pain (Greene et al., 2005).

A more advantageous way to educate patients with chronic OA-related pain might be PNE (Louw et al., 2011; Nijs et al., 2001b). PNE is a cognitive-based educational intervention performed by musculoskeletal therapists that aims to desensitize the CNS and consequently reduce pain and disability, through a reconceptualization of pain (Louw et al., 2011). PNE is therapeutic on its own, with level A evidence (evidence from meta-analysis of randomized controlled trials) supporting its use for changing pain beliefs and improving health status in patients with CS pain (Louw et al., 2011). Evidence supporting the capacity of PNE to desensitize the CNS comes from a recent trial in patients with fibromyalgia (Van Oosterwijck et al., 2013).

Though sometimes provided separately, PNE seems to be more effective when administered in conjunction with other physical therapy interventions (Louw et al., 2011). Likewise, manual therapy is more beneficial for patients with OA if not used as a stand-alone treatment (Page et al., 2011). However, clinicians may encounter several practical problems when trying to combine PNE and manual therapy in the context of a patient with chronic OA-related pain.

The problem of the "conflicting" messages or "contradictory" messages

Manual therapy is often presented to a patient with chronic OA-related pain within a biomedical model of pain. Traditionally, the main objective of manual therapy has been to find the structure at fault, reproduce the patient's pain if possible and fix that pain thorough joint mobilization/manipulation techniques (Bialosky et al., 2008). However, this "find it and fix it" model could perpetuate the notion of the joint as a single fault for

OA-related pain, fueling the biomedical beliefs (Nijs et al., 2013) and contradicting (when applied together) the PNE message that de-emphasizes a specific tissue as the solely cause of pain. To make the message provided during the combined application of manual therapy and PNE more consistent, musculoskeletal therapists may want to consider the following recommendations.

Instead of "fixing a structure", OA patients should be educated about manual therapy according to the current understanding of its mechanisms of action (Bialosky et al., 2009). Besides peripheral effects (i.e. increase in range of motion), joint mobilization has shown to generate (temporal) activation of descending inhibitory pain mechanisms (Schmid et al., 2008). Hence, manual therapy should be presented to OA patients as a transient technique used to gain movement and activate endogenous analgesia found to be dysfunctional in chronic OA-related pain (Kosek and Ordeberg, 2000). Manual therapy might be a priori capable of restoring one of the mechanisms related to CS in chronic OA pain, namely the impaired descending inhibition, although this hypothesis has not been formally tested.

Still, it is important for OA patients to understand that the central analgesic effects of manual therapy are short-lived. CS is a complex mechanism unlikely to be resolved by a single modality of treatment (Nijs et al., 2011a), so other "desensitizing" techniques such as exercise therapy may be required (Uthman et al., 2013) or PNE. That's why the combination of manual therapy and PNE, which potentially targets CS through modulation of enhanced descending facilitatory mechanisms [i.e. inappropriate beliefs (Zusman, 2002)], could be worthwhile.

Moreover, several types of manual therapy interventions applied for chronic OA patients rely on pain relief as a guide for application and treatment outcome (Takasaki et al., 2013). Repetitive use of the word "pain" during the manual treatment may again come into conflict with the PNE message, where achieving functional gains is advocated over resolution of symptoms. A solution to this conflict may be to replace the use of threatening words such as "pain" during the application of manual therapy techniques by other less frightening terms such as "symptoms" or "loss of function". This might improve the uniformity of the message provided and avoid confusion in patients. It is therefore crucial not to increase vigilance by a priori asking the patient to report any pain experienced (or aggravated) during the hands-on treatment. Relying on the joint end-feel or the baseline outcome of the joint examination (e.g. joint mobility tests) for guiding the hands-on treatment is preferred for patients with CS as a dominant pain mechanism.

The problem of the order of interventions: should manual therapy precede PNE or vice versa?

The question that may arise in the musculoskeletal therapists' clinical reasoning when combining both interventions (i.e. manual therapy and PNE) is: What should I apply first? From the previous section on conflicting messages, maybe keen readers familiarized with both interventions have already deduced that PNE should be logically applied before manual therapy. Both explanation of the impaired descending pain inhibition and enhanced facilitatory mechanisms potentially addressed with this combined approach (with manual therapy and PNE, respectively), are part of the typical PNE message (Louw et al., 2011). Therefore, it would seem logical to first explain to

chronic OA patients that their pain system has become sensitized before presenting them desensitizing techniques, such as manual therapy, as potentially helpful.

In addition, there are other reasons why the message from PNE should be introduced first. Unlike education focused on the biomedical model (Eschalier et al., 2013), PNE is beneficial in changing patients' cognition regarding their pain state resulting in decreased fear and, consequently, promoting better adherence to subsequent movement-based approaches such as manual therapy (Louw et al., 2011). In line with this, the seemingly most logical choice when dealing with patients affected by chronic OA-related pain would be to implement manual therapy after having educated the patient about modern pain neuroscience. Moreover, the occasional reproduction of symptoms when applying joint mobilizations (and the consequent "danger messages" arriving to the brain), would be interpreted differently by the patient if PNE was applied first. As one of the key messages of PNE is that in a chronic pain situation (like chronic OA-related pain) pain is not a true reflection of what's happening at the tissues, but is more related to hyperexcitability of the CNS and deconditioning of the tissues (Louw et al., 2011), the threatening value of pain is decreased.

The problem of cognitive and educational barriers when applying PNE to elderly people affected by chronic OA-related pain

One of the factors associated with reporting more symptoms and responding less to treatment in people with chronic OA-related pain is the socioeconomic status, including low educational attainment (Callahan et al., 2010). In that sense, musculoskeletal therapists can encounter some problems when conveying the key messages of PNE to

elderly patients, mostly due to cognitive and/or educational barriers. In addition, as on average clinicians underestimate the ability of patients to understand the PNE message (Moseley, 2003), this may be more evident when dealing with elderly people affected by OA. Some elderly people with OA have blind faith in (bio)medical information, which often makes it more difficult to reconceptualize pain through PNE. This should be taken into consideration and clinicians are encouraged to adapt the information provided during the PNE to these patients, in order to make it more easily understood.

An example of a musculoskeletal therapist discussing the patient's perceptions about OA pain as part of a PNE session and the rationale of the combination of PNE with manual therapy can be found online at http://www.paininmotion.be/EN/sem-tools.html (Table 1).

Table 1. Example of the communication between a musculoskeletal therapist applying PNE with an elderly patient with chronic knee OA-related pain and CS as the main dominant pain mechanism. Note how the musculoskeletal therapist challenges the patient's biomedical beliefs and presents the patient with a rationale for a combined application of manual therapy with PNE.

- **Therapist (T):** '*So, I would like to start this session asking you about the cause of the pain at your knee. Why do you think your knee is painful?*'
- **Patient (P):** '*I think my knee pain is provoked by the cartilage degeneration in my knee. My surgeon explained it to me in that way. I was able to see it myself when he showed me the X-ray: there was no space between the two bones of my knee! Sorry, I can't remember the names of the bones, but what I could see is*

that they are rubbing together. That's the reason of my pain.'

- **T:** '*I totally understand you; it's a logical way of thinking. But let me ask you one question. If your way of thinking was totally true, how would you then explain the fact that there are people with a lot of degeneration in their knees, a lot of friction, but without feeling any pain?*'
- **P:** '*I don't know… does that actually happen? Gosh, maybe not everybody feels pain in the same way? I remember that I heard or read something like that. There are persons with more or less tendency to feel pain, no?*'
- **T:** '*That could be one of the reasons, yes. Each person experiences pain differently. But let me continue. If you were on the right way of thinking about your pain, then surgery, such as a total knee replacement, would be like a magic bullet for knee osteoarthritis. It should completely eliminate the knee pain. However, how would you then explain that some people continue experiencing pain even after surgery if it's supposed that the source of pain has been eliminated?*'
- **P:** '*Perhaps because the surgery is not well-performed or there is some kind of complication? A good friend of mine had to be operated three times for the same knee due to loosening of the prosthesis and later because of an infection. And even now he is still very much in pain! I cannot understand…*'
- **T:** '*A failed surgery or complications post-surgery could explain that persistent pain, absolutely. But there are people who underwent surgery without complication and even so still have pain. So, there must be other factors explaining the pain, don't you agree?*'
- **P:** '*Yes, I suppose… but I don't totally understand what you are trying to say. Do you mean that the surgeon's opinion is not right, that my knee pain is not*

due to cartilage loss?'

- **T:** '*What I'm trying to say is that cartilage degeneration is in part responsible for your pain, but not the sole reason. That's why we often find discordances between the degree of cartilage degeneration and the intensity of pain experienced, or why some people still feel pain even after surgery.*'
- **P:** '*Ok, but then… where is my pain coming from if it is not coming from my knee? I'm now becoming a little bit confused.*'
- **T:** '*That's what we are going to explain to you in this session. What we actually know is that in a chronic pain situation like yours your nervous system, which works like an alarm system of your body, is not working in the normal way. Specifically, nerves transmitting the message of damage from your knee to higher regions of your body, like the brain, have become too sensitive or overactive. These nerves have been working for a long time, day after day, sending up danger messages of what was happening at your knee. Now, after so much time working in this way, your nerves have turned into a sensitized state. It is as if the volume button of your nervous system is turned up*'
- **P:** '*And what can I or you do to get me better now? It doesn't sound very good. You said sensi… what? Is there any cure for that?*'
- **T:** '*Sensitization of your nerves. What we are going to do with treatment is to try to calm down this excess of sensitivity of your nervous system. To do that we will combine some educational sessions to explain in more detail the chronic pain you feel at your knee with a series of mobilizations applied to your knee. We currently know that both interventions are capable of decreasing the sensitivity of an overactive nervous system like yours so we will use them in combination.*

Are you happy with that?'

- **P:** '*Yes. Let's try and see*'.

CONCLUSION

The aim of this paper is to present a sound scientific rationale and practical guidelines for the application of a combined manual therapy and PNE approach in patients with chronic OA-related pain and CS as their dominant pain mechanism. Musculoskeletal therapists may find some practical problems when combining these two interventions in a clinical setting. Future studies should test these promising avenues for the treatment of chronic OA-related pain against current approaches, in order to determine if they can increase therapeutic outcomes.

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PREOPERATIVE PAIN NEUROSCIENCE EDUCATION COMBINED WITH KNEE JOINT MOBILIZATION FOR KNEE OSTEOARTHRITIS: A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Objectives: To compare the effects of a pre-operative treatment combining pain neuroscience education (PNE) with knee joint mobilization versus biomedical education with knee joint mobilization on central sensitization (CS) in subjects with knee osteoarthritis (KOA). Secondarily, to investigate the effects of both interventions on knee pain, disability and psychosocial variables.

Methods: Forty-four subjects with KOA were allocated to receive four sessions of either PNE combined with knee joint mobilization or biomedical education with knee joint mobilization before surgery. All participants completed self-administered questionnaires and performed quantitative sensory testing at baseline, after treatment and at one month follow-up (all before surgery) and at three months after surgery.

Results: Significant and clinically relevant differences over time were found after both treatments for knee pain and disability and some measures of CS (i.e. widespread hyperalgesia, central sensitization inventory), with no significant between-group differences. Other indicators of CS (i.e. conditioned pain modulation, temporal summation) did not change over time in either treatment or even the observed changes were not in the expected direction. Subjects receiving PNE with knee joint mobilization achieved greater improvements in psychosocial variables (pain catastrophizing, kinesiophobia) at short and long follow-ups.

Discussion: Pre-operative PNE combined with knee joint mobilization did not produce any additional benefits over time in knee pain and disability and CS measures compared with biomedical education with knee joint mobilization. Superior effects in the PNE with knee joint mobilization group were only observed for psychosocial variables related to pain catastrophizing and kinesiophobia.

Key words: Knee osteoarthritis, central sensitization syndromes, physical therapy, education

INTRODUCTION

The pain experience in knee osteoarthritis (KOA) is a multifactorial phenomenon comprising knee structural changes ocurring together with psychosocial and pain neurophysiology factors[1]. Regarding the latter, there is compelling evidence that central sensitization (CS) is a prominent phenomenon in a subgroup of people with KOA[2]. Despite the increased emphasis on the importance of CS in KOA[3], current KOA treatments don't usually specifically address altered nociceptive processing mechanisms[4]. Indeed most evidence-based recommendations for KOA management[5,6] don't consider pain mechanisms and its possible modulation by treatment.

Some studies have investigated the effects of treatments used for KOA on central pain modulation using outcome measures related to CS [e.g., the flexor withdrawal reflex[7] and conditioned pain modulation (CPM)[8]]. In those studies, CS was down-modulated after knee joint mobilization[7-9], exercise[10], TENS[11], surgery[12] or a combination of interventions[13]. Combined treatments consisting of locally-applied and centrally-oriented interventions have been proposed for KOA[14,15], aiming for synergistic effects and consequently an improvement of outcomes.

Within this view of combined treatments, the rationale for applying pain neuroscience education (PNE) together with knee joint mobilization was recently presented[14], but requires experimental testing. On one hand, knee joint mobilization may produce beneficial effects on pain and function in KOA[16,17] as well as modulating effects on CS[7-9]. On the other hand, PNE is a useful intervention for chronic pain populations characterized by CS, especially when administered with other physical therapy interventions[18]. Enhancement of CPM was shown following PNE[19] and, when applied

before surgery, PNE produced favorable post-surgical outcomes in people with lumbar radiculopathy[20]. As the pre-surgical presence of CS in KOA contributes to poor outcomes after total knee replacement[21], preoperative PNE combined with other interventions[18] might be beneficial.

The primary aim of this study was to compare the effects of a pre-operative treatment combining PNE with knee joint mobilization versus biomedical education with knee joint mobilization on measures of CS in people with KOA. Secondarily, the effects of both interventions on knee pain, disability and psychosocial variables were investigated. We hypothesized that PNE with knee joint mobilization would result in significantly greater improvements in CS and psychosocial measures.

MATERIALS AND METHODS

Study design

A two-arm, parallel group, assessor blinded, randomized controlled trial conforming to CONSORT guidelines[22] was performed between January 2014 and February 2015, at the Hospital Universitario La Ribera (Alzira, Spain). The study was approved by the Human Research Ethics Committee of the Hospital Universitario La Ribera and conducted in accordance with the Declaration of Helsinki. The study was registered at ClinicalTrials.gov (Trial Registration NCT02246088).

Participants

People with KOA pain of more than 3 months duration and scheduled to undergo total knee replacement were enrolled. They were recruited from the Orthopedic Surgery Service of the Hospital Universitario La Ribera, Spain.

Individuals were included if they had symptomatic KOA according to the American College of Rheumatology classification criteria[23]. All participants underwent weight bearing, fixed flexion posteroanterior and lateral X-rays of their affected knee. Radiographic disease severity of the tibiofemoral (Kellgren–Lawrence 0–4 grading scale[24]) and patellofemoral (Ahlbäck 0-5 grading scale[25]) compartments were evaluated for each participant.

Subjects were excluded if they had previous total knee replacement or any other lower limb surgery within the past six months of the affected knee, co-existing inflammatory, metabolic or neurological disease, cognitive impairment, illiteracy, or were unable to speak or write Spanish.Subjects were informed about the procedures and gave written informed consent prior to participation.

Procedure

Demographic information was first collected by self-report. Participants additionally completed an 11-point numeric rating scale to quantify their current pain intensity overall during the last week.

They then completed the following self-administrated questionnaires: the Western Ontario and McMaster Universities Arthritis Index (WOMAC), Central Sensitization Inventory (CSI), Pain Catastrophizing Scale (PCS) and 11-item version of the Tampa Scale for Kinesiophobia (TSK-11). Finally, all participants were assessed by quantitative sensory testing to examine pressure pain thresholds (PPTs), temporal summation and CPM in one individual session. Participants were requested not to take analgesic medication 24h before the assessment.

A physical therapist, specifically trained in all aspects of assessments, was responsible for all the measurements. This assessor was blinded to questionnaire data and treatment allocation.

Outcome Measurements

The primary outcome measure was CPM which is a recognized objective biomarker of CS[3]. Secondary outcomes were PPTs, temporal summation and results from the questionnaires. Every outcome was measured at baseline (2 months before surgery), immediately after four treatment sessions (1 month before surgery), at one month follow-up (just before surgery) and three months after surgery.

Assessment of CS

Pressure pain thresholds

A standardized protocol for evaluating PPTs was used[26]. Two test sites in the peripatellar region (3 cm medial and lateral to the midpoint of the medial and lateral edge of patella, respectively) and one distant site on the ipsilateral extensor carpi radialis longus (5 cm distal to lateral epicondyle) were selected for measurement[27]. The PPT was measured using an analogue Fisher algometer (Force Dial model FDK 40) with a surface area of 1cm^2. The algometer probe tip was applied perpendicular to the skin at a rate of 1kg/cm^2/s until the first onset of pain. Three measures were performed on each site with a 30 s interstimulus interval between each measurement and the mean was taken for analysis. For PPTs, a 1.62-1.53 kg/cm^2 is the minimum detectable change required to be clinically meaningful in subjects with KOA[28].

Temporal summation and Conditioned pain modulation

The protocol described by Cathcart and colleagues was used for measuring temporal summation and CPM[29], which are established ways of measuring excitability of nociceptive pathways and descending pain inhibition, respectively[30,31].

First, PPTs were measured at the local and distal sites as described above. Second, temporal summation was provoked by means of 10 consecutive pulses at the previously determined PPT at each location. For each pulse, pressure was gradually increased at a rate of 2 kg/s to the determined PPT and maintained for 1 s before being released (1 s interstimulus interval). Pain intensity of the 1st, 5th, and 10th pulse was rated on a numerical rating scale (0: no pain to 10: worst possible pain). Afterwards, a rest period of 5 min was given.

Third, CPM was induced by combining the temporal summation procedure (test stimulus) and an inflated occlusion cuff around the subject's arm, contralateral to the side of the affected knee, to a painful intensity (conditioning stimulus). The occlusion cuff was inflated at a rate of 20 mm Hg/s until 'the first sensation of pain' and maintained for 30 s. Following, pain intensity, as a result of cuff inflation, was rated on a numerical rating scale. Next, cuff inflation was increased or decreased until the pain intensity was rated as 3/10. Temporal summation assessment was then repeated during maintenance of the cuff inflation[29].

The details and data supporting the test-retest reliability and validity of the protocol for examining temporal summation and CPM are described elsewhere[29].

Central Sensitization Inventory (CSI)

The CSI is a self-report screening instrument that helps to identify key symptoms associated with CS[32]. Part A of the CSI assesses increased responsiveness to a variety of stimuli and is comprised of 25 items each ranged on a 5-point scale with the end points "never" (0) and "always" (4) (range: 0-100). It has high reliability and validity[32]. A cutoff score of 40 distinguished between individuals with central sensitivity syndromes and a non-patient comparison sample (sensitivity = 81%, specificity = 75%)[33]. The following CSI severity levels have been established for interpreting CSI scores: subclinical = 0 to 29; mild = 30 to 39; moderate = 40 to 49; severe = 50 to 59; and extreme = 60 to 100[34]. The Spanish version of the CSI was used in this study.

Knee pain and disability

The total WOMAC score (range 0-96) was considered with higher scores indicating worse knee pain and disability. Test-retest reliability, internal consistency, convergent validity and responsiveness of the Spanish version of the WOMAC has been demonstrated in people with KOA[35]. A 7.9-point change is required for the result of WOMAC to be clinically meaningful[36].

Psychosocial variables

Pain catastrophizing

The Pain Catastrophizing Scale (PCS), which is a valid and reliable instrument to measure pain catastrophizing, was used[37]. It consists of 13 items each ranged on a 5-point scale with the end points (0) "not at all" and (4) "all the time" (range: 0-52). Higher scores indicate higher pain catastrophizing. The Spanish version of the PCS

showed appropriate internal consistency, test-retest reliability and sensitivity to change[38].

Kinesiophobia

The Spanish version of the TSK-11 was used to measure fear of movement[39]. It is comprised of 11 items each ranged on a 4-point scale with the end points (1) "totally agree" and (4) "totally disagree" (range: 11-44). The TSK-11 has demonstrated acceptable internal consistency and validity (convergent and predictive)[39]. Higher scores indicate more fear-avoidance behavior. The minimal detectable change score for the TSK-11 is 5.6[40].

Interventions

An equal number of participants were randomly allocated by the computer program EPIDAT version 3.1, to receive either PNE plus knee joint mobilization (experimental treatment) or biomedical education plus knee joint mobilization (control treatment). The researcher administering the randomization schedule was different from those who recruited the participants.

In both groups, the educational part of the intervention preceded knee mobilization[14] and participants were blinded to the type of education they received. Both programmes involved a total of four treatment sessions (one session per week), starting two months prior to surgery and finishing one month prior to surgery in all participants. All interventions were applied by a physiotherapist experienced in providing educational and knee joint mobilization procedures. This therapist was blinded to the results of the measurements and questionnaires which were used as outcome measures.

All participants were instructed to continue to take any current medications but not to start new medications or initiate new treatments during the treatment period.

PNE with knee joint mobilization

PNE and knee joint mobilization were applied following previous published guidelines[14]. The therapist avoided conflicting or contradictory messages between these two interventions, for instance, not using pain relief as the guide and threatening words such as "pain" during knee joint mobilization[14]. In addition, key messages of PNE were adapted to elderly patients in order to make it more easily understood[14].

PNE was provided in accordance with published guidelines[41]. Educational information was presented verbally and visually with the aid of a computer. The content and pictures of the sessions were based on the book *Explicando el dolor*[42] and a booklet designed for patients having knee replacement surgery[43].

Four sessions on pain neurophysiology were delivered. The first session was a longer session lasting 50 to 60 minutes whereas the second, third and fourth follow-up sessions lasted 20-30 minutes. After the first session, participants were asked to read *Explicando el dolor*[42] at home. During the second, third and fourth sessions the therapist answered questions that had arisen after the first session and reading the book, tailoring these sessions and emphasizing the topics needed additional explanation.

Knee joint mobilization was applied using Mulligan's mobilization with movement following the protocol from Takasaki et al[16]. Mobilization with movement during active knee flexion and/or extension, depending on which was the limited/painful movements

for each patient, was applied progressing from non-weight-bearing to weight-bearing positions[16]. All the mobilizations were performed for three sets of 10 repetitions and patients were asked to perform self-applied mobilizations at home involving four series of 20 movement repetitions per day[16]. Home treatment adherence was recorded by means of a timetable.

Biomedical education with knee joint mobilization

Individuals assigned to this group received information regarding anatomy and biomechanics of the knee, and etiology, symptoms, recommended treatments and surgical procedure of KOA. That information was provided through visualization of several videos which were presented on a computer. No information about mechanisms underlying pain was included in order to establish a clear difference with information provided from the PNE. The total duration of education was the same as PNE. After the education, these participants received the same mobilization protocol as the other group, except that all the mobilization techniques were pain-guided.

Statistical analysis

Sample size

The required sample size was calculated using G*Power 3.0.18 Software based on CPM as the primary outcome measure. The effect size for the CPM was considered at 0.25. The correlation between repeated measurements assumed was assumed in 0.5. Considering four measures in two treatment groups, the sphericity correction was determined at 0.5. We estimated a sample size of 44 participants with a statistical power of 0.95 and an alpha level of 0.05. Considering a possible loss to follow-up of up to 20%, a total of 53 patients with KOA were recruited.

Analysis

Descriptive statistics were used to describe the baseline characteristics of individuals in each group. Student's t-test or Mann-Whitney U-test (for continuous variables) and chi-square or Fisher exact tests (for categorical variables) were applied to determine if there were baseline differences between groups.

Temporal summation was calculated as the difference in percentage between the 10th and the 1st pain rating score before occlusion using the formula: ((Temporal summation10th temporal summation1st)/temporal summation1st)*100[44]. CPM was calculated as the difference between the 10th pain rating score before occlusion and the 10th during occlusion[29].

In order to analyze the effectiveness of the two interventions, a per protocol analysis was performed. Analysis of variance (ANOVA) was performed for each of the patient-related outcomes. Three-way ANOVA was used to evaluate differences in PPTs, CPM and temporal summation. The between subject factor was treatment (experimental treatment, control treatment), with time (baseline, immediately post treatment, 1 month post treatment, 3 months post-surgery) and location (lateral knee, medial knee, epicondyle) as within subject factors.

Data from the self-administration questionnaires were each analyzed with a two-way ANOVA with treatment (experimental treatment, control treatment) as the between-subject factor, and time (baseline, immediately post treatment, 1 month post treatment, 3 months post-surgery) as the within subject factor. In each case, significant differences revealed by ANOVA were followed by post-hoc Student-Newman-Keuls (SNK) pair-

wise comparisons. The effect size was calculated as the Partial Eta Squared (η^2_p) when significant. An effect size of 0.01 was considered small, 0.06 medium and 0.14 large[45].

Statistical analyses were performed using SPSS 22 (SPSS INc, Chicago, IL, USA). The significance level was set at $p < 0.05$.

RESULTS

The participant flow and retention is depicted in Figure 1. A total of 44 participants were finally analyzed [experimental treatment (n=22); control treatment (n=22)]. All these participants completed the four treatment sessions including the home task performance of mobilizations with movement and reading of the book if allocated to PNE.

Baseline characteristics of both groups are presented in Table 1. There were no significant differences in baseline variables between the groups (all $p>0.05$).

Figure 1. Participants flow and retention.

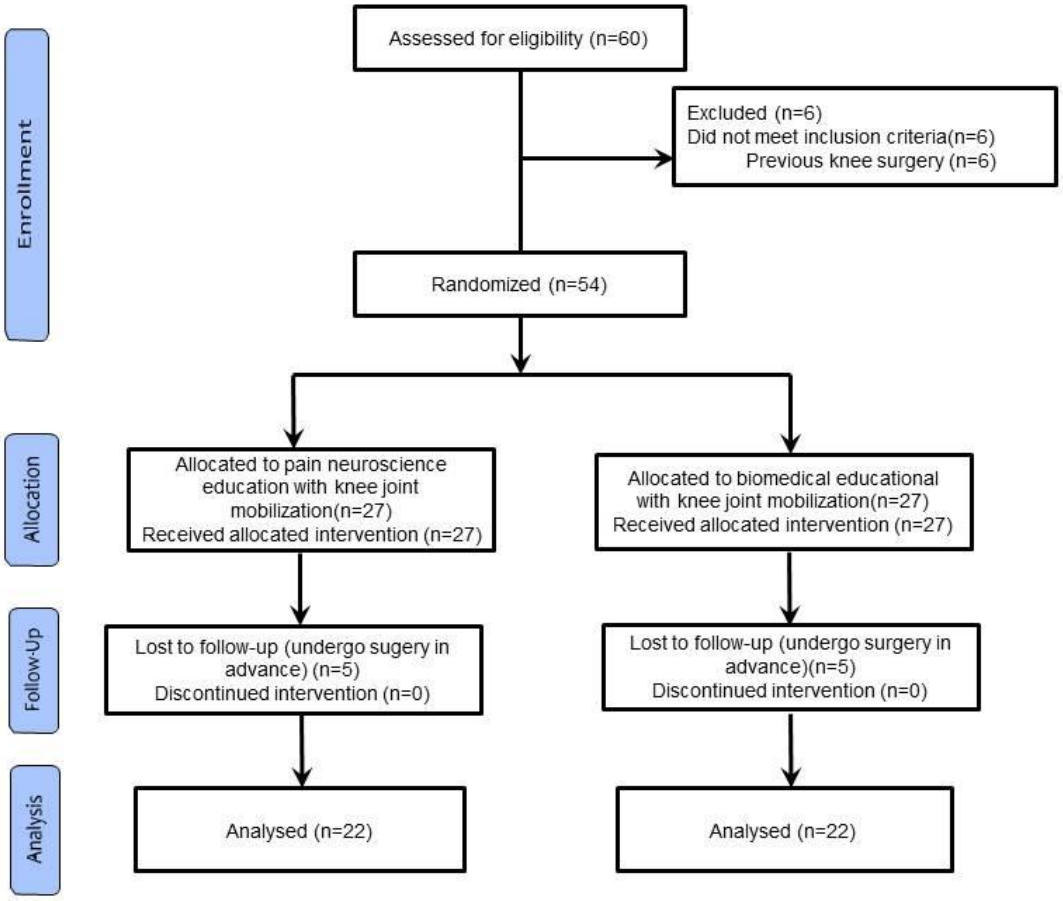


Table 1. Baseline characteristics of the patient groups. Values are presented as Mean ± SD.

Baseline demographic characteristics of OA patients	Biomedical education with knee joint mobilization	Pain neuroscience education with knee joint mobilization
Age (years)	72.8 ± 5.6	67.7 ± 7.8
Gender (% female)	68	59
Height (cm)	160.9 ± 7.4	163.5 ± 7.6
Weight (kg)	80.0 ± 10.3	79.1 ± 14.9
Duration of Pain (years)	7.2 ± 5.2	8.3 ± 6.1
Numeric Rating Pain Scale (0-10)	5.4 ± 1.6	6.2 ± 1.5
Kellgren–Lawrence grade (tibiofemoral joint) n (%)		
0	0 (0)	0 (0)
1	0 (0)	0 (0)
2	6 (27.3)	6 (27.3)
3	11 (50)	10 (45.4)
4	5 (22.7)	6 (27.3)
Ahlbäck grade (patellofemoral joint) n (%)		
1	2 (9.1)	3 (13.6)
2	6 (27.3)	7 (31.8)
3	13 (59.1)	12 (54.6)
4	1 (4.5)	0 (0)
5	0 (0)	0 (0)

Primary outcome: conditioned pain modulation

CPM scores differed across locations ($F=4.92$, $p=0.007$, $\eta^2_{p:}$ 0.02) and were significantly lower at both the lateral knee (SNK: $p<0.01$) and epicondyle (SNK: $p<0.05$) compared to the medial knee. Regardless of the location, there was an interaction between treatment and time ($F=4.66$, $p<0.01$, $\eta^2_{p:}$ 0.02; Figure 2). However, the only significant change was observed for the experimental treatment between baseline CPM value and the value measured 3 months post-surgery (SNK: $p<0.05$) with lower values of CPM noted 3 months after surgery. No other changes were observed for the experimental treatment and no statistically significant changes were observed for the control treatment.

Figure 2. Mean ± SE of conditioned pain modulation at baseline, immediately post-treatment, 1 month post treatment and 3 months after surgery for individuals with knee osteoarthritis performing pain neuroscience education with knee joint mobilization versus subjects receiving biomedical education with knee joint mobilization

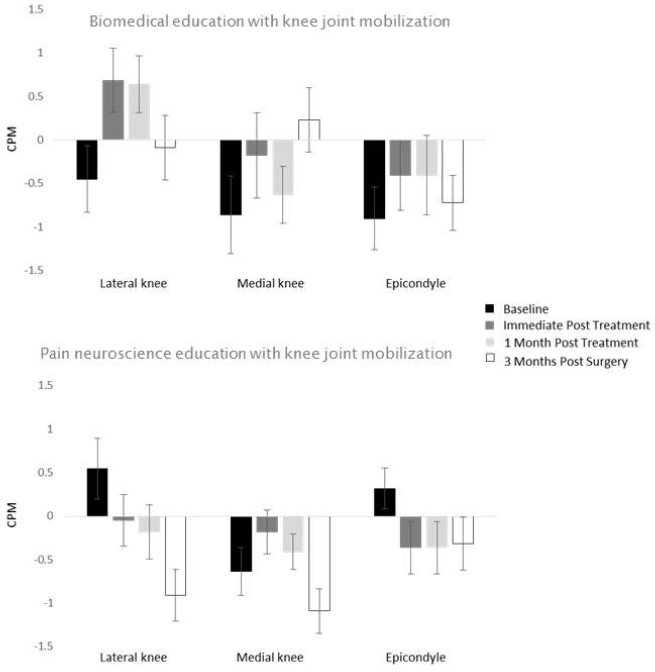
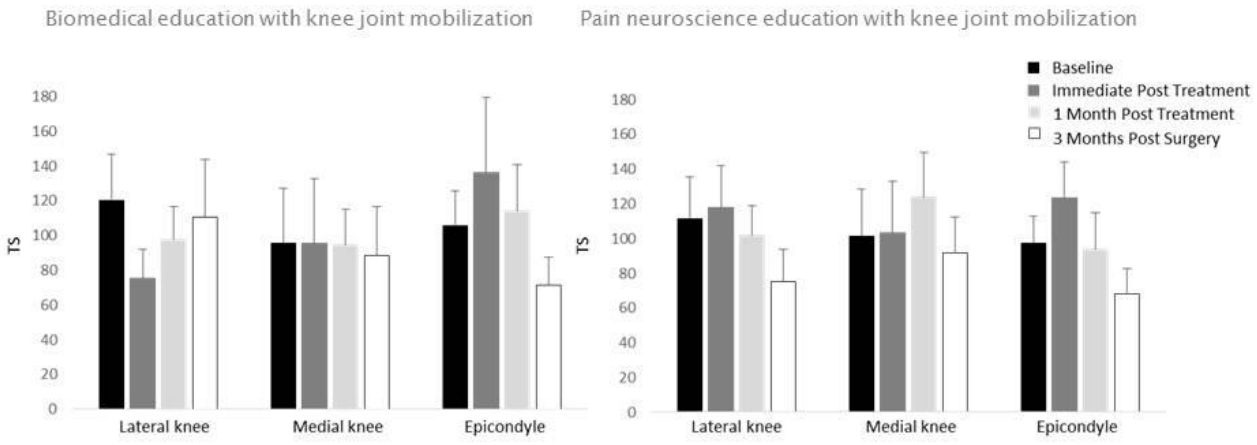


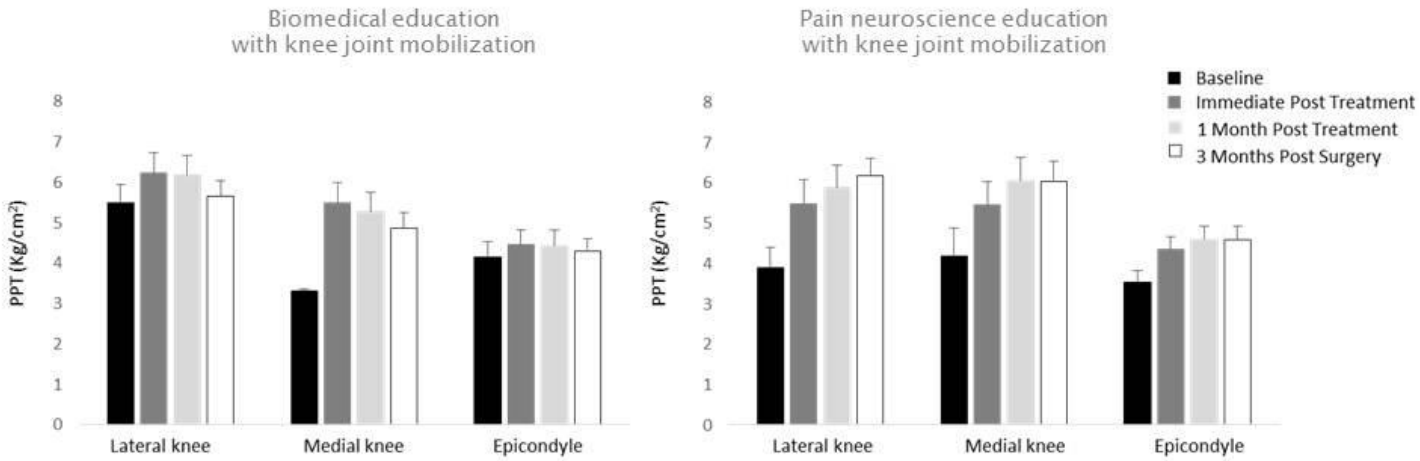
Figure 3. Mean ± SE of temporal summation of pain at baseline, immediately post-treatment, 1 month post treatment and 3 months after surgery for individuals with knee osteoarthritis performing pain neuroscience education with knee joint mobilization versus subjects receiving biomedical education with knee joint mobilization.



PPTs differed across locations (F=18.28, p<0.0001, $\eta^2_{p:}$ 0.06) with higher PPTs at the lateral knee compared to the medial knee (SNK: p<0.01) and epicondyle (SNK: p<0.0001) and higher values at the medial knee compared to the epicondyle (SNK: p<0.0001). PPTs did not differ between treatments but changed over time (F=11.28, p<0.0001, $\eta^2_{p:}$ 0.06). For both treatments there was a significant increase in PPTs at all locations immediately post treatment (percent change in PPTs averaged across all sites: experimental treatment: 40.6 ± 31.2%; control treatment: 27.3 ± 41.7%), at 1 month after treatment (experimental treatment: 49.6 ± 30.3%; control treatment: 24.4 ± 34.2%)

and at 3 months after surgery (experimental treatment: 53.4 ± 45.3%; control treatment: 17.1 ± 30.5%) compared to baseline (SNK: all $p<0.00001$, Figure 4). However, there was no significant change for either treatment between the time points of immediately post treatment, at 1 month after treatment and at 3 months after surgery.

Figure 4. Mean ± SE of the pressure pain thresholds at baseline, immediately post-treatment, 1 month post treatment and 3 months after surgery for individuals with knee osteoarthritis performing pain neuroscience education with knee joint mobilization versus subjects receiving biomedical education with knee joint mobilization.



Secondary outcomes: symptoms of central sensitization, knee pain and disability

Table 2 shows results from the questionnaire data at each measurement time. The CSI score improved over time with both treatments ($F=5.51$, $p<0.001$, $\eta^2_{p:}$ 0.09), with no significant difference between treatments ($F=0.80$, $p=0.49$). For both treatments, the CSI score did not change from baseline to immediately post treatment or 1 month post treatment (all SNK: $p>0.05$). However it was significantly lower with both treatments when measured 3 months post-surgery compared to baseline, immediately post treatment, and 1 month after treatment (all SNK: $p<0.05$). The percent change at 3 months compared to baseline was -37.3 ± 24.0% and -11.7 ± 80.1% for the experimental and control treatment, respectively.

Table 2. Scores obtained in the questionnaire data at each time point for the experimental treatment (pain neuroscience education plus knee joint mobilization) and control treatment (biomedical education plus knee joint mobilization). All values are expressed as Mean ± SD.

VARIABLE	TREATMENT	Baseline	Immediately post treatment	1 month post treatment	3 months post surgery
CSI (0-100)	Experimental treatment N=22	37.6±17.2	30.3±10.2	27.8±11.1	21.5±10.1
	Control treatment N=22	38.3±15.6	38.1±15.7	36.2±15.7	30.3±16.1
WOMAC (0-96)	Experimental treatment N=22	52.4±14.6	41.4±13.7	38.1±11.6	21.1±10.9
	Control treatment N=22	52.1±18.4	50.1±18.5	46.0±18.0	32.6±20.6
PCS (0-52)	Experimental treatment N=22	22.6±11.5	12.5±10.3	10.7±8.4	6±5.3
	Control treatment N=22	25.9±13.6	24.5±13.6	25±13.6	22.7±13
TSK-11 (11-44)	Experimental treatment N=22	34.3±7	25.9±5.9	24±5.4	21.5±5.1
	Control treatment N=22	33.7±5.6	33.6±6.7	33.6±6.6	30.8±6

The WOMAC total score decreased over time ($F=19.46$, $p<0.0001$, $\eta^2_{p:}$ 0.26) for both treatments but was not dependent on the interaction between treatment and time ($F=1.07$, $p=0.35$). For both treatments, the WOMAC score decreased 3 months post-surgery compared to baseline (experimental treatment: -58.3 ± 21.9%; control treatment: -38.6 ± 31.5%), immediately post treatment and at 1 month after treatment (all SNK: $p<0.0001$). The WOMAC score was also lower for both treatments 1 month after treatment compared to baseline (SNK: $p<0.01$; experimental treatment: -24.6 ± 21.9%; control treatment: -9.7 ± 23.9%).

Secondary outcome: psychosocial variables

There was an interaction for the PCS score between treatment and time ($F=7.26$, $p<0.001$, $\eta^2_{p:}$ 0.11). For the experimental treatment, there was a significant reduction in the PCS 3 months post-surgery, immediately post treatment and at 1 month after treatment (all SNK: $p<0.001$) compared to the baseline scores. Whereas for the control treatment, PCS score were the same three months post-surgery as they were at baseline (SNK: $p=0.59$). The only reduction in PCS score with control treatment was noted at 1 month after treatment versus baseline and immediately post treatment (SNK: both $p<0.0001$), but by three months post-surgery the PCS score had returned to baseline values. Significantly lower values of the PCS were seen with the experimental compared to control treatment immediately post treatment and at 3 months post-surgery (all SNK: $p<0.01$).

The TSK-11, which was dependent on the interaction between treatment and time ($F=6.81$, $p<0.001$, $\eta^2_{p:}$ 0.11), also showed no improvement with the control treatment. However, the TSK-11 score decreased with the experimental treatment immediately post treatment, at 1 month after treatment and 3 months post-surgery (all SNK: $p<0.0001$) compared to baseline score. The TSK-11 score was also significantly lower 3 months post-surgery compared to immediately post treatment (SNK: $p<0.05$). The reduction of the TSK-11 score with the experimental treatment resulted in significantly lower values compared to the control treatment immediately post treatment, at 1 month after treatment and at 3 months post-surgery (all SNK: $p<0.00001$).

DISCUSSION

This study showed that a pre-operative treatment combining PNE with knee joint mobilization did not produce any significant superior effect in CS measures and knee pain and disability compared to biomedical education plus knee joint mobilization in people with KOA. Greater improvements in the PNE with knee joint mobilization group were observed for psychosocial variables related to pain catastrophizing and kinesiophobia, which confirms part of our hypothesis. Regarding CS measures, only some CS correlates (i.e. widespread hyperalgesia, CSI score) achieved significant improvement after both interventions with no additional benefits for the experimental group, while other indicators of CS such as CPM and temporal summation did not change over time in either treatment or even the observed changes were not in the expected direction.

Central sensitization

A significant increase in local and remote PPTs was demonstrated with both treatments over time with a moderate effect size. However, as seen in Figure 4, these changes were only clinically meaningful [28] for the local PPTs. The increase in remote PPTs after both interventions may provide evidence of modulation of central pain mechanisms[3]. Our findings are consistent with previous studies using knee joint mobilization[8,9] or PNE[46] in isolation, where both a local and global increase of PPTs was demonstrated after treatment. In studies assessing knee joint mobilization[8,9], passive oscillatory mobilization techniques were applied and only immediate effects on PPTs were evaluated. The current study expands the knowledge regarding the neurophysiological effects of manual therapy techniques for KOA, by showing short and long-term peripheral and central modulatory improvements over time when using mobilization with movement techniques preceded by education, regardless of the type of education provided.

To our knowledge, this is the first time that CSI has been used in a trial as an outcome measure. A decrease in symptoms of CS, as reflected by lower CSI scores, was observed after both treatments at all measurement times with a medium effect size. On the contrary, other variables related to CS did not change over time with either intervention, or the changes were in the opposite direction to our a priori hypothesis (i.e. CPM). Conflicting results on CS measures were also reported by Skou et al[13] who concluded that, when assessing treatment effects through multiple pain-related measures including CS, results may differ depending on what measures are being evaluated[13].

Our results regarding CPM differ with previous research showing an enhancement of CPM after knee joint mobilization[8] or PNE[19]. We found no enhancement of CPM after either intervention. Differences in the nature of the mobilization technique (mobilization with movement versus passive oscillatory mobilization[8]) may have accounted for this discrepancy. Passive oscillatory mobilizations might be a preferable option for activation of descending nociceptive inhibitory pathways for KOA, either alone or in combination with other interventions such as PNE. In addition, unlike previous research[8,19], mobilization with movement was always combined with prior education in the current study.

Knee pain and disability

Measures related to knee pain and disability improved for both treatments at all-time points with large effect sizes, but no significant differences were observed between treatments. Compared to baseline, improvements in knee pain and disability for both groups (Table 2) were not only statistically significant, but also clinically meaningful[36] at one month after treatment and three months post-surgery. These results are important as function of people waiting for surgery is significantly worse than that of the reference population[47]. Previous research showed beneficial effects in pain and disability following knee joint mobilization[8,9,16,17] and biomedical education[48].

Psychosocial variables

Only the experimental treatment achieved significant improvements in psychosocial measures, with overall medium effect sizes. In addition, changes observed in the TSK-11 were clinically meaningful[40] immediately post-treatment and 3 months after surgery when compared to baseline. Our results are consistent with known favorable effects of

PNE on decreasing catastrophism and kinesiophobia observed in other chronic pain populations[18-20,46]. In addition, the post-surgical benefits observed after pre-operative PNE are in line with other studies[20].

Pre-operative educational programs for KOA, as applied in the control group, are centered on a biomedical model and don't normally include a pain science education component. This type of education was ineffective for changing psychosocial factors in people with KOA. One possible reason may be that threatening terminology characteristic of this kind of education had elicited negative emotional responses.

Limitations

The main limitation of this study is the lack of a control group not receiving any pre-operative intervention and undergoing surgery which would have allowed us to compare the results of both interventions with the natural history of KOA. In addition, given the small sample size, definitive conclusions cannot be extracted so further replication in a bigger sample is warranted. The per protocol analysis may have introduced bias as participants who underwent surgery earlier were not included in the analysis. Minimal clinically important difference was only established for some variables, but not for others. Therefore, firm conclusions about clinical relevance of findings related to the variables where no data existed could not be made.

Due to the multimodal setup of the two interventions investigated, it is not possible to determine individually the efficacy of each treatment. In addition, treatment was not matched to pain phenotype the participants presented when entering the study. Individuals with a higher degree of CS might have responded better if assigned to the

experimental treatment, as PNE is especially indicated when the clinical picture is dominated by CS[18,41]. Future studies could define subgroups of people with KOA having similar pain phenotype and evaluate whether matching interventions to subgroups improve outcome.

In conclusion, a pre-operative treatment for people with KOA combining PNE with knee joint mobilization did not produce any additional benefits in knee pain and disability and CS measures, when compared to biomedical education with knee joint mobilization. Superior effects were observed in the PNE and knee joint mobilization group for psychosocial variables related to pain catastrophizing and kinesiophobia.

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CHAPTER 5

CHAPTER 5
General discussion

GENERAL DISCUSSION

Our understanding of the pathophysiology of pain has increased substantially over the last years. Nowadays pain is no longer considered a proxy to nociception but a conscious experience that can be associated with nociception, but that it is always modulated by a myriad of neurobiological, environmental, and cognitive factors [1]. Historically, pain in knee OA has been attributed to peripheral nociception possibly because the majority of physiotherapists have received a biomedical-focused training or education [2]. However, the poor association between objective measures of disease severity and clinical symptoms [3,4], the lack of complete resolution of symptoms in some patients even after eliminating the nociceptive source (i.e., knee replacement surgery) [5-8] or changes observed in some biomarkers of CS such as temporal summation of pain or conditioned pain modulation [9] suggests that non-local factors, such as altered central processing of painful stimuli , also contribute to clinical pain in knee OA.

In this dissertation, central pain mechanisms related to the pain experience of people with osteoarthritis including those affected by knee OA were studied. The first part of the dissertation focused on revising the existing evidence regarding the presence of CS in people with osteoarthritis pain and current interventions addressing pain sensitization in this population. The second part consists of a study assessing whether the area of pain assessed using pain drawings relates to CS and clinical symptoms including the level of pain, disability and psychosocial factors in people with knee OA. In the third part, the theoretical rationale of a combined intervention comprising PNE together with knee joint mobilization and the clinical effectiveness of this combined approach when applied pre-operatively in people with knee OA was investigated.

The following research questions were addressed in the general introduction of this dissertation:

- What is the role central sensitization plays in people with osteoarthritis including those with knee OA and which options do we have for treatment?
- Are measures of central sensitization associated with the area of pain and clinical symptoms in subjects with knee osteoarthritis?
- Is a combined intervention of manual therapy addressing the knee and pain neuroscience education targeted to the central nervous system effective for people with knee osteoarthritis?

In this final chapter, we will answer these research questions, and discuss the main findings and conclusions of the studies included in the dissertation. In addition, recommendations for further research will be formulated.

Main findings and discussion of the research questions

What is the role central sensitization plays in people with osteoarthritis including those with knee OA and which options do we have for treatment?

In addition to the pathological changes in the knee joint, changes in central pain processing or CS appear to be involved in osteoarthritis pain. This is reflected by the great number of narrative reviews regarding CS in osteoarthritis published in the scientific literature [10-14]. However, prior to the initiation of the present dissertation, a study that systematically reviewed the literature related to the presence of CS in osteoarthritis pain was unavailable. Likewise, the scientific literature offered hardly any information addressing the (conservative) treatment of CS specifically in osteoarthritis

patients. It seemed therefore valuable to conduct a systematic review on this topic and to explore rehabilitation options for patients with OA pain having CS as their dominant mechanism.

A non-systematic review of the literature was performed aiming to summarize current evidence regarding CS in osteoarthritis pain [15]. In that review, it was concluded that a significant proportion (approximately 30%) of patients with OA show signs of CS. In addition, it was recognized that osteoarthritis pain is a heterogeneous pathology characterized by a complex and multifactorial nature so strategies to allow reliable and systematic recognition of the subgroup of patients with OA whose pain has a CS component were needed. Since that review, researchers have put a lot of effort into profiling clinical pain phenotype within the knee OA population as indicated by the high number of studies looking at classification of patients with knee OA in terms of pain mechanisms [16-22]. Distinct clinical phenotypes in the knee OA population have been recognized based on several factors such as serological biochemical and pain biomarkers [17,18], biomarkers confirming the presence of CS such as PPTs, temporal summation or conditioned pain modulation resulting in a pain sensitivity index [19], psychological, health and sensory assessments [20] or contribution of different domains to pain experience (i.e. knee joint, psychosocial factors, altered pain neurophysiology) [21]. Overall all these classifications systems have supported the presence of a subgroup of chronic knee OA pain in which central mechanisms (e.g., CS) are prominent. Kittelson et al. [21] found that 24% of their sample was composed of subjects with higher knee joint sensitivity. The pain sensitivity index developed by Arendt-Nielsen et al. [19] was able to classify 27-38% of the patients with knee OA and 3% of the controls as highly sensitive with no association to radiographic knee joint degeneration.

In addition, higher scores in this index were found in those subjects with high knee pain intensities and long pain duration. A high matrix metalloproteinase (MMP)-mediated breakdown of CRP (CRPM) level, a serologic biomarker measured in serum, was associated with CS measures (temporal summation and CPM) in another study [17]. Finally, Wright et al. [22] identified a specific subgroup of patients with knee OA who exhibited widespread, multimodality hyperalgesia (to cold, heat and pressure stimuli), more pain, more features of neuropathic pain, and greater functional impairment. All these findings are in accordance with conclusions raised in the non-systematic review [15] that altered central processing of pain is particularly characteristic of some individuals with knee OA pain. Based on results from a systematic review [9] and later research [21] the percentage of people with a dominant CS pain in knee OA seems to be around 30%.

After the publication of the narrative [15] and systematic review [9] that form part of this dissertation, other authors have performed similar research reaching comparable conclusions. For instance, Akinci et al. [23] wrote a narrative literature review on clinical studies, systematic reviews and narrative reviews regarding the evidence for CS in chronic OA pain. They also concluded that there is good evidence for a role of CS in chronic OA pain in a subgroup of patients and raised the issue of a lack of diagnostic criteria for CS specific to OA. These authors recommend the use of pain biomarkers for confirming the presence of CS and alert clinicians to be aware of CS in patients with chronic OA pain, especially in subjects presenting with severe pain with unusual features [23].

Unlike the systematic review comprising this dissertation [9] which was focused in knee OA, a recent systematic review and meta-analysis conducted by Fingleton and colleagues [24] examined the evidence for pain sensitization specifically in people with knee OA and the relationship between pain sensitization and symptom severity. Only studies using QST measures of central hyperexcitability were considered for inclusion. Authors pointed to evidence supporting the presence of pain sensitization in people with knee OA and an association between pain sensitization with knee OA symptom severity [24]. In line with the latter, altered central processing of pain has been shown to be particularly characteristic of individuals with moderate to severe symptomatic knee OA [25] and especially if high knee pain is associated with an absence of moderate-to-severe radiographic evidence of pathologic changes at the knee [4,19]. It is currently known that CS dominates the clinical picture in a subgroup of the musculoskeletal pain population including, not only people with knee OA, but also patients with other complaints ranging from tennis elbow over shoulder pain to whiplash [26]. Physical therapists should therefore implement modern pain neuroscience including the role of CS in amplifying and explaining the pain experience of people with knee OA within their clinical reasoning framework.

Optimum treatment for people with knee OA pain requires determination of how peripheral and central factors are contributing to pain in each patient, to enable individualization of treatment strategies [15]. In this regard, physical therapists are considered to be in a good position to deliver such individualized intervention because they are cognizant of the need for a biopsychosocial approach to management [15]. A recent study has accounted for this issue investigating the effects of a combined intervention addressing physical and psychological impairments associated with knee

OA [27]. In particular, a 12-week physical therapist-delivered combined pain coping skills training and exercise program was compared with either treatment alone. Significantly greater improvements in function but not pain were found for the combined intervention at the end of treatment that persisted at long-term follow-up. In addition, benefits favoring the combined intervention were seen on several secondary outcomes [27]. Interestingly, physical therapists were intensively trained in this study to deliver the pain coping skills training program, which is a psychological intervention belonging to the group of cognitive-behavioral therapies, by a psychologist [28, 29]. Therefore physical therapists are probably in the best position to deliver treatments that integrate physical and psychosocial elements for people with knee OA.

Are measures of central sensitization associated with the area of pain and clinical symptoms in subjects with knee osteoarthritis?

Despite growing awareness of the important contribution of central pain mechanisms to knee OA pain, routine evaluation of CS is yet to be incorporated into clinical practice. This is partly due to the historically laboratory-based focus of CS research, where the equipment and protocols used to identify features are relatively sophisticated, time-consuming, expensive and not well-suited for clinical settings. Insight in clinical screening tools for assessing pain sensitization in people with knee OA is thus needed. With this in mind, an experimental study was performed to investigate whether the area of pain assessed with a novel method for obtaining and quantifying the area of pain had any association with direct (QST) and indirect (self-reported questionnaires, neuropathic pain) measures of CS in people with knee OA [30]. In addition, the association between pain drawings and clinical symptoms was also studied. Pain frequency maps showed enlarged areas of pain, especially in women. An expanded distribution of pain is a well-recognized sign of CS [31-33]. Our finding agrees with other reports of greater

spreading of pain in women with knee OA as compared to men [17,34]. Bartley et al. [34] found that women with knee OA exhibited greater sensitivity to multiple pain modalities and greater widespread pain when compared to men, although no sex differences in clinical pain were observed. Overall, these findings provide evidence for greater pain sensitivity in women with symptomatic knee OA compared to men, suggesting that enhanced central sensitivity may be an important contributor to pain in this group.

In our study [30] enlarged areas of pain were associated with widespread mechanical hyperalgesia (lower pressure pain thresholds at the epicondyle) and higher scores with the Central Sensitization Inventory, considered direct and indirect biomarkers of CS, respectively. Pain drawings were proposed as a simple way for identifying CS in people with knee OA waiting for further research. In line with our investigation, a recent study by Visser et al. [35] explored the hypothesis that chronic widespread pain drawn by patients on a body diagram could be used as a screening tool for some variables including increased pain sensitization, psycho-social load, and utilization of pain management strategies. The percentage pain surface area drawn on the body diagrams of a total of 144 patients attending a chronic pain outpatients' clinic was calculated. Outcomes were measured using the painDETECT Questionnaire and other indices and compared. Significantly more subjects with chronic widespread pain defined as a percentage pain surface area ≥ 20% reported high (≥ 19) PD-Q scores (suggesting pain "sensitization" or neuropathic pain), high anxiety scores on the Depression, Anxiety and Stress Scale-21 Items Questionnaire, ≥ 5 psycho-social stressors, ≥ 5 significant life events and used ≥ 7 pain management strategies, compared to control subjects with a lower percentage pain surface area. In additions, significant and independent

associations were observed between the presence of chronic widespread pain and Widespread Pain Index score ≥ 7, PD-Q score ≥ 19 and use of ≥ 7 pain management strategies. The authors concluded that calculating percentage pain surface area on a body diagram is an optimal "snapshot" screening tool to identify patients with an increased likelihood of pain sensitization, maladaptive psycho-social factors, and utilizing pain management resources [35]. In another study, Cruz-Almeida et al. [20], using a hierarchical cluster analysis, determined the presence of a subgroup of subjects with knee OA with a psychological profile consisting on high levels of pain vigilance, reactivity, negative affect, anger, and depression. These individuals experienced the highest levels of widespread pain and were the most sensitive to mechanical, pressure, and thermal stimuli thus reflecting CS mechanisms [20]. Skou et al. [8] reported significantly more pain sites in participants with pain after revised total knee arthroplasty as compared to participants without pain, and Dave et al. [36] found that pre-operative widespread pain as assessed by a pain diagram was associated with greater pain at 12-months post total knee arthroplasty. Overall, findings from the above-mentioned studies and from this dissertation [30] support a role for pain drawings in order to record pain distribution in people with knee OA and to raise suspicion about the presence of altered central processing mechanisms in case of an expanded distribution of symptoms.

Different alternatives to experimental pain sensitivity for assessing CS in patients with knee OA have been suggested in the literature. Besides the Central Sensitization Inventory, PainDETECT questionnaire or pain drawings used in this dissertation, other screening tools for assessing pain sensitization in knee OA have been explored. For instance, assessment of exercise-induced hipoalgesia has recently been proposed as a novel preoperative screening tool for predicting chronic postoperative pain in people

with knee OA [37]. In a normal physiological situation, pain sensitivity should decrease (i.e., increase of PPTs) during physical activity and stay in that way for up to 30 min post-exercise as a result of endogenous opioid release and related activation of several (supra)spinal anti-nociceptive mechanisms [38]. Oppositely, reporting of an strong increase in symptoms and a decrease of PPTs in response to low to moderate exercise may point towards impaired anti-nociceptive mechanisms during exercise and hence CS [39]. Vaegter et al. [37] found that hypoalgesia after aerobic exercise assessed preoperatively was associated with pain relief six months after total knee replacement in knee OA patients. The assessment of PPTs in response to exercise could be of great value in the future for recognizing CS in people with knee OA, but evidence at this point is limited.

An expanded distribution of pain has been linked to the presence of CS [31-33]. One term used to describe the presence of enlarged referred areas of pain in people with musculoskeletal pain disorders is widespread pain including the definition of a measure of the number of painful body regions, the so called widespread pain index [40]. The American College of Rheumatology (ACR) defines widespread pain as concurrent pain in the axial region, above and below the waist, and pain on the right and left sides of the body [41]. According to this definition the pain frequency maps determined in our sample of patients with knee OA [30] cannot be considered widespread as participants don't report pain above the waist or in the axial region. The ACR originally defined widespread pain as a diagnostic criterion for recognizing people with fibromyalgia, but widespread pain also has been found in patients with knee OA among other disorders [12]. Especially subjects with bilateral knee OA pain with high levels of knee pain but either no or minimal knee OA are at high risk for simultaneously occurring widespread

pain [42]. Different theories have been proposed to explain the relationship between widespread pain, abnormal pain processing and rheumatic disorders including OA [11, 32, 43, 44]. For instance, Gerhardt et al. [45] found that chronic localized pain and chronic widespread pain were produced by different mechanisms in people with chronic low back pain. In particular, patients with chronic widespread pain show widespread ongoing pain and hyperalgesia for different stimuli that was generalized in space, suggesting the involvement of descending control systems, as also suggested for patients with fibromyalgia. Currently however the underlying mechanisms of widespread pain remain unknown as well as validated cutoff scores for inferring whether pain is widespread or not are not available [46]. Given that widespread pain is associated with psychologically based impairments, abnormal pain processing, and poor outcomes [42], some authors have recommended assessment for the presence of widespread pain in people with knee OA [42]. Concretely, identifying the presence of widespread pain in people with knee OA seeking physical therapy may assist in establishing prognosis and in considering the use of psychologically based interventions [42].

Is a combined intervention of manual therapy addressing the knee and pain neuroscience education targeted to the central nervous system effective for people with knee osteoarthritis?

Conventional rehabilitation of patients with chronic pain including people with chronic knee OA pain is often not successful and is frustrating for physical therapists dealing with these patients [47]. One solution for people with late stage knee OA is total knee replacement (TKR) surgery, which has been traditionally thought to be an effective and cost-effective intervention for severe symptomatic OA of the knee joint [48]. However, recent evidence suggests that although treatment with TKR followed by 12-weeks of

nonsurgical treatment (exercise, education, dietary advice, use of insoles, and pain medication) resulted in greater pain relief and functional improvement after 12 months than did nonsurgical treatment alone, TKR was associated with a greater number of serious adverse events than nonsurgical treatment. Furthermore, most patients who were assigned to receive nonsurgical treatment alone did not undergo TKR before the 12-month follow-up [49]. In addition to this high-quality evidence regarding TKR utilization, there are currently no clear indications for surgery (it is difficult to know when in the course of knee OA is best to operate) [48] and a significant proportion of patients (≈ 20%) experience chronic knee pain, functional disability, a poor quality of life and dissatisfaction after TKR [5,6]. Outcomes can be even worse after revision TKR in comparison with primary TKA surgery [50]. It has been proposed that a biological explanation for continuing pain after TKR could involve a dysfunction of pain modulation by the central nervous system (i.e. CS) [5,7,8, 50-54]. As the pre-surgical presence of CS in knee OA contributes to poor outcomes after TKR [51-57], treatment strategies addressing CS in the pre-operative phase seemed valuable to be investigated [58]. Affected knee OA patients therefore require effective management to address their knee pain while waiting for TKR [58] as intense and continued nociceptive input proceeding from knee OA joint may cause CS [59-61].

In order to address the aforementioned necessity, a randomized controlled trial investigating the effects of a pre-operative treatment combining PNE with knee joint mobilization, both having previously demonstrated a modulating effects on CS [62,63], in subjects with knee OA was performed [64]. Guidelines for application of this combined intervention (i.e., the published treatment protocol), which also form part of this dissertation, were adhered [65]. The experimental group receiving PNE with knee

joint mobilization was compared with another treatment group where biomedical education with knee joint mobilization was combined, as we were especially interested in revealing differences if any between two totally opposite types of education. On one hand, preoperative biomedical education was centered on anatomy and pathoanatomy as well as procedural information regarding TKR. This kind of education has shown limited effects in reducing postoperative pain after TKA surgery [66]. On the other hand, PNE aims to shift one's conceptualization of pain from that of a marker of tissue damage or disease to that of a marker of the perceived need to protect body tissue [67]. Knee joint mobilization was selected as a treatment modality due to supporting evidence for endorsement in subjects with knee OA [68]. After four sessions of either PNE combined with knee joint mobilization or biomedical education with knee joint mobilization before surgery, significant and clinically relevant differences over time were found for both treatments in knee pain and disability and some measures of CS (i.e., widespread hyperalgesia, Central Sensitization Inventory), with no significant between-group differences. However, other indicators of CS (i.e., conditioned pain modulation, temporal summation) did not change over time in either treatment or even the observed changes were not in the expected direction. Reductions in pain pain-related measures were not parallel to changes in pain processing in other similar studies [69], indicating that mechanisms other than pain sensitization may contribute to the perceived pain of people with knee OA. This may justify the conflicting results encountered on CS measures in our randomized controlled trial [64]. When assessing treatment effects through multiple pain-related measures including CS, results may be different depending on what measures are being evaluated [69].

Concurrently with our research and responding to the call for evidence on treatment of CS in osteoarthritis patients [15], interest in research has grown regarding the application of treatments addressing CS in subjects with knee OA [62, 69-73]. In particular, the effects on pain sensitization of multimodal treatments combining interventions applied locally at the knee and addressing the CNS have been planned [73] or have been already investigated [69,72]. This paradigm shift in management of knee OA (combining CNS interventions with peripheral) is also being observed for other chronic musculoskeletal pain disorders such as chronic low back pain, where the effects achieved with most available physical therapy treatments is moderate at best [74]. Our research [64] is in accordance with previous studies by Skou and colleagues who found positive effects in reducing clinical pain and pain sensitization with application of a 3-month multimodal treatment program (neuromuscular exercise, education, diet, insoles and pain medication) [69] and when combining TKR with that same multimodal treatment [72] in people with knee OA. It has been argued that due to the complex multidimensional nature of knee OA pain and the moderate effects that physical therapies have in isolation in knee OA, combination of treatments addressing both the knee and the CNS may bolster each other thus further improving outcomes [73]. It is unlikely that a single modality of treatment is identified as being capable of treating such a complex mechanism as CS when dominant in subjects with knee OA so using a combination of different strategies, each targeting a different "desensitizing mechanism", could be useful [75]. Further studies using combination of treatments addressed to subgroups of people with knee OA characterized by a dominant CS pain mechanism are warranted.

Currently there is insufficient quality evidence to support the efficacy of any preoperative physiotherapy in older adults who undergo TKR due to knee OA, as found in a recent systematic review [76]. Of the ten studies which were included in that review, no studies included any intervention addressing specifically CS and pain sensitization measures were not considered as outcome measures but knee strength, ambulation, and pain [76]. The most used intervention was preoperative exercise (n = 5) followed by combined exercise and education applied in two studies. Previous systematic reviews also agree with these conclusions showing that evidence for implementation of either pre-operative education or physiotherapy programmes in people with knee OA is insufficient [77-80]. Regarding the content of education, no consensus exists about the optimal content of preoperative patient information for people with knee OA waiting for surgery [81]. Explaining pain biology to patients is not included within the contents of education programs for subjects with knee OA [79] and indeed is not considered a key issue to convey such kind of education to patients with OA pain [82]. In line with this, Louw et al. [66] evaluated the content and methods of delivery of preoperative education addressing postoperative pain targeted to people waiting for a total joint arthroplasty of the hip and knee. They found that most of the educational models for OA were based on a biomedical model discussing aspects such as anatomy, biomechanics and pathoanatomy. Concretely, the content of education was mainly centered on descriptions of preparation for surgery, hospital stay, surgical procedure, expectations following surgery, rehabilitation, reassurance, and answering common question associated with the surgical procedure [66]. It was concluded that preoperative education centered on a biomedical model has limited effect in reducing postoperative pain after total hip or knee arthroplasties. But importantly, not only have these models shown a limited efficacy in minimizing OA pain and disability, but they

may increase anxiety and fear having a negative impact on patient prognosis [83-85]. The terminology used to describe pathophysiology of knee OA within the biomedical model can be provocative for the patient with knee OA and may induce misunderstandings, unintended meanings and negative emotional responses [83]. Physiotherapists should therefore be careful with the words they use to explain OA to their patients. Instead of using a biomedical model, educational sessions administered before surgery aiming to increase patient knowledge of pain science (PNE) as used in this dissertation may be more effective in managing postoperative pain [66]. Further research with large samples could evaluate the role PNE when applied before knee OA surgery to reduce postoperative pain and CS in the same way as has been demonstrated for other conditions such as lumbar radiculopathy [86,89]

A better understanding of the neural mechanisms underpinning chronic pain including chronic pain related to knee OA has favored the development of new therapeutic approaches, one of these is PNE. In fact, the scientific interest in PNE for treating chronic musculoskeletal pain has grown over the last years as reflected by the great number of publications in this topic [67, 86-99], despite this rise in popularity of PNE has not still been corresponded with improved care [89]. Strong evidence is now available for effectiveness of PNE for treatment of several chronic pain conditions and, interestingly, the effectiveness of PNE is greater when it is combined with movement-based interventions versus education-alone [67, 93,95]. However, as recently stated by Blickenstaff and Pearson [99] and published guidelines [65], in order to integrate PNE with exercise and movement, messages given to patients with PNE and those of other therapeutic interventions should be consistent. In this sense, aligning the communication than surrounds the application of other physical therapies (i.e. manual

therapy) is recommended [26, 65]. When inconsistent messages exist between education and movement therapies, patient outcomes may be adversely impacted [65, 99]. In order to be compliant with these recommendations, PNE and knee joint mobilization were combined in our randomized controlled trial in such way that the therapists avoided contradictory messages between these two interventions, for instance, not using pain relief as the guide for treatment and threatening words such as "pain" during knee joint mobilization [64]. This balanced approach between PNE and manual therapy that we rationally presented [65] and used experimentally for knee OA [64], has been now suggested by other authors for treating other chronic pain conditions such as chronic low back pain [91].Further guidelines for application of PNE including not only merging PNE with movement but also other key elements such as examination, educational content, delivery methods, goal setting, and progression have been recently discussed [100].

Future research

In this dissertation, we attempted to broaden the framework for understanding the role of CS in people with OA pain and exploring new avenues for treating patients with chronic knee OA pain. While our results raised important issues in this regard, there are still many questions that remain unanswered and that would be valuable to investigate in future research.

Only superior effects pre and post-operatively for psychosocial variables related to pain catastrophizing and kinesiophobia were observed when using PNE with knee joint mobilization as compared to biomedical education and knee joint mobilization [64]. These results reported in people with knee OA are consistent with known favorable

effects of PNE on decreasing catastrophizing, excessive attention to pain and activity-related fear observed in other chronic pain populations [93,101]. In addition, the post-surgical benefits observed from pre-operative PNE are in line with recent reports applying PNE before surgery for lumbar radiculopathy [86, 88]. However, no attempt was made to understand the mechanisms underpinning these effects. One possible reason for the less beneficial effect in psychosocial variables in the group receiving biomedical education may be that the use of threatening and provocative terminology characteristic of this kind of education may have elicited negative emotional responses thus having a negative impact in psychosocial variables. In contrast, PNE may have targeted the cognitive emotional component of pain in the other group and therefore reducing pain catastrophizing and kinesiophobia. Despite clinical effectiveness of various treatments including PNE in chronic pain disorders characterized by CS has been proven, little is known about the effect of those treatments on the mechanism of CS [75]. The mechanisms underlying treatment effects of PNE are not totally understood but some recent studies are enquiring into this issue. For instance, Lee and colleagues explored into the mechanisms why improvement in pain biology knowledge was associated with a reduction in pain intensity and function using mediating analysis [102]. Mediation analysis of clinical trials can estimate how much the total effect of a treatment on the outcome is carried through an indirect path. Change in catastrophizing in a cohort of 799 patients who were exposed to a pain education intervention did not mediate the effect of pain knowledge acquisition on change in pain or function [102]. Same authors have planned a study to determine whether the effect of pain education on pain and disability is mediated by changes in self-efficacy, catastrophisation and back pain beliefs in people with acute low back pain [97]. Puentedura and Flynn [91] hypothesized that providing manual therapy within a PNE context as done in this

dissertation, besides producing local mechanical effects, can be a form of meeting or enhancing patient expectations and refreshing body schema maps within the brain. To our knowledge, the mechanisms underlying treatment effects of PNE, or the effect of PNE on an intermediate factor and its subsequent effect on outcome, have not been investigated in any clinical trial related to OA pain. Future research may estimate the causal mediation effects of a pain education intervention for people with chronic knee OA pain. Further examination of combination of treatments addressed to the periphery and the CNS for synergistic effects in people with knee OA is also warranted.

Classification of patients in terms of pain mechanisms including CS pain is considered a research priority in chronic musculoskeletal pain [103]. Identifying the specific mechanisms operating in the nervous system to produce chronic pain in individual with knee OA could provide the basis for a targeted and rational individualized approach to pain therapy. Participants from our randomized controlled trial were not previously stratified as having CS dominant pain and thus being optimal to be included for instance in the group receiving PNE with knee joint mobilization. PNE is especially indicated when the clinical picture of a patient is dominated by CS [104]. Diener et al. [96] have developed an interview process within a pain science framework in order to screen patients, establish maladaptive psychosocial barriers for poor prognosis and enquire into pain mechanism including altered pain processing mechanisms. Furthermore, Wijma et al. [98] recommend prior to PNE to perform an exhaustive biopsychosocial assessment in order to allow proper explanation of pain biology. They propose to follow a model [i.e. Pain - Somatic factors - Cognitive factors - Emotional factors - Behavioral factors - Social factors - Motivation - model (PSCEBSM-model)] that aims to determine the dominant pain mechanism of the patient (predominant nociceptive, neuropathic, or non-

neuropathic central sensitization pain) and evaluate the main provoking and perpetuating biopsychosocial factors. Therefore, future studies may use this model to specifically classify patients with chronic knee OA pain and tailor the plan of care, including PNE, to individual patients. Future research should also implement pain phenotyping as an inclusion or stratification criteria. This would reduce heterogeneicity by defining subgroups of people with knee OA with a similar pain phenotype and would allow to evaluate whether matching interventions to these subgroups improve outcome.

Detection of altered central pain processing in humans is a challenge as there is no diagnostic gold standard [105, 106]. This implies that the construct validity of clinical screening tools for CS, such as determining the presence of extended areas of pain with pain drawings, cannot be tested. In addition, it is still unclear to what extent disturbances in central pain processing are relevant for the determination of symptoms in individual patients [105, 106]. Despite classification criteria of pain types have been published for musculoskeletal pain in general [107], people with low back pain [108] and pain following cancer treatment [109], no guidelines exist in relation to knee OA. A group of osteoarthritis researchers from different countries have currently adapted these criteria for knee OA pain [110]. Although based on research data, the psychometric properties (i.e. inter- and intra-examiner reliability, sensitivity, specificity) of the criteria proposed for identifying CS [107-110] should be the subject of future research. Furthermore, other easily applicable and user-friendly clinical screening tools such as pain drawings that permit clinical identification of pain mechanisms including CS in patients with knee OA pain are needed.

Several neurophysiological changes across different areas of the peripheral and central nervous system have been recently detected in people with knee OA. For instance, differences in the organization of the motor cortex (i.e. a shift in the cortical representation of the knee and a swap of the relative position of the knee and ankle representations in the motor cortex), were found in subjects with knee OA [111]. Disrupted representation of the knee in primary sensory cortex has also been found in patients with knee OA as manifested by a decrease in tactile acuity [112]. These findings may provide direction for future treatments addressing these specific neuroplastic changes such as sensory discrimination training or graded motor imagery, because there are documented associations between treatments that normalize cortical organization and improvement of symptoms in other chronic pain musculoskeletal conditions [113-115].

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CHAPTER 6

CHAPTER 6
Conclusions

CONCLUSIONS

General conclusions achieved after this Doctoral Thesis are:

1. Substantial scientific evidence indicates a role for central sensitization in osteoarthritis pain including those with knee osteoarthritis, yet it is necessary to develop strategies to allow reliable and systematic recognition of patients with osteoarthritis whose pain has a (predominant) central sensitization component.

2. Optimum treatment for people with knee osteoarthritis pain requires a biopsychosocial approach and determination of how peripheral and central factors are contributing to pain in each patient in order to enable individualization of treatment strategies. Physical therapists are well positioned to deliver an individualized intervention because they are cognizant of the need for a biopsychosocial approach to management.

3. The area of pain reported by individuals with knee osteoarthritis pain is associated with some measures of central sensitization. Clinicians should be attentive for individuals with knee osteoarthritis showing extended areas of pain as this may be an indicator of altered nociceptive processing mechanisms. Pain drawings may constitute an easy and cheap way for the early identification of central sensitization in people with knee osteoarthritis pain.

4. Physical therapists are encouraged to find an equilibrium between hands-on and hands-off interventions in patients with knee osteoarthritis-related pain dominated by central sensitization. In light of evidence supporting a key role of central sensitization in a subgroup of patients with knee osteoarthritis pain, physical therapists are urged to

reconsider (their communication surrounding) hands-on interventions for the management of osteoarthritis, and emphasize the use of hands-off interventions for improving pain coping, self-efficacy and pain cognition.

5. Sound scientific rationale and practical guidelines have been developed for the application of a combined manual therapy and pain neuroscience education approach in patients with chronic osteoarthritis-related pain and central sensitization as their dominant pain mechanism.

6. In subjects with knee osteoarthritis waiting for knee joint replacement, pre-operative pain neuroscience education combined with knee joint mobilization did not produce any additional benefits over time in knee pain and disability and central sensitization measures compared with biomedical education with knee joint mobilization. Superior effects in the pain neuroscience education with knee joint mobilization group were only observed for psychosocial variables related to pain catastrophizing and kinesiophobia.