TESIS DOCTORAL

Actualización de la fisiopatología de las neuropatías por atrapamiento y propuesta de nuevos métodos de intervención.

Autor

Luis Matesanz García

Directores

Dr. Carlos Goicoechea García

Dr. Josué Fernández Carnero

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RESUMEN

Resumen

Introducción: En Europa se calcula que en torno a un 20% de la población sufre dolor crónico, de ellos entorno al 7% encajaría con un dolor crónico con características neuropáticas. Dentro de las neuropatías periféricas más comunes y que pueden ser frecuente causa de dolor neuropático están las neuropatías por atrapamiento. La etiología de las neuropatías por atrapamiento sigue siendo en gran medida desconocida.

Objetivos: Identificar cambios estructurales y funcionales en el sistema somato-sensorial en función de la presencia y la severidad del dolor neuropático. Identificar alteraciones centrales en el procesamiento del dolor en pacientes con Síndrome del Túnel del Carpo (STC) mediante medidas sensoriales, psicofisiológicas y mapas de dolor. Describir la eficacia que las diferentes intervenciones de fisioterapia tienen sobre los principales biomarcadores de dolor neuropático periférico en modelos preclínicos. Comprobar la eficacia de la movilización neural activa, la movilización neural mediante terapia espejo, movilización neural mediante observación de acciones y un protocolo clásico de ejercicios de mano (movilidad y fuerza) sobre la mecanosensibilidad neural, umbral de dolor a la presión a nivel proximal y distal.

Métodos: Se realizaron cuatro estudios. Dos observacionales transversales con cohortes de pacientes con síndrome del túnel del carpo. En estos dos se realizaron diferentes pruebas somatosensoriales y de procesamiento del dolor, así como la realización de diferentes cuestionarios relacionados con la función y la salud emocional. En otro ensayo se llevó a cabo una revisión sistemática para analizar los efectos de la fisioterapia en modelos animales de dolor neuropático periférico. Por último, se llevó a cabo un ensayo clínico aleatorizado ciego simple. En él se realizaron pruebas de mecanosensibilidad neural, procesamiento del dolor,

pruebas funcionales y de capacidad de imaginar movimiento en voluntarios sanos. Éstos fueron sometidos a tratamiento de movilización neural mediante técnicas de representación de imagen.

Resultados: Los pacientes con síndrome del túnel del carpo, presentaron perdida de función correspondiente tanto a neuropatías de fibras grandes como pequeñas. Además, presentaron alteraciones en el procesamiento del dolor a nivel central mediante la presencia de hiperalgesia extraterritorial y alteraciones en la modulación condicionada de dolor. En comparación con los sujetos sanos, presentaron una peor salud emocional, aunque estas no fueran puntuaciones clínicamente relevantes. El cuestionario de sensibilización central no es útil para detectar esa característica en este tipo de pacientes.

Los modelos animales de dolor neuropático periférico presentan alteraciones en distintos tipos de biomarcadores. Las distintas técnicas de fisioterapia se han mostrado eficaces a la hora de regular las sobreexpresiones de los diferentes sistemas que se asocian a la presencia de dolor neuropático.

Todas las intervenciones (movilizaciones neurales activas, movilizaciones neurales a través de terapia de espejo y observación de acciones y un protocolo de fuerza y movilidad de muñeca) testadas fueron capaces de disminuir la mecanosenbilidad neural y la hiperalgesia proximal, sin embargo, no consiguieron mejorar el procesamiento del dolor o la hiperalgesia al frío. Tampoco fueron eficientes en la mejora de la capacidad de imaginar.

Conclusiones: Los pacientes con síndrome del túnel del carpo presentan una alteración de ambos tipos de fibras (mielínicas y amielínicas). Además, presentan síntomas extraterritoriales que podrían deberse a alteraciones en el sistema nervioso central y la

presencia de neuroinflamación u otros biomarcadores. Estos biomarcadores descritos en los modelos preclínicos de dolor neuropático periférico son susceptibles de modularse mediante los diferentes tratamientos de fisioterapia (ej.: ejercicio o movilizaciones). Las nuevas técnicas de representación de imagen pueden mejorar el procesamiento del dolor y la mecanosensibildad neural en sujetos sanos en el área del nervio mediano. Aunque estas se necesitarían testar en pacientes con lesión focal de nervio, podrían ser una buena opción terapéutica en el futuro.

Abstract

Introduction: In Europe it is estimated that around 20% of the population suffers from chronic pain, of which around 7% would qualify as chronic pain with neuropathic characteristics. Among the most common peripheral neuropathies that can lead to neuropathic pain are entrapment neuropathies. The etiology of entrapment neuropathies remains largely unknown.

Objectives: To identify structural and functional changes in the somatosensory system depending on the presence and severity of neuropathic pain. To identify central alterations in pain processing in patients with CTS by means of sensory and psychophysiological measures and pain maps. To describe the efficacy of different physiotherapy interventions on the main biomarkers of peripheral neuropathic pain in preclinical models. To test the efficacy of active neural mobilization, neural mobilization by mirror therapy, neural mobilization by action observation and a classical hand exercise protocol (mobility and strength) on neural mechanosensitivity, proximal and distal pressure pain threshold.

Methods: Four studies were conducted. Two cross-sectional observational cohorts of patients with carpal tunnel syndrome. Different somatosensory and pain processing tests were performed as well as different questionnaires related to function and emotional health. A systematic review was also conducted to analyze the effects of physiotherapy in animal models of peripheral neuropathic pain. Finally, a single-blind, randomized clinical trial was conducted. Neural mechanosensitivity, pain processing, functional tests and imagery were performed on healthy volunteers. Healthy volunteers underwent neural mobilization treatment using motor imagery techniques.

Results: Patients with carpal tunnel syndrome showed loss of function depending on both large and small fiber neuropathies. They also presented alterations in central pain processing through the presence of extra-territorial hyperalgesia and alterations in conditioned pain modulation. Compared to healthy subjects, they had higher scores on the emotional health questionnaires even though they were not scores exceeding the cutoff. The central sensitization questionnaire is not useful to detect this feature in this type of patients.

Animal models of peripheral neuropathic pain show alterations in different types of biomarkers. Different physiotherapy techniques have been shown to be effective in regulating the overexpression of the different systems associated with the presence of neuropathic pain.

All the interventions tested were able to reduce neural mechanosensitivity and proximal hyperalgesia but failed to improve pain processing or cold hyperalgesia. They were also ineffective in improving the ability to imagine.

Conclusions: Patients with carpal tunnel syndrome present a mixed fiber type alteration. They also have extra-territorial symptoms that could be due to alterations in the central nervous system and the presence of neuroinflammation or other biomarkers. These biomarkers described in preclinical models of peripheral neuropathic pain are susceptible to modulation by different physiotherapy treatments (e.g., exercise or mobilization). New imaging techniques may improve pain processing and neural mechanosensitivity in healthy subjects in the median nerve area. Although these would need to be tested in patients with focal nerve injury, they could be a good therapeutic option.

Índice General

Abreviaturas

AO: Observación de la acción

BDNF: Factor Neurotrófico Derivado del Cerebro

BECK: Cuestionario de Depresión

CB2: receptor cannabinoide

Cdc2: Quinasa dependiente de ciclina 2

CDT: Umbral de detección de frío

CPM: Modulación Condicionada de Dolor

CPT: umbral de dolor por frío

CR: Rehabilitación clásica

CSI: cuestionario de sensibilización central

DN4: Cuestionario de Dolor Neuropático

DP: Dolor Neuropático

DRG: Ganglio de la Raíz Dorsal

ETK: Escala Tampa de Kinesiofobia

EVA: escala visual analógica

GAP-43: Proteína 43 asociada al crecimiento

GDNF: Factor Neurotrófico Derivado de células Gliales

GRD: ganglio de la raíz dorsal

HPT: umbral de dolor por calor

IENFD: Densidad de Fibras Nerviosas Intraepidérmicas

Il-1β: Interleuquina 1β

IL-6: Interleuquina 6

IM: imaginería motora

IQR: Rango Intercuartil

ISI: Índice de gravedad del insomnio

MBP: Proteína básica de mielina

MCD: modulación condicionada de dolor

MDT: umbral de detección mecánica

MIQ-R: Cuestionario de Imagen de Movimiento Revisado (MIQ-R)

MOR: receptor opioide

MPS: sensibilidad al dolor mecánico

MPT: umbral de dolor mecánico

MRC: Escala de Fuerza Muscular del Consejo de Investigación Médica

MT: Terapia Espejo

NGF: Factor de Crecimiento Nervioso

NM: movilización neural

NMDA: N-nitrosodimetilamina

NPSI: Inventario de Síntomas de Dolor Neuropático

NT-3: Neurotrofina 3

PASS 20: Escala breve de Síntomas de Dolor y Ansiedad

PASS: Escala de Síntomas de Dolor y Ansiedad

PCS: Catastrofismo del Dolor

PGP: protein gene product

PPT: Umbral de Dolor a la Presión

QST: Prueba Sensorial Cuantitativa

SC: Sensibilización central

SCDH: spinal cord dorsal horn

SD: Desviación estandar

STAI, STAI-ES: Cuestionario de ansiedad (State and Trait Anxiety Inventory, version castellano)

STC: Síndrome del Túnel del Carpo

SYRCLE: Escala de Riesgo de Sesgo

tDCS: trasncraneal direct current stimulation

TNF: Factor de Necrosis Tumoral

TRPV1: Miembro 1 de la subfamilia V del canal catiónico potencial transitorio del receptor

TRPV8: Miembro 8 de la subfamilia V del canal catiónico potencial transitorio del receptor

TSK: Cuestionario de miedo al movimiento

TSL: límite sensorial térmico

ULTN1: Prueba Neurodinámica del miembro superior 1

VDT: umbral de detección de vibración

VEGF: Factor de Crecimiento del Endotelio Vascular

WDT: umbral de detección de calor

WUR: ratio de wind-up

Listado de publicaciones originales

Esta tesis está basada en las siguientes publicaciones originales que forman parte de una línea de investigación cuyo fin es esclarecer los diferentes procesos patológicos que pueden ocurrir en pacientes con neuropatía periférica, así como identificar los distintos fenotipos asociados al dolor neuropático. Escogiendo una población de pacientes con síndrome del túnel del carpo. Además, de proponer nuevas líneas posibles de tratamiento para este tipo de pacientes. Estas publicaciones se exponen de forma completa en los apartados de la presente tesis doctoral:

I. **Matesanz, L.**, Hausheer, A. C., Baskozos, G., Bennett, D. L., & Schmid, A. B. (2021). Somatosensory and psychological phenotypes associated with neuropathic pain in entrapment neuropathy. *Pain*, *162*(4), 1211.

II. **Matesanz-García, L.**, Schmid, A. B, Cáceres-Pajuelo, J. E, Cuenca-Martínez, F., Arribas-Romano, A., González-Zamorano, Y., Goicoechea-García, C., & Fernández-Carnero, J. "Effect of Physiotherapeutic Interventions on Biomarkers of Neuropathic Pain: A Systematic Review of Preclinical Literature" (Aceptado en The Journal of Pain)

III. **Matesanz-García, L.**, Cuenca-Martínez, F., Simón A-I., Cecilia, D., Goicoechea-García, C., Fernández-Carnero, J & Schmid, A. B.(2022) Signs indicative of central sensitization are present but not associated with the Central Sensitization Inventory in patients with focal nerve injury. The Journal Of Clinical Medicine *11*(4), 1075.

IV. **Matesanz-García, L**., Cáceres-Pajuelo, J. E., Cuenca-Martínez, F., La Touche, R., Goicoechea-García, C., & Fernández-Carnero, J. (2021). Effects of neural mobilizations through movement representation techniques for the improvement of neural mechanosensitivity of the median nerve region: a randomized controlled trial. *Somatosensory & Motor Research*, 1-10.

1. INTRODUCCIÓN

1.1 Dolor neuropático

El dolor neuropático (DN) se define, según la IASP (Asociación Internacional para el Estudio del Dolor) como " dolor causado por una lesión o enfermedad del sistema somatosensorial" (Jensen et al., 2011). El sistema somatosensorial permite percibir estímulos tales como la presión, el dolor, o la temperatura la vibración. Estos son recogidos por las terminaciones nerviosas como los mecanorreceptores, termorreceptores o nociceptores que envían las señales a la medula espinal, núcleo talámico y finalmente a la corteza cerebral (Colloca et al., 2017).

Normalmente, tras una afectación en los tejidos, se puede producir cambios adaptativos en el sistema nervioso sensorial que pueden conducir a una hipersensibilidad al dolor. Un mecanismo de protección para garantizar la cicatrización. En cambio, puede haber ciertas situaciones en las que lo que esté afectado sea el propio sistema nervioso, generando una hipersensibilidad, dolor espontáneo o descenso de umbrales, que pueden llegar a provocar que estímulos inocuos como una caricia produzcan sensación de dolor, en definitiva, manifestaciones propias de DN (von Hehn et al., 2012).

El DN suele ser un tipo de dolor crónico o persistente. Puede tener diferentes etiologías que pueden afectar al sistema nervioso. Las más comunes suelen ser metabólicas, enfermedades degenerativas, autoinmune, tumor, traumatismo etc. (Colloca et al., 2017; Scholz et al., 2019) (Fig. 1).

Independiente de la etiología, los pacientes con dolor neuropático experimentan dolor más severo que los pacientes sin él, con una intensidad de 6,4 versus 4,6 en una escala del 0 al 10, siendo en el 60% de los casos dolor localizado (Mick et al., 2011).La depresión, ansiedad y trastornos del sueño son también significativamente más prevalentes en pacientes con dolor neuropático comparado con otros tipos de dolor. Es así como el impacto del dolor neuropático en diversos aspectos de la vida es relevante, el 41% de los pacientes han sufrido dolor por más de 5 años, el 60% tiene trastornos del sueño, 34% se siente deprimido, 25% está ansioso, 27% se siente constantemente debilitado, 65% ha restringido sus actividades diarias y el 82% refiere impacto significativo en su calidad de vida debido al dolor (Freynhagen et al., 2006; O´connor, 2009)

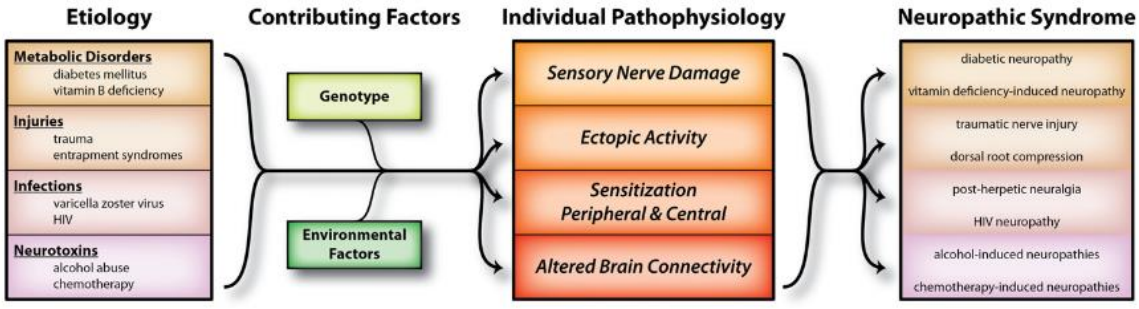


Figura 1. Etiología de los síndromes neuropáticos (von Hehn et al., 2012)

Debido a la complejidad de este tipo de dolor la IASP en colaboración con la Organización Mundial de la salud introdujo una clasificación acorde a la CIE. La clasificación está dedicada a síndromes de dolor crónico o recurrente de más de tres meses. Por ello la mayor diferenciación será en función de la localización, pudiendo distinguir entre dolor neuropático central y dolor neuropático periférico (figura 2). El diagnóstico del DN crónico requiere una

historia de lesión o enfermedad del sistema nervioso y una distribución neuro-anatómica plausible del dolor. Suele ir asociado a una presencia de síntomas o signos negativos (pérdida de función) y positivos (ganancia de función) que indican el mal funcionamiento del sistema somatosensorial (Scholz et al., 2019).

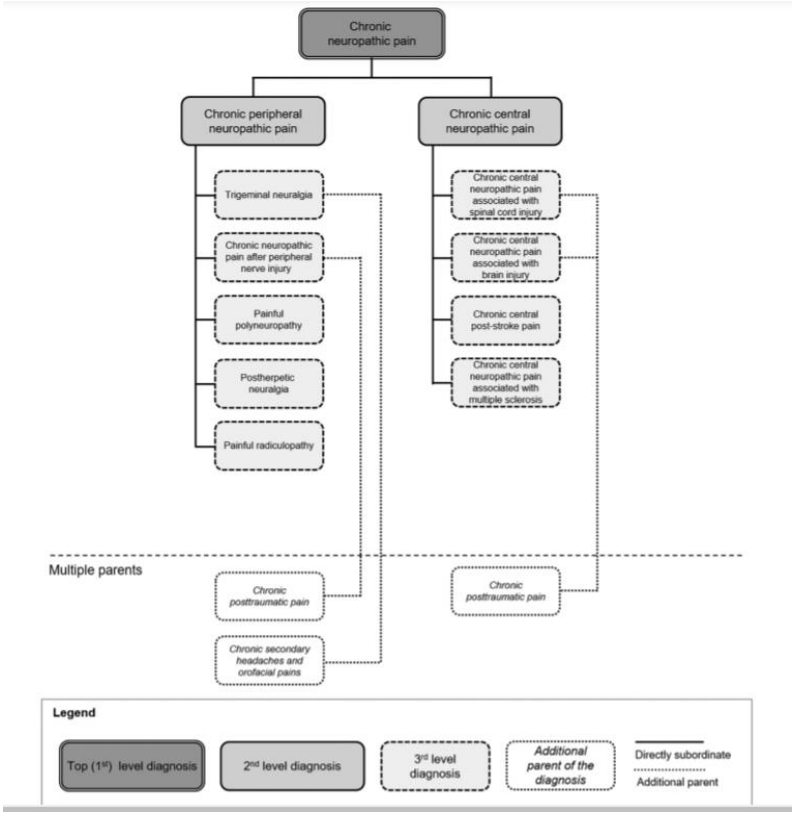


***Figura 2**. Clasificación dolor neuropático ICD-11 de la IASP.* (Scholz et al., 2019)

1.2 Mecanismos patobiológicos del DN

El DN central se desarrolla como consecuencia de una lesión o enfermedad a nivel medular y/o cerebro. Las más comunes suelen ser enfermedades cerebrovasculares, enfermedades neurodegenerativas o trastornos cerebrales capaces de provocar cambios en el procesamiento del dolor (Borsook, 2012). Las patologías más comunes a nivel medular,

capaces de desarrollar DN incluyen enfermedades desmielinizantes como la mielielitis transversa o la esclerosis múltiple o lesiones como la siringomielia (Watson & Sandroni, 2016).

El dolor neuropático periférico responde a una afectación de las fibras nerviosas C, Aδ y Aβ (Finnerup et al., 2016). Será sobre este tipo de DN sobre el que nos centraremos en este trabajo de tesis doctoral.

Es común que una vez que se manifiesta el DN, persista aun cuando la causa etiológica original haya desaparecido hace tiempo. No obstante, el síndrome puede progresar si la enfermedad primaria sigue dañando el sistema nervioso. El dolor asociado a una lesión neural aguda suele convertirse en dolor neuropático crónico en una minoría de los pacientes. Esta transición a la cronicidad es más evidente tras las lesiones nerviosas quirúrgicas (Kehlet et al., 2006; Michael Costigan, Joachim Scholz, 2009).

Una característica importante del DN es el dolor en ausencia de un estímulo identificable. El dolor espontáneo surge como resultado de la generación de potenciales de acción ectópicos dentro de las vías nociceptivas y no se origina en los terminales periféricos en respuesta a un estímulo (Michael Costigan, Joachim Scholz, 2009). Aunque normalmente, las sensaciones espontáneas suelen generarse como resultado de la hiperexcitabilidad de la neurona sensorial primaria, provocando una descarga ectópica del potencial de acción en el lugar de la lesión y en regiones próximas (Amir et al., 2005). Este tipo de impulsos anormales es una de las principales actividades espontaneas consecuencia de lesión/enfermedad del sistema nervioso. Suele generar dolor que puede presentarse a ráfagas, aunque puede presentarse también con otras características (continuo, superficial/profundo, quemante…)

lo que pone de manifiesto la actividad de los distintos tipos de fibras (Figura 3) (von Hehn et al., 2012).

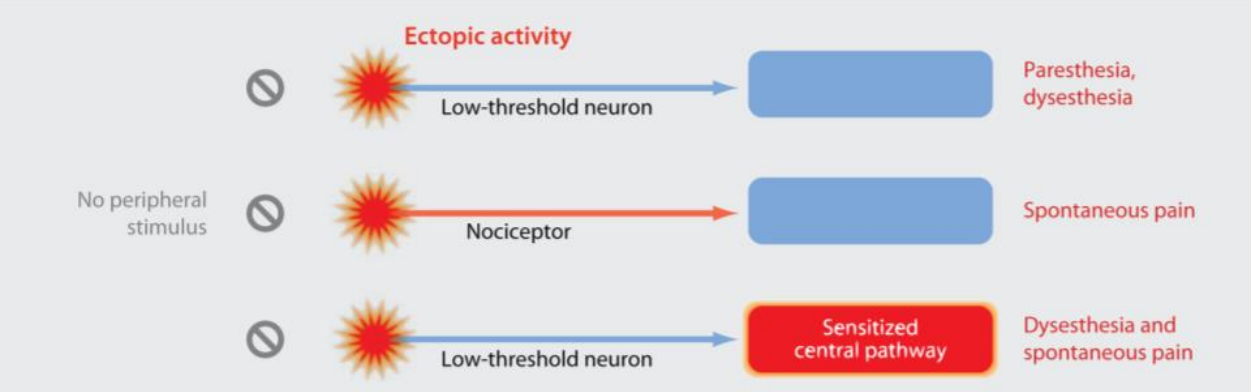


Figura 3. *Actividad ectópica tras lesión de nervio periférico* (Michael Costigan, Joachim Scholz, 2009)

El aumento de la sensibilidad de las neuronas sensoriales lesionadas a los estímulos térmicos y químicos endógenos puede iniciar un dolor espontáneo, mientras que el aumento de la sensibilidad mecánica puede provocar disestesia o dolor en respuesta a la punción de un nervio lesionado (signo de Tinel) (Michael Costigan, Joachim Scholz, 2009).

El DN implica un cambio en la sensibilidad, por lo que un estímulo de baja intensidad puede generar dolor, una alteración del patrón normal de dolor (Perl, 2007). La sensibilización periférica suele venir precedida de inflamación, lo que lleva a una reducción de los umbrales y un aumento de la excitabilidad de las terminaciones nociceptivas debido a los mediadores inflamatorios. En ocasiones puede producir alodinia o hiperalgesia en la zona de la inflamación. Por otro lado, también puede producirse la sensibilización periférica en ausencia de inflamación en los tejidos y que sea por una lesión en el nervio, lo que daría lugar a un aumento de la sensibilidad en el dermatoma correspondiente (von Hehn et al., 2012) .

La neuropatía puede provocar alteraciones en los canales iónicos de los nervios afectos. Pudiendo afectar a los tres tipos de fibras aferentes (Yang et al., 2004). Estas

alteraciones pueden llevar al desarrollo de síntomas relacionados con ganancia de función como los impulsos ectópicos o de pérdida de función como el adormecimiento del área correspondiente (Tesfaye et al., 2013).

Las lesiones axonales periféricas impulsan a las neuronas sensoriales a un estado de crecimiento activo al aumentar la expresión de genes asociados a la regeneración (Costigan et al., 2002). El aumento de la concentración de estas sustancias ayuda a la reconexión de los axones periféricos dañados con sus objetivos. Sin embargo, el aumento de la capacidad de crecimiento también puede conducir a un aumento de los axones centrales terminales de las neuronas lesionadas en la médula espinal (Woolf et al., 1992). Estos cambios en la proliferalización de axones en la médula junto con la actividad ectópica y el aumento de biomarcadores inflamatorios y de regeneración axonal podría dar lugar a la sensibilización central, sin que el sistema nervioso central esté directamente involucrado (Baron et al., 2010).

El aumento de la excitabilidad de las neuronas espinales produce un incremento de las respuestas sensoriales, provocando que fibras aferentes de bajo umbral (Aβ y Aδ) activen neuronas de nociceptivas de segundo orden, ampliando la señal para que un estímulo concreto excite a más neuronas nociceptivas de segundo orden, dando lugar a la sensibilización central (Baron et al., 2013; Woolf, 2011).

Las fibras Aβ, mielinizadas, normalmente hacen sinapsis en las láminas ventrales del cuerno dorsal (lámina III-V), mientras que las fibras Aδ menos mielinizadas y los nociceptores de fibras C, amielínicas, terminan en las láminas superficiales (I y II). Tras la lesión del nervio periférico, se ha sugerido que las fibras Aβ pueden generar nuevas conexiones en la lámina II (Kohama et al., 2000; Woolf et al., 1992).

Tras una lesión nerviosa, las aferentes primarias reducen su expresión de receptores μ opioides, y las neuronas del asta dorsal son menos sensibles a la inhibición de los agonistas μ opioides (Kohno et al., 2005). Además de una pérdida de la inhibición GABAérgica pre y postsináptica en la médula espinal (Michael Costigan, Joachim Scholz, 2009). Lo que produce una reducción de la actividad inhibitoria nociceptiva.

En el SNP, la vigilancia inmunitaria corre a cargo de los macrófagos, que identifican y eliminan residuos celulares y presentan antígenos de superficie para activar los linfocitos T. Tanto los macrófagos como los linfocitos T se comunican a través de citocinas y quimiocinas con las neuronas, las células de Schwann y las células satélite del ganglio de la raíz dorsal (GRD). Esta activación contribuye a la hipersensibilidad al dolor (Marchand et al., 2005; Scholz & Woolf, 2007). Tras una lesión neural se produce una respuesta inmunitaria que provoca un aumento de sustancias proinflamatorias (Figura 4) (J. N. Campbell & Meyer, 2006).

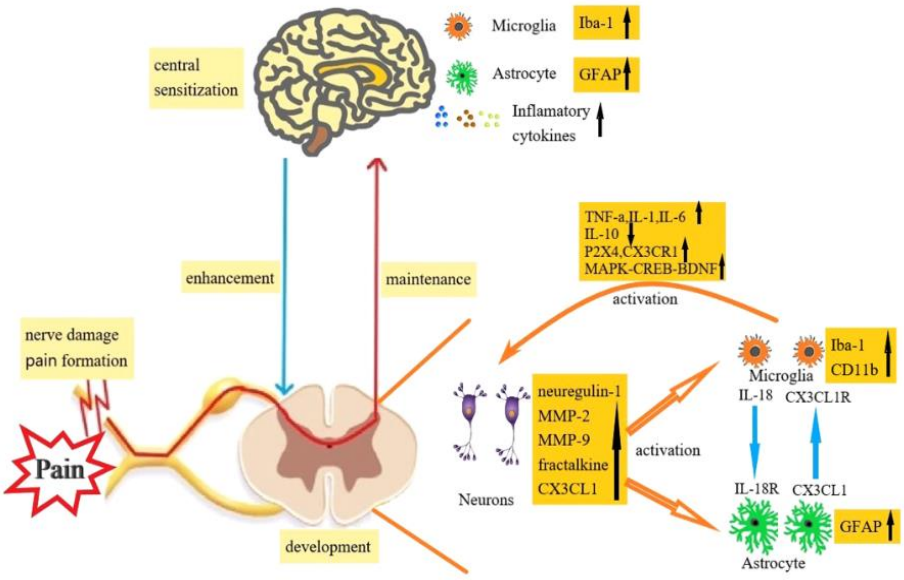


Figura 4*. Rol de la neuroglía y sistema inmune en el mantenimiento del dolor neuropático.* (J. N. Campbell & Meyer, 2006).

1.3 Prevalencia del Dolor Neuropático

Aunque la prevalencia exacta del DN es desconocida, se estima que puede afectar entre un 6,9 y 10% de la población general (Song et al., 2017; van Hecke et al., 2014). En Europa se calcula que en torno a un 20% de la población sufre dolor crónico, de ellos entorno al 7% encajaría con un dolor crónico con características neuropáticas. De los pacientes afectados, entre el 40-60% llegarían a alcanzar un alivio adecuado del mismo (Dieleman et al., 2008). El dolor neuropático periférico se está volviendo más prevalente debido al envejecimiento de la población mundial, el impacto de la diabetes y por el aumento de la supervivencia al cáncer debido a la quimioterapia (Colloca et al., 2017).

Dentro de las neuropatías periféricas más comunes y que puede ser frecuente causa de dolor neuropático están las neuropatías por atrapamiento (Matesanz et al., 2021). La lesión focal de nervio de este tipo más prevalente es el síndrome del túnel del carpo, con una incidencia de 276 casos por cada 100.000 habitantes cada año (Ibrahim et al., 2012), lo que podría llegar a suponer entorno a un 10% de la población mundial. Esta cifra podría aumentar al 85% en personas diabéticas (Singh et al., 2005). La segunda neuropatía por atrapamiento más común es el síndrome del túnel del cubital (Mondelli et al., 2005). Otra condición común es la "ciática", con prevalencia que oscila entre el 1,6% y el 43% (Konstantinou & Dunn, 2008).

1.4 Neuropatías por atrapamiento

La etiología de las neuropatías por atrapamiento sigue siendo en gran medida desconocida. Comparten varios factores de riesgo entre las afecciones, como el aumento del índice de masa corporal, factores laborales o físicos y enfermedades sistémicas predisponentes, como la mencionada diabetes o el hipotiroidismo. Recientemente, la predisposición genética está

emergiendo como uno de los factores de riesgo más fuertes para neuropatías por atrapamiento (Kozak et al., 2015; Lemmelä et al., 2016; Parreira et al., 2018; Pourmemari & Shiri, 2016; Wiberg et al., 2019).

La fisiopatología de este tipo de lesión neural suele tener un origen multifactorial (Figura 5.)

Figura 5. *Factores relacionados con el origen y mantenimiento de las neuropatías por atrapamiento* (Schmid et al., 2020)

Gracias a modelos animales de neuropatías por atrapamiento, ha quedado claro la influencia de la neuro-inflamación en el lugar de la lesión mediada por los linfocitos T y los macrófagos en el mantenimiento del DN (Moalem et al., 2004). La presencia de citoquinas reduce el umbral de disparo e inducen la actividad ectópica de las neuronas mecanosensibles y nociceptivas (Sorkin et al., 1997). Dicha inflamación también puede extenderse al ganglio de la raíz dorsal, donde las células del sistema inmune junto con las células gliales pueden seguir aumentando la señal eléctrica (Hu & McLachlan, 2002). En la tabla 1 se puede ver un resumen de los principales mediadores del sistema inmune y su función. La actividad glial y

del sistema inmune no solo se ha descrito en lugares anatómicos pertenecientes al sistema nervioso periférico tales como el nervio o el ganglio de la raíz dorsal (GRD), también se ha podido observar el aumento de la señal de dichas sustancias en lugares pertenecientes al sistema nervioso central como son la asta posterior de la médula (APM) (Rothman et al., 2010; Rothman & Winkelstein, 2007), el tálamo o el cerebro (LeBlanc et al., 2011; Mor et al., 2010).

Tabla 1. *Células del sistema inmune y su ro l*(Schmid et al., 2013)*).*

Overview of the role of the most common immune cells and immune competent cells after peripheral nerve injury.

	Cell type	Role after peripheral nerve injury
Neutrophils	Leukocytes	Acute local immune response. Phagocytic function and secretion of inflammatory mediators (e.g., TNF, IL-1β, IL-2 and IL-6) that attract other immune cells.
Mast cells		Acute local immune response. Secretion of mediators, which sensitise nociceptors (e.g. histamine, TNF) or directly activate them (e.g. serotonin). Recruitment of other immune cells.
Macrophages	Leukocytes	Acute and chronic immune response. Phagocytosis and antigen presentation to other immune cells. Secretion of mediators that sensitise nociceptors or attract other immune cells (e.g., prostaglandins, IL1β, IL-6, IL12, TNF and reactive oxygen species).
T-lymphocytes	Leukocytes	Acute and chronic immune response. Destruction of pathogens or cells directly or by secreting cytokines (e.g. IL-1β, IL-2 and TNF or IL-4, IL-5, IL-10). Activation of other immune cells (e.g., B-cells, macrophages and other leukocytes).
Schwann cells	Glial cells of the peripheral nervous system	Secretion of nerve growth factors, proinflammatory cytokines (e.g. IL-1, IL-6, IL-8) as well as prostaglandins and ATP which can directly sensitise nociceptors. Recruitment of other immune cells and presentation of antigens.
Satellite glial cells	Glial cells in the DRGs	Secretion of cytokines and chemokines (e.g. IL-1β, TNF) that increase ectopic firing of neurones
Astrocytes	Glial cells in the central nervous system	Release of substances (ATP, nitric oxide, IL-1β, TNF and IL-6), which modulate the firing threshold of neurons. Facilitation of synaptic transmission and communication with other immune cells.
Microglia	Glial cells in the central nervous system	Tissue repair by phagocytosing cellular debris and pathogens. Communication with neurones and immune cells, release of several neuro-active mediators including cytokines, chemokines and growth factors.

Estos cambios a nivel bioquímico también han sido medidos en humanos, presentando cambios similares a los modelos de dolor animal aumento de las sustancias pro-nociceptivas y disminución de las citoquinas anti-inflamatorias (Held et al., 2019). La diferencia es que en humanos las medidas son indirectas, puesto que no somos capaces de medirlas en el lugar de la lesión y los resultados hay que interpretarlos con precaución, puesto que los biomarcadores podrían cambiar de rol dependiendo de donde se encuentren presentes. Por ejemplo, para el factor de crecimiento derivado del cerebro (BDNF), se ha descrito un efecto de hiperalgesia cuando está presente en el GDR o en el APM (Siniscalco et al., 2011), mientras que si está en el cerebro tiene un carácter neuro-protector asociado a neuroplasticidad (Knaepen et al., 2010; Szuhany et al., 2015).

La isquemia intraneural es típica de las neuropatías por atrapamiento leves (Schmid et al., 2020). En animales demuestran que presiones extraneurales tan bajas como 20 a 30 mm Hg interrumpen la circulación venosa intraneural (Rydevik et al., 1981). En humanos también se ha registrado alteraciones en la presión del túnel, incluso variando está en distintas posiciones. El mayor aumento de presión dentro del túnel del carpo se asocia a posiciones que impliquen una flexión dorsal de muñeca, pudiendo alcanzar hasta 110mmHg, cuando los valores registrados en posiciones neutras de muñeca están en torno a 2,5mmHg (Gelberman et al., 1981). También se han registrado valores altos en la prueba ortopédica clásica de phalen 100-150mmHg (Williams et al., 1992).

La isquemia prolongada y el compromiso mecánico pueden inducir efectos posteriores como la desmielinización y, finalmente, la degeneración de los axones (Schmid et al., 2020). Por ello en un principio, también en base a los modelos animales de lesión por constricción crónica, se pensaba que solo podía afectar a las fibras más mielínicas (Basbaum et al., 1991). Aunque investigaciones más recientes han demostrado la afectación de fibras C en este tipo de neuropatías (Schmid et al., 2014). Además, se ha descrito un cambio en la morfología que afecta a los nodos de Ranvier tras la compresión pudiendo afectar esto a los canales iónicos (Calvo et al., 2016; Schmid et al., 2014).

La compresión de los nervios periféricos junto con la posible inflamación puede llegar a bloquear el nervio, provocando un aumento de la mecano-sensibilidad asociado al aumento de los canales iónicos en el lugar de la lesión (Ando, 1990; Armstrong et al., 2004; Dilley & Bove, 2008).

La perpetuación de todos los procesos anteriormente descritos puede dar lugar a la

manifestación de signos clínicos compatibles con sensibilización central, pese a que en origen la lesión tuviese lugar en la periferia. La sensibilización central se define como un aumento de la respuesta a un estímulo doloroso, amplificando la señal en el sistema nervioso central, esto puede ocurrir por dos vías: aumentando la señal dolorosa (sensibilización) o reduciendo las señales de inhibición del dolor (modulación descendente) (Fernández-de-las-Peñas et al., 2016). Primero presenta un aumento de la actividad neuronal que conlleva hipersensibilidad al dolor y alodinia, posteriormente hiperalgesia a la presión y aumento de la sumación temporal (Woolf, 2011).

La primera demostración de la sensibilización central en dolor neuropático fue la realizada por Campbell con una presión isquémica de fibras mielinizadas, produce una reducción de la movilidad del nervio causando alodinia (J. Campbell et al., 1988). Desde entonces estudios de distintas patologías han demostrado sensibilidad bilateral y extraterritorial.

En el sistema nervioso central se produce un aumento de la excitabilidad neuronal, hipersensibilidad y cambios estructurales y sinápticos mediados por receptores de N-metil-D-aspartato y glutamato, junto con la muerte de neuronas inhibitorias que son remplazadas por neuronas excitadoras estableciendo conexiones sinápticas aberrantes (Melzack & Wall, 1965). Estos cambios son en mayor o menor medida, influenciados por comorbilidades como la depresión, ansiedad, el grado de actividad física o la medicación (Henry et al., 2011).

1.5 Síndrome del túnel del Carpo (STC)

Como ya hemos señalado con anterioridad, el síndrome del túnel del carpo es la neuropatía por atrapamiento más común (Jenkins et al., 2012; Singh et al., 2005). Dicho síndrome se

define como la compresión o tracción del nervio mediano a su paso por la muñeca (Bland, 2007).

La prevalencia del STC en la población general es del 3.8%, si se diagnostica atendiendo a su clínica y de 2.7% cuando se realizan estudios neurofisiológicos (Atroshi et al., 1999), siendo más prevalente en mujeres que en hombres (Gelfman et al., 2009) y afectando en un rango de edad comprendida entre los 40 y los 60 años (Chammas et al., 2014)

El túnel carpiano se sitúa en la cara palmar de la muñeca. Está delimitado por el pisiforme y el ganchoso en la parte medial y la tuberosidad del escafoides y del trapecio en la parte radial. Cubriendo estos cuatro huesos hay una fina capa de tejido conectivo, el retináculo flexor, que crea el túnel por el que pasa el flexor profundo de los dedos, el flexor superficial de los dedos y el flexor largo del pulgar. El nervio mediano es el mayor nervio periférico de la extremidad superior. Inerva la eminencia tenar, la palma de la mano, el dedo índice, el medio y la parte media del anular (Newington et al., 2015). El nervio mediano a su paso por la muñeca va acompañado por los cuatro tendones de los flexores superficiales de los dedos, los cuatro tendones de los flexores profundos y el flexor largo del pulgar (Chammas et al., 2014)

Los pacientes clínicamente presentan síntomas sensoriales y/o motores en la mano y en la muñeca. Y frecuentemente experimentan dolor, parestesias u hormigueo en una distribución distal del pulgar, el índice y el dedo medio y la mitad radial del anular. Los síntomas sensoriales y el dolor en regiones extra- territoriales del nervio mediano se han encontrado en el 37,5% de los pacientes (Fan et al., 2015; Zanette et al., 2010). En estadios avanzados se observa atrofia de la zona tenar y debilidad de musculatura de la mano (Ibrahim

et al., 2012).

Las teorías más comunes sobre la patología señalan que viene provocada por compresión mecánica, insuficiencia microvascular o vibraciones (Aroori & Spence, 2008). Es probable que el origen sea multifactorial y que influyen varios procesos: fuerzas mecánicas, compresión isquémica, inflamación, edema e hipoxia (Duncan et al., 2017). Se ha comprobado en laboratorio que una presión aguda afecta más a las fibras Aβ (fibras mielínicas sensitivas de mayor tamaño, mientras que las de menor tamaño, mielínicas o no (Aδ y C respectivamente), son más sensibles a la hipoxia (Osborne et al., 2018). Investigaciones han encontrado hipoestesia o pérdida de sensibilidad en la mano patológica de los pacientes de túnel del carpo, lo que indica que podrían estar afectadas ambos tipos de fibras. El aumento de detección mecánica o vibración se asociaría con daño de las fibras Aβ mientras que los cambios térmicos (calor o frío) tendrán mayor relación con las fibras C y Aδ (Clarke et al., 2017).

En la región cerebral también se ha encontrado alteraciones, por ejemplo, en imágenes del cerebro de los pacientes con síndrome del túnel del carpo han demostrado alteraciones corticales en el área de representación de la mano afectada en el córtex somatosensorial primario (S1) (Maeda et al., 2013). Estudios con resonancia magnética funcional muestran que el mapa cerebral en estos pacientes está amplificado con respecto a los sujetos sanos (Tecchio et al., 2002). También se han observado cambios estructurales, disminución de la sustancia gris en varias regiones del córtex somatosensorial. Una pérdida en dicha área está relacionada con la velocidad de conducción nerviosa del nervio mediano (Maeda et al., 2013). Otro estudio con este tipo de pacientes demostró que los sujetos con STC presentaban una disminución de la velocidad a la hora de reconocer si las imágenes que

les presentaban pertenecían a MMSS e MMII de izquierda o derecha (Schmid & Coppieters, 2012).

1.6 Tratamiento

Para su tratamiento, las posibilidades terapéuticas contemplan tanto el abordaje quirúrgico como el conservador. Las intervenciones quirúrgicas se dividen en dos tipos: la liberación abierta y las endoscópicas. En las cirugías abiertas el ligamento del túnel del carpo es dividido por una incisión palmar, en los últimos años se han comenzado a realizar cirugías mínimamente invasivas, para minimizar los efectos adversos de la cirugía y mejorar la recuperación. Las cirugías endoscópicas llevan a la incisión del ligamento transverso del carpo, pudiendo dejar intactas las otras estructuras. Se cree que se reduce el dolor postoperatorio y un retorno más rápido al trabajo (Sanati et al., 2011). La cirugía está indicada principalmente en individuos que tienen síntomas persistentes que no han respondido a un tratamiento conservador, aquellos que tienen síntomas más severos (mayor frecuencia de adormecimiento o pérdida de fuerza de la musculatura tenar) o en aquellos que el estudio electrofisiológico determina un deterioro de conducción neural severa (Scholten et al., 2007; Verdugo et al., 2008).

Por otro lado, en las cirugías del túnel del carpo, se han observado complicaciones postquirúrgicas que incluyen: lesiones nerviosas, formación de neuromas, lesiones del arco palmar, hematomas, síndrome de dolor regional complejo, adherencias de los tendones, acortamiento de los tendones flexores, dolor en la base de la mano, dolor de la incisión y otras complicaciones de la cirugía (Braun et al., 2002).

Las posibles razones para la persistencia de los síntomas después de la cirugía son: diagnóstico incorrecto, descompresión inadecuada del nervio mediano, lesión nerviosa o

compresión iatrogénica, síndrome del doble atrapamiento o la patología en etapa terminal (Louie et al., 2012).

Por el contrario, el tratamiento conservador se ofrece a pacientes que presentan síntomas leves o intermitentes, embarazadas o aquellos que no pueden o no quieren una intervención quirúrgica (Page, O'Connor, et al., 2012). Dentro de las opciones terapéuticas conservadoras se han propuesto: el ultrasonido, inmovilización con férula, prescripción de ejercicio, movilización neural, modificación ergonómica, medicación vía oral, inyección de corticosteroides y vitaminas (Marshall et al., 2007; Page, Massy-Westropp, et al., 2012; Page, O'Connor, et al., 2012)

En los últimos años, se han utilizado dentro de las terapias conservadoras los ejercicios dirigidos a los nervios mediante movilizaciones o automovilizaciones (Brininger et al., 2007; Huisstede et al., 2010; Piazzini et al., 2007). Estos ejercicios van dirigidos a la mejora de las características mecánicas y fisiológicas del nervio. Una característica mecánica esencial de los nervios periféricos es su capacidad de deslizamiento longitudinal (Millesi, 1984; Millesi et al., 1990) y una disminución de la movilidad del nervio tanto local como general desencadenará lesión nerviosa. Los pacientes con STC presentan reducida la capacidad de deslizamiento del nervio mediano (Hough et al., 2007; Korstanje et al., 2012). Por tanto y relacionado con estos hechos, los ejercicios de deslizamiento del nervio podrían beneficiar a los pacientes que lo padecen.

Se ha demostrado que el nervio mediano sufre un deslizamiento cuando se realizan los ejercicios de deslizamiento de los nervios. La mayoría de los estudios han evaluado el deslizamiento del nervio mediano a la altura del antebrazo (Coppieters et al., 2009; Dilley et al., 2003). Un grupo diferente ha evaluado el movimiento del nervio mediano en diferentes

niveles del brazo entre el túnel de carpo y el músculo pronador redondo. En este estudio, han medido la cantidad de deslizamiento del nervio cuando se realizan unos ejercicios nuevos de deslizamiento neural que consisten en la abducción y aducción de los dedos de la mano, previa puesta en tensión del recorrido de los nervios del miembro superior en abducción de hombro de 90º con rotación externa y flexión de codo. Los autores han demostrado que los ejercicios convencionales suponen una movilización del nervio proximal en el túnel del carpo y a nivel de la cabeza del pronador redondo (12 y 13.8mm, respectivamente) pero menor dentro del túnel del carpo (6.6mm). En cambio, el nuevo diseño de ejercicios, consistentes en realizar la abducción y aducción de los dedos, en sustitución de la flexo-extensión de muñeca, llega a producir un desplazamiento de 13.8mm dentro del túnel del carpo, sin detectarse mayores deslizamientos del nervio cuando se añaden inclinaciones de la cabeza (Meng et al., 2015). Sin embargo, los efectos de estos nuevos ejercicios no se han probado todavía en pacientes con STC.

En cuanto a comparación de los beneficios del tratamiento quirúrgico frente al conservador, presenta resultados contradictorios, una revisión sistemática muestra que el tratamiento quirúrgico es superior al conservador a medio y largo plazo, pero no a corto plazo (3 meses) (Shi & MacDermid, 2011) .En cambio, en un estudio en el que someten a pacientes de forma aleatoria a tratamiento quirúrgico o conservador mediante técnicas de terapia manual en el cuello y ejercicios de movilización neural en el miembro superior, demuestran que los dos grupos tienen los mismos resultados de mejora a medio-largo plazo (6-12 meses), pero el grupo de tratamiento conservador mejora mucho más en los primeros 3 meses (Fernández-de-las Peñas et al., 2015). Sin embargo, existen datos contradictorios a esos resultados en una revisión Cochrane donde comparan las férulas nocturnas con la cirugía;

encuentran que la cirugía es mejor al principio hasta el 6º mes, pero al año los dos tratamientos producen efectos similares (Page, Massy-Westropp, et al., 2012). Además, en otro ensayo realizado en 2009 en el que comparan la terapia manual multimodal frente a la cirugía obtuvieron muy pocas diferencias (Jarvik et al., 2009). Y en una revisión sistemática han comprobado que ambos tratamientos son similares a los 3 meses, pero concluyen que la cirugía tiene un efecto superior entre los 6 a 12 meses, en la disminución en la sensación del dolor y mejora de la función (Shi & MacDermid, 2011). Recientemente un estudio donde realizaban educación al paciente con tratamiento activo combinado con férulas logró reducir la lista de espera de cirugía al mejor la percepción de los pacientes sobre su estado y satisfacción sobre el tratamiento conservador (K. J. Lewis et al., 2020).

El tratamiento conservador no solo se ha aplicado de forma aislada, sino como tratamiento posterior a la cirugía. En una revisión Cochrane publicada en 2016 (Peters et al., 2016); evaluaron la efectividad y seguridad de la rehabilitación postquirúrgica en pacientes con STC. Concluyen que hay una evidencia muy baja que apoye el uso de rehabilitación después de la cirugía del túnel del carpo, mostrando que los estudios eran heterogéneos en cuanto a la intensidad, el tipo de terapia, la dosis, la duración del tratamiento, el tiempo y los resultados. Recomiendan en futuras investigaciones el uso de la cirugía, estudios con tamaños muestrales más grandes y mejor diseñados, con el fin de poder detectar diferencias estadísticamente significativas entre los grupos. Por otro lado, hay una variedad de resultados pobres con la cirugía en los que no se alivian los síntomas o se producen complicaciones postquirúrgicas, por tanto, en esos pacientes que pueden seguir teniendo dolor, es importante que se investiguen los efectos de la rehabilitación post cirugía del STC.

La justificación para realizar rehabilitación postquirúrgica es la de acelerar la resolución de los

síntomas y la recuperación funcional de los pacientes.

Las terapias más recomendadas son:

1.- La inmovilización con órtesis para minimizar el dolor postquirúrgico, el atrapamiento del nervio, adherencias tendinosas de los flexores.

2.- El Laser y la electroterapia, para estimular la cicatrización de la herida y la regeneración neuronal y el control del dolor postoperatorio (Gordon et al., 2010).

3.- También se ha utilizado la movilización precoz de la mano y la muñeca (Ritting et al., 2012). Todos los consejos de la movilización precoz después de la cirugía de la muñeca y de los dedos promueven el deslizamiento longitudinal del nervio mediano a través de lecho quirúrgico y previenen adherencias entre el nervio y los tendones flexores (Nathan et al., 1993) y la irritación neural (Santos et al., 2012).

4.- El masaje, la presión y la aplicación de productos de base de silicio se han propuesto para disminuir adherencias entre la piel y tejidos profundos y ayudar a la mejora de la sensibilidad en la zona de la incisión. Posteriormente se incorporan ejercicios de fortalecimiento y actividades funcionales progresivas para mejora la realización ocupacional(Nathan et al., 1993)

2. Justificación

A día de hoy no está claro por qué algunos pacientes con neuropatías por atrapamiento manifiestan dolor neuropático y otro dolor nociceptivo. Se ha teorizado sobre este fenómeno planteando que la neuropatía es más severa en aquellos pacientes con síntomas de DN. La gran parte de los estudios no han encontrado correlaciones entre la severidad ni ningún tipo de prueba, principalmente neurofisiológica (Gürsoy et al., 2013; Oteo-Álvaro & Marín, 2018; Sonohata et al., 2014). Hay que tener en cuenta que las pruebas electrofisiológicas solo aportan información sobre la pérdida de sensibilidad.

La sensibilización central es un mecanismo que no se puede medir directamente en seres humanos. La propagación de los síntomas, la valoración psicofisiológica y sensorial puede darnos una idea sobre los mecanismos del dolor presentes en los pacientes. Un clásico ejemplo es la utilización de los umbrales de dolor a la presión, donde la presencia de hiperalgesia mecánica está asociada a la sensibilización central (Sorkin & Willis, 1991; Treede et al., 1992). Otra de las pruebas más extendidas es la sumación temporal, que valora la plasticidad dependiente del sistema nervioso central (Arendt-Nielsen et al., 1994; Koltzenburg & Handwerker, 1994). En el STC se han reportado resultados contradictorios al respecto (Nir & Yarnitsky, 2015; Schmid et al., 2012).

La alteración de los procesos inhibitorios del dolor es uno de los mecanismos principales que pueden acarrear un aumento de la intensidad del dolor. La variable que se utiliza más frecuentemente es la modulación condicionada de dolor (CPM). Que evaluar los mecanismos endógenos de modulación (Nir & Yarnitsky, 2015). Y que consiste en comprobar si un estímulo doloroso puede ser influido por un estímulo condicionante nocivo aplicado en

una parte remota del cuerpo. Se ha reportado que aproximadamente el 70% de los pacientes con dolor crónico muestran una reducción en la eficacia de dicho sistema (G. N. Lewis et al., 2012).

El cuestionario de sensibilización central se ha utilizado en los últimos años para identificar pacientes con estas características como por ejemplo la fibromialgia o la fatiga crónica. Recientemente ha estado en el punto de mira por su validez de constructo. Estudios realizados sobre diferentes patologías, tales como dolores temporomandibulares, dolor de hombro, latigazo cervical o dolor de espalda, no han encontrado relación entre esta herramienta y las variables fisiológicas (dos Santos Proençaa et al., 2021; Hendriks et al., 2020; Kregel et al., 2018; Rogelio A. Coronado, 2018).

Para hacer frente al DN la primera línea de tratamiento suele ser el tratamiento conservador (Colloca et al., 2017). Entre ellos el grupo especial sobre dolor neuropático de la IASP, " THE NEUROPATHIC PAIN SPECIAL INTEREST GROUP " recomienda la farmacología como primera opción, pero esta opción ha mostrado en ocasiones no ser muy eficaz y con efectos secundarios importantes en su uso a largo plazo (Finnerup et al., 2010, 2018; Percie Du Sert & Rice, 2014). En la última década la fisioterapia ha ganado terreno y crecido en interés como nueva herramienta de tratamiento para hacer frente al dolor neuropático (Jesson et al., 2020). Aunque la fisioterapia, como nueva opción terapéutica ha mostrado resultados prometedores en la mejora de la calidad de vida y el dolor (Cleland et al., 2006; Fernández-De-Las Peñas et al., 2015), poco se sabe de los mecanismos de acción. Un mejor entendimiento de estos mecanismos podría ayudar a ser más efectivos en el tratamiento de estos pacientes tan complejos.

La movilización neural (MN) ha mostrado ser eficaz a la hora de reducir la alodinia mecánica, las citoquinas proinflamatorias, modular el sistema opioide endógeno en la sustancia gris periacueductal y reducir la expresión de las células gliales y del factor neurotrófico derivado del cerebro en modelos animales de DN (G.-C. et al., 2018; Giardini et al., 2017; Santos et al., 2012; Zhu et al., 2018). En humanos los resultados han sido contradictorios (Basson et al., 2017).

El uso de técnicas de representación de movimiento como la observación de acciones (OA) o la terapia espejo han crecido en popularidad en los últimos años. Las dos han obtenido resultados interesantes y prometedores en voluntarios sanos y en pacientes con dolor musculoesquelético (Sarasso et al., 2015; Suso-Martí et al., 2020) La OA simula el movimiento motor en tiempo real de los movimientos visualizados (Buccino 2014). Consiguen activar áreas relacionadas con el movimiento y respuestas autonómicas similares al movimiento real (Shinoura et al., 2008).

3. Hipótesis

La hipótesis principal de esta tesis es que en las neuropatías por atrapamiento existen procesos periféricos que pueden llevar a desarrollar alteraciones centrales del procesamiento del dolor y a disfunciones somatosensoriales fuera de sus dermatomas correspondientes. Y que, una vez detectada la presencia de dichos fenómenos, estos pueden ser revertidos mediante técnicas de imagen dirigidas a la reorganización del sistema nervioso central.

De la hipótesis surgieron 4 hipótesis distintas que fueron puestas a prueba a través de los siguientes estudios:

- Estudio I: Se llevó a cabo un estudio observacional transversal en el cual la hipótesis planteada consistía en que existían distintos fenotipos sensoriales dentro de los pacientes diagnosticados de síndrome del túnel del capo, siendo estos dependientes de la intensidad y el tipo de dolor que sufrían los pacientes.

- Estudio II: Se realizó un estudio observacional transversal en pacientes con síndrome del túnel del carpo en el cual la hipótesis era que en dichos pacientes presentaban una alteración de los mecanismos centrales de procesamiento del dolor que podría contribuir a la extraterritorialidad de los síntomas.

- Estudio III: Se realizó una revisión sistemática en modelos animales de dolor neuropático periférico cuya hipótesis principal era evaluar los efectos de la terapia física sobre los biomarcadores moleculares de dolor neuropático.

- Estudio IV: Se realizó un ensayo clínico aleatorizado a simple ciego. En el cual, la hipótesis consistía en verificar la posibilidad de que técnicas clásicamente dirigidas al sistema nervioso periférico como es la movilización neural, presentadas en el paciente mediante técnicas de imagen, más dirigidas al sistema nervioso central, eran capaces de mejorar el procesamiento del dolor.

4. Objetivos

El objetivo principal de esta tesis doctoral es describir los distintos procesos fisiológicos que ocurren durante el dolor neuropático periférico. Así como intentar hallar una nueva línea de tratamiento que pueda ser efectiva frente a las neuropatías por atrapamiento.

Con dicho fin se llevaron a cabo los siguientes estudios de investigación:

Estudio I:

Objetivo principal: Identificar cambios estructurales y funcionales en el sistema somato-sensorial en función de la presencia y la severidad del dolor neuropático.

Objetivo secundario: Explorar las diferencias demográficas, clínicas y salud emocional relacionados con la severidad del dolor neuropático.

Estudio II:

Objetivo principal: Identificar alteraciones centrales en el procesamiento del dolor en pacientes con STC mediante medidas sensoriales, psicofisiológicas y mapas de dolor.

Objetivos secundarios: Investigar si el cuestionario de sensibilización central tiene alguna asociación con las variables psicofisiológicas y la distribución del dolor que indican la presencia de sensibilización central. Investigar la asociación del cuestionario de sensibilización central a través de los parámetros psicológicos.

Estudio III:

Objetivo principal: Describir la eficacia que las diferentes intervenciones de fisioterapia tienen sobre los principales biomarcadores de dolor neuropático periférico en modelos preclínicos.

Estudio IV:

Objetivo principal: Comprobar la eficacia de la movilización neural activa, la movilización neural mediante terapia espejo, movilización neural mediante observación de acciones y un protocolo clásico de ejercicios de mano (movilidad y fuerza) sobre la mecanosensibilidad neural, umbral de dolor a la presión a nivel proximal y distal.

Objetivo secundario: Valorar el efecto de las terapias sobre la fuerza de presión manual, hiperalgesia al frío, modulación condicionada, tolerancia al dolor y sumación temporal.

5. MATERIAL Y MÉTODOS

Los estudios de la presente tesis fueron realizados en laboratorios de distintos centros. El **estudio I** tuvo lugar en el centro de investigación de la universidad de Oxford, John Radcliffe of Clinical Neuroscience. El **estudio II** se llevó a cabo de manera conjunta entre los hospitales Severo Ochoa y 12 de Octubre y la Universidad Rey Juan Carlos. El **estudio III** tuvo lugar en la Universidad Rey Juan Carlos, en el campus de Alcorcón. El **estudio IV** se realizó en las universidades Rey Juan Carlos y La Salle Campus Madrid.

El **estudio I** contaba con la aprobación del comité ético nacional de ética (London Riverside, Ref. 10/H0706/35). El **estudio II** contaba con la aprobación de los hospitales del servicio de Salud de la Comunidad de Madrid, Hospital Universitario Severo Ochoa y el Hospital Universitario 12 de Octubre (ANEXO I, nº aprobación CPMP/ICH/135/95 y 20/092) El **estudio III** se registró previamente a su realización en la página de registro de revisiones sistemáticas PROSPEORO (nº CDR42019142878). El **estudio IV** contaba con la pertinente aprobación del comité de ética de la Universidad Rey Juan Carlos (ANEXO II, nº aprobación (2703201906919) y se registró debidamente en la página Clinicaltrials.org (nº (NCT04086563).

Todos los estudios se llevaron a cabo conforme a la declaración de la Asociación Médica Mundial de Helsinki y su posterior actualización en Fortaleza. Se informó a cada sujeto acerca de la naturaleza de los estudios, voluntariedad de la participación en los mismos, de los objetivos propuestos, así como de los posibles efectos adversos que pudieran tener lugar durante su realización. A cada sujeto se le solicitó que diera su consentimiento a participar en los estudios por escrito. Los experimentos eran suspendidos en cualquier momento, si así lo deseaba el paciente.

De esta manera se llevaron a cabo los siguientes estudios que componen esta tesis:

I. **Matesanz, L.**, Hausheer, A. C., Baskozos, G., Bennett, D. L., & Schmid, A. B. (2021). Somatosensory and psychological phenotypes associated with neuropathic pain in entrapment neuropathy. *Pain*, *162*(4), 1211.

II. **Matesanz-García, L.**, Cuenca-Martínez, F., Simón A-I., Cecilia, D., Goicoechea-García, C., Fernández-Carnero, J & Schmid, A. B. (2022). Signs indicative of central sensitization are present but not associated with the Central Sensitization Inventory in patients with focal nerve injury. The Journal of Clinical Medicine *11*(4), 1075.

III. **Matesanz-García, L.**, Schmid, A. B, Cáceres-Pajuelo, J. E, Cuenca-Martínez, F., Arribas-Romano, A., González-Zamorano, Y., Goicoechea-García, C., Fernández-Carnero, J. "Effect of Physiotherapeutic Interventions on Biomarkers of Neuropathic Pain: A Systematic Review of Preclinical Literature" (Aceptado en la revista The Journal of Pain)

IV. **Matesanz-García, L**., Cáceres-Pajuelo, J. E., Cuenca-Martínez, F., La Touche, R., Goicoechea-García, C., & Fernández-Carnero, J. (2021). Effects of neural mobilizations through movement representation techniques for the improvement of neural mechanosensitivity of the median nerve region: a randomized controlled trial. *Somatosensory & Motor Research*, 1-10.

5.1 Sujetos de Estudio

5.1.1 Participantes estudio I

Para este estudio se incluyeron 108 pacientes. Los participantes que cumplían los criterios electrodiagnósticos y criterios clínicos de STC. Los pacientes fueron reclutados en los departamentos de neurofisiología y de cirugía de la mano de los hospitales universitarios de Oxford. También se utilizaron medios de comunicación locales y los tablones de anuncios públicos. Los pacientes fueron excluidos si los hallazgos electrodiagnósticos eran indicativos de otras neuropatías periféricas distintas del STC, si existía otra enfermedad que afecta a las extremidades superiores o el cuello (por ejemplo, codo de tenista o artrosis osteoartritis de la mano), si existían antecedentes de cirugía o traumatismo en la extremidad superior o el cuello, o si el STC estaba causado por el embarazo o la diabetes. Controles sanos (n=32) proporcionalmente emparejados por edad y sexo fueron reclutados a través de tablones de anuncios públicos y anuncios en los medios de comunicación. Todos los participantes dieron su consentimiento informado por escrito antes de participar.

5.1.2 Participantes en el estudio II

Para este estudio se reclutaron 30 pacientes con STC unilateral de las unidades de cirugía de mano y codo del Hospital 12 de Octubre y del Hospital Severo Ochoa, ambos situados en Madrid. Para determinar ese número se realizó el cálculo del tamaño muestral en base a la potencia del efecto de 0,74 de los PPTs del estudio de Llave Rincón et al. (Llave-rincón et al., 2011), con un poder estadístico del 80% (alpha=0.05, independent t-test). La muestra fue de 30 sujetos, suficiente para detectar grandes cambios en el análisis de correlación. (rho=0.44, power 80%, alpha 0.05). Todos los pacientes estaban en lista de espera quirúrgica, con al menos un año de persistencia de los síntomas, tenían signo de Tinel y Phalen positivos y

tenían confirmación electro diagnóstica de STC de moderado a grave según la Asociación Americana de Medicina Neuromuscular y Electrodiagnóstica. Los pacientes fueron excluidos si las pruebas electro diagnósticas identificaban déficits sensoriales y/o motores del nervio radial y/o cubital, o si los pacientes informaban de cirugías previas de la mano, infiltraciones previas de esteroides, fracturas de muñeca, diagnósticos relacionados con la columna cervical y la extremidad superior (por ejemplo: radiculopatías cervicales, lesiones de hombro), u otras comorbilidades musculoesqueléticas (por ejemplo: artritis reumatoide y fibromialgia). Y por último se excluyeron del estudio las mujeres embarazadas.

Los pacientes fueron emparejados en edad y sexo con controles sanos (HC, n=30). Estos fueron reclutados a través de anuncios en los hospitales y la universidad y de los familiares de los pacientes participantes. Todos los participantes dieron su consentimiento informado por escrito antes de participar y el estudio recibió la autorización ética de los dos comités de los hospitales participantes.

Los datos de este estudio fueron extraídos del "baseline" de un estudio de intervención que cuenta con la aprobación de los comités de ética de ambos hospitales Severo Ochoa y 12 de Octubre.

5.1.3 Participantes estudio III

Se incluyeron ensayos clínicos en animales, sin limitación en cuanto al tipo de animal o sexo del mismo. El idioma se restringió a inglés y castellano. El modelo animal debía ser de dolor neuropático periférico, admitiendo cualquier tipo de modelo (ej.: neuropatía diabética, neuropatía por tratamiento, neuropatía post-quimioterapia). Los estudios deberían incluir al menos un grupo control y un grupo que solo hubiese sido tratado con fisioterapia (ej.:

movilización neural, ejercicio, electroestimulación, etc.). Como variables deberían reportar un algún biomarcador relacionado con el dolor neuropático (ej.: sistema neuro-inmune, factores neurotróficos, sistema opioide, etc.). Como criterios de exclusión se tuvieron en cuenta: que el modelo fuese de dolor neuropático central, las intervenciones de fisioterapia estuviesen en combinación con tratamiento farmacológico (ej.: opioides) u otra técnica invasiva (ej.: electroestimulación espinal).

5.1.4. Participantes estudio IV

El tamaño de la muestra se estimó utilizando el programa GPower 3.1.7 para Windows (GPower de la Universidad de Dusseldorf, Alemania) (Faul et al. 2007). El cálculo del tamaño de la muestra se consideró como un cálculo de potencia para detectar diferencias entre grupos en una medida de resultado primaria (ULTN1). Se consideraron tres grupos y dos mediciones para los resultados primarios, para obtener una potencia estadística del 80% (probabilidad de error 1-b) con una probabilidad de nivel de error de 0,05 utilizando el análisis de la varianza (ANOVA) de medidas repetidas, la interacción intra-entre, y un tamaño del efecto de gp2 ¼ 0,202 (Tamaño del efecto f ¼ 0,503) obtenido a partir de los resultados de un ensayo clínico anterior (Suso-Martı et al. 2019). Esto generó un tamaño de muestra de un total de 48 participantes más una pérdida estimada del 20% en el seguimiento, lo que arrojó un total de 57 participantes (12 por grupo). Entre septiembre de 2019 y febrero de 2020, se reclutaron participantes voluntarios sanos. Para ello se utilizaron anuncios, redes sociales y correos electrónicos. Antes de la inclusión final, todos firmaron el consentimiento informado. Los criterios de inclusión fueron 1) tener entre 18 y 65 años. Los criterios de exclusión fueron 1) padecer cualquier patología que presente dolor, 2) padecer patologías de origen neurológico, 3) tener algún trastorno musculoesquelético en las extremidades superiores y 4)

enfermedades metabólicas. La aleatorización se llevó a cabo mediante una tabla de secuencias aleatorias generada por ordenador y proporcionada por GraphPad Software Inc, CA, USA. Un miembro del equipo no implicado en el tratamiento o las evaluaciones se encargó de generar y mantener la lista.

5.2 Diseño de los estudios

5.2.1 Estudio I

El diseño experimental consistió en un estudio observacional de sección transversal. Los pacientes fueron divididos en aquellos que presentaban dolor neuropático o no mediante el cuestionario DN4. Para la posterior subdivisión de la intensidad de dolor (leve y moderado/severo) se utilizó la escala visual analógica de dolor. Se pidió al paciente que marcase la intensidad del dolor durante las 24 horas previas a la medición.

Para la valoración de la severidad de los síntomas, los déficits funcionales y las características del dolor neuropático se utilizaron los siguientes cuestionarios: BOSTON, cuestionario de los síntomas de dolor neuropático y un diagrama corporal. También se pasaron los cuestionarios correspondientes a la salud emocional: Depresión, ansiedad y perspectivas positivas, el cuestionario de catastrofismo de dolor y alteraciones del sueño.

Una vez completado todos los cuestionarios se realizó el examen clínico consistente en valorar el tacto fino, pinprick, tinnel, phalel, presencia de hipotonía en la eminencia tenar y el balance muscular. La siguiente variable registrada fue el test cuantitativo sensorial, se realizó tal y como establece el protocolo marcado por la German Research Network on Neuropathic Pain (Rolke et al., 2006). El electromiograma fue realizado con el ADVANCE System (NEUROMATRIX) y unos electrodos convencionales y se utilizó la clasificación

publicada por Bland en el 2000 (Bland, 2000). Para terminar, se realizó una biopsia de piel bajo anestesia local de la falange proximal del dedo índice. El análisis de inervación intradermal se realizó bajo microscopio.

5.2.2 Estudio II

El diseño experimental consistió en un estudio observacional de sección transversal. Los pacientes fueron reclutados durante sus visitas a la consulta del traumatólogo especialista de la unidad. Durante esa visita se le ofrecía la posibilidad de participación. Una vez firmado el consentimiento informado, se realizan las mediciones psicofisiológicas. Las primeras mediciones realizadas fueron los PPTS en ambas manos, entre mediciones se realizó una pausa de 30 segundos para evitar el efecto sumatorio de sensibilización en el tiempo. Seguidamente se realizó la modulación condicionada de dolor y la sumación temporal. Para la CPM se midió el umbral de dolor a la presión en la falange distal del 1º dedo, tras la cual, con la ayuda de un esfingomanómetro se realizó el estímulo condicionante en el brazo contralateral hasta que el paciente refería dolor en dicho brazo. Con el estímulo aún presente, se vuelven a medir los PPTs en la misma área del dedo. Un resultado negativo al realizar la diferencia entre ambas mediciones sería indicativo de un mal funcionamiento del sistema inhibitorio. La sumación temporal se realizó mediante la observación entre la diferencia del dolor percibido durante un estímulo aislado y un estímulo en tren. En la misma consulta el paciente también dejó constancia mediante la EVA de su intensidad de dolor. El resto de los cuestionarios y mapas de dolor, debido a la situación de pandemia en la que se desarrolló el estudio se permitió que los pacientes lo pudiesen rellenar en sus domicilios, previa explicación de las instrucciones pertinentes y permitiendo el contacto telefónico para la resolución de dudas.

5.2.3 Estudio III

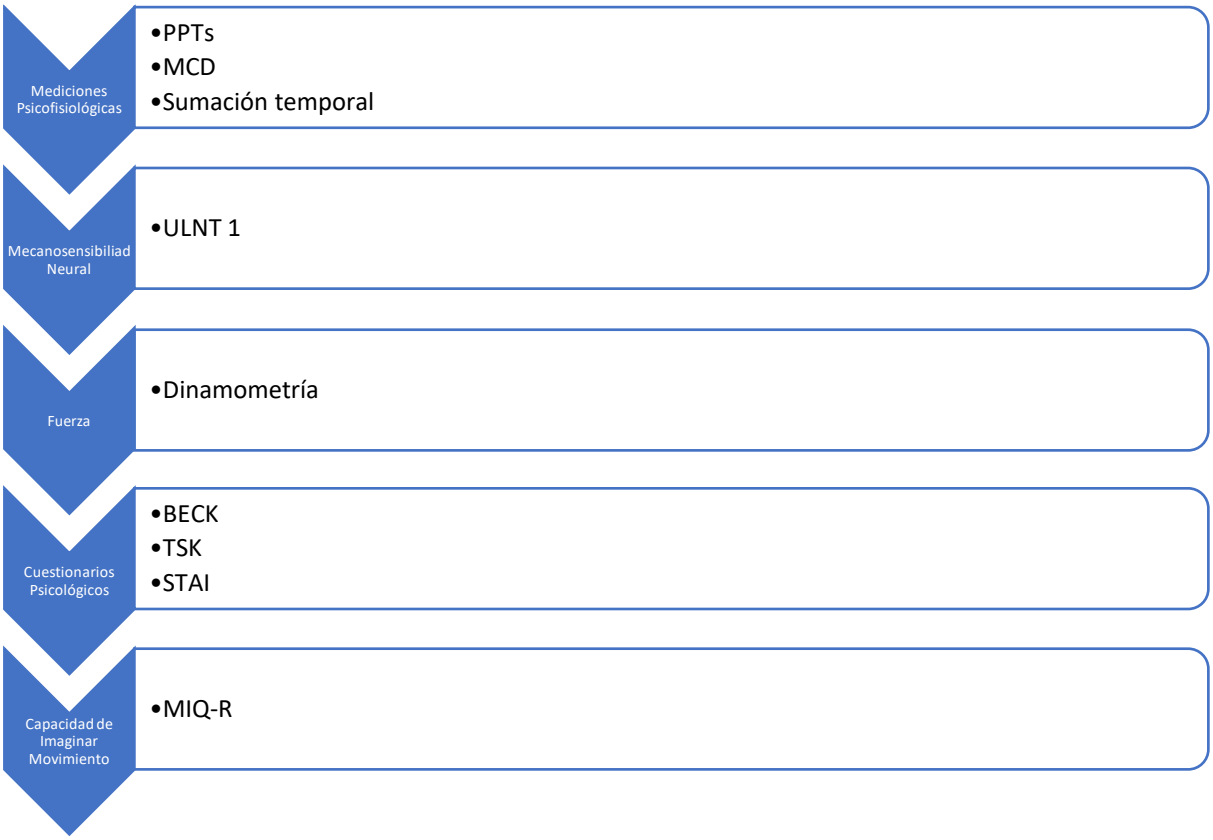
El diseño de este estudio fue una revisión sistemática. Debido a la heterogeneidad de los biomarcadores, formas de medirlos y lugar donde se llevaron a cabo dichas mediciones no fue posible realizar el metaanálisis. Dicha revisión, se llevó a cabo mediante una búsqueda en las bases de datos "Pubmed" "MEDLINE", "EMBASE", "CINAHL", "Web of Science", "PsycInfo", "Scopus", y "Cochrane". Se utilizó una combinación de términos (MeSH) y palabras clave (ANEXO III). Dos investigadores revisaron independientemente los títulos y los resúmenes de los estudios de la búsqueda para identificar inicialmente si estos cumplían los criterios de selección establecidos. Cualquier desacuerdo entre los revisores fue resuelto mediante consenso. Debido a la alta heterogeneidad de los biomarcadores, así como de los medios utilizados para su valoración y localización anatómica, se hizo imposible meta-analizar los resultados. Finalmente, los resultados fueron reportados en un mapa de calor que analizaba la frecuencia de cambios en las concentraciones en los distintos tejidos.

5.2.4 Estudio IV

El estudio se realizó como un ensayo controlado, aleatorio y a ciegas, de acuerdo con las normas de las directrices CONSORT. La aleatorización se llevó a cabo mediante una tabla de secuencias aleatorias generada por ordenador y proporcionada por GraphPad Software Inc, CA, USA. Un miembro del equipo no involucrado en el tratamiento o las evaluaciones fue responsable de generar y mantener la lista. Las mediciones y los tratamientos fueron realizados por dos investigadores independientes. Las mediciones fueron realizadas por un terapeuta experimentado. El miembro encargado de las mediciones no conocía el tratamiento que seguían los participantes. Y se realizaron seis sesiones a razón de 3 sesiones por semana a cada uno de los participantes.

Una vez firmado el consentimiento informado. Se realizaron las mediciones basales, tal y como viene reflejado en la Figura 6:

Figura 6



Tras las mediciones basales el voluntario pasaba a una sala contigua para iniciar las 6 sesiones de tratamiento correspondientes a la intervención que le hubiese tocado.

-Movilización neural activa consistía en la realización de los ejercicios neurales propuestos por Totten and Hunter (Totten & Hunter, 1991). Los ejercicios se realizaron a un ritmo de 0.5Hz marcados por un metrónomo. Una duración de 3 minutos por ejercicio descansando 5 segundos cada minuto y 30 segundos entre ejercicios.

-La terapia de espejo consistía en realizar los mismos ejercicios que durante la movilización neural activa, pero con unas gafas modelo Prims Glases^{TM}. Los ejercicios se realizaron con la

mano contralateral, pues el efecto de esas gafas consiste en crear una ilusión óptica de que se mueve el mano objetivo (contralateral). La dosis de tratamiento es la misma que en el grupo anterior (cumpliendo los mismos tiempos).

-La observación de acciones consistió en la visualización de una grabación de una mano realizando los mismos ejercicios al mismo ritmo y dosis que los dos grupos anteriores (con una duración igual al tiempo invertido en los ejercicios del primer grupo).

-El grupo del programa clásico de rehabilitación consistió en realizar una combinación de ejercicios de movilidad de muñeca y mano junto con ejercicios de fuerza.

Los ejercicios detallados se encuentran en el ANEXO IV.

Seguidamente de la última sesión se realizó la valoración post tratamiento. Ésta siguió el mismo orden de la valoración basal.

5.3 Equipos y procedimientos empleados:

5.3.1 Estudio I

Los siguientes aparatos componen la valoración cuantitativa sensorial utilizada en el estudio I:

Figura 7. Termotest modelo Somedic, Sweden, 25x 50mm thermode.

Utilizado para las variables de detección térmica y umbrales de dolor térmico. También registramos sensaciones de calor parciales sensaciones de calor durante la prueba del límite sensorial térmico.

Figura 8. *Filamentos de Von Frey utilizados para la detección mecánica.*

Figura 9. *Pinprick utilizado para la sumación temporal.*

La sensibilidad al dolor mecánico se examinó con una escala numérica del dolor (0-100) durante 5 series de 7 estimulaciones de pinchazos pseudoaleatorios. Entremezclados con estas estimulaciones de pinchazos, se realizaron 5 series de 3 estimulaciones con una mecha de algodón, una punta de algodón y un cepillo estandarizado cepillo normalizado (Sense-lab) para determinar la presencia de alodinia. El coeficiente de wind-up se midió como la calificación numérica media del dolor de 5 trenes de 10 estímulos de pinchazos, dividida por la puntuación media de 5 estímulos individuales.

Figura 10. *Algómetro digital Wagner Instruments, Greenwich, CT.*

Utilizado para evaluar los umbrales de dolor a la presión.

Figura 11. *Diapasón Rydel-Seiffer.*

Utilizado para medir los umbrales de detección a la vibración. Los pacientes se familiarizaron con la prueba sensorial cuantitativa (QST) en el dorso de la mano no experimental, seguida de una prueba en la cara palmar del dedo índice afectado (inervado

por el nervio mediano). También se evaluó la QST en una zona extraterritorial sobre el dorso de la mano (inervada por el nervio radial). Mientras que la zona de prueba de los umbrales de temperatura era más pequeña en el dedo índice (10 x 50 mm) que en el dorso de la mano (25x 50 mm), las áreas eran comparables entre los grupos de grupos de participantes, por lo que no influyen en nuestros resultados. Los umbrales de dolor por presión se registraron en la eminencia tenar y en el músculo braquiorradial y los umbrales de detección de vibraciones en la cara palmar del extremo distal del segundo metacarpiano o la estiloides cubital para las zonas mediana y extramediana, respectivamente.

Figura 12. *Electromiograma.*

La temperatura de la mano se estandarizó a 31°C. Los registros ortódromos sensoriales se realizaron estimulando el dedo índice y registrando desde la muñeca. Los estudios motores se realizaron registrando desde el abductor pollicis brevis estimulado desde la muñeca y la fosa antecubital. Para determinar la presencia de una anomalía muy leve del TCE, se consideró anormal una latencia mixta aumentada del potencial de acción del nervio sensorial mediano en comparación con el potencial de acción del nervio sensorial cubital en la estimulación del dígito IV, mostrada por un "doble pico". Además, una diferencia de 0,4 ms en la latencia motora mediana frente a la cubital, medida en una distancia fija de 8 cm y registrada en los músculos interóseos lumbricales y palmares, se consideró anormal. La gravedad de la prueba de electrodiagnóstico se calificó en una escala de 1 (muy leve) a 6 (extremadamente severa) según los criterios publicados anteriormente.

Figura 13. *Microscopio Axio LSM 700 con sistema de observación Z1 (Zeiss, Cambridge, United Kingdom).*

Se utilizó para determinar el número de fibras intradermales. Se tomó una biopsia de piel de 3 mm de diámetro bajo anestesia subcutánea en la cara ventromedial de la falange proximal del dedo índice inervada por el nervio mediano. La biopsia se fijó en periodato-lisina-paraformaldehído fresco durante 30 minutos. A continuación, se lavó el tejido en tampón fosfato y se almacenó durante 2 o 3 días. Después de la incrustación en gel a temperatura de corte óptima, el tejido se congeló y se almacenó a 280˚C. La tinción se realizó mediante el método de flotación libre descrito anteriormente, utilizando el producto genético de la proteína 9.5 (PGP 9.5 Ultraclone, Isle of Wight, United Kingdom, 1:1000; Zytomed, Berlin,

Germany 1:200) y la proteína de mielina básica (Abcam, Cambridge, United Kingdom 1:500) como anticuerpo primario y Cy3 (Stratech, Ely, United Kingdom 1:1000) junto con Alexa Fluor 488 (Abcam, 1:500) como anticuerpos secundarios. La densidad de fibras nerviosas intraepidérmicas (IENFD) se cuantificó en secciones de piel de 50- mm determinando la cantidad de fibras por milímetro de epidermis según las directrices actuales. También cuantificamos la inervación dérmica de Meissner por milímetro de epidermis, el porcentaje de milímetro de epidermis, el porcentaje de haces nerviosos dérmicos PGP1 que contienen MBP, y la longitud media de los nódulos.

5.3.2 Estudio II

En este estudio se utilizó el mismo algómetro que el mostrado en la figura 10 del estudio I. Este instrumento utiliza kg/cm² como unidad de medida. Las mediciones se realizaron bilateralmente (lado afecto y lado no afecto). Se calculó la media de tres mediciones sobre el túnel del carpo que se realizaron con un intervalo de 30 segundos para evitar la sumación temporal. La sumación temporal se aplicó mediante los PPTs en el punto medio de la cara dorsal de la primera interfalángica de la mano afectada. Se le pidió al paciente que cuantificara la intensidad de dolor en una escala numérica de 0-10. Seguidamente se realizaron 10 mediciones con la misma intensidad y a un ritmo de 1 Hz. Tras el estímulo en trenes se volvió a preguntar por la intensidad de dolor. La sumación temporal se calculó como el ratio de dolor durante el tren entre el estímulo aislado.

Figura 14. *Esfigmomanómetro Riester.*

Modulación condicionada del dolor: Para realizar el estímulo condicionado de dolor en el brazo no afecto de los pacientes se utilizó el esfigmomanómetro Riester (figura 14). Para la evaluación de la modulación condicionada de dolor, se utilizaron la media de tres mediciones de los PPTs sobre la falange distal del primer dedo, en la cara dorsal de la mano afectada. El estímulo condicionante se aplicó en el lado no afecto mediante el esfigmomanómetro. Se insufló hasta 200 mmHg, hasta provocar un dolor de una intensidad 5/7 sobre 10 en la escala de dolor. Una vez alcanzada esa intensidad y con el manguito puesto, se vuelve a realizar la medición de los PPT. El protocolo ha demostrado ser adecuado para valorar la modulación condicionada previamente en otras patologías (Foucher et al., 2019). La eficacia de la CPM se calculó restando los PPT después del estímulo condicionante menos el PPT aislado. Valores positivos indicarían un buen funcionamiento del sistema inhibitorio descendente (Tuveson et al., 2006).

5.3.3 Estudio IV

Los materiales y protocolos utilizados para la medición de las variables psico-fisiológicas fueron los mismos que los empleados para el estudio III.

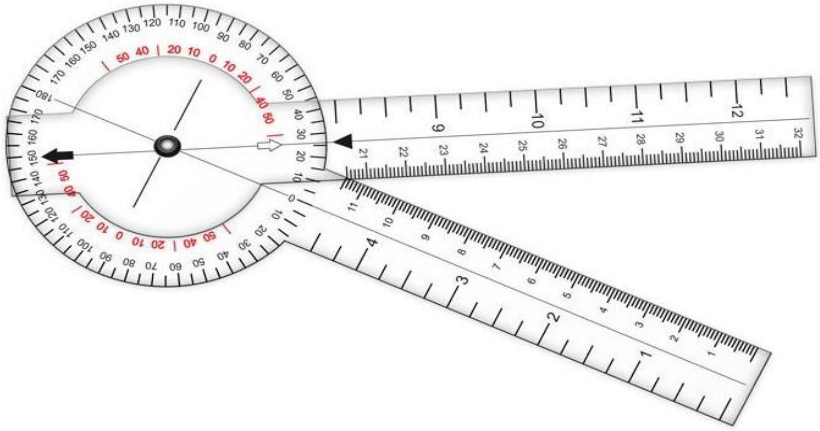


Figura 15. *Goniómetro.*

La mecanosensibilidad neural fue evaluada a partir de la amplitud valorada en grados de extensión del codo con un goniómetro convencional, utilizando la prueba neurodinámica del miembro superior 1, que es una herramienta de diagnóstico para evaluar la mecanosensibilidad del nervio mediano (Schmid et al., 2009). Para medir el ángulo del codo, el eje se colocó en el epicóndilo medial con el brazo fijo del goniómetro mirando hacia el acromion y el brazo móvil hacia la apófisis estiloides cubital. Un cambio superior a 7,16 puede considerarse debido a la intervención (Oliver & Rushton, 2011).

Figura 16. *Dinamómetro Jamar, Sammon Preston, Canada.*

La fuerza de prensión manual se midió utilizando el dinamómetro JAMAR. Este dinamómetro presenta una excelente fiabilidad intra-observador (ICC 1⁄4 0,94 y 0,98) y una excelente fiabilidad intercalar (ICC 1⁄4 0,98) (Peolsson et al., 2001). El dinamómetro se ajustó a la mano dominante del sujeto. Se ha establecido que el cambio mínimo significativo sería una diferencia de 2,8 kg (Baldwin et al., 2013).

5.4 Instrumentos de recogida de datos y análisis de estudios.

Durante las investigaciones que componen este proyecto de tesis se utilizaron los siguientes instrumentos de recogida de datos.

-Cuestionario DN4 de dolor neuropático: la versión española de la Douleur Neuropathique 4 (DN4). Esta versión ha mostrado una buena consistencia interna (Pérez et al., 2007). El cuestionario consta de una parte inicial con preguntas que evalúan una serie de descriptores de síntomas neuropáticos (dolor ardiente y frío, descarga eléctrica, hormigueo, pinchazos, entumecimiento, picor), seguida de una breve exploración clínica sensorial (hipoestesia al tacto, hipoestesia al pinchazo y alodinia por cepillado). Una puntuación de DN4 >=4 se

interpretó como dolor neuropático (Bouhassira et al., 2005) y una puntuación <4 se interpretó como dolor nociceptivo.

-Cuestionario del síndrome túnel del carpo BOSTON: se utilizó para evaluar la gravedad de los síntomas y los déficits funcionales. El cuestionario del túnel carpiano de Boston consta de una subescala de síntomas y otra de función (Levine et al., 1993). Este cuestionario ha sido validado en español, con buenos niveles de consistencia interna y reproducibilidad (Oteo-Álvaro et al., 2016). La intensidad del dolor actual de la mano se registró mediante una escala visual analógica (EVA), siendo 0 la ausencia de dolor y 100 el peor dolor imaginable.

-Cuestionario de síntomas de dolor neuropático: distingue el dolor superficial, profundo, paroxístico o evocado, así como la parestesia y la disestesia. Cada una de ellas en una escala de 0 a 10, con una puntuación total que va de 0 a 100 (Bouhassira et al., 2004).

-Diagramas corporales: los pacientes marcaron la localización de los síntomas en un diagrama de manos y cuerpo (Katz et al., 1990). Los resultados se dicotomizaron en distribución mediana y extramediana.

-Cuestionario de sensibilización central: es una herramienta diseñada originalmente para identificar a los pacientes con "síndrome de sensibilidad central" (Moser et al., 2012). La traducción al español muestra una buena fiabilidad y consistencia interna (Cuesta-Vargas et al., 2016). El paciente puntúa cada pregunta de 0 a 4: nunca, rara vez, a veces, continuamente y siempre. La puntuación total oscila entre 0 y 100, y se considera que los valores superiores a 40 indican la presencia del "síndrome de sensibilidad central" (Moser et al., 2012).

-Índice de la severidad de insomnio: esta escala clasifica a los pacientes en sin insomnio (0-7), subumbral (8-14), moderado (15-21) o insomnio grave (22-28). El cuestionario demostró

que tiene una consistencia interna adecuada y es una medida de autoinforme fiable para evaluar las dificultades de sueño percibidas (Bastien et al., 2001).

-Cuestionario sobre catastrofismo de dolor: está compuesta por 13 ítems, cada ítem puntúa del 0 al 4. El rango de puntuación total se encuentra de 0 a 52, donde las puntuaciones mayores indican mayor nivel de catastrofismo. Este instrumento presentó la misma estructura factorial original presentando tres factores (rumiación, magnificación y desesperanza), así como unas adecuadas propiedades psicométricas (García Campayo et al., 2008)

-Cuestionario de depresión BECK: es el cuestionario más empleado a nivel mundial y nacional para evaluar la depresión (Whisman, Perez, & Ramel, 2000). Empleamos la adaptación al castellano del inventario de depresión de Beck II, que consta de 21 ítems para medir la situación afectiva, cognitiva y los signos y síntomas de depresión durante las dos últimas semanas. Altas puntuaciones indican niveles altos de síntomas depresivos. Este inventario ha demostrado unas excelentes propiedades psicométricas con una buena consistencia interna (Cronbach $\alpha = 0{,}89$) con una divergencia adecuada y validez divergente (Melipillán Araneda, Cova Solar, Rincón González, & Valdivia Peralta, 2008). Con respecto al punto de corte, no se puede establecer uno concreto, ya que depende de la población a estudio y el propósito de este, pero se sitúa en un rango de 12 a 19 para indicar la presencia de sintomatología depresiva (Melipillán Araneda et al., 2008; Sanz, García-Vera, Espinosa, Fortún, & Vázquez, 2005)

-Cuestionario Ansiedad (Stai): Se utilizó la versión adaptada al castellano del "State and Trait Anxiety Inventory" (STAIES) (Rossi & Pourtois, 2012; Charles D Spielberger, 1983). El "STAI-

ES" es una escala bien conocida de autoinforme, que comprende dos subescalas de autoevaluación que miden dos conceptos de la ansiedad: estado (E) y rasgo (R). Está compuesto por 40 ítems con 4 posibles respuestas cada uno (puntuación de 0 a 3). Las puntuaciones totales de cada una de las subescalas oscilan entre 0 y 60 puntos. Concretamente la "STAI-ES" es apta para evaluar la ansiedad-estado en una gran variedad de situaciones (Rossi & Pourtois, 2012). Además, presenta una buena fiabilidad y validez demostrada previamente (C. D. Spielberger & Vagg, 1984). La consistencia interna oscila entre 0,90 y 0,93 para la escala de estado, y entre 0,84 y 0,87 para la escala de rasgo (C. D. Spielberger & Vagg, 1984; Vélez, Garzón, & Ortíz, 2008)

-Cuestionario miedo al movimiento TSK: Para evaluar el miedo al movimiento o a la (re)lesión relacionada con el dolor se utilizará la *escala Tampa de kinesiofobia* (ETK) validada al Castellano (Gómez-Pérez, López-Martínez and Ruiz-Párraga, 2011). Se usará la versión de 11 ítems que mostró buenas propiedades de fiabilidad en pacientes con dolor crónico (Gómez-Pérez, López-Martínez and Ruiz-Párraga, 2011). Cada ítem se califica en una escala de cuatro puntos tipo Likert que va desde "muy de acuerdo" a "totalmente en desacuerdo". Las puntuaciones totales oscilan entre 11 y 44, y las puntuaciones más altas indican más miedo de movimiento y/o (re) lesión. Para el dolor crónico en la versión inglesa, el cambio mínimo detectable es de 5,6 puntos (Hapidou *et al.*, 2012).

-Habilidad de imaginar movimiento (MIQ-R): Para evaluar la capacidad de imaginar movimiento, se utilizó la versión española del Cuestionario de Imagen de Movimiento Revisado (MIQ-R) que consiste en 4 movimientos repetidos en 2 dominios (visual y cinestésico). Los participantes puntúan los movimientos de 1 a 7, siendo 1 la máxima dificultad y 7 la menor o mínima dificultad. Las características psicométricas del de la MIQ-R

han sido consistentemente adecuadas, con coeficientes de Cronbach superiores a 0,84 para toda la escala (Campos y González 2010).

-Escala de riesgo de sesgo SYRCLE: para valorar el riesgo de sesgo de los estudios en animales se utilizó la escala SYRCLE. Dicha escala valora los diferentes tipos de sesgos: selección, realización, detección, pérdidas y reporte. También deja la opción abierta a otro tipo de sesgos que se pudiesen identificar. La escala no cuenta con un puntaje, por lo que lo deja abierto a la interpretación de los investigadores (Hooijmans et al., 2014)

5.5 Análisis de datos

Para todos los estudios incluidos en este proyecto de tesis se utilizó el programa Statistics Package for Social Science (SPSS 20.00 o 27.00, IBM Inc.).

5.5.1 Estudio I

La normalidad de los datos se evaluó mediante inspección visual y utilizando la prueba de normalidad de Shapiro-Wilk.

Se compararon variables demográficas, datos histológicos de la piel, cuestionarios psicológicos del sueño y parámetros de la electromiografía de los grupos (sanos, sin DN, DN leve y DN moderado/grave) con un análisis de varianza de una vía (ANOVA) o estadísticas de Kruskal-Wallis seguido de contrastes planificados. Como estábamos interesados en efectos de 1) la presencia de DN y 2) la gravedad del DN, utilizamos contrastes de Helmert para las comparaciones de seguimiento previstas. Este tipo de contraste compara cada nivel de nuestra variable categórica "grupo de grupo de pacientes" con la media de los niveles siguientes. Los contrastes previstos incluían 1) grupos sanos frente a grupos combinados de pacientes (para confirmar diferencias entre los pacientes y los controles sanos), 2) grupos sin

DN vs grupos combinados de DN (para evaluar el efecto de la presencia de DN y 3) DN leve frente a DN moderado/grave (para evaluar el efecto de la gravedad del DN). El equivalente no paramétrico del contraste de Helmert se utilizó para datos no distribuidos normalmente, y el punto de corte de la significación se ajustó para las pruebas múltiples (corrección de Bonferroni). La gravedad de los síntomas y de la función sólo se evaluó en los 3 subgrupos de pacientes mediante pruebas de Kruskal-Wallis seguidas de 2 contrastes de Helmert (grupos sin DN frente a DN combinado y DN leve frente a moderado/grave). Los resultados del examen clínico y de la medicación se comparó entre los grupos con la estadística chi-cuadrado o pruebas exactas de Fisher, según el caso. A continuación, se realizaron 2 comparaciones planificadas, ajustadas por Bonferroni para pruebas múltiples (grupos sin DN vs. grupos combinados de DN y DN leve vs DN moderado/grave), reflejando los contrastes de Helmert.

Las puntuaciones z de las pruebas sensoriales cuantitativas se analizaron con 4 ANOVAs multivariantes de una vía (MANOVAs) utilizando los umbrales de combinados de detección de QST o umbrales de dolor como variables de respuesta y grupo de pacientes como variable independiente para los territorios mediano como para los territorios medianos y radiales. Se realizó la estadística de rastreo de Pillai, que es robusta para los diseños desequilibrados. Los MANOVAs significativos fueron acompañados de ANOVAs unidireccionales seguidos de Helmert para comprobar la hipótesis de que los fenotipos clínicos son más pronunciados en los pacientes con DN moderado/grave, seguidos de los que tienen DN leve y no tienen DN, mientras que los participantes sanos muestran los menores déficits.

También utilizamos un algoritmo publicado recientemente que incluye a cada paciente en 1 de 3 fenotipos sensoriales: 1) pérdida de detección térmica y mecánica

("pérdida sensorial"), 2) función sensorial intacta, a menudo combinada con hiperalgesia o alodinia térmica ("hiperalgesia térmica"), y 3) pérdida de detección térmica, pero no mecánica, acompañada de hiperalgesia o alodinia mecánica ("hiperalgesia mecánica"). Se utilizó la versión determinista en la que cada paciente se clasifica en un fenotipo y no son posibles los fenotipos mixtos. Se utilizaron las pruebas exactas de Fisher para comparar la frecuencia de los fenotipos de QST entre los grupos.

5.5.2 Estudio II

No se pudo realizar el meta-análisis. Se realizó un análisis descriptivo mediante mapas de calor.

5.5.3 Estudio III

Se comprobó la normalidad de los datos mediante la inspección visual de los histogramas y la prueba de Kolmogorov-Smirnov. Las características sociodemográficas y clínicas de los participantes se resumieron mediante estadísticas descriptivas.

Para determinar la presencia de signos indicativos de un procesamiento central del dolor alterado, se emplearon pruebas t de Student independientes para identificar las diferencias entre los grupos de sanos y de pacientes para las variables psicofísicas. Se informó de la frecuencia de propagación extraterritorial de los síntomas (mediana/extramediana).

Para identificar las asociaciones entre el CSI y los signos psicofísicos indicativos de una alteración del procesamiento del dolor, realizamos estadísticas de correlación de Pearson sólo en los datos de los pacientes. Los coeficientes de 0,5 o superiores se interpretaron como una correlación fuerte, 0,3 moderada y 0,1 pequeña. Se corrigió la tasa de falsos descubrimientos mediante la corrección de Benjamini Hochberg (FDR=25%). También agrupamos a los

pacientes con STC en aquellos con CSI >=40 y <40 y exploramos las diferencias en las pruebas psicofísicas y la propagación de los síntomas con pruebas t independientes y estadísticas de la prueba de Chi cuadrado o exacta de Fisher, según el caso.

Para explorar la relación entre el CSI y el bienestar emocional (BECK, TSK, STAI) en los datos de los pacientes, se calcularon los coeficientes de correlación de Pearson y se utilizó la corrección de Benjamini Hochberg para corregir la tasa de falsos descubrimientos. Los valores p no ajustados se presentan para facilitar la interpretación.

5.5.4 Estudio IV

Se empleó un intervalo de confianza del 95% y considerando estadísticamente significativos todos los valores con un valor p inferior a 0,05. La estadística descriptiva se empleó para resumir los datos de las variables continuas, se presentaron como media ± desviación estándar y el intervalo de confianza del 95%. Se realizó un ANOVA de medidas repetidas para estudiar el efecto del factor inter-sujeto "grupo de intervención" con 4 categorías (NM activo, MT, AO y CR) y el factor intra-sujeto tiempo", también con 2 categorías (pre y post) sobre las variables dependientes. Se realizó un análisis post hoc con corrección de Bonferroni en el caso de resultados significativos del ANOVA para comparaciones múltiples entre variables.

El tamaño del efecto se calculó mediante el Eta Cuadrado Parcial (gp2) cuando era significativo. Un tamaño del efecto de 0,01 se consideró pequeño, 0,06 como medio y 0,14 como grande (Gray y Kinnear, 2012).

Se realizó un análisis por protocolo porque nos interesaba conocer los datos de los participantes que completaron el estudio asumiendo que en la realidad clínica se producen pérdidas. De este modo, se conoce con mayor precisión el efecto de la intervención, ya que

se ha demostrado que los pacientes con niveles bajos de adherencia tienden a tener un peor pronóstico que los que tienen mayores niveles de adherencia. Esto fue considerado como una pequeña limitación porque se trata de personas sanas y no pacientes.

6. Resultados

6.1 Resultados del estudio I

Research Paper

PAIN

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Somatosensory and psychological phenotypes associated with neuropathic pain in entrapment neuropathy

Luis Matesanz[a,b], Andrea C Hausheer[a,c], Georgios Baskozos[a], David L.H. Bennett[a], Annina B. Schmid[a,*]

Abstract

It currently remains unclear why some patients with entrapment neuropathies develop neuropathic pain (neuP), whereas others have non-neuP, presumably of nociceptive character. Studying patients with carpal tunnel syndrome (CTS), this cross-sectional cohort study investigated changes in somatosensory structure and function as well as emotional well-being specific to the presence and severity of neuP. Patients with CTS (n = 108) were subgrouped by the DN4 questionnaire into those without and with neuP. The latter group was further subdivided into mild and moderate/severe neuP using a pain visual analogue scale. N = 32 participants served as healthy controls. All participants underwent a clinical examination, quantitative sensory testing, electrodiagnostic testing (EDT), and skin biopsy to determine the structural integrity of dermal and intraepidermal nerve fibres. Patients also completed questionnaires evaluating symptom severity and functional deficits, pain distribution, sleep quality, and emotional well-being. The overall prevalence of neuP in patients with CTS was 80%, of which 63% had mild neuP. Symptom severity and functional deficits as well as somatosensory dysfunction was more pronounced with the presence and increasing severity of neuP. No difference was identified among patient groups for EDT and nerve fibre integrity on biopsies. The severity of neuP was accompanied by more pronounced deficits in emotional well-being and sleep quality. Intriguingly, extraterritorial spread of symptoms was more prevalent in patients with moderate/severe neuP, indicating the presence of central mechanisms. NeuP is common in patients with CTS, and its severity is related to the extent of somatosensory dysfunction and a compromise of emotional well-being.

Keywords: Neuropathic pain, Quantitative sensory testing, Entrapment neuropathy, Carpal tunnel syndrome

1. Background

Entrapment neuropathies represent the most prevalent peripheral neuropathy and are the most common cause of neuropathic pain (neuP). Carpal tunnel syndrome (CTS) is the most prevalent entrapment neuropathy with a lifetime risk of ~10% that increases to 85% in patients with diabetes.[48] Patients mostly experience tingling and numbness in the hand and loss of dexterity. In addition, some patients experience pain, which can impact on their daily functioning.

According to the neuP grading system,[16] patients with electrodiagnostically confirmed CTS and symptoms in their hand are automatically classed as having at least probable neuP and definite neuP if sensory abnormalities are present. However, the patients' description of their pain sometimes indicates the presence of nociceptive rather than neuP.[31] Indeed, the use of screening questionnaires revealed that the prevalence of neuP in patients with CTS varies with values reported from 31% to 77%.[21,37,49,50,56] This together with the absence or at best weak correlation between pain and measures of nerve pathology (eg, nerve conduction studies)[20,51] has led to the hypothesis that in some patients, pain may originate from structures other than the nerve such as the flexor tendons.[24]

It currently remains unclear why some patients with CTS develop neuP, whereas others do not experience neuP but pain of predominant nociceptive character. One hypothesis is that neuropathy is more severe in patients with neuP compared with those without neuP. However, the evidence for this is currently controversial,[21,37,50] with most studies reporting no association between electrodiagnostic test severity and the presence of neuP. Of note, electrodiagnostic testing only examines loss of function of large nerve fibres, thus providing only limited information on the potential spectrum of nerve pathology.

A better understanding of the prevalence of neuP and its underlying disease process is crucial to determine risk factors and guide management for these patients. This cross-sectional cohort study provides an in-depth evaluation of the somatosensory phenotype of patients with CTS with and without neuP. We thereby

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L. Matesanz and A.C. Hausheer contributed equally.

[a] *Nuffield Department for Clinical Neurosciences, University of Oxford, Oxford, United Kingdom,* [b] *Department of Physical Therapy, Occupational Therapy, Rehabilitation and Physical Medicine, Escuela Internacional de Doctorado, Universidad Rey Juan Carlos, Alcorcón, Spain,* [c] *School of Health Professions, Institute of Physiotherapy, Zurich University of Applied Sciences, Winterthur, Switzerland*

**Corresponding author. Address: Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, West Wing Level 6, Oxford OX39DU, United Kingdom. Tel: +44 01865 223254. E-mail address: Annina.schmid@neuro-research.ch (A. Schmid).*

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aim to (1) identify changes in the somatosensory structure and function specific to the presence and severity of neuP and (2) explore whether differences in demographic, clinical, and emotional well-being are related to the presence and severity of neuP.

2. Methods

2.1. Participants

One hundred and eight patients who met electrodiagnostic[1] and clinical criteria[2] for CTS participated in the study. Patients were recruited through the neurophysiology and hand surgery departments at Oxford University Hospitals, local print media, and public notice boards. Patients were excluded if electrodiagnostic findings were indicative of other peripheral neuropathies than CTS, if another medical condition affecting the upper extremity or neck was present (eg, tennis elbow or hand osteoarthritis), if a previous history of surgery or trauma to the upper limb or neck existed, or if CTS was caused by pregnancy or diabetes. Proportionally age- and sex-matched healthy controls (n = 32) were recruited through public notice boards and media advertisements. The study was approved by the national ethics committee (London Riverside, Ref 10/H0706/35), and all participants gave informed written consent before participating. Primary publications containing parts of the Oxford CTS cohort have been previously published.[6,46]

2.2. Patient subgroups

Patients were divided into those with and without neuP using the DN4 questionnaire.[10] This questionnaire is composed of questions evaluating a range of sensory descriptors and a short sensory examination. Sensory descriptors include the presence or absence of burning and painfully cold-like pain, electric shocks, tingling, pins and needles, numbness, and itching. The sensory examination evaluates the presence or absence of hypoesthesia to touch, hypoesthesia to pinprick, and brush allodynia. A DN4 score of ≥4 was interpreted as neuP. Because the DN4 was designed to differentiate neuropathic from somatic pain, we interpreted a score of <4 (no neuP) to represent pain of likely nociceptive character. We specifically decided against the use of the neuP grading system,[16] which has previously been applied to classify patients in similar studies.[22,42,55] This was particularly important in our cohort, as the grading system would automatically classify all patients with CTS as having at least probable neuP because of the presence of nerve conduction abnormalities. Moreover, our question was focused on neuP vs no neuP (nociceptive pain) rather than painful vs pain-free neuropathies as in previous studies.

To examine the impact of neuP severity on the clinical phenotype, we further classed those with neuP as having mild (<4) or moderate/severe neuP using a cutoff of ≥4 on a visual analogue scale for average pain during the past 24 hours.[55]

2.3. Symptom severity, functional deficits, and characteristics of neuropathic pain

The Boston Carpal Tunnel Questionnaire was used to assess symptom severity and functional deficits in patients with CTS.[32] Characteristics of neuP were evaluated with the Neuropathic Pain Symptom Inventory,[11] which distinguishes superficial, deep, paroxysmal, or evoked pain as well as paraesthesia and dysaesthesia each on a scale from 0 to 10 with the total score ranging from 0 to 100.[17] Patients also marked their spread of symptoms on a hand and body diagram. The patterns were dichotomized into median and extramedian spread and the presence or absence of proximal spread of symptoms beyond the hand.[26] Spread of symptoms outside the distribution of the median nerve has previously been associated with central sensitisation in patients with CTS.[62]

2.4. Clinical examination

Light touch and pinprick were tested with cotton wool and a neurotip over the palmar surface of the index fingertip. As sensation may be altered even in hand areas not innervated by the affected median nerve in patients with CTS,[46] sensation was recorded as normal or reduced compared with the proximal ventral forearm. We further performed 3 commonly used clinical provocation tests: Tinel sign involved light percussion over the median nerve just proximal to the carpal tunnel. A positive test was recorded if characteristic paraesthesia or shooting pain radiating into the fingers was provoked. The Phalen test involved active end of range wrist flexion. A reproduction of symptoms (eg, paraesthesia and numbness) in the median nerve territory within 1 minute was considered a positive test.[39] For the carpal compression test, moderate pressure was exerted with the investigators' thumbs over the transverse carpal ligament with the wrist in a neutral position.[19] The test was deemed positive if paraesthesia or numbness was provoked in the median nerve territory of the hand within a maximum period of 30 seconds. Thenar wasting was graded as present or absent. Muscle strength of the abductor pollicis brevis was graded according to the Medical Research Council Manual Muscle Testing scale ranging from M0 to M5, with M3 indicating full range against gravity and M5 indicating activation against the examiner's full resistance with a full range of motion.[35]

2.5. Emotional well-being and sleep quality

To evaluate emotional well-being, participants completed the Depression Anxiety and Positive Outlook Scale.[40] They also completed the 13-item Pain Catastrophizing Scale,[52] which contains subscales for rumination, magnification, and helplessness, as well as the short form Pain Anxiety Symptoms Scale (PASS-20)[34] with subscales describing cognitive factors, escape, fear, and physiological anxiety. Sleep disturbance was evaluated with the Insomnia Severity Index, which classifies patients into no insomnia (0-7), subthreshold (8-14), moderate (15-21), or severe insomnia (22-28).[7]

2.6. Quantitative sensory testing

Quantitative sensory testing was used to determine somatosensory phenotypes according to the previously published protocol by the German Research Network on Neuropathic Pain.[45] Cold and warm detection thresholds as well as cold and heat pain thresholds and thermal sensory limen were measured with a ThermoTester (Somedic, Sweden, 25 × 50 mm thermode). We also recorded paradoxical heat sensations during thermal sensory limen testing. Mechanical detection was measured with von Frey hairs and mechanical pain thresholds with weighted pin-prick stimulators. Mechanical pain sensitivity was examined with a numerical pain rating scale (0-100) during 5 sets of 7 pseudorandom pin-prick stimulations. Intermingled with these pin-prick stimulations were 5 sets of 3 light touch stimulations with a cotton wisp, a cotton wool tip, and a standardized brush (Sense-lab) to determine the presence of allodynia. Pressure pain thresholds were evaluated with a manual algometer (Wagner Instruments, Greenwich, CT) and vibration detection threshold with a Rydel–Seiffer tuning fork. The wind-up ratio was measured as the

mean numerical pain rating of 5 trains of 10 pin-prick stimuli divided by the mean rating of 5 single stimuli.

The patients were familiarised with the quantitative sensory testing (QST) on the dorsum of the nonexperimental hand followed by testing on the palmar side of the affected index finger (innervated by the median nerve). We also evaluated QST in an extraterritorial area over the dorsum of the hand (innervated by the radial nerve). Whereas the testing area for temperature thresholds was smaller over the index finger (~10 × 50 mm) than the dorsum of the hand (25 × 50 mm), the areas were comparable between participant groups, hence not influencing our findings. Pressure pain thresholds were recorded over the thenar eminence and brachioradial muscle and vibration detection thresholds over the palmar side of the distal end of the second metacarpal or ulnar styloid for the median and extramedian areas, respectively.

Quantitative sensory testing data (except for cold and heat pain and vibration detection thresholds) were log transformed to achieve normally distributed data.[33,38] *Z* scores ((value of the participant-mean value of healthy controls)/SD of healthy controls)[45] were calculated using the proportionally matched healthy control group. A small constant of 0.1 was added to the MPS to avoid loss of zero rating values.[45]

2.7. Electrodiagnostic tests

Electrodiagnostic testing (EDT) was performed with an ADVANCE system (Neurometrix) and conventional reusable electrodes. Hand temperature was standardized to >31°C. Sensory orthodromic recordings were made by stimulating the index finger and recording from the wrist. Motor studies were performed by recording from the abductor pollicis brevis stimulated from the wrist and antecubital fossa. To determine the presence of a very mild EDT abnormality, an increased mixed latency of the median sensory nerve action potential compared with ulnar sensory nerve action potential on digit IV stimulation shown by a "double peak" was considered abnormal.[58] In addition, a difference of >0.4 ms in median vs ulnar motor latency measured over a fixed distance of 8 cm and recorded over the lumbrical and palmar interossei muscles was considered abnormal.[41] Electrodiagnostic test severity was graded on a scale from 1 (very mild) to 6 (extremely severe) according to previously published criteria.[8]

2.8. Skin histology

A 3-mm diameter skin biopsy was taken under subcutaneous anaesthesia on the ventroradial side of the proximal phalanx of the index finger innervated by the median nerve. The biopsy was fixed in fresh periodate-lysine-paraformaldehyde for 30 minutes. The tissue was then washed in phosphate buffer and stored for 2 to 3 days in sucrose in phosphate buffer. After embedding in optimal cutting temperature gel, the tissue was frozen and stored at −80°C. Staining was performed using a previously described free-floating method,[46] using protein gene product 9.5 (PGP 9.5 Ultraclone, Isle of Wight, United Kingdom, 1:1000; Zytomed, Berlin, Germany 1:200) and myelin basic protein (Abcam, Cambridge, United Kingdom 1:500) as primary antibodies and Cy3 (Stratech, Ely, United Kingdom 1:1000) and Alexa Fluor 488 (Abcam, 1:500) as secondary antibodies.

Intraepidermal nerve fibre density (IENFD) was quantified in 50-µm skin sections using an Axio LSM 700 microscope with an Observer Z1 imaging system (Zeiss, Cambridge, United Kingdom) by determining the amount of fibres per millimeter epidermis according to current guidelines.[30] We also quantified dermal innervation by evaluating the number of Meissner corpuscles per millimeter epidermis, the percentage of PGP^+ dermal nerve bundles containing MBP, and the mean nodal length as previously reported.[46]

2.9. Statistical analysis

SPSS Version 27 (IBM) was used for statistical analyses. Normality of data was assessed by visual inspection and using the Shapiro–Wilk test for normality.

Demographic variables, skin histology data, psychological and sleep questionnaires, and EDT parameters were compared among groups (healthy, no neuP, mild neuP, and moderate/severe neuP) with one-way analysis of variance (ANOVA) or Kruskal–Wallis statistics followed by planned contrasts. As we were interested in effects of (1) the presence of neuP and (2) the severity of neuP, we used Helmert contrasts for planned follow-up comparisons. This type of contrast compares each level of our categorical variable "patient group" with the mean of the subsequent levels. As such, the planned contrasts included (1) healthy vs combined patient groups (to confirm differences between patients and healthy controls), (2) no neuP vs combined neuP groups (to evaluate the effect of the presence of neuP), and (3) mild neuP vs moderate/severe neuP (to evaluate the effect of neuP severity). The nonparametric equivalent for the Helmert contrast was used for non-normally distributed data,[47] and the significance cutoff was adjusted for multiple testing (Bonferroni correction). Symptom and function severity were only evaluated in the 3 patient subgroups using Kruskal–Wallis tests followed by 2 Helmert contrasts (no neuP vs combined neuP groups and mild neuP vs moderate/severe neuP). Findings of the clinical examination and medication intake were compared among groups with chi-square statistics or Fisher exact tests as appropriate. This was followed by 2 planned comparisons, Bonferroni adjusted for multiple testing (no neuP vs combined neuP groups and mild neuP vs moderate/severe neuP), reflecting Helmert contrasts.

Quantitative sensory testing *z* scores were analysed with 4 one-way multivariate ANOVAs (MANOVAs) using the combined QST detection or pain thresholds as the response variables and patient group as the independent variable for both the median and radial territories. Pilai's trace statistics, which is robust to unbalanced designs, is reported. We followed the significant MANOVAs up with one-way univariate ANOVAs followed by Helmert contrasts to test the hypothesis that clinical phenotypes are most pronounced in patients with moderate/severe neuP, followed by those with mild and no neuP, whereas healthy participants show the least deficits.

We also used a recently published algorithm[5,59] that allocates each patient into 1 of 3 sensory phenotypes: (1) loss of thermal and mechanical detection ("sensory loss"), (2) intact sensory function, often combined with thermal hyperalgesia or allodynia ("thermal hyperalgesia"), and (3) loss of thermal detection, but not mechanical detection, accompanied by mechanical hyperalgesia or allodynia ("mechanical hyperalgesia").[59] The deterministic version of the algorithm was used, in which each patient is sorted to 1 phenotype and no mixed phenotypes are possible. Fisher exact tests were used to compare the frequency of QST phenotypes among groups.

3. Results

3.1. Most patients with carpal tunnel syndrome have neuropathic pain

The demographic data are described in **Table 1**. Most patients with CTS had likely neuP (80%), whereas 20% were classified as unlikely neuP by the DN4 and therefore presumably have pain of nociceptive character. Of those patients with neuP, 63% were classified as having

mild neuP, whereas 37% had moderate/severe neuP. The groups were comparable in regard to age, sex, height, and weight. Duration of symptoms was different among groups ($H(2) = 10.1$, $P = 0.006$), with Helmert contrasts demonstrating that this was caused by shorter symptom duration in patients with moderate/severe neuP than those with mild neuP.

Pain medication to alleviate CTS symptoms was taken by 36% of patients (Supplementary Table 1, available at http://links.lww.com/PAIN/B203). Whereas no differences were apparent between patients with and without neuP, patients with moderate/severe neuP reported more analgesic drug use than those with mild neuP; however, this marginally failed to reach statistical significance. There were no differences among groups for the types of medications used apart from paracetamol and opioids, which were more frequently taken by patients with moderate/severe neuP compared with those with mild neuP.

3.2. Symptom severity and functional deficits are more pronounced with the presence and increasing severity of neuropathic pain

Data for symptom severity and functional deficits are summarised in **Table 2**. Planned contrasts revealed that patients with neuP (combined group) experienced more pronounced symptoms than those with no neuP, except for the deep and evoked pain domain of the NPSI. In addition, symptom severity was consistently higher in patients with moderate/severe neuP compared with those with mild neuP. Similarly, functional deficits measured by the Boston Functional Status Scale were higher in patients with neuP compared with those without neuP.

Patients with moderate/severe neuP had a higher tendency to have extraterritorial symptoms (66%) compared with patients with mild neuP (35%) but not those without neuP (46%, $P = 0.024$).

3.3. Clinical examination findings

Patients with neuP exhibited more sensory abnormalities on light touch and pin-prick testing compared with those without neuP (**Table 2**). The frequencies of motor signs as well as a positive Phalen test and compression sign were comparable among groups. The overall chi-square test for Tinel sign was significant; however, planned contrasts were not significant after Bonferroni correction for the number of planned comparisons.

3.4. Somatosensory dysfunction of some parameters is greater in neuropathic pain

Quantitative sensory testing data are shown in **Figure 1**. The most common somatosensory phenotype in patients with CTS was thermal hyperalgesia (45.4%), followed by sensory loss (33.3%) and mechanical hyperalgesia (21.3%).

In the median nerve territory, the MANOVA for the detection thresholds showed a significant effect ($V = 0.32$, $F(15, 402) = 0.327$, $P < 0.0001$). Univariate ANOVAs followed by Helmert contrasts (**Fig. 1A**) revealed deficits in all detection thresholds in the combined patient groups compared with healthy controls ($t(136) > 3.20$, $P < 0.002$). Patients with moderate/severe neuP were different from those with mild neuP for cold detection ($t(136) = 2.09$, $P = 0.032$). Of note, all 3 Helmert contrasts were significant for mechanical detection thresholds in the median nerve territory, indicating that mechanical sensory deficits intensify with the presence and increasing severity of neuP ($t(136) > 2.18$, $P < 0.03$).

In the radial nerve territory, the MANOVA for detection thresholds was significant ($V = 0.24$, $F(15,402) = 2.36$, $P = 0.003$). Univariate ANOVAs followed by Helmert contrasts (**Fig. 1B**) demonstrated deficits in all detection thresholds except for vibration in the combined patient groups compared with healthy controls ($t(136) > 2.98$, $P < 0.003$). In addition, patients with moderate/severe neuP had stronger deficits in mechanical detection and thermal sensory limen compared with patients with mild neuP ($t(136) > 3.65$, $P < 0.012$).

No differences between groups were apparent for pain thresholds in both the median ($V = 0.13$, $F(18,387) = 1.00$, $P = 0.452$, **Fig. 1C**) and radial ($V = 0.14$, $F(18,384) = 1.01$, $P = 0.452$, **Fig. 1D**) territories. Paradoxical heat sensations in the median territory were only experienced by 3 patients, all of which had neuP (2 mild and 1 moderate/severe). In the radial nerve area, 6 participants (3 moderate/severe, 1 mild, 1 no neuP, and 1 healthy control) had paradoxical heat sensations. None of the patients presented with allodynia in either innervation territory.

There was no difference in the proportions of somatosensory profiles among patient subgroups (Fisher exact test, $P = 0.540$, Supplementary Table 2, available at http://links.lww.com/PAIN/B203).

3.5. Electrodiagnostic test severity is comparable

There were no differences in electrodiagnostic test severity among patient groups (no neuP median [interquartile range] 3.0 [2.0], mild neuP 3.0 [2.0], and moderate/severe neuP 3.0 [2.0], $P = 0.744$, Supplemental Fig 1, available at http://links.lww.com/PAIN/B203).

Kruskal–Wallis tests showed significant group effects for sensory nerve action potential amplitudes ($H(3) = 33.3$, $P < 0.0001$), sensory nerve conduction velocities ($H(3) = 51.67$, $P < 0.0001$), and compound motor latencies ($H(3) = 40.57$, $P < 0.0001$), but not motor action potential

Table 1
Demographic data.

	Healthy	No neuP	Mild neuP	Mod/sev neuP	*P*
No. of participants, n (%)	32	22 (20)	54 (50)	32 (30)	
Sex female (%)	24 (75)	12 (55)	37 (69)	23 (72)	0.426#
Mean age (SD), yrs	57.2 (12.4)	59.0 (14.5)	59.9 (13.5)	57.2 (10.1)	0.725*
Mean height (SD), cm	163.02 (29.9)	168.3 (9.6)	165.7 (10.4)	168.0 (9.0)	0.599*
Mean weight (SD), kg	73.8 (16.9)	75.1 (9.8)	73.0 (17.0)	79.6 (16.8)	0.307*
Median symptom duration [QR], mo		40 [83]	48 [42]†	18 [30]	**0.006***

* *P* values are presented for one-way ANOVAs. # P value represents χ^2 test association values. Significant overall comparisons are highlighted in bold.
† Significant Bonferroni-adjusted Helmert contrasts are indicated for mild vs moderate/severe neuP groups. Contrasts between no neuP vs combined neuP groups were not significant.
ANOVA, analysis of variance; IQR, interquartile range.; neuP, neuropathic pain; SD, standard deviation

Table 2

Symptom severity, functional deficits, and clinical findings.

	No neuP	Mild neuP	Mod/sev neuP	*P*
Symptom severity, median [IQR]				
Boston Symptom Scale	2.1 [1.1]‡	2.4 [0.9]§	3.2 [0.9]	**<0.0001#**
NPSI total	10.0 [17.5]‡	16.0 [15.8]§	38.5 [20.8]	**<0.0001#**
NPSI burning	0.0 [0.0]‡	0.0 [4.0]	2.0 [6.0]	**0.001#**
NPSI deep	0.0 [2.1]	0.0 [2.0]§	2.5 [4.0]	**0.007#**
NPSI paroxysmal	0.0 [0.1]‡	0.0 [2.1]§	3.0 [4.0]	**<0.0001#**
NPSI evoked	0.0 [0.1]	0.0 [2.0]§	2.7 [3.7]	**<0.0001#**
NPSI paraesthesia	3.5 [3.1]‡	5.3 [5.5]§	7.0 [4.3]	**<0.0001#**
Functional deficits, median [IQR]				
Boston Function Scale	1.6 [0.9]‡	1.9 [0.9]	2.6 [1.4]	**0.004#**
Symptom distribution, n (%)				
Extramedian spread	10 (46)	19 (35)§	21 (66)	**0.024***
Proximal spread	11 (50)	31 (57)	23 (72)	0.229*
Clinical examination, n (%) abnormal				
Light touch	1 (5)‡	30 (56)	16 (50)	**0.004†**
Pinprick	6 (27)‡	38 (72)	19 (59)	**<0.0001***
Phalen test	13 (62)	37 (82)	24 (80)	0.169*
Tinel sign	7 (33)	23 (46)	20 (67)	**0.050***
Compression sign	8 (38)	27 (55)	13 (43)	0.354*
Muscle strength‖				
MRC3	0 (0)	0 (0)	1 (4)	
MRC4	3 (20)	12 (30)	5 (20)	0.617†
MRC5	12 (80)	29 (71)	19 (76)	
Thenar wasting	6 (29)	19 (35)	7 (22)	0.423*

Data are shown as median [IQR] or n (%)

* *P* values reflect χ^2 associations. #*P* values reflect Kruskal Wallis results.

† *P* values reflect Fisher exact test associations.Significant overall comparisons are highlighted in bold.

‡ Significant Bonferroni-adjusted Helmert contrasts are indicated for no neuP vs combined neuP groups.

§ Significant Bonferroni-adjusted Helmert contrasts are indicated for mild vs moderate/severe neuP groups.

‖ Data for 27 patients not recorded.

IQR, interquartile range; MRC, Medical Research Council Muscle Strength Scale; neuP, neuropathic pain; NPSI, Neuropathic Pain Symptom Inventory.

amplitudes for the median nerve (Supplementary Table 3, available at http://links.lww.com/PAIN/B203). Planned contrasts revealed differences between healthy controls and the combined patient groups for all parameters (sensory nerve action potential amplitude: U = 557, z = −5.72, $P < 0.0001$; sensory nerve conduction velocity, U = 102, z = −7.18, $P < 0.0001$; distal motor latencies, U = 3084.5, z = 7.29, $P < 0.0001$; compound motor action potentials, U = 1178, z = −2.73, $P = 0.006$), but no other contrasts were significant ($P > 0.451$).

3.6. Nerve structure is comparable

There was an effect of group on IENFD (H(3) = 25.34, $P < 0.0001$), with planned contrasts confirming a reduction in IENFD in patients with CTS compared with healthy controls (U = 755, z = −4.75, $P < 0.0001$, Supplemental Fig. 2, available at http://links.lww.com/PAIN/B203), with no other contrasts being significant ($P > 0.137$, **Table 3**). No differences were present among groups for dermal measures including density of Meissner corpuscles, dermal nerve bundles containing myelin, or nodal length.

3.7. Emotional well-being and sleep quality are more impaired with increasing neuropathic pain severity

Data of questionnaires evaluating the psychological domain and sleep disturbance are shown in **Table 4** and **Figure 2**.

Whereas no differences among groups were apparent for all domains of the Depression Anxiety and Positive Outlook Scale, significant effects were identified for the PASS-20 total score (H(3) = 18.061, $P < 0.0001$) and the cognitive (H(3) = 23.65, $P < 0.0001$) and escape domains (H(3) = 12.93 m $P = 0.005$). Planned contrasts confirmed higher ratings in patients with CTS compared with healthy controls in 2 PASS-20 measures (total U = 2379, z = 3.35, $P = 0.01$; cognitive U = 2509.5, z = 4.02, $P < 0.0001$). In addition, patients with moderate/severe neuP had higher ratings than patients with mild neuP in several PASS-20 domains (total U = 1125, z = 2.52, $P = 0.012$; cognition U = 1124.5, z = 2.51, $P = 0.01$; escape U = 1114.5, z = 2.44, $P = 0.015$), indicating a stronger compromise in emotional well-being with increasing neuP severity. No other planned contrasts were significant.

There was also an effect of group on the PCS (total score H(3) = 8.72, $P = 0.033$; rumination H(3) = 8.20, $P = 0.042$; helplessness H(3) = 11.64, $P = 0.009$), with more severe rumination (U = 1114.5, z = 2.45, $P = 0.014$), helplessness (U = 1160, z = 2.86, $P = 0.004$), and total PCS scores (U = 1130, z = 2.57, $P = 0.10$) in patients with moderate/severe neuP compared with those with mild neuP, although the other contrasts were not significant.

For the Insomnia Severity Index (H(3) = 26.24, $P < 0.0001$), a more pronounced sleep disturbance was apparent in the combined patient groups compared with healthy controls (U = 2478, z = 3.839, $P < 0.0001$) and in patients with moderate/severe neuP compared with those with mild neuP (U = 1222.5, z = 3.402, $P = 0.001$), indicating more pronounced sleep difficulty with increasing intensity of neuP.

4. Discussion

In our cohort of patients with CTS, 20% have no neuP, 50% have mild neuP, and 30% have moderate/severe neuP. The presence

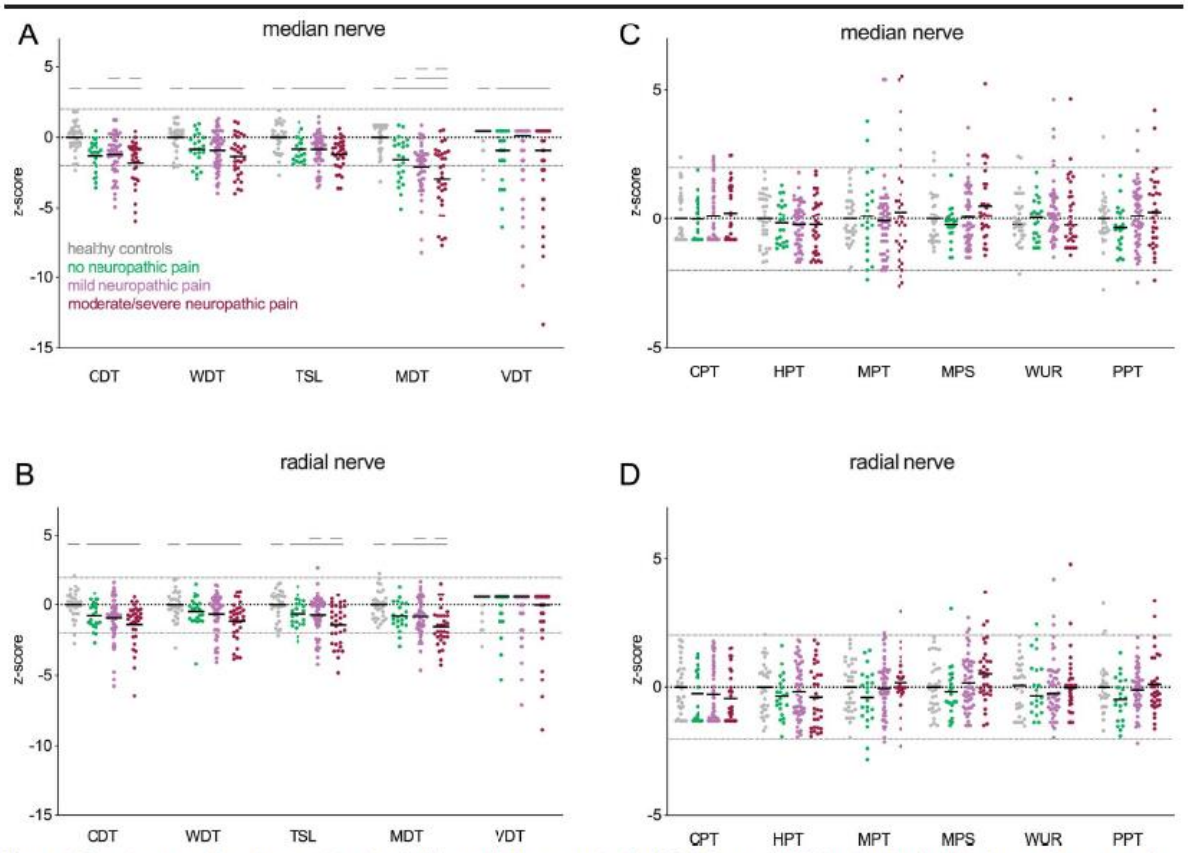

Figure 1. Somatosensory phenotypes as determined with quantitative sensory testing (QST Z-scores): (A) Detection thresholds in the median nerve territory demonstrating a larger deficit for all detection thresholds in patients with carpal tunnel syndrome compared with healthy controls. Patients with moderate/severe neuP have more pronounced CDT deficits compared to patients with mild neuP. All Helmert contrasts were significant for MDT, suggesting that mechanical deficits intensify with the presence and increasing severity of neuP. (B) Detection thresholds in the radial nerve territory demonstrating a larger deficit in CDT, WDT, TSL, and MDT for patients with carpal tunnel syndrome compared with healthy controls. Patients with moderate/severe neuP have a more pronounced deficit in TSL and MDT compared with those with mild neuP. (C) Pain thresholds in the median nerve territory are comparable among groups. (D) Pain thresholds in the radial nerve territory are comparable among groups. Straight lines represent significant Helmert contrasts. CDT, cold detection threshold; CPT, cold pain threshold; HPT, heat pain threshold; MDT, mechanical detection threshold; MPS, mechanical pain sensitivity; MPT, mechanical pain threshold; neuP, neuropathic pain; PPT, pressure pain threshold; TSL, thermal sensory limen; VDT, vibration detection threshold; WDT, warm detection threshold; WUR, wind-up ratio.

of neuP was associated with increased symptom severity and functional deficits as well as deficits in bedside sensory testing. Apart from a more pronounced deficit in mechanical detection, somatosensory profiles were largely comparable among patients with and without neuP. However, an increasing neuP severity was associated with more pronounced loss of function deficits in both the median and radial nerve territories. By contrast, no differences were identified in neurophysiological variables or structural nerve fibre integrity in skin biopsies among patient groups. Notably, many aspects of emotional well-being (eg, PCS rumination and helplessness, as well as PASS cognition and escape) and sleep were more affected with increasing neuP severity. Our findings indicate that apart from clear differences in symptom severity and function deficits, structural and functional somatosensory measures are largely comparable in patients with and without neuP. The severity of neuP is associated with somatosensory nerve

Table 3

Histological findings in skin biopsies.

	Healthy	No neuP	Mild neuP	Mod/sev neuP	*P*
IENFD (per mm epidermis)	7.8 [3.5]*	4.0 [3.0]	4.6 [4.1]	3.6 [3.8]	**<0.0001**
Meissner corpuscle density (per mm epidermis)	0.4 [0.4]	0.3 [0.5]	0.3 [0.5]	0.4 [0.6]	0.454
PGP+ bundles containing MBP	1.2 [0.4]	1.1 [0.6]	1.2 [0.3]	1.2 [0.4]	0.621
Nodal length	2.5 [0.9]	2.5 [1.5]	2.5 [1.7]	2.3 [1.0]	0.442

Data are presented as median [IQR]. *P* values reflect Kruskal–Wallis results. Significant overall comparisons are highlighted in bold.
No significant contrasts were found between no neuP vs combined neuP groups and mild vs moderate/severe neuP groups.
* Significant Bonferroni-adjusted Helmert contrasts ($P < 0.017$) are indicated for healthy vs combined patient groups.
IENFD, intraepidermal nerve fibre density; MBP, myelin basic protein; neuP, neuropathic pain; PGP, protein gene product 9.5.

Table 4

Emotional well-being and sleep quality.

	Healthy	No neuP	Mild neuP	Mod/sev neuP	*P*
Insomnia severity	3.0 [6.0]*	6.5 [7.8]	7.0 [7.0]†	13.0 [8.5]	**<0.0001**
PCS total	6.5 [13.0]	7.5 [11.0]	3.5 [13.0]†	11.0 [23.0]	**0.033**
Rumination	2.5 [6.0]	3.5 [5.0]	1.5 [6.0]†	4.0 [10.0]	**0.042**
Magnification	0.5 [3.0]	2.0 [2.0]	1.0 [3.0]	2.0 [3.0]	0.244
Helplessness	1.5 [6.0]	2.5 [4.0]	1.0 [5.0]†	4.0 [8.0]	**0.009**
DAPOS					
Depression	5.0 [2.0]	5.0 [3.0]	6.0 [2.0]	6.0 [6.0]	0.555
Anxiety	3.0 [1.0]	3.0 [2.0]	3.0 [1.0]	3.0 [3.0]	0.572
Outlook	12.5 [4.0]	14.0 [4.0]	12.0 [3.0]	12.0 [5.0]	0.128
PASS-20					
Total	1.5 [18.8]*	13.0 [18.5]	10.5 [29.8]†	19.0 [47.0]	**<0.0001**
Cognition	0.0 [6.0]*	7.0 [13.0]	6.5 [16.0]†	13.0 [24.0]	**<0.0001**
Escape	0.5 [7.0]	3.0 [4.0]	2.5 [6.0]†	8.0 [10.0]	**0.005**
Fear	0.0 [4.0]	2.0 [5.0]	1.0 [5.0]	1.0 [6.0]	0.245
Anxiety	0.0 [1.0]	0.0 [2.0]	0.0 [1.0]	1.0 [5.0]	0.060

Data are shown as median [IQR]. *P* values reflect Kruskal–Wallis test results.Significant overall comparisons are highlighted in bold.
* Significant nonparametric Helmert contrasts Bonferroni adjusted for multiple testing are indicated for healthy vs combined patient groups.
† Significant nonparametric Helmert contrasts Bonferroni adjusted for multiple testing are indicated for mild vs moderate/severe neuP groups. No significant contrasts were apparent between no neuP vs combined neuP groups.
DAPOS, Depression Anxiety and Positive Outlook Scale; IQR, interquartile range; neuP, neuropathic pain; PASS-20, Short Form Pain Anxiety Symptoms Scale; PCS, Pain Catastrophizing Scale.

dysfunction, but not structural nerve integrity. Of note, an increasing severity of neuP was accompanied by reduced emotional well-being, increased sleep disturbance, and the presence of extraterritorial symptoms, indicating a more dominant contribution of central mechanisms.

The reported prevalence of neuP in patients with CTS varies substantially (31%–77%).[21,49,50,54] This is most likely attributable to the different screening tools used to detect neuP, none of which has been validated in patients with CTS. In the absence of a validated screening tool for patients with CTS, we decided to use the DN4. Unlike the painDETECT, it focuses on the number of neuropathic features rather than their severity, which is often low in patients with CTS and may thus underestimate the prevalence of neuP. Furthermore, the painDETECT was originaly developed for spinally referred leg pain,[18] whereas the DN4 was validated in a mixed group of nerve disorders,[10] thus increasing its generalisability. The here-identified 80% of patients having neuP is comparable with other studies that also used the DN4 tool in patients with CTS (65%–77%).[37,56] The sample of convenience used in our study does not allow inferences about the general prevalence of neuP in CTS. Nevertheless, our data suggest that although most patients have neuP, a significant proportion has non-neuP, presumably of nociceptive origin.

Compared with healthy controls, patients with CTS show loss of function to thermal and mechanical stimuli in the median nerve innervation territory independent of the presence of neuP. This represents the characteristic dysfunction of both small and large nerve fibers as previously reported in CTS[29,46] and other focal and systemic peripheral neuropathies.[22,42,54,55,57] Although somatosensory function was largely comparable between patients with and without neuP except for mechanical detection, the increasing severity of neuP was associated with a mechanical and thermal

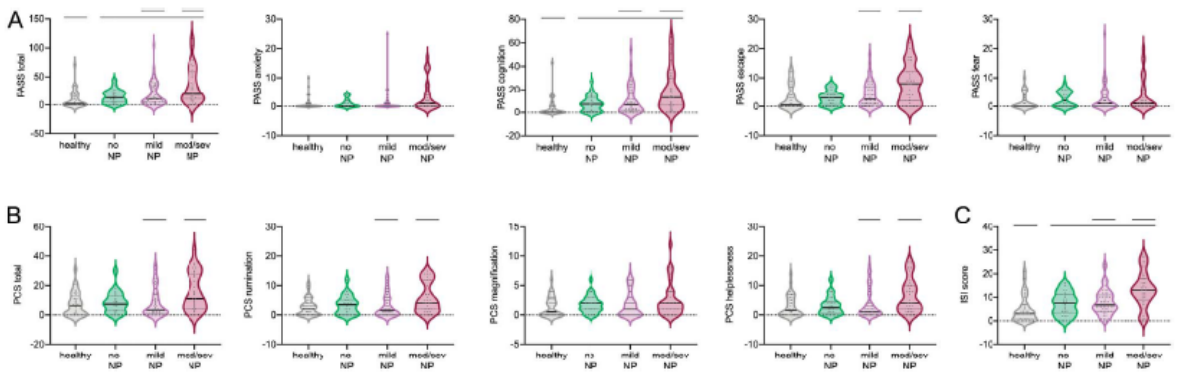

Figure 2. Emotional well-being and sleep quality: (A) The PASS-20 and its subscales demonstrate higher scores for the PASS total and the cognition subscale in patients with carpal tunnel syndrome compared with healthy controls. Patients with moderate/severe neuP have higher scores on PASS total as well as escape and cognition subscores than those with mild neuP. (B) Pain Catastrophizing Scale (PCS) showing mostly higher scores in patients with moderate/severe neuropathic pain compared with those with mild neuP. (C) The Insomnia Severity Index indicates that patients with carpal tunnel syndrome have higher insomnia ratings than healthy controls. Patients with moderate/severe neuP have a more pronounced sleep deficit compared with patients with mild neuP. Violin plots depicting median (solid line), first and third quantiles (dotted lines), and single data points; straight lines represent significant Helmert contrasts. ISI, Insomnia Severity Index; neuP, neuropathic pain; PASS-20, Pain Anxiety Symptoms Scale.

loss of function phenotype. This progressive loss of function phenotype with increasing neuP severity is in line with previous reports in patients with focal and systemic peripheral nerve injuries[22,42,55] and has been interpreted as an indication that increasing neuP severity is associated with a more pronounced neuropathy. Intriguingly and consistent with previous reports from systemic polyneuropathies,[42,55] changes in nerve fibre integrity in the skin or the extent of neurophysiological changes were not associated with the presence or severity of neuP.

Extramedian but not proximal spread of symptoms was more common in patients with moderate/severe neuP. Such extramedian spread of symptoms has previously been shown to be associated with extramedian mechanical and thermal hyperalgesia[62] and has thus been attributed to central mechanisms.[62,63] In addition, we found a more pronounced hypoaesthesia in the radial nerve territory in patients with moderate/severe neuP compared with those with mild neuP. We have previously reported such extramedian hyposensitivity in a smaller cohort of patients with CTS.[46] Although widespread hyperalgesia is commonly accepted as a sign of central mechanisms, hyposensitivity as a sign of nerve dysfunction is usually expected to be restricted to the area of the affected nerve. There is, however, growing evidence that sensory loss can also be found in unaffected areas in patients with neuP.[23,27,28,53,60,61] In such instances, the extraterritorial sensory loss has been attributed to centrally mediated mechanisms, for instance, to the suppression of normal sensitivity by ongoing pain.[60] Taken together, our data suggest that central mechanisms are more prominent in patients with moderate/severe neuP. More pronounced central mechanisms may thus be an alternative interpretation to an increased neuropathy severity in driving symptoms in patients with more severe neuP.

Patients with neuP had more pronounced symptom severity and functional deficits than patients without neuP throughout a range of questionnaires. This is in line with previous reports in a range of chronic pain conditions.[4] As expected due to the neuP subgroup allocation being governed by symptom severity, increasing neuP severity was associated with more pronounced symptoms, but this was also the case for functional deficits. In addition, emotional well-being and sleep impairment was more compromised with increasing neuP severity. These results are in line with previous reports of patients with CTS[37] and other peripheral neuropathies.[4,22,42,55] Nevertheless, the average ratings in our cohort were low. Also, it remains unanswered whether the deficits in emotional well-being are a consequence of or a risk factor for more severe neuP. The previously reported decrease of depressive symptoms after carpal tunnel decompression and its correlation with symptom resolution[13] suggests that depression may be secondary to CTS. This is further corroborated in our own prospective data, which confirm improvements in most emotional well-being parameters after carpal tunnel decompression (Supplementary Table 4, available at http://links.lww.com/PAIN/B203).

Some limitations of this study need to be considered. Our study is a post hoc analysis of 2 published cohorts of exploratory character and did therefore not include an a priori sample size calculation. Nevertheless, our study contains the largest deeply phenotyped CTS cohort to date, and its size was large enough to detect moderate effect sizes among patient groups. However, numbers in some patient subgroups were relatively low. This may have contributed to the absence of group differences for instance in the planned contrasts of neuP and no neuP groups. Another limitation to consider is that analgesic intake was not stopped before somatosensory profiling and may thus have influenced our readings, particularly related to hyperalgesia.

4.1. Clinical implications

Although it is clear that there are a proportion of patients with CTS who do not experience neuP (20%), most patients do. Treatment for patients with CTS is currently not stratified for the presence of neuP. Our data suggest that particularly patients with moderate/severe neuP have a distinct phenotype characterised by a more pronounced and widespread somatosensory dysfunction and exacerbated deficits in emotional well-being and sleep quality. Given the excessive wait times for carpal tunnel surgery[3] and the detrimental effects of poor emotional well-being and sleep quality on general health and quality of life,[12,44] these patients may need to be prioritised. Indeed, in our cohort that was mostly recruited from surgery waitlists, symptom duration was over two-fold shorter in the moderate/severe subgroup, potentially reflecting an earlier escalation to surgery.

Although surgical decompression is successful in around 75% of patients,[9] nonsurgical management including pharmacological options remains first-line treatment.[43] Current guidelines recommend corticosteroid injections but not oral nonsteroidal anti-inflammatory drugs without mentioning neuP drugs.[36] In our cohort, patients with moderate/severe neuP took more paracetamol and opioids, which are not first-line pharmacological options for neuP.[14] It could be argued that patients with moderate/severe neuP may benefit from specific neuP drugs, which often target central mechanisms that seemed common in that group. However, trials into neuP medications such as gabapentin for patients with CTS show controversial results.[15,25] Future studies are required to determine whether stratification by the neuP phenotype may lead to more promising effects of these medications for patients with CTS and whether the risk/benefit of neuP medications outweighs that of surgery.

Of note, our results suggest that the routine diagnostic tests for CTS (Phalen test, Tinel sign, carpal compression test, and electrodiagnostic tests) are not able to identify the presence of neuP. Therefore, simple screening tools such as the DN4 will facilitate the identification of patients who are more severely affected by neuP and may help guide management.

4.2. Conclusions

Our cohort has shown that neuP is common in patients with CTS and its presence is accompanied by more severe symptom and function deficits. Apart from a deficit in mechanical detection, the presence of neuP was not associated with substantial changes in somatosensory function or structural nerve pathology. The severity of neuP was accompanied by a more pronounced somatosensory dysfunction. Of note, neuP severity was related to more pronounced deficits in emotional well-being and sleep quality and the presence of extraterritorial spread of symptoms suggesting a more dominant contribution of central mechanisms. These differences between subgroups raise the question whether treatment stratification may help improve management for patients with CTS.

Conflict of interest statement

D.L.H. Bennett has acted as a consultant on behalf of Oxford Innovation in the past 2 years for Amgen, CODA therapeutic,

Bristows, Lilly, Mundipharma, and Theranexus. The remaining authors have no conflicts of interest to declare.

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Author contributions: A.B. Schmid and D.L.H. Bennett conceptualized the study. A.B. Schmid collected the data. A.C. Hausheer, L. Matesanz, G. Baskozos, and A.B. Schmid analysed the data. A.B. Schmid, L. Matesanz, and A.C. Hausheer wrote the first draft of the manuscript, and all authors provided input to the final manuscript.

Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/B203.

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6.2 Resultados del estudio II

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Article

Signs Indicative of Central Sensitization Are Present but Not Associated with the Central Sensitization Inventory in Patients with Focal Nerve Injury

Luis Matesanz-García [1,2], Ferran Cuenca-Martínez [3], Ana Isabel Simón [4], David Cecilia [5,6,7], Carlos Goicoechea-García [8,9], Josué Fernández-Carnero [9,10,*,†] and Annina B. Schmid [11,*,†]

1 Escuela Internacional de Doctorado, Department of Physical Therapy, Occupational Therapy, Rehabilitation and Physical Medicine, Rey Juan Carlos University, 28922 Alcorcón, Spain; luis.matesanz.garcia@gmail.com
2 Department of Physiotherap, Centro Superior de Estudios Universitarios La Salle, Universidad Autónoma de Madrid, 28023 Madrid, Spain
3 Exercise Intervention for Health Research Group (EXINH-RG), Department of Physiotherapy, University of Valencia, 46010 Valencia, Spain; fecuen2@gmail.com
4 Unit of Elbow-Hand, Service de Traumatologia, Hospital Severo Ochoa, 28911 Leganés, Spain; ai.simoncarrascal@gmail.com
5 Unit of Elbow-Hand, Service de Traumatologia, Hospital 12 de Octubre, 28048 Madrid, Spain; dacecilia@hotmail.com
6 Complutense University of Madrid, 28040 Madrid, Spain
7 Department of Surgery, Hospital Vithas La Milagrosa, 28010 Madrid, Spain
8 Department Basic Health Sciences, Rey Juan Carlos University, 28922 Alcorcón, Spain; carlos.goicoechea@urjc.es
9 Grupo Multidisciplinar de Investigación y Tratamiento del Dolor, Grupo de Excelencia Investigadora URJC-Banco de Santander, 28922 Madrid, Spain
10 Department of Physical Therapy, Occupational Therapy, Rehabilitation and Physical Medicine, Rey Juan Carlos University, 28922 Alcorcón, Spain
11 Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford OX3 9DU, UK
* Correspondence: josue.fernandez@urjc.es (J.F.-C.); annina.schmid@neuro-research.ch (A.B.S.)
† These authors contributed equally to this work.

Abstract: Objective: Carpal tunnel syndrome (CTS) is the most common focal nerve injury. People with CTS may show alterations in central processing of nociceptive information. It remains unclear whether the central sensitization inventory (CSI) is capable of detecting such altered central pain processing. Methods: Thirty healthy volunteers were matched with 30 people with unilateral CTS from the orthopaedic waitlist. Changes to central pain processing were established through psychophysical sensory testing (bilateral pressure pain thresholds (PPT), conditioned pain modulation, temporal summation) and pain distribution on body charts. Patients also completed pain severity and function questionnaires, psychological questionnaires and the CSI. Results: Compared to healthy volunteers, patients with CTS have lower PPTs over the carpal tunnel bilaterally ($t = -4.06$, $p < 0.0001$ ipsilateral and $t = -4.58$, $p < 0.0001$ contralateral) and reduced conditioned pain modulation efficacy ($t = -7.31$, $p < 0.0001$) but no differences in temporal summation ($t = 0.52$, $p = 0.60$). The CSI was not associated with psychophysical measures or pain distributions indicative of altered central pain processing. However, there was a correlation of the CSI with the Beck Depression Inventory ($r = 0.426$; $p = 0.019$). Conclusion: Patients with CTS show signs of altered central pain mechanisms. The CSI seems unsuitable to detect changes in central pain processing but is rather associated with psychological factors in people with focal nerve injuries.

Keywords: entrapment neuropathy; conditioned pain modulation; temporal summation; pain measurement; carpal tunnel syndrome; pressure pain threshold; central sensitization; central sensitization inventory

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1. Introduction

Carpal tunnel syndrome (CTS) is the most common focal nerve injury [1,2]. It is defined as a compression of the median nerve as it passes through the carpal tunnel in the wrist. Classically, CTS symptoms manifest themselves in the median nerve area, although extramedian or proximal spread of symptoms is frequently reported [3]. This spread of symptoms has been attributed to changes in the central nervous system such as central sensitization [4].

Central sensitization is a neurophysiological mechanism that cannot be directly determined in humans. However, in addition to the spread of symptoms, psychophysical sensory testing can be used to infer the contribution of central pain mechanisms to patients' presentations. For instance, local and remote mechanical hyperalgesia such as measured with pain thresholds has been associated with central sensitization [5,6]. Additionally, temporal summation is related to activity-dependent plasticity within the central nervous system [7,8]. Several studies have examined the presence of such local and widespread hyperalgesia in patients with CTS with conflicting results [9,10].

In addition to increased facilitation, a disruption of inhibitory mechanisms is another central mechanism that can lead to hyperexcitability. Conditioned pain modulation (CPM) is a psychophysical measure that examines the efficacy of endogenous inhibitory systems [11]. CPM evaluates whether a painful test stimulus can be modulated by a noxious conditioning stimulus applied at a remote part of the body. About 70% of patients with chronic pain show signs of reduced CPM efficacy [12]. To date, only one publication has examined possible alterations of the descending inhibitory system by means of CPM in patients with CTS and found reduced efficacy [13].

Whereas these psychophysical sensory tests can provide information about the potential involvement of central pain mechanisms, they are time consuming and involve costly equipment. Thus, self-completed questionnaires have been developed to identify the presence of "central sensitization". For instance, the central sensitization inventory (CSI) has been suggested to identify patients with "central sensitivity syndrome" such as fibromyalgia, chronic fatigue syndrome, irritable bowel or temporomandibular joint disorders [14]. In addition, the CSI is associated with outcomes after spinal surgery [15]. However, recent studies question its construct validity. The CSI was originally validated by demonstrating increasing CSI scores in conditions thought to represent increasing degrees of central sensitization (e.g., healthy controls, regional chronic low back pain, chronic widespread pain, fibromyalgia) [14]. Similarly, the cutoff to identify "central sensitivity syndrome" was determined by receiver operating curve analyses, best distinguishing patients with diagnoses that are thought to be characterised by central mechanisms (e.g., fibromyalgia) from healthy controls [16]. Arguably, a more compelling way of evaluating the construct validity of a tool that is meant to identify central sensitisation is to examine its associations with psychophysical testing. However, recent studies in patients with temporomandibular disorders, shoulder pain, chronic whiplash and chronic spinal pain found no relationship between the CSI and psychophysical tests indicating the presence of central pain mechanisms [17–20]. In contrast, other studies have identified a weak correlation of the CSI with mechanical hyperalgesia and CPM in patients with knee osteoarthritis [21], and CSI scores seem higher in patients with musculoskeletal pain and more impaired CPM [22]. Of note, evidence is growing that the CSI is more strongly associated with psychological measures rather than psychophysical measures indicating central pain mechanisms [18–21,23]. To date, construct validity of the CSI has only been evaluated in populations with musculoskeletal pain. It remains unclear how the CSI performs in patients with peripheral nerve injuries.

To improve our knowledge of alterations in pain processing in focal nerve injuries and the construct validity of the CSI, this study has the following objectives: (1) Identify alterations in central pain mechanisms in patients with CTS using psychophysical sensory testing and pain mapping. (2) Investigate whether the CSI is associated with psychophysical parameters and pain distributions indicative of central pain mechanisms. (3) Investigate whether the CSI is associated with psychological parameters.

2. Materials and Methods

2.1. Participants

Thirty patients with unilateral CTS were recruited from Hand and Elbow surgery units from 12 Octubre Hospital and Severo Ochoa Hospital, both located in Madrid. All patients were on the orthopaedic surgery waitlist, with at least one year of persistency of symptoms, had positive Tinel's and Phalen's sign and had electrodiagnostic confirmation of moderate to severe CTS on the affected side according to the American Association of Neuromuscular and Electrodiagnostic Medicine [24]. Patients were excluded if the electrodiagnostic testing identified sensory and/or motor deficits of the radial and/or ulnar nerve, if any indication for nerve root involvement was present (e.g., needle EMG) or if patients reported previous hand surgeries, previous steroid infiltrations, wrist fractures, diagnoses related to the cervical spine and upper limb (e.g., cervical radiculopathies, shoulder injuries), or other musculoskeletal comorbidities (e.g., rheumatoid arthritis and fibromyalgia). Women who were pregnant were excluded from the study.

The patients were matched for age and sex with healthy controls (HC, n = 30). Those were recruited through advertisements around the hospitals and university and through relatives of participating patients. All participants gave informed written consent prior to participating, and the study received ethical clearance from the two committees of the participating hospitals CPMP/ICH/135/95 (Severo Ochoa Hospital, December 2017) and 20/092 (12 Octubre Hospital, March 2020).

2.2. Symptom Characteristics and Functional Deficits

The Boston carpal tunnel questionnaire was used to assess symptom severity and functional deficits. The Boston carpal tunnel questionnaire consists of a symptom and a function subscale [25]. This questionnaire has been validated in Spanish, with good levels of internal consistency and reproducibility [26]. The current hand pain intensity was recorded using a visual analogue scale (VAS), with 0 being no pain and 100 being the worst pain imaginable.

The presence of neuropathic pain was assessed with the Spanish version of Douleur Neuropathique 4 (DN4). This version has shown good internal consistency [27]. The questionnaire consists of an initial part with questions that evaluate a series of neuropathic symptom descriptors (burning and cold-like pain, electric shock, tingling, pins and needles, numbness, itching) followed by a short sensory clinical examination (hypoesthesia to touch, hypoesthesia to pin prick and brush allodynia). A DN4 score of ≥ 4 was interpreted as neuropathic pain [28] and a score < 4 was interpreted as nociceptive pain.

The central sensitization inventory (CSI) is a tool originally designed to identify patients with "central sensitivity syndrome" [14]. It includes a wide range of 25 questions covering pain and stiffness, daily function, psychological factors (e.g., anxiety, depression), fatigue and memory. The Spanish translation shows good reliability and internal consistency [29]. The patient scores each question from 0 to 4: never, rarely, sometimes, continuously and always. The total score ranges from 0 to 100 with values over 40 thought to indicate the presence of "central sensitivity syndrome" [14].

2.3. Signs Indicative of Altered Central Pain Processing

2.3.1. Pressure Pain Threshold (PPT)

PPT is defined as the minimum amount of pressure needed to elicit pain. Measurements of PPT were made using a digital algometer (Model FDX 10®, Wagner Instruments, Greenwich, CT, USA). This instrument measures the pressure in kg/cm^2. The measurements were made bilaterally (affected and unaffected side) over the carpal tunnel (Supplementary Figure S1). The average of three measurements was recorded, with an interval of 30 s between each measurement to avoid a temporal summation effect. PPT has shown good reliability and internal consistency [30].

2.3.2. CPM

For the evaluation of CPM efficiency, an average of three PPT measures was used as a test stimulus over the base of the dorsal side of the distal phalanx of the thumb of the affected side (Supplementary Figure S1). The conditioning stimulus involved ischemic pain using a sphygmomanometer applied on the unaffected arm with a pressure of 200 mmHg until the subjects reported pain intensity between 5–7/10 on a numerical pain rating scale. While the sphygmomanometer was still inflated, the PPT measurements were repeated on the dorsal side of the distal phalanx of the thumb on the affected side. This protocol has been shown to be adequate to assess the endogenous inhibitory system in patients with knee osteoarthritis [31]. CPM efficacy was calculated by deducting the PPT after applying the conditioning stimulus from the PPT obtained before the conditioning stimulus. Positive values indicate effective pain modulation [32].

2.3.3. Temporal Summation

The measurement of temporal summation was performed using a Model FDX 10® digital algometer, Wagner Instruments, Greenwich, CT, USA applied to the intensity of the PPT at the midpoint between the nail and the interphalangeal joint on the dorsal side of the distal phalanx of the first finger of the affected side (Supplementary Figure S1). Numerical pain ratings from 0–10 were obtained for a single stimulus followed by a rating after 10 stimuli with a repetition rate of 1 Hz. For the isolated stimuli, the patients were asked to indicate the onset of pain and rate it from 0–10. The repetitive stimuli were performed in an area around the same point of the finger with the same pressure that induced the first onset of pain during the isolated stimulus. The average pain intensity after 10 repetitions was recorded. The temporal summation ratio was calculated by dividing the average pain produced by the train of stimuli by the pain produced by the single stimulus. A similar method has been used and validated previously [33].

2.3.4. Symptom Spread

Patients marked the localization of symptoms on a hand and body diagram [34]. Results were dichotomized into median and extramedian distribution.

2.4. *Emotional Wellbeing*

To evaluate emotional wellbeing, patients completed the Beck Depression Inventory (BECK) and the State-Trait Anxiety Inventory (STAI). The BECK consists of 21 elements related to depressive symptoms (e.g., hopelessness and irritability), specific thoughts (e.g., guilt or feelings of being punished) and physical symptoms [35,36]. STAI has demonstrated acceptable psychometric properties in its Spanish version [37].

To assess pain-related fear of movement, the validated Tampa kinesiophobia scale (TSK) was used. Each item is rated on a four-point Likert scale ranging from "strongly agree" to "strongly disagree" with a cutoff of 29 points. This questionnaire has shown a good consistency [38,39].

2.5. *Statistical Analyses*

The sample size was estimated using the program G*Power 3.1.7 (G*power from University of Dusseldorf, Germany) [40]. The sample size calculation was powered to detect between-group differences in PPT measures. Using previously published data measured over the carpal tunnel area in healthy controls and patients with CTS [41], n = 30 participants are required in each group to detect an effect size of 0.74 with 80% statistical power (alpha = 0.05, independent *t*-test). This sample size is sufficient to detect large effects in correlation analyses (rho = 0.44, power 80%, alpha 0.05).

We performed the data analysis using the Statistics Package for Social Science (SPSS 20.00, IBM Inc., Armonk, NY, USA). We checked data normality by visual inspection of histograms and the Kolmogorov–Smirnov test. Participants' sociodemographic and clinical characteristics were summarized using descriptive statistics and summary tables.

To determine the presence of signs indicative of altered central pain processing, we employed independent Student's *t*-tests to identify differences between healthy and patient groups for psychophysical variables. The frequency of extraterritorial spread of symptoms (median/extramedian) was reported.

To identify associations between CSI and psychophysical signs indicative of altered pain processing, we performed Pearson's correlation statistics in patient data only. Coefficients of 0.5 or above were interpreted as a strong correlation, 0.3 moderate and 0.1 small correlation. We corrected for false discovery rate using the Benjamini–Hochberg correction (FDR = 25%). We also grouped patients with CTS into those with CSI $\geq$ 40 and <40 and explored differences in psychophysical tests and symptom spread with independent *t*-tests and Chi squared or Fisher's exact test statistics as appropriate.

To explore the relationship between CSI and emotional wellbeing (BECK, TSK, STAI) in patient data, we calculated Pearson correlations coefficients and used Benjamini–Hochberg correction to correct for a false discovery rate. Unadjusted *p*-values are reported for ease of interpretation.

3. Results

Thirty participants were healthy controls (8 men and 22 women with a mean age of 46.23 ± 1.36 years), and 30 patients diagnosed with CTS (8 men and 22 women with a mean age of 48.67 ± 1.19 years, Table 1). According to the Boston questionnaire, patients had on average mild to moderate symptoms and moderate to severe function deficits. The mean pain intensity was 4.2/10 (SD 2.7). Using the DN4 questionnaire, the most common pain descriptor was tingling (100%), followed by numbness (96.6%) and electric shocks (90%). In contrast, hypoesthesia to touch and pinprick was present only in 50% and 60% of patients, respectively. Twenty-eight patients (93.3%) were classified as having neuropathic pain according to the DN4.

Table 1. Participant characteristics.

	Healthy (n = 30)	**CTS (n = 30)**
Female, n (%)	22 (77.3)	22 (77.3)
Age (Years)	46.2 ± 1.36	48.7 ± 1.2
Boston		
Severity		2.6 ± 0.11
Functional deficits		3.5 ± 0.11
Visual Analogue Scale		4.2 (2.7)
DN4 total score		5.9 (1.6)
Burning, n (%)		11 (36.6)
Painful cold, n (%)		9 (30.0)
Electric shocks, n (%)		27 (90.0)
Tingling, n (%)		30 (100.0)
Pins and needles, n (%)		22 (73.3)
Numbness, n (%)		29 (96.6)
Itching, n (%)		9 (30.0)
Hypoesthesia to touch, n (%)		15 (50.0)
Hypoesthesia to pinprick, n (%)		18 (60.0)
DN4 neuropathic, n (%)		28 (93.3)

Data are shown as mean and standard deviation or n (%).

3.1. Patients with CTS Have Signs Indicative of Altered Central Pain Processing

There were statistically significant differences between patients with CTS and healthy participants in the psychophysical variables related to central pain processing. PPTs were reduced in patients with CTS, indicative of mechanical hyperalgesia compared to healthy controls both on the ipsilateral ($t = -4.06$; $p < 0.0001$) and contralateral side ($t = -4.58$; $p < 0.0001$).

Similarly, CPM efficiency was reduced in patients with CTS compared to healthy controls ($t = -7.31$; $p < 0.01$). No differences were found for temporal summation ($t = 0.52$, $p = 0.60$). Data are shown in Table 2.

Table 2. Variables indicative of changes in central pain processing.

	Healthy (n = 30)	CTS (n = 30)	*p*-Value
PPT affected side (Kg/cm^2)	5.9 (2.0)	3.4 (1.7)	$p < 0.0001$
PPT contralateral side (Kg/cm^2)	5.9 (2.0)	3.8 (2.0)	$p < 0.0001$
CPM	2.1 (2.0)	0.1 (0.9)	$p < 0.0001$
Temporal summation ratio	1.5 (0.9)	1.6 (0.9)	$p = 0.60$

Data are shown as mean (standard deviation); PPT: pressure pain threshold; CPM: conditioned pain modulation; *p*-values reflect Student's *t*-tests.

3.2. Association between Central Sensitization Inventory and Signs of Altered Central Pain Processing

The mean CSI in patients with CTS was 32.4 (SD 11.8). Eight patients (26.67%) had a score ≥ 40.

The CSI did not correlate with any psychophysical signs of altered pain processing (Table 3). Similarly, there were no differences in psychophysical signs of altered pain processing if patients were grouped according to the CSI cutoff of ≥ 40 ($p > 0.600$).

Table 3. Correlations between CSI and signs of altered central pain processing in patients with CTS.

	Pearson Correlation Coefficient	Unadj *p*-Value
CSI vs. PPT affected side	0.023	0.903
CSI vs. PPT unaffected side	−0.042	0.828
CSI vs. CPM	0.276	0.140
CSI vs. temporal summation	0.069	0.719

CSI: central sensitization inventory; PPT: pain pressure threshold; CPM: conditioned pain modulation.

Extramedian distribution of symptoms was reported by 25 (83%) of patients with the remaining patients reporting a median distribution. No difference was identified for the proportion of patients with median/extramedian spread of symptoms according to the CSI cutoff (Table 4).

Table 4. Association between CSI and symptom spread.

CSI	Median	Extramedian	*p*-Value
≥40	1	8	0.521
<40	4	17	

p-values reflect Fisher exact test. CSI: central sensitization inventory.

3.3. Association between Central Sensitization Inventory and Emotional Wellbeing

The mean BECK, STAI and TSK scores in patients with CTS were 7.87 (SD 4.91), 24.30 (SD 5.05), and 25.93 (SD 7.62), respectively (Supplementary Table S1). The CSI did not correlate with the level of anxiety according to STAI ($r = 0.026$; $p = 0.893$) and kinesiophobia according to TSK ($r = 0.109$; $p = 0.566$). There was, however, a moderate correlation between CSI and depression according to BECK ($r = 0.426$; $p = 0.019$, Table 5), which survived the Benjamini–Hochberg correction.

Table 5. Correlations between CSI and emotional wellbeing.

	CTS	
	Pearson Correlation Coefficient	**Unadj *p*-Value**
CSI with BECK	0.426	0.019 *
CSI with STAI	0.026	0.893
CSI with TSK	0.109	0.566

* reflects *p*-value that remains significant after Benjamini–Hochberg correction.

4. Discussion

Our cohort of patients with CTS has clear indications for the presence of central pain mechanisms as apparent by local and widespread mechanical hyperalgesia and impaired CPM compared to healthy volunteers. No changes were apparent for temporal summation. Of note, there was no association of the CSI with psychophysical measures or symptom spread indicative of central pain mechanisms. There was, however, a moderate correlation between the CSI and depression scores, suggesting that the CSI may be more closely related to psychological parameters than psychophysical measures indicative of central pain mechanisms in patients with focal nerve injury.

Our cohort of patients with CTS had clear indication of a presence of central pain mechanisms, although there was heterogeneity among patients. We identified mechanical hyperalgesia both locally as well as remotely, extraterritorial spread of symptoms and lower efficacy of CPM. Extraterritorial spread of symptoms in patients with CTS is consistently reported in the literature [4,42,43] and has been associated with the presence of central mechanisms. Mechanical hyperalgesia is also commonly interpreted as a sign of central sensitization [44,45]. Local (and remote) mechanical hyperalgesia has previously been reported in focal peripheral neuropathies including CTS [9,43,46]. However other patient cohorts could not confirm this at group level [47,48]. This discrepancy may be attributed to different recruitment pathways as well as different sites of PPT measurements (e.g., palmar aspect of index finger, carpal tunnel). Importantly, the large variation in mechanical hyperalgesia within patients with CTS suggests differing extents of central contributions in individual patients.

Intriguingly, this is the second study demonstrating impaired CPM efficacy in patients with CTS (see also Soon et al., 2017) [13]. On the other hand, temporal summation, which is related to activity-dependent plasticity within the central nervous system [7,8] remained unaltered in patients with CTS. Whereas we assessed temporal summation with PPTs as used in other cohorts [33], more established protocols using pinprick stimulators also did not find group differences between patients with CTS and healthy participants [47]. In line with our results, temporal summation is often found to be comparable at group level in other peripheral neuropathies including systemic polyneuropathies [49,50] and other focal nerve injuries [46,51]. Again though, there is variation within patients, suggesting that some patients have elevated temporal summation, which may be washed out in group comparisons.

Of note, we did not identify an association between the CSI and psychophysical measures and symptom location indicative of altered central pain processing. The CSI was originally developed as a tool to identify central sensitization characteristics [52]. It was developed in patients with fibromyalgia, chronic widespread pain and chronic low back pain, who presumably have stronger clinical phenotypes than the here studied patients with entrapment neuropathies. Some studies in musculoskeletal pain report a correlation between the CSI and the spread of pain [21,53]. However, similar to our findings in patients with peripheral nerve injury, other studies do not find a correlation of the CSI with symptom spread in people with shoulder pain [20] and whiplash injury [18], questioning its construct validity.

A recent systematic review reports a high construct validity of the CSI [54]. However, the included studies compared the CSI to other questionnaires related to pain severity,

general health, emotional wellbeing or sleep. There may be a reciprocal relationship of these measures with central pain mechanisms. However, these constructs are not measures of central sensitisation, which the CSI is meant to evaluate. Surprisingly, not even the original development of the CSI involved psychophysical measures of central pain mechanisms, which are considered to be best practice when assessing the manifestation of central sensitisation in humans [55]. Recent studies have compared the CSI with psychophysical tests indicative of central pain mechanisms. Of note, most studies find no [17–19] or only a weak correlation [21,53] between the CSI and psychophysical tests in patients with musculoskeletal pain. This, together with our findings of no association between the CSI and psychophysical tests in patients with focal nerve injury, further questions the validity of the CSI in detecting human correlates of central sensitization.

Intriguingly though, the CSI was associated with depressive symptoms determined on the BECK in our cohort. Such an association of CSI with psychological wellbeing has been consistently reported in the literature [17–21,23]. This may not be surprising as several questions of the CSI explore psychological constructs such as anxiety, feeling sad or depressed. Whereas, indeed, a decrease in emotional wellbeing is frequently associated with chronic pain including neuropathic pain [46,49,50,56–58], care has to be taken to not confuse changes in emotional wellbeing with the presence of central sensitisation [59]. Unfortunately, these two distinct principles are often equated in the clinical literature. We should note though that whereas psychological parameters were more pronounced in patients with CTS compared to healthy volunteers in our study, average scores were not considered clinically relevant. These findings are in line with previous reports in patients with CTS [42].

4.1. Limitations

Some limitations have to be taken into account. The sample size was calculated to detect differences in central pain processing between healthy people and patients with CTS. Whereas it was adequately powered to detect large effects on correlations between the CSI and psychophysical testing, small or moderate correlations would have been missed. Inspection of the data, however, clearly demonstrated the absence of trends, and even if larger samples may have detected significant correlations, these would likely have been weak.

We recruited patients from surgery waiting lists, which is likely to include more severe profiles. However, symptom and function severity in our study was comparable with previous CTS cohorts from primary care [60] and secondary care [42]. The examiner who performed psychophysical testing could not be blinded to group allocation (CTS vs. healthy). To minimise bias, the examiner was not aware of the outcome of the CSI and other questionnaires until after psychophysical testing was performed. As per routine practice in participating hospitals, the electrodiagnostic test was only performed on the affected side. Subclinical cases of CTS on the contralateral side may therefore have been missed [61].

4.2. Clinical Implications

Our study confirms the presence of central pain mechanisms in patients with focal nerve injury. This is of clinical relevance as their presence may be associated with poorer prognosis in some musculoskeletal conditions [62]. It has also been suggested that the identification of central pain mechanisms may help personalise management strategies [63], an area of active research. For instance, duloxetine may be particularly effective in patients with peripheral diabetic neuropathy who have altered CPM efficacy [64]. Similarly, CPM efficacy may predict the analgesic effect of non-steroidal antirheumatic inflammatory drugs plus acetaminophen in patients with knee osteoarthritis [65], and temporal summation seems to predict pain relief from ketamine in patients with neuropathic pain [66]. Future studies will have to examine whether the identification of central pain mechanisms may be important not only for pharmacological management but also beyond (e.g., physiotherapy).

Most studies of personalised management according to central pain mechanisms use time-consuming psychophysical testing. A low-cost self-reported questionnaire that identifies central sensitisation as measured by psychophysical tools would be ideal. Unfortunately, our study adds to the increasing body of evidence that questions the usefulness of the CSI in identifying central sensitisation according to psychophysical measures. Rather, our data, together with other studies, consistently suggest that the CSI better reflects emotional wellbeing. It is crucial that the distinct concept of emotional wellbeing is not conflated with the neurophysiological concept of central sensitisation in clinical practice. Nevertheless, even though the CSI may not be detecting "central sensitisation" in a strict sense, it may still be of value clinically. For instance, CSI scores seem to be associated with prognostic outcome in certain musculoskeletal conditions [67,68], and this could be further explored in focal nerve injuries.

5. Conclusions

Our results suggest that patients with CTS have changes indicative of altered central pain processing. The CSI does not seem to be associated with psychophysical measures of central sensitization. Rather, the CSI correlates with emotional wellbeing, in particular, depression scores. These data question the construct validity of the CSI in detecting central sensitisation in patients with focal peripheral nerve injury.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/jcm11041075/s1, Figure S1: Three psychophysical measurements. Table S1: Results of emotional wellbeing questionnaires.

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6.3 Resultados del estudio III

The Journal of Pain

Effect of Physiotherapeutic Interventions on Biomarkers of Neuropathic Pain: A Systematic Review of Preclinical Literature

--Manuscript Draft--

Manuscript Number:	JPAIN-D-21-00845
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Corresponding Author:	Ferran Cuenca-Martínez SPAIN
First Author:	Luis Matesanz-García
Order of Authors:	Luis Matesanz-García
	Annina B Schmid
	Julio Eduardo Cáceres-Pajuelo
	Ferran Cuenca-Martínez
	Alberto Arribas-Romano
	Yeray González-Zamorano
	Carlos Goicoechea-García
	Josué Fernández-Carnero
Abstract:	I would appreciate if you review the submitted research paper entitled "Effect of Physiotherapeutic Interventions on Biomarkers of The purpose of this systematic review was to evaluate the effects of physiotherapeutic interventions on biomarkers of neuropathic pain in preclinical models of peripheral neuropathic pain (PNP). The search was performed in Pubmed, Web of Science, EMBASE, Cochrane, Cinhal, Psycinfo, Scopus, Medline and Science Direct. Studies evaluating any type of physiotherapy intervention for PNP (systemic or traumatic) were included. Eighty-one articles were included in this review. The most common PNP model was chronic constriction injury, and the most frequently studied biomarkers were related to neuro-immune processes. Exercise therapy and Electro-acupuncture were the two most frequently studied physiotherapy interventions while acupuncture and joint mobilization were less frequently examined. Most physiotherapeutic interventions modulated the expression of biomarkers related to neuropathic pain. Whereas the results seem promising; they have to be considered with caution due to the high risk of bias of included studies and high heterogeneity of the type and anatomical localization of biomarkers reported. The review protocol is registered on PROSPERO (CRD42019142878) . Perspective: This article presents the current evidence about physiotherapeutic interventions on biomarkers of neuropathic pain in preclinical models of peripheral neuropathic pain. Existing findings are reviewed, and relevant data are provided on the effectiveness of each physiotherapeutic modality, as well as its certainty of evidence and clinical applicability.
Suggested Reviewers:	Roy La Touche roylatouche@yahoo.es
	Jose Casaña-Granell jose.casana@uv.es
	cesar Calvo-Lobo cescalvo@ucm.es

17/11/2021

Dear Editor-in-Chief,

Journal of Pain

I would appreciate if you review the submitted research paper entitled **"Effect of Physiotherapeutic Interventions on Biomarkers of Neuropathic Pain: A Systematic Review of Preclinical Literature"** to be considered for publication in *Journal of Pain*.

The authors of this paper certify full contribution to all aspects of the research and writing process, and take final responsibility for the paper, that we agree with the paper content, that such content was not previously published, and that the paper will not be submitted to any other journal before the Editorial Board decision is taken.

Corresponding author Prof. Dr. Ferran Cuenca-Martínez.

Department of Physiotherapy, University of Valencia, 46010 Valencia, Spain. Tel : 963 98 38 55. Email: fecuen2@gmail.com

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Effect of Physiotherapeutic Interventions on Biomarkers of Neuropathic Pain: A Systematic Review of Preclinical Literature

Luis Matesanz-García[a], Annina B. Schmid[b], Julio Eduardo Cáceres-Pajuelo[c], Ferran Cuenca-Martínez[d,*], Alberto Arribas-Romano[a,e], Yeray González-Zamorano[a,f], Carlos Goicoechea-García[g], & Josué Fernández-Carnero[e,f,h,i,j]

a. Escuela Internacional de Doctorado, Department of Physical Therapy, Occupational Therapy, Rehabilitation and Physical Medicine, Universidad Rey Juan Carlos, Alcorcón, Spain.
b. Nuffield Department for Clinical Neurosciences, University of Oxford, Oxford, United Kingdom.
c. Kapalua fisioterapia S.L., Madrid, Spain.
d. Exercise Intervention for Health Research Group (EXINH-RG), Department of Physiotherapy, University of Valencia, Valencia, Spain.
e. Department of Physical Therapy, Occupational Therapy, Rehabilitation and Physical Medicine. Rey Juan Carlos University, Madrid, Spain.
f. Grupo de Investigación de Neurorrehabilitación del Daño Cerebral y los Trastornos del Movimiento (GINDAT), Facultad de Ciencias Experimentales, Universidad Francisco de Vitoria, Pozuelo de Alarcón, Madrid, Spain
g. Departament basic health sciences Rey Juan Carlos University, Madrid, Spain.
h. Motion in Brains Research Group, Institute of Neuroscience and Sciences of the Movement (INCIMOV), Centro Superior de Estudios Universitarios La Salle, Universidad Autónoma de Madrid, Madrid, Spain.
i. Grupo Multidisciplinar de Investigación y Tratamiento del Dolor. Grupo de Excelencia Investigadora URJC-Banco de Santander.
j. La Paz Hospital Institute for Health Research, IdiPAZ, Madrid, Spain.

***Corresponding author:** *Prof. Dr. Ferran Cuenca-Martínez*

Address: Department of Physiotherapy, University of Valencia, 46010 Valencia, Spain

Tel : 963 98 38 55. Email: fecuen2@gmail.com / Ferran.Cuenca@uv.es

Conflict of interest

None declared.

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ABSTRACT

The purpose of this systematic review was to evaluate the effects of physiotherapeutic interventions on biomarkers of neuropathic pain in preclinical models of peripheral neuropathic pain (PNP). The search was performed in Pubmed, Web of Science, EMBASE, Cochrane, Cinhal, Psycinfo, Scopus, Medline and Science Direct. Studies evaluating any type of physiotherapy intervention for PNP (systemic or traumatic) were included. Eighty-one articles were included in this review. The most common PNP model was chronic constriction injury, and the most frequently studied biomarkers were related to neuro-immune processes. Exercise therapy and Electro-acupuncture were the two most frequently studied physiotherapy interventions while acupuncture and joint mobilization were less frequently examined. Most physiotherapeutic interventions modulated the expression of biomarkers related to neuropathic pain. Whereas the results seem promising; they have to be considered with caution due to the high risk of bias of included studies and high heterogeneity of the type and anatomical localization of biomarkers reported. The review protocol is registered on PROSPERO (CRD42019142878).

Perspective: This article presents the current evidence about physiotherapeutic interventions on biomarkers of neuropathic pain in preclinical models of peripheral neuropathic pain. Existing findings are reviewed, and relevant data are provided on the effectiveness of each physiotherapeutic modality, as well as its certainty of evidence and clinical applicability.

KEYWORDS: Neuropathic pain; Physical Therapy Modalities; Animal model; Preclinical study; Biological factor; Pain measurement

Introduction

Neuropathic pain (NP) is defined as pain caused by a lesion or a disease of the somatosensory system[118] and is estimated to affect between 6.9 and 10% of the general population.[53,107] Peripheral neuropathic pain is becoming more prevalent due to an ageing world population, the rising impact of diabetes mellitus as well as higher survival rates of cancer and the implications of chemotherapy.[31] Management of NP remains challenging, as many patients do not experience adequate pain relief.

Treatment of neuropathic pain usually focuses on symptom management.[31] Non-surgical interventions are recommended as first-line treatments for patients with neuropathic pain.[51] Among the non-surgical interventions, the Neuropathic Pain Special Interest Group of the International Association for the Study of Pain recommends pharmacology as first-line treatment.[32,65] However, efficacy is limited[41] with often unacceptable side effects.[40,41,95]

Over the past decade, the role of Physiotherapy has gained increasing interest in the treatment of neuropathic pain.[66] Several studies have been published on the efficacy of physiotherapy on peripheral neuropathic pain resulting from systemic[70] or focal nerve damage.[38,66] Although some studies suggest that physiotherapy provides significant improvements in pain, quality of life and disability in patients with peripheral neuropathies and neuropathic pain,[28,37] other studies did not report similar findings[66] and the mixed quality of studies prevents firm conclusions.[66] Whereas human studies evaluating physiotherapy for neuropathic pain focus on improving pain, function and quality of life, the mechanisms by which physiotherapy interventions work remains poorly understood. A better understanding of the mechanisms of action of physiotherapy would help the selection of the most promising disease modulating physiotherapy interventions for future clinical trials.

The body of literature exploring the mechanisms of action of physiotherapeutic interventions using preclinical models has grown substantially over the past years. The main objective of this systematic review is therefore to summarise this literature by assessing the effect of physiotherapeutic interventions on biomarkers of neuropathic pain in pre-clinical models.

Methods

This systematic review was conducted following the guidelines of the Systematic Review Center for Laboratory Animal Experimentation (SYRCLE), the Cochrane Handbook for Systematic Review of Intervention,[56] the original guide "Preferred Reporting Items for Systematic Reviews, PRISMA" and the most recent update from 2021 (Page, McKenzie, Bossuyt, Boutron, Hoffmann, Mulrow, Shamseer, Tetzlaff, 2021). The protocol has been prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO, CRD42019142878).

Literature search

A systematic search was developed following the step by step guide suggested by Leenaars et al.[75] The following databases were searched from inception to 13th January 2020: MEDLINE EMBASE, CINAHL, SCOPUS, Web of Science, PubMed, Cochrane library and PsycINFO. The search strategy is described in **Appendix 1.**

Selection Criteria

Types of studies

Original animal studies reporting the effect of physiotherapeutic interventions compared to a control group on peripheral neuropathic pain were included. Case studies, cross-over studies, and studies without a separate control group were excluded. Letters, reports, or abstracts from congresses were not included. Only articles with access to the full-text in English and Spanish language were included.

Animal models

In-vivo animal models of neuropathic pain induced by both systemic (e.g., diabetic or chemotherapy induced neuropathy) and focal nerve injury (e.g., nerve ligation, crushing or transection) were included. We excluded studies where due to the model or validation tests (e.g., sensory thresholds), we could not ascertain that the animals had developed neuropathic pain. We also excluded studies with animals with co-morbidities (eg: pre-ischemic physiologic conditions such as ischemic injury) and studies that evaluated the prevention rather than the treatment of already existing neuropathic pain.

Interventions

We included any physiotherapy intervention (e.g., exercise, acupuncture, electro-acupuncture, joint mobilization, neural mobilization, physical agents), independent of timings and dosage. Studies evaluating invasive treatments (e.g., radiofrequency or spinal stimulation) or pharmacological treatments were excluded.

Comparator

The control population was defined as a cohort of animals in which the same neuropathic pain model was induced, but who did either receive no treatment or a sham intervention (e.g., electroacupuncture without electrical stimulation). Studies comparing physiotherapy interventions to other substantive control interventions such as pharmacology were excluded.

Outcome measures

Studies were included if they reported on the effect of the physiotherapy interventions on biomarkers related to neuropathic pain. Studies were not included if they only reported behavioral outcomes. Examples of neuropathic pain biomarkers could include:

a) Immune system: Immune cell markers (e.g., CD68, CD3), markers of immune competent cells (e.g., OX-42, GFAP), cytokines/chemokines

b) Neurotrohpins (eg: NGF)

c) Opioid system: Neuropeptides (eg: β-endorphine) and receptors (eg: MOR)

d) Neurotrasnmitters (eg: substance P)

e) Ion channels (eg: TRPV1, TRPV8)

Study Selection

Before carrying out the article selection procedure, a search for duplicates was carried out with MENDELEY©. In a first phase, two independent reviewers (L.M and A.A.) assessed the eligibility of the studies based on information from title, abstract and keywords. During the second phase, the full text was independently reviewed by both revierwers for eligibility. A third reviewer (C.G.) acted as a mediator when there were differences of opinion between the two reviewers, with the three reviewers reaching consensus.[42]

Data Extraction and management

Data of included studies were extracted by two independent reviewers (L.M and A.A.). This involved registered bibliographic data such as first author and year of publication, animal characteristic (species, age, weight, and gender), neuropathic pain model, treatment groups and intervention characteristics (physiotherapeutic intervention, timing of intervention, number of treatment sessions, duration, dose and location). We also extracted the type of biomarkers including in wich tissue they were measured. We attempted to extract means, standard deviations, and p values for all biomakers. If available, we recorded behavioural test outcomes to confirm the presence of neuropathic pain. Finally, both authors reached consensus on each item of extracted data. In case of disagreement between the authors, a third author (C.G.) made the final decision.

Methodological quality assessment

Risk of bias assessment

The risk of bias of each study was assessed using SYRCLE's risk of bias tool [57] scored by two independent reviewers (Y.G and E.C.). If there was any disagreement or discrepancy, it was resolved by a third reviewer (J.F.). The tool does not give any cutoff, however we considered studies to have low risk of bias if they were rated as high bias on less than the half of the scoring criteria (≤ 4 out of 10).

Reporting quality

To evaluate the reporting quality of the studies we used the "Animals in research: reporting in vivo experiments" (ARRIVE) guidelines[71] scored by two independent reviewers (Y.G and E.C.). Any discrepancies were resolved by consensus with a third reviewer (F.C.M). Each ARRIVE item was graduated into three descriptive levels: complete (green) when all sub-items in the topic have been described; partial (yellow) when one or more of the sub-items have been described; and incomplete (red) when none of the sub-items have been described. We considered articles to have good reporting quality if they report at least 60% of items completely.

Qualitative analysis

For the description of the results, the studies were grouped by type of intervention (e.g., exercise, electro-acupuncture) as well as type and location of reported biomarkers.

Due to the heterogeneity of reported biomarkers, anatomical measurement sites and measurement methods (e.g., gene expression, immunohistochemistry, protein level), and the missing summary statistics in many studies, a meta-analysis could not be carried out.

Instead, we report these findings with heat maps for each intervention and at each location (eg.: spinal cord, dorsal root ganglia): colour coding was assigned according to

the frequency of studies reporting any change on individual biomarker expression (eg.: increase, decrease or no change) after the intervention.

Results

Selection of the Studies

The database search retrieved a total of 4633 articles. After reviewing the titles and abstracts, 175 studies were assessed for eligibility. Of those, 94 were excluded because they did not satisfy the eligibility criteria. This resulted in the inclusion of 81 full-text articles. The flow diagram is shown in **Figure 1**. The country that produced most eligible studies is China (35.8%), followed by Brazil (20.9%) and Taiwan (17.3%). Italy, the United States and Japan contributed with 4.9% each, while Spain, South Korea and Turkey produced 3.7% of included studies.

Risk of Bias Analysis

Only two of the 81 papers had a low risk of bias, obtaining a 5/10 score on the SYRCLE tool. The remaining articles had a high risk of bias **(Table 1)**.

Reporting Quality according to ARRIVE

Fifty-eight (71.6%) out of 81 articles were rated as 60% or more "complete" according to the ARRIVE guidelines. Twenty-one (80.8%) of the 26 articles exploring the effect of exercise are of good quality. Fifty percent (1 out of 2) of the acupuncture and joint mobilization articles have low quality. Of the reports on electroacupuncture, 26.9% (7 of the 26) have low methodological quality. All articles on neural mobilisation showed good methodological quality (5 out of 5). Of studies including physical agents, 57.9 % (11 out of 19) were of good quality **(Supplementary table 1)**.

Characteristics of the Studies

Characteristics of the included articles such as details of animal species, neuropathic pain models and treatment groups and interventions are shown in **supplementary table 2.**

The majority of studies reported on electroacupuncture, and exercise (32%) followed by physical agents (23.5%), neural mobilization (6.2%) and acupuncture and joint mobilization (2.5%).

The most widely used model of neuropatic pain was traumatic nerve injury (78.9%), with chronic constriction injury being the most studied model (55.8%) followed by sciatic nerve cut (13%). Other models reported were diabetic neuropathy, complex regional pain and chemotherapy induced neuropathy. 82.72% of the articles confirmed the presence of NeuP with behavioural tests before treatment started.

Rats were the most prevalent species studied (85.2%) followed by mice (14.8%). Only one report with rabbits was included. Whereas 92.5% of studies included only male animals, 7.4 % of studies studied female animals. None of the studies included both sexes.

Biomarkers type and site examined

The main biomarkers reported related to the immune system (67.9%) followed by neurotrophins (27.2%), neurotransmitters (16%) and opioid pathways (7.4%, **Supplementary table 3**). The anatomical sites where the biomarkers were measured included spinal cord (53.0% of studies), followed by the peripheral nerve and dorsal root ganglia (both 30.9%), the brain (13.6%) and blood (4.9%) **(Table 2).**

Qualitative analysis

Tables 3a-3f contain heat maps reflecting the frequency of studies showing specific directions of effects (up vs downregulation vs no change) of each physiotherapy intervention on biomarkers of neuropathic pain.

Exercise

Two types of exercises were investigated in the studies, swimming and treadmill running.

Swimming was one of the two activities studied by 4 out of 26 studies (15.4%). The dose for swimming exercise ranged from 40 to 60 minutes and was perfomed on 5 days per week. Swimming reduced the concentration of pro-inflammatory cytokines in the injured nerve tissue,[20] as well as the concentration of neuroptrophins in spinal cord, dorsal root ganglia and peripheral nerve tissue in the medium term.[4,117] Only one article found no post-treatment differences in BDFN concentrations.[33] One paper found an increase of GAP-43 in the peripheral nerve.[33]

Treadmill aerobic training was the most used by the studies (23 out of 26 studies, 88.5%), both in isolation and using it against other therapies. The dose of treadmill running ranged from 60 minutes to exhaustion and was performed between 3 to 5 days per week over a period of 3 to 8 weeks. Treadmill running was able to reduce pro-inflammatory cytokines and increase anti-inflamatory cytokines mainly in peripheral nerves,[18,19,61,119] with changes in DRG and spinal cord also reported.[12–14,19,49,74,116] Only one article found increased pro-inflammatory cytokines in nerve and dorsal horn of the spinal cord.[14] Only one study found no difference in the sub-group "other inflammatory markers" of the immune system[68] The concentration of neurotrophins was lowered after treadmill exercise.[29,81,114,117] One study reported increased expression of at least one of these biomarkers when treadmill running was combined with electrical stimulation.[29] Treadmill running was also effective in reducing the activation of glial cells in DRG and spinal cord.[14,23,30,68,81] Only one article did not find changes in the spinal cord after intervention.[30] In that experiment, the animals ran until exhaustion,[30] while in the others it was of a fixed duration.[14,23,30,68,81] Studies reported a direct relationship between

increased expression of inhibitory neurotransmitters such as serotonin in the brain and spinal cord and exposure to treadmill running.[72,82,114] Only one study found a decrease in neurotrophin expression in the peripheral nerve.[18] In contrast, the effect on excitatory neurotransmitters was only evaluated in two articles, with mixed results, however different neurotransmitters were measured (GABA and Sustance P).[69,126] Two articles reported a decline in the expression of inflammatory markers in the dorsal horn.[30,116]

Neural mobilization

Five articles studied neural mobilization. The most frequently reported dose was 20 oscillations per minute for 2 minutes and 25 seconds of rest, for 10 minutes for a total of 10 sessions. Only one showed no difference in post-treatment biomarkers of neuropathic pain.[45] Whereas Giardini et al.[45] evaluated changes in the thalamus, midbrain and PAG, the other studies examined biomarkers in SCDH, DRG and sciatic nerve. Neural mobilization consistently reduced the concentration of neurotrophic factors and the expression of substance P, TRPV1 and MOR[98,99] in the spinal cord. One article reported an increased concentration of NGF in the sciatic nerve [104]. Whereas most studies used the chronic constriction model, one used a diabetic neuropathy model [135] and reported a decrease in intraneural pro-inflammatory cytokines on the treated side.

Joint mobilization

Two studies evaluated the effect of joint moblisation on biomarkers of neuropathic pain. The dose for joint mobilization ranged from 1 series of 10 repetitions to 3 minutes series with 30 seconds' rest. The frequency ranged from every 2 days to 5 consecutive days for a total of 12 to 15 days. Joint mobilization consistently reduced activation of the immune system (glial cells mainly) in the SCDH.[34] Their effect on cytokine expression revealed controversial results; while the concentration of cytokines in the

DRG remained the same after treatment, only anti-inflamatory cytokines increased their expression in the spinal cord.[111] One of the 2 studies used rhythmic mobilization techniques[86] and the other high-speed manipulations.[111] The place of application was different as well as the dose, so the results must be interpreted with caution.

Physical agents

Nineteen studies investigated a range of physical agents including laser, therapeuthic ultrasound, and transcranial direct current stimulation. The dose for ultrasound most frequently reported was 1MHz 0.5-1 w/cm^2 during 5 min.

Therapeutic ultrasound reduced the expression of substance P in both studies.[22,60] Further, a reduction of cytokines (TNF and IL-6)[21] and TRPV1 expression [60] was apparent at sciatic nerve and dorsal root ganglia respectively.

Of the 5 articles including laser therapy, only one measured the changes generated on enkephalines[48] with no changes after treatment. Three papers report a decrease of cytokine concentration.[25,58,59] All laser treatments increased the concentration of NGF in the sciatic nerve regardless of the time of intervention or parameters applied.[58,59,105] Cidral et al.[25] found a decrease in the concentration of TNF but not Il-1β in the SC and the sciatic nerve while Hsieh et al.[58] reported a decrease of several cytokines measured in the sciatic nerve. This difference could be due to the different intensities applied in the studies. Cidral et al.[25] used 80 mW/cm2 and 2.5 J/cm2 vs 30 mW/cm2 and 9 J/cm2 used by Hsieh et al.[58] in both studies.

2 studies investigated tDCS. tDCS increased TNF-a concentrations in the brain and spinal cord, whereas IL-1b and IL-10 only changed significantly in the spinal cord, with a decreasing concentration of both cytokines.[26] tDCS also reduced the activation of glial cells in spinal cord dorsal horn[133] and decreased BDNF concentrations both in the central nervous system and in blood serum.[39]

Three studies reported on the effect of TENS therapy. TENS could not reduce proinflammatory cytokines (TNF-a) in the sciatic nerve,[79] in fact one study reported an increase in that biomarker.[113] However, TENS did reduce the concentration of pro-inflammatory cytokines in the spinal cord.[87] The glial activity in the spinal cord was reduced after the application of TENS, and the expression of opioid receptors increased in the same location.[87] Contradictory results were reported regarding the presence of excitatory neurotransmitters in the spinal cord.[108]

The pulse electromagnetic field was consistent in modulating the cytokine concentrations, in both the spinal cord and the peripheral nerve tissue that caused the injury.[88,89]

Electro-acupuncture

Electroacupuncture reduced the concentrations of proinflammatory cykines. The doses reported ranged from 1-2 mA, fluctuating between 2 and 100 Hz, 1.05-2.85 ms for 30 min. Most of the changes seem to occur in the dorsal horn[80,123,125,132] although changes in the nerve,[16] blood[44] and DRG[129] were also reported. In contrast, four articles did not find changes in cytokine concentrations following electroacupuncture.[16,44,78,123]

The effect of electroacupuncture reported on neurotrophins has been mixed. Articles reported decreased concentrations of nerve growth factors (NGF and BDNF) in dorsal root ganglia and spinal cord dorsal horn[85,92,123,128] while others obtained significant increases in the same anatomical sites for NGF,[129] BDNF[24] and GDNF.[35] These differences may be due to the starting times and duration of treatment. It seems that most of the articles that reported a decreased concentration[85,92,123,128] had a treatment duration greater or equal to 2 weeks. In contrast those that increased pain markers expression only treated the animals for one week.[24,129]

Acupuncture

The two acupuncture articles included were very heterogeneous. Only Wang et al.[127] found a significant decrease in the concentrations of cytokines. While Wang et al. performed the treatment one day after surgery and for a period of 14 days,[127] Chang et al. started the intervention 24 days after surgery, during a period of 5 days.[17] The location of biomarker measurement were different; Wang et al. measured cytokines in the blood, Chang et al. measured Cdc2 and P-vim in the sciatic nerve and DRG with no difference after treatment.[17] In both articles, the same 30-minute daily dose was applied, but the duration of treatment varied between one and two weeks.

Discussion

This systematic review summarises the results of 81 studies that report the influence of differents types of physiotherapy modalities on biomarkers of peripheral neuropathic pain in pre-clinical models. The two most studied interventions were electro-acupuncture and exercise, with neural mobilization, joint mobilisation and physical agents being less commonly studied. The most frequently measured biomarker group was related to the neuro-immune system, specifically cytokines. The dorsal horn is the anatomical site where biomarkers were measured most frequently. Most studies, despite their heterogeneous nature, report significant post-intervention changes of the biomarkers of neuropathic pain. Our findings indicate that physiotherapy interventions downregulate the expression of pro-nociceptive (eg. immune system or neurotrophins) markers and upregulate the expression of markers that dampen neuropathic pain (eg. opioid system). However, risk of bias was high in 97.5% of studies.

Our findings about the most common model is similar to previous reviews about pre-clinical models of NP were traumatic injury (78.9%) is the most commun.[5] Although neuropathic pain induced by chemotherapy[110] or diabetic painful neuropathy are growing problems,[1] the models of neuropathic pain induced by chemotherapy and

diabetic neuropathy have not been used very often in preclinical physiotherapy studies (2.5% and 11.1% respectively).

Effects of Physiotherapy

Exercise was one of the main interventions studied, specifically swimming and running (treadmill). It is well established that aerobic exercise induces analgesic effects in pre-clinical models.[50] Our results demonstrate that aerobic exercise has promising effects on biomarker modulation in neuropathic pain. There seems to be a consistent effect of aerobic exercise on the modulation of markers of neuro-inflammation in the peripheral and central nervous system. Other biomarkers such as neurotrophins and neurotransmitters are also modulated by exercise. Of note, studies which did not demonstrate an effect on biomarkers used exercise duration of less than 40 min,[4,33] perhaps insufficient time to generate changes. In contrast, studies showing an effect on biomarkers included sessions with a duration between 60 to 90 min.[20,117] For treadmill running, only one article did not find changes after intervention.[30] In this experiment the animals ran until exhausntion,[30] while in the others it was of a fixed duration.[14,23,30,68,81] It could thus be speculated that reaching exhaustion may counteract the positive effects of physical activity in regulating glial cell activity.

Neural Mobilizations have shown efficacy in human trials of patients with referred leg or arm pain of neural origin,[8] however their exact mechanisms of action remain speculative. In line with findings in animal models,[99,135] neural mobilizations improve mechanical hyperalgesia in patients after neural mobilization intervention.[10] Our findings indicate that neural mobilisations may exert their beneficial effect through modulating neuroinflammation, opioid system and neurotrophins. The ability of neural mobilisation to disperse fluids has been reported with cadaveric models.[15] In patients, there is also some indication that neuroinflammation may be a target. Schmid et al

reported a reduction of intreanueral edema after one week of neural mobilization in patients with carpal tunnel syndrome.[101]

Although Joint mobilization techniques are often used, they seem to have only short term analgesic effects in humans.[11,100] In addition they are not usually used for neuropathic pain, but for nociceptive pain.[9,90] Both preclinical studies included in our systematic review reported a decrease of mechanical hyperalgesia after the interventions.[86,111] Similarly, Krouwel et al. reported an increase on the pain preassure thresholds in humans after a lumbar joint mobilization.[73,100] Interestingly, our data indicate that joint mobilization may exert their beneficial effects through modulation of glial cells and cytokines. However, only two articles were included, both using different techniques which make it difficult to draw firm conclusions.

Physical agents are often used clinically as analgetic treatments. However, their clinical benefit remains contradictory. For instance, a Cochrane review about the use of TENS in adults with neuropapthic pain could not draw firm conclusions whether TENS is effective for pain control due to the very low quality of the evidence.[46] Another review from Akyuz et al. conclude that physical modalities such as ultraound or laser are not effective for the treatment of neuropathic pain when applied alone.[3] Our data suggest that physical agents mainly seems to modulate neuropathic pain through regulation of neuroinflammation such as a downregulation of TNF and IL-1β wich are associated with the maintenance of neuropathic pain after peripheral injury.[102] Nevertheless, physical agents could also modulate other biomarkers, for instance neurotrophins or neurotransmitters.

Electroacupunture has shown some evidence in reducing pain in patients with osteoarthritis mediated by β-endorphins.[2] Human evidence for the effect of electroacupuncture on neuropathic pain remains controversial. Penza et al. did not find

pain improvements following electroacupunture treatment in patients with sixteen[94] whereas Galantino et al. reported some improvement in patients with HIV-related peripheral neuropathy.[43] In both reports the number of patients included was small, so these results remain preliminary. Our findings indicate that electroacupuncture may exert beneficial effects through modulating neuroinflammation, regulating neurotropins and neutrotransmitters as well as decreasing ATP and ion channels such as TRPV1.[76–78,122–124,130–132,134] Another possible mechanism is that this type of electrical stimulation may be activating the endogenus opioid system by the release of enkephalins and b-endorphins.[52]

As we only identified two articles about acupuncture, it is difficult to hypothesize about its mechanisms of action. Preliminary data suggest that similar to electro-acupuncture this technique might modulate the activation of the neuro-immune system,[17,127] but further research is needed. In line with our preclinical findings, a Cochrane review about the use of acupuncture in humas with any type of neuropathic pain reports limited evidence.[67] Another review about acupuncture and its effect on pain could also not establish a clear relationship between the technique and the analgesics effects in humans.[84]

Implications for humans

The importance of specific biomarkers to mantain neuropathic pain is not only clear in preclinical models,[27] but also in humans.[109] Our findings suggest that Physiotherapy can modulate biomarkers related to neuropathic pain in preclinical models. Although the most studied biomarkers related to the immune system and neurotrophins, this review identified other targets such as neurotransmitters or the opioid system. In recent years, several publications have reported the possible relationship between the presence of neuropathic pain and some of the here reported biomarkers humans. For instance,

neuroinflammation is thought to play a crucial role in the generation and maintenance of neuropathic pain in preclinical models[6] Similarly, there is a growing body of evidence confirming the importance of neuroinflammation in neuropathic pain in humans.[109] This is apparent both in patients with focal nerve injuries [54], but also in patients with polyneuropathies.[62,136] As such, our findings indicate that physiotherapy can modulate biomarkers that are relevant in patients with neuropathic pain.

In addition to the neuroimmune system, other systems may influence the presence of NP. For example, neurotrohpins have been implicated with neuropathic pain. For Instance, NGF acts as a pathogenic pain mediator[55] and also in humans, high levels of NGF have been associated with pain.[115] BDNF shows similar hyperalgesic effects and its presence in the dorsal root ganglia and the spinal cord correlate with neuropathic pain behaviour.[106] The dysfunction of the opioid system has been describe in preclinical[96] and in humans with NP [36]. An ohter indirect measure from the opioid system is the conditioned pain modulation wich is mediated by the endogenus opioid system.[120] This type of alteration has been reported in patients with different types of NP such as complex regional pain syndrome[103] or carpal tunnel syndrome.[112] These two systems look like a promising target which required further investigation in human trials.

So far, pharmacological managent has been the first line of treatment for NP in humans. Tricyclic antidepressants (eg amitriptilyne), and serotonin-noradrenaline reuptake inhibitors (eg duloxetine) or anticonvulsants (eg pregabaline) have been use as first line option.[31] Also opioids, like tramadol have been use to target the opioid system.[32] Even Combination therapy have been used in these kind of patients, for instance the use mixed of morphine and gabapentin provided better pain relief together but that gain was also modest.[47] Despite of this evidence, some trials have report controversial

resoults[7,63] in addition of the concerns about side effects reported of long term used [64] advises on looking for new, safer treatment options.

Future targets to investigate are the endogenous cannabionides such as CB2 receptor wich recently have been shown to increase hypersensitivity in models of neuropathic pain[91] and we have not found this to have been evaluated in physiotherapy studies.

Whereas the results of this study seem to suggest promising effects of biomarker modulation of physiotherapy interventions for peripheral neuropathic pain, these findings cannot be directly translated to understand the mechanism of these therapies in humans. Nevertheless, these findings can provide guidance on the type and design of future physiotherapy interventions in clinical trials.

Limitations

We have identified some limitations in our review. Only studies written in English were included. The heterogeneity of the measurement methods as well as the large number of different biomarkers analyzed challenges the interpretation. Of note, 92.5% of studies only included male rats. It is well established that pain behavior and underlying mechanisms differ according to sex,[97] thus limiting the generalizability of our findings. Importantly, risk of bias was high and reporting according to the ARRIVE guidelines was poor in the majority of studies. The inconsistent reporting of summary statistics prevented a meta-analysis. Poor reporting and methodological quality have been identified as major challenges in preclinical research including in the pain field.[83,121] With the recent publication of the ARRIVE guidelines, it is hoped that the quality of preclinical studies and their reporting will improve, thus facilitating future systematic reviews.[71]

Conclusion

Our results suggest that exercises, electro-acupuncture, neural mobilization, and physical agents modulate biomarkers of neuropathic pain in preclinical models.

Only few studies were available for joint mobilization and acupuncture, thus preventing firm conclusions. Physiotherapy interventions seem to regulate the expression of a range of biomarkers particularly associated with the neuro-immune system, opioid system, neurotrasnmitters, neurotrophins and receptors. The high risk of bias and poor reporting quality however prevents firm conclusions. Nevertheless, our findings may be used to inform the design of future human studies. Future preclinical studies need to follow higher standards of methodological quality and reporting to advance this promising field.

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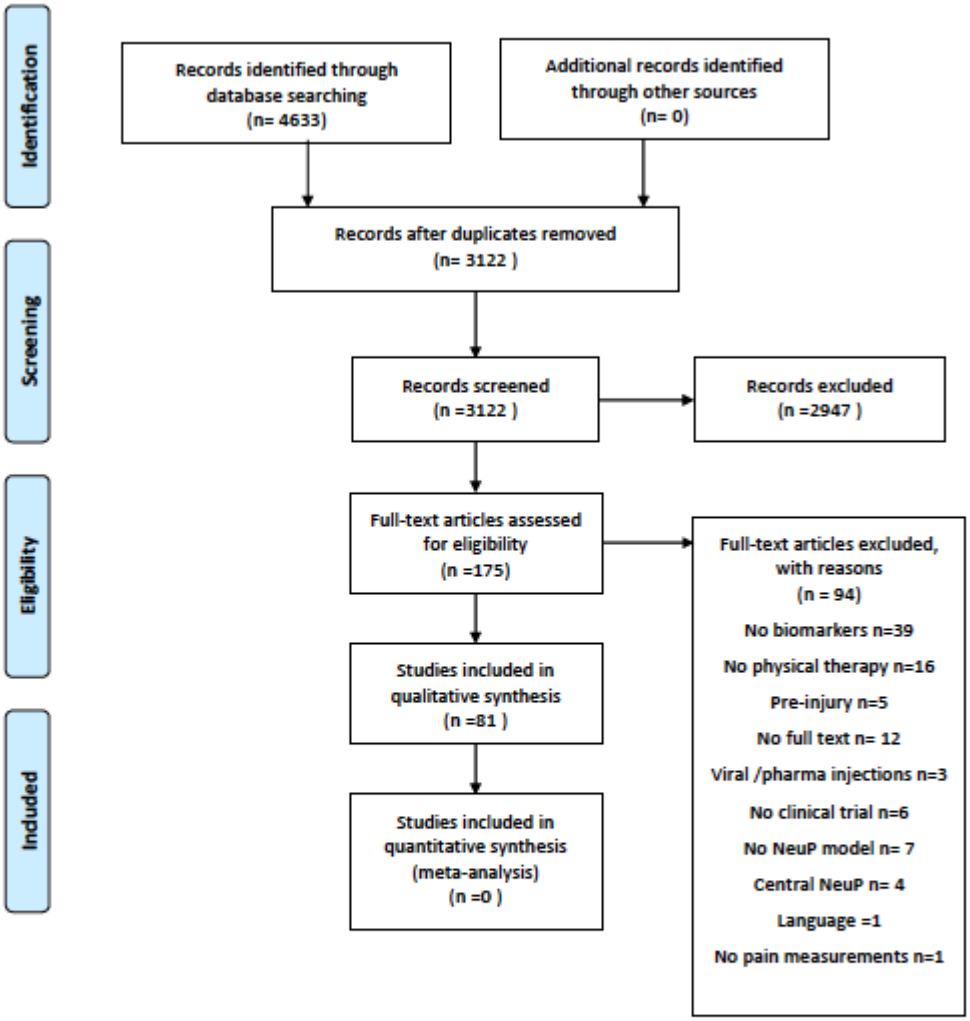
Identification
Screening
Eligibility
Included
Records identified through database searching (n= 4633)
Additional records identified through other sources (n= 0)
Records after duplicates removed (n= 3122)
Records screened (n =3122)
Records excluded (n =2947)
Full-text articles assessed for eligibility (n =175)
Full-text articles excluded, with reasons (n = 94)
No biomarkers n=39
No physical therapy n=16
Pre-injury n=5
No full text n= 12
Viral /pharma injections n=3
No clinical trial n=6
No NeuP model n= 7
Central NeuP n= 4
Language =1
No pain measurements n=1
Studies included in qualitative synthesis (n =81)
Studies included in quantitative synthesis (meta-analysis) (n =0)

Tables

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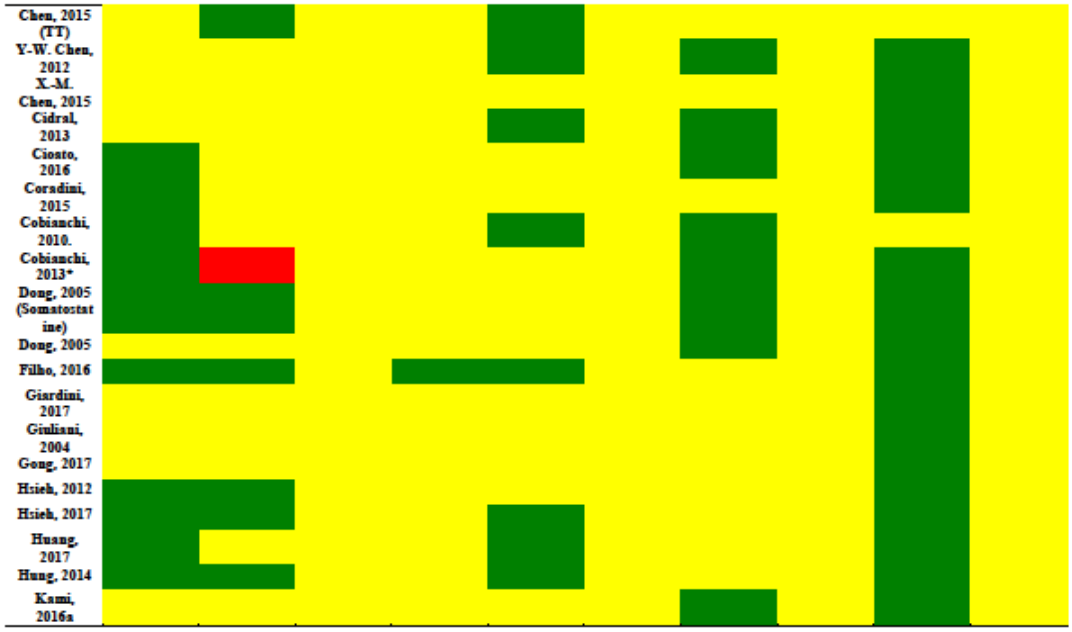
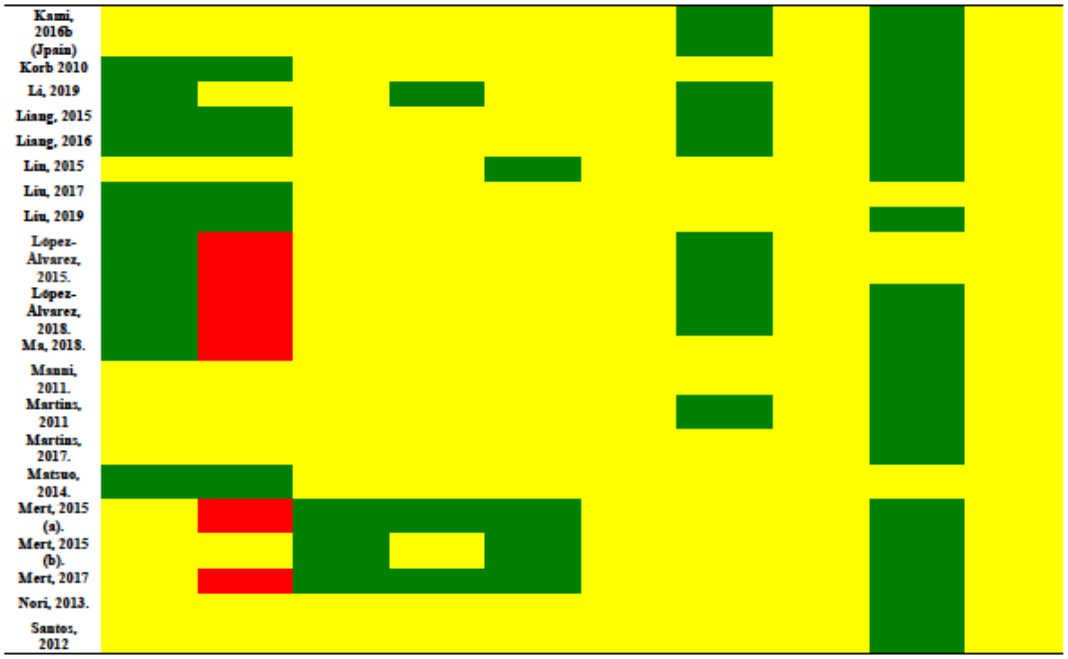
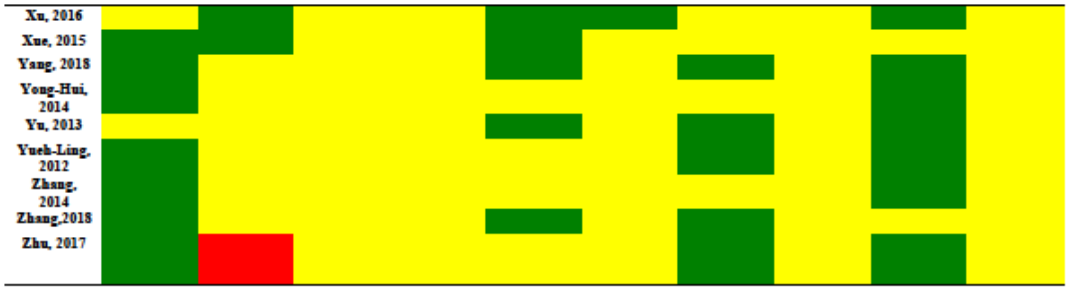
Table 1. Risk of bias assessment using the SYRCLE tool

-	Selection bias	Selection bias	Selection bias	Performance bias	Performance bias	Detection bias	Detection bias	Attrition bias	Reporting bias	Other
Reference	Was the allocation sequence adequately generated and applied?	Were the groups similar at baseline or were they adjusted for confounders in the analysis?	Was the allocation adequately concealed?	Were the animals randomly housed during the experiment?	Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?	Were animals selected at random for outcome assessment?	Was the outcome assessor blinded?	Was incomplete outcome data adequately addressed? (*) of selective outcome reporting?	Are reports of the study free of selective outcome reporting?	Was the study apparently free of other problems that could result in high risk of bias?
Almeida, 2015										
Belmonte, 2018										
Bobinsky, 2011										
Bobinsky, 2015										
Bobinsky, 2018										
Cha, 2010										
Cha, 2012										
Chang, 2013										
Y-W. Chen, 2013										
Y-W. Chen, 2015 (US)										


Chen, 2015 (TT)
Y-W. Chen, 2012
X.-M. Chen, 2015
Cidral, 2013
Ciosto, 2016
Coradini, 2015
Cobianchi, 2010.
Cobianchi, 2013*
Dong, 2005 (Somatostatine)
Dong, 2005
Filho, 2016
Girardini, 2017
Giuliani, 2004
Gong, 2017
Hsieh, 2012
Hsieh, 2017
Huang, 2017
Hung, 2014
Kami, 2016a


Kumi, 2016b (Jpain)
Korb 2010
Li, 2019
Liang, 2015
Liang, 2016
Lin, 2015
Liu, 2017
Liu, 2019
López-Álvarez, 2015.
López-Álvarez, 2018.
Ma, 2018.
Manni, 2011.
Martins, 2011
Martins, 2017.
Matsuo, 2014.
Mert, 2015 (a).
Mert, 2015 (b).
Mert, 2017
Nori, 2013.
Santos, 2012


Santos, 2018
Shao, 2015
Shi, 2013
da Silva, 2015
da Silva Oliveira, 2018
Somers, 2003
Somers, 2009
Song, 2016
Su, 2018
Sumizono, 2018
Sun, 2004
Thakur, 2016
Tian, 2018
Tsai, 2017
Tu, 2015
Tu, 2018
Wang, 2009
Wang, 2014
Wang, 2016 (a)
Wang, 2016
Wang, 2018
Xia, 2019



Green: low risk of bias; yellow: unclear risk of bias; red: high risk of bias

Tables

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Table 2. Characteristics and findings of the included studies in relation to biomarkers

Reference	Groups	Anatomical Level	Biomarkers	Main Results	P value
Chang, 2013	NC NC + acupuncture	**POD 7** Sciatic nerve DRG Sciatic Nerve	NF-200-stained axons (Quantification of axonal regeneration) % number of labelled neurons Quantification of Hoechst-stained nuclei Cdc2 P-vim	Increased by acupuncture No difference ? ?	p<0.05
Wang, 2009	CCI CCI+acupuncture	**POD** 15 blood	IL-1B	Decrease CCI+acupuncture	p<0.01
Cha, 2010	NT NT+EA	**POD** ? Spinal cord	Neuronal nitric oxide synthase-positive neurons	Decrease by EA in Rexed area I–II but no difference in Rexed area III–V and X	p<0.05
Cha, 2012	NT NT+EA	**POD?** Peripheral nerves DRG 	IL-1b IL-6 TNF-Alfa IL-1beta IL-6 TNF-Alfa	Decrease by EA Decrease by EA Decrease by EA Decrease by EA No difference No difference	p<0.05 p<0.05 p<0.05 p<0.05 . .
X.-M. Chen, 2015	CCI CCI+EA	**POD 14** Spinal cord	P2X4R IFN-g	Decrease by EA Decrease by EA	p<0.01 p<0.01
Dong, 2005 (a)	CCI CCI+EA	**POD 14, 21 and 28** DRG Spinal cord	GDNF (WB) GDNF (IR) GDNF (PCR) GFRα-1 (WB) GFRα-1 (PCR) GDNF (IR)	Increase by EA at day 14 Increase by EA at days 21 and 28 Increase by EA at day 21 Increase by EA at day 28 Increase by EA at days 14 and 21 Increase by EA at day 28 Increase by EA at day 14 Increase by EA at days 21 and 28 Increase by EA at days 14 and 21 Increase by EA at day 28 Increase by EA at days 14 and 21 Increase by EA at day 28	p<0.05 p<0.01 p<0.05 p<0.01 p<0.01 p<0.001 p<0.05 p<0.01 p<0.05 p<0.01 p<0.01 p<0.001
Dong, 2005 (b)	CCI CCI+EA	**POD 14, 21 and 28** DRG Spinal cord	SOM (IR) SOM (PCR) SOM (IR)	Increase by EA at days 14, 21 and 28 Increase by EA at days 14 and 21 Increase by EA at day 28 Increase by EA at day 14 Increase by EA at days 21 and 28	p<0.01 p<0.01 p<0.001 p<0.05 p<0.01

Li, 2019	CIPN	**POD 14**			
	CIPN + EA	L4–6 DRGs	TRPV1 (normalized fluorescence intensity(%))	Decreased by EA vs sham EA	p<0.01
	CIPN + sham EA		TRPV1 (% of TRPV1 + Neuron(among neuron+))	Decreased by EA vs sham EA	p<0.01
			TRPV1 (Western blotting)	Decreased by EA vs sham EA	p<0.01
		Spinal cord dorsal horn (SCDH)	TLR4	Decreased by EA vs sham EA	p<0.01
			MyD88	Decreased by EA vs sham EA	p<0.01
			GFAP (staining intensity)	Decreased by EA vs sham EA	p<0.01
			GFAP (number of positive cells)	Decreased by EA vs sham EA	p<0.01
			OX42 (staining intensity)		
			OX42 (number of positive cells)		
Liang, 2015	CCI	**POD 3-14**			
	CCI+EA	Dorsal Horn I -II ipsilateral	GFAP	CCI+EA decrease 3, 7 and 14 days	p<0.05
			OX-42	CCI+EA decrease 3,7, day	p<0.01
			IL-1B /IL-6	no change,	
			OX-42	CCI+EA decrease day 3	p<0.01
		Dorsal Horn I -II contralateral	OX-42	CCI+EA decrease	p <0.01
Liang, 2016	CCI	**POD After 73 hours**			
	CCI + EA	Laminae I-II of ipsilateral Spinal cord dorsal horn (SCDH)	p-p38 MAPK	Decreased by EA	p<0.01
	CCI + sham EA		OX--42	Decreased by EA	p<0.05
				Decreased by EA	p<0.01

Liu, 2019	CCI	POD 8			
	CCI+EA	Spinal cord	TNF-a	Decreased by EA	p<0.01
			IL-1B	Decreased by EA	p<0.001
			IL-6	Decreased by EA	p<0.001
			CX3CR1	Decreased by EA	p<0.001
Manni, 2011.	12 STZ group	**POD 28**		No difference	
	12 STZ group+EA	skin	NGF skin	Decreased by EA	p<0.05
		DRG	NGF Spinal Cord	Decreased by EA	
			substance P (SP) skin	Decreased by EA	
			substance P (SP) spinal cord	Decreased by EA	
			NGF receptor TrkA skin	Decreased by EA	
			pTyr496-TrkA	Increased by EA	
			transient receptor potential vanilloid 1 (TRPV1) skin	Decreased by EA	
			spinal TrkA	Decreased by EA	
			pTyr496-TrkA in the spinal cord	Decreased by EA	
			TRPV1 in spinal cord	Increased by EA	
			GABA--GAD-67		

Nori, 2013.	DN DN+EA	**POD:28** DRG	NGF Protein. NGF mRNA production. **NGF Receptor:** TrkA mRNA TrkA protein pTyr496-TrkA mRNA-p75NTR p75NTR protein ERK1-2 Akt JNKp38 phospho-IκB-α phosphorylation of the IκB-α TRPV-1 phosphorylated p38	Decreased by EA No difference Decreased by EA No difference Decreased by EA No difference Decreased by EA No difference No difference Increased by EA Increased by EA Increased by EA Decreased by EA No difference	p<0.05
Shao, 2015	CCI EA strong manual acupuncture (smA) mild manual acupuncture (MA)	**POD ?** Spinal cord Brain (anterior cingulate cortex)	p-ERK GFAP p-ERK OX42	Decrease (smA =MA)	p< 0.01 smA=MA

Shi, 2013	Diabetes Diabetes+EA	**POD 30** Dorsal root ganglia L4-L5	. CBS (cystathionine b synthase) p65 b-actin NF-kB	. Decrease EA Decrease EA Decrease EA No difference	. P < 0.05. P < 0.05. P < 0.05.
Sun, 2004	CCI+ PES CCI+ needling	**POD 48** L5 spinal superficial laminae I-II	NMDA (NR1)	Decrease PES group	P <0.001
Tu, 2015	CCI CCI + EA	**POD 14** ipsilateral L4-6 DRGs L4-L5 lumbar spinal cords, dorsal horn	NT-3 NT-3 IL-1β GFAP OX-42	Increase EA Increase EA Decrease EA Decrease EA Decrease EA Decrease EA	p< 0.001 p < 0.001 p < 0.001 p = 0.001 p = 0.003
Tu, 2018	CCI CCI+EA	**POD 14** Spinal Cord L4-L6	BDNF TrkB	Decrease EA Decrease EA	p<0.001 p<0.001
Wang, 2014	CCI CCI + contralateral EA CCI +ipsilateral EA	**POD 14** L4-L6 Dorsal Root Ganglia ipsilateral contralateral (P2X3)	ATP ATP	Decrease EA Drecrease EA	p<0.001 p<0.001

Wang, 2016	**CCI**	**POD 14**			
	CCI + sham EA	L4-L5 spinal cord	IL-B	decrease EA	p<0.05
	CCI +EA	(dorsal horn)	GFAP	decrease EA	p<0.05
			TNF-a	EA no difference	
			IL-6	decrease EA	p<0.05
			BDNF	decrease EA	p<0.05
			NGF	decrease EA	p <0.05
			NT3	decrease EA	p <0.05
			NT4	decrease EA	p <0.05
Wang, 2018	**CCI**	**POD 21**			
	CCI+EA	Spinal Cord L4-L6	a7nAChR	Increase EA	p< 0.01,
			IL-1B	Decrease EA	p< 0.001
Xia, 2019	**CCI**	**POD 21**			
	CCI+EA	L4-L6.	HMGB1	Decrease EA	p<0.01
			TLR4	Decrease EA	p<0.001
			CD1	Suppressed EA	p<0.01
			MyD88	Suppressed EA	p<0.05
			NF-kB	Inhibited EA	p<0.05
Xu, 2016	**CCI**	**POD 14**			
	CCI+EA	L4-L5 Spinal cord ipsilateral	P2X7R	Decrease EA	p< 0.0001
			IL-1B	Decrease EA	p= 0.0026
			IL-18	Decrease EA	p= 0.0023
Xue, 2015	**CCI**	**POD ?**			
	CCI+EA	Spinal cord	BDNF	Increase CCI+EA	p<0.05
			P2X4	No significant difference	

Yong-Hui, 2014	**CCI**	**POD ?**			
	CCI +3 EA	Blood	IL1-B	Decrease 12 EA	p < 0.05
	CCI+5EA		IL-2	No significant difference	
	CCI+12EA		IL-12	No significant difference CCI	
			IL-15	No significant difference CCI	
			INF-y	12 EA reduce to normal	p < 0.05
			IL-4-Il-10	No significant upregulated	
			TGF-B	EA 12 EA upregulated	p< 0.05
			beta-endorphin	All EA upregulated	p< 0.05
		Hypothalamus	beta-endorphin	All EA upregulated	p< 0.05
Yu, 2013	CCI group	**POD 10**			
	CCI+low-frequency EA	Spinal Cord	P2X3 protein	EA decrease	LEA p=0,045
	CCI+ high-frequency EA		P2X3 receptor	EA decrease	HEA p=0.047 Lea vs Hea p<0.05 to LEA
Zhang, 2014	**NT**	**POD 7-28**			
	NT+EA	Brain (arcuate nucleus)	β-endorphin	EA increase	p <0.05
Zhang,2018	**CCI**	**POD 7**			
	CCI+EA	L4-L6 spinal cord	GFAP	CCI+EA decrease	p < 0.01
			IL-6	CCI+EA decrease	p < 0.01
			TNF-α	CCI+EA decrease	p < 0.01
			IL-1β	CCI+EA decrease	p < 0.01

Almeida, 2015	CCI	**POD 42 and 70**			
	CCI+Swimming	DRG	BDNF	Decrease by swimming at day 42;	
	CCI+Swimming+ Detraining		GDNF	Decrease by swimming+detraining at day 70	P< 0.05
			NGF	No difference	P<0.05
				Decrease by swimming at day 42; No difference by swimming+detraining	
Belmonte, 2018	CPIP	**POD 11**			
	CPIP+Exercise continous	Spinal cord	TNF-alfa	Decrease by Exercise continuous protocol and Exercise interval protocol	P<0.05
	CPIP+Exercise interval protocol		IL-1beta	No difference	P<0.05
			IL-6	Decrease by Exercise continuous protocol and Exercise interval protocol	P<0.05
			IL-10	Increase by Exercise continuous protocol and Exercise interval protocol	P<0.05
			ERK1/2	Increase by Exercise continuous protocol; decrease by Exercise interval protocol	
			AKT1/2/3	No difference	

Bobinsky, 2011	Non-Exer	**POD 15**			
	NC+Exercise-preoperative (Exer 1)	Sciatic nerve	TNF-alfa	Decrease by Exer 2 and Exer 3	P<0.05
			IL-1beta	Decrease by Exer 1, Exer 2 and Exer 3	P<0.05
			IL-6R	No difference	
	NC+Exercise-preoperative-postoperative (Exer 2)	Spinal cord	TNF-alfa	No difference	
			IL-1beta	Decrease by Exer 2 and Exer 3	P<0.01
			IL-6R	Decrease by Exer 1, Exer 2 and Exer 3	P<0.05
			IL-10	Decrease by Exer 1, Exer 2 and Exer 3	P<0.05
	NC+Exercise-postoperative (Exer 3)			No difference	
Bobinsky, 2015	NC+Sedentary	**POD 15**			
	NC+Exercise	Brainstem	5-HT	Increase by exercise	P<0.001
			5-HIAA	Increase by exercise	P<0.01
			5-HT1A	No difference	
			5-HT1B	Increase by exercise	P<0.05
			5-HT2A	Increase by exercise	P<0.05
			5-HT2C	Increase by exercise	P<0.05
			5-HT3A	No difference	
			TNF-alfa	Decrease by exercise	P<0.05
			IL-1beta	Decrease by exercise	P<0.05
			SERT	Decrease by exercise	P<0.01
		Medullary raphe	SERT	Decrease by exercise	P<0.05

Bobinsky, 2018	NC+Sedentary NC+Exercise	**POD 15** Sciatic nerve	IL-4	Increase by exercise	P<0.05
			IL-1ra	Increase by exercise	P<0.05
			IL-5	No difference	
			IL-6	No difference	
		Spinal cord	IL-4	Increase by exercise	P<0.01
			IL-1ra	Increase by exercise	P<0.01
			IL-5	Increase by exercise	P<0.05
			IL-6	No difference	
			BDNF	Decrease by exercise	P<0.01
			β-NGF	Decrease by exercise	P<0.001
			GFAP	Decrease by exercise bilateral I-II/ ipsilateral III-VI	P<0.05
			Iba-1		P<0.05
				Decrease by exercise bilateral I-II/ ipsilateral III-VI	p <0.01
Y-W. Chen, 2013	Sedentary+DN Exercise+DN	**POD 14, 28 or 56** Spinal cord	Hsp72	Increase by exercise	P<0.05
			TNF-alfa	No difference	
			IL-6	No difference	
		Peripheral nerves	Hsp72	Increase by exercise	P<0.05
			TNF-alfa	No difference	
			IL-6	No difference	

Y-W. Chen, 2015	Sedentary+DN Exercise+DN	**POD 14 and 28** Sciatic nerve	IL-10	Increase by Exercise at days 14 and 28	P<0.0051
			IL-6	Decrease by Exercise at days 14 and 28	P<0.01
			TNF-α	Decrease by Exercise at days 14 and 28	P<0.01
			MDA	Decrease by Exercise at day 14 but not 28	P<0.01
Y-W. Chen, 2012	CCI CCI+Swimming Exercise (CCISE) CCI+Treadmill Exercise (CCITE)	**POD 21** Sciatic nerve	Hsp72	Increase by CCISE	P<0.05
				Increase by CCITE	P<0.01
			TNF-alfa	Decrease by CCISE and CCITE	P<0.05
			IL-1beta	Decrease by CCISE	P<0.05
				Decrease by CCITE	P<0.01
Cobianchi, 2010.	CCI CCI+EX day3-7 CCI+Ex day3-56	**POD: 7 AND 17** Dorsal horn ipsilateral Ventral horn ipsilateral Dorsal horn contralateral Ventral horn contralateral	Cd11b IR	7 days: Decreased by exercise 17 days: Decreased by exercise	p<0.01
			GFAP IR	7 days: decreased by exercise 17 days: No difference	

Cobianchi, 2013*	NT NT+TR NT+ES	**POD 1, 3 and 8** DRG	NGF NT-3 BDNF GDNF	Decrease by ES at day 3 but not at day 1; No difference at day 8 No difference at day 1, day 3 and day 8 Decrease by ES at day 3 but not at day 1; Decrease by TR at day 8	P<0.01 P<0.05 P<0.01
		Spinal cord	NGF NT-3 BDNF GDNF	No difference at day 1 and day 3; Decrease by TR (compared to NT and ES) at day 8 No difference Increase by ES at day 1 but not at day 3; No difference at day 8 No difference at day 1 and day 3 Increase by ES at day 8 Decrease by TR (compared to NT+ES) at day 8 Decrease by ES+TR (compared to ES) at day 8 No difference Increase by ES+TR (compared to NT and TR) at day 8 Increase by ES+TR (compared to ES) at day 8	P<0.05 P<0.01 P<0.01 P<0.05 P<0.001 P<0.01

Coradini, 2015	CCI CCI+Swim CCI (Obese) CCI+Swim (Obese)	**POD ?** Right median nerve	GAP43 BDNF	Increased by CCI + swim vs CCI No difference between CCI + swim (obese) and CCI (obese) No difference between CCI + swim and CCI No difference between CCI + swim (obese) and CCI (obese)	p<0.05
Gong, 2017	CCI CCI+exercise	**POD 31 (Postnatal day 41)** Spinal dorsal horn	IL-1B TNF-a CD86 CD68 INOS IL-4 IL-10 CD2016 Arg Yml CD206 + Microglia proportion	Decreased by exercise Decreased by exercise No difference Decreased by exercise Decreased by exercise Increased by exercise Increased by exercise Increased by exercise Increased by exercise Increased by exercise Increased by exercise Increased by exercise	p<0,05 p<0,05 p>0,05 p<0,05 p<0,05 p<0,05 p<0,05 p<0,05 p<0,05 p<0,05 p<0,05 p<0,05
		Ipsilateral spinal cord.	IL-10 (western blot) TNF-a (western blot)	Decreased by exercise	p<0,05

Huang, 2017	CCI CCI + TU0 CCI + TU CCI + TE CCI + TU0 + TE CCI + TU + TE	**PODs 14 and 28** Sciatic nerve	TNF-a IL-6 IL-10	PODs 14 and 28: Decreased by TU, TE, TU0+TE, TU+TE POD14: Decreased by TU, TE, TU0+TE, TU+TE POD28: Decreased by TE, TU0+TE, TU+TE POD14: Increased by TU, TE, TU0+TE, TU+TE POD28: No difference	p<0.05 p<0.05 p<0.05 p<0.05 P>0.36
Hung, 2014	CCI CCI+TT CCI+TU CCI+TT+TU	**POD 14 or 28** Spinal cord	IL-6 IL-10 Iba-1	Decrease by TT,TU and TT+TU at day 14 and 28 No difference at day 14; Increase by TT, TU and TT+TU at day 28 Decrease by TT,TU and TT+TU; Decrease by TT+TU (compared to CCI+TT and CCI+TU)	p<0.008 p<0.01 p<0.01

Hung, 2016	CCI CCI+TU CCI+TT CCI+TT+TU	**PODs 14 and 28** Spinal cords (L4 –L5)	IL-6 IL-10 Iba1 IR	PODs 14 and 28: Decreased by TT, TU, TT+TU POD28: Greater decrease with TT+TU compared to TT and TU POD14: No difference POD28: Increased by TT, TU and TT+TU POD28: Greater increase with TT+TU compared to TT and TU PODs 14 and 28: Decreased by TT, TU and TT+TU POD28: Greater decrease with TT+TU compared to TT and TU	p<0.008 p<0.05 p>0.58 p<0.01 p<0.05 p<0.01 p<0.01
Kami, 2016a	CCI-sedentary CCI + running	**POD 7** Lumbar spinal cord (L4-5), superficial dorsal horns	GABA GAD65/67	Increased by running Increased by running	p<0.01 p<0.01
Kami, 2016b	CC_PI-sedentary CCI_P+ running	**POD 7** Lumbar spinal cord (L4-5), superficial dorsal horns	HDAC1+ nuclei HDAC1+/GFAP+ astrocytes HDAC1+/CD11b+ microglia CD11b+ H3K9ace+/CD11b+ microglia CD11b+	Decreased by running No difference Decreased by running No difference Increased by running No difference	p<0.01 p<0.01 p<0.01

Korb 2010	NT+trained NT sedentary	**POD 35-36** SC, lumbosacral ventral horn SC, lumbosacral, dorsal horn, superficial laminae Magnus raphe nucleus Dorsal raphe nucleus Soleus muscles	Serotonin (5-HT) immunoreactivity (lumbosacral ventral horn) Serotonin inmunoreactivity (superficial laminae of lumbosacral SC) Serotonin inmunoreactivity (magnus raphe nucleus) Serotonin inmunoreactivity (dorsal raphe nucleus) Citrate synthase enzyme activity (soleus muscle)	Increased by training No difference No difference No difference Increases by training	p<0.05 p<0.05

López-Álvarez, 2015.	CCI+ITR1 CCI+ITR2 CCI	**POD 8 and 15** paw skin L3-L5 dorsal root ganglia	NGF ski Western blot of NGF NGF in DRG GAP43 in DRG pNKCC1 NKCC1 pKCC2 KCC2 BDNF L3 BDNF L5 Iba1 l3 Iba1 l5	8 days: Decreased by ITR1 15 days: Decreased by ITR1/ITR2 8 days: Decreased by ITR1 8 days: Decreased by ITR1 8 days: Decreased by ITR1 8 days: Decreased by ITR1 15 days: Decreased by ITR1 8 days: Decreased by ITR1 8 days: Decreased by ITR1 15 days: Decreased by ITR1 15 days: Increased by ITR1 8 days: Decreased by ITR1 15 days: Decreased by ITR1 8 days: Decreased by ITR1 15 days: Decreased by ITR1/ITR2 8 days: Decrease by ITR1 15 days: Decreased by ITR1 8 days: Decreased by ITR1 15 days Decreased by iTR1 15 days Decreased by ITR2	p<0,05 p<0,05 p<0,05 p<0,05 p<0,01 p<0,01 p<0,001 p<0,05 p<0,01 p<0,05 p<0,05 p<0,05 p<0,01 p<0,05 p<0,0001 p<0,05 p<0,05 p<0,01 p<0,05 p<0,01

López-Álvarez, 2018.	SNTR-iTR SNTR-sedentary	**POD 14** Spinal Cord DH lamiae I-II. Brain. (periaqueductal grey matter (PAG) the locus coeruleus (LC) the dorsal raphe (DRN) the raphe magnus nucleus (RM)	. α1A immunoreactivity α2A β2 receptor 5HT2A	. . ipsilateral horn: Increased by ITR LC and DRN: Increased by ITR No difference lamina II: increased by ITR the contralateral lamina I: Increased by ITR LC: Increased by ITR lamina II: Increased by ITR Ipsilateral lamina I: Increased by ITR PAG and DRN: Increased by ITR	. . p<0,001 p<0,05 p<0,001 p<001 p<0,01 p<0,01 p<0,05 p<0,01
Ma, 2018.	DN DN+EX	**POD 35** DRG	IL-1b IL-6 TNF-a IL1R IL6R TNFR1	Decreased by exercise Decreased by exercise Decreased by exercise Decreased by exercise Decreased by exercise Decreased by exercise	p<0,05

Martins, 2017.	NC NC+ eccentric exercise 6 m/min NC + eccentric exercise 10 m/min NC + eccentric exercise 14 m/min	**POD 63** sciatic nerve tissues triceps surae	IL-1β TNF-α IL-4 IL-1Ra IGF-1	No difference Muscle: Decreased by Exercise Nerve: No difference No difference No difference Nerve: Increased by exercise Muscle: no difference	 p<0.03 p<0.01
Sumizono, 2018	CCI CCI + high-frequency exercise CCI + low-frequency exercise	**POD 21 and 35** Dorsal HORN laminae I-III midbrain PAG	BDNF MOR GFAP Iba1 B-endorphin met-enkephalin	Decrease HFE 5w Decrease all exercise 5 w Decrease all exercise 5 w Decrease all exercise 5 w Increase all exercise 3w 5 w Increase all exercise 3w 5 w	p < 0.05 p < 0.05 p < 0.05 p < 0.05 p < 0.05 p < 0.05

Tian, 2018	NT NT+swimming	**PODs 21, 42 and 49** SC L4–L6	NGF (protein levels, ipsilateral SC)	Day42: Decreased by swimming Day49: Decrease by swimming Day21: No difference	p<0.01 p<0.05
			BDNF (protein levels, ipsilateral SC)	Days 42 and 49: Decreased by swimming Day21: No difference Day21: Decreased by swimming Days 42 and 49: No difference	p<0.01 p<0.05 p>0.05
		DRG L4–L5	NGF (protein expression, ipsilateral DRG)	Day21: Decreased by swimming Days 42 and 49: No difference	p<0.01 p>0.05
		Tibial nerve (neuroma)	BDNF (protein expression, ipsilateral DRG)	Day21: Decreased by swimming Days 42 and 49: No difference	p<0.05 p>0.05
			NGF (protein expression, ipsilateral neuroma)	Day21: Decreased by swimming Days 42 and 49: No difference	p<0.01 p>0.05
			BDNF (protein expression, ipsilateral neuroma)		
Thakur, 2016	1diabetes 2diabetic+exercise	POD 42 Spinal cord dorsal horn	IL-1B macrophage(CD11b,CD6) CGRP	Decrease exercise Decrease exercise Preservation exercise	p<0.05 p<0.001

Tsai, 2017	CCI CCI + 0%-incline treadmill CCI + 8%-incline treadmill	POD 26 sciatic nerve	IL-10 IL-6 TNF-a	Increase 8% treadmill Decrease 8% treadmill Decrease 8% treadmill	p <0.05 p< 0.01 p<0.05
Wang, 2016	NC NC+Ex NC+EX+EA	**POD 31** Tibia	. Substance P	Decrease by exercise and exercise+EA Decrease exercise+EA vs exercise	p<0.05 p<0.05
Martins, 2011	NC NC+Anesthesia NC+AJM	**POD 35** Spinal cord	GFAP CD11b/c	Decrease by AJM Decrease by AJM (compared to Anesthesia) Decrease by AJM Decrease by AJM (compared to Anesthesia)	p<0.01 p<0.05 p<0.01 p<0.05
Song, 2016	CCI de-CCI de-CCI+ASMT	**POD 28** Dorsal Root Ganglia neurons L4-L5 Blood Spinal cord L3-L6	c-FOS IL-10 DRG IL-1B,IL-10, Tonfa IL-1B (DRG and SC) TNF-a (DRG and SC) IL-10 (SC)	Decrease de-CCD+SMT Suppressed de-CCD+SMT SMT same SMT reduce SMT same SMT increase	p< 0.01 p< 0.01 P <0.05 p< 0.01
da Silva, 2015	CCI CCI+NM	**POD 24** Sciatic nerve	NGF MPZ	Increase by NM Increase by NM	p<0.01 p<0.01

Giardini, 2017	CCI	**POD ?**			
	CCI+NM	Thalamus	GFAP	No difference	P>0,05
			OX-42	No difference	P>0,05
			BDNF	No difference	P>0,05
		Midbrain	GFAP	No difference	P>0,05
			OX-42	No difference	P>0,05
			BDNF	No difference	P>0,05
		VPL and PAG	GFAP		
			OX42		
			BDNF		
Santos, 2012	CCI	**POD 24**			
	CCI+ NM	Dorsal root ganglia	NGF	Decrease NM	P <0.05
			GFAP		
		Spinal cord	NGF		
			GFAP		
Santos, 2018	CCI	**POD 24**			
	CCI+ NM	Dorsal root ganglia L4-L6	substance P	Decrease NM	p < 0.001
			expression of TRPV1	Decrease NM	p < 0.001
			protein expression MOR	Decrease NM	p < 0.001
			protein expression DOR	Not observe immunoreactivity of	
			protein expression KOR	These receptors not observe	
			b-actin	Immunoreactivity of these receptors	
				No differences were observed	

Zhu, 2017	diabetes	**POD 31**	.		
	diabetes+neural mobilization	Sciatic nerve left (no treatment)	IL-1B	No significant different	
			TNF-a		
			IL-1B	MN decrease vs contralateral side	P = .023
		Sciatic nerve right (treatment)	TNF-a	MN decrease vs contralateral side	P = .004
			IL-1B		
			TNF-a		
		Dorsal root ganglion			
Chen, 2015	CC I	**POD 28**	TNF-a		
	CCI+ TU-0	sciatic nerve	IL-6	TU-1 decrease	p < 0.01
	CCI + TU-0.25		NK-1R	TU-1 decrease	p < 0.05
	CCI+TU-0.5		substance P	All TU decrease	p < 0.05
	CCI+TU-1			All TU decrease	p < 0.05
Cidral, 2013	NC	**POD 13**			
	NC+LEDT	Spinal cord	TNF-alfa	Decrease by LEDT	p<0.05
			IL-1beta	No difference	
			IL-10	No difference	
		Sciatic nerve	TNF-alfa	Decrease by LEDT	p<0.05
			IL-1beta	No difference	
			IL-10	No difference	

Cioato, 2016	CCI CCI+sham tDCS CCI+tDCS	**POD 24 and 29** Cortex Spinal cord Brainstem	 TNF-alfa IL-1beta IL-10 TNF-alfa IL-1beta IL-10 TNF-alfa IL-1beta IL-10	 Increase by tDCS at day 29 but not at 24 No difference No difference Increase by tDCS at day 29 day but not at 24 Decrease by tDCS at days 24 and 29 Decrease by tDCS at day 29 but not at24 No difference No difference No difference	 P<0.05 P<0.05 P<0.05 P<0.05
Filho, 2016	CCI CCI+Sham tDCS CCI+tDCS	**POD 24 or 29** Serum Spinal cord Cortex Brainstem	 BDNF BDNF BDNF BDNF	 Decrease by tDCS at day 29 but not at 24 Increase by tDCS at day 29 but not at 24 Decrease by tDCS at day 24 but not at 29 Decrease by tDCS at days 24 and 29	 P<0.05 P<0.05 P<0.05 P<0.05
Giuliani, 2004	CCI CCI + laser	**POD?** Laminae I and II of the dorsal horn of spinal cord (L3-L5)	Enkephalin mRNA	No difference	

Hsieh, 2012	CCI+laser CCI+sham	**POD 14** Sciatic nerve	H&E study (nuclei percentage) ED1 immunoreactivity TNF-a IL-1B Cytokine HIF-1a-positive cells (inmunoreactivity) HIF-1a (protein levels, immunoblotting) VEGF positive cells (inmunoreactivity) NGF positive cells (inmunoreactivity) S100 positive cells (inmunoreactivity) VEGF (protein levels, immunoblotting) NGF (protein levels, immunoblotting)	Decreased by laser Decreased by laser Decreased by laser Decreased by laser Decreased by laser Decreased by laser Decreased by laser Increased by laser Increased by laser Increased by laser Increased by laser Increased by laser Increased by laser	p<0.05 p<0.05 p<0.05 p<0.05 p< 0.0001 p=0.006 p=0.006 p=0.009 p=0.002 p=0.005 p=0.009 p=0.002
Hsieh, 2017	Oxaliplatin+TUS Oxaliplatin+sham TUS	**POD 24** L2–L6 DRG. Superficial laminae (dorsal horn) in lumbar spinal cord (at	TRPM8 TRPV1 SP-like immunoreactivity	Decreased by TUS No difference Decreased by TUS	p<0.05 p>0.05 P<0.05

		segments L2–L6)			
Lin, 2015	CCI CCI+ HFS	**POD 7** affected sciatic nerve	TNF-a	No difference	
Liu, 2017	CCI + sham PEMF CCI + PEMF	**POD 14** Sciatic nerve Dorsal root ganglion Spinal cord	HCN1 mRNA HCN2 mRNA	No difference No difference	
Matsuo, 2014.	CCI CCI+TENS 1 w CCI+TENS 2 w	**POD 8** spinal cord dorsal horn	Iba1 immunoreactivity BrdU-positive/Iba1-positive GFAP immunoreactivity p-p38 in microglia PKC-y p-CREB MAP kinases (p-p38, p-ERK1/2, p-JNK) proinflammatory cytokines (IL-1, TNF-, IL-6) opioid receptors (μOR and OR)	decreased by TENS decreased by TENS decreased by TENS decreased by TENS decreased by TENS decreased by TENS decreased by TENS decreased by TENS increased by TENS	p<0,05
Mert, 2015 (a).	sham PMF (SPMF) PMF-AD PMF-AW	**POD 28-35** sciatic nerve tissues	IL-1 beta IL-6 IL-10	Decreased by PMF Decreased by PMF increased by PMF PMF-AD > PMF-AW	p<0.05
Mert, 2015 (b).	STZ-induced diabetic L-PMF-treated diabetic H-PMF-treated diabetic	**POD: 35** Spinal cord sciatic nerve tissues	TNF-alpha IL-1 beta IL-6 IL-10	 Spinal cord: decreased L-PMF decreased by H-PMF Sciatic nerve: decreased by L-PMF No difference by H-PMF Spinal cord: decreased by L-PMF increased by H-PMF Sciatic nerve: decreased by L-PMF decreased by H-PMF Spinal cord: decreased by L-PMF No difference by H-PMF Sciatic nerve: No difference by L-PMF Increased by H-PMF Spinal cord: increased by L-PMF No difference by H-PMF Sciatic never: No difference by L-PMF decreased by H-PMF	p<0.05
Mert, 2017	CCI+PMF CCI+SPMF	**POD: 35** sciatic nerve tissues	IL-1b IL-6 IL-10	Decreased by PMF Decreased by PMF Increase by PMF	p<0.05 p<0.05 p<0.05

da Silva Oliveira, 2018	DN+Sham DN+PBM	**POD 35** Sciatic nerve	NGF	Increase by PBM	p=0.0133
Somers, 2003	CCI CCI+TENS	**POD 12** Spinal cord	Aspartate Glutamate Glycine GABBA	Decrease by TENS Decrease by TENS Decrease by TENS No difference	p<0.05 p<0.05 p<0.05
Somers, 2009	CCI CCI+ high frequency TENS contralateral CCI + low-frequency TENS CCI +randomly TENS	**POD ?** Dorsal Horn	Aspartate Glutamate Glycine GABA	Increase randomly TENS Increase randomly TENS Increase randomly TENS Increase high frequency TENS	p < .001 p <.001 p< .001 p< .014
Su, 2018	NC NC + High-frequency immediately(HFI) NC + High-frequency 7 days after(HFL) NC + Low-frequency immediately (LFI) NC + Low-frequency 7 days after (HFL)	POD:4 weeks after treatments The distal end of the nerve Dorsal root ganglion Somatosensory cortex and hippocampus	S-100 Neurofilament (NF) TNF-a Synaptophysin TNF-a Synaptophysin	Increased by HFI and HFL vs NC and LFI Increased by HFI and HFL vs NC and LFI Increased by HFI vs NC and HFL Increased by HFI vs NC and HFL Increased by HFI vs NC and HFL Increased by HFI vs NC and HFL	p<0.01 p<0.01 p<0.01 p<0.01 p<0.01 p<0.01
Yang, 2018	CCI+sham-rTMS group CCI+ 1 Hz group CCI+ 20 Hz group	POD 13 L4-L6 Dorsal Root Ganglia ipsilateral Dorsal horn I-IV	nNOs/B-actin GFAP	CCI+ 20HZ Decrease 20HZ CCI+20 Hz decrease	P<0.01 p <0.05
Yueh-Ling, 2012	CCI and treated with laser CCI and treated with sham irradiation	POD sciatic nerve	IL-1B TNF-a HIF-1a VEGF NFG	Decrese after laser Decrease after laser Decreased after laser Increase in laser Increase in laser	P < 0.0001 P < 0.0001 P =0.006 P = 0.009 P = 0.002

NC nerve crush; CCI chronic constriction injury ; NT nerve transection; CPIP chronic post-ischemia pain; STZ streptozocin DN diabetic neuropathy; SNTR sciatic nerve transection and repair; POD post operative day; ? not reported;ES electrical stimulation; PES percutaneus electrical stimulation ; HFE high frecuency exercise; PMF pulse magnetic field; SPMF sham pulse magnetic field; EX exercise; EA electro-acupuncture; AJM ankle joint mobilization; SMT spinal manipulative therapy; HFI High-frequency immediately; HFL Low-frecuency immediately; tDCS trasncraneal direct current stimulation DRG dorsal root ganglia; PAG periaqueductal grey; SC spinal cord; SCDH spinal cord dorsal horn; WB western blot; PCR polymerase chain reaction; IL interleukin TNF tumor necrosis factor, TGF transformin growth factor MyD-88 myeloid differentiation primary response 88, NGF nerve growth factor, NT-3 neurotrophin 3, BDNF brain derived neurotrophic factor, GDNF glial cell derived neurotrophic factor, GAP-43 growth asociated protein 43
VEGF vascular endothelial growth factor, GFAP glial fribillary acidic protein, MDA, mor M-opioid receptor, ,dor D-opioid receptor, kor k-opioid receptor,
TRPV1 transient receptor potential cation channel subfamily V member 1, NMDA N-nitrosodimethylamine, TRPV8 transient receptor potential cation channel subfamily V member 8, ATP adenosine triphosphate, OX-42, IFN-γ interferon gamma, NF-kb nuclear factor-kb, CX3CR1 chemoline receptor 1, cd11b, CD68, cluster of differentiation 68 , CD86 cluster of differentiation 86

Tables

Click here to access/download;Tables;Table 3.docx

Table 3a. Variation in the concentration of biomarkers after Exercise depending on the measurement site. Biomarker frequency is colour coded with red representing not measured, yellow low concentration, green high concentration.

	Increase				Decrease				No difference			
	Nerve	DRG	Dorsal Horn	Brain	Nerve	DRG	Dorsal Horn	Brain	Nerve	DRG	Dorsal Horn	Brain
Immune system												
Immune competent cells												
Cytokines/chemokines												
Other inflamatory markers												
Neurotrohins												
NGF/NT-3												
BDNF												
GDNF												
GAP-43												
VEGF												
Neurotransmitters												
Excitador												
Inhibitor												
Opioid pathways												
Receptors												
Peptides*												
Receptors												
Ionic (TRPV1 /NMDA)												
Cationic												
ATP												
Heat shck protein												

NGF nerve growth factor; NT-3 neurotrophin 3; BDNF brain derived neurotrophic factor; GDNF glial cell derived neurotrophic factor; GAP-43 growth asociated protein 43;VEGF vascular endothelial growth factor TRPV1 transient receptor potential cation channel subfamily V member 1, NMDA N-nitrosodimethylamine, TRPV8 transient receptor potential cation channel subfamily V member 8; ATP adenosine triphosphate

Table 3b. Variation in the concentration of biomarkers after Neural Mobilization depending on the measurement site. Biomarker frequency is colour coded with red representing not measured, yellow low concentration green high concentration

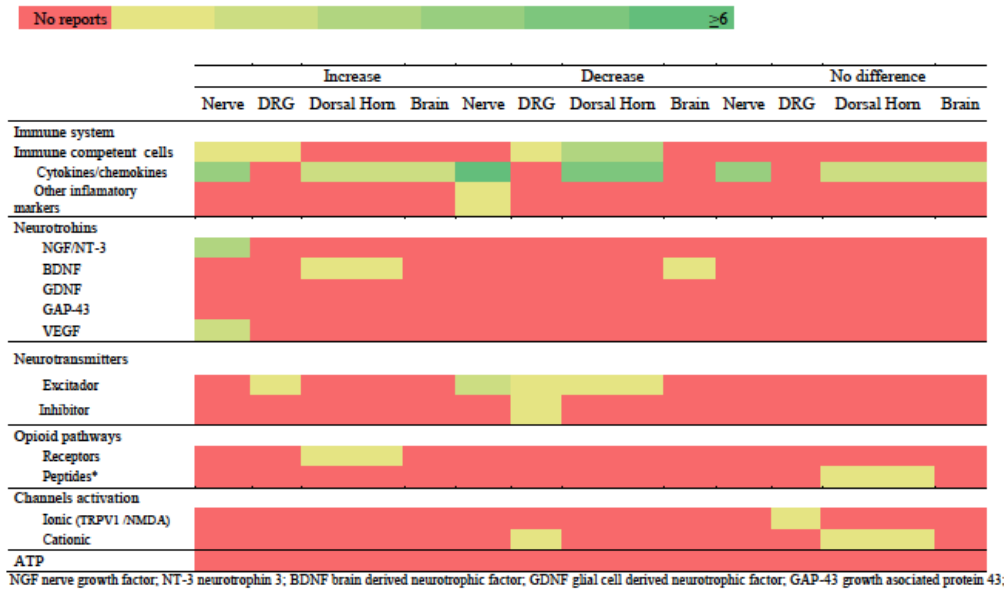
	Increase				Decrease				No difference			
	Nerve	DRG	Dorsal Horn	Brain	Nerve	DRG	Dorsal Horn	Brain	Nerve	DRG	Dorsal Horn	Brain
Immune system												
Immune competent cells												
Cytokines/chemokines												
Other inflamatory markers												
Neurotrohins												
NGF/NT-3												
BDNF												
GDNF												
GAP-43												
VEGF												
Neurotransmitters												
Excitador												
Inhibitor												
Opioid pathways												
Receptors												
Peptides*												
Receptors												
Ionic (TRPV1 /NMDA)												
Cationic												
ATP												
Actins (b-actin)												

NGF nerve growth factor; NT-3 neurotrophin 3; BDNF brain derived neurotrophic factor; GDNF glial cell derived neurotrophic factor; GAP-43 growth asociated protein 43;VEGF vascular endothelial growth factor TRPV1 transient receptor potential cation channel subfamily V member 1, NMDA N-nitrosodimethylamine, TRPV8 transient receptor potential cation channel subfamily V member 8

Table 3c. Variation in the concentration of biomarkers after Joint Mobilization depending on the measurement site. Biomarker frequency is colour coded with red representing not measured, yellow low concentration green high concentration

NGF nerve growth factor; NT-3 neurotrophin 3; BDNF brain derived neurotrophic factor; GDNF glial cell derived neurotrophic factor; GAP-43 growth asociated protein 43;VEGF vascular endothelial growth factor TRPV1 transient receptor potential cation channel subfamily V member 1, NMDA N-nitrosodimethylamine, TRPV8 transient receptor potential cation channel subfamily V member 8

Table 3d. Variation in the concentration of biomarkers after Physical Agents depending on the measurement site. Biomarker frequency is colour coded with red representing not measured, yellow low concentration green high concentration



NGF nerve growth factor; NT-3 neurotrophin 3; BDNF brain derived neurotrophic factor; GDNF glial cell derived neurotrophic factor; GAP-43 growth asociated protein 43;VEGF vascular endothelial growth factor TRPV1 transient receptor potential cation channel subfamily V member 1, NMDA N-nitrosodimethylamine, TRPV8 transient receptor potential cation channel subfamily V member 8

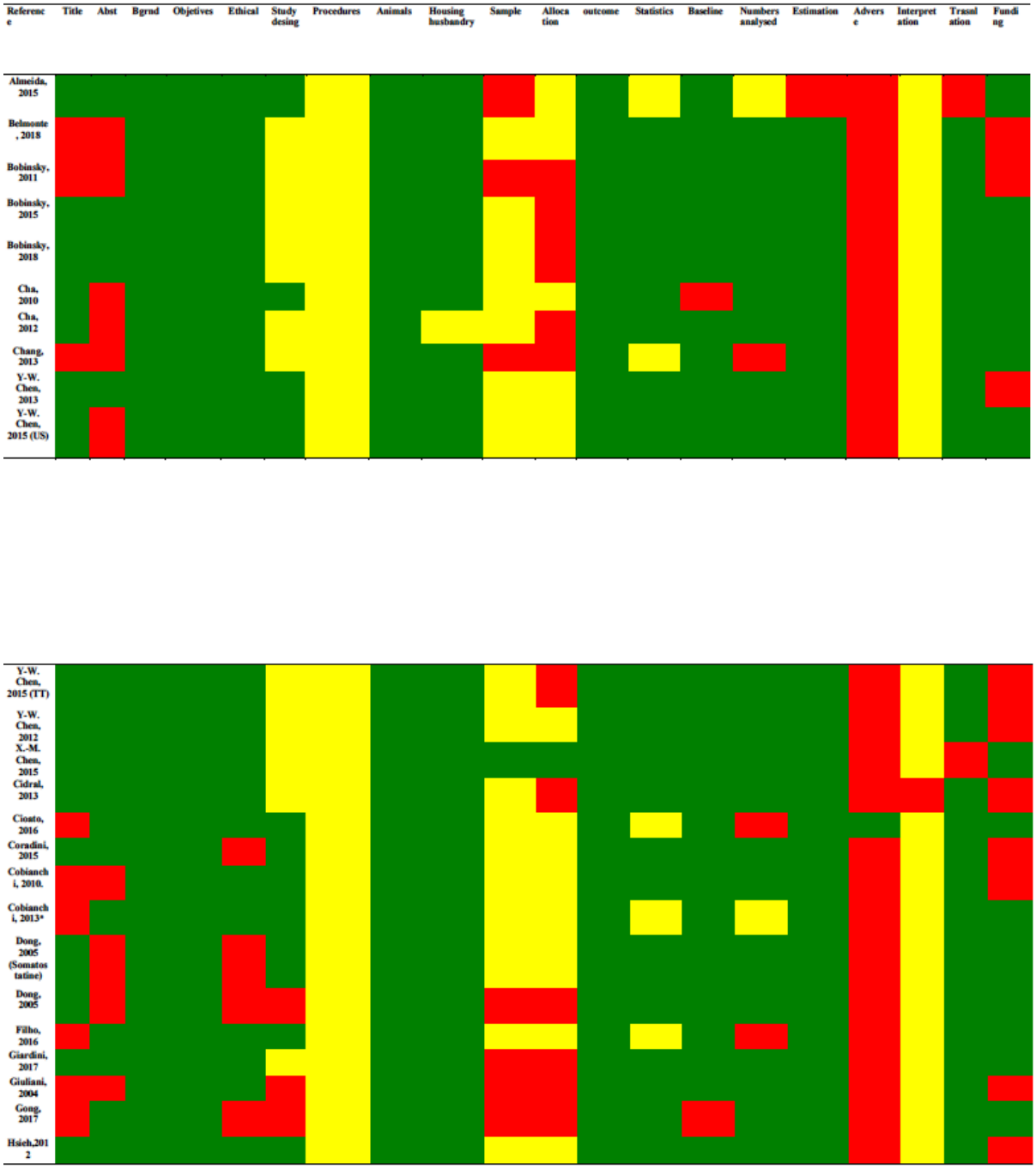
Table 3e. Variation in the concentration of biomarkers after Electro-acupucture depending on the measurement site. Biomarker frequency is colour coded with red representing not measured, yellow low concentration - green high concentration.

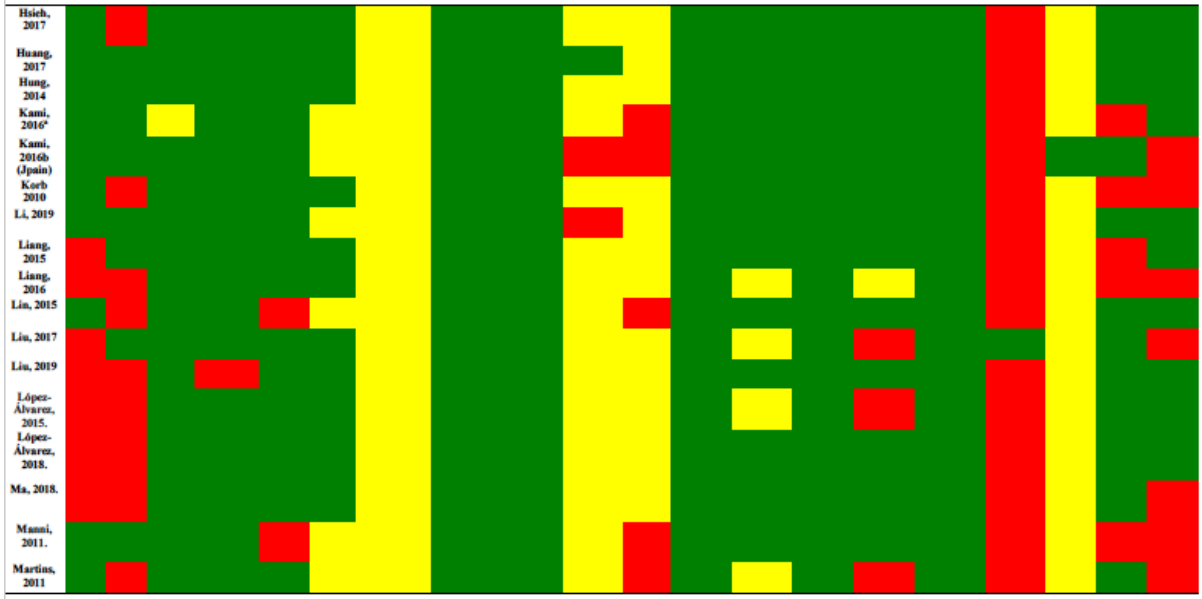
NGF nerve growth factor; NT-3 neurotrophin 3; BDNF brain derived neurotrophic factor; GDNF glial cell derived neurotrophic factor; GAP-43 growth asociated protein 43;VEGF vascular endothelial growth factor

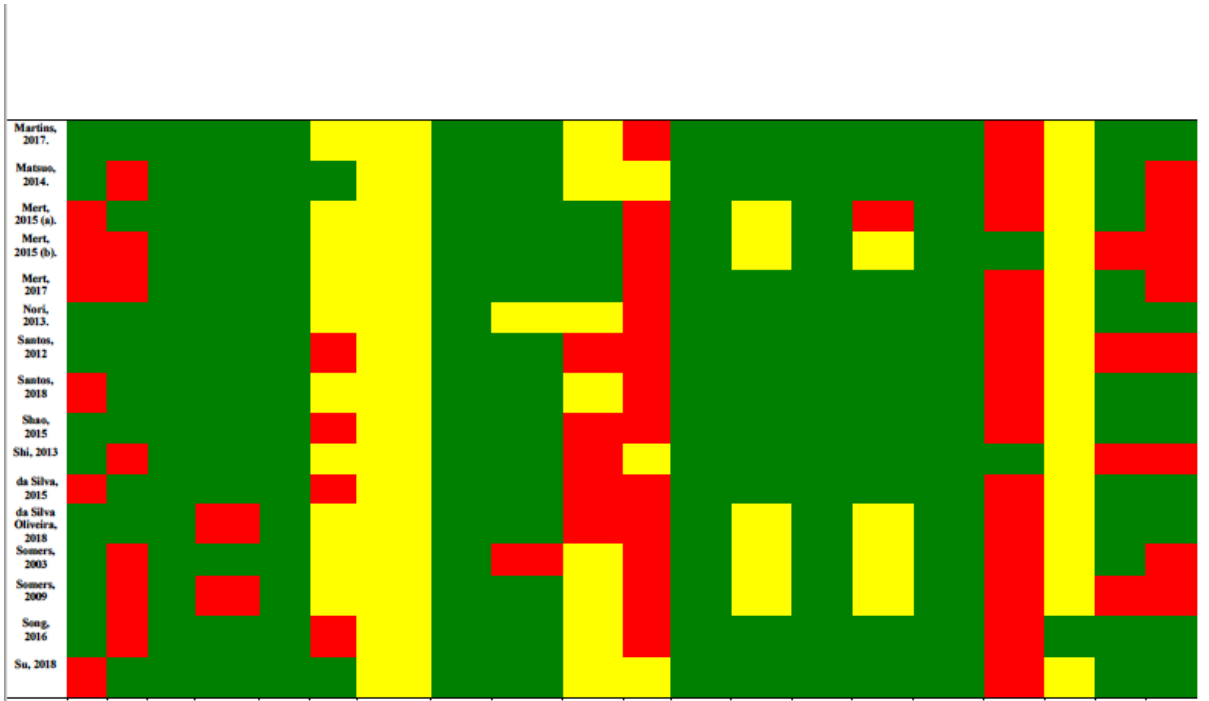
Table 3f. Variation in the concentration of biomarkers after Acupucture depending on the measurement site. Biomarker frequency is colour coded with red representing not measured, yellow low concentration - green high concentration.

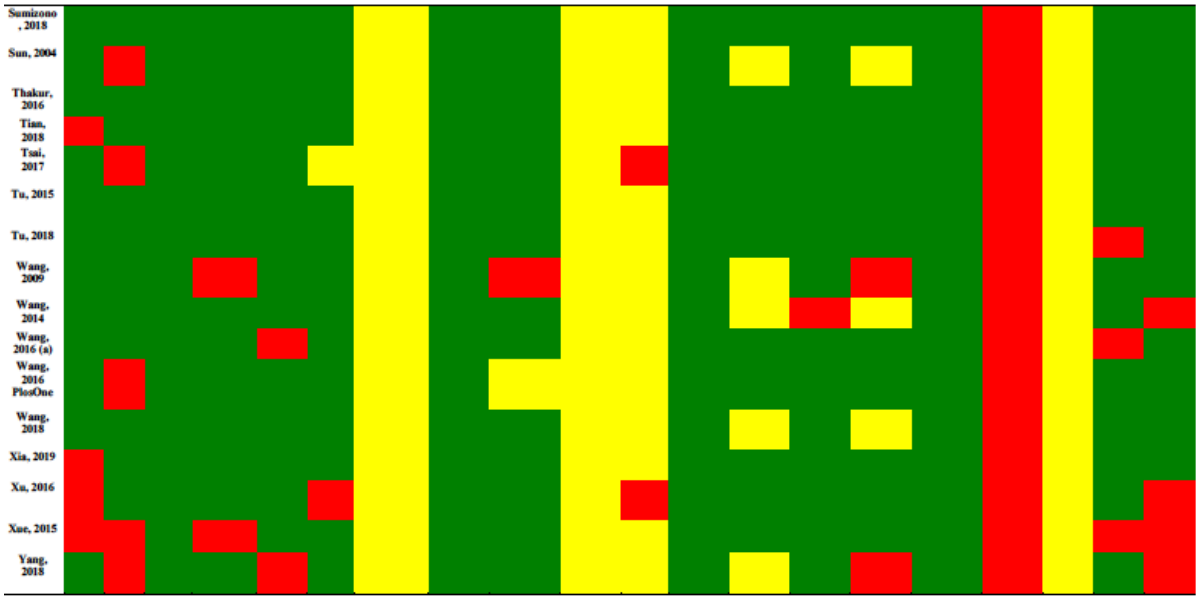
NGF nerve growth factor; NT-3 neurotrophin 3; BDNF brain derived neurotrophic factor; GDNF glial cell derived neurotrophic factor; GAP-43 growth asociated protein 43;VEGF vascular endothelial growth factor

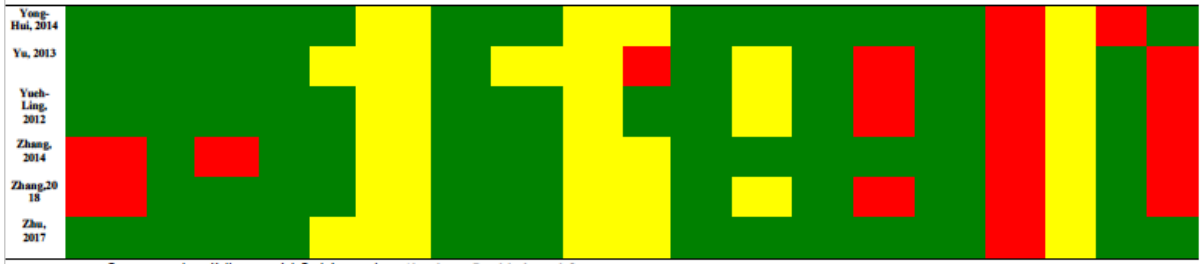
Supplementary 1. ARRIVE reporting quality.




Hsieh, 2017
Huang, 2017
Hung, 2014
Kami, 2016a
Kami, 2016b (Jpain)
Korb 2010
Li, 2019
Liang, 2015
Liang, 2016
Liu, 2015
Liu, 2017
Liu, 2019
López-Álvarez, 2015.
López-Álvarez, 2018.
Ma, 2018.
Manni, 2011.
Martins, 2011


Martins, 2017.
Matsuo, 2014.
Mert, 2015 (a).
Mert, 2015 (b).
Mert, 2017
Nori, 2013.
Santos, 2012
Santos, 2018
Shao, 2015
Shi, 2013
da Silva, 2015
da Silva Oliveira, 2018
Somers, 2003
Somers, 2009
Song, 2016
Su, 2018





Green: complete; Yellow: partial; Red: Incomplete; Abst: abstract; Bgrnd: background; Outc: outcomes

Supplementary 2. Characteristics of the included studies (I)

	Animals	NeuP Model	Groups	Intervention
Chang, 2013	Sprague-Dawley rats, male, 200-250g	Nerve crush injury; NC-sciatic nerve NeuP not confirmed by behavioural test	NC NC + acupuncture	**Acupuncture:** POD 24. 30 min with a slow rotation every 5 mi. GB30 Once a day for 5 days
Wang, 2009	Sprague-Dawley, male, adult, 220 ± 10g	Chronic constriction injury; CCI-L5 NeuP confirmed by behavioural test	CCI CCI+ acupuncture	**Acupuncture:** POD 1 lumbago pain, hip pain" point. Daily for 30 min 14 days
Cha, 2010	Sprague-Dawley rats, male, young adult, 200-250g	Nerve transection; NT-Sural and tibial nerves NeuP confirmed by behavioural test	NT NT+EA	**Electroacupuncture:** POD 14. 1 Hz, 0.1 ms pulse, 0.6 mA, 10 min, acupuncture points ST36 (Choksamni) and SP9 (Eumleungcheon). ?weeks ?sessions
Cha, 2012	Sprague-Dawley rats, male, adult, 220-250g	Nerve transection; NT-sural and tibial nerves NeuP confirmed by behavioural test	NT NT+EA	**Electroacupuncture:** POD 14. 1 Hz, 0.1 ms pulse 0.6 mA, 10 min, acupuncture points ST36 (Choksamni) and SP9 (Eumleungcheon). ?weeks ?sessions
X.-M. Chen, 2015	Sprague-Dawley rats, male, adult, 200-250g	Chronic constriction injury; CCI-Sciatic nerve NeuP confirmed by behavioural test	CCI CCI+EA	**Electroacupuncture**: POD 1, 2 Hz, 2 mA, 30 min, acupuncture points GB 30 (Huantiao) 2 weeks, ?sessions
Dong, 2005 (a)	Sprague-Dawley rats, male, adult, 200-220g	Chronic constriction injury CCI-Sciatic nerve NeuP not confirmed by behavioural test	CCI CCI+EA	**Electroacupuncture**: POD 7, ≤1 mA, 60 Hz for 1.05 s and 2Hz for 2.85 s alternately, 30 min, acupoints GB-30 and GB-34 Daily to the end of experiment
Dong, 2005 (b)	Sprague-Dawley rats, male, adult, 200-220g	Chronic constriction injury CCI-Sciatic nerve NeuP confirmed by behavioural test	CCI CCI+EA	**Electroacupuncture**: POD 7, ≤1 mA, 60 Hz for 1.05 s and 2Hz for 2.85 s alternately, 30 min, acupoints GB-30 and GB-34 Daily to the end of experiment
Li, 2019	Sprague–Dawley rats, male, 5–8 weeks, 180–220 g	Model of paclitaxel-induced peripheral neuropathic pain CIPN Antineoplastic neuropathy NeuP confirmed by behavioural test	CIPN CIPN + EA CIPN + sham EA	**Electroacupuncture**: 2 Hz, square wave 0.2 ms pulse from 0.5 to 1.5mA (increased by 0.5 mA every 10 min, for a total of 30 min). Needles of 0.25mm, inserted 5 mm in bilateral ST36 and BL60.Once daily for 7 consecutive days.
Liang, 2015	Sprague-Dawley, male, 220–260	Chronic constriction injury; CCI-L5 NeuP confirmed by behavioural test	CCI CCI+EA	**Electroacupuncture:** POD 1 . square wave current output (pulse width: 0.6 ms at 2 Hz, 0.2 ms at 100 Hz); intensities from 1 to 2 mA (15 min each, total 30 min); 2 and 100 Hz alternating frequencies y shifting between 2 and 100 Hz stimulation for 3 s each). ST36 bilaterally. BL60 bilaterally 11 days daily session.
Liang, 2016	Sprague–Dawley rats, male, 220–240 g	Chronic constriction injury; CCI L4-L6 spinal nerves NeuP confirmed by behavioural test	CCI CCI + EA CCI + sham EA	**Electroacupuncture**: POD 1. square wave: 0.2 ms pulse intensities from 1to 2 mA (15 min each, totalling 30 min) at alternating (automatically shifting every 3 s) frequencies of 2and 100 Hz. Bilateral ST36 and BL60The stimulation was given at 24, 48 and72 h once per day.
Liu, 2019	Sprague-Dawley rats, male, 180-220g	Chronic constriction injury; CCI-sciatic nerve NeuP confirmed by behavioural test	CCI CCI+EA	**Electroacupuncture:** POD 1„" . 2 Hz/100Hz pulses for 30 minutes. The intensity ≤ 1 mA. "Weizhong Acupoint" and "Huantiao Acupoint 3 days 1 w

Manni, 2011.	Sprague–Dawley rats, female, 200–220 g	Diabetes Neuropathy NeuP confirmed by behavioural test	12 STZ group 12 STZ group +EA	**Electroacupuncture** POD 7 square wave with duration 0.18 ms, a burst length 0.1 s, and internal burst frequency of 80 Hz. The intensity (1.0–1.5 mA burst frequency of 2 Hz30 min bilaterally at the traditional acupoint Zusanl twice a week for 3 weeks.
Nori, 2013.	Sprague-Dawley rats, Female, 200-220 gr	Diabetes Neuropathy NeuP not confirmed by behavioural test	DN DN+EA	**Electroacupuncture:** POD 7 30 minutes low burst frequency of 2Hz; pulse square electric wave f 180 μsec, a length of 0.1 sec, and internal burst frequency of 80 Hz, intensity (1.0–1.5mA) bilaterally ST36. twice a week for 3 weeks
Shao, 2015	Sprague-Dawley, male, adult 70 days old, 220–250 g	Chronic constriction injury; CCI- L5 NeuP confirmed by behavioural test	CCI EA strong manual acupuncture mild manual acupuncture	**Electroacupuncture**: POD 3 GB30. 0.6ms at 2Hz, 0.2ms at 100Hz,; intensities at 1 ± 0.5mA; alternating frequencies of 2Hz and 100Hz. 2min at a rate of 180 times per min, followed by an interval of 13min with needles retained and then another 2 min twisting stimulation. Daily session, 9 days.
Shi, 2013	Sprague-Dawley, female, 160–180 g	Diabetes Neuropathy NeuP confirmed by behavioural test	Diabetes Diabetes +EA	**Electroacupuncture**: POD 21. 100 Hz for 1.05 s and 2 Hz for 2.85 s alternately, pulse 0.1 ms.30 min each day ST-361 week.
Sun, 2004	Sprague–Dawley, Male, 230–250g	Chronic constriction injury; CCI-L5 and L6 spinal nerves NeuP confirmed by behavioural test	CCI+ PES CCI+needling	**Peripheral electrical stimulation**, POD 8 frequency 2 Hz, pulse 0.6 ms. The intensity 3,increasing order (0.5, 1 and 2 mA) 10 min each, ST 36 , and Jiaji on both sides. ST 36 and Jiaji on the same side. 30 min. Once every 4 days 10 session
Tu, 2015	Sprague Dawley, male, 200–250 g	Chronic constriction injury; CCI- sciatic nerve NeuP confirmed by behavioural test	CCI CCI + EA	**Electroacupuncture:** POD 7. square wave at 2/100Hz, intensity 2 mA for 30 min. ST36 and GB34. Daily session, 1 week.
Tu, 2018	Sprague Dawley, male, 200-250g	Chronic constriction injury; CCI- sciatic nerve NeuP confirmed by behavioural test	CCI CCI+EA	**electroacupuncture:** POD 8. low (2 Hz) and high (100 Hz) frequencies 2/100 EA ST-36 and GB-34. Daily session, 1 week
Wang, 2014	Sprague Dawley, male, 130–150g	Chronic constriction injury; CCI- sciatic nerve NeuP confirmed by behavioural test	CCI CCI + contralateral EA CCI +ipsilateral EA	**Electroacupuncture:** POD 7. 4 Square wave at 2/100 Hz, intensity 2 mA 30 min ST-3 and GB-3. Daily session, 1 week
Wang, 2016	Wistar, male, adult, 200–250 g	Chronic constriction injury; CCI- sciatic nerve NeuP not confirmed by behavioural test	CCI CCI + sham EA CCI +EA	**Electroacupuncture:** POD 5. (2/100Hz, 1mA) was applied for 30 min ST36 and GB34 daily, for 2 weeks

Wang, 2018	Sprague–Dawley, male, adult, 180–220 g	Chronic constriction injury; CCI-sural and tibial nerve NeuP confirmed by behavioural test	CCI CCI+EA	**Electroacupuncture: POD** 1. frequency 2 Hz pulse 0.6 Ms, intensity increased in a stepwise manner at 1–2–3 mA, each lasting for 10 min.30. min ST36 and SP6. Daily session, 3 weeks
Xia, 2019	Sprague-Dawley, male, adult 7 to 8 weeks old, 160–180g	Chronic constriction injury; CCI-sural and tibial nerve NeuP not confirmed by behavioural test	CCI CCI+EA	**Electroacupuncture:** POD1 day. 2Hz pulse f 0.6 Ms, at 1-2-3 mA, each intensity 10 min ST36 Daily 21 days.
Xu, 2016	Sprague-Dawley, male, adult, 200 to 250 g	Chronic constriction injury; CCI- sciatic nerve NeuP confirmed by behavioural test	CCI CCI+EA	**Electroacupuncture:** POD 1 A 2-Hz frequency and a 2-mA. 30 minutes. GB30. Daily session, 2week
Xue, 2015	Sprague Dawley, male, 220-250g	Chronic constriction injury; CCI- L5 NeuP confirmed by behavioural test	CCI CCI+EA	**Electroacupuncture:** POD 7. 2 Hz -1 mA 30 min. Huantiao and zusanli Daily session, 2week.
Yong-Hui, 2014	Wistar, male, 240–300 g	Chronic constriction injury; CCI- sciatic nerve NeuP confirmed by behavioural test	CCI CCI +3 EA CCI+5EA CCI+12EA	**Electroacupuncture:** POD 7 1 mA and 15 Hz, 30 min ST36 and GB34. once daily continuously for 3, 5 or 12 consecutive days
Yu, 2013	Sprague Dawley, male, 200 ± 20	Chronic constriction injury; CCI- sciatic nerve NeuP confirmed by behavioural test	CCI group CCI+low-frequency EA CCI+ high-frequency EA	**Electroacupuncture:** POD 4. frequency 2 Hz or 15 Hz intensity f less than 1.5 mA. 30 min ST36 and GB34. Daily session, 5 days.
Zhang, 2014	Sprague- Dawley, male, 220 ± 1.38g	Nerve transection; NT-C4/T1 NeuP confirmed by behavioural test	NT NT+EA	**Electroacupuncture**: POD 2 . Dilatational wave (8 mA, 2–100 Hz) 15–20 minutes. LI11, LI04, ST36, GB34. Alternating the injured and uninjured sides on different days of the week. 3 sessions/week 2 weeks.

Zhang,2018	Sprague-Dawley, male, 200–250,	Chronic constriction injury; CCI- sciatic nerve NeuP confirmed by behavioural test	CCI CCI+EA	**Electroacupuncture:** POD 7. 1 mm intensity and 2/15 Hz frequency11. 30 minutes. St 36and Lr 3. ? Session, ? week
Almeida, 2015	BALB/c mice, male, 23.5-60.24g	Chronic constriction injury; CCI-Sciatic nerve NeuP confirmed by behavioural test	CCI CCI+ Swimming CCI+ Swimming+ Detraining	**Swimming:** POD7s. 12 in 3 sessions of 10, 20, 30, 40 minutes and 13 of 50 minutes). 25 session 5 ssesions/week 2 day rest
Belmonte, 2018	Swiss mice, male, 40-50g	Complex pain syndrome; CPIP NeuP confirmed by behavioural test	CPIP CPIP+ Exercise continuous CPIP+ Exercise interval protocol	**Continous and interval treadmill** :, day 7, for 1, 3 alternate days or 5 consecutive days with 2 (two) days interval. Continuous exercise was at 16m/min. The interval exercise was 3:1 ratio at 16 and 19 m/min. Each session 30 min
Bobinsky, 2011	Swiss mice, male, 8-9 weeks old,25-35g	Nerve crush injury; NC-Sciatic nerve NeuP confirmed by behavioural test	Non-Exer NC+ Exercise-preoperative (Exer 1) NC+ Exercise-preoperative-postoperative (Exer 2) NC+ Exercise-postoperative (Exer 3)	**Low-intensity aerobic treadmill** :POD 3, 30 min at 10m/min with no inclination 5 days per week 2 weeks
Bobinsky, 2015	Swiss mice, male, 8-9 weeks old,25-35g	Nerve crush injury; NC-Sciatic nerve NeuP confirmed by behavioural test	NC+ Sedentary NC+ Exercise	**Low-intensity aerobic treadmill:**, POD 3, k for 30 min at 10m/min with no inclination. 5 days per wee

Bobinsky, 2018	Swiss mice, male, 20-30g	Nerve crush injury; NC-Sciatic nerve NeuP confirmed by behavioural test	NC+ Sedentary NC+ Exercise	**Low-intensity aerobic treadmill:**, POD 3, 5 for 30 min at 10m/min with no inclination days per week
Y-W. Chen, 2013	Wistar rats, male, 285-335g	Diabetes Neuropathy NeuP confirmed by behavioural test	Sedentary +DN Exercise +DN	**Treadmill:**, POD? starting at 20 m/min for 30 min and gradually increasing to 20 m/ min for 60 min first 2 weeks. ? Sessions/week 8 weeks
Y-W. Chen, 2015	Wistar rats, male, 290-340g	Diabetes Neuropathy NeuP confirmed by behavioural test	Sedentary +DN Exercise +DN	**Treadmill:** POD3, , 1.2 km/h for 30 min (first 2 weeks), 1.5 km/h for 60 min (second 2 weeks) ? Sessions/week 4 weeks
Y-W. Chen, 2012	Sprague-Dawley rats, male, 250-300g	Chronic constriction injury; CCI-Sciatic nerve NeuP confirmed by behavioural test	CCI CCI+ Swimming Exercise (CCISE) CCI+ Treadmill Exercise (CCITE)	**Swimming**: POD 1,, starting with 9 sessions of 10 min /15 min rest increasing day 7: 1 session of 90 min without res. 39 weeks, 5 days per week **Treadmill**: POD 1 , starting at 1.2 km/h during 15-30 min increasing 1.8 km/h during 60 min at days 33-39. 39 weeks, 5 days per week
Cobianchi, 2010.	CD1 mice, Male, 40-45 gr	Chronic constriction injury; CCI-sciatic nerve NeuP confirmed by behavioural test	CCI CCI+EX day3-7 CCI+Ex day3-56	**TREADMILL**. POD 3 20cm/s that were increased 2 cm/s every 5 min (cut off 60 min). speed at the end of running was 52 cm/s. Running continued until exhaustion. 5 dasy/week 53 days.
Cobianchi, 2013*	Sprague-Dawley rats, female, adult, 210-270g	Nerve transection; NT-Sciatic nerve NeuP confirmed by behavioural test (only in Treadmill)	NT NT+TR	Electrical stimulation: start immediately, 1 session, 0.1 Ms, 3V, 2Hz, 4 h, anode: needle near muscle, cathode: wire bared at the tip **Treadmill** POD, 5 e days, 10 cm/s increasing 2 cm/s every 5 min until 32 cm/s, 1h
Coradini, 2015	Wistar, male, 73 ± 4 days	Chronic constriction injury; CCI Median nerve NeuP confirmed by behavioural test	CCI CCI+ Swim CCI (Obese) CCI+ Swim (Obese)	**Swimming**: POD 3 loads adjusted for swimming. first week, started with 20 min second week 30 min and in the third week they exercised for 40 min, with a load of 10% of BW. Daily 5/week
Gong, 2017	Wistar, male, 10 days	Chronic constriction injury; CCI-tibial and peroneal NeuP confirmed by behavioural test	CCI CCI+ exercise	**Treadmill:** Initiated 11 days after the injury. Postnatal day (P) 21P. 21-23 (P): 5m/min x 10 min 24-26 (P): 8m/min x 20 min 28-33 (P): 10m/min x 30 min 35-40 (P): 15m/min x 30 min
Huang, 2017	Sprague-Dawley rats, male, 220-270g	Chronic constriction injury; CCI of the sciatic nerve NeuP confirmed by behavioural test	CCI CCI + TU0 CCI + TU CCI + TE CCI + TU0 + TE CCI + TU + TE	**Ultrasound:** POD 8 1 MHz with pulse (20% duty cycle) 1 W/cm2 intensity and 100-Hz frequency (beam no uniformity ratio = 3.6) for 5 minutes a day TU0: therapeutic ultrasound turned off **TE: Treadmill exercise**. 30 minutes Starting on postoperative day 8 and lasting daily for the next 3 weeks

Hung, 2014	Sprague-Dawley rats, male, 220-270g	Chronic constriction injury; CCI-Sciatic nerve NeuP confirmed by behavioural test	CCI CCI+TT CCI+TU CCI+TT+TU	**Treadmill Training** :POD 3,, at 14-16 m/min, 8% inclination, 30 min 5 days per week during 4 weeks **Ultrasound** :POD 3,, 1 MHz with pulse (20% duty cycle), 1-W/cm2 intensity, 100-Hz frequency 5 minutes. 5 days per week during 4 weeks
Hung, 2016	Sprague-Dawley rats, male, 220-270g	Chronic constriction injury; CCI-sciatic nerve NeuP confirmed by behavioural test	CCI CCI+TU CCI+TT CCI+TT+TU	**Ultrasound:** The parameters were 1 MHz with pulse (20% duty cycle), 1-W/cm2 intensity, and 100-Hz frequency (beam no uniformity ratio 3.6) for 5 minutes a day. **TT: treadmill training: POD 3**t 14 to 16 m/min with an 8% incline for 30 minutes. 5 days a week for the next 4 weeks.
Kami, 2016a	Adult C57BL/6 J mice	CCI partial sciatic nerve ligation; CCI_P-sciatic NeuP confirmed by behavioural test	CCI-sedentary CCI + running	**Treadmill**: POD 2. 1° week 7 m/min for 10 min/day ,2° week 7 m/min for 20–60 min/day 3° week7 m/min for 60 min/day. 5 days/week
Kami, 2016b (Jpain)	Adult C57BL/6 J mice, male, 12 week	CCI partial sciatic nerve ligation; CCI_P-sciatic NeuP confirmed by behavioural test	CC_PI-sedentary CCI_P+ running	**Treadmill**: POD 2. 1° week 7 m/min for 10 min/day ,2° week 7 m/min for 20–60 min/day 3° week7 m/min for 60 min/day. 5 days/week

Korb 2010	Wistar, adult male, 200-250g	Nerve transection; NT- Sciatic nerve NeuP confirmed by behavioural test	NT+ trained NT sedentary	**Treadmill:** r 20 min on the first day, increased every day up to 50 min 5 day and 60 min in the next 4 weeks. warm-up period of 5 min running at 30% of the maximal speed reached in the MET (5.5 m/min), 10–50 min running at 45–55% (*9 m/min) and 5 min recovery at 30% again (5.5 m/min), 5 sessions per week, once a day during 4 weeks.
López-Álvarez, 2015.	Sprague-Dawley, female, 240 +- 30 g	Chronic constriction injury; CCI- sciatic nerve NeuP confirmed by behavioural test	CCI+ITR1 CCI+ITR2 CCI	**Treadmill:** starting speed of 10 cm/s increased 2 cm/s every 5 minutes, until a maximal speed ofv32 cm/s. 60 min.. G1 POD3 daily session 5 days. G 2 POD 10-14
López-Álvarez, 2018.	Sprague-Dawley rats, female, 240 ± 30 g	Sciatic nerve transection and repair SNTR NeuP confirmed by behavioural test	SNTR-iTR SNTR-sedentary	**Treadmill:** POD 3startting speed of 10 cm/s increased 2 cm/s every 5 minutes, until a maximal speed ofv32 cm/s. 60 min. daily session 12 days
Ma, 2018.	Sprague-Dawley rats, Male, 200-250 gr	Diabetes Neuroapathy NeuP confirmed by behavioural test	DN DN+EX	**Treadmill:** POD 4 . speed was gradually increased from 5 m/min at a 10% grade, and exercise duration was maintained at 10 min. By the third week, the intensity increased to 10 m/min for 10 min, 4 days/week for 5 weeks

Martins, 2017.	Swiss mice, 8 weeks old, Male, 25-30 gr	Nerve crush injury; NC-sciatic NeuP confirmed by behavioural test	NC NC+ eccentric exercise 6 m/min NC + eccentric exercise 10 m/min NC + eccentric exercise 14 m/min	**Eccentric:** (Downhill Running) Program:30 min at a speed of 6, 10, or 14 m/min with − 16° slope, 5 days per week, for 8 weeks.
Sumizono, 2018	Sprague Dawley, male, 8 weeks, 274.3 ± 21.2 g	Chronic constriction injury; CCI-sciatic nerve NeuP confirmed by behavioural test	CCI CCI + high-frequency exercise CCI + low-frequency exercise	**Treadmill**: speed of 20 m/min, for either 5 days (HFE) or 3 days (LFE) a week, for a total of 5 weeks
Tian, 2018	Sprague-Dawley rats, male, 200-250g	Nerve transacted; NT- Tibial nerve NeuP confirmed by behavioural test	NT NT+ swimming	**Swim**: POD 7 1°week,10-min swimming exercise 1° day, gradually increased r 60 min. In the following 4 wk, rats swam daily for 5 d followed by 2-d rest. weeks swimming exercise
Thakur, 2016	SpragueDawley, male, 250–280 g	Diabetes Neuropathy NeuP not confirmed by behavioural test	1diabetes 2diabetic+exercise	**Treadmill**: POD 14, speed10m/min, 60min per day five days/week, for 6 weeks break for waterafter20min
Tsai, 2017	Sprague-Dawley, male, 285–335 g.	Chronic constriction injury; CCI- sciatic nerve NeuP confirmed by behavioural test	CCI CCI + 0%-incline treadmill CCI + 8%-incline treadmill	**Treadmill:** POD 6. 14–16 m/min with/without 8% incline grade for 30 min . Daily sessions 3 weeks

Wang, 2016	New Zealand white rabbit, male, 11±12 weeks-old, 1.78 ±0.12 kg	Nerve crush injury; NC-sciatic nerve NeuP not confirmed by behavioural test	NC NC+Ex NC+EX+EA	**Treadmill:** POD 3 for 20 minutes a day at a rate of 10m/min for 3 days, at a rate of 15m/min for 20 min/day from the fourth to sixth day, and then at a rate of 20m/min for 20 min/day from the seventh day onward, 6 days/week for a total treatment cycle duration of 4 weeks **EX+EA**:3 days post-surgery, 6 Jiaji acupoints3Hz/s electrical current for 30 min/day, 6 days/week for a total treatment duration of 4 weeks
Martins, 2011	Wistar rats, male, adult, 250-280g	Nerve crush; NC-Sciatic nerve NeuP confirmed by behavioural test	NC NC+Anesthesia NC+AJM	**Ankle joint mobilisation:** POD1 dorsal and plantar flexion,, s, 3 treatments of 3 minutes with 30 seconds rest, 48 h rest between sessions. 15 session
Song, 2016	Sprague-Dawley, male, adult, 200-250	Chronic constriction injury and decompresion CCI-DRG de-CCI-DRG NeuP confirmed by behavioural test	CCI de-CCI de-CCI+SMT	**Chiropractic spinal manipulative therapy**. POD10. b0.1 ms mechanical force, manually assisted spinal manipulative thrusts, L5 and L6. 10 ASMT. Daily for consecutive 5 days
da Silva, 2015	Wistar rats, male, two weeks, 180-220g	Chronic constriction injury; CCI-Sciatic nerve NeuP not confirmed by behavioural test	CCI CCI+NM	**Neural mobilisation:** POD 14, 10 sessions, 20 oscillations per minute during 2min, followed by a 25-s pause, total of 10 minutes, ankle joint in dorsiflexion (30–45 degrees)

Giardini, 2017	Wistar, male, 2 month, 200-220g	Chronic constriction injury; CCI-sciatic nerve NeuP not confirmed by behavioural test	CCI CCI+NM	**Neural Mobilization:** POD14 20 oscillations per minute for 2 minutes 25-second rest. ten minutes total. initiated 14 days after the injury. Every other day for a total of 10 sessions.
Santos, 2012	wistar, male, 2 months-old,180 and 220 g	Chronic constriction injury; CCI-sciatic nerve NeuP confirmed by behavioural test	CCI CCI+ NM	**Neural Mobilization**: POD14. 20 oscillations/ min 2 min, 25-sr rest.10 min total last minute the cervical spine was fully flexed, 10 sessions.
Santos, 2018	wistar, male, 200 and 220 g	Chronic constriction injury; CCI-sciatic nerve NeuP not confirmed by behavioural test	CCI CCI+ NM	**Neural Mobilization**: 10 sessions. 20 oscillations/ min 2 min, 25-sr rest.
Zhu, 2017	Sprague-Dawley, male, mature, 300 to 320g	Diabetes Neuropthy NeuP confirmed by behavioural test	Diabetes Diabetes +neural mobilization	**Neural Mobilization**: POD 10. . 20 times/min. 2-min oscillation, 25-s break; 5 repetitions for each treatment session. 1 session/d, 5 d/wk. 3 weeks
Chen, 2015	Sprague–Dawley, male, 200–250 g	Chronic constriction injury; CCI- sciatic nerve NeuP confirmed by behavioural test	CC I CCI+ TU-0 CCI + TU-0.25 CCI+TU-0.5 CCI+TU-1	**Ultrasound:** POD 5. 1-MHz frequency intensity of 70.25, 0.5 or 1 W/cm2 and 100% on–off cycle 5 min once a day, 22 days
Cidral, 2013	Swiss mice, male, adult, 25-35g	Nerve crush injury; NC-Sciatic nerve NeuP confirmed by behavioural test	NC NC+LEDT	**Light-emitting diode therapy:** POD 7, 950 nm, 80 mW/cm2 and 2.5 J/cm2, Daily sessions 15 days.
Cioato, 2016	Wistar rats, male, 55-65 days, 200-250g	Chronic constriction injury; CCI-Sciatic nerve NeuP confirmed by behavioural test	CCI CCI+s ham tDCS CCI+ tDCS	**Transcranial direct current stimulation:** POD15. , 0.5 mA, 1.5 cm2 electrodes, 20 min, anode: head, cathode: supraorbital area. Daily 8 day
Filho, 2016	Wistar rats, male, 55-65 days, ≥ 250g	Chronic constriction injury; CCI-Sciatic nerve NeuP not confirmed by behavioural test	CCI CCI+ Sham tDCS CCI+t DCS	**Transcranial direct current stimulation:**.POD 14, 8 days, 0.5 mA, 1.5 cm2 electrodes, 20 min, anode: parietal cortex, cathode: supraorbital area. Daily 8 days
Giuliani, 2004	Sprague-Dawley rats, male, 2 month, 250-275g	Chronic constriction injury; CCI-sciatic nerve NeuP confirmed by behavioural test	CCI CCI + laser	**Laser:** POD 8 power 0.03 mW, wavelength of 670nm, 1% duty cycle modulation of a 3-mW peak power diode, frequency 100Hz. each point lasted 35 sec (1.05mJ) t area is less than 5mm2. Density less than 0,21 mJ/mm2 2 selected points every 3 days
Hsieh, 2012	Sprague-Dawley rats, male, 250-300g	Chronic constriction injury; CCI-sciatic nerve NeuP confirmed by behavioural test	CCI+laser CCI+sham	**Laser:** POD 7 continuous 660 nm Ga-Al- or sham size was 0.2 cm2 aprox. power irradiation was 30 mW per session for 60 seconds per spot, 4 spots . The energy density was 9 J/cm2. Control group with power set at 0. daily 1 week
Hsieh, 2017	Sprague-Dawley rats, male, 200-250g	Oxaliplatin administration: Antineoplasic neuropathy NeuP not confirmed by behavioural test	Oxaliplatin +TUS Oxaliplatin +shamTUS	**Ultrasound:** POD 4 hours Pulsed-mode TUS (1 MHz, spatial average/temporal average intensity [ISATA] 5 0.5 W/cm2, 50% duty cycle) was applied for 5 min. sonication/non-sonication times of 2 ms/2 ms. Daily 10 sessions.

Lin, 2015	Sprague-Dawley rats, male, 200-250g	Chronic constriction injury; CCI- sciatic nerve NeuP confirmed by behavioural test	CCI CCI+ HFS	**TENS**: POD 1 80% of that enough to elicit an obvious muscle contraction. The pulse duration was set at 100us for 20 min Daily 13 d
Liu, 2017	Sprague-Dawley rats, male, 300-350g	Chronic constriction injury; CCI- sciatic nerve NeuP confirmed by behavioural test	CCI + sham PEMF CCI + PEMF	**Pulsed electromagnetic field therapy:** POD 1 Set as 3.8mT, 8Hz, 30min. The treatment began from the first day and sustained 2 weeks
Matsuo, 2014.	ICR mice (Clea, Tokyo), 9 weeks, male, 39.6±3.0 g	Chronic constriction injury; CCI-tibial and peroneal nerves NeuP confirmed by behavioural test	CCI CCI+TENS 1 w CCI+TENS 2 w	**TENS:** POD 7 frequency 100 Hz and the intensity defined by the sensory threshold. 30min. Of 1w or 2w
Mert, 2015 (a).	Wistar rats, 8-12 weeks, Male, 270-280 gr	Chronic constriction injury; CCI-sciatic nerve NeuP confirmed by behavioural test	sham PMF (SPMF) PMF-AD PMF-AW	**Pulse magnetic field:** POD 1- 7. Three sequences. Each sequence included four different consecutive pulse trains (1, 10, 20, 40 Hz). The each pulse train was 4 min, and the interval 1 min. 60 min. dailyl for 4 weeks
Mert, 2015 (b).	Wistar rats, 10-12 weeks, Male, 280-300 gr	Diabetes Neuropathy NeuP confirmed by behavioural test	STZ-induced diabetic L-PMF-treated diabetic H-PMF-treated diabetic	**Pulsed magnetic field**. POD3 Three sequences. Each sequence included four different consecutive pulse trains (1, 10, 20, 40 Hz). The each pulse train was 4 min, and the interval 1 min. 60 min. daily for 5 weeks

Mert, 2017	Wistar rats, 10-12 weeks, Male, 280-290 gr	Chronic constriction injury; CCI-sciatic nerve NeuP confirmed by behavioural test	CCI+PMF CCI+SPMF	**Pulsed Magnetic Field:** POD1 Three sequences. Each sequence included four different consecutive pulse trains (1, 10, 20, 40 Hz). The each pulse train was 4 min, and the interval 1 min. 60 min. daily for 4 weeks.
da Silva Oliveira, 2018	C57BL6 mice, male, 20-26g	Diabetes Neuropathy NeuP confirmed by behavioural test	DN+ Sham DN+PBM	**Photobiomodulation**: POD 14. , 660 nm, 0.28 cm2, 30 mW, 1.6 J/cm2, 15 sec in a continuous frequency, plantar region of the left hind paw. 21 sessions
Somers, 2003	Sprague-Dawley rats, male, adult, 150-165g	Chronic constriction injury; CCI-Sciatic nerve NeuP not confirmed by behavioural test	CCI CCI+TENS	**High-Frequency TENS,** POD 0 , s, 30 to 40 uA, 100Hz, 60 min per day, Para spinal musculature. 11 days.
Somers, 2009	Sprague-Dawley rats, male, 150 to 175 g	Chronic constriction injury; CCI-sciatic nerve NeuP not confirmed by behavioural test	CCI CCI+ high frequency TENS contralateral CCI + low-frequency TENS CCI +randomly TENS	**Electrical Nerve Stimulation**: POD 0 s. 1 day90 min 10 days 60 min 100 Hz high frequency 30-40 microamperes delivered through 45 mm 5-mm electrodes 2 Hz Low frequency 30-40 microamperes delivered through 45 mm 5-mm electrodes 11 Daily days

Su, 2018	Sprague-Dawley rats, male, 250-300g	Nerve crush injury; NC- sciatic nerve NeuP confirmed by behavioural test	NC NC + High-frequency immediately(HFI) NC + High-frequency 7 days after(HFL) NC + Low-frequency immediately (LFI) NC + Low-frequency 7 days after (HFL)	**Electrical stimulation**: POD 400 ms of biphasic pulses at 200 μs per phase. HF use 100hz and LF 5 Hz frequency and with 6 s of rest 30 min per day for 1ws
Yang, 2018	Sprague-Dawley, male, 180 to250 g	Chronic constriction injury; CCI- sciatic nerve NeuP confirmed by behavioural test	CCI+ sham-rTMS group CCI+ 1 Hz group CCI+ 20 Hz group	**Transcranial Magnetic Stimulation**: POD 3. right primary motor cortex (M1) contralateral to the pain side with 90% RMT stimulation intensity (40% of the maximum output), and 1600 pulses for each treatment. 1 Hz group was 1 Hz with continuous stimulation for total 26.7 min, and that of 20 Hz group was 20 Hz, with 4 s for each sequence and a 30 s interval, 20 sequences in total for each treatmen Daily 10 days
Yueh-Ling, 2012	Sprague–Dawley, male, adult, 250–300 g	Chronic constriction injury; CCI- sciatic nerve NeuP confirmed by behavioural test	CCI and treated with laser CCI and treated with sham irradiation	**Laser**: POD 7 day. continuous 660 nm Ga-Al-As diode laser. Size 0.2 cm2. 30 mW per session for 60 seconds per spot . The energy density was 9 J/cm 7 days

NC nerve crush; CCI chronic constriction injury ; NT nerve transection; CPIP chronic post-ischemia pain; STZ streptozocin DN diabetic neuropathy; SNTR sciatic nerve transection and repair; POD post operative day; ? not reported; PMF pulse magnetic field; SPMF sham pulse magnetic field; EX exercise; EA electro-acupuncture; AJM ankle joint mobilization; SMT spinal manipulative therapy; HFI High-frequency immediately; HFL Low-frequency immediately

Supplementary 3. The number [%] of each biomarker type according to intervention

	Acupuncture	Electro-acupuncture	Exercise	Joint mobilization	Neural mobilization	Physical Agents
Immune system	2 [100.0]	16 [61.5]	20 [76.9]	1 [50.0]	2 [40.0]	14 [73.7]
Immune competent cells (eg: astrocytes)	1 [50.0]	5 [31.3]	7 [35]	1 [100.0]	1 [50.0]	3 [21.4]
Immune cells (eg: macrophagues)		1 [6.3]	3 [15]	1 [100.0]		
Cytokines/chemokines (IL-1β)	1[50.0]	8 [50]	15 [75]	1 [100.0]	1 [50.0]	11[78.6]
Other inflammatory markers (IFN-γ)		1 [6.3]	3 [15]			
Neurotrophins (eg: NGF, BDNF)		8 [30.8]	8 [30.8]		1 [20.0]	5 [26.3]
Opioid system (eg: β -endorphin)		2 [7.7]	1 [3.9]		1 [20.0]	2 [10.5]
Neurotransmitters (eg: serotonin)		2 [7.7]	7 [26.9]		1 [20.0]	3 [15.8]
Enzymes (eg:HDAC1)		1 [3.9]	1 [3.9]	1 [50.0]		
Receptors (eg: TRPV1)		5 [19.3]	1 [3.9]		1 [20.0]	1[5.3]
Actins (β-actin)		1 [3.9]			1 [20.0]	1 [5.3]
Hormone (Arg)		1[3.9]	1 [3.9]			
Oxidative markers (eg: MDA)			1 [3.9]			
Heat shock protein			2 [7.7]			

6.4 Resultados del estudio IV

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Effects of neural mobilizations through movement representation techniques for the improvement of neural mechanosensitivity of the median nerve region: a randomized controlled trial

Luis Matesanz-García, Julio Eduardo Cáceres-Pajuelo, Ferran Cuenca-Martínez, Roy La Touche, Carlos Goicoechea-García & Josué Fernández-Carnero

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ARTICLE

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Effects of neural mobilizations through movement representation techniques for the improvement of neural mechanosensitivity of the median nerve region: a randomized controlled trial

Luis Matesanz-García[a], Julio Eduardo Cáceres-Pajuelo[b], Ferran Cuenca-Martínez[c,d], Roy La Touche[c,d,e], Carlos Goicoechea-García[f] and Josué Fernández-Carnero[d,g,h,i]

[a]Escuela Internacional de Doctorado, Department of Physical Therapy, Occupational Therapy, Rehabilitation and Physical Medicine, Universidad Rey Juan Carlos, Alcorcón, Spain; [b]Kapalua fisioterapia S.L., Madrid, Spain; [c]Departamento de Fisioterapia, Centro Superior de Estudios Universitarios La Salle. Universidad Autónoma de Madrid, Madrid, Spain; [d]Motion in Brains Research Group, Institute of Neuroscience and Sciences of the Movement (INCIMOV), Centro Superior de Estudios Universitarios La Salle. Universidad Autónoma de Madrid, Madrid, Spain; [e]Instituto de Dolor Craneofacial y Neuromusculoesquelético (INDCRAN), Madrid, Spain; [f]Departament basic health sciences, Rey Juan Carlos University, Madrid, Spain; [g]Grupo Multidisciplinar de Investigación y Tratamiento del Dolor, Grupo de Excelencia Investigadora URJC-Banco de Santander, Madrid, Spain; [h]La Paz Hospital Institute for Health Research, IdiPAZ, Madrid, Spain; [i]Department of Physical Therapy, Occupational Therapy, Rehabilitation and Physical Medicine, Rey Juan Carlos University, Madrid, Spain

ABSTRACT

Purpose: The main objective was to compare the effects of neural mobilization (NM), NM performed through mirror therapy (MT), NM performed through action observation (AO) training and finally classic rehabilitation program (mobility and strength) exercises on neural mechanosensitivity, widespread of proximal and distal pain and pressure pain thresholds (PPT). The second objective was to assess the effects of these interventions on handgrip strength, conditioned pain modulation, motor imagery ability and temporal summation.

Materials and methods: Single-blinded randomized controlled trial. Fifty-four healthy subjects were randomly assigned to each group. Neural mechanosensitivity, widespread pain and PPT were the main variables. The secondary variables included handgrip strength, conditioned pain modulation, motor imagery ability and temporal summation.

Results: All groups showed significant differences in time*factor for neural mechanosensitivity ($p = 0.001$), PPT in the dermatome of the median nerve ($p = 0.007$), PPT at carpal tunnel ($p < 0.05$) and proximal widespread ($p = 0.01$). No differences were found for distal widespread, conditioned pain modulation, handgrip strength motor imagery ability or temporal summation ($p > 0.05$). There is an absence of statistically significant differences between groups.

Conclusions: NM through movement representation techniques can reduce mechanosensitivity and mechanical hyperalgesia in the median nerve dermatome and forearm, although no differences were found between groups.

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Movement representation techniques; therapeutic exercise; mechanosensitivity; median nerve; neurodynamic mobilization; pressure pain threshold

Introduction

The incidence of Carpal Tunnel Syndrome (CTS) is 276 cases per 100,000 people each year (Ibrahim et al. 2012). Enhancing perineural inflammation without axonal nerve damage increases spontaneous activity and mostly induces a mechano-sensitivity in the myelinated axon (Eliav et al. 2001). Intraneural ischaemia is characteristic of mild entrapment neuropathies. Mechanical entrapment can induce subsequent effects such as demyelination and eventually axon degeneration (Schmid et al. 2020). This mechanosensitivity in the median nerve was not always higher in subjects with a clinical diagnosis of CTS. Some patients have negative neurodynamic tests even though there is a clear impairment of the median nerve as proven by electrodiagnostic tests (Baselgia et al. 2017).

Patients with mild to moderate diagnosed CTS, demonstrated altered pain facilitation and inhibition process and normally tend to show the extraterritorial spread of the symptoms, affecting the whole hand or the proximal upper limb and increased pain sensitivity in the upper region of the shoulder (Zanette et al. 2007, 2010; Soon et al. 2017), besides presenting bilateral thermal hyperalgesia (De La Llave-Rincón et al. 2009).

In several trials, neurodynamic mobilization (NM) with neuropathic pain models, attenuates mechanical allodynia and decreases proinflammatory cytokines, modulates the expression of endogenous opioids in the periaqueductal

CONTACT Ferran Cuenca-Martínez fecuen2@gmail.com Motion in Brains Research Group, Institute of Neuroscience and Sciences of the Movement (INCIMOV), Centro Superior de Estudios Universitarios La Salle, Universidad Autónoma de Madrid, Madrid, Spain

Supplemental data for this article can be accessed here.

grey matter, and decreases the expression of glial cells and brain-derived neurotrophic factor (Santos et al. 2012; Giardini et al. 2017; Zhu et al. 2018). NM has shown therapeutic effects in the treatment of CTS, being one of the main techniques regarding a conservative treatment (Wolny 2017). Although the findings of some reviews suggest contradictory results (Basson et al. 2017; Lim et al. 2017).

The use of movement representation techniques such as action observation (AO) or mirror therapy (MT) has increased in recent years. Both techniques have shown promising results in healthy subjects and patients with musculoskeletal conditions improving motor function (Sarasso et al. 2015; Cuenca-Martínez et al. 2020b) and pain intensity (Park et al. 2014; Boesch et al. 2016).

AO evokes a real-time internal motor simulation of the movements that the observer perceives visually (Buccino 2014). MT is defined as the reflective illusory movement perception in one limb upon viewing the moving opposite limb in a midsagittal mirror (Ramachandran et al. 1995; Ramachandran and Altschuler 2009). These techniques have in common they lead to an activation of planning-related areas, as well as, adjustment and automation of voluntary movement in a very similar manner as to when the movement occurs in a real way (Shinoura et al. 2008; Ge et al. 2018).

The authors hypothesize that this neurophysiological activity can produce somatosensory and sensorimotor peripheral changes, leading to a decrease in neural mechanosensitivity in a very similar way to a real NM.

It is therefore that the main objective of the present study was to compare the effects of NM, NM performed through MT, NM performed through AO training and finally classic rehabilitation program (mobility and strength) on neural mechanosensitivity, widespread of proximal and distal pain and pressure pain thresholds (PPT). The second objective was to assess the effects of these interventions on handgrip strength, cold hyperalgesia, conditioned pain modulation, pain tolerance and temporal summation.

Methods

The study was conducted as a single-blind, randomized, controlled trial, according to the CONSORT guidelines standards (Moher et al. 2010). The trial was approved by the ethics committee [removed for peer review] and subsequently registered in clinicaltrial.gov [removed for peer review].

Participants

Between September 2019 and February 2020, healthy volunteer participants were recruited. Advertisements, social networks, and emails were used for this purpose. Prior to final inclusion, all signed the informed consent. All the procedures were carried out according to ethical procedures for medical research with human beings, in accordance with The Helsinki Declaration.

Inclusion and exclusion criteria

The criteria for inclusion were: 1) be aged between 18 and 65. The exclusion criteria were: 1) suffering from any pathology that presents pain, 2) suffering pathologies of a neurological origin, 3) having any musculoskeletal disorders in the upper limbs and 4) Metabolic diseases.

Randomization

Randomization was conducted using a computer-generated random sequence table provided by GraphPad Software Inc., CA, USA. A team member not involved in treatment or assessments was responsible for generating and maintaining the list.

Blinding

Measurements and treatments were performed by two independent researchers. The measurements were carried out by an experienced therapist. The member in charge of the measurements was blind to the treatment followed by the participants.

Interventions

All the volunteers had six sessions at the rate of 3 sessions per week.

Active NM

The subjects performed an active mobilization of the median nerve according to (Totten and Hunter 1991). NM was performed at a rate of 0.5 Hz following the rhythm of a metronome, 3 min per exercise, resting 5 s every minute and 30 s between exercises. This group acted as the control group (CG).

MT. For the MT, Prims Glasses™ was used. The glasses were placed so that they focussed on the non-dominant upper limb. The exercises focussed on the hand on the dominant side. The glasses create the illusion for the patients that they are moving their dominant hand, but in reality, the exercises are performed by the non-dominant one. Mobilizations were performed in the same parameters as the NM group but on the non-dominant upper limb.

AO. The subjects were shown videos with the same exercises and on the same parameters as the previous groups. These videos showed upper limb performing exercises aimed at mobilizing the median nerve at carpal tunnel level.

Classic rehabilitation program (CR)

Participants performed a combination of exercises of mobility and strength of wrist and fingers with their dominant hand. The protocol is detailed in Supplementary data.

Outcome measures

Primary outcomes

Neural mechanosensitivity. Neural mechanosensitivity was evaluated from the amplitude assessed in degrees of extension of the elbow with a conventional goniometer, using the upper limb neurodynamic test 1 which is a diagnostic tool used to assess the mechanosensitivity of the median nerve (Schmid et al. 2009). To measure the angle of the elbow, the axis was positioned on the medial epicondyle with the stationary arm pointing to the acromion and the mobile arm to the ulnar styloid process. A change greater than 7.16° can be considered due to intervention (Oliver and Rushton 2011).

Widespread proximal and distal pain. The three PPT measurements were made with a Model FDX 10® digital algometer, Wagner Instruments, Greenwich, CT, USA. Subjects were placed in a seated position with their arms supported and their elbows bent to 90°. The proximal widespread was defined by three points: metacarpophalangeal joint of the Index finger, carpal tunnel, and the trunk of the median nerve at the elbow. The first point was in the metacarpophalangeal joint of the Index finger, the second in the trunk of the median nerve as it passes through the carpal tunnel, the third was located in the medial ulnar fossa just next to the tendon of the biceps. Two complete measurements of the path of each point were made, leaving 30 s of resting to avoid temporal summation (Binderup et al. 2010). Regarding the widespread distal pain, two PPT measurements were made. The first point was in the acromioclavicular joint and the second at the C2 spinous process. Two complete measurements of the path of each point were made, leaving 30 s of rest to avoid temporal summation (Binderup et al. 2010).

PPT. PPT is defined as the minimum amount of pressure needed to cause pain. Measurements of PPT were made using a digital algometer (Model FDX 10®, Wagner Instruments, Greenwich, CT, USA). This instrument measures the pressure in kg, with the pain threshold being expressed in kg/cm^2. Three measurements were recorded, within an interval of 30 s between each measurement to avoid a temporal summation effect. The measurements were made bilaterally on the carpal tunnel.

Secondary outcomes

Handgrip strength (HGS). The HGS was carried out with a dynamometer (JAMAR, Sammon Preston, Canada). The Jamar Dynamometer presents excellent intra-rater reliability (ICC = 0.94 and 0.98) and excellent inter-rater reliability (ICC = 0.98) (Peolsson et al. 2001). The dynamometer was adjusted to the dominant hand of the subject. It has been established that the minimum significant change would be a difference of 2.8 kg (Baldwin et al. 2013).

Conditional pain modulation (CPM). For the evaluation of the diffuse descending inhibitory system, tonic pain was provoked in a non-painful area. Measurements were made with a Model FDX 10® digital algometer, Wagner Instruments, Greenwich, CT, USA. Firstly, the PPT was measured on the base of the dorsal side of the distal phalanx of the thumb. Followed by the PPT a conditioned stimulus by an ischaemic pain with an intensity between 5 and 7/10, using a sphygmomanometer. While the sphygmomanometer was inflated, the PPT measurement was repeated on the dorsal side of the distal phalanx of the thumb. This procedure has shown to be an adequate stimulus to assess the endogenous inhibitory system. Once the data was obtained, the thresholds during the conditioned stimulus were deducted minus the thresholds obtained in the pre-stimulation (Tuveson et al. 2006; Lindstedt et al. 2011).

Motor imagery (MI) ability. To assess MI ability, the Spanish version of the Revised Movement-Image Questionnaire (MIQ-R) was used which consists of 4 movements repeated in 2 domains (visual and kinesthetic). Participants score the movements from 1 to 7, with being 1 the maximum difficulty and 7 the least or minimum difficulty. The psychometric properties of MIQ-R have been consistently adequate, with Cronbach's α coefficients ranging above 0.84 for the entire scale (Campos and Gonzalez 2010).

Temporal summation (TS). The measurement of the TS was done using a Model FDX 10® digital algometer, Wagner Instruments, Greenwich, CT, USA. The TS was obtained from 10 applications with the algometer to the intensity of the PPT, applied at the midpoint between the nail and the interphalangeal joint on the dorsal side of the distal phalanx of the first finger at a repetition rate of 1 Hz. Before the first pulse, subjects were instructed to verbally rate the pain level of the isolated stimulus and the tenth pulse according to a visual analogue scale (VAS). The stimuli were performed in an area of 1 cm^2. The ratio was calculated by dividing the average pain produced by the training stimulus by the pain produced by the individual stimulus. This method has been used and validated in several investigations on time addition (Magerl et al. 1998).

Sample size calculation

The sample size was estimated using the program G*Power 3.1.7 for Windows (G*Power from University of Dusseldorf, Germany) (Faul et al. 2007). The sample size calculation was considered as a power calculation to detect between-group differences in a primary outcome measure (ULTN1). Three groups and two measurements for primary outcomes were considered, to obtain 80% statistical power (1-β error probability) with an α error level probability of 0.05 using analysis of variance (ANOVA) of repeated measures, within-between interaction, and an effect size of $\eta p^2 = 0.202$ (Effect size $f = 0.503$) obtained from the results of a previous clinical trial (Suso-Martí et al. 2019). This generated a sample size of a total of 48 participants plus an estimated 20% loss in follow-up, yielding a total of 57 participants (12 per group).

Data analysis

We performed the data analysis with the Statistics Package for Social Science (SPSS 25.00, IBM Chicago, IL, USA), employing a 95% confidence interval and considering all values with a *p*-value less than 0.05 to be statistically significant. The descriptive statistics employed to summarize the data for continuous variables are presented as mean ± standard deviation and the 95% confidence interval. We performed a repeated-measure ANOVA to study the effect of the between-subject factor 'intervention group' with 4 categories (active NM, MT, AO, and CR) and the within-subject factor 'time', also with 2 categories (pre and post) on the dependent variables. The partial eta was calculated squared as a measure of effect size (strength of association) for each main effect and interaction in the ANOVAs, with 0.01–0.059 representing a small effect, 0.06–0.139 a medium effect, and >0.14 a large effect. A *post hoc* analysis with Bonferroni correction in the case of significant ANOVA findings for multiple comparisons between variables was performed too. The effect size was calculated using the Partial Eta Squared (ηp2) when significant. An effect size of 0.01 was considered as small, 0.06 as a medium, and 0.14 as large (Gray and Kinnear 2012). It was performed a per-protocol analysis because we were interested in knowing the data of the participants who completed the study assuming that in clinical reality we have losses. In this way, we know more precisely the effect of the intervention as it has been shown that patients with lower levels of adherence tend to have a worse prognosis than those with higher levels of adherence. We consider this as a small limitation because they are healthy and not patients.

Results

A total of 55 participants were included and randomly assigned to 4 groups (15 participants in the AO group, 12 participants in the MT group, and 15 in the CR and finally 13 participants in the CG). Figure 1 shows the process of recruitment and dropouts. No adverse events were reported in any of the groups. There were no statistically significant differences in the demographic data among the groups or the self-report variables in the baseline measurement (Table 1). All primary and secondary measures presented a normal distribution, and there were no differences among the groups in the pre-intervention measurement ($p > 0.05$).

Primary outcomes

Neural mechanosensitivity

The ANOVA did not reveal significant differences in the group*time interaction ($F = 0.23$, $p = 0.871$, $\eta p^2 = 0.014$) all groups improved over time ($F = 35.40$, $p = 0.0001$, $\eta p^2 = 0.419$) for the neural tension test. Figure 2 shows the results for each of the groups. The *post hoc* analysis revealed significant within-group differences in all groups between pre- and post-intervention measures, with a medium-large effect size for the AO group ($p = 0.014$, $d = -0.77$), MT group ($p = 0.007$, $d = -0.85$), CR ($p = 0.003$, $d = -0.76$) and NM ($p = 0.001$, $d = -0.83$) (Table 2).

Local hyperalgesia PPT over carpal tunnel

The ANOVA did not reveal significant differences in the group*time interaction ($F = 2.12$, $p = 0.11$, $\eta p^2 = 0.11$) all groups improved over time ($F = 3.98$, $p < 0.05$, $\eta p^2 = 0.075$) for PPT in the carpal tunnel. Figure 3 shows the comparative results for each of the groups. The *post hoc* analysis revealed significant within-group differences in the MT group between pre- and post-intervention measures, with a medium effect size ($p = 0.024$, $d = -0.67$) (Table 2).

Proximal widespread

The ANOVA did not reveal significant differences in the group*time interaction ($F = 1.236$, $p = 0.30$, $\eta p^2 = 0.06$) all groups improved over time ($F = 4.31$, $p = 0.04$, $\eta p^2 = 0.079$) for PPT in hand + forearm. The *post hoc* analysis revealed significant within-group differences in all groups between pre- and post-intervention measures, with a medium-large effect size for the NM group ($p = 0.011$, $\eta p^2 = 0.124$). The *post hoc* analysis revealed significant within-group differences in the NM group between pre- and post-intervention measures, with a medium effect size ($p = 0.011$, $d = -0.50$) (Table 2). Figure 4 shows the comparative results for each of the groups.

Distal widespread

The ANOVA did not reveal significant differences over time ($F = 0.62$, $p = 0.433$, $\eta p^2 = 0.013$) and neither in the group*time interaction ($F = 2.267$, $p = 0.092$, $\eta p^2 = 0.122$) for distal widespread (shoulder + cervical spine).

Secondary outcomes

HGS and MI ability variables

The ANOVA did not show significant differences over time for HGS ($F = 3.02$, $p = 0.08$, $\eta p^2 = 0.06$) and also for MI ability ($F = 0.04$, $p = 0.83$, $\eta p^2 = 0.01$) and neither in the group*time interaction ($F = 0.25$, $p = 0.85$, $\eta p^2 = 0.01$) for HGS measurements and ($F = 0.69$, $p = 0.55$, $\eta p^2 = 0.03$) for MI ability. Table 2 shows the results for each of the groups.

CPM and TS

The ANOVA did not show significant differences over time for CPM ($F = 1.82$, $p = 0.18$, $\eta p^2 = 0.03$) or TS ($F = 0.001$, $p = 0.97$, $\eta p^2 = 0.0$), and neither in the group*time interaction for CPM ($F = 0.32$, $p = 0.81$, $\eta p^2 = 0.01$) or TS ($F = 2.00$, $p = 0.12$, $\eta p^2 = 0.11$) (Table 2).

Discussion

As far as the authors know, the present study is the first to combine NM with movement representation techniques. Overall, the results showed that neural hand exercises applied through AO and MT, as well as the classic

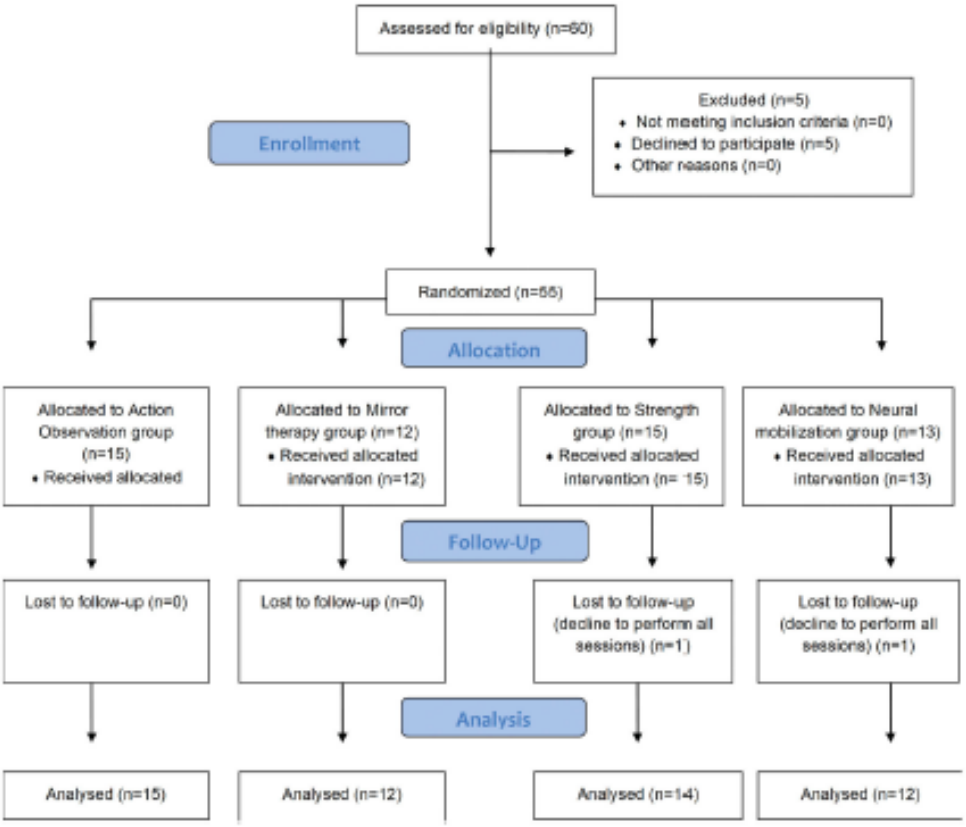

Figure 1. Study flow chart.

Table 1. Baseline outcomes.

	Action observation	Mirror therapy	Classic rehabilitation	Neural mobilization	*p*-value
Age	21.6 (±2.6)	23.3 (±5.2)	22.8 (±2.3)	22.5 (±3.4)	0.636
Height (m)	1.67 (±0.07)	1.7 (±0.12)	1.7 (±0.06	1.7 (±0.07)	0.605
Weight (KG)	63.9 (±8.1)	71.5 (±25.1)	66.9 (±11.6)	69.3 (±11.6)	0.606
BMI	22.6 (±1.8)	24.3 (±5.8)	22.5(±2.8)	23.5 (±2.8)	0.572
ULNT1	115.6 (±18.4)	118.0 (±18.1)	116.8 (±24.5)	121.6 (±25.2)	0.900
Carpal tunnel PPT_rigth (kg/cm^2)	6.1 (±1.7)	6.0 (±1.3)	6.5 (±2.5)	6.3 (±2.9)	0.918
PPT_left (kg/cm^2)	6.1 (±2.3)	5.9 (2.3)	6.4 (±2.8)	6.2 (±2.9)	0.950
Widespread proximal 2° MCJ (kg/cm^2)	5.9 (±1.5)	5.9 (±1.1)	5.8 (±2.4)	6.1 (±2.2)	0.982
BT (kg/cm^2)	4.5 (±1.8)	4.2 (±1.2)	4.5 (±1.3)	4.6 (±1.5)	0.947
Widespread distal AC (kg/cm^2)	5.9 (±1.5)	5.6 (±1.4)	6.0 (±3.2)	5.8 (±2.7)	0.974
C2 (kg/cm^2)	3.1 (±1.0)	3.5 (±1.9)	3.3 (±1.0)	3.4 (±1.5)	0.886
HGS	35.1 (±8.1)	30.5 (±6.9)	38.1 (±13)	35.7 (±10.3)	0.284
MI	48.3 (±8.2)	50.9 (±4.3)	49.4 (±6.1)	46.6 (±7.9)	0.458
CPM	1.5 (±1.3)	1.1 (±1.3)	1.8 (±1.6)	1.7 (±1.5)	0.586
TS	1.2 (±0.7)	1.8 (±1.1)	1.4 (±0.8)	2.9 (±2.6)	0.97

Abbreviations: BMI: body mass index; ULNT1: upper limb neurodynamic test 1; PPT: pain pressure threshold; CPM: conditioned pain modulation; TS: temporal summation; MCJ: metacarpophalangeal joint; BT: biceps tendon; AC: acromioclavicular joint; C2: second cervical vertebrae.
Data shown as mean (standard deviation). *p*-values reflect one-way ANOVA . *

rehabilitation program, showed an improvement in the mechanosensitivity and local and proximal hypoalgesia as well as the application of active NM. No changes in CPM, TS, HGS and MI ability were obtained in the four groups.

Regarding neural mechanosensitivity and mechanical hyperalgesia, results showed that all groups can produce a positive effect. In this regard, NM of the median nerve had already shown positive effects in reducing neural mechanosensitivity in healthy subjects. Beneciuk et al. found that NM of the medial nerve showed an increase of the range of motion (ROM) with a change magnitude percentage of approximately 6% (Beneciuk et al. 2009). In the actual study's

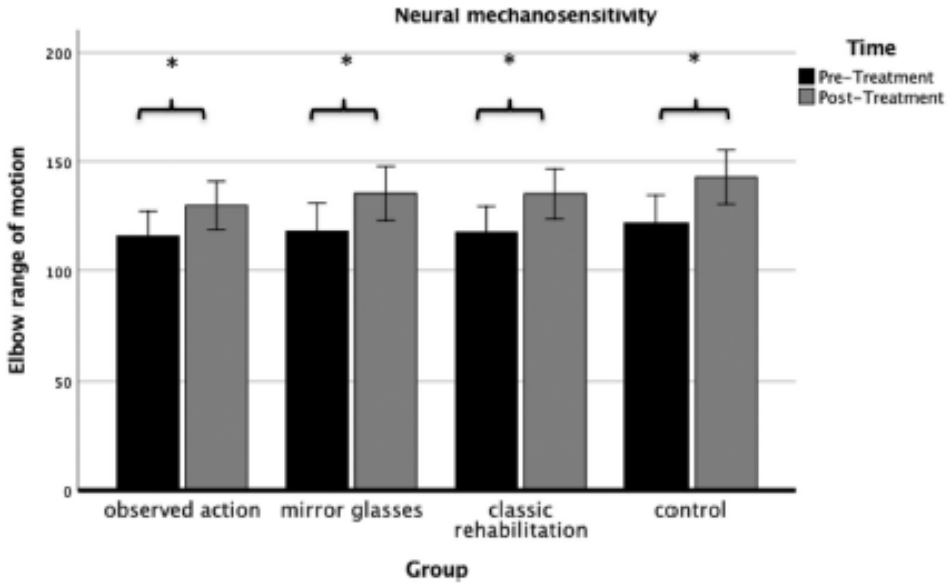

Figure 2. Within-group differences in neural mechanosensitivity outcome measure. *$p < 0.05$.

Table 2. Post-intervention results.

	Action observation		Mirror therapy		Classic rehabilitation		Neural mobilization		*p*	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	time	group
ULNT1	115.6 (±18.4)	129.8 (±18.5)	118.0 (±18.1)	135.4 (±22.5)	116.8 (±24.5)	135.2 (±20.9)	121.6 (±25.2)	142.9 (±24.3)	0.0001*	0.87
CT PPT_rigth (kg/cm^2)	6.1 (±1.7)	6.8 (±1.6)	6.0 (±1.3)	7.2 (±2.2)	6.5 (±2.5)	6.1 (±1.7)	6.3 (±2.9)	6.9 (±2.8)	<0.05*	0.11
CT PPT_left (kg/cm^2)	6.1 (±2.3)	6.8 (±1.7)	5.9 (2.3)	6.1 (±1.9)	6.4 (±2.8)	6.0 (±1.8)	6.2 (±2.9)	6.6 (±2.8)	0.43	0.55
Proximal widespread (kg/cm^2)	16.4 (±3.5)	18.6 (±3.7)	16.6 (±3.3)	18.2 (±4.2)	16.9 (±5.8)	17.7 (±3.8)	16.8 (±4.5)	25.27 (±22.9)	0.04*	0.30
2° MCJ (kg/cm^2)	5.9 (±1.5)	7.1 (±1.7)	5.9 (±1.1)	6.2 (±1.4)	5.8 (±2.4)	6.6 (±1.4)	6.1(±2.2)	6.8 (±2.6)	0.007*	0.69
BT (kg/cm^2)	4.5 (±1.8)	4.6 (±1.3)	4.2 (±1.2)	4.8 (±1.0)	4.5 (±1.3)	5.2 (±1.4)	4.6 (±1.5)	5.3 (±1.7)	0.010*	0.56
Distal Widespread AC (kg/cm^2)	5.9 (±1.5)	6.8 (±1.9)	5.6 (±1.4)	5.2 (±1.7)	6.0 (±3.2)	5.6 (±1.7)	5.8 (±2.7)	6.7 (±2.3)	0.415	0.26
C2 (kg/cm^2)	3.1 (±1.0)	3.5 (±1.2)	3.5 (±1.9)	3.1 (±0.8)	3.3 (±1.0)	3.4 (±0.8)	3.4 (±1.5)	3.9 (±2.1)	0.312	0.44
CPM	1.5 (±1.3)	1.6 (±1.2)	1.1 (±1.3)	1.7 (±1.3)	1.8 (±1.6)	1.7 (±1.1)	1.7 (±1.5)	2.2 (±1.6)	0.18	0.81
TS	1.2 (±0.7)	1.4 (±0.8)	1.8 (±1.1)	2.1 (±0.9)	1.4 (±0.8)	1.7 (±0.9)	2.9 (±2.6)	1.9 (±1.4)	0.97	0.12
HGS	35.1 (±8.1)	36.5 (±9.2)	30.5 (±6.9)	32.2 (±8.1)	38.1(±13)	38.9 (±14)	35.7 (±10.3)	37.1 (±12.1)	0.08	0.85
MI	48.3 (±8.2)	51.47 (±4.4)	50.9 (±4.3)	52.1 (±5.4)	49.4(±6.1)	47.1 (±14.3)	48.8 (6.9)	45.8 (15.2)	0.834	0.55

Abbreviations: ULNT1: upper limb neurodynamic test 1; PPT: pain pressure threshold; CPM: conditioned pain modulation; TS: temporal summation; MCJ: metacarpophalangeal joint; BT: biceps tendon; AC: acromioclavicular joint; C2: second cervical vertebrae
Data shown as mean (standard deviation). *p*-values reflect on ANOVA *$p < 0.05$.

case, the change magnitude percentage was superior, with a total value of 17.5% in the NM group. In the AO, MT, and CR groups, the values were slightly inferior to the previous highlighted one, however, these differences were not statistically significant.

These findings appear to suggest that both real exercise and that performed through movement representation techniques seem to share neurophysiological unspecific mechanisms mediated at least by a central level component due to the fact that AO training lacks real movement. Movement representation techniques produce an activity of the cerebral cortex similar to the one that produces when performing a real movement (Wright et al. 2014), and it is possible that this is associated with a hypoalgesic effect and as well to a reduction of the mechanosensitivity (Hardwick et al. 2018).

Researched evidence suggests that an MT intervention may have a positive impact on pain management (Wittkopf and Johnson 2017). Larsen et al. (2019) have shown an analgesic effect of the AO and the motor imagery associated with pain perception. These studies can help us understand why mechanosensitivity could change for a modification of cortical excitability.

Regarding local and proximal widespread hyperalgesia, one first study (Nunes et al. 2016), where mechanical hyperalgesia pre and post-NM were measured (using the VAS), it was obtained a percentage change of the variables measured of a 25.58%, then obtaining statistically positive and significant results in this case. In addition, Beltran-Alacreu et al. (2015) did measurements of the PPT in different areas, also involving pre and post-treatment with neural gliding.

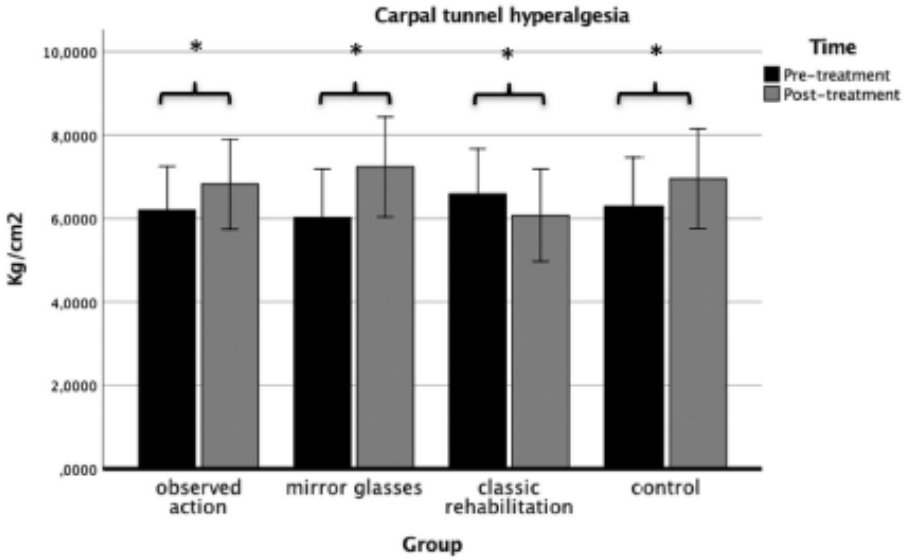

Figure 3. Comparative results in local hyperalgesia PPT over carpal tunnel variable. *$p < 0.05$.

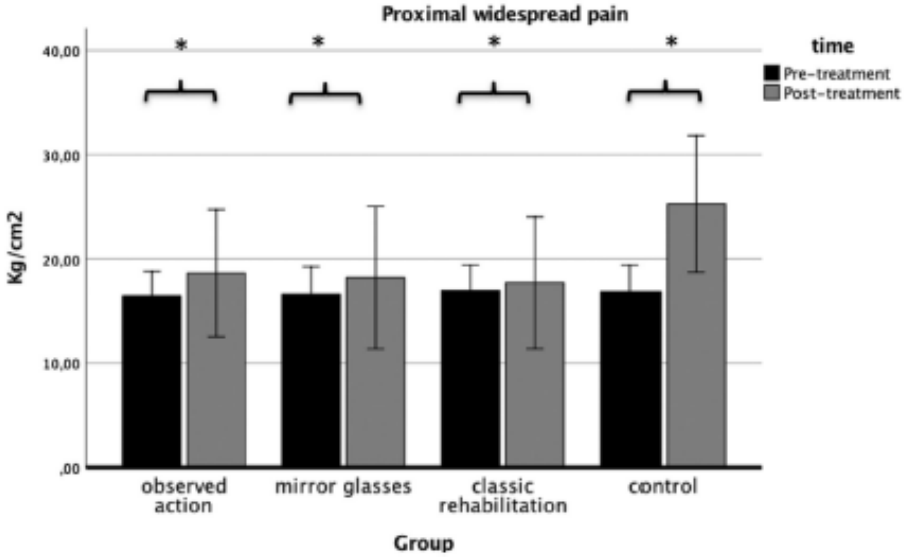

Figure 4. Within-group differences in proximal widespread outcome measure. *$p < 0.05$.

Change percentages (valued in the suboccipital zone, then valuing a distal joint) were 2.48% (right side) and 5.24% (left side). Our study, however, threw values of 14.7% partially caused by the measurement in the carpal tunnel region of the PPTs. In these studies, NM was performed in other areas of the arm than our intervention, so the results should be compared with caution.

So, therefore, it can be affirmed that the valuables obtained regarding hyperalgesia, and PPTs measurement, including proximal and distal ones, in this study, are fairly superior to the ones done in previous studies and in which the same variables are measured (being concerned that some of them are measured in different joints to the present study).

Regarding secondary outcomes, the results obtained on CPM are contradictory to those obtained in a previous study conducted by Morales Tejera et al. (2020) in which they found that both AO and MI have a positive effect similar to

the exercise in the cervical region. In this study, we have found no effect on the time*factor but the NM group obtained a percentage of change of 29.41%, while the MT group obtained a percentage of change greater than 54.54% and the SG showed a negative effect with a percentage of change of −5.5%. This may be because it has been applied in different areas, as well as the type of exercise is also different. In addition, in another study that applied NM versus a placebo in patients with neck pain, there was an improvement in CPM (Fernández-Carnero et al. 2019).

On the other hand, in the TS, all the groups obtain an increase or a worsening of it, except the NM group, which obtains a reduction of 34.48%. These results do not reach those obtained in the study conducted by Beneciuk et al. (2009) where they found a percentage of change of 87.7% in the temporal summation after applying nine NM sessions in healthy subjects.

Regarding the improvement of MI ability, no significant differences were found in any of the groups. The scientific literature has reported that introducing visual inputs can favour the imagination process (Holmes and Calmels 2008). In addition, motor variables such as strength, activity levels or the person's general physical condition can modulate the imagination activity (Cuenca-Martínez et al. 2020a). Therefore, the results seem to be contradictory in this aspect since an improvement in the cognitive process could be expected. However, it is likely that healthy subjects, also showing a good ability to imagine could be the factors that explain the absence of improvement in this variable despite the intervention performed.

Finally, regarding HGS, it seems that NMs, as well as NMs carried out through AO or MT, were not able to promote significant changes in this variable. AO has been shown to engage the motor system. Di Rienzo et al. (2019) found an improvement of the maximum isometric force in an AO session. These findings were also found when AO was combined with MI (Shimada et al. 2019) or both with real exercise compared to only real exercise (Losana-Ferrer et al. 2018). It seems, therefore, that there may be some level of specificity in causing peripheral sensorimotor changes according to the type of exercise-trained.

Clinical implications

The impact of the findings suggests that neural exercises using movement representation techniques could be used in entrapment neuropathies such as carpal tunnel syndrome, especially in patients with severe or recalcitrant neuropathic pain with an inability to perform physiological movements.

Limitations

Some limitations must be considered in this study, the first one, has been carried out in asymptomatic subjects, and the results cannot be extrapolated to a population in the presence of pathology. Secondly, it has only been measured immediately, and it is necessary to evaluate their medium- and long-term effects.

Conclusion

Results showed that AO, MT, strength exercises and active NM could induce within-group changes in neural mechanosensitivity and local and proximal hyperalgesia in a similar way. However, there was no difference in CPM, TS, HGS and MI ability. Although it seems that neural mechanosensitivity can be improved with movement representation techniques, it is unpredictable to verify this in patients with entrapment neuropathy such as carpal tunnel syndrome.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

Ethical approval

The trial was approved by the ethics committee of the Rey Juan Carlos University (2703201906919) and subsequently registered in clinicaltrial.gov (NCT04086563).

ORCID

Luis Matesanz-García http://orcid.org/0000-0001-5148-6336
Julio Eduardo Cáceres-Pajuelo http://orcid.org/0000-0001-5733-1247
Ferran Cuenca-Martínez http://orcid.org/0000-0003-4644-3758
Roy La Touche http://orcid.org/0000-0001-6379-6155
Carlos Goicoechea-García http://orcid.org/0000-0002-6226-6934
Josué Fernández-Carnero http://orcid.org/0000-0002-1314-624X

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7. Discusión

En las dos cohortes de pacientes con STC (n_{total}= 138) incluidas en esta tesis, la mayoría de estos presentaba DN. Con respecto al primer grupo de pacientes (del estudio I) el 20% no tiene DN, el 50% tiene DN leve y el 30% tiene DN moderada/grave. En el estudio II el porcentaje de pacientes con características neuropáticas ascendió al 93%. La presencia de DN se asoció con una mayor gravedad de los síntomas y déficits funcionales, así como con déficits en las pruebas sensoriales. Las pérdidas más pronunciadas se dieron en la detección mecánica. Los perfiles somatosensoriales eran en gran medida comparables entre los pacientes con y sin DN. Sin embargo, un aumento de la gravedad del DN se asoció a una pérdida más pronunciada de las capacidades funcionales en los territorios de los nervios mediano y radial. Por el contrario, no se identificaron diferencias en las variables neurofisiológicas ni en la integridad estructural de las fibras nerviosas en las biopsias de piel entre los grupos de pacientes. Para completar los perfiles sensoriales, en el estudio II se realizaron pruebas de procesamiento del dolor. En esta segunda cohorte, los pacientes mostraron claros indicios de la presencia de mecanismos de dolor central, tal y como se desprende de la hiperalgesia mecánica local y de la MCD en comparación con los voluntarios sanos. Por el contrario, no se observaron cambios en la sumación temporal. Cabe destacar que no hubo asociación del CSI con las medidas psicofísicas o la propagación de los síntomas indicativos de los mecanismos centrales del dolor. Con relación a los cuestionarios, muchos aspectos del bienestar emocional (p. ej., la rumiación y la impotencia del PCS, así como la cognición y la evasión del PASS) y el sueño se vieron más afectados con el aumento de la gravedad del DN. Nuestros resultados indican que, aparte de las claras diferencias en la gravedad de los síntomas y los déficits funcionales, las medidas somatosensoriales

estructurales y funcionales son en gran medida comparables en los pacientes con y sin DN.

La gravedad de la DN está asociada a la disfunción nerviosa somatosensorial, pero no a la integridad nerviosa estructural. Cabe destacar que el aumento de la gravedad del DN se acompañó de una reducción del bienestar emocional, un aumento de los trastornos del sueño y la presencia de síntomas extraterritoriales, lo que indica una contribución más dominante de los mecanismos centrales. Hay que reseñar que, el CSI sí tuvo una correlación con la salud emocional. Se halló una correlación moderada entre el CSI y las puntuaciones de depresión, lo que sugiere que el CSI puede estar más estrechamente ligado a parámetros psicológicos que las medidas psicofísicas indicativas de los mecanismos centrales del dolor en pacientes con lesiones nerviosas focales que cursen con dolor.

En ambos estudios encontramos una presencia de DN alta del 80% (Matesanz et al., 2021) y el 93% (Matesanz-garcia et al., 2022) respectivamente. Estudios previos mostraron una prevalencia de DN en neuropatías por atrapamiento más bajas y con amplias diferencias (31-77%) (Gürsoy et al., 2013; Sonohata et al., 2014, 2017; Tampin et al., 2018b). Esto se ha atribuido al uso de distintos cuestionarios, a lo que se añade que ninguno de ellos ha sido validado en la patología del STC.

Los pacientes con STC mostraron una pérdida de función ante estímulos térmicos y mecánicos en el territorio de inervación del nervio mediano, dicha pérdida es independiente de la presencia de DN. Las alteraciones previamente mencionadas, concuerdan con la disfunción de fibras nerviosas pequeñas y grandes. Esto confirma resultados previamente descritos en otros grupos de pacientes con STC (Lang et al., 1995; Schmid et al., 2014) y en otras neuropatías periféricas focales y sistémicas (Held et al., 2019; Raputova et al., 2017; Tampin et al., 2018a; Themistocleous et al., 2016; Tschugg et al., 2015).

La expansión fuera del territorio del mediano de los síntomas fue más frecuente en los pacientes con DN moderada/grave (Matesanz et al., 2021). Dicha propagación ha demostrado estar asociada con la hiperalgesia mecánica (Matesanz et al., 2021; Matesanz-garcia et al., 2022) y térmica (Zanette et al., 2010) y, por tanto, se ha atribuido a mecanismos centrales (Zanette et al., 2006, 2010). La severidad del dolor también se asocia a la hipoestesia presente en el territorio del nervio radial (Matesanz et al., 2021). Este fenómeno se había observado previamente fuera del territorio del nervio mediano en una cohorte más pequeña de pacientes con STC (Schmid et al., 2014).

Aunque la hiperalgesia generalizada suele aceptarse como signo de mecanismos centrales, normalmente se espera que la hiposensibilidad como signo de disfunción nerviosa se restrinja a la zona del nervio afectado. Sin embargo, cada vez hay más pruebas de que la pérdida sensorial también puede encontrarse en zonas no afectadas en pacientes con DN (Krause et al., 2016; Landmann et al., 2017; Matesanz-garcia et al., 2022; Tampin et al., 2012; Westermann et al., 2011; Younis et al., 2016).

En el segundo estudio de esta tesis, se describe la presencia de hiperalgesia mecánica tanto local como remota y una menor eficacia de la MCD (Matesanz-garcia et al., 2022). La propagación extraterritorial de los síntomas en pacientes con STC se ha descrito previamente (Zanette et al., 2006, 2010) en la literatura y se ha confirmado en dos estudios de la presente tesis (Matesanz et al., 2021; Matesanz-garcia et al., 2022). Este fenómeno se ha asociado a la presencia de mecanismos centrales. La hiperalgesia mecánica también suele interpretarse como un signo de sensibilización central (Baron et al., 2017; Baumann et al., 1991). La hiperalgesia mecánica local (y remota) se ha descrito anteriormente en neuropatías periféricas focales, incluido el STC (Fernandez-De-Las-Peñas et al., 2009; Held et al., 2019;

Zanette et al., 2010). Sin embargo, otras cohortes de pacientes no pudieron confirmarlo (Baskozos et al., 2020; Schmid et al., 2014). Esta discrepancia puede atribuirse a diferentes vías de reclutamiento, así como a las diferentes localizaciones de las mediciones del PPT (por ejemplo, la cara palmar del dedo índice, el túnel carpiano, etc.).

Los resultados somatosensoriales descritos en esta tesis se ven reforzados tras la reciente publicación de una revisión sistemática en la que concluyen que en general, los pacientes con STC presentan aumento significativo de la sensibilidad al dolor mecánico en los territorios del nervio mediano y a distancia en el antebrazo ($P < 0,05$) y un aumento significativo de los umbrales de dolor por presión y calor en la zona del carpo ($P < 0,05$) (Sobeeh et al., 2021).

Una de las herramientas más utilizadas en el ámbito clínico para evaluar la presencia de sensibilización central es el CSI. Esto se debe a una mayor facilidad para el diagnóstico, y que los equipos utilizados en investigación suelen ser caros y con protocolos muy largos. Una reciente revisión sistemática informa de una alta validez de constructo del CSI (Scerbo et al., 2018). Sin embargo, los estudios incluidos compararon el CSI con otros cuestionarios relacionados con la intensidad del dolor, la salud general, el bienestar emocional o el sueño. Es posible que exista una relación recíproca de estas medidas con los mecanismos centrales del dolor. Sin embargo, estos constructos no son medidas de sensibilización central, que es lo que pretende evaluar el CSI. Sorprendentemente, ni siquiera el desarrollo original del desarrollo del CSI incluía medidas psicofísicas de los mecanismos centrales del dolor, que se consideran las mejores prácticas para evaluar la manifestación de la sensibilización central en humanos (Arendt-Nielsen et al., 2018). En los últimos años, diversos trabajos han comparado el CSI con pruebas psicofísicas indicativas de los mecanismos centrales del dolor. Cabe

destacar que la mayoría de los estudios no lo encontraron (dos Santos Proençaa et al., 2021; Hendriks et al., 2020; Kregel et al., 2018) o esta era una correlación débil (Gervais-Hupé et al., 2018; Zafereo et al., 2021) entre el CSI y las pruebas psicofísicas en pacientes con dolor musculoesquelético. Esto, junto con nuestros hallazgos de ausencia de asociación entre el CSI y las pruebas psicofísicas en pacientes con lesiones nerviosas focales, cuestiona aún más la validez del CSI para detectar los correlatos humanos de la sensibilización central.

Hay que tener en cuenta algunas limitaciones en el estudio I. Es un análisis post hoc de 2 cohortes publicadas de carácter exploratorio y, por tanto, no incluyó un cálculo del tamaño de la muestra a priori. No obstante, nuestro estudio contiene la mayor cohorte de STC profundamente fenotipada hasta la fecha, y su tamaño fue lo suficientemente grande como para detectar tamaños de efecto moderados entre los grupos de pacientes. Sin embargo, las cifras de algunos subgrupos de pacientes fueron relativamente bajas. Esto puede haber contribuido a la ausencia de diferencias de grupo, por ejemplo, en los contrastes previstos de los grupos con DN y sin DN. Otra limitación a tener en cuenta es que la ingesta de analgésicos no se interrumpió antes de la elaboración del perfil somatosensorial y, por lo tanto, puede haber influido en nuestras lecturas, en particular las relacionadas con la hiperalgesia.

Para el estudio II, el tamaño de la muestra se calculó para detectar diferencias en el procesamiento central del dolor entre personas sanas y pacientes con STC. Mientras que tenía una potencia adecuada para detectar grandes efectos en las correlaciones entre el CSI y las pruebas psicofísicas, se habrían pasado por alto correlaciones pequeñas o moderadas. Sin embargo, la inspección de los datos demostró claramente la ausencia de tendencias e incluso

si muestras más grandes pudieran haber detectado correlaciones significativas, éstas habrían sido probablemente débiles.

Se reclutaron pacientes de las listas de espera de cirugía, lo que probablemente incluya perfiles más graves. Sin embargo, la gravedad de los síntomas y de la función en nuestro estudio era comparable con cohortes anteriores de STC de atención primaria (Shetty et al., 2020) y de atención secundaria (Zanette et al., 2010). El examinador que realizó las pruebas psicofísicas no podía estar cegado a la asignación de grupos (STC frente a sanos). Para minimizar el sesgo, el examinador no conocía el resultado del CSI y otros cuestionarios hasta después de realizar las pruebas psicofísicas. Según la práctica habitual en los hospitales participantes, la prueba de electrodiagnóstico sólo se realizó en el lado afectado. Por lo tanto, es posible que no se hayan detectado casos subclínicos de STC en el lado contralateral (Enax-Krumova et al., 2021).

Con el fin de analizar los efectos fisiológicos de la fisioterapia y poder entender mejor los cambios bioquímicos, se realizó una revisión sistemática en modelos animales de dolor neuropático periférico (estudio III). Las dos intervenciones más comunes fueron electro-acupuntura y ejercicio. También se identificaron estudios con intervenciones tales como movilización neural, movilizaciones articulares y diferentes agentes físicos como ultrasonidos o laser. La mayoría de los trabajos analizados observaron que las distintas intervenciones de fisioterapia son capaces de regular la sobreexpresión de sustancias pro-nociceptivas. Pese a los resultados tan prometedores, hay que tener cierta cautela, debido al alto riesgo de sesgo presentado en la mayoría de los trabajos.

La importancia de los biomarcadores específicos para mantener el dolor neuropático no sólo lo sabemos gracias a modelos preclínicos (Clark et al., 2013), sino también en humanos (Sommer et al., 2018). Los hallazgos pertenecientes a nuestro estudio III sugieren que la fisioterapia puede modular los biomarcadores relacionados con el dolor neuropático en modelos preclínicos. Aunque los biomarcadores más estudiados están relacionados con el sistema inmunitario y los neurotrofinas, esta revisión identificó otras dianas como los neurotransmisores o el sistema opioide. En los últimos años varias publicaciones han informado de la posible relación entre la presencia de dolor neuropático y algunos de los biomarcadores humanos aquí señalados. Por ejemplo, se cree que la neuroinflamación desempeña un papel crucial en la generación y el mantenimiento del dolor neuropático en modelos preclínicos (Austin & Moalem-Taylor, 2010). Asimismo, cada vez hay más pruebas que confirman la importancia de la neuroinflamación en el dolor neuropático en humanos (Sommer et al., 2018). Esto es evidente tanto en pacientes con lesiones nerviosas focales (Held et al., 2019) pero también en pacientes con polineuropatías (Hubertus Köller, M.D., Bernd C. Kieseier, M.D., Sebastian Jander, M.D., and Hans-Peter Hartung, 2019; Ziegler et al., 2019). Por tanto, nuestros hallazgos indican que la fisioterapia puede modular biomarcadores que son relevantes en pacientes con dolor neuropático.

Además del sistema neuroinmune, otros sistemas pueden influir en la presencia de DN. Por ejemplo, las neurotrofinas se han relacionado con este tipo de dolor. Para ejemplo, el NGF actúa como mediador del dolor patológico (Herzberg et al., 1997) y también en humanos, los niveles elevados de NGF se han asociado con el dolor (Svensson et al., 2003). El BDNF ha mostrado efectos hiperalgésicos similares, además su presencia en los ganglios de la raíz dorsal y la médula espinal se correlaciona con el comportamiento del dolor neuropático

(Siniscalco et al., 2011). La disfunción del sistema opioide se ha descrito en preclínica (Porreca et al., 1998) y en humanos con DN (DosSantos et al., 2012). Otra medida indirecta del sistema opioide es la modulación condicionada del dolor. Esta disfunción ha sido tratada y descrita en el estudio II de la presente tesis.

Aunque el estudio III arroja resultados prometedores no está libre de limitaciones. Sólo se incluyeron estudios escritos en inglés. La heterogeneidad de los métodos de medición, así como el gran número de diferentes biomarcadores analizados desafía la interpretación. Cabe destacar que el 92,5% de los estudios sólo incluía ratas macho. Está bien establecido que el comportamiento del dolor y los mecanismos subyacentes difieren según el sexo (Rosen et al., 2017), lo que limita la generalización de nuestros resultados. Es importante destacar que el riesgo de sesgo fue alto y que la información según las directrices ARRIVE fue deficiente en la mayoría de los estudios. El informe inconsistente de los datos estadísticos de resumen impidió realizar un metaanálisis. La mala información y la baja calidad metodológica se han identificado como retos importantes en la investigación preclínica, incluso en el campo del dolor (Macleod et al., 2009; Vollert et al., 2020). Con la reciente publicación de las directrices ARRIVE, se espera que la calidad de los estudios preclínicos y sus informes mejore, facilitando así futuras revisiones sistemáticas (Kilkenny et al., 2010).

Debido a las características centrales que sufren la mayoría de los pacientes con neuropatía periférica por atrapamiento. Se planteó la posibilidad de empezar a testar una nueva intervención. En el estudio IV, se planteó la combinación de técnicas de imaginería motora y terapia de espejo con la movilización neural tan utilizada previamente y con resultados a veces contradictorios (Basson et al., 2017). La combinación de dichas técnicas redujo la mecanosensibilidad neural y la hiperalgesia mecánica tanto proximal como distal.

Estos resultados parecen sugerir que tanto el ejercicio real como el realizado mediante técnicas de representación del movimiento parecen compartir mecanismos neurofisiológicos específicos mediados al menos, por un componente de nivel central, debido al hecho de que el entrenamiento de AO carece de movimiento real. Las técnicas de representación del movimiento producen una actividad de la corteza cerebral similar a la que se produce al realizar un movimiento real (Wright et al., 2014).

Cabe la posibilidad que la modulación de los síntomas encontrados en nuestro estudio IV (Matesanz-garcía et al., 2021) esté asociada a un efecto hipoalgésico y también a una reducción de la mecanosensibilidad, los cual reforzaría las conclusiones planteadas por Hardwick y col. (Hardwick et al., 2018). Otros autores con Priscilla y col. o Larson y col. también apuntan en esa dirección, sugieren que una intervención de terapia espejo puede tener un impacto positivo en el manejo del dolor. Han demostrado un efecto hipoalgésico de la OA y la imaginería motora asociada con la percepción del dolor (Larsen et al., 2019; Priscilla & Johnson, 2017). Estos estudios, en los que todo gira en torno al movimiento, pueden ayudarnos a entender por qué la mecanosensibilidad y el dolor podría cambiar por una modificación de la excitabilidad cortical.

8. Conclusiones

Estudio I

Our cohort has shown that neuP is common in patients with CTS and its presence is accompanied by more severe symptom and function deficits. Apart from a deficit in mechanical detection, the presence of neuP was not associated with substantial changes in somatosensory function or structural nerve pathology. The severity of neuP was accompanied by a more pronounced somatosensory dysfunction. Of note, neuP severity was related to more pronounced deficits in emotional well-being and sleep quality and the presence of extraterritorial spread of symptoms suggesting a more dominant contribution of central mechanisms. These differences between subgroups raise the question whether treatment stratification may help improve management for patients with CTS.

Estudio II

Our results suggest that patients with CTS have changes indicative of altered central pain processing. The CSI does not seem to be associated with psychophysical measures of central sensitization. Rather, the CSI correlates with emotional wellbeing, in particular depression scores. These data question the construct validity of the CSI in detecting central sensitization in patients with focal peripheral nerve injury.

Estudio III

Our results suggest that exercises, electro-acupuncture, neural mobilization, and physical agents modulate biomarkers of neuropathic pain in preclinical models. Only few studies were available for joint mobilization and acupuncture, thus preventing firm conclusions.

Physiotherapy interventions seem to regulate the expression of a range of biomarkers particularly associated with the neuro-immune system, opioid system, neurotrasnmitters, neurotrophins and receptors. The high risk of bias and poor reporting quality however prevents firm conclusions. Nevertheless, our findings may be used to inform the design of future human studies. Future preclinical studies need to follow higher standards of methodological quality and reporting to advance this promising field.

Estudio IV

Results showed that AO, MT, strength exercises and active NM could induce within-group changes in neural mechano-sensitivity and local and proximal hyperalgesia in a similar way. However, there was no difference in CPM, TS, HGS and MI ability. Although it seems that neural mechanosensitivity can be improved with movement representation techniques, it is unpredictable to verify this in patients with entrapment neuropathy such as carpal tunnel syndrome.

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10. Publicaciones en congresos relacionados con la tesis

- *Imaginería Motora vs ejercicio en la mejora del dolor en área del nervio Mediano Imaginería Motora vs ejercicio en la mejora del dolor en área del nervio Mediano.* **V Congreso Fisioterapia y Dolor 14 feb. 2020**

- *Comparación de la efectividad de "ejercicios neurales post cirugía" vs "ejercicios neurales" vs "cirugía" para la mejora del dolor y la activación del sistema inhibitorio descendente del dolor en pacientes con síndrome del túnel del carpo: Ensayo clínico Comparación de la efectividad de "ejercicios neurales post cirugía" vs "ejercicios neurales" vs "cirugía" para la mejora del dolor y la activación del sistema inhibitorio descendente del dolor en pacientes con síndrome del túnel del carpo: Ensayo clínico.* **V Jornadas Doctorales Universidad de Murcia 29 may. 2019**

- *Influencia del ejercicio en la modulación de biomarcadores de dolor en modelos preclínicos de dolor neuropático periférico. Revisión sistemática****. I Congreso Internacional de Fisioterapia "Movimiento y Dolor". 22 abr. 2022***

11. Anexos

ANEXO I Comités de Ética Hospitales:

Hospital Universitario 12 de Octubre

Comunidad de Madrid

i+12 Instituto de Investigación Hospital 12 de Octubre

Nº CEIm: 20/092

INFORME DE VIABILIDAD PARA LA REALIZACION DEL ESTUDIO EN EL HOSPITAL 12 DE OCTUBRE

La Secretaría Técnica del Comité de Ética de la Investigación con medicamentos (CEIm)

C E R T I F I C A

El estudio cuenta con un dictamen favorable de un CEIm acreditado en España y tras evaluar los aspectos locales del estudio titulado: **Comparación de la efectividad de "ejercicios neurales post cirugía" vs "cirugía" para la mejora del dolor y la activación del sistema inhibitorio descendente del dolor en pacientes con síndrome del túnel del carpo: Ensayo clínico, alateorizado, en condiciones de práctica clínica habitual.**

Del cual es Investigador Principal el ***CECILIA LOPEZ, David*** del Servicio de ***CIRUGIA ORTOPEDICA Y TRAUMATOLOGIA***.

Entendiendo que dicho estudio se ajusta a las normas éticas esenciales y criterios deontológicos que rigen en este Centro, y siendo correctos los aspectos locales necesarios, esta Secretaría ***INFORMA FAVORABLEMENTE*** a la realización de dicho proyecto en este Centro.

Lo que firmo en Madrid, a 4 de marzo de 2020.

Hospital Universitario 12 de Octubre

SECRETARIA TÉCNICA - CEIm

Secretaría Técnica del CEIm Hospital 12 de Octubre

Secretaría Técnica del Comité de Ética de la Investigación CEIm, Hospital 12 de Octubre • Av. de Córdoba s/n 28041 Madrid
Centro Actividades Ambulatoria, Bloque D, Planta 6ª • e-mail: ceicdoc@h12o.es

Hospital Universitario Severo Ochoa

C.E.I.C

Dña. Ana López Martín, Secretaria del Comité Ético de Investigación Clínica del Hospital Universitario Severo Ochoa,

CERTIFICA

Que el Ensayo Clínico sin medicamento con título:

"Comparación de la efectividad de "ejercicios neurales post cirugía" vs "ejercicios neurales" vs "cirugía" para la mejora del dolor y la activación del sistema inhibitorio descendente del dolor en pacientes con síndrome del túnel del carpo: Ensayo clínico, aleatorizado,en condiciones de práctica clínica habitual"

Ha sido valorada por este Comité la respuesta a las aclaraciones solicitadas en el Acta 09/17 (25/10/2017), considerándole **FAVORABLE** en su reunión de fecha **29 de diciembre de 2017.**

Éste Comité acepta que sea llevada a cabo por la **Dra. Ana Isabel Simón Carrascal,** del servicio de **Traumatología y Cirugía Ortopédica del Hospital Universitario Severo Ochoa.**

Además, se hace constar que:
1º. El CEIC, tanto en su composición, como en los PNTs cumple las normas de BPC (CPMP/ICH/135/95) y con el RD 1090/2015.
2º. La composición actual del CEIC es la siguiente:

D. Adolfo Ramos Luengo	Presidente, adjunto del Servicio de Anestesiología
D. Carlos González Juárez	Vicepresidente, adjunto de Psiquiatría
Dª. Ana López Martín	Secretaria Técnica, adjunta del servicio de Oncología.
Dª Amparo Lucena Campillo	Vocal, adjunta del servicio de Farmacia
Dª Beatriz Medina Bustillo	Vocal, Farmacéutica Atención Primaria Dirección Asistencial Sur
D. Miguel Cervero Jiménez	Vocal, Presidente de la Comisión de Investigación
D. Sergio Quevedo Teruel	Vocal, adjunto de Pediatría y Áreas Específicas.
D. Daniel Ordorica Rubiano	Vocal, enfermero, Especialista en Geriatría.
Dª. Lucía Llanos Jiménez	Vocal, Farmacóloga Clínica
Dª. Mª Teresa Rodríguez Monje	Vocal, médico de Atención Primaria.
Dª Isabel Herranz Lama Noriega	Vocal lego, Lda. en Derecho, Especialista en Derecho sanitario.
Dª Ana Isabel Martín Cuesta	Vocal, miembro lego, administrativa del CEIC
D. Manuel Martínez Domínguez	Vocal, miembro lego representante de los pacientes

Leganés, 12 de diciembre de 2017

Fdo.: Ana López Martín

ANEXO II Comités ética URJC

Universidad Rey Juan Carlos

Rectorado

Doña. Adriana Izquierdo Lahuerta, Secretaria del Comité de Ética de la Investigación de la Universidad Rey Juan Carlos,

CERTIFICA

Que este Comité ha evaluado el proyecto de investigación titulado:

PROYECTO DE INVESTIGACIÓN EN IMAGINERÍA MOTORA SOBRE LAS CARACTERÍSTICAS DE SENSIBILIZACIÓN CENTRAL EN SUJETOS SANOS

Con número de registro interno: 2703201906919

y considera que:

- Se cumplen los requisitos éticos necesarios del protocolo en relación con los objetivos del estudio y están justificados los riesgos y molestias previsibles para los participantes.
- La capacidad del investigador y los medios disponibles son apropiados para llevar a cabo el estudio.

Por lo que ha decidido emitir un dictamen **FAVORABLE** para la realización de dicho proyecto, cuyo investigador principal es Don **JOSUÉ FERNÁNDEZ CARNERO** de la Facultad de Ciencias de la Salud de la URJC.

Lo que firmo en Móstoles a 27 de junio de 2019.

Firmado: Dña. Adriana Izquierdo Lahuerta.

- Este informe sólo tiene validez para el proyecto o procedimiento propuesto y en las condiciones en ellos descritas. Cualquier cambio que afecte a las implicaciones éticas y/o de seguridad del mismo y de los participantes, invalida este informe y deberá ser puesto en conocimiento de este Comité de Ética para su valoración.
- El Comité de Ética de la Investigación puede instar a las autoridades autonómicas para que proceda a la suspensión cautelar de la investigación autorizada en los casos en los que no se hayan observado los requisitos que establece la legislación vigente y sea necesaria para proteger los derechos de los ciudadanos.

Tulipán s/n - 28933 Móstoles Madrid España Tel. 34 91 665 50 63 Fax 34 91 664 71 25

ANEXO III Estrategia de búsqueda estudio III

CINAHL Search Formula vía EBSCO. Results: 165

("Models, Animal"[Mesh] OR "animal*" OR "mice" OR "rat*" OR "transgenic mice") AND ("nerve block method*" OR "nerve crush" OR "nerve constriction" OR "nerve crush" OR "nerve cut" OR "nerve constriction" OR "nerve injury" OR "nerve ligation" OR "constriction pathologic*" OR "chronic constriction injury" OR "peripheral neuropathy" OR "nerve inflammation" OR "neuropathy" OR "diabetic*" OR "chemotherapy" OR "metabolic*") AND ("neuropathic pain" OR "Neuralgia" [Mesh] OR "neuropathic*" OR "sciatica" OR "pain") AND ("Physical therapy modalities"[Mesh] OR "physical therap*" OR "physiotherap*" OR "Musculoskeletal manipulations" OR "Manual therap*" OR "exercise therapy" OR "exercise*" OR "run*" OR "swim*" OR "strength*" OR "endurance" OR "resistance" OR "physical conditioning" OR "neural tension technique*" OR "neural mobilization*" OR "neural mobilisation" OR "neural stretching" OR "neural gliding" OR "massage*" OR "massotherapy" OR "peripheral nerve therapy" OR "Electric Stimulation Therapy"[Mesh] OR electrotherap* OR "TENS" OR "Acupuncture"[Mesh] OR "dry needling" OR "manipulation*" OR "mobilization*" OR "mobilisation*") AND ("biomarker*" OR "biological factor*" OR "nerve tissue protein" OR "nerve regeneration" OR "pain measurement" OR "glial cell line-derived neurotrophic factor" OR "glial cell line-derived neurotrophic factor receptor*" OR "brain-derived neurotrophic factor" OR "nerve growth factor receptor*" OR "receptor trkB" OR "nerve growth factor*" OR "neurotrophin*" OR "receptor trkA" OR "receptor trkC" OR "neuropeptide*" OR "cytokine*" OR "interleukin*" OR "interleukin receptor" OR "macrophage*" OR "immunology*" OR "glial cell*" OR "astrocyte*" OR "schwann cell*" OR "microglia" OR "oligodendroglia*" OR "satellite cell*")

PsycINFO Search Formula vía EBSCO: Results:180

("Models, Animal"[Mesh] OR "animal*" OR "mice" OR "rat*" OR "transgenic mice") AND ("nerve block method*" OR "nerve crush" OR "nerve constriction" OR "nerve crush" OR "nerve cut" OR "nerve constriction" OR "nerve injury" OR "nerve ligation" OR "constriction pathologic*" OR "chronic constriction injury" OR "peripheral neuropathy" OR "nerve inflammation" OR "neuropathy" OR "diabetic*" OR "chemotherapy" OR "metabolic*") AND ("neuropathic pain" OR "Neuralgia" [Mesh] OR "neuropathic*" OR "sciatica" OR "pain") AND ("Physical therapy modalities"[Mesh] OR "physical therap*" OR "physiotherap*" OR "Musculoskeletal manipulations" OR "Manual therap*" OR "exercise therapy" OR "exercise*" OR "run*" OR "swim*" OR "strength*" OR "endurance" OR "resistance" OR "physical conditioning" OR "neural tension technique*" OR "neural mobilization*" OR "neural mobilisation" OR "neural stretching" OR "neural gliding" OR "massage*" OR "massotherapy" OR "peripheral nerve therapy" OR "Electric Stimulation Therapy"[Mesh] OR electrotherap* OR "TENS" OR "Acupuncture"[Mesh] OR "dry needling" OR "manipulation*" OR "mobilization*" OR "mobilisation*") AND ("biomarker*" OR "biological factor*" OR "nerve tissue protein" OR "nerve regeneration" OR "pain measurement" OR "glial cell line-derived neurotrophic factor" OR "glial cell line-derived neurotrophic factor receptor*" OR "brain-derived neurotrophic factor" OR "nerve growth factor receptor*" OR "receptor trkB" OR "nerve growth factor*" OR "neurotrophin*" OR "receptor trkA" OR "receptor trkC" OR "neuropeptide*" OR "cytokine*" OR "interleukin*" OR "interleukin receptor" OR "macrophage*" OR "immunology*" OR "glial cell*" OR "astrocyte*" OR "schwann cell*" OR "microglia" OR "oligodendroglia*" OR "satellite cell*")

Medline Search Formula (EBSCO). Results: 489

("Models, Animal"[Mesh] OR "animal*" OR "mice" OR "rat*" OR "transgenic mice") AND ("nerve block method*" OR "nerve crush" OR "nerve constriction" OR "nerve crush" OR "nerve cut" OR "nerve constriction" OR "nerve injury" OR "nerve ligation" OR "constriction pathologic*" OR "chronic constriction injury" OR "peripheral neuropathy" OR "nerve inflammation" OR

“neuropathy” OR "diabetic*" OR "chemotherapy" OR "metabolic*") AND (“neuropathic pain” OR “Neuralgia” [Mesh] OR “neuropathic*” OR “sciatica” OR “pain”) AND (“Physical therapy modalities”[Mesh] OR “physical therap*” OR “physiotherap*” OR "Musculoskeletal manipulations" OR "Manual therap*” OR “exercise therapy” OR “exercise*” OR “run*” OR “swim*” OR “strength*” OR “endurance” OR “resistance” OR “physical conditioning” OR "neural tension technique*" OR “neural mobilization*” OR “neural mobilisation” OR “neural stretching” OR “neural gliding” OR “massage*” OR “massotherapy” OR “peripheral nerve therapy” OR "Electric Stimulation Therapy"[Mesh] OR electrotherap* OR “TENS” OR “Acupuncture”[Mesh] OR “dry needling” OR "manipulation*” OR ”mobilization*" OR "mobilisation*") AND (“biomarker*” OR “biological factor*” OR “nerve tissue protein” OR “nerve regeneration” OR “pain measurement” OR “glial cell line-derived neurotrophic factor” OR “glial cell line-derived neurotrophic factor receptor*” OR “brain-derived neurotrophic factor” OR “nerve growth factor receptor*” OR “receptor trkB” OR “nerve growth factor*” OR “neurotrophin*” OR “receptor trkA” OR “receptor trkC” OR “neuropeptide*” OR “cytokine*” OR “interleukin*” OR “interleukin receptor” OR “macrophage*” OR “immunology*” OR “glial cell*” OR “astrocyte*” OR “schwann cell*” OR “microglia” OR “oligodendroglia*” OR “satellite cell*”)

PubMed Search Formula vía NLM. Results: 1405

("Models, Animal"[Mesh] OR "animal*" OR "mice" OR "rat*" OR "transgenic mice") AND ("nerve block method*" OR "nerve crush" OR "nerve constriction" OR "nerve crush" OR "nerve cut" OR "nerve constriction" OR "nerve injury" OR "nerve ligation" OR "constriction pathologic*" OR "chronic constriction injury" OR "peripheral neuropathy" OR "nerve inflammation" OR "neuropathy" OR "diabetic*" OR "chemotherapy" OR "metabolic*") AND ("neuropathic pain" OR "Neuralgia" [Mesh] OR "neuropathic*" OR "sciatica" OR "pain") AND ("Physical therapy modalities"[Mesh] OR "physical therap*" OR "physiotherap*" OR "Musculoskeletal manipulations" OR "Manual therap*" OR "exercise therapy" OR "exercise*" OR "run*" OR "swim*" OR "strength*" OR "endurance" OR "resistance" OR "physical conditioning" OR "neural tension technique*" OR "neural mobilization*" OR "neural mobilisation" OR "neural stretching" OR "neural gliding" OR "massage*" OR "massotherapy" OR "peripheral nerve therapy" OR "Electric Stimulation Therapy"[Mesh] OR electrotherap* OR "TENS" OR "Acupuncture"[Mesh] OR "dry needling" OR "manipulation*" OR "mobilization*" OR "mobilisation*") AND ("biomarker*" OR "biological factor*" OR "nerve tissue protein" OR "nerve regeneration" OR "pain measurement" OR "glial cell line-derived neurotrophic factor" OR "glial cell line-derived neurotrophic factor receptor*" OR "brain-derived neurotrophic factor" OR "nerve growth factor receptor*" OR "receptor trkB" OR "nerve growth factor*" OR "neurotrophin*" OR "receptor trkA" OR "receptor trkC" OR "neuropeptide*" OR "cytokine*" OR "interleukin*" OR "interleukin receptor" OR "macrophage*" OR "immunology*" OR "glial cell*" OR "astrocyte*" OR "schwann cell*" OR "microglia" OR "oligodendroglia*" OR "satellite cell*")

Scopus Search Formula vía ELSEVIER: Results: 1046

TITLE-ABS method*" OR "nerve crush" OR "nerve constriction" OR "nerve crush" OR "nerve cut" OR "nerve constriction" OR "nerve injury" OR "nerve ligation" OR "constriction pathologic*" OR "chronic constriction injury" OR "peripheral neuropathy" OR "nerve inflammation" OR "neuropathy" OR "diabetic*" OR "chemotherapy" OR "metabolic*") TITLE-ABS-KEY ("neuropathic pain" OR "Neuralgia" OR "neuropathic*" OR "sciatica" OR "pain") AND TITLE-ABS-KEY ("Physical therapy modalities" OR "physical therap*" OR "physiotherap*" OR "Musculoskeletal manipulations" OR "Manual therap*" OR "exercise therapy" OR "exercise*" OR "run*" OR "swim*" OR "strength*" OR "endurance" OR "resistance" OR "physical conditioning" OR "neural tension technique*" OR "neural mobilization*" OR "neural mobilisation" OR "neural stretching" OR "neural gliding" OR "massage*" OR "massotherapy" OR "peripheral nerve therapy" OR "Electric Stimulation Therapy" OR electrotherap* OR "TENS" OR "Acupuncture" OR "dry needling" OR "manipulation*" OR "mobilization*" OR "mobilisation*") TITLE-ABS-KEY ("biomarker*" OR "biological factor*" OR "nerve tissue protein" OR "nerve regeneration" OR "pain measurement" OR "glial cell line-derived neurotrophic factor" OR "glial cell line-derived neurotrophic factor receptor*" OR "brain-derived neurotrophic factor" OR "nerve growth factor recept-KEY ("animal*" OR "mice" OR "rat*" OR "transgenic mice") AND TITLE-ABS-KEY ("nerve block or*" OR "receptor trkB" OR "nerve growth factor*" OR "neurotrophin*" OR "receptor trkA" OR "receptor trkC" OR "neuropeptide*" OR "cytokine*" OR "interleukin*" OR "interleukin receptor" OR "macrophage*" OR "immunology*" OR "glial cell*" OR "astrocyte*" OR "schwann cell*" OR "microglia" OR "oligodendroglia*" OR "satellite cell*")

Wos Searh Formula vía ELSEVIER: Results: 327

Índices=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Período de tiempo=Todos los años

1 11.064.724 TS= ("animal*" OR "mice" OR "rat*" OR "transgenic mice")

Índices=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Período de tiempo=Todos los años

2 1.380.208 TS=("nerve block method*" OR "nerve crush" OR "nerve constriction" OR "nerve crush" OR "nerve cut" OR "nerve constriction" OR "nerve injury" OR "nerve ligation" OR "constriction pathologic*" OR "chronic constriction injury" OR "peripheral neuropathy" OR "nerve inflammation" OR "neuropathy" OR "diabetic*" OR "chemotherapy" OR "metabolic*")

Índices=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Período de tiempo=Todos los años

3 642.424 TS=(“neuropathic pain” OR"neuralgia" OR “neuropathic*” OR “sciatica” OR “pain”)

Índices=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Período de tiempo=Todos los años

4 4.273.448 TS= (“Physical therapy modalities” OR “physical therap*” OR “physiotherap*” OR "Musculoskeletal manipulations" OR "Manual therap*” OR “exercise therapy” OR “exercise*” OR “run*” OR “swim*” OR “strength*” OR “endurance” OR “resistance” OR “physical conditioning” OR "neural tension technique*" OR “neural mobilization*” OR “neural mobilisation” OR “neural stretching” OR “neural gliding” OR “massage*” OR “massotherapy” OR “peripheral nerve therapy” OR "Electric Stimulation Therapy" OR electrotherap* OR “TENS” OR “Acupuncture” OR “dry needling” OR "manipulation*” OR ”mobilization*" OR "mobilisation*")

5 1.387.467 TS=("biomarker*" OR "biological factor*" OR "nerve tissue protein" OR "nerve regeneration" OR "pain measurement" OR "glial cell line-derived neurotrophic factor" OR "glial cell line-derived neurotrophic factor receptor*" OR "brain-derived neurotrophic factor" OR "nerve growth factor receptor*" OR "receptor trkB" OR "nerve growth factor*" OR "neurotrophin*" OR "receptor trkA" OR "receptor trkC" OR "neuropeptide*" OR "cytokine*" OR "interleukin*" OR "interleukin receptor" OR "macrophage*" OR "immunology*" OR "glial cell*" OR "astrocyte*" OR "schwann cell*" OR "microglia" OR "oligodendroglia*" OR "satellite cell*")

Índices=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Período de tiempo=Todos los años

6 327 #5 AND #4 AND #3 AND #2 AND #1

Índices=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Período de tiempo=Todos los años

# 6	**327**	#5 AND #4 AND #3 AND #2 AND #1	Editar		

		Índices=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Período de tiempo=Todos los años			
# 5	**1.387.467**	TS=("biomarker*" OR "biological factor*" OR "nerve tissue protein" OR "nerve regeneration" OR "pain measurement" OR "glial cell line-derived neurotrophic factor" OR "glial cell line-derived neurotrophic factor receptor*" OR "brain-derived	Editar		

		neurotrophic factor" OR "nerve growth factor receptor*" OR "receptor trkB" OR "nerve growth factor*" OR "neurotrophin*" OR "receptor trkA" OR "receptor trkC" OR "neuropeptide*" OR "cytokine*" OR "interleukin*" OR "interleukin receptor" OR "macrophage*" OR "immunology*" OR "glial cell*" OR "astrocyte*" OR "schwann cell*" OR "microglia" OR "oligodendroglia*" OR "satellite cell*")			

		Índices=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Período de tiempo=Todos los años			
# 4	**4.273.448**	TS= (“Physical therapy modalities” OR “physical therap*” OR “physiotherap*” OR "Musculoskeletal manipulations" OR "Manual therap*” OR “exercise therapy” OR “exercise*” OR “run*” OR “swim*” OR “strength*” OR “endurance” OR	Editar		

		“resistance” OR “physical conditioning” OR "neural tension technique*" OR “neural mobilization*” OR “neural mobilisation” OR “neural stretching” OR “neural gliding” OR “massage*” OR “massotherapy” OR “peripheral nerve therapy” OR "Electric Stimulation Therapy" OR electrotherap* OR “TENS” OR “Acupuncture” OR “dry needling” OR "manipulation*” OR ”mobilization*"			

		OR "mobilisation*") *Índices=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Período de tiempo=Todos los años*			
# 3	**642.424**	TS=("neuropathic pain" OR"neuralgia" OR "neuropathic*" OR "sciatica" OR "pain") *Índices=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Período de tiempo=Todos los años*	Editar		

# 2	**1.380.208**	TS=("nerve block method*" OR "nerve crush" OR "nerve constriction" OR "nerve crush" OR "nerve cut" OR "nerve constriction" OR "nerve injury" OR "nerve ligation" OR "constriction pathologic*" OR "chronic constriction injury" OR "peripheral neuropathy" OR "nerve inflammation" OR "neuropathy" OR "diabetic*" OR "chemotherapy" OR "metabolic*")	Editar		

		Índices=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Período de tiempo=Todos los años			
# 1	**11.064.724**	TS= ("animal*" OR "mice" OR "rat*" OR "transgenic mice") *Índices=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Período de tiempo=Todos los años*			

EMBASE: Results:897

No.	Query	Results
#90	**#30** OR **#31** OR **#32** OR **#33** OR **#34** OR **#35** OR **#36** OR **#37** OR **#38** OR **#39** OR **#40** OR **#41** OR **#42** OR **#43** OR **#44** OR **#45** OR **#46** OR **#47**OR **#48** OR **#49** OR **#50** OR **#51** OR **#52** OR **#53** OR **#54** OR **#55** OR **#56** OR **#57** OR **#58**	**2,901,286**
#89	**#25** OR **#26** OR **#27** OR **#28** OR **#29**	**1,308,928**
#88	**#8** OR **#9** OR **#10** OR **#11** OR **#12** OR **#13** OR **#14** OR **#15** OR **#16** OR **#17** OR **#18** OR **#19** OR **#20** OR **#21** OR **#22** OR **#23** OR **#24**	**2,305,231**
#87	**#1** OR **#2** OR **#3** OR **#4** OR **#5** OR **#6** OR **#7**	**12,278,126**
#86	**'cytokine receptor'**	**11,838**
#85	**'glial cell line derived neurotrophic factor receptor'**	**702**
#84	**'nerve growth factor receptor'**	**4,512**
#83	**'satellite cell'**	**6,305**
		21,647

#82

'oligodendroglia'

53,164

#81

'microglia'

17,266

#80

'schwann cell'

69,005

#79

'astrocyte'

34,553

#78

'glia cell'

1,262,931

#77

'immunology'

370,799

#76

'macrophage'

1,515

#75

'cytokine receptor antagonist'

3,402

#74

'interleukin receptor'

669,310

#73

interleukin

523,111

#72

'cytokine'

56,941

#71	
'neuropeptide'	
	18,438
#70	
'neurotrophin'	
	5,329
#69	
'brain derived neurotrophic factor receptor'	
	3,217
#68	
'protein tyrosine kinase a'	
	1,033
#67	
'receptor trkb'	
	33,151
#66	
'nerve growth factor'	
	39,314
#65	
'brain derived neurotrophic factor'	
	9,029
#64	
'glial cell line derived neurotrophic factor'	
	8,865
#63	
'pain measurement'	
	26,469
#62	
'nerve regeneration'	
	44
#61	
'nerve tissue protein'	
	4,816

#60

'biological factor'

291,640

#59

'biological marker'

93,459

#58

'mobilization'

9,272

#57

mobilisation

144,443

#56

manipulation*

674

#55

'dry needling'

49,637

#54

'acupuncture'

16,019

#53

tens

85,616

#52

'electrostimulation'

14,461

#51

'electrotherapy'

2

#50

'peripheral nerve therapy'

23,397

#49 'massage'	11
#48 'neural gliding'	3
#47 'neural stretching'	15
#46 'neural mobilisation'	113
#45 'neural mobilization'	2
#44 'neural tension technique'	1,130
#43 'physical conditioning'	1,195,994
#42 resistance	45,855
#41 'endurance'	395,263
#40 'strength'	54,887
#39 swim*	47,871

#38	
'treadmill'	
	337,640
#37	
run*	
	568,836
#36	
exercise*	
	33,694
#35	
'kinesiotherapy'	
	11,028
#34	
'manipulative medicine'	
	5,740
#33	
'manual therap*'	
	318
#32	
'musculoskeletal manipulation'	
	89,891
#31	
'physical therap*'	
	133,444
#30	
'physiotherapy'	
	1,285,188
#29	
'pain'	
	6,476
#28	
'sciatica'	
	52,626

#27 **'neuropathic*'**	**31,397**
#26 **'neuralgia'**	**40,160**
#25 **'neuropathic pain'**	**72,223**
#24 **'metabolic disorder'**	**866,443**
#23 **metabolic***	**886,136**
#22 **'chemotherapy'**	**430,426**
#21 **'diabetic*'**	**197,530**
#20 **'neuropathy'**	**307**
#19 **'nerve inflammation'**	**57,586**
#18 **'peripheral neuropathy'**	**2,469**
#17 **'chronic constriction injury'**	**7,254**

#16	
'stenosis, occlusion and obstruction'	
	102
#15	
'constriction pathologic*'	
	3,051
#14	
'nerve ligation'	
	54,329
#13	
'nerve injury'	
	248
#12	
'nerve cut'	
	228
#11	
'nerve constriction'	
	15,583
#10	
'nerve compression'	
	3,943
#9	
'nerve crush'	
	154
#8	
'nerve block method*'	
	65,081
#7	
'transgenic mice'	
	8,107,007
#6	
rat*	
	1,177,969

#5	**mice**	**82,727**
#4	**'transgenic mouse'**	**1,963,922**
#3	**'mouse'**	**6,274,624**
#2	**animal***	**1,372,929**
#1	**'animal model'**/exp OR **'animal model'**	

Final del formulario

Cochrane Library Search Formula. Results: 124

1. MeSH descriptor: [Models, Animal] explode all tres
2. (“animal*”):ti,ab,kw
3. (“mice”):ti,ab,kw
4. (“mice”):ti,ab,kw
5. (“transgenic mice”):ti,ab,kw
6. (“nerve block method*”):ti,ab,kw
7. (“nerve block method*”):ti,ab,kw
8. (“nerve constriction”):ti,ab,kw
9. (“nerve crush”):ti,ab,kw
10. (“nerve cut”):ti,ab,kw
11. (“nerve constriction”):ti,ab,kw
12. ("Nerve injury"):ti,ab,kw
13. (“nerve ligation”):ti,ab,kw
14. (“constriction pathologic*”):ti,ab,kw
15. (“chronic constriction injury”):ti,ab,kw
16. (“peripheral neuropathy”):ti,ab,kw

17. (“nerve inflammation”):ti,ab,kw
18. (“neuropathy”):ti,ab,kw
19. ("diabetic*"):ti,ab,kw
20. ("chemotherapy*"):ti,ab,kw
21. ("metabolic*"):ti,ab,kw
22. MeSH descriptor: [Neuralgia] explode all tres
23. (“neuropathic pain”):ti,ab,kw
24. (“neuropathic*”):ti,ab,kw
25. (“sciatica”):ti,ab,kw
26. (“pain”):ti,ab,kw
27. MeSH descriptor: [Physical Therapy Modalities] explode all tres
28. (“physical therapy”):ti,ab,kw
29. (“physiotherapy”):ti,ab,kw
30. ("Musculoskeletal manipulations"):ti,ab,kw
31. (Manual therap*):ti,ab,kw
32. (“exercise therapy”):ti,ab,kw
33. (“exercise*”):ti,ab,kw
34. (“run*”):ti,ab,kw
35. (“swim*”):ti,ab,kw
36. (“strength*”):ti,ab,kw
37. (“endurance”):ti,ab,kw
38. (“resistance”):ti,ab,kw
39. (“physical conditioning”):ti,ab,kw
40. ("neural tension technique"):ti,ab,kw
41. (“neural mobilization*”):ti,ab,kw
42. (“neural stretching”):ti,ab,kw
43. (“neural stretching”):ti,ab,kw
44. (“massage*”):ti,ab,kw
45. (“massotherapy”):ti,ab,kw
46. (“peripheral nerve therapy”):ti,ab,kw
47. MeSH descriptor: [Electric Stimulation Therapy] explode all tres
48. (electrotherap*):ti,ab,kw
49. (“TENS”):ti,ab,kw
50. MeSH descriptor: [Acupuncture] explode all tres
51. (“dry needling”):ti,ab,kw
52. (manipulation):ti,ab,kw
53. (mobilization*):ti,ab,kw
54. ("mobilisation*"):ti,ab,kw
55. (“biomarker*”):ti,ab,kw
56. (“biological factor*”):ti,ab,kw
57. (“nerve tissue protein”):ti,ab,kw
58. (“nerve regeneration”):ti,ab,kw
59. (“pain measurement”):ti,ab,kw
60. (“glial cell line-derived neurotrophic factor”):ti,ab,kw
61. (“glial cell line-derived neurotrophic factor receptor*”):ti,ab,kw
62. (“receptor trkB”):ti,ab,kw

63. (“nerve growth factor*”):ti,ab,kw
64. (“neurotrophin*”):ti,ab,kw
65. (“receptor trkA”):ti,ab,kw
66. (“receptor trkC”):ti,ab,kw
67. (“neuropeptide*”):ti,ab,kw
68. (“cytokine*”):ti,ab,kw
69. (“interleukin*”):ti,ab,kw
70. (“interleukin receptor”):ti,ab,kw
71. (“macrophage*”):ti,ab,kw
72. (“immunology*”):ti,ab,kw
73. (“glial cell*”):ti,ab,kw
74. (“astrocyte*”):ti,ab,kw
75. (“schwann cell*”):ti,ab,kw
76. (“microglia”):ti,ab,kw
77. (“oligodendroglia*”):ti,ab,kw
78. (“satellite cell*”):ti,ab,kw

{OR #1-#5} AND {OR #6-#26} AND {OR #27-#54} AND {OR #55-#78}

ANEXO IV Ejercicios estudio IV

Active neural mobilization

The movements will be made at a rate of 0.5 HZ. 3 minutes per exercise, resting 5 seconds every minute. And 30 seconds between exercises.

- Open and close your fingers.
- Forearm supported on the table, neutral prone/supination position, perform finger extensión.
- From a neutral prone-supination position. Performing wrist and finger flexo-extension.

- Hand in supination, back of the hand resting on the table and in cubital deviation. Perform ABD of the 1st finger.

- Forearm in neutral prone/supination position and wrist neutral. Perform flexion of the metacarpophalangeal joints.

- Forearm in neutral prone/supination position and neutral wrist perform flexion of the interphalangeal joints.

- Forearm supported on the table and supination. Perform ABD/ADD of the fingers of the hand.

Action observation and Mirror glasses will be base on the same exercise tan active neural mobilization.

ANEXO V Carta de invitación estancia internacional

NUFFIELD DEPARTMENT OF CLINICAL NEUROSCIENCES

UNIVERSITY OF OXFORD

West Wing, Level 6, John Radcliffe Hospital, Oxford, OX3 9DU
Web: www.ndcn.ox.ac.uk | Tel: +44(0)1865 223254 | Email: annina.schmid@ndcn.ox.ac.uk

Oxford, 29/09/2020

Re: Internship of Luis Matesanz García at Oxford University

To whom it may concern,

Unfortunately, the already organised internship of Luis Matesanz to the Nuffield Department of Clinical Neurosciences at Oxford University, which was meant to start in April 2020, had to be postponed due to COVID-19. Our department at Oxford University has completely closed to external visitors and is only just now starting to reopen at reduced capacity.
We have now approval from the head of department to start Luis' internship on the 18th of January 2021 for 3 months. Of course, this internship remains subject of most recent developments in regards to COVID-19 restrictions, but I am hopeful that it will go ahead as planned.

I am delighted to host doctoral candidate Luis Matesanz García for this international internship and predoctoral training in my laboratory. Luis will be working alongside my team on one of our current projects, with the aim to gain experience in translational neurosciences. We look forward to welcoming Luis in Oxford.

Yours sincerely,

A/Prof Annina Schmid

University of Oxford
Nuffield Department of Clinical Neurosciences
Level 6 West Wing
John Radcliffe Hospital
Oxford OX3 9DU

ANEXO VI Informe de estancia internacional

NUFFIELD DEPARTMENT OF CLINICAL NEUROSCIENCES

UNIVERSITY OF OXFORD

West Wing, Level 6, John Radcliffe Hospital, Oxford, OX3 9DU
Web: www.ndcn.ox.ac.uk | Tel: +44(0)1865 223254 | Email: annina.schmid@ndcn.ox.ac.uk

18/05/2021

Re: Activity report doctoral candidate Luis Matesanz García

To whom it may concern,

I confirm that the doctoral candidate Luis Matesanz García has completed his international internship with me at the Nuffield Department of Clinical Neuroscience at the University of Oxford from 18th of January to 18th of April 2021. During his international research internship, he carried out the following activities:

- Active collaboration with different members of my research group during the development of a preclinical systematic review and meta-analysis about the efficacy of exercise in neuropathic pain.
- Participation in research group sessions including presentations and journal clubs.
- Training in research methodology.
- Co-supervision of a MSc student

I have been impressed by Luis' enthusiasm, commitment and careful scientific work and I am looking forward to continuing my collaboration with Luis beyond his internship.

Yours sincerely,

A. Schmid

Annina Schmid, Ph.D.

Wellcome Clinical Career Development Fellow, Medical Research Foundation Fellow, Senior NIHR BRC fellow

Associate Professor in Clinical Neurosciences