VNIVERSITAT DE VALÈNCIA

Facultat de Fisioteràpia

PROGRAMA DE DOCTORADO EN FISIOTERAPIA 3165

# "ENFOQUE DE TRATAMIENTO CENTRADO EN EL SISTEMA NERVIOSO CENTRAL PARA PERSONAS CON HOMBRO CONGELADO"

TESIS DOCTORAL

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VALENCIA, JUNIO 2023

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HACEN CONSTAR:

Que el presente trabajo, titulado "Enfoque de tratamiento centrado en el Sistema Nervioso Central para personas con hombro congelado", ha sido realizado bajo su dirección, por Dña. Silvia Mena del Horno, para optar al grado de Doctor por la *Universitat de València*. Habiéndose concluido, y reuniendo a su juicio las condiciones de originalidad y rigor científico necesarias, autoriza su presentación a fin de que pueda ser defendido ante el tribunal correspondiente.

Y para que así conste expide y firma la presente documentación en Valencia a 29 de Mayo de 2023.

Fdo: Lirios Dueñas Moscardó

Fdo: Enrique Lluch Girbes

Fdo: Mercè Balasch i Bernat

Deseo expresar mi agradecimiento:

En primer lugar, quiero agradecer a todos los participantes de este estudio que compartieron su tiempo conmigo y se mostraron siempre dispuestos y colaboradores. Me han ayudado a crecer y mejorar tanto en lo profesional como en lo personal.

A mis directores de tesis, Lirios, Mercè y Quique, mis tres mosqueteros. No podría haber estado rodeada de mejores profesionales y amigos. Nunca ha sido un camino solitario, me han ayudado a mejorar, a superarme, y crecer con cada reto que suponía este trabajo.

A los traumatólogos José Enrique Aroca y Marta Navarro Bosch por su colaboración en el reclutamiento de pacientes.

A mis amigos Mª Luz y Juanma, por sus consejos y su ayuda incondicional, habéis sido apoyo moral y técnico de este trabajo en varias ocasiones.

Quiero dar las gracias a mi familia. A mis padres y mi hermana, por respaldarme siempre en todo lo que me propongo, creer en mí, por su cariño y los valores que me han inculcado.

Y por último, dar las gracias a mi marido Pablo y mis hijos, Adrián y Alba, por estar siempre en los momentos buenos y no tan buenos, por hacerme ver que con esfuerzo y constancia todo es posible y acompañarme incondicionalmente durante este largo camino. Gracias por la paciencia, os pido disculpas por las incontables horas robadas.

Gracias.

## ÍNDICE DE CONTENIDOS

**ANEXOS**

## INCIDE DE FIGURAS

### SECCIÓN SEGUNDA: PROCEDIMIENTO GENERAL



### ESTUDIO 1

**ESTUDIO 2**



**ESTUDIO 3**



**ESTUDIO 4**

## INDICE DE TABLAS

### SECCIÓN PRIMERA: INTRODUCCIÓN GENERAL



### SECCIÓN SEGUNDA: PROCEDIMIENTO GENERAL



### ESTUDIO 1



### ESTUDIO 2



### ESTUDIO 3



### ESTUDIO 4

## INDICE DE ABREVIATURAS

| | |
|---|---|
| BNSE: | Bloqueo del nervio supraescapular. |
| CSI: | Central Sensitization Inventory. |
| DASH: | Disabilities of the Arm, Shoulder and Hand. |
| DM: | Diabetes mellitus. |
| DMCI: | Diferencia mínima clínicamente importante. |
| ECA: | Estudio clínico aleatorizado. |
| EVA: | Escala Visual analógica. |
| GMI: | Imaginería motora graduada. |
| HC: | Hombro congelado. |
| ICC: | Coeficiente de correlación intraclase. |
| MBA: | Manipulación bajo anestesia. |
| MCD: | Mínimo cambio detectable. |
| PCS: | Pain Catastrophizing Scale. |
| PSFS: | Patient Specific Functional Scale. |
| RNM: | Resonancia Nuclear Magnética. |
| ROM: | Rango de movilidad articular. |
| SC: | Sensibilización central. |
| SD: | Desviación estándar. |
| SDT: | Sensory Discrimination Training. |
| SPADI: | Shoulder Pain and Disability Index Questionnaire. |
| ST: | Sumación temporal del dolor. |
| STAR: | Staged Approach for Rehabilitation Classification. |
| TPDT: | Umbral de discriminación entre dos puntos. |
| TSK-11: | Tampa Scale for Kinesiophobia. |
| UDP: | Umbral de dolor a la presión. |

# PRESENTACIÓN DE LOS ESTUDIOS

# PRESENTACIÓN DE LOS ESTUDIOS

El presente documento comprende la tesis doctoral realizada por Silvia Mena del Horno, en el marco del programa de doctorado en Fisioterapia, código 3165, de la *Universitat de València*, R.D. 99/2011. La memoria que se presenta a continuación se acoge a la modalidad por compendio de publicaciones. Los artículos que conforman el documento han sido publicados durante los años del programa de doctorado y se engloban dentro de una misma línea de investigación.

El trabajo de investigación pretende estudiar los efectos de un enfoque de tratamiento centrado en el Sistema Nervioso Central para pacientes con hombro congelado. Para ello, se diseñaron varios estudios dentro del proyecto de investigación con los objetivos de:

- Estudiar la factibilidad de un enfoque de tratamiento orientado al Sistema Nervioso Central en sujetos con hombro congelado.
- Definir el protocolo para la realización de un estudio clínico aleatorizado que compare los efectos de añadir un programa de tratamiento dirigido al Sistema Nervioso Central a un programa de terapia manual para pacientes con hombro congelado.
- Realizar el estudio clínico aleatorizado que compare el impacto clínico de añadir las técnicas de tratamiento orientadas al Sistema Nervioso Central a un protocolo de terapia manual en sujetos con hombro congelado.
- Profundizar en el conocimiento sobre los mecanismos de dolor presentes en pacientes con hombro congelado.

Los resultados de dichos estudios fueron publicados en revistas indexadas en el Journal Citation Reports de la Web of Knowledge, cuyo factor de impacto, cuartil y área de conocimiento (año 2021) se muestra a continuación.

**Estudio 1.** Laterality judgement and tactile acuity in patients with frozen shoulder: A cross-sectional study.

Revista: *Musculoskeletal Science and Practice.*

ISSSN: 2468-7812

DOI: 10.1016/j.msksp.2020.102136

Catergoría: Rehabilitation

| Factor de impacto | Ranking | Cuartil | Percentil de factor de impacto |
|---|---|---|---|
| 2.520 | 27/68 | 2 | 61.03 |

**Estudio 2.** A Central Nervous System Focused Treatment Program for People with Frozen Shoulder: A Feasibility Study

Revista: *International Journal of Environmental Research and Public Health.*

ISSSN: 1660-4601

DOI: https://doi.org/10.3390/ijerph19052628

Catergoría: Public, environmental and occupational health.

| Factor de impacto | Ranking | Cuartil | Percentil de factor de impacto |
|---|---|---|---|
| 4.614 | 45/182 | 1 | 75.55 |

**Estudio 3.** A central nervous system focused treatment approach for people with Frozen Shoulder: Protocol for a randomised clinical trial

Revista:.*Trials.*

ISSSN: 1745-6215

DOI: https://doi.org/10.1186/s13063-019-3585-z

Catergoría: Medicine, research and experimental.

| Factor de impacto | Ranking | Cuartil | Percentil de factor de impacto |
|---|---|---|---|
| 1.883 | 102/139 | 3 | 26.98 |

**Estudio 4.** Is there any benefit of adding a Central Nervous System focused intervention to a manual therapy and home stretching program for people with frozen shoulder? A randomized controlled trial.

Revista: *Journal of Shoulder and Elbow Surgery.*

ISSSN: 1532-6500

DOI: https://doi.org/10.1016/j.jse.2023.02.134

Categoría: Orthopedics.

| Factor de impacto | Ranking | Cuartil | Percentil de factor de impacto |
|---|---|---|---|
| 3.507 | 24/86 | 2 | 72.67 |

# SECCIÓN PRIMERA:

# MARCO TEÓRICO

# INTRODUCCIÓN GENERAL

# 1. DESCRIPCIÓN DEL HOMBRO CONGELADO

## 1.1. Concepto y clasificación

El hombro congelado (HC) es una condición musculoesquelética de etiología desconocida que afecta a la articulación glenohumeral y se caracteriza por dolor de inicio espontáneo acompañado de pérdida progresiva del rango de movilidad articular (ROM). El dolor, por lo general es muy intenso y, junto con la pérdida de ROM, conduce a discapacidad y alteraciones del sueño (1).

A lo largo de las últimas décadas, se han empleado diferentes términos, definiciones y criterios diagnósticos para esta condición del hombro. La primera descripción fue dada por Duplay en 1896, quien le atribuyó el término de "periartritis escapulohumeral" (2). Posteriormente, Codman (3) introdujo el concepto de "hombro congelado" en 1934, describiendo del siguiente cuadro clínico: dolor idiopático de inicio lento situado en la región de inserción del músculo deltoides, incapacidad de dormir sobre el lado afecto y restricción en el ROM del hombro a la elevación y a la rotación externa, tanto activa como pasiva y de apariencia radiológica normal. Sin embargo, dado que este concepto de "hombro congelado" es muy amplio y dentro del mismo se pueden contemplar diferentes condiciones del hombro que cursan con rigidez articular y dolor, existía una clara necesidad de describir de forma más precisa los criterios diagnósticos. Fue Nevaiser (4) quien introdujo entonces el concepto de "capsulitis adhesiva" para describir el cuadro clínico resultado de la inflamación crónica de la membrana sinovial y fibrosis de la cápsula articular del hombro, así como adherencias intraarticulares en el hombro. Sin embargo, los resultados de estudios artroscópicos posteriores descartaron la presencia de dichas adherencias intraarticulares (5,6), asociando el dolor y la rigidez articular a sinovitis y contractura progresiva de la cápsula (7). En 1994, la *American Shoulder and Elbow Surgeons*, definió el HC como una condición de etiología desconocida, caracterizada por una restricción significativa del ROM activo y pasivo del hombro en ausencia de una patología intrínseca conocida (8).

Zuckerman (8,9) propuso la clasificación del HC e

- Primario o idiopático cuando no se asocia a una condición sistémica o a una causa aparente que justifique el cuadro y que, por tanto, la etiología asociada o subyacente no pueda ser identificada.
- Secundario: incluye todos los casos de HC en los que se puede identificar una etiología subyacente o una condición asociada. Se subdivide a su vez en tres categorías:
    - Sistémico: cuando se presenta en pacientes con trastornos sistémicos, como diabetes mellitus, hiper o hipotiroidismo, hipoadrenalismo o cualquier otra condición cuya asociación haya sido demostrada con el desarrollo de HC.
    - Intrínseco: en esta categoría se incluyen aquellos casos de HC que presentan limitación del ROM activo y pasivo asociado a alteraciones del manguito rotador (tendinitis y rotura parcial o total) tendinitis del bíceps o tendinitis calcificante (en el caso de tendinitis calcificante, una radiografía aceptable incluiría depósitos de calcio dentro del espacio subacromial/tendones del manguito rotador).
    - Extrínseco: son aquellos casos en los que existe una asociación entre el desarrollo del HC con una anomalía externa al hombro. Por ejemplo, aquellos pacientes que presentan limitación del ROM activo y pasivo del hombro como consecuencia de cirugía de mama ipsilateral previa, radiculopatía cervical, tumor de la pared torácica, accidente cerebrovascular previo o problemas extrínsecos más locales, como fractura de la diáfisis humeral, anomalías escapulotorácicas, artritis acromioclavicular o fractura de clavícula.

### 1.2. Historia natural

En cuanto a la historia natural del HC, son varios los estudios que la han descrito a lo largo de los años a medida que se ha ido profundizando en el conocimiento de su evolución. Inicialmente, Reeves et al. (10) describieron 3 fases o estadios: fase dolorosa, fase de rigidez y fase de

recuperación. Posteriormente, Hannafin y Chiaia (11) añadieron una cuarta etapa, teniendo en cuenta los hallazgos clínicos, histológicos y las etapas artroscópicas descritas por Neviaser (12). La etapa 1, descrita como etapa "pre adhesiva" se caracteriza por dolor a la movilidad activa y pasiva y limitación gradual en el ROM medio y final de todos los movimientos del hombro, apareciendo a nivel histológico sinovitis glenohumeral difusa. A esta primera etapa se le atribuye una duración aproximada de tres meses y se caracteriza por dolor agudo en el ROM final, dolor intenso en reposo y trastornos del sueño (1). En esta etapa, a través de la exploración artroscópica se puede observar reacción sinovial difusa sin adherencias ni contractura (11,13). Además, la pérdida temprana de rotación externa, en presencia de manguito rotador intacto, se ha considerado como signo precoz de HC en esta primera etapa (13,14).

Posteriormente, de los 3 a los 9 meses de evolución, se describe la etapa 2 o fase de "congelamiento", caracterizada por dolor intenso y limitaciones significativas en el ROM global del hombro, presentando a nivel histológico sinovitis hipertrófica hipervascularizada, fibroplasia y pérdida de movilidad incluso bajo anestesia (11–13).

La etapa 3 o "adhesiva" suele tener una duración aproximada de 9 a 15 meses, el dolor ya es leve/moderado pero la restricción del ROM global del hombro continúa siendo significativa. En las pruebas de imagen durante esta etapa ya no se observa apenas sinovitis ni hipervascularización, pero existen hallazgos de aumento la fibrosis capsulo-ligamentosa, así como limitación en la movilidad bajo anestesia al igual que en la fase 2 (11–13).

Finalmente, la etapa 4, también denominada de resolución o "descongelación", se sitúa desde los 15 hasta los 24 meses, en los cuales, el paciente describe mejoría gradual del dolor y la rigidez articular (1,13). Sin embargo, esta mejoría es variable entre sujetos y de una duración indeterminada, ya que, aunque en esta última etapa el dolor suele resolverse por completo en la mayoría de los casos, frecuentemente pueden persistir ciertas restricciones de la movilidad articular incluso bajo anestesia, observándose a nivel histológico fibrosis capsulo-ligamentosa (12,13).

Esta clasificación fue aceptada clásicamente, sin embargo, su utilidad en la práctica clínica es limitada, dado que no todos los pacientes presentan la sintomatología en el orden cronológico y duración descritos, existiendo una amplia variabilidad entre casos.

Otro modelo de clasificación que resulta más aplicable en la práctica clínica es el propuesto por McClure *et al.* (15) en el modelo STAR-hombro (*Staged Approach for Rehabilitation Classification*) (16), el cual tiene en cuenta además de los factores patoanatómicos, el nivel de irritabilidad del paciente. Esta clasificación se basa en la percepción del dolor por parte del paciente mediante una escala visual analógica (EVA) de 10 puntos, en si éste está presente durante el descanso nocturno, en reposo y/o en movimiento y en si existe limitación del ROM tanto activo como pasivo. Por tanto, tiene en cuenta diferentes variaciones en el cuadro clínico que pueden presentar los pacientes a lo largo de la progresión del HC, como, p. ej., si existe predominancia del dolor frente a la limitación, o viceversa (Tabla 1).

*Tabla 1. Estrategias de clasificación y tratamiento basadas en el nivel de irritabilidad*

| | **Irritabilidad alta** | **Irritabilidad moderada** | **Irritabilidad baja** |
|---|---|---|---|
| **Historia y hallazgos clínicos** | Nivel de dolor alto (≥7/10).<br><br>Dolor nocturno o de reposo permanente.<br><br>Dolor antes del final ROM AROM menor que PROM debido al dolor. | Nivel de dolor moderado (4-6/10).<br><br>Dolor nocturno o de reposo intermitente.<br><br>Dolor al final ROM AROM similar a PROM. | Nivel de dolor bajo (≤ 3/10).<br><br>No dolor nocturno o de reposo.<br><br>Mínimo dolor al final ROM con sobrepresión AROM y PROM iguales. |
| **ROM/estiramiento** | Corta duración (1-5 s), sin dolor, AAROM pasiva. | Corta duración (5-15 s), AAROM a AROM. | Final recorrido/sobrepresión, aumento de la duración, carga cíclica. |
| **Técnicas de terapia manual** | Movilizaciones de bajo grado (grados I-II). | Movilizaciones de bajo a alto grado (grados I-IV). | Movilizaciones de alto grado / sostenidas (grados III-IV). |

Abreviaturas: AAROM, rango de movilidad activa asistida; AROM rango de movilidad activa; PROM, rango de movilidad pasiva; ROM, rango de movilidad.

Adaptada de Kelley *et al., 2009 (16)*

Según la evidencia consultada, la duración del HC varía entre 1 y 3 años, aunque hay una recuperación incompleta en el 7-50% de los pacientes, que mantienen un leve dolor y restricción del ROM (17–20) y el 6% todavía presenta síntomas severos más allá de los 3 años de evolución (17). Asimismo, se ha observado que los pacientes con diabetes que sufren HC secundario pueden tener plazos de recuperación más prolongados y con peores resultados (21).

La gran variabilidad en la duración de los síntomas del HC puede deberse a que tanto el tratamiento más eficaz (22–24) como los criterios diagnósticos y la historia natural de la patología, siguen siendo poco claros en la actualidad (25–27).

### 1.3. Fisiopatología

El HC es un proceso multifactorial bastante complejo por lo que su etiología y fisiopatología son aún poco conocidas. Diversos estudios han intentado aclarar la patogenia del HC, coincidiendo en que intervienen en su desarrollo diversos factores metabólicos, la inflamación crónica de bajo grado, el estrés mecánico y la neovascularización (5,28–30).

En cuanto a los factores metabólicos, diversos autores han estudiado la alta prevalencia de síndrome metabólico, diabetes mellitus o enfermedades cardiovasculares en pacientes con HC, sugiriendo que podrían compartir una etiología en común (29,31). Lo más característico del síndrome metabólico es el exceso de grasa abdominal, triglicéridos y presión arterial elevados, el aumento de la glucemia basal y la disminución en los niveles de colesterol de alta densidad en sangre (32). Varios estudios han demostrado la presencia de niveles elevados de glucosa en sangre, lípidos y colesterol en pacientes con HC (33,34). No existe una conclusión firme al respecto, sin embargo, ante la evidencia existente se sugiere la relación del síndrome metabólico como factor etiológico subyacente en el desarrollo del HC secundario sistémico. Además, cada vez existe mayor evidencia de la relación que guarda la presencia de inflamación crónica o de bajo grado con el desarrollo del HC (31,34–36). Al igual que los sujetos con síndrome metabólico o enfermedad cardiovascular, los marcadores de inflamación crónica y las lipoproteínas proinflamatorias están elevados en pacientes con HC (31,37). De hecho, estudios histológicos de biopsias tomadas en pacientes con HC han hallado inflamación crónica o de bajo grado así como un aumento en la presencia de citocinas y células inmunes (29,38).

En términos anatómicos, Neviaser (4) cuando introdujo el término de "capsulitis adhesiva" se basó en sus hallazgos de inflamación y adherencias capsulares y sinoviales durante cirugía abierta, las cuales conducían a la adherencia del pliegue axilar a sí mismo y al cuello anatómico del húmero. Sin embargo, la literatura más actual, defiende el engrosamiento y la contractura de la cápsula en lugar de la adherencia del pliegue axilar (39).

La articulación glenohumeral normal presenta un volumen mínimo de 15 ml y suele presentar un volumen medio de 20 ml , sin embargo, en el HC puede llegar a ser menor a 5 ml (40). En este sentido, varios autores han medido y comparado la presión intraarticular durante la distensión de la cápsula tanto en sujetos con HC como en controles sanos. Los sujetos con HC, presentaron un aumento de la presión mucho más brusco y ruptura de la cápsula ante volúmenes menores que los sujetos de los grupos de control (41–43).

Por otro lado, la rigidez del hombro a la movilidad pasiva en pacientes con HC se ha relacionado no sólo con la contractura anterior de la cápsula, sino con otras estructuras anatómicas. Diversos estudios coinciden en la presencia de contractura del intervalo rotador y del ligamento coracohumeral (44–47) (dado que el este se expande por la parte extra-articular del intervalo rotador y se tensa durante la rotación externa glenohumeral). La liberación de dicho ligamento es uno de los factores clave en la liberación quirúrgica de la cápsula en sujetos con HC (48,49). Otro hallazgo al respecto que defiende el importante papel de estas estructuras anatómicas en la patogenia del HC, es la mejoría del dolor y la movilidad que experimentan los pacientes tras infiltrar corticoesteroides de forma ecoguiada en el intervalo rotador y los alrededores del ligamento coracohumeral en comparación con los pacientes que son infiltrados con corticoesteroides mediante abordaje posterior de la cápsula (47).

En cuanto a los cambios histológicos, en las fases tempranas del desarrollo del HC, se observan cambios inflamatorios junto con hiperplasia sinovial e hipervascularización subsinovial. Mientras que en estadios más avanzados, desaparece gradualmente la inflamación y aumenta la fibrosis de los tejidos y la presencia de fibroblastos en la matriz extracelular de colágeno tipo III (40).

Algunos autores han cuestionado si la presencia de inflamación es parte del proceso, sugiriendo que el origen del HC sea exclusivamente debido a la fibrosis, como ocurre en la enfermedad de Dupuytren de la mano (5). Sin embargo, la biopsia de pacientes con HC en las primeras tres etapas de la patología presenta niveles aumentados de factor de crecimiento y otras citoquinas que favorecen la fibrosis; demostrando por tanto una clara progresión de un proceso inflamatorio que

deriva en fibrosis capsular, confirmando así el origen inflamatorio del HC (50). No obstante, el factor o los factores que desencadenan este proceso inflamatorio, siguen siendo desconocidos.

En definitiva, a pesar de la amplia literatura al respecto, los factores que influyen en la aparición y desarrollo del HC son diversos y no se pueden atribuir a una única causa o mecanismo patogénico.

### 1.4. Epidemiología

*Prevalencia en la población general*

Se calcula que de entre un 2,4% y un 26% de la población general que padece dolor de hombro (16), entre un 2% y un 5% sufre HC primario o idiopático (51,52).

*Prevalencia por sexo y edad*

El HC afecta más comúnmente a mujeres de entre los 40 y 65 años de edad, con un pico de incidencia mayor entre los 51 y 55 años (1,50).

Aproximadamente en 1 de cada 6 sujetos se presenta de forma bilateral (alrededor del 17% de los casos) (7,21), pudiendo aparecer en el hombro contralateral incluso años después del inicio de los síntomas del primer hombro afectado (17,39). Asimismo, las cifras sugieren que existe mayor incidencia de HC en el hombro no dominante (alrededor del 60% de los casos) (17,53).

*Prevalencia de comorbilidades*

En cuanto al HC secundario, se ha asociado mayor incidencia en pacientes que sufren diferentes alteraciones sistémicas como: diabetes mellitus (DM), disfunciones tiroideas, enfermedad cardiovascular o accidentes cerebro-vasculares (50). Concretamente, se estima que los pacientes con DM o trastornos tiroideos tienen un riesgo de padecer HC de 5 a 7 veces mayor (54,55), estando presente entre un 10% y un 20% en sujetos diabéticos (56) y en un 10,9% en pacientes con problemas de tiroides (57). Milgrom *et al.* (55), en un estudio de prevalencia de DM en pacientes con HC idiopático, compararon 126 pacientes (76 mujeres, edad media desviación estándar

(SD)=55.0; 50 hombres edad media SD=54.7), encontrando diferencias significativas en la presencia de DM tanto en hombres (38.0% frente a 6.5%) como en mujeres (23.7% frente a 4.7%) en comparación con la población emparejada en sexo y edad. Además, encontraron prevalencia significativa de hipotiroidismo en mujeres con HC en comparación con la muestra emparejada en sexo y edad (21.1% frente a un 4.7%) (55).

Por otro lado, también se ha comprobado que existe una mayor probabilidad de desarrollar HC (hasta 8 veces mayor) en pacientes que padecen enfermedad de Dupuytren (58). De hecho, un estudio que realizó análisis histológico de una biopsia intraoperatoria mostró que el proceso patológico subyacente del HC es similar a la de la enfermedad de Dupuytren de la mano (5).

Finalmente, la incidencia de HC post-traumatismo es de un 9-33% (59).

## 2. DIAGNÓSTICO DEL HOMBRO CONGELADO

En la actualidad no existe una prueba específica para diagnosticar el HC, si no que el diagnóstico definitivo se basa en: i) el examen físico e historia clínica, ii) la exclusión de otras patologías que cursan con dolor y restricción del movimiento pudiendo simular HC e iii) imágenes diagnósticas glenohumerales normales (9).

Los pacientes con HC suelen referir dolor localizado de inicio insidioso, a veces precedido por una lesión mínima. Dicho dolor suele afectar a la realización de las actividades de la vida diaria y puede interferir en el descanso nocturno. Además, los pacientes presentan restricción dolorosa del ROM en múltiples planos, especialmente en la elevación (menor de $100^0$) y la rotación externa (restricción mayor al 50%), tanto pasiva como activa durante al menos un mes de duración y que no mejora o incluso ha empeorado (1). Por consenso, el criterio más simple para el diagnóstico del HC, es la restricción del ROM en la rotación externa del hombro tanto activa como pasiva acompañada de imágenes radiográficas normales (a excepción de la osteopenia de la cabeza humeral y las tendinosis calcificante) (60).

El hecho de complementar la exploración física con imágenes diagnósticas como la radiografía permite descartar otras patologías como artrosis, necrosis avascular o fracturas, las cuales también suelen presentar restricción dolorosa del movimiento y pueden ser erróneamente diagnosticadas como HC (61,62). Si se desea mayor precisión en el diagnóstico, la ecografía o la resonancia nuclear magnética (RNM) pueden ser de gran utilidad. Mediante ecografía por ejemplo, puede observarse engrosamiento de las estructuras del intervalo rotador, especialmente del ligamento coracohumeral y restricción de la movilidad del tendón del supraespinoso en la abducción de hombro (61). Por otro lado, el uso de RNM no solo proporciona información para un diagnóstico diferencial del HC, si no que puede orientarnos sobre la fase de la patología en que se encuentra el/la paciente, ya que algunos estudios indican que el grado de engrosamiento de la capsula medido en el receso axilar, puede correlacionarse con el estadio clínico del HC (62). En la RNM se pueden detectar aspectos

característicos del HC como: engrosamiento del ligamento coracohumeral y capsular en el intervalo rotador y el receso axilar (mayor de 4mm) así como obliteración del espacio subcoracoideo por el engrosamiento de la capsula (61,63).

Por tanto, el diagnóstico del HC está determinado principalmente por la anamnesis y la exploración física, pero los estudios de imagen pueden utilizarse para confirmar la presencia de HC mediante el descarte de patología subyacente.

En conclusión, es necesario seguir investigando el origen y mecanismos patológicos del HC para poder realizar un diagnóstico precoz que permita identificar esta condición de hombro en fases tempranas para un abordaje terapéutico eficaz y asimismo tratar de acortar el tiempo de resolución de esta patología.

## 3. SENSIBILIZACIÓN CENTRAL Y HOMBRO CONGELADO

En los últimos años se ha estudiado el procesamiento central del dolor y el posible papel que puede desempeñar la sensibilización central (SC) en pacientes con dolor de hombro (64–67). Concretamente, en las primeras etapas del HC, la presencia de mediadores inflamatorios crónicos como las citoquinas, pueden proporcionar una estimulación prolongada de las neuronas en el asta dorsal, así como de las células gliales de la médula espinal, siendo estas responsables de la sensibilización tanto central como periférica (68,69). La presencia de SC, por tanto, puede obstaculizar las vías descendentes de inhibición del dolor, alterando el procesamiento de la información sensorial y produciendo hipersensibilidad o aumento en la respuesta a los estímulos sensitivos, llevando a que los estímulos inocuos y/o repetitivos puedan interpretarse a nivel central como dolorosos (70). En definitiva, los mecanismos fisiopatológicos de la SC son múltiples y complejos, pero podrían definirse como una "amplificación de las señales neurales dentro del sistema nervioso central (SNC) que provoca hipersensibilidad al dolor" (71,72).

Aunque algunos estudios han mostrado evidencia del papel que desempeñan los mecanismos de procesamiento central del dolor en pacientes con dolor de hombro de diferente etiología (65,66), otras investigaciones cuestionan estos hallazgos (73). Además, no se ha estudiado concretamente en pacientes con HC, por lo que su papel sigue siendo especulativo. Sin embargo, esto podría explicar por qué algunos pacientes no mejoran con algunas de las intervenciones actuales y plantea la cuestión de si éstos podrían beneficiarse de un enfoque terapéutico orientado al SNC, incluyendo técnicas como la educación en la neurociencia del dolor, la imaginería motora graduada ("*Graded Motor Imagery"*, GMI) o el entrenamiento de la discriminación sensorial (69). Este tipo de enfoque terapéutico se ha postulado como una opción prometedora en el tratamiento tanto de pacientes con SC (p. ej., síndrome doloroso regional complejo, miembro fantasma o hemiplejia) (74–77) como en patologías musculoesqueléticas que cursan con dolor crónico (78,79).

Concretamente, los estudios en esta línea de tratamiento para dolor crónico de hombro y HC son escasos, pero presentan resultados preliminares satisfactorios. Louw *et al*. (80) aplicaron terapia en espejo a 69 pacientes con dolor y limitación de la movilidad de hombro (8.7% de los sujetos diagnosticados de HC) obteniendo mejoría significativa en el dolor, el catastrofismo, las conductas de miedo-evitación y la flexión activa de hombro. Başkaya *et al*. (81) realizaron un estudio clínico aleatorizado (ECA) controlado, comparando un grupo que recibió un programa estándar de fisioterapia con otro grupo de pacientes que recibió este mismo tratamiento junto con terapia en espejo. Aquellos pacientes que recibieron la terapia en espejo mostraron un aumento significativo de la abducción activa y pasiva y de la flexión activa y pasiva del hombro, así como en la función física, el dolor y diferentes variables de índole psicosocial. Sawyer *et al*. (70) publicaron un caso de una paciente con HC que recibió 20 sesiones durante 12 semanas de un tratamiento multimodal que incluía educación en neurociencia del dolor, entrenamiento de la discriminación sensorial y GMI. Tras la finalización del programa terapéutico, la paciente reportó mejoras en el dolor, en la conducta de miedo-evitación y en el ROM activo.

En resumen, el reducido número de estudios al respecto no permite establecer conclusiones firmes sobre el papel que desempeña la SC en el HC y la efectividad de las terapias enfocadas al SNC en estos pacientes, pero abre un interesante campo de investigación que se está desarrollando durante los últimos años.

## 4. TRATAMIENTO DEL HOMBRO CONGELADO

Existen diversas opciones terapéuticas para el tratamiento del HC, todas ellas orientadas en primera instancia a aliviar el dolor, especialmente en las fases iniciales de la patología, así como a recuperar la movilidad y mejorar la función del hombro. Dichas técnicas incluyen un amplio abanico de intervenciones que incluyen tanto opciones conservadoras como invasivas (82). Habitualmente, la primera elección suele ser aplicar un enfoque conservador obteniendo por lo general buenos resultados. Sin embargo, como ya se ha comentado con anterioridad, algunos pacientes pueden seguir presentando dolor y restricción del ROM varios años después del inicio de los síntomas (39). Por otro lado, como también se ha comentado en el apartado anterior, las últimas investigaciones se han centrado en abordar el papel que desempeña la SC y los cambios a nivel del SNC en el dolor de hombro crónico y concretamente en el HC. Esto es debido a que las lesiones musculoesqueléticas no solo presentan daño e inflamación a nivel tisular, sino que pueden producir cambios y adaptaciones tanto funcionales como estructurales en el SNC que pueden contribuir a la perpetuación del dolor pese a la resolución de la lesión de los tejidos (83). Este fenómeno se conoce como neuroplasticidad maladaptativa del SNC, y se considera que puede tener un papel fundamental en la cronificación del dolor musculoesquelético. Se postula que esta podría ser la causa por la que en ocasiones, la aplicación de ciertas técnicas de fisioterapia convencionales no obtenga resultados satisfactorios en algunos pacientes con dolor musculoesquelético crónico (83). Basándonos en estos mecanismos de adaptación al dolor del SNC podemos dividir las diferentes estrategias de tratamiento fisioterapéutico en dos grandes ramas: técnicas *"top-down"* o *"hands-off"* y técnicas *"bottom-up"* o *"hands on"*.

Las intervenciones *"top-down"* o *"hands-off"* son aquellas dirigidas específicamente al SNC con el fin de repercutir en los tejidos periféricos, como, p. ej., la educación del paciente en neurociencia del dolor o la GMI. En cambio, las estrategias *"bottom-up"* o *"hands on"* son aquellas enfocadas directamente en el tratamiento de los tejidos periféricos, como puede ser la terapia manual (84).

Sin embargo, no se han descrito guías de práctica clínica que orienten al fisioterapeuta en el tratamiento de pacientes que presentan dolor nociplástico o SC. Es más, la compleja naturaleza y mecanismos que dan lugar a la SC sugieren que la combinación de varias técnicas de tratamiento enfocadas a los tejidos periféricos *("bottom up")* y técnicas dirigidas al SNC *("top-down")*, sea lo más efectivo para tratar la SC (84).

Además, debido a la variabilidad de criterios de inclusión, protocolos aplicados y variables medidas en los distintos estudios, actualmente no existe consenso sobre las mejores técnicas de tratamiento para el HC. Independientemente del enfoque terapéutico que se escoja, se recomienda aplicar un mínimo de 6 meses de tratamiento conservador supervisado antes de pasar a la aplicación de técnicas invasivas (82).

A continuación se describen las principales opciones terapéuticas que suelen aplicarse en el tratamiento del HC y la evidencia sobre su eficacia:

## 4.1. Tratamiento conservador

### 4.1.1. Técnicas *"bottom-up"* o *"hands on"*

*Terapia manual y ejercicio*

La terapia manual suele ser la primera opción de tratamiento, pudiendo aplicarse de forma aislada o complementaria a otras técnicas terapéuticas, pero siendo considerada crucial para un abordaje exitoso del HC (85). Varios estudios sobre la aplicación de terapia manual en HC, han demostrado resultados positivos sobre el dolor y mejora de la función del hombro tras la aplicación de diversas técnicas como: movilizaciones angulares (86), movilizaciones de columna (combinadas con estiramiento glenohumeral y movilizaciones angulares y traslacionales) (87), movilizaciones con movimiento de Mulligan (88–90) o técnicas de Maitland que incluyen movilizaciones pasivas de alto, medio y bajo rango de movilidad (89–92). Sin embargo, de acuerdo con las recomendaciones basadas en Guías de Práctica Clínica, en la actualidad no existe evidencia que apoye el tratamiento

del HC mediante el empleo de unas u otras técnicas de terapia manual ni superioridad de éstas respecto a otras intervenciones (16,93).

Por otro lado, la aplicación de diferentes modalidades de ejercicio terapéutico en el tratamiento del HC tanto de forma aislada cómo en combinación con otras técnicas de fisioterapia también ha sido estudiada por varios autores con resultados satisfactorios. Jewell *et al.* (94), tras un estudio de cohorte retrospectivo en 2370 pacientes con HC, reportaron que tanto las técnicas de terapia manual como los estiramientos y los programas de ejercicio domiciliarios son efectivos para el tratamiento del HC. Kaddah *et al.* (95) compararon dos grupos de pacientes con HC: un grupo recibió tratamiento mediante movilizaciones en el rango final de movimiento y movilización escapular y el otro ejercicio de estiramiento pasivo. Los resultados mostraron mejoras significativas para ambos grupos en la severidad del dolor, la discapacidad y el dolor medidos mediante la escala SPADI (*Shoulder Pain and Disability Index*) y el ROM pasivo en flexión, abducción y rotaciones interna y externa de hombro. Sin embargo, el grupo que recibió el tratamiento mediante movilizaciones mostró mejorías superiores en cuanto a la severidad del dolor, la discapacidad funcional (SPADI) y el ROM pasivo en flexión y abducción (pero no para las rotaciones de hombro). Dueñas *et al*. (96) aplicaron un enfoque de terapia manual multimodal que incluía ejercicios de estiramiento en el domicilio en 11 pacientes con HC. Dicho tratamiento se adaptó de forma individualizada en función del nivel de irritabilidad y funcionalidad del hombro a cada paciente. Tras el tratamiento, los pacientes mostraron mejoras significativas en cuanto al dolor, discapacidad medida mediante el cuestionario DASH (*Disabilities of the Arm, Shoulder and Hand*), el ROM glenohumeral (abducción y rotación externa activas) y la fuerza.

*Electroterapia*

Otras técnicas de fisioterapia como la electroterapia también son aplicadas en el tratamiento del HC con los objetivos reducir el dolor y la inflamación y mejorar la movilidad glenohumeral. Por ejemplo, los ultrasonidos, TENS, laser, corrientes interferenciales, ondas de choque o

radiofrecuencia (97–100). Algunos de estos estudios que han investigado el efecto de las técnicas de electroterapia en pacientes con HC concluyen que estas técnicas presentan resultados satisfactorios cuando son aplicadas junto con ejercicio terapéutico o terapia manual y en ocasiones se muestran superiores al placebo. Sin embargo, existe falta de consenso de un protocolo específico (dosis, duración del tratamiento, parámetros específicos de la electroterapia aplicada…) y algunos estudios no presentan diferencias significativas al añadir electroterapia al tratamiento del HC (94,97,101–103). Por tanto, es necesario seguir investigando para poder definir de forma más precisa los beneficios de la electroterapia combinada con otras técnicas de fisioterapia.

*Masaje*

Finalmente, varios estudios también incluyen otras técnicas como el masaje o la técnica de Cyriax en combinación con ejercicio terapéutico o crioterapia con resultados positivos en el alivio de los síntomas del HC (104–106). Sin embargo, de nuevo, la variabilidad en las técnicas y dosis aplicadas en dichos estudios debido a la falta de protocolización dificulta establecer conclusiones firmes sobre la eficacia aislada de estas modalidades terapéuticas (107).

### 4.1.2. Técnicas *"top-down"* o *"hands off"*

*Educación del paciente*

La educación del paciente sobre la historia natural del HC debería ser clave en el tratamiento del mismo y aunque ningún estudio ha abordado este aspecto de forma específica en esta condición de hombro, la evidencia disponible señala que la educación en fisiología del dolor es efectiva para cambiar la percepción del dolor e incluso el estado de salud en pacientes con diversas patologías musculoesqueléticas con dolor crónico (p. ej., lumbalgia, fibromialgia o síndrome de fatiga crónica) (108).

La naturaleza insidiosa del HC y el intenso dolor que le caracteriza sobre todo en las etapas iniciales puede resultar desconcertante para los pacientes. Por tanto, explicar de forma clara la naturaleza y curso de la patología nos ayudará a preparar al paciente e implicarle en el proceso de la rehabilitación, así como mejorar la adherencia al tratamiento, especialmente si incluye ejercicios domiciliarios (16).

Kelley *et al*. (109) publicaron en la sección de ortopedia de la *American Physical Therapy Association* una Guía de Práctica Clínica para el HC basada en la Clasificación Internacional del Funcionamiento, la Discapacidad y la Salud (CIF). En esta guía, los autores recomiendan la educación del paciente para fomentar la modificación de la actividad, al mismo tiempo que enfatiza el ROM funcional sin dolor, es importante para prevenir la inmovilización autoimpuesta.

*Imaginería motora graduada*

La GMI es un programa integral diseñado para activar y reorganizar secuencialmente las redes motoras a nivel cortical en tres pasos: entrenamiento del reconocimiento de la lateralidad, movimientos imaginarios y terapia en espejo (110,111). El objetivo de la GMI por tanto, es "entrenar el cerebro", partiendo de la premisa de que si los cambios a nivel cortical son clave en el manejo del dolor crónico, entonces la reorganización de la corteza motora ayudará a disminuir el dolor (112). Como se ha comentado en apartados anteriores de esta tesis, este enfoque terapéutico se presenta como una opción prometedora en el tratamiento tanto de sujetos con SC (74–77) como en patologías musculoesqueléticas con dolor crónico (78,79) pero su evidencia para el tratamiento del dolor de hombro y HC es escasa. Los estudios de Louw *et al*. (80), Başkaya *et al*. (81) y Sawyer *et al*. (70) han presentado resultados preliminares satisfactorios sugiriendo que este enfoque terapéutico puede ser efectivo en la población con dolor de hombro y HC. Sin embargo, debido al reducido número de investigaciones, es necesario seguir investigando el efecto de este tipo de enfoque terapéutico para establecer conclusiones firmes al respecto.

### 4.2. Farmacoterapia y técnicas invasivas

*Fármacos e infiltraciones intraarticulares*

Aunque no existe evidencia suficiente que respalde el uso de fármacos antiinflamatorios no esteroideos (AINES) para el tratamiento del HC, a menudo los corticoesteroides orales y las infiltraciones intraarticulares en el espacio glenohumeral o subacromial son prescritos en las fases tempranas de la patología para proporcionar alivio del dolor y la inflamación (82). La mayoría de los estudios al respecto sólo han mostrado una reducción transitoria del dolor (de 3 a 6 semanas) sin mejoría del ROM (50). Por otro lado, las infiltraciones guiadas mediante ecografía o fluoroscopia han demostrado resultados mucho más favorables al inicio de los síntomas, pero es necesaria mayor evidencia que respalde su uso preferentemente en una u otra fase del desarrollo del HC (39,113,114). A este respecto, Challoumas *et al*. (115), en una reciente revisión sistemática y metaanálisis, recomiendan el uso de infiltraciones de corticoesteroides en sujetos con HC de un tiempo de evolución inferior a un año, ya que parecen tener beneficios más tempranos en comparación con otras intervenciones y sus efectos pueden alargarse hasta 6 meses. No obstante, los autores de dicho estudio recomiendan complementar las infiltraciones con un programa de ejercicios de movilidad y estiramiento domiciliarios y enfatizan la importancia de la educación al paciente sobre la historia natural del HC y las alternativas terapéuticas para que éstos decidan si desean someterse a esta técnica invasiva (115).

En conclusión, los corticoesteroides orales y las infiltraciones intraarticulares pueden estar indicadas en las fases tempranas de la patología para mejorar el dolor y la inflamación. Sin embargo, no se ha demostrado que el uso de AINES mejore la función o el dolor frente al uso del placebo (39).

*Bloqueo del nervio supraescapular*

El nervio supraescapular proporciona el 70% de la inervación sensorial de la articulación glenohumeral (116). Por tanto, sus fibras aferentes pueden quedar atrapadas por los tejidos lesionados o sensibilizados en pacientes con dolor crónico de hombro (64). En ocasiones se emplea el bloqueo del nervio supraescapular (BNSE) como tratamiento del dolor de hombro en patologías agudas y crónicas (117), el cual consiste en la infiltración de fármacos anestésicos en la fosa supraescapular, suponiendo un método terapéutico simple y rentable que no suele presentar complicaciones asociadas (118–120). Diversos estudios han presentado resultados satisfactorios en cuanto al alivio del dolor y mejora del ROM en pacientes con HC mediante BNSE (116,121,122) y apoyan priorizar su aplicación con respecto a las infiltraciones intraarticulares por tener resultados similares pero menos contraindicaciones y efectos secundarios, así como por ser de fácil aplicación, especialmente de forma ecoguiada.

Sin embargo, se requieren más ensayos clínicos aleatorizados que comparen el BNSE con otros tratamientos para poder concretar su función y el momento más adecuado para emplear esta herramienta terapéutica en el tratamiento del HC (122).

*Manipulación bajo anestesia*

La manipulación bajo anestesia (MBA) es un proceso relativamente rápido y sencillo mediante el cual se pretende romper las adherencias capsulares para tratar de recuperar el ROM del hombro y mejorar los síntomas en un corto plazo de tiempo (123).

La MBA frecuentemente se combina con la aplicación de infiltración de corticoesteroides para minimizar la respuesta inflamatoria de esta intervención, aunque la literatura no es muy concluyente respecto a sus beneficios añadidos (124). En ocasiones también se combina la MBA con liberación capsular bajo artroscopia, ya que parece obtener resultados superiores a corto plazo en comparación con la aplicación de la MBA de forma aislada (125). Rangan *et al.* (126), en el mayor ECA

publicado en los últimos años, compararon la efectividad de tres tratamientos en 503 pacientes con HC primario: MBA + fisioterapia post-intervención, liberación capsular bajo artroscopia + fisioterapia post-intervención y fisioterapia + infiltración de esteroides. Ninguna de estas intervenciones se mostró superior al resto en cuanto a mejoría en el dolor y la función del hombro, sin embargo la MBA resultó la opción con mejor coste-efectividad (126).

Por otro lado, cabe destacar que el papel de la MBA en el tratamiento del HC sigue siendo controvertido por las complicaciones que puede acarrear, como pueden ser la lesión del plexo braquial por la distensión y, en casos más graves, la fractura humeral, de la glenoides o de la clavícula (127,128).

*Hidrodilatación capsular*

La hidrodilatación capsular es una intervención no quirúrgica que se emplea en el tratamiento del HC. Aunque la composición puede variar, básicamente consiste en la infiltración ecoguiada de un gran volumen de solución salina que contiene anestésico local, corticoesteroides y material de contraste en la articulación glenohumeral (generalmente alrededor de 30 ml) (129). Mediante esta técnica se produce una distensión de la cápsula con el fin de aumentar el volumen dentro de la articulación y disminuir la rigidez produciéndose frecuentemente como consecuencia una rotura de la cápsula (130). No obstante, existe controversia sobre el mecanismo de acción de la hidrodilatación capsular, ya que no hay evidencia firme que apoye que los beneficios de esta intervención se deban a la dilatación de la cápsula o a la rotura de la misma (129) y las investigaciones sobre la eficacia de esta técnica presenta resultados contradictorios. Buchbinder *et al*. (131), compararon en un ECA el tratamiento mediante hidrodilatación capsular con placebo mostrando una mejoría estadística y clínicamente significativa en el dolor de hombro e índice de discapacidad 6 semanas después de la intervención, pero no durante el seguimiento. Por otro lado, varios estudios han comparado la hidrodilatación capsular con esteroides con la infiltración intraarticular de esteroides de forma aislada sin obtener diferencias estadísticamente significativas. Khan *et al.* (132), compararon los

efectos añadidos de la hidrodilatación capsular a un tratamiento de fisioterapia convencional en 36 pacientes con HC obteniendo mejoras estadísticamente significativas en el ROM a las 8 semanas, pero no en cuanto a la intensidad del dolor. Quraishi *et al.* (133), compararon en un ECA la hidrodilatación capsular con la MBA obteniendo mejoría clínicamente significativa de la función, el ROM y el dolor después de la intervención en ambos grupos; sin embargo, ninguno de los enfoques terapéuticos mostró superioridad respecto al otro.

Por otro lado, además de los beneficios reportados varios autores han indicado que el principal efecto secundario de este procedimiento es el dolor asociado a la aplicación de esta técnica (131,134,135). Por lo tanto, aunque es una técnica de tratamiento que se aplica en el HC con resultados aparentemente satisfactorios, aún es necesario investigar en mayor profundidad sus beneficios y protocolo de aplicación ya que tampoco existe evidencia que sugiera su superioridad con respecto a otros tratamientos.

*Liberación capsular bajo artroscopia:*

La liberación capsular bajo artroscopia es una técnica quirúrgica que puede emplearse como tratamiento del HC, generalmente en última instancia y tras el fracaso del tratamiento conservador (136,137). Se ha demostrado su efectividad en la mejoría de los síntomas y presenta ciertas ventajas, como minimizar el trauma en los tejidos y un mejor acceso a la cápsula glenohumeral y control en su liberación, así como menos complicaciones asociadas que otras técnicas como la MBA (138,139). Los estudios al respecto han mostrado que la liberación capsular bajo artroscopia ayuda a la reducción de la severidad y frecuencia del dolor y a la mejoría del ROM y función del hombro (140,141). Sin embargo, esta técnica no parece reportar resultados clínicos superiores a otras intervenciones como la MBA o la fisioterapia combinada con infiltración de esteroides (126) y su aplicación puede conllevar más riesgos y/o complicaciones como inestabilidad articular (126,142).

Además, aunque los resultados de esta intervención quirúrgica sean satisfactorios, aún existen cuestiones como son el momento y la técnica apropiados así como los pacientes candidatos a beneficiarse de esta cirugía (143).

En definitiva, aunque todas estas técnicas invasivas han sido estudiadas y se aplican en la práctica clínica para el tratamiento del HC, ninguno de estos métodos presenta resultados superiores al resto (144). De hecho, en la actualidad, no existe un protocolo de tratamiento estandarizado y aceptado universalmente para el manejo del HC, siendo los objetivos terapéuticos principales disminuir el dolor y mejorar el ROM y la función del hombro (109,122).

En este sentido, Kelley *et al*. publicaron en 2013 unas recomendaciones y Guía de Práctica Clínica para el diagnóstico y tratamiento de pacientes con HC basadas en el nivel de evidencia de las diferentes intervenciones tanto conservadoras como invasivas (109).

## 5. OBJETIVOS

Por todo lo expuesto en el contexto del marco teórico, en esta sección se detallan los objetivos del presente trabajo de investigación.

### 5.1. Objetivo general

Determinar la efectividad de incluir un enfoque terapéutico centrado en el SNC en el tratamiento de pacientes con HC.

### 5.2. Objetivos específicos

**Estudio 1**

1. Estudiar si los pacientes con HC presentan alteración en los mapas corticales y en el esquema corporal a causa del dolor mediante la valoración de la agudeza táctil (discriminación entre dos puntos) y el reconocimiento de la lateralidad.
2. Comparar la agudeza táctil y el reconocimiento de la lateralidad del hombro afecto con el hombro sano en sujetos con HC.
3. Comparar la agudeza táctil y el reconocimiento de la lateralidad entre hombro afecto y no afecto en sujetos con HC y respecto al hombro dominante en sujetos controles sanos.
4. Determinar si existe correlación entre la agudeza táctil y el reconocimiento de la lateralidad y la severidad y duración de los síntomas en los sujetos con HC.

La hipótesis de este estudio es que los pacientes con HC muestran alteración en los mapas corticales y en el esquema corporal a causa del dolor al comparar el hombro sano con el hombro afecto, así como al comparar el hombro afecto con el hombro del brazo dominante en sujetos controles sanos. Asimismo, se espera encontrar relación entre dichas alteraciones y la severidad y duración de los síntomas de los sujetos con HC.

**Estudio 2**

1. Evaluar la factibilidad de implementar un programa de tratamiento centrado en el SNC para pacientes con HC.
2. Valorar la adherencia al tratamiento orientado al SNC en sujetos con HC.
3. Estudiar el impacto clínico de este programa sobre el dolor, el ROM, la función y los aspectos psicosociales.
4. Establecer la base de un ECA que estudie si existen diferencias al añadir el tratamiento enfocado al SNC a un programa de terapia manual en pacientes con HC.

La hipótesis de este estudio es que los pacientes con HC pueden ser candidatos a recibir un enfoque de tratamiento orientado al SNC con resultados satisfactorios en cuanto a la adherencia al tratamiento, la mejora del dolor, el ROM y la función, y a diferentes aspectos psicosociales.

**Estudio 3**

1. Definir el protocolo de un ECA que compare la efectividad de añadir las técnicas orientadas al SNC a un programa de terapia manual en pacientes con HC.

**Estudio 4**

1. Analizar y comparar dos tratamientos para el HC: uno que consiste en terapia manual y estiramientos domiciliarios y otro grupo tratamiento combinado de terapia manual y estiramientos domiciliarios + el enfoque orientado al SNC.
2. Determinar si los pacientes con HC que reciben también el enfoque terapéutico centrado en el SNC presentan mejores resultados en cuanto a funcionalidad y dolor que el grupo que solamente recibe terapia manual y estiramientos domiciliarios.

La hipótesis de este estudio es que el grupo de pacientes que reciben el tratamiento de terapia manual y estiramientos domiciliarios junto con las técnicas orientadas al SNC presentarán mejores resultados clínicos en términos de funcionalidad y dolor, en comparación con los pacientes que reciben únicamente el tratamiento de terapia manual y estiramientos en domicilio.

# SECCIÓN SEGUNDA: PROCEDIMIENTO GENERAL

## 6. PARTICIPANTES

### 6.1. Divulgación del proyecto

Después de ser aprobada la propuesta de investigación por la Comisión de Ética en Investigación Experimental de la *Universitat de València* (Anexo I), se comenzó la búsqueda de participantes. Para ello, se preparó la documentación necesaria sobre el estudio para alcanzar la mayor difusión posible con el objetivo de reclutar pacientes con HC. Por un lado, se organizaron varias entrevistas con fisioterapeutas tanto de centros privados como públicos, así como con dos traumatólogos del Hospital Universitario la Fe de Valencia. En las reuniones con los profesionales sanitarios, se les informó sobre el proyecto, los criterios de inclusión y exclusión del estudio y los datos de contacto del equipo investigador. Para ello, se les proporcionó unos folletos para poder informar a aquellos pacientes que considerasen posibles candidatos de la muestra de estudio. Asimismo, el estudio se publicitó por varias redes sociales y se envió la información por email a diversos centros de fisioterapia que pudieran estar interesados en colaborar con el reclutamiento de pacientes.

Una vez los pacientes eran derivados al equipo investigador, se les contactaba telefónicamente para informarles sobre los detalles y objetivos del proyecto, y la forma de realización del mismo. Si los pacientes accedían a participar en el estudio, se les citaba formalmente en uno de los laboratorios del *Departament de Fisioteràpia* de la *Universitat de València*.

Durante la primera entrevista personal, se explicó a los candidatos en qué consistían las valoraciones y el tipo de tratamiento que iban a recibir. Además, se resolvieron las posibles dudas que pudieran tener y a continuación, si presentaban conformidad, se les proporcionaba el consentimiento informado (Anexo II) y el consentimiento del uso de la imagen para su firma (Anexo III). Asimismo, el estudio se registró previamente en *Clinical Trials* (www.clinicaltrials.gov) (Anexo IV).

### 6.2. Reclutamiento de participantes

A lo largo de este proyecto, un total de 67 sujetos candidatos al estudio fueron remitidos al equipo investigador. 21 sujetos no formaron parte del estudio debido a que presentaban algún criterio de exclusión, no cogieron el teléfono o no quisieron participar. De los 46 participantes que accedieron y firmaron el consentimiento informado, 10 formaron parte de la muestra del estudio de factibilidad del enfoque de tratamiento centrado en el SNC y los otros 36 formaron parte del ECA que se realizó con posterioridad y que fue completado por un total de 34 participantes (Figura 1).

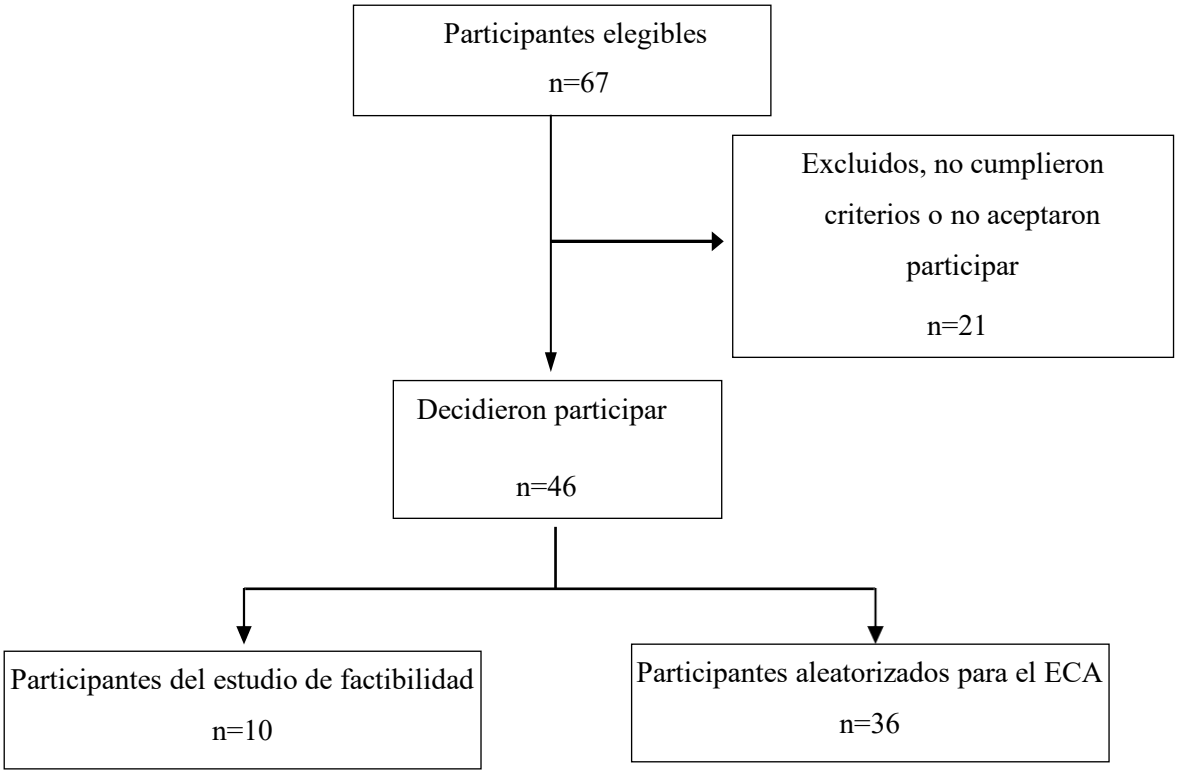


*Figura 1. Esquema del reclutamiento de participantes del estudio. Fuente: elaboración propia.*

Para la realización del ECA, se asignó a los participantes de forma aleatoria en dos grupos con el mismo número de sujetos. Se equilibró la muestra de participantes para que los grupos tuvieran características similares en cuanto a edad y sexo con el fin de favorecer la comparación de resultados

entre grupos. Esta aleatorización se realizó mediante un generador de números aleatorios con el ordenador (www.random.org).

Además, los investigadores responsables de todas las valoraciones estuvieron cegados al grupo de intervención asignado a cada participante. Asimismo, a cada consentimiento informado firmado se le asignó un código alfanumérico, que lo identificaba, asegurando la confidencialidad de los datos personales tal como estipula la ley Orgánica 15/1999, de 13 de diciembre, de Protección de Datos de Carácter Personal, siendo custodiado este documento por separado de los datos obtenidos del estudio.

### 6.3. Tamaño de la muestra

El tamaño muestral del ECA se calculó utilizando el software G*Power 3.0.18, considerando el SPADI como medida de resultado primaria. Además, se basó en estudios que aplicaron intervenciones de fisioterapia en pacientes con HC (promedio SPADI de 66 puntos; SD = 16) (145) y el mínimo cambio detectable (MCD) indicado en el estudio de Tveita *et al*. (146) (17 puntos) para detectar una diferencia entre grupos de 17 puntos (SD = 16). Con un poder del 80% y un nivel alfa de 0.05, se estimó un tamaño de muestra total de 30 pacientes (15 por grupo). Finalmente, se tuvo en cuenta una tasa de abandono del 15%, aumentando el tamaño de la muestra a 34 pacientes (17 por grupo).

### 6.4. Criterios de inclusión / exclusión

Los criterios de inclusión / exclusión (147) del presente estudio se presentan en la Tabla 2:

*Tabla 2. Criterios de inclusión y exclusión del estudio. Fuente: elaboración propia.*

| Criterios de inclusión | Criterios de exclusión |
|---|---|
| • Presentar restricción mayor al 50% en la rotación externa pasiva de hombro en comparación con el lado no afectado o bien menos de $30^0$ rotación externa de hombro en posición anatómica.<br>• Pérdida de ROM mayor al 25% en al menos dos planos de movimiento en comparación con el hombro no afectado.<br>• Dolor y restricción del ROM presentes y que hayan alcanzado una meseta o que hayan empeorado al menos durante el último mes. | • Dificultades para entender el idioma español escrito o hablado.<br>• Cirugía en el cuadrante superior durante el último año (hombro, cuello, miembro superior).<br>• Problemas de la piel o condiciones médicas que impidan la aplicación de estímulos táctiles en el hombro.<br>• Trastornos de la visión, psicopatologías o problemas motores o neurológicos que puedan dificultar el desempeño de tareas de denominación rápida.<br>• Diagnóstico de luxación cerrada, artritis, fracturas o necrosis avascular.<br>• Infiltración de corticoesteroides en el hombro afectado o haber recibido previamente otros tratamientos que hayan mejorado la sintomatología.<br>• Hombro congelado bilateral.<br>• Embarazo o lactancia.<br>• Enfermedad cardiovascular. |

Abreviaturas: ROM, rango de movilidad.

# 7. MATERIAL Y MÉTODOS

El equipo investigador estuvo compuesto por 4 fisioterapeutas, 3 de ellos a cargo de las valoraciones periódicas de los pacientes y la cuarta, doctoranda de esta tesis, encargada de la aleatorización y de implementar el tratamiento de fisioterapia. Los evaluadores, con 20, 20 y 10 años de experiencia clínica en valoración y tratamiento de pacientes con HC, fueron instruidos sobre cómo realizar las mediciones por uno de los evaluadores con el fin de utilizar todo el mismo protocolo. Asimismo, se realizó un entrenamiento bajo la supervisión del instructor con participantes voluntarios durante tres sesiones durante la semana previa al inicio del estudio. Con el fin de garantizar la coherencia en la recogida de datos, el mismo examinador fue responsable de todas las medidas tomadas en un sujeto desde el principio hasta el final del estudio.

Las valoraciones se realizaron en el periodo comprendido entre octubre de 2017 y febrero de 2021. A continuación, se detalla el protocolo seguido durante las sesiones de valoración de los participantes.

## 7.1. Protocolo de las valoraciones

Las valoraciones se realizaron al inicio y después de un período de 2 semanas de "lavado" sin intervención (148). Después de esta valoración inicial, los participantes comenzaron el tratamiento y volvieron a ser valorados al final del tratamiento y a los tres meses de su finalización, a modo de seguimiento (Figura 2).

En las sesiones de valoración se recogió información relativa a:

a) Datos sociodemográficos.
b) Intensidad del dolor de hombro.
c) Agudeza táctil y reconocimiento de la lateralidad.
d) Algometría: umbral de dolor a la presión (UDP), sumación temporal del dolor (ST).
e) Valoración del ROM activo y pasivo mediante inclinómetro.

f) Administración de cuestionarios.

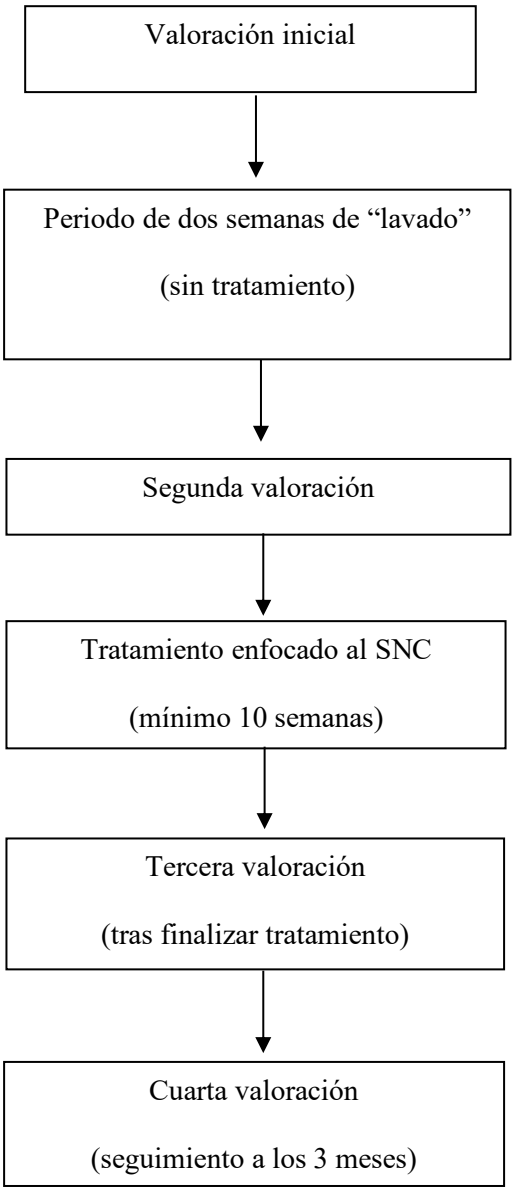


*Figura 2. Esquema del reclutamiento de participantes del estudio. Fuente: elaboración propia.*

A continuación, se detallan las herramientas y métodos empleados durante las sesiones de valoración de los participantes.

### 7.2. Formulario de registro

Se cumplimentó un formulario de registro (Anexo V) para cada participante con el fin de realizar las diferentes valoraciones periódicas a lo largo del estudio. Dicho formulario incluyó la recogida de los siguientes datos sociodemográficos: edad, sexo, peso, altura, lado afectado, HC primario o secundario, inicio de la sintomatología y progresión, diabetes, trastornos tiroides, tratamientos recibidos con anterioridad, toma de medicación y aspectos relacionados con la funcionalidad (trabajo, actividad deportiva, …etc.).

### 7.3. Intensidad del dolor

Para la valoración de la intensidad del dolor de hombro se empleó la EVA de 0 mm ("*no dolor*") a 100 mm ("*el peor dolor que puedas imaginar*") para registrar el dolor en reposo, en movimiento y en las últimas 24h (149). La EVA ha demostrado ser una herramienta válida y fiable para medir la intensidad del dolor en sujetos con dolor de hombro, siendo su diferencia mínima clínicamente importante (DMCI) de 30 mm (150).

### 7.4. Agudeza táctil

La agudeza táctil valoró mediante el umbral de discriminación entre dos puntos (*"Two point discrimination threshold"*, TPDT). Para su cálculo se utilizó un pie de rey mecánico deslizante con una precisión de 1 mm (Duratech TA-2081). Los participantes estaban sentados y se les marcó un punto 5 cm distal al borde lateral del acromion del hombro afectado. Con el fin de estandarizar esta valoración, dicho punto siempre se mantuvo entre los dos puntos del pie de rey y las mediciones se realizaron en dirección longitudinal (151) (Figura 3). Durante el proceso, se completaban una serie de mediciones ascendentes y descendentes. Primero, la distancia del calibre se aumentó gradualmente de 5 en 5 mm, comenzando desde 0 mm, hasta que el participante reportó la percepción de dos puntos en lugar de uno (Figura 3). La valoración descendente comenzó con los

puntos del calibre separados 30 mm más que el valor obtenido en la medición ascendente, seguido de decrementos en la distancia del calibre de 5 mm. Para el análisis posterior se empleó el valor medio del TPDT a partir de las dos puntuaciones anteriores.

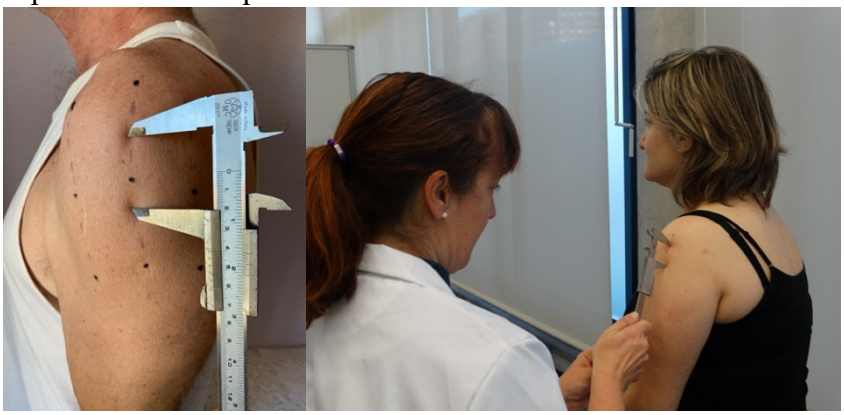

*Figura 3. Valoración de la agudeza táctil. Izquierda, demostración del protocolo de valoración. Derecha, valoración de la agudeza táctil de una participante.*

### 7.5. Reconocimiento de la lateralidad

El reconocimiento de lateralidad se valoró con una tarea de discriminación izquierda/derecha utilizando la aplicación *Recognise*™ del *Neuro Orthopaedic Institute* (www.noigroup.com). Para ello se presentaron un total de 30 imágenes de hombros (modo contextual) en un teléfono móvil a los participantes en un orden aleatorio que establece la propia aplicación y se les pidió que indicaran lo más rápido posible si la imagen mostraba un hombro derecho o izquierdo (Figura 4). Se registró el tiempo medio de respuesta y se calculó tanto la precisión como el porcentaje de imágenes evaluadas correctamente. Los participantes realizaron la prueba dos veces (se les mostraron dos bloques idénticos de 30 imágenes) con un descanso de 2 minutos entre cada bloque para lograr medidas precisas de reconocimiento de lateralidad. El primer bloque se realizó a modo de entrenamiento de la tarea para comprobar que los sujetos habían comprendido su ejecución, por lo que los datos de este bloque se descartaron y se emplearon para el posterior análisis los datos del segundo bloque (152). Este protocolo de medición ha demostrado ser muy fiable en sujetos sanos,

presentando un tiempo de respuesta media (SD) y precisión media (SD) para el reconocimiento de la lateralidad del hombro de 1738 (741) ms y 93,5 % (9,2) %, respectivamente (153).

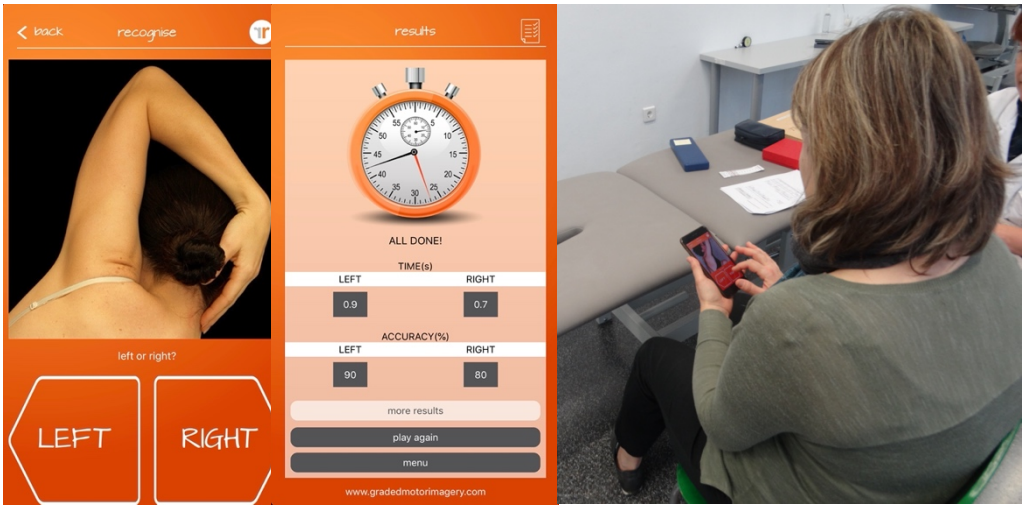


*Figura 4. Valoración del reconocimiento de la lateralidad. Izquierda, aplicación Recognise™. Derecha, valoración del reconocimiento de la lateralidad de una participante.*

### 7.6. Umbral de dolor a la presión

Para evaluar el umbral de dolor a la presión (UDP) se siguió un protocolo estandarizado (154) mediante el cual se valoró el hombro afectado y el sano (sobre el vientre medio del deltoides anterior, 5 cm caudal al borde anterior del acromion) y en una región corporal alejada, concretamente en el cuádriceps ipsilateral.

Para este proceso se empleó un algómetro *Fisher* analógico (*Force Dial* modelo FDK, *Wagner Instruments*) con un área de superficie en la punta redonda de 1 $cm^2$ **(**Figura 5**)**. La valoración se realizó aplicando la punta de la sonda del algómetro perpendicular a la piel, a razón de 1 $kg/cm^2/s$ hasta la primera aparición de dolor (155). Para estandarizar la velocidad de aplicación, los investigadores responsables de las mediciones practicaron una semana antes del comienzo del estudio, aumentando la presión linealmente a 5 $kg/cm^2$ durante 5 s según lo recomendado por otros autores (155).

El UDP se midió tres veces en cada una de las regiones anatómicas a valorar, con un período de descanso de 30 s entre repeticiones. Para el posterior análisis estadístico, se utilizó la media de estas tres mediciones. La algometría por medio de aplicación de presión es un método válido y fiable para medir el UDP, existiendo estudios que muestran una buena repetibilidad de las mediciones para el hombro en sujetos controles sanos (156,157).

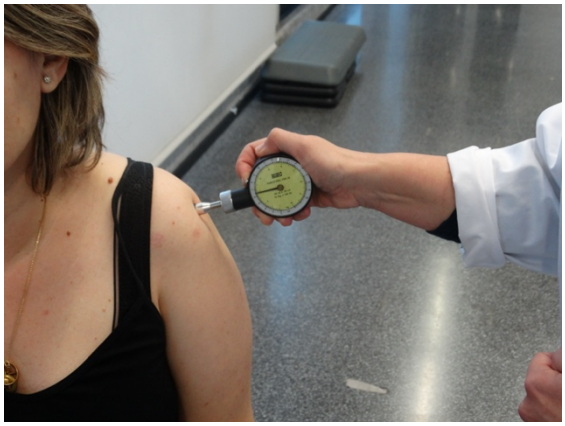

*Figura 5. Valoración del umbral de dolor a la presión de una participante.*

### 7.7. Sumación temporal del dolor

Para calcular la sumación temporal del dolor (ST), se comparó la intensidad de dolor percibida en un solo estímulo doloroso (pinchazo aplicado con un Pinprick de 256mN) sobre el músculo trapecio superior con la intensidad de dolor percibida sobre el hombro afectado tras aplicar una serie de 10 estímulos dolorosos repetitivos de la misma fuerza a una velocidad de uno por segundo (Figura 6). Para valorar la intensidad del dolor tras la aplicación del estímulo doloroso se le mostró al paciente una escala EVA donde indicaba el nivel de dolor de 0 a 100. Este procedimiento completo, se repitió 5 veces y para el cálculo final del resultado y el consiguiente análisis estadístico, se siguió la fórmula: ST= media 5 series / media 5 estímulos individuales (154). La ST es ampliamente utilizada para valorar la presencia de SC, sin embargo, se requieren más estudios y de mayor calidad metodológica para determinar sus propiedades psicométricas, especialmente en sujetos con dolor de hombro (158,159).

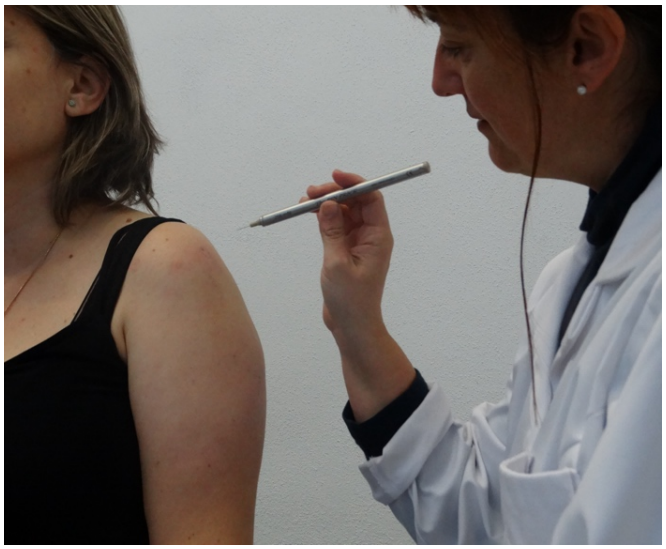

*Figura 6. Valoración de la sumación temporal del dolor de una participante.*

### 7.8. Rango de movimiento (ROM)

El ROM activo y pasivo del hombro afectado se evaluó mediante un inclinómetro *Plurimeter-V* (*Plurimeter 164 dr Rippstein*) siguiendo el protocolo de guías publicadas al respecto (160,161) (Figura 7). Los siguientes movimientos fueron evaluados:

a) Rotación externa de forma activa y pasiva en posición anatómica.

b) Flexión activa y pasiva.

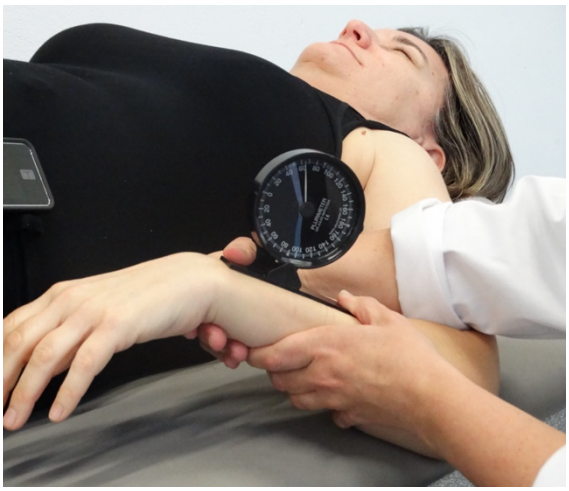

*Figura 7. Valoración del ROM de una participante.*

Los datos del ROM de cada participante se anotaron al formulario de registro (Anexo V) y además se tomaron anotaciones para cada movimiento evaluado respecto a dolor reportado por el participante o si no había sido posible de evaluar y el motivo.

Para evaluar el ROM en flexión de hombro, los participantes permanecieron de pie con el inclinómetro sobre el tercio proximal del húmero en la porción superior del bíceps braquial. Primero se pidió a los participantes que elevaran activamente el hombro hasta que apareciera dolor o resistencia y luego el/la evaluador/a movilizó el hombro de forma pasiva, hasta que se alcanzó la tolerancia al dolor o el ROM máximo. Los inclinómetros han mostrado una alta sensibilidad al cambio para la flexión pasiva y activa del hombro en pacientes con HC, presentando un MCD para

la flexión activa del hombro de $8^0$ en sujetos asintomáticos (162) y buena fiabilidad y validez para medir la flexión activa del hombro en el plano escapular (163).

Por otro lado, para valorar la rotación externa glenohumeral, los participantes permanecieron en decúbito supino con el brazo apoyado sobre la camilla. El brazo estuvo en $0^0$ de abducción de hombro, flexión de codo $90^0$ y pronosupinación neutra del antebrazo y se colocó inclinómetro en la parte distal y dorsal del antebrazo. Igual que en la valoración de la flexión de hombro, primero se pidió a los participantes que realizaran de forma activa rotación externa del hombro hasta que apareciera dolor o resistencia y luego el/la evaluador/a movilizó de forma pasiva hasta el límite por tolerancia al dolor o se alcanzara el ROM máximo. Se ha reportado un MCD para la valoración de la rotación externa activa con inclinómetro de $9^0$ en sujetos asintomáticos y es una herramienta de evaluación que presenta una buena fiabilidad intra e inter-observador para la rotación externa activa y pasiva en sujetos sanos y pacientes con dolor de hombro de diferentes etiologías (162).

### 7.9. Escalas y cuestionarios

Al final de la valoración, se le proporcionó a cada paciente un formulario compuesto por los siguientes cuestionarios y escalas (Anexo VI):

*Shoulder Pain and Disability Index questionnaire*

El dolor de hombro y la discapacidad se valoraron mediante la versión en español del "*Shoulder Pain and Disability Index questionnaire"* (SPADI) (164). Este cuestionario está compuesto por 13 items, los cuales se puntúan mediante una escala numérica que va de 0 (sin dolor/sin dificultad) a 10 (el peor dolor imaginable/tan difícil que requirió ayuda). La puntuación total oscila entre 0 y 100 puntos (puntuaciones más altas indican mayor discapacidad o disfunción del hombro) (165). La versión española del SPADI presenta alta consistencia interna (α de Cronbach: 0,916), excelente fiabilidad test-retest (ICC (coeficiente de correlación intraclase): 0.91) (166) y su DMCI oscila entre 8 y 13 puntos (167).

*Patient Specific Functional Scale*

Los participantes completaron la versión en español de la "*Patient Specific Functional Scale"* (PSFS) para valorar los cambios en el estado funcional de la extremidad superior afectada después del tratamiento. Para completarla, los sujetos escogieron de tres a cinco actividades que no podían hacer o en las cuales presentaban dificultades debido al HC y las calificaron en una escala de 11 puntos, que oscila entre 0 ("incapaz de realizar la actividad") y 10 ("capaz de realizar la actividad al nivel previo a la lesión"). Se obtuvo una puntuación total mediante la suma de las puntuaciones de las actividades divididas por el número de actividades evaluadas, obteniendo una puntuación global de 0-10 ,donde las puntuaciones más altas indican un mejor desempeño de las actividades.
La PSFS ha demostrado ser una herramienta de valoración válida y fiable en sujetos con problemas musculoesqueléticos en las extremidades superiores y presenta una DMCI de 1.16 puntos (168).

*Tampa Scale for Kinesiophobia*

La conducta de miedo-evitación de los participantes fue valorada a través de la versión validada en español de la "*Tampa Scale for Kinesiophobia"* (TSK-11) (169). Este cuestionario consta de 11 ítems para evaluar el miedo al movimiento o el miedo a volverse a lesionar durante el movimiento (170). Cada ítem se puntúa en una escala de 4 puntos, de 1 = "totalmente de acuerdo" a 4 = "totalmente en desacuerdo" (las posibles puntuaciones totales oscilan entre 11-44 y puntuaciones más altas indican mayor comportamiento de evitación del miedo). Esta herramienta ha mostrado una aceptable consistencia interna y validez (convergente y predictiva) tanto en sujetos con dolor musculoesquelético agudo (alfa de Cronbach= 0.79) como crónico (alfa de Cronbach= 0.79) (171). El MCD para el TSK-11 es 5.6 (172).

*Central Sensitization Inventory*

Con el objetivo de valorar el nivel de SC (173) se empleó la versión en español del "*Central Sensitization Inventory"* (CSI), el cual es un inventario de autoinforme que fue diseñado para identificar diferentes síntomas que pueden estar relacionados con la SC (174). El CSI tiene dos dimensiones: la parte A, que evalúa 25 síntomas relacionados con la salud comunes en la SC, con una puntuación total que va de 0 a 100; la parte B, que no tiene puntuación, ya que consiste en una pregunta sobre si el paciente ha sido diagnosticado previamente con uno o más trastornos específicos que incluye siete síndromes de SC (175). El CSI ha mostrado una consistencia interna aceptable en sujetos con dolor musculoesquelético de diferentes etiologías (alfa de Cronbach= 0.872), una alta confiabilidad test-retest (ICC = 0.91) y un MCD de 7.83% (173).

*Pain Catastrophizing Scale*

Para valorar la catastrofización se empleó la versión en español de la *"Pain Catastrophizing Scale"* (PCS), una herramienta válida y fiable que consiste en 13 ítems, que se evalúan de 0 (nada en absoluto) a 4 (todo el tiempo) (176). Su puntuación total va de 0-52 y puntuaciones más altas indican mayor nivel de catastrofización. Esta escala presenta apropiada consistencia interna, fiabilidad test-retest y sensibilidad al cambio (177).

### 7.10. Protocolo de tratamiento

Los participantes de este estudio recibieron dos tratamientos diferentes de fisioterapia con el fin de estudiar el objetivo principal planteado en este trabajo: determinar la efectividad de incluir un enfoque terapéutico centrado en el SNC en el tratamiento de pacientes con HC.

Por tanto, aquellos sujetos que cumplieron los criterios de inclusión y accedieron a participar en el estudio fueron aleatorizados en dos grupos de tratamiento:

I. Terapia manual y programa de estiramientos domiciliarios.
II. Terapia manual y programa de estiramientos en domiciliarios + enfoque centrado en el SNC.

Ambos tratamientos fueron aplicados por la misma fisioterapeuta, quien fue previamente entrenada por el equipo investigador para la aplicación y realización de ambos protocolos.

*Terapia manual y programa de estiramientos domiciliarios*

Los participantes de este grupo recibieron un programa de terapia manual y estiramientos domiciliarios descrito previamente por Dueñas *et al.* (96). Esta intervención consistió en 12 sesiones de terapia manual de una hora de duración por sesión en clínica, un día a la semana y un programa de estiramientos domiciliarios una vez al día, cinco días a la semana durante toda la intervención.

Tanto las técnicas de terapia manual como los ejercicios de estiramiento domiciliarios se adaptaron específicamente a cada participante, en base a su capacidad funcional medida a través del ROM (178) y al sistema de calificación de irritabilidad de los tejidos del hombro STAR (15) (Tabla 1). Por ejemplo, en pacientes que presentaron alta irritabilidad, se aplicaron técnicas manuales de movilización pasiva oscilatoria de bajo grado (p. ej., movilizaciones de Maitland grado I-II) y realizaron ejercicios de estiramiento en el domicilio sin dolor, de baja intensidad y corta duración (1-5 s).

Con el fin de determinar el tipo de técnicas que se iban a aplicar en la clínica y los estiramientos a realizar en el domicilio, al inicio de cada sesión la fisioterapeuta testaba el ROM del hombro activo

y pasivo (especialmente las rotaciones interna y externa) de cada participante en diferentes planos de movimiento y con distintos grados de abducción de hombro. Además, si el sujeto presentaba limitaciones en el ROM al llevar la mano a la espalda y/o la flexión de hombro, se aplicaban técnicas de movilización con movimiento de Mulligan (179).

Las movilizaciones oscilatorias pasivas (p. ej., movilizaciones de Maitland) (180) se aplicaron en 5 series de 1 minuto (grados I-IV) y las técnicas Mulligan en 3 series de 10 repeticiones.

En cuanto a los ejercicios de estiramiento domiciliarios, en base a la valoración del ROM y la irritabilidad, se indicaba a los participantes en cada sesión los ejercicios que debían realizar en casa una vez al día, 5 días a la semana y se les enseñaba a adaptar la intensidad y duración de los mismos en función del nivel de irritabilidad.

Los participantes con irritabilidad alta realizaron estiramientos de corta duración y sin dolor (cinco series de 1 a 5 segundos), los sujetos con irritabilidad moderada realizaron estiramientos de corta duración (cinco series de 5 a 15 segundos) y a aquellos que presentaron irritabilidad baja se les indicó que realizasen los estiramientos de mayor duración pudiendo experimentar dolor leve o molestia (16).

El protocolo completo del tratamiento de terapia manual y programa de estiramientos en domicilio pueden observarse en el Anexo VII.

La adherencia al programa de estiramientos domiciliarios se controló mediante un diario de tratamiento individual donde cada participante registraba la fecha y la duración de cada sesión, así como un apartado de comentarios si necesitaban hacer mención a algún aspecto concreto (181).

La progresión del tratamiento se fue basando en la reevaluación de las limitaciones del ROM y la irritabilidad de los tejidos presentada por cada participante en cada sesión clínica.

Además, para asegurar una buena tolerancia por parte de los participantes a las técnicas de terapia manual y al programa de estiramiento domiciliarios, la intensidad y la duración de las técnicas de terapia manual se adaptaron continuamente durante y entre sesiones según la respuesta del paciente y los niveles de irritabilidad.

*Enfoque de tratamiento centrado en el sistema nervioso central*

Los participantes de este grupo recibieron el programa de terapia manual y estiramientos domiciliarios descrito previamente, junto con las técnicas orientadas al SNC que se detallan a continuación:

En la primera sesión se hizo a los participantes una breve explicación sobre el procesamiento central del dolor y se les mostró una imagen del "mapa cerebral" (homúnculo) para explicarles como este mapa se vuelve "menos nítido" cuando existe dolor debido a la falta de movimiento de la zona afectada y se cree que cuando el mapa se agudiza, incluso el movimiento puede ayudar a reducir el dolor. A continuación, se les explicó que el enfoque de tratamiento centrado en el SNC que iban a recibir tenía como objetivo "afinar" el mapa cortical del hombro y por tanto disminuir su percepción de dolor y mejorar su ROM mediante el uso del entrenamiento de la discriminación sensorial (*Sensory Discrimination Training,* SDT) y de la GMI. Además, cuando se citó a los pacientes para su primera visita, se les pidió que acudieran con la persona que les fuese a asistir en las tareas a realizar en el domicilio. En este sentido, la fisioterapeuta encargada del tratamiento destacó la importancia de contar con un asistente colaborador para la realización de los ejercicios en el domicilio. Además, si algún participante presentó exacerbación de los síntomas en alguna de las etapas de tratamiento se revisaron y adecuaron los parámetros adecuados del mismo.

El tratamiento incluyó una sesión a la semana con la fisioterapeuta durante un mínimo de 10 semanas y entrenamiento en domicilio al menos 5 días a la semana.

La adherencia a los ejercicios de entrenamiento domiciliarios de este protocolo orientado al SNC también se registró mediante un diario de tratamiento individual donde cada participante registró la fecha y la duración de cada sesión domiciliaria, así como un apartado de comentarios (181).

*Entrenamiento de la discriminación sensorial*

Se implementó un programa de SDT graduado basado en el modelo utilizado por Wand *et al*. (182). Dicho programa de entrenamiento incluyó la discriminación del tipo de estímulo y su ubicación y el entrenamiento de la grafestesia en 5 etapas diferentes (clasificadas según el nivel de dificultad y de compromiso cortical). Cada etapa tuvo una duración mínima de 2 semanas (10 semanas en total), pero se prolongó una semana más en los casos en que los participantes no dominaban la tarea correspondiente a esa etapa.

Para el SDT en la primera etapa (semana 0-2), los participantes permanecían sentados en una posición cómoda con un espejo entre las extremidades superiores, (183). Por lo tanto, durante la primera semana de entrenamiento en casa y en la clínica, los participantes se colocaron de manera que pudieran ver el reflejo de su brazo no afectado en un espejo mientras se estimulaba el hombro afectado. Se colocó al paciente de tal manera que las extremidades estuvieran alineadas. Esta retroalimentación visual se retiró después de la primera semana y no se volvió a utilizar en el resto del programa de SDT. En esta primera etapa se entrenó la localización del estímulo. Para ello se mostró a los participantes una fotografía de un hombro en la que se marcaron 9 cuadrículas numeradas. El espaciado de las cuadrículas se basó en los datos normativos relacionados con la discriminación de dos puntos de la articulación afectada (184). El borde superior se fijó a 1 cm proximal a la articulación acromioclavicular y el borde inferior hasta la inserción del deltoides (Figura 8). Primero, para familiarizarse con esta tarea, se les mostró la fotografía y, mediante estímulos táctiles con el borde romo de un lápiz, se les iba indicando dónde se correspondía la numeración de cada bloque con cada zona de su hombro (182,185). Después de este período de familiarización, la fisioterapeuta encargada del tratamiento aplicó secuencias de números aleatorios siguiendo unas plantillas diseñadas con anterioridad específicamente para esta tarea (Anexo VIII).

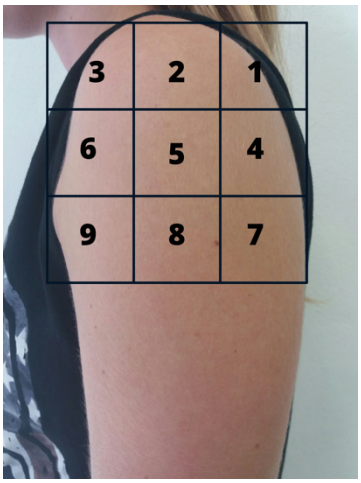


*Figura 8. Cuadrícula de 9 puntos que se entregó a los participantes para el entrenamiento de discriminación sensorial en el domicilio durante las semanas 0-2.*

Estas secuencias consistieron en presionar ligeramente el punto que indicaba la plantilla con el borde romo de un lápiz durante aproximadamente 2 segundos. La presión se mantenía al mínimo para evitar la provocación de dolor. Se indicaba a los participantes que debían identificar qué número de la cuadrícula se correspondía con el lugar del estímulo, y, si acertaban, la fisioterapeuta pasaba a la siguiente localización de la plantilla. En caso de no identificar el estímulo correctamente, se les decía cuál era el número de cuadrícula correcto y, a continuación, se les indicaba con un estímulo táctil con el lápiz sobre el número de la cuadrícula que ellos habían reportado. De esta manera, se pretendía ayudar a los participantes a desarrollar una mayor capacidad de identificar el área del estímulo. Se emplearon bloques de 60 estímulos con un intervalo de 15 s entre estímulos y un período de descanso de 3 minutos entre bloques (182).

Como se ha comentado en apartados anteriores, en la primera sesión los participantes vinieron acompañados por la persona que iba a asistirles en las tareas de entrenamiento en casa con el fin de asegurar la comprensión de la tarea y su correcta realización. Para la realización del entrenamiento en el domicilio se proporcionó a cada participante una fotografía de un hombro estándar con el dibujo de la cuadrícula de los puntos de estimulación (correspondiente con su género y lado afectado), y varias plantillas con bloques de 60 números aleatorios (Anexo VIII). Si al final de la

segunda semana (primera etapa) los participantes presentaban una precisión menor al 80% tras un bloque de prueba de 60 estímulos, el entrenamiento se prolongaba durante una semana más.

La segunda etapa (semanas 2-4) consistió en aumentar la dificultad de la tarea y se pidió a los participantes identificar el lugar del estímulo y también el tipo de estímulo. Para ello el protocolo a seguir fue el mismo, pero se emplearon plantillas diseñadas específicamente que presentaban bloques de 60 estímulos aleatorios tanto en la ubicación como el tipo de estímulo, empleando en unas ocasiones la parte roma del lápiz y en otras un tapón de corcho. En la primera semana de esta etapa, se siguió empleando la cuadrícula de 9 puntos de la fase anterior y durante la segunda semana se empleó una cuadrícula de 12 puntos para hacer más compleja la tarea, de forma que, a pesar de ser el área a estimular la misma, los puntos de discriminación sensorial se encontraban más juntos (Figura 9).

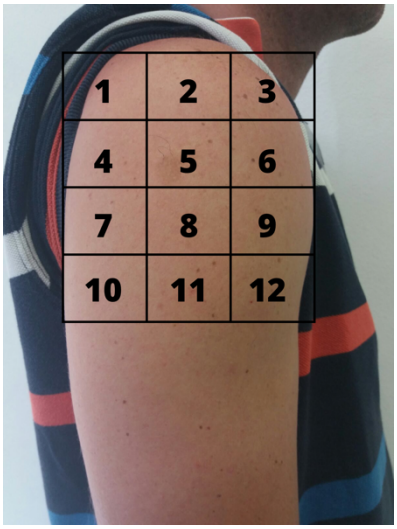


*Figura 9. Cuadricula de 12 puntos que se entregó a los participantes para el entrenamiento de discriminación sensorial en el domicilio durante las semanas 2-4.*

De nuevo, se informaba a los participantes sobre cada error que cometían. Del mismo modo, si al final de la segunda semana de esta etapa los participantes tenían menos del 80 % de precisión con un bloque de prueba de 60 estímulos, el entrenamiento de esta tarea se prolongaba por una semana más.

Para el entrenamiento en casa en esta segunda etapa, se entregó a los participantes una fotografía del hombro con los puntos de estimulación y un tapón corcho del mismo grosor que el empleado en la consulta. Se les proporcionó también diversas plantillas de combinaciones aleatorias de números (del 1 al 9 o del 1 al 12) y estímulos (tapón de corcho o borde romo del lápiz) (Anexo VIII). Se instó a los participantes a que hiciesen 15 minutos de esta tarea en casa al menos 5 días en semana.

Las siguientes 3 etapas (semanas 4-10) consistieron en tareas de grafestesia de dificultad creciente. En esta tercera etapa (semanas 4-6), los participantes debían reconocer letras dibujadas en el hombro de forma aleatoria en base a plantillas de bloques de 60 letras diseñadas específicamente para esta tarea. Inicialmente, la fisioterapeuta dibujó letras mayúsculas en el hombro del paciente con su dedo índice y se les pidió que la identificasen. Si se equivocaban, se les decía la letra real que se había dibujado y luego se dibujaba la letra que habían indicado incorrectamente. La progresión dentro de este bloque de 2 semanas consistió en disminuir progresivamente el tamaño de las letras, alternar su orientación y aumentar la velocidad a la que se dibujaban. Nuevamente, esta etapa se prolongó 1 semana más en aquellos participantes que tuvieron menos del 80% de precisión con un bloque de prueba al final de esta etapa. Para el entrenamiento en el domicilio, se pidió a los participantes que realizaran esta tarea al menos 15 minutos utilizando varias secuencias aleatorias de letras que se les había proporcionado (Anexo VIII).

La cuarta etapa (semanas 6-8) consistió en el reconocimiento de palabras de 3 letras dibujadas en el hombro. El protocolo y la progresión fueron similares a los descritos para la tarea de una sola letra, incluido el criterio para avanzar a la siguiente etapa.

La última etapa añadía una progresión adicional en las últimas dos semanas de tratamiento (semana 8-10) que consistió en la superposición de las letras de la palabra, de modo que todas se dibujaron sobre la misma parte del hombro. La última tarea de entrenamiento sensorial fue el cálculo de sumas simples dibujadas en el hombro con el mismo protocolo. Como en todas las etapas anteriores, en caso de no alcanzar un mínimo del 80 % de precisión al final de las 2 semanas, la tarea se prolongaba por una semana más. Igualmente, se indicó a los participantes que debían realizar estas tareas en

casa al menos 15 minutos al día, 5 días a la semana utilizando las plantillas con secuencias aleatorias de letras que les había proporcionado la fisioterapeuta (Anexo VIII).

La descripción completa del programa de SDT se muestra en la tabla 3.

*Tabla 3. Resumen de la progresión empleada en el programa de discriminación sensorial graduada.*

*Fuente: Adaptada de Lluch et al., (2019) (147)*

| **ETAPA** | **DISCRIMINACIÓN SENSORIAL GRADUADA** |
|---|---|
| **1 (semanas 0-2)** | **Ubicación del estímulo**<br>Determinar lugar del estímulo<br>Con feedback visual mediante espejo la primera semana<br>Sin feedback visual la segunda semana |
| **2 (semanas 2-4)** | **Ubicación y tipo de estímulo**<br>Determinar lugar del estímulo<br>Determinar tipo de estímulo<br>Progresión añadiendo puntos de estimulación |
| **3 (semanas 4-6)** | **Entrenamiento grafestesia**<br>Reconocer letras<br>Progresar disminuyendo tamaño<br>Progresar variando orientación<br>Progresar aumentando velocidad |
| **4 (semanas 6-8)** | **Entrenamiento grafestesia**<br>Reconocer palabras de 3 letras<br>Progresar disminuyendo tamaño<br>Progresar variando orientación<br>Progresar aumentando velocidad<br>Progresar superponiendo las letras de la palabra |
| **5 (semanas 8-10)** | **Entrenamiento grafestesia**<br>Calcular sumas simples<br>Progresar disminuyendo tamaño<br>Progresar variando orientación<br>Progresar aumentando velocidad<br>Progresar superponiendo los números |

*Entrenamiento imaginería motora graduada*

Se implementó un programa de GMI basado en trabajos previos de Wand *et al.* (182) y siguiendo las directrices publicadas por Moseley *et al.* (186). Este programa de GMI también se compuso de 5 etapas diferentes (clasificadas según el nivel de dificultad y de compromiso cortical). Cada etapa tuvo una duración mínima de 2 semanas (10 semanas en total).

La etapa inicial (semanas 0-2) del programa de GMI incluyó tareas de entrenamiento del reconocimiento de la lateralidad mediante el uso del mismo programa (*Recognise*™ del *Neuro Orthopaedic Institute*) que se empleó en las valoraciones de los participantes. Mediante esta aplicación se les mostraba a los pacientes en el móvil 3 bloques aleatorios de 30 imágenes contextualizadas de hombros tanto izquierdos como derechos en diferentes posiciones y orientaciones con 1 minuto de descanso entre bloques. Se indicó a los participantes que debían presionar 1 de los 2 botones (izquierdo o derecho), en función de la imagen mostrada, y que debían ejecutarlo dando su respuesta lo más rápido posible (111). Esta tarea requiere que hagan coincidir mentalmente su propia parte del cuerpo para que coincida con la posición que se muestra en la imagen y, por lo tanto, permite involucrar las áreas corticales motoras correspondientes a esa parte del cuerpo (111).

La progresión en dificultad de esta etapa del GMI se realizó reduciendo el tiempo de presentación de las imágenes y cambiando el contexto de las mismas (dichas acciones se pueden modificar de forma sencilla desde la propia aplicación *Recognise*™. Tras la primera sesión clínica, se instaló la aplicación *Recognise*™ en el móvil de cada participante para realizar esta tarea de entrenamiento en el domicilio al menos 15 minutos / 5 días a la semana.

La segunda etapa (semanas 3-4) consistió en la realización de tareas de movimientos imaginados. Para ello el equipo investigador grabó 4 vídeos en los que se presentaba a una persona realizando lentamente 10 repeticiones de una variedad de movimientos de hombro. Cada video tuvo una duración aproximada de 7 minutos. Durante la primera semana de esta etapa (semana 3), el video

mostraba movimientos de inicio de ROM del hombro (flexión, extensión y abducción unilateral del hombro), rotaciones externa e interna del hombro en $0^0$ de abducción, mano detrás de la espalda, mano a la cabeza y aducción horizontal. En la segunda semana de esta etapa (semana 4), el video mostró los mismos movimientos pero en rango completo y en posiciones más difíciles (p. ej., rotación interna y externa del hombro en $90^0$ de abducción) y usando algunos objetos para cambiar el contexto (p. ej., lanzar una pelota mediante rotación externa del hombro a $90^0$ de abducción). A los participantes se les indicó que visualizaran el video sentados en una posición relajada y cómoda y que a continuación cerrasen los ojos y se imaginaran a sí mismos en primera persona realizando esos movimientos de una manera suave, controlada y sin dolor con su hombro afectado. Esta tarea la realizaron en dos series de 20 repeticiones por cada movimiento y en cada sesión. Los vídeos fueron enviados a los participantes para que pudieran realizar esta tarea en casa durante al menos 15 minutos al día 5 días en semana.

La siguiente etapa (semanas 5-6) incluyó la realización de ejercicios de contracción isométrica del manguito rotador y los músculos escápulo-torácicos mediante ejercicios dinámicos de control neuromuscular glenohumeral y escápulo-torácico. El trabajo de activación de estos músculos facilitó la progresión entre los movimientos imaginarios y los movimientos reales del hombro que se emplearían en etapas posteriores mediante terapia en espejo, ya que no implicaban movimiento del hombro, minimizando así el potencial de incongruencia sensoriomotora. Además, la activación de dichos músculos podría agudizar la representación cortical del hombro (182). Durante la primera semana (semana 5), se enseñó a los participantes a realizar ejercicios de contracción isométrica de los músculos del manguito rotador (187) y de los músculos escápulo-torácicos (188) de forma aislada. Durante la segunda semana de esta etapa (semana 6), la progresión consistió en mantener la contracción muscular isométrica mientras realizaban movimientos de hombro lentos, controlados y libres de dolor en diferentes direcciones. Al igual que con el resto de tareas del entrenamiento de GMI, se indicó a los participantes que practicaran en su domicilio estos ejercicios, durante 15 minutos cada día, al menos 5 días a la semana.

Las dos últimas etapas (semanas 7-10) consistieron en implementar tareas de terapia en espejo siguiendo la progresión que se explica a continuación. Los participantes se sentaban de forma cómoda en una silla con un espejo con ruedas delante y centrado con su tronco, de manera que el lado reflectante se orientase hacia el lado no afectado para poder visualizarlo. Se pidió a los pacientes que se inclinasen ligeramente hacia adelante para poder ver por completo el brazo no afectado en el espejo. Los ejercicios comenzaron simplemente observando el reflejo del brazo no afectado en el espejo y en semanas posteriores progresaron a la realización de movimientos activos y funcionales. En las últimas semanas y si era posible según la sintomatología del paciente, se incluyeron movimientos suaves y sincrónicos del brazo afectado detrás del espejo. Todos estos movimientos eran explicados y mostrados a los sujetos por la fisioterapeuta. En cada sesión se realizaron dos series de 15 minutos, con 2 minutos entre series para permitir el descanso y relajación del brazo. Además, se explicó a los participantes que debían realizar los movimientos lentamente, con control, observando el espejo en todo momento y concentrándose en la tarea (Figura 10). De esta manera, este tipo de ejercicios proporcionaba a los sujetos la "ilusión" de estar moviendo su brazo afectado en un ROM completo y libre de dolor. Se proporcionó a cada participante un espejo de pie para que practicase esta tarea durante 15 minutos cada día, al menos 5 días a la semana en el domicilio. Por otra parte, se les aconsejó que se detuvieran si experimentaban aumento del dolor, ya fuera durante o inmediatamente después de la terapia en espejo y lo anotasen en el diario.

*Figura 10. Paciente realizando ejercicios de terapia en espejo en la clínica.*

La descripción completa del programa de GMI se muestra en la tabla 4.

*Tabla 4. Resumen de la progresión empleada en el programa de GMI. Fuente: Adaptada de Lluch et al., (2019) (146)*

| ETAPA | ENTRENAMIENTO GMI |
|---|---|
| **1 (semana 0-2)** | **Reconocimiento de la lateralidad**<br>Uso del software *Recognise*™<br>Determinar si se trata del hombro derecho o izquierdo<br>Progresar disminuyendo el tiempo que se muestran las imagenes |
| **2 (semana 2-4)** | **Movimientos imaginados**<br>Vídeos de movimientos de hombro<br>Movimientos de bajo rango primera semana<br>Movimientos en el rango completo segunda semana |
| **3 (semana 4-6)** | **Contracción muscular isomètrica analítica**<br>Músculos manguito rotador<br>Músculos escápulo-torácicos<br>Añadir pequeños movimientos libres de dolor a la contracción isométrica |
| **4 (semana 6-8)** | **Terapia en espejo**<br>Mantener el brazo del hombro afectado apoyado de forma cómoda / Mantener el brazo del hombro no afectado apoyado igual que el otro y observar el reflejo (primera semana)<br>Progresión segunda semana, igual que anterior pero el hombro no afectado realiza moviemientos en ROM completo mientras se observa el reflejo |
| **5 (semana 8-10)** | **Terapia en espejo**<br>Mover el brazo afectado en los rangos limitados o dolorosos hasta el límite de dolor, mantener la posición y realizar el mismo movimiento en su ROM completo con el hombro no afectado mientras es observado en el espejo<br>Movimientos simétricos con ambos brazos, llevando el hombro afectado hasta el límite del dolor en la(s) dirección(es) de movimiento restringido/doloroso (el brazo no afectado se mueve en su ROM completo y es observado en el espejo) |

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# SECCIÓN TERCERA: TRABAJOS PUBLICADOS

# ESTUDIO 1

# Estudio 1

# Laterality judgement and tactile acuity in patients with frozen shoulder: A cross-sectional study

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**ABSTRACT**

**Background:** Disrupted tactile acuity and poor performance in laterality judgement have been shown in a variety of chronic musculoskeletal pain conditions. Whether they are also impaired in people with frozen shoulder (FS) remains unknown.

**Objectives:** To determine whether there is impairment in tactile acuity and laterality judgement in subjects with FS.

**Methods:** Thirty-eight subjects with idiopathic FS and 38 sex and age-matched healthy controls were enrolled. Two-point discrimination threshold (TPDT) and a left/right discrimination task over the affected shoulder, unaffected shoulder, and shoulder of healthy controls were evaluated. Independent and dependent t-tests were used to compare group means. Spearman rho correlations between pain duration and pain intensity and results from the left/right discrimination task and TPDT were calculated for the patient group.

**Results:** The TPDT over the affected shoulder in participants with FS was significantly increased when compared to their unaffected shoulder (mean difference, 3.82 mm; 95% confidence interval [CI]:0.53, 7.10; p=0.24), but no significantly different to healthy controls. A statistically significant difference between the affected and unaffected shoulder in subjects with FS was found for accuracy (mean difference, 5.90 %; 95% CI: .36, 11.43; p = .03) and reaction time (mean difference, 0.26 seconds; 95% CI: .06, .45; p=0.01) and between patients and healthy controls in reaction time for the left/right discrimination task (mean difference, .23 seconds; 95% CI: .04, .41; p=0.01). No correlations were found between pain intensity and duration of pain and either TPDT or laterality judgement in the FS group.

**Conclusions:** Tactile acuity and laterality judgment impairment was observed in the affected shoulder in comparison to the unaffected shoulder in subjects with FS. When compared to pain-free individuals, subjects with FS showed a delayed reaction time in laterality judgment.

**Keywords:** shoulder pain, body image, left/right judgement task, two-point discrimination.

## 1. Introduction

Shoulder pain is a highly prevalent condition among general population (Kelley et al., 2013). Specifically, frozen shoulder (FS) is a disabling musculoskeletal condition characterized by intense pain and large mobility deficits (Walmsley et al., 2014). Although FS has been widely studied, its epidemiology, aetiology, diagnosis and assessment are still poorly understood (Ryan et al., 2016). To a large extent, physiotherapy management of FS has traditionally focused on structural dysfunctions found around the shoulder joint (Kelley et al., 2009, 2013). Although some physiotherapeutic interventions have shown to be effective in terms of pain reduction or mobility gains, there is currently little evidence that these interventions positively influence the disease natural history of FS (Struyf and Meeus, 2014). Some authors have argued that this fact raises the need for innovative research in the role central pain mechanisms might play in this chronic disorder (Struyf and Meeus, 2014). An example of maladaptive central pain mechanisms is structural reorganisation in the brain. Neuroimaging studies have provided evidence of alterations in brain morphology and functional activity associated to chronic pain (Baliki et al., 2011; Kuner and Flor, 2017; Morton et al., 2016) in people with fibromyalgia (Schmidt-Wilcke et al., 2007), complex regional pain syndrome (CRPS) (Juottonen et al., 2002; Maihöfner et al., 2003), osteoarthritis (Rodriguez-Raecke et al., 2009), and low back pain (Flor et al., 1997). Similarly, studies composed of participants with shoulder pain identified abnormal neuronal activity in multiple brain regions involved in the integration and processing of pain signals (Niddam et al., 2019; Yu et al., 2017) and changes in motor excitability and cortical motor representation (Ngomo et al., 2015). Among the maladaptive structural changes, reorganisation in the primary somatosensory cortex (S1) (i.e. shrinkage or shifting of the representation of the affected body region) have been observed in different chronic pain populations (Flor et al., 1997; Lotze and Moseley, 2007; Maihöfner et al., 2003). This brain area holds a somatotopic map of the body's surface (Penfield and Boldrey, 1937). However, the awareness of the body's position in space is a multisensory representation that

involves the somatosensory cortices and multiple areas of the brain that code for visual, tactile, and proprioceptive inputs (Moseley et al., 2012). The extent of S1 cortical reorganisation (Flor et al., 1997) has been shown to correlate with a decrease tactile acuity (Flor et al., 1997) and is clinically expressed as an increased in the two-point discrimination threshold (TPDT) (Catley et al., 2013; Lotze and Moseley, 2007). Tactile acuity is altered in patients with several chronic pain conditions such as osteoarthritis (Stanton et al., 2013) and low back pain (Adamczyk et al., 2018a) where larger TPDTs were found in patients compared to controls. Additionally, the sensory and motor cortices are functionally linked to form our perception of the body and provide internal organization for movement. The so called "body schema" is suggested to be the link between brain sensoriomotor maps (Moseley and Flor, 2012). Since the integrity of the body schema depends on correct input from S1, cortical reorganisation of S1 may provoke incongruence between predicted and actual sensory feedback and motor output thus negatively influencing proprioception (Ager et al., 2019) and motor performance (Elsig et al., 2014; Luomajoki and Moseley, 2011). The integrity of the body schema can be indirectly measured by performing a left/right judgment task (LRJT) (Lotze and Moseley, 2007). The LRJT consists in viewing images of a body part and determining whether each image belongs to, i.e., the left or right side of the body. Two recent systematic reviews have provided evidence of impaired laterality judgement of the affected limb in different chronic pain populations (Breckenridge et al., 2019; Ravat et al., 2019). Regarding shoulder pain, a small sample study found a faster reaction time in a LRJT and decreased tactile acuity at the painful arm in patients with chronic nonspecific complaints of arm, neck and shoulder, which might imply disturbed information processing of sensory and motor feedback (Heerkens et al., 2018). Interestingly, in people with chronic pain, tactile acuity and LRJT impairments can be related to clinical aspects such as pain intensity and duration of symptoms. For instance, in people with CRPS, tactile acuity was reduced on the affected limb compared to the unaffected limb and the difference between limbs was correlated to pain intensity (Maihöfner et al., 2003; Pleger et al., 2004). Similarly, delayed recognition in hand laterality was correlated to the duration of symptoms

(Moseley, 2004). Taking into account the evidence provided by the literature and considering that FS is a long-lasting musculoskeletal condition with continuous nociceptive activity in the early stages, it is plausible to observe cortical reorganisation of S1 and disruption of the body schema in this population (Moseley and Flor, 2012; Pelletier et al., 2015). Apart from recent case studies and case-series (Louw et al., 2017; Sawyer et al., 2018), the maladaptive brain changes in people with FS has not been fully studied and remains speculative. Acquiring further knowledge on the pain mechanisms of chronic pain conditions such as FS is essential for designing better diagnosis and treatment strategies (Moseley and Flor, 2012). In addition, central alterations have demonstrated to have a crucial role in the pathophysiology and clinical manifestations of many musculoskeletal disorders (Armijo-Olivo, 2018; Roy et al., 2017). Therefore, the primary aim of this study was to explore whether people with FS presented with clinical evidence of disrupted cortical maps specific to the site of pain and disrupted working body schema. We used the TPDT to assess tactile acuity and a LRJT for laterality judgement. These measurements were compared between the affected and unaffected side in the FS group and the affected side in the FS group and dominant side in a healthy control group. We hypothesized that tactile acuity and laterality judgement would be impaired over the painful side in people with FS in comparison to the unaffected side and in comparison to controls. As a secondary aim of this study, possible associations between tactile acuity and laterality judgement and clinical aspects (severity and duration of symptoms) in subjects with FS were also investigated.

## 2. Methods

### 2.1. Design

The study was a cross-sectional case-control study undertaken at the University of Valencia (Spain) examining tactile acuity and laterality judgement in patients with FS and an age and gender-matched comparison group. The paper is reported following the STROBE statement (Von Elm et al., 2007).

### 2.2. Participants

Thirty-eight participants diagnosed by a physician with primary or idiopathic FS were consecutively recruited in Valencia (Spain) together with thirty-eight sex and age-matched healthy volunteers. Recruitment of both groups occurred between July 2018 and June 2019 by advertising posters at the physiotherapy department of the University of Valencia and private physiotherapy centers. The sample size was calculated using G*Power 3.1 software based on the TPDT as the primary outcome measure. To the best of our knowledge, there are no studies investigating differences in TPDT between participants with FS and healthy subjects. We determined our sample size based on the study of Botnmark et al. (2016) which reported a TPDT of the dominant and non-dominant shoulder of healthy subjects of 44.8 (13.1) mm and 39.3 (9.5) mm, respectively, with a statistically significant mean side-to-side difference of 5.5 (13.5). Considering a 80% power and an alpha level of 0.05, a total sample size of 72 patients was estimated (36 per group). An allowance was made for a 5% dropout rate, increasing the sample size to 76 patients (38 per group). The specific inclusion criteria for the FS group were: (1) having greater than 50% limitation of passive external rotation in the affected shoulder compared to the unaffected shoulder or less than $30^0$ of external rotation in the affected shoulder (Breckenridge et al., 2017); (2) range of motion loss greater than 25% in at least two movement planes in the affected shoulder compared to the unaffected shoulder (Breckenridge et al., 2017); (3) pain and movement restriction should be present for at least one month either having

reached a plateau or worsened (Kelley et al., 2009); and (4) shoulder radiographs had to be normal (with the exception of osteopenia of the humeral head and calcific tendinosis). (Zuckerman and Rokito, 2011). The specific inclusion criterion for the controls was no actual shoulder pain or previous history of shoulder complaints including FS. Exclusion criteria for both groups were locked dislocations, arthritis, fractures or avascular necrosis on shoulder radiographs or previous surgery in the upper quadrant region during the last year. Moreover, those subjects not understanding written or spoken Spanish language, having any skin or medical condition preventing them from receiving tactile stimuli on the shoulder, any neurological or motor disorder including a diagnosis of dyslexia or difficulty performing a rapid naming task (Silva et al., 2012), visually impaired or having a diagnosed psychopathology were excluded from the study. The study was approved by the Ethical Committee of the University of Valencia the (reference number H1532330957968) and all procedures were performed in accordance with the Declaration of Helsinki. All participants gave their written informed consent prior to participate in the study.

### 2.3. Procedures

A researcher (MB), who assessed suitability of each participant via the inclusion and exclusion criteria, initially examined participants. This researcher was different to that one involved in TPDT and LRJT measurements. Prior to testing, both groups provided demographic information. In addition, symptoms' duration and self-perceived shoulder pain using a visual analogue scale (VAS) were recorded in the FS group. In particular, participants were asked to mark on a 10-cm line their average shoulder pain in the last 24 h between 0 ("no pain") and 10 ("worst possible pain"). Tactile acuity and LRJT were then assessed in all participants, in the same session, by a physiotherapist with a post-graduate degree in manual therapy and 10 years working experience with the use of tactile acuity and LRJT. The examiner was not blinded to the participants' clinical status but was blinded to the side of pain in the FS group.

### 2.4. Tactile acuity

Tactile acuity was assessed by means of the TPDT. A mechanical sliding calliper with precision of 1 mm (Duratech™ TA-2081), was used to measure TPDT. Prior to formal testing, one familiarization trial was conducted on the participant's forearm. During formal testing, participants were positioned in sitting with the arm in a relaxed neutral position. A point 5 cm distal to the lateral border of the acromion was marked on the painful and non-painful shoulder for participants with FS. The same point was marked in the dominant shoulder for healthy controls (Botnmark et al., 2016). In order to standardise the testing region, a vertical line was drawn from the middle edge of the acromion towards the elbow and the TPDT was performed following that line, in the longitudinal direction of the arm (**Fig. 1**) (Adamczyk et al., 2018b). The 5 cm mark below the lateral border the acromion process was kept between the two calliper points in all assessments (Botnmark et al., 2016).

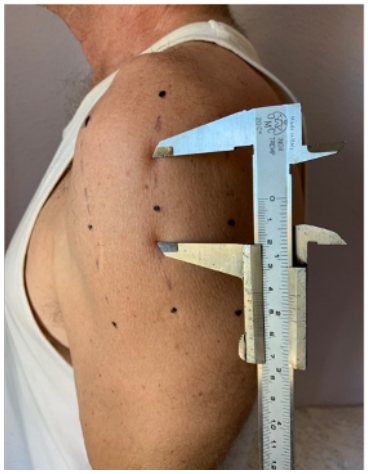

*Figure 1. Region for TPDT testing. Anterior and posterior edges and mid-point of the acromion process were marked. From these bony landmarks, vertical lines in the longitudinal direction of the arm and 5-cm marks below the bony landmarks were drawn. The 5 cm mark below the mid-point of the acromion process was used for TPDT testing and kept between the two calliper points to standardise the testing region.*

The calliper was applied with even pressure through both tips, until the very first blanching of the skin (Moberg, 1990). Participants were instructed to inform the tester whether they could feel one or two points. The TPDT was defined as the smallest distance between calliper points that was

perceived as two points instead of one. An ascending and a descending run was completed for each shoulder tested following the staircase method (Yarnitsky, 1997).

The test began in 0 mm and the distance was first gradually increased in 5 mm increments until the participant perceived two points instead of one. Once the subject reported perceiving two points, the following responses established the TPDT: (i) the subject reported a single point when the distance between calliper points was decreased below threshold, (ii) the subject reported two points when the distance between calliper points was increased back to the determined threshold, and (iii) the subject reported a single point when a single point was applied (Stanton et al., 2013). In case participants don't comply with all these three criteria (i-iii), the distance between calliper points was incremented further 5 mm. Descending runs began with the calliper points separated 30 mm more than the TPDT value obtained from the ascending run, followed by decrements of 5 mm. A similar protocol as described above (i.e. i-iii) was used to establish the threshold value in this descending run (Lotze and Moseley, 2007). Stimuli out of sequence were included (contracting the callipers instead of expanding them with ascending runs or vice versa) to verify that participants were not guessing. Subjects were instructed to report if they felt one or two points after each application. If they were unsure, they were instructed to report one point. In addition, participants were asked to inform the researcher if they perceived two points because of a temporal delay in the presentation of the two points and, in this case, that trial was repeated. A mean TPDT value was obtained from the two threshold scores and used for subsequent analysis. In participants with FS, both shoulders were tested in a random order. In the healthy controls, only the dominant shoulder was tested.

### 2.5. Left/right judgement task (LRJT)

Laterality judgement was assessed with a LRJT using the Neuro Orthopaedic Institute (NOI) Recognise™ online program (www.noigroup. com). A total of 30 shoulder pictures using the Context mode of the NOI program were presented on a laptop to participants in a random order.

They were instructed to decide whether the picture showed a right or left shoulder giving a response as quickly as possible without guessing. Both accuracy and response time were recorded in this LRJT. Accuracy was defined as the percentage of images correctly judged and response time as the time employed to decide whether the picture showed a right or left shoulder. If participants timed out (>5 s) for four or more images in a row this fact was taken as reflecting distraction from the task and the test was then repeated. The test was performed twice (two identical blocks of 30 images) with a 2-min break between each block to obtain a real sense of laterality judgement. The first block was considered for task training and consequently data from this block was discarded. Data from the second block were then used for analysis (Wallwork et al., 2013). The protocol used in this study has proved to be highly reliable in healthy subjects with a mean (SD) normative response time and accuracy for this shoulder specific LRJT of 1738 (741) ms and 93.5 (9.2)%, respectively (Breckenridge et al., 2017).

### 2.6. Statistical analysis

All statistical analyses were performed using SPSS 24.0. Descriptive statistics were used to present demographic and clinical information. Normality of the TPDT and LRJT data was explored using the Shapiro- Wilk test. Dependent t tests were used to compare TPDT and LRJT (accuracy and response time) between the affected and unaffected shoulder in the FS group. Independent t tests were used to compare participants with FS (affected shoulder) and healthy controls (dominant shoulder) in those two clinical measurements. Pearson-product moment coefficient correlations were calculated in the FS group between symptoms duration and pain intensity (VAS 24 h) and results from the LRJT (accuracy and response time) and TPDT. Effect sizes were calculated through Cohens' d according to the formula d = mean difference/SD. Differences were deemed significant at $p < .05$.

## 3. Results

All participants completed all parts of the study. All TPDT and LRJT values were normally distributed. Demographic data of participants are summarized in **Table 1**. No statistically significant differences were found between groups at baseline (all $p > .05$). In the FS group, the mean (SD) TPDT over the affected shoulder was 41.71 (10.88) mm and 37.89 (8.92) mm for the unaffected side. This difference was statistically significant (mean difference, 3.82 mm; 95% CI: 0.53, 7.10; $t(37) = 2.35$, $p = .02$) . Moderate effect sizes were observed for the TPDT in the FS group ($d = 0.38$). In the healthy control group, the mean (SD) TPDT value was 35.91 (9.72) mm. A statistically significant difference was found between the TPDT measured at the affected shoulder in the FS group and the TPDT of the dominant shoulder in the healthy control group (mean difference, 5.80 mm; 95% CI: 1.09, 10.52; $t(74) = 2.45$, $p = .02$) (**Fig. 2**).

*Table 1. Characteristics of participants with frozen shoulder (n = 38) and health age and sex matched control participants (n = 38)*

| | **Frozen shoulder (n=38)** | **Control (n=38)** | **Differences between groups (p-values)** |
|---|---|---|---|
| Age (years) | 52.5 (7.3) | 52.9 (7.3) | 0.8 |
| Sex (male/female) | 12/26 | 12/26 | N/A |
| Hand dominance (left/right) | 1/37 | 1/37 | N/A |
| Shoulder affected (left/right) | 21/17 | N/A | N/A |
| Symptoms' duration (months) | 8.5 (5.9) | N/A | N/A |
| VAS 24h* (0-100mm) | 46.5 (27.2) | N/A | N/A |

*VAS 24h: visual analogue scale in the last 24h. Data are reported as mean (standard deviation).

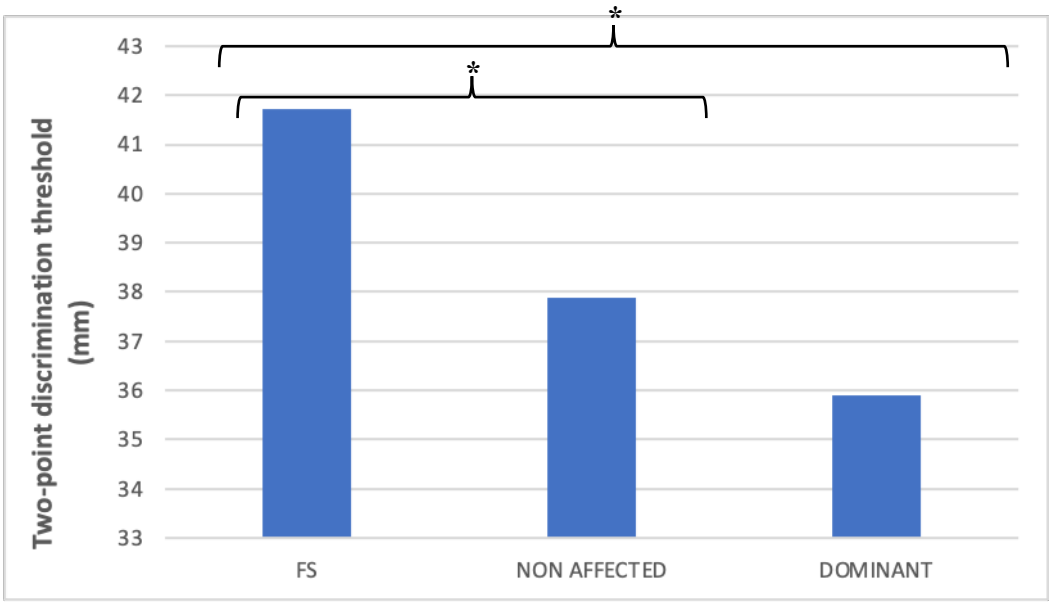


*Figure 2. Mean and SD of the TPDT in the affected and unaffected shoulder of the FS group and dominant shoulder of the control group.* ****p<.05***.

This TPDT comparison presented a medium effect size (d = 0.56). In the FS group, mean (SD) accuracy and response time of the affected shoulder in the LRJT was 80.73 (21.47) % and 1.88 (0.46) seconds, respectively. In the unaffected side, mean (SD) accuracy and response time was 86.63 (15.53) % and 1.62 (0.41) seconds. A statistically significant difference between the affected and unaffected shoulder in subjects with FS was found for accuracy (mean difference, 5.90%; 95% CI: 0.36, 11.43; t(37) = 2.16, p = .03) and response time (mean difference, -0.26 s; 95% CI: 0.06, 0.45; t(37) = 2.69, p = .01) (Fig. 3 and 4), with moderate effect sizes (d = 0.32 and d = 0.59 respectively for accuracy and response time) The mean (SD) accuracy and response time of the dominant shoulder for the healthy controls was 87.66 (15.36)% and 1.85 (0.39) seconds, respectively. Compared to values obtained in the affected shoulder of the FS group, no significant differences were found for accuracy (t(74) = 1.62, p = .1) or response time (t(74) = 0.32, p = .7) in the LRJT (**Fig. 3 and 4**).

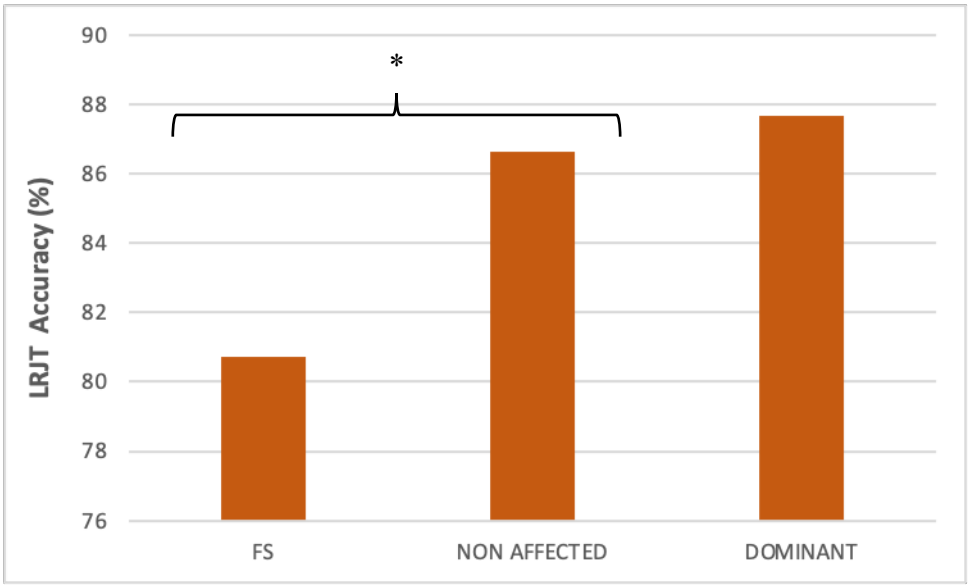


*Figure 3. Mean and SD of the accuracy in LRJT in the affected and unaffected shoulder of the FS group and dominant shoulder of the control group.* ***p<.05**.

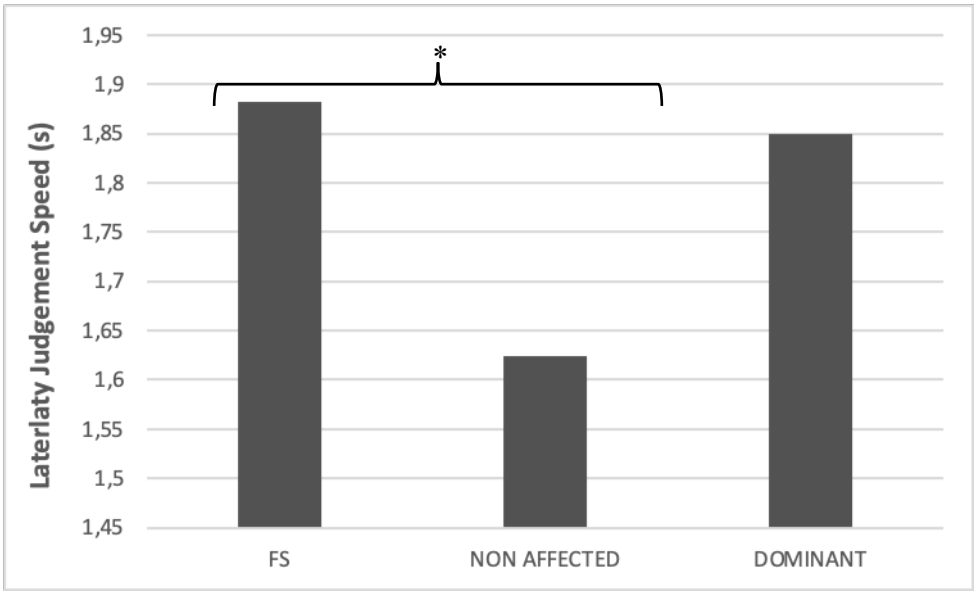


*Figure 4. Mean and SD of the speed in LRJT in the affected and unaffected shoulder of the FS group and dominant shoulder of the control group.* ***p<.05**.

**Table 2** summarizes the mean (SD) values for the TPDT and LRJT in participants with FS and healthy controls. No significant correlations were observed between pain intensity and TPDT ($r_p$ = -0.02, p = .91) or accuracy ($r_p$ = -0.03, p = .85) and response time ($r_p$ =c -0.05, p = .76) in the LRJT in the FS group. Similarly, no correlations were found between symptom duration and TPDT ($r_p$ = -0.08, p = .61) or accuracy ($r_p$ = -0.03, p = .88) and response time ($r_p$ = -0.01 p = .98) in the LRJT in the FS group.

*Table 2. TPDT and laterality judgement in FS and healthy control group.*

| Shoulder | TPDT | | Laterality judgement (right shoulder) | | | |
|---|---|---|---|---|---|---|
| | | | Accuracy (%) | | Speed (s) | |
| | Mean±SD | p value | Mean±SD | p value | Mean±SD | p value |
| FS affected | 41.71 (10.88) | **.02** | 80.73 (21.47) | **.04** | 1.88 (0.46) | **.01** |
| FS unnaffected | 37.89 (8.92) | | 86.63 (15.53) | | 1.62 (0.41) | |
| Dominant | 35.91 (9.72) | **.01** | 87.66 (15.36) | .1 | 1.85 (0.39) | .7 |

TPDT, two point discrimination threshold. Bold values mean statistically significant difference. Data are reported as mean (standard deviation).

## 4. Discussion

The purpose of this study was to determine whether tactile acuity alterations are associated to pain severity and symptoms duration. Our findings may indicate that tactile acuity is impaired in people with FS over the affected shoulder in comparison to the unaffected shoulder and when compared to healthy controls. Furthermore, in comparison to the unaffected shoulder, people with FS had less accuracy and a delayed reaction time in the affected shoulder in a LRJT. Neither pain intensity nor symptoms duration were correlated with either tactile acuity or laterality judgement in the FS group. Our data regarding TPDT are in accordance with those obtained by Heerkens and colleagues at the painful arm in patients with chronic nonspecific shoulder complaints (Heerkens et al., 2018) and with a large body of evidence that suggests that tactile acuity is diminished in people with several chronic musculoskeletal pain conditions (i.e. osteoarthritis, CRPS, chronic low back pain) at the site of pain in comparison to pain-free controls (Catley et al., 2014). In addition, when consider patients as their own control and comparing tactile acuity at the painful shoulder to the corresponding site on the non-painful shoulder, a larger TPDT in the affected shoulder was observed. Previous studies performed in people with unilateral chronic pain (i.e. CRPS) also found larger TPDT values at the affected side in comparison with the contralateral unaffected side (Catley et al., 2014). Clinical interpretation of our results is challenging because the cut-off value at which tactile acuity deficit become clinically meaningful remains unknown. Botnmark et al. (2016), using the same protocol as in our study, reported a side-to-side TPDT mean (SD) difference of 5.5 (13.5) mm between the dominant and non-dominant shoulder of pain-free subjects. The TPDT difference that we found when comparing the affected and unaffected shoulder of people with FS (3.82 mm), was lower than the value reported by Botnmark et al. (2016) Although statistically significant, we could thus argue that this within-group difference might not be clinically relevant. To further support this argument, the mean TPDT value that we obtained in the affected shoulder in the FS group (i.e. 41.71 mm) would be considered a “normal” value according to the TPDT previously reported for healthy

subjects (i.e. 44.8 mm) (Botnmark et al., 2016). Despite we also found a higher TPDT in the affected shoulder of people with FS compared to healthy controls, the TPDT value obtained in the painful shoulder of people with FS was similar to that reported for healthy shoulders. These conflicting results regarding tactile acuity are in line with the criticism raised in the literature due to the unexplained variability observed in TPDT within subjects, between subjects and between studies. Indeed some researchers even argue that TPDT should not be used as a scientific measure of acuity (Craig and Johnson, 2000). Further research may calculate the TPDT standard error of measurement or the reliable change index in the shoulder area as done for instance in the lumbar region (Wand et al., 2014). This would contribute to determine the size of the TPDT difference needed to be distinguishable from measurement errors in people with shoulder pain. People with FS had less accuracy and a delayed response time in their affected shoulder in comparison to the unaffected shoulder in the LRJT. This finding contrasts with the study results of Heerkens et al. (2018) where a faster reaction time at the painful arm was observed in patients with chronic nonspecific shoulder complaints. However we are in line with current literature which has shown that people with several chronic pain disorders tend to be less accurate and slower in a LRJT on the injured site (Breckenridge et al., 2019; Ravat et al., 2019). A recent systematic review concluded that patients with upper limb pain are slower and less accurate at recognising images that correspond to the side of their painful body part and at discriminating between left and right images compared to healthy controls (Breckenridge et al., 2019). However, heterogeneity of the studies included in that review was substantial. Abnormally long response times in the LRJT are thought to reflect delayed processing of body/spatial representations. In particular, they are thought to reflect a bias in information processing away from the delayed side or toward the opposite side (Hudson et al., 2006; Moseley, 2004). Reduced accuracy is thought to reflect disrupted cortical proprioceptive representations (Moseley and Flor, 2012). However, similar to TPDT, one should be cautious when interpreting our laterality judgement scores. Mean (SD) normative values for accuracy and response time in healthy subjects have been reported to be 93.5(9.2) % and 1.7 (0.7) seconds using the same

shoulder specific LRJT as we used in this study (Breckenridge et al., 2017). Our within and between-group differences in the LRJT are again difficult to be interpreted because the values we obtained for accuracy in the unaffected shoulder (i.e. mean = 86.63; SD = 15.53%) would be considered "abnormal" based on those normative values. In addition, the difference observed in accuracy and response time between the affected and unaffected shoulder of participants with FS (i.e. 5.90% and 0.26s) is probably too small to be considered clinically meaningful. Therefore, more research is needed to reach firm conclusions on the role of body schema disruption in people with FS. Our study shows that tactile acuity and laterality performance deficits are independent of the perceived intensity of the pain or pain duration in people with FS. Analysis of the pooled data of a systematic review about tactile acuity in people with chronic pain showed no significant associations between tactile acuity and either pain intensity or pain duration which would support our findings (Catley et al., 2014). However, correlations in that review were reported for people with chronic pain (Botnmark et al., 2016). Recent studies assessing tactile acuity in response to acute pain induction have demonstrated a site-specific sensory adaptation to pain (Adamczyk et al., 2018b, 2019). While tactile acuity decreased immediately after experimentally induced low back pain (Adamczyk et al., 2018b), experimental neck pain did not elicit changes in tactile acuity (Adamczyk et al., 2019). Influence of pain intensity and duration in laterality judgement has not been fully elucidated yet (Ravat et al., 2019). Further research might also investigate the possible relationships between tactile acuity, body schema integrity, shoulder proprioception and physical performance in people with FS. One strength of this study is age and sex-matching. Although the link between age-sex and tactile acuity and laterality judgement is still unclear, it has been recommended to match patients with chronic pain and pain-free participants in terms of age and gender when performing these measurements (Catley et al., 2014; Ravat et al., 2019). Consideration must be given to the limitations of this study. Deviating from normal laterality judgement or tactile acuity values may indicate changes in somatosensory homunculus but may also be due to other factors such as impaired touch perception, slow processing or difficulty with coordination, attention or decision-making process

(Catley et al., 2014; Ravat et al., 2019). It is not possible to infer how these confounding factors which were not considered in this study may have influenced our results. The assessor made subjective assessment as to when the TPDT was determined which might have introduced assessor bias. Laterality judgement was tested using a mobile phone, which differ to the majority of studies where a computer-based assessment was performed (Ravat et al., 2019). Only a practice run of 30 pictures before formal laterality testing was done but a practice round of approximately 80 pictures is needed for the LRJT becoming implicit (Bray and Moseley, 2011). Further work should formulate standardized protocols for laterality judgment tasks (i.e. number of trials, number of pictures) and tactile acuity to be used in people with chronic pain including those with FS. We did not assess remote sites to investigate if impairment in laterality judgement and tactile acuity were restricted to the area of pain or were generally altered in other regions of the body. Whether patients were with pain during assessments was not registered. Both tactile acuity and laterality judgement might be pain-dependent so the presence of pain during assessments might have influenced our results. Other potential confounding factors (i.e. activity levels/arm usage, age) should also be considered when interpreting the results of this study. For instance, tactile acuity performance declines with increasing age (Woodward, 1993). While the researcher testing the participants with FS was blinded to side (affected vs unaffected) in the FS group, no blinding to clinical status was possible as only one side (the dominant side) was assessed in the control group. The inclusion of two testers, one for the cases and one for the controls, might have been useful for controlling for this fact but at the same time might have introduced additional error to the measurements.

## 5. Conclusions

Participants with FS demonstrated reduced tactile acuity over their affected shoulder when compared to their unaffected shoulder and controls. In comparison to the unaffected shoulder, less accuracy and a delayed response time in a LRJT was found in the affected shoulder of the FS group. However, our results should be interpreted with caution as the clinical meaningfulness of these findings remains unknown. This consideration is especially important before physical therapists fully implement strategies targeting the CNS in people with FS. **Funding** The authors affirm that they have no affiliations with or financial involvement in any organization or entity with a direct financial interest in any matter included in this manuscript. This cross-sectional study received approval from the Institutional Review Board at the University of Valencia, Spain (reference number H1532330957968).

### Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.msksp.2020.102136.

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# ESTUDIO 2

# Estudio 2

# A Central Nervous System Focused Treatment Program for People with Frozen Shoulder: A Feasibility Study

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**ABSTRACT:**

**Background:** Frozen shoulder (FS) is a highly disabling pathology of poorly understood etiology, which is characterized by the presence of intense pain and progressive loss of range of motion (ROM). The aim of this study is to evaluate the feasibility and clinical impact of a CNS-focused treatment program for people with FS.

**Methods:** 10 subjects with primary FS received a 10-week CNS-focused intervention including sensory discrimination training and graded motor imagery techniques delivered as clinic sessions (60 min) and home therapy (30 min five times per week). Measurements were taken at baseline, after a 2-week "washout" period, after treatment, and at three months follow-up. The Shoulder Pain and Disability Index (SPADI) was the primary outcome. Secondary measures were feasibility-related outcomes, self-reported shoulder pain, active and passive range of motion, two-point discrimination threshold (TPDT), left/right judgement task (LRJT), fear-avoidance (Tampa Scale for Kinesiophobia), pain catastrophization (Pain Catastrophizing Scale), and pain sensitization (Central Sensitization Inventory). A Student's t-test was used to assess the "washout" period. A repeated measure analysis of variance (ANOVA) was used to evaluate within-subjects' differences for all outcome measures in the different assessment periods and a pairwise analysis was used to compare between the different assessment points. Statistical significance was set at $p < 0.05$.

**Results:** 70% of participants completed the treatment. No significant changes were found after "washout" period except for TPDT ($p = 0.02$) and SPADI ($p = 0.025$). Improvements in self-reported shoulder pain ($p = 0.028$) and active shoulder flexion ($p = 0.016$) were shown after treatment ($p = 0.028$) and follow-up ($p = 0.001$) and in SPADI at follow-up ($p = 0.008$). No significant changes were observed in TPDT, LRJT, fear-avoidance, pain catastrophization, and pain sensitization.

**Conclusions:** a CNS-focused treatment program might be a suitable approach to improve pain and disability in FS, but further research is needed to draw firm conclusions.

**Keywords:** adhesive capsulitis; feasibility study; frozen shoulder; motor imagery; patient compliance; tactile discrimination training.

## 1. Introduction

Frozen shoulder (FS) is a highly disabling pathology of poorly understood etiology [1], which is characterized by the presence of intense pain and progressive loss of range of motion (ROM) [2]. FS is present in 2–5% of the general population, especially in women aged between 40 and 65 years and its exact etiology is currently unknown [3]. The pathophysiology of FS is a complex and multifactorial process encompassing several mechanisms such as an upregulation of grown factors and inflammatory cytokines, which stimulate fibroblast proliferation and differentiation into myofibroblasts. This in turn leads to an imbalance of extracellular matrix turnover and a resultant stiff and thickened glenohumeral capsule with an abundance of type III collagen [4]. Accumulation of advanced glycation end products (AGEs) has also been shown in people with FS [5]. In addition, a state of low grade inflammation, which is associated with diabetes, cardiovascular disease, and thyroid disorders, seems also to predispose to the development of FS [6]. Many treatments have been proposed for FS including conservative (i.e., manual therapy) [7] and non-conservative approaches (i.e., arthroscopic capsular release) [8]. The most common and recommended physical therapy interventions used for treating these patients are mobilization techniques and exercises, while the utility of other suggested interventions such as aerobic exercise, lifestyle changes, or pain neuroscience education is still hypothetical [9]. To date, none of these interventions has demonstrated to have an influence on the natural history of this condition, therefore innovative research seems necessary [10]. Some authors have suggested an involvement of central pain mechanisms secondary to continuous nociception characteristic of the early stages of FS [10]. In line with this, two systematic reviews showed preliminary evidence that central pain mechanisms may contribute to shoulder pain of different etiologies [11,12], but recent studies questioned those findings [13,14]. Importantly, these reviews did not include people with FS, so the role of the central nervous system (CNS) in this clinical condition remains speculative.

Different approaches targeting the CNS (e.g., graded motor imagery (GMI) and tactile discrimination training) have been applied in a variety of chronic musculoskeletal pain disorders with promising results [15,16]. Specific to shoulder pain, only a few studies have investigated the clinical effectiveness of CNS-focused interventions. Louw et al. [17] presented a case-series where a CNS-focused treatment program based on a brief mirror therapy intervention was applied in subjects with shoulder pain and limited active ROM. This approach showed statistically significant improvements in pain, pain catastrophization, fear-avoidance, and shoulder flexion active ROM [17]. However, only 8.7% of the sample presented a diagnosis of FS. Similarly, Sawyer et al. [18] applied a combination of pain neuroscience education, tactile discrimination training, and GMI in an individual with FS. The patient reported significant improvements in pain, fear of movement, and active ROM. Further high-quality research about the effectiveness of CNS-focused treatments in peoplewith FS is thus needed.

The aim of this study is to evaluate the feasibility and clinical impact when implementing a CNS-focused treatment program for people with FS. The results of this study will inform of the appropriateness to conduct a randomized controlled trial on this topic.

## 2. Materials and methods

### 2.1. Sample recruitment

A convenience sample of 10 subjects diagnosed with FS was recruited. Since there is no gold standard to diagnose FS, diagnosis was established by a physician based on clinical examination, exclusion of other pathologies, and imaging [19]. Patients included had to present with primary or idiopathic FS, a limitation in passive external rotation >50% compared to the unaffected shoulder or less than 30 of passive external rotation, and a ROM loss >25% in at least two movement planes [20]. Additionally, pain and movement restriction had to be present for at least one month having either reached a plateau or worsened [20] and radiographs had to be normal (with the exception of osteopenia of the humeral head and calcific tendinosis) [21].

Patients that presented with locked dislocations, arthritis, fractures, or avascular necrosis were excluded. Furthermore, those subjects not understanding Spanish language, having previous upper quadrant region surgery during the last year, any skin or medical condition preventing them from receiving tactile stimuli on the shoulder, any neurological or motor disorder, visually impaired, or having a diagnosed psychopathology were excluded from the study. All participants were instructed to continue taking any current medications, but not to start new medications or initiate new treatments during the treatment period.

### 2.2. Procedures

This feasibility study involved a 10-week CNS-focused intervention and periodic assessment of the participants. All outcome measurements were performed at baseline and after a two-week period of "washout" with no intervention (T0) [22]. After this initial assessment, participants began the treatment and were again measured at the end of treatment (3 months after baseline (T1) and at three months follow-up (T2) (Figure 1)).

The CNS-focused intervention consisted of a 10-week treatment program (1 session per week) delivered as 60 min sessions. In addition, participants performed a 30-min home training program five times per week during those 10 weeks. The CNS-focused intervention included discussion of the participant's shoulder pain experience from a pain neuroscience perspective provided in the first session plus graded sensory discrimination training and GMI [23]. The physiotherapist performing treatment (S.M.) had a post-graduate degree in manual therapy and was trained in how to perform the treatment by another researcher (E.LL.) with 10 years working experience in the use of these intervention

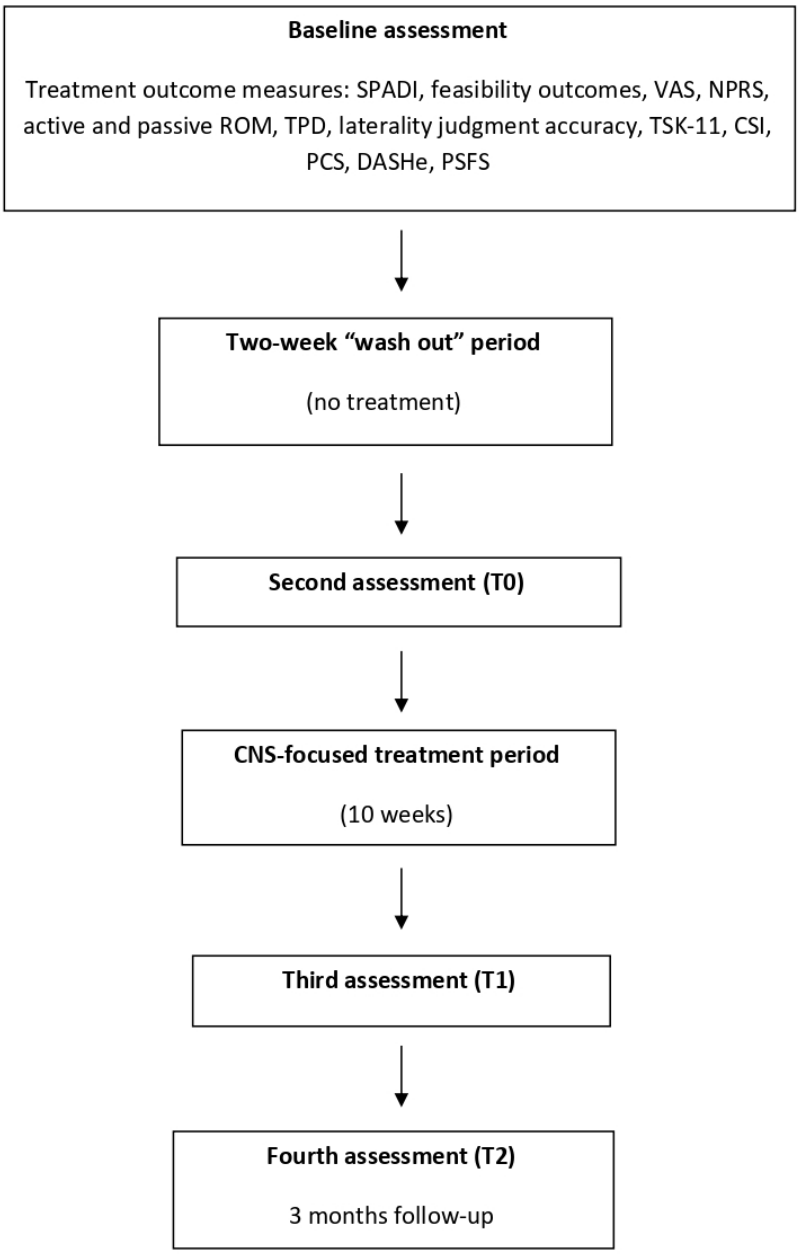


*Figure 1. Assessment and treatment flowchart diagram.*

### 2.3. Primary outcome measure

The primary outcome was self-reported shoulder pain and disability measured with the Shoulder Pain and Disability Index (SPADI) [1]. The SPADI is a 13-item shoulder function index assessing pain and disability related to shoulder dysfunction [2]. Each item is scored by a numeric scale (0–10) and the total score ranges from 0 to 100 points. A higher score indicates greater disability. The Spanish version of the SPADI has shown high internal consistency and excellent test-retest reliability [3]. The Minimal Clinically Important Difference (MCID) for the SPADI ranges from 8 to 13 points [4].

### 2.4. Secondary outcome measures

Different feasibility outcomes were considered as secondary: timely recruitment, number of participants completing treatment, treatment compliance and barriers (with clinic and home training sessions), and number of patients measured at follow-up. To assess treatment adherence, patients were provided with a diary to record their compliance with therapy [5]. After treatment completion, patients provided the diary to the physiotherapist performing the intervention to monitor adherence to the home training program for later analysis. In addition, patients were asked whether any difficulties with treatment compliance had appeared from one session to another. Additionally, other secondary outcome measures were collected: self-perceived shoulder pain, active and passive ROM, tactile acuity and laterality judgement performance, Tampa Scale for Kinesiophobia (TSK-11), Central Sensitization Inventory (CSI), and Pain Catastrophizing Scale (PCS).

#### *2.4.1. Self-perceived shoulder pain*

Participants' self-perceived shoulder pain was evaluated with the Numeric Pain Rating Scale (NPRS) anchored between 0 ("no pain") and 10 ("pain as bad as you can imagine"). Patients reported their most intense pain over the last week, least intense pain over the last week, average pain intensity over the last week, and pain at that moment. The scores were averaged to calculate a

final pain intensity score [6]. NPRS is a valid and reliable measure in patients with shoulder pain [7]. The minimal detectable change (MDC) of the NRPS for patients with shoulder pain is 2.5 points and the MCID is 1.1 points [7].

*2.4.2. Shoulder range of motion*

Shoulder flexion and active and passive external rotation at 0° of abduction of the affected shoulder were measured with a goniometer with the patient seated. To allow consistency of pre- and post-therapy measurements, skin marks were placed for goniometric measurements. A good reliability and validity of goniometric shoulder ROM measurements has been previously reported [8]. The MDC for shoulder flexion, abduction, and external rotation ranges from 11° to 16° [9].

*2.4.3. Tactile acuity*

Tactile acuity was assessed with the two-point discrimination threshold (TPDT). A mechanical sliding calliper with a 1-mm precision (Duratech TA-2081) was used to calculate the TPDT. Participants were placed in a sitting position and a point 5 cm distal to the lateral border of the acromion was marked on the painful shoulder. In order to standardize the testing region, this point was always kept between the two calliper points and measurements were performed in the longitudinal direction of the arm [10]. An ascending and a descending run of measurements were completed. The calliper distance was first gradually increased from 0 mm in 5 mm steps until the participant perceived two points instead of one. The descending run began with the calliper points separated 30 mm more than the TPDT value obtained from the ascending run, followed by decrements of 5 mm. A mean TPDT value was obtained from the two threshold scores and used for analysis.

*2.4.4. Laterality judgement*

Laterality judgement was assessed with a left/right judgement task (LRJT) using the NOI™ online program. A total of 30 shoulder pictures (context mode) were presented to participants on a laptop

in a random order and they were instructed to decide as quickly as possible, but without guessing, whether the picture showed the right or left shoulder thus making a response. Accuracy and mean response time were recorded. The LRJT was performed twice. The first block of images was used for task familiarization and data from the second block was used for analysis [11]. The normative mean (SD) response time and mean (SD) accuracy of this LRJT is 1738 (741) ms and 93.5 (9.2)%, respectively [12].

*2.4.5. Questionnaires*

Fear-avoidance was assessed with the Spanish version of the TSK-11 [13]. The TSK-11 is an 11-item questionnaire used to assess fear of movement or (re)injury during movement [14]. The total score ranges from 11 to 44, with higher scores indicating more fear-avoidance behavior. The TSK-11 has shown acceptable internal consistency and validity in both subjects with acute and chronic musculoskeletal pain [13]. The MDC for the TSK-11 is 5.6 [15]. The Spanish version of the CSI was used to assess different symptom dimensions related to central sensitization [16]. The CSI has high test-retest reliability and internal consistency [16]. Moreover, pain catastrophization was assessed with the Pain Catastrophizing Scale (PCS). PCS consists of 13 items and the total score ranges from 0 to 52. [17]. A total PCS score of 30 represents a clinically relevant level of catastrophizing [17].

### 2.5. CNS-focused treatment program

Prior to starting treatment, participants were given an explanation of the study. Patients were shown a picture of the 'brain map' (homunculus) and taught how, when people are in pain, the map becomes "less sharp" since it is not being moved and it is believed that when the map is sharpened, it may help reduce their pain and even movements [18]. By using sensory discrimination training and GMI, the therapy aimed to sharpen the brain shoulder map and thus improve pain and

movement. The CNS-focused treatment included graded sensory discrimination training and GMI training techniques. A full description of the treatment can be found elsewhere [19].

### 2.6. Statistical analysis

Statistical analysis was conducted using IBM SPSS Statistics 21. Normality of the data was assessed using the Shapiro–Wilk test. Study findings are expressed as the mean and standard deviation or 95% confidence interval, or as percentage frequencies. A Student's t-test was used to assess differences between baseline and T0 ("washout" period). A repeated measure analysis of variance (ANOVA) was used to evaluate within-subjects' differences for all outcome measures in the different assessment periods and a pairwise analysis was used to compare between the different assessment times. Statistical significance was set at $p < 0.05$.

## 3. Results

### 3.1. Participants' clinical and demographic data

The clinical and demographic characteristics of the participants at baseline are presented in Table 1. Only three patients (1, 8, and 9) presented moderate levels of pain (NPRS ≤ 5). Symptom duration ranged between two months and two years. Three patients (3, 8, and 10) demonstrated impaired tactile acuity (i.e., larger TPDT) at baseline in the affected shoulder compared to normative values reported for healthy individuals [i.e., 44.8 (13.1) mm] [10]. A total of 80% of the subjects presented lower accuracy in the LRJT at baseline compared to normative values [12]. This lower accuracy was observed bilaterally in 50% of the subjects and in the affected side in 30%. Only two patients (1 and 8) were slower in the LRJT in the affected shoulder compared to normative values [12]. Six patients were slower in the LRJT in the non-dominant shoulder.

*Table 1. Clinical and demographic characteristics of the participants at baseline.*

| | | Patient | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** |
| Age (years) | | 51 | 51 | 49 | 49 | 46 | 63 | 59 | 58 | 48 | 47 |
| Sex (male/female) | | f | f | f | f | f | f | m | f | f | M |
| Weight (kg) | | 53 | 57 | 85 | 55 | 55 | 74 | 60 | 63 | 63 | 75 |
| Length (cm) | | 169 | 164 | 175 | 166 | 155 | 164 | 170 | 162 | 168 | 189 |
| Affected shoulder | | left | right | right | right | right | right | right | left | left | Left |
| Dominant Side | | right | right | right | right | right | right | right | right | right | Right |
| Symptoms duration (months) | | 2 | 15 | 6 | 6 | 16 | 12 | 3 | 3 | 24 | 10 |
| SPADI (0–100) | | 91.54 | 26.15 | 20 | 59.23 | 20 | 74.62 | 40.77 | 75.38 | 62.31 | 54.62 |
| NPRS (0–10) | | 5 | 2 | 1 | 3 | 3 | 0 | 1 | 5 | 5 | 2 |
| PER ROM (degrees) | | 6 | 24 | 34 | 0 | 56 | 55 | 14 | 28 | 18 | 43 |
| AF ROM (degrees) | | 60 | 110 | 102 | 66 | 156 | 150 | 86 | 78 | 118 | 140 |
| TPD threshold (mm) | | 22.5 | 35 | 120 | 37.5 | 35 | 20 | 27.5 | 50 | 20 | 57.5 |
| Left/right accuracy (%) | Left | 87 | 100 | 100 | 100 | 100 | 73 | 93 | 93 | 100 | 93 |
| | Right | 87 | 93 | 80 | 10 | 80 | 67 | 87 | 73 | 100 | 93 |
| Left/right speed (s) | Left | 1.8 | 1.9 | 1.8 | 1.8 | 2.2 | 2 | 1.4 | 2.5 | 1.2 | 1.6 |
| | Right | 2 | 1.6 | 1.2 | 1.4 | 1.4 | 1.4 | 1.3 | 1.7 | 1.3 | 1.8 |
| PCS (0–52) | | 11 | 4 | 0 | 2 | 35 | 13 | 23 | 18 | 19 | 18 |
| CSI (0–100) | | 47 | 16 | 29 | 16 | 54 | 36 | 21 | 45 | 15 | 10 |
| TSK-11 (11–44) | | 35 | 16 | 15 | 15 | 32 | 21 | 27 | 20 | 33 | 36 |

SPADI, Shoulder Pain and Disability Index; NPRS, Numeric Pain Rating Scale; PER, passive external rotation; AF, active flexion; TPDT, Two Point Discrimination Threshold; PCS, Pain Catastrophizing Scale; CSI, Central Sensitization Inventory; TSK-11, Tampa Scale for Kinesiophobia.

### 3.2. Primary outcomes

The SPADI scores improved after treatment in the different assessment times ($p$ = 0.001). Significant changes in SPADI scores between baseline and follow-up (baseline-T2) ($p$ = 0.008), but not between baseline and post-treatment (baseline-T1) or between post treatment and follow-up (T1-T2) were observed (Table 2).

*Table 2. Questionnaires results at baseline, two-week "washout" period (T0), post treatment (T1), and follow-up (T2).*

| | | Mean ± SD | MD |
|---|---|---|---|
| SPADI (0–100) | Baseline | 47.6 ± 25 | |
| | T0 | 52.4 ± 24.9 | 4.8 |
| | T1 | 31.6 ± 31.5 | −16 |
| | T2 | 19.4 ± 24.5# | −28.2 |
| TSK-11 (11–44) | Baseline | 23.9 ± 8.3 | |
| | T0 | 23.6 ± 8 | −0.3 |
| | T1 | 19.9 ± 8.5 | −4 |
| | T2 | 19.4 ± 8.9 | −4.5 |
| CSI (0–100) | Baseline | 28.9 ± 15.7 | |
| | T0 | 28.8 ± 14.7 | −0.1 |
| | T1 | 24.4 ± 13.04 | −4.5 |
| | T2 | 21.9 ± 16.1 | −7 |
| PCS (0–52) | Baseline | 14.3 ± 10.7 | |
| | T0 | 11.4 ± 8.6 | −2.9 |
| | T1 | 5.8 ± 6.5 | −8.5 |
| | T2 | 6.3 ± 7.9 | −8 |

SPADI, Shoulder Pain and Disability Index; TSK-11, Tampa Scale for Kinesiophobia; CSI, Central Sensitization Inventory; PCS, Pain Catastrophizing Scale; MD, mean difference. #: significantly different between baseline and follow-up, $p < 0.05$.

### 3.3. Secondary outcomes

Seven participants (70%) completed the treatment and all the measurements. The three patients (3, 5, and 8) not completing the treatment attended three, four, and six sessions, respectively. They dropped-out due to either difficulty for assisting to clinic sessions or lack of support from relatives to comply with home training. No adverse effects were found during or after the intervention. All patients completed the daily treatment diaries consistently.

No significant changes were found after the "washout" period for all outcome measures except for TPDT ($p = 0.02$) and SPADI ($p = 0.025$). A significant decrease in shoulder pain was found after treatment ($p = 0.028$), between post-treatment and follow-up ($p = 0.028$), and between baseline and follow-up ($p = 0.004$) (Table 3). Significant improvements were found for active shoulder flexion ($p < 0.001$).

Additionally, a significant improvement in active shoulder flexion after treatment ($p$ = 0.016), between post-treatment and follow-up ($p$ = 0.020), and between baseline and follow-up ($p$ = 0.001) was found (Table 3).

*Table 3. Self-reported shoulder pain and range-of-motion outcomes at baseline, two-week "washout" period (T0), posttreatment (T1), and follow-up (T2).*

| | | **Mean ± SD** | **MD** |
|---|---|---|---|
| NPRS (0–10) | Baseline | 2.6 ± 1.9 | |
| | T0 | 2.9 ± 1.8 * | 0.3 |
| | T1 | 1.4 ± 1.1 † | −1.2 |
| | T2 | 0.3 ± 0.4 # | −2.3 |
| PER ROM (degrees) | Baseline | 27.6 ± 19.6 | |
| | T0 | 32.4 ± 25.9 | 4.8 |
| | T1 | 30.9 ± 22.3 | 3.3 |
| | T2 | 40.6 ± 24.4 | 13 |
| AF ROM (degrees) | Baseline | 106.6 ± 34.4 | |
| | T0 | 105.8 ± 32.1 * | −0.8 |
| | T1 | 120.1 ± 35.3 † | 13.5 |
| | T2 | 138.3 ± 33.1 # | 31.7 |

NPRS, numeric pain rating scale; PER ROM, passive external rotation range of motion; ASF ROM, active shoulder flexion range of motion; MD, mean difference.*: significantly different after treatment compared to baseline; †: significantly different between post-treatment and follow-up, $p$ <0.05; #: significantly different between baseline and follow-up, $p$ <0.05.

There were no significant changes in tactile acuity or laterality judgement performance over time (Table 4). No significant changes were found in TSK-11, PCS, or CSI at any assessment time.

*Table 4. TPDT and laterality judgement at baseline, two-week "washout" period (T0), post-treatment (T1), and follow-up (T2).*

| | | | **Mean ± SD** | **MD** |
|---|---|---|---|---|
| TPD threshold | | Baseline | 42.5 ± 29.9 | |
| | | T0 | 35.8 ± 26.1 | −6.7 |
| | | T1 | 28.1 ± 11.5 | −14.4 |
| | | T2 | 27.5 ± 11.5 | −15 |
| Laterality judgement (right shoulder) | Accuracy (%) | Baseline | 86 ± 11.03 | |
| | | T0 | 90 ± 16.6 | 4 |
| | | T1 | 95.9 ± 5.9 | 9.9 |
| | | T2 | 96.6 ± 5.01 | 10.6 |
| | Speed (s) | Baseline | 1.5 ± 0.3 | |
| | | T0 | 1.4 ± 0.3 | −0.1 |
| | | T1 | 1.3 ± 0.2 | −0.2 |
| | | T2 | 1.4 ± 0.2 | −0.1 |
| Laterality judgement (left shoulder) | Accuracy (%) | Baseline | 93.9 ± 8.7 | |
| | | T0 | 94.6 ± 5.2 | 0.7 |
| | | T1 | 99.1 ± 2.5 | 5.2 |
| | | T2 | 93.3 ± 11.2 | −0.6 |
| | Speed (s) | Baseline | 1.8 ± 0.4 | |
| | | T0 | 1.8 ± 0.7 | 0 |
| | | T1 | 1.6 ± 0.5 | −0.2 |
| | | T2 | 1.4 ± 0.3 | −0.4 |

TPDT, Two Point Discrimination Threshold; MD, mean difference.

## 4. Discussion

The main goal of this study was to evaluate the feasibility of implementing a CNS-focused treatment program for people with FS. Furthermore, we aimed to assess the clinical impact of this program on pain and function. Overall, no significant changes were found after the "washout" period thus suggesting minimal changes in the participants' clinical condition before treatment. Our findings revealed medium adherence of participants (70%) to the CNS-focused treatment and follow-up measurements. Regarding clinical impact, improvements in shoulder pain and active shoulder flexion were shown after treatment and at three months follow-up and in disability at three months follow-up. No significant changes were observed in tactile acuity, laterality judgement, pain catastrophization, fear-avoidance, or central sensitization after treatment or at follow-up.

Average participants' compliance with treatment was lower than expected. Participants' compliance was recorded with a treatment diary which was consistently fulfilled by all participants, but it was

not enough for them to comply with the totality of treatment as previously reported by Moseley et al. [5]. Nevertheless, all participants who attended the totality of treatment sessions at the clinic also met the home training dosage. In the current study, drop-outs were mainly due to a lack of support from relatives to assist participants with their home training tasks. Previous studies have also emphasized the difficulties with implementing CNS-focused techniques, in particular home training tasks, due to the lack of "helpers" availability or lack of time from participants [20,21]. These findings highlight the importance of having a cooperative context when using this kind of therapeutic approach at home. Long-term follow-up of participants was almost feasible as eight participants were followed-up. Only two participants were lost to follow-up, as they decided to discontinue the clinical sessions due to difficulties in the conciliation of their work schedules or lack of assistance with home training tasks.

Regarding clinical outcomes, positive effects on pain and shoulder function were observed after treatment, which is in accordance with previous studies using a similar protocol [22]. Specifically, improvements were found in shoulder pain and active shoulder flexion both after treatment and follow-up measurements and in disability scores at follow-up. Regarding disability, the change in SPADI scores at follow-up exceeded both the MDC and MCID established for individuals with FS and non-specific shoulder pain, respectively [4,23]. Likewise, changes in pain intensity after treatment and at follow-up and in active shoulder flexion after treatment and at follow-up also surpassed the MCID established for pain intensity (1.1 points) and MDC for active shoulder flexion (11°) in people with shoulder pain, respectively [7,9]. No significant changes were found in LRJT and TPDT neither after treatment nor at follow-up. To our knowledge, responsiveness to treatment of these two variables in people with FS had not been previously investigated except in a single case report [22], where a 10 mm TPDT reduction and improvement of accuracy and response time in the LRJT task were observed after intervention. A case-series study [24] investigated the efficacy of a treatment combining GMI with mirror therapy in five patients with different shoulder painful conditions, including one patient with FS. After treatment, all patients showed significant

improvements in pain intensity, active shoulder flexion, and motor imagery ability, but no significant changes on laterality judgement were found.

No significant changes in fear-avoidance or pain catastrophization were found after treatment. This is not surprising given the nature of the CNS-focused treatment program, which mainly included sensory discrimination training and GMI. These two interventions were not expected to address fear or pain catastrophization. In this regard, pain neuroscience education has demonstrated clinically relevant effects in reducing psychosocial factors, in particular kinesiophobia and pain catastrophizing [25], but only a short discussion of pain from a pain neuroscience perspective was implemented in this study. This may explain the lack of change in psychosocial variables. Future studies could explore the role of pain neuroscience education in this population as recently recommended by some authors [26].

On the other hand, the duration of symptoms of our sample spanned over a wide range (2–24 months), meaning that participants may have entered the study at different stages of the disease. It is known that larger improvements in the natural history of FS are often found in the early stages of the disease (e.g., during the first year) [27]. The results of the current study cannot determine whether this CNS-focused approach would be more suitable to subjects with FS either in their early or late stage of the disease.

To our knowledge, a CNS-focused treatment had not been used before specifically for people with FS, except in a case report [22]. However, the aforementioned study did not include home training sessions. In contrast, the present study integrated both clinic and home training sessions, which was considered essential to properly investigate the feasibility of applying this kind of approach in clinical practice.

## 5. Study limitations

Our results need to be interpreted in light of some limitations. This feasibility study recruited a sample of only ten participants with FS. Despite the reported significant improvements in pain, disability, and ROM, clinical effects must be interpreted with caution as a greater sample of participants is needed to better estimate the utility of this treatment for people with FS. Another important limitation is the lack of a control group with no intervention, which has not allowed to reveal the natural history of FS, so future research should overcome this issue.

Moreover, the heterogeneity of the recruited participants at baseline in terms of pain intensity and symptom duration limits the generalization of our results.

As participants completed the questionnaires alone and not in the presence of any researcher, this may have been one of the causes of the observed drop-outs.

Even though participants were allowed to continue with their current medication, the presence and absence of concomitant treatments, including specific medication intake, was not recorded. How these concomitant treatments may have influenced the results of this study is unknown.

Overall, this study identified key feasibility issues related to home training compliance that should lead one to reflect when using this approach, especially concerning the need of support from relatives.

## 6. Conclusions

The results of this feasibility study suggest that a CNS-focused treatment program might be a suitable approach to improve pain and disability in people with FS, but further research with a greater sample of participants is needed to draw firm conclusions. Although a high percentage of the sample completed the whole treatment program, some fulfillment issues arose, such as the need for the patient to have a cooperative context when implementing this treatment at home.

**Author contributions:** Conceptualization, L.D., M.B.B., E.L. and A.L.S.; methodology, E.L., A.L.S., M.G.M. and L.D.; formal analysis, S.M.d.H.; investigation, S.M.d.H., M.B.B., E.L. and L.D.; data curation, L.F.A.; writing original draft preparation, S.M.d.H.; writing review and editing L.F.A., E.L., L.D., M.G.M., A.L. and M.B.B.; supervision, A.L.S. and M.B.-B. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Institutional review board statement:** The study was approved by the Ethical Committee of the University of Valencia (reference number H1532330957968) and all procedures were performed in accordance with the Declaration of Helsinki.

**Informed consent statement:** Informed consent was obtained from all subjects involved in the study.

**Data availability statement:** The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

**Acknowledgments:** The authors would like to thank all the participants who took part in the study. We would also like to thank Jose Enrique Aroca and Marta Navarro for their assistance with participants recruitment.

**Conflicts of interest:** Declare conflicts of interest or state “The authors declare no conflict of interest.” Authors must identify and declare any personal circumstances or interest that may be perceived as inappropriately influencing the representation or interpretation of reported research results. Any role of the funders in the design of the study; in the collection, analyses or interpretation of data; in the writing of the manuscript, or in the decision to publish the results must be declared in this section. If there is no role, please state “The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results”.

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# ESTUDIO 3

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# A central nervous system focused treatment approach for people with Frozen Shoulder: Protocol for a randomised clinical trial

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**ABSTRACT**

**Background:** Frozen shoulder (FS) is a musculoskeletal condition of poorly understood etiology that results in shoulder pain and large mobility deficits. Despite some physical therapy interventions such as joint mobilization and exercise have shown therapeutic benefit, a definitive treatment does not currently exist. The aim of this study will be to compare the effectiveness of a central nervous system (CNS)-directed treatment program versus a standard medical and physical therapy care program on outcomes in participants with FS.

**Methods/Design:** The study is a two-group randomised clinical trial with blinding of participants and assessors. Participants will be recruited via referrals from orthopaedic surgeons and physical therapists, community-based advertisements, private care practices and hospitals. Participants will be randomized to receive either a CNS-focused treatment program or standard medical and physical therapy care. The shoulder pain and disability index (SPADI) will be the primary outcome, while the numeric pain rating scale (NPRS), shoulder range of movement (ROM), The Patient Specific Functional Scale, two point discrimination threshold and laterality judgement accuracy. Assessment will occur at baseline, at the end of the treatment program (week 10), and at 3 and 6 months follow-up.

**Discussion:** Preliminary data suggest that treatments that target CNS function are a promising approach to the treatment of people with shoulder pain including patients with FS. In the context of modest effects from most available physical therapy treatments for FS, this CNS-focused approach may lead to improved clinical outcomes. The trial will determine if the CNS-directed program is more effective than traditional interventions at reducing pain intensity and improving function in a FS cohort and will follow up participants for 6 months, providing important information on the persistence of any treatment effects.

**Trial registration number**: NCT03320200. Registered on October 25, 2017.

**Key words**: shoulder pain; shoulder adhesive capsulitis; central nervous system; physiotherapy

**Key points**

- The effects of central nervous system treatment on frozen shoulder will be analyzed
- Graded Sensory discrimination and Graded Motor imagery trainings will be applied
- Outcome measures will be shoulder pain and disability

## 1. Background

Frozen shoulder (FS) is a musculoskeletal condition of poorly understood etiology that results in shoulder pain and large mobility deficits (1). Obtaining pain relief and improving shoulder function are of significant concern to people with FS. Unfortunately, a definitive treatment for this condition does not currently exist and there is little consensus as to what constitutes optimal evidence-based (2). Despite some physical therapy interventions such as joint mobilization and exercise have shown therapeutic benefit (3-5), there is little evidence to suggest that the disease prognosis is affected (6). Other interventions such as guided intra-articular corticosteroid injections appear to show more promising outcomes in the short-term than stand-alone physical therapy interventions (7). Evidence also suggests the injection benefit being enhanced both in the short term and medium term when combined with physical therapy (8). The current state of evidence for the various physical therapy treatments suggest that further and alternative approaches for managing FS might be investigated (6).

There is preliminary evidence from two systematic reviews showing that central pain processing mechanisms can contribute to the pain experience in a subgroup of patients with shoulder pain of different etiologies, including those with chronic subacromial impingement syndrome and post-stroke shoulder pain (9,10). Similarly, it could be argued that continuously nociceptive barrage, as in the early stages of FS, could lead to peripheral and subsequently long-lasting central sensitization. However, up to now the involvement of central mechanisms in FS remains speculative (6). Interventions such as pain neuroscience education and graded motor imagery, which are thought to target the central nervous system (CNS) have been developed and tested in people with chronic musculoskeletal disorders with some promising results (11-15). To our knowledge, only two case-series studies have used a CNS-focused treatment program in people with shoulder pain (16,17). In one study, a brief mirror therapy intervention resulted in statistically significant improvements in pain, pain catastrophization, fear-avoidance and shoulder flexion active range of motion (ROM) in

patients presenting with shoulder pain and limited active motion (16). However, only 8.7% of the studied sample was diagnosed with FS and immediate post-intervention effects were solely assessed. In a second case series, Louw and colleagues showed that a sensory discrimination task applied to fifty-five patients with shoulder pain and limited ROM (including FS) resulted in an immediate increase of shoulder ROM ($p = 0.001$) with 25 patients (40%) meeting or exceeding minimal detectable change, but the study failed to report on the specific number of patients with FS (17). Despite the positive effects shown in these two case series, the potential benefits of adding other approaches addressing the CNS (e.g. sensory discrimination training) remains largely unknown. Hence, further investigation of these preliminary findings in adequately powered randomised controlled trials together with exploration of longer term effects of centrally-focused interventions for people with FS, is needed.

The aim of this study is to compare the effectiveness of a CNS-directed treatment program versus a standard medical and physical therapy care program on outcomes in participants with FS.

## 2. Methods

### 2.1. Design

This is a two-group, randomized clinical trial with blinding of participants and assessors.

### 2.2. Setting

Participants will be recruited via referrals from orthopaedic surgeons and physical therapists, community-based advertisements, private care practices and hospitals in Valencia, Spain. Potential referrals will be informed of the trial and the referral process via formal meetings and trial information sheets. This study is reported in line with the Standard Protocol Items; Recommendations for Interventional Trials (SPIRIT) statement (18) (Additional file 1).

### 2.3. Participants

Participants will be screened to determine whether they meet the following inclusion and exclusion criteria:

*Inclusion criteria:*

Primary or idiopathic FS, defined as FS not associated with a systemic condition or history of injury (19); greater than 50% reduction in passive external rotation when compared to the uninvolved shoulder or less than 30° of external rotation (20); range of motion loss of greater than 25% in at least two movement planes in comparison to the uninvolved shoulder (20); pain and restricted movement present for at least one month reaching a plateau or worsening (20); normal shoulder X-rays (with the exception of osteopenia of the humeral head and calcific tendinosis) (21).

*Exclusion criteria*

Locked dislocations, rheumatic disease, fractures or avascular necrosis on radiographs; surgery in the upper quadrant region <12 months prior to the study; skin or medical conditions that prevents from receiving tactile stimuli on the shoulder; neurological or motor disorders including a diagnosis of dyslexia or difficulty performing a rapid naming task; visually and mental health conditions that precludes successful participation.

### 2.4. Details of the interventions

Participants will be randomized to receive either a CNS-focused treatment program or standard medical and physical therapy care. Adherence to both interventions will be monitored using an individual treatment diary where the time of day and duration of each clinic and home session will be recorded (22). Adverse events will be recorded through passive capture. Patients will be requested to not participate in other treatments for their shoulder during the 10-week study period and any change in medication type or dosage during the study period will be recorded.

Trial physical therapists performing both interventions will have worked in private or public practice for at least 2 years. The clinicians performing the CNS-focused treatment will be engaged with a 1-day training session led by the author (ELL) for specific training in delivery of the interverventions comprising the program. This training session will include group discussions and quarterly workshops to review specific cases in the context of the CNS-focused treatment program. In addition, these physical therapists will be provided with a treatment manual outlining the CNS-focused treatment protocol and the details of each intervention included in the protocol. In order to ensure a good level of proficiency with the treatment protocol, trial physical therapists will go through a theoretical test and a practical exam with questions and techniques included in the protocol. The interventions are described in detail according to recommendatios of Template for Intervention Description and Replication (TIDieR) Checklist recommendations (23).

### 2.5. CNS-focused treatment program

Participants randomized to this treatment will receive a CNS-focused intervention consisting of a 10-session treatment program delivered as 60 minute sessions, scheduled once a week, over a period of 10 weeks. All treatment sessions are one-on-one. In addition, participants will complete a home treatment program entailing 30 minutes of training, five times per week that finishes at session 10. The intervention includes discussion of the participant's shoulder pain experience from a pain neuroscience perspective (e.g. pain neuroscience education) (24), graded sensory discrimination training and graded motor imagery (GMI) training. These interventions are likely to overlap due to variable allocation of time to each of the treatments within the clinic and home treatment sessions. Prior to training, participants will be given an explanation of the proposed treatment and the aim of the study. Patients will be shown a picture of the 'brain map' (homunculus) and taught how the map becomes "less sharp" when people are in pain, since the affected shoulder is not being moved (16). They will be told that when the map is sharpened, it may help to reduce not only their pain but also

mobility (16). By using sensory discrimination training and GMI, the therapy aims to sharpen the map of the shoulder in the brain and thus improve pain and movement.

*Graded Sensory discrimination training*

A graded sensory discrimination training program based on previous work by Wand et al. (13) will be implemented. In this model, participants undertake a training regimen that involves discrimination of stimulus type and location and graphestesia training in five different stages, graded according to level of theoretical cortical engagement and complexity. Each stage is planned to last a minimum of 2 weeks (10 weeks in total), but can be extended by some days if participants appear not to have sufficiently mastered that stage.

For tactile discrimination training in the first stage (week 0-2), participants will be seated in a comfortable position with a mirror between their upper limbs. Evidence has shown that tactile acuity is enhanced with visualization of the reflected image of the unaffected limb (that is, patients look towards the stimulated body part and can see the skin of the opposite body part in the mirror) (25). Therefore, during the first week of training at home and in the clinic, participants will be positioned so that they can see the reflection of their unaffected arm in a mirror while the affected arm is stimulated. The limbs will be positioned in such a way that the reflected image of the opposite arm is in line with the stimulated arm. Visual feedback will be withdrawn after the first week and will not be used again in any part of the sensory training program.

In this first stage, only localization of the stimulus will be trained. Participants will be shown a digital standard photograph of the shoulder on which 9 numbered grids will be marked. The spacing of the grids will be based on the current normative data pertaining to two-point discrimination of the affected joint (e.g. (45.9mm ± 18.4mm) (26). For the shoulder localization blocks, the superior border will be set as one centimetre proximal to the acromioclavicular joint and the lower border reaching the deltoid insertion. While the participant views the photograph and nine-block grids, they will be taught via tactile stimulus with the back of a blunt end of a pencil, where each block is in

relation to their shoulder, thus familiarizing them with the nine-block grid (13,27). After the familiarization period, the therapist using a random number sequence will press lightly on a particular point with the blunt end of a pencil for about 2 seconds. Pressure will be kept to a minimum to avoid pain provocation. Participants will be instructed to refer to the picture and to indicate which grid has been stimulated. With a correct identification of the area, the therapist will proceed to the next block for identification. If the participants make an error, they will be told which grid (number) has in fact been stimulated, and then the actual position of the grid that they have incorrectly indicated will be stimulated. This in essence will help the participant to develop a greater ability to identify the stimulated grid. Three blocks of 60 stimuli with an interstimulus interval of 15 s and a 3-min rest period between blocks will be used during the treatment session.

At the first session, participants will be accompanied by someone who can assist them to undertake training at home. This assistant will be trained in the task and participants will be advised to undertake 15 minutes of training at home in addition to the clinic session. Participants will be given a photograph of a standard shoulder on which the stimulation points will be marked and several sets of 60 random number sequences to use for training at home. If at the end of the second week (first stage), participants have less than 80% accuracy with one test block of 60 stimuli, then the training will be extended for an additional week.

In the next stage (week 2-4), participants will be asked to discern both the localization of the stimulus (i.e. the corresponding number on the photograph) and the size of the probe used (type of stimulus). The experimental setup will be similar to that used in the first stage, but this time a probe with a sharp end (pen cap) and a blunt end (cork) will be used. A random number table will be used to randomize both position and probe size. Participants initially will be shown a picture with nine numbered grids marked on the shoulder; the number of grids will be increased to 12 in the second week of this stage. Again, participants will be given feedback about each error they make. Three blocks of 60 stimuli with an interstimulus interval of 15 s and a three-min rest period between blocks will be used during the treatment session.

Should participants be less than 80% accurate with 1 test block of 60 stimuli at the end of the second week of this stage, then the training will be extended for an additional week. For home training in this second stage, participants will be given a photograph of the shoulder with the stimulation points and a wine cork and a pen lid to use as stimulus type. They will be given five lists of random combinations of numbers (1–9 or 1-12) and stimuli (cork or pen lid), and will be advised to use a different list each day. Participants will be advised to undertake 15 minutes of training at home in addition to the clinic session.

The next three stages (weeks 4–10) will involve graphesthesia tasks of increasing difficulty. In this third stage, participants will have to simply recognize letters drawn on the shoulder. Several random sequences of 60 letters will be generated, and three lots of 60 letters will be used in each treatment session with a interstimulus interval of 15 s and a 3-min rest period between blocs. Initially, uppercase letters will be drawn on the shoulder by the therapist with his index finger. Participants will be asked to indicate the letter drawn; if they guessed incorrectly, they will be told the actual letter that has been drawn, and then the letter that they have incorrectly indicated will be re-drawn. Progression within this 2-week block will be undertaken by decreasing the size of the letters, altering the orientation of the letters, and altering the speed at which the letters are drawn. Again, this stage may be extended by one week if participants are less than 80% accurate with a test block at the end of two weeks. Participants will be advised to undertake 15 minutes of graphesthesia training at home by using several random sequences of letters.

The next 2-week stage (week 6-8) will involve the recognition of 3-letter words drawn on the shoulder. The protocol and progression will be almost identical to those outlined for the single-letter task, including the criterion for advancement to the next stage. One additional progression in the last two weeks (week 8-10) will involve overlapping the letters of the word such that they are all drawn on the same part of the shoulder. Again, this stage can be extended for an additional week if participants were less than 80% accurate at the end of two weeks. Participants will be advised to

undertake 15 minutes of graphesthesia training at home by using several random sequences of letters.

A full description of the Graded Sensory discrimination training program is provided in **Table 1**.

*Table 1. Summary of progressions used for the Graded Sensory Discrimination Training program*

| **STAGE** | **Sensory Discrimination training** |
|---|---|
| **1 (week 0-2)** | **Localization training**<br>Determine site of stimulus<br>With visual feedback during first week<br>Without visual feedback during second week |
| **2 (week 2-4)** | **Localization and stimulus type**<br>Determine site of stimulus<br>Determine size of probe<br>Progress by adding points |
| **3 (week 4-6)** | **Graphesthesia training**<br>Recognize letters<br>Progress by size<br>Progress by orientation<br>Progress by speed of drawing |
| **4 (week 6-8)** | **Graphesthesia training**<br>Recognize 3-letter words<br>Progress by size<br>Progress by orientation<br>Progress by speed of drawing<br>Progress by overlapping letters |
| **5 (week 8-10)** | **Graphesthesia training**<br>Progress by size<br>Progress by orientation<br>Progress by speed of drawing<br>Progress by overlapping numbers |

*Graded Motor Imagery (GMI) Training*

A graded motor cortical retraining program based on previous work by Wand et al. (13) and published guidelines (28) will be implemented.

The initial stage (week 1-2) of the GMI will involve laterality recognition training (Implicit Motor Imagery). An online computer program (Recognise Online, NOIgroup, Adelaide, Australia) will be used to present participants with a random selection of photographs of either left or right shoulders (28). The photographs will be presented in a variety of positions and orientations. Participants will respond by pressing one of two keys to indicate whether a picture shows the left or right shoulder, a process that require them to mentally rotate their own body part to match the position shown in the picture and, thereby, to engage motor cortical areas corresponding to that body part. An important aspect of the test is that it is performed unconsciously (relatively) so it should be done as quickly as possible, almost as though the patient was guessing (28). The photographs will be presented in groups of 30 for a duration of five seconds each photograph , and progression will involve reducing the time for which the photographs are presented and changing the photographs background. During an initial familiarization session conducted during the first formal treatment, three lots of 30 photographs will be presented with a 1-min rest period between lots. Participants will be asked to practice this task at home for 15 minutes each day.

The next stage (week 3-4) will involve imagined movements (Explicit Motor Imagery). Two videos each lasting approximately seven minutes will be made of a person slowly performing a variety of shoulder movements from simple, low-load movements to more complex, behaviourally relevant movements. During the first week of this stage (week 3), the video will show small-range shoulder movements (e.g. unilateral shoulder flexion, extension, abduction, shoulder external and internal rotation in 0º of abduction). In the second week of this stage (week 4), the video will show the a person performing the same movements as before but in full-range and more challenging and functional tasks (e.g. hand behind back, hand to curl hair). Participants will be in sitting in a relaxed position for imaging movements. They will be instructed to watch the videos and then close their

eyes and to imagine themselves performing the same movements in a smooth and pain-free manner as if it was real in all its aspects, including the timing taken to move. Participants will be advised not to imagine watching themselves performing the movement but to imagine actually performing the movement in the first person. They will execute two series of 20 repetitions for every imagined movement in each session. Additionally, participants will be asked at home to watch the videos twice and to practice for a total of 15 minutes each day.

The next stage (week 5-6) will involve isometric contraction of the rotator cuff and scapulo-thoracic muscles using dynamic glenohumeral and scapulo-thoracic neuromuscular control exercises. It is believed that the activation of these muscles will serve as an ideal bridge between imagined movements and actual shoulder movements used in the next stage using mirror therapy (because there would not be shoulder movement, thus minimizing the potential for sensorimotor incongruence) and that the activation of these muscles might sharpen the cortical representation of the shoulder (13). During the first week (week 5), participants will receive instruction on dynamic glenohumeral neuromuscular control exercises aiming to contract the rotator cuff muscles (29) and scapulo-thoracic muscles (30) in isolation. They will perform neuromuscular control exercises for three sets of 10s repetitions with a 2-min rest period between sets. During the second week of this stage (week 6), the progression will involve maintenance of the local muscle contraction while participants move their shoulder in a pain-free manner in different directions. Exercise dose will be the same as during week 5. Participants will be asked to practice at home these tasks for a total of 15 minutes each day.

The next 4-week stage (week 7-10) will involve the use of mirror therapy with different progressions. Participants will be seated in a comfortable chair, towards the end of the chair allowing for movement, but also providing some trunk support. The proposed mirror therapy will be demonstrated and explained to the subjects by the physiotherapist. Next, a standing mirror on wheels will be placed in front of the participant with the reflective side facing the uninvolved side. The affected arm will be placed behind the mirror. The participant will be asked to lean forward slightly,

allowing them to view the complete uninvolved arm in the mirror. Mirror exercises will begin with simply watching the reflection of the unaffected arm in the mirror and then progressed from static to active and functional movements. When possible, gentle and synchronous movements of the affected arm will be encouraged behind the mirror. Two series of 12-15 minutes will be performed in each session, with 2 minutes between series to allow for resting and relaxing the arm. Additionally, participants will be asked to practice this task at home for 15 minutes each day with a mirror provided by researchers conducting the study.

Participants will be encouraged to move slowly and easily, breathing comfortably and focusing on the movement of the uninvolved arm. The intervention will allow subjects to move the uninvolved arm giving the "illusion" that their involved arm is moving through full active ROM. Participants will be advised to stop if they have an increase in pain either during or directly after mirror therapy. A full description of the Graded Motor Imagery training program is provided in **Table 2**.

Should sustained symptom exacerbation occur in any of the stages, the appropiate parameters will be reviewed and possibly reduced.

*Table 2. Summary of progressions used for the Graded Motor Imagery training program*

| STAGE | GMI training |
|---|---|
| **1 (week 0-2)** | **Laterality recognition**<br>Using Recognise software<br>Determine whether left or right side of shoulder<br>Progress by time for which image was presented |
| **2 (week 2-4)** | **Imagined moviments**<br>Using video of model performing movements<br>Small-range movements during first week<br>Full-range movements during second week |
| **3 (week 4-6)** | **Isometric local muscle recruitment**<br>Rotator cuff muscles<br>Scapular muscles<br>Add pain-free movement to local contraction |
| **4 (week 6-8)** | **Mirror therapy**<br>Keep the affected arm still in a comfortable position/ Keep the unaffected arm still in the same position and just observe the reflect<br>Keep the affected arm still in a comfortable position/ Move the unaffected arm through its full ROM in different directions. |
| **5 (week 8-10)** | **Mirror therapy**<br>Move the affected arm towards the limit of pain in the restricted/painful direction(s) of movement and keep that position/ Move the unaffected arm through its full ROM in the painful/limited directions<br>Move the affected arm towards the limit of pain in the restricted/painful direction(s) of movement / Copy with the unaffected arm through a full range of movement (synchronous moviments) |

### 2.6. Standard medical and physical therapy care program

Participants randomised to standard medical and physical therapy care will receive a 10-session treatment program of the same duration as the CNS-focused treatment. This standard treatment will include one corticosteroid infiltration provided in the early acute stage followed by a multimodal physical therapy program including analgesic modalities (e.g. TENS, cryotherapy) and exercise and manual therapy techniques addressing the specific mobility deficits of each patient (31). Physical therapists will be instructed not to include interventions that were similar to those used in the group receiving the CNS-focused protocol (e.g. using mirrors or imagined movements) and to include a home program that involves a training load comparable to that in the other group.

### 2.7. Primary and secondary outcome measures and assessment points

The primary outcome measured is self-reported shoulder pain-related disability as measured on the SPADI questionnaire. The Spanish version of the SPADI has high internal consistency (Cronbach α: 0.916) and excellent test-retest reliability (ICC: 0.91).[32] Secondary outcomes are as follows:

1. The Numeric Pain Rating Scale (NPRS), a valid and reliable measure of shoulder pain (33).
2. Goniometric assessment of active shoulder ROM which is valid and reliable (34,35).
3. Two point discrimination threshold measured at one standardize site on the affected shoulder (5cm distal to the lateral border of the acromion),[36] following an established protocol (37).
4. Laterality judgement accuracy using the NOI Recognise online program (www.noigroup.com) and following and established protocol (38).
5. The Spanish version of the Tampa Scale of Kinesophobia, a valid and reliable measure of fear of movement (39).
6. The Patient Specific Functional Scale, a reliable, valid, and responsive instrument that can be used in patients with a primary shoulder complaint (40).

Assessment will occur at baseline, at the end of the treatment program (week 10), and at 3 and 6 months follow-up. At baseline, a clinical assessment of symptom distribution, history of the present and previous shoulder complaints, red flag screening, medical history and general health status will also be performed.

### 2.8. Recruitment procedures

Participants will be recruited from different outpatient private clinics and rehabilitation services of different hospitals of the region of Valencia (Spain). In addition, posters will be distributed in the community and advertisement in social media will be performed to increase potential number of participants in the study. Physical therapists and primary care practitioners will be contacted and invited to recruit participants after providing them brief information about the study. Involved practitioners will identifiy potentially suitable patients and, after providing them with information about the study, will invite them to contact with the research team. Upon contact by potential participants, a researcher will explain the study and assess them for study eligilibily via telephone. If the potential participant remains interested in participating in the study, they will be invited to a baseline session. During that session, one researcher will provide to the patient an information leaflet, confirm eligibility, and obtain consent form. Baseline outcome data will be collected during this session, following which the participant will be randomised.

Adherence to treatment will be enhanced by careful explanation of the time demands of participation and regular contact by a researcher who will send repeated reminders to participants by email and make phone calls to ensure adherence to the time schedule including follow-up sessions.

The schedule of the enrolment, interventions and assessments are shown in **Fig. 1**.

| | STUDY PERIOD | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Enrolment | Allocation | Post-allocation | | | | | Close-out |
| **TIMEPOINT** | $-t_1$ | 0 | $t_1$ | $t_2$ | $t_3$ | $t_4$ | *etc.* | $t_x$ |
| **ENROLMENT:** | | | | | | | | |
| **Eligibility screen** | X | | | | | | | |
| **Informed consent** | X | | | | | | | |
| **Allocation** | | X | | | | | | |
| **INTERVENTIONS:** | | | | | | | | |
| *[*CNS-focused treatment program*]* | | | — | — | — | | | |
| *[*standard medical and physical therapy care*]* | | | — | — | — | | | |
| **ASSESSMENTS:** | | | | | | | | |
| ***[Demographic data]*** | X | X | | | | | | |
| ***[Shoulder pain and disability, ROM, discrimination, laterality, kinesiophobia, functionality]*** | | | X | X | X | | | |

*Figure 1. Schedule of enrollment, interventions and assessments*

### 2.9. Randomisation procedures

Randomization will be conducted using computer-generated random numbers (Epidat® version 3.1). The allocation sequence will be prepared by a researcher with no involvement in the study by using a blocked randomization model. Allocation concealment will be ensured using 34 sequentially numbered opaque and sealed envelopes. After performing the baseline assessments the treating clinician will open the envelope and reveal each participant group allocation.

### 2.10. Blinding

Participants will be blinded to both study hypothesis and group allocation. It will not be possible to blind the treating physical therapists who are responsable of performing the interventions . All the assessments will be conducted by researchers who will be blinded to group allocation. Statitistical analysis will be performed by a statistician blinded to the study aims.

### 2.11. Statistical analysis including sample size calculation

*Sample size calculations*

The sample size will be calculated using G*Power 3.0.18 Software based on the SPADI as the primary outcome measure. To our knowledge, there are not studies investigating the effects of GMI or graded sensory discrimination training on FS. Based on similar studies applying physiotherapy on FS (SPADI mean of 66 points; SD:16) (8), and the minimal detectable change attained in the study of Tveita et al (17 points) (41), to detect a 17 points (SD=16) between-group difference, with 80% power and an alpha level of 0.05, a total sample size of 30 patients is estimated (15 per group). An allowance will be made for a 15% drop out rate, increasing the sample size to 34 patients (17 per group). However, since this calculation is not based in the use of GMI, to assure an adequate sample size, we will carry out a pilot study with 20 participants (10 per group) to test these assumptions. Mean differences and standard deviations from the intergroup comparison on the primary outcome (SPADI) will then be used to recalculate the sample size, if necessary.

*Statistical analysis*

Data will be analyzed using the statistical package SPSS 21.00 for Windows. Statistical significance will be set at $p<0.05$. Prior to statistical comparisons, all data will be tested for normal distribution. Then, a descriptive analysis of the data will be obtained for the dependent variables in the different assessment times. Subsequently, homogeneity of the two intervention groups will be studied. To confirm if there are differences in each group (intra-group comparisons), considering each group in isolation, between the four assessments in each of the variables (baseline, post-treatment, 3 month follow-up, 6 month follow-up), repeated measures ANOVA will be used. To calculate inter-group differences between baseline and follow-ups, a four-way repeated measures ANOVA will be conducted, with the scores of every primary and secondary outcomes as dependent factors, with 4 levels corresponding to every time of assessment (t1, t2, t3 and t4), and the two intervention groups (CNS-focused treatment vs standard care treatment) as independent factors. Between- and within-

group effect sizes for all quantitative variables will be measured with the Cohen *d* coefficient according to the formula $d = 2t/\sqrt{g}$. An effect size greater than 0.8 will be considered large, around 0.5 moderate, and less than 0.2 small (42). In cases of missing data, an intention-to-treat analysis will be performed. Double data entry will be carried out in order to promote data quality.

### 2.12. Data management

Data from the study will be only accessible to the research team and will be stored on password-protected computers at the University of Valencia. Paper-form data will be stored in locking cabinets located at the Department of Physiotherapy of that same University. In order to preserve data confidentiality study participants will be assigned an identification number which will be kept for the duration of the study. A list of participant identification numbers will be created and separated from the de-identified data. Statistical analyses will be performed keeping participants anonymity by using patient identification numbers and the statistician will be blinded to group allocation. Confidenciality will also be preserved when dissemination results by using group data.

## 3. Significance and implications for practice

Preliminary data suggest that treatments that target CNS function are a promising approach to the treatment of people with shoulder pain including patients with FS. In the context of modest effects from most available physical therapy treatments for FS, this CNS-focused approach may lead to improved clinical outcomes. The trial will determine if the CNS-directed program is more effective than traditional interventions at reducing pain intensity and improving function in a FS cohort and will follow up participants for 6 months, providing important information on the persistence of any treatment effects. The inclusion of variables related to functional reorganization of the brain such as the two-point discrimination threshold and laterality judgement accuracy will also allow for the first time to explore responsiveness to change of these tests after treatment in a population with shoulder

pain. In addition, this study provide a good oportunity to explore the relationship between shoulder pain, cortical changes and clinical markers in people with FS. Finally, the flexible structure of the interventions comprising the CNS-focused approach closely reflects the real-world clinical practice. CNS-directed interventions constitute a completely new treatment paradigm for management of shoulder pain and in particular people with FS. Feelings of stiffness in the back have been recently demonstrated to be a multisensory perceptual inference consistent with protection rather than reflecting biomechanical properties of the back (43). Stiffness is a main characteristic in people with FS and the prevailing view is that it is related to a capsular fibrosis despite the cause is still unknown (44). The positive effects in ROM observed in preliminary research conducted in people with FS after brief interventions targeting the CNS challenge the prevailing view that stiffness in FS is an isomorphic marker of the biomechanical characteristics of the shoulder. The results of this study will have the potential to address this issue and change current physiotherapy management of FS.

## 4. Anticipation dates of trial commencement and completion

Commencement March 2018. Completion September 2020.

## 5. Ethics and dissemination

The trial has been registerd in Clinicaltrials.gov, with the number NCT03320200. The results of the study will be disseminated at several research conferences and as published articles in peer-reviewed journals. The full protocol, participant-level dataset, and statistical code will be available when this study will be finished.

**Acknowledegements**

Not applicable.

## 6. Trials status

Protocol version number and date: NCT03320200 March 2018

Recruitment has begun on March 2018. Recrutiment will be completed on October 2019.

## Authors' contributions

ELG designed this protocol study. All the authors have contributed to the writting of this manuscript. All authors read and approved the final manuscript.

## Funding

This work is funded by the Conselleria de Educación, Investigación, Cultura y Deporte de la Generalitat Valenciana, Spain (GV/2016). (http://www.ceice.gva.es/es). The study sponsor and funders will be not involved in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication. Provisions for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation will be provided by the aforementioned organization.

## Availability of data and materials

Not applicable.

## Ethics Approval and consent to participate

This study protocol has received Ethic approval by Ethics Committee of Research in Humans of the University of Valencia, Spain (H153233095796). All the participants have accepted and signed an informed consent before beginning the study. Protocol modifications will be notified to relevant parties. All the research team will have access to the final trial dataset. There will not have any responsabilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial.

## Consent for publication

All authors have approved the manuscript for submission.

**Competing interests**

AL receives royalties for books about pain and rehabilitation. AL receives speaker's fees for lectures on pain and rehabilitation. To minimize the risk of conflict, AL will have no role in data collection or analysis in the current trial. The rest of the authors declare to have no conflicts of interest.

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# ESTUDIO 4

# Estudio 4

# Is there any benefit of adding a Central Nervous System focused intervention to a manual therapy and home stretching program for people with frozen shoulder? A randomized controlled trial.

**Short title: Central-focused intervention for frozen shoulder**

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This study was approved by the Ethical Committee of the University of Valencia (reference number H1532330957968) and all procedures were performed in accordance with the Declaration of Helsinki. All participants gave their written informed consent prior to participate in the study.

**Disclaimers**

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest: The authors, their immediate, and any research Foundation with which they are affiliated have not received any financial payments or other benefits from any commercial entity related to the subject of this article.

**Acknowledgments**

The authors thank the participants for taking part in the study. They would also like to thank Dr. Jose Enrique Aroca and Dr. Marta Navarro for their role in recruiting participants.

**ABSTRACT:**

**Background:** Frozen shoulder (FS) is a highly disabling pathology of poorly understood etiology, which is characterized by the presence of intense pain and progressive loss of range of motion (ROM). The aim of this study was to evaluate the effect of adding a central nervous system-focused (CNS) approach to a manual therapy and a home stretching program in people with frozen shoulder (FS).

**Methods:** 34 subjects diagnosed with primary FS were randomly allocated to receive a 12-weeks manual therapy and home stretching program or manual therapy and home stretching program plus a CNS-focused approach including Graded Motor Imagery and sensory discrimination training. The Shoulder Pain and Disability Index (SPADI), self-perceived shoulder pain (VAS), shoulder range of motion and the Patient Specific Functional Scale (PSFS) were measured at baseline, after a 2-weeks washout period just before starting treatment, after treatment and at three months follow-up.

**Results:** No significant between-groups differences in any outcome were found either after treatment or at three months follow-up.

**Conclusion:** A CNS-focused approach provided no additional benefit to a manual therapy and home stretching program in terms of shoulder pain and function in people with FS.

**Keywords:** Exercise; Frozen shoulder; manual therapy; motor imagery; physical therapy; tactile discrimination training.

**Level of evidence:** Level; Randomized Controlled Trial; Treatment Study

## 1. INTRODUCTION

Frozen shoulder (FS) is one of the most challenging musculoskeletal conditions that physiotherapists face in their clinical practice. It is characterized by an spontaneous onset of shoulder pain followed by a gradual and generalized decrease of both active and passive range of motion (ROM) [44]. In 2011, the American Shoulder and Elbow Surgeons society proposed to classify FS into primary or idiopathic FS and secondary FS, with this latter in turn being subclassified into one of three categories: intrinsic (i.e. secondary to any other shoulder pathology such as a rotator cuff tear), extrinsic (i.e. secondary to any pathology outside the shoulder such as a cervical radiculopathy) and systemic (i.e. secondary to diabetes) [44].

The underlying physiopathology of FS is still poorly understood, although some mechanisms such as low grade inflammation and immune system dysregulation have gained scientific interest in the last years [16,31].

The effectiveness of different interventions has been investigated in people with FS. For instance, a wide variety of mobilization techniques have shown beneficial effects in this clinical condition [29,30]. However, to date no intervention has demonstrated superiority over others, except the early use of intraarticular corticosteroids injections in patients with FS of less than 1-year duration [6]. Additionally, the effect sizes of currently applied interventions are modest at best and the natural history of FS does not seem to be influenced by any treatment [27]. This fact has prompted some authors to claim the need for innovative research in the area of management for FS [41].

In the last years, growing evidence is showing that central pain mechanisms may play a key role in a wide variety of chronic musculoskeletal pain conditions [14,21,38]. Considering the long-lasting nature of FS, it was postulated that this could also be the case for this condition [41]. In line with this, some recent studies have investigated the contribution of altered central pain processing mechanisms in people with FS. Mena et al [23] found that people with FS had a reduced tactile acuity and impaired laterality judgement in their affected shoulder when compared to their unaffected shoulder and

controls. These results were later replicated by Breckenridge et al [2]. In another case series study, Louw et al [21] investigated the effects of a brief mirror therapy intervention in subjects with shoulder pain and limited active ROM, including people with FS. Significant improvements were found in pain intensity, pain catastrophizing, fear-avoidance and shoulder ROM (active flexion) after treatment. Similar results were shown by Sawyer et al in a case report with FS after implementing a combined intervention comprising pain neuroscience education, sensory discrimination training and graded motor imagery (GMI). Due to the small sample sizes, low level of evidence study designs (i.e. case report, case series) and the short-term follow-up of the aforementioned studies, further research on the role of CNS-focused interventions in this population seems warranted.

The aim of this study was to investigate the effect of adding a combined CNS-focused intervention including sensory discrimination training and GMI to a manual therapy and home stretching program in people with FS. It was hypothesized that patients receiving the combined peripheral and CNS-focused interventions would report better outcomes when compared to those receiving only the peripheral-focused intervention (i.e. manual therapy and stretching).

## 2. METHODS

### 2.1. Study Design

This study was a randomized controlled trial analyzing the comparative effectiveness of two physiotherapy interventions for FS. The study was previously registered at clinicaltrials.gov (NCT03320200). Ethical approval was obtained from the Committee of the University of Valencia and all procedures were performed in accordance with the Declaration of Helsinki. All participants gave their written informed consent prior to their participation in the study. This study has been reported following the CONSORT guidelines [25] (APPENDIX I) and interventions are described in accordance with the Template for Intervention Description and Replication (TIDieR) checklist (APPENDIX II) [13].

### 2.2. Participants

Participants with primary FS were recruited between October 2017 and March 2020. Participants had to comply with the following inclusion criteria:[3](1) to have either a loss of passive external rotation greater than 50% in the affected shoulder compared to the unaffected shoulder or less than 30° of external rotation in the affected shoulder as measured in 0º of shoulder abduction, (2) to have a ROM loss greater than 25% in at least two movement planes in the affected shoulder when compared to the unaffected shoulder, and (3) shoulder pain and restricted ROM had to be present and reached a plateau or be worsening for at least one month.

Participants were excluded if they had received shoulder surgery during the last year; had a locked dislocation, arthritis, fracture or avascular necrosis; presented difficulties to understand written or spoken Spanish language; had any skin or medical condition preventing them from receiving tactile stimuli on the shoulder; any neurological or motor disorder (i.e. dyslexia); were visually impaired; or had any diagnosed psychopathology.

Prior to inclusion, none of the participants had received a corticosteroid injection in their affected shoulder or reported satisfactory results from previous physical therapy treatments. All participants were instructed to continue taking any current medications, but not to start new medications or initiate new treatments during the treatment period.

### 2.3. Procedure

All participants were interviewed at baseline to collect sociodemographic and clinical information. Then, participants' shoulder ROM and self-perceived shoulder pain were measured and the Shoulder Pain and Disability Index (SPADI) and the Patient Specific Functional Scale (PSFS) questionnaires were fulfilled.

All assessments were performed by three researchers (MB, LD and ELL), with 20, 20 and 10 years of clinical experience, respectively, in assessing and treating people with FS. Prior to the study commencement, all measurements were practised and agreed between the researchers to ensure consistency.

### 2.4. Outcome measures

The primary outcome measure was the SPADI. Secondarily, self-perceived shoulder pain (Visual Analogue Scale – VAS), shoulder active and passive ROM and the PSFS were also measured. All outcomes were recorded at baseline and after a 2-weeks period of washout to evaluate whether changes in participants' clinical condition could occur during a "non-intervention" period [13]. Participants were again measured after treatment and at three months follow-up. If no significant differences in outcomes were observed between the baseline and 2-weeks assessments, any change in the following measurements could be more attributable to the intervention [10].

*Shoulder pain and disability*

Participants' shoulder pain and disability was measured with the Spanish version of the SPADI. The SPADI is a 13-items shoulder function index which assesses pain and disability related to shoulder dysfunction [33]. Each item is scored using a numeric scale ranging from 0 ("*no pain / no difficulty*") to 10 ("*worst pain imaginable / so difficult it required help*"). The total score ranges from 0 to 100 points with higher scores indicating greater disability.

The Spanish version of the SPADI has shown high internal consistency (Cronbach α: 0.916) and excellent test-retest reliability (ICC: 0.91) [22]. Its Minimal Clinically Important Difference (MCID) ranges from 8 to 13 points [35].

*Self-perceived shoulder pain*

Participants' self-perceived shoulder pain was assessed with a VAS anchored with 0 ("*no pain*") and 100 ("*pain as bad as you can imagine*"). They were asked to indicate their average pain experienced over the 24 hours prior to assessment [11].

The VAS has been shown to be a valid and reliable tool to measure pain intensity in people with shoulder pain. The MCID for the VAS is 30 mm [17].

*Shoulder range of motion (ROM)*

Active and passive shoulder flexion and external rotation at 0° of shoulder abduction were measured at the affected shoulder using a Plurimeter-V gravity inclinometer (Plurimeter 164 dr Rippstein) following previous guidelines [28,37].

For shoulder flexion, participants were standing with the inclinometer placed in the proximal third of the humerus, over the superior portion of the biceps brachii muscle. Participants were first asked to actively elevate their shoulder until either pain or resistance appeared and then the shoulder was forced passively, until pain tolerance or maximum ROM was reached. Inclinometers have shown high responsiveness in measuring change for both passive and active flexion of the shoulder in FS and the minimal detectable change (MDC) for active shoulder flexion is 8º in asymptomatic subjects

[34]. In addition, active shoulder flexion in the scapular plane has demonstrated good reliability and validity [15].

For shoulder external rotation, participants laid in supine with their arm entirely supported by the plinth. The arm was placed in 0º of shoulder abduction, elbow flexion 90° and neutral forearm pronosupination. The inclinometer was placed in the distal part of the dorsal forearm. Participants were first asked to actively rotate into external rotation until either pain or resistance appeared and then the shoulder was forced passively, until pain tolerance or maximum ROM was achieved. MDC for active external rotation is 9º in asymptomatic subjects while good intra-rater and inter-rater reliability have been reported for both active and passive external rotation in healthy subjects and patients with shoulder pain disorders [34].

*Patient Specific Functional Scale (PSFS)*

Participants completed the PSFS to assess for changes in the functional status of their affected upper limb after treatment. Participants nominated three to five activities they were unable to do or had difficulties because of their current shoulder problem and rated them on an 11-point scale ranging from 0 ("*unable to perform the activity*") to 10 ("*able to perform the activity at preinjury level*"). A total PSFS score was obtained by the sum of the activities' scores divided by the number of limited activities (range 0-10), with higher scores indicating better performance.

The PSFS has been shown to be a valid, reliable and responsive outcome measure in people with upper limb musculoskeletal problems [12]. The MCID of the PSFS is 1.16 points [12].

*Adherence to treatment*

Adherence to home treatment was assessed after each session with a diary where participants marked their compliance with the assigned home exercises [26].

### 2.5. Randomization and blinding

Participants were randomized to receive one of two 12-weeks interventions: a manual therapy and home stretching program or a manual therapy and home stretching program plus a CNS-focused approach including GMI and sensory discrimination training. Randomization was performed using sealed envelopes by a researcher who was blinded to the aim of the study. Additionally, the researchers responsible of all the assessments were blinded to treatment allocation.

### 2.6. Interventions

*Manual therapy and home stretching program*

Participants of this group received a manual therapy and home stretching program previously described by Dueñas et al [8]. This intervention included 12 sessions of supervised manual therapy applied once a week and a home stretching program performed once a day, five days per week, during the whole intervention period. The selection of specific manual therapy and home stretching techniques for each patient was based on individual shoulder ROM impairments [7] and the STAR-shoulder tissue irritability rating system [8]. Details about how treatment techniques were individualized based on the two aforementioned factors can be found elsewhere [8].

*Manual therapy and home stretching program plus CNS-focused approach*

Participants in this group received the same manual therapy and home stretching program plus a CNS-focused approach as previously described by Lluch et al [19]. This latter included discussion of the participant's shoulder pain experience from a pain neuroscience perspective provided in the first session plus 12 supervised sessions of GMI and sensory discrimination training performed once a week [20,43]. Additionally, participants performed a home exercise program once a day, five days per week, of GMI and sensory discrimination training during the whole intervention. These home sessions approximately lasted 45-60 minutes until tasks completion. The feasibility of this CNS-focused treatment program for people with FS has recently been demonstrated [24].

The physiotherapist performing all the interventions (SM) had a post-graduate degree in manual therapy and was trained by two experienced researchers (LD and ELL) in the use of these techniques before starting the study.

### 2.7. Sample size calculation

The sample size was calculated using G*Power 3.0.18 Software based on the SPADI as the primary outcome measure. Based on studies which applied physiotherapy interventions in people with FS (SPADI mean of 66 points; standard deviation (SD) = 16) [4], and the MDC attained in the study by Tveita et al. (17 points) [42], to detect a 17-point (SD = 16) between-group difference, with 80% power and an alpha level of 0.05, a total sample size of 30 patients was estimated (15 per group). An allowance was made for a 15% dropout rate, increasing the sample size to 34 patients (17 per group).

**Statistical analysis**

Statistical analysis was performed using R in accordance with intention-to-treat approach. Linear mixed-models with repeated-measures analysis and random effect models were used to model the intervention effect over assessment timepoints for primary and secondary outcome measures. We modeled the random effects of individuals and fixed effects of group (Manual therapy and home stretching, manual therapy and home stretching plus CNS-focused approach), assessment timepoint (baseline, after treatment and three months follow-up) and group x assessment timepoint. Pairwise comparisons with Bonferroni adjustment were used when interaction effect group x assessment timepoint or timepoint was significant and change scores between baseline, after treatment and three months follow-up were computed to examine if MDC or MCID was exceeded.

## 3. RESULTS

Fifty-four participants were initially assessed for eligibility and 34 completed the study. (**FIGURE 1)**. Both intervention groups were comparable at baseline in terms of patients' characteristics and outcomes (**TABLES 1 and 2**).

**TABLE 2** shows the results of each outcome for both groups, as well as within- and between-group changes. No timepoint-by-group interaction was observed for any of the assessed outcomes. Main effect for timepoint was found for SPADI ($p<0.001$), with manual therapy and home stretching and manual therapy and home stretching plus CNS-focused approach showing similar improvements after treatment (within-group mean difference [MD]= -27.36; 95% Confidence Interval [CI]: -40.37, -14.34 and -28.59; 95% CI: -41.21, -15.96 respectively) and at three months follow-up (-35.47; 95% CI: -47.63, -23.30 and -38.32; 95% CI: -50.86, -25.78), both exceeding the MCID.

A main effect for timepoint was also observed for PSFS ($p<0.001$), with both intervention groups showing comparable improvements after treatment (within-group MD= -7.42; 95% CI: -9.50, -5.11 and -6.05; 95% CI: -8.80, -4.04 respectively) and at three months follow-up (-8.18; 95%CI: -13.48, -2.88 and -11.06; 95%CI: -9.60, 1.31), which exceeded the MCID. Both groups also improved in VAS through the study (main effect for timepoint, $p<0.001$) (within-group MD= -18.58; 95% CI: -34.91, -2.26 and -33.68; 95% CI: -50.50, -16.85 respectively) and at three months follow-up (-28.58; 95% CI: -46.03, -11.14 and -27.93; 95% CI: -45.91, -9.95), which exceeded the MCID in the manual therapy and home stretching plus CNS-focused approach group. Between-group comparison for PSFS, SPADI and VAS are shown in **FIGURE 2**.

In terms of shoulder ROM, a similar improvement was observed in both groups (no timepoint-by-group interaction, but significant main effect for timepoint) for active and passive shoulder flexion ($p<0.001$) and active and passive shoulder external rotation ($p<0.001$) (see within-group MD for each outcome in **TABLE 2**). Active shoulder flexion did not improve in the manual therapy and home stretching group after treatment compared to baseline (within-group MD=13.47; 95% CI: -

0.75, 27.69), whereas a significant improvement was observed in the manual therapy and home stretching plus CNS-focused approach (within-group MD=21.56; 95% CI: 6.89, 36.22). Significant improvement in active shoulder flexion was observed in the manual therapy and home stretching group between after treatment and at three months follow-up (within-group MD=11.65; 95% CI: 1.59, 21.69). Between-group comparison for shoulder ROM are shown in **FIGURE 3**.

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*Figure 1. CONSORT diagram showing participant flow through the study, from enrollment to allocation, follow-up and analysis.*

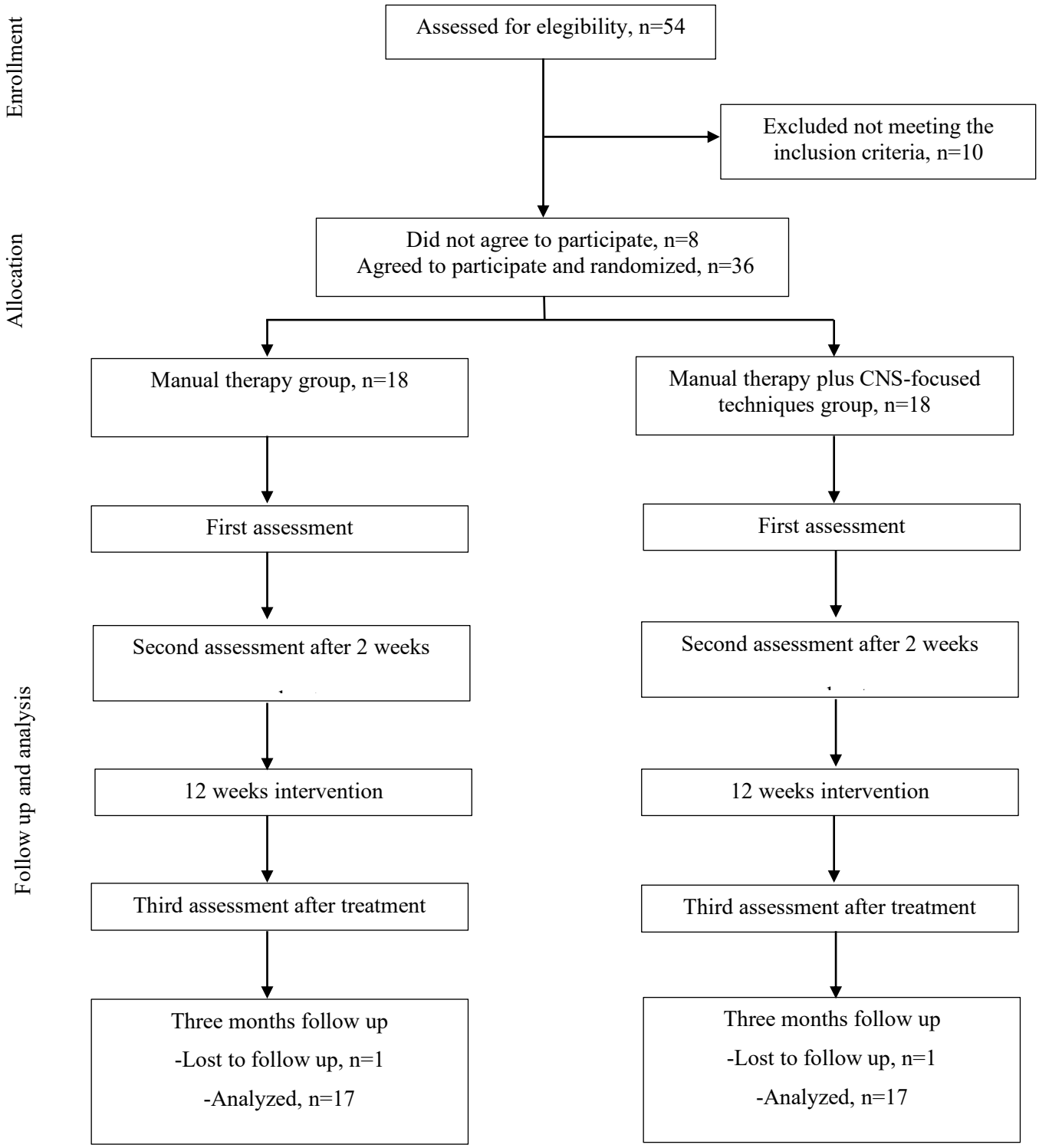


*Table 1. Demographic characteristics*

| | Manual Therapy (N=17) | Manual Therapy + CNS-focused approach (N=17) | Total (N=34) |
|---|---|---|---|
| **Gender** | | | |
| Female | 9 (52.9%) | 15 (88.2%) | 24 (70.6%) |
| Male | 8 (47.1%) | 2 (11.8%) | 10 (29.4%) |
| **Age (years)** | 53.4 (7.87) | 54.2 (7.48) | 53.8 (7.57) |
| **BMI** | 24.2 (3.31) | 23.1 (2.28) | 23.7 (2.85) |
| **Dominant side** | | | |
| Right-handed | 0 (0%) | 1 (5.9%) | 1 (2.9%) |
| Left-handed | 17 (100%) | 16 (94.1%) | 33 (97.1%) |
| **Painful side** | | | |
| Left side | 9 (52.9%) | 10 (58.8%) | 19 (55.9%) |
| Right side | 8 (47.1%) | 7 (41.2%) | 15 (44.1%) |
| **FS type** | | | |
| Primary adhesive capsulitis | 15 (88.2%) | 11 (64.7%) | 26 (76.5%) |
| Secondary adhesive capsulitis | 2 (11.8%) | 6 (35.3%) | 8 (23.5%) |
| **Symptoms duration (months)** | 9.82 (8.54) | 8.00 (5.41) | 8.91 (7.10) |
| **Diabetes** | | | |
| No | 14 (82.4%) | 16 (94.1%) | 30 (88.2%) |
| Yes | 3 (17.6%) | 1 (5.9%) | 4 (11.8%) |
| **Hypo/hyper thyroidism** | | | |
| No | 15 (88.2%) | 16 (94.1%) | 31 (91.2%) |
| Yes | 2 (11.8%) | 1 (5.9%) | 3 (8.8%) |

Data are mean ± standard deviation or frequency (proportion)

Abbreviations: BMI, body max index; FS, frozen shoulder

*Table 2. Results of each outcome for both groups and within- and between-group changes.*

| Outcome | Manual Therapy | Manual Therapy + CNS-focused approach | Between-group change score |
|---|---|---|---|
| **Active shoulder flexion (°)** | | | |
| Baseline | 112.6±5.9 | 103.1±6.1 | |
| After treatment | 126.1± 5.1 | 124.6±5.3 | 1.4 (-13.5, 16.4) |
| Within-group change I | 13.5 (-0.8, 27.7) | 21.6 (6.9, 36.2) | |
| Three months follow-up | 137.7±5.4 | 134.3±5.6 | 3.4 (-12.5, 19.3) |
| Within-group change II | 25.1 (12.2, 38.1) | 31.3 (17.9, 44.6) | |
| Within-group change III | 11.6 (1.6, 21.7) | 9.7 (-0.7, 20) | |
| **Passive shoulder flexion (°)** | | | |
| Baseline | 122.5±6.3 | 119±6.5 | |
| After treatment | 139.1±5.6 | 134.8±5.8 | 4.3 (-12.2, 20.8) |
| Within-group change I | 16.5 (3.9, 29.2) | 15.8 (2.7, 28.8) | |
| Three months follow-up | 147±5.7 | 145.4±5.8 | 1.6 (-15, 18.2) |
| Within-group change II | 24.5 (12.3, 36.6) | 26.4 (13.9, 39) | |
| Within-group change III | 7.9 (-2.3, 18.2) | 10.687 (0.2, 21.2) | |
| **Active shoulder external rotation (°)** | | | |
| Baseline | 10.1±2.9 | 13.1±2.9 | |
| After treatment | 23.4±4.3 | 26.5±4.3 | -3.1 (-15.4, 9.2) |
| Within-group change I | 13.3 (4.8, 21.9) | 13.4 (4.8, 21.9) | |
| Three months follow-up | 30.2±4.8 | 32.6±4.8 | -2.4 (-16.1, 11.4) |
| Within-group change II | 20.1 (10.3, 29.9) | 19.4 (9.6, 29.3) | |
| Within-group change III | 6.8 (-0.4, 14) | 6.1 (-1.2, 13.3) | |
| **Passive shoulder external rotation (°)** | | | |
| Baseline | 16.8±3.2 | 20.7±3.3 | |
| After treatment | 37.6±6.1 | 36.8±6.3 | 0.8 (-17, 18.6) |
| Within-group change I | 20.9 (8, 33.8) | 16.1 (2.8, 29.4) | |
| Three months follow-up | 42.1±5.1 | 40.8±5.3 | 1.3 (-13.6, 16.3) |
| Within-group change II | 25.3(14.1, 36.5) | 20.1 (8.5, 31.6) | |
| Within-group change III | 4.4 (-4.2, 13) | 3.9 (-4.9, 12.8) | |
| **SPADI (0-100)** | | | |
| Baseline | 57.6±4.4 | 61.2±4.5 | |
| After treatment | 29±5.3 | 33.8±5.5 | -4.8 (-20.4, 10.7) |
| Within-group change I | -28.6 (-41.2, -16) | -27.4(-40.4, -14.3) | |
| Three months follow-up | 22.1±4.8 | 22.9±4.9 | -0.8 (-14.7, 13.2) |
| Within-group change II | -35.5 (-47.6, -23.3) | -38.3 (-50.9, -25.8) | |
| Within-group change III | -6.9 (-17.9, 4.2) | -11 (-22.4, 0.4) | |
| **PSFS*** | | | |

| | | | |
|---|---|---|---|
| Baseline | 38.6±4 | 37.5±4.2 | |
| After treatment | 31.2±3.2 | 31.1±3.3 | 0.1 (-9.3, 9.5) |
| Within-group change I | -7.4 (-9.5, -5.1) | -6.1 (-8.8, -4) | |
| Three months follow-up | 30.4±2.6 | 33.3± 3 | -2.9 (-11.4, 5.5) |
| Within-group change II | -8.2 (-13.5, -2.9) | -11.1 (-9.6, 1.3) | |
| Within-group change III | -0.8 (-9.8, -5.1) | 5 (-1.3, 5.9) | |
| **VAS** | | | |
| Baseline | 41.6±5.5 | 49.3±5.6 | |
| After treatment | 23.1±5 | 15.6±5.2 | 7.4 (-7.3, 22.1) |
| Within-group change I | -18.6 (-34.9, -2.3) | -33.7 (-50.5, -16.9) | |
| Three months follow-up | 13.1±5.1 | 21.4±5.2 | -8.3 (-23.2, 6.5) |
| Within-group change II | -28.6 (-46, -11.1) | -27.9 (-45.9, -10) | |
| Within-group change III | -10 (-23.3, 3.3) | 5.7 (-8, 19.5) | |

Data are mean ± standard error or mean difference (95% confidence interval).

Abbreviations: SPADI, Shoulder Pain and Disability Index; PSFS, Patient Specific Functional Scale. Within-group change I (baseline – after treatment); Within-group change II (baseline – three months follow-up); Within-group change III (after treatment– three months follow-up)

* Total score is obtained by the sum of the activities scores divided by the number of activities (range 0-10)

*Figure 2. Between-group comparison for PSFS, SPADI and VAS throughout the study*

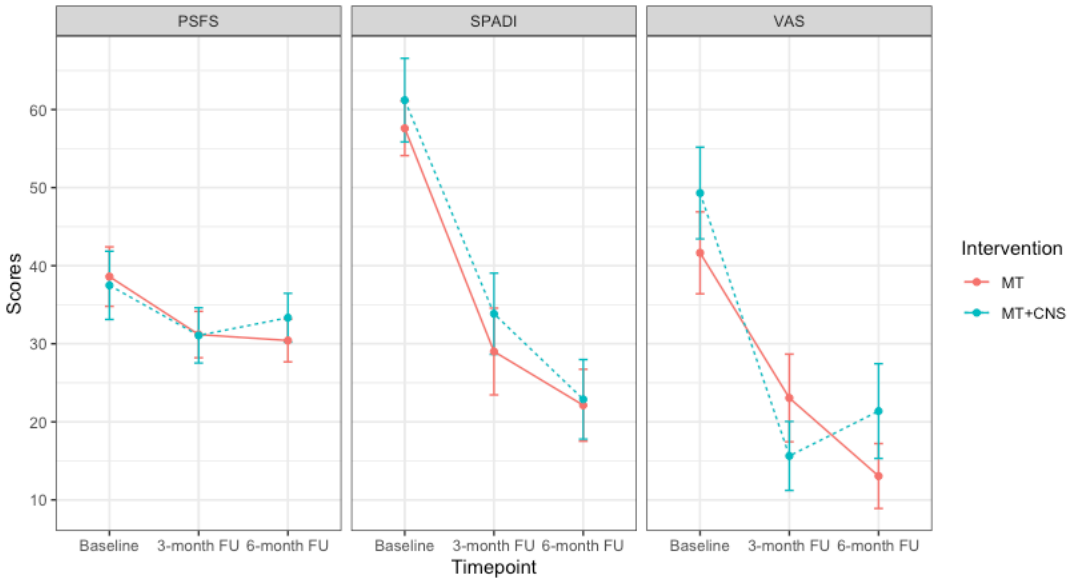
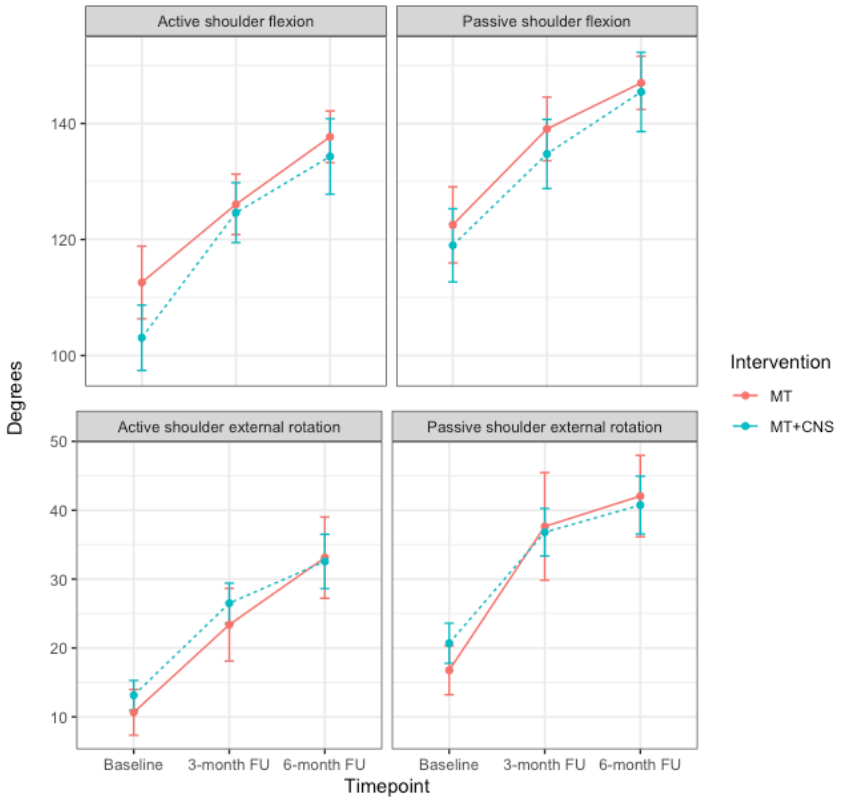



*Figure 3. Between-group comparison for shoulder range of motion throughout the study*



## 4. DISCUSSION

The aim of this study was to evaluate the additive effect of a CNS-focused approach to a manual therapy and home stretching program in people with FS. Overall, the results indicate that both interventions are equally effective in improving shoulder ROM and reducing shoulder pain and disability thus suggesting that a CNS-focused approach has no additional benefit to a more peripheral-focused treatment in people with FS.

In the last years, CNS-focused physiotherapy approaches have been successfully implemented, both in isolation or within a multimodal treatment, in people with several chronic musculoskeletal conditions [1,9,18]. Regarding shoulder pain, only a preliminary study and a case report had previously investigated the effect of CNS-focused interventions in FS [21,38]. The improvements we observed in shoulder pain and function in the group receiving the CNS-focused intervention group are in line with the aforementioned studies. For instance, Louw et al.[21] and Sawyer et al.[38] reported a mean improvement of 14.5°and 101° in active shoulder flexion, respectively, whereas a gain of 21.56° in active shoulder flexion after treatment was observed in our CNS-focused group. Similarly, improvements in the SPADI and in shoulder pain after treatment (27.36 and 33.68 points, respectively) observed in the group receiving the CNS-focused approach are comparable to those reported by Sawyer et al.[38] (22 points in SPADI) and by both Louw et al.[21] and Sawyer et al.[38] (0.48 and 7 points in a numerical rating pain scale).

The positive effects in shoulder pain and function reported in our study by the manual therapy and home stretching group are in accordance with those previously obtained in a case-series by this research group [8] and with current literature [29,30,32]. However, contrary to our hypothesis, both intervention groups showed comparable improvements in terms of shoulder pain, function, disability and ROM after treatment and three months follow-up, suggesting that a CNS-focused approach had no additional benefit to a more peripherally-targeted treatment in patients with FS. Several reasons might explain these results. Firstly, our participants were randomly assigned to one

of two intervention groups following a "one size fits all" approach without establishing their predominant pain mechanism at baseline. Recent evidence has shown that cortical representations were not present in people with shoulder pain with a primary nociceptive pain mechanism [5]. Most of our sample could have consisted of patients with a dominant nociceptive pain mechanism thus explaining why they did not show the expected benefit with an additional CNS-focused approach. Secondly, it cannot be discarded that the theoretically summative therapeutic effect of the combined peripheral and the CNS-focused interventions might have been annulated due to participants in this group perceiving a contradictory message between both treatments [9]. Additionally, better outcomes may have been obtained by adding other CNS-focused interventions different to those used in the current study (i.e. pain neuroscience education). Further, pain and functional limitations in people with FS are largely related to pathophysiological changes occurring at the peripheral tissue level (e.g. inflammation and subsequent capsular contracture) [16,36]. This may be the reason why CNS approaches such as GMI, sensory discrimination training or PNE would have not added any value to the manual therapy and exercise treatment, as no influence on the pathological changes reported in the joint capsule and related structures may be expected after implementing the aforementioned CNS interventions.

*Study limitations*

The present study has several limitations that need to be acknowledged. First, the lack of a control group without intervention prevents from establishing firm conclusions about the superiority of the two studied interventions over natural history. Second, as previously mentioned, no stratification of participants was done at baseline in terms of pain mechanisms so interventions were not individually tailored. Future studies could classify participants with FS at baseline in terms of predominant pain mechanisms [39,40] in order to establish more specific inclusion criteria before treatment.

## 5. CONCLUSION

A CNS-focused approach provided no additional benefit to a manual therapy and home stretching program in terms of shoulder pain and function in people with FS. Future studies should evaluate the effectiveness of CNS-interventions in people with FS with a predominant nociplastic pain mechanisms to assess their potential benefits.

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# SECCIÓN CUARTA

# DISCUSIÓN, CONCLUSIONES GENERALES Y LÍNEAS FUTURAS

# DISCUSIÓN

El dolor de hombro es una condición clínica con una alta prevalencia entre la población general (1). En concreto, el HC ha sido ampliamente estudiado ya que se caracteriza por la aparición de dolor intenso y déficits importantes en la movilidad del hombro (2). Sin embargo, hasta la fecha, su epidemiología, etiología y diagnóstico no se conocen en profundidad (3). Asimismo, se ha investigado sobre la efectividad de diversos enfoques terapéuticos tanto conservadores como invasivos sin que exista actualmente ninguna intervención que haya demostrado superioridad respecto al resto ni en relación a la propia historia natural de la patología (1,4). En base a esto, en los últimos años se ha profundizado en la investigación de los mecanismos centrales de dolor implicados en los sujetos que padecen dolor crónico musculoesquelético (incluido el dolor de hombro) así como en técnicas de tratamiento enfocadas al SNC dentro del abordaje de dichas patologías (5,6).

En esta tesis, se fijó como objetivo general estudiar la efectividad de un programa de tratamiento que incluyera un enfoque terapéutico centrado en el SNC en pacientes con HC, y, como objetivos secundarios, estudiar la implicación de los mecanismos centrales de dolor en esta patología. Por este motivo se realizaron 4 estudios dentro de esta investigación, con el fin de dar respuesta a las hipótesis planteadas y analizar en profundidad aspectos relevantes para la consecución de los objetivos de esta tesis.

El primer estudio, investigó la posible alteración en los mapas corticales y en el esquema corporal en pacientes con HC mediante la valoración del TPDT y el reconocimiento de la lateralidad en el hombro afecto en comparación con el no afecto y respecto a sujetos sanos emparejados en edad y sexo.

El segundo estudio, tuvo como objetivo estudiar la factibilidad de aplicar un enfoque terapéutico centrado en el SNC en sujetos con HC partiendo de la hipótesis de que dicho enfoque podría dar

lugar a resultados satisfactorios en términos de adherencia al tratamiento y mejoría del dolor, la función y diferentes aspectos psicosociales.

En el tercer estudio, se presentó el protocolo de un ECA que comparase la efectividad de un programa de tratamiento basado en terapia manual y estiramientos domiciliarios junto con técnicas orientadas al SNC, frente a un programa basado únicamente en terapia manual y estiramientos domiciliarios en pacientes con HC.

Por último, el cuarto estudio consistió en la realización de un ECA que buscó estudiar los efectos añadidos de incluir técnicas orientadas al SNC a un programa de terapia manual y estiramientos domiciliarios en sujetos con HC y valorar si la combinación de estas técnicas presentaba resultados superiores en cuanto a discapacidad, ROM y dolor.

En este capítulo final, se va a dar respuesta a las hipótesis planteadas, se van a discutir los principales hallazgos y conclusiones de los estudios incluidos en la tesis y, por último, se van a plantear futuras líneas de investigación.

## 1. PRINCIPALES CONCLUSIONES Y DISCUSIÓN DE LAS HIPÓTESIS

### 1.1. Estudio 1:

En base a los estudios existentes, se ha demostrado que los pacientes con HC pueden presentar una reorganización cortical de la corteza somatosensorial primaria así como alteraciones del esquema corporal como consecuencia de la larga duración de la actividad nociceptiva, sobre todo en las primeras etapas de la patología (7,8). Sin embargo, la literatura al respecto es muy escasa. En concreto, sólo dos estudios han analizado de forma indirecta la existencia de estos cambios cerebrales, observando una respuesta positiva de los sujetos con HC a intervenciones dirigidas a dichas alteraciones centrales (9,10). Cabe destacar que el *gold estándar* diagnóstico para determinar la presencia de cambios estructurales y funcionales en el SNC en pacientes con dolor musculoesquelético crónico son las técnicas de neuroimagen. Ninguno de los estudios citados (9,10) han medido de forma directa qué cambios se producen a nivel del cerebro como consecuencia del

HC ni si dichos cambios son reversibles con la implementación de estrategias de tratamiento dirigidas al SNC. Por consiguiente, el objetivo principal de este primer estudio fue conocer si las personas con HC presentaban una evidencia indirecta de una reorganización cortical y una alteración del esquema corporal. Para ello se valoró el TPDT para evaluar la agudeza táctil y una tarea de reconocimiento de la lateralidad. Estas medidas se compararon entre el hombro afecto y el no afecto en el grupo de HC y con el hombro del miembro superior dominante de un grupo de control sano emparejado en sexo y edad. Además, como objetivo secundario de este estudio, se investigaron también las posibles asociaciones existentes entre el TPDT y el reconocimiento de la lateralidad y determinados aspectos clínicos como la gravedad y la duración de los síntomas en sujetos con HC. Los resultados de este primer estudio mostraron que el TPDT del hombro afecto está alterado en sujetos con HC en comparación con el hombro no afecto y sujetos controles sanos. Además, en comparación con el hombro no afecto, los participantes con HC mostraron una menor precisión y un mayor tiempo de reacción en la tarea de reconocimiento de la lateralidad en el hombro afecto. Por otro lado, ni la intensidad del dolor ni la duración de los síntomas se correlacionaron con el TPDT o el reconocimiento de la lateralidad. Los datos obtenidos en cuanto al TPDT, están en la línea de los obtenidos por Heerkens *et al.* (11) en el brazo afecto de pacientes con dolor crónico inespecífico de hombro. Asimismo, coinciden con otros estudios que han reportado disminución del TPDT en diversos cuadros de dolor musculoesquelético crónico (p. ej., osteoartritis, síndrome doloroso regional complejo o dolor lumbar crónico) en comparación con sujetos controles (12). Además, el TPDT entre el lado afecto y el no afecto de los sujetos con HC también se encontró disminuida en estudios previos realizados en personas con dolor crónico, como por Ejemplo, Pacientes afectos de síndrome doloroso regional complejo (12). Sin embargo, hay que ser cautelosos a la hora de interpretar estos resultados, dado que no existe un valor de corte normativo del TPDT que permita determinar la existencia de una alteración en dicha variable. En este sentido, Botnmark *et al.* (13), usando el mismo protocolo empleado en este primer estudio, reportaron una diferencia de medias (SD) para el TPDT de 5.5 (13,5) mm entre el hombro dominante y el no dominante de

sujetos sin dolor. La diferencia en el TPDT reportado en el presente estudio al comparar el hombro afecto y no afecto de sujetos con HC fue de 3.82 mm, inferior por tanto al valor del estudio de Botnmark *et al.* (13). Por tanto, aunque la diferencia del TPDT resultó ser estadísticamente significativa en nuestro estudio, se podría argumentar que esta diferencia podría no ser clínicamente relevante. De hecho, el valor medio del TPDT que se obtuvo en el presente estudio para el hombro afecto en el grupo de HC fue de 41.71 mm, el cual se encuentra muy cercano al valor "normal" reportado en sujetos sanos (44.8 mm) (13). A pesar de que también se encontró un TPDT más alto en el hombro afecto de sujetos con HC en comparación con controles sanos, el valor del TPDT obtenido en el hombro doloroso de los sujetos con HC fue similar al obtenido en los sujetos controles sanos. Esta contradicción en los resultados obtenidos en el TPDT está en la misma línea de lo que refleja la literatura científica, que ha puesto de manifiesto la gran variabilidad tanto intra como inter-sujetos que existe en la medida del TPDT. De hecho, algunos autores han llegado a sugerir que el TPDT no debería usarse como una medida objetiva de la agudeza táctil (14). Esta variabilidad en los resultados entre los diferentes estudios respecto a la variable TPDT, pone de manifiesto la necesidad de realizar estudios que estimen el error estándar de medición del TPDT o la DMCI de dicha variable en la región del hombro, de forma similar a como ya se ha hecho en la región lumbar (15). De esta forma, se podría determinar la diferencia en el valor del TPDT que puede considerarse clínicamente relevante en sujetos con dolor de hombro y que no es debida a errores en la propia medición.

Por otro lado, en nuestro estudio se encontró que los participantes con HC tenían una menor precisión y un mayor tiempo de respuesta en una tarea de reconocimiento de la lateralidad en el hombro afecto en comparación con el no afecto. En cambio, Heerkens *et al.* (11) reportaron tiempos de reacción más rápidos en el lado afecto en sujetos con dolor crónico inespecífico de hombro. Sin embargo, otros estudios han encontrado una menor precisión y un mayor tiempo de respuesta en la zona afectada en sujetos con diferentes cuadros de dolor crónico (16,17). Además, una revisión sistemática reciente concluyó que los pacientes con dolor musculoesquelético crónico en el miembro

superior son más lentos y menos precisos a la hora de reconocer imágenes de la parte del cuerpo que les duele y para discriminar entre las imágenes izquierda y derecha en comparación con sujetos controles sanos (16). No obstante, se debe tener en cuenta la heterogeneidad de los estudios incluidos en dicha revisión. Se cree que los tiempos de respuesta anormalmente largos en el reconocimiento de la lateralidad reflejan un procesamiento alterado de la representación espacial y corporal. Por todo esto, es difícil interpretar nuestros resultados y establecer conclusiones firmes sobre el posible papel de la alteración del esquema corporal en personas con HC. Los valores medios para la precisión y el tiempo de respuesta en sujetos sanos descritos en la literatura usando la misma tarea de reconocimiento de la lateralidad que se empleó en nuestro estudio son de 93.5 (9,2) % y 1.7 (0,7) s, respectivamente (18). En nuestro estudio, la precisión en el reconocimiento de la lateralidad fue menor con respecto a los valores normativos descritos. Sin embargo, la diferencia observada en la precisión y el tiempo de respuesta entre el hombro afecto y el no afecto de los participantes con HC es probablemente demasiado pequeña para considerarse clínicamente relevante.

Por otro lado, en el presente estudio no se encontró ninguna correlación entre las alteraciones del TPDT o el reconocimiento de la lateralidad y la intensidad percibida del dolor o la duración de los síntomas. Dichos hallazgos se corresponden, en líneas generales, con los reportados por la literatura en sujetos con dolor crónico (12). Estudios recientes han evaluado los cambios en la agudeza táctil en respuesta a la inducción de dolor agudo. Por ejemplo, en el estudio de Adamczyk *et al.* (19), el TPDT disminuyó inmediatamente después de inducir de forma experimental dolor lumbar. Sin embargo, en otro estudio similar de los mismos autores, la inducción experimental de dolor cervical no provocó cambios en el TPDT (20). Por tanto, es necesario investigar este aspecto en mayor profundidad para establecer conclusiones firmes respecto a la influencia de la intensidad y duración del dolor en la agudeza táctil. Además, debería estudiarse también la posible asociación entre el TPDT, la integridad del esquema corporal, la propiocepción del hombro y el rendimiento físico en sujetos con HC.

Un aspecto a destacar de nuestro estudio es el emparejamiento en edad y sexo de los sujetos experimentales con controles sanos ya que, aunque la relación entre estas variables y el TPDT y el reconocimiento de la lateralidad no está del todo clara, la literatura científica recomienda llevar a cabo comparativas entre sujetos con dolor crónico y controles sanos (12,17).

Como limitaciones de este estudio, cabe destacar que las desviaciones del reconocimiento de la lateralidad y el TPDT respecto a los valores normativos, pueden indicar cambios en el homúnculo somatosensorial pero también pueden deberse a otros factores como una percepción táctil alterada, un procesamiento lento o dificultad con la coordinación, la atención o el proceso de toma de decisiones (12,17). Sin embargo, el diseño de nuestro estudio no permitió determinar cómo estos factores podrían haber influido en los resultados obtenidos.

Otra posible limitación a considerar es que nuestro estudio valoró el reconocimiento de la lateralidad mediante una aplicación en un teléfono móvil y en la mayoría de los estudios se ha hecho con la ayuda de un ordenador (17). Además, el protocolo de nuestro estudio sólo incluyó un bloque de prueba de 30 imágenes antes de la valoración formal de la lateralidad, mientras que lo recomendado por la literatura son aproximadamente 80 imágenes (21). Por tanto, futuras investigaciones deberían establecer protocolos estandarizados para la valoración del reconocimiento de lateralidad y la agudeza táctil en sujetos con dolor crónico. En el presente estudio no se evaluaron las variables investigadas en otras zonas del cuerpo para establecer una comparativa ni se registró si los pacientes presentaban dolor en el momento de la evaluación, lo cual podría haber influido tanto en el TPDT como en el reconocimiento de la lateralidad. Otro posible factor que no fue considerado en nuestro estudio fue la influencia de la edad, ya que la agudeza táctil disminuye con el aumento de la misma (22).

Por último, los investigadores que evaluaron a los sujetos con HC estuvieron cegados respecto al hombro que estaba afecto, pero el grupo control fue evaluado únicamente en el lado dominante. Para minimizar este sesgo, un evaluador se encargó de valorar a los sujetos con HC y otro realizó las

mediciones de los sujetos de control. Sin embargo, este hecho pudo haber introducido algún error adicional en las mediciones.

### 1.2. Estudio 2:

El objetivo de este estudio fue evaluar la factibilidad y el impacto clínico sobre el dolor y la función del hombro de un programa de tratamiento centrado en el SNC en sujetos con HC.

En general, no se encontraron cambios significativos después de un período de "lavado", lo que aseguró que no se produjeran cambios importantes en la condición clínica de los participantes antes de empezar con el tratamiento. Los resultados revelaron una adherencia de los participantes de un 70% al tratamiento centrado en el SNC y las medidas de seguimiento. En cuanto al impacto clínico, se observaron mejorías en el dolor y la flexión activa del hombro después del tratamiento y a los tres meses de seguimiento y en la discapacidad a los tres meses de seguimiento. Sin embargo, no se observaron cambios significativos en el TPDT, el reconocimiento de la lateralidad, el catastrofismo, la conducta miedo-evitación o la SC después del tratamiento o durante el seguimiento.

En primer lugar, la adherencia al tratamiento de los participantes fue menor de lo esperado a pesar de que se intentó reforzar este aspecto proporcionando un diario para el registro de las sesiones domiciliarias (23). No obstante, todos los participantes que asistieron a la totalidad de las sesiones de tratamiento en la clínica cumplieron también con la dosis de entrenamiento domiciliario. Los abandonos se debieron principalmente a la falta de apoyo de los familiares para ayudar a los participantes con sus tareas de entrenamiento en casa. En este sentido, estudios previos también han puesto de manifiesto las dificultades que existen a la hora de implementar técnicas centradas en el SNC a nivel domiciliario debido a la falta de disponibilidad de un asistente o la falta de tiempo de los participantes (24,25). En consecuencia, cabe destacar la importancia de contar con un ambiente socio-familiar cooperativo que permita mejorar la adherencia en este tipo de enfoques terapéuticos.

En cuanto a la adherencia a las mediciones, sólo dos participantes no acudieron a las sesiones de valoración de seguimiento puesto que decidieron suspender las sesiones clínicas por dificultades en

la conciliación de sus horarios de trabajo o por falta de ayuda con las tareas de entrenamiento domiciliario.

En segundo lugar, en cuanto a los resultados clínicos, se obtuvieron mejorías en el nivel de dolor y la función del hombro tras el tratamiento, lo cual coincide con los resultados reportados por el estudio de Sawyer *et al.* (10), que aplicaron un protocolo similar al de este estudio a un único sujeto con HC. Concretamente, en nuestro estudio, los pacientes presentaron mejoría en el dolor y la flexión activa del hombro tanto después del tratamiento como en las mediciones de seguimiento y en el nivel de discapacidad (SPADI) en el seguimiento a los tres meses. Estos cambios en el SPADI superaron tanto el MCD como la DMCI establecidos para el HC y dolor de hombro inespecífico, respectivamente (26,27). Asimismo, los cambios en la intensidad del dolor y en la flexión activa del hombro después del tratamiento y en el seguimiento superaron también la DMCI establecida para la intensidad del dolor (1.1 puntos) y el MCD para la flexión activa del hombro (11°) en sujetos con dolor de hombro, respectivamente (28,29).

Por otro lado, no se encontraron cambios significativos para el reconocimiento de la lateralidad y el TPDT ni después del tratamiento ni durante el seguimiento. La contrastación e interpretación de estos resultados es compleja ya que, en la actualidad, la capacidad de respuesta al tratamiento de estas dos variables en sujetos con HC ha sido apenas investigada en dos estudios. En un reporte de un caso (30), se obtuvo una reducción de 10 mm en el TPDT y una mejoría de la precisión y el tiempo de respuesta en la tarea del reconocimiento de la lateralidad tras la intervención. Asimismo, en una serie de casos (31) se investigó la eficacia de un tratamiento que combinó GMI con terapia en espejo en cinco pacientes con diferentes patologías que cursaban con dolor de hombro, incluido un paciente con HC. Tras el tratamiento, todos los pacientes mostraron mejorías significativas en la intensidad del dolor, la flexión activa del hombro y la capacidad de visualización motora, pero no se encontraron cambios significativos en el reconocimiento de la lateralidad. En el presente estudio tampoco se encontraron cambios significativos en la conducta de miedo-evitación o el catastrofismo después del tratamiento. En este sentido, la educación en neurociencia del dolor ha demostrado

efectos clínicamente relevantes en la reducción de factores psicosociales como la kinesiofobia y el catastrofismo (32). Sin embargo, en nuestro estudio solo se implementó una breve discusión sobre el dolor desde la perspectiva de la neurociencia del dolor, lo cual puede justificar que no se obtuvieran cambios significativos en las variables psicosociales. Sería recomendable, por tanto, que investigaciones futuras estudiaran el papel de la educación en neurociencia del dolor en el HC como ya se ha sugerido en algún estudio reciente (33).

Otro factor a tener en cuenta es la heterogeneidad en la duración de los síntomas que presentó la muestra de nuestro estudio (2 a 24 meses), aspecto que pudo haber influido en los resultados obtenidos al encontrarse los participantes en diferentes etapas del HC.

Los sujetos con HC suelen mostrar mejores resultados tras el tratamiento en las primeras fases del desarrollo de la patología, especialmente durante el primer año (34). Este aspecto no estuvo contemplado en el diseño de nuestro estudio, sin embargo, futuras investigaciones deberían estar orientadas a determinar en qué etapa(s) de la historia natural del HC (en el caso de que haya alguna) podría ser más efectiva la implementación del enfoque terapéutico centrado en el SNC.

Como ya se ha citado con anterioridad, únicamente existe un estudio de un caso de Sawyer *et al.* (30) dónde se aplicó un tratamiento centrado en el SNC específicamente para sujetos con HC, el cual no incluyó sesiones de entrenamiento domiciliario. En este sentido, cabe resaltar que nuestro estudio sí que empleó tratamiento domiciliario para poder investigar adecuadamente la viabilidad de aplicar este tipo de enfoque terapéutico en la práctica clínica. De hecho, algunos autores indican que los pacientes con patologías musculoesqueléticas de hombro, incluido HC, probablemente obtienen mayores mejorías en el dolor y la función si además del tratamiento de fisioterapia en clínica realizan ejercicios domiciliarios (35,36).

Por otro lado, para poder interpretar adecuadamente los resultados del presente estudio, cabe tener en cuenta también sus limitaciones. Por ejemplo, aunque se obtuvieron mejorías significativas en el dolor, la discapacidad y el ROM, la muestra tan solo estuvo formada por 10 participantes y no hubo un grupo control sin intervención. Por tanto, no podemos asegurar que los cambios obtenidos tras

el tratamiento no fueran debidos por ejemplo a la historia natural de la patología. En futuros estudios sería recomendable aplicar este tipo de tratamiento a una muestra mayor de participantes y comparar los resultados con un grupo control sin tratamiento.

Otra limitación de nuestro estudio es la heterogeneidad en la intensidad del dolor y la duración de los síntomas de los participantes, lo cual impide llevar a cabo una generalización de los resultados. Además, aunque a los participantes se les permitió continuar con su medicación, no se hizo un registro de posibles tratamientos concomitantes, incluida la toma de medicación específica. Por tanto, no se puede determinar si este hecho podría haber influido en los resultados obtenidos.

### 1.3. Estudio 3:

Como ya se ha comentado anteriormente en otros apartados, en la actualidad no existe evidencia de que exista un "mejor" enfoque de tratamiento para el HC (37). Los datos aportados por el estudio 2 de esta tesis doctoral y la literatura existente al respecto, sugieren que los tratamientos dirigidos al SNC podrían ser una opción válida y factible para los pacientes con HC. Como consecuencia, el objetivo del estudio 3 fue definir un protocolo de tratamiento que combinara la aplicación de técnicas orientadas al SNC con un programa de terapia manual y estiramientos domiciliarios. La efectividad de dicho programa se compararía posteriormente con un programa de terapia manual y estiramientos domiciliarios aplicado de forma aislada en sujetos con HC (estudio 4 de esta tesis doctoral).

Al tratarse este estudio de un protocolo, no podemos establecer discusión al respecto, pero sí que destacaremos en este apartado las fortalezas y justificación del mismo en el contexto de esta tesis doctoral. Este protocolo se describió siguiendo la lista de verificación para el diseño de ECAs "*Standard Protocol Items"*, SPIRIT (38) y nos permitió describir los objetivos, diseño, metodología, consideraciones estadísticas y aspectos relacionados con la organización del ECA. Por último, cabe destacar que el diseño y publicación de protocolos proporciona la base y justificación para la

posterior realización de estudios clínicos así como el planteamiento de las preguntas de investigación específicas (39).

### 1.4. Estudio 4:

Tras la realización del estudio de factibilidad de un enfoque terapéutico centrado en el SNC y la elaboración del protocolo para llevar a cabo un ECA, se realizó dicho ensayo, que constituye el cuarto estudio de esta tesis doctoral. Su objetivo fue evaluar los efectos añadidos de un enfoque centrado en el SNC a un programa de terapia manual y estiramientos domiciliarios en sujetos con HC. En general, ambos grupos de intervención (terapia manual y estiramientos domiciliarios + tratamiento dirigido al SNC vs terapia manual y estiramientos domiciliarios) mostraron resultados similares sobre la mejoría del ROM del hombro, la reducción del dolor y la discapacidad, lo que sugiere que el enfoque centrado en el SNC no presenta beneficios adicionales a un tratamiento de terapia manual con estiramientos domiciliarios en sujetos con HC.

En los últimos años, se han implementado con éxito enfoques de fisioterapia centrados en el SNC, tanto de forma aislada como dentro de un tratamiento multimodal en sujetos con diferentes cuadros de dolor musculoesquelético crónico (40–42). Sin embargo, sólo un estudio preliminar y un informe de un caso habían investigado previamente el efecto de dichas intervenciones en sujetos con dolor de hombro, incluido el HC (9,30). Los resultados obtenidos en nuestro estudio respecto a las mejorías en el dolor y la función del hombro del grupo que recibió la intervención centrada en el SNC están en la misma línea de los estudios mencionados anteriormente. De hecho, en nuestro estudio observamos una ganancia de 21.56° en la flexión activa del hombro después del tratamiento centrado en el SNC, mientras que Louw *et al.* (9) y Sawyer *et al.* (30) reportaron unos cambios de 14.5° y 101° en la flexión activa del hombro, respectivamente. Del mismo modo, el grupo que recibió el enfoque centrado en el SNC mostró mejorías en el SPADI y el dolor de hombro después del tratamiento (27.36 y 33.68 puntos, respectivamente). Estos cambios fueron similares a los

reportados por Sawyer *et al.* (30) (22 puntos en SPADI) y por Louw *et al.* (9) y Sawyer *et al.* (30) (0.48 y 7 puntos) en una escala numérica del dolor.

Por otro lado, como se ha comentado previamente, el grupo que recibió únicamente el tratamiento de terapia manual y estiramientos domiciliarios también mostró mejorías en el dolor y la función del hombro. Estos resultados contrastan con los obtenidos previamente por este grupo de investigación en un estudio de casos (43) así como con los reportados por otros autores (44–46). No obstante, contrariamente a nuestra hipótesis, ambos grupos de intervención mostraron mejorías similares en el dolor de hombro, función, discapacidad y ROM después del tratamiento y a los tres meses de seguimiento, lo que sugiere que el enfoque centrado en el SNC no tuvo ningún beneficio adicional en los sujetos con HC.

Estos resultados podrían deberse a diferentes motivos. En primer lugar, los participantes del estudio fueron asignados aleatoriamente a uno de los dos grupos de intervención sin tener en cuenta cual era el mecanismo de dolor dominante de cada sujeto. Hasta dónde llega nuestro conocimiento, no existen estudios que hayan evaluado la prevalencia de los tres tipos de dolor (nociceptivo, neuropático, nociplástico) en grupos de población con dolor de hombro. Estudios recientes han mostrado que en sujetos con dolor de hombro el dolor nociplástico no suele ser el mecanismo de dolor dominante (47), pero no sabemos si estas conclusiones son extrapolables de forma específica a sujetos con HC. Es posible que la mayor parte de la muestra de nuestro estudio presentara un dolor de tipo nociceptivo dominante, lo que explicaría por qué no se obtuvieron beneficios adicionales con el enfoque centrado en el SNC.

En segundo lugar, no se puede descartar que el posible efecto sumativo de ambas intervenciones (terapia manual + estiramientos junto con el enfoque centrado en el SNC) se hubiera anulado debido a que los participantes de ese grupo hubieran percibido un mensaje contradictorio al recibir ambos tratamientos (41). De hecho, una de las principales dificultades que se puede encontrar el clínico al aplicar de forma simultánea técnicas de "*hands on*" y de "*hands off*" es precisamente transmitir al paciente un mensaje congruente y no contradictorio (48). Futuros estudios podrían evaluar la

posibilidad de agregar otras intervenciones centradas en el SNC diferentes a las utilizadas en el estudio actual (p. ej., educación en neurociencia del dolor), para ver si se obtienen mejores resultados.

Por otra parte, aunque algunos estudios han respaldado la importancia del papel que desempeñan los mecanismos centrales en el dolor de hombro (6,49), otros autores lo han cuestionado (47) y, concretamente en sujetos con HC, la contribución del SNC sigue siendo especulativa a día de hoy. Por último, el dolor y las limitaciones funcionales de los sujetos con HC están relacionados en gran medida con los cambios fisiopatológicos que se producen a nivel tisular (p. ej., inflamación y contractura de la cápsula) (3,49). Este podría ser otro motivo por el cual el enfoque centrado en el SNC no mostró ningún valor añadido a la terapia manual y los ejercicios de estiramiento domiciliario.

Como limitaciones de este estudio, cabe destacar la falta de un grupo control sin intervención que permitiera establecer conclusiones firmes sobre la superioridad de las dos intervenciones estudiadas respecto a la historia natural de la patología. En segundo lugar, como ya se ha mencionado anteriormente, no se estratificó a los participantes al inicio del estudio según su mecanismo de dolor dominante. Futuros estudios deberían clasificar a los participantes al inicio del estudio en función del mecanismo de dolor dominante (50,51) con el fin de establecer criterios de inclusión más específicos.

## 2. CONCLUSIÓN GENERAL

Con el presente trabajo de investigación se ha profundizado en el conocimiento sobre la etiopatogenia, mecanismos de dolor y tratamiento del HC.

El objetivo principal fue estudiar el valor añadido de aplicar técnicas de tratamiento enfocadas al SNC en pacientes con HC. Asimismo, esta tesis doctoral estudió la efectividad de implementar protocolos estandarizados de tratamiento y la aplicación de herramientas terapéuticas personalizadas con el fin de obtener mejores resultados en términos de funcionalidad, dolor y diferentes aspectos psicosociales presentes en esta patología de hombro.

## 3. CONCLUSIONES ESPECÍFICAS

### Estudio 1

1. Los participantes con HC mostraron una agudeza táctil reducida en el hombro afecto en comparación con el hombro sano y con sujetos controles sanos emparejados por edad y sexo.
2. En comparación con el hombro sano, se encontró una menor precisión y un mayor tiempo de respuesta en las tareas de reconocimiento de la lateralidad en el hombro afecto de los sujetos con HC.
3. Las implicaciones clínicas de los resultados anteriores se desconocen, por lo que dichos hallazgos deben interpretarse con cautela.

### Estudio 2

1. Los resultados de este estudio de factibilidad sugieren que un programa de tratamiento centrado en el SNC podría ser un enfoque adecuado para mejorar el dolor y la función en sujetos con HC.
2. Aunque un alto porcentaje de la muestra completó todo el programa de tratamiento y valoraciones, se detectaron aspectos importantes respecto a la adherencia como la necesidad de apoyo socio-familiar del paciente para la realización de las tareas de entrenamiento en el hogar.
3. Con el fin de establecer conclusiones firmes sobre la utilidad de un enfoque terapéutico centrado en el SNC en sujetos con HC, se requiere seguir investigando su aplicación con mayores tamaños muestrales.

### Estudio 3

1. Se ha definido un protocolo para realización de un ECA con el fin de estudiar el efecto añadido a un programa de terapia manual y estiramientos domiciliarios de un enfoque de tratamiento orientado al SNC sobre el dolor y la función en pacientes con HC.

**Estudio 4**

1. Un enfoque terapéutico centrado en el SNC no proporcionó beneficios adicionales a un programa de terapia manual y estiramientos domiciliarios en términos de dolor y función en sujetos con HC.
2. Futuras líneas de investigación deberían evaluar la efectividad de las intervenciones orientadas al SNC en sujetos con HC con un mecanismo de dolor nociplástico dominante para evaluar sus beneficios potenciales.
3. Futuros estudios deberían incluir también un grupo control sin tratamiento para determinar si las mejorías obtenidas con el tratamiento son superiores a la historia natural de la patología.

## 4. LÍNEAS PRESENTES Y FUTURAS

En base a este proyecto y sus resultados, nuestro grupo de investigación ha seguido estudiando el efecto añadido de implementar estrategias terapéuticas orientadas al SNC en pacientes con HC. En este sentido, esperamos poder publicar próximamente los resultados de un análisis secundario de los datos del ECA, concretamente para ver el impacto del enfoque terapéutico dirigido al SNC sobre los aspectos psicosociales en pacientes con HC.

Asimismo y ante los resultados y conclusiones extraídos del presente trabajo, se plantea como línea futura de investigación la estratificación de los pacientes de HC en función de su mecanismo de dolor dominante y la inclusión de un grupo control sin tratamiento. De este modo, se podría determinar si los efectos de un enfoque centrado en el SNC son dependientes del tipo de dolor del paciente y si dicho enfoque es superior o no a la propia evolución natural de la patología.

Finalmente, sería interesante investigar los posibles cambios estructurales y funcionales en el SNC en pacientes con HC a través de técnicas de neuroimagen. De hecho, hasta donde alcanza nuestro conocimiento, en la literatura actual no existen estudios que hayan medido de forma directa los cambios que se producen a nivel central como consecuencia del HC ni la influencia sobre dichos cambios de la implementación de estrategias de tratamiento dirigidas al SNC.

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# ANEXOS

# Anexo I: Aprobación comité de ética

VNIVERSITAT DE VALÈNCIA Vicerectorat d'Investigació i Política Científica

D. Francesc Francés Bozal, Profesor Contratado Doctor del Departamentode Medicina Preventiva y Salud Publica, Ciencias de la Alimentación, Toxicología y Medicina Legal, y Secretario, del Comité Ético de Investigación en Humanos de la Comisión de Ética en Investigación Experimental de la Universitat de Valencia,

CERTIFICA:

Que el Comité Ético de Investigación en Humanos, en la reunión celebrada el día 1 de Junio de 2017, una vez estudiado el proyecto de investigación titulado: *"Tratamiento enfocado al sistema nervioso central para personas con hombro congelado: un ensayo clínico aleatorizado ", número de procedimiento H1532330957968,* cuyo responsable es D. Enrique Lluch Girbés, ha acordado informar favorablemente el mismo dado que se respetan los principios fundamentales establecidos en la Declaración de Helsinki, en el Convenio del Consejo de Europa relativo a los derechos humanos y cumple los requisitos establecidos en la legislación española en el ámbito de la investigación biomédica, la protecci6n de datos de carácter personal y la bioética.

Y para que conste, se firma el presente certificado en Valencia, a uno dejunio de dos mil diecisiete.

# Anexo II: Consentimiento informado

## 1. IDENTIFICACIÓN Y DESCRIPCIÓN DEL PROCEDIMIENTO

Se solicita su autorización para utilizar los datos clínicos y de la evolución del tratamiento que se le aplicará para la capsulitis adhesiva de hombro y que se hallan recogidos en su historia clínica para el trabajo de investigación: "Tratamiento enfocado al sistema nervioso central para personas con hombro congelado: Protocolo para un ensayo clínico aleatorizado"**,** cuya finalidad es evaluar la efectividad de un programa de tratamiento dirigido al sistema nervioso central frente a un programa de tratamiento estándar de fisioterapia en pacientes con capsulitis adhesiva.

## 2. OBJETIVO

Los resultados de este proyecto de investigación pueden contribuir a la mejora en el diagnóstico y tratamiento de la capsulitis adhesiva. Los datos de su historia clínica serán custodiados en los términos previstos en la Ley 14/2007, de 3 de julio, y en el Real Decreto 1716/2011, de 18 de noviembre.

## 3. BENEFICIOS ESPERADOS

No percibirá ninguna compensación económica o de otro tipo por participar en esta investigación. Sin embargo, si las investigaciones que se pudieran realizar tuvieran éxito, podrían ayudar en el futuro a pacientes que tienen la misma patología que usted. La información no será vendida o distribuida a terceros con fines comerciales.

## 4. CONSECUENCIAS PREVISIBLES DE SU NO PARTICIPACIÓN Y DERECHO DE REVOCACIÓN DEL CONSENTIMIENTO

La participación en este proyecto de investigación es voluntaria y puede cancelarse en cualquier momento. Si rechaza participar, no habrá consecuencias negativas para usted. Si se retira del proyecto, puede decidir si los datos utilizados hasta ese momento, deben borrarse o si se pueden seguir utilizando siendo totalmente anónimos.

## 5. PROTECCIÓN DE DATOS PERSONALES Y CONFIDENCIALIDAD

La gestión y distribución de los datos personales, cuestionarios, escalas, consentimientos informados e imágenes será llevada a cabo por el investigador principal, el cual asignará un código a cada sujeto y custodiará la ficha personal de cada uno de los participantes en un documento separado de los datos del estudio para asegurar la confidencialidad de éstos.
La relación entre el código asignado y el documento que contiene los datos personales de los sujetos, permanecerán en todo momento bajo la protección del investigador principal. Ningún dato personal será transferido por cualquier medio a terceros.
Todo ello de acuerdo con lo estipulado en la Ley Orgánica 15/1999 de Protección de datos de Carácter Personal, de 13 de diciembre (LOPD). El titular de los datos personales podrá ejercitar los derechos de acceso, rectificación, cancelación y oposición al tratamiento de datos de carácter personal, y de revocación del consentimiento, en los términos previstos en la normativa aplicable.

## 6. INFORMACIÓN DE CONTACTO

Si tienen alguna pregunta sobre este proyecto de investigación, puede consultar en cualquier momento al investigador: Enrique Lluch Girbés.

Si decide participar en este estudio, rellene y firme el formulario de consentimiento que aparece a continuación.

## DECLARACIÓN DE CONSENTIMIENTO *EJEMPLAR PARA EL PACIENTE*

## 9. DECLARACIÓN DE CONSENTIMIENTO

D./Dña.....de.....años de edad, con DNI.....

D./Dña.....de.....años de edad, con DNI……en calidad de representante (en caso de minoría legal o incapacidad) de.....…

con DNI.....

**DECLARO**

- Que he leído la hoja de información que se me ha entregado.
- Que he comprendido las explicaciones que se me han facilitado.
- Que he podido realizar observaciones y me han sido aclaradas las dudas que he planteado.
- Que puedo revocar el consentimiento en cualquier momento sin tener que dar explicaciones y sin que esto repercuta en mis cuidados médicos.
- Que de forma libre y voluntaria cedo los datos que se hallan recogidos en mi historia clínica para el

estudio que se me ha propuesto

- Que puedo incluir restricciones sobre el uso de las mismas.

**CONSIENTO**

Que se utilicen los datos que se hallan recopilados en mi historia clínica para el mencionado estudio.
Que el investigador pueda acceder a mis datos en la medida en que sea necesario y manteniendo siempre su confidencialidad.
Que el personal del centro me contacte en el futuro en caso de que se estime oportuno añadir nuevos datos a los recogidos y/o tomar nuevas muestras. ☐ Sí ☐ No
☐ Deseo incluir la siguiente restricción al uso de mis datos:
……

Fdo.: D./Dña .....
En ..... a..... de ..... de 20……

**Declaración Investigador:**

He informado debidamente al donante
Fdo.: ..... DNI .....
En ..... a ..... de ..... de 20…

**REVOCACIÓN**

Fdo.: D./Dña .....
Revoco el consentimiento cedido para la utilización de mis datos para el estudio propuesto
En ..... a..... de ..... de 20……

**DECLARACIÓN DE CONSENTIMIENTO** *EJEMPLAR PARA EL CENTRO*

D./Dña.....de.....años de edad, con DNI.....

D./Dña.....de.....años de edad, con DNI……en calidad de representante (en caso de minoría legal o incapacidad) de.....…

con DNI.....

**DECLARO**

- Que he leído la hoja de información que se me ha entregado.
- Que he comprendido las explicaciones que se me han facilitado.
- Que he podido realizar observaciones y me han sido aclaradas las dudas que he planteado.
- Que puedo revocar el consentimiento en cualquier momento sin tener que dar explicaciones y sin que esto repercuta en mis cuidados médicos.
- Que de forma libre y voluntaria cedo los datos que se hallan recogidos en mi historia clínica para el estudio que se me ha propuesto
- Que puedo incluir restricciones sobre el uso de las mismas.

**CONSIENTO**

Que se utilicen los datos que se hallan recopilados en mi historia clínica para el mencionado estudio.
Que el investigador pueda acceder a mis datos en la medida en que sea necesario y manteniendo siempre su confidencialidad.
Que el personal del centro me contacte en el futuro en caso de que se estime oportuno añadir nuevos datos a los recogidos y/o tomar nuevas muestras. ☐ Sí ☐ No
☐ Deseo incluir la siguiente restricción al uso de mis datos:
……

Fdo.: D./Dña .....
En ..... a..... de ..... de 20……

**Declaración del investigador:**
He informado debidamente al donante
Fdo.: ..... DNI
En ..... a ..... de ..... de 20…

**REVOCACIÓN**

Fdo.: D./Dña .....
Revoco el consentimiento cedido para la utilización de mis datos para el estudio propuesto
En ..... a..... de ..... de 20……

# Anexo III: Consentimiento para la toma de imágenes

## CONSENTIMIENTO PARA LA TOMA DE IMÁGENES Y AUTORIZACIÓN PARA SU USO

Nombre de la persona: _____

Teléfono: _____ Dirección: _____

Nombre del padre, madre o tutor/a: _____

### CONSENTIMIENTO PARA LA TOMA DE IMÁGENES

Por la presente, doy mi consentimiento para que se me tomen fotografías. El término "imagen" incluye video o fotografía fija, en formato digital o de otro tipo, y cualquier otro medio de registro o reproducción de imágenes.
Por la presente, autorizo el uso con fines didácticos o educativos.

### PROPÓSITO

Por la presente, autorizo el uso de la(s) imágenes(s) para el propósito de difusión al personal del hospital, médicos, profesionales de la salud y miembros del público con fines educativos, de tratamiento, de investigación y científicos.

Doy mi consentimiento para que se tomen imágenes de mi hijo/a o tutorizado/a y autorizo el uso o la divulgación de tal(es) fotografía(s) a fin de contribuir con los objetivos científicos, de tratamiento, educativos, y por la presente renuncio a cualquier derecho a recibir compensación por tales usos en virtud de la autorización precedente. Por la presente, yo y mis sucesores o cesionarios eximimos al centro y a sus empleados, a mi(s) médico(s) y a cualquier otra persona que participe en mi atención, y a sus sucesores y cesionarios, de toda responsabilidad ante cualquier reclamo por daños o de indemnización que surja de las actividades autorizadas por este acuerdo.

### REESCISIÓN

Si yo decido rescindir esta autorización, no se permitirá posteriores usos de mi fotografía o la de mi hijo/a, tutorizado/a, pero no podrá pedir que se devuelvan las fotografías o la información ya utilizadas.

## DERECHOS

Puedo solicitar que cese la filmación o grabación en cualquier momento.

Puedo rescindir esta autorización hasta una fecha razonable antes de que se utilice la imagen, pero debo hacerlo por escrito, remitido a _____

Puedo inspeccionar u obtener una copia de las imágenes cuyo uso estoy autorizando.

Puedo negarme a firmar esta autorización. Mi negativa no afectará a las posibilidades de mi hijo de recibir atención.

Tengo derecho a recibir una copia de esta autorización.

Entiendo que no recibiré ningún tipo de compensación financiera.

FIRMA

Fecha: _____

Firma: _____ Firma: _____ Firma: _____

*Paciente si es mayor de 12 años* *representante legal* *Investigador prinicpal*

FIRMA REESCISIÓN

Fecha: _____

Firma: _____ Firma: _____ Firma: _____

*Paciente si es mayor de 12 años* *representante legal* *Investigador principal*

# Anexo IV: Registro del estudio en Clinical Trials

ClinicalTrials.gov PRS
*Protocol Registration and Results System*

**ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt**
Release Date: July 9, 2022

**ClinicalTrials.gov ID: NCT03320200**

## Study Identification

| | |
|---|---|
| Unique Protocol ID: | H1507114540624 |
| Brief Title: | A Central Nervous System Focused Treatment Approach for Frozen Shoulder |
| Official Title: | A Central Nervous System Focused Treatment Approach for People With Frozen Shoulder: Protocol for a Randomised Clinical Trial |
| Secondary IDs: | |

## Study Status

| | |
|---|---|
| Record Verification: | July 2022 |
| Overall Status: | Completed |
| Study Start: | October 1, 2017 [Actual] |
| Primary Completion: | February 18, 2021 [Actual] |
| Study Completion: | February 18, 2021 [Actual] |

## Sponsor/Collaborators

| | |
|---|---|
| Sponsor: | University of Valencia |
| Responsible Party: | Principal Investigator<br>Investigator: Enrique Lluch Girbés [egirbés]<br>Official Title: PhD Professor<br>Affiliation: University of Valencia |
| Collaborators: | |

## Oversight

| | |
|---|---|
| U.S. FDA-regulated Drug: | No |
| U.S. FDA-regulated Device: | No |
| U.S. FDA IND/IDE: | No |
| Human Subjects Review: | Board Status: Approved<br>Approval Number: H1507114540624<br>Board Name: Mª José Vidal García<br>Board Affiliation: Commisió d'Ética en Investigació Experimental Universitat de València<br>Phone: 96 38 64109<br>Email: maria.j.vidal@uv.es<br>Address: |

Av. de Blasco Ibáñez, 13, 46010 València

Data Monitoring: No

FDA Regulated Intervention: No

## Study Description

Brief Summary: The aim of this study is to compare the effectiveness of a CNS-directed treatment program versus a standard medical and physiotherapy care program on outcomes in participants with FS.Participants will be randomized to receive either a 10 weeks CNS-focused treatment program or standard medical and physiotherapy care.To evaluate the results of the interventions, the subjects will be assessed at the beginning, at the end of the treatment program (week 10) and at 3 and 6 months of follow-up.

Detailed Description: The aim of this study is to compare the effectiveness of a CNS-directed treatment program versus a standard medical and physiotherapy care program on outcomes in participants with Frozen Shoulder (FS). It will consist of a randomized double-blind clinical trial (both participants and evaluators). The sample will consist of subjects with primary or idiopathic FS.

Once the sample is selected, participants will be randomly assigned to receive either a CNS-centered treatment program or a standard physiotherapy program. The CNS-centered treatment program will last for 10 weeks, conducted in 60-minute sessions on a weekly basis. In addition, participants in this group will complete a home treatment program for 30 minutes, five times a week. On the other hand, subjects assigned to the standard physiotherapy group will receive a 10-session treatment program, such as the CNS-centered treatment group. This standard treatment will include one corticosteroid infiltration provided in the early acute stage followed by a multimodal physiotherapy program including analgesic modalities (e.g. TENS, cryotherapy) and exercise and manual therapy techniques addressing the specific mobility deficits of each patient. Physiotherapists will be instructed not to include interventions that were similar to those used in the group receiving the CNS-focused protocol (e.g. using mirrors or imagined movements) and to include a home program that involves a training load comparable to that in the other group. Adherence to both interventions will be monitored using an individual treatment diary where the time of day and duration of each clinic and home session will be recorded To evaluate the results of the interventions, the subjects will be assessed at the beginning, at the end of the treatment program (week 10) and at 3 and 6 months of follow-up.

## Conditions

Conditions: Adhesive Capsulitis of Shoulder
Frozen Shoulder

Keywords:

## Study Design

Study Type: Interventional

Primary Purpose: Treatment

Study Phase: N/A

Interventional Study Model: Parallel Assignment

| | |
|---|---|
| Number of Arms: | 2 |
| Masking: | Double (Participant, Investigator) |
| Allocation: | Randomized |
| Enrollment: | 34 [Actual] |

## Arms and Interventions

| Arms | Assigned Interventions |
|---|---|
| Experimental: CNS-focused treatment<br>Group of subjects receiving a 10 week CNS (Central Nervous System) -focused treatment program for frozen shoulder in addition to 5 days per week home treatment program | CNS-focused treatment<br>The CNS-focused treatment will last for 10 weeks, conducted in 60-minute sessions on a weekly basis. In addition, participants in this group will complete a home treatment program for 30 minutes, five times a week.<br>Other Names:<br>• graded motor and sensory imagery traininng |
| Experimental: Standard Care Treatment<br>Group of subjects receiving a 10 week standard care treatment program for frozen shoulder in addition to 5 days per week home treatment program based on conventional physiotherapy | Standard Care Treatment<br>The standard physiotherapy group will receive a 10-session treatment program that will include one corticosteroid infiltration provided in the early acute stage followed by a multimodal physiotherapy program including analgesic modalities (e.g. TENS, cryotherapy) and exercise and manual therapy techniques addressing the specific mobility deficits of each patient. This program also include a home treatment based on conventional physiotherapy that involves a training load comparable to that in the CNS-focused group.<br>Other Names:<br>• Conventional physiotherapy treatment |

## Outcome Measures

Primary Outcome Measure:

1. shoulder pain-related disability questionnaire (SPADI)
   The SPADI is a 13-items shoulder function index assessing pain and disability related to shoulder dysfunction. Each item is scored by a numeric rate scale ranging from 0 (no pain/no difficulty) to 10 (worst pain imaginable/so difficult it required help). The total score ranges from 0 to 100 points where a higher score indicates greater disability.

   [Time Frame: Baseline]
2. shoulder pain-related disability questionnaire (SPADI)
   The SPADI is a 13-items shoulder function index assessing pain and disability related to shoulder dysfunction. Each item is scored by a numeric rate scale ranging from 0 (no pain/no difficulty) to 10 (worst pain imaginable/so difficult it required help). The total score ranges from 0 to 100 points where a higher score indicates greater disability.

   [Time Frame: Change from baseline SPADI at 10 weeks]
3. shoulder pain-related disability questionnaire (SPADI)
   The SPADI is a 13-items shoulder function index assessing pain and disability related to shoulder dysfunction. Each item is scored by a numeric rate scale ranging from 0 (no pain/no difficulty) to 10 (worst pain imaginable/so difficult it required help). The total score ranges from 0 to 100 points where a higher score indicates greater disability.

   [Time Frame: Change from baseline SPADI at 3 months]
4. shoulder pain-related disability questionnaire (SPADI)

The SPADI is a 13-items shoulder function index assessing pain and disability related to shoulder dysfunction. Each item is scored by a numeric rate scale ranging from 0 (no pain/no difficulty) to 10 (worst pain imaginable/so difficult it required help). The total score ranges from 0 to 100 points where a higher score indicates greater disability.

[Time Frame: Change from baseline SPADI at 6 months]

Secondary Outcome Measure:

5. Numeric Pain Rating Scale
   a valid and reliable measure of shoulder pain. Participants will be presented with numerical rating scales anchored with 0 (“no pain”) and 10 (“pain as bad as you can imagine”).

   [Time Frame: Baseline]
6. Numeric Pain Rating Scale
   a valid and reliable measure of shoulder pain. Participants will be presented with numerical rating scales anchored with 0 (“no pain”) and 10 (“pain as bad as you can imagine”).

   [Time Frame: Change from baseline Numeric Rating Pain Scale at 10 weeks]
7. Numeric Pain Rating Scale
   a valid and reliable measure of shoulder pain. Participants will be presented with numerical rating scales anchored with 0 (“no pain”) and 10 (“pain as bad as you can imagine”).

   [Time Frame: Change from baseline Numeric Rating Pain Scale at 3 months]
8. Numeric Pain Rating Scale
   a valid and reliable measure of shoulder pain. Participants will be presented with numerical rating scales anchored with 0 (“no pain”) and 10 (“pain as bad as you can imagine”).

   [Time Frame: Change from baseline Numeric Rating Pain Scale at 6 months]
9. Goniometric assessment of active shoulder ROM (range of motion)
   Degrees of active range of motion

   [Time Frame: Baseline]
10. Goniometric assessment of active shoulder ROM (range of motion)
    Degrees of active range of motion

    [Time Frame: Change from baseline ROM at 10 weeks]
11. Goniometric assessment of active shoulder ROM (range of motion)
    Degrees of active range of motion

    [Time Frame: Change from baseline ROM at 3 months]
12. Goniometric assessment of active shoulder ROM (range of motion)
    Degrees of active range of motion

    [Time Frame: Change from baseline ROM at 6 months]
13. Two point discrimination threshold
    Two point discrimination threshold measured at one standardize site on the affected shoulder (5cm distal to the lateral border of the acromion) 33, following an established protocol

    [Time Frame: Baseline]
14. Two point discrimination threshold
    Two point discrimination threshold measured at one standardize site on the affected shoulder (5cm distal to the lateral border of the acromion) 33, following an established protocol

    [Time Frame: Change from baseline two point discrimination threshold at 10 weeks]
15. Two point discrimination threshold
    Two point discrimination threshold measured at one standardize site on the affected shoulder (5cm distal to the lateral border of the acromion) 33, following an established protocol

    [Time Frame: Change from baseline two point discrimination threshold at 3 months]
16. Two point discrimination threshold

Two point discrimination threshold measured at one standardize site on the affected shoulder (5cm distal to the lateral border of the acromion) 33, following an established protocol

[Time Frame: Change from baseline two point discrimination threshold at 6 months]

17. Laterality judgement accuracy
Laterality judgement accuracy using the NOI Recognise online program (www.noigroup.com) and following and established protocol

[Time Frame: Baseline]

18. Laterality judgement accuracy
Laterality judgement accuracy using the NOI Recognise online program (www.noigroup.com) and following and established protocol

[Time Frame: Change from baseline laterality judgement accuracy at 10 weeks]

19. Laterality judgement accuracy
Laterality judgement accuracy using the NOI Recognise online program (www.noigroup.com) and following and established protocol

[Time Frame: Change from baseline laterality judgement accuracy at 3 months]

20. Laterality judgement accuracy
Laterality judgement accuracy using the NOI Recognise online program (www.noigroup.com) and following and established protocol

[Time Frame: Change from baseline laterality judgement accuracy at 6 months]

21. The Spanish version of the Tampa Scale of Kinesophobia (TSK-11)
The TSK-11 is an 11-item questionnaire assessing fear of movement or fear of (re)injury during movement. It is comprised of 11 items each ranged on a 4-point scale with the end points (1) “totally agree” and (4) “totally disagree” (range: 11-44). Higher scores indicate more fear-avoidance behavior.

[Time Frame: Baseline]

22. The Spanish version of the Tampa Scale of Kinesophobia
The TSK-11 is an 11-item questionnaire assessing fear of movement or fear of (re)injury during movement. It is comprised of 11 items each ranged on a 4-point scale with the end points (1) “totally agree” and (4) “totally disagree” (range: 11-44). Higher scores indicate more fear-avoidance behavior.

[Time Frame: Change from baseline Tampa Scale of Kinesophobia at 10 weeks]

23. The Spanish version of the Tampa Scale of Kinesophobia
The TSK-11 is an 11-item questionnaire assessing fear of movement or fear of (re)injury during movement. It is comprised of 11 items each ranged on a 4-point scale with the end points (1) “totally agree” and (4) “totally disagree” (range: 11-44). Higher scores indicate more fear-avoidance behavior.

[Time Frame: Change from baseline Tampa Scale of Kinesophobia at 3 months]

24. The Spanish version of the Tampa Scale of Kinesophobia
The TSK-11 is an 11-item questionnaire assessing fear of movement or fear of (re)injury during movement. It is comprised of 11 items each ranged on a 4-point scale with the end points (1) “totally agree” and (4) “totally disagree” (range: 11-44). Higher scores indicate more fear-avoidance behavior.

[Time Frame: Change from baseline Tampa Scale of Kinesophobia at 6 months]

25. The Patient Specific Functional Scale
A list of activities and movements is shown to the patients and they are asked to identify the activities that he/she experience difficulty with because of his/her complaints in the shoulder. The patient selects the 3 most important activities and rank them by degree of importance from 0 (no difficulty at all) to 10 (impossible). The total score range from 0 to 30. Higher score indicates higher difficulty in performance on daily activities.

[Time Frame: Baseline]

26. The Patient Specific Functional Scale
A list of activities and movements is shown to the patients and they are asked to identify the activities that he/she experience difficulty with because of his/her complaints in the shoulder. The patient selects the 3 most important

activities and rank them by degree of importance from 0 (no difficulty at all) to 10 (impossible). The total score range from 0 to 30. Higher score indicates higher difficulty in performance on daily activities.

[Time Frame: Change from baseline Patient Specific Functional Scale at 10 weeks]

27. The Patient Specific Functional Scale
A list of activities and movements is shown to the patients and they are asked to identify the activities that he/she experience difficulty with because of his/her complaints in the shoulder. The patient selects the 3 most important activities and rank them by degree of importance from 0 (no difficulty at all) to 10 (impossible). The total score range from 0 to 30. Higher score indicates higher difficulty in performance on daily activities.

[Time Frame: Change from baseline Patient Specific Functional Scale at 3 months]

28. The Patient Specific Functional Scale
A list of activities and movements is shown to the patients and they are asked to identify the activities that he/she experience difficulty with because of his/her complaints in the shoulder. The patient selects the 3 most important activities and rank them by degree of importance from 0 (no difficulty at all) to 10 (impossible). The total score range from 0 to 30. Higher score indicates higher difficulty in performance on daily activities.

[Time Frame: Change from baseline Patient Specific Functional Scale at 6 months]

## Eligibility

| | |
|---|---|
| Minimum Age: | 18 Years |
| Maximum Age: | |
| Sex: | All |
| Gender Based: | No |
| Accepts Healthy Volunteers: | No |
| Criteria: | Inclusion Criteria: |

- Primary or idiopathic Frozen Shoulder (FS), defined as FS not associated with a systemic condition or history of injury
- greater than 50% reduction in passive external rotation when compared to the uninvolved shoulder or less than 30° of external rotation
- range of motion loss of greater than 25% in at least two movement planes in comparison to the uninvolved shoulder
- pain and restricted movement present for at least one month reaching a plateau or worsening
- normal shoulder X-rays (with the exception of osteopenia of the humeral head and calcific tendinosis)

Exclusion Criteria:

- Locked dislocations, arthritis, fractures or avascular necrosis on radiographs
- surgery in the upper quadrant region <12 months prior to the study
- skin or medical conditions that prevents from receiving tactile stimuli on the shoulder
- neurological or motor disorders including a diagnosis of dyslexia or difficulty performing a rapid naming task
- visually and mental health conditions that precludes successful participation.

## Contacts/Locations

Central Contact Person: Silvia Mena, PhD student
Telephone: +34646362194

Email: silmedel@uv.es

Central Contact Backup:

Study Officials: Enrique Lluch, PhD
Study Director
Physiotherapy Department University of Valencia

Locations: **Spain**
University of Valencia
Valencia, Spain, 46010
Contact: Lirios Dueñas, PhD 96 398 37 84 lirios.duenas@uv.es

## IPDSharing

Plan to Share IPD:

## References

Citations: **[Study Results]** Wand BM, O'Connell NE, Di Pietro F, Bulsara M. Managing chronic nonspecific low back pain with a sensorimotor retraining approach: exploratory multiple-baseline study of 3 participants. Phys Ther. 2011 Apr;91(4):535-46. doi: 10.2522/ptj.20100150. Epub 2011 Feb 24. PubMed 21350034

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Links:

Available IPD/Information:

# Anexo V: Formulario de registro de valoración

## 1. PERSONAL INFORMATION

Date:_____

Rater:_____

Number:_____ Date of birth:_____

Gender: Male /Female Left-handed/Right-handed Measurement:_____

Weight:_____kg Length:_____cm

Frozen Shoulder: Left/right Cause: Primary/secondary/…_____

Start shoulder complaints:_____

Progression (in terms of pain and restriction):_____

_____

_____

_____

Current VAS (0-100mm) AT REST: _____DURING MOVEMENT: _____

VAS last 24 hours (0-100mm)_____

Previous treatments (Report everything, how many times a week, which treatment, when was the last one, injections, etc): physiotherapy / osteopathy/ acupuncture /

_____

_____

_____

Diabetes: yes/no; Type: _____

-Date diagnosis:_____

-Treatment: ☐ standard medical and physiotherapy care
☐ corticosteroid infiltration
☐ TENS
☐ Cryotherapy
☐ Graded motor and sensory discrimination training

Thyroid disease: yes/no; Type:_____

Usage of medicines: (during the last 2 weeks, underline medication taken today):

**Functionality**

- ✓ Do you still work?
  - ☐ No. Why not?_____
    When did you stop?_____

- ☐ Yes, part-time ( days:_____, hours in total:_____)
- ☐ Yes, fulltime
- ☐ Student

✓ What is your profession?_____

✓ Do you practice sport?

- ☐ No. Why not?_____
- ☐ Yes, (days:_____, hours total:_____, sport:_____)

✓ Do you want to receive your study results?

- ☐ No, not necessary
- ☐ Yes, please
  - E-mail address:_____
  - Home address (optional): _____
    _____
  - Phone number:_____

**Remarks, important things to notice?**

_____
_____
_____
_____
_____

## Patient-specific functional scale (PSFS): ___ TWO-POINT DISCRIMINATION THRESHOLD

| | **TDP Threshold** (mm.) | | | | | |
|---|---|---|---|---|---|---|
| | **Affected side** | | | **Unaffected side** | | |
| **5cm distal to the lateral border of the acromion** | ↑ | ↓ | mean | ↑ | ↓ | mean |

**LATERALITY JUDGEMENT ACCURACY (**randomize and make one trial as practice before testing**).**

| | **ACCURACY** | | **SPEED** | |
|---|---|---|---|---|
| | **LEFT** | **RIGHT** | **LEFT** | **RIGHT** |
| **CONTEXT**<br>**30 images. 5 sec.**<br>**Current NPRS** | | | | |

**PRESSURE PAIN MEASUREMENTS (ALGOMETRY)**

| | **Shoulder (affected)*** | | | | **Quadriceps**** | | | | **Non affected*** | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ***1. PPT*** **(UDP)** | *PPT A* | *PPT B* | *PPT C* | ***PPT MEAN*** | *PPT A* | *PPT B* | *PPT C* | ***PPT MEAN*** | *PPT A* | *PPT B* | *PPT C* | ***PPT MEAN*** |
| **Kg/cm²** | | | | | | | | | | | | |
| ***2. TS*** *(Pinprik)* | **Shoulder*** | | *1* | *10* | *1* | *10* | *1* | *10* | *1* | *10* | *1* | *10* |
| *(No rest btw series)* | **(affected)** | | | | | | | | | | | |

* 2 cm lateral border acromion

** 1/2 between ASIS and superior pole of patella

**SHOULDER TESTING**

| **Mobility** | **Affected** | **Remarks** Report pain or if position is not possible, because of belly or other reasons |
|---|---|---|
| Active: External rotation 0° abduction | | |
| Passive: External rotation 0° abduction | | |
| Active: Elevation | | |
| Passive: Elevation | | |

# Anexo VI: Cuestionarios y escalas de valoración

## SHOULDER PAIN AND DISABILITY INDEX (SPADI) SPANISH VERSION

## ESCALA DE DOLOR Y DISCAPACIDAD DE HOMBRO

Nombre del paciente _____ Fecha _____

**Por favor, léalo con atención:**

Instrucciones: Por favor, rodeé con un círculo el número que mejor describa la respuesta a la pregunta que se le formula.

**Escala de Dolor:**

Ningún dolor 0 1 2 3 4 5 6 7 8 9 10 El peor dolor imaginable

**¿Cómo de severo es su dolor?**

1. Su peor dolor
   0 1 2 3 4 5 6 7 8 9 10

2. Cuando está tumbado/a sobre el lado afecto
   0 1 2 3 4 5 6 7 8 9 10

3. Cuando coge algo de un estante alto
   0 1 2 3 4 5 6 7 8 9 10

4. Cuando se toca la zona posterior del cuello
   0 1 2 3 4 5 6 7 8 9 10

5. Cuando empuja con el brazo afecto
   0 1 2 3 4 5 6 7 8 9 10

**Escala de Discapacidad:**
Sin dificultad 0 1 2 3 4 5 6 7 8 9 10 Tan difícil que necesita ayuda

**¿Cuánta dificultad tiene usted?**

1. Cando se lava el pelo
   0 1 2 3 4 5 6 7 8 9 10

2. Cuando se lava la espalda
   0 1 2 3 4 5 6 7 8 9 10

3. Cuando se pone una camiseta o jersey
0 1 2 3 4 5 6 7 8 9 10

4. Cuando se pone una camisa abotonada por delante
0 1 2 3 4 5 6 7 8 9 10

5. Cuando se pone unos pantalones
0 1 2 3 4 5 6 7 8 9 10

6. Cuando coloca un objeto en un estante alto
0 1 2 3 4 5 6 7 8 9 10

7. Cuando lleva un objeto pesado de 4 kilos y medio
0 1 2 3 4 5 6 7 8 9 10

8. Cuando coge algo de su bolsillo trasero
0 1 2 3 4 5 6 7 8 9 10

OTROS COMENTARIOS:

_____
_____
_____
_____

Evaluador: _____

_____
_____
_____
_____

## The patient-specific functional scale (PSFS)

**Name:**

_____

**Read at Baseline Assessment:**

I'm going to ask you to identify up to 5 important activities that you are unable to do or have difficulty with as a result of your problem.

Today, are there any activities that you are unable to do or have difficulty with because of your problem? (show scale to patient).

**Read at Follow-up Visits**

When I assessed you on (state previous assessment date), you told me that you had difficulty with (read 1, 2, 3, 4, 5 from list).

Today, do you still have difficulty with 1; 2; 3; 4; 5 (have patient score each activity).

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Unable to perform activity | | | | | | | | | | Able to perform activity at preinjury level |

| Activity | T /date | score | T /date | score | T /date | score | T /date | score |
|---|---|---|---|---|---|---|---|---|
| 1 | | | | | | | | |
| 2 | | | | | | | | |
| 3 | | | | | | | | |
| 4 | | | | | | | | |
| 5 | | | | | | | | |
| Additional | | | | | | | | |
| Additional | | | | | | | | |

# CUESTIONARIO TSK-11SV

*Tampa Scale for Kinesiophobia* (Spanish adaptation. Gómez-Pérez, López-Martínez y Ruiz-Párraga, 2011)

**INSTRUCCIONES:** a continuación se enumeran una serie de afirmaciones. Lo que Ud. ha de hacer es indicar hasta qué punto eso ocurre en su caso según la siguiente escala:

1 **Totalmente en desacuerdo** 2 3 4 **Totalmente de acuerdo**

| | | | | |
|---|---|---|---|---|
| **1. Tengo miedo de lesionarme si hago ejercicio físico.** | 1 | 2 | 3 | 4 |
| **2. Si me dejara vencer por el dolor, el dolor aumentaría.** | 1 | 2 | 3 | 4 |
| **3. Mi cuerpo me está diciendo que tengo algo serio.** | 1 | 2 | 3 | 4 |
| **4. Tener dolor siempre quiere decir que en el cuerpo hay una lesión.** | 1 | 2 | 3 | 4 |
| **5. Tengo miedo a lesionarme sin querer.** | 1 | 2 | 3 | 4 |
| **6. Lo más seguro para evitar que aumente el dolor es tener cuidado y no hacer movimientos innecesarios.** | 1 | 2 | 3 | 4 |
| **7. No me dolería tanto si no tuviese algo serio en mi cuerpo.** | 1 | 2 | 3 | 4 |
| **8. El dolor me dice cuándo debo parar la actividad para no lesionarme.** | 1 | 2 | 3 | 4 |
| **9. No es seguro para una persona con mi enfermedad hacer actividades físicas.** | 1 | 2 | 3 | 4 |
| **10. No puedo hacer todo lo que la gente normal hace porque me podría lesionar con facilidad.** | 1 | 2 | 3 | 4 |
| **11. Nadie debería hacer actividades físicas cuando tiene dolor.** | 1 | 2 | 3 | 4 |

**APÉNDICE A: INVENTARIO DE SENSIBILIZACIÓN CENTRAL: PARTE A**

| | | | | | | |
|---|---|---|---|---|---|---|
| 1 | Me siento cansado cuando me levanto por la mañana. | Nunca | Rara vez | A veces | A menudo | Siempre |
| 2 | Siento mis músculos rígidos y doloridos. | Nunca | Rara vez | A veces | A menudo | Siempre |
| 3 | Tengo ataques de ansiedad. | Nunca | Rara vez | A veces | A menudo | Siempre |
| 4 | Rechino o aprieto los dientes. | Nunca | Rara vez | A veces | A menudo | Siempre |
| 5 | Tengo problemas de diarrea y/o estreñimiento. | Nunca | Rara vez | A veces | A menudo | Siempre |
| 6 | Necesito ayuda para hacer mis actividades de la vida diaria. | Nunca | Rara vez | A veces | A menudo | Siempre |
| 7 | Soy sensible a las luces brillantes o intensas. | Nunca | Rara vez | A veces | A menudo | Siempre |
| 8 | Me canso muy fácilmente cuando estoy físicamente activo. | Nunca | Rara vez | A veces | A menudo | Siempre |
| 9 | Siento dolor en todo mi cuerpo. | Nunca | Rara vez | A veces | A menudo | Siempre |
| 10 | Tengo dolores de cabeza. | Nunca | Rara vez | A veces | A menudo | Siempre |
| 11 | Siento molestia en la vejiga y/o quemazón al orinar. | Nunca | Rara vez | A veces | A menudo | Siempre |
| 12 | No duermo bien. | Nunca | Rara vez | A veces | A menudo | Siempre |
| 13 | Tengo dificultad para concentrarme. | Nunca | Rara vez | A veces | A menudo | Siempre |
| 14 | Tengo problemas en la piel como sequedad, picor o sarpullido. | Nunca | Rara vez | A veces | A menudo | Siempre |
| 15 | El estrés hace que mi dolor empeore. | Nunca | Rara vez | A veces | A menudo | Siempre |
| 16 | Me siento triste o deprimido. | Nunca | Rara vez | A veces | A menudo | Siempre |
| 17 | Tengo poca energía. | Nunca | Rara vez | A veces | A menudo | Siempre |
| 18 | Tengo tensión muscular en mi cuello y hombros. | Nunca | Rara vez | A veces | A menudo | Siempre |

| | | | | | | |
|---|---|---|---|---|---|---|
| 19 | Tengo dolor en mi mandíbula. | Nunca | Rara vez | A veces | A menudo | Siempre |
| 20 | Algunos olores, como los perfumes, hacen que me sienta mareado y con nauseas. | Nunca | Rara vez | A veces | A menudo | Siempre |
| 21 | Tengo que orinar frecuentemente. | Nunca | Rara vez | A veces | A menudo | Siempre |
| 22 | Siento molestias en las piernas y las muevo constantemente cuando estoy en la cama. | Nunca | Rara vez | A veces | A menudo | Siempre |
| 23 | Tengo dificultad para recordar cosas. | Nunca | Rara vez | A veces | A menudo | Siempre |
| 24 | Sufrí un trauma psíquico de niño/a. | Nunca | Rara vez | A veces | A menudo | Siempre |
| 25 | Tengo dolor en la zona de la pelvis. | Nunca | Rara vez | A veces | A menudo | Siempre |

**APÉNDICE B: INVENTARIO DE SENSIBILIZACIÓN CENTRAL: PARTE B**

¿Ha sido diagnosticado por un médico de alguna de las siguientes enfermedades?
Por favor, revise el cuadro de la derecha para cada diagnóstico y anote el año del diagnóstico

| | | |
|---|---|---|
| 1 | Síndrome de piernas inquietas. | **SÍ No** |
| 2 | Síndrome de fatiga crónica. | **SÍ No** |
| 3 | Fibromialgia. | **SÍ No** |
| 4 | Enfermedad de la articulación temporo-mandibular. | **SÍ No** |
| 5 | Migraña o cefalea tensional. | **SÍ No** |
| 6 | Síndrome de colon irritable. | **SÍ No** |
| 7 | Sensibilidad química múltiple. | **SÍ No** |
| 8 | Lesión cervical (incluyendo latigazo cervical). | **SÍ No** |
| 9 | Ansiedad o ataques de pánico. | **SÍ No** |
| 10 | Depresión. | **SÍ No** |

## MUCHAS GRACIAS POR SU COLABORACIÓN

**PAIN CATASTROPHIZING SCALE**

Todas las personas experimentamos situaciones de dolor en algún momento de nuestra vida. Las personas estamos a menudo expuestas a situaciones que pueden causar dolor como las enfermedades, las heridas, los tratamientos dentales o las intervenciones quirúrgicas.
Estamos interesados en conocer el tipo de pensamientos y sentimientos que usted tiene cuando siente dolor. A continuación se presenta una lista de 13 frases que describen diferentes pensamientos y sentimientos que pueden estar asociados al dolor. Utilizando la siguiente escala, por favor, indique el grado en que usted tiene esos pensamientos y sentimientos cuando siente dolor.

Cuando siento dolor…

1. Estoy preocupado todo el tiempo pensando en si el dolor desaparecerá
   0: Nada en absoluto
   1: Un poco
   2: Moderadamente
   3: Mucho
   4: Todo el tiempo

2. Siento que ya no puedo más
   0: Nada en absoluto
   1: Un poco
   2: Moderadamente
   3: Mucho
   4: Todo el tiempo

3. Es terrible y pienso que esto nunca va a mejorar
   0: Nada en absoluto
   1: Un poco
   2: Moderadamente
   3: Mucho
   4: Todo el tiempo

4. Es horrible y siento que esto es más fuerte que yo
   0: Nada en absoluto
   1: Un poco
   2: Moderadamente
   3: Mucho
   4: Todo el tiempo

5. Siento que no puedo soportarlo más
   0: Nada en absoluto
   1: Un poco
   2: Moderadamente
   3: Mucho
   4: Todo el tiempo

6. Temo que el dolor empeore
    0: Nada en absoluto
    1: Un poco
    2: Moderadamente
    3: Mucho
    4: Todo el tiempo

7. No dejo de pensar en otras situaciones en las que experimento dolor
    0: Nada en absoluto
    1: Un poco
    2: Moderadamente
    3: Mucho
    4: Todo el tiempo

8. Deseo desesperadamente que desaparezca el dolor
    0: Nada en absoluto
    1: Un poco
    2: Moderadamente
    3: Mucho
    4: Todo el tiempo

9. No puedo apartar el dolor de mi mente
    0: Nada en absoluto
    1: Un poco
    2: Moderadamente
    3: Mucho
    4: Todo el tiempo

10. No dejo de pensar en lo mucho que me duele
    0: Nada en absoluto
    1: Un poco
    2: Moderadamente
    3: Mucho
    4: Todo el tiempo

11. No dejo de pensar en lo mucho que deseo que desaparezca el dolor
    0: Nada en absoluto
    1: Un poco
    2: Moderadamente
    3: Mucho
    4: Todo el tiempo

12. No hay nada que pueda hacer para aliviar la intensidad del dolor
    0: Nada en absoluto
    1: Un poco
    2: Moderadamente
    3: Mucho
    4: Todo el tiempo

13. Me pregunto si me puede pasar algo grave
    0: Nada en absoluto
    1: Un poco
    2: Moderadamente
    3: Mucho
    4: Todo el tiempo

# Anexo VII: Protocolo de tratamiento terapia manual y estiramientos domiciliarios

[ CASE REPORT ]

**APPENDIX A**

## MANUAL THERAPY TECHNIQUES*

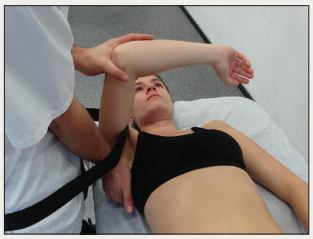
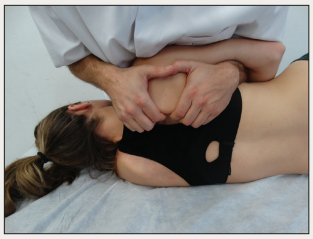
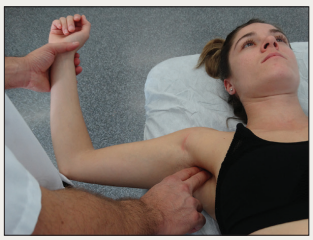
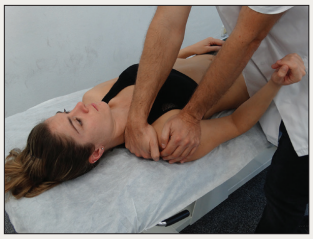
| Technique | Description | Illustration |
|---|---|---|
| General capsule-stretching technique | | |
| Lateral humerus distraction[58] | The patient is in supine, with the involved extremity close to the edge of the table and the shoulder flexed to 90°. The therapist's hands stabilize the elbow and lateral border of the scapula. The therapist uses body weight to provide a lateral humerus distraction through a belt<br>This technique is applied in all patients at the beginning of the treatment<br>Perform 5 repetitions as a sustained mobilization, holding each repetition 1 minute |  |
| Limitation: ER at 0° of humeral abduction | | |
| Scapular tilt and distraction[7] (**ONLINE VIDEO**) | The patient is in sidelying, with the upper extremity relaxed at the side. The therapist's caudal hand holds the inferior angle of the scapula and the cephalad hand grasps its vertebral border. The therapist's sternum is the third contact point to assist the tilt. A distraction force to the scapula away from the thoracic wall is performed to patient tolerance. Perform 5-second holds, alternating with 5-second rests, during 5 minutes<br>After 2 weeks, progress to 10-second holds, alternating with 10-second rests |  |
| Subscapularis soft tissue techniques[54] | With the patient in supine, the following techniques are applied<br>• Moderate sustained pressure for 3 sets of 90-second cycles applied over myofascial trigger point(s). Pressure level is modified from moderate to deep, according to patient's tolerance<br>• Soft tissue mobilizations parallel and perpendicular to muscular fiber orientation. Perform during 1 minute<br>• Continuous pressure over myofascial trigger points while the therapist holds and assists the shoulder in flexion and abduction until end range. Perform 5 sets of 30 movements |  |
| Oscillatory anterior/posterior mobilization[58] | The patient is in supine, with the arm placed at 0° of humeral abduction. The therapist's hand on the anterior part of the shoulder applies an anterior/posterior oscillatory force over the humeral head, with the scapula stabilized. The patient concurrently holds the shoulder in end-range ER with the mobilization technique<br>Perform 5 sets of 1-minute duration |  |

*Table continues on page D2.*

## APPENDIX A

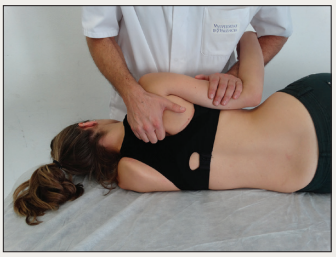
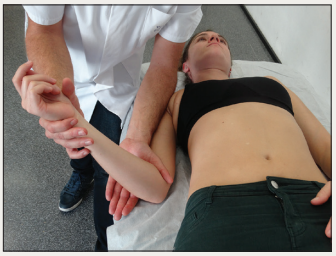
| Technique | Description | Illustration |
|---|---|---|
| Anterior/posterior mobilization with movement[33] (**ONLINE VIDEO**) | The patient is in supine, with the arm placed at 0° of humeral abduction. The therapist's hand on the anterior part of the shoulder applies an anterior/posterior sustained force over the humeral head, with the scapula stabilized. The patient concurrently performs active ER to the end of the pain-free range (ie, 0/10 on an NPRS) with the mobilization technique<br>Perform 3 sets of 10 repetitions |  |
| Coracohumeral ligament mobilization[7] (**ONLINE VIDEO**) | The patient is in sidelying. The therapist's caudal hand grasps the patient's arm above the elbow while the patient's forearm rests on the therapist's arm. The cephalad hand grasps the vertebral border of the scapula and tilts it away from the thoracic wall. The caudal hand takes the patient's arm into end-range ER and applies an inferior glide through the long axis of the humerus. Once the barrier is felt, the therapist tilts the scapula. Then, the humerus can be externally rotated further and the scapular tilt can be repeated<br>Perform 3 sets of 10 repetitions |  |
| Superior/inferior glide mobilization[25] | The patient is in supine, with the arm at the side. The therapist's caudal hand holds the patient's wrist. The cephalad hand grasps the patient's arm above the elbow crease and applies an inferior glide while the patient's arm is positioned into end-range ER<br>Perform 5 repetitions as a sustained mobilization, holding each repetition 1 minute |  |
| Rotator cuff interval stretch[25] | The patient is in sidelying, with the arm at the side. The therapist's caudal hand fixes the patient's hand. The cephalad hand moves the patient's elbow toward the table<br>Perform 5 repetitions as a sustained mobilization, holding each repetition 1 minute |  |

*Table continues on page D3.*

## APPENDIX A

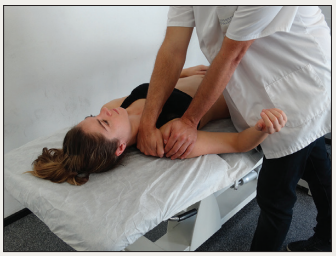
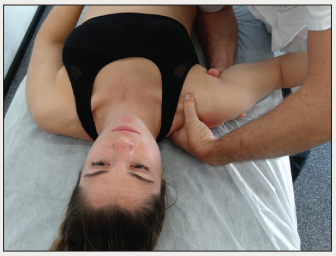
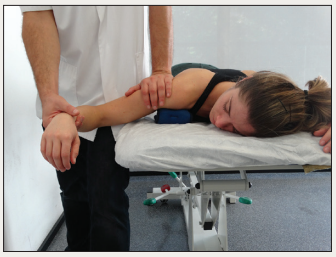
| Technique | Description | Illustration |
|---|---|---|
| Limitation: ER at 45° of humeral abduction | | |
| Oscillatory anterior/posterior mobilization[58] | The patient is in supine, with the arm placed at 45° of humeral abduction. The therapist's hand on the anterior part of the shoulder applies an anterior/posterior oscillatory force over the humeral head, with the scapula stabilized. The patient concurrently holds the shoulder in end-range ER with the mobilization technique<br>Perform 5 sets of 1-minute duration |  |
| Anterior/posterior mobilization with movement[33] | The patient is in supine, with the arm placed at 45° of humeral abduction. The therapist's hand on the anterior part of the shoulder applies an anterior/posterior sustained force over the humeral head, with the scapula stabilized. The patient concurrently performs active ER to the end of the pain-free range (ie, 0/10 on an NPRS) with the mobilization technique<br>Perform 3 sets of 10 repetitions |  |
| Middle glenohumeral mobilization[7] | The patient is in supine, with the involved extremity close to the edge of the table. The patient's arm is placed at 45° of humeral abduction. The therapist's caudal hand on the posterior glenohumeral joint glides the head of the humerus anteriorly. The cephalad hand stabilizes the scapula<br>Perform 5 repetitions as a sustained mobilization, holding each repetition 1 minute |  |
| Limitation: ER at 90° of humeral abduction | | |
| Posterior/anterior humeral head mobilization[23] | The patient is in prone, with the arm placed at 90° of humeral abduction, the elbow flexed, the glenohumeral joint off the table, and a fulcrum over the coracoid process. The therapist's lateral hand grasps the patient's arm above the elbow crease and takes the patient's arm into end-range ER. Simultaneously, the cephalad hand on the posterior part of the humerus applies a posterior/anterior force over the humeral head, with the scapula stabilized<br>Perform 5 repetitions as a sustained mobilization, holding each repetition 1 minute |  |

*Table continues on page D4.*

[ CASE REPORT ]

## APPENDIX A

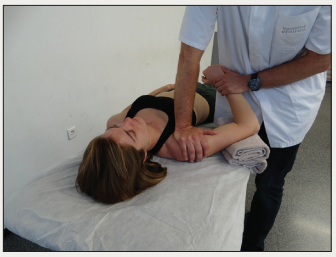
| Technique | Description | Illustration |
|---|---|---|
| Superior/inferior glenohumeral glide[7] (**ONLINE VIDEO**) | The patient is in supine, with the involved extremity close to the edge of the table. The patient's arm is in 90° of humeral abduction. The cephalad hand on the superior glenohumeral joint, inferior to the acromion, applies a superior/inferior force over the humeral head. The therapist concurrently holds the shoulder in end-range ER with the mobilization technique<br>Perform 5 repetitions as a sustained mobilization, holding each repetition 1 minute |  |
| Superior/inferior mobilization with movement[22] | The patient is in supine, with the arm placed at 90° of humeral abduction. The therapist's cephalad hand performs a sustained superior/inferior passive shoulder mobilization while the caudal hand stabilizes the humerus. The patient concurrently performs active ER to the end of the pain-free range (ie, 0/10 on an NPRS) with the mobilization technique<br>Perform 3 sets of 10 repetitions |  |
| Limitation: IR at 30° of humeral abduction | | |
| Anterior/posterior mobilization[58] | The patient is in supine, with the arm placed at 30° of humeral abduction. The therapist's hand on the anterior part of the shoulder applies an anterior/posterior force over the humeral head, with the scapula stabilized. While sustaining the anterior/posterior force, the therapist moves the shoulder to end-range IR<br>Perform 5 repetitions as a sustained mobilization, holding each repetition 1 minute |  |
| Limitation: IR at 60° of humeral abduction | | |
| Anterior/posterior mobilization[58] | The patient is in supine, with the arm placed at 60° of humeral abduction. The therapist's hand on the anterior part of the shoulder applies an anterior/posterior force over the humeral head, with the scapula stabilized. While sustaining the anterior/posterior force, the therapist moves the shoulder to end-range IR<br>Perform 5 repetitions as a sustained mobilization, holding each repetition 1 minute |  |

*Table continues on page D5.*

## APPENDIX A

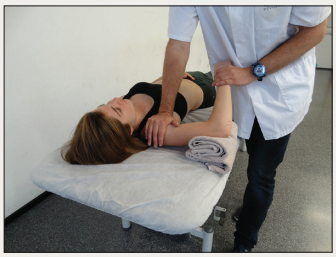
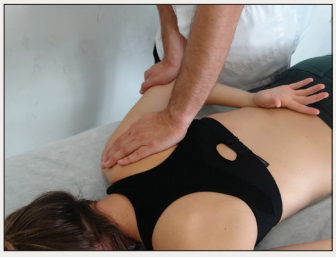
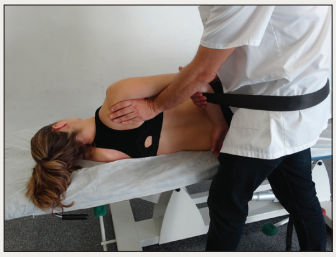
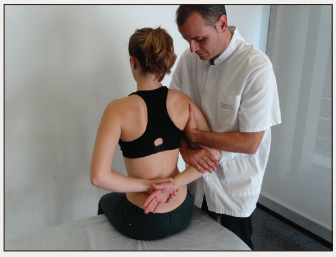
| Technique | Description | Illustration |
|---|---|---|
| Limitation: IR at 90° of humeral abduction | | |
| Anterior/posterior mobilization[58] (**ONLINE VIDEO**) | The patient is in supine, with the arm placed at 90° of humeral abduction. The therapist's hand on the anterior part of the shoulder applies an anterior/posterior force over the humeral head, with the scapula stabilized. While sustaining the anterior/posterior force, the therapist moves the shoulder to end-range IR<br>Perform 5 repetitions as a sustained mobilization, holding each repetition 1 minute |  |
| Limitation: IR at 30° of humeral abduction and extension | | |
| Prone IR hang[7] | The patient is in prone, with the dorsum of the hand on the lumbar spine (if the patient is unable to internally rotate enough, place the hand on the table). The therapist's cephalad hand stabilizes the scapula along the spinal border. The caudal hand applies a downward force on the patient's medial elbow<br>Perform 5 repetitions as a sustained mobilization, holding each repetition 1 minute |  |
| Limitation: IR with hand behind back | | |
| Superior/inferior glenohumeral glide: hand behind back[33] (**ONLINE VIDEO**) | The patient is in sidelying, with the hand placed at the end-range position of "hand behind back." The therapist's cephalad hand stabilizes the scapula. The caudal hand holds the forearm and applies a superior/inferior force. The technique may be enhanced by using a mobilization belt<br>Perform 5 repetitions as a sustained mobilization, holding each repetition 1 minute |  |
| Hand-behind-back mobilization with movement[22] | The patient is in sitting, with the hand behind the back at the end-range position. One hand is placed on the forearm just distal to the elbow crease. The other hand is placed dorsally to stabilize the scapula. The therapist provides a sustained caudal glide along the line of the humerus<br>The patient concurrently moves the arm behind the back, assisted by the therapist's abdomen, to the end of the pain-free range (ie, 0/10 on an NPRS) with the mobilization technique. Overpressure is applied by the patient's hand, assisting the affected shoulder further into the pain-free range<br>Perform 3 sets of 10 repetitions |  |

*Table continues on page D6.*

[ CASE REPORT ]

## APPENDIX A

| Technique | Description | Illustration |
|---|---|---|
| Limitation: shoulder flexion | | |
| Posterolateral mobilization with movement[22] | The patient is seated and the therapist stands beside the patient on the opposite side of the affected shoulder. One hand is placed posteriorly over the scapula, while the thenar eminence of the other hand is placed over the anterior aspect of the humeral head. A sustained posterolateral gliding force is applied to the humeral head along the plane of the glenohumeral joint. The patient is then asked to raise the affected arm in the scapular plane to the end of the pain-free range (ie, 0/10 on an NPRS) simultaneously with the mobilization technique<br>Perform 3 sets of 10 repetitions |  <br>  |

*Abbreviations: ER, external rotation; IR, internal rotation; NPRS, numeric pain-rating scale.*
**Each technique is adapted, in intensity and duration, to the patient's irritability level.*

## APPENDIX B

### HOME STRETCHING TECHNIQUES*

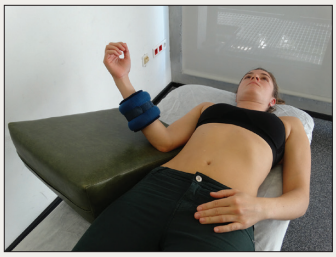
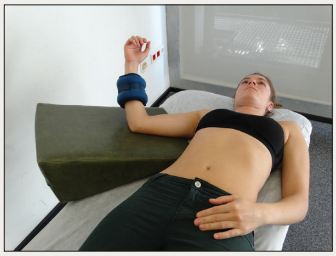
| Exercise Objectives | Soft Tissue Targeted | Description | Illustration |
|---|---|---|---|
| Stretch into ER at 0° of abduction[9] | Subscapularis muscle | The patient is in supine, with the shoulder supported on a foam wedge in 0° of abduction in the scapular plane, allowing gravity to produce the intended stretch into glenohumeral ER |  |
| Stretch into ER at 45° of abduction[9] (**ONLINE VIDEO**) | Subscapularis muscle and middle glenohumeral ligament | The patient is in supine, with the shoulder supported on a foam wedge in 45° of abduction in the scapular plane, allowing gravity to produce the intended stretch into glenohumeral ER |  |
| Stretch into ER at 90° of abduction[9] | Inferior glenohumeral ligament complex | The patient is in prone, with the shoulder at 90° of abduction and the forearm resting on a foam wedge, maintaining the intended stretch into glenohumeral ER |  |
| Stretch into IR at 30° of abduction[9] | Superior portion of the posterior capsule | The patient is in sidelying, with the shoulder supported on a foam wedge in 30° of abduction in the scapular plane, allowing gravity to produce the intended stretch into glenohumeral IR |  |

*Table continues on page D8.*

## APPENDIX B

| Exercise Objectives | Soft Tissue Targeted | Description | Illustration |
|---|---|---|---|
| Stretch into IR at 60° of abduction[9] | Superior portion of the posterior capsule | The patient is in sidelying, with the shoulder supported on a foam wedge in 60° of abduction in the scapular plane, allowing gravity to produce the intended stretch into glenohumeral IR |  |
| Stretch into IR at 90° of abduction[9] | Posterior capsule | The patient is in sidelying, with the shoulder supported on a foam wedge in 90° of abduction in the scapular plane, allowing gravity to produce the intended stretch into glenohumeral IR |  |

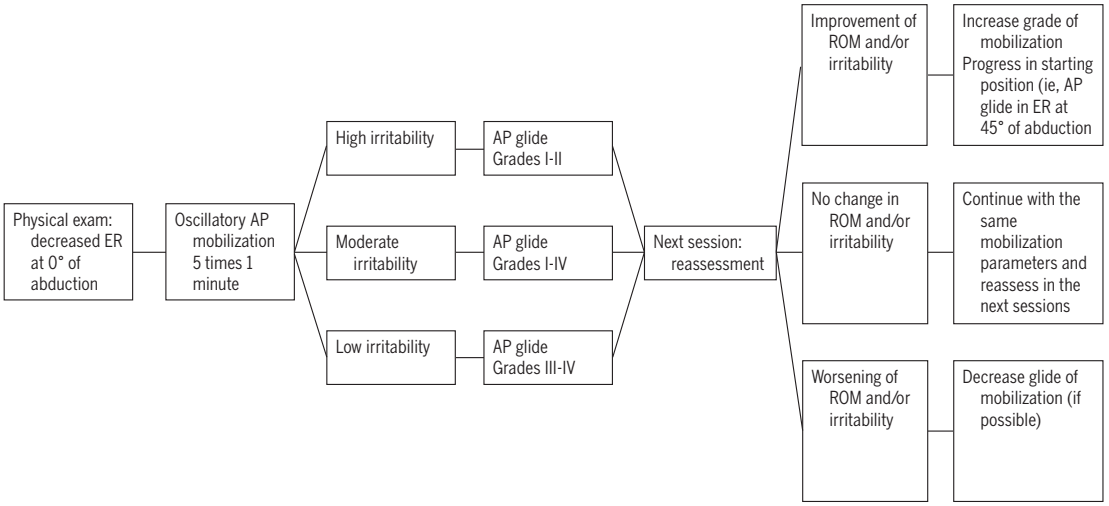
*Abbreviations: ER, external rotation; IR, internal rotation.*
**Patients performed the corresponding stretching exercises according to their glenohumeral limitations. Each stretching exercise was adapted, in intensity and duration, to the patient's irritability level. Each exercise lasted for 10 minutes. A 1.5-kg weight was used. In patients with high irritability, the stretching exercises need to be performed at low intensity, with a short duration (1-5 seconds) and no pain (ie, 0/10 on a numeric pain-rating scale).*

## APPENDIX C

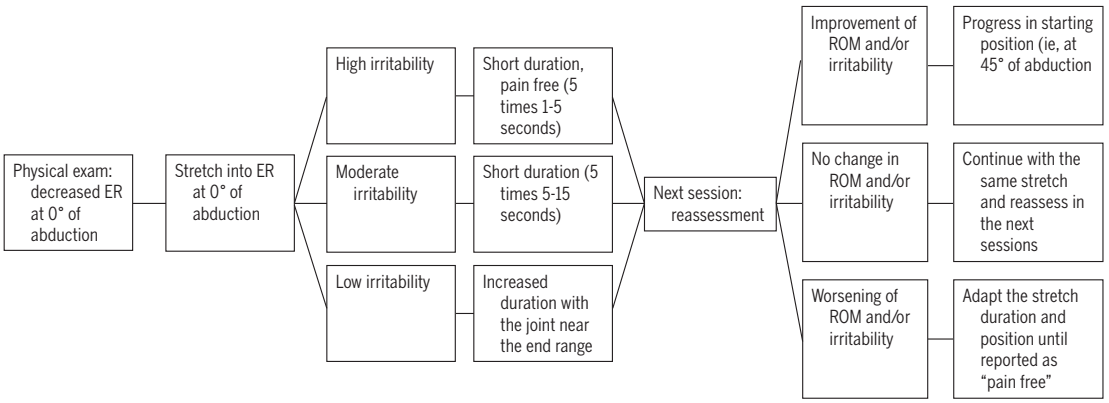
### PROGRESSION OF TECHNIQUES

Improvement of ER at 0° of abduction.

**Typical progression of the oscillatory AP mobilization technique used in this case series**




**Typical progression of the stretch into ER at 0° of abduction used in this case series**




*Abbreviations: AP, anteroposterior; ER, external rotation; ROM, range of motion.*

# Anexo VIII: Plantillas de entrenamiento domiciliario de la discriminación sensorial

EJEMPLO PLANTILLA ENTRENAMIENTO DOMICILIARIO DISCRIMINACIÓN SENSORIAL GRADUADA: SEMANA

| NÚMERO | CORRECTO | INCORRECTO |
|---|---|---|
| **7** | | |
| **9** | | |
| **7** | | |
| **5** | | |
| **8** | | |
| **2** | | |
| **1** | | |
| **5** | | |
| **7** | | |
| **6** | | |
| **9** | | |
| **1** | | |
| **2** | | |
| **4** | | |
| **6** | | |
| **1** | | |
| **7** | | |
| **4** | | |
| **8** | | |
| **3** | | |
| **3** | | |
| **6** | | |
| **5** | | |
| **7** | | |
| **2** | | |

| **NÚMERO** | CORRECTO | INCORRECTO |
|---|---|---|
| **5** | | |
| **8** | | |
| **2** | | |
| **9** | | |
| **8** | | |
| **5** | | |
| **2** | | |
| **3** | | |
| **7** | | |
| **3** | | |
| **9** | | |
| **4** | | |
| **9** | | |
| **5** | | |
| **9** | | |
| **5** | | |
| **5** | | |
| **4** | | |
| **3** | | |
| **8** | | |
| **8** | | |
| **9** | | |
| **1** | | |
| **7** | | |
| **7** | | |

EJEMPLO PLANTILLA ENTRENAMIENTO DOMICILIARIO DISCRIMINACIÓN SENSORIAL GRADUADA: SEMANA 2-4

| | | NÚMERO | | TIPO DE ESTÍMULO | |
|---|---|---|---|---|---|
| NÚMERO | ESTÍMULO | CORRECTO | INCORRECTO | CORRECTO | INCORRECTO |
| **4** | **boli** | | | | |
| **8** | **boli** | | | | |
| **5** | **boli** | | | | |
| **5** | **boli** | | | | |
| **9** | **corcho** | | | | |
| **9** | **corcho** | | | | |
| **3** | **boli** | | | | |
| **7** | **corcho** | | | | |
| **8** | **corcho** | | | | |
| **1** | **corcho** | | | | |
| **6** | **corcho** | | | | |
| **8** | **corcho** | | | | |
| **3** | **boli** | | | | |
| **4** | **corcho** | | | | |
| **3** | **corcho** | | | | |
| **9** | **boli** | | | | |
| **8** | **boli** | | | | |
| **4** | **boli** | | | | |
| **2** | **boli** | | | | |
| **5** | **boli** | | | | |
| **5** | **corcho** | | | | |
| **7** | **boli** | | | | |
| **8** | **corcho** | | | | |

EJEMPLO PLANTILLA ENTRENAMIENTO DOMICILIARIO DISCRIMINACIÓN SENSORIAL GRADUADA: SEMANA 2-4 (PROGRESIÓN)

| | | NÚMERO | | TIPO DE ESTÍMULO | |
|---|---|---|---|---|---|
| NÚMERO | ESTÍMULO | CORRECTO | INCORRECTO | CORRECTO | INCORRECTO |
| **12** | **corcho** | | | | |
| **5** | **corcho** | | | | |
| **12** | **corcho** | | | | |
| **3** | **boli** | | | | |
| **5** | **boli** | | | | |
| **4** | **corcho** | | | | |
| **7** | **corcho** | | | | |
| **9** | **corcho** | | | | |
| **12** | **boli** | | | | |
| **10** | **boli** | | | | |
| **2** | **boli** | | | | |
| **7** | **boli** | | | | |
| **12** | **boli** | | | | |
| **5** | **corcho** | | | | |
| **7** | **boli** | | | | |
| **4** | **corcho** | | | | |
| **8** | **corcho** | | | | |
| **4** | **corcho** | | | | |
| **10** | **corcho** | | | | |
| **9** | **corcho** | | | | |
| **4** | **boli** | | | | |
| **5** | **boli** | | | | |
| **9** | **corcho** | | | | |
| **9** | **boli** | | | | |
| **5** | **corcho** | | | | |
| **12** | **corcho** | | | | |
| **4** | **corcho** | | | | |

EJEMPLO PLANTILLA ENTRENAMIENTO DOMICILIARIO DISCRIMINACIÓN SENSORIAL GRADUADA: SEMANA 4-6

| LETRA | CORRECTO | INCORRECTO |
|---|---|---|
| **I** | | |
| **S** | | |
| **P** | | |
| **R** | | |
| **W** | | |
| **B** | | |
| **C** | | |
| **D** | | |
| **S** | | |
| **N** | | |
| **F** | | |
| **Z** | | |
| **U** | | |
| **P** | | |
| **X** | | |
| **L** | | |
| **F** | | |
| **G** | | |
| **Y** | | |
| **K** | | |
| **Q** | | |
| **C** | | |
| **Q** | | |
| **V** | | |
| **U** | | |
| **J** | | |
| **L** | | |
| **P** | | |

| LETRA | CORRECTO | INCORRECTO |
|---|---|---|
| **H** | | |
| **J** | | |
| **P** | | |
| **I** | | |
| **W** | | |
| **L** | | |
| **S** | | |
| **R** | | |
| **C** | | |
| **D** | | |
| **B** | | |
| **F** | | |
| **G** | | |
| **K** | | |
| **A** | | |
| **E** | | |
| **V** | | |
| **P** | | |
| **Y** | | |
| **M** | | |
| **K** | | |
| **P** | | |
| **W** | | |
| **D** | | |
| **X** | | |
| **F** | | |
| **B** | | |
| **T** | | |

EJEMPLO PLANTILLA ENTRENAMIENTO DOMICILIARIO DISCRIMINACIÓN SENSORIAL GRADUADA: SEMANAS 6-10

| PALABRA | CORRECTO | INCORRECTO |
|---|---|---|
| TIO | | |
| ALA | | |
| PIE | | |
| BAR | | |
| TEZ | | |
| TUL | | |
| OLA | | |
| AJO | | |
| BUS | | |
| MES | | |
| SUR | | |
| PUA | | |
| OCA | | |
| PAR | | |
| SED | | |
| ASA | | |
| FAN | | |
| ROE | | |
| BOL | | |
| DOS | | |
| ERA | | |
| LUZ | | |
| IRA | | |
| RES | | |
| MAR | | |
| GEL | | |
| LEO | | |

| PALABRA | CORRECTO | INCORRECTO |
|---|---|---|
| VOZ | | |
| TOS | | |
| MAS | | |
| PAZ | | |
| ASA | | |
| UÑA | | |
| VIA | | |
| OJO | | |
| OSO | | |
| PEZ | | |
| SAL | | |
| FEO | | |
| ARO | | |
| UNO | | |
| AMO | | |
| RIE | | |
| UVA | | |
| LIO | | |
| AÑO | | |
| CAN | | |
| SOL | | |
| FAZ | | |
| PAN | | |
| SIN | | |
| OSA | | |
| REY | | |
| RON | | |

# Anexo IX: Copia original del estudio 1

**Laterality judgement and tactile acuity in patients with frozen shoulder: A cross-sectional study, en la revista**

***Musculoskeletal Science and Practice***

Musculoskeletal Science and Practice 47 (2020) 102136

Contents lists available at ScienceDirect

Musculoskeletal Science and Practice

journal homepage: www.elsevier.com/locate/msksp

Original article

# Laterality judgement and tactile acuity in patients with frozen shoulder: A cross-sectional study

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ARTICLE INFO

*Keywords:*
Shoulder pain
Body image
Left/right judgement task
Two-point discrimination

ABSTRACT

*Background:* Disrupted tactile acuity and poor laterality judgement have been shown in several chronic musculoskeletal pain conditions. Whether they are impaired in people with frozen shoulder (FS) remains unknown.
*Objectives:* To determine whether there is impairment in tactile acuity and laterality judgement in subjects with FS.
*Methods:* Thirty-eight subjects with idiopathic FS and 38 sex and age-matched healthy controls were enrolled. The two-point discrimination threshold (TPDT) over the affected and unaffected shoulder of patients with FS and shoulder of healthy controls was evaluated. In addition, all participants performed a left/right judgment task (LRJT). Independent and dependent t-tests were used to compare group means. Pearson-product moment coefficient correlations between pain intensity and duration and LRJT and TPDT were calculated for the FS group.
*Results:* The TPDT over the affected shoulder was significantly increased compared to the unaffected shoulder (mean difference, 3.82 mm; 95% confidence interval [CI]:0.53, 7.10; p = .02) and controls (mean difference, 5.80 mm; 95% CI: 1.09, 10.52; p = .02). Patients with FS were less accurate (mean difference, 5.90%; 95% CI: 0.36, 11.43; p = .03) and slower (mean difference, −0.26 s; 95% CI: 0.06, 0.45; p = .01) responding to images of their affected shoulder compared to their unaffected shoulder. No associations were found between pain intensity and duration and either TPDT or laterality judgement.
*Conclusions:* Participants with FS demonstrated reduced tactile acuity and impaired laterality judgement over their affected shoulder compared to their unaffected shoulder. When compared to controls, subjects with FS showed reduced tactile acuity.
*Trial registration ClinicalTrials.gov Identifier:* NCT03320200.

## 1. Introduction

Shoulder pain is a highly prevalent condition among general population (Kelley et al., 2013). Specifically, frozen shoulder (FS) is a disabling musculoskeletal condition characterized by intense pain and large mobility deficits (Walmsley et al., 2014). Although FS has been widely studied, its epidemiology, aetiology, diagnosis and assessment are still poorly understood (Ryan et al., 2016).

To a large extent, physiotherapy management of FS has traditionally focused on structural dysfunctions found around the shoulder joint (Kelley et al., 2009, 2013). Although some physiotherapeutic interventions have shown to be effective in terms of pain reduction or mobility gains, there is currently little evidence that these interventions positively influence the disease natural history of FS (Struyf and Meeus, 2014). Some authors have argued that this fact raises the need for innovative research in the role central pain mechanisms might play in

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[1] www.paininmotion.be

https://doi.org/10.1016/j.msksp.2020.102136
Received 1 October 2019; Received in revised form 19 February 2020; Accepted 22 February 2020
Available online 24 February 2020

this chronic disorder (Struyf and Meeus, 2014). An example of maladaptive central pain mechanisms is structural reorganisation in the brain. Neuroimaging studies have provided evidence of alterations in brain morphology and functional activity associated to chronic pain (Baliki et al., 2011; Kuner and Flor, 2017; Morton et al., 2016) in people with fibromyalgia (Schmidt-Wilcke et al., 2007), complex regional pain syndrome (CRPS) (Juottonen et al., 2002; Maihöfner et al., 2003), osteoarthritis (Rodriguez-Raecke et al., 2009), and low back pain (Flor et al., 1997). Similarly, studies composed of participants with shoulder pain identified abnormal neuronal activity in multiple brain regions involved in the integration and processing of pain signals (Niddam et al., 2019; Yu et al., 2017) and changes in motor excitability and cortical motor representation (Ngomo et al., 2015).

Among the maladaptive structural changes, reorganisation in the primary somatosensory cortex (S1) (i.e. shrinkage or shifting of the representation of the affected body region) have been observed in different chronic pain populations (Flor et al., 1997; Lotze and Moseley, 2007; Maihöfner et al., 2003). This brain area holds a somatotopic map of the body's surface (Penfield and Boldrey, 1937). However, the awareness of the body's position in space is a multisensory representation that involves the somatosensory cortices and multiple areas of the brain that code for visual, tactile, and proprioceptive inputs (Moseley et al., 2012). The extent of S1 cortical reorganisation (Flor et al., 1997) has been shown to correlate with a decrease tactile acuity (Flor et al., 1997) and is clinically expressed as an increased in the two-point discrimination threshold (TPDT) (Catley et al., 2013; Lotze and Moseley, 2007). Tactile acuity is altered in patients with several chronic pain conditions such as osteoarthritis (Stanton et al., 2013) and low back pain (Adamczyk et al., 2018a) where larger TPDTs were found in patients compared to controls. Additionally, the sensory and motor cortices are functionally linked to form our perception of the body and provide internal organization for movement. The so called "body schema" is suggested to be the link between brain sensoriomotor maps (Moseley and Flor, 2012). Since the integrity of the body schema depends on correct input from S1, cortical reorganisation of S1 may provoke incongruence between predicted and actual sensory feedback and motor output thus negatively influencing proprioception (Ager et al., 2019) and motor performance (Elsig et al., 2014; Luomajoki and Moseley, 2011). The integrity of the body schema can be indirectly measured by performing a left/right judgment task (LRJT) (Lotze and Moseley, 2007). The LRJT consists in viewing images of a body part and determining whether each image belongs to, i.e., the left or right side of the body. Two recent systematic reviews have provided evidence of impaired laterality judgement of the affected limb in different chronic pain populations (Breckenridge et al., 2019; Ravat et al., 2019). Regarding shoulder pain, a small sample study found a faster reaction time in a LRJT and decreased tactile acuity at the painful arm in patients with chronic nonspecific complaints of arm, neck and shoulder, which might imply disturbed information processing of sensory and motor feedback (Heerkens et al., 2018).

Interestingly, in people with chronic pain, tactile acuity and LRJT impairments can be related to clinical aspects such as pain intensity and duration of symptoms. For instance, in people with CRPS, tactile acuity was reduced on the affected limb compared to the unaffected limb and the difference between limbs was correlated to pain intensity (Maihöfner et al., 2003; Pleger et al., 2004). Similarly, delayed recognition in hand laterality was correlated to the duration of symptoms (Moseley, 2004).

Taking into account the evidence provided by the literature and considering that FS is a long-lasting musculoskeletal condition with continuous nociceptive activity in the early stages, it is plausible to observe cortical reorganisation of S1 and disruption of the body schema in this population (Moseley and Flor, 2012; Pelletier et al., 2015). Apart from recent case studies and case-series (Louw et al., 2017; Sawyer et al., 2018), the maladaptive brain changes in people with FS has not been fully studied and remains speculative. Acquiring further knowledge on the pain mechanisms of chronic pain conditions such as FS is essential for designing better diagnosis and treatment strategies (Moseley and Flor, 2012). In addition, central alterations have demonstrated to have a crucial role in the pathophysiology and clinical manifestations of many musculoskeletal disorders (Armijo-Olivo, 2018; Roy et al., 2017).

Therefore, the primary aim of this study was to explore whether people with FS presented with clinical evidence of disrupted cortical maps specific to the site of pain and disrupted working body schema. We used the TPDT to assess tactile acuity and a LRJT for laterality judgement. These measurements were compared between the affected and unaffected side in the FS group and the affected side in the FS group and dominant side in a healthy control group. We hypothesized that tactile acuity and laterality judgement would be impaired over the painful side in people with FS in comparison to the unaffected side and in comparison to controls. As a secondary aim of this study, possible associations between tactile acuity and laterality judgement and clinical aspects (severity and duration of symptoms) in subjects with FS were also investigated.

## 2. Methods

### 2.1. Design

The study was a cross-sectional case-control study undertaken at the University of Valencia (Spain) examining tactile acuity and laterality judgement in patients with FS and an age and gender-matched comparison group. The paper is reported following the STROBE statement (Von Elm et al., 2007).

### 2.2. Participants

Thirty-eight participants diagnosed by a physician with primary or idiopathic FS were consecutively recruited in Valencia (Spain) together with thirty-eight sex and age-matched healthy volunteers. Recruitment of both groups occurred between July 2018 and June 2019 by advertising posters at the physiotherapy department of the University of Valencia and private physiotherapy centers.

The sample size was calculated using G*Power 3.1 software based on the TPDT as the primary outcome measure. To the best of our knowledge, there are no studies investigating differences in TPDT between participants with FS and healthy subjects. We determined our sample size based on the study of Botnmark et al. (2016) which reported a TPDT of the dominant and non-dominant shoulder of healthy subjects of 44.8 (13.1) mm and 39.3 (9.5) mm, respectively, with a statistically significant mean side-to-side difference of 5.5 (13.5). Considering a 80% power and an alpha level of 0.05, a total sample size of 72 patients was estimated (36 per group). An allowance was made for a 5% dropout rate, increasing the sample size to 76 patients (38 per group).

The specific inclusion criteria for the FS group were: (1) having greater than 50% limitation of passive external rotation in the affected shoulder compared to the unaffected shoulder or less than 30° of external rotation in the affected shoulder (Breckenridge et al., 2017); (2) range of motion loss greater than 25% in at least two movement planes in the affected shoulder compared to the unaffected shoulder (Breckenridge et al., 2017); (3) pain and movement restriction should be present for at least one month either having reached a plateau or worsened (Kelley et al., 2009); and (4) shoulder radiographs had to be normal (with the exception of osteopenia of the humeral head and calcific tendinosis). (Zuckerman and Rokito, 2011).

The specific inclusion criterion for the controls was no actual shoulder pain or previous history of shoulder complaints including FS. Exclusion criteria for both groups were locked dislocations, arthritis, fractures or avascular necrosis on shoulder radiographs or previous surgery in the upper quadrant region during the last year. Moreover, those subjects not understanding written or spoken Spanish language, having any skin or medical condition preventing them from receiving

tactile stimuli on the shoulder, any neurological or motor disorder including a diagnosis of dyslexia or difficulty performing a rapid naming task (Silva et al., 2012), visually impaired or having a diagnosed psychopathology were excluded from the study.

The study was approved by the Ethical Committee of the University of Valencia the (reference number H1532330957968) and all procedures were performed in accordance with the Declaration of Helsinki. All participants gave their written informed consent prior to participate in the study.

### 2.3. Procedures

A researcher (MB), who assessed suitability of each participant via the inclusion and exclusion criteria, initially examined participants. This researcher was different to that one involved in TPDT and LRJT measurements. Prior to testing, both groups provided demographic information. In addition, symptoms' duration and self-perceived shoulder pain using a visual analogue scale (VAS) were recorded in the FS group. In particular, participants were asked to mark on a 10-cm line their average shoulder pain in the last 24 h between 0 ("no pain") and 10 ("worst possible pain"). Tactile acuity and LRJT were then assessed in all participants, in the same session, by a physiotherapist with a postgraduate degree in manual therapy and 10 years working experience with the use of tactile acuity and LRJT. The examiner was not blinded to the participants' clinical status but was blinded to the side of pain in the FS group.

### 2.4. Tactile acuity

Tactile acuity was assessed by means of the TPDT. A mechanical sliding calliper with precision of 1 mm (Duratech™ TA-2081), was used to measure TPDT. Prior to formal testing, one familiarization trial was conducted on the participant's forearm. During formal testing, participants were positioned in sitting with the arm in a relaxed neutral position. A point 5 cm distal to the lateral border of the acromion was marked on the painful and non-painful shoulder for participants with FS. The same point was marked in the dominant shoulder for healthy controls (Botnmark et al., 2016). In order to standardise the testing region, a vertical line was drawn from the middle edge of the acromion towards the elbow and the TPDT was performed following that line, in the longitudinal direction of the arm (Fig. 1). (Adamczyk et al., 2018b) The 5 cm mark below the lateral border the acromion process was kept between the two calliper points in all assessments (Botnmark et al., 2016).

The calliper was applied with even pressure through both tips, until the very first blanching of the skin (Moberg, 1990). Participants were instructed to inform the tester whether they could feel one or two points. The TPDT was defined as the smallest distance between calliper points that was perceived as two points instead of one. An ascending and a descending run was completed for each shoulder tested following the staircase method (Yarnitsky, 1997). The test began in 0 mm and the distance was first gradually increased in 5 mm increments until the participant perceived two points instead of one. Once the subject reported perceiving two points, the following responses established the TPDT: (i) the subject reported a single point when the distance between calliper points was decreased below threshold, (ii) the subject reported two points when the distance between calliper points was increased back to the determined threshold, and (iii) the subject reported a single point when a single point was applied (Stanton et al., 2013). In case participants don't comply with all these three criteria (i-iii), the distance between calliper points was incremented further 5 mm. Descending runs began with the calliper points separated 30 mm more than the TPDT value obtained from the ascending run, followed by decrements of 5 mm. A similar protocol as described above (i.e. i-iii) was used to establish the threshold value in this descending run (Lotze and Moseley, 2007). Stimuli out of sequence were included (contracting the callipers instead of expanding them with ascending runs or vice versa) to verify that participants were not guessing. Subjects were instructed to report if they felt one or two points after each application. If they were unsure, they were instructed to report one point. In addition, participants were asked to inform the researcher if they perceived two points because of a temporal delay in the presentation of the two points and, in this case, that trial was repeated. A mean TPDT value was obtained from the two threshold scores and used for subsequent analysis. In participants with FS, both shoulders were tested in a random order. In the healthy controls, only the dominant shoulder was tested.

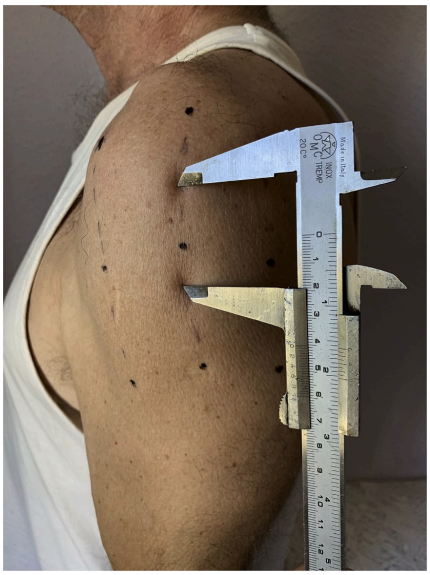

**Fig. 1.** Region for TPDT testing. Anterior and posterior edges and mid-point of the acromion process were marked. From these bony landmarks, vertical lines in the longitudinal direction of the arm and 5-cm marks below the bony landmarks were drawn. The 5 cm mark below the mid-point of the acromion process was used for TPDT testing and kept between the two calliper points to standardise the testing region.

### 2.5. Left/right judgement task (LRJT)

Laterality judgement was assessed with a LRJT using the Neuro Orthopaedic Institute (NOI) Recognise™ online program (www.noigroup.com). A total of 30 shoulder pictures using the Context mode of the NOI program were presented on a laptop to participants in a random order. They were instructed to decide whether the picture showed a right or left shoulder giving a response as quickly as possible without guessing. Both accuracy and response time were recorded in this LRJT. Accuracy was defined as the percentage of images correctly judged and response time as the time employed to decide whether the picture showed a right or left shoulder. If participants timed out (>5 s) for four or more images in a row this fact was taken as reflecting distraction from the task and the test was then repeated. The test was performed twice (two identical blocks of 30 images) with a 2-min break between each block to obtain a real sense of laterality judgement. The first block was considered for task training and consequently data from this block was discarded. Data from the second block were then used for analysis (Wallwork et al., 2013).

The protocol used in this study has proved to be highly reliable in healthy subjects with a mean (SD) normative response time and accuracy for this shoulder specific LRJT of 1738 (741) ms and 93.5 (9.2)%, respectively (Breckenridge et al., 2017).

**Table 1**
Characteristics of participants with frozen shoulder (n = 38) and health age and sex matched control participants (n = 38).

| | Frozen shoulder (n = 38) | Control (n = 38) | Differences between groups (p-values) |
|---|---|---|---|
| Age (years) | 52.5 (7.3) | 52.9 (7.3) | 0.8 |
| Sex (male/female) | 12/26 | 12/26 | N/A |
| Hand dominance (left/right) | 1/37 | 1/37 | N/A |
| Shoulder affected (left/right) | 21/17 | N/A | N/A |
| Symptoms' duration (months) | 8.5 (5.9) | N/A | N/A |
| VAS 24 h[a] (0–100 mm) | 46.5 (27.2) | N/A | N/A |

[a] VAS 24 h: visual analogue scale in the last 24 h. Data are reported as mean (standard deviation).

### 2.6. Statistical analysis

All statistical analyses were performed using SPSS 24.0. Descriptive statistics were used to present demographic and clinical information. Normality of the TPDT and LRJT data was explored using the Shapiro-Wilk test. Dependent t tests were used to compare TPDT and LRJT (accuracy and response time) between the affected and unaffected shoulder in the FS group. Independent t tests were used to compare participants with FS (affected shoulder) and healthy controls (dominant shoulder) in those two clinical measurements. Pearson-product moment coefficient correlations were calculated in the FS group between symptoms duration and pain intensity (VAS 24 h) and results from the LRJT (accuracy and response time) and TPDT. Effect sizes were calculated through Cohens' d according to the formula d = mean difference/SD. Differences were deemed significant at $p < .05$.

## 3. Results

All participants completed all parts of the study. All TPDT and LRJT values were normally distributed. Demographic data of participants are summarized in Table 1. No statistically significant differences were found between groups at baseline (all $p > .05$).

In the FS group, the mean (SD) TPDT over the affected shoulder was 41.71 (10.88) mm and 37.89 (8.92) mm for the unaffected side. This difference was statistically significant (mean difference, 3.82 mm; 95% CI: 0.53, 7.10; $t(37) = 2.35$, $p = .02$) . Moderate effect sizes were observed for the TPDT in the FS group (d = 0.38). In the healthy control group, the mean (SD) TPDT value was 35.91 (9.72) mm. A statistically significant difference was found between the TPDT measured at the affected shoulder in the FS group and the TPDT of the dominant shoulder in the healthy control group (mean difference, 5.80 mm; 95% CI: 1.09, 10.52; $t(74) = 2.45$, $p = .02$) (Fig. 2). This TPDT comparison presented a medium effect size (d = 0.56).

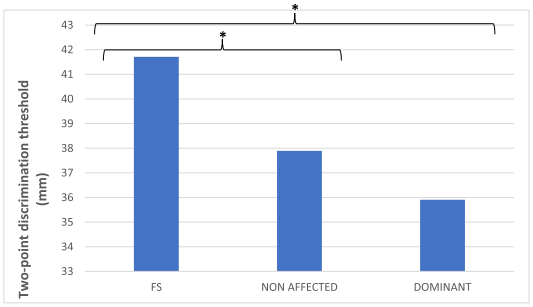


**Fig. 2.** Mean and SD of the TPDT in the affected and unaffected shoulder of the FS group and dominant shoulder of the control group.***p<.05**.

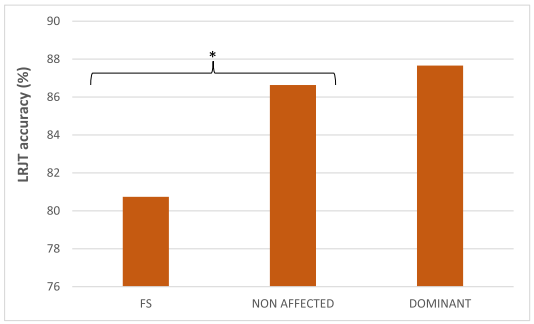


**Fig. 3.** Mean and SD of the accuracy in LRJT in the affected and unaffected shoulder of the FS group and dominant shoulder of the control group. ***p<.05**.

In the FS group, mean (SD) accuracy and response time of the affected shoulder in the LRJT was 80.73 (21.47) % and 1.88 (0.46) seconds, respectively. In the unaffected side, mean (SD) accuracy and response time was 86.63 (15.53) % and 1.62 (0.41) seconds. A statistically significant difference between the affected and unaffected shoulder in subjects with FS was found for accuracy (mean difference, 5.90%; 95% CI: 0.36, 11.43; $t(37) = 2.16$, $p = .03$) and response time (mean difference, −0.26 s; 95% CI: 0.06, 0.45; $t(37) = 2.69$, $p = .01$) (Fig. 3 and 4), with moderate effect sizes (d = 0.32 and d = 0.59 respectively for accuracy and response time) The mean (SD) accuracy and response time of the dominant shoulder for the healthy controls was 87.66 (15.36)% and 1.85 (0.39) seconds, respectively. Compared to values obtained in the affected shoulder of the FS group, no significant differences were found for accuracy ($t(74) = 1.62$, $p = .1$) or response time ($t(74) = 0.32$, $p = .7$) in the LRJT (Fig. 3 and 4). Table 2 summarizes the mean (SD) values for the TPDT and LRJT in participants with FS and healthy controls. No significant correlations were observed between pain intensity and TPDT ($r_p = -0.02$, $p = .91$) or accuracy ($r_p = -0.03$, $p = .85$) and response time ($r_p = -0.05$, $p = .76$) in the LRJT in the FS group. Similarly, no correlations were found between symptom duration and TPDT ($r_p = -0.08$, $p = .61$) or accuracy ($r_p = -0.03$, $p = .88$) and response time ($r_p = -0.01$ $p = .98$) in the LRJT in the FS group.

## 4. Discussion

The purpose of this study was to determine whether tactile acuity

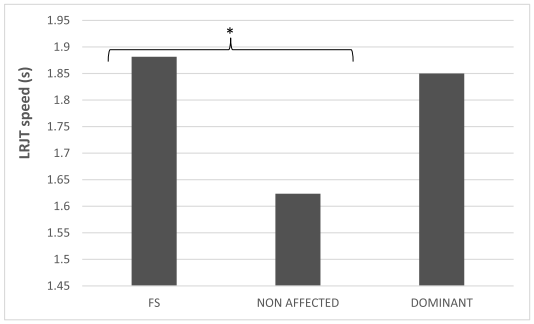


**Fig. 4.** Mean and SD of the speed in LRJT in the affected and unaffected shoulder of the FS group and dominant shoulder of the control group. .***p<.05**.

**Table 2**
TPDT and laterality judgement in FS and healthy control group.

| Shoulder | TPDT | | Laterality judgement (right shoulder) | | | |
|---|---|---|---|---|---|---|
| | | | Accuracy (%) | | Speed (s) | |
| | Mean ± SD | p value | Mean ± SD | p value | Mean ± SD | p value |
| FS affected | 41.7 (10.9) | **.02** | 80.7 (21.5) | **.04** | 1.88 (0.5) | **.01** |
| FS unaffected | 37.9 (8.9) | | 86.6 (15.5) | | 1.62 (0.4) | |
| Dominant | 35.9 (9.7) | **.01** | 87.7 (15.4) | .1 | 1.85 (0.4) | .7 |

TPDT, two point discrimination threshold. Bold values mean statistically significant difference. Data are reported as mean (standard deviation).

and laterality judgement are altered in people with FS and whether any alterations are associated to pain severity and symptoms duration. Our findings may indicate that tactile acuity is impaired in people with FS over the affected shoulder in comparison to the unaffected shoulder and when compared to healthy controls. Furthermore, in comparison to the unaffected shoulder, people with FS had less accuracy and a delayed reaction time in the affected shoulder in a LRJT. Neither pain intensity nor symptoms duration were correlated with either tactile acuity or laterality judgement in the FS group.

Our data regarding TPDT are in accordance with those obtained by Heerkens and colleagues at the painful arm in patients with chronic nonspecific shoulder complaints (Heerkens et al., 2018) and with a large body of evidence that suggests that tactile acuity is diminished in people with several chronic musculoskeletal pain conditions (i.e. osteoarthritis, CRPS, chronic low back pain) at the site of pain in comparison to pain-free controls (Catley et al., 2014). In addition, when consider patients as their own control and comparing tactile acuity at the painful shoulder to the corresponding site on the non-painful shoulder, a larger TPDT in the affected shoulder was observed. Previous studies performed in people with unilateral chronic pain (i.e. CRPS) also found larger TPDT values at the affected side in comparison with the contralateral unaffected side (Catley et al., 2014). Clinical interpretation of our results is challenging because the cut-off value at which tactile acuity deficit become clinically meaningful remains unknown. Botnmark et al. (2016), using the same protocol as in our study, reported a side-to-side TPDT mean (SD) difference of 5.5 (13.5) mm between the dominant and non-dominant shoulder of pain-free subjects. The TPDT difference that we found when comparing the affected and unaffected shoulder of people with FS (3.82 mm), was lower than the value reported by Botnmark et al. (2016) Although statistically significant, we could thus argue that this within-group difference might not be clinically relevant. To further support this argument, the mean TPDT value that we obtained in the affected shoulder in the FS group (i.e. 41.71 mm) would be considered a "normal" value according to the TPDT previously reported for healthy subjects (i.e. 44.8 mm) (Botnmark et al., 2016). Despite we also found a higher TPDT in the affected shoulder of people with FS compared to healthy controls, the TPDT value obtained in the painful shoulder of people with FS was similar to that reported for healthy shoulders. These conflicting results regarding tactile acuity are in line with the criticism raised in the literature due to the unexplained variability observed in TPDT within subjects, between subjects and between studies. Indeed some researchers even argue that TPDT should not be used as a scientific measure of acuity (Craig and Johnson, 2000). Further research may calculate the TPDT standard error of measurement or the reliable change index in the shoulder area as done for instance in the lumbar region (Wand et al., 2014). This would contribute to determine the size of the TPDT difference needed to be distinguishable from measurement errors in people with shoulder pain.

People with FS had less accuracy and a delayed response time in their affected shoulder in comparison to the unaffected shoulder in the LRJT. This finding contrasts with the study results of Heerkens et al. (2018) where a faster reaction time at the painful arm was observed in patients with chronic nonspecific shoulder complaints. However we are in line with current literature which has shown that people with several chronic pain disorders tend to be less accurate and slower in a LRJT on the injured site (Breckenridge et al., 2019; Ravat et al., 2019). A recent systematic review concluded that patients with upper limb pain are slower and less accurate at recognising images that correspond to the side of their painful body part and at discriminating between left and right images compared to healthy controls (Breckenridge et al., 2019). However, heterogeneity of the studies included in that review was substantial.

Abnormally long response times in the LRJT are thought to reflect delayed processing of body/spatial representations. In particular, they are thought to reflect a bias in information processing away from the delayed side or toward the opposite side (Hudson et al., 2006; Moseley, 2004). Reduced accuracy is thought to reflect disrupted cortical proprioceptive representations (Moseley and Flor, 2012). However, similar to TPDT, one should be cautious when interpreting our laterality judgement scores. Mean (SD) normative values for accuracy and response time in healthy subjects have been reported to be 93.5(9.2)% and 1.7 (0.7) seconds using the same shoulder specific LRJT as we used in this study (Breckenridge et al., 2017). Our within and between-group differences in the LRJT are again difficult to be interpreted because the values we obtained for accuracy in the unaffected shoulder (i.e. mean = 86.63; SD = 15.53%) would be considered "abnormal" based on those normative values. In addition, the difference observed in accuracy and response time between the affected and unaffected shoulder of participants with FS (i.e. 5.90% and 0.26s) is probably too small to be considered clinically meaningful. Therefore, more research is needed to reach firm conclusions on the role of body schema disruption in people with FS.

Our study shows that tactile acuity and laterality performance deficits are independent of the perceived intensity of the pain or pain duration in people with FS. Analysis of the pooled data of a systematic review about tactile acuity in people with chronic pain showed no significant associations between tactile acuity and either pain intensity or pain duration which would support our findings (Catley et al., 2014). However, correlations in that review were reported for people with chronic pain (Botnmark et al., 2016). Recent studies assessing tactile acuity in response to acute pain induction have demonstrated a site-specific sensory adaptation to pain (Adamczyk et al., 2018b, 2019). While tactile acuity decreased immediately after experimentally induced low back pain (Adamczyk et al., 2018b), experimental neck pain did not elicit changes in tactile acuity (Adamczyk et al., 2019). Influence of pain intensity and duration in laterality judgement has not been fully elucidated yet (Ravat et al., 2019). Further research might also investigate the possible relationships between tactile acuity, body schema integrity, shoulder proprioception and physical performance in people with FS.

One strength of this study is age and sex-matching. Although the link between age-sex and tactile acuity and laterality judgement is still unclear, it has been recommended to match patients with chronic pain and pain-free participants in terms of age and gender when performing these measurements (Catley et al., 2014; Ravat et al., 2019). Consideration must be given to the limitations of this study. Deviating from normal laterality judgement or tactile acuity values may indicate changes in somatosensory homunculus but may also be due to other factors such as

impaired touch perception, slow processing or difficulty with coordination, attention or decision-making process (Catley et al., 2014; Ravat et al., 2019). It is not possible to infer how these confounding factors which were not considered in this study may have influenced our results. The assessor made subjective assessment as to when the TPDT was determined which might have introduced assessor bias. Laterality judgement was tested using a mobile phone, which differ to the majority of studies where a computer-based assessment was performed (Ravat et al., 2019). Only a practice run of 30 pictures before formal laterality testing was done but a practice round of approximately 80 pictures is needed for the LRJT becoming implicit (Bray and Moseley, 2011). Further work should formulate standardized protocols for laterality judgment tasks (i.e. number of trials, number of pictures) and tactile acuity to be used in people with chronic pain including those with FS. We did not assess remote sites to investigate if impairment in laterality judgement and tactile acuity were restricted to the area of pain or were generally altered in other regions of the body. Whether patients were with pain during assessments was not registered. Both tactile acuity and laterality judgement might be pain-dependent so the presence of pain during assessments might have influenced our results. Other potential confounding factors (i.e. activity levels/arm usage, age) should also be considered when interpreting the results of this study. For instance, tactile acuity performance declines with increasing age (Woodward, 1993). While the researcher testing the participants with FS was blinded to side (affected vs unaffected) in the FS group, no blinding to clinical status was possible as only one side (the dominant side) was assessed in the control group. The inclusion of two testers, one for the cases and one for the controls, might have been useful for controlling for this fact but at the same time might have introduced additional error to the measurements.

## 5. Conclusions

Participants with FS demonstrated reduced tactile acuity over their affected shoulder when compared to their unaffected shoulder and controls. In comparison to the unaffected shoulder, less accuracy and a delayed response time in a LRJT was found in the affected shoulder of the FS group. However, our results should be interpreted with caution as the clinical meaningfulness of these findings remains unknown. This consideration is especially important before physical therapists fully implement strategies targeting the CNS in people with FS.

## Funding

The authors affirm that they have no affiliations with or financial involvement in any organization or entity with a direct financial interest in any matter included in this manuscript.

This cross-sectional study received approval from the Institutional Review Board at the University of Valencia, Spain (reference number H1532330957968).

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.msksp.2020.102136.

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# Anexo X: Copia original del estudio 2

**A Central Nervous System Focused Treatment Program for People with Frozen Shoulder: A Feasibility Study,** en la revista ***International Journal of Environmental Research and Public Health***

International Journal of
*Environmental Research and Public Health*

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MDPI

https://doi.org/10.3390/ijerph19052628

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# A Central Nervous System Focused Treatment Program for People with Frozen Shoulder: A Feasibility Study

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**Abstract:** Background: Frozen shoulder (FS) is a highly disabling pathology of poorly understood etiology, which is characterized by the presence of intense pain and progressive loss of range of motion (ROM). The aim of this study is to evaluate the feasibility and clinical impact of a CNS-focused treatment program for people with FS. Methods: 10 subjects with primary FS received a 10-week CNS-focused intervention including sensory discrimination training and graded motor imagery techniques delivered as clinic sessions (60 min) and home therapy (30 min five times per week). Measurements were taken at baseline, after a 2-week "washout" period, after treatment, and at three months follow-up. The Shoulder Pain and Disability Index (SPADI) was the primary outcome. Secondary measures were feasibility-related outcomes, self-reported shoulder pain, active and passive range of motion, two-point discrimination threshold (TPDT), left/right judgement task (LRJT), fear-avoidance (Tampa Scale for Kinesiophobia), pain catastrophization (Pain Catastrophizing Scale), and pain sensitization (Central Sensitization Inventory). A Student's *t*-test was used to assess the "washout" period. A repeated measure analysis of variance (ANOVA) was used to evaluate within-subjects' differences for all outcome measures in the different assessment periods and a pairwise analysis was used to compare between the different assessment points. Statistical significance was set at $p < 0.05$. Results: 70% of participants completed the treatment. No significant changes were found after "washout" period except for TPDT ($p = 0.02$) and SPADI ($p = 0.025$). Improvements in self-reported shoulder pain ($p = 0.028$) and active shoulder flexion ($p = 0.016$) were shown after treatment ($p = 0.028$) and follow-up ($p = 0.001$) and in SPADI at follow-up ($p = 0.008$). No significant changes were observed in TPDT, LRJT, fear-avoidance, pain catastrophization, and pain sensitization. Conclusions: a CNS-focused treatment program might be a suitable approach to improve pain and disability in FS, but further research is needed to draw firm conclusions.

**Keywords:** adhesive capsulitis; feasibility study; frozen shoulder; motor imagery; patient compliance; tactile discrimination training

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**Citation:** Mena-del Horno, S.; Dueñas, L.; Lluch, E.; Louw, A.; Luque-Suarez, A.; Mertens, M.G.; Fuentes-Aparicio, L.; Balasch-Bernat, M. A Central Nervous System Focused Treatment Program for People with Frozen Shoulder: A Feasibility Study. *Int. J. Environ. Res. Public Health* **2022**, *19*, 2628. https://doi.org/10.3390/ijerph19052628

Academic Editors: César Fernández De Las Peñas and Paul B. Tchounwou

Received: 29 December 2021
Accepted: 21 February 2022
Published: 24 February 2022

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## 1. Introduction

Frozen shoulder (FS) is a highly disabling pathology of poorly understood etiology [1], which is characterized by the presence of intense pain and progressive loss of range of

motion (ROM) [2]. FS is present in 2–5% of the general population, especially in women aged between 40 and 65 years and its exact etiology is currently unknown [3]. The pathophysiology of FS is a complex and multifactorial process encompassing several mechanisms such as an upregulation of grown factors and inflammatory cytokines, which stimulate fibroblast proliferation and differentiation into myofibroblasts. This in turn leads to an imbalance of extracellular matrix turnover and a resultant stiff and thickened glenohumeral capsule with an abundance of type III collagen [4]. Accumulation of advanced glycation end products (AGEs) has also been shown in people with FS [5]. In addition, a state of low grade inflammation, which is associated with diabetes, cardiovascular disease, and thyroid disorders, seems also to predispose to the development of FS [6]. Many treatments have been proposed for FS including conservative (i.e., manual therapy) [7] and non-conservative approaches (i.e., arthroscopic capsular release) [8]. The most common and recommended physical therapy interventions used for treating these patients are mobilization techniques and exercises, while the utility of other suggested interventions such as aerobic exercise, lifestyle changes, or pain neuroscience education is still hypothetical [9]. To date, none of these interventions has demonstrated to have an influence on the natural history of this condition, therefore innovative research seems necessary [10]. Some authors have suggested an involvement of central pain mechanisms secondary to continuous nociception characteristic of the early stages of FS [10]. In line with this, two systematic reviews showed preliminary evidence that central pain mechanisms may contribute to shoulder pain of different etiologies [11,12], but recent studies questioned those findings [13,14]. Importantly, these reviews did not include people with FS, so the role of the central nervous system (CNS) in this clinical condition remains speculative.

Different approaches targeting the CNS (e.g., graded motor imagery (GMI) and tactile discrimination training) have been applied in a variety of chronic musculoskeletal pain disorders with promising results [15,16]. Specific to shoulder pain, only a few studies have investigated the clinical effectiveness of CNS-focused interventions. Louw et al. [17] presented a case-series where a CNS-focused treatment program based on a brief mirror therapy intervention was applied in subjects with shoulder pain and limited active ROM. This approach showed statistically significant improvements in pain, pain catastrophization, fear-avoidance, and shoulder flexion active ROM [17]. However, only 8.7% of the sample presented a diagnosis of FS. Similarly, Sawyer et al. [18] applied a combination of pain neuroscience education, tactile discrimination training, and GMI in an individual with FS. The patient reported significant improvements in pain, fear of movement, and active ROM. Further high-quality research about the effectiveness of CNS-focused treatments in people with FS is thus needed.

The aim of this study is to evaluate the feasibility and clinical impact when implementing a CNS-focused treatment program for people with FS. The results of this study will inform of the appropriateness to conduct a randomized controlled trial on this topic.

## 2. Materials and Methods

### *2.1. Sample Recruitment*

A convenience sample of 10 subjects diagnosed with FS was recruited. Since there is no gold standard to diagnose FS, diagnosis was established by a physician based on clinical examination, exclusion of other pathologies, and imaging [19]. Patients included had to present with primary or idiopathic FS, a limitation in passive external rotation >50% compared to the unaffected shoulder or less than 30° of passive external rotation, and a ROM loss >25% in at least two movement planes [20]. Additionally, pain and movement restriction had to be present for at least one month having either reached a plateau or worsened [20] and radiographs had to be normal (with the exception of osteopenia of the humeral head and calcific tendinosis) [21].

Patients that presented with locked dislocations, arthritis, fractures, or avascular necrosis were excluded. Furthermore, those subjects not understanding Spanish language, having previous upper quadrant region surgery during the last year, any skin or medical

condition preventing them from receiving tactile stimuli on the shoulder, any neurological or motor disorder, visually impaired, or having a diagnosed psychopathology were excluded from the study. All participants were instructed to continue taking any current medications, but not to start new medications or initiate new treatments during the treatment period.

*2.2. Procedures*

This feasibility study involved a 10-week CNS-focused intervention and periodic assessment of the participants. All outcome measurements were performed at baseline and after a two-week period of "washout" with no intervention (T0) [22]. After this initial assessment, participants began the treatment and were again measured at the end of treatment (3 months after baseline (T1) and at three months follow-up (T2) (Figure 1)).

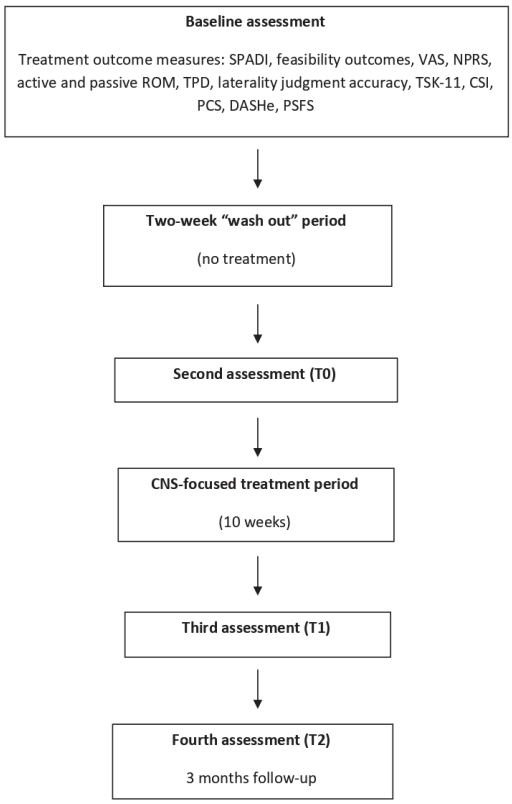


**Figure 1.** Assessment and treatment flowchart diagram.

The CNS-focused intervention consisted of a 10-week treatment program (1 session per week) delivered as 60 min sessions. In addition, participants performed a 30-min home training program five times per week during those 10 weeks. The CNS-focused intervention included discussion of the participant's shoulder pain experience from a pain neuroscience perspective provided in the first session plus graded sensory discrimination training and GMI [23]. The physiotherapist performing treatment (S.M.) had a post-graduate degree in manual therapy and was trained in how to perform the treatment by another researcher (E.LL.) with 10 years working experience in the use of these interventions.

### 2.3. Primary Outcome Measure

The primary outcome was self-reported shoulder pain and disability measured with the Shoulder Pain and Disability Index (SPADI) [24]. The SPADI is a 13-item shoulder function index assessing pain and disability related to shoulder dysfunction [25]. Each item is scored by a numeric scale (0–10) and the total score ranges from 0 to 100 points. A higher score indicates greater disability. The Spanish version of the SPADI has shown high internal consistency and excellent test-retest reliability [26]. The Minimal Clinically Important Difference (MCID) for the SPADI ranges from 8 to 13 points [27].

### 2.4. Secondary Outcome Measures

Different feasibility outcomes were considered as secondary: timely recruitment, number of participants completing treatment, treatment compliance and barriers (with clinic and home training sessions), and number of patients measured at follow-up. To assess treatment adherence, patients were provided with a diary to record their compliance with therapy [28]. After treatment completion, patients provided the diary to the physiotherapist performing the intervention to monitor adherence to the home training program for later analysis. In addition, patients were asked whether any difficulties with treatment compliance had appeared from one session to another. Additionally, other secondary outcome measures were collected: self-perceived shoulder pain, active and passive ROM, tactile acuity and laterality judgement performance, Tampa Scale for Kinesiophobia (TSK-11), Central Sensitization Inventory (CSI), and Pain Catastrophizing Scale (PCS).

#### 2.4.1. Self-Perceived Shoulder Pain

Participants' self-perceived shoulder pain was evaluated with the Numeric Pain Rating Scale (NPRS) anchored between 0 ("no pain") and 10 ("pain as bad as you can imagine"). Patients reported their most intense pain over the last week, least intense pain over the last week, average pain intensity over the last week, and pain at that moment. The scores were averaged to calculate a final pain intensity score [29]. NPRS is a valid and reliable measure in patients with shoulder pain [30]. The minimal detectable change (MDC) of the NRPS for patients with shoulder pain is 2.5 points and the MCID is 1.1 points [30].

#### 2.4.2. Shoulder Range of Motion

Shoulder flexion and active and passive external rotation at 0° of abduction of the affected shoulder were measured with a goniometer with the patient seated. To allow consistency of pre- and post-therapy measurements, skin marks were placed for goniometric measurements. A good reliability and validity of goniometric shoulder ROM measurements has been previously reported [31]. The MDC for shoulder flexion, abduction, and external rotation ranges from 11° to 16° [32].

#### 2.4.3. Tactile Acuity

Tactile acuity was assessed with the two-point discrimination threshold (TPDT). A mechanical sliding calliper with a 1-mm precision (Duratech TA-2081) was used to calculate the TPDT. Participants were placed in a sitting position and a point 5 cm distal to the lateral border of the acromion was marked on the painful shoulder. In order to standardize the testing region, this point was always kept between the two calliper points and measurements were performed in the longitudinal direction of the arm [33]. An ascending and a descending run of measurements were completed. The calliper distance was first gradually increased from 0 mm in 5 mm steps until the participant perceived two points instead of one. The descending run began with the calliper points separated 30 mm more than the TPDT value obtained from the ascending run, followed by decrements of 5 mm. A mean TPDT value was obtained from the two threshold scores and used for analysis.

2.4.4. Laterality Judgement

Laterality judgement was assessed with a left/right judgement task (LRJT) using the NOI™ online program. A total of 30 shoulder pictures (context mode) were presented to participants on a laptop in a random order and they were instructed to decide as quickly as possible, but without guessing, whether the picture showed the right or left shoulder thus making a response. Accuracy and mean response time were recorded. The LRJT was performed twice. The first block of images was used for task familiarization and data from the second block was used for analysis [34]. The normative mean (SD) response time and mean (SD) accuracy of this LRJT is 1738 (741) ms and 93.5 (9.2)%, respectively [35].

2.4.5. Questionnaires

Fear-avoidance was assessed with the Spanish version of the TSK-11 [36]. The TSK-11 is an 11-item questionnaire used to assess fear of movement or (re)injury during movement [37]. The total score ranges from 11 to 44, with higher scores indicating more fear-avoidance behavior. The TSK-11 has shown acceptable internal consistency and validity in both subjects with acute and chronic musculoskeletal pain [36]. The MDC for the TSK-11 is 5.6 [38]. The Spanish version of the CSI was used to assess different symptom dimensions related to central sensitization [39]. The CSI has high test-retest reliability and internal consistency [39]. Moreover, pain catastrophization was assessed with the Pain Catastrophizing Scale (PCS). PCS consists of 13 items and the total score ranges from 0 to 52 [40]. A total PCS score of 30 represents a clinically relevant level of catastrophizing [40].

*2.5. CNS-Focused Treatment Program*

Prior to starting treatment, participants were given an explanation of the study. Patients were shown a picture of the 'brain map' (homunculus) and taught how, when people are in pain, the map becomes "less sharp" since it is not being moved and it is believed that when the map is sharpened, it may help reduce their pain and even movements [17]. By using sensory discrimination training and GMI, the therapy aimed to sharpen the brain shoulder map and thus improve pain and movement. The CNS-focused treatment included graded sensory discrimination training and GMI training techniques. A full description of the treatment can be found elsewhere [41].

*2.6. Statistical Analysis*

Statistical analysis was conducted using IBM SPSS Statistics 21. Normality of the data was assessed using the Shapiro–Wilk test. Study findings are expressed as the mean and standard deviation or 95% confidence interval, or as percentage frequencies. A Student's *t*-test was used to assess differences between baseline and T0 ("washout" period). A repeated measure analysis of variance (ANOVA) was used to evaluate within-subjects' differences for all outcome measures in the different assessment periods and a pairwise analysis was used to compare between the different assessment times. Statistical significance was set at $p < 0.05$.

## 3. Results

*3.1. Participants' Clinical and Demographic Data*

The clinical and demographic characteristics of the participants at baseline are presented in Table 1. Only three patients (1, 8, and 9) presented moderate levels of pain (NPRS $\leq$ 5). Symptom duration ranged between two months and two years. Three patients (3, 8, and 10) demonstrated impaired tactile acuity (i.e., larger TPDT) at baseline in the affected shoulder compared to normative values reported for healthy individuals [i.e., 44.8 (13.1) mm] [33]. A total of 80% of the subjects presented lower accuracy in the LRJT at baseline compared to normative values [35]. This lower accuracy was observed bilaterally in 50% of the subjects and in the affected side in 30%. Only two patients (1 and 8) were slower in the LRJT in the affected shoulder compared to normative values [35]. Six patients were slower in the LRJT in the non-dominant shoulder.

**Table 1.** Clinical and demographic characteristics of the participants at baseline.

| | | Patient | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** |
| Age (years) | | 51 | 51 | 49 | 49 | 46 | 63 | 59 | 58 | 48 | 47 |
| Sex (male/female) | | f | f | f | f | f | f | m | f | f | M |
| Weight (kg) | | 53 | 57 | 85 | 55 | 55 | 74 | 60 | 63 | 63 | 75 |
| Length (cm) | | 169 | 164 | 175 | 166 | 155 | 164 | 170 | 162 | 168 | 189 |
| Affected shoulder | | left | right | right | right | right | right | right | left | left | left |
| Dominant Side | | right | right | right | right | right | right | right | right | right | right |
| Symptoms duration (months) | | 2 | 15 | 6 | 6 | 16 | 12 | 3 | 3 | 24 | 10 |
| SPADI (0–100) | | 91.54 | 26.15 | 20 | 59.23 | 20 | 74.62 | 40.77 | 75.38 | 62.31 | 54.62 |
| NPRS (0–10) | | 5 | 2 | 1 | 3 | 3 | 0 | 1 | 5 | 5 | 2 |
| PER ROM(degrees) | | 6 | 24 | 34 | 0 | 56 | 55 | 14 | 28 | 18 | 43 |
| AF ROM (degrees) | | 60 | 110 | 102 | 66 | 156 | 150 | 86 | 78 | 118 | 140 |
| TPD threshold (mm) | | 22.5 | 35 | 120 | 37.5 | 35 | 20 | 27.5 | 50 | 20 | 57.5 |
| Left/right accuracy (%) | Left | 87 | 100 | 100 | 100 | 100 | 73 | 93 | 93 | 100 | 93 |
| | Right | 87 | 93 | 80 | 10 | 80 | 67 | 87 | 73 | 100 | 93 |
| Left/right speed (s) | Left | 1.8 | 1.9 | 1.8 | 1.8 | 2.2 | 2 | 1.4 | 2.5 | 1.2 | 1.6 |
| | Right | 2 | 1.6 | 1.2 | 1.4 | 1.4 | 1.4 | 1.3 | 1.7 | 1.3 | 1.8 |
| PCS (0–52) | | 11 | 4 | 0 | 2 | 35 | 13 | 23 | 18 | 19 | 18 |
| CSI (0–100) | | 47 | 16 | 29 | 16 | 54 | 36 | 21 | 45 | 15 | 10 |
| TSK-11 (11–44) | | 35 | 16 | 15 | 15 | 32 | 21 | 27 | 20 | 33 | 36 |

SPADI, Shoulder Pain and Disability Index; NPRS, Numeric Pain Rating Scale; PER, passive external rotation; AF, active flexion; TPDT, Two Point Discrimination Threshold; PCS, Pain Catastrophizing Scale; CSI, Central Sensitization Inventory; TSK-11, Tampa Scale for Kinesiophobia.

### 3.2. Primary Outcomes

The SPADI scores improved after treatment in the different assessment times ($p = 0.001$). Significant changes in SPADI scores between baseline and follow-up (baseline-T2) ($p = 0.008$), but not between baseline and post-treatment (baseline-T1) or between post-treatment and follow-up (T1-T2) were observed (Table 2).

**Table 2.** Questionnaires results at baseline, two-week "washout" period (T0), post treatment (T1), and follow-up (T2).

| | | **Mean ± SD** | **MD** |
|---|---|---|---|
| SPADI (0–100) | Baseline | 47.6 ± 25 | |
| | T0 | 52.4 ± 24.9 | 4.8 |
| | T1 | 31.6 ± 31.5 | −16 |
| | T2 | 19.4 ± 24.5 # | −28.2 |
| TSK-11 (11–44) | Baseline | 23.9 ± 8.3 | |
| | T0 | 23.6 ± 8 | −0.3 |
| | T1 | 19.9 ± 8.5 | −4 |
| | T2 | 19.4 ± 8.9 | −4.5 |
| CSI (0–100) | Baseline | 28.9 ± 15.7 | |
| | T0 | 28.8 ± 14.7 | −0.1 |
| | T1 | 24.4 ± 13.04 | −4.5 |
| | T2 | 21.9 ± 16.1 | −7 |
| PCS (0–52) | Baseline | 14.3 ± 10.7 | |
| | T0 | 11.4 ± 8.6 | −2.9 |
| | T1 | 5.8 ± 6.5 | −8.5 |
| | T2 | 6.3 ± 7.9 | −8 |

SPADI, Shoulder Pain and Disability Index; TSK-11, Tampa Scale for Kinesiophobia; CSI, Central Sensitization Inventory; PCS, Pain Catastrophizing Scale; MD, mean difference. #: significantly different between baseline and follow-up, $p < 0.05$.

### 3.3. Secondary Outcomes

Seven participants (70%) completed the treatment and all the measurements. The three patients (3, 5, and 8) not completing the treatment attended three, four, and six sessions, respectively. They dropped-out due to either difficulty for assisting to clinic sessions or lack of support from relatives to comply with home training. No adverse effects were found during or after the intervention. All patients completed the daily treatment diaries consistently.

No significant changes were found after the "washout" period for all outcome measures except for TPDT ($p = 0.02$) and SPADI ($p = 0.025$). A significant decrease in shoulder pain was found after treatment ($p = 0.028$), between post-treatment and follow-up ($p = 0.028$), and between baseline and follow-up ($p = 0.004$) (Table 3). Significant improvements were found for active shoulder flexion ($p < 0.001$).

**Table 3.** Self-reported shoulder pain and range-of-motion outcomes at baseline, two-week "washout" period (T0), posttreatment (T1), and follow-up (T2).

| | | Mean ± SD | MD |
|---|---|---|---|
| NPRS (0–10) | Baseline | 2.6 ± 1.9 | |
| | T0 | 2.9 ± 1.8 * | 0.3 |
| | T1 | 1.4 ± 1.1 † | −1.2 |
| | T2 | 0.3 ± 0.4 # | −2.3 |
| PER ROM (degrees) | Baseline | 27.6 ± 19.6 | |
| | T0 | 32.4 ± 25.9 | 4.8 |
| | T1 | 30.9 ± 22.3 | 3.3 |
| | T2 | 40.6 ± 24.4 | 13 |
| AF ROM (degrees) | Baseline | 106.6 ± 34.4 | |
| | T0 | 105.8 ± 32.1 * | −0.8 |
| | T1 | 120.1 ± 35.3 † | 13.5 |
| | T2 | 138.3 ± 33.1 # | 31.7 |

NPRS, numeric pain rating scale; PER ROM, passive external rotation range of motion; ASF ROM, active shoulder flexion range of motion; MD, mean difference. *: significantly different after treatment compared to baseline; †: significantly different between post-treatment and follow-up, $p < 0.05$; #: significantly different between baseline and follow-up, $p < 0.05$.

Additionally, a significant improvement in active shoulder flexion after treatment ($p = 0.016$), between post-treatment and follow-up ($p = 0.020$), and between baseline and follow-up ($p = 0.001$) was found (Table 3).

There were no significant changes in tactile acuity or laterality judgement performance over time (Table 4). No significant changes were found in TSK-11, PCS, or CSI at any assessment time.

**Table 4.** TPDT and laterality judgement at baseline, two-week "washout" period (T0), post-treatment (T1), and follow-up (T2).

| | | | Mean ± SD | MD |
|---|---|---|---|---|
| TPD threshold | | Baseline | 42.5 ± 29.9 | |
| | | T0 | 35.8 ± 26.1 | −6.7 |
| | | T1 | 28.1 ± 11.5 | −14.4 |
| | | T2 | 27.5 ± 11.5 | −15 |
| Laterality judgement (right shoulder) | Accuracy (%) | Baseline | 86 ± 11.03 | |
| | | T0 | 90 ± 16.6 | 4 |
| | | T1 | 95.9 ± 5.9 | 9.9 |
| | | T2 | 96.6 ± 5.01 | 10.6 |
| | Speed (s) | Baseline | 1.5 ± 0.3 | |
| | | T0 | 1.4 ± 0.3 | −0.1 |
| | | T1 | 1.3 ± 0.2 | −0.2 |
| | | T2 | 1.4 ± 0.2 | −0.1 |

**Table 4.** *Cont.*

| | | | Mean ± SD | MD |
|---|---|---|---|---|
| Laterality judgement (left shoulder) | Accuracy (%) | Baseline | 93.9 ± 8.7 | |
| | | T0 | 94.6 ± 5.2 | 0.7 |
| | | T1 | 99.1 ± 2.5 | 5.2 |
| | | T2 | 93.3 ± 11.2 | −0.6 |
| | Speed (s) | Baseline | 1.8 ± 0.4 | |
| | | T0 | 1.8 ± 0.7 | 0 |
| | | T1 | 1.6 ± 0.5 | −0.2 |
| | | T2 | 1.4 ± 0.3 | −0.4 |

TPDT, Two Point Discrimination Threshold; MD, mean difference.

## 4. Discussion

The main goal of this study was to evaluate the feasibility of implementing a CNS-focused treatment program for people with FS. Furthermore, we aimed to assess the clinical impact of this program on pain and function. Overall, no significant changes were found after the "washout" period thus suggesting minimal changes in the participants' clinical condition before treatment. Our findings revealed medium adherence of participants (70%) to the CNS-focused treatment and follow-up measurements. Regarding clinical impact, improvements in shoulder pain and active shoulder flexion were shown after treatment and at three months follow-up and in disability at three months follow-up. No significant changes were observed in tactile acuity, laterality judgement, pain catastrophization, fear-avoidance, or central sensitization after treatment or at follow-up.

Average participants' compliance with treatment was lower than expected. Participants' compliance was recorded with a treatment diary which was consistently fulfilled by all participants, but it was not enough for them to comply with the totality of treatment as previously reported by Moseley et al. [28]. Nevertheless, all participants who attended the totality of treatment sessions at the clinic also met the home training dosage. In the current study, drop-outs were mainly due to a lack of support from relatives to assist participants with their home training tasks. Previous studies have also emphasized the difficulties with implementing CNS-focused techniques, in particular home training tasks, due to the lack of "helpers" availability or lack of time from participants [22,42]. These findings highlight the importance of having a cooperative context when using this kind of therapeutic approach at home. Long-term follow-up of participants was almost feasible as eight participants were followed-up. Only two participants were lost to follow-up, as they decided to discontinue the clinical sessions due to difficulties in the conciliation of their work schedules or lack of assistance with home training tasks.

Regarding clinical outcomes, positive effects on pain and shoulder function were observed after treatment, which is in accordance with previous studies using a similar protocol [18]. Specifically, improvements were found in shoulder pain and active shoulder flexion both after treatment and follow-up measurements and in disability scores at follow-up. Regarding disability, the change in SPADI scores at follow-up exceeded both the MDC and MCID established for individuals with FS and non-specific shoulder pain, respectively [27,43]. Likewise, changes in pain intensity after treatment and at follow-up and in active shoulder flexion after treatment and at follow-up also surpassed the MCID established for pain intensity (1.1 points) and MDC for active shoulder flexion (11°) in people with shoulder pain, respectively [30,32]. No significant changes were found in LRJT and TPDT neither after treatment nor at follow-up. To our knowledge, responsiveness to treatment of these two variables in people with FS had not been previously investigated except in a single case report [18], where a 10 mm TPDT reduction and improvement of accuracy and response time in the LRJT task were observed after intervention. A case-series study [44] investigated the efficacy of a treatment combining GMI with mirror therapy in five patients with different shoulder painful conditions, including one patient with FS. After treatment, all patients showed significant improvements in pain intensity, active shoulder

flexion, and motor imagery ability, but no significant changes on laterality judgement were found.

No significant changes in fear-avoidance or pain catastrophization were found after treatment. This is not surprising given the nature of the CNS-focused treatment program, which mainly included sensory discrimination training and GMI. These two interventions were not expected to address fear or pain catastrophization. In this regard, pain neuroscience education has demonstrated clinically relevant effects in reducing psychosocial factors, in particular kinesiophobia and pain catastrophizing [45], but only a short discussion of pain from a pain neuroscience perspective was implemented in this study. This may explain the lack of change in psychosocial variables. Future studies could explore the role of pain neuroscience education in this population as recently recommended by some authors [9].

On the other hand, the duration of symptoms of our sample spanned over a wide range (2–24 months), meaning that participants may have entered the study at different stages of the disease. It is known that larger improvements in the natural history of FS are often found in the early stages of the disease (e.g., during the first year) [46]. The results of the current study cannot determine whether this CNS-focused approach would be more suitable to subjects with FS either in their early or late stage of the disease.

To our knowledge, a CNS-focused treatment had not been used before specifically for people with FS, except in a case report [18]. However, the aforementioned study did not include home training sessions. In contrast, the present study integrated both clinic and home training sessions, which was considered essential to properly investigate the feasibility of applying this kind of approach in clinical practice.

## 5. Study Limitations

Our results need to be interpreted in light of some limitations. This feasibility study recruited a sample of only ten participants with FS. Despite the reported significant improvements in pain, disability, and ROM, clinical effects must be interpreted with caution as a greater sample of participants is needed to better estimate the utility of this treatment for people with FS. Another important limitation is the lack of a control group with no intervention, which has not allowed to reveal the natural history of FS, so future research should overcome this issue.

Moreover, the heterogeneity of the recruited participants at baseline in terms of pain intensity and symptom duration limits the generalization of our results.

As participants completed the questionnaires alone and not in the presence of any researcher, this may have been one of the causes of the observed drop-outs.

Even though participants were allowed to continue with their current medication, the presence and absence of concomitant treatments, including specific medication intake, was not recorded. How these concomitant treatments may have influenced the results of this study is unknown.

Overall, this study identified key feasibility issues related to home training compliance that should lead one to reflect when using this approach, especially concerning the need of support from relatives.

## 6. Conclusions

The results of this feasibility study suggest that a CNS-focused treatment program might be a suitable approach to improve pain and disability in people with FS, but further research with a greater sample of participants is needed to draw firm conclusions. Although a high percentage of the sample completed the whole treatment program, some fulfillment issues arose, such as the need for the patient to have a cooperative context when implementing this treatment at home.

**Author Contributions:** Conceptualization, L.D., M.B.-B., E.L. and A.L.-S.; methodology, E.L., A.L.-S., M.G.M. and L.D.; formal analysis, S.M.-d.H.; investigation, S.M.-d.H., M.B.-B., E.L. and L.D.; data curation, L.F.-A.; writing—original draft preparation, S.M.-d.H.; writing—review and editing L.F.-A., E.L., L.D., M.G.M., A.L. and M.B.-B.; supervision, A.L.-S. and M.B.-B. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Institutional Review Board Statement:** The study was approved by the Ethical Committee of the University of Valencia (reference number H1532330957968) and all procedures were performed in accordance with the Declaration of Helsinki.

**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study.

**Data Availability Statement:** The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

**Acknowledgments:** The authors would like to thank all the participants who took part in the study. We would also like to thank Jose Enrique Aroca and Marta Navarro for their assistance with participants recruitment.

**Conflicts of Interest:** The authors declare no conflict of interest.

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# Anexo XI: Copia original del estudio 3

## A central nervous system-focused treatment approach for people with frozen shoulder: protocol for a randomized clinical trial, en la revista *Trials*

Lluch-Girbés et al. Trials (2019) 20:498
https://doi.org/10.1186/s13063-019-3585-z

Trials

STUDY PROTOCOL Open Access

# A central nervous system-focused treatment approach for people with frozen shoulder: protocol for a randomized clinical trial

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**Abstract**

**Background:** Frozen shoulder (FS) is a musculoskeletal condition of poorly understood etiology that results in shoulder pain and large mobility deficits. Despite some physical therapy interventions, such as joint mobilization and exercise, having shown therapeutic benefit, a definitive treatment does not currently exist. The aim of this study will be to compare the effectiveness of a central nervous system (CNS)-directed treatment program versus a standard medical and physical therapy care program on outcomes in participants with FS.

**Methods/design:** The study is a two-group, randomized clinical trial with blinding of participants and assessors. Participants will be recruited via referrals from orthopedic surgeons and physical therapists, community-based advertisements, private care practices and hospitals. Participants will be randomized to receive either a CNS-focused treatment program or standard medical and physical therapy care. The Shoulder Pain And Disability Index (SPADI) will be the primary outcome, while the Numeric Pain Rating Scale (NPRS), shoulder range of movement (ROM), The Patient Specific Functional Scale, two-point discrimination threshold and laterality judgement accuracy will be the secondary outcomes. Assessment will occur at baseline, at the end of the treatment program (week 10), and at 3 and 6 months' follow-up.

**Discussion:** Preliminary data suggest that treatments that target CNS function are a promising approach to the treatment of people with shoulder pain including patients with FS. In the context of modest effects from most available physical therapy treatments for FS, this CNS-focused approach may lead to improved clinical outcomes. The trial should determine if the CNS-directed program is more effective than traditional interventions at reducing pain intensity and improving function in a FS cohort and will follow up participants for 6 months, providing important information on the persistence of any treatment effects.

**Trial registration:** NCT03320200. Registered on October 25, 2017.

**Keywords:** Shoulder pain, Shoulder adhesive capsulitis, Central nervous system, Physiotherapy

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## Key points

- The effects of central nervous system (CNS) treatment on frozen shoulder will be analyzed
- Graded sensory discrimination and Graded Motor Imagery trainings will be applied
- Outcome measures will be shoulder pain and disability

## Background

Frozen shoulder (FS) is a musculoskeletal condition of poorly understood etiology that results in shoulder pain and large mobility deficits [1]. Obtaining pain relief and improving shoulder function are of significant concern to people with FS. Unfortunately, a definitive treatment for this condition does not currently exist and there is little consensus as to what constitutes optimal evidence-based treatment [2]. Despite some physical therapy interventions, such as joint mobilization and exercise, having shown therapeutic benefit [3–5], there is little evidence to suggest that the disease prognosis is affected [6]. Other interventions, such as guided intra-articular corticosteroid injections, appear to show more promising outcomes in the short-term than stand-alone physical therapy interventions [7]. Evidence also suggests the injection benefit being enhanced both in the short term and medium term when combined with physical therapy [8]. The current state of evidence for the various physical therapy treatments suggest that further and alternative approaches for managing FS might be investigated [6].

There is preliminary evidence from two systematic reviews showing that central pain processing mechanisms can contribute to the pain experience in a subgroup of patients with shoulder pain of different etiologies, including those with chronic subacromial impingement syndrome and post-stroke shoulder pain [9, 10]. Similarly, it could be argued that continuous nociceptive barrage, as in the early stages of FS, could lead to peripheral and subsequently long-lasting central sensitization. However, up to now the involvement of central mechanisms in FS remains speculative [6]. Interventions, such as pain neuroscience education and Graded Motor Imagery (GMI), which are thought to target the CNS, have been developed and tested in people with chronic musculoskeletal disorders with some promising results [11–15]. To our knowledge, only two case-series studies have used a CNS-focused treatment program in people with shoulder pain [16, 17]. In one study, a brief mirror therapy intervention resulted in statistically significant improvements in pain, pain catastrophization, fear avoidance and shoulder flexion active range of motion (ROM) in patients presenting with shoulder pain and limited active motion [16]. However, only 8.7% of the studied sample was diagnosed with FS and immediate post-intervention effects were solely assessed. In a second case series, Louw et al. showed that a sensory discrimination task applied to 55 patients with shoulder pain and limited ROM (including FS) resulted in an immediate increase of shoulder ROM ($p = 0.001$) with 25 patients (40%) meeting or exceeding minimal detectable change, but the study failed to report on the specific number of patients with FS [17]. Despite the positive effects shown in these two case series, the potential benefits of adding other approaches addressing the CNS (e.g., sensory discrimination training) remains largely unknown. Hence, further investigation of these preliminary findings in adequately powered randomized controlled trials together with exploration of the longer-term effects of centrally focused interventions for people with FS, is needed.

The aim of this study is to compare the effectiveness of a CNS-directed treatment program versus a standard medical and physical therapy care program on outcomes in participants with FS.

## Methods

### Design

This is a two-group, randomized clinical trial with blinding of participants and assessors.

### Setting

Participants will be recruited via referrals from orthopedic surgeons and physical therapists, community-based advertisements, private care practices and hospitals in Valencia, Spain. Potential referrals will be informed of the trial and the referral process via formal meetings and trial information sheets. This study is reported in line with the Standard Protocol Items; Recommendations for Interventional Trials (SPIRIT) Statement [18] (Additional file 1).

### Participants

Participants will be screened to determine whether they meet the following inclusion and exclusion criteria:

#### *Inclusion criteria*

Primary or idiopathic FS, defined as FS not associated with a systemic condition or history of injury [19]; greater than 50% reduction in passive external rotation when compared to the uninvolved shoulder or less than 30° of external rotation [20]; range of motion loss of greater than 25% in at least two movement planes in comparison to the uninvolved shoulder [20]; pain and restricted movement present for at least 1 month reaching a plateau or worsening [20]; normal shoulder x-rays (with the exception of osteopenia of the humeral head and calcific tendinosis) [21].

#### *Exclusion criteria*

Locked dislocations, rheumatic disease, fractures or avascular necrosis on radiographs; surgery in the upper quadrant region < 12 months prior to the study; skin or medical conditions that prevent patients from receiving tactile stimuli on the shoulder; neurological or motor disorders including a diagnosis of dyslexia or difficulty performing a rapid naming task; visual and mental health conditions that preclude successful participation.

### Details of the interventions

Participants will be randomized to receive either a CNS-focused treatment program or.

standard medical and physical therapy care. Adherence to both interventions will be monitored using an individual treatment diary where the time of day and duration of each clinic and home session will be recorded [22]. Adverse events will be recorded through passive capture. Patients will be requested to not participate in other treatments for their shoulder during the 10-week study period and any change in medication type or dosage during the study period will be recorded.

Trial physical therapists performing both interventions will have worked in private or public practice for at least 2 years. The clinicians performing the CNS-focused treatment will be engaged in a 1-day training session led by the author (ELL) for specific training in delivery of the interverventions comprising the program. This training session will include group discussions and quarterly workshops to review specific cases in the context of the CNS-focused treatment program. In addition, these physical therapists will be provided with a treatment manual outlining the CNS-focused treatment protocol and the details of each intervention included in the protocol. In order to ensure a good level of proficiency with the treatment protocol, trial physical therapists will go through a theoretical test and a practical exam with questions and techniques included in the protocol. The interventions are described in detail according to Template for Intervention Description and Replication (TIDieR) Checklist recommendations [23].

### CNS-focused treatment program

Participants randomized to this treatment will receive a CNS-focused intervention consisting of a 10-session treatment program delivered as 60-min sessions, scheduled once a week, over a period of 10 weeks. All treatment sessions are one-on-one. In addition, participants will complete a home treatment program entailing 30 min of training, five times per week that finishes at session 10. The intervention includes discussion of the participant's shoulder pain experience from a pain neuroscience perspective (e.g., pain neuroscience education) [24], graded sensory discrimination training and GMI training. These interventions are likely to overlap due to variable allocation of time to each of the treatments within the clinic and home treatment sessions.

Prior to training, participants will be given an explanation of the proposed treatment and the aim of the study. Patients will be shown a picture of the "brain map" (homunculus) and taught how the map becomes "less sharp" when people are in pain, since the affected shoulder is not being moved [16]. They will be told that when the map is sharpened, it may help to reduce not only their pain but also their mobility [16]. By using sensory discrimination training and GMI, the therapy aims to sharpen the map of the shoulder in the brain and thus improve pain and movement.

#### *Graded sensory discrimination training*

A graded sensory discrimination training program based on previous work by Wand et al. [13] will be implemented. In this model, participants undertake a training regimen that involves discrimination of stimulus type and location and graphesthesia training in five different stages, graded according to level of theoretical cortical engagement and complexity. Each stage is planned to last a minimum of 2 weeks (10 weeks in total), but can be extended by some days if participants appear not to have sufficiently mastered that stage.

For tactile discrimination training in the first stage (weeks 0–2), participants will be seated in a comfortable position with a mirror between their upper limbs. Evidence has shown that tactile acuity is enhanced with visualization of the reflected image of the unaffected limb (that is, patients look towards the stimulated body part and can see the skin of the opposite body part in the mirror) [25]. Therefore, during the first week of training at home and in the clinic, participants will be positioned so that they can see the reflection of their unaffected arm in a mirror while the affected arm is stimulated. The limbs will be positioned in such a way that the reflected image of the opposite arm is in line with the stimulated arm. Visual feedback will be withdrawn after the first week and will not be used again in any part of the sensory training program.

In this first stage, only localization of the stimulus will be trained. Participants will be shown a digital standard photograph of the shoulder on which nine numbered grids will be marked. The spacing of the grids will be based on the current normative data pertaining to two-point discrimination of the affected joint (e.g., (45.9 mm ± 18.4 mm) [26]. For the shoulder localization blocks, the superior border will be set as 1 cm proximal to the acromioclavicular joint and the lower border reaching the deltoid insertion. While the participant views the photograph and nine-block grids, they will be taught via tactile stimulus with the back of the blunt end

of a pencil, where each block is in relation to their shoulder, thus familiarizing them with the nine-block grid [13, 27]. After the familiarization period, the therapist, using a random number sequence, will press lightly on a particular point with the blunt end of a pencil for about 2 s. Pressure will be kept to a minimum to avoid pain provocation. Participants will be instructed to refer to the picture and to indicate which grid has been stimulated. With a correct identification of the area, the therapist will proceed to the next block for identification. If the participants make an error, they will be told which grid (number) has in fact been stimulated, and then the actual position of the grid that they have incorrectly indicated will be stimulated. This in essence will help the participant to develop a greater ability to identify the stimulated grid. Three blocks of 60 stimuli with an interstimulus interval of 15 s and a 3-min rest period between blocks will be used during the treatment session.

At the first session, participants will be accompanied by someone who can assist them to undertake training at home. This assistant will be trained in the task and participants will be advised to undertake 15 min of training at home in addition to the clinic session. Participants will be given a photograph of a standard shoulder on which the stimulation points will be marked and several sets of 60 random number sequences to use for training at home. If at the end of the second week (first stage), for participants who have less than 80% accuracy with one test block of 60 stimuli, the training will be extended for an additional week.

In the next stage (weeks 2–4), participants will be asked to discern both the localization of the stimulus (i.e., the corresponding number on the photograph) and the size of the probe used (type of stimulus). The experimental setup will be similar to that used in the first stage, but this time a probe with a sharp end (pen cap) and a blunt end (cork) will be used. A random number table will be used to randomize both position and probe size. Participants initially will be shown a picture with nine numbered grids marked on the shoulder; the number of grids will be increased to 12 in the second week of this stage. Again, participants will be given feedback about each error they make. Three blocks of 60 stimuli with an interstimulus interval of 15 s and a 3-min rest period between blocks will be used during the treatment session.

Should participants be less than 80% accurate with one test block of 60 stimuli at the end of the second week of this stage, then the training will be extended for an additional week. For home training in this second stage, participants will be given a photograph of the shoulder with the stimulation points and a wine cork and a pen lid to use as stimulus type. They will be given five lists of random combinations of numbers (1–9 or 1–12) and stimuli (cork or pen lid), and will be advised to use a different list each day. Participants will be advised to undertake 15 min of training at home in addition to the clinic session.

The next three stages (weeks 4–10) will involve graphesthesia tasks of increasing difficulty. In this third stage, participants will have to simply recognize letters drawn on the shoulder. Several random sequences of 60 letters will be generated, and three lots of 60 letters will be used in each treatment session with a interstimulus interval of 15 s and a 3-min rest period between blocks. Initially, uppercase letters will be drawn on the shoulder by the therapist with his index finger. Participants will be asked to indicate the letter drawn; if they guessed incorrectly, they will be told the actual letter that has been drawn, and then the letter that they have incorrectly indicated will be re-drawn. Progression within this 2-week block will be undertaken by decreasing the size of the letters, altering the orientation of the letters, and altering the speed at which the letters are drawn. Again, this stage may be extended by 1 week if participants are less than 80% accurate with a test block at the end of 2 weeks. Participants will be advised to undertake 15 min of graphesthesia training at home by using several random sequences of letters.

The next 2-week stage (weeks 6–8) will involve the recognition of three-letter words drawn on the shoulder. The protocol and progression will be almost identical to those outlined for the single-letter task, including the criterion for advancement to the next stage. One additional progression in the last 2 weeks (weeks 8–10) will involve overlapping the letters of the word such that they are all drawn on the same part of the shoulder. Again, this stage can be extended for an additional week if participants were less than 80% accurate at the end of 2 weeks. Participants will be advised to undertake 15 min of graphesthesia training at home by using several random sequences of letters.

A full description of the graded sensory discrimination training program is provided in Table 1.

#### *Graded Motor Imagery (GMI) training*

A graded motor cortical retraining program based on previous work by Wand et al. [13] and published guidelines [28] will be implemented.

The initial stage (weeks 1–2) of the GMI will involve laterality recognition training (Implicit Motor Imagery). An online computer program (Recognise Online, NOI Group, Adelaide, SA, Australia) will be used to present participants with a random selection of photographs of either their left or right shoulders [28]. The photographs will be presented in a variety of positions and orientations. Participants will respond by pressing one of two keys to indicate whether a picture shows the left or right

**Table 1** Summary of progressions used for the graded sensory discrimination training program

| Stage | Sensory discrimination training |
|---|---|
| 1 (weeks 0–2) | *Localization training*<br>Determine site of stimulus<br>With visual feedback during first week<br>Without visual feedback during second week |
| 2 (weeks 2–4) | *Localization and stimulus type*<br>Determine site of stimulus<br>Determine size of probe<br>Progress by adding points |
| 3 (weeks 4–6) | *Graphesthesia training*<br>Recognize letters<br>Progress by size<br>Progress by orientation<br>Progress by speed of drawing |
| 4 (weeks 6–8) | *Graphesthesia training*<br>Recognize 3-letter words<br>Progress by size<br>Progress by orientation<br>Progress by speed of drawing<br>Progress by overlapping letters |
| 5 (weeks 8–10) | *Graphesthesia training*<br>Progress by size<br>Progress by orientation<br>Progress by speed of drawing<br>Progress by overlapping numbers |

shoulder, a process that require them to mentally rotate their own body part to match the position shown in the picture and, thereby, to engage motor cortical areas corresponding to that body part. An important aspect of the test is that it is performed unconsciously (relatively) so it should be done as quickly as possible, almost as though the patient was guessing [28]. The photographs will be presented in groups of 30 for a duration of 5 s for each photograph, and progression will involve reducing the time for which the photographs are presented and changing the background of the photographs. During an initial familiarization session conducted during the first formal treatment, three lots of 30 photographs will be presented with a 1-min rest period between lots. Participants will be asked to practice this task at home for 15 min each day.

The next stage (weeks 3–4) will involve imagined movements (Explicit Motor Imagery). Two videos, each lasting approximately 7 min will be made of a person slowly performing a variety of shoulder movements from simple, low-load movements to more complex, behaviourally relevant movements. During the first week of this stage (week 3), the video will show small-range shoulder movements (e.g., unilateral shoulder flexion, extension, abduction, shoulder external and internal rotation in 0° of abduction). In the second week of this stage (week 4), the video will show a person performing the same movements as before but in full-range and more challenging and functional tasks (e.g., hand behind back, hand to curl hair). Participants will be in sitting in a relaxed position for imaging movements. They will be instructed to watch the videos and then close their eyes and to imagine themselves performing the same movements in a smooth and pain-free manner as if it was real in all its aspects, including the timing taken to move. Participants will be advised not to imagine watching themselves performing the movement but to imagine actually performing the movement in the first person. They will execute two series of 20 repetitions for every imagined movement in each session. Additionally, participants will be asked at home to watch the videos twice and to practice for a total of 15 min each day.

The next stage (weeks 5–6) will involve isometric contraction of the rotator cuff and scapulo-thoracic muscles using dynamic glenohumeral and scapulo-thoracic neuromuscular control exercises. It is believed that the activation of these muscles will serve as an ideal bridge between imagined movements and actual shoulder movements used in the next stage using mirror therapy (because there would not be shoulder movement, thus minimizing the potential for sensorimotor incongruence) and that the activation of these muscles might sharpen the cortical representation of the shoulder [13]. During the first week (week 5), participants will receive instruction on dynamic glenohumeral neuromuscular control exercises aiming to contract the rotator cuff muscles [29] and scapulo-thoracic muscles [30] in isolation. They will perform neuromuscular control exercises for three sets of 10-s repetitions with a 2-min rest period between sets. During the second week of this stage (week 6), the progression will involve maintenance of the local muscle contraction while participants move their shoulder in a pain-free manner in different directions. Exercise dose will be the same as during week 5. Participants will be asked to practice at home these tasks for a total of 15 min each day.

The next 4-week stage (weeks 7–10) will involve the use of mirror therapy with different progressions. Participants will be seated in a comfortable chair, towards the edge of the chair seat allowing for movement, but also providing some trunk support. The proposed mirror therapy will be demonstrated and explained to the subjects by the physiotherapist. Next, a standing mirror on wheels will be placed in front of the participant with the reflective side facing the uninvolved side. The affected arm will be placed behind the mirror. The participant will be asked to lean forward slightly, allowing them to view the complete uninvolved arm in the mirror. Mirror exercises will begin with simply watching the reflection of the unaffected arm in the mirror and then progressed from static to active and functional movements. When possible, gentle and synchronous movements of the

affected arm will be encouraged behind the mirror. Two series of 12–15 min will be performed in each session, with 2 min between series to allow for resting and relaxing the arm. Additionally, participants will be asked to practice this task at home for 15 min each day with a mirror provided by researchers conducting the study.

Participants will be encouraged to move slowly and easily, breathing comfortably and focusing on the movement of the uninvolved arm. The intervention will allow subjects to move the uninvolved arm giving the "illusion" that their involved arm is moving through the full active ROM. Participants will be advised to stop if they have an increase in pain either during or directly after mirror therapy.

A full description of the GMI training program is provided in Table 2.

Should sustained symptom exacerbation occur in any of the stages, the appropiate parameters will be reviewed and possibly reduced.

**Table 2** Summary of progressions used for the Graded Motor Imagery (GMI) training program

| Stage | GMI training |
|---|---|
| 1 (weeks 0–2) | *Laterality recognition*<br>Using Recognise software<br>Determine whether left or right side of shoulder<br>Progress by time for which image was presented |
| 2 (weeks 2–4) | *Imagined movements*<br>Using video of model performing movements<br>Small-range movements during first week<br>Full-range movements during second week |
| 3 (weeks 4–6) | *Isometric local muscle recruitment*<br>Rotator cuff muscles<br>Scapular muscles<br>Add pain-free movement to local contraction |
| 4 (weeks 6–8) | *Mirror therapy*<br>Keep the affected arm still i n a comfortable position/ keep the unaffected arm still in the same position and just observe the reflection<br>Keep the affected arm still in a comfortable position/ move the unaffected arm through its full-range of movement (ROM) in different directions |
| 5 (weeks 8–10) | *Mirror therapy*<br>Move the affected arm towards the limit of pain in the restricted/painful direction(s) of movement and keep that position/ move the unaffected arm through its full ROM in the painful/limited directions<br>Move the affected arm towards the limit of pain in the restricted/painful direction(s) of movement/copy with the unaffected arm through a full ROM (synchronous movements) |

### Standard medical and physical therapy care program

Participants randomized to standard medical and physical therapy care will receive a 10-session treatment program of the same duration as the CNS-focused treatment. This standard treatment will include one corticosteroid infiltration provided in the early acute stage followed by a multimodal physical therapy program including analgesic modalities (e.g., TENS, cryotherapy) and exercise and manual therapy techniques addressing the specific mobility deficits of each patient [31]. Physical therapists will be instructed not to include interventions that were similar to those used in the group receiving the CNS-focused protocol (e.g., using mirrors or imagined movements) and to include a home program that involves a training load comparable to that in the other group.

### Primary and secondary outcome measures and assessment points

The primary outcome measured is self-reported shoulder pain-related disability as measured on the Shoulder Pain And Disability Index (SPADI) questionnaire. The Spanish version of the SPADI has high internal consistency (Cronbach α: 0.916) and excellent test-retest reliability (ICC 0.91) [32]. Secondary outcomes are as follows:

1. The Numeric Pain Rating Scale (NPRS), a valid and reliable measure of shoulder pain [33]
2. Goniometric assessment of active shoulder ROM which is valid and reliable [34, 35]
3. Two-point discrimination threshold measured at one standardize site on the affected shoulder (5 cm distal to the lateral border of the acromion) [36], following an established protocol [37]
4. Laterality judgement accuracy using the NOI Recognize online program (www.noigroup.com) and following an established protocol [38]
5. The Spanish version of the Tampa Scale of Kinesophobia, a valid and reliable measure of fear of movement [39]
6. The Patient Specific Functional Scale, a reliable, valid and responsive instrument that can be used in patients with a primary shoulder complaint [40]

Assessment will occur at baseline, at the end of the treatment program (week 10), and at 3 and 6 months' follow-up. At baseline, a clinical assessment of symptom distribution, history of the present and previous shoulder complaints, red flag screening, medical history and general health status will also be performed.

### Recruitment procedures

Participants will be recruited from different outpatient private clinics and rehabilitation services of different hospitals of the region of Valencia (Spain). In addition, posters will be distributed in the community and advertisements in social media will be placed to increase the potential number of participants in the study. Physical therapists and primary care practitioners will be contacted and invited to recruit participants after providing them with brief information about the study. Involved practitioners will identifiy potentially suitable patients and, after providing them with information about the study, will invite them to contact the research team. Upon contact by potential participants, a researcher will explain the study and assess them for study eligilibily via telephone. If the potential participant remains interested in participating in the study, they will be invited to a baseline session. During that session, one researcher will provide to the patient an information leaflet, confirm eligibility, and obtain a signed consent form. Baseline outcome data will be collected during this session, following which the participant will be randomized.

Adherence to treatment will be enhanced by careful explanation of the time demands of participation and regular contact by a researcher who will send repeated reminders to participants by email and make telephone calls to ensure adherence to the time schedule including follow-up sessions.

The schedule of the enrollment, interventions and assessments is shown in Fig. 1.

### Randomization procedures

Randomization will be conducted using computer-generated random numbers (Epidat® version 3.1). The allocation sequence will be prepared by a researcher with no involvement in the study by using a blocked randomization model. Allocation concealment will be ensured using 34 sequentially numbered opaque and sealed envelopes. After performing the baseline assessments the treating clinician will open the envelope and reveal each participant's group allocation.

### Blinding

Participants will be blinded to both study hypothesis and group allocation. It will not be possible to blind the treating physical therapists who are responsable of performing the interventions. All the assessments will be conducted by researchers who will be blinded to group allocation. Statitistical analysis will be performed by a statistician blinded to the study aims.

### Statistical analysis including sample size calculation

#### *Sample size calculations*

The sample size will be calculated using G*Power 3.0.18 Software based on the SPADI as the primary outcome measure. To our knowledge, there are no studies investigating the effects of GMI or graded sensory discrimination training on FS. Based on similar studies applying physiotherapy on FS (SPADI mean of 66 points; standard deviation (SD) = 16) [8], and the minimal detectable change attained in the study by Tveita et al. (17 points) [41], to detect a 17-point (SD = 16) between-group difference, with 80% power and an alpha level of 0.05, a total sample size of 30 patients is estimated (15 per group). An allowance will be made for a 15% dropout rate, increasing the sample size to 34 patients (17 per group). However, since this calculation is not based in the use of GMI, to assure an adequate sample size, we will carry out a pilot study with 20 participants (10 per group) to test these assumptions. Mean differences and standard deviations from the inter-group comparison on the primary outcome (SPADI) will then be used to recalculate the sample size, if necessary.

#### *Statistical analysis*

Data will be analyzed using the statistical package SPSS 21.00 for Windows. Statistical significance will be set at $p < 0.05$. Prior to statistical comparisons, all data will be tested for normal distribution. Then, a descriptive analysis of the data will be obtained for the dependent variables in the different assessment times. Subsequently, homogeneity of the two intervention groups will be studied. To confirm if there are differences in each group (intra-group comparisons), considering each group in isolation, between the four assessments in each of the variables (baseline, post treatment, 3-month follow-up, 6-month follow-up), repeated measures analysis of variance ANOVA will be used. To calculate inter-group differences between baseline and follow-ups, a four-way repeated-measures ANOVA will be conducted, with the scores of every primary and secondary outcome as dependent factors, with four levels corresponding to every time of assessment (t1, t2, t3 and t4), and the two intervention groups (CNS-focused treatment vs standard care treatment) as independent factors. Between- and within-group effect sizes for all quantitative variables will be measured with the Cohen *d* coefficient. An effect size greater than 0.8 will be considered large, around 0.5 moderate, and less than 0.2 small [42]. In cases of missing data, an intention-to-treat analysis will be performed. Double data entry will be carried out in order to promote data quality.

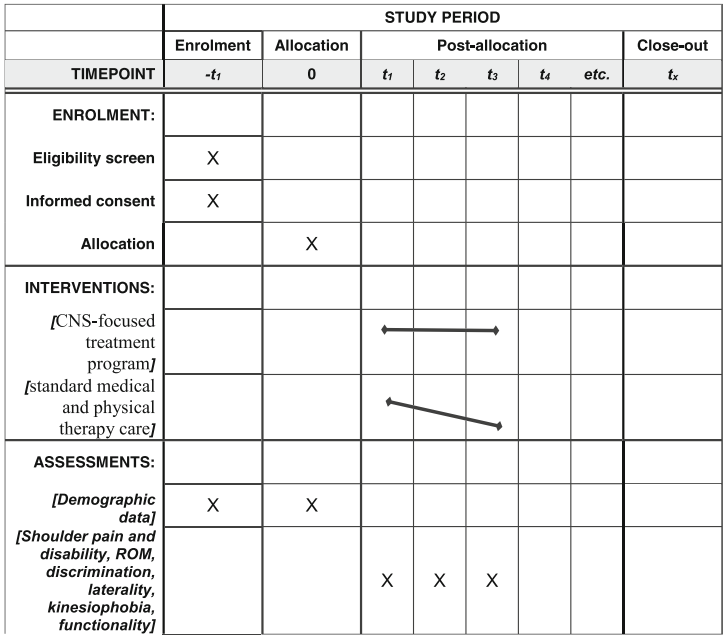


**Fig. 1** Schedule of enrollment, interventions and assessments

### Data management

Data from the study will be only accessible to the research team and will be stored on password-protected computers at the University of Valencia. Paper-form data will be stored in locked cabinets located at the Department of Physiotherapy of that same university. In order to preserve data confidentiality study participants will be assigned an identification number which will be kept for the duration of the study. A list of participant identification numbers will be created and separated from the de-identified data. Statistical analyses will be performed keeping participant anonymity by using patient identification numbers and the statistician will be blinded to group allocation. Confidentiality will also be preserved when disseminating results by using group data.

### Significance and implications for practice

Preliminary data suggest that treatments that target CNS function are a promising approach to the treatment of people with shoulder pain including patients with FS. In the context of modest effects from most available physical therapy treatments for FS, this CNS-focused approach may lead to improved clinical outcomes. The trial should determine if the CNS-directed program is more effective than traditional interventions at reducing pain intensity and improving function in a FS cohort and will follow up participants for 6 months, providing important information on the persistence of any treatment effects. The inclusion of variables related to functional reorganization of the brain, such as the two-point discrimination threshold and laterality judgement accuracy, will also allow for the first time to explore responsiveness to change of these tests after treatment in a population with shoulder pain. In addition, this study provide a good oportunity to explore the relationship between shoulder pain, cortical changes and clinical markers in people with FS. Finally, the flexible structure of the interventions comprising the CNS-focused approach closely reflects the real-world clinical practice.

CNS-directed interventions constitute a completely new treatment paradigm for the management of shoulder pain and, in particular, people with FS. Feelings of stiffness in the back have been recently demonstrated to be a multisensory perceptual inference consistent with protection rather than reflecting biomechanical properties of the back [43]. Stiffness is a main characteristic in people with FS and the prevailing view is that it is related to a capsular fibrosis despite the cause being still unknown [44]. The positive effects in ROM observed in preliminary research conducted in people with FS after brief interventions targeting the CNS challenge the prevailing view that stiffness in FS is an isomorphic marker of the biomechanical characteristics of the shoulder. The results of this study should

have the potential to address this issue and change the current physiotherapy management of FS.

### Anticipation dates of trial commencement and completion

Commencement March 2018. Completion September 2020.

### Ethics and dissemination

The trial has been registerd at Clinicaltrials.gov with the identifier: NCT03320200. The results of the study will be disseminated at several research conferences and as published articles in peer-reviewed journals. The full protocol, participant-level dataset, and statistical code will be available when this study will be finished.

## Additional file

**Additional file 1:** Standard Protocol Items; Recommendations for Interventional Trials (SPIRIT) 2013 Checklist: recommended items to address in a clinical trial protocol and related documents. (DOC 125 kb)

#### Acknowledgements
Not applicable.

#### Trials status
Protocol version number and date: NCT03320200 March 2018. Recruitment begun in March 2018. Recrutiment will be completed in October 2019.

#### Authors' contributions
ELG designed this protocol study. All the authors have contributed to the writing of this manuscript. All authors read and approved the final manuscript.

#### Funding
This work is funded by the Conselleria de Educación, Investigación, Cultura y Deporte de la Generalitat Valenciana, Spain (GV/2016). (http://www.ceice.gva.es/es). The study sponsor and funders will be not involved in study design; collection, management, analysis and interpretation of data; writing of the report; and the decision to submit the report for publication. Provisions for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation, will be provided by the aforementioned organization.

#### Availability of data and materials
Not applicable.

#### Ethics approval and consent to participate
This study protocol has received ethical approval by Ethics Committee of Research in Humans of the University of Valencia, Spain (H153233095796). All the participants have accepted and signed an informed consent before beginning the study. Protocol modifications will be notified to relevant parties. All members of the Research Team will have access to the final trial dataset. They will not have any responsability for the coordinating centre, Steering Committee, Endpoint Adjudication Committee, Data Management Team, and other individuals or groups overseeing the trial.

#### Consent for publication
All authors have approved the manuscript for submission.

#### Competing interests
AL receives royalties for books about pain and rehabilitation. AL receives speaker's fees for lectures on pain and rehabilitation. To minimize the risk of conflict, AL will have no role in data collection or analysis in the current trial. The other authors declare that they have no conflicts of interest.

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Received: 27 October 2018 Accepted: 16 July 2019
Published online: 13 August 2019

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## Publisher's Note

# Anexo XII: Copia original del estudio 4

**Is there any benefit of adding a Central Nervous System focused intervention to a manual therapy and home stretching program for people with frozen shoulder? A randomized controlled trial, en la revista *Journal of Shoulder and Elbow Surgery***

J Shoulder Elbow Surg (2023) 32, 1401–1411

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# Is there any benefit of adding a central nervous system–focused intervention to a manual therapy and home stretching program for people with frozen shoulder? A randomized controlled trial

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**Background:** Frozen shoulder (FS) is a highly disabling pathology of poorly understood etiology, which is characterized by the presence of intense pain and progressive loss of range of motion. The aim of this study was to evaluate the effect of adding a central nervous system (CNS)–focused approach to a manual therapy and home stretching program in people with FS.
**Methods:** A total of 34 patients with a diagnosis of primary FS were randomly allocated to receive a 12-week manual therapy and home stretching program or manual therapy and home stretching program plus a CNS-focused approach including graded motor imagery and sensory discrimination training. The Shoulder Pain and Disability Index score, self-perceived shoulder pain (visual analog scale score),

This study was approved by the Ethical Committee of the University of Valencia (reference no. H1532330957968), and all procedures were performed in accordance with the Declaration of Helsinki. All participants gave their written informed consent prior to study participation. The study was previously registered on clinicaltrials.gov (no. NCT03320200).

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https://doi.org/10.1016/j.jse.2023.02.134

shoulder range of motion, and the Patient-Specific Functional Scale score were measured at baseline, after a 2-week washout period just before starting treatment, after treatment, and at 3 months' follow-up.
**Results:** No significant between-group differences in any outcome were found either after treatment or at 3 months' follow-up.
**Conclusion:** A CNS-focused approach provided no additional benefit to a manual therapy and home stretching program in terms of shoulder pain and function in people with FS.
**Level of evidence:** Level I; Randomized Controlled Trial; Treatment Study


**Keywords:** Exercise; frozen shoulder; manual therapy; motor imagery; physical therapy; tactile discrimination training

Frozen shoulder (FS) is one of the most challenging musculoskeletal conditions that physiotherapists face in their clinical practice. It is characterized by a spontaneous onset of shoulder pain, followed by a gradual and generalized decrease in both active and passive range of motion (ROM).[44] In 2011, the American Shoulder and Elbow Surgeons proposed to classify FS into primary or idiopathic FS and secondary FS, with the latter in turn being subclassified into 1 of 3 categories: intrinsic (ie, due to any other shoulder pathology, eg, rotator cuff tear), extrinsic (ie, due to any pathology outside the shoulder, eg, cervical radiculopathy), and systemic (ie, due to diabetes).[44] The underlying physiopathology of FS is still poorly understood, although some mechanisms such as low-grade inflammation and immune system dysregulation have gained scientific interest in recent years.[16,31]

The effectiveness of different interventions in people with FS has been investigated. For instance, a wide variety of mobilization techniques have shown beneficial effects in patients with this clinical condition.[29,30] However, to date, no intervention has demonstrated superiority over the other interventions, except the early use of intra-articular corticosteroid injections in patients with FS of <1 year in duration.[6] Additionally, the effect sizes of currently applied interventions are modest at best, and the natural history of FS does not seem to be influenced by any treatment.[27] This fact has prompted some authors to claim the need for innovative research in the area of management of FS.[41]

In recent years, growing evidence has shown that central pain mechanisms may play a key role in a wide variety of chronic musculoskeletal pain conditions.[14,21,38] Considering the long-lasting nature of FS, it was postulated that this could also be the case for this condition.[41] In line with this, some recent studies have investigated the contribution of altered central pain-processing mechanisms in people with FS. Mena-del Horno et al[23] found that people with FS had reduced tactile acuity and impaired laterality judgment in their affected shoulders when compared with their unaffected shoulders and controls. These results were later replicated by Breckenridge et al.[2] In a case-series study, Louw et al[21] investigated the effects of a brief mirror therapy intervention in subjects with shoulder pain and limited active ROM, including people with FS. Significant improvements in pain intensity, pain catastrophizing, fear avoidance, and shoulder ROM (active flexion) were found after treatment. Similar results were shown by Sawyer et al[38] in a case report of FS after implementing a combined intervention comprising pain neuroscience education, sensory discrimination training, and graded motor imagery (GMI). Because of the small sample sizes, low level-of-evidence study designs (ie, case reports and case series), and short-term follow-up of the aforementioned studies, further research on the role of central nervous system (CNS)–focused interventions in this population seems warranted.

The aim of this study was to investigate the effect of adding a combined CNS-focused intervention including sensory discrimination training and GMI to a manual therapy and home stretching program in people with FS. It was hypothesized that patients receiving the combined peripheral and CNS-focused intervention would report better outcomes than patients receiving only the peripheral-focused intervention (ie, manual therapy and stretching).

## Methods

### Study design

We performed a randomized controlled trial analyzing the comparative effectiveness of 2 physiotherapy interventions for FS. This study has been reported following the CONSORT (Consolidated Standards of Reporting Trials) guidelines[25] (Supplementary Appendix S1), and interventions are described in accordance with the Template for Intervention Description and Replication (TIDieR) checklist (Supplementary Appendix S2).[13]

### Participants

Participants with primary FS were recruited between October 2017 and March 2020. Participants had to comply with the following inclusion criteria[3]: (1) either loss of passive external rotation in the affected shoulder >50% compared with the unaffected shoulder or >30° of external rotation in the affected shoulder as measured in 0° of shoulder abduction, (2) ROM loss >25% in ≥2 movement planes in the affected shoulder when compared with the unaffected shoulder, and (3) presence of

shoulder pain and restricted ROM that had reached a plateau or had been worsening for ≥1 month. Patients were excluded if they had received shoulder surgery during the past year; had a locked dislocation, arthritis, a fracture, or avascular necrosis; presented difficulties in understanding the written or spoken Spanish language; had any skin or medical condition preventing them from receiving tactile stimuli on the shoulder; had any neurologic or motor disorder (eg, dyslexia); were visually impaired; or had any diagnosis of psychopathology.

Prior to inclusion, none of the participants had received a corticosteroid injection in the affected shoulder or reported satisfactory results from previous physical therapy treatments. All participants were instructed to continue taking any current medications but not to start new medications or initiate new treatments during the treatment period.

## Procedure

All participants were interviewed at baseline to collect sociodemographic and clinical information. Then, participants' shoulder ROM and self-perceived shoulder pain were measured, and the Shoulder Pain and Disability Index (SPADI) and Patient-Specific Functional Scale (PSFS) questionnaires were completed.

All assessments were performed by 3 researchers (M.B.-B., L.D., and E.L.), with 20 years, 20 years, and 10 years of clinical experience, respectively, in assessing and treating patients with FS. Prior to study commencement, the researchers practiced all measurements and agreed on them to ensure consistency.

## Outcome measures

The primary outcome measure was the SPADI score. Secondarily, self-perceived shoulder pain (visual analog scale [VAS] score), shoulder active and passive ROM, and PSFS score were also measured. All outcomes were recorded at baseline and after a 2-week washout period to evaluate whether changes in participants' clinical condition could occur during a "non-intervention" period.[13] Participants again underwent measurements after treatment and at 3 months' follow-up. If no significant differences in outcomes were observed between the baseline and 2-week assessments, any change in the following measurements could be more attributable to the intervention.[10]

### Shoulder pain and disability

Participants' shoulder pain and disability were measured with the Spanish version of the SPADI. The SPADI is a 13-item shoulder function index that assesses pain and disability related to shoulder dysfunction.[33] Each item is scored using a numeric scale ranging from 0 ("no pain/no difficulty") to 10 ("worst pain imaginable/so difficult it required help"). The total score ranges from 0 to 100 points, with higher scores indicating greater disability.

The Spanish version of the SPADI has shown high internal consistency (Cronbach α, 0.916) and excellent test-retest reliability (intraclass correlation coefficient, 0.91).[22] The minimal clinically important difference (MCID) for the SPADI score ranges from 8 to 13 points.[35]

### Self-perceived shoulder pain

Participants' self-perceived shoulder pain was assessed with a VAS anchored at 0 ("no pain") and 100 ("pain as bad as you can imagine"). Participants were asked to indicate their average pain experienced over the 24 hours prior to assessment.[11]

The VAS score has been shown to be a valid and reliable tool to measure pain intensity in people with shoulder pain. The MCID for the VAS score is 30 mm.[17]

### Shoulder ROM

Active and passive shoulder flexion and external rotation at 0° of shoulder abduction in the affected shoulder were measured using a Plurimeter-V gravity inclinometer (Plurimeter 164 Dr Rippstein, La Conversion, Switzerland) following previous guidelines.[28,37] For shoulder flexion, participants were standing with the inclinometer placed on the proximal third of the humerus, over the superior portion of the biceps brachii muscle. Participants were first asked to actively elevate the shoulder until either pain or resistance appeared; then, the shoulder was forced passively until pain tolerance or maximum ROM was reached. Inclinometers have shown high responsiveness in measuring change in both passive and active flexion of the shoulder in FS patients, and the minimal detectable change (MDC) for active shoulder flexion is 8° in asymptomatic subjects.[34] In addition, active shoulder flexion in the scapular plane has demonstrated good reliability and validity.[15]

For shoulder external rotation, participants laid supine with the arm entirely supported by a plinth. The arm was placed in 0° of shoulder abduction, 90° of elbow flexion, and neutral forearm prono-supination. The inclinometer was placed on the distal part of the dorsal forearm. Participants were first asked to actively rotate into external rotation until either pain or resistance appeared; then, the shoulder was forced passively until pain tolerance or maximum ROM was achieved. The MDC for active external rotation is 9° in asymptomatic subjects, and good intrarater reliability and inter-rater reliability have been reported for both active and passive external rotation in healthy subjects and patients with shoulder pain disorders.[34]

### PSFS score

Participants completed the PSFS questionnaire to assess for changes in the functional status of the affected upper limb after treatment. Participants selected 3-5 activities they had difficulties doing or were unable to do because of their current shoulder problem and rated these activities on an 11-point scale ranging from 0 ("unable to perform the activity") to 10 ("able to perform the activity at preinjury level"). The total PSFS score was calculated as the sum of the activities' scores divided by the number of limited activities (range, 0-10), with higher scores indicating better performance.

The PSFS score has been shown to be a valid, reliable, and responsive outcome measure in people with upper-limb musculoskeletal problems.[12] The MCID for the PSFS score is 1.16 points.[12]

### Adherence to treatment

Adherence to home treatment was assessed after each session with a diary in which participants marked their compliance with the assigned home exercises.[26]

## Randomization and blinding

Participants were randomized to receive one of two 12-week interventions: a manual therapy and home stretching program or a manual therapy and home stretching program plus a CNS-focused approach including GMI and sensory discrimination training. Randomization was performed via sealed envelopes by a researcher who was blinded to the aim of the study. Additionally, the researchers responsible for all the assessments were blinded to treatment allocation.

## Interventions

### Manual therapy and home stretching program

Participants in one group received a manual therapy and home stretching program previously described by Dueñas et al.[8] This intervention included 12 sessions of supervised manual therapy applied once a week and a home stretching program performed once a day, 5 days per week, during the whole intervention period. The selection of specific manual therapy and home stretching techniques for each patient was based on individual shoulder ROM impairments[7] and the staged approach for rehabilitation (STAR)-shoulder tissue irritability rating system.[8] Details about how treatment techniques were individualized based on the 2 aforementioned factors can be found elsewhere.[8]

### Manual therapy and home stretching program plus CNS-focused approach

Participants in the other group received the same manual therapy and home stretching program plus a CNS-focused approach as previously described by Lluch-Girbés et al.[19] The latter approach included a discussion of the participant's shoulder pain experience from a pain neuroscience perspective, provided in the first session, plus 12 supervised sessions of GMI and sensory discrimination training performed once a week.[20,43] Additionally, participants performed a home exercise program once a day, 5 days per week, consisting of GMI and sensory discrimination training, during the whole intervention. These home sessions lasted approximately 45-60 minutes until task completion. The feasibility of this CNS-focused treatment program for people with FS has recently been demonstrated.[24] The physiotherapist performing all the interventions (S.M.-d.H.) received a postgraduate degree in manual therapy and was trained by 2 experienced researchers (L.D. and E.L.) in the use of these techniques before starting the study.

## Sample size calculation

The sample size was calculated using G*Power software (version 3.0.18) based on the SPADI score as the primary outcome measure. On the basis of studies that applied physiotherapy interventions in people with FS (mean SPADI score of 66 points; standard deviation, 16 points),[4] as well as the MDC attained in the study by Tveita et al[42] (17 points), to detect a 17-point between-group difference (standard deviation, 16 points), with 80% power and an $\alpha$ level of .05, a total sample size of 30 patients was estimated (15 per group). An allowance for a 15% dropout rate was made, increasing the sample size to 34 patients (17 per group).

## Statistical analysis

Statistical analysis was performed using the R program (R Foundation for Statistical Computing, Vienna, Austria) in accordance with an intention-to-treat approach. Linear mixed models with repeated-measures analysis and random-effect models were used to model the intervention effect over the assessment time points for the primary and secondary outcome measures. We modeled the random effects of individuals and fixed effects of group (manual therapy and home stretching and manual therapy and home stretching plus CNS-focused approach), assessment time point (baseline, after treatment, and at 3 months' follow-up), and group × assessment time point. Pair-wise comparisons with Bonferroni adjustment were used when the interaction effect (ie, group × assessment time point) or the time point was significant and change scores between evaluations at baseline, after treatment, and at 3 months' follow-up were computed to examine whether the MDC or MCID was exceeded.

## Results

Fifty-four participants were initially assessed for eligibility, and 34 completed the study (Fig. 1). Both intervention groups were comparable at baseline in terms of patients' characteristics and outcomes (Tables I and II).

Table II shows the results of each outcome for both groups, as well as within- and between-group changes. No time point–by–group interaction was observed for any of the assessed outcomes. A main effect for time point was found for the SPADI score ($P < .001$), with the group receiving manual therapy and home stretching and the group receiving manual therapy and home stretching plus a CNS-focused approach showing similar improvements after treatment (within-group mean difference [MD], −27.36 [95% confidence interval (CI), −40.37 to −14.34] and −28.59 [95% CI, −41.21 to −15.96], respectively) and at 3 months' follow-up (−35.47 [95% CI, −47.63 to −23.30] and −38.32 [95% CI, −50.86 to −25.78], respectively), both exceeding the MCID.

A main effect for time point was also observed for the PSFS score ($P < .001$), with both intervention groups showing comparable improvements after treatment (within-group MD, −7.42 [95% CI, −9.50 to −5.11] and −6.05 [95% CI, −8.80 to −4.04], respectively) and at 3 months' follow-up (−8.18 [95% CI, −13.48 to −2.88] and −11.06 [95% CI, −9.60 to 1.31], respectively), which exceeded the MCID. Both groups also showed improvement in the VAS score through the study (main effect for time point, $P < .001$) (within-group MD, −18.58 [95% CI, −34.91 to −2.26] and −33.68 [95% CI, −50.50 to −16.85], respectively) and at 3 months' follow-up (−28.58 [95% CI, −46.03 to −11.14] and −27.93 [95% CI, −45.91 to −9.95], respectively), which exceeded the MCID in the group receiving manual therapy and home stretching plus a CNS-focused approach. Between-group comparisons of PSFS, SPADI, and VAS scores are shown in Figure 2.

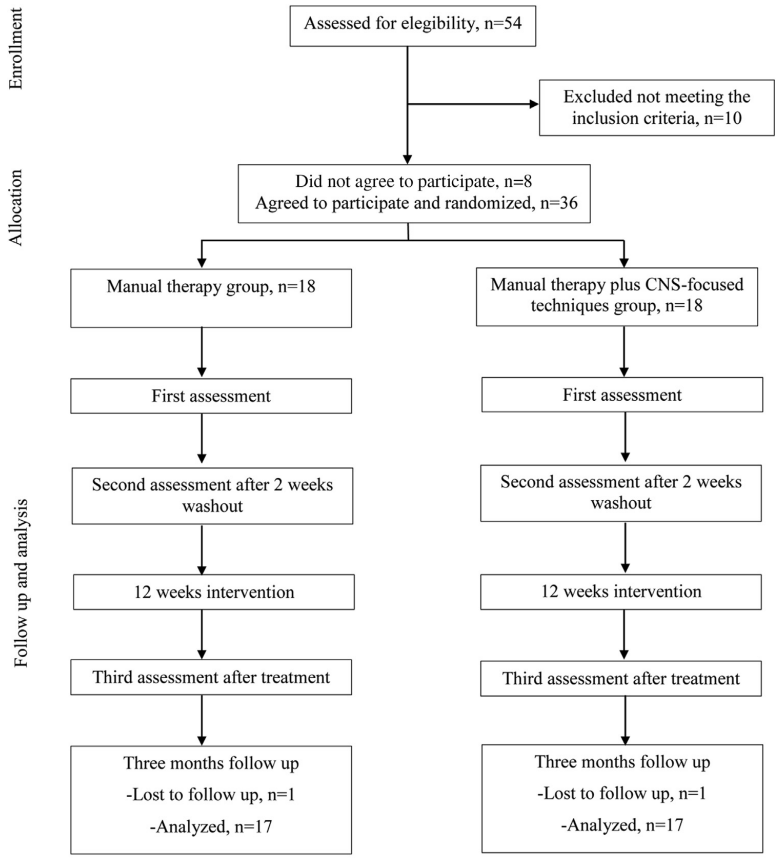


**Figure 1** CONSORT (Consolidated Standards of Reporting Trials) diagram showing participant flow through study, from enrollment to allocation, follow-up, and analysis. *CNS*, central nervous system.

In terms of shoulder ROM, a similar improvement was observed in both groups (no time point–by–group interaction but a significant main effect for time point) for active and passive shoulder flexion ($P < .001$) and active and passive shoulder external rotation ($P < .001$) (the within-group MD for each outcome is shown in Table II). In the group receiving manual therapy and home stretching, active shoulder flexion did not improve after treatment compared with baseline (within-group MD, 13.5°; 95% CI, −0.8° to 27.7°), whereas a significant improvement was observed in the group receiving manual therapy and home stretching plus a CNS-focused approach (within-group MD, 21.6°; 95% CI, 6.9°-36.2°). Significant improvement in active shoulder flexion was observed in the group receiving manual therapy and home stretching between the evaluations after treatment and at 3 months' follow-up (within-group MD, 11.6°; 95% CI, 1.6°-21.7°). Between-group comparisons of shoulder ROM are shown in Figure 3.

## Discussion

The aim of this study was to evaluate the additive effect of a CNS-focused approach to a manual therapy and home stretching program in people with FS. Overall, the results indicate that both interventions are equally effective in improving shoulder ROM and reducing shoulder pain and disability, thus suggesting that a CNS-focused approach has no additional benefit to a more peripheral-focused treatment in people with FS.

In recent years, CNS-focused physiotherapy approaches have been successfully implemented, both in isolation or within a multimodal treatment, in people with several chronic musculoskeletal conditions.[1,9,18] Regarding shoulder pain, only a preliminary study and a case report have previously investigated the effect of CNS-focused interventions in FS.[21,38] The improvements in shoulder pain and function in the group receiving the CNS-focused

**Table I** Demographic characteristics

| Characteristic | Manual therapy (n = 17) | Manual therapy + CNS-focused approach (n = 17) | Total (N = 34) |
|---|---|---|---|
| Sex, n (%) | | | |
| Female | 9 (52.9) | 15 (88.2) | 24 (70.6) |
| Male | 8 (47.1) | 2 (11.8) | 10 (29.4) |
| Age, yr | 53.4 (7.87) | 54.2 (7.48) | 53.8 (7.57) |
| BMI | 24.2 (3.31) | 23.1 (2.28) | 23.7 (2.85) |
| Dominant side, n (%) | | | |
| Right | 0 (0) | 1 (5.9) | 1 (2.9) |
| Left | 17 (100) | 16 (94.1) | 33 (97.1) |
| Painful side, n (%) | | | |
| Left | 9 (52.9) | 10 (58.8) | 19 (55.9) |
| Right | 8 (47.1) | 7 (41.2) | 15 (44.1) |
| FS type, n (%) | | | |
| Primary adhesive capsulitis | 15 (88.2) | 11 (64.7) | 26 (76.5) |
| Secondary adhesive capsulitis | 2 (11.8) | 6 (35.3) | 8 (23.5) |
| Symptom duration, mo | 9.82 (8.54) | 8.00 (5.41) | 8.91 (7.10) |
| Diabetes, n (%) | | | |
| No | 14 (82.4) | 16 (94.1) | 30 (88.2) |
| Yes | 3 (17.6) | 1 (5.9) | 4 (11.8) |
| Hypothyroidism or hyperthyroidism, n (%) | | | |
| No | 15 (88.2) | 16 (94.1) | 31 (91.2) |
| Yes | 2 (11.8) | 1 (5.9) | 3 (8.8) |

*CNS*, central nervous system; *BMI*, body max index; *FS*, frozen shoulder.
Data are presented as mean ± standard deviation or frequency (proportion).

intervention group that we observed are in line with the findings of the aforementioned studies. For instance, Louw et al[21] and Sawyer et al[38] reported a mean improvement of 14.5° and 101°, respectively, in active shoulder flexion, whereas a gain of 21.56° in active shoulder flexion after treatment was observed in our CNS-focused group. Similarly, the improvements in the SPADI and shoulder pain scores after treatment (27.36 points and 33.68 points, respectively) observed in the group receiving the CNS-focused approach are comparable to those reported by Sawyer et al for the SPADI score (22 points) and by both Louw et al[21] and Sawyer et al[38] for pain scores on a numerical rating scale (0.48 points and 7 points, respectively).

The positive effects on shoulder pain and function reported in our study by the group receiving manual therapy and home stretching are in accordance with those previously obtained in a case series by our research group[8] and with the recent literature.[29,30,32] However, contrary to our hypothesis, both intervention groups showed comparable improvements in terms of shoulder pain, function, disability, and ROM after treatment and at 3 months' follow-up, suggesting that a CNS-focused approach had no additional benefit to a more peripherally targeted treatment in patients with FS. Several reasons might explain these results. First, we randomly assigned our participants to 1 of 2 intervention groups following a one-size-fits-all approach without establishing their predominant pain mechanism at baseline. Recent evidence has shown that cortical representations were not present in people with shoulder pain with a primary nociceptive pain mechanism.[5] Most of our sample could have consisted of patients with a dominant nociceptive pain mechanism, thus explaining why they did not show the expected benefit with an additional CNS-focused approach. Second, it cannot be discarded that the theoretically summative therapeutic effect of the combined peripheral and CNS-focused intervention might have been annulated owing to participants in this group perceiving a contradictory message between the 2 treatments.[9] Additionally, better outcomes may have been obtained by adding CNS-focused interventions other than those used in this study (eg, pain neuroscience education). Furthermore, pain and functional limitations in people with FS are largely related to pathophysiological changes occurring at the peripheral tissue level (eg, inflammation and subsequent capsular contracture).[16,36] This may be the reason CNS approaches such as GMI, sensory discrimination training, or pain neuroscience education would have not added any value to the manual therapy and exercise treatment, as no influence on the pathologic changes reported in the joint capsule and related structures may be expected after implementing the aforementioned CNS-focused interventions.

## Study limitations

This study has several limitations that need to be acknowledged. First, the lack of a control group without intervention prevents us from establishing firm conclusions

**Table II** Results of each outcome for both groups and within- and between-group changes

| Outcome | Manual therapy | Manual therapy + CNS-focused approach | Between-group change score |
|---|---|---|---|
| Active shoulder flexion, ° | | | |
| Baseline | 112.6 ± 5.9 | 103.1 ± 6.1 | |
| After treatment | 126.1 ± 5.1 | 124.6 ± 5.3 | 1.4 (−13.5 to 16.4) |
| Within-group change from baseline to after treatment | 13.5 (−0.8 to 27.7) | 21.6 (6.9-36.2) | |
| 3-mo follow-up | 137.7 ± 5.4 | 134.3 ± 5.6 | 3.4 (−12.5 to 19.3) |
| Within-group change from baseline to 3-mo follow-up | 25.1 (12.2-38.1) | 31.3 (17.9-44.6) | |
| Within-group change from after treatment to 3-mo follow-up | 11.6 (1.6-21.7) | 9.7 (−0.7 to 20) | |
| Passive shoulder flexion, ° | | | |
| Baseline | 122.5 ± 6.3 | 119.0 ± 6.5 | |
| After treatment | 139.1 ± 5.6 | 134.8 ± 5.8 | 4.3 (−12.2 to 20.8) |
| Within-group change from baseline to after treatment | 16.5 (3.9-29.2) | 15.8 (2.7-28.8) | |
| 3-mo follow-up | 147.0 ± 5.7 | 145.4 ± 5.8 | 1.6 (−15 to 18.2) |
| Within-group change from baseline to 3-mo follow-up | 24.5 (12.3-36.6) | 26.4 (13.9-39) | |
| Within-group change from after treatment to 3-mo follow-up | 7.9 (−2.3 to 18.2) | 10.687 (0.2-21.2) | |
| Active shoulder external rotation, ° | | | |
| Baseline | 10.1 ± 2.9 | 13.1 ± 2.9 | |
| After treatment | 23.4 ± 4.3 | 26.5 ± 4.3 | −3.1 (−15.4 to 9.2) |
| Within-group change from baseline to after treatment | 13.3 (4.8-21.9) | 13.4 (4.8-21.9) | |
| 3-mo follow-up | 30.2 ± 4.8 | 32.6 ± 4.8 | −2.4 (−16.1 to 11.4) |
| Within-group change from baseline to 3-mo follow-up | 20.1 (10.3-29.9) | 19.4 (9.6-29.3) | |
| Within-group change from after treatment to 3-mo follow-up | 6.8 (−0.4 to 14) | 6.1 (−1.2 to 13.3) | |
| Passive shoulder external rotation, ° | | | |
| Baseline | 16.8 ± 3.2 | 20.7 ± 3.3 | |
| After treatment | 37.6 ± 6.1 | 36.8 ± 6.3 | 0.8 (−17 to 18.6) |
| Within-group change from baseline to after treatment | 20.9 (8-33.8) | 16.1 (2.8-29.4) | |
| 3-mo follow-up | 42.1 ± 5.1 | 40.8 ± 5.3 | 1.3 (−13.6 to 16.3) |
| Within-group change from baseline to 3-mo follow-up | 25.3 (14.1-36.5) | 20.1 (8.5-31.6) | |
| Within-group change from after treatment to 3-mo follow-up | 4.4 (−4.2 to 13) | 3.9 (−4.9 to 12.8) | |
| SPADI score (0-100) | | | |
| Baseline | 57.6 ± 4.4 | 61.2 ± 4.5 | |
| After treatment | 29.0 ± 5.3 | 33.8 ± 5.5 | −4.8 (−20.4 to 10.7) |
| Within-group change from baseline to after treatment | −28.6 (−41.2 to −16) | −27.4 (−40.4 to −14.3) | |
| 3-mo follow-up | 22.1 ± 4.8 | 22.9 ± 4.9 | −0.8 (−14.7 to 13.2) |
| Within-group change from baseline to 3-mo follow-up | −35.5 (−47.6 to −23.3) | −38.3 (−50.9 to −25.8) | |
| Within-group change from after treatment to 3-mo follow-up | −6.9 (−17.9 to 4.2) | −11.0 (−22.4 to 0.4) | |
| PSFS score* | | | |
| Baseline | 38.6 ± 4 | 37.5 ± 4.2 | |
| After treatment | 31.2 ± 3.2 | 31.1 ± 3.3 | 0.1 (−9.3 to 9.5) |

(*continued on next page*)

**Table II** Results of each outcome for both groups and within- and between-group changes (*continued*)

| Outcome | Manual therapy | Manual therapy + CNS-focused approach | Between-group change score |
|---|---|---|---|
| Within-group change from baseline to after treatment | −7.4 (−9.5 to −5.1) | −6.1 (−8.8 to −4) | |
| 3-mo follow-up | 30.4 ± 2.6 | 33.3 ± 3 | −2.9 (−11.4 to 5.5) |
| Within-group change from baseline to 3-mo follow-up | −8.2 (−13.5 to −2.9) | −11.1 (−9.6 to 1.3) | |
| Within-group change from after treatment to 3-mo follow-up | −0.8 (−9.8 to −5.1) | 5.0 (−1.3 to 5.9) | |
| VAS score | | | |
| Baseline | 41.6 ± 5.5 | 49.3 ± 5.6 | |
| After treatment | 23.1 ± 5 | 15.6 ± 5.2 | 7.4 (−7.3 to 22.1) |
| Within-group change from baseline to after treatment | −18.6 (−34.9 to −2.3) | −33.7 (−50.5 to −16.9) | |
| 3-mo follow-up | 13.1 ± 5.1 | 21.4 ± 5.2 | −8.3 (−23.2 to 6.5) |
| Within-group change from baseline to 3-mo follow-up | −28.6 (−46 to −11.1) | −27.9 (−45.9 to −10) | |
| Within-group change from after treatment to 3-mo follow-up | −10.0 (−23.3 to 3.3) | 5.7 (−8 to 19.5) | |

*CNS*, central nervous system; *SPADI*, shoulder pain and disability index; *PSFS*, Patient-Specific Functional Scale; *VAS*, visual analog scale.
Data are presented as mean ± standard error or mean difference (95% confidence interval).
* The total score is calculated as the sum of the activities' scores divided by the number of activities (range, 0-10).

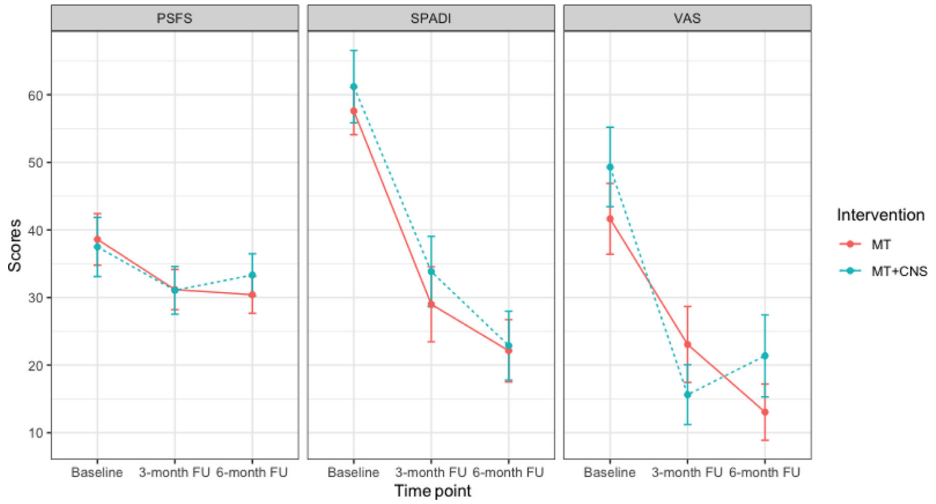


**Figure 2** Between-group comparisons of Patient-Specific Functional Scale (PSFS), Shoulder Pain and Disability Index (SPADI), and visual analog scale (VAS) scores throughout study. *MT*, manual therapy and home stretching program; *MT+CNS*, manual therapy and home stretching program plus central nervous system–focused approach; *FU*, follow-up.

about the superiority of the 2 studied interventions over natural history. Second, as previously mentioned, no stratification of participants was performed at baseline in terms of pain mechanisms, so interventions were not individually tailored. Future studies could classify participants with FS at baseline in terms of predominant pain mechanisms[39,40] to establish more specific inclusion criteria before treatment.

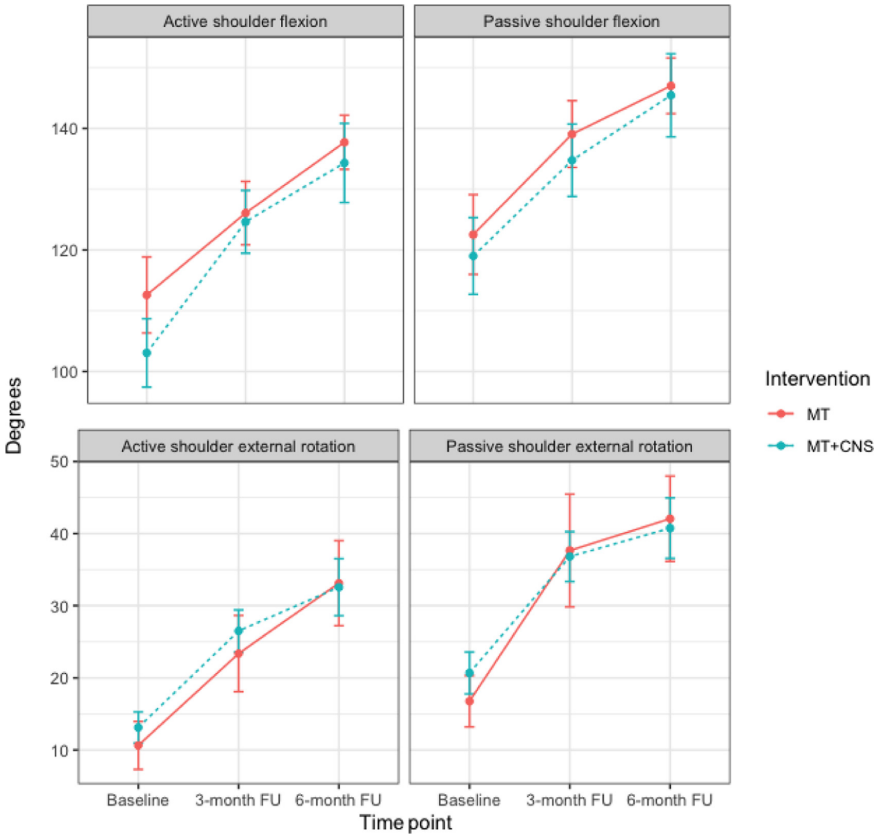


**Figure 3** Between-group comparisons of shoulder range of motion throughout study. *MT*, manual therapy and home stretching program; *MT+CNS*, manual therapy and home stretching program plus central nervous system–focused approach; *FU*, follow-up.

## Conclusion

A CNS-focused approach provided no additional benefit to a manual therapy and home stretching program in terms of shoulder pain and function in people with FS. Future studies should evaluate the effectiveness of CNS-focused interventions in people with FS with a predominant nociplastic pain mechanism to assess their potential benefits.

## Acknowledgment

The authors thank the participants for taking part in this study. They also thank Dr. Jose Enrique Aroca and Dr. Marta Navarro for their role in recruiting participants.

## Disclaimers:

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sector.
Conflicts of interest: The authors, their immediate families, and any research foundations with which they are affiliated have not received any financial payments or other benefits from any commercial entity related to the subject of this article.

## Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jse.2023.02.134.

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