UNIVERSIDAD DE EXTREMADURA

TESIS DOCTORAL

EFECTOS DE UN PROGRAMA DE EJERCICIO FÍSICO MEDIANTE REALIDAD VIRTUALSOBRE LA ESTRUCTURA CEREBRAL Y ANÁLISIS DE LAS FUNCIONES MOTORA Y COGNITIVA EN PERSONAS CON FIBROMIALGIA

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PROGRAMA DE DOCTORADO EN CIENCIAS DEL DEPORTE

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Ítaca

Cuando emprendas tu viaje a Ítaca
pide que el camino sea largo,
lleno de aventuras, lleno de experiencias.
No temas a los lestrigones ni a los cíclopes
ni al colérico Poseidón,
seres tales jamás hallarás en tu camino,
si tu pensar es elevado, si selecta
es la emoción que toca tu espíritu y tu cuerpo.
Ni a los lestrigones ni a los cíclopes
ni al salvaje Poseidón encontrarás,
si no los llevas dentro de tu alma,
si no los yergue tu alma ante ti.

Pide que el camino sea largo.
Que muchas sean las mañanas de verano
en que llegues -¡con qué placer y alegría!-
a puertos nunca vistos antes.
Detente en los emporios de Fenicia
y hazte con hermosas mercancías,
nácar y coral, ámbar y ébano
y toda suerte de perfumes sensuales,
cuantos más abundantes perfumes sensuales puedas.
Ve a muchas ciudades egipcias
a aprender, a aprender de sus sabios.

Ten siempre a Ítaca en tu mente.
Llegar allí es tu destino.
Mas no apresures nunca el viaje.
Mejor que dure muchos años
y atracar, viejo ya, en la isla,
enriquecido de cuanto ganaste en el camino
sin aguantar a que Ítaca te enriquezca.

Ítaca te brindó tan hermoso viaje.
Sin ella no habrías emprendido el camino.
Pero no tiene ya nada que darte.

Aunque la halles pobre, Ítaca no te ha engañado.
Así, sabio como te has vuelto, con tanta experiencia,
entenderás ya qué significan las Ítacas.

Konstantinos Kavafis (1863-1933)

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Una manera de hacer Europa

Fondo Europeo de Desarrollo Regional

Contenido

Resumen

Antecedentes: la fibromialgia es una enfermedad compleja que se caracteriza por la presencia de dolor musculoesquelético crónico generalizado, difuso y persistente que se asocia a un número de síntomas entre los que se encuentran la fatiga, trastornos de sueño, ansiedad, depresión, problemas cognitivos y una condición física baja. Todos estos síntomas limitan la salud de la persona repercutiendo en las actividades de la vida diaria y conduciendo a una reducción de la calidad de vida.

La realización de dos o más tareas de manera simultánea, es una acción que ocurre de manera continua en nuestras vidas. En la fibromialgia, esta capacidad se encuentra deteriorada y ha generado un interés en el campo de la investigación. Tradicionalmente, la mayoría de pruebas que evalúan la condición física en esta población lo han hecho incluyendo exclusivamente el componente físico. Sin embargo, la fiabilidad de estas pruebas agregando una segunda tarea cognitiva ha sido poco estudiada.

En cuanto al impacto de la enfermedad, casi el 80% de las personas con fibromialgia han reportado problemas de sueño. La glándula pineal es un órgano neuroendocrino que produce y segrega melatonina, hormona que se encuentra involucrada en los procesos de sueño-vigilia. El conocimiento del volumen que tiene este órgano y su relación con la producción de melatonina, así como con las horas de sueño parece que puede aportar información muy interesante en el estudio del sueño. Sin embargo, hasta el momento estos aspectos no han sido tratados en fibromialgia.

Los problemas cognitivos y los problemas de concentración se presentan de manera habitual en personas con fibromialgia. Una de las principales estructuras cerebrales involucradas en estos procesos además del dolor es el hipocampo. Parece que la sintomatología puede empeorar o incrementar en base a la atrofia de esta estructura y son varios los estudios que han analizado los cambios volumétricos. Sin embargo, el hipocampo se compone de diferentes subregiones que aún no han sido estudiadas en esta población y podrían aportar información relevante en el campo de la investigación.

La kinesiofobia o miedo al movimiento también es otra característica común que se da en la fibromialgia. Su relación con acciones de la vida diaria, el miedo a las caídas y el impacto de la enfermedad no ha sido ampliamente estudiado. Conocer estos aspectos ayudaría en gran medida al manejo de la patología.

El ejercicio físico se considera la terapia no farmacológica que ha mostrado el mayor nivel de evidencia para el tratamiento de la fibromialgia. En este sentido, los *exergames* han mostrado ser una propuesta interesante en el manejo de la fibromialgia, ya que, han manifestado resultados positivos que han mejorado la función general, la percepción del dolor, la calidad de vida, la capacidad de ejercicio, la salud percibida, la severidad de la fatiga, el control autónomo y la dinámica cerebral. Sin embargo, los cambios volumétricos producidos en estructuras cerebrales involucradas en la red del dolor tras una intervención basada en *exergames* en población con fibromialgia no han sido estudiados hasta la fecha.

Objetivos: para la presente tesis doctoral se pueden diferenciar cuatro objetivos generales: 1) Evaluar las propiedades psicométricas de diferentes pruebas para la evaluación de la función motora y cognitiva en mujeres con fibromialgia; 2) Evaluar el impacto que tiene la fibromialgia sobre estructuras cerebrales involucradas en los procesos de sueño y memoria, así como variables relacionadas en los mismos; 3) Evaluar el impacto que tiene la fibromialgia sobre la kinesiofobia y su relación con pruebas de evaluación que guardan relación con actividades de la vida diaria y el miedo a las caídas; y 4) Evaluar los efectos de los *exergames* sobre el volumen de materia gris de determinadas estructuras cerebrales involucradas en la red del dolor en mujeres con fibromialgia.

Métodos: se llevaron a cabo cinco estudios transversales. Dos de estos estudios se centraron en el análisis de las propiedades psicométricas de tres pruebas de evaluación bajo el paradigma de la doble tarea. Los tres estudios restantes se centraron en el impacto de la fibromialgia sobre aspectos relacionados con la sintomatología de la enfermedad. En este sentido, dos estudios se centraron en los cambios volumétricos en la glándula pineal y los subcampos del hipocampo medidos a través de imagen por resonancia magnética. El otro estudio se centró en la relación existente entre la kinesiofobia, pruebas de evaluación físicas que guardan una estrecha relación con actividades de la vida diaria y el miedo a las caídas. Finalmente, se realizó un ensayo controlado aleatorizado con el fin de estudiar los cambios volumétricos producidos en estructuras cerebrales involucradas en la red del dolor tras una intervención de 24 semanas basada en *exergames* que incluía ejercicios de danza, control postural, coordinación y marcha.

Resultados y discusión: un total de cinco artículos publicados en revistas indexadas en el *Journal Citation Reports* y un artículo fuera de índice se han incluido en la presente tesis doctoral. Los principales hallazgos extraídos han sido los siguientes: 1) las pruebas *30 seconds chair stand*, *30 seconds arm curl* y una variable de rendimiento total que involucraba el aspecto físico y cognitivo, obtuvieron buenos valores de fiabilidad bajo condiciones de doble tarea; 2) la prueba *3-meters backwards walking test* mostró buenos valores de fiabilidad en condición simple y de doble tarea, además de mostrar una fuerte validez concurrente con la prueba *Timed Up and Go* y mostrar una relación con el impacto de la enfermedad; 3) el análisis volumétrico de la glándula pineal no mostró diferencias significativas entre mujeres sanas y con fibromialgia. Sin embargo, se observaron diferencias en la prevalencia de quistes entre los dos grupos. Parece que las horas de sueño y los niveles de melatonina se encuentran relacionados con el volumen del parénquima pineal en mujeres con fibromialgia; 4) las mujeres con fibromialgia mostraron reducciones significativas de volumen en la mayoría de los subcampos que componen el hipocampo en comparación con mujeres sanas. Covariables como la edad, el deterioro cognitivo o la depresión se encontraron relacionadas con subcampos específicos; 5) El análisis de la kinesiofobia reveló que las mujeres con fibromialgia mostraron peores puntuaciones en comparación con las mujeres sanas. Además, mostraron un peor rendimiento en los test de movilidad y mayor miedo a las caídas. La puntuación de la kinesiofobia se relacionó con el rendimiento obtenido en las pruebas de movilidad (i.e. *Timed Up and Go* y *10-step stair ascent test*), miedo a las caídas y el impacto de la enfermedad en las mujeres con fibromialgia. Sin embargo, la kinesofobia no se relacionó con la prueba de prensión manual que requiere de un patrón motor menos complejo que las otras pruebas físicas. Por último, el programa basado en *exergames* con una duración de 24 semanas parece no haber producido cambios en el volumen de materia gris de diferentes estructuras cerebrales involucradas en la red del dolor en mujeres con fibromialgia. De la misma forma, tampoco se detectaron mejoras en el pico del consumo de oxígeno estimado y el deterioro cognitivo. No obstante, se observa una relación entre el pico de consumo de oxígeno estimado y las regiones izquierda y derecha del hipocampo, así como de la amígdala, pudiendo estar estos resultados relacionados con el flujo sanguíneo y la frecuencia respiratoria.

Palabras clave: dolor crónico; valoración; doble tarea; sueño; kinesiofobia; danza; imagen por resonancia magnética.

Abstract

Background: Fibromyalgia is a complex disease characterized by widespread, diffuse, and persistent chronic musculoskeletal pain associated with some symptoms, including fatigue, sleep disorders, anxiety, depression, cognitive problems, and poor physical condition. All these symptoms limit the person's health, impacting activities of daily living and reducing the quality of life.

The performance of two or more tasks simultaneously is an action that occurs continuously in our lives. In fibromyalgia, this ability is impaired and has generated research interest. Traditionally, most tests assessing physical fitness in this population have done so by including the physical component exclusively. However, the reliability of these tests with the addition of a second cognitive task has been little studied.

Regarding the impact of the disease, almost 80% of people with fibromyalgia have reported sleep problems. The pineal gland is a neuroendocrine organ that produces and secretes melatonin, a hormone involved in the sleep-wake cycle. Knowledge of the volume of this organ and its relationship with melatonin production and the hours of sleep provides exciting information in the study of sleep. However, so far, these aspects have not been treated in fibromyalgia.

Cognitive problems and concentration problems are common in people with fibromyalgia. The hippocampus is one of the primary brain structures involved in these processes besides pain. Symptomatology may worsen or increase based on the atrophy of this structure, and several studies have analyzed volumetric changes. However, the hippocampus is composed of different subregions that still need to be studied in this population and could provide relevant information in the field of research.

Kinesiophobia, or fear of movement, is another common characteristic of fibromyalgia. Its relationship with activities of daily living, fear of falling, and the impact of the disease has not been extensively studied. Knowing these aspects would greatly help in the management of the pathology.

Physical exercise is considered the non-pharmacological therapy that has shown the highest level of evidence for treating fibromyalgia. Exergames are an exciting proposal for managing fibromyalgia since they have manifested positive results that have improved general function, pain perception, quality of life, exercise capacity, perceived health, fatigue severity, autonomic control, and brain dynamics. However, the volumetric changes produced in brain structures involved in the pain matrix after an exergame-based intervention in the fibromyalgia population have not been studied to date.

Objectives: For the present doctoral thesis, four general objectives can be distinguished: 1) To evaluate the psychometric properties of different tests for assessing motor and cognitive function in women with fibromyalgia; 2) To evaluate the impact of fibromyalgia on brain structures involved in sleep and memory processes, as well as related variables; 3) To evaluate the impact of fibromyalgia on kinesiophobia and its relationship with assessment tests related to activities of daily living and fear of falling; 4) To evaluate the effects of exergames on the gray matter volume of specific brain structures involved in the pain matrix in women with fibromyalgia.

Methods: Five cross-sectional studies were carried out. Two of these studies analyzed the psychometric properties of three assessment tests under the dual-task paradigm. The remaining three studies focused on the impact of fibromyalgia on aspects related to disease symptomatology. Two studies focused on volumetric changes in the pineal gland and hippocampal subfields measured through magnetic resonance imaging. The other study focused on the relationship between kinesiophobia, physical assessment tests closely related to activities of daily living, and fear of falling. Finally, a randomized controlled trial was conducted to study volumetric changes in brain structures involved in the pain matrix after a 24-week exergame-based intervention involving dance, postural control, coordination, and gait exercises.

Results and discussion: A total of five articles published in journals indexed in the Journal Citation Reports and one non-indexed article have been included in this doctoral thesis. The main findings extracted have been the following: 1) The 30 seconds chair stand test, 30 seconds arm curl test, and a total performance variable involving physical and cognitive aspects obtained good reliability values under dual-task conditions; 2) The 3-meter backward walking test showed good reliability values in single and dual-task conditions, besides showing strong concurrent validity with the Timed Up and Go test and a relationship with the impact of the disease; 3) The volumetric analysis of the pineal gland showed no significant differences between healthy and fibromyalgia women. However, differences in the prevalence of cysts were observed between the two groups. Sleep hours and melatonin levels are related to pineal parenchymal volume in women with fibromyalgia; 4) women with fibromyalgia showed significant volume reductions in most of the subfields composing the hippocampus compared to healthy women. Covariates such as age, cognitive impairment, or depression were found to be related to specific subfields; 5) Analysis of kinesiophobia revealed that women with fibromyalgia showed worse scores compared to healthy women. In addition, they showed worse performance on mobility tests and greater fear of falling. The kinesiophobia score was related to the performance obtained in mobility tests (i.e., Timed Up and Go and 10-step stair ascent test), fear of falling, and the impact of the disease in women with fibromyalgia. However, kinesophobia was unrelated to the manual handgrip strength test, which requires a less complex motor pattern than the other physical tests. Finally, the exergame-based intervention with a duration of 24 weeks seems not to have produced changes in the gray matter volume of different brain structures involved in the pain matrix in women with fibromyalgia. Similarly, no peak estimated oxygen consumption and cognitive impairment improvements were detected. However, a relationship was observed between peak estimated oxygen consumption and the left and right regions of the hippocampus and the amygdala. These results could be related to blood flow and respiratory rate.

Keywords: chronic pain; assessment; dual-task; sleep; kinesiophobia; dance; magnetic resonance imaging.

Lista de siglas

Sigla	Comunidad Científica Internacional	Castellano
3MBWT	3 Meters Backward Test	Test de 3 metros caminando hacia atrás
BDNF	Brain Derived Neurotrophic Factor	Factor Neurotrófico Derivado del Cerebro
CA	Cornus Ammonis	Cuerno de Ammon
DTE	Dual Task Effect	Efecto de la doble tarea
EEG	Electroencephalography	Electroencefalografía
EULAR	European League Against Rheumatism	Liga Europea contra el Reumatismo
EXERNET	Red de Investigación en Ejercicio Físico y Salud para Poblaciones Especiales	Red de Investigación en Ejercicio Físico y Salud para Poblaciones Especiales
FES-I	Falls Efficacy Scale International	Escala Internacional de Eficacia de las Caídas
FIQ	Fibromyalgia Impact Questionnaire	Cuestionario del Impacto de la Fibromialgia
FIQR	Fibromyalgia Impact Questionnaire Revised	Cuestionario del Impacto de la Fibromialgia Revisado
FM	Fibromyalgia	Fibromialgia
GCDG	Granule Cell layer of the Dentate Gyrus	Capa de Células Glanulares del Giro Dentado
GDS	Geriatric Depression Scale	Escala de Depresión Geriátrica
JCR	Journal Citation Reports	Journal Citation Reports
MDC	Minimal Detectable Change	Cambio Mínimo Detectable
MMSE	Mini-Mental State Examination	Miniexamen del Estado Mental
PPV	Pineal Parenchima Volume	Volumen del Parénquima Pineal
PSQI	Pittsburgh Sleep Quality Index	Índice de Calidad del Sueño de Pittsburgh
SEM	Standard Error of Measurement	Error Estándar de Medida
SFT	Senior Fitness Test	Senior Fitness Test
SRD	Smallest Real Difference	Diferencia Mínima Real
SSS	Symptom Severity Scale	Escala de Severidad de los Síntomas
TSK	Tampa Scale of Kinesiophobia	Escala de Kinesiofobia de Tampa
TUG	Timed Up and Go	Timed Up and Go
WPI	Widespread Pain Index	Índice de Dolor Generalizado
HATA	Hippocampus-Amygdala-Transition-Area	Área de Transición del Hipocampo-Amígdala
eTIV	Estimated Total Intracranial Volume	Volumen Intracraneal Total Estimado

Contextualización

La presente tesis doctoral se enmarca en dos proyectos del Plan Nacional de Investigación Científica y Técnica y de Innovación. En este sentido, los proyectos son: "Coste-efectividad de un programa de ejercicio físico de realidad virtual sobre el envejecimiento cerebral y motor en fibromialgia (DEP2015-70356)" y "Coste-efectividad de programas de ejercicio físico basados en plantilla inteligente autónoma sobre el cerebro, patrón motor y calidad de vida en fibromialgia (referencia: PID2019-107191RB-I00/AEI/10.13039/501100011033)". Esta tesis doctoral se ha desarrollado en el grupo de investigación Actividad Física, Calidad de Vida y Salud (AFYCAV, CTS011) en la Facultad de Ciencias del Deporte de Cáceres de la Universidad de Extremadura entre los años 2019-2023 y cuenta con la aprobación de la Comisión de Bioética y Bioseguridad de la Universidad de Extremadura (5/2020).

El grupo de investigación AFYCAV se encuentra dentro de los 26 grupos de investigación que componen la Red de Investigación en Ejercicio Físico y Salud para Poblaciones Especiales (EXERNET), siendo el único representante en el nodo de Extremadura. El objetivo principal que persigue esta red es el de desarrollar acciones conjuntas que potencien los resultados de la investigación y proporcionen una transferencia inmediata a la sociedad y a los órganos de decisión en materia de salud pública, con una clara vocación innovadora en las propuestas. Además, la Red EXERNET tiene firmado desde el año 2014 con el Colegio Americano de Medicina del Deporte la representación exclusiva en España de la iniciativa global de salud "*Exercise Is Medicine*" cuya visión es hacer de la evaluación de la actividad física y de su promoción un estándar en el ámbito clínico, conectando el cuidado de la salud con los recursos basados en la evidencia científica disponibles para todos los miembros de la sociedad. *Exercise Is Medicine Spain* incluye diferentes instituciones públicas y asociaciones médicas de ámbito estatal.

En base al artículo 33 de la Normativa de Doctorado de la Universidad de Extremadura, las tesis doctorales que se presenten como compendio de publicaciones deben contar con diferentes requisitos:

a) Una introducción general, en la que se presenten temáticamente las publicaciones y se justifique la coherencia e importancia unitaria de la Tesis.

b) Un resumen global estructurado de los resultados y de la discusión de los mismos, así como las conclusiones finales.

c) Una copia completa de los trabajos publicados, haciendo constar claramente el nombre y la filiación de todas las coautorías de los trabajos y la referencia completa de las revistas en que se han publicado o aceptado para su publicación. En este último caso deberá aportar la *documentación justificativa de la aceptación, así como la referencia completa de la revista a la que se ha enviado el trabajo para su publicación. En caso de que se presente algún trabajo realizado en coautoría, hay que incluir también el informe a que hace referencia el apartado 2 de este artículo.*

d) En caso de que alguno de los trabajos presentados se haya publicado en una lengua distinta de las especificadas en el Programa de Doctorado, debe adjuntar un resumen del trabajo en cuestión redactado en alguna de las lenguas del Programa.

e) De estas aportaciones al menos dos tendrán que estar publicadas en revistas indexadas en el ISI-JCR o tratarse de alguna contribución relevante en su campo científico según los criterios de la Comisión Nacional Evaluadora de la Actividad Investigadora (CNEAI). Al menos en una de ellas el estudiante de doctorado deberá ocupar una posición relevante, entendiendo como tales, la primera, la última o la autoría de correspondencia.

f) Cualquier otro requisito que pueda establecer la Comisión Académica del Programa de Doctorado.

En este último punto, la Comisión Académica del Programa de Doctorado en Ciencias del Deporte de la Universidad de Extremadura, establece que, si la Tesis se realiza por compendio de publicaciones *"es necesario que se presenten un mínimo de 4 artículos en los que el doctorando aparezca como primer autor, debiendo estar todos ellos publicados en revistas indexadas, y estando como mínimo, 2 de ellos publicados en revistas indexadas en el JCR"* (Acta 18/04/2017).

En este sentido, la presente tesis doctoral incluye 5 artículos científicos indexados en el *Journal Citation Reports* (JCR) y 1 artículo fuera de índice en los que el doctorando figura como primer autor en todos ellos.

Artículos	**Cuartil y factor de impacto**
Leon-Llamas, J. L., Villafaina, S., Murillo-Garcia, A., Collado-Mateo, D., Domínguez-Muñoz, F. J., Sánchez-Gómez, J., & Gusi, N. (2019). Strength assessment under dual task conditions in women with fibromyalgia: a test–retest reliability study. *International Journal of Environmental Research and Public Health*, *16*(24), 4971.	Q1 (FI: 2.85)
Leon-Llamas, J. L., Villafaina, S., Murillo-Garcia, A., Domínguez-Muñoz, F. J., & Gusi, N. (2023). Test–Retest Reliability and Concurrent Validity of the 3 m Backward Walk Test under Single and Dual-Task Conditions in Women with Fibromyalgia. *Journal of Clinical Medicine*, *12*(1), 212.	Q2 (FI: 3.90)
Leon-Llamas, J. L., Villafaina, S., Murillo-Garcia, A., Domínguez, P. R., & Gusi, N. (2022). Relationship between pineal gland, sleep and melatonin in fibromyalgia women: a magnetic resonance imaging study. *Acta Neuropsychiatrica*, *34*(2), 77-85.	Q2 (FI: 3.80)
Leon-Llamas, J. L., Villafaina, S., Murillo-Garcia, A., & Gusi, N. (2021). Impact of fibromyalgia in the hippocampal subfields volumes of women—An MRI study. *International Journal of Environmental Research and Public Health*, *18*(4), 1549.	Q1 (FI: 4.61)
Leon-Llamas, J. L., Murillo-Garcia, A., Villafaina, S., Domínguez-Muñoz, F. J., Morenas, J., & Gusi, N. (2022). Relationship between kinesiophobia and mobility, impact of the disease, and fear of falling in women with and without fibromyalgia: a cross-sectional study. *International Journal of Environmental Research and Public Health*, *19*(14), 8257.	Fuera de índice
Leon-Llamas, J. L., Villafaina, S., Murillo-Garcia, A., Dominguez-Muñoz, F. J., & Gusi, N. (2020). Effects of 24-week exergame intervention on the gray matter volume of different brain structures in women with fibromyalgia: A single-blind, randomized controlled trial. *Journal of Clinical Medicine*, *9*(8), 2436.	Q1 (FI: 4.24)

Esquema de la tesis doctoral

La presente tesis doctoral está estructurada en diez capítulos. De manera previa, se ha recogido el resumen en castellano e inglés presentando una visión general del trabajo. Además, se ofrece una breve contextualización de los proyectos donde se enmarca este trabajo. Posteriormente, se establece el listado de artículos científicos que componen la presente tesis doctoral incluyendo el cuartil y el factor de impacto de los mismos.

El primer capítulo desarrolla el marco teórico sobre el cual se sustenta la presente tesis doctoral. En él se expondrán las definiciones, conceptos y antecedentes que permitirán contextualizar el trabajo realizado. En primer lugar, se describe la fibromialgia, especificando la prevalencia y la forma de diagnóstico. Tras ello, se exponen tres apartados que versan sobre el impacto que tiene la fibromialgia en determinadas estructuras cerebrales involucradas en la red del dolor, el sueño y la kinesiofobia. Posteriormente, se muestran las principales terapias que existen en esta enfermedad y se dedica una atención especial al ejercicio físico, remarcando de manera concreta la actividad física implementada a través de realidad virtual, denominada en la literatura científica como *exergames*. Finalmente se presenta la justificación y coherencia de la tesis doctoral exponiendo los tres bloques temáticos sobre los que se sustentará el documento para una mejor comprensión de los capítulos restantes.

El segundo capítulo expone los objetivos generales que se persiguen con esta tesis doctoral. De manera adicional, se establecen los objetivos específicos, ordenados en base a los bloques temáticos en los que se divide este trabajo para una mejor comprensión. Finalmente, aparecen de manera enumerada las hipótesis principales que se pretendían verificar en base a los estudios desarrollados.

El tercer capítulo presenta de manera resumida la metodología y los resultados derivados de las diferentes publicaciones que componen el presente trabajo ordenados por bloques temáticos. Además, se establece la relación de estos estudios con los objetivos e hipótesis planteadas, así como una breve interpretación de los hallazgos.

En el cuarto capítulo se realiza una discusión de los resultados obtenidos en los diferentes estudios desarrollados. Para una mejor comprensión, este apartado también se encuentra dividido en base a los diferentes bloques temáticos en los que se ha dividido la presente tesis doctoral.

En el quinto capítulo se recogen las fortalezas del trabajo.

En el sexto capítulo aparecen las limitaciones encontradas.

El séptimo capítulo propone las perspectivas futuras de trabajo que podrían seguir indagándose tras el conocimiento obtenido de los trabajos desarrollados, así como las brechas detectadas que podrían seguir investigándose.

El octavo capítulo expone las conclusiones de la presente tesis doctoral. Este capítulo también se encuentra redactado en lengua inglesa al igual que el resumen del presente trabajo, ya que, para la mención de doctorado internacional, en el artículo 43 de la normativa de los estudios de doctorado de la Universidad de Extremadura se establece que parte de la Tesis doctoral, al menos el resumen y las conclusiones, se hayan redactado en una de las lenguas habituales para la comunicación científica, distinta a cualquiera de las lenguas oficiales en España.

El noveno capítulo recopila las referencias bibliográficas utilizadas para la elaboración de la presente tesis doctoral.

En último lugar, el décimo capítulo permite visualizar los 6 artículos científicos que han conformado la presente tesis doctoral. Todos los documentos son de acceso abierto y se encuentran en la versión original en la que fueron publicados.

Capítulo 1

Marco teórico y contexto de la investigación

Capítulo 1. Marco teórico y contexto de la investigación

1.1. Fibromialgia: definición, prevalencia y diagnóstico

La fibromialgia (FM) es una enfermedad crónica caracterizada principalmente por dolor musculoesquelético persistente y difuso. Este dolor se acompaña de numerosos síntomas entre los que se destacan la ansiedad, depresión, rigidez, trastornos de sueño, una reducida condición física, problemas de equilibrio, de movilidad y deterioro cognitivo entre otros [1-3]. Todos estos síntomas conducen a que los pacientes experimenten una reducida calidad de vida [4, 5] y dificultades para llevar a cabo actividades de la vida diaria [6, 7].

Históricamente se ha cuestionado la existencia de la FM, ya que, la etiología y la fisiopatología es compleja al intervenir diferentes factores como los biológicos, psicológicos y sociales. A esto hay que añadir que el diagnóstico es difícil de realizar debido a que la clasificación y los criterios que se emplean siguen en evolución y no se encuentran biomarcadores específicos asociados a esta patología [8]. No obstante, en las últimas dos décadas se han llevado a cabo investigaciones que han proporcionado pruebas consistentes que indican un funcionamiento anormal en el sistema nervioso en individuos con FM [9]. Los estudios de neuroimagen han revelado respuestas incrementadas en la percepción del dolor [10-12], así como alteraciones en la estructura cerebral, actividad metabólica y conectividad funcional en reposo en áreas que están involucradas en el procesamiento del dolor [13-19]. No obstante, además de estas características, se propone que la FM podría estar influenciada por la combinación de factores genéticos, metabólicos, neurofisiológicos e inmunológicos, que van desde niveles elevados de estrés oxidativo que pueden desencadenar una respuesta inflamatoria y causar daño en el ADN mitocondrial de las células, hasta alteraciones en la microbiota intestinal que pueden alterar la producción de melatonina y serotonina [20].

A nivel mundial, la prevalencia de la FM se sitúa entre un 0,2% y un 6,6%, mostrando las mujeres una mayor prevalencia que los hombres, situándose entre un 2,4% y un 6,8% [21] y dándose principalmente en mujeres mayores de 50 años [22]. En Europa, la prevalencia se muestra similar, oscilando entre un 2,9% y un 4,7% en la población general [23], presentando una mayor incidencia en las mujeres con una prevalencia que se sitúa entre los 35 y 84 años. Los niveles superiores se sitúan en rangos que van desde los 55 a 64 años y los muy superiores entre 75 y 84 años [23]. En España, se estima una prevalencia general de un 2,45%, del cual las mujeres presentan un 4,49% frente a un 0,29% en los hombres [24]. El pico de prevalencia en mujeres se da en edades comprendidas entre los 60 y 69 años, seguido de rangos de edad comprendidos entre 40-49 años y 50-59 años [24].

En términos económicos, se estima que la FM supone un gasto de 12 billones de euros anuales para una población de 80 millones de habitantes [25]. En España, la FM supone un gasto medio de casi 10000 euros al año por paciente, de los cuales el 32,5% se atribuyen a costes sanitarios (e.g.

visitas médicas, test complementarios, terapias farmacológicas) y el 67,5% a costes indirectos (e.g. reducción de las horas de trabajo, bajas por enfermedad y discapacidad permanente) [26].

En 1990, el Colegio Americano de Reumatología aprobó por primera vez los criterios para la clasificación de la FM [27]. Estos criterios sufrieron una serie de modificaciones en 2010 que se caracterizaron por no requerir de un examen físico específico de los puntos sensibles por parte del médico, dado que, ocasionaban una serie de dificultades pragmáticas para aplicarlos. Sin embargo, este conjunto de criterios se reemplazó por el recuento de 19 regiones dolorosas y una serie de síntomas de la FM. En 2011, los mismos autores de los criterios de 2010 publicaron una modificación de los criterios de 2010 que permitía establecer el diagnóstico de la enfermedad en su totalidad de manera autoinformada. En este sentido, se advirtió que estas modificaciones sólo debían usarse para fines de investigación y no como una herramienta de diagnóstico clínico. Los criterios de 2011 introdujeron una puntuación a través de la gravedad de la FM, la suma del índice de dolor generalizado y la escala de gravedad de los síntomas, lo que permitió una medición cuantitativa de la gravedad de los síntomas de la FM.

La última actualización aprobada es la que se estableció en el año 2016 [28] y contempla cuatro criterios de diagnóstico:

1) Existe dolor generalizado, definido como dolor en al menos 4 o 5 regiones.
2) Los síntomas se han presentado en un nivel similar al menos durante 3 meses.
3) El índice de dolor general (WPI) es mayor o igual a 7 y la puntuación en la escala de severidad de los síntomas (SSS) es mayor o igual a 5. Aunque también se puede establecer un WPI entre 4-6 puntos y una puntuación en SSS mayor o igual a 9.
4) Un diagnóstico de FM es válido independientemente de otros diagnósticos. Un diagnóstico de FM no excluye la presencia de otras enfermedades clínicamente importantes.

1.2. Impacto de la fibromialgia sobre estructuras cerebrales involucradas en la red del dolor

Investigaciones previas han informado de anomalías en el sistema nervioso central en personas con FM [9], incluyendo alteraciones funcionales, metabólicas y estructurales en regiones cerebrales involucradas en el procesamiento del dolor [13, 16, 17, 29-31]. Dado que la FM tiene una sintomatología variada, las alteraciones en el sistema inmunológico, la fatiga, los patrones de sueño y los estados de ánimo pueden contribuir a experimentar dolor con la disfunción que ello conlleva. Esta cascada de síntomas puede conducir a experimentar alodinia e hiperalgesia [32] que se relacionan con la amplificación de las señales sensoriales (e.g. periféricas y centrales) que se encuentran involucradas en la percepción del dolor [33], afectando a la funcionalidad y estructura del sistema nervioso central. En este sentido, las personas con FM han mostrado reducciones de volumen en la materia gris de numerosas estructuras cerebrales que forman parte de la matriz del dolor o *pain matrix* [34], entre las que se destacan el hipocampo [16, 35], la amígdala [36], la corteza prefrontal [36], las cortezas cingulada anterior y cingulada media [14, 36, 37], así como la ínsula media [14].

En este sentido, el hipocampo se trata de una de las estructuras cerebrales más estudiadas y desempeña un papel fundamental en diversos procesos entre los que se destacan la memoria, la navegación, la cognición, el estrés, los estados de ánimo y el dolor [38-41]. Todos estos procesos se encuentran relacionados con la sintomatología de la FM. Aunque los estudios sobre la alteración volumétrica del hipocampo en el dolor crónico son escasos, parece que existe una disminución en su volumen [16, 35]. Además, se propone que las proporciones anormales de N-acetilaspartato/creatina pueden estar relacionadas con la disfunción y atrofia del mismo, ya que, se han reportado niveles inferiores de estas proporciones en individuos con FM en comparación con individuos sanos en el hipocampo derecho. Además, estas proporciones se han correlacionado con la gravedad de los síntomas de la FM [42]. En la misma línea también se han hallado resultados similares de la colina y el índice N-acetilaspartato + N-acetilaspartato glutamato en el hipocampo izquierdo, así como un descenso del mioinositol y mioinositol/creatina en ambos hipocampos [43]. También se detectaron valores inferiores en ambos hipocampos para la colina y solo en el izquierdo para el glutamato [44]. Por el contrario, también se observaron niveles reducidos de N-actilaspartato en ambos hemisferios y colina elevada solo en el derecho [45]. En este sentido, parece que existe una relación entre las alteraciones volumétricas y los niveles de metabolitos en el hipocampo [13].

Llegados a este punto, se puede considerar que la atrofia del hipocampo en la FM puede empeorar o incrementar la sintomatología en esta población. En esta línea, las personas que sufren FM comúnmente experimentan un deterioro de la función cognitiva que se caracteriza por problemas de memoria a corto plazo y concentración que reciben el nombre de *fibrofog* [46]. Además, el dolor, la sensación de incomodidad y la ansiedad en personas con FM se pueden incrementar al retroalimentarse esta atrofia y disfunción en el hipocampo, debido al papel central que desempeñan en los circuitos límbicos y las redes de modulación del dolor [47].

Aunque existen estudios que han analizado los cambios volumétricos del hipocampo en la FM, es importante remarcar que esta estructura está compuesta de diferentes subregiones como el subículo, la circunvolución dentada y el cornus ammonis (CA) entre otras [48]. Los avances que se han desarrollado en neuroimagen han permitido el estudio de estas subregiones [49], mostrando que cada una tiene diferencias en función, conectividad e histología con otras regiones del cerebro, así como vulnerabilidad a la enfermedad [50-52]. Estudios previos también han demostrado que estas subregiones se encuentran alteradas en el dolor crónico [53], los trastornos psiquiátricos [54, 55], los trastornos cognitivos [56-58] y la vida adulta [59]. Por lo tanto, la evaluación del volumen de los subcampos del hipocampo en FM parece fundamental en la comprensión de la patología y puede ayudar a la detección de posibles biomarcadores para esta enfermedad.

1.3. Impacto de la fibromialgia sobre el sueño

El sueño es un proceso vital y fundamental, necesario para la función física y mental. Mientras dormimos se producen cambios importantes en nuestro organismo. Se estima que cerca del 80% de las personas afectadas por FM han reportado problemas de sueño [60, 61], experimentando desordenes [27] y trastornos [62] en el mismo. Las manifestaciones más comunes incluyen movimientos involuntarios de las piernas, inquietud nocturna, despertares numerosos y sensaciones de sueño ligero y no reparador, con fatiga y rigidez al despertar. Son varios los estudios que han encontrado correlaciones entre una baja calidad del sueño y el empeoramiento de los síntomas de la FM [63-67] y parece que una reducida calidad de sueño tiende a generar un mayor riesgo de desarrollar síntomas asociados a esta patología como ansiedad, depresión y dolor crónico [68].

Hay diferentes estructuras cerebrales que desempeñan un papel crucial en la regulación del sueño. En este sentido, el hipotálamo y concretamente el núcleo supraquiasmático, considerado como el reloj biológico del cuerpo humano, se encarga de regular la secreción de hormonas durante las veinticuatro horas del día en base a la entrada de luz a través del sistema visual [69]. No obstante, la glándula pineal es el principal órgano neuroendocrino que se encarga de sintetizar melatonina (N -acetil-5-metoxitriptamina) [70] conocida como la hormona del sueño y que es fundamental en la regulación de los ritmos circadianos [71, 72], así como los ritmos de sueño vigilia [72, 73]. Esta hormona también se encuentra implicada en otros procesos relevantes como son la regulación del estado de ánimo, la ansiedad, el apetito, las respuestas inmunitarias, determinadas funciones cardíacas [74], el dolor [75] y tiene la capacidad de actuar como neuroprotector y antioxidante [76].

La literatura muestra resultados mixtos en los niveles de melatonina al comparar personas con FM y controles sanos, encontrando niveles normales [77, 78], niveles aumentados [79] y niveles reducidos [80]. En este sentido, conocer la actividad de la melatonina es fundamental, ya que, permite comprender otro proceso biológico que se experimenta en la FM y los trastornos de depresión mayor, demostrando que existe una relación positiva entre la disrupción en la liberación de melatonina y los síntomas clínicos [81].

Dado que la glándula pineal es el principal órgano que se encarga de producir y secretar melatonina [70], conocer su morfología también es interesante, ya que, se han reportado alteraciones en diferentes condiciones y patologías, encontrando volúmenes reducidos de la glándula pineal en personas obesas en comparación con personas delgadas [82], personas con insomnio primario [83], Alzheimer [84], esquizofrenia [85] y trastorno depresivo mayor [86]. Además, Liebrich, Schredl, Findeisen, Groden, Bumb and Nölte [87] encontraron que en individuos sanos, la alteración del ritmo del sueño se correlacionó con volúmenes pineales más pequeños.

Un hallazgo que se suele producir cuando se realiza una resonancia magnética o una tomografía axial computarizada en la glándula pineal es la calcificación, que se suele encontrar asociada a condiciones patológicas y de envejecimiento [88]. Aunque el proceso de calcificación no se conoce de manera certera, hay una serie de teorías que se proponen en el campo científico [88]. No obstante, se sabe que la glándula pineal posee una de las tasas de calcificación más elevadas entre los órganos y tejidos [88, 89]. En esta línea, en la enfermedad de Alzheimer se ha observado que la reducción del volumen de la glándula pineal y la presencia de calcificaciones pueden contribuir a la reducción de la secreción de melatonina, problemas de sueño [90] y, en consecuencia, a un deterioro cognitivo [91].

Por otro lado, también es frecuente encontrar quistes pineales cuando se lleva a cabo una resonancia magnética nuclear, los cuales suelen presentarse entre los 21 y los 30 años y disminuyen su prevalencia con la edad [92]. Parece que estos quistes también pueden tener un efecto negativo en la secreción de melatonina al comprimir el parénquima pineal [93]. Tanto los quistes como las calcificaciones se consideran tejidos hormonalmente inactivos y su volumen suele excluirse del volumen pineal total. Esta idea se basa en los resultados obtenidos en investigaciones previas [87, 93, 94] que mostraron que las alteraciones volumétricas pueden alterar la actividad de la melatonina, principalmente en relación con el volumen del parénquima pineal (PPV), que se refiere al tejido pineal hormonalmente activo.

Aunque los trastornos del sueño en la FM han sido ampliamente estudiados, debido a la falta de conocimiento científico sobre el volumen de la glándula pineal, su relación con las horas de sueño y los niveles de melatonina en mujeres con FM, se precisa de más investigación que permita explorar estas cuestiones.

1.4. Impacto de la fibromialgia sobre la kinesiofobia

Como se ha comentado en párrafos anteriores, la FM se caracteriza por la presencia de dolor crónico generalizado, persistente y difuso asociado a otro gran número de síntomas. La kinesiofobia es otra característica que suele encontrarse en la FM y consiste en un miedo excesivo, irracional y debilitante al movimiento y a la actividad física que surge de una sensación de vulnerabilidad o de fragilidad debido a una lesión dolorosa o a poder sufrir una nueva lesión [95].

En este sentido, el modelo de evitación del miedo cobra una especial relevancia en el contexto de la FM, ya que, postula que las experiencias dolorosas pueden generar en pacientes un miedo al movimiento y, en consecuencia, a generar comportamientos de evitación desadaptativos como respuesta a ese dolor. Si estos comportamientos se prolongan en el tiempo, se pueden llegar a estados de discapacidad, desuso y depresión que facilitan la entrada en un ciclo de retroalimentación que contribuye al mantenimiento y progresión de la enfermedad [96-98]. Esta situación se ve agravada por la actividad física reducida y el alto nivel de sedentarismo que se observa en personas con FM, las cuales tienden a presentar una condición física reducida [99], problemas de equilibrio que conllevan a un mayor riesgo de sufrir caídas [100] y un mayor miedo a caer. Todas estas alteraciones de la función física podrían dificultar la práctica de actividad física, aumentando aún más el tiempo de sedentarismo y, en consecuencia, la prevalencia de sobrepeso y obesidad en esta patología [101].

En la FM, es relevante conocer el miedo al dolor que se experimenta en la actividad física, ya que, parece que la sintomatología empeora tras su ejecución [102]. En este sentido, es comprensible que las personas con FM desarrollen un miedo hacia la realización de estas actividades y, en consecuencia, un comportamiento de rechazo o evitación hacia la actividad física [96, 103]. No obstante, es importante mencionar que el nivel inicial de dolor asociado con la actividad determina el nivel de actividad física que una persona que padece FM está dispuesta a realizar [104].

Investigaciones previas han revelado que la kinesiofobia perjudica las actividades de la vida diaria en personas mayores institucionalizadas que padecen dolor crónico [105], y también limita el estado de actividad física en pacientes con dolor lumbar crónico [106]. Adicionalmente, se ha visto que la kinesiofobia predice la movilidad y el equilibrio en personas mayores que padecen dolor lumbar [107]. Teniendo en cuenta esta información y la mencionada anteriormente, parece relevante evaluar la kinesiofobia en el contexto clínico para identificar las barreras que pueden interferir con la adhesión a los programas de rehabilitación [107] que tan beneficiosos serían en esta patología. En el caso de la FM, el 40% de los pacientes han mostrado un alto grado de miedo al movimiento y comportamientos con tendencia a evitar la actividad física [103]. De hecho, la adhesión al tratamiento en personas con FM se ve influenciada por altos niveles de dolor, una calidad de vida reducida en los dominios físicos y sociales y miedo al movimiento [108].

Hasta la fecha, la mayoría de estudios en FM que han tenido en cuenta la kinesiofobia se han basado en los efectos que han tenido diferentes tipos de terapia sobre diferentes variables, incluida la kinesiofobia. Sin embargo, son pocos los estudios que han indagado sobre la relación que existe entre la kinesiofobia y la discapacidad medida a través de cuestionarios [109-112]. Este tema es interesante desde una perspectiva de aplicación práctica con pocos recursos, pero debe tenerse en cuenta el sesgo que se puede generar al utilizar este tipo de instrumentos, ya que, no ofrecen medidas objetivas de la aptitud física al tener los participantes que recordar lo que hicieron o cómo se sintieron en un periodo de varios días. Por otra parte, sólo dos estudios han examinado la relación entre la kinesiofobia y la discapacidad medida a través de pruebas de aptitud física, aunque no encontraron correlaciones significativas entre estas variables [7, 113].

En la literatura, no se han encontrado estudios que hayan analizado la relación entre la kinesiofobia, el miedo a las caídas y el número de caídas, ni se han incluido grupos de control sanos. De los pocos estudios mencionados anteriormente, solo uno investigó la relación entre la kinesiofobia y el impacto de la enfermedad usando el cuestionario revisado del impacto de la fibromialgia (FIQR) [109] que se trata de la versión actualizada del cuestionario de impacto de la fibromialgia (FIQ). Los estudios restantes usaron el FIQ o no lo utilizaron.

Llegados a este punto, parece interesante contribuir a la literatura con nueva información que analice la relación entre la kinesiofobia, el número de caídas, el miedo a caer, el impacto de la FM y pruebas de condición física que guarden una relación con actividades de la vida diaria. Además, parece relevante la incorporación de un grupo control sano que permita profundizar en estos aspectos y pueda compararse con población con FM. La información que se obtenga es importante desde un punto de vista clínico, ya que, permitirá aumentar el conocimiento en este campo, pudiendo identificar aquellas actividades que se consideren más desafiantes y permitiendo diseñar actividades más amigables para mejorar el manejo de la FM.

1.5. Principales terapias en fibromialgia

La carga que supone vivir con FM es más elevada en comparación con otros trastornos reumáticos y más alta con respecto a la mayoría de otras enfermedades crónicas [114-116]. A esto hay que añadir que el manejo de la patología es complejo y a menudo muestra resultados mixtos en los tratamientos aplicados, haciendo difícil conseguir un éxito total [117]. En este sentido es fundamental que los profesionales de la salud proporcionen un apoyo y educación continua a los pacientes con el fin de conseguir que estas personas conozcan mejor cómo manejar su condición. Esta es sin duda una de las intervenciones más importante que hay que conseguir con estas personas para permitir una vida exitosa con esta patología multidimensional y debilitante [118].

La *European League Against Rheumatism* (EULAR) considera que los tratamientos actuales para tratar la FM se dividen en terapias farmacológicas y terapias no farmacológicas [117]. A continuación, se mostrarán los hallazgos más actuales que se conocen en este tipo de terapias:

Terapias farmacológicas

En Estados Unidos sólo tres medicamentos han sido aprobados para su uso en el tratamiento de la FM. En este sentido, encontramos dos antidepresivos como son la duloxetina y el milnaciprán y un anticonvulsivo que es la pregabalina [119]. Además de estos medicamentos, se encuentran otros que se engloban dentro de los antidepresivos tricíclicos, los inhibidores de la recaptación de la serotonina-norepinefrina, los anticonvulsivos y los relajantes musculares tricíclicos [120].

Entre los antidepresivos tricíclicos, la amitriptilina se muestra como un medicamento interesante, ya que, reduce el dolor, mejora el sueño y aumenta la satisfacción del paciente [121]. Por otra parte, la nortriptilina muestra menos efectos secundarios que la amitriptilina y parece que es mejor tolerado por los pacientes [122]. No obstante, se necesita más investigación, ya que, no hay muchos estudios de este fármaco en FM. En el caso de que no se tolere bien la amitriptilina, el relajante muscular tricíclico ciclobenzaprina, muestra reducciones moderadas del dolor sin afectar al sueño y la fatiga, por lo que su uso, también se muestra interesante [123].

Los inhibidores selectivos de la recaptación de serotonina y norepinefrina como la venlafaxina, no han sido estudiados en profundidad, por lo que su uso no está recomendado. En la misma línea, el anticonvulsivo gabapentina, tampoco muestra niveles de evidencia altos para confirmar si su uso es efectivo [124]. No obstante, parece que los inhibidores selectivos de la recaptación de serotonina y norepinefrina son efectivos para el tratamiento de la depresión [125].

Finalmente, los opioides parecen no ser aconsejables en el tratamiento de la FM al no actuar sobre los mecanismos implicados en la sensibilización central y pueden provocar dependencia, aumento de la hiperalgesia y otros efectos secundarios [126]. De la misma forma, los antiinflamatorios no esteroideos tampoco han demostrado ser más efectivos que el placebo en el alivio del dolor y pueden generar efectos secundarios importantes [127].

En el caso de que haya que administrar tratamiento farmacológico, se recomienda iniciar con una dosis baja e incrementarla de manera progresiva durante al menos tres meses para evaluar su efectividad. Si el tratamiento se muestra eficaz, se recomienda prolongarlo hasta los doce meses. En caso de no obtener resultados positivos con el tratamiento aplicado se recomienda suprimir el mismo y probar otras terapias no farmacológicas que no se hayan realizado hasta el momento [120].

Terapias no farmacológicas

La EULAR recomienda que el manejo de la FM se debe hacer desde un enfoque gradual para mejorar la calidad de vida relacionada con la salud, teniendo en cuenta el beneficio y el riesgo de las modalidades de tratamiento existentes adaptadas a las características individuales de la persona. No obstante, considera que el manejo inicial de la FM debe centrarse en terapias no farmacológicas en base al coste, disponibilidad, seguridad y preferencia del paciente [117].

Entre las diferentes terapias no farmacológicas, el ejercicio físico se concibe como la principal recomendación, ya que, proporciona el mayor nivel de evidencia en base a sus efectos positivos sobre el dolor, el bienestar, la función física, su amplia disponibilidad, la seguridad y su bajo coste [117]. No hay una conclusión clara para establecer qué tipo de ejercicio es más efectivo para el tratamiento de la FM. Sin embargo, parece que el ejercicio aeróbico y de fuerza son los más recomendados para reducir el dolor y la gravedad de los síntomas, mientras que los ejercicios de estiramiento y aeróbicos producen los mayores beneficios en la calidad de vida relacionada con la salud. Para la mejora de los síntomas de depresión en FM, parece que el ejercicio combinado, que incluiría las tres modalidades mencionadas anteriormente, se muestra como la forma más eficaz [128].

No obstante, existen otras terapias no farmacológicas que también muestran reducciones en la sintomatología de la FM, aunque su nivel de evidencia es un tanto más limitado. En este sentido, podemos destacar las terapias cognitivo-conductuales [129-131], las terapias multicomponente [132, 133], la acupuntura [134-136], la punción seca [136], la hidroterapia [137, 138], las terapias de movimiento meditativo [139] como el qigong, yoga y tai chi, las terapias centradas en la reducción de estrés mediante mindfulness [140, 141], el entrenamiento vibratorio de cuerpo completo [142, 143], la estimulación transcraneal de corriente directa [144] y las intervenciones basadas en danza [145] y concretamente las basadas en danza creativa [146].

Es importante recordar que cada persona con FM experimenta diferentes síntomas y niveles de dolor, y lo que funciona para una persona puede no funcionar para otra. Es imprescindible trabajar de manera conjunta y multidisciplinar entre varios profesionales del sector de la salud para conseguir el plan de tratamiento más adecuado con el fin de obtener los mayores beneficios, consiguiendo llevar a la persona de un estado A hacia un estado B cualitativamente mejor.

1.6. Ejercicio físico en personas con fibromialgia

En 2018 la asamblea mundial de la salud aprobó el plan de acción mundial sobre actividad física 2018-2030 y estableció una meta mundial voluntaria en la que se establecía que la inactividad física en adultos y adolescentes debía reducirse un 15% para el año 2030 [147]. En esta línea, la organización mundial de la salud mantiene actualizadas las directrices sobre actividad física y comportamiento sedentario para que se pueda conseguir el objetivo propuesto [148]. Estas recomendaciones son interesantes y recalcan la importancia de la realización de actividad física de manera regular para alcanzar los rangos propuestos de 150 a 300 minutos de actividad física de intensidad moderada y de 75 a 150 minutos de actividad física de intensidad vigorosa en personas adultas, así como la reducción de comportamientos sedentarios [148]. Aunque estas directrices ofrecen beneficios significativos y mitigan los riesgos para la salud, las enfermedades crónicas en general y la FM en particular precisa de un manejo más específico que es fundamental comprender para mejorar la salud de este colectivo.

La última revisión general sobre los efectos del ejercicio en pacientes con FM publicada hasta la fecha muestra la importancia de la realización de ejercicio físico como una forma eficaz de tratar la sintomatología de la FM sin generar efectos adversos para la salud [149]. Además, recalca que el ejercicio aeróbico y el entrenamiento de fuerza se presentan como las modalidades más efectivas para el tratamiento de esta patología en lo que al tratamiento de dolor y calidad de vida se refiere tal y como se había mencionado anteriormente en el apartado 1.5. No obstante, otras intervenciones de ejercicio han mostrado efectos beneficiosos sobre otros componentes de la sintomatología de la FM. En esta línea, encontramos los ejercicios acuáticos que parecen mejorar el bienestar, los síntomas y el estado físico. Las terapias de movimiento como el yoga, tai chi, Pilates y otras terapias alternativas muestran efectos sobre la calidad de vida y la intensidad de dolor. Los ejercicios múltiples o ejercicios combinados parecen afectar a la respuesta inflamatoria y a la ansiedad. No obstante, entre estas últimas modalidades citadas, resulta complicado realizar una comparación entre los distintos protocolos debido a diversos factores metodológicos, como el reducido tamaño de la muestra, la amplia variedad de resultados analizados y la falta de evidencia concluyente.

De forma general el envejecimiento normal tiende a generar una atrofia cerebral global con los respectivos cambios funcionales que ello conlleva y por consiguiente el deterioro cognitivo que puede experimentarse [150]. No obstante, este envejecimiento es variable de manera individual y parece estar relacionado con los hábitos de vida [151]. En este sentido, el ejercicio físico tiene un papel fundamental sobre el envejecimiento desde el punto de vista físico y cognitivo [152, 153] al tratarse, en muchos casos, de una herramienta de fácil acceso, segura y rentable. Además promueve el aumento de la neurogénesis, angiogénesis y sinaptogénesis [154]. Estas acciones son principalmente inducidas por el factor neurotrófico derivado del cerebro (BDNF), el factor de crecimiento y diferenciación 11 o GDF11 y el factor de crecimiento del endotelio vascular o VEGF, que afectan directamente a la plasticidad cerebral [155]. Estudios previos han hallado aumentos volumétricos, principalmente en el hipocampo tras intervenciones de ejercicio en personas sanas [156, 157], personas con deterioro cognitivo [158, 159], adultos mayores [153, 159, 160], personas con esclerosis múltiple [161] y personas con esquizofrenia [159, 162, 163]. Sin embargo, en FM no se encontraban estudios que hubieran analizado los cambios volumétricos cerebrales inducidos por el ejercicio físico.

Uno de los principales desafíos y aspectos fundamentales a tener en cuenta en las intervenciones de ejercicio físico es la baja adherencia y la alta tasa de abandono que experimentan las personas con FM [164], principalmente cuando finaliza la fase supervisada de la intervención [165-167]. Esto conduce a que los síntomas de la FM empeoren y se entre en un círculo vicioso que retroalimenta y contribuye al mantenimiento y progresión de la enfermedad [168]. Para intentar reducir estas cuestiones Sanz-Banos, Pastor-Mira, Lledó, Lopez-Roig, Penacoba and Sánchez-Meca [169] destacaron puntos importantes para favorecer la adherencia a programas que se basaban en caminar, pero que pueden ser extrapolables a otras modalidades de cara a mejorar la salud del individuo. En este sentido, recalcaron que la adherencia a este programa fue mayor si los médicos recomendaban la asistencia a los pacientes, se combinaban otras actividades junto a la tarea de caminar y finalmente se contemplaba la evaluación de la adherencia durante el tratamiento, así como de las sesiones. Teniendo esto en cuenta, se requiere seguir profundizando en diferentes moderadores que puedan influir en estas características, así como en la elaboración de programas que permitan la realización de ejercicio a través de programas que sean atractivos para los usuarios.

1.7. Ejercicio físico basado en realidad virtual en personas con fibromialgia

La gamificación, definida como la aplicación de elementos de juego en contextos que no son de juego [170] se ha mostrado como una herramienta útil en el contexto de la salud incentivando una mejor autogestión por parte de pacientes con enfermedades crónicas [171]. Una reciente revisión narrativa [172], mostró los estudios que han utilizado la gamificación en la rehabilitación musculoesquelética en base a las posibilidades que ofrece sobre la condición física, la salud y la calidad de vida, además de permitir una mejora de la motivación y adherencia a los tratamientos que se proponen mostrándose seguros y rentables. En este sentido, parece que propuestas que incluyan la gamificación en FM pueden ser interesantes para el tratamiento.

Además de la gamificación, se han desarrollado otras propuestas como la realidad virtual, la realidad aumentada o la tele rehabilitación, que generan diferentes desafíos para los pacientes y proporcionan una mayor gama de recursos para los profesionales sanitarios, consiguiendo generar procesos más atractivos y dinámicos en lo que a rehabilitación se refiere [173] y que también tienen la posibilidad de gamificarse.

La realidad virtual es un tipo de interfaz usuario-computadora que permite conseguir una experiencia tecnológica, ofreciendo una inmersión en un entorno virtual en el cual el usuario puede interactuar a través de un hardware específico o usando su propio cuerpo [174]. La característica fundamental de cualquier aplicación que involucre realidad virtual es la interacción. En este sentido, los usuarios pueden interactuar con los entornos virtuales generados por el software y también pueden interaccionar con objetos virtuales incluidos en dicho entorno [175]. Para conseguir esta interacción los sistemas utilizan diferentes dispositivos como punteros o joystick, aunque también se puede utilizar la mano u otra parte del cuerpo del usuario dentro del entorno virtual [176].

Dependiendo del grado de aislamiento que tenga el usuario con respecto a la interacción con el entorno virtual, se pueden distinguir tres tipos de realidad virtual: la inmersiva, la no inmersiva y la semi-inmersiva [177, 178]. La realidad virtual inmersiva generalmente utiliza un visor que se coloca en la cabeza del usuario y diferentes sistemas de seguimiento de movimiento que generan una experiencia totalmente inmersiva e interactiva con el entorno virtual. Por otra parte, la realidad virtual no inmersiva utiliza generalmente dispositivos como pantallas de proyección de grandes dimensiones o paredes para mostrar la escena virtual, que suelen incluir un avatar frente al usuario [179] como el que se puede observar en los juegos de Nintendo ™ Wii Fit. Finalmente, la realidad virtual semi-inmersiva utiliza la superposición de imágenes virtuales sobre elementos reales como podría ser la cabina de simulación que se utiliza en simuladores de aviación. La diferencia más notable entre estos tres tipos de realidad virtual radica en el punto de vista del participante, así como en la experiencia que se genera durante su uso. No obstante, dependiendo del tipo de población con el que se trabaje y los objetivos que se quieran conseguir, se podrá utilizar un tipo u otro. En este sentido, parece que la realidad virtual no inmersiva y semi-inmersiva tienen un mayor grado de aceptación por parte de las personas mayores debido a la menor sensación de efectos secundarios derivados del uso de la realidad virtual inmersiva o *cibersikness* [178] (e.g. dolor de cabeza, náuseas, desorientación e inestabilidad), por lo que su uso en población con FM puede ser interesante.

Cuando se habla de actividad física implementada a través de realidad virtual, hablamos de *exergames*, aunque en la literatura también se pueden encontrar otras terminologías que se refieren al mismo término y son las siguientes: exertion games, serious video games, exertainment, interactive computer games, active-play videogames o game-based technology-mediated physical activity [180]. Este tipo de intervenciones ha mostrado efectos beneficiosos sobre la función ejecutiva, la cognición, la memoria y la depresión en adultos mayores [181, 182]. De la misma forma, también ha mostrado efectos beneficiosos sobre el control del equilibrio y la reducción de caídas en personas mayores sanas, sobre todo si se combina con entrenamiento de equilibrio y fuerza [183]. Aunque parece que los *exergames* pueden reducir los niveles de dolor en pacientes con dolor musculo esquelético [184, 185], la evidencia disponible sigue siendo limitada, aun así se considera que los *exergames* se pueden utilizar como alternativa al entrenamiento tradicional. En este sentido, se sigue precisando de más investigación que contenga diseños de programas más específicos y mayores tamaños de muestra [185].

En FM una reciente revisión sistemática y meta-análisis [186] evaluó los efectos que tenía el entrenamiento basado en *exergames* en mujeres con FM, encontrando resultados positivos en la función general, la percepción del dolor, la calidad de vida, la capacidad de ejercicio, la salud percibida y la severidad de la fatiga. Además, se han encontrado efectos positivos en el control autónomo en mujeres con FM tras una intervención de *exergames* con una duración de 24 semanas [187] al igual que se han hallado mejoras en la dinámica cerebral, concretamente en la banda beta que pueden estar relacionadas con un aumento del flujo sanguíneo cerebral [188]. No obstante, aunque existen investigaciones que han evaluado cambios en la estructura cerebral tras un programa de *exergames* en adultos mayores [189-191], hasta la fecha de inicio de este plan nacional no se disponía de investigaciones que contemplasen los efectos de este tipo de intervención en población con FM.

1.8. Evaluación de la condición física en fibromialgia

La evaluación es un proceso fundamental que permite conocer el estado en el que se encuentra un individuo, brindando información fundamental para los profesionales de la salud, así como para la propia persona que será evaluada.

Para que una evaluación sea útil para los investigadores y para los profesionales clínicos, es fundamental que las medidas que se obtengan de las pruebas ejecutadas sean precisas y significativas. En este sentido, el primer requisito que debe de cumplirse es que exista fiabilidad, la cual puede definirse como el grado en que una medida u observación puede obtenerse de manera sistemática, consistente y repetitiva sin mostrar un comportamiento variable bajo las mismas condiciones [192]. Por otra parte, es fundamental que exista validez, que se refiere a la confianza de que las herramientas de medición aporten información precisa sobre un constructo para que se puedan establecer los resultados de manera significativa. La validez se refiere al significado o la interpretación que se da a una medida [192], aunque también se define como el grado en que una prueba mide lo que pretende medir.

Estas dos características son fundamentales cuando se llevan a cabo evaluaciones, ya que, permitirán conocer los resultados de manera objetiva y facilitarán el proceso de toma de decisiones para alcanzar los objetivos que se planteen con el individuo.

La evaluación de la condición física en personas con FM se compone de protocolos variados e incluyen diferentes test [193]. Las pruebas de condición física que se emplean de manera habitual que presentan fiabilidad en personas con FM y que mayoritariamente derivan de la batería *Senior Fitness Test* (SFT) [194] son las siguientes: *6 minute walk* [195, 196], *30 seconds chair stand* [196, 197], *30 seconds arm curl* [196], *handgrip strength* [196], *timed-up and go* (TUG) [198], *back scratch* [196] y *chair sit and reach* [196]. Existen otros métodos para evaluar la condición física, sin embargo, estas pruebas tienen la característica de ser económicas, rápidas y de fácil administración en un entorno clínico o de investigación [196].

Todas las cualidades físicas son importantes, sin embargo, la agilidad, el equilibrio y la fuerza de las extremidades inferiores se encuentran reducidas en la FM [199]. La fuerza cobra un especial interés, ya que, determina la capacidad para llevar a cabo diferentes trabajos, así como las actividades de la vida diaria [200, 201]. Además, se ha visto como el rendimiento muscular se encuentra reducido en esta población [202, 203]. Como se ha mencionado anteriormente, existen numerosas pruebas para evaluar la condición física en la FM. No obstante, para la evaluación de la fuerza, los test empleados habitualmente son el *30 seconds arm curl* y *30 seconds chair stand* que también se han utilizado para establecer clasificaciones en base a la presencia o ausencia de la FM, así como la gravedad de sus síntomas [204, 205].

Puesto que los problemas de equilibrio y de movilidad son comunes en FM [60, 206, 207], el estudio de esta capacidad es relevante para el contexto clínico y de investigación. El TUG se trata de una de las herramientas más empleada para valorar estas capacidades [208] y se muestra fiable en población con FM [198]. No obstante, esta tarea no contempla caminar hacia atrás en toda su ejecución. En este sentido, hay evidencia que sugiere que caminar hacia atrás se trata de una tarea compleja que requiere un alto control neuromuscular y propioceptivo [209]. Además, se trata de una acción que se desarrolla de manera habitual en las actividades de la vida diaria (e.g. abrir una puerta, sentarse en una silla, apartarse de un lavabo, etc) [210]. Una prueba que se encarga de medir el rendimiento cuando una persona camina hacia atrás es el *3-meters backwards walk test* (3MBWT) que ha mostrado ser fiable y válida en diferentes grupos poblacionales que presentan dificultades en la movilidad y el equilibrio [211-215]. Conocer este tipo de información en FM es relevante, ya que, puede ofrecer una medida sensible que permita evaluar los déficits de rendimiento que pudiesen existir en las variables mencionadas.

Tradicionalmente, las pruebas de evaluación de la condición física se han llevado a cabo involucrando únicamente al participante en una tarea física. Sin embargo, las actividades de la vida diaria suelen implicar dos o más tareas de manera simultánea [216, 217]. Siguiendo esta idea, surge lo que se denomina el paradigma de la doble tarea [218] que básicamente se define como la realización de dos tareas de manera simultánea, que pueden combinarse de diferente forma y pueden clasificarse como tareas motoras-cognitivas, motoras-motoras y cognitivas-cognitivas.

Dado que las personas con FM tienen dificultades para llevar a cabo actividades de la vida diaria [7] y, que este tipo de actividades frecuentemente se realizan junto a otra actividad secundaria (e.g. hablar con alguien mientras se camina, ver la televisión mientras se cocina o incluso pensar en lo que se tiene que realizar en un día habitual mientras se pasea), las evaluaciones de la condición física parece que pueden estar un tanto más alejadas de la realidad al no contemplar ese aspecto cognitivo que se puede incluir en las actividades cotidianas. Este aspecto es fundamental en esta patología, puesto que, estudios previos han analizado la alteración del rendimiento en pruebas de aptitud física al incluir tareas cognitivas en mujeres con FM [219-223]. Sin embargo, ninguna de estas investigaciones ha informado sobre la fiabilidad y validez. Por tanto, debido a la falta de conocimiento sobre las propiedades psicométricas de pruebas de evaluación bajo el paradigma de la doble tarea, se precisan estudios que permitan explorar esta cuestión.

1.9. Justificación y coherencia de la tesis doctoral

Considerando en conjunto el marco teórico presentado, se detecta la pertinencia y necesidad de profundizar en algunos aspectos fundamentales que permitiesen mejorar el manejo de la FM y mejorar la calidad de vida de las personas que la padecen. En este sentido, surge la idea de analizar la fiabilidad y la validez de diferentes pruebas que evalúan la fuerza y la movilidad desde el paradigma de la doble tarea, permitiendo obtener resultados más ecológicos y cercanos a contextos de la vida diaria que son fundamentales para el campo clínico y de la investigación. Dado que la sintomatología de la fibromialgia es muy variada y afecta a diferentes factores, resultaría interesante ofrecer nueva información a la literatura en aspectos relacionados con los procesos de sueño y memoria que se dan de manera frecuente en esta población. Llegados a este punto, emerge la idea de analizar la morfometría de estructuras cerebrales involucradas en estos procesos como son la glándula pineal y el hipocampo, para comprender como el impacto de la FM puede estar involucrado en la atrofia de estas estructuras. De la misma forma, la kinesiofobia también es una condición frecuente en esta patología y hasta el momento, había una serie de cuestiones que no se habían tratado en profundidad como era la comparación de este miedo al movimiento con pruebas físicas que involucran acciones que se desarrollan en la vida diaria, así como la relación de este miedo al movimiento con el riesgo de caídas y el impacto de la enfermedad. Incluir a un grupo de personas sanas para la comparación de estas variables sería un aspecto diferenciador con respecto a los estudios previos que no lo habían tenido en cuenta. Estos hallazgos proporcionarían información interesante y adicional al campo científico. En último lugar, dado que el ejercicio físico es la terapia no farmacológica con mayor nivel de evidencia hasta la fecha en población con FM y teniendo en cuenta que los *exergames* ofrecen gran cantidad de efectos positivos para esta condición, conocer los efectos de este tipo de entrenamiento sobre el volumen cerebral de estructuras involucradas en la red del dolor parecía una idea interesante que podría aportar conocimiento a la neurociencia y al campo del entrenamiento para la mejora de esta enfermedad.

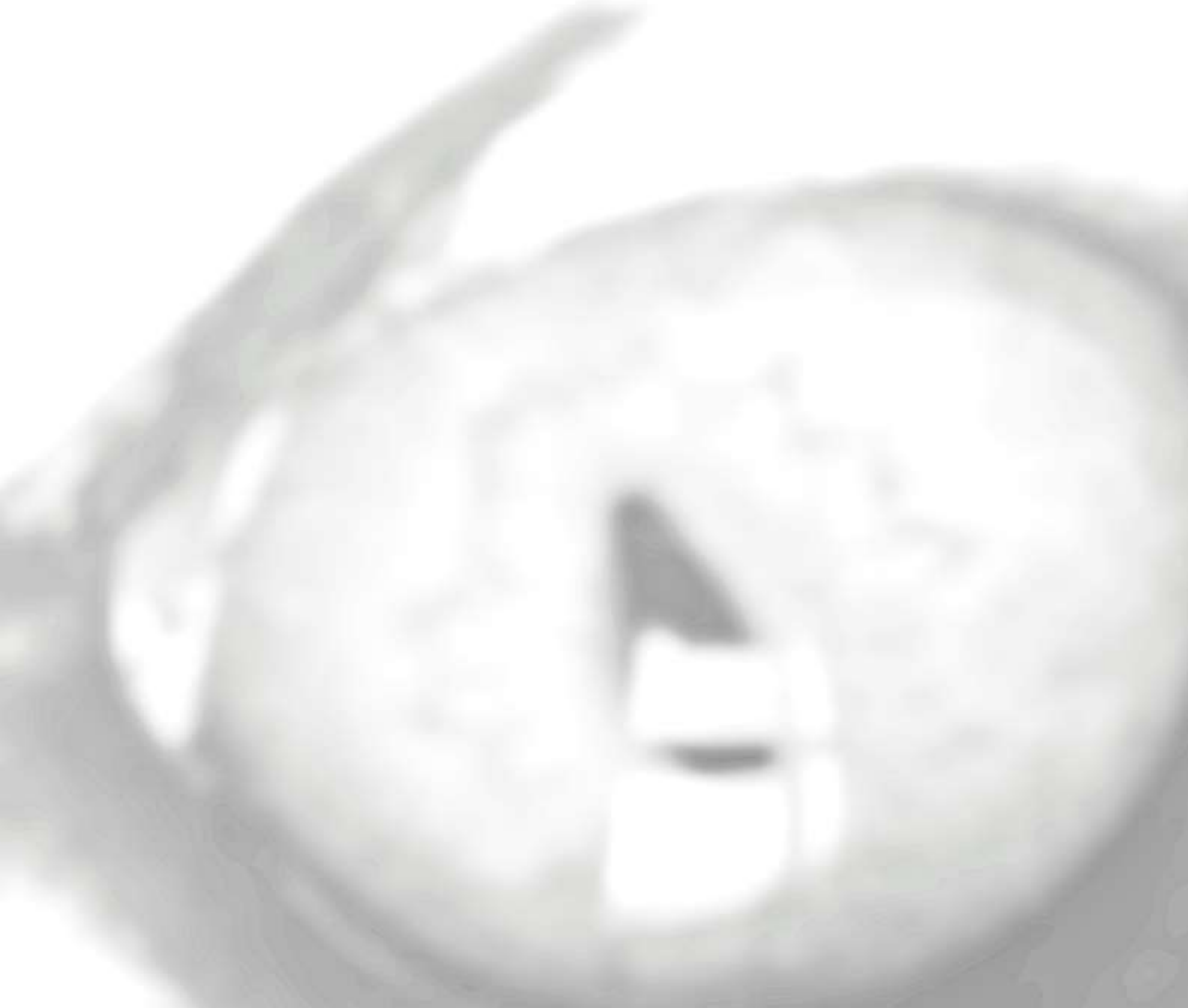
Para dar respuesta a estas cuestiones, era preciso llevar a cabo diferentes investigaciones que culminaron con la escritura de diferentes artículos científicos. En este sentido, y como se mostró previamente en el contexto de la tesis doctoral, un total de seis estudios forman el cuerpo de este trabajo. Para una mejor comprensión de la información que se ha dado en este apartado y que ayudará a entender el resto del documento, se ha optado por dividir a los estudios científicos en tres bloques temáticos que son los siguientes:

- Bloque I. Propiedades psicométricas de diferentes pruebas de evaluación de la condición físico-cognitiva en la FM.
- Bloque II. Impacto de la FM sobre determinadas estructuras cerebrales y la kinesiofobia.
- Bloque III. *Exergames* como terapia no farmacológica en la FM.

Estos bloques ofrecerán en su conjunto información relevante sobre cuestiones que no han sido estudiadas hasta el momento en el campo de la FM y que podrían suponer un avance importante en el contexto clínico y de la investigación.

Capítulo 2

Objetivos e hipótesis



Capítulo 2. Objetivos e hipótesis

Los objetivos generales que se establecieron para la presente tesis doctoral fueron los siguientes:

1. Evaluar las propiedades psicométricas de diferentes pruebas para la evaluación de la función motora y cognitiva en mujeres con FM.
2. Evaluar el impacto que tiene la FM sobre estructuras cerebrales involucradas en los procesos de sueño y memoria, así como variables relacionadas en los mismos.
3. Evaluar el impacto que tiene la FM sobre la kinesiofobia y su relación con pruebas de evaluación que guardan relación con actividades de la vida diaria y el miedo a las caídas.
4. Evaluar los efectos de los *exergames* sobre el volumen de materia gris de determinadas estructuras cerebrales involucradas en la red del dolor en mujeres con FM.

A continuación, aparecen de manera específica los diferentes objetivos que se propusieron para los diferentes estudios que componen la presente tesis doctoral. Estos objetivos aparecen divididos en los diferentes bloques temáticos que componen el trabajo para una mejor comprensión:

Bloque I. Propiedades psicométricas de diferentes pruebas de evaluación de la condición físico-cognitiva en la FM.

a) Evaluar la fiabilidad test-retest de las pruebas de evaluación *30 seconds arm curl* y *30 seconds chair stand* en condición simple y de doble tarea en mujeres con FM.
b) Evaluar y comparar la fiabilidad test-retest de la prueba 3MBWT usando un cronómetro manual y un cronómetro automático bajo condición simple y de doble tarea en mujeres con FM.
c) Comprobar la validez concurrente entre la prueba 3MBWT y la prueba TUG en mujeres con FM.

Bloque II. Impacto de la FM sobre determinadas estructuras cerebrales y la kinesiofobia.

d) Evaluar el volumen de la glándula pineal y la prevalencia de quistes pineales entre mujeres sanas y mujeres con FM.
e) Comprobar la relación entre el volumen de la glándula pineal y los niveles de melatonina y calidad de sueño en mujeres con FM.
f) Evaluar el volumen de los subcampos del hipocampo entre mujeres sanas y mujeres con FM.
g) Analizar las variables que se relacionan de manera específica con los subcampos del hipocampo.
h) Comparar los niveles de kinesiofobia entre mujeres sanas y mujeres con FM.

i) Analizar la relación entre la kinesiofobia, el miedo a las caídas, el impacto de la FM y las pruebas de dinamometría manual, TUG y *10-step stair ascent test* entre mujeres sanas y mujeres con FM.

Bloque III. *Exergames* como terapia no farmacológica en la FM.

j) Evaluar los efectos de un programa de actividad física de 24 semanas basado en *exergames* sobre el volumen cerebral de materia gris en determinadas estructuras cerebrales que componen la red del dolor en mujeres con FM.
k) Analizar la relación entre las capacidades aeróbica y cognitiva y el volumen de materia gris en determinadas estructuras cerebrales que componen la red del dolor en mujeres con FM.

En base a estos objetivos, las principales hipótesis que se pretendían verificar fueron las siguientes:

1. Las pruebas *30 seconds chair stand* y *30 seconds arm curl* en condición de doble tarea se mostrarán fiables en mujeres con FM.
2. La variable desarrollada para evaluar el rendimiento total, que engloba el rendimiento físico y cognitivo, se mostrará fiable.
3. La prueba 3MBWT mostrará buenos valores de fiabilidad en condición de tarea simple y de doble tarea en mujeres con FM.
4. Las pruebas 3MBWT y TUG mostrarán una elevada validez concurrente.
5. Las mujeres con FM tendrán volúmenes reducidos de la glándula pineal en comparación con las mujeres sanas.
6. Los volúmenes de la glándula pineal de las mujeres con FM se correlacionarán con los niveles de melatonina y las horas de sueño.
7. Las mujeres con FM tendrán volúmenes reducidos de los subcampos del hipocampo en comparación con las mujeres sanas.
8. Las mujeres con FM obtendrán mayores puntuaciones de kinesiofobia en comparación con las mujeres sanas.
9. La puntuación de la kinesiofobia se correlacionará con el rendimiento en el TUG y en el *10-step stair ascent test*, pero no lo hará con la fuerza de prensión manual al no implicar una traslación del cuerpo importante.
10. La puntuación de la kinesiofobia se correlacionará con el miedo a las caídas y el impacto de la FM.
11. Las mujeres con FM que realizaron el programa de ejercicio basado en *exergames* mostrarán un aumento del volumen de materia gris en determinadas estructuras que componen la red del dolor.

Capítulo 3

Metodología y resultados de los artículos publicados

Capítulo 3. Metodología y resultados de los artículos publicados.

A continuación, se presentan brevemente los seis artículos científicos que componen la presente tesis doctoral (cinco estudios transversales y un ensayo controlado aleatorizado). En este sentido, aparece el título, los objetivos e hipótesis relacionadas, así como un breve resumen de la metodología, los resultados principales y la interpretación de los mismos. Para una mejor comprensión, estos estudios aparecen clasificados en los tres bloques temáticos en los que se estructura el presente trabajo y que han sido comentados anteriormente:

Bloque I. Propiedades psicométricas de diferentes pruebas de evaluación de la condición físico-cognitiva en la FM.

Estudio I: Strength assessment under dual task conditions in women with fibromyalgia: a test–retest reliability study.

Relacionado con el objetivo: a)

Relacionado con las hipótesis: 1 y 2

Diseño y participantes: Un total de 37 mujeres con FM diagnosticadas por un especialista en reumatología participaron en este estudio transversal.

Procedimiento: en primer lugar, se tomaron medidas antropométricas de las participantes e información sociodemográfica como la edad y número de años con FM. Posteriormente, se completó el cuestionario FIQ que evalúa el impacto de la enfermedad. Finalmente, se llevaron a cabo dos pruebas físicas: a) *30 senconds arm curl test* y b) *30 seconds chair stand test*. Estas pruebas se realizaron bajo condición simple y condición de doble tarea. La condición de doble tarea consistió en la realización de una tarea cognitiva que implicaba la ejecución de restas numéricas de dos en dos desde un número aleatorio mayor de 100 mientras se realizaba la prueba física. Tanto la condición simple como la de doble tarea tuvieron una duración de 30 segundos. El orden entre la condición simple o de doble tarea fue aleatorizado. Para evitar posibles efectos de aprendizaje, las evaluaciones se volvieron a repetir transcurridos siete días.

Resultados: en la prueba *30 seconds chair stand* en condición de doble tarea se obtuvo una fiabilidad de baja a buena, mientras que la variable de rendimiento total obtuvo una fiabilidad de baja a moderada. La prueba *30 seconds arm curl* en condición de doble tarea, así como la variable de rendimiento total, obtuvieron una fiabilidad de buena a moderada.

Interpretación: Tanto la prueba *30 seconds chair stand* como la prueba *30 seconds arm curl* en condición de doble tarea, así como las variables de rendimiento total, obtuvieron buenos valores de fiabilidad, permitiendo su uso como herramienta de evaluación. Sin embargo, es necesario tener en cuenta el rango de fluctuación del índice de correlación intraclase (ICC).

Estudio II: Test–Retest Reliability and Concurrent Validity of the 3 m Backward Walk Test under Single and Dual-Task Conditions in Women with Fibromyalgia.

Relacionado con los objetivos: b) y c)

Relacionado con las hipótesis: 3 y 4

Diseño y participantes: un total de 21 mujeres con FM participaron en este estudio transversal. Las mujeres fueron diagnosticadas de FM por un especialista en reumatología.

Procedimiento: se obtuvieron medidas antropométricas de las participantes e información sociodemográfica de las participantes. A continuación, las participantes cumplimentaron el cuestionario FIQR que evalúa el impacto de la FM. Posteriormente, se realizaron dos pruebas físicas: a) TUG y b) 3MBWT. Estas pruebas se realizaron bajo condición simple y de doble tarea. La condición de doble tarea consistió en realizar una tarea cognitiva que implicaba llevar a cabo restas de dos en dos desde un número aleatorio menor de 100 mientras se realizaba la prueba física. El orden entre los test fue aleatorizado, así como los tipos de condición. Las evaluaciones se volvieron a realizar transcurrida una semana.

Resultados: en la prueba 3MBWT para la condición simple se obtuvieron valores de fiabilidad de bajos a buenos y de moderados a excelentes para el cronómetro y Chronopic, respectivamente. En la condición de doble tarea, los valores de fiabilidad para el cronómetro fueron de moderado a excelente, y para el Chronopic de bueno a excelente. Por otra parte, al comparar los diferentes dispositivos en ambas condiciones, los valores de fiabilidad obtenidos oscilaron de buenos a excelentes para el test y excelentes para el retest. En cuanto a la validez concurrente entre el 3MBWT y el TUG, las correlaciones obtenidas se clasificaron como fuertes. Finalmente, las corelaciones obtenidas entre el rendimiento en el 3MBWT y el impacto de la enfermedad fueron fuertes, excepto el rendimiento obtenido en el 3MBWT bajo condición simple en el test medido con cronómetro que fue moderado. De manera específica, se analizaron las correlaciones entre las dimensiones del cuestionario FIQR y el rendimiento obtenido en el 3MBWT. En este sentido se obtuvieron correlaciones fuertes entre la dimensión "síntomas" y el 3MBWT. En la misma línea se obtuvieron los mismos resultados para la dimensión "impacto general" excepto para la condición simple y de doble tarea en el test medidas con cronómetro y Chronopic, respectivamente, donde se hallaron correlaciones moderadas. En cuanto a la dimensión "función", sólo se encontraron correlaciones moderadas en la condición simple en test y retest, medidas con cronómetro y Chronopic, respectivamente.

Interpretación: La prueba 3MBWT es fiable en condición simple y de doble tarea en mujeres con FM. Esta herramienta muestra mayores valores de fiabilidad cuando el tiempo se obtiene utilizando un cronómetro automático (Chronopic). Además, muestra una alta validez concurrente con la prueba TUG, y el rendimiento en la prueba 3MBWT se relaciona con el impacto de la enfermedad.

Bloque II. Impacto de la FM sobre determinadas estructuras cerebrales y la kinesiofobia.

Estudio III: Relationship between pineal gland, sleep and melatonin in fibromyalgia women: a magnetic resonance imaging study.

Relacionado con los objetivos: d) y e)

Relacionado con las hipótesis: 5 y 6

Diseño y participantes: un total de 50 mujeres participaron en este estudio transversal (30 mujeres con FM y 20 mujeres sanas). Las participantes con FM fueron reclutadas de una asociación local de FM mediante llamadas telefónicas y las mujeres sanas fueron seleccionadas desde la base de datos abierta OASIS-3.

Procedimiento: para las mujeres con FM, se obtuvieron medidas antropométricas de altura, peso e índice de masa corporal. Además, se solicitó la edad y el número de años con la enfermedad. Posteriormente cumplimentaron la versión española del cuestionario del impacto de la fibromialgia y el índice de calidad de sueño de Pittsburgh (PSQI). Para determinar los niveles de melatonina, las participantes recolectaron en casa mediante un tubo estéril sus muestras salivares en dos días consecutivos y posteriormente se refrigeraban en un congelador. La adquisición de la imagen por resonancia magnética se realizó con un escáner de 3 teslas usando una secuencia ponderada T1 eco turbo de campo. Para el grupo de mujeres sanas se obtuvo la información a través de la base de datos OASIS-3. Sin embargo, no se pudo obtener información sobre la calidad del sueño, número de horas de sueño y niveles de melatonina, ya que, no se disponía de esta información. Se descargaron de manera aleatoria 20 mujeres a las cuales se les había aplicado una secuencia T1 eco de gradiente de adquisición rápido preparado por magnetización para la obtención de la imagen por resonancia magnética. El procesamiento de las imágenes se realizó a través del software 3D Slicer y se obtuvo el volumen pineal total, el volumen pineal quístico y el volumen del parénquima pineal (PPV).

Resultados: El PPV se relacionó significativamente con las horas de sueño y con los niveles de melatonina nocturnos. Sin embargo, no se vio una relación entre el PPV y el índice de calidad del sueño. Se observó un PPV de 102mm^3 con una prevalencia de quistes del 29,6% en las mujeres con FM.

Interpretación: no se observaron diferencias significativas de los volúmenes pineales al comparar las mujeres sanas con las mujeres con FM. Sin embargo, se observaron diferencias en la prevalencia de quistes entre los dos grupos. Disponer de más horas de sueño y mayores niveles de melatonina parece relacionarse con el PPV en mujeres con FM.

Estudio IV: Impact of fibromyalgia in the hippocampal subfields volumes of women—An MRI study.

Relacionado con los objetivos: f) y g)

Relacionado con la hipótesis: 7

Diseño y participantes: 50 mujeres con FM de una asociación local diagnosticadas por un especialista en reumatología y 43 mujeres sanas de la base de datos abierta OASIS-3 participaron en este estudio transversal.

Procedimiento: para las mujeres con FM, se obtuvieron medidas de altura y peso, así como la edad, el número de años con la enfermedad y el número de años desde el diagnóstico de la enfermedad. Posteriormente se cumplimentó el FIQ, la escala de depresión geriátrica de 15 ítems (GDS-15) y el mini examen del estado mental (MMSE). Para la adquisición de la imagen por resonancia magnética se utilizó un escáner de 3 teslas usando una secuencia ponderada T1 eco turbo de campo. Para el grupo de mujeres sanas se obtuvo la información a través de la base de datos OASIS-3. Se descargaron de manera aleatoria 43 mujeres a las cuales se les había aplicado una secuencia T1 eco de gradiente de adquisición rápido preparado por magnetización para la obtención de la imagen por resonancia magnética. El procesamiento de las imágenes se llevó a cabo mediante el software FreeSurfer que mostró los diferentes subcampos que componen el hipocampo.

Resultados: la prueba ANOVA mostró que todos los modelos estadísticos de la regresión lineal múltiple fueron válidos excepto para los subcampos de la fisura del hipocampo izquierdo, CA1 bilateral, fimbria izquierda y en el área de transición del hipocampo-amígdala (HATA) bilateral, que no pudieron ser estudiados por no cumplir con los supuestos necesarios para llevar a cabo el análisis de regresión lineal múltiple. Para el hemisferio derecho, las variables edad, volumen intracraneal total estimado (eTIV) y grupo, predijeron el volumen de la ML; las variables eTIV, grupo y MMSE, predijeron el volumen de CA3; las variables edad, eTIV y grupo, predijeron el volumen de GCDG. Para el hemisferio izquierdo, las variables edad, eTIV y grupo, predijeron el volumen de la cola, presubículo y parasubículo; las variables edad, eTIV, grupo y MMSE, predijeron el volumen de ML. Tomando al hipocampo completo en el hemisferio izquierdo y derecho, las variables que predijeron su volumen fueron edad, eTIV y grupo. Al realizar un análisis individualizado de la edad, por cada año, se producía una disminución en la mayoría de las estructuras, excepto en la cola y presubículo derecho, CA3 izquierdo, CA4 y subículo bilateral. En esta línea, también se encontraron disminuciones en el hipocampo completo bilateral. Finalmente, las mujeres sanas mostraron mayores volúmenes en la mayoría de los subcampos, aunque en la fimbria derecha se observó una disminución.

Interpretación: las mujeres con FM mostraron reducciones significativas de volumen en la mayoría de los subcampos que componen el hipocampo en comparación con mujeres sanas. Covariables como la edad, el deterioro cognitivo o la depresión se encontraron relacionadas con subcampos específicos.

Bloque III. *Exergames* como terapia no farmacológica en la FM.

Estudio V: Relationship between kinesiophobia and mobility, impact of the disease, and fear of falling in women with and without fibromyalgia: a cross-sectional study.

Relacionado con los objetivos: h) y i)

Relacionado con las hipótesis: 8, 9 y 10

Diseño y participantes: un total de 51 mujeres de una muestra por conveniencia participaron en este estudio transversal (25 mujeres con FM y 26 mujeres sanas). Las participantes fueron reclutadas mediante llamadas telefónicas. Se contactó con una asociación local de FM, las instalaciones de la Universidad y contactos cercanos de las mujeres con FM.

Procedimiento: en primer lugar, se obtuvieron medidas de peso, altura, edad y composición corporal mediante bioimpedancia. Posteriormente, las participantes completaron el cuestionario de impacto de la enfermedad FIQR (si tenían FM), la escala de Tampa de 11 ítems de kinesiofobia (TSK-11) y la escala internacional de eficacia de las caídas (FES-I). Tras estos primeros pasos, las participantes llevaron a cabo las pruebas físicas TUG, fuerza de prensión manual y *10-step stair ascent test*. Todas las pruebas se realizaron el mismo día y se llevaron a cabo en el orden indicado con la finalidad de prevenir la fatiga local en los miembros superiores e inferiores. La intervención se llevó a cabo en la Facultad de Ciencias del Deporte de la Universidad de Extremadura.

Resultados: las mujeres con FM mostraron diferencias significativas en la puntuación de kinesiofobia y el miedo a las caídas en comparación con las mujeres sanas. Se observó un rendimiento inferior para las mujeres con FM en las pruebas físicas TUG y *10-step stair ascent test* en comparación con las mujeres sanas. No obstante, la prueba de prensión manual mantuvo resultados similares entre los dos grupos analizados. Finalmente, se encontraron relaciones significativas en el grupo de FM entre la kinesiofobia, el impacto de la enfermedad, el miedo a las caídas y el rendimiento obtenido en las pruebas TUG y *10-step stair ascent test*.

Interpretación: las mujeres con FM mostraron mayores puntuaciones de kinesiofobia, peor rendimiento en los test de movilidad y mayor miedo a las caídas en comparación con las mujeres sanas. La puntuación de la kinesiofobia se relaciona con el rendimiento obtenido en las pruebas TUG, *10-step stair ascent test*, miedo a las caídas y el impacto de la enfermedad en las mujeres con FM. Sin embargo, la kinesofobia no se relaciona con la prueba de prensión manual, que requiere de un patrón motor menos complejo que las otras pruebas. La evaluación de la kinesiofobia en la evaluación de pacientes con dolor crónico parece relevante en el entorno clínico, ya que, puede ayudar al manejo de la enfermedad.

Estudio VI: Effects of 24-week exergame intervention on the gray matter volume of different brain structures in women with fibromyalgia: A single-blind, randomized controlled trial.

Relacionado con los objetivos: j) y k)

Relacionado con la hipótesis: 11

Diseño y participantes: un total de 55 mujeres con FM diagnosticadas por un especialista en reumatología participaron en este estudio controlado aleatorizado simple ciego. Las participantes fueron aleatorizadas en dos grupos: grupo de ejercicio y grupo control.

Procedimiento: el grupo de ejercicio realizó dos sesiones a la semana con una duración de 60 minutos cada una, durante 24 semanas. La intervención se basó en *exergames* y se componía de ejercicios de movilidad articular, una parte aeróbica basada en ejercicios de danza, ejercicios de movilidad y control postural a través de un avatar gráfico, coordinación de movimientos del tren superior e inferior y fuerza. El grupo control tenía que mantener su rutina de vida habitual. Se obtuvieron antes y después de la intervención: medidas antropométricas, cuestiones sociodemográficas, puntuación en FIQ, deterioro cognitivo a través del MMSE, capacidad aeróbica mediante el *6-minute walk test* e imágenes de resonancia magnética.

Resultados: no se encontraron diferencias significativas entre el grupo control y el grupo experimental en el volumen de materia gris de las diferentes estructuras cerebrales analizadas, el volumen total de materia gris, el consumo de oxígeno estimado y el deterioro cognitivo tras la intervención del programa. Las mujeres con FM mostraron relaciones significativas entre el pico de consumo de oxígeno estimado y las regiones izquierda y derecha del hipocampo, así como de la amígdala.

Interpretación: el programa basado en *exergames* con una duración de 24 semanas parece no haber producido cambios en el volumen de materia gris de determinadas estructuras cerebrales involucradas en la red del dolor en las mujeres con FM. De la misma forma, tampoco se detectaron mejoras en el pico del consumo de oxígeno estimado y el deterioro cognitivo. No obstante, se observa una relación entre el pico de consumo de oxígeno estimado y las regiones izquierda y derecha del hipocampo, así como de la amígdala, pudiendo estar estos resultados relacionados con el flujo sanguíneo y la frecuencia respiratoria. Se precisan investigaciones futuras sobre los determinantes de la sensibilidad al ejercicio físico sobre los cambios volumétricos cerebrales.

Capítulo 4

Discusión

Capítulo 4. Discusión

La motivación de la presente tesis doctoral vino dada por la escasez de conocimiento existente sobre las propiedades psicométricas en pruebas que valoran la agilidad, el equilibrio y la fuerza bajo el paradigma de la doble tarea. Se compone de dos estudios transversales que abordan esta cuestión. Adicionalmente, se pretendía investigar el impacto que puede tener la FM sobre la kinesiofobia y la morfometría de ciertas estructuras cerebrales involucradas en procesos que se encuentran alterados en esta patología como pueden ser el sueño y el deterioro cognitivo, lo que se expone a través de tres estudios transversales adicionales. Finalmente, se pretendía contemplar el análisis de los efectos de un programa de ejercicio basado en *exergames* con una duración de 24 semanas, sobre el volumen de la materia gris de estructuras cerebrales que forman parte de la red del dolor a través de un ensayo controlado aleatorizado.

4.1. Propiedades psicométricas de diferentes pruebas de evaluación de la condición físico-cognitiva en la FM.

La evaluación es un proceso fundamental que permite conocer el estado en el que se encuentra un individuo, aportando información relevante para los profesionales de la salud y para la persona que será evaluada. En la presente tesis doctoral se llevaron a cabo los estudios I y II que pretendían aportar información relevante sobre las propiedades psicométricas de tres pruebas que evaluaron la fuerza y el equilibrio/movilidad desde el paradigma de la doble tarea.

Tradicionalmente, la evaluación de la condición física se ha llevado a cabo involucrando al participante exclusivamente en el desarrollo de una tarea física. Sin embargo, la mayor parte de actividades que se desarrollan en la vida diaria involucran que un individuo realice más de dos tareas al mismo tiempo, siendo estas principalmente tareas físicas y cognitivas (e.g. mantener una conversación telefónica mientras se camina por la calle). Conocer el rendimiento de una persona desde un punto de vista que involucre la capacidad física y la cognitiva es interesante para establecer pruebas que se aproximen a un contexto más ecológico. Esto es fundamental en FM, ya que, en esta población el rendimiento de las actividades diarias y con doble tarea se ve deteriorado.

Dos de los tres test (*30 seconds chair stand test* y 3MBWT), por su naturaleza, se midieron utilizando un cronómetro manual y uno automático (Chronopic). La incorporación del cronómetro automático se basó en la idea de estudios previos, que informaron que de esta manera se reducía el error asociado a la persona que realizaba la evaluación, consiguiendo una medida más precisa y fiable que de forma manual [198].

En el estudio I, se analizó la fiabilidad de dos pruebas que miden la fuerza del tren superior (*30 seconds arm curl test*) e inferior (*30 seconds chair stand test*) y forman parte de la batería SFT, ampliamente utilizada en el mundo de la investigación y de la salud. Los resultados obtenidos indican que ambas pruebas pueden considerarse fiables cuando se llevan a cabo bajo la condición de doble tarea, sin embargo, se debe tener en cuenta el rango de fluctuación del ICC obtenido. Esta investigación reportó dos términos relevantes a la hora de analizar la fiabilidad test-retest que son el error estándar de medida (SEM) y el cambio mínimo detectable (MDC) o la diferencia mínima real (SRD). El primero hace referencia a la variabilidad de los resultados de una prueba debido al error de medición, siendo una forma de cuantificar la precisión de las puntuaciones. Por otro lado, el segundo término, representa la cantidad mínima de cambio que se debe observar en una puntuación para que se pueda considerar que es un cambio real o significativo, más allá del error de medición [192].

Los resultados obtenidos a partir del MDC indicaron que una mejora en la condición de doble tarea superior a 3,93 repeticiones en la prueba *30 seconds chair stand* y 5,12 repeticiones en la prueba *30 seconds arm curl* indicaría un cambio en la medida que no se debe al error de medición [224, 225] y por tanto se considerarían cambios significativos en estas pruebas a la hora de evaluar a mujeres con FM. Esta información es relevante, ya que, los investigadores y profesionales de la salud pueden identificar cambios relevantes en esta población llevando a cabo estas pruebas bajo la condición de doble tarea.

En la vida diaria generalmente se llevan a cabo varias tareas a la vez (e.g. caminar y hablar, pensar en la lista de la compra mientras se camina hacia el mercado, etc.), lo que se conoce como doble tarea [218]. Puesto que la atención es un recurso limitado, el rendimiento en alguna de las dos acciones puede disminuir cuando se llevan a cabo dos tareas de manera simultánea en comparación a realizarlas individualmente, especialmente si una de las tareas requiere de bastante atención [226]. Este cambio relativo en el rendimiento asociado con la doble tarea se denomina interferencia de doble tarea o efecto de doble tarea (DTE) y su estudio se muestra interesante, ya que, permite detectar los recursos de atención disponibles [227]. En este sentido, conocer la fiabilidad de estas variables bajo el paradigma de la doble tarea era fundamental en el contexto clínico y de la investigación.

Para cuantificar el rendimiento total de las pruebas se desarrolló una variable específica que combinaba el número de aciertos, errores y repeticiones realizadas por las participantes en la doble tarea. En este sentido, se daba la misma importancia a la parte motora y a la parte cognitiva, ya que, ambas funciones son relevantes en las actividades de la vida diaria y ofrecen información importante cuando se llevan a cabo este tipo de evaluaciones en esta población. Son varios los estudios que han cuantificado como disminuye el rendimiento físico tras agregar una tarea cognitiva en estas pruebas y en esta población [219, 221]. Además, Tomas-Carus, Biehl-Printes, Pereira, Vieiga, Costa and Collado-Mateo [228] crearon una variable que contemplaba el rendimiento físico y cognitivo en personas mayores a través del tiempo obtenido en la prueba

TUG, el número de paradas cognitivas y el número de errores, sin embargo, no reportaron la fiabilidad de este indicador. En este sentido, nuestro estudio analizó la fiabilidad de una variable similar que mostró unos valores de bajos a moderados y de buenos a moderados en las pruebas de *30 seconds chair stand* y *30 seconds arm curl*, respectivamente. La MDC para la variable de rendimiento total en la prueba *30 seconds chair stand* fue de 13,44 unidades, mostrando un SEM de 4,85 puntos. Por otra parte, en la prueba de *30 seconds arm curl* se obtuvo una MDC de 9,03 unidades y un SEM de 11,19 puntos. Investigaciones futuras que evalúen pruebas bajo el paradigma de la doble tarea deberían contemplar el cálculo de esta variable para evaluar el rendimiento total de las pruebas que se lleven a cabo.

En el estudio II, se analizó la fiabilidad y validez concurrente del 3MBWT que evalúa el rendimiento de una persona cuando camina hacia atrás. Se decidió analizar este tipo de acción, ya que, se trata de una tarea compleja que requiere un alto control neuromuscular y propioceptivo además de correcciones de equilibrio más rápidas y frecuentes [209, 229]. Además, caminar hacia atrás es una acción que muestra una mayor o igual sensibilidad que caminar hacia adelante, y está fuertemente relacionada con el riesgo de caídas [210]. De la misma forma, se desarrolla de manera habitual en la vida diaria de una persona como cuando se abre una puerta, se intenta sortear algún obstáculo y cuando se procede a sentarse en una silla [210]. Conocer este tipo de información es importante, ya que, ofrece una medida sensible que permite evaluar los déficits en la movilidad y el equilibrio [230, 231], factores fundamentales que se deben de conocer en la FM para evitar una pérdida del rendimiento en los mismos y que lleven a situaciones de discapacidad.

Estudios previos han destacado la importancia de evaluar la marcha hacia atrás en adultos mayores y han mostrado una reducción en el rendimiento de diferentes parámetros tras realizar una comparación con adultos jóvenes y de mediana edad [230, 231].

Uno de los principales test que se ha usado hasta la fecha para evaluar la movilidad y el equilibrio en población con FM ha sido el TUG [198, 207, 232]. Sin embargo, este test no incluye la acción de caminar hacia atrás en toda su ejecución. En este sentido, conocer las propiedades psicométricas de la prueba 3MBWT en personas con FM parecía relevante, ya que, estudios previos se han centrado en otras poblaciones que también experimentan problemas de movilidad y equilibrio y han obtenido buenos resultados de fiabilidad y de validez [211-214, 233, 234]. Además, como factor diferenciador y dado que la mayoría de las actividades de la vida diaria se llevan a cabo realizando más de una tarea de forma simultánea como se había indicado anteriormente, también se decidió incorporar el paradigma de la doble tarea en esta prueba [218].

Los resultados de este estudio mostraron que el 3MBWT se puede considerar fiable en condición simple y de doble tarea cuando el rendimiento en la prueba se mide con un cronómetro o con un cronómetro automático (i.e. Chronopic), aunque debe considerarse el rango de fluctuación del

ICC obtenido [235]. No obstante, el ICC registrado en la condición simple con el cronómetro mostró valores inferiores con respecto a otras investigaciones que evaluaron la fiabilidad en poblaciones con accidente cerebrovascular [211], artroplastia total de rodilla [236] y adultos mayores que vivían en comunidad [212]. Para observar la concordancia entre el test y retest, este estudio también proporcionó los gráficos de Bland-Altman, mostrando resultados consistentes, ya que, la mayor parte de los valores del 3MBWT se encontraban cercanos a la media de las diferencias, indicando un sesgo cercano a cero y una variabilidad reducida en base a los límites de acuerdo.

Es probable que la variabilidad hallada en los resultados del estudio estuviese influenciada por la propia sintomatología de la FM [237], caracterizada por dolor y fatiga principalmente, que puede variar en su intensidad y severidad a lo largo del tiempo [238, 239]. En base a estas fluctuaciones, es posible que el rendimiento físico [104, 240] y cognitivo [3] se vea alterado y pueda cambiar de día a día. Estas variaciones pueden haber contribuido a la obtención de resultados diferentes entre el test y retest. Sin embargo, los ICC obtenidos en el estudio se pueden considerar aceptables, sugiriendo que el 3MBWT es fiable para usarse en población de mujeres con FM.

Tal y como se esperaba, el ICC fue ligeramente superior al emplear Chronopic en comparación con el cronómetro manual, dado que este último dispositivo introduce variabilidad humana en la medición [198, 241]. En este sentido y al igual que en el estudio I, la utilización de un cronómetro automático puede ser una opción económica y precisa para medir el rendimiento en el 3MBWT bajo condición simple y de doble tarea. No obstante, aunque los ICC obtenidos con el cronómetro manual sean ligeramente inferiores a los obtenidos por el Chronopic, los hallazgos en este estudio sugieren que el uso de un cronómetro manual también proporciona valores de fiabilidad aceptables en las condiciones simple y de doble tarea.

En este estudio, al igual que en el estudio I también se proporcionaron los valores de SEM y MDC, solo que en este caso fue para el 3MBWT. Como se explicó anteriormente estos valores pueden aportar información valiosa a los profesionales del ámbito clínico y de la investigación con el objetivo de determinar si existen cambios significativos en el rendimiento de esta prueba. Como era de esperar, El SEM y la MDC fueron inferiores al usar Chronopic, hallazgo que coincide con investigaciones previas que evaluaron la fiabilidad test-retest de las pruebas *30 seconds chair stand* y TUG en condición simple [198, 241].

Para probar la validez concurrente en el 3MBWT, en esta investigación se empleó el TUG, ya que, se trata de una herramienta muy utilizada en la práctica clínica [208, 242] y ha demostrado una alta fiabilidad en FM tanto en condición simple [198] como en doble tarea [207]. Aunque la prueba TUG no contempla en toda su ejecución caminar hacia atrás, otros estudios la han incluido en sus investigaciones para probar la validez [211-214], obteniendo los valores de correlación más fuertes en la mayoría de los casos [211, 212, 214]. Los resultados del estudio II mostraron correlaciones fuertes en la condición simple empleando el cronómetro manual entre el 3MBWT y el TUG al igual que en estudios previos en accidente cerebrovascular [211], adultos [210] y personas mayores que vivían en comunidad [212]. Además, también se obtuvieron correlaciones fuertes en la condición simple y de doble tarea cuando se utilizó el cronómetro manual y el Chronopic.

En este estudio también se decidió analizar la relación entre el rendimiento en el 3MBWT y el impacto de la FM medido a través del cuestionario FIQR. Se hallaron correlaciones que fluctuaron de fuertes a moderadas entre el rendimiento medido a través de los diferentes dispositivos y entre las diferentes condiciones en el 3MBWT y la puntuación total obtenida en el FIQR. Además, para ofrecer una observación más detallada se decidió analizar las correlaciones entre el rendimiento en el 3MBWT y las dimensiones que componen el FIQR. En este sentido, las correlaciones más fuertes se encontraron en la dimensión de "síntomas", seguida de la dimensión de "impacto general", que mostró una correlación moderada. Sin embargo, la dimensión de "función" no mostró una correlación significativa con el rendimiento en el 3MBWT en la mayoría de los casos. Estos hallazgos pueden indicar que el rendimiento en el 3MBWT no se correlaciona de manera adecuada con las acciones incluidas en la dimensión de "función", ya que, hay actividades que componen esta dimensión que no guardan una similitud con la acción de caminar hacia atrás (e.g. peinarse, preparar la comida y comprar). Sin embargo, las dimensiones de sintomatología e impacto general si mostraron buenas correlaciones. Sería interesante que futuras investigaciones tuvieran en cuenta y contemplasen este hallazgo.

Por tanto, evaluar la marcha hacia atrás a través del 3MBWT en FM puede ser de interés para los profesionales de la salud y de la investigación con el fin de observar cambios en la movilidad y el equilibrio. En este sentido, el 3MBWT puede utilizarse como una herramienta útil y aplicable en población con FM.

Finalmente, es interesante remarcar que el intervalo de tiempo óptimo entre las condiciones test y retest pueden variar según el constructo que se mide, la estabilidad del constructo a lo largo del tiempo y la población a la que se dirija el estudio [243]. En este sentido, para el estudio I y para el estudio II se estableció un periodo de siete días entre el test y retest, de la misma forma que hicieron investigaciones previas en personas con FM [196, 207, 244], con el fin de minimizar el impacto de posibles variables de confusión como los efectos de recuperación o de aprendizaje [245].

4.2. Impacto de la FM sobre determinadas estructuras cerebrales y la kinesiofobia.

El sueño, el deterioro cognitivo y el miedo al movimiento son factores que se encuentran alterados en gran parte de la población con FM. En este apartado se comentarán los hallazgos encontrados en los estudios III, IV y V que se centran principalmente en el impacto que genera la FM sobre el volumen de la glándula pineal y su relación con el sueño (estudio III), el impacto de la FM sobre el volumen de los subcampos del hipocampo (estudio IV) y la relación existente entre la kinesiofobia, el rendimiento en test físicos que guardan una estrecha relación con actividades de la vida diaria, el miedo a las caídas y el impacto de la FM (estudio V).

Los pacientes con FM suelen experimentar problemas de sueño [60, 61] que se suelen vincular a la severidad de los síntomas de esta enfermedad [27, 68]. La glándula pineal, un órgano neuroendocrino esencial en la producción de la melatonina [70] y se encuentra involucrado en los ritmos circadianos [71, 72], los procesos de sueño vigilia [72, 73] y la calidad del sueño [246], ya que, se encarga de sintetizar y segregar esta hormona. Investigaciones previas han propuesto que la reducción del volumen pineal suele encontrarse asociada a una disminución en los niveles de melatonina en personas sanas [87, 93], en personas mayores [94] y en personas con insomnio primario [247], pudiendo afectar a la falta de sueño [90] y el dolor [75]. En este sentido, en el estudio III se propuso examinar el volumen de la glándula pineal y determinar su relación con las horas de sueño, la calidad de sueño, los niveles de melatonina y la prevalencia de tipos de quiste en la glándula pineal en mujeres con FM, ya que, hasta la fecha no existían datos de referencia.

Los resultados mostraron un PPV medio de 102,00 mm^3 y una prevalencia de quistes de un 29,60% en mujeres con FM. Además, se hallaron correlaciones significativas entre el PPV, las horas de sueño, y el nivel de melatonina nocturno. Sin embargo, se observó una tendencia, aunque no fue significativa entre el PPV y el índice de calidad de sueño medido a través del cuestionario PSQI. Al analizar las diferencias entre el grupo FM y el grupo control sano, no se encontraron diferencias significativas en el PPV, el volumen pineal total y el volumen real, aunque sí se detectaron en la prevalencia de quistes.

Investigaciones previas también han mostrado correlaciones significativas entre la calidad del sueño y el volumen de la glándula pineal en población con insomnio primario [83], trastorno depresivo mayor y participantes sanos [86]. De la misma forma, nuestros hallazgos se encuentran en línea con estudios previos que se han centrado en los niveles de melatonina. En este sentido, encontramos investigaciones que ha mostrado asociaciones entre la producción de melatonina y el PPV [87, 93]. Una de estas investigaciones llevada a cabo por Liebrich, Schredl, Findeisen, Groden, Bumb and Nölte [87] detectó que existía una correlación inversa entre el PPV y los trastornos en el ritmo del sueño. De igual forma, se puede destacar el trabajo de Sigurdardottir, Markt, Sigurdsson, Aspelund, Fall, Schernhammer, Rider, Launer, Harris and Stampfer [94] en el que hallaron una correlación entre el volumen pineal y los niveles matutinos de 6-sulfatoximelatonina (i.e. metabolito de la melatonina que se excreta por la orina) en adultos mayores. Otra investigación, encontró niveles reducidos de melatonina plasmática nocturna en personas con insomnio primario tras llevar a cabo una comparación con un grupo de personas sanas [247]. Tomando esta información en conjunto y los resultados obtenidos en el estudio III, parece que el volumen de la glándula pineal en mujeres con FM podría estar relacionado con la disminución de las horas de sueño y la reducción de los niveles de melatonina, llevando a un posible deterioro en la calidad del sueño. No obstante, se necesitan más investigaciones en este campo que ayuden a dilucidar estas cuestiones.

En cuanto al PPV, nuestro estudio mostró un valor medio de 102,00 (41,46) mm^3 para el grupo de FM y 94,98 (37,87) mm^3 para el grupo control sano. En comparación con otras investigaciones, encontramos que el volumen de la glándula pineal de nuestras participantes era ligeramente inferior al de las poblaciones de hombres jóvenes sanos [87, 93], pero ligeramente superior a los valores reportados por el grupo control sano. Otros estudios que se centraron en población con insomnio primario [83], Alzheimer, deterioro cognitivo leve y personas sanas [84] reportaron volúmenes de glándula pineal inferiores en comparación con nuestros resultados. Dada la alta variabilidad de los métodos de adquisición de imagen y las poblaciones implicadas en los estudios previos que se han centrado en el estudio del volumen de la glándula pineal, las comparaciones entre nuestros hallazgos y la literatura previa deben tomarse con cautela. Por tanto, nuestro estudio no puede concluir que las mujeres con FM tienen un volumen de la glándula pineal más reducido que la población sana. En este sentido, se precisa de más investigación que ayude a la determinación de los mecanismos que puede generar el impacto de la FM sobre el volumen de esta importante glándula neuroendocrina.

Puesto que existen varias formas de analizar el volumen pineal, en este estudio también se empleó el método de Hasegawa [248]. Sin embargo, debido a la variabilidad de la forma de la glándula y los resultados obtenidos en el volumen, se puede decir que este método no es el más adecuado para determinar el volumen, ya que, tiende a subestimar los resultados, hallazgo que también se ha encontrado en una investigación previa [249]. Para evaluar los volúmenes de la glándula pineal, excluyendo el tejido quístico, que se considera hormonalmente inactivo [93], en nuestro estudio, se usaron secuencias de imágenes 3D ponderatas T1 eco turbo de campo. En este sentido, se pudo observar una prevalencia de quistes en la glándula pineal en el 29.60% de las mujeres con FM, resultados similares a los reportados en estudios previos en adultos sanos [249, 250]. Sin embargo, sólo el 5% de las mujeres sanas en este estudio mostraron la presencia de un quiste. Aunque la detección de quistes pineales se trata de un hallazgo común y a menudo se detecta de manera accidental [92, 251], las participantes con FM que tenían quiste informaron de más horas de sueño que aquellas con FM que no tenían quiste. Sin embargo, no se observaron diferencias significativas en el PPV y los niveles de melatonina nocturna. De manera adicional, cuando se dividió la muestra de FM entre participantes que no tenían quiste, participantes que tenían un quiste de menos de 2 mm y participantes que tenían un quiste de más de 2 mm, tampoco se encontraron diferencias significativas en ninguna de las variables estudiadas (PPV, años con FM, PSQI y horas de sueño). Aunque los quistes pineales se consideran tejido hormonalmente inactivo, es necesario investigar con más detalle posibles efectos que pueda generar este cuerpo sobre la función pineal [93]. En este estudio, no se estimaron las calcificaciones pineales cuando se usaban secuencias T1, ya que no permiten una identificación fiable [252]. Por tanto, futuros estudios deberían contemplar la evaluación del impacto que pueden generar los quistes pineales en la producción de melatonina, así como la prevalencia de las calcificaciones pineales. En este sentido, sería interesante utilizar tomografía computarizada y/o resonancia magnética ponderada de susceptibilidad, que permitirían la detección de calcificaciones de la glándula pineal [252].

Tal y como se indicó anteriormente las personas con FM suelen experimentar problemas de memoria, estados de ánimo alterados, estrés y dolor. En este sentido, el hipocampo es una de las estructuras cerebrales más estudiadas y que desempeña un papel fundamental en estos procesos [38-41]. El estudio IV tuvo como objetivo evaluar las diferencias volumétricas en los subcampos del hipocampo, así como, el hipocampo completo en mujeres sanas y mujeres con FM, controlando la edad, la depresión, el deterioro cognitivo y el volumen total intracraneal estimado. Dado que esta información no era conocida hasta la fecha, se trata del primer estudio que analiza la morfometría de los subcampos que componen el hipocampo en mujeres con FM en comparación con un grupo control sano.

Los hallazgos obtenidos en este estudio revelan que todos los modelos de regresión que se probaron fueron válidos. Además, se encontró que tanto los subcampos del hipocampo como el hipocampo en su totalidad mostraron volúmenes considerablemente inferiores en las mujeres con FM en comparación con las mujeres sanas. La única excepción que se detectó fue en la fisura derecha del hipocampo, la cual no mostró diferencias significativas. Al considerar el hipocampo en su totalidad, nuestros resultados se encuentran en línea con los de investigaciones previas en FM que también reportaron disminuciones volumétricas de materia gris en toda la estructura [13, 16, 35]. Además, estudios que aplicaron electroencefalografía (EEG) sugirieron este hallazgo a partir de la identificación de alteraciones en las ondas theta, mostrando que las mujeres con FM que habían sufrido los síntomas durante un periodo de tiempo más prolongado presentaban un espectro de potencia theta más elevado [253, 254]. Esta información es relevante, ya que, el espectro de potencia theta se asocia con funciones cognitivas superiores, plasticidad sináptica y atrofia del hipocampo [255].

Parece que las reducciones en el volumen del hipocampo comienzan a manifestarse desde la mediana edad, mostrando una atrofia progresiva de la estructura a medida que incrementan los años [256]. Nuestros hallazgos, guardan similitud con la literatura previa, mostrando disminuciones volumétricas en el hipocampo derecho e izquierdo a medida que aumenta la edad. De manera similar, se identificaron reducciones volumétricas en gran parte de los subcampos del hipocampo a excepción de la cola derecha, parasubículo derecho, CA3 izquierdo y CA4 y subículo en ambos hemisferios. Estos resultados se encuentran en línea con una investigación previa que reportó la disminución de volumen de estos subcampos con la edad, siendo el CA el más afectado [58]. Sin embargo, en nuestro estudio, estas disminuciones relacionadas con la edad no fueron halladas en este subcampo, pudiendo ser consecuencia de la edad relativamente baja de la muestra del estudio, que se situaba en 53,37 (4,47) años para el grupo control sano y 54,18 (10,12) para el grupo FM. No obstante, en base a la variabilidad metodológica utilizada en los diferentes estudios [58], se requiere más investigación para confirmar estos hallazgos.

La FM se asocia con una incidencia de depresión y deterioro cognitivo [257, 258], y se ha documentado que pacientes con trastorno depresivo mayor [259] y enfermedad de Alzheimer [56] presentan un tamaño del hipocampo reducido. Sin embargo, se sigue observando un patrón no uniforme de atrofia en esta condición. En este sentido, nuestros resultados fueron controlados para el efecto del deterioro cognitivo y la depresión, incluyendo estos datos como covariables en los análisis estadísticos. Las puntuaciones más altas en el MMSE se relacionaron con un aumento del volumen en el subcampo CA3 derecho. Sin embargo, no se hallaron diferencias significativas entre las puntuaciones en la GDS y los volúmenes de los subcampos del hipocampo. En la misma línea, una investigación previa no encontró diferencias entre mujeres sanas y con FM cuando controló la depresión [16]. En cuanto al trastorno depresivo mayor, una revisión previa sobre los subcampos del hipocampo, informó que las reducciones volumétricas ocurrieron principalmente en los subcampos CA y células granuladas del giro dentado (GCDG) [57]. En nuestro estudio, no se llegaron a detectar cambios volumétricos en estas subestructuras, lo que podría explicarse por los niveles de depresión más elevados que se dan en el trastorno depresivo mayor en comparación con la FM y la edad de los participantes. Además, se ha señalado que las alteraciones del hipocampo relacionadas con la depresión son más pronunciadas en adultos mayores debido al efecto acumulativo de la depresión [260] y la atrofia del hipocampo relacionada con la edad [261].

Zhao, Wang, Yin, He, Li and Han [56] llevaron a cabo la comparación de los subcampos del hipocampo en diferentes grupos de participantes entre los que se encontraban personas con Alzheimer, pacientes con deterioro cognitivo leve amnésico, pacientes con deterioro cognitivo subjetivo y controles sanos. Al comparar estos resultados con nuestros hallazgos, se puede observar que los volúmenes obtenidos en nuestro grupo de mujeres con FM eran inferiores a los del grupo de deterioro cognitivo subjetivo pero superiores que los del grupo de deterioro cognitivo leve amnésico, así como el grupo de Alzheimer. Esto es relevante, ya que, los problemas recurrentes de memoria y concentración conocidos como *fibrofog* son habituales y se consideran un aspecto clínicamente importante en FM [262]. No obstante, nuestra investigación no detectó ningún efecto específico del deterioro cognitivo en los subcampos del hipocampo. Este hecho pudo haber estado propiciado porque no se llevaron a cabo pruebas neuropsicológicas específicas para evaluar el rendimiento cognitivo en diferentes dominios que se podrían encontrar alterados [263]. En este sentido, es interesante que futuras investigaciones examinen la relación de la variación de los cambios volumétricos de los subcampos del hipocampo con diferentes dominios cognitivos aplicando diferentes pruebas neuropsicológicas. Se sabe que la depresión, la ansiedad, el dolor y los trastornos del sueño pueden afectar de manera negativa a los síntomas cognitivos, aunque no explican completamente todos los síntomas cognitivos de la FM [264]. Aun así, estudios morfológicos muestran reducciones de materia gris en FM en áreas vinculadas a componentes cognitivos [265, 266]. Como esperábamos, las puntuaciones de depresión y deterioro cognitivo fueron peores en el grupo de FM que en el grupo control, estando en línea con investigaciones previas [16, 258, 267, 268]. Sin embargo, se requieren más estudios para comprender los mecanismos subyacentes a estas observaciones.

El miedo al movimiento, también conocido en la literatura como kinesiofobia, es otro factor que suele experimentarse en la FM. En este sentido, el estudio V tuvo como objetivo evaluar la diferencia existente en esta variable entre mujeres con FM y mujeres aparentemente sanas. Además, se analizaron las correlaciones entre el impacto de la FM, el miedo a las caídas, diferentes pruebas físicas que se asemejan a tareas de la vida diaria (i.e. TUG, prueba de prensión manual y *10-step stair ascent test*) y la kinesiofobia. Aunque la kinesiofobia ha sido estudiada en la FM, solo cuatro estudios han explorado su relación con la discapacidad medida a través de cuestionarios [109-112], pudiendo introducir sesgos en la información por parte de los participantes al recordar lo que hicieron o como se sintieron. Por el lado contrario, solo dos estudios exploraron esta relación a través de la realización de pruebas de aptitud física [7, 113]. Ninguna de las investigaciones analizó la relación entre la kinesiofobia y el miedo a caer. Además, estos estudios tampoco incorporaron un grupo de comparación con personas aparentemente sanas, y solo un estudio comparó la kinesiofobia con el impacto de la enfermedad medido a través del cuestionario FIQR [109]. Puesto que no hay un cuerpo de conocimiento extenso en este tema, el estudio V pretendía contribuir a la literatura con nueva información teniendo en cuenta los aspectos mencionados.

Los resultados obtenidos en nuestra investigación indicaron que las mujeres con FM mostraron puntuaciones más elevadas de kinesiofobia (i.e. miedo al movimiento) y miedo a las caídas en comparación con el grupo de mujeres aparentemente sanas. Estos hallazgos se encuentran en línea con una investigación previa que también registró un mayor miedo a las caídas en personas con FM en comparación con individuos sanos [269]. Estas variaciones podrían estar asociadas con el número de caídas experimentadas [269], la sintomatología de la FM y otros problemas relacionados, como el bajo rendimiento en el equilibrio [269, 270], la inestabilidad postural [271] y un reducido rendimiento funcional [270]. Además, un dato interesante reportado por Peinado-Rubia, Osuna-Pérez, Rodríguez-Almagro, Zagalaz-Anula, López-Ruiz and Lomas-Vega [110] contemplaba que los días con episodios de inestabilidad, kinesiofobia y vértigo explicaron más de la mitad de la variación en la confianza en el equilibrio en los pacientes con FM. En relación a la kinesiofobia, estudios anteriores han obtenido resultados similares. Sin embargo, las investigaciones de Koçyiğit and Akaltun [112] y Meeus, Ickmans, Struyf, Kos, Lambrecht, Willekens, Cras and Nijs [272] a pesar de mostrar resultados parecidos a los de nuestra investigación, no emplearon la versión de 11 ítems de la TSK.

El análisis de la kinesiofobia es fundamental porque tiene un efecto considerable sobre los niveles de actividad física [273], las actividades de la vida diaria [105] y la calidad de vida [274]. En esta línea, la kinesiofobia puede llevar a las personas con FM a entrar en un círculo vicioso donde el miedo puede generar temor al dolor, y este temor al dolor conduce a la discapacidad, en parte debida a un incremento del estilo de vida sedentario [97, 98, 275]. En este sentido, las intervenciones que promueven la actividad física son esenciales en esta población, ya que, ayudan a romper este círculo vicioso disminuyendo el dolor y mejorando la calidad de vida relacionada con la salud [276, 277]. Llegados a este punto, la evaluación de la kinesiofobia en contextos clínicos resulta de gran interés, dado que podría suponer un obstáculo para los programas de rehabilitación [107] y se ha visto que las personas con FM que han experimentado dolor severo, miedo al movimiento y disminución en la calidad de vida en los ámbitos físico y social, han reportado menores niveles de adherencia al tratamiento [108]. Investigaciones futuras deberían contemplar y establecer puntos de corte para la TSK en personas con FM para lograr interpretaciones más precisas.

Las personas con FM sufren un deterioro físico que puede limitar la capacidad para desarrollar actividades de la vida diaria [6, 7]. Nuestros resultados coinciden con este hallazgo, mostrando un rendimiento inferior en el grupo con FM comparado con el grupo aparentemente sano en las pruebas TUG y la prueba *10-step stair ascent test*, las cuales simulan acciones próximas a tareas que se desarrollan de manera común en el día a día de una persona [198, 278, 279]. Por lo general, las personas con FM presentan menor fuerza de prensión manual en comparación con individuos sanos. No obstante, nuestro estudio mostró fuerzas de prensión similares entre ambos grupos, al igual que lo hizo la investigación de Panton, Kingsley, Toole, Cress, Abboud, Sirithienthad, Mathis and McMillan [280]. Es posible que no se hayan encontrado diferencias debido a que el grupo aparentemente sano mostró niveles más bajos de fuerza en comparación con otros estudios que tenían un rango de edad similar y que usaron el mismo instrumento de medición [281-283]. En este sentido, parece fundamental seguir unificando los protocolos de medición de la fuerza de prensión manual para facilitar comparaciones precisas entre las investigaciones que se sigan desarrollando [284].

En este estudio, se hallaron relaciones significativas en el grupo de FM entre la kinesiofobia, el miedo a las caídas, las pruebas de movilidad TUG y *10-step stair ascent*, así como el impacto general de la FM. Estas conexiones podrían explicarse por el modelo de evitación del miedo [96, 97], donde las experiencias dolorosas pueden generar altos niveles de kinesiofobia e inducir cambios en las redes corticales que se encuentran involucradas en el manejo de las funciones motoras [285]. En la misma línea, es posible que los valores de kinesiofobia se hayan correlacionado de manera significativa con las pruebas TUG y *10-step stair ascent*, ya que, este miedo al movimiento puede evitar la realización de determinadas actividades que se encuentren relacionadas con la vida diaria, generando ese círculo vicioso que se comentaba anteriormente y que puede contribuir a perpetuar y agravar la enfermedad. Esta relación se observó anteriormente en investigaciones que usaron la prueba TUG [113], pero no con la prueba *10-step stair ascent* [7], posiblemente debido al ritmo cómodo que se permitió a los participantes utilizar para subir las escaleras. El impacto general de la enfermedad también está relacionado con la kinesiofobia en base a los resultados obtenidos en esta investigación y los proporcionados por Russek, Gardner, Maguire, Stevens, Brown, Jayawardana and Mondal [109]. Para un análisis más detallado, nuestro estudio examinó las preguntas específicas de los dominios que componen el FIQR, y encontró que el dolor y ciertas actividades como peinarse, levantar y cargar una bolsa de la compra, y subir escaleras se correlacionaron con la puntuación obtenida en la TSK-11. No obstante, no se encontraron resultados significativos entre la kinesiofobia y la prueba de fuerza de prensión manual, lo que está en línea con una investigación previa [113]. Además, Ishak, Zahari and Justine [107] informaron de correlaciones significativas entre la kinesiofobia y la movilidad y el equilibrio medidos a través del TUG, sin embargo, estas correlaciones no se observaron con la fuerza de prensión manual. En este sentido, suponemos que los hallazgos obtenidos en nuestro estudio puedan deberse al hecho de que la prueba de fuerza de prensión manual es una prueba estática que no implica un movimiento significativo del cuerpo, por lo tanto, es posible que las mujeres no lleguen a experimentar esa sensación de miedo durante esta prueba. Finalmente, es importante comentar que en este estudio, el miedo a caer se relaciona con la kinesiofobia, posiblemente debido al recuerdo doloroso de una caída o al temor de sufrir dolor debido a una caída futura [286]. Sin embargo, se requieren más investigaciones para aclarar estos aspectos interesantes.

4.3. *Exergames* como terapia no farmacológica en la FM.

Tal y como proponen Wu, Chen, Zheng, Huang and Ren [186] en una reciente revisión sistemática y meta análisis, las intervenciones basadas en *exergames* han mostrado resultados positivos en la función general, la percepción del dolor, la calidad de vida, la capacidad de ejercicio, la salud percibida y la severidad de la fatiga en mujeres con FM. Además, la literatura también ha mostrado efectos positivos en el control autónomo en mujeres con FM tras una intervención de *exergames* con una duración de 24 semanas [187] al igual que se han hallado mejoras en la dinámica cerebral, concretamente en la banda beta, que pueden estar relacionadas con un aumento del flujo sanguíneo cerebral [188]. Sin embargo, los efectos de intervenciones basadas en *exergames* sobre el volumen de materia gris de estructuras cerebrales involucradas en la red del dolor eran desconocidos y ofrecer información en esta área era relevante en el campo de la neurociencia para seguir profundizando en el manejo de la FM.

Los resultados del estudio VI indicaron que tras la intervención de ejercicio basada en *exergames* con una duración de 24 semanas, no se encontraron efectos significativos sobre el volumen de materia gris en estructuras cerebrales involucradas en la red del dolor (i.e. hipocampo, amígdala, tálamo, ínsula y cerebelo), así como en el volumen total de materia gris del cerebro. En la misma línea, aunque en una población de adultos mayores, la investigación llevada a cabo por Adcock, Fankhauser, Post, Lutz, Zizlsperger, Luft, Guimarães, Schättin and de Bruin [191] que incluía un programa de entrenamiento multicomponente basado en *exergames* con 16 semanas de duración tampoco mostró aumentos en la materia gris total ni en el hipocampo. En contraposición, dos estudios que incluían una población de personas mayores hallaron aumentos en el volumen cerebral en áreas frontales tras intervenciones basadas en *exergames* que utilizaron Nintendo Wii [190] y un programa específico con bicicletas estáticas que incorporaban pantallas de realidad virtual [189].

Fuera del contexto de los *exergames*, en la literatura se encuentran varias revisiones que han investigado los efectos del ejercicio físico sobre la morfología cerebral [159, 287-291]. En este sentido, la investigación de Hvid, Harwood, Eskildsen and Dalgas [291] se puede considerar como uno de los trabajos más relevantes hasta la fecha y muestra la evidencia de los efectos del ejercicio físico de tipo aeróbico, de fuerza y concurrente sobre el volumen cerebral total y regional de materia gris en poblaciones con riesgo de neurodegeneración. En este sentido, los autores informan que la investigación hasta la fecha es escasa y poco concluyente, por tanto, se precisa más investigación para respaldar la potencialidad del ejercicio físico sobre el aumento del volumen de materia gris, ya que, parece ser que este volumen no aumenta ni se conserva significativamente tras programas que han utilizado intervenciones que se han desarrollado en un periodo de 3 a 12 meses. Por otra parte, en la literatura también se encuentran investigaciones que han mostrado alteraciones a nivel estructural tras la realización de programas de ejercicio que incluían actividades de coordinación [292, 293], baile [294-296] y Tai Chi [297].

Los mecanismos fisiológicos que explican como el entrenamiento aeróbico y de fuerza afectan al cerebro no se comprenden por completo. Sin embargo, se sugiere que pueden existir varios mecanismos.

En primer lugar, parece que este tipo de entrenamiento aumenta los niveles del BDNF así como otros factores dentro del sistema nervioso central entre los que se incluyen el factor de crecimiento nervioso, el factor 1 de crecimiento de la insulina, y las neurotrofinas 3 y 4/5 [298-300]. Se cree que estos procesos se pueden dar directamente a través de la actividad neuronal o indirectamente por medio de la elevación de mioquinas en el músculo esquelético, que tendrán un recorrido hacia el cerebro por medio de la sangre y el líquido cefalorraquídeo, consiguiendo finalmente un aumento de los niveles de BDNF [301] que facilitará los procesos de gliogénesis [302], sinaptogénesis [303], neurogénesis [304] y angiogénesis [305]. En segundo lugar, se propone que el ejercicio físico tiene efectos positivos sobre las citocinas que llegan a reducir la neuroinflamación, que es un factor clave en la neurodegeneración [306, 307]. En este sentido, se precisa de más investigación en el campo, aunque se propone a la interleucina-6 como el marcador más prometedor [308, 309]. Finalmente, parece que el ejercicio aumenta el flujo sanguíneo cerebral y la biogénesis mitocondrial, optimizando el metabolismo energético y la eliminación de desechos y la señalización de factores como el BDNF. En este sentido, parece que el ejercicio podría contrarrestar el hipometabolismo que se encuentra asociado con el deterioro cognitivo y una posible atrofia cerebral [310].

En nuestro estudio no se obtuvieron cambios volumétricos en estructuras cerebrales involucradas en la red del dolor. Sin embargo, es interesante considerar una serie de cuestiones metodológicas a la hora de desarrollar programas de intervención, aunque es necesario seguir investigando en las mismas.

La intensidad del ejercicio parece un factor interesante, ya que, en estudios con animales se ha encontrado una mayor expresión de los niveles de BDNF vinculados a la intensidad del ejercicio [311]. Este hallazgo lleva a plantearse que los entrenamientos a intensidades elevadas pueden generar efectos positivos sobre la expresión de BDNF. Sin embargo, Ruscheweyh, Willemer, Krüger, Duning, Warnecke, Sommer, Völker, Ho, Mooren and Knecht [312] mostraron que los beneficios de la actividad física sobre las funciones cognitivas y estructuras cerebrales ubicadas en la parte frontal se pueden obtener independientemente de la intensidad del ejercicio realizado. En la misma línea, Lövdén, Schaefer, Noack, Bodammer, Kühn, Heinze, Düzel, Bäckman and Lindenberger [313] hallaron efectos positivos sobre el volumen del hipocampo tras la realización de un programa de *exergames* pero a una baja intensidad. Aunque los ejercicios a intensidades elevadas generan adaptaciones en el sistema respiratorio, cardiovascular, metabólico e inmunológico, y estos pueden afectar indirectamente a los procesos cerebrales, parece que la relación entre los cambios volumétricos y la intensidad del ejercicio sigue sin estar clara.

Aunque parece que el volumen de materia gris cerebral no aumenta ni se conserva tras programas que han utilizado intervenciones de ejercicio que se han desarrollado en un periodo de 3 a 12 meses [291], especulamos que la duración de la intervención ha podido en parte influir en la no obtención de resultados significativos. En este sentido, investigaciones previas han reportado incrementos en diferentes estructuras cerebrales, principalmente en el hipocampo tras de doce meses de intervención [160, 293, 314]. Además, este argumento puede verse reforzado por los resultados de Niemann, Godde and Voelcker-Rehage [293], donde no se encontraron cambios volumétricos tras seis meses de intervención pero sí después de 12 meses. Nuestra intervención basada en *exergames* de 24 semanas de duración ha mostrado previamente efectos significativos en la aptitud física [206, 232], la calidad de vida y el dolor [232], la modulación autonómica [187], e incluso en el espectro de potencia beta de EEG [188] en mujeres con FM. Estos hallazgos podrían indicar que los cambios relacionados con el volumen cerebral necesitan más tiempo para alcanzarse con este tipo de protocolo de ejercicio físico

Teniendo en cuenta la gran variabilidad de intensidades, duración, volúmenes o tipos de entrenamiento que han informado cambios volumétricos tras las intervenciones de ejercicio físico, la investigación futura debería dilucidar cómo estas variables (i.e. volumen, intensidad, duración y tipo de entrenamiento) modulan los cambios en la morfometría cerebral. Además, si se realizan intervenciones de baile, se debe considerar si los ejercicios realizados son creativos o repetitivos, ya que, influyen en la supervivencia neuronal y en los cambios del volumen cerebral [294].

Al analizar de forma intragrupal la muestra del estudio, se identificaron cambios significativos tanto en los grupos de intervención como en los de control. Un estudio detallado de los cambios en los volúmenes cerebrales en el mismo grupo de pacientes puede ser crucial para comprender parte de los mecanismos centrales de la FM. Los resultados significativos obtenidos dentro de los grupos están en línea con un informe morfométrico previo que indicaba variaciones en los volúmenes de materia gris en pacientes con FM [315]. Otro estudio destacó que los cambios en el volumen cerebral son más pronunciados tras una exposición prolongada al dolor en la FM. En ese sentido, los autores sugirieron que una mayor duración de FM puede reflejar un mecanismo compensatorio en el que el cerebro intenta prevenir los efectos negativos de la entrada nociceptiva constante [37]. También es posible pensar que los cambios morfométricos representan un incremento en el procesamiento afectivo-evaluativo del dolor, como se ha propuesto en pacientes con dolor lumbar crónico [316].

Finalmente, las correlaciones significativas encontradas entre el pico de consumo de oxígeno y las regiones derecha e izquierda del hipocampo y las regiones derecha e izquierda de la amígdala brindan una información interesante. En este sentido y de manera paralela a nuestros hallazgos, la investigación de Erickson, Prakash, Voss, Chaddock, Hu, Morris, White, Wójcicki, McAuley and Kramer [317] mostró que los niveles más elevados de condición física aeróbica se encontraban asociados a mayores volúmenes del hipocampo en personas mayores. Además, se sabe que el ejercicio aeróbico aumenta el volumen sanguíneo cerebral en el giro dentado de los adultos, lo que está relacionado con la neurogénesis [318]. Por otra parte, las correlaciones halladas entre el pico de consumo de oxígeno y las regiones derecha e izquierda de la amígdala pueden coincidir con los resultados de un estudio que analizó la actividad neuronal y la frecuencia respiratoria en relación con la anticipación de la ansiedad. En el sujeto más ansioso, se detectaron fuentes de corriente eléctrica en la amígdala izquierda, cuya activación contribuye a la mejora de la frecuencia respiratoria [319]. Por lo tanto, podría ser relevante explorar la relación entre el sistema aeróbico y la amígdala, teniendo en cuenta que la población con FM a menudo presenta síntomas de ansiedad [320-322].

Capítulo 5

Fortalezas

Capítulo 5. Fortalezas

La presente tesis doctoral tiene una serie de fortalezas que deben tenerse en cuenta:

1. Las investigaciones realizadas se han llevado a cabo de manera multidisciplinar utilizando conocimientos y técnicas desde una variedad de campos de investigación como la medicina, la psicología y las ciencias del deporte.
2. La duración de la intervención mediante *exergames* en FM sigue siendo la más extensa que existe en la literatura contando con 24 semanas. Además, se han proporcionado por primera vez los efectos sobre la morfometría de estructuras cerebrales involucradas en la red del dolor tras una intervención de *exergames*.
3. Se ha observado por primera vez el impacto que tiene la sintomatología de la FM sobre el volumen de los subcampos del hipocampo.
4. Se ha observado por primera vez el impacto que tiene la FM sobre el volumen de la glándula pineal, la prevalencia de quistes y la posible relación que puede existir entre el PPV, las horas de sueño y los niveles de melatonina.
5. Se ha contribuido a la literatura con nueva información analizando la relación entre la kinesiofobia, el impacto de la FM medido a través del cuestionario FIQR, el miedo a las caídas y diferentes pruebas de evaluación que guardan una estrecha relación con situaciones de la vida cotidiana.
6. Se han obtenido por primera vez los resultados de las propiedades psicométricas de tres pruebas de valoración que involucran tareas físicas y cognitivas en FM desde un punto de vista de la doble tarea. Esto abre nuevas posibilidades de evaluación desde un punto de vista más ecológico en el tratamiento de la FM.

Capítulo 6

Limitaciones

Capítulo 6. Limitaciones

La presente tesis doctoral tiene una serie de limitaciones que deberían tenerse en cuenta:

- Los resultados obtenidos en los diferentes estudios no pueden generalizarse para la población masculina, ya que, la muestra de todas las investigaciones presentadas en esta tesis doctoral se compuso exclusivamente de mujeres.
- En los estudios III y IV no se pudieron evaluar los posibles efectos de los escáneres de resonancia magnética, ya que, la muestra no se pudo aleatorizar para obtener las imágenes en los diferentes dispositivos al provenir el grupo control de la base de datos abierta OASIS-3.
- En el estudio III no se pudo llevar a cabo ningún análisis con las horas de sueño ni con los niveles de melatonina, ya que, el conjunto de datos de OASIS-3 no dispone de esta información.
- En el estudio III también hay factores como los medicamentos, el ciclo menstrual y algunas comorbilidades asociadas a la FM que podrían influir en la producción y secreción de melatonina.
- En el estudio III es posible que, al realizar la segmentación manual de la glándula pineal, parte de estructuras adyacentes se hayan incluido en los cortes y puedan afectar al volumen final reportado.
- En el estudio IV no se pudieron analizar las diferencias volumétricas en la fisura del hipocampo izquierdo, CA1 izquierdo y derecho, fimbria izquierda, y HATA izquierdo y derecho, ya que, no se cumplieron los supuestos para llevar a cabo el análisis de regresión lineal múltiple.
- Hubiera sido interesante incluir en el estudio VI un grupo de participantes que realizase un entrenamiento tradicional para conseguir aislar el efecto de la intervención basada en *exergames*.
- En el estudio VI se podría haber incluido un grupo de participantes sanas que hubiese permitido una comparación con el grupo de FM.

Capítulo 7

Perspectivas futuras

Capítulo 7. Perspectivas futuras

En base a los resultados y las limitaciones de los estudios que componen la presente tesis doctoral, las futuras investigaciones que se desarrollen podrían tener en cuenta las siguientes consideraciones:

1. Futuros estudios deberían incluir sujetos masculinos con el fin de generalizar los resultados a esta población.
2. Se precisan investigaciones longitudinales que exploren el rendimiento físico y cognitivo mediante evaluaciones que incluyan el paradigma de la doble tarea debido a la dificultad específica que genera la realización de este tipo de tareas en población con FM en comparación con personas sanas.
3. Investigaciones futuras deberían contemplar la inclusión de programas de ejercicio físico que se encuentren compuestos de actividades motoras creativas, ya que, requieren de la realización de tareas simultáneas y procesos que involucran coordinación, orientación espacial, equilibrio, fuerza, interacción y comunicación [295]. Además, si se pretenden incluir programas de danza, sería interesante apostar por intervenciones de danza creativa, que parecen mostrar mejores resultados en la reducción del dolor y el impacto de la FM con respecto a intervenciones de danza repetitiva (i.e. Zumba o aeróbic) [146].
4. Explorar los cambios volumétricos en los subcampos del hipocampo tras programas de ejercicio que involucren diferentes tipos de actividades y que estas variables se puedan controlar, se muestra como una idea interesante de cara a conocer la implicación que pueda tener la actividad física en estas subestructuras.
5. Se ha encontrado evidencia moderada de pequeños efectos del ejercicio sobre el sueño [323]. Evaluar los cambios en el volumen en la glándula pineal, la producción de melatonina y la calidad del sueño, se muestra interesante para comprobar los efectos de programas de ejercicio físico que se encuentren bien diseñados y controlados para determinar si existe una influencia sobre las variables mencionadas.
6. Dado que la sintomatología de la FM es cambiante con el paso de los días, sigue siendo fundamental establecer programas de entrenamiento específicos con el fin de replicar los estudios llevados a cabo o conocer que intervenciones son las más adecuadas para mejorar aquellos aspectos que se quieran tratar en la enfermedad. En este sentido, recomendamos encarecidamente que los autores determinen de la manera más clara posible la carga de entrenamiento y el tipo de ejercicios que se apliquen en un programa de ejercicio físico. Para ello, recomendamos el uso de la Consensus on Exercise Reporting Template o CERT [324, 325] disponible en la red EQUATOR.

Capítulo 8

Conclusiones

Capítulo 8. Conclusiones

En base a los resultados obtenidos en los diferentes estudios que componen la presente tesis doctoral, se pueden destacar las siguientes conclusiones:

1. Un programa de 24 semanas basado en una intervención de ejercicio mediante *exergames* no produjo cambios morfométricos en el volumen de materia gris de estructuras cerebrales que componen la red del dolor.
2. Tras una intervención de un programa de ejercicio basado en *exergames* de 24 semanas de duración se obtuvieron relaciones significativas entre el pico de consumo de oxígeno y las regiones izquierda y derecha del hipocampo y la amígdala.
3. Las mujeres con FM no mostraron diferencias en el volumen de la glándula pineal con respecto a mujeres sanas.
4. Las mujeres con FM poseen una mayor prevalencia de quistes en la glándula pineal en comparación con las mujeres sanas.
5. Las mujeres con FM mostraron relaciones significativas entre el PPV, las horas de sueño y los niveles de melatonina.
6. Se han encontrado volúmenes reducidos en los subcampos del hipocampo en mujeres con FM en comparación con mujeres sanas.
7. Parece que la edad, el deterioro cognitivo y la depresión se encuentran relacionados con algunos de los subcampos del hipocampo en base a los modelos de regresión obtenidos durante el análisis.
8. Las mujeres con FM mostraron mayores puntuaciones de kinesiofobia, un peor rendimiento en pruebas que evaluaban la movilidad y un mayor miedo a las caídas en comparación con mujeres sanas.
9. En mujeres con FM las puntuaciones de kinesiofobia se relacionan con el rendimiento obtenido en el TUG, el rendimiento obtenido en la prueba *10-step stair ascent*, el miedo a las caídas y el impacto de la enfermedad.
10. Las pruebas de evaluación de la fuerza *30 seconds chair stand* y *30 seconds arm curl* bajo condición de doble tarea, así como la variable calculada de rendimiento total mostraron buenos valores de fiabilidad test-retest.
11. La prueba de evaluación 3MBWT se muestra fiable y válida en condiciones simple y de doble tarea en mujeres con FM. Para obtener valores más altos de fiabilidad se requiere el uso de un cronómetro automático Chronopic. Además, el rendimiento obtenido en la prueba se relaciona con el impacto de la FM.

Capítulo 8. Conclusions

Based on the results obtained in the different studies included in this doctoral thesis, the following conclusions can be highlighted:

1. A 24-week of exergame-based intervention did not produce morphometric changes in the gray matter volume of brain structures composing the matrix pain.
2. Following a 24-week of exergame-based intervention, significant relationships were obtained between peak oxygen consumption and the left and right regions of the hippocampus and amygdala.
3. Women with FM did not show differences in pineal gland volume compared to healthy women.
4. Women with FM exhibit a higher prevalence of pineal gland cyst compared to healthy women.
5. Women with FM showed significant relationships between PPV, hours of sleep and melatonin levels.
6. Reduced hippocampal subfield volumes have been found in women with FM compared to healthy women.
7. It seems that age, cognitive impairment and depression are related with some of the hippocampal subfields based on the regression models obtained during the analysis.
8. Women with FM showed higher kinesiophobia scores, worse performance on tests assessing mobility, and higher fear of falling compared to healthy women.
9. In women with FM, kinesiophobia scores are related to performance on the TUG, performance on the 10-step stair ascent test, fear of falling and the impact of the disease.
10. The 30 seconds chair stand test and 30 seconds arm curl test under dual-task condition, as well as the calculated variable of total performance showed good test-retest reliability values.
11. The 3MBWT test is shown to be reliable and valid under single and dual-task conditions in women with FM. To obtain higher reliability values, the use of an automatic stopwatch is required. In addition, the performance obtained in the test is related to the impact of FM.

“Es preciso sacudir enérgicamente el bosque de las neuronas cerebrales adormecidas; es menester hacerlas vibrar con la emoción de lo nuevo e infundirles nobles y elevadas inquietudes”

Santiago Ramón y Cajal (1852-1934)

Capítulo 9

Referencias

Capítulo 9. Referencias

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Capítulo 10

Artículos científicos

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Article

Strength Assessment Under Dual Task Conditions in Women with Fibromyalgia: A Test–Retest Reliability Study

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Abstract: The present study aimed to: (1) analyze the test–retest reliability of the 30 s chair stand test and the 30 s arm curl test under dual-task conditions; (2) analyze the test–retest reliability of a new variable which assesses the total performance (cognitive + physical) in both tests. A total of 37 women with fibromyalgia participated in the study. Participants completed the 30 s arm curl test and 30 s chair stand test in both simple and dual-task conditions. These tests were repeated after seven days. In the 30 s chair stand dual-task test the reliability was low to good whereas that of the total performance variable was low to moderate. The reliability in both the 30 s arm curl dual-task test and the total performance variable were good to moderate. Both the 30 s chair stand test and 30 s arm curl test under dual-task conditions and the total performance variables had good test–retest reliability. However, it is necessary to consider the fluctuations of the intraclass correlation coefficient (ICC).

Keywords: dual-task; chronic pain; activities of daily living; strength

1. Introduction

Fibromyalgia (FM) is defined as a chronic disease characterized by persistent, diffuse, and widespread pain associated with several symptoms. Amongst others, these symptoms include non-recovery sleep, anxiety, depression, stiffness, fatigue, cognitive problems, and mobility or balance problems [1]. Therefore, most people who suffer from FM tend to experience a reduced quality of life [2–5], as well as a series of difficulties related to activities of daily living [6–8].

In Europe, the prevalence of this disease is somewhere between 2.9% and 4.7% of the general population [9], showing higher incidence in women aged 40–59 years [2,10]. In economic terms, it is estimated that FM represents twelve billion euros annually for a population of 80 million inhabitants [11]. In Spain, FM represents a total average of 9982 euros per patient, of which 32.5% is attributable to health care costs and 67.5% to indirect costs [12]. Physical exercise is shown as an interesting tool that improves fitness and wellness in this population [13], therefore reducing health economic costs. Several studies have analyzed the importance of fitness in people with FM with regards to pain [14], quality of life [15], psychological disorders [16], and fear of falling [17].

Chronic pain significantly affects function and quality of life for patients with FM. This leads to a reduction in lower limb strength, agility, and balance [18]. In this regard, strength takes a particular interest because it determines the ability to carry out work, as well as activities of daily living [19,20]. Moreover, previous studies have demonstrated reduced muscle performance in patients with FM [21,22].

In an adult population, the most commonly used tests in the assessment of strength are the 30 s chair stand test and the 30 s arm curl test [23]. The first involves repeated sitting down and rising from a chair. The second involves flexing and extending the elbow throughout its range of motion, with an external weight of 2.5 kg [23]. In women with FM, these tests have been used to establish classifications based on the presence or absence of the disease as well as the severity of the symptoms [24,25].

Traditionally, physical fitness tests have been carried out by only involving the participant in a physical task. However, it would be interesting to approach these tests through activities of daily living. Activities of daily living usually involve two or more tasks simultaneously [26]. The dual-task paradigm proposes the accomplishment of two tasks simultaneously—a first cognitive task directs or focuses the attention of the participant towards an external source of attention (i.e., performing a mathematical operation) whilst performing a second motor task (i.e., climbing stairs). The different task combinations are motor–motor, cognitive–cognitive, and motor–cognitive. Previous studies have analyzed the influence of adding a cognitive task when performing physical fitness tests in women with FM [27–29], but none of them have reported test–retest reliability. A test is considered reliable when, on two or more occasions under the same conditions, a subject obtains similar results [30]. Therefore, the aim of the present study was to analyze the test–retest reliability of the 30 s chair stand test and 30 s arm curl test under dual-task conditions. This would allow us to determine whether the application of this kind of test closer to typical conditions of activities of daily living, could be reliable in women with FM. The secondary aim was to analyze the test–retest reliability of the new variable created, which assesses the total performance (cognitive + physical). Accordingly, the hypotheses of the present study were: (1) that the 30 s chair stand test and the 30 s arm curl test under dual-task conditions are reliable in women with FM; (2) that the variable which assesses the total performance (cognitive + physical) is reliable in both tests.

2. Materials and Methods

2.1. Participants

A total of 37 women from a local FM association participated in this study. This sample size with two observations per subject achieves 91% power to detect an intraclass correlation of 0.90 under the alternative hypothesis, when the intraclass correlation under the null hypothesis is 0.75 using an F-test with a significance level of 0.05 [31,32]. The PASS software for performing power and sample size calculations (version 11.0; PASS; Kaysville, Utah) was employed.

The main characteristics are shown in Table 1. The following inclusion criteria were established for this study: (a) female between 30 and 75 years old; (b) diagnosed with FM by a rheumatologist according to the 2010 criteria established by the American College of Rheumatology [1]; (c) able to communicate effectively with the study staff; and (d) understood and signed informed consent in accordance with the updated Declaration of Helsinki. Participants were excluded if they: (a) were pregnant; (b) could not sit down and get up from a chair without help; or (c) had an arm injury that prevented flexion and extension of the elbow. This study obtained the agreement of the Biomedical Ethics Committee of the University of Extremadura (Spain) (62/2017).

Table 1. Descriptive characteristics of the participants.

Participants	Mean (SD)
Sample size	37
Age (years)	54.76 (8.64)
Years with fibromyalgia	12.73 (6.75)
BMI (kg/m^2)	28.30 (3.43)
FIQ-100	53.61 (19.88)

FIQ: Fibromyalgia Impact Questionnaire; SD: standard deviation.

2.2. Procedure

First, anthropometric measurements of the participants were taken to calculate the body mass index (BMI), as well as age and years with FM. Subsequently, participants completed the Spanish version of the Fibromyalgia Impact Questionnaire (FIQ), which evaluates the impact of symptoms of the disease from 0 to 100, indicating the minimum to maximum impact respectively [3,33,34]. Finally, two physical fitness tests were performed: (1) the 30 s arm curl test and (2) the 30 s chair stand test. Tests were performed in two conditions—simple and dual-task. The dual-task conditions consisted of subtracting two by two from a random number greater than 100. The cognitive task was completed continuously throughout each 30 s physical performance. The order of simple and dual-task was randomized in the test and retest. In the same sense, in order to avoid a learning effect, the evaluations were repeated after seven days [35].

2.3. 30 s Arm Curl Test

The 30 s arm curl test was performed according to the recommendations of Boneth Collantes et al. [36]. Participants sat in a chair with a straight back supported by a backrest, with the trunk perpendicular to the floor and the feet placed fully on the floor. A weight of 2.5 kg was given to the participants. They held the weight in the dominant hand with the wrist in a neutral position and the elbow in extension. To complete the exercise, the participant was asked to flex the elbow and then return to full extension with the wrist in a neutral position. This cycle was repeated as many times as possible in 30 s. Before starting the test, a member of the study staff demonstrated the execution and allowed it to be practiced twice by the participant, to ensure it was correctly performed and to serve as a familiarization for the test. The test began to the command of "ready, go". The number of flexions and extensions of the elbow joint that were performed in 30 s were recorded so long as the participant performed a correct movement.

2.4. 30 s Chair Stand Test

The 30 s chair stand test was performed according to the recommendations of Boneth Collantes et al. [36]. Participants started by sitting in a chair with their arms crossed and fixed at chest level, placing their hands on their shoulders. They stood up from the sitting position to full knee extension, and then returned to the initial position until the back was supported by the backrest. This cycle was repeated as many times as possible in 30 s. The time and the repetitions were measured by using the free software Chrono-jump (Chronojump-BoscoSystem, Barcelona, Spain) with the open hardware Chronopic [37]. Before starting the test, a member of the study staff demonstrated the execution and allowed it to be practiced twice by the participant to ensure it was correctly performed and to serve as familiarization for the test. The test began to the command of "ready, go". The number of times that the participant sat in the chair in a period of 30 s was recorded, so long as the participant performed a correct movement.

2.5. Statistical Analysis

The SPSS statistical package (version 24.0; IBM Corp., Armonk, NY, USA) was employed. Parametric and non-parametric tests were conducted based on the results obtained in the Shapiro–Wilk test. The differences between test and retest were evaluated using the independent *t*-test or Wilcoxon signed-rank test when appropriate.

Reliability was estimated and their 95% confidence intervals are reported using recommendations by Weir [38]. The intraclass correlation coefficient (ICC) two-way random effects, consistency, and single measurement [39] were chosen. In the same way, recommendations by Koo et al. [39] were used for the interpretation of the ICC estimates and their 95% confidence intervals. Therefore, the 95% confidence intervals of the ICC estimates should be used to interpret the level of reliability. Values lower than 0.5 indicate poor reliability, values between 0.5 and 0.75 indicate moderate reliability, values between 0.75 and 0.9 indicate good reliability, and values greater than 0.9 indicate excellent reliability. Absolute reliability was established by calculating the standard error of measurement (SEM) following this formula:

$$SEM = SD\ \sqrt{1 - ICC}, \tag{1}$$

where *SD* is the mean standard deviation of the two repetitions (test–retest). The smallest real difference (SRD) was calculated according to the formula:

$$SRD = 1.96 \times SEM \times \sqrt{2}. \tag{2}$$

Both SEM and SRD were expressed in percentages in order to facilitate comparison with previous and future studies.

Total performance (TP) was calculated taking into account the physical performance (number of repetitions) and the cognitive performance (number of successes and errors in the cognitive test) through the formula:

$$TP = \text{number of repetitions test} + (\text{number of successes} - \text{number of errors}). \tag{3}$$

3. Results

Table 1 shows the main characteristics of the participants. The mean age was 54.76 (8.64) years, with a BMI of 28.30 (3.43) and a FIQ score of 53.61 (19.88).

Table 2 shows the reliability parameters obtained for each of the tests performed. Following the recommendations of Koo et al. [39], the lower and upper bound of the 95% confidence interval of the ICC estimate was used to interpret the level of reliability. Therefore, a moderate to excellent reliability index (95% CI: 0.726 to 0.921) was observed for the number of repetitions in the 30 s chair stand test during the single-task conditions. A low to good reliability index (95% CI: 0.399 to 0.799) was observed for the number of repetitions in the 30 s chair stand test during the dual-task conditions. A low to moderate reliability index (95% CI: 0.151 to 0.678) was observed for the variable total performance (TP) in the 30 s chair stand test during the dual-task conditions. Furthermore, a moderate to excellent reliability index (95% CI: 0.718 to 0.918) was observed for the number of repetitions in the 30 s arm curl test during the single-task conditions. A good to moderate reliability index (95% CI: 0.650 to 0.895) was observed for the number of repetitions in the 30 s arm curl test during the dual-task conditions. Finally, a good to moderate reliability index (0.564 to 0.867) was observed for the variable TP in the 30 s arm curl test during the dual-task conditions.

Table 2. Reliability of the 30 s chair stand test and arm curl test under single and dual-task conditions (n = 37).

Variable		Test	Retest	p-Value	Distribution Value	ICC (95% CI)	SEM	%SEM	SRD	%SRD
30 s Chair Stand Test	M (SD)	11.14 (2.65)	11.73 (2.36)	0.011	0.060	0.85 (0.726–0.921)	0.97	8.48	2.69	23.52
	Md (IQR)	11.00 (3)	12.00 (3)							
30 s Chair Stand dual Test	M (SD)	9.97 (2.45)	10.54 (2.28)	0.072	0.117	0.64 (0.399–0.799)	1.42	13.82	3.93	38.30
	Md (IQR)	10.00 (4)	10.00 (3)							
TP 30 s Chair Stand Test	M (SD)	22.70 (7.84)	23.16 (7.97)	0.776	0.782	0.62 (0.151–0.678)	4.85	21.14	13.44	58.60
	Md (IQR)	24.00 (12.00)	23.00 (11.50)							
30 s Arm Curl Test	M (SD)	16.64 (4.41)	16.24 (4.71)	0.471	0.005	0.85 (0.718–0.918)	1.79	10.88	4.96	30.17
	Md (IQR)	16.00 (6)	16.00 (5)							
30 s Arm Curl Dual Test	M (SD)	14.35 (4.34)	14.59 (4.03)	0.618	0.312	0.81 (0.650–0.895)	1.85	12.77	5.12	35.40
	Md (IQR)	14.00 (5)	14.00 (5)							
TP 30 s Arm Curl Test	M (SD)	28.31 (9.60)	29.95 (7.76)	0.070	0.024	0.86 (0.564–0.867)	3.26	11.19	9.03	31.01
	Md (IQR)	28.00 (10.25)	30.00 (8.50)							

M: mean; SD: standard deviation; Md: median; IQR: interquartile range; ICC: intraclass correlation coefficient; SEM: standard error of measurement; SRD: smallest real difference; TP: total performance. Paired t-test or Wilcoxon tests were conducted depending on the distribution (variables with a p-value lower than 0.05 in the Shapiro–Wilk test were considered for a non-parametric analysis).

4. Discussion

The main objective of this study was to establish the test–retest reliability in the 30 s arm curl and 30 s chair stand tests during dual-task conditions. Results indicate that both tests can be considered reliable, as can the total performance (TP) variable calculated for both tests. However, it is necessary to take into account the ICC fluctuation range. This is the first study to analyze the test–retest reliability of the 30 s arm curl and 30 s chair stand tests under dual-task conditions in women with fibromyalgia (FM). The results confirm the idea of applying dual-task conditions as a reliable and ecological tool to approach physical fitness evaluation in real-life conditions.

Regarding absolute reliability, the SEM results can be considered high in the dual-task conditions. There was an 86.18% probability (with a 95% CI) that a repeated measure in the 30 s chair stand dual test differed 1.42 repetitions from the initial score. In the same way, there was an 87.23% probability that a repeated measure in the 30 s arm curl test differed 1.85 repetitions from the initial score.

The results obtained in the SRD indicate that improvements in the dual-task conditions higher than 3.93 in the 30 s chair stand test and 5.12 in the 30 s arm curl test would indicate a change in the measure that is not due to the error of the measure or the variability of the subject [40,41]. This is pertinent to helping healthcare professionals and researchers identify relevant functional changes in women with FM.

In order to quantify the TP of the tests, a specific variable, "total performance" was developed. This variable combines the number of successes, errors, and repetitions performed by the participants in the time test. Our method gives the same importance to the motor and cognitive parts since these components are crucial in activities of daily living and could provide us with relevant information when evaluating women with FM. Several studies have quantified the physical performance in these tests and this population [27,29]. Other studies have also measured test–retest reliability, but only in simple-task conditions [35,37]. Although previous research created a variable that included both physical and cognitive performance, the reliability of this method was not evaluated [42]. In this regard, this is the first study that demonstrates a low to moderate reliability in the 30 s chair stand test and a good to moderate reliability in the 30 s arm curl test, under dual-task conditions, in a variable that includes both physical and cognitive performance. Therefore, future studies that assess physical fitness under the dual-task paradigm can use this method to evaluate the total performance.

Previous studies have analyzed the impact of pain on the performance of activities of daily living in chronic pain populations such as rheumatoid arthritis [43] and FM [44]. Similarly, increases in pain and fatigue have been observed after dual-task conditions in patients with FM versus healthy subjects [45], concluding that pain can exert some negative influence on the development of activities of daily living. In this way, we can observe the impact that pain can have in patients with FM and the "conflict of objectives" [46] that can be generated in their daily life (e.g. to avoid personal pain or to meet with friends). In this regard, previous studies confirmed that pain is able to affect brain areas involved in attention processes, cognitive processing, memory and nociception [47,48], which could reduce the performance of activities of daily living. A previous study evaluated the relationship between fear of pain and physical performance under dual-task conditions [49]. The authors showed that baseline pain determines the level of physical activity that the person was willing to perform regardless of the pain that was generated in the test or the instructions given to reduce the pain. In this sense, our research did not specifically record the degree of pain that participants felt during the physical fitness tests, as in the study by Gier et al. [49]. However, future research is needed to clarify the effects of pain on dual-tasks and how pain can modulate the physical or cognitive performance of patients with FM, since it is a common feature in their daily life.

Given that activities of daily living simultaneously involve the performance of physical and cognitive tasks, the clinical relevance of the current study is due to the potential advantages of dual-task assessment by health professionals and researchers. This study also reports the number of repetitions that should be considered as a real change when these physical tests are performed along with the cognitive task, and can serve as reference values for the interpretation of results in future research. In the same way, the variable created to know the physical and cognitive performance of the participants can be used in both FM and other populations.

The present study has some limitations. First, the relatively small sample size that was only composed of women, means that the findings cannot be generalized to men. Secondly, data from cognitive tasks, under single-task conditions, were not included in the analysis, so the interference caused by the physical test on the cognitive test was not evaluated. The third limitation could be related to the potential learning from the test to the retest, which is a common limitation in test–retest reliability studies. Finally, the sample age ranged between 30 and 75 years old, which could have influenced the physical and cognitive performance.

5. Conclusions

Both the 30 s chair stand test and the 30 s arm curl test under dual-task conditions obtained good levels of test–retest reliability. Therefore, these tests could be considered as reliable tools for the evaluation of strength in women with fibromyalgia. In the same way, the total performance variable presented good levels of reliability. Future research with larger samples is required in order to generalize these results.

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Test–Retest Reliability and Concurrent Validity of the 3 m Backward Walk Test under Single and Dual-Task Conditions in Women with Fibromyalgia

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Abstract: Background: Previous studies have reported good test–retest reliability for the 3 m backward test (3MBWT) in different populations. However, reliability of the 3MBWT has not been studied in fibromyalgia (FM) under single and dual-task conditions; Methods: A total of 21 women with FM participated in this study. Participants completed the Revised Fibromyalgia Impact Questionnaire and two physical fitness tests: the 3MBWT and the Timed Up and Go (TUG). The dual-task condition consisted of subtracting two by two while performing the test, starting from a random number less than 100; Results: Values showed that the 3MBWT can be considered reliable under single and dual-task conditions when measured with both a manual stopwatch and a Chronopic automatic stopwatch. A strong concurrent validity was shown of 3MBWT and TUG results in the test and retest and the different devices. The relationship between the performance of the 3MBWT in test and retest conditions under single and dual-task conditions measured with different devices and the impact of the disease were high; Conclusions: The 3MBWT is a reliable tool under the single and dual-task conditions in women with FM. It shows higher reliability values when time is taken using a Chronopic. This test also shows high concurrent validity with the TUG test. Its performance is related to the impact of the disease.

Keywords: reproducibility; assessment; chronic pain; activities of daily living; mobility

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1. Introduction

Fibromyalgia (FM) is a chronic disease that is characterized by chronic widespread, diffuse, and persistent musculoskeletal pain, often accompanied by other symptoms, such as fatigue, sleep disorders, mood disturbance, anxiety, depression, cognitive problems, low physical activity, and balance problems [1–3]. All these symptoms have an important influence on the activities of daily living [4] and tend to reduce the health-related quality of life in this population [5]. It is estimated that FM affects 0.2% to 6.6% of the general population and mainly women over 50 years old [6].

One of the ten most debilitating symptoms of FM is balance impairments, which is experienced by 45% of this population [7]. Moreover, people with FM usually report nonspecific postural balance disorder, an increased prevalence of falls [8], a reduced performance in mobility [9–11], a higher risk of falling [12–14], and, therefore, a lower performance on balance tests [12,14]. In addition, gait disturbances [15] that are influenced by attention and executive function [16] have been also detected.

One of the most important objectives that a rehabilitation or training program should follow is to increase the individual's performance to minimize the risks associated with the condition. Therefore, previous studies have evaluated the physical fitness of people with FM using different tests to assess flexibility [17], endurance [10], strength [10,17–19], balance [9], or mobility [11,17]. Among the physical fitness tests used to assess functional mobility, the Timed Up and Go test (TUG) has been used in different populations [20,21], including FM [9,11,17]. This test involves walking forward, balance, and turning tasks. Nevertheless, walking backward, which is not contemplated in the TUG test, is more complex and requires higher neuromuscular and proprioceptive control [22]. Moreover, it is a task that can occur in everyday life situations, such as opening a door, avoiding an obstacle, or backing up to a chair [23]. Additionally, walking backward is considered a more sensitive measure for assessing mobility and balance deficits [24,25]. In this regard, Carter et al. [23] proposed the 3 m walking backward test (3MBWT). This is a clinical tool developed in healthy older adults to identify the risk of falling that appears to be more accurate or equal to other existing tests such as TUG, Five Times Sit-to-Stand, and Four Square Step Test. Regarding the 3MBWT, it has shown high test–retest reliability and validity in the stroke population [26], community-dwelling older adults [27], multiple sclerosis [28,29], and patients with advanced knee osteoarthritis [30]. However, this test has yet to be studied in people with FM. Interestingly, it could become an important clinical tool due to the characteristics of this population since it is essential to perform a functional assessment of mobility and balance to aid in diagnosing and managing the disease.

Due to the similarities to real-life conditions and activities of daily living requirements [31], previous studies have included a simultaneous cognitive task (dual-task paradigm). Therefore, assessing these activities is essential in clinical and ecological settings since they require significant attention and executive processes [31]. In this regard, people with FM have exhibited a considerable impairment in dual-task performance compared to healthy controls [32–34]. Furthermore, the reliability of the chair stand test [18], 10-m walking test [11], TUG [11], and arm curl test [18] under dual-task conditions have been explored for people with FM. Nevertheless, the reliability of walking backward while performing a cognitive task has yet to be assessed. This issue is crucial since healthcare professionals and researchers can better understand an individual's symptoms and develop a more effective treatment plan to address their specific needs.

To our knowledge, previous investigations have not explored the reliability and validity of the 3MBWT in people with FM. Therefore, this study aimed to analyze the test–retest reliability of the 3MBWT under single and dual-task conditions. As a secondary objective, we also aimed to evaluate the test–rest reliability using different instruments (stopwatch and Chronopic). Lastly, we also aimed to assess the concurrent validity of the TUG and 3MBWT as well as the relationship between the 3MBWT test and the impact of the disease. We hypothesized that good test–retest reliability values would be obtained with both Chronopic and stopwatch, with higher scores when using a Chronopic, as previous studies suggested [9,11]. Additionally, a high concurrent validity between the 3MBWT and TUG test would be obtained considering the results reported in previous research [26–29], and a significant correlation between the 3MBWT and the impact of the disease would be observed.

2. Materials and Methods

2.1. Participants

Twenty-one women with FM were enrolled in this cross-sectional study. The sample size and statistical power were calculated using the PASS software (version 11.0; PASS; Kaysville, Utah). In this regard, with two samples per participant, there is a 98% power to detect an intra-class correlation of 0.95 under the alternative hypothesis when the intraclass correlation under the null hypothesis is 0.75, using an F-test with a significance level of 0.05.

The participants fulfilled the following inclusion criteria for this study: (a) to be a female between 35 and 65 years old, (b) to be diagnosed with FM by a rheumatologist according to the criteria established by the American College of Rheumatology [35], and (c) to understand the physical fitness protocols. Participants were excluded if they: (a) were pregnant, (b) were enrolled in another clinical trial or research that could impact the results, and (c) had any condition where exercise is contraindicated.

All the participants gave written informed consent. The Research Ethics Committee of the University of Extremadura approved the protocols of the current study (approval reference: 51/2021).

2.2. Procedure

The Spanish version of the Revised Fibromyalgia Impact Questionnaire (FIQR) was administered [36]. This instrument is composed of 21 items divided into three domains (function, overall impact, and symptoms). The maximum score is 100, which corresponds to the worst overall impact. In addition, age and anthropometric measurements were acquired using a Tanita Body Composition Analyzer BC-418 MA (Tanita Corp., Tokyo, Japan).

The 3MBWT and (2) the TUG were performed under single and dual-task conditions. The dual-task condition consisted of subtracting two by two (a random number lower than 100) while performing the physical fitness tests.

The 3 m Backward Walk Test (3MBWT) was performed according to the procedure proposed by Carter et al. [23]. A distance of three meters was measured with black tape establishing the start and finish. Participants were asked to place their heels on the start mark. Then, they had to walk backward as fast and safely as possible at the "go" signal. Running was not allowed, and they could look behind themselves if they wished.

In the Timed Up and Go (TUG) test, participants had to get up from a chair without armrests, walk a distance of 3 m without running, turn around a cone, walk back to the chair, and sit down [37].

Simultaneous stopwatch and automatic timer records were obtained. For the TUG, the Chronopic (Chronojump, BoscoSystem®, Barcelona, Spain) time was obtained using a DIN A4-sized contact platform placed on the back of the chair, which was used to open and close the circuit to obtain the test time [9,11]. For the 3MBWT a DIN A2-sized contact platform on the start line combined with a photocell on the end line was used. Physical tests were repeated after seven days to avoid learning effect [11,18,38,39]. Participants performed three trials for each condition (single and dual-task), and the order of TUG test and 3MBWT was randomized.

2.3. Statistical Analysis

Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS, version 24.0; IBM Corp., Armonk, NY, USA) software. Based on data provided by the Shapiro–Wilk test, parametric tests were employed. The statistical significance was established at the $p \leq 0.05$ level. To estimate the intraclass correlation coefficient (ICC) and its 95% confidence intervals of the 3MBWT in the single and dual-task conditions at test and retest times, the 3,1 (Two-way mixed effects, consistency, single rater/measurement) model was used following the recommendations by Weir [40] and Koo [41]. Regarding the ICC classification, an ICC value lower than 0.50 indicates "poor" reliability, an ICC value between 0.50 and 0.75 indicates "moderate" reliability, an ICC value between 0.75 and 0.90 indicates "good" reliability, and an ICC value higher than 0.90 indicates "excellent" reliability. This ICC classification was interpreted according to the guideline proposed by Koo [41].

The standard error of measurement (SEM) was calculated using the following formula:

$$\text{SEM} = \text{SD} \times \sqrt{1 - \text{ICC}} \quad (1)$$

The minimal detectable change (MDC) was obtained according to the formula:

$$\text{MDC} = 1.96 \times \text{SEM} \times \sqrt{2} \quad (2)$$

The SEM and MDC were expressed as a percentage according to the following formula, SEM% or MCD% $=$ (SEM or MCD/mean) $\times$ 100, where the mean is the average of the test and retest.

To identify the level of agreement between the test and retest, and the measuring devices in the 3MBWT under single and dual-task conditions, Bland–Altman plots were performed [42].

The Pearson's product–moment correlation coefficient (r) was used to explore the concurrent validity comparing the 3MBWT and the TUG. Finally, the relationship between 3MBWT and the impact of the disease was also analyzed through the total value of the FIQR. Cohen's recommendations [43] were followed to interpret the correlation coefficient. A score $\geq$ 0.5 was strong, moderate if the score was between 0.5 and 0.35, and poor if the score was $\leq$0.35.

3. Results

A total of 21 women with FM from a local association participated in this study. The main characteristics of the participants are shown in Table 1.

Table 1. Descriptive characteristics of the participants.

Variables (N = 21)	Mean (SD)
Age (years)	52.48 (5.99)
Height (cm)	160.10 (0.07)
Weight (kg)	73.50 (14.37)
BMI (kg/m^2)	28.67 (5.53)
FIQR	59.68 (22.07)
FIQR-Function	16.06 (7.74)
FIQR-Overall impact	10.71 (6.90)
FIQR-Symptoms	32.90 (9.77)
Falls in the last six months (number)	0.95 (1.20)

Abbreviations: N, sample; SD, standard deviation; BMI, body mass index, FIQR, Fibromyalgia Impact Questionnaire Revised.

Table 2 shows the relative reliability (ICC) and absolute reliability (SEM and MDC) of the performance obtained in the 3MBWT, under the single and dual-task conditions in both test and retest with the different devices. Following the recommendations by Koo et al. [41], the 95% confidence intervals of the ICC were used to interpret the reliability values. Regarding the single condition, "poor" to "good" and "moderate" to "excellent" reliability values were obtained for the stopwatch and Chronopic, respectively. On the other hand, in the dual-task condition, the reliability values for the stopwatch were "moderate" to "excellent" and for the Chronopic were "good" to "excellent".

Table 2. Reliability of the 3MBWT under single and dual-task conditions.

Variables		Test	Retest	ICC (95% CI)	SEM	%SEM	MDC	%MDC
3MBWT (s)	Stopwatch	2.90 (0.87)	2.85 (1.13)	0.71 (0.283–0.882)	0.54	18.73	1.49	51.92
	Chronopic	2.80 (0.88)	2.75 (1.09)	0.85 (0.619–0.937)	0.38	13.75	1.06	38.11
3MBWT DT (s)	Stopwatch	3.21 (0.95)	2.81 (1.10)	0.89 (0.718–0.954)	0.34	11.29	0.94	31.31
	Chronopic	3.06 (1.03)	2.90 (1.03)	0.93 (0.817–0.970)	0.27	9.14	0.76	25.35

Abbreviations: 3MBWT, 3 m backward test; s, seconds; SD, standard deviation; ICC, intraclass correlation coefficient; CI, confidence interval; SEM, standard error of measurement; MDC, minimal detectable change; DT, dual-task.

Reliability values obtained by comparing the different devices in both the single and dual-task conditions in the test and retest are shown in Table 3. Taking into account the 95% confidence intervals of the ICC, a reliability value of "good" to "excellent" was obtained for the test, and an "excellent" value was obtained for the retest in the single and dual-task condition.

Table 3. Reliability of the 3MBWT under single and dual-task conditions using stopwatch and Chronopic in the test and retest.

Variables		Stopwatch Mean (SD)	Chronopic Mean (SD)	ICC (95% CI)
3MBWT (s)	Test	2.90 (0.87)	2.80 (0.88)	0.92 (0.811–0.969)
	Retest	2.85 (1.13)	2.75 (1.09)	0.974 (0.937–0.990)
3MBWT DT (s)	Test	3.21 (0.95)	3.06 (1.03)	0.91 (0.779–0.964)
	Retest	2.81 (1.10)	2.90 (1.03)	0.974 (0.937–0.990)

Abbreviations: 3MBWT, 3 m backward test; s, seconds; SD, standard deviation; ICC, intraclass correlation coefficient; CI, confidence interval; DT, dual-task.

Figure 1 shows the Bland–Altman plots of the times obtained by stopwatch and Chronopic in test and retest in the single and dual-task conditions, and the times obtained between the two devices in both the single and dual-task conditions in the test and retest, respectively.

Table 4 shows the concurrent validity analysis results of 3MBWT and TUG test. All correlation values obtained were classified as strong [43] in the test and retest and the different devices.

Table 4. Concurrent validity between 3MBWT and TUG under single and dual-task conditions, in test and retests, with stopwatch and Chronopic.

		Stopwatch	
		Test Condition	Retest Condition
	Variables	TUG	TUG
Single	3MBWT	0.735 ***	0.831 ***
Dual	3MBWT	0.679 ***	0.875 ***
		Chronopic	
		Test Condition	Retest Condition
	Variables	TUG	TUG
Single	3MBWT	0.834 ***	0.794 ***
Dual	3MBWT	0.845 ***	0.906 ***

Abbreviations: 3MBWT, 3-m backward test; TUG, timed up and go. *** *p*-value < 0.001.

Finally, the relationship between the performance of the 3MBWT in test and retest conditions under single and dual-task conditions measured with different devices and the impact of the disease were strong, excepting the 3MBWT in test condition under single condition measured with a stopwatch (r: 0.488), which was moderate. In analyzing the dimensions that make up the FIQR questionnaire, strong correlations were obtained between the "symptoms" dimension and all the conditions and devices. Similarly, strong correlations were also obtained between the dimension "overall impact" except for the single and dual-task conditions in the test period, measured with the stopwatch and the Chronopic, respectively, where moderate correlations were reported. As for the dimension "function," only moderate correlations were found in the single condition in the retest and test periods, measured with a stopwatch and Chronopic, respectively. Results are shown in Table 5.

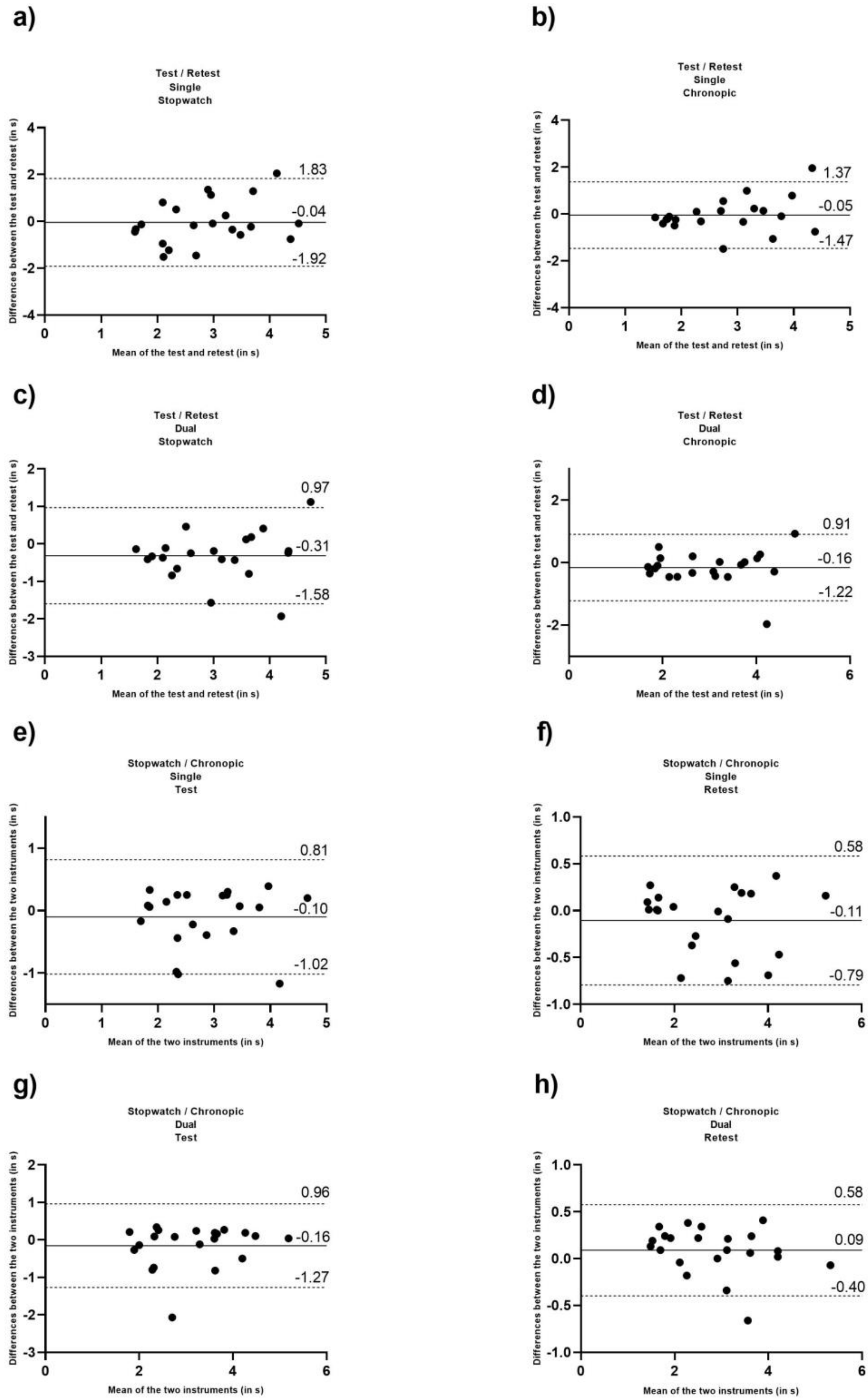

Figure 1. (**a**) differences between test and retest vs. the mean of the two measurements under the single condition using a stopwatch; (**b**) differences between test and retest vs. the mean of the two measurements

under the single condition using a Chronopic; (**c**) differences between test and retest vs. the mean of the two measurements under the dual-task condition using a stopwatch; and (**d**) differences between test and retest vs. the mean of the two measurements under the dual-task condition using a Chronopic; (**e**) differences between stopwatch and Chronopic vs. the mean of the two measurements under the single condition in test; (**f**) differences between stopwatch and Chronopic vs. the mean of the two measurements under the single condition in retest; (**g**) differences between stopwatch and Chronopic vs. the mean of the two measurements under the dual-task condition in test; and (**h**) differences between stopwatch and Chronopic vs. the mean of the two measurements under the dual-task condition in retest.

Table 5. Correlation between 3MBWT and FIQR under single and dual-task conditions, in test and retest, with stopwatch and Chronopic.

	Stopwatch Variables	FIQR	FIQR-Function	FIQR-Overall impact	FIQR-Symptoms
Single	3MBWT (test)	0.488 *	0.273	0.488 *	0.543 *
	3MBWT (retest)	0.659 ***	0.461 *	0.652 **	0.663 ***
Dual	3MBWT (test)	0.527 *	0.396	0.513 *	0.514 *
	3MBWT (retest)	0.614 ***	0.389	0.630 **	0.634 **
	Chronopic Variables	FIQR	FIQR-Function	FIQR-Overall impact	FIQR-Symptoms
Single	3MBWT (test)	0.654 ***	0.448 *	0.558 **	0.729 ***
	3MBWT (retest)	0.577 ***	0.325	0.624 **	0.604 **
Dual	3MBWT (test)	0.532 *	0.356	0.444 *	0.607 **
	3MBWT (retest)	0.636 ***	0.394	0.631 **	0.679 ***

Abbreviations: 3MBWT, 3-m backward test; FIQR, fibromyalgia impact questionnaire revised. * p-value < 0.05; ** p-value < 0.01; *** p-value < 0.001.

Figure 1 Bland–Altman plots of the times obtained by stopwatch and Chronopic in test and retest under the single and dual-task conditions and Bland–Altman plots of the times obtained between the two devices under the single and dual-task conditions in the test and retest.

4. Discussion

This study aimed to investigate the test–retest reliability and concurrent validity of the 3MBWT in women with FM under single and dual-task conditions. We also aimed to investigate the agreement between a manual stopwatch and a Chronopic automatic stopwatch. In order to provide clinical and objective directions, the SEM, MDC, and Bland–Altman plots were reported. Generally, good reliability values were obtained for the 3MBWT test when measured with a stopwatch and Chronopic in both single and dual-task conditions. Similarly, the 3MBWT and the TUG achieved good concurrent validity. Lastly, performance between 3MBWT and the impact of the disease were analyzed, and consistent relationships were found between both.

In the present study, walking backward has been analyzed because it is a complex task that requires high neuromuscular and proprioceptive control [22]. Walking backward usually occurs in activities of daily living, such as opening a door, avoiding an obstacle, or backing up to a chair [23]. Therefore, it is a sensitive measure for assessing mobility and balance deficits [24,25]. In people with FM, performing a functional assessment of mobility and balance is essential to manage the disease. However, one of the main tests used to evaluate these characteristics in this population is the TUG [9,11,17]. However, this test does not include backward gait. In this sense, we consider it relevant to analyze the psychometric properties of the 3MBWT in people with FM since previous studies have focused on other populations obtaining good reliability and validity values [26–29]. Therefore, the 3MBWT is a tool that can be used elsewhere in the clinical and research context. Moreover, due to the fact that more than one task is performed at the same time in activities of daily living, and the impairment in dual-task ability detected on people with FM [32,44,45], we decided to incorporate the dual-task paradigm in this cross-sectional study.

Results showed that the 3MBWT could be considered reliable under single and dual-task conditions when measured with both a stopwatch and a Chronopic. However, it is necessary to consider the ICC fluctuation range [41]. Nevertheless, the data presented in the Bland–Altman plots (Figure 1) showed that most of the 3MBWT values were close to the mean of the test–retest differences in both single and dual-task conditions, having a bias close to zero and a reduced variability seeing the limits of agreement. Therefore, there is a high level of agreement between the test–retest measures evaluated in the 3MBWT since the values obtained provide consistent results. The reported ICC in the single condition with a stopwatch (0.71, 95% CI 0.283–0.882) is lower than those reported in previous studies that investigated test–retest reliability in stroke [26] (0.985, 95% CI 0.973–0.992), community-dwelling older adults [27] (0.940, 95% CI 0.90–0.96), and primary total knee arthroplasty [46] (0.942).

Our findings might be due to the symptomatology of FM [47], characterized by widespread pain and fatigue, which can fluctuate in intensity and severity over time [48,49]. For this reason, a person's symptoms and level of functioning can vary daily and affect the physical fitness performance. In this regard, previous studies highlighted what can affect performance in physical fitness tests [50,51]. The same rationale can also affect cognitive function [52], including attention, memory, and information processing. These factors may have contributed to the variability of results between the test and retest. Nevertheless, the ICC values obtained in the present study are acceptable, so the test analyzed seems to be stable enough to be used in the characterization of people with FM.

The optimal time interval between tests may vary depending on the construct being measured, the stability of the construct over time, and the target population [53]. For this study, a seven-day period was selected, the same as previous studies conducted in people with FM [11,18,38,39], to minimize the impact of potential confounding variables, such as recovery or learning effects [54]. However, other studies have used shorter test–retest times to assess test–retest reliability on the 3MBWT [26–29]. In addition, the tests (TUG and 3MBWT), as well as the conditions (single and dual-task), were randomized to ensure that the order of administration may not bias the results. In this way, obtaining more accurate and reliable results is possible by eliminating biases and reducing the influence of external factors that may affect the results.

As expected, the ICC values were slightly higher when using Chronopic versus stopwatch, since the use of a manual stopwatch adds human variability to the measurement by the evaluator [9,55]. Therefore, using an automatic timer can be a cost-effective alternative to assess performance in the 3MBWT in both single and dual conditions. However, although the ICC values obtained by the stopwatch are slightly lower than those obtained by the Chronopic, our data suggest that the use of a manual stopwatch could be also very useful for this test, since it yields relatively good reliability values in both single (0.71, 95% CI 0.283–0.882) and dual-task conditions (0.89, 95% CI 0.718–0.954) (see Table 2). Similarly, the lower ICC obtained in the single and dual-task conditions in the test performance was probably due to human error experienced when using a manual stopwatch. This may be suggested since the scores between the stopwatch and the Chronopic differed slightly, unlike the values obtained in the new test. Nevertheless, the ICC values obtained are classified as good to excellent (see Table 3).

Our study also provided the SEM and MDC values of the 3MBWT under all conditions and devices. These values are important for interpreting the results of the 3MBWT, because they can help clinicians and researchers to determine if there are meaningful changes in the performance of this test. Furthermore, the estimate of random variation in the data (SEM) and the minimum detectable change (MDC) are both lower when the Chronopic is used. Previous research has also observed this trend assessing test–retest reliability under the single condition in TUG and 30 s chair stand test [9,55]. Bland–Altman plots were also reported for a more comprehensive analysis of the results, showing bias and limits of agreement.

In our study, the TUG test was used to test the validity of the 3MBWT since it is a tool frequently used in clinical practice [56,57], showing high reliability in FM in both single [9] and dual-task conditions [11]. Although the TUG test does not contemplate walking backward, as previous studies did [26–29], in the present study we have used the TUG test to conduct the concurrent validity. Moreover, this test has obtained the highest relationship values in most cases [26,27,29]. Significant correlations between 3MBWT and TUG tests were obtained, which can be considered relevant since the TUG test comprises movements that can occur in activities of daily living, including walking, turning, and sitting [37]. In addition, correlation analyses showed a strong correlation in the single condition between the 3MBWT and TUG test measured with a stopwatch, as in previous studies in stroke [26], community-dwelling older adults [27], and adults [23]. In our study, the correlation in single conditions between 3MBWT and TUG measured through the automatic timer also showed strong correlation values. Similarly, the correlation in the dual-task conditions also obtained strong values in the test and retest measured by a stopwatch and a Chronopic.

Our results also found a positive correlation between the 3MBWT performance and the impact of FM obtained through the FIQR questionnaire. Strong to moderate correlations were found between FIQR total score and the performance obtained in single and dual-task conditions using manual stopwatch and Chronopic. Additionally, correlations between FIQR dimensions and 3MBWT have been reported. In this line, the strongest correlations were found in the symptoms dimension, followed by overall impact, where moderate correlations were also found. However, function dimension did not show significant correlation with 3MBWT performance in most cases. These findings could indicate that performance on the 3MBWT does not correlate well with the actions included in the function dimension by including activities that are not highly associated with walking backward (i.e., combing hair, preparing food, shopping) but do correlate with symptomatology and overall impact. Nevertheless, future studies should corroborate this hypothesis.

Previous studies have highlighted the importance of assessing backward gait in older adults [24,25], showing a reduction in performance in different parameters when comparing to young and middle-aged adults. In this regard, during backward gait, greater neuromuscular and proprioceptive control is required, in addition to faster and more frequent balance corrections due to the elimination of visual feedback [22,58]. Additionally, it has been shown that walking backward shows greater or equal sensibility than walking forward, and it is strongly related to the risk of falling [23]. In this sense, assessing backward gait, via the 3MBWT, in FM may be of interest to clinicians to observe changes in mobility and balance due to the balance impairment manifested in this population [59]. Thus, a previous study [60] conducted a physical exercise intervention based on walking backward in community-dwelling older adults. Given these reasons and the strong relationships between the impact of the disease and the performance obtained in the 3MBWT, this test can be used as a useful tool in FM populations to assess exercise-based interventions.

The present study has some limitations. In this regard, the relatively small sample size did not allow us to generalize results to all women with FM. Moreover, only women were included in this cross-sectional study. Thus, results cannot be extrapolated to men with this disease. Therefore, it would be interesting to extend the sample with different age ranges, which allow us to establish cut-off points.

5. Conclusions

The results obtained from this study show that the 3MBWT is a reliable tool under the single and dual-task conditions in women with FM. It shows higher reliability values when time is taken using a Chronopic. This test also shows high concurrent validity with the TUG test, and its performance is related to the impact of the disease. These results may help clinicians and researchers in the assessment of balance and functional mobility and to interpret the effect of interventions in this population.

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Relationship between pineal gland, sleep and melatonin in fibromyalgia women: a magnetic resonance imaging study

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Abstract

A total of 80% of fibromyalgia (FM) population have reported poor sleep. In this regard, the pineal gland, involved in circadian rhythm processes as a key neuroendocrine organ which mainly synthesises and secretes melatonin, has never been studied before in this population. Therefore, this study aimed to evaluate the parenchyma pineal volume and its relation to sleep hours, sleep quality index and melatonin level at night. A total of 50 participants, 30 women with FM and 20 healthy control women underwent cranial magnetic resonance imaging. The total pineal volume, cyst pineal volume and parenchyma pineal volume were manually calculated in cubic millimetres. Also, the total pineal volume was estimated using Hasehawa method. Parenchyma pineal volume was significantly correlated with sleep hours (p-value = 0.041) and nocturnal melatonin level (p-value = 0.027). Moreover, there was also a non-significant correlation between parenchyma pineal volume and sleep quality index (p-value = 0.055). Furthermore, a mean parenchyma pineal volume of 102.00 (41.46) mm^3 was observed, with a prevalence of 29.60% cyst in FM group. This is the first study that has reported pineal gland volumes, cyst prevalence and correlative relationships between parenchyma pineal volume and sleep hours and melatonin levels in women with FM.

Significant outcomes

- Fibromyalgia women showed a correlation between sleep hours and melatonin levels.
- Fibromyalgia and healthy control groups did not show differences in pineal gland volumes.
- Fibromyalgia and healthy control groups show differences in cyst prevalence.

Limitations

- Only the correlation study between melatonin and pineal volume in the fibromyalgia population could be performed.
- The study sample consisted only of women and was relatively small.
- During manual segmentation, adjacent structures can be included, which may affect pineal volume.
- Some drugs used and comorbidities associated with FM can alter the production and secretion of melatonin.
- This study did not consider the influence of the menstrual cycle on melatonin variation.

Introduction

Fibromyalgia (FM) is a chronic disease, which affects between 2.9% and 4.7% of the European population (Branco et al., 2010), most of them being women (Walitt et al., 2015). FM is characterised by widespread musculoskeletal pain associated with different symptoms, such as sleeping problems, fatigue, depression, anxiety, stiffness and poor physical fitness (Wolfe et al., 2010). All these symptoms have a significant impact on both the ability to perform activities of daily living (Huijnen et al., 2015) and the quality of life of women with FM (Mas et al., 2008). Sleeping problems have become one of the most important associated symptoms. In this regard, FM patients experience sleep disorder (Wolfe et al., 1990) and sleep disturbances (Wu et al., 2017), and almost 80% of FM population have reported poor sleep (Bennett et al., 2007; Jacobson et al., 2015). This is relevant since sleep-related problems are strongly associated with the severity of the symptoms (Choy, 2015).

The pineal gland is a key neuroendocrine organ which mainly synthesises and secretes melatonin (*N*-acetyl-5-methoxytryptamine; Macchi & Bruce, 2004). This relevant hormone is involved in several processes, such as the circadian rhythm (Korf, 1994; Acer et al., 2011), the sleep–wake rhythm (Arendt, 2005; Acer et al., 2011), mood regulation, anxiety, appetite, immune responses, cardiac functions (Comai & Gobbi, 2014) and pain (Danilov & Kurganova, 2016). It acts as a neuroprotector or antioxidant (Alghamdi, 2018). In this regard, reliable non-invasive methods, such as saliva sampling, and urinary metabolite of melatonin sampling have been developed in both research and clinical fields (Benloucif et al., 2008). These methods allow us to evaluate the levels of melatonin production. In this regard, salivary melatonin can be considered as a biomarker of circadian rhythm, thus improving the diagnosis and treatment of circadian rhythm sleep–wake disorders (Keijzer et al., 2014). Regarding melatonin levels of FM patients, controversial results have been found when compared with healthy controls (HCs), thus showing normal (Press et al., 1998; Senel et al., 2013), increased (Korszun et al., 1999) and decreased (Wikner et al., 1998) melatonin levels.

Regarding pineal gland morphology, alterations have been reported in physiological and pathological conditions, including a decrease of the pineal gland in obese people compared to lean people (Grosshans et al., 2016) and a reduced pineal volume in people with primary insomnia (Bumb et al., 2014), Alzheimer's disease (Matsuoka et al., 2017), schizophrenia (Fındıklı et al., 2015) and major depressive disorder (Zhao et al., 2019). Moreover, in healthy individuals, sleep rhythm disturbance correlated with smaller pineal volume (Liebrich et al., 2014).

As previously mentioned, the main function of the pineal gland is the production and secretion of melatonin (Macchi & Bruce, 2004). However, this function is altered by the calcification, a frequent clinical finding that occurs in this small structure and which has been associated with pathological conditions and ageing (Tan et al., 2018). The pineal gland has one of the highest calcification rates among organs and tissues (Yalcin et al., 2016; Tan et al., 2018). Nevertheless, the mechanism that produces calcification is not known with certainty, although several theories have been proposed (Tan et al., 2018).

In the case of Alzheimer's disease, it has also been observed that reduced pineal volume and pineal gland calcifications may contribute to reduce melatonin secretion, sleep problems (Song, 2019) and, therefore, cognitive impairment (Krause et al., 2017).

Another frequent magnetic resonance imaging (MRI) finding is pineal cysts that usually occur between the ages of 21 and 30 years, decreasing, its prevalence, with age (Nolte et al., 2010). It appears that cysts may also have a negative effect on melatonin secretion by compressing the pineal parenchyma (Nölte et al., 2009). In this regard, both calcifications and cysts are considered hormonally inactive tissues and its volume is usually excluded from the total pineal volume. This is based on the results of previous studies (Nölte et al., 2009; Liebrich et al., 2014; Sigurdardottir et al., 2016) which showed that volumetric alterations may affect melatonin activity, mainly related to the pineal parenchymal volume (PPV) which is referred to hormonal active pineal tissue.

Although sleep disorders in FM have been widely studied there is, to the best of our knowledge, no study that evaluates the volume of the pineal gland and its relation to sleep hours and melatonin levels in women with FM. Therefore, this study was aimed to assess the volume of the pineal gland as well as the relation between this gland and levels of melatonin and sleep quality in women with FM. We hypothesised that reduced pineal volumes would be correlated with reduced levels of melatonin and sleep hours.

Subjects and methods

Participants

In this study, a total of 50 participants participated in this study. A total of 30 women with FM were recruited by the Extremadura Association of Fibromyalgia (AFIBROEX) in Cáceres by telephone calls. All participants met the following inclusion criteria: (a) being a 30- to 75 years old woman; (b) have been diagnosed with FM by a rheumatologist according to American College of Rheumatology 2010 criteria (Wolfe et al., 2010) and (c) being able to communicate with the study staff effectively; and (d) have understood and signed an informed consent conform to the updated Declaration of Helsinki. Moreover, participants were excluded if: (a) they were pregnant; (b) they had any cerebral injury and (c) illegible MRI sequences were obtained. In this sense, three participants were excluded due to poor visibility of the pineal gland. Therefore, a total of 27 participants of the FM were included in the present study.

A total of 20 HC participants were selected by the OASIS-3 data set (LaMontagne et al., 2018). The participants met the following inclusion criteria: (a) female and ages between 42 and 60 years, (b) height between 152 and 178 cm, (c) weight between 40 and 120 kg, (d) being cognitively normal and (e) have T1w MRI scan with 3 tesla scanner.

According to the power calculation estimates using the PASS-11 software (version 11; NCSS, LLC, Kaysville, UT, USA), a group sample of 27 and 20 achieve a 100% power to detect a difference of −7.7 at the 0.05 significance level (alpha) using a two-sided Mann–Whitney test after 2000 Monte Carlo simulations.

All participants were verbally informed about the details of the study and gave written informed consent to participate. Participants underwent MRI in January 2018. All procedures were approved by the Research Ethics Committee of the University of Extremadura (approval reference: 62/2017) and were conducted in accordance with the tenets of the updated Declaration of Helsinki.

Image acquisition

The FM MRI scans were performed with a 3.0 tesla (T) system (Achieva 3.0T TX, Philips Medical Systems, Best, Netherlands) with eight channel receiver head coil. MRI data were obtained using 3D T1-weighted Turbo Field Echo (T1-w TFE) sequence (time repetition/time to echo = 11.51/2.8 ms; matrix size= 288×288; flip angle= 10°; slice thickness= 0.9 mm; number of averages = 1). For the HC group, a system equipped with a 16-channel head coil (Siemens TIM Trio or BioGraph mMR PET-MR, Erlangen, Germany) was used. The MP-RAGE protocol of TIM Trio scanner used the following parameters: TR/TE = 2400/3.16 ms, ± 176 axial slices without slice gap and 1.0 mm nominal isotropic resolution (Field-of-view (FOV) = 256×256 mm). The MP-RAGE sequence of BioGraph

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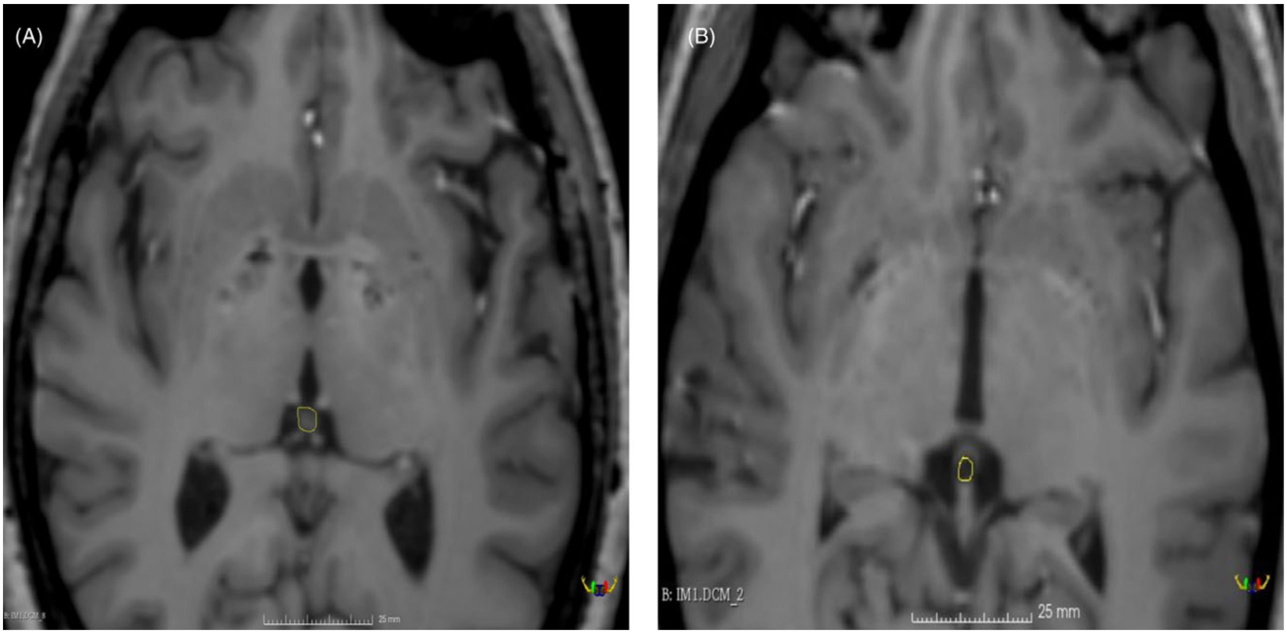

Fig. 1. T1-weighted Turbo Field Echo (T1-w TFE) imaging of pineal region illustrating: (A) solid pineal gland measured manually (hiperintense) and (B) cystic pineal gland measured manually (hipointense).

mMR PET-MR scanner used the following parameters: TR/TE = 2300/2.95 ms, ± 176 axial slices without slice gap and 1.2-mm nominal isotropic resolution (FOV = 256 × 256 mm).

Image processing

The 3D Slicer version 4.11.0 Nightly Build free software, to see at https://www.slicer.org/, was used for processing the imaging data. The 3D mask of each pineal gland was manually drawn by one researcher (J.L.L.-L.), who was blind to the diagnosis and supervised by an experienced neuroradiologist, 10 years in neuroradiology. Anatomical structures, such as the quadrigeminal cisterna posteriorly, the posterior part of the third ventricle anteriorly, the corpus callosum above, the superior colliculus below and pulvinars laterally (Moeller & Reif, 2007), were used as limits to draw the pineal gland. The pineal glands were also classified according to the size of the cyst, following the recommendations by Pu et al. (2007): type 1 (pineal gland with no visible cyst), type 2 (pineal gland with a visible cyst < 2 mm) and type 3 (pineal gland with a visible cyst > 2 mm).

Volumetric measurements of each pineal gland were manually drawn via slice-by-slice segmentation using the 'Draw Effect' tool in the axial plane, with simultaneous side-by-side view of the sagittal and coronal plane. The sum of these areas was added up to determine the volumes of the pineal gland. The total pineal gland area was obtained using 'Segment Statistics' module to determine the real volume (RV) of the pineal gland in cubic millimetres (see Fig. 1). The cyst pineal volume (CPV) was also measured following the same procedure used to measure the RV (see Fig. 1). Additionally, the reference value of the pineal gland volume (TPV) was estimated using the Hasegawa method by the formula $0.5 \times H \times L \times W$ (where W is the maximum width, L is the maximum length and H is the maximum height of the gland; Hasegawa et al., 1987).

PPV was calculated as the subtraction of CPV-RV in the cases where cysts were found. Moreover, when no cyst was observed the PPV was calculated as follows: PPV = RV. Pineal calcifications were not estimated when using T1 sequences, since it does not allow a reliable identification (Adams et al., 2017).

A total of 20 participants, from the whole sample, were randomly selected to determine the reliability of the pineal gland measurements. These participants were measured twice with a time gap of one month.

All T1-weighted images were analysed on a HP 840 eliteBook (Version Windows 10, 8 GB, 2.60 GHz, Intel Core i7).

Fibromyalgia Impact Questionnaire

The revised Spanish version of the Fibromyalgia Impact Questionnaire was used (Salgueiro et al., 2013) to evaluate the impact of FM-related symptoms on daily living skills and general health status. The questionnaire has 21-item, and it is self-administered. The total score was measured from 0 to 100, thus indicating the impact of the disease, 100 being the highest score and meaning the worst state.

Pittsburgh sleep quality index

The Pittsburgh sleep quality index (PSQI) enabled us to assess the sleep quality and disturbances of the participants over 1 month. Seven components, with subscales ranging from 0 to 3, make up the global score, which ranges from 0 to 21: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication and daytime dysfunction (Buysse et al., 1989). Higher scores represent poorer subjective sleep quality. We used the Spanish version of the PSQI, which has been validated for its use in patients with FM. (Hita-Contreras et al., 2014).

Melatonin measurement

Participants' salivary samples were collected in sterile biological liquid collection tubes (Deltalab, Barcelona, Spain) on two consecutive days at home (24 p.m.) in order to measure melatonin levels. All collected samples were directly stored in a refrigerator at −80°C. In order to avoid variability, all samples were analysed in the same batch. Direct

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Table 1. Descriptive characteristics of the participants

Variables	Mean (SD)	Mean (SD)	Value of the contrast	*p*-value
	Demographic characteristics			
	FM	HC		
Sample size	27	20		
Age (years)	53.56 (8.42)	53.45 (4.51)	−0.280	0.779
Years with fibromyalgia n = 24	10.46 (6.10)	N.A		
Height (cm)	159.78 (6.47)	165.30 (6.17)	−2.861	0.004
Weight (kg)	73.12 (16.91)	75.09 (19.00)	−0.409	0.683
BMI (kg/m^2)	28.55 (6.08)	27.47 (6.43)	−0.280	0.780
	Fibromyalgia impact and sleep quality			
FIQ-R total score	56.01 (17.94)	N.A		
Hours of sleep	5.54 (0.97)	N.A		
Pittsburgh sleep quality index n = 21	11.71 (3.28)	N.A		
	Melatonin levels and pineal gland volumes			
Melatonin levels at night (pg/ml) n = 21	14.56 (9.92)	N.A		
Total pineal volume (mm^3)	97.92 (49.75)	91.51 (56.51)	−0.796	0.426
Real volume (mm^3)	108.60 (52.14)	94.28 (37.87)	−0.839	0.401
PPV (mm^3)	102.00 (41.46)	94.28 (37.87)	−0.559	0.576
Cyst pineal volume (mm^3)	22.28 (21.35)	67.00	−1.162	0.245

BMI, body mass index; FIQ-R, fibromyalgia impact questionnaire revised; FM, fibromyalgia; HC, healthy control; PPV, pineal parenchymal volume.

Saliva Melatonin ELISA (Bühlmann, Schönenbuch, Switzerland) was used to measure melatonin concentrations.

Participants were requested to follow their usual sleep habits and to collect the salivary sample with dim lighting (<30 lux). Moreover, they were instructed not to smoke, eat or drink during the 60 min before the collection and to rinse their mouths with water before collecting saliva.

No data were obtained on melatonin and sleep hours in HC since this information was not available in the OASIS-3 data set. In the same way, no data were available on the impact of FM, since it did not apply to this population.

Statistical analysis

The SPSS statistical package (version 24.0 SPSS, Inc., Chicago, IL, USA) was used to analyse the data. The data were analysed with non-parametric methods for the results obtained from the Shapiro–Wilk test. Intraclass correlation coefficient (ICC) two-way random effects, consistency, single measurement was used to explore the reliability of the measures (Weir, 2005).

The Mann–Whitney *U*-test was conducted to examine the differences between groups (FM vs. HCs and FM with and without pineal cyst) for each variable. Furthermore, chi-square test was used to evaluate the prevalence of the existence of cysts between groups as well as to evaluate the impact of the type of cyst on PPV, years with FM, PSQI and sleep hours in people with FM.

Finally, Spearman's correlation coefficient was used for correlation analysis of PPV with sleep hours, melatonin level at night and sleep quality index in FM. Statistical significance was set at $p = 0.05$.

Results

Reliability or the pineal gland measurements

The reliability of the PGV and the RV was high. For the RV, the ICC was 0.97 (95% CI 0.92–0.98), showing 'excellent' reliability. Moreover, the ICC for the PGV was 0.90 (95% CI 0.76–0.96), showing 'moderate to excellent' reliability. The classification by Koo and Li (2016) was used for reliability estimation.

Demographic characteristics of the participants and differences between groups, fibromyalgia impact and sleep quality

Table 1 shows the main characteristics of the participants of both groups. Differences between FM and HC group were only observed in height (p-value < 0.004; see Table 1). FM participants had a mean of 10.46 (6.10) years from FM diagnosis. The fibromyalgia impact questionnaire revised (FIQ-R) indicated that participants had a value of 56.01 (17.94), which corresponds to mild severity symptoms. The mean hours of sleep were 5.54 (0.97) (see Table 1).

Pineal gland volumes and melatonin levels

Table 1 shows the different pineal volumes measured by Hasegawa method (TPV) and manually (RV and PPV). Cyst volume is also reported (see Table 1).

The mean levels of melatonin at night were 14.56 (9.92) pg/ml (see Table 1).

Table 2 shows the differences, within the FM group, between those people in whom a cyst was detected or not. In this regard, people with FM with a pineal cyst showed statistically significant more sleep hours than people with FM without pineal cyst (p-value < 0.028).

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Table 2. Differences between people with fibromyalgia in whom a cyst was detected or not in the pineal parenchymal volume, years with fibromyalgia, Pittsburgh sleep quality index and sleep hours in people with fibromyalgia

Variables	FM without pineal cyst	FM with pineal cyst	Value of the contrast	*p*-Value
PPV (mm^3)	92.14 (31.98)	125.44 (53.51)	−1.168	0.260
Years with FM	12.06 (6.41)	11.86 (3.48)	−1.181	0.070
PSQI	11.65 (3.30)	11.86 (3.48)	−0.224	0.852
Sleep hours	5.26 (0.77)	6.21 (1.11)	−2.221	0.028
Melatonin levels at night (pg/ml)	15.17 (10.60)	13.35 (9.08)	−0.373	0.743

FM, fibromyalgia; PPV, pineal parenchymal volume; PSQI: Pittsburgh sleep quality index.

Table 3. Prevalence and types of cysts found among different groups

Variable	FM n (%)	HC n (%)	χ^2	*p*-Value
Cyst prevalence	8 (29.60)	1 (5.00)	4.502	0.034
Type I cyst	19 (70.38)	19 (95.00)	3.562	0.059
Type II cyst	2 (7.40)	0 (0.00)	1.547	0.214
Type III cyst	6 (22.22)	1 (5.00)	2.689	0.101

FM, fibromyalgia; HC, healthy control; n, number of participants.

Prevalence and types of cyst

In the visualisation MRI sequences, 19 types I cyst (no visible cyst), 2 types II (< 2 mm) cyst and 6 types III (>2 mm) cyst were found in the FM. Therefore, a 29.60% of cyst prevalence was established in the FM group sample evaluated. On the other hand, 19 types I cyst and 1 type III cyst were found in the HC group, showing a 5.00% of cyst prevalence (see Table 3). Differences between FM and HC group were only observed in cyst prevalence (*p*-value = 0.034).

Table 4 shows the impact, within the FM group, of the type of pineal cyst on PPV years with FM, PSQI and sleep hours in people with FM. Significant differences were not found in any of the studied variables (*p*-value > 0.05).

Correlation analyses

Table 5 shows the correlation analyses between pineal gland volumes, sleep hours and melatonin levels in the FM group. A significant correlation was found between PPV and sleep hours (*p*-value = 0.041). Furthermore, a significant correlation was also found between melatonin levels and the PPV (*p*-value = 0.027).

Discussion

The present study was aimed to investigate the pineal volume of women with FM as well as to establish relationships between sleep hours and nocturnal melatonin levels in this population.

To date, no volume reference data have been found in women with this age range analysed by MRI. As a result, the mean PPV was 102.00 with a prevalence of 29.60% cyst between women with FM. Moreover, significant correlations were found between the PPV and both sleep hours and melatonin level at night. In

Table 4. Impact of type of cyst on pineal parenchymal volume, years with fibromyalgia, Pittsburgh sleep quality index and sleep hours in people with fibromyalgia

Type of cyst	N (%)	Years with FM	*p*-Value	PPV	*p*-Value	PSQI	*p*-Value	Sleep hours	*p*-Value	Melatonine	*p*-Value
Type I cyst	19 (70.37%)	12.06 (6.41)	0.636	92.14 (31.98)	0.398	5.26 (0.77)	0.169	11.65 (3.30)	0.230	12165.5 (10595.49)	0.384
Type II cyst (<2 mm)	2 (7.41%)	10 (2.83)		98.14 (31.98)		6.25 (0.35)		10 (2.83)		8602.50 (8481.74)	
Type III cyst (>2 mm)	6 (22.22 %)	6.33 (4.18)		134.54 (56.02)		6.20 (1.35)		12.60 (3.71)		15260 (9480.77)	

FM, fibromyalgia group; PPV, pineal parenchymal volume; PSQI, Pittsburgh sleep quality index.

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Table 5. Relationship between pineal parenchyma volume (PPV) with sleep hours, nocturnal average melatonin level and total score in the PSQI in the FMG

Variable		Sleep hours (n = 24)	Melatonin at night (n = 21)	PSQI (n = 21)
PPV	Correlation coefficient	0.419*	0.481*	−0.396
	p-Value	0.041	0.027	0.055

FM, fibromyalgia; PPV, pineal parenchymal volume; PSQI: Pittsburgh sleep quality index. *p-value lower than 0.05. For correlation analyses, Spearman's correlation coefficient was used.

addition, a non-significant tendency between PPV and the sleep quality index obtained by PSQI was also noticed. Finally, no significant differences were observed in PPV, TPV and RV between the FM and the HC group. Only differences were observed in the prevalence of cysts between the groups. Results from the present study are relevant, since this is the first study that has reported on correlations between variables, such as pineal gland volumes, cyst prevalence and relationships between PPV and sleep hours and melatonin levels in women with FM. In addition, no difference in pineal volume was observed in comparison with healthy women.

Our study showed a significant correlation between the active pineal gland tissue (PPV) and both hours of sleep and melatonin levels. Regarding pineal gland volume and sleep hours, previous studies showed a significant correlation between sleep quality and pineal gland volume in primary insomnia (Bumb et al., 2014), major depressive disorder and HCs (Zhao et al., 2019). Moreover, our results are also in line with previous studies focused on melatonin levels. In particular, these previous studies found associations between the production of melatonin and the PPV in healthy people (Liebrich et al., 2014; Nölte et al., 2009). In addition, Liebrich et al. (2014) found an inverse correlation between active pineal tissue and sleep rhythm disorder. In the same way, the pineal volume was correlated with the morning 6-sulfatoxymelatonin levels (Sigurdardottir et al., 2016) in older adults. Moreover, Riemann et al., (2002) found reduced nocturnal plasma melatonin levels comparing primary insomnia and healthy individuals and poor quality of sleep in primary insomnia patients. In a whole, considering our study and previous studies, the pineal gland volume of women with FM could be related to reduced sleep hours. Moreover, it might be associated with reduced nocturnal melatonin releases, which may lead to a reduced quality of sleep. However, more studies are needed to confirm this hypothesis.

FM patients usually experience sleep disorders (Bennett et al., 2007; Jacobson et al., 2015), and this is associated with the severity of the symptoms (Wolfe et al., 1990; C-oté & Moldofsky, 1997; Mease et al., 2009; Mork & Nilsen, 2012; Choy, 2015). The pineal gland is a key neuroendocrine organ that is located in the centre of the brain and synthesises and secretes melatonin (*N*-acetyl-5-methoxytryptamine; Macchi & Bruce, 2004) in its active tissue (PPV). The melatonin is involved in circadian rhythm processes (Korf, 1994; Acer et al., 2011), and therefore it is in relation with sleep quality (Ferracioli-Oda et al., 2013). Thus, the reduction of pineal volume is usually associated with a decrease in melatonin levels, which can affect the lack of sleep (Song, 2019) and pain (Danilov & Kurganova, 2016). Therefore, we hypothesised that women with FM would show a reduced pineal gland volume. Previous studies using MRI in healthy populations reported that women have slight smaller pineal gland volumes than men (Sun et al., 2009) and old males have bigger volumes than young (Sigurdardottir et al., 2016). Results from our study show that the average PPV, 102.00 (41.46), is consistent with previous literature and with the values obtained in the HC group. Comparing this result with previous studies, we found that participants' pineal gland volumes were slightly lower than the pineal gland volumes reported by Liebrich et al. (2014) 113 mm³ with 3.0 T MR and Nölte et al. (2009) 125 mm³ by 1.5 T MR in healthy young male population, but slightly high compared to the HC values 94.28 (37.87). Bumb et al. (2014) reported a pineal gland volumes much smaller than us in primary insomnia, and Matsuoka et al. (2017) controlling cyst volumes found 70, 90 and 111 mm³ in adults (mixed men and women) older than 70 years old with Alzheimer's disease, mild cognitive impairment and healthy, respectively. Due to the high variability of methods (e.g. MRI with different brands and analysis) and populations in previous studies regarding pineal gland volumes, the comparisons between studies have been cautious. Therefore, the current study could not conclude that women with FM have smaller pineal gland than healthy population, thought women with FM reported sleep disorders and pain. Further studies are warranted to fully determine the mechanisms of the impact of FM in the size of this relevant neuroendocrine gland.

Due to the shape variability of the pineal gland through the volume data obtained in this study using the Hasegawa method, it seems that it is not the most appropriate method to establish the volume since an underestimation is performed, finding similarities with previous studies (Sun et al., 2009). In the present study, 3D T1-w TFE image sequences were used to assess pineal gland volumes, excluding cystic tissue, since it can be considered as hormonally inactive (Nölte et al., 2009). A pineal gland cyst was observed in the 29.60% of women with FM. These results are similar to the findings reported by Pu et al. (2007) 23% and Sun et al. (2009) 25% in healthy adults. However, only 5% of the sample of healthy women in this study showed a cyst. Pineal cyst is common and frequently detected as an incidental finding (Petitcolin et al., 2002; Nolte et al., 2010). Our results showed that people with FM whom a cyst was detected reported more sleep hours than those with FM in whom a pineal cyst was detected. However, no significant differences in PPV and melatonin levels at night were observed. Furthermore, when the FM sample was divided between those who did not have a cyst, who had a cyst of less than 2 mm and those who had a cyst of more than 2 mm, no significant differences were observed in any of the variables studied (PPV, years with FM, PSQI and sleep hours in people with FM). In this regard, although pineal cysts are considered a hormonally inactive tissue, further research on the effects of pineal cyst on pineal function is needed to elucidate this question (Nölte et al., 2009). Moreover, pineal calcifications were not estimated when using T1 sequences, since it does not allow a reliable identification (Adams et al., 2017). Therefore, future studies should evaluate the impact of pineal cysts in the melatonin releases as well as the prevalence of pineal calcifications increasing the sample size of women with FM. For that it would be interesting to use computed tomography and/or susceptibility-weighted MRI, which allow detection of pineal gland calcifications (Adams et al., 2017).

The present study has some limitations, which should be considered. First, no analysis could be performed in the HC group on sleep hours and melatonin levels since the OASIS-3 data set does not have this information. Second, we included only women, so our results cannot be generalised to male patients with FM. Third, the

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relatively small sample size likely reduced the statistical significance of some of our results; it is possible that only the largest differences had enough statistical power to reach significance. Fourth, when performing manual segmentation, it is possible to include adjacent structures to the pineal gland, and this affects the final volume value. Therefore, we recommend to increase sample size and to include male patients with FM. Fifth, there are numerous factors that can influence the production and secretion of melatonin, such as age, pathologies, pharmacotherapy, exposure to light and consumption of substances (alcohol or caffeine; Aulinas, 2019). In people with FM, one of the most important factors might be pharmacotherapy, since some medications are used to reduce some symptoms of FM and have been shown to cause an alteration in the secretion and production of melatonin. For example, some drugs used for the treatment of anxiety and depression show increases in melatonin production. In the same line, other drugs such as benzodiazepines, also used for the treatment of anxiety, have shown a decrease in melatonin levels. On the other hand, some non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen or aspirin, often used to reduce pain, have been shown to decrease melatonin production and secretion (Aulinas, 2019). Nevertheless, both serotonin noradrenaline reuptake inhibitors and NSAIDs are commonly used in the treatment of FM (Derry et al., 2017; Welsch et al., 2018) and it is rare to find patients who do not use these drugs. Sixth, there are possibly a number of comorbidities, which could be manifested along lifetime, associated with insomnia that could impact FM symptoms such as depression, anxiety and chronic pain. In this regard, it is important that future studies take into account medications and comorbidities to clarify how they can alter melatonin production and secretion. Finally, another aspect that has not been controlled in this study has been the menstrual period of the participants; however, to the best of our knowledge, it appears that the current data to date on melatonin and its variation during the menstrual cycle are inconsistent (Aulinas, 2019).

Our present study found significant correlations between the PPV and both sleep hours and melatonin levels at night in women with FM. Moreover, a mean PPV of 102.00 (41.46) mm^3 was observed, with a prevalence of 29.62% cyst in this population. Results from the present study are relevant, since this is the first study that has reported pineal gland volumes, cyst prevalence and correlative relationships between PPV and sleep hours and melatonin levels in women with FM.

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Author contributions. JLLL: design, drafting the article, analysis and interpretation of data. NG: concept, design, and drafting the article. SV: acquisition of data, analysis and interpretation of data. PRD: review of literature. AMG: design, analysis and interpretation of data. NG, SV, AMG and PRD: reviewing and revising the manuscript. SV: consultation and reviewing statistical analysis and interpretation of data. All authors contributed to and approved the final version.

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Impact of Fibromyalgia in the Hippocampal Subfields Volumes of Women—An MRI Study

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Abstract: Patients with fibromyalgia (FM) show widespread pain associated with other symptoms such as cognitive problems, depression, and anxiety among others associated with alterations in the central nervous system. The hippocampal subfields had differences in function, histology, and connectivity with other brain regions, and are altered in different diseases. This study evaluates the volumetric differences between patients with FM compared with a healthy control group. A total of 49 women with, and 43 healthy women completed this study. T1-weighted MRI was used to assess brain volume, and FreeSurfer software was used to segment the hippocampal subfields. Women with FM had a significant reduction in most of the hippocampal subfields. The regression equation models were obtained to predict the volume of specific subfields of the right and left hippocampus. These findings provide that women with FM have lower hippocampal subfields volumes compared with healthy women. Besides, regression models show that different covariates, such as age, cognitive impairment, or depression, are related to specific subfields.

Keywords: chronic pain; hippocampus; brain; cognitive impairment

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1. Introduction

Fibromyalgia (FM) is a chronic, persistent, and diffuse disease that fluctuates in intensity, characterized by widespread pain and tenderness, accompanied by other numerous symptoms like cognitive problems, depression, anxiety, non-recovery sleep, fatigue, stiffness, poor physical fitness, and mobility or balance problems [1–3]. These symptoms lead to a reduced quality of life [4,5] and difficulties in carrying out activities of daily living [6,7]. The prevalence of FM in the general population is between 0.2 and 6.6% [8], occurring mostly in women over 50 years old [9].

Previous research has reported central nervous system (CNS) abnormalities in people with FM [10], including functional, metabolic, and structural alterations in brain regions involved in pain processing [11–16]. Besides, alterations in the immune system, sleep patterns, fatigue, and moods contributed to pain and dysfunction in people with FM. This alteration can lead to allodynia (increased pain from a normally non-painful stimulus) and hyperalgesia (increased response to painful stimuli) [17] associated with amplification of peripheral and central sensory signals involved in pain perception [18], affecting the functionality and structure of CNS. In this regard, people with FM show volume reductions in the gray matter of numerous brain regions involved in the "pain matrix" like hippocampus [13,19], prefrontal cortex [20], amygdala [20], anterior cingulate [20–22], midcingulate, and midinsula [21] cortices.

The hippocampus is one of the most studied brain structures that play an important role in numerous processes, including memory, navigation, cognition, moods, stress, and pain [23–26] related to FM symptomatology. A previous review focused on FM showed alterations in the volume and metabolite levels of the hippocampus [12]. This region is composed of a series of sub-regions such as the subiculum, the dentate gyrus and cornus ammonis [27] among others. Advances in neuroimaging have allowed their study [28], showing that each sub-region had differences in function, histology, connectivity with other brain regions, and vulnerability to disease [29–31]. Furthermore, previous studies showed that these sub-regions are altered in chronic pain [32], cognitive disorders [33–35], psychiatric disorders [36,37], and adult lifespan [38] being able to become possible biomarkers.

To our knowledge, no studies have been evaluated the hippocampal subfields volume in people with FM compared with a healthy control group. It seems more relevant to consider the subfields of the hippocampus, rather than just evaluating the whole hippocampus, to more deeply understand the neurobiology of FM. Thereby, this study aims to evaluate the changes in the volume of the hippocampal subfields in women with FM compared with a healthy control group by magnetic resonance imaging (MRI) analysis.

2. Materials and Methods

2.1. Participants

A total of 50 women with FM from a local association (AFIBROEX) and 43 healthy women from the Open Access Series of Imaging Studies (OASIS-3) participated in this study and, therefore, were divided into two groups: (1) FM group and (2) healthy control group (HC). FM participants met the following inclusion criteria: (a) female and ages between 30 and 75 years, (b) diagnosed with FM by a rheumatologist according to the 2010 American College of Rheumatology criteria [1], (c) able to communicate, and (d) have read and signed the written informed consent. On the other hand, the FM participants were excluded if they: (a) were pregnant, (b) had any cerebral injury (traumatic brain disease, cerebral stroke, brain tumor, or any other diagnosed pathology), and (c) illegible MRI sequences were obtained.

The HC group was obtained by using the OASIS-3 data set. OASIS-3 is a compilation of MRI and PET imaging and related clinical data from 1098 participants, of which 605 are cognitively normal adults, and 493 have various cognitive decline stages. Since different studies have shown brain structural changes associated with cognitive impairment, the sample was filtered to obtain healthy subjects of similar age and gender to the FM group to homogenize the sample. The following inclusion criteria were established: (a) be female and ages between 42 and 60 years, (b) have completed the Mini-Mental State Examination score between 28 to 30, (c) have completed the Geriatric Depression Scale score between 0 to 5, (d) height between 152 to 178 cm, (e) weight between 40 to 120 kg, and (f) have been assessed by a T1w MRI scan with a 3.0 Tesla scanner.

The study was approved by the Research Ethics Committee of the University of Extremadura (approval reference: 62/2017). All participants gave their written informed consent following the updated Declaration of Helsinki.

2.2. Image Acquisition

T1-weighted images were obtained using a 3.0 Tesla scanner. For the FM group, a system equipped with an 8-channel head coil (Achieva 3.0 TX, Philips Medical Systems, Best, The Netherlands) was used to obtain the structural images. T1-weighted images were acquired using a 3D T1-weighted Turbo Field Echo (T1-w TFE) sequence with the following parameters: repetition time (TR) of 11.51 ms; echo time (TE) of 2.8 ms; 288 $\times$ 288 matrix size; 0.9 mm slice thickness; 10° flip angle; 1 number of averages. For the HC group, a system equipped with a 16-channel head coil (Siemens TIM Trio or BioGraph mMR PET-MR, Erlangen, Germany) was used. The MP-RAGE protocol of TIM Trio scanner used the following parameters: TR/TE = 2400/3.16 ms, $\pm$176 axial slices without slice gap, and 1.0 mm nominal isotropic resolution (FOV = 256 $\times$ 256 mm). The MP-RAGE sequence of BioGraph mMR PET-MR scanner used the following parameters: TR/TE = 2300/2.95 ms, $\pm$176 axial slices without slice gap, and 1.2 mm nominal isotropic resolution (FOV = 256 $\times$ 256 mm).

2.3. Image Processing

All T1-weighted images were processed using the FreeSurfer software [39] 6.0 version (Laboratory for Computational Neuroimaging, Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA, USA; http://surfer.nmr.mgh.harvard.edu). The command *recon-all* (http://surfer.nmr.mgh.harvard.edu/fswiki/recon-all) was used for automated segmentation of the T1-weighted images on a MacBook Pro (Version OS X 10.14, 8GB, 2.30 GHz, Intel Core i5). The following steps were followed for the pre-processing of the image data: (a) head motion correction and averaging [40]; (b) removal of non-brain tissue by a hybrid watershed/surface deformation algorithm [41]; (c) automated Talairach space transformation [42]; (d) segmentation of the subcortical and cortical structures using a probabilistic brain atlas [43]; (e) intensity normalization [44]; (f) tessellation of the gray matter and white matter boundary [45]; (g) topology correction; and (h) surface deformation following intensity gradients to reconstruction [43]. Finally, the Iglesias et al. [28] validated method was used to obtain the hippocampal subfields segmentation and volumetric measurements of participants. This procedure uses a probabilistic atlas of the hippocampus combining ex vivo and in vivo MRI data through Bayesian inference, which can automatically segment the hippocampal regions in vivo. For a detailed overview, see Iglesias et al. [28]. The automated segmentation allows to obtain twelve subfields separated by right and left hemisphere: hippocampal tail, parasubiculum, presubiculum, subiculum, cornu ammonis 1 (CA1), cornu ammonis 2/3 (CA2/3), cornu ammonis 4 (CA4), hippocampus-amygdala transition area (HATA), granule cell layer of dentate gyrus (GC-DG), molecular layer, fimbria, and hippocampal fissure. It also includes the total volume of the left and right hippocampus. Figure 1 shows the different hippocampal subfields of a healthy participant and a participant with FM.

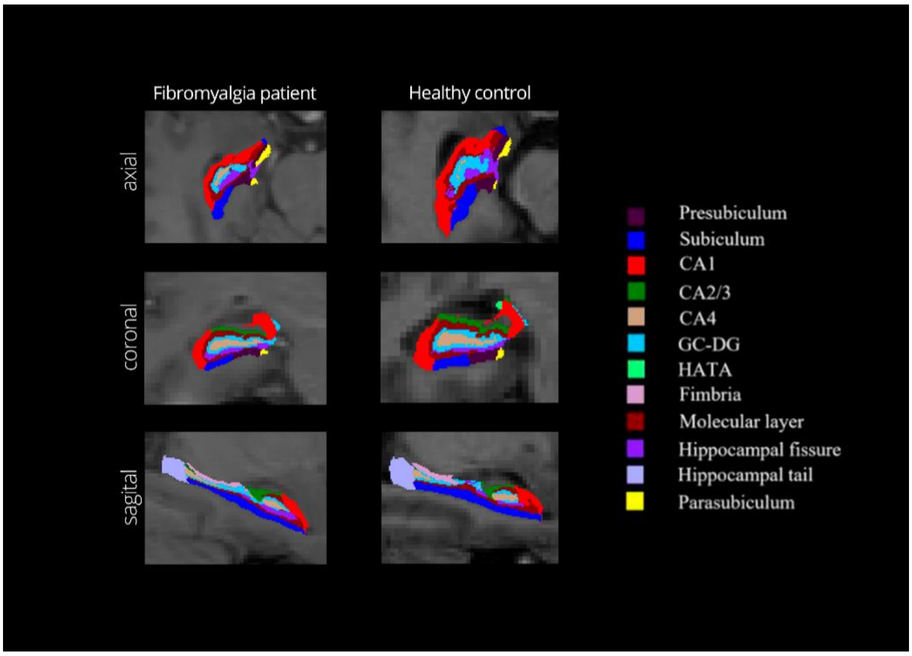

Figure 1. Subfields of the right hippocampus obtained from the FreeSurfer viewer in axial, coronal, and sagittal planes. One participant with fibromyalgia and one control participant with similar characteristics and age 59 years are shown.

2.4. Outcome Measurements

Height, weight, age, general depressive state, and cognitive impairment were collected in both groups (FM and HC). HC group outcomes were obtained from the OASIS-3 database. The FM group was assessed through a standardized interview. The following instruments were used for this purpose:

The 15-items Geriatric Depression Scale (GDS) [46] is a questionnaire that allows assessing symptoms of depression. Items are marked with a simple yes/no format. To consider the possible existence of depression symptoms, the cut-off point is set at 5 or higher. For the FM group, the Spanish version was administrated [47].

The Mini-Mental State Examination (MMSE) [48] is a wide dementia screening tool used in clinical practice and different types of studies. This is a written test with a maximum score of 30 points, with lower scores indicating more severe cognitive impairments. The cut-off point is usually set at 24 for "normal" cognitive function. However, it has several limitations depending on the education and age of the participants that must be taken into account [49]. The Spanish version was used with the 30-point version to establish international comparisons [50].

Furthermore, the Fibromyalgia Impact Questionnaire (FIQ) [51] in the Spanish version [52] was used to assess the disease impact. This instrument has 10 items with 3 domains: function, overall impact, and symptoms.

2.5. Statistical Analysis

Statistical analysis was carried out using Statistical Package for Social Sciences software (SPSS, version 24.0, IBM Corp, Armonk, New York, NY, USA). Parametric and non-parametric tests were conducted based on the results of the Shapiro-Wilk test.

Mann Whitney *U* test was conducted to examine differences between groups (FM and HC) in depression levels and cognitive functions through the GDS-15 and MMSE questionnaires.

To predict the value of the hippocampal subfields and the whole hippocampus, and determine if there were volumetric differences between the groups the multiple linear regression was used. This analysis also allows determining the relative contribution of independent or predictor variables to the total variance explained in the same direction. Before carrying out the multiple linear regression analysis, it was necessary to comply with the necessary assumptions to obtain valid results. Among these assumptions, the dependent variable needed to be measured on a continuous scale, there are two or more independent variables, there is independence of residues, there is a linear relationship between the dependent variable and each of the independent variables, there is homoscedasticity in the data, and they do not show multicollinearity. Finally, the residuals (errors) follow a normal distribution. The independent variables selected were age, estimated intracranial volume (eTIV), group, GDS-15 score, and MMSE score [33,38].

ANOVA test was performed to test whether the regression model had a good fit for the data. The values of the statistics obtained in the multiple linear regression model were R^2 or coefficient of determination representing the proportion of variance in the dependent variable that can be explained by the independent variables. The unstandardized coefficients or B indicate how much the dependent variable varies with an independent variable when all other independent variables are held constant.

The level of statistical significance was set at 0.05.

3. Results

The demographic characteristics of the FM and HC groups are shown in Table 1. The Mann-Whitney *U* test showed that HC group obtained significantly better results than the FM group in the GDS-15 and MMSE scores (see Table 1). Moreover, FM participants had a moderate effect on the impact of the FM [53].

Table 1. Characteristics of the participants.

Variables	HC (n = 43)	FM (n = 49)	Z	p-Value
Age (years)	53.37 (4.47)	54.18 (10.12)	−0.051	0.959
Height (cm)	165.07 (6.30)	159.61 (6.24)	−3.972	<0.001
Weight (Kg)	73.92 (6.30)	71.57 (14.05)	−0.767	0.443
GDS-15	2.55 (1.71)	6.88 (4.07)	−5.338	<0.001
MMSE	29.51 (0.63)	28.47 (1.42)	−3.809	<0.001
FIQ-100	-	58.05 (17.85)		
Years with FM Diagnosed	-	10.80 (6.33)		
Years with FM Symptoms	-	19.38 (12.70)		

GDS: Geriatric Depression Scale; MMSE: Mini Mental State Examination; FIQ: Fibromyalgia. Impact Questionnaire; n: number of participants; FM: Fibromyalgia; HC: Healthy Control.

One subject from the FM group was eliminated from the study because an illegible MRI sequence was obtained. Table 2 shows the statistical results of the multiple linear regression of the hippocampal subfields and hippocampal volumes of the FM and HC groups. ANOVA test showed that all models were valid except in the left hippocampal fissure, CA1 bilateral, left fimbria, and HATA bilateral subfields that could not be studied because they did not meet the necessary assumptions to carry out the analysis.

Table 2. Volume measures and multiple linear regression analysis of the hippocampal subfields and the whole hippocampus.

Structures		FM Mean (SD)	HC Mean (SD)	ANOVA F	ANOVA p	Covariates	R^2	Constant	B	β	t	p
Tail	L	402.28 (51.76)	499.09 (67.58)	26.93	<0.001	Age	0.48	152.11	−1.52	−0.16	−2.02	0.046
						eTIV			0.00	0.28	3.33	0.001
						Group			110.41	0.72	8.72	<0.001
	R	397.11 (60.20)	526.63 (76.40)	38.23	<0.001	Age	0.57	4.53	−1.23	−0.10	−1.46	0.148
						eTIV			0.00	0.31	4.15	<0.001
						Group			149.73	0.79	10.57	<0.001
Fissure	L $_a$	145.84 (25.58)	147.71 (24.56)									
	R	156.69 (25.52)	143.50 (24.69)	5.79	<0.001	Age	0.17	68.00	0.86	0.27	2.70	0.008
						eTIV			0.00	0.19	1.76	0.081
						Group			−8.65	−0.17	−1.60	0.113
ML	L	513.41 (47.02)	530.38 (59.16)	8.65	<0.001	Age	0.29	99.63	−1.50	−0.22	−2.40	0.019
						eTIV			0.00	0.47	4.85	<0.001
						Group			26.21	0.24	2.30	0.024
						MMSE			7.13	0.17	1.60	0.112
	R	526.55 (51.20)	539.68 (62.52)	11.27	<0.001	Age	0.28	316.88	−2.04	−0.29	−3.11	0.003
						eTIV			0.00	0.49	5.00	<0.001
						Group			29.78	0.26	2.69	0.009
CA1	L $_a$	597.81 (68.26)	586.52 (64.12)									
	R $_a$	615.80 (67.30)	605.79 (68.15)									

Table 2. *Cont.*

				ANOVA		Multiple Linear Regression						
CA3	L	172.80 (21.51)	193.25 (30.17)	11.30	<0.001	Age	0.28	60.52	−0.52	−0.15	−1.62	0.109
						eTIV			0.00	0.39	4.01	<0.001
						Group			27.21	0.49	5.06	<0.001
	R	196.23 (21.99)	205.73 (32.92)	11.56	<0.001	eTIV	0.29	−114.59	0.00	0.50	5.14	<0.001
						Grupo			12.42	0.22	2.11	0.038
						MMSE			5.43	0.24	2.40	0.019
CA4	L	216.59 (22.12)	239.00 (29.54)	13.48	<0.001	Age	0.39	−13.78	−0.57	−0.16	−1.89	0.062
						eTIV			0.00	0.47	5.22	<0.001
						Group			26.70	0.48	4.84	<0.001
						MMSE			3.42	0.15	1.59	0.116
	R	233.31 (22.21)	243.08 (30.98)	12.13	<0.001	Age	0.30	94.36	−0.55	−0.16	−1.81	0.074
						eTIV			0.00	0.54	5.58	<0.001
						Group			18.51	0.30	3.15	0.002
Subiculum	L	395.72 (40.41)	402.66 (49.56)	6.68	<0.001	Age	0.19	219.47	−0.90	−0.16	−1.64	0.104
						eTIV			0.00	0.43	4.19	<0.001
						Group			20.15	0.22	2.17	0.033
	R	394.96 (38.44)	405.08 (47.62)	5.39	0.002	Age	0.16	245.46	−0.83	−0.15	−1.53	0.129
						eTIV			0.00	0.38	3.61	0.001
						Group			21.24	0.25	2.34	0.022
Presubiculum	L	271.72 (32.29)	285.32 (34.14)	10.47	<0.001	Age	0.27	159.66	−1.17	−0.28	−2.99	0.004
						eTIV			0.00	0.43	4.37	<0.001
						Group			23.26	0.35	3.52	0.001
	R	257.34 (30.47)	276.78 (32.49)	8.05	<0.001	eTIV	0.22	91.36	0.00	0.34	3.37	0.001
						Group			35.46	0.54	4.45	<0.001
						GDS			1.82	0.21	1.80	0.076
GC-DG	L	256.51 (25.87)	277.44 (33.87)	11.52	<0.001	Age	0.35	22.67	−0.89	−0.23	−2.54	0.013
						eTIV			0.00	0.46	4.90	<0.001
						Group			25.50	0.41	4.00	<0.001
						MMSE			3.42	0.15	1.59	0.116
	R	273.89 (25.30)	282.61 (35.25)	12.36	<0.001	Age	0.30	129.11	−0.84	−0.22	−2.40	0.018
						eTIV			0.00	0.54	5.58	<0.001
						Group			18.51	0.30	3.15	0.002
Fimbria	L a	102.73 (18.72)	75.33 (16.50)			Age						
						Group						
	R	107.37 (18.99)	73.42 (14.38)	48.64	<0.001	eTIV	0.53	102.12	0.00	0.15	1.91	0.060
						Group			−31.96	−0.66	−8.47	<0.001
Parasubiculum	L	45.91 (8.20)	57.24 (11.65)	16.16	<0.001	Age	0.36	17.20	−0.31	−0.22	−2.49	0.015
						eTIV			0.00	0.27	2.88	0.005
						Group			13.47	0.59	6.44	<0.001
	R	45.97 (8.63)	56.20 (11.02)	13.88	<0.001	Age	0.22	46.85	−0.20	−0.15	−1.57	0.119
						Group			10.07	0.46	4.94	<0.001

Table 2. *Cont.*

				ANOVA		Multiple Linear Regression						
HATA	L a	58.09 (7.48)	56.49 (9.80)									
	R a	61.12 (7.70)	58.52 (8.98)									
Hippocampus	L	3033.93 (263.48)	3202.74 (334.79)	14.84	<0.001	Age	0.34	1737.96	−10.43	−0.27	−3.05	0.003
						eTIV			0.00	0.49	5.25	<0.001
						Group			266.52	0.43	4.62	<0.001
	R	3109.64 (286.93)	3273.53 (346.07)	15.19	<0.001	Age	0.35	1583.24	−9.93	−0.24	−2.77	0.007
						eTIV			0.00	0.53	5.66	<0.001
						Group			270.91	0.42	4.48	<0.001

Abbreviations: FM, fibromyalgia; HC, healthy control; SD, standard deviation; ML, molecular layer; CA, cornus ammonis; GC-DG, granule cell-dentate gyrus; HATA, hippocampus—amygdala-transition-area; eTIV, estimated total intracranial volume; MMSE, mini-mental state examination; GDS, geriatric depression scale; R^2, coefficient of determination; B, unstandardized coefficient; β, standardized coefficient; *p*, *p*-value. $_a$ The assumptions for performing the multiple linear regression are not met, FM = 1; HC = 2.

Multiple regressions to predict the volume of the hippocampal subfields that obtained statistical significance in the independent variables were as follows:

For the right hippocampal subfields, it was found that the variables age, etiv, group, and MMSE predict the LH volume from the equation:

$$\textit{Predicted ML volume} = 99.63 - (1.50 \times \textit{age}) + (\textit{0.00} \times \textit{eTIV}) + (7.13 \times \textit{MMSE}) + (26.21 \times \textit{group}).$$

The variables eTIV, group and, MMSE predict the CA3 volume, from the equation:

$$\textit{Predicted CA3} = -114.59 + (0.00 \times \textit{eTIV}) + (5.43 \times \textit{MMSE}) + (12.42 \times \textit{group})$$

The age, eTIV, and group predict the CG volume from the equation:

$$\textit{Predicted GCDG} = 129.11 - (0.84 \times \textit{age}) + (0.00 \times \textit{eTIV}) + (18.51 \times \textit{group})$$

For the subfields of the left hippocampus, the variables *age*, *eTIV*, and *group* predicted the volume in the tail, presubiculum, and parasubiculum, from the equations:

$$\textit{Predicted Tail} = 152.11 - (1.52 \times \textit{age}) + (0.00 \times \textit{eTIV}) + (110.41 \times \textit{group}).$$

$$\textit{Predicted presubiculum} = 159.66 - (1.17 \times \textit{age}) + (0.00 \times \textit{eTIV}) + (23.26 \times \textit{group}).$$

$$\textit{Predicted Parasubiculum} = 17.20 - (0.31 \times \textit{age}) + (0.00 \times \textit{eTIV}) + (13.47 \times \textit{group}).$$

As for predicting the volume of the whole hippocampus, the variables predicting volume are age, eTIV, and group for both the left and the right, with the equation *Predicted left hippocampus* = 1737.96 − (10.43 × *age*) + (0.00 × *eTIV*) + (266.52 × *group*) for the left and the equation *Predicted right hippocampus* = 1583.24 − (9.93 × *age*) + (0.00 × *eTIV*) + (270.91 × *group*) for the right.

By performing an individualized analysis of the variables, for each year of age, the volume of the structures decreases in almost all the structures, except the right tail, left CA3, CA4 bilateral, subiculum bilateral, and right presubiculum. In the whole hippocampus, there is also a decrease in volume for each year of age of 10.43 mm^3 in the left and 9.93 mm^3 in the right. In contrast, the right fissure presents a volume increase of 0.86 mm^3 for each year of age.

When visualizing the variable of participation in the HC or FM group, in almost all the subfields, healthy women present a greater volume than women with FM. However, the HC group has 31.96 mm^3 less than the FM group in the fimbria.

As for the score obtained in MMSE, for each point obtained in MMSE, the volume of right CA3 increases by 5.43 mm^3.

There are no volumetric changes in the subfields of the hippocampus based on eTIV and GDS scores.

The differences and regression models in the left hippocampal fissure, left and right CA1, left fimbria, and left and right HATA could not be analyzed because the assumptions for conducting the multiple linear regression analysis were not met.

4. Discussion

This study aimed to evaluate the volumetric differences in the hippocampal subfields and the whole hippocampus in healthy women and women with FM controlling for age, eTIV, depression, and cognitive impairment. Besides, regression equation models were obtained to predict the volume of the hippocampal subfields and the whole hippocampus. This is the first study that analyzes the hippocampal subfields in women with FM compared to a healthy control group.

Our results indicated that all regression models were valid. Moreover, the hippocampal subfields and the whole hippocampus had significantly lower volumes in FM than healthy controls except in the right fissure of the hippocampus, where no significant differences were achieved. Considering the whole hippocampus, our results are in line with previous research in FM that also found volumetric reductions in the gray matter of the whole hippocampus [12,13,19]. This has also been suggested in EEG studies through an altered theta, showing that women with FM with more years suffering from symptoms exhibited greater theta power spectrum [54,55]. This is relevant since theta power spectrum is related to higher cognitive functions, synaptic plasticity, and atrophy of the hippocampus [56].

It is now known that reductions in the volume of the hippocampus begin to occur from mid-adulthood. From this point, progressive atrophy of the hippocampus begins to be found as age increases [57]. In this sense, our findings are consistent with the literature since a decrease in volume has been observed in the left and right hippocampus with increasing age. Similarly, these reductions have been detected in most subfields except right tail, left CA3, CA4 bilateral, subiculum bilateral, and right presubiculum. These findings are related to a previous study that has reported a reduction of these subfields with age [35] being the CA subfield the most affected by age. In our study, age-induced decreases in this subfield have not been found. This could be due to the age of participants which was relatively low HC 53.37 (4.47) and FM 54.18 (10.12). Since there is controversy due to the methodological variability among the studies [35], further research is needed to confirm these findings.

The incidence of depression and cognitive impairment in FM is known [58,59], and findings have been reported confirming that patients with major depressive disorder [60] and Alzheimer's disease (AD) [33] have a smaller hippocampus. However, there is still a non-homogeneous pattern of atrophy in this disease. Thus, our results were controlled for the effect of cognitive impairment and depression, introducing these outcomes as covariates in the statistical analyses. Therefore, findings suggest that higher MMSE scores are associated with volume increases in the right CA3. However, no significant differences were found between GDS scores and hippocampal subfield volumes. In this regard, McCrae et al. [13] found differences in depression comparing HC females and FM females, but no volumetric differences were found in the hippocampus controlling for depression. A previous review of the hippocampal subfields in major depressive disorder [34] reported that volume reductions occurred mainly in the CA and GCDG subfields. Our results did not show volumetric changes in these subfields, which could hypothetically be explained by the higher levels of depression symptoms in major depressive disorder than in FM and the age of participants. In this regard, a previous study reported the most pronounced depression-related alterations of the hippocampus in older adults than young people due to the cumulative effect of depression [61] and age-related atrophy of the hippocampus [62].

When comparing our results with the results obtained by Zhao et al. [33], in which the hippocampal subfields were compared in different groups of patients, including AD patients, normal controls, amnestic mild cognitive impairment patients, and subjective cognitive decline patients, we can observe that the volumes obtained in our population of women with FM are lower than the subjective cognitive decline group and higher than the amnestic mild cognitive impairment group as well as the AD group. This is relevant since, among the symptoms of FM, memory and concentration problems known in the literature as "fibrofog" are recurrent and are considered a clinically important aspect of FM [63]. However, our study found no specific effect caused by cognitive impairment in the hippocampal subfields. This effect was probably not found, as no specific neuropsychological tests were carried out in our research to control for cognitive performance in different domains that have been altered [64]. Therefore, future research should study the possible volumetric changes in hippocampal subfields associated with different cognitive domains in FM through different neuropsychological tests. It is known that depression, anxiety, pain, or sleeping disturbances can negatively affect cognitive symptoms. However, they do not entirely explain all the cognitive symptoms of FM [65]. Nevertheless, morphological investigations show decreases of grey material in FM in regions related to cognitive components [66,67]. As we expected, the values obtained in depression and cognitive impairment were worse in the FM group than the HC group, being in line with previous studies that obtained similar results [13,59,68,69]. However, more studies are needed to know the mechanisms involved in their origin.

Regarding the volumetric results obtained in the HC group in some structures are lower when compared to the subjective cognitive decline patient group. These differences could be due to the segmentation methods used.

While the findings of this study are promising, some limitations must be taken into account. The differences in the left hippocampal fissure, left and right CA1, left fimbria, and left and right HATA could not be analyzed because the assumptions for conducting the multiple linear regression analysis were not met. We only evaluated a sample of women, so these results cannot be generalized to men with FM. The MRI scanners' possible effects could not be assessed since the sample was not randomized to be measured on the different devices. Furthermore, the pharmacological history of subjects was not an inclusion criterion in the present study. On the other hand, this study was based on cross-sectional data; future research is requested to conduct longitudinal follow-up studies of the same cohort to determine the evolution of these structures to identify possible biomarkers in FM. Finally, we know that the segmentation method is based on an atlas developed from elderly subjects [28], which may present slight hippocampal atrophy. However, this method has shown test–retest reliability in estimating hippocampal volumes and hippocampal subfields [70]. Future research should also be conducted to monitor the stress level and the levels of glucocorticoids generated in the hippocampus. These elements seem to negatively affect the neuronal plasticity of the hippocampus and may influence the reduction of the volume of this structure [12]. In the same way, it would be interesting to consider whether the subjects are medicated to establish possible relationships between decreases or increases in volume in the subfields of the hippocampus [34].

5. Conclusions

To our knowledge, this is the first study to analyze volume differences in the subfields of the hippocampus between healthy controls and women with FM. Our findings showed that women with FM had a significant reduction in most of the hippocampal subfields. Besides, regression models show that different covariates, such as age, cognitive impairment, or depression, are related to specific subfields.

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Article

Relationship between Kinesiophobia and Mobility, Impact of the Disease, and Fear of Falling in Women with and without Fibromyalgia: A Cross-Sectional Study

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Abstract: Background: Kinesiophobia is defined as fear of movement due to the painful experience of it. The main symptom of fibromyalgia is persistent and widespread pain associated with other symptoms. This study analyzes the kinesiophobia between women with fibromyalgia and apparently healthy women and investigates the relationship between kinesiophobia and physical fitness tests, fear of falling, and the impact of the fibromyalgia. Methods: Fifty-one women participated in this study were divided into two groups: (1) women with fibromyalgia and (2) apparently healthy women. Participants completed questionnaires to assess kinesiophobia, fear of falling, and the impact of fibromyalgia. Subsequently, participants completed the physical tests Timed Up and Go, 10-step stair ascent, and handgrip strength. Results: Women with fibromyalgia had significant differences in kinesiophobia and fear of falling compared to apparently healthy women. Similarly, performance in the physical tests was lower, except for the handgrip strength, which maintained similar values to the apparently healthy women. Significant relationships were found only in the fibromyalgia group between kinesiophobia, the impact of the disease, fear of falling, and the Timed Up and Go and 10-step stair ascent tests. Conclusions: Women with fibromyalgia showed higher kinesiophobia scores, worse performance in mobility tests, and higher fear of falling than apparently healthy women. Kinesiophobia score is related to Timed Up and Go performance, the 10-step stair ascent, the fear of falling, and the impact of the disease in women with fibromyalgia.

Keywords: activities of daily living; chronic pain; movement; pain; physical fitness

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1. Introduction

Fibromyalgia (FM) is a complex disease characterized by chronic widespread pain, and it is often associated with fatigue, disrupted sleep, anxiety, depression, cognitive dysfunction, and poor physical fitness, among other symptoms [1,2]. These symptoms limit physical function, daily living activities, and emotional well-being [3,4], leading to a reduced health-related quality of life [5]. FM affects 0.2% to 6.6% of the general population, mainly in women over 50 years [6]. In Europe, the prevalence ranges from 2.9% to 4.7% of the general population and mainly occurs in women between 35 and 84 years [7]. In Spain, the global prevalence is estimated at 2.45%, of which women present 4.49% while men present 0.29% [8].

Due to reduced physical activity and a higher level of sedentarism, people with FM tend to present a relatively low physical condition [9]. Furthermore, people with FM commonly present balance problems that lead to a greater risk of suffering falls and a greater fear of falling [10]. All these physical function impairments could make the practice of physical activity difficult, increasing sedentary time and, consequently, the prevalence of overweight and obesity [11].

The Fear Avoidance Model proposes that pain-related fear activates mechanisms that lead to movement and activity avoidance, which, in the long-term, cause disability, disuse, and depression, entering a cycle that feedbacks and contributes to the maintenance and progression of the disability [12–14]. In FM, the fear of pain plays a crucial role in physical activity habits. In this regard, the initial level of pain associated with activities determines the level of physical activity a person with FM is willing to perform [15].

Kinesiophobia plays a fundamental role in the Fear Avoidance Model, since it consists of an irrational, excessive, and debilitating fear of movement arising from a sense of fragility or vulnerability due to injury or (re)injury [16]. Higher kinesiophobia has been consistently associated patients with chronic pain with higher levels of intensity of pain, disability [17], and lower quality of life [18]. Importantly, recent evidence highlighted the mediating role of kinesiophobia in the relationship between pain intensity and self-reported disability, suggesting the pivotal role of these factors in modulating the response to pain stimuli [19].

Previous studies have shown that kinesiophobia has a negative impact on activities of daily living in elder institutionalized people with chronic pain [20] as well as limited the physical activity status of patients with chronic low back pain [21]. Furthermore, kinesiophobia predicts mobility and balance in older people with low back pain [22]. Thus, the evaluation of kinesiophobia in clinical practice is relevant to recognize barriers that may affect compliance with rehabilitation programs [22]. In FM, 40% of patients exhibited high levels of fear of movement and avoidance behaviors toward physical activity [23]. In fact, treatment compliance in people with FM is affected by high pain levels, lower quality of life in the physical and social domains, and fear of movement [24].

In order to explore previous studies in the field of kinesiophobia and FM, a literature review was conducted in the PubMed database. The search string used was: "(kinesiophobia) AND (fibromyalgia)". A total of 45 articles were retrieved on 19 June 2022 (date of the search). Of the 45 articles, most of them were focused on the effects of different therapies on different variables, including kinesiophobia. Only four studies explored the relationship between kinesiophobia and disability using questionnaires [25–28] that consider the physical activity performed (the last weeks or days) or how the person would feel performing an activity. However, these studies may lead to possible biases when participants remembered what they did or how they felt, since objective measures of physical fitness were not registered. In contrast, two studies explored the relationship between kinesiophobia and disability through the performance of physical fitness tests [3,29]. In this regard, Cigarán-Méndez et al. [29] did not show significant correlation between handgrip performance and kinesiophobia. In the same line, Huijnen, Verbunt, Meeus and Smeets [3] did not report significant correlation between climbing stair performance (three times up and down a ten-step-high stair at a self-chosen, comfortable speed) and kinesiophobia. None of these studies analyzed the relationship between kinesiophobia, number of falls, and fear of falling. Furthermore, an apparently healthy group that examined the relationship between kinesiophobia and disability was not included in the analyzed studies. In addition, of the previously mentioned six articles [3,25–29], only one study examined the relationship between kinesiophobia and the impact of the disease through the Revised Fibromyalgia Impact Questionnaire (FIQR) [25] (the updated version of the Fibromyalgia Impact Questionnaire (FIQ)). The rest either did so with FIQ or did not use it.

In this sense, the present study aimed to contribute to the literature with new information by analyzing the relationship between kinesiophobia with the number of falls, fear of falling, the impact of FM, and physical fitness tests closely related to activities of daily living, such as the Timed Up and Go test (TUG) [30,31], the 10-step stair ascent test [32], or handgrip strength [33]. In addition, an apparently healthy group was incorporated. It is important from a clinical point of view since increasing the knowledge in this field can identify those activities that are considered challenging, allowing the design of more friendly activities to improve the management of this disease. Therefore, this study aimed: (1) to compare the kinesiophobia between women with FM and apparently healthy women and (2) to investigate the relationship between kinesiophobia and TUG, 10-step stair ascent test, handgrip strength, number of falls, fear of falling, and the impact of FM. We hypothesized that (1) kinesiophobia will be significantly higher in the FM group than in the apparently healthy group; (2) kinesiophobia will positively correlate with the performance in TUG and the 10-step stair ascent test but not correlate with the handgrip strength since the motor pattern required in the TUG and 10-step stair ascent tests are more challenging than handgrip strength; and (3) kinesiophobia will positively correlate with the fear of falling and the impact of the FM.

2. Materials and Methods

2.1. Participants

A total of fifty-one women (n = 25 women with FM; n = 26 apparently healthy women) from a convenience sample participated in this cross-sectional study. The sample size was calculated using G*Power 3.1 and based on the kinesiophobia results from Peinado-Rubia, et al. [26] (28.88 (7.11) for FM group) and Osumi et al. [34] (21.0 (4.1) for healthy participants). A total of 38 participants (19 both in the FM and the comparison group) were necessary to achieve a 99% statistical power. Assuming they did not participate in the measurements or some inconvenience occurred, 25% of the participants were added to each group. Therefore, 25 and 26 women were recruited for the FM group and the apparently healthy group, respectively. The flow chart of participants is depicted in Figure 1. Participants were recruited from a local association of FM in Cáceres (Spain), university facilities, and close contacts of FM patients by telephone calls. All the recruited participants fulfilled the following inclusion criteria: (a) female and aged between 30 and 75 years; (b) able to communicate with the research staff; (c) for the FM group, they have to be diagnosed by a rheumatologist according to the 2010 criteria established by the American College of Rheumatology [1]; and (d) have read, understood, and signed the written informed consent conforming to the updated Declaration of Helsinki. In addition, participants were excluded if they: (a) were pregnant, (b) had contraindications for physical exercise, and (c) have neurological diseases or psychiatric diagnosis. All procedures were approved by the University Research Ethics Committee (approval number: 62/2017), and all participants were verbally informed and gave written informed consent to participate in this study.

2.2. Procedure

First, age of the participants, height, weight, and body composition measured by bioimpedance (Tanita Body Composition Analyzer BC-418 MA, Tokyo, Japan) were assessed. Then, participants answered the Revised Fibromyalgia Impact Questionnaire (FIQR) [35], 11-item Tampa Scale of Kinesiophobia (TSK-11) [36], and Falls Efficacy Scale International (FES-I) [37].

After these first steps, participants carried out the physical Timed Up and Go (TUG) [38], 10-Step stair ascent [32], and handgrip strength [39] tests in the same day. Before starting the measurements, participants were informed about instructions and considerations for the correct development of the different physical fitness tests. The order of these tests were TUG, handgrip strength, and 10-Step stair ascent to prevent local fatigue in the upper and lower body. The procedure took place in the University facilities (Faculty of Sport Science, University of Extremadura, Cáceres) between January and March 2018.

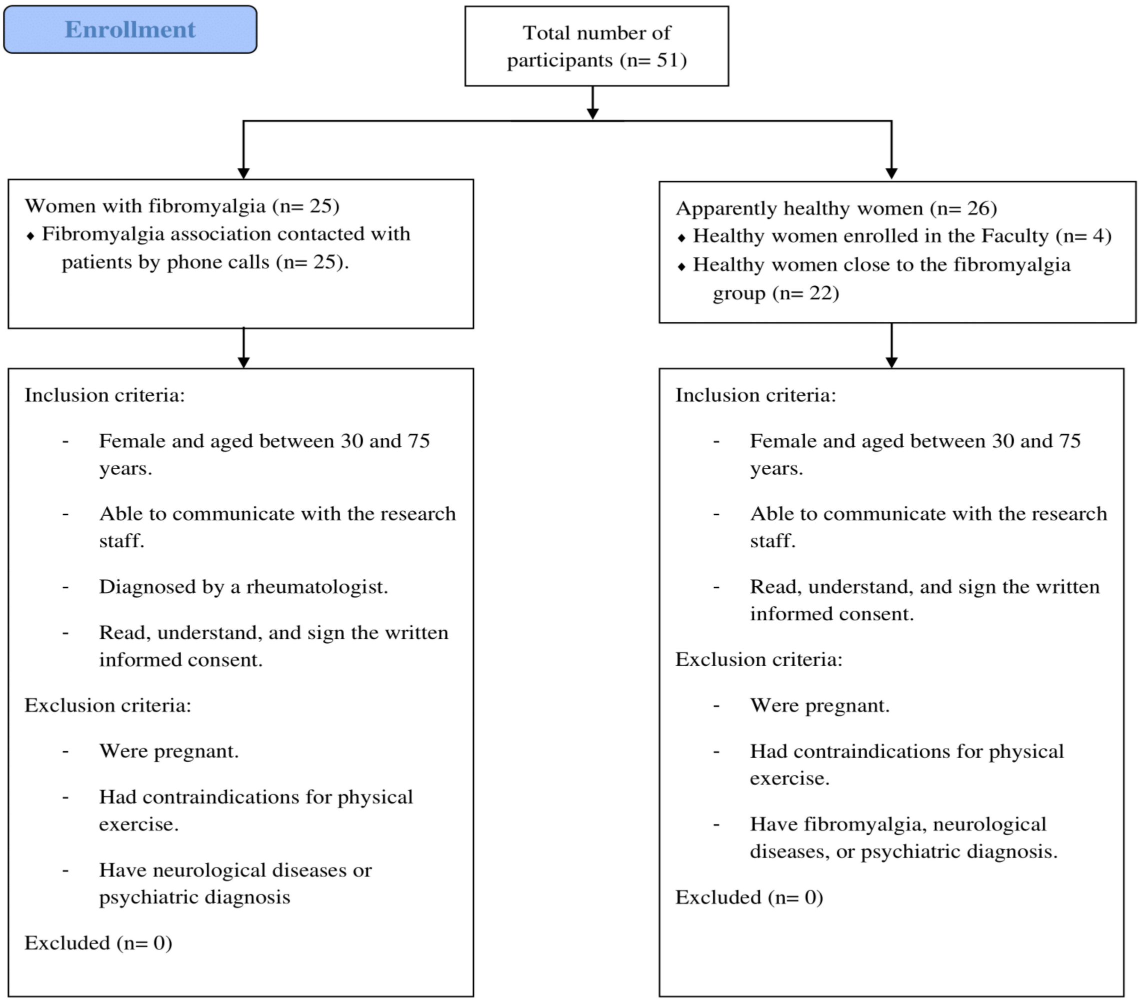

Figure 1. Flow chart of participants.

2.3. Outcomes

(a) Impact of the disease, kinesiophobia, and fear of falling.

Revised Fibromyalgia Impact Questionnaire (FIQR). This extensively validated FM-specific tool is divided into three domains focusing on function, overall impact, and symptoms that evaluates the general impact of the disease from 0 to 100, where 0 indicates no impact and 100 indicates the highest impact [35]. The validated FIQR Spanish version was used in this study [40].

Tampa Scale of Kinesiophobia (TSK-11). TSK-11 is a robust predictor of disability based on fear of movement and injury [16,41]. This instrument has been used in patients with FM [28], chronic pain [42], and chronic low back pain [43], and it is used as a clinical diagnostic tool [28,36,44]. Kinesiophobia was measured by TSK 11-item [36] in its Spanish version [45]. Each of the 11 items has 4 answer options (1 = "strongly disagree", 4 = "strongly agree"). The total score is calculated by adding the items. This total score can range from 11 to 44 points, with 11 indicating the lowest level of kinesiophobia and 44 the highest level of kinesiophobia.

Falls Efficacy Scale International (FES-I). This tool is a self-report questionnaire developed and validated by the Prevention of Falls Network Europe (ProFaNE), providing information on the level of concern about falls for a range of activities of daily living inside and outside the home, providing excellent reliability and validity [37,46]. This questionnaire has been previously used in the FM population [47]. The FES-I contains 16 items scored on a four-point scale (1 = not at all concerned, 4 = very concerned), and a higher score is associated with a greater fear of falling [46]. The Spanish version was used in this study [48].

(b) Physical Fitness Tests

Timed Up and Go (TUG). This test has been previously used in the FM population, showing excellent reliability [38]. Participants have to get up from a chair without armrests, walk 3 m, turn around a cone, walk back, and sit down without using armrests. The time was measured using a manual stopwatch by one of the researchers.

The 10-Step stair ascent. In the FM population, this test has been previously used showing excellent reliability [32]. Participants have to climb 10 stairs with the instruction "as quickly and safely as you can", but they cannot use handrails. The test starts with the subject in a static position. The recording time starts when the participant starts the movement and stops with the first step at the last stair. The time was measured using a manual stopwatch by one of the researchers.

Upper body muscular strength. A hand dynamometer (Takei TKK 5401 Digital Handgrip Dynamometer, Tokyo, Japan) was used to obtain the handgrip strength. This test has been previously used in FM patients [39,49]. The participant squeezes gradually and continuously for at least 2 s. The test was performed with the right and left hand twice, using a comfortable grip-span with the elbow fully extended and the palm of the hand perpendicular to the line of the shoulders in a standing position. The maximum score in kilograms for each hand was recorded.

The researcher who evaluated the physical fitness tests was blinded to group allocation. The participants were called to perform the physical tests on their assigned day. However, the researcher did not know the group to which the participants belonged, since he was only focused on evaluating.

2.4. Statistical Analysis

The SPSS statistical package (version 24.0; IBM Corp, Armonk, NY, USA) was used to analyze the data. Shapiro–Wilk test was conducted to analyze the distribution of the data. Variables with a p-value > 0.05 for each group (FM group and apparently healthy group) were required to consider a normal distribution. In this regard, non-parametric tests were conducted since some variables (age, number of falls, FES-I total score, 10-Step stair ascent, and handgrip strength) did not follow a Gaussian distribution. Furthermore, non-parametric tests are recommended in biomedical sciences [50].

Mann–Whitney U tests were performed to examine differences between groups in age, body mass index (BMI), time of the tests, strength, and total score tests. Furthermore, effect size [r] was calculated. It was classified as follows: 0.5 is a large effect, 0.3 is a medium effect, and 0.1 is a small effect [51].

Moreover, Spearman's rho correlation analyses were used to evaluate the relationship between TSK-11, TUG, 10-Step stair ascent, handgrip strength, and FES-I.

The alpha level of significance was set at 0.05.

3. Results

The main characteristics of the participants and the differences between groups are shown in Table 1. The results indicated that the FM group had a moderate impact on the disease according to the classification by Bennett et al. [52].

The Mann–Whitney U test showed that the FM group reported higher kinesiophobia than the apparently healthy group, showing significant differences. The FM group also reported higher values of fear of falling than apparently healthy group measured through the FES-I. In the same line, FM group also reported a higher number of falls in the last year than apparently healthy group. Regarding physical fitness tests, lower levels of physical performance were found in the TUG and 10-Step stair ascent, showing significant differences when comparing the FM group with the apparently healthy group. These changes were not found in handgrip strength (see Table 1).

Table 1. Differences between groups in demographic, total score questionnaires, and physical fitness tests.

Variable		Women with FM (n = 25) Mean (SD)	Apparently Healthy Women (n = 26) Mean (SD)	Value of Contrast	*p*-Value	Effect Size
Age (years)		56.36 (8.39)	54.69 (6.78)	−0.293	0.770	−0.041
Height (cm)		160.04 (7.02)	160.12 (6.92)	−0.661	0.509	−0.093
Weight (Kg)		68.64 (12.22)	62.99 (8.18)	−1.630	0.103	−0.228
BMI (Kg/m^2)		26.79 (4.48)	24.72 (3.95)	−1.592	0.111	−0.222
Number of falls in the last year		1.52 (2.24)	0.42 (0.76)	−2.131	0.033	−0.298
FIQR		51.45 (17.71)	N.A.			
TSK-11		25.68 (6.54)	20.54 (6.20)	−2.394	0.017	−0.335
FES-I		28.22 (7.55)	18.88 (4.75)	−4.779	<0.001	−0.669
TUG (s)		6.42 (0.84)	5.92 (0.74)	−2.196	0.028	−0.308
10-Step stair ascent (s)		4.72 (1.04)	3.83 (0.68)	−3.241	0.001	−0.454
Handgrip strength (Kg)	L	23.03 (4.48)	24.32 (3.86)	−0.914	0.361	−0.128
	R	24.52 (4.69)	25.99 (3.89)	−1.159	0.246	−0.162

Abbreviations: FM, Fibromyalgia; BMI, Body Mass Index; FIQR, Revised Fibromyalgia Impact Questionnaire; TSK-11, 11-item Tampa Scale of Kinesiophobia; FES-I, Falls Efficacy Scale International; TUG, Timed Up and Go; SD, Standard Deviation; s, seconds; Kg, Kilograms; L, Left; R, Right; N.A., Not Applicable.

Correlation analyses between the values of kinesiophobia, the impact of FM, the fear of falling, and the performance developed in the physical tests were performed in the two groups. Only the values which correspond to the women with FM significantly correlated. However, significant correlation was not found for the handgrip strength for the apparently healthy group or the FM group. These results are shown in Table 2.

Table 2. Relationship between kinesiophobia, impact of FM, fear of falling, and physical fitness tests.

Variable			FIQR	FES-I	TUG	10-Step Stair Ascent	Handgrip Strength	
	Group						L	R
TSK-11	Women with FM	Correlation coefficient	0.458	0.543	0.441	0.470	−0.265	−0.178
		p-value	0.028	0.005	0.027	0.018	0.201	0.395
	Apparently healthy women	Correlation coefficient	N.A.	0.122	0.310	0.283	0.183	0.045
		p-value	N.A.	0.572	0.140	0.180	0.393	0.836

Abbreviations: FM, Fibromyalgia; FIQR, Revised Fibromyalgia Impact Questionnaire; TSK-11, 11-item Tampa Scale of Kinesiophobia; FES-I, Falls Efficacy Scale International; TUG, Timed Up and Go; L, Left, R, Right; N.A., Not Applicable.

To obtain a more comprehensive analysis of the impact of fibromyalgia, the relationships between the score obtained in the TSK-11 and the specific questions that make up the domains of the FIQR are also shown. In this regard, within the "function" domain, a relationship was found with combing hair (r = 0.49, p = 0.013), lifting and carrying a bag full of groceries (r = 0.48, p = 0.015), and climbing stairs (r = 0.43, p = 0.032). A relationship was found with the overwhelming state of symptoms question inside the "overall impact" domain (r = 0.49, p = 0.012). Finally, in the "symptoms" domain, the pain question also showed a relationship with the score obtained in the TSK-11 (r = 0.49, p = 0.014). The rest of the questions did not show significant relationships.

4. Discussion

The present study aimed to evaluate the differences between apparently healthy women and women with FM in kinesiophobia. It also evaluated correlations between kinesiophobia and physical fitness tests (TUG, 10-step stair ascent test, and handgrip strength), fear of falling, and the impact of the FM. As we hypothesized, results showed that women with FM showed higher values of kinesiophobia and fear of falling than apparently healthy group. Furthermore, significant correlations were found in the FM group between kinesiophobia and impact of the disease, fear of falling, and performance in both TUG and 10-step stair ascent tests. Interestingly, a significant correlation was not found between kinesiophobia and handgrip strength in the FM group. Moreover, in the apparently healthy group, significant correlations were not found for any variable.

As commented above, our results showed that women with FM exhibited a higher level of kinesiophobia and fear of falling than the apparently healthy group. In this regard, our results are in line with a previous study that showed higher fear of falling levels in people with FM than in healthy controls [10]. These changes are probably due to the number of falls suffered [10], the symptomatology of FM, and other associated problems, including poor balance performance [10,53], postural instability [54], and poor functional performance [53]. Similarly, days with episodes of instability, kinesiophobia, and dizziness also explained more than half of the variance in the confidence in balance in FM patients [26]. Regarding kinesiophobia, previous studies found similar results [26,29]. However, Koçyiğit et al. [28] and Meeus et al. [55] found similar results but these investigations did not use the 11-item version of TSK.

In this sense, kinesiophobia is relevant as it dramatically affects the levels of physical activity [42], the activities of daily living [20], and the quality of life [18]. This would make people with FM enter a vicious circle where fear induces fear of pain, and fear of pain leads to disability partly due to increased sedentary time [13,14,56]. Thus, physical activity interventions are quite relevant in this population since it is a way to break this vicious circle, reducing pain levels and increasing the health-related quality of life [57,58]. The assessment of kinesiophobia seems essential in clinical settings since it could act as a barrier to rehabilitation programs [22]. In this line, people with FM characterized by severe pain, high fear of movement, and a reduced quality of life in the physical and social domains reported reduced levels of adherence to treatment [24]. Nevertheless, future studies should establish cut-offs levels for TSK-11 in people with FM to make better interpretations.

Previous studies have shown that people with FM showed a physical impairment that could reduce their ability to perform activities of daily living [3,4]. In this regard, our results showed lower performance in the FM group than in the apparently healthy group in the TUG and the 10-step stair ascent tests. This information is in line with previous studies [32,53]. Moreover, these tests are relatively close to tasks which have to be performed in daily living where people with FM find difficulties [32,59]. Patients with FM generally show low handgrip strength levels compared to healthy subjects [39,49,60,61]. However, our results have shown similar handgrip strengths between the groups and are in line with a previous research [62]. It is possible that these differences may not have been found, since the apparently healthy group showed lower levels of strength in comparison with other studies that had a similar age range and used the same measurement instrument [49,60,61]. In this regard, it seems essential to homogenize the handgrip strength protocols used in order to be able to perform accurate comparisons between studies [63].

Considering the relationships between TSK-11 and the variables analyzed in this study, there are significant relationships in the FM group between kinesiophobia and fear of falling, TUG, 10-step stair ascent, and the impact of FM. These relationships can be explained through the Fear Avoidance Model [12,13]. Pain, the main symptom of FM, is associated with high values of kinesiophobia [12,18,42,56,64,65] and may induce changes in cortical networks that perceive and regulate motor functions [66]. The physical performance obtained in the TUG and 10-step stair ascent significantly correlated with kinesiophobia. This may be since kinesiophobia can cause the avoidance of physical activity during activities of daily living, inducing a vicious cycle that contributes to the maintenance and progression of the disease [67]. This relationship has also been previously observed in the TUG [29] but not in the 10-step stair ascent test [3], probably due to the comfortable pace used by the participants to climb the stairs. In addition, this vicious cycle can explain the relationship between kinesiophobia and the impact of the disease. In this regard, Russek et al. [25] also found significant correlation between kinesiophobia and the impact of the disease. Our study analyzed the specific questions of the domains that constitute the FIQR. Pain is related to the score obtained in the TSK-11, as are activities such as combing hair, lifting and carrying a bag full of groceries, climbing stairs, and the overwhelming state of symptoms. However, a significant correlation was not found between kinesiophobia and the handgrip strength test. This result is consistent with a previous study that did not find significant correlation between kinesiophobia and handgrip strength in people with FM [29]. Furthermore, Ishak et al. [22], in older people with low back pain, reported significant correlation between kinesiophobia and mobility and balance measured through the TUG but not with the handgrip strength. We hypothesized that this could be due to the context and the motor pattern involved in this task since it is a static test that does not involve a translation of the body in space, and therefore, women may not feel "fear" during this test. Finally, fear of falling is another variable related to kinesiophobia in the present study. This association may be due to the painful memory of having suffered a fall or the possible pain generated by a future fall based on the fear-avoidance model of falling and functional disability [68]. However, more research is needed to clarify these interesting aspects.

The current study has some limitations. First, the sample was relatively small and only composed of women, so we cannot generalize the results to men. The second limitation was this cross-sectional design study could not establish causality, requiring longitudinal research or a randomized controlled trial to clarify these questions.

Furthermore, some recommendations for future research directions can emerge from this study. Firstly, it is necessary to continue using the 11-item TSK to assess kinesiophobia, establish cut-off points to identify the severity of kinesiophobia, and facilitate comparison between studies. Secondly, further research is needed into different treatment methods to improve physical performance, fear of falling, the impact of the disease, and kinesiophobia in this population through interventions that include larger samples based on size estimation, well-defined protocols, and long-term data. Similarly, future research should also include other significant factors associated with functioning, pain catastrophizing, and pain acceptance in FM. In this regard, a multidisciplinary approach is required due to the wide range of variables that could affect FM.

5. Conclusions

Women with FM showed higher kinesiophobia score, worse performance in mobility tests, and higher fear of falling than apparently healthy women. Kinesiophobia score is related to TUG performance, the 10-step stair ascent test, and the FES-I score and the impact of the disease in women with FM. However, this correlation was not observed in a physical fitness test with a less complex motor pattern such as handgrip strength test. The apparently healthy women did not show a significant correlation between kinesiophobia and any variables. The influence of kinesiophobia on conducting assessments in patients with chronic pain is relevant for healthcare professionals.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Research Ethics Committee of the University of Extremadura (approval number: 62/2017).

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

Data Availability Statement: The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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Effects of 24-Week Exergame Intervention on the Gray Matter Volume of Different Brain Structures in Women with Fibromyalgia: A Single-Blind, Randomized Controlled Trial

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Abstract: Background: Exergame-induced changes in the volume of brain gray matter have not been studied in fibromyalgia (FM). This study evaluates the effects of a 24-week exergame-based intervention on the gray matter volume of different brain structures in patients with FM through magnetic resonance imaging (MRI). Methods: A total of 25 FM patients completed 24 weeks of intervention program, and another 25 FM patients did not receive any intervention. T1-weighted MRI was used to assess brain volume, and FreeSurfer software was used to segment the brain regions. Results: No significant effects on gray matter volume of different structures and total gray matter were found. Conclusions: FM patients did not show significant changes in gray matter brain volume between the control and experimental groups after 24 weeks. FM patients showed significant relationships between peak oxygen consumption (pVO2) and the left and right regions of the hippocampus and the left and right regions of the amygdala.

Keywords: MRI; physical exercise; pain; virtual reality

1. Introduction

Fibromyalgia (FM) is a chronic disease characterized by widespread pain associated with other symptoms such as sleep disorders, fatigue, anxiety, depression, stiffness, poor physical fitness, or cognitive dysfunction [1], among others. These symptoms lead to a reduction in the health-related quality of life [2], mainly in women between 40 and 59 years old [3].

Previous studies in FM have shown alterations in metabolic activity, functional connectivity, and regions involved in processing pain (i.e., insula, thalamus, amygdala, hippocampus, among others), known as the "pain matrix" [4], and brain structures [5–11]. Moreover, patients with FM have shown lower thresholds and higher pain ratios, as well as changes in brain activity [12,13] and brain morphology in gray matter [13]. For example, a study found that FM patients have an accelerated brain gray matter loss, and it was related to the duration of the disease [8]. The authors of another study concluded that there is evidence that volumetric changes of gray matter in the frontal-cingulate cortex and the amygdala might reflect both neurobiological preconditions for central sensitization in FM and plastic changes as consequences of chronic pain input [14].

Pharmacological and nonpharmacological therapies have been used in the management of FM symptoms [15]. In this regard, physical exercise is the one that has accumulated the highest level of evidence to date in reducing the symptoms of this disease. In addition, it has been considered a cheap and effective tool for enhancing pain relief, physical function, and well-being [16–18]. It is important to emphasize that exercise has a fundamental role in avoiding the physiological effects of aging, as well as promoting the increase of neurogenesis, angiogenesis, and synaptogenesis [19]. These effects are mainly induced by the brain-derived neurotrophic factor (BDNF), growth and differentiation factor 11 (GDF11), and the vascular endothelial growth factor (VEGF), which directly affect brain plasticity [20].

To our knowledge, no studies have evaluated the exercise-induced changes in brain volume in people with FM. Nevertheless, previous longitudinal studies on exercise-based interventions [21], as well as in other populations such as healthy subjects [22], cognitive impairment [23,24], older adults [24,25], multiple sclerosis [26], or schizophrenia [24,27], have shown volume increases in the hippocampus.

Virtual reality-based exercise (VRE), also known as exergames, has shown benefits in the different populations [28,29]. In patients with FM, this type of intervention has been previously used in a nonimmersive version, obtaining improvements in the overall quality of life, pain, disease, mobility, balance, and fear of falling [30,31]. Furthermore, the effects of exergame-based interventions on the brain dynamics of patients with fibromyalgia have previously been studied, finding changes in brain dynamics that could be related to increased cerebral blood flow [32]. On the other hand, two studies have assessed changes in brain structure after exergame training in older adults [33,34]. Therefore, the effects of exergames on the brain are of great interest to the field of neuroscience. However, the effects of exergame-based interventions on brain volume in patients with FM have not previously been studied. Thereby, this study aims (1) to evaluate the effects of a 24-week exergame-based intervention on the gray matter volume of different brain structures of women with FM by magnetic resonance imaging (MRI) analysis, and (2) to analyze the relationship between aerobic and cognitive capacities with the gray matter volume brain structures. As exercise-based interventions can produce changes in brain morphometry, it is hypothesized that participants would show increased gray matter volumes in the different brain structures after the exergame intervention.

2. Materials and Methods

2.1. Trial Design

This study was a single-blinded randomized controlled trial. Participants were randomly assigned numbers by one of the researchers who did not participate in the statistical analysis or data acquisition and they were randomly allocated into two groups: the control group (CG) and the exercise group (EG). All evaluations were performed by another researcher who was blinded to the grouping allocation. Participants were not blinded since they were informed of the procedures and knew whether or not they were performing the exercise intervention. All procedures were approved by the University Research Ethics Committee (62/2017). The trial was registered at the International Standard Randomized Controlled Trial Number Registry (ISRCTN65034180), and the protocol is available in BioMed Central website [35]. Participants gave their written consent for the procedures in the study.

Different articles focused on the primary outcomes (i.e., electroencephalography, physical fitness, and quality of life) of the trial have been recently published [32,36–38]. Nevertheless, the hypothesis in the present study is entirely novel (improvements in different volumetric brain structures after an exergame intervention) and significantly differs from the other articles. This enables us to deeply examine the findings in the brain volume of women with FM. Furthermore, the scope, audience, and research professionals that this article involves are different and complementary.

2.2. Participants

A total of 56 women from a local FM association were recruited for this study and fulfilled the following inclusion criteria: (1) female between 30 and 75 years old; (2) diagnosed with FM by a rheumatologist according to the 2010 criteria established by the American College of Rheumatology; (3) able to communicate with research staff; (4) have read and signed the written informed consent conforming to the updated Declaration of Helsinki. Moreover, participants were excluded if (1) they were pregnant, (2) they had any cerebral injury, (3) illegible MRI sequences were obtained, (4) they had contraindications for physical exercise, or (5) they had changed their usual care therapies during the intervention program. The intervention was carried out in the University facilities (Faculty of Sport Science, Caceres, Spain) from January 2018 to June 2018.

2.3. Interventions

The EG participants completed a 24-week training program, whereas the CG participants continued their daily routine. The intervention consisted of two sessions per week (60 min per session). All sessions were conducted in groups of two or three participants in the university facilities, and there were no important adverse events as a result of the intervention. A specialized physical therapist, who conducted participant evaluations, also supervised all the sessions.

The exercise intervention was based on an exergame called VirtualEx-FM that was created by the research group, which aims to improve the ability to develop activities of daily living as well as physical conditioning in FM patients. VirtualEx-FM meets the key points of VR rehabilitation therapy [39] and has been used previously [30,31]. The program focuses on balance, postural control, coordination, mobility, aerobic conditioning, and strengthening of the upper and lower body, providing visual feedback and maintaining the correct execution of movements [31].

A typical session contained the following parts: (1) a video warm-up, where an expert performs joint movements and participants imitate these movements. The speed could be controlled by the expert at 0.5×, 1×, 1.5×, and 2×. (2) An aerobic component through dance steps (Zumba) performed by a dance teacher. (3) A game in which participants have to reach an apple with an avatar, getting to work on postural control and coordination, which was controlled and modified by the physical therapist. (4) Walking training, where participants must complete a virtual trail of footprints on a virtual floor. The interface allows the selection of different types of steps (i.e., normal, heel walking, tiptoe, raised knees, and raised heels; see Collado-Mateo et al. [31] for further details).

2.4. Data Collection and Outcomes

All the tests were carried out in the laboratory of the research group. Thus, tests were implemented at the beginning and the end of the intervention program by the same researchers. The variables measured were anthropometric measures, disease impact, cognitive decline, aerobic domain, and gray matter brain volumes.

First, anthropometric measurements of the participants were taken to report the body mass index (BMI). Subsequently, participants completed the Spanish version of the Fibromyalgia Impact Questionnaire (FIQ), which evaluates the impact of symptoms of the disease from 0 to 100, indicating the minimum to maximum impacts, respectively. FIQ is an extensively validated fibromyalgia-specific tool that captures the overall effects of fibromyalgia symptomatology (i.e., pain, fatigue, rested, stiffness, anxiety, depression, physical impairment, feeling good, or work missed) [40–42]. After that, trained research staff administered the Mini-Mental State Examination (MMSE), previously used in patients with fibromyalgia [43,44]. MMSE is a widely used test of cognitive function; it includes tests of orientation, attention, memory, language, and visual–spatial skills. A higher score represents a better cognitive state.

The 6-min walk test is a reliable measure in people with fibromyalgia [45]. The results of the 6-min walk test were used to predict peak oxygen consumption (pVO2) [46] through an equation from the distance covered in 6 min [47]. The regression equation to predict pVO2 from 6-min walk distance and BMI is pVO2 (ml/Kg/min) = $21.48 + (-0.4316 \times \text{BMI}) + (0.0304 \times \text{distance (m)})$.

2.5. Image Acquisition

T1-weighted structural MRI scans were acquired from a 3.0 Tesla (T) system (Achieva 3.0T TX, Philips Medical Systems, Best, Netherlands) with an 8-channel receiver head coil. For each T1-weighted structural scan, the parameters were set as follows: 196 slices were acquired; the turbo field echo (TFE) imaging sequence (time repetition/time to echo = 11.51/2.8 ms; matrix size = 256 × 256; flip angle = 10°; slice thickness = 0.9 mm; number of averages = 1) was used.

2.6. Image Processing

All T1-weighted images were processed using the FreeSurfer software 6.0 version, a program freely available for download (Laboratory for Computational Neuroimaging, Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA, USA) [48]. Automated segmentation of the T1-weighted images was used employing the recon-all command [49] on a MacBook Pro (Version OS X 10.14, 8GB, 2.30 GHz, Intel Core i5).

Preprocessing data include the following steps: (1) motion correction and averaging [50]; (2) removal of nonbrain tissue [51]; (3) automated Talairach transformation [52]; (4) segmentation of subcortical white matter and deep gray matter structures [53]; (5) intensity normalization [54]; (6) tessellation of the gray matter and white matter boundary [55]; (7) topology correction; (8) surface deformation following intensity gradients to reconstruction [53]. Structures that are part of the "pain matrix" (left and right regions of the hippocampus, insula, thalamus, amygdala, and cerebellum, in addition to total gray matter) and have an interest in the study of FM [56,57] were selected.

2.7. Statistical Analyses

The SPSS statistical package version 24 (IBM Corp, Armonk, New York, United States) was used to analyze the data.

To conduct the intention-to-treat analysis by multiple imputations (MIs) of missing values, the data from all 55 participants were used following the Sterne et al. guidelines [58]. Our missing data were classified as missing at random. The SPSS software package was used for the MIs of data.

Nonparametric tests were conducted because the dataset was not large and the data were not always Gaussian. To explore the effectiveness of the exergame-based intervention, the Mann–Whitney U-test was conducted to examine the differences between groups for each variable. Moreover, within-group comparisons were conducted by the Wilcoxon signed-rank test.

The Benjamini–Hochberg false discovery rate correction for multiple comparisons was applied in each comparison to avoid Type I errors. The partial eta-squared effect size was reported for each statistical test [59]. According to Cohen [60], effect sizes could be classified as small ($0.01 \leq \eta^2 < 0.06$), medium ($0.06 \leq \eta^2 < 0.14$), and large ($\eta^2 \geq 0.14$).

Furthermore, Spearman's rho correlation analyses were used to evaluate the relationship between pVO2, MMSE, and brain structure volumes.

3. Results

The flow diagram for participants is represented in Figure 1. A total of 56 women with FM were screened for eligibility. One participant was excluded for not meeting with the inclusion criteria. Therefore, 55 women were randomly allocated into two groups: CG and EG. Two women were not able to attend the final evaluations for CG. On the other hand, three women from EG were excluded by lack of time ($n = 2$) and a surgery unrelated to the exercise intervention ($n = 1$).

Table 1 shows the baseline characteristics of the participants of both groups. Differences between EG and CG were not observed in age, the impact of the disease, years with FM symptoms, peak volume oxygen consumption, MMSE, anthropometric characteristics, and gray matter brain volumes (p-value > 0.05).

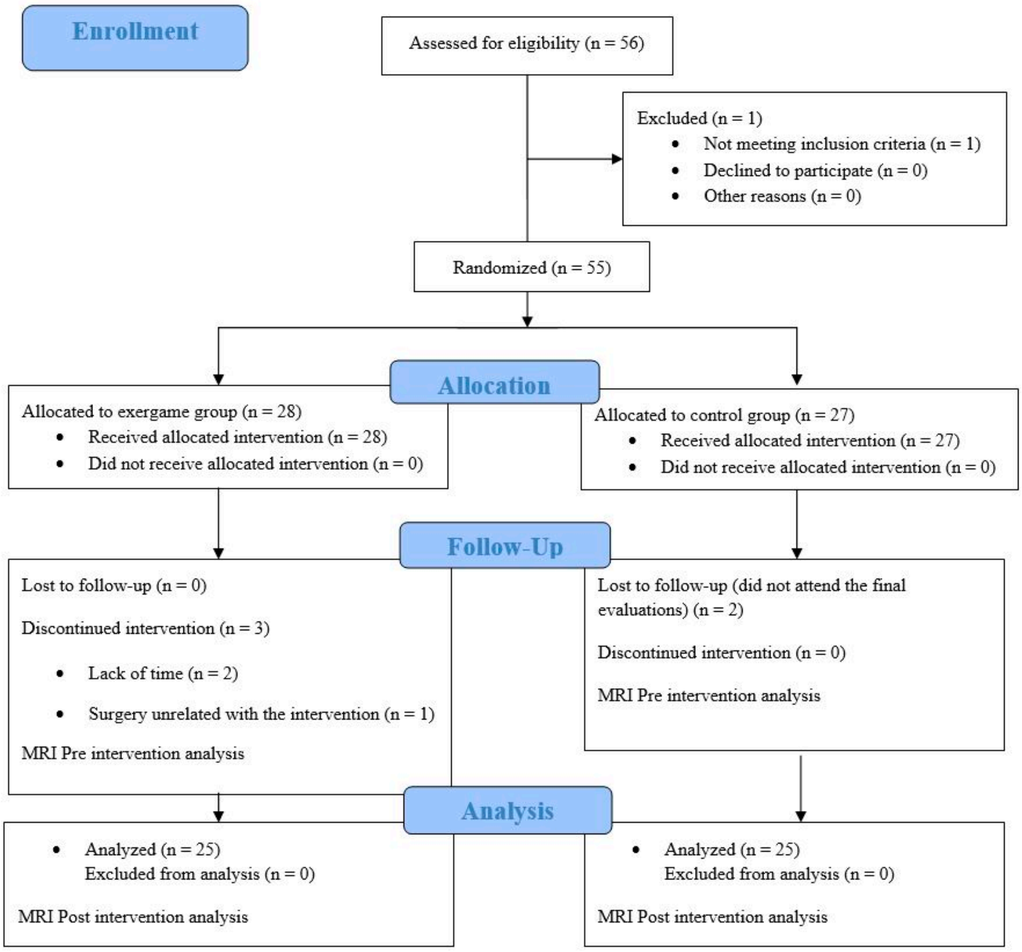

Figure 1. Flow chart of participants.

Table 1. Descriptive characteristics of participants and differences between groups at the baseline of fibromyalgia patients.

Variable	Exercise Group Median (IQR)	Control Group Median (IQR)	Value of the Contrast	*p*-Value
Sample size	25	25		
Age (Years)	54.00 (16.00)	53.00 (13.00)	−0.351	0.800
Height (cm)	160.00 (11.00)	159.00 (7.00)	−0.351	0.800
Weight (Kg)	69.30 (16.20)	72.35 (19.40)	−0.470	0.800
BMI (Kg/m^2)	27.00 (4.30)	28.35 (7.40)	−0.650	0.800
FIQ-100	57.58 (28.47)	63.90 (23.56)	−0.490	0.800
Years with FM	8.50 (10.75)	11.00 (10.25)	−0.308	0.800
pVO2 (ml/Kg/min)	23.77 (4.24)	24.46 (5.38)	−0.019	0.985
MMSE	29.00 (1.00)	28.50 (2.25)	−2.151	0.460
Left Hippocampus	3.04 (0.43)	2.93 (0.36)	−1.660	0.460
Right Hippocampus	3.08 (0.31)	3.07 (0.33)	−0.760	0.800
Left Insula	3.35 (2.06)	3.34 (2.49)	−0.919	0.800
Right Insula	3.82 (1.70)	4.28 (1.21)	−0.809	0.800
Left Amygdala	1.37 (0.19)	1.41 (0.16)	−0.319	0.800
Right Amygdala	1.63 (0.18)	1.64 (0.22)	−0.873	0.800
Left Thalamus	7.83 (0.94)	7.51 (0.61)	−1.532	0.477

Table 1. *Cont.*

Variable	Exercise Group Median (IQR)	Control Group Median (IQR)	Value of the Contrast	*p*-Value
Right Thalamus	7.07 (0.81)	6.81 (0.66)	−1.724	0.460
Left Cerebellum	48.37 (9.92)	46.12 (8.09)	−0.958	0.800
Right Cerebellum	51.39 (13.14)	49.04 (11.27)	−1.681	0.460
Total Cerebral GM	436.10 (72.50)	428.35 (126.54)	−0.319	0.800

Abbreviations: IQR, interquartile range; BMI, body mass index; FIQ, fibromyalgia impact questionnaire; FM, fibromyalgia; pVO2, peak volume oxygen consumption; MMSE, mini-mental state examination; GM, gray matter.

Tables 2 and 3 show the efficacy and the intent-to-treat analyses, respectively. Significant differences in the effect of the exergame-based intervention were not found for the gray matter volumes of the different brain structures, the total volume of gray matter, the pVO2, and the MMSE score.

Table 2. Efficacy analysis of the effects of exergame intervention in patients with fibromyalgia on the different brain structures, the pVO2, and the MMSE.

Variables				Between Group Comparison			Within Group Comparison		
Brain Areas (cm^3)	Groups	Pre Median (IQR)	Post Median (IQR)	Value of the Contrast	*p*-Value	Effect Size	Value of the Contrast	*p*-Value	Effect Size
L. Hippocampus	EG	3.04 (0.43)	3.15 (0.22)	−0.342	0.925	−0.020	−2.738	0.016	−0.323
	CG	2.93 (0.36)	3.07 (0.24)				−2.372	0.039	−0.438
R. Hippocampus	EG	3.08 (0.31)	3.26 (0.36)	−0.075	0.925	0.071	−3.011	0.013	−0.354
	CG	3.07 (0.33)	3.15 (0.26)				−2.220	0.048	−0.354
L. Insula	EG	3.35 (2.06)	5.08 (3.16)	0.013	0.925	0.053	−3.320	0.007	−1.037
	CG	3.34 (2.49)	5.93 (1.12)				−2.896	0.016	−1.245
R. Insula	EG	3.82 (1.70)	5.76 (2.41)	−0.450	0.925	0.000	−2.516	0.022	−0.578
	CG	4.28 (1.21)	5.87 (1.23)				−2.451	0.036	−0.751
L. Amygdala	EG	1.37 (0.19)	1.39 (0.17)	−0.501	0.925	-0.090	−0.633	0.527	0.088
	CG	1.41 (0.16)	1.39 (0.11)				−0.087	0.931	0.003
R. Amygdala	EG	1.63 (0.18)	1.68 (0.27)	−0.103	0.925	0.197	−2.776	0.016	−0.329
	CG	1.64 (0.22)	1.65 (0.15)				−1.860	0.091	−0.290
L. Thalamus	EG	7.83 (0.94)	7.72 (0.80)	−0.918	0.925	−0.145	−4.107	0.020	0.272
	CG	7.51 (0.61)	7.41 (0.65)				−4.074	0.075	0.208
R. Thalamus	EG	7.07 (0.81)	6.95 (0.73)	−1.599	0.371	−0.338	−1.834	0.097	0.153
	CG	6.81 (0.66)	6.74 (0.48)				−0.991	0.373	−0.037
L. Cerebellum	EG	48.37 (9.92)	50.80 (8.43)	1.601	0.706	-0.397	−1.705	0.114	−0.158
	CG	46.12 (8.09)	48.27 (5.87)				−2.833	0.016	−0.466

Table 2. *Cont.*

Variables				Between Group Comparison			Within Group Comparison		
Brain Areas (cm^3)	Groups	Pre Median (IQR)	Post Median (IQR)	Value of the Contrast	*p*-Value	Effect Size	Value of the Contrast	*p*-Value	Effect Size
R. Cerebellum	EG	51.39 (13.14)	52.00 (6.91)	−1.483	0.377	-0.489	−1.282	0.236	−0.093
	CG	49.04 (11.27)	50.36 (8.96)				−2.798	0.016	−0.426
Total Cerebral GM	EG	436.10 (72.50)	507.24 (92.04)	−0.595	0.814	-0.177	−3.750	< 0.001	−0.939
	CG	428.35 (126.54)	521.54 (71.29)				−2.972	0.016	−0.965
pVO2 (ml/Kg/min)	EG	23.77 (4.24)	24.51 (3.86)	−1.911	0.371	0.462	−0.807	0.455	−0.108
	CG	23.62 (5.23)	23.02 (5.52)				−1.601	0.142	0.132
MMSE	EG	29.00 (1.00)	29.00 (2.50)	−0.983	0.706	−0.108	−1.996	0.075	0.404
	CG	28.00 (2.00)	28.00 (4.00)				−0.945	0.373	0.248

Abbreviations: IQR, interquartile range; GM, gray matter; pVO2, peak volume oxygen consumption; MMSE, mini-mental state examination; EG, exercise group; CG, control group; L, left; R, right.

Table 3. Intent-to-treat analysis of the effects of exergame intervention on the different brain structures, the pVO2, and the MMSE.

Variables				Between Group Comparison			Within Group Comparison		
Brain Areas (cm^3)	Groups	Pre Median (IQR)	Post Median (IQR)	Value of the Contrast	*p*-Value	Effect Size	Value of the Contrast	*p*-Value	Effect Size
L. Hippocampus	EG (*N* = 28)	3.10 (0.44)	3.17 (0.27)	−0.511	0.853	−0.057	−2.846	0.011	−0.304
	CG (*N* = 27)	2.95 (0.37)	3.07 (0.23)				−2.560	0.026	−0.434
R. Hippocampus	EG (*N* = 28)	3.11 (0.31)	3.28 (0.36)	−0.435	0.853	0.086	−3.155	0.009	−0.348
	CG (*N* = 27)	3.09 (0.35)	3.16 (0.29)				−2.239	0.058	−0.369
L. Insula	EG (*N* = 28)	3.44 (1.98)	5.20 (2.64)	−0.549	0.853	0.107	−3.628	< 0.001	−1.031
	CG (*N* = 27)	3.57 (2.10)	5.76 (1.24)				−3.628	< 0.001	−1.283
R. Insula	EG (*N* = 28)	4.00 (1.73)	5.71 (2.26)	−0.261	0.853	0.023	−2.951	0.011	−0.611
	CG (*N* = 27)	4.24 (1.66)	5.78 (1.24)				−2.600	0.026	−0.724
L. Amygdala	EG (*N* = 28)	1.37 (0.19)	1.39 (0.17)	−0.301	0.853	−0.150	−0.557	0.593	0.127
	CG (*N* = 27)	1.39 (0.16)	1.39 (0.13)				−0.237	0.816	−0.025
R. Amygdala	EG (*N* = 28)	1.64 (0.19)	1.69 (0.27)	−0.187	0.853	0.155	−2.900	0.011	-0.302
	CG (*N* = 27)	1.63 (0.22)	1.65 (0.17)				−1.989	0.088	−0.309

Table 3. *Cont.*

Variables				Between Group Comparison			Within Group Comparison		
Brain Areas (cm^3)	Groups	Pre Median (IQR)	Post Median (IQR)	Value of the Contrast	*p*-Value	Effect Size	Value of the Contrast	*p*-Value	Effect Size
L. Thalamus	EG (*N* = 28)	7.92 (0.97)	7.73 (0.83)	−0.559	0.853	−0.159	−2.774	0.030	0.288
	CG (*N* = 27)	7.53 (0.63)	7.41 (0.66)				−2.050	0.088	0.222
R. Thalamus	EG (*N* = 28)	7.09 (0.81)	6.95 (0.75)	−1.832	0.355	−0.330	−1.957	0.082	0.161
	CG (*N* = 27)	6.86 (0.68)	6.74 (0.50)				−0.836	0.468	−0.012
L. Cerebellum	EG (*N* = 28)	48.18 (8.60)	50.53 (8.12)	−1.138	0.712	−0.368	−1.878	0.098	−1.169
	CG (*N* = 27)	46.36 (7.46)	49.01 (6.09)				−3.031	0.013	−0.447
R. Cerebellum	EG (*N* = 28)	52.25 (11.40)	52.18 (7.39)	−1.851	0.355	−0.514	−1.087	0.360	−0.066
	CG (*N* = 27)	49.41 (10.03)	50.36 (7.63)				−2.991	0.016	−0.408
Total Cerebral GM	EG (*N* = 28)	438.64 (80.28)	498.36 (88.08)	−0.962	0.787	−0.177	−3.821	< 0.001	−0.852
	CG (*N* = 27)	432.38 (125.40)	520.53 (68.98)				−3.211	0.007	−0.935
pVO2 (ml/Kg/min)	EG (*N* = 28)	23.87 (4.28)	24.62 (3.88)	−2.189	0.355	0.466	−1.139	0.301	−0.126
	CG (*N* = 27)	24.08 (5.19)	23.02 (5.37)				−1.685	0.126	0.134
MMSE	EG (*N* = 28)	29.00 (2.00)	29.00 (2.50)	−1.098	0.712	-0.109	−2.113	0.055	0.388
	CG (*N* = 27)	29.00 (2.00)	28.00 (4.00)				−0.945	0.407	0.231

Abbreviations: IQR, interquartile range; GM, gray matter; pVO2, peak volume oxygen consumption; MMSE, mini-mental state examination; EG, exercise group; CG, control group; L, left; R, right.

Table 4 shows the relationship at baseline between the pVO2, the MMSE, and the gray matter brain volumes. The analyses revealed a relationship between the pVO2, the left and right regions of the hippocampus, and the left and right regions of the amygdala (*p*-value < 0.05).

Table 4. Relationships between the pVO2, the MMSE, and the brain structure volumes.

Variables		pVO2	MMSE
L. Hippocampus	Correlation coefficient	0.349	0.229
	p-value	0.017	0.125
R. Hippocampus	Correlation coefficient	0.478	0.205
	p-value	0.001	0.173
L. Insula	Correlation coefficient	0.102	0.248
	p-value	0.531	0.122
R. Insula	Correlation coefficient	0.102	−0.137
	p-value	0.506	0.369
L. Amygdala	Correlation coefficient	0.363	0.144
	p-value	0.014	0.346

Table 4. *Cont.*

Variables		pVO2	MMSE
R. Amygdala	Correlation coefficient	0.360	0.054
	p-value	0.015	0.723
L. Thalamus	Correlation coefficient	0.265	0.146
	p-value	0.079	0.339
R. Thalamus	Correlation coefficient	0.249	0.259
	p-value	0.099	0.085
L. Cerebellum	Correlation coefficient	0.214	0.113
	p-value	0.158	0.458
R. Cerebellum	Correlation coefficient	0.288	0.179
	p-value	0.055	0.238
Total Cerebral GM	Correlation coefficient	0.194	0.246
	p-value	0.201	0.103

Abbreviations: L, left; R, right; pVO2, peak volume oxygen consumption; GM, gray matter; MMSE, mini-mental state examination.

4. Discussion

This study is the first randomized controlled trial that examines the effects of an exergame-based intervention on the gray matter volume of different brain structures in patients with FM. The intervention did not show any overall effect in the volume of some brain structures involved in the "pain matrix" (hippocampus, amygdala, thalamus, insula, and cerebellum) as well as the total gray matter of the brain in the comparison of CG and EG.

Results showed that no statistically significant effects were found after 24 weeks of exergame intervention in the brain volumes studied. In line with our results, Firth et al. [24] reported in a review that aerobic exercise did not increase the hippocampus gray matter volumes, but produced retention of gray matter in the left hippocampus. However, this information should be taken with caution due to the heterogeneity of the groups and the programs included in this review. Along the same lines, a recent exergame-based study did not show increases in total gray matter and the hippocampus in older adults [61]. Regarding the thalamus, three studies did not show increases in volume after physical exercise interventions [25,26,62]. However, there are previous studies that have reported significant brain volume changes after exercise interventions. In this regard, Wittfeld et al. [63] found volumetric increases in the thalamus as well as in the cerebellum after an intervention with 2103 adults. Moreover, other previous studies have reported effects on the insula volume after aerobic [64] and dance interventions [65]. Considering the large variability of intensities, volumes, or types of training that have reported volumetric changes after physical exercise interventions, future research should elucidate how these variables (i.e., volume, intensity, and type of training) modulate brain volume changes. In addition, if dance interventions are performed, consideration should be given to whether the exercises performed are creative or repetitive, as they influence neuronal survival and brain volume changes [65].

The duration of the intervention might explain why significant results were not achieved. In this regard, previous studies have reported increases in different brain structures, mainly in the hippocampus, after twelve months of an intervention [25,66,67]. Furthermore, this hypothesis may be reinforced by the results of Nieman et al. [66], where they did not find volumetric changes after six months of intervention but did after 12 months. However, the 24-week exergame-based intervention has previously shown significant effects in physical fitness [36,38], quality of life and pain [36], autonomic modulation [37], and even in the EEG beta power spectrum [32] in women with FM. Interestingly, this could indicate that brain volume-related changes need more time to be achieved. Therefore, future studies should investigate the role of intervention duration in brain volume changes.

However, the within-group analysis showed significant changes in both intervention and control groups. An analysis of different brain volumes in the same group of patients may represent a critical step in elucidating the central mechanisms of FM. The significant changes within groups are in line with previous morphometric reports of changed gray matter volumes in FM patients [68]. Another study has reported volumetric changes to be more pronounced with longer exposure to FM pain. In that case, the authors explained that a longer FM duration reflects a compensatory mechanism in which the brain may attempt to prevent the negative effects of constant nociceptive input [69]. It is also possible that the morphometric changes reflect an increase in the affective–evaluative processing of pain, as has been suggested to occur in patients with chronic lower back pain [70].

The correlations of the present study provide interesting information regarding the significant relationships found between pVO2 and the right and left regions of the hippocampus and the right and left regions of the amygdala. Similar to our results, another study has indicated that higher levels of aerobic fitness are associated with higher hippocampal volumes in older humans [71]. Consequently, it is known that aerobic exercise increases cerebral blood volume in the dentate gyrus of adults, which is related to neurogenesis [72]. On the other hand, the significant relationships found between pVO2 and the right and left regions of the amygdala may be in line with the results of a study that analyzed neural activity and respiratory frequency on anticipation of anxiety. In the most anxious subject, electric current sources were found in the left amygdala. The activation of this area participates in the enhancement of respiratory frequency [73]. Thus, it could be interesting to study the relationship between the aerobic system and the amygdala, also taking into account that the population with FM is a population related to anxiety symptoms [74–76].

The present study has some limitations. First, we only included women with FM, so we cannot generalize the results to men with FM. In addition, the women of the present study have different ages, being an aspect to consider in gray matter studies [77]. Second, the effect of the exergame intervention cannot be isolated since no group performed traditional exercise training. Finally, the intensity of training was not specified since the personal conditions of the participants were changing due to the disease. However, this is the first study that evaluates the effects of an exergame tool on different gray matter volumes of brain structures in women with FM.

5. Conclusions

The exergame-based intervention did not induce significant changes in gray matter brain volume when comparing CG and EG of women with FM. The patients of the present study showed significant relationships between pVO2 with the left and right regions of the hippocampus and the left and right regions of the amygdala. Future research on the determinants of the sensitivity to exercise-specific brain changes are warranted.

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