UNIVERSIDAD DE EXTREMADURA

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SANTOS VILLAFAINA DOMÍNGUEZ

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DOCTORAL THESIS

EFFECTS OF AN EXERGAME-BASED INTERVENTION ON PHYSICAL, BRAIN AND HEART VARIABLES IN WOMEN WITH FIBROMIALGIA

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Que la Tesis Doctoral realizada por **D. Santos Villafaina Domínguez**, con el título **"Efectos de un programa de ejercicio físico mediante realidad virtual sobre variables físicas, cerebrales y cardíacas en mujeres con fibromialgia"**, bajo mi co-dirección, reúne los requisitos necesarios de calidad, originalidad y presentación para optar al grado de Doctor, y está en condiciones de ser sometida a valoración de la Comisión encargada de juzgarla.

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“If the human brain were so simple
that we could understand it,
we would be so simple that we couldn’t”

– **Emerson M. Pugh** –

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La Tesis Doctoral es un camino largo, plagado de incertidumbre y con muchas bifurcaciones ante las que tienes que tomar decisiones rápidas sin saber muy bien hacia dónde te van a llevar. Por ello, es importante contar con un equipo detrás, cada miembro con una pequeña-gran función, para lograr que la suma de sus aportaciones concluya con la culminación de un proyecto exitoso, como así ha sido. Así, me gustaría agradecer a cada una de esas PERSONAS su contribución.

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ABSTRACT

Background: Fibromyalgia is a chronic disease which is characterised by widespread musculoskeletal pain, with an estimated prevalence of 2.45% in Spain. Moreover, it is accompanied by several symptoms such as fatigue, stiffness, sleep disturbance, and cognitive impairments. In addition, abnormalities in autonomic modulation (dysautonomia) or even in the brain electrical activity have been detected in this population. Therefore, the impact of fibromyalgia symptoms led to a significant reduction of the health-related quality of life and the ability to perform activities of daily living. These activities are rarely presented as single-task, but requiring the ability to perform two simultaneous tasks involving motor and cognitive demands. This paradigm is known as dual-task and has been poorly studied in people with fibromyalgia.

Objective: Three different overall objectives can be differentiated in this project: a) To study the impact of dual-tasks on the physical fitness test performance in women with fibromyalgia; b) To analyse the electroencephalographic power spectrum of women with fibromyalgia; and c) To evaluate the effects of a 24-week exergame-based intervention in women with fibromyalgia in the quality of life, pain, physical function, autonomic modulation and brain electrical activity.

Methods: A total of six cross-sectional studies were conducted. Three of them were carried out to evaluate the impact of dual-task on physical fitness test performance, balance and upper-limb range of motion respectively. Other three of them were focused on the study of the impact of fibromyalgia or its related symptoms to the electroencephalographic power spectrum. In addition, a randomized controlled trial was conducted to study the effectiveness of a 24-weeks of exergame-based intervention on

the quality of life, pain, physical function, autonomic modulation and brain electrical activity. In this regard, four different articles were written to discuss all these outcomes.

Results and discussion: A total of ten articles published in journals indexed in the Journal Citation Reports have been included in this thesis. The main findings are: 1) women with fibromyalgia have lower physical fitness performance in both single and dual-task conditions than healthy controls. Moreover, the impact of dual-tasks seems to be greater in women with fibromyalgia than in healthy controls; 2) Women with fibromyalgia have an altered electroencephalographic power spectrum compared with healthy controls. Furthermore, years since patients were suffering from fibromyalgia have a significant association (more than the age of the patient) with the electroencephalographic response. Also, women with fibromyalgia with untreated depression showed an hypoactivation of the left hemisphere while eliciting depression symptoms; 3) A 24-week of exergame-based intervention has a significant effect on the quality of life, pain, physical function, autonomic modulation and brain electrical dynamics. In addition, the exergames-based intervention has greater benefits in those women with fibromyalgia with worse quality of life and pain level at baseline as well as in those with less time suffering from fibromyalgia symptoms. Lastly, improvements in the cardiorespiratory fitness remained after six months of detraining which could indicate that this long-term intervention (24 weeks) may have changed the lifestyle of women with fibromyalgia, being more physically active.

Keywords: Fibromyalgia; virtual reality; electhroencephalography; EEG; health; quality of life; heart rate variability; pain; physical exercise.

RESUMEN

Antecedentes: La fibromialgia es una enfermedad crónica que cursa con dolor musculoesquelético generalizado y que tiene una prevalencia estimada del 2,45% en España. Además, se acompaña de síntomas como pueden ser fatiga, rigidez, trastornos del sueño y trastornos cognitivos. Además, se han detectado anormalidades en la modulación autónoma (disautonomía) o incluso en la actividad eléctrica cerebral en esta población. Todos estos síntomas hacen que el impacto de la fibromialgia provoque una reducción significativa de la calidad de vida relacionada con la salud, así como de la capacidad de realizar actividades de la vida diaria. En este sentido, estas actividades rara vez se presentan como una sola tarea, requiriendo la capacidad de realizar dos tareas simultáneamente. Este paradigma se conoce como doble tarea y ha sido poco estudiado en personas con fibromialgia.

Objetivos: Se pueden diferenciar tres objetivos generales en esta Tesis Doctoral: a) Estudiar el impacto de las tareas duales en el rendimiento de las pruebas de condición física en mujeres con fibromialgia; b) Analizar el espectro de potencia electroencefalográfica de mujeres con fibromialgia; y c) Evaluar los efectos de una intervención de 24 semanas basada en *exergames* en la calidad de vida, dolor, función física, modulación autónoma y actividad eléctrica cerebral en mujeres con fibromialgia.

Métodos: Se realizaron un total de seis estudios transversales. Tres de ellos se llevaron a cabo para evaluar el impacto de la tarea dual en pruebas de condición física, el equilibrio y el rango de movimiento de las extremidades superiores, respectivamente. Los otros tres se centraron en el estudio del impacto de la fibromialgia o sus síntomas con el espectro de potencia electroencefalográfica. Además, se realizó un ensayo controlado aleatorizado con el fin de estudiar la efectividad de una intervención de 24 semanas

basada en *exergames* sobre la calidad de vida, el dolor, la función física, la modulación autónoma y la actividad eléctrica cerebral. En este sentido, se redactaron cuatro artículos diferentes para discutir todos estos resultados.

Resultados y discusión: Se han incluido en esta Tesis un total de diez artículos publicados en revistas indexadas en *Journal Citation Reports*. Los principales hallazgos son: 1) las mujeres con fibromialgia presentan un rendimiento físico más bajo, tanto en condición de tarea simple como dual, que controles sanos. Además, el impacto de las tareas duales parece ser mayor en mujeres con fibromialgia que en controles sanos; 2) las mujeres con fibromialgia muestran un espectro de potencia electroencefalográfica alterado en comparación con los controles sanos. Por otra parte, los años transcurridos desde que los pacientes padecían síntomas de fibromialgia se asocian significativamente (más que la edad del paciente) con la respuesta electroencefalográfica. También, las mujeres con fibromialgia con depresión no tratada mostraron una hipoactividad del hemisferio izquierdo mientras se provocaron sentimientos depresivos; 3) Una intervención de 24 semanas basada en el ejercicio ejerce un efecto significativo en la calidad de vida, el dolor, la función física, la modulación autónoma y la dinámica eléctrica del cerebro. Asimismo, la intervención basada en el ejercicio tiene mayores beneficios en aquellas mujeres con fibromialgia con peor calidad de vida y nivel de dolor al inicio del estudio, así como en aquellas que hace menos tiempo que padecen síntomas de fibromialgia. Por último, las mejoras en el *fitness* cardiorrespiratorio se mantuvieron después de seis meses de desentrenamiento, lo que podría indicar que esta intervención a largo plazo (24 semanas) puede haber cambiado el estilo de vida de las mujeres con fibromialgia, siendo físicamente más activas.

Palabras Clave:

Fibromialgia; realidad virtual; electroencefalografía; salud; calidad de vida; variabilidad de la frecuencia cardíaca; dolor; ejercicio físico.

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This Ph.D. thesis is based on ten studies which have been performed in the period from 2015-2020 at the Physical Activity, Quality of Life and Health Research Group (AFYCAV, CTS011), Faculty of Sport Sciences, University of Extremadura, Cáceres, Spain.

The studies published are:

Studies:		***Quartile and Impact Factor:***
Study I:	Villafaina, S., Collado-Mateo, D., Domínguez-Muñoz, F. J., Fuentes-García, J. P., & Gusi, N. (2018). Impact of adding a cognitive task while performing physical fitness tests in women with fibromyalgia: a cross-sectional descriptive study. *Medicine*, *97*(51). DOI: 10.1097/MD.0000000000013791.	Q2 (IF:1.87)
Study II:	Villafaina, S., Gusi, N., Rodriguez-Generelo, S., Martin-Gallego, J. D. D., Fuentes-García, J. P., & Collado-Mateo, D. (2019). Influence of a Cell-Phone Conversation on Balance Performance in Women with Fibromyalgia: A Cross-Sectional Descriptive Study. *BioMed Research International*, *2019*. DOI: 10.1155/2019/5132802.	Q3 (IF:2.197)

Study III:	Villafaina, S., Polero, P., Collado-Mateo, D., Fuentes-García, J. P., & Gusi, N. (2019). Impact of adding a simultaneous cognitive task in the elbow's range of movement during arm curl test in women with fibromyalgia. *Clinical Biomechanics*, *65*, 110-115. DOI: 10.1016/j.clinbiomech.2019.04.006.	Q2 (IF:1.863)
Study IV:	Villafaina, S., Collado-Mateo, D., Fuentes-García, J. P., Cano-Plasencia, R., & Gusi, N. (2019). Impact of Fibromyalgia on Alpha-2 EEG Power Spectrum in the Resting Condition: A Descriptive Correlational Study. *BioMed research international*, *2019*. DOI: 10.1155/2019/7851047.	Q2 (IF:2.583)
Study V:	Villafaina, S., Collado-Mateo, D., Fuentes-García, J. P., Domínguez-Muñoz, F. J., & Gusi, N. (2019). Duration of the Symptoms and Brain Aging in Women with Fibromyalgia: A Cross-Sectional Study. *Applied Sciences*, *9*(10), 2106. DOI: 10.3390/app9102106.	Q2 (IF:2.217)
Study VI:	Villafaina, S., Sitges, C., Collado-Mateo, D., Fuentes-García, J. P., & Gusi, N. (2019). Influence of depressive feelings in the brain processing of women with fibromyalgia: An EEG study. *Medicine*, *98*(19). DOI: 10.1097/MD.0000000000015564.	Q2 (IF:1.87)

Study VII:	Villafaina, S., Collado-Mateo, D., Dominguez-Munoz, F. J., Fuentes-Garcia, J. P., & Gusi, N. (2019). Benefits of 24-Week Exergame Intervention on Health-Related Quality of Life and Pain in Women with Fibromyalgia: A Single-Blind, Randomized Controlled Trial. *Games for health journal*, *8*(6), 380-386. DOI: 10.1089/g4h.2019.0023.	Q1 (IF:1.782)
Study VIII:	Villafaina, S., Collado-Mateo, D., Fuentes, J. P., Rohlfs-Domínguez, P., & Gusi, N. (2019). Effects of Exergames on Brain Dynamics in Women with Fibromyalgia: A Randomized Controlled Trial. *Journal of clinical medicine*, *8*(7), 1015. DOI: 10.3390/jcm8071015.	Q1 (IF:5.597)
Study IX:	Villafaina, S., Collado-Mateo, D., Domínguez-Muñoz, F. J., Gusi, N., & Fuentes-Garcia, J. P. (2020). Effects of exergames on heart rate variability of women with fibromyalgia: A randomized controlled trial. *Scientific Reports*, *10*(1), 1-8. DOI: 10.1038/s41598-020-61617-8.	Q1 (IF:4.011)
Study X:	Villafaina, S., Borrega-Mouquinho, Y., Fuentes-García, J. P., Collado-Mateo, D., & Gusi, N. (2020). Effect of Exergame Training and Detraining on Lower-Body Strength, Agility, and Cardiorespiratory Fitness in Women with	Q1 (IF:2.468)

Fibromyalgia: Single-Blinded Randomized Controlled Trial. *International Journal of Environmental Research and Public Health*, *17*(1), 161. DOI: 10.3390/ijerph17010161.

ABBREVIATIONS

DMN	Default mode network
DT	Dual-task
DTC	Dual-task cost
EEG	Electroencephalography
EQ-5D-5L	5-level EQ-5D version
EULAR	European League Against Rheumatism
FM	Fibromyalgia
fMIR	Functional magnetic resonance imaging
GDS	Geriatric Depression Scale
HFD	Higuchi fractal dimension analysis
HF	Relative power of the high-frequency band
HRQoL	Health-related quality of life
HRV	Heart rate variability
LF	Relative power of the high-frequency band
MRI	Magnetic resonance imaging
Pnn50	Percentage of successive RR intervals that differ by more than 50 ms
RMSSD	Square root of differences between adjacent RR intervals
SD1	Poincaré plot standard deviation perpendicular the line of identity
SD2	Poincaré plot standard deviation along the line of identity
SDNN	Standard deviation of NN intervals
SSS	Symptoms severity score
ST	Single-task
TPN	Task-positive network
VAS	Visual analogue scale
VR	Virtual reality
WPI	Widespread pain index

MAIN FINDINGS

What is already known about the topic?

- Fibromyalgia-related symptoms led to a reduction in the ability to perform activities of daily living.
- Dual-task paradigm is close to activities of daily living since two tasks are simultaneously presented.
- Contradictory results were reported about the impact of fibromyalgia on dual-task performance in people with fibromyalgia.
- Pain and motor control could compete for brain resources.
- People with fibromyalgia have alterations on the autonomic modulation and electroencephalic (EEG) response even at rest. However, little evidence has been reported yet.
- Exergame-based interventions have been shown to be effective in enhancing health-related quality of life, pain or physical function. However, effects on autonomic modulation, electrical brain response, quality of life, pain or the detraining effects on physical function have not been studied in longer interventions.

What this project adds:

- Physical fitness, balance or elbow´s range of motion is reduced when a cognitive task or an activity of the daily living is simultaneously added.
- Dual-task interference is greater in fibromyalgia than in healthy controls.

- Alpha-2 EEG power spectrum is altered in the resting condition in people with fibromyalgia when compared with healthy controls. Moreover, it is correlated with pain intensity levels in people with fibromyalgia.
- EEG theta power spectrum seems to be altered in those people with fibromyalgia who had more years suffering from fibromyalgia. This could indicate a premature brain ageing derived from fibromyalgia condition.
- Left hemisphere hypoactivation was observed in fibromyalgia patients with untreated depression depressive feelings were elicited. in women with fibromyalgia. Differences were not found between fibromyalgia patients without depression and women with both fibromyalgia and depression who were under antidepressant medication.
- Significant effects on the health-related quality of life, pain, physical function, autonomic modulation and EEG power spectrum were observed after 24-weeks of exergame-based intervention.
- Subgroup analyses showed that this exergame-based intervention could be more effective in those people with fibromyalgia, which fewer duration of the symptoms and with lower quality of level before the intervention.
- Cardiorespiratory fitness improvements remained after 24-weeks of detraining, which could indicate that this long-term intervention (24 weeks) may have changed the lifestyle of women with fibromyalgia, being more physically active.

Chapter 1 | BACKGROUND

Chapter 1. BACKGROUND

1.1. Fibromyalgia: Definition, prevalence and diagnostic

Fibromyalgia (FM) is a chronic disease which is mainly characterised by widespread musculoskeletal pain. This is accompanied by several symptoms which include the social, the mental and the physical health of patients. In this regard, fatigue, stiffness, sleep disturbance, and cognitive impairments are the most common symptoms [1]. The cause of this syndrome is still unknown. However, previous studies pointed out that the genetics [2,3] and/or stress [4-6] could be behind the cause of FM.

The estimated prevalence of FM in Spain is 2.45% [7], being more prevalent in women than in men in a ratio 20:1 [8]. This is in line with the prevalence estimated in Europe (2.9-4.7%) [9]. Moreover, 2.1% of the worldwide population suffer from FM [10]. These number together with the significant incapacity of the FM make that the health-costs are around to 10.000 dollars per year [11]. In Spain, the extra-cost of FM is around 5.000 €/year per patient [12]. This is more than 14.000 million euros per year [10].

Since in 1990 appeared the first diagnostic criteria of FM [13], these criteria have been evolved in order to be less affected by cultural or social constructs. Nowadays, the last update [14] consider four diagnostic criteria:

- (1) Widespread pain index (WPI) ≥ 7 and symptoms severity score (SSS) ≥ 5 OR WPI of 4–6 and SSS score ≥ 9.
- (2) Generalized pain, defined as pain in at least 4 of 5 regions, must be present. Jaw, chest, and abdominal pain are not included in generalized pain definition.
- (3) Symptoms have generally been present for at least 3 months.

- (4) A diagnosis of FM is valid irrespective of other diagnoses

However, as Ablin and Wolfe [15] stated: *"FM and FM criteria are inherently subjective, culture- and context-driven, and subject to measurement error.*

1.2. Impact of fibromyalgia on the activities of daily living: The dual-task paradigm

The impact of FM symptoms led to a significant reduction of the health-related quality of life (HRQoL) of patients with FM [16]. Moreover, women with FM are more prone to falling than healthy controls since their strength, balance and functionality levels are quite similar to older women [17,18]. All these aspects make that people with FM have a reduced ability to perform activities of daily living [19]. In this regard, activities of daily living are rarely presented as a single-task (ST), but requiring the ability to perform two or more tasks simultaneously [20]. This paradigm is called dual-task (DT), and it is defined as the simultaneous execution of two tasks. In this regard, different combinations are possible such as motor-cognitive, motor-motor or cognitive-cognitive tasks.

However, traditionally, physical fitness tests have been carried out only involving the participant physically (only in an ST condition). This is relevant since people with FM have impaired the ability to perform activities of daily living and given that daily tasks are often performed along with other secondary activities (like talking, watching TV or merely thinking about something), traditional testing could be inappropriate for assessing the ability to perform activities of daily living. Thus, using physical tests in ST condition may be limited to the evaluation of physical fitness, while DT may be recommended to evaluate performance in the activities of daily living. This is a growing field of research, for example, a recent study investigates the test-retest reliability of the 30s arm curl test and 30s chair stand test in people with FM [21]. Results showed a "good

to moderate" reliability, so these tests are a reliable tool to evaluate the strength in a more ecological way than in ST condition.

As we can imagine, when we simultaneously performed two tasks, the performance of these tasks will be affected in some ways. Thus, Lacour*, et al.* [22] explored three different DT performance models:

1. The cross-domain competition model, where posture control and cognitive activity compete for attentional resources in DT conditions [23]. Therefore, postural performance in DT conditions is altered when compared to the ST postural performance. The adverse effects on posture are higher in older adults than in younger adults due to diminished cognitive and attentional capacities [24,25].
2. The U-shaped interaction model, where physical performances can be improved or diminished depending on the difficulty of the secondary task. For example, in young people, standing quietly on a force platform [26,27], when the cognitive load increased, balance improvements were observed. This may be due to a shift in the focus of attention away from posture control, increasing the automatic processing system of posture [28-30].
3. The task prioritization competition model, where it is predicted that older adults prioritize postural stability and balance to cognitive performance in DT conditions. In this regard, older adults will follow the selection, optimization and compensation model [31,32]. Therefore, they will select the goal that is crucial for the individual, then they will optimize the performance level of the selected goal by all relevant means, and lastly, they will use alternative strategies for maintaining the performance level. Thus, older adults allocate resources to posture

control instead of cognitive performance since they select the postural domain as more vital to them, particularly when postural-task complexity increased [33,34].

Previous studies have explored the impact of DT in people with FM [35-38]. In this regard, two studies reported a significant influence of adding a DT, showing a decrease in physical and cognitive performance [35,36]. Sempere-Rubio, Lopez-Pascual, Aguilar-Rodriguez, Cortes-Amador, Espi-Lopez, Villarrasa-Sapina and Serra-Ano [36] showed that the postural control worsens during DT condition in people with FM. In the same line, de Gier, Peters and Vlaeyen [35], observed that the pain at baseline will determine the physical performance. However, there are some studies in people with FM which did not report significant differences between ST and DT conditions. Peters, Vlaeyen and van Drunen [38] did not find significant differences when studying the hypervigilance for somatosensory signals under ST and DT conditions. Moreover, in the study of Rasouli, Fors, Vasseljen and Stensdotter [37], although, differences did not reach the significance level, an insufficient postural control in people with FM was observed.

Due to the lack of scientific knowledge about the impact of DT in people with FM, further investigation is needed to explore how the addition of a cognitive task or an activity of daily living (such as holding of a cell-phone conversation) modifies the performance of physical fitness in both upper and lower limbs.

1.3. Impact of the fibromyalgia on the nervous system: Brain and autonomic modulation

Some studies have suggested that people with FM suffer from an autonomic nervous system dysfunction (dysautonomia) [39-43]. It is characterized by persistent autonomic nervous system hyperactivity at rest as well as hyporeactivity during stressful situations [44]. According to Martinez-Lavin [43], dysautonomia could explain the different clinical

manifestation of FM. In this regard, because of a ceiling effect and adrenergic receptor desensitization and downregulation, the hyperactive sympathetic nervous system of such patients becomes unable to further respond to different stressors. This could explain the constant fatigue and morning stiffness of people with FM. Moreover, relentless sympathetic hyperactivity may explain sleep disorders or anxiety in these patients [45].

The heart rate variability (HRV) is defined as the beat-to-beat variation in the R-R interval. It is a reproducible and non-invasive measure of the autonomic nervous system function which provides information about the autonomic modulation (balance between the parasympathetic and the sympathetic nervous system) [46]. Low HRV values are associated with an increased risk of death from several causes [47] and in people with FM, HRV has been used to analyze the dysautonomia [39,40,42,43]. Moreover, the HRV has been considered as a measure of heart-brain interaction [48] since it could be altered by cognitive, attentional tasks or anxiogenic response [49-53]. HRV can be described using time-domain (quantify the amount of variability in measurements of the interbeat interval), frequency-domain (estimate the distribution of absolute or relative power into frequency bands) and non-linear measurements (quantify the unpredictability of a time series) [54]. Some of the variables used in this thesis are summarized in Table 1.

Table 1 | HRV parameters.

Parameter	Units	Description
		Time-domain measures
SDNN	ms	Standard deviation of NN intervals.
Pnn50	%	Percentage of successive RR intervals that differ by more than 50 ms.
RMSSD	ms	Square root of differences between adjacent RR intervals.
		Frequency-Domain measures
LF power	nu	Relative power of the low-frequency band in normal units (0.04- 0.15 Hz).
HF power	nu	Relative power of the high-frequency band in normal units (0.15- 0.4 Hz).
LF/HF	%	Ratio of LF to HF power.
		Non-linear measures
SD1	ms	Poincaré plot standard deviation perpendicular the line of identity.
SD2	ms	Poincaré plot standard deviation along the line of identity
SD1/SD2	%	Ratio of SD1 to SD2.
HFD		Higuchi fractal dimension analysis.

The widespread pain suffered which people with FM suffered from leads to somatic (fatigue or stiffness), psychiatric and psychological symptoms (sleep disturbance, depression, and cognitive impairment) [1,55]. Regarding cognitive impairments, people with FM have shown a reduced memory [56], processing speed [57], cognitive flexibility [58], and decision making [59]. Moreover, the prevalence of depression is higher in comparison with people without FM [60], and a bidirectional association between depression and FM has been observed [61]. These are the reasons why previous investigations have been focused on the brain and its functioning. Regarding brain

functioning, patients with FM showed alterations in the functional connectivity [62] and grey matter atrophy in the default mode network (DMN) regions [63]. The DMN comprises the posterior cingulate cortex and precuneus, the anterior medial prefrontal cortex, and the angular gyrus [64]. This circuit is active during task-free conditions (i.e. eyes-closed) or when participants are instructed to generate their own thoughts [65,66]. In this regard, people with FM showed an altered brain activity when observing negative emotions like facial expression of pain [67].

Moreover, previous studies have proposed that central nervous system hyperexcitability is an essential mechanism in the maintenance of the chronic pain of people with FM [68,69]. In this regard, several studies have reported significant differences between people with FM and healthy controls in terms of brain dynamics. In particular, people with FM patients shown abnormal activation in the thalamic nuclei, somatosensory cortex, anterior cingulate, insula, and prefrontal cortices during pain processing [70-72]. Moreover, compared to healthy groups, people with FM displayed altered brain dynamics [73] even at rest [74,75].

Electroencephalography (EEG) is a technic to record the electrical activity in the brain generated by firing between neurons. The EEG is commonly recorded by the use of EEG electrodes placed on the scalp. In this dissertation the International 10-20 system distribution has been used with 19 scalp location as shown in Figure 1.

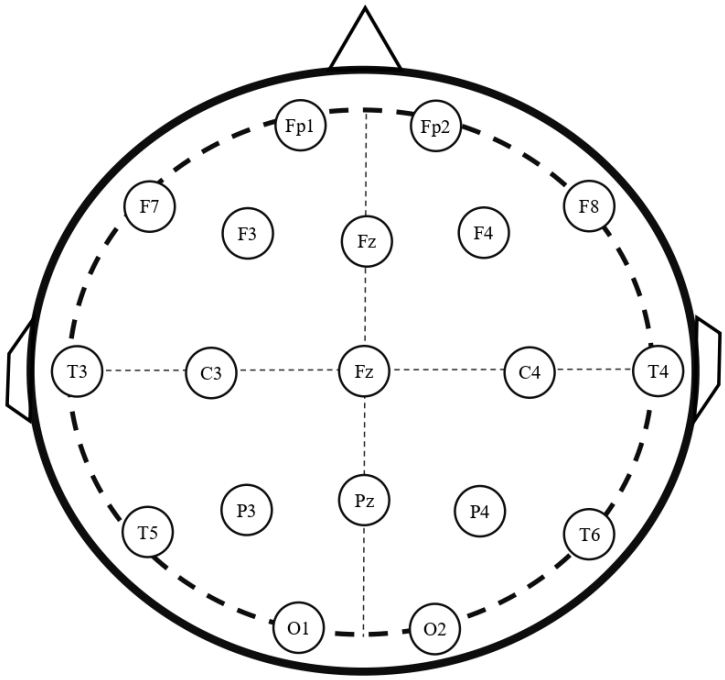

Figure 1. The 19 EEG electrodes locations according to the International 10–20 system: frontal (Fz, Fp1, Fp2, F3, F4, F7 and F8), central (Cz, C3, and C4), temporal (T3, T4, T5 and T6), parietal (Pz, P3, and P4), and occipital (O1 and O2). Source: Own elaboration.

The EEG has, as the main advantage, an excellent temporal resolution [75,76] and it is well established as a technic in the pain research [77]. In this regard, the electrical brain activity can be analyzed and recorded by several approaches such as resting EEG or evoked brain potentials. The resting EEG approach (recorded when the participant is relaxed without external stimulus) that has been used in this thesis, offers an analysis of the ongoing brain activity. The resting EEG has traditionally been analyzed in terms of frequency domains. In this regard, the EEG signal is decomposed into sine waves (through the Fourier analysis), constructing a compressed representation of the relative dominance of the various frequencies [78]. This is known as the power spectrum. The analysis of EEG data in this thesis is based on frequency analysis described by the

following standard bands: delta (0.5 – 4 Hz), theta (4–8 Hz), alpha (8-12) (which can be divided into alpha-1, 8–10 Hz, and alpha-2, 11–12 Hz), beta (12-30) (which can also be divided into beta-1, 13–18 Hz, beta-2, 19–21 Hz, and beta-3, 22–30 Hz). Table 2 summarizes some studies focused on the pain in different populations which have previously used these bands.

Table 2 | Pain studies and results in typical EEG frequency bands

Frequency bands	Observation	References
Delta	Increased after painful stimulus and in people with diabetes mellitus.	[79] [80]
	Decreased in people with FM.	[75]
Theta	Increased in neurogenic pain and in people with diabetes mellitus.	[81] [80]
	Increased in people with FM.	[73]
Alpha	Decreased by painful stimulus.	[82]
	Correlated to subjective pain perception.	[83]
	Decreased in people with FM.	[84]
Beta	Increased in neurogenic pain patients.	[81]
	Increased in people with FM.	[75]

In this regard, previous EEG studies in FM have focused on frequency domain analyses. People with FM showed greater power density in the beta band over the right middle frontal lobe and midcingulate gyrus [75] as well as significantly reduced delta, theta, and alpha bands in the frontal areas [74]. Moreover, Navarro Lopez, del Moral Bergos and Marijuan [84] stated that lower alpha EEG power band may associate with diminished

sensorimotor integration in brain processing in people with FM. Therefore, this could be an indicator of the need of people with FM to make extra efforts to attenuate the chronic pain sensation [84].

However, further studies are needed to deeply explore the brain dynamics at rest, while eliciting feelings or even after exercise interventions.

1.4. Treatment of fibromyalgia

The burden of living with FM is higher than with other rheumatic disorders and even higher than with other chronic diseases [85-87]. Thus, since medical management is not completely successful, people with FM usually become expert and active self-managers [88].

Following the division of the original European League Against Rheumatism (EULAR) [89], the main pharmacological and non-pharmacological therapies in the treatment of FM are summarized in this section.

1.4.1. Pharmacological approach

Before providing a list with the main pharmacological treatments in people with FM, it is important to remind that drug therapy only has a supportive role in the management of the symptoms so, it should be chosen to manage the individual´s predominant symptoms (mainly pain, sleep disturbance and psychological distress) [88].

Antidepressants drugs

Low-dose **amitriptyline** has traditionally been used for treating pain and sleep disturbance in people with FM. However, the evidence supporting this treatment is low quality [90].

Milnacipran which inhibits the reuptake of serotonin and noradrenaline (norepinephrine), showed modest efficacy [91].

Duloxetine treatment shows pain relief in moderate-quality studies [92].

Antiepileptic drugs

Pregabalin showed a small effect reducing the pain level and also has a small benefit for sleep [93]. It is administered since the concentrations of the pain facilitatory neurotransmitter glutamate, and substance P (targets of pregabalin) are elevated in people of FM.

Other drugs

Tramadol [94], pramipexole [95], and memantine [96] have preliminary evidence in the treatment of FM symptoms. Pure mu-opioid receptor agonist like codeine, fentanyl or oxycodone are strongly contraindicated due to a risk of opioid-induced hyperalgesia [94].

There is weak evidence that non-steroidal anti-inflammatory drugs are ineffective, and no trial evidence supports the efficacy of paracetamol [89].

1.4.2. Non-pharmacological approach

Non-pharmacological therapies have emerged as more effective in the treatment of FM than the pharmacological approach [89,97]. We can find a wide variety of non-pharmacological interventions which have achieved improvements in these populations. It is important to mention that this intervention usually increases the number of outcomes than pharmacological intervention. For instance, a pharmacological study probably would explore the effect of a drug in the quality of life, pain level, depression or impact of the disease. Meanwhile, a non-pharmacological intervention could incorporate the evaluation of the physical fitness or risk of falling among others.

Of all the therapies above, including both the pharmacological and non-pharmacological approaches, the physical exercise seems to be the only therapeutic recommendation which presents strong evidence reducing the FM symptoms [89].

Nevertheless, there are other non-pharmacological therapies which also present evidence reducing the FM symptoms, although its evidence is smaller or its limited to specific symptoms. Among other, we can highlight the acupuncture (reducing pain or fatigue) [98], nutrition or supplementation (improving the quality of life, physical function, pain or sleep quality) [99-101], whole-body vibration (improving balance) [102], cognitive behavioural therapy (enhancing pain level, the impact of the disease or mood) [103] or psychoeducational programs (enhancing pain level) [104].

1.5. Physical exercise for people with FM

As commented above, physical exercise is the treatment approach which presents strong evidence against the FM symptoms [89]. In this regard, Bidonde, *et al.* [105] in an systematic umbrella review and in a review focused on aerobic exercise [106], highlighted the characteristics that physical exercise interventions for people with FM should include. Therefore:

- Frequency of interventions should be at least three times per week.
- Duration of the physical exercise sessions of 31-60 min.
- Light and moderate intensity between 57-76% of the maximum heart rate.
- At least seven weeks of intervention.
- Physical interventions should be supervised.

In this regard, aerobic exercise has shown to improve the quality of life, pain or stiffness as well as the physical function or the cardiorespiratory fitness [106]. Moreover, the strength training has also shown to be more effective reducing the FM symptoms and improving the wellness and physical function than the usual care [107]. Physical exercise intervention based on strength training should include.

- A duration between 16-21 weeks.
- Mild to high intensity.
- Using resistance machines, free weight or body weight.
- Intervention should be supervised.

Importantly, women with FM can tolerate and benefit from resistance training. Nevertheless, there is evidence that eight weeks of aerobic exercise may be superior to moderate-intensity resistance training for reducing pain and sleep disorders in people with FM. However, there is also evidence that twelve weeks of low-intensity resistance training led to better results (in pain, fatigue or sleep) than flexibility exercises [107]. Previous studies did not evaluate the effects of DT in the physical or cognitive performances of people with FM.

Moreover, there are other types of exercise interventions that have shown to be effective in the management of FM symptoms. For example, the aquatic training could improve the wellness, physical function, or reducing the impact of the disease [108,109]. In this regard, previous studies based on tai-chi, yoga or Pilates [110-112] have shown to be beneficial. However, the comparison between protocols is complex due to methodological issues, small sample size, the wide variety of analysed outcomes or the evidence is inconclusive for new modalities of exercise.

However, poor adherence and high rate of dropouts to physical exercise are the main challenges of interventions in people with FM [113,114]. Thus, future studies should also explore motivating alternatives to face this problem.

1.6. Virtual Reality-based interventions: Exergames and fibromyalgia

According to Schultheis and Rizzo [115] virtual reality (VR) is "*an advanced form of human-computer interface that allows the user to "interact" with and become "immersed" in a computer-generated environment in a naturalistic fashion*". This emerging technology has been successfully integrated into several fields of such rehabilitation assessments, treatment and research. Two types of VR can be distinct [116]: 1) immersive where participants feel as they are inside the environment while 2) non-immersive environments that only allow participants to see the contents based on how the device in use – PC, smartphone, or tablet – is held and moved.

The introduction of new technologies and, specifically, VR could have a relevant impact on the motivation of participants in the promoting health context [117,118]. This is important since, a more motivating physical exercise program could lead to greater long-term effects on different variables, due to both greater adherence and probability of continuing to carry out physical activity once the intervention was completed [113]. Moreover, in the field of rehabilitation, VR reality interventions could be a key distractor tool for pain sensation [119]. These effects are higher in immersive VR, although in non-immersive VR has also been shown this distractor effect [120]. Therefore, in chronic pain population VR could be a useful tool to practice physical exercise diverting attention from pain in a motivating environment.

In this regard, the games which incorporate technology, play, and physical activity are named as exergames (also can be found as serious video games, exertion games,

exertainment, active-play videogames, interactive computer games, or game-based technology-mediated physical activity) [117]. Some of the better-known exergames devices are: Nintendo WiiTM (Redmon, WA, USA), Microsoft® Kinect (Redmond, WA, USA) y PlayStation® EyeToys (Sony Computer Entertainment America LLC, San Mateo, CA, USA).

The use of exergames has some advantages when compared with conventional physical exercise, for instance [117,121]:

- Exergames could be more motivating than conventional physical exercise.
- Difficulty and intensity of the programmed exercises in the simulated environment could be regulated.
- Exergames easily allow home-based intervention.
- Exergames could provide automatic feedback which implies less clinician or physical therapist dependence.
- Since exercise load are known and controlled, exergames intervention can be replicated.

The use of exergames in rehabilitation and health context is a growing research field. In this regard, exergame-based training involved a constantly changing environment where participant have to pay attention to some stimulus at the same time. Therefore, exergame interventions could be considered as a DT-based training [122]. Thus, previous studies have shown the effectiveness of this kind of interventions in different populations such as Parkinson´s disease [123], obesity [124] or chronic pain populations as back and neck pain [125]. Moreover, a systematic review and meta-analysis showed that exergames could reduce pain levels in patients with musculoskeletal pain [126]. In addition, exergames interventions have been introduced in people with FM [127,128]. Results from these studies indicated that an exergames program based on Zumba and other mobility

and gait tasks significantly improved mobility skills, HRQoL and pain. However, the duration of these interventions was only 8-weeks, and the effects of exergames on autonomic modulation, brain electrical activity are still unknown.

Chapter 2 | OBJECTIVES AND HYPOTHESES

Chapter 2. OBJECTIVES AND HYPOTHESES

Due to the lack of scientific evidence on: 1) the impact of FM on DT performance, 2) the impact of FM on EEG power spectrum, and 3) the effects of a long exergame-based intervention (24 weeks) in women with FM, the following objective emerged:

1. To study the impact of DT on the physical fitness test performance in women with FM.
    a. To evaluate the impact an ecological simultaneous task (such as holding on a cell-phone conversation) on the balance performance of women with FM while performing.
    b. To explore the impact of DT with particular focus on the upper-limbs of women with FM.

2. To analyse the EEG power spectrum of women with FM.
    a. To compare the EEG power spectrum at rest of women with FM with healthy controls.
    b. To identify correlations between pain intensity level at rest and EEG power spectrum.
    c. To study the influence of the age and the symptoms durations on the EEG power spectrum of women with FM.
    d. To explore the modifications of the EEG power spectrum when depressive feelings are elicited in women with FM as well as the effect of antidepressant medication intake on this response.

3. To evaluate the effects of a 24-week exergame-based intervention in women with FM.
    a. To evaluate the effects of a 24-week exergame-based intervention on the HRQoL and pain level of women with FM.
    b. To study the effects of a 24-week exergame-based intervention on the EEG power spectrum of women with FM.
    c. To evaluate the effects of a 24-week exergame-based intervention on the HRV of women with FM.
    d. To study the effects of a 24-week exergame-based intervention and 24-week of detraining on the physical fitness of women with FM.

Consistently, the major hypotheses to be tested are:

1. People with FM will have a decreased DT performance than healthy controls.
2. People with FM will show an abnormal EEG power at rest.
3. Pain intensity level will correlate with EEG power at rest.
4. Symptoms duration will have a significant impact on EEG power at rest.
5. Women with FM who present depression symptoms will show an altered EEG power spectrum when depressive symptoms are elicited.
6. A 24-week exergame intervention will enhance pain, physical fitness and HRQoL of women with FM
7. A 24-week exergame intervention will induce HRV and EEG changes in women with FM.

Chapter 3 | METHODOLOGY AND RESULTS OF PUBLISHED STUDIES

Chapter 3. METHODOLOGY AND RESULTS OF PUBLISHED STUDIES

In this section, all the main characteristics of both, the methodology and the results of all the published studies, are summarised. In this regard, a total of ten articles have been published elsewhere (six cross-sectional studies and four single-blinded randomised controlled trials). These articles have been divided into three sections:

1. Cross-sectional studies regarding DT and FM.
    a. *Impact of adding a cognitive task while performing physical fitness tests in women with fibromyalgia: A cross-sectional descriptive study.*
    b. *Influence of a Cell-Phone Conversation on Balance Performance in Women with Fibromyalgia: A Cross-Sectional Descriptive Study.*
    c. *Impact of adding a simultaneous cognitive task in the elbow's range of movement during arm curl test in women with fibromyalgia.*

2. Cross-sectional studies regarding EEG and FM.
    a. *Impact of Fibromyalgia on Alpha-2 EEG Power Spectrum in the Resting Condition: A Descriptive Correlational Study.*
    b. *Duration of the Symptoms and Brain Aging in Women with Fibromyalgia: A Cross-Sectional Study.*
    c. *Influence of depressive feelings in the brain processing of women with fibromyalgia: An EEG study.*

3. Randomised control trial on the effects of 24-week of exergame-based intervention.
    a. *Benefits of 24-Week Exergame Intervention on Health-Related Quality of Life and Pain in Women with Fibromyalgia: A Single-Blind, Randomized Controlled Trial.*
    b. *Effects of Exergames on Brain Dynamics in Women with Fibromyalgia: A Randomized Controlled Trial.*
    c. *Effects of exergames on heart rate variability of women with fibromyalgia: A randomized controlled trial.*
    d. *Effect of Exergame Training and Detraining on Lower-Body Strength, Agility, and Cardiorespiratory Fitness in Women with Fibromyalgia: Single-Blinded Randomized Controlled Trial.*

In order to facilitate the comprehension, each study will be accompanied by a QR code which redirect to the web site where each of the manuscript has been published.

Importantly, all procedures were previously approved by the University research ethics committee (approval number: 62/2017). Moreover, the randomised controlled trial was prospectively registered at the International Standard Randomised Controlled Trial Number Registry (ISRCTN65034180). The protocol is available on the following website: https://doi.org/10.1186/ISRCTN65034180.

3.1. Cross-sectional studies regarding dual-task and fibromyalgia

Study I: *Impact of adding a cognitive task while performing physical fitness tests in women with fibromyalgia: A cross-sectional descriptive study*

Objective. To investigate how the addition of a cognitive task modifies the performance in physical fitness tests in people with FM and healthy controls.

Linked to objective: 1 **Linked to hypothesis**: 1

Design and participants. A total of 61 women participated in this cross-sectional study, where 31 of them diagnosed with FM (age= 55.27 [9.49]) by a rheumatologist and 30 were healthy controls (age=50.84 [8.51]).

Procedure. Participants performed three physical fitness tests (arm curl test, handgrip, and 10-steps stair test) in 2 conditions: a) regular (ST condition) and b) while thinking in 3 words that were given before each test and had to be recalled and verbalised after the execution of each test (DT condition).

Results. Women with FM showed lower physical performance than healthy controls in both ST and DT conditions (p-value<0.05). In addition, differences between ST and DT conditions were observed in the 10-steps stair test in women with FM (p-value=0.004).

Interpretation. People with FM have diminished physical fitness, and this reduction is even higher when a cognitive task is added. This might be closely related to the reduction in the ability to perform daily life activities showed in people suffering from FM.

Study II: *Influence of a Cell-Phone Conversation on Balance Performance in Women with Fibromyalgia: A Cross-Sectional Descriptive Study*

Objective. To evaluate the impact of a simultaneous cell-phone conversation on balance performance in women with FM and healthy pain-free controls.

Linked to objective: 1 and 1a **Linked to hypothesis**: 1

Design and participants. This cross-sectional case-control study was performed in 34 women recruited from local self-help organizations and university facilities (n= 18; age= 54.83 (8.99) FM cases; n =16; age= 58.44 (10.55) healthy, pain-free controls).

Procedure. The participants had to perform a postural stability test (30 s) where the degree of stability was altered during the course of the task. The DT condition consisted in an active cell-phone conversation. The sway index, which is the root mean square distance for the *X*, *Y* coordinates during the test, was used in the statistical analyses because it does not depend on the starting distance from the centre of the platform.

Results. Compared with controls, women with FM showed higher dual-task cost (DTC) in balance variables, such as overall sway (p-value = 0.039) and anterior/posterior sway (p-value = 0.007). In the DT condition, overall (p-value =0.004) and anterior/posterior (p-value = 0.012) sway indices significantly decreased in women with FM but not in controls.

Interpretation. In women with FM, balance performance was adversely impacted by the holding of a simultaneous cell-phone conversation. The inability to conduct two tasks simultaneously may be related to reduced attention and may increase the risk of falling in this population.

Study III: *Impact of adding a simultaneous cognitive task in the elbow's range of movement during arm curl test in women with fibromyalgia*

Objective. To evaluate how DT could modify the range of movement, duration of repetitions and performance in the arm curl test in healthy controls and people with FM.

Linked to objective: 1 and 1b **Linked to hypothesis**: 1

Design and participants. Twenty women participated in this cross-sectional study, divided into two groups: 1) people with FM (N=10, age=52.00 [5.08]) and 2) age- and gender-matched healthy controls (N=10; age=51.60 [4.09]).

Procedure. The participants had to perform the arm curl test in two conditions: ST condition and performing a DT. The DT condition consisted of remembering three random unrelated words.

Results. Women with FM completed fewer repetitions than controls during DT condition (p-value= 0.015). Furthermore, both groups showed a significant decrease in the range of movement in the DT condition when comparing the mean of the three first repetitions with the three last ones (p-value < 0.05).

Interpretation. At the beginning of the test, the motor task might be prioritised over the cognitive task. However, at the end of the test, the cognitive task could require more attention due to the increased time since the words were heard, and also the motor task could require less attention after some repetitions have been performed. Thus, the addition of a cognitive task could lead to a less conscious execution of the motor task at the end of the test, which may be consistent with a reduced range of movement.

3.2. Cross-sectional studies regarding EEG and fibromyalgia

Study IV: *Impact of Fibromyalgia on Alpha-2 EEG Power Spectrum in the Resting Condition: A Descriptive Correlational Study*

Objective. To analyse the differences between people with FM and non-pain controls in terms of EEG power in the eyes-closed resting state. This study also aims to evaluate potential correlations between EEG power and subjective pain.

Linked to objective: 2, 2a and 2b **Linked to hypothesis**: 2 and 3

Design and participants. A total of 62 women participated in this cross-sectional study, where 31 of them diagnosed with FM (ager= 54.52 [10.23]) by a rheumatologist and 31 were healthy controls (age=50.84 [8.51]).

Procedure. The participants were instructed to rest on a chair in a quiet room with their eyes closed. The EEG signals were assessed during a 1-minute period by using the Enobio device, which is a wireless electrode system (Neuroelectrics, Cambridge, MA, USA). EEG was recorded from 19 scalp locations according to the International 10–20 system, namely, from seven frontal locations (Fz, Fp1, Fp2, F3, F4, F7, and F8), three central locations (Cz, C3, and C4), four temporal locations (T3, T4, T5, and T6), three parietal locations (Pz, P3, and P4), and two occipital locations (O1 and O2). The data were banded into the theta (4–7 Hz), alpha-1 (8–10 Hz), alpha-2 (11–12 Hz), beta-1 (13–18Hz), beta-2 (19–21Hz), and beta-3 (22–30) frequency bands.

Results. FM group exhibited a significantly lower (p-value<0.05) alpha-2 in C4, T3, P4, Pz, and O2 compared to the healthy controls. Interestingly, pain correlated negatively with alpha-2 in Cz, P4, and Pz only in the FM group (p-value<0.05).

Interpretation. Results could suggest that the chronic pain of people with FM acts like a noxious stimulus and could eventually decrease the alpha-2 power band in the resting condition.

Study V: *Duration of the Symptoms and Brain Aging in Women with Fibromyalgia: A Cross-Sectional Study*

Objective. To evaluate the effects of age and the duration of the symptoms on the brain dynamics of women with FM, by using EEG power spectrum analyses in an eye-closed resting state.

Linked to objective: 2 and 2c **Linked to hypothesis**: 4

Design and participants. A total of 29 women (ager= 55.89 [9.50]) participated in this cross-sectional study. Participants were divided into two groups (longer, N=14 and shorter duration of symptoms, N=15), taking into account the median duration of symptoms: 17 years.

Procedure. The participants were instructed to rest on a chair in a quiet room with their eyes closed. The EEG signals were assessed during a 1-minute period by using the Enobio device, which is a wireless electrode system (Neuroelectrics, Cambridge, MA, USA). EEG was recorded from 19 scalp locations according to the International 10–20 system, namely, from seven frontal locations (Fz, Fp1, Fp2, F3, F4, F7, and F8), three central locations (Cz, C3, and C4), four temporal locations (T3, T4, T5, and T6), three parietal locations (Pz, P3, and P4), and two occipital locations (O1 and O2). The data were banded into the delta (1.5-6), theta (6.5–8 Hz), alpha-1 (8.5–10 Hz), alpha-2 (10.5–12 Hz), beta-1 (12.5–18Hz), beta-2 (18.5–21Hz), and beta-3 (21.5–30) frequency bands.

Results. Theta power significantly correlated (p-value<0.05) with the duration of the symptoms, but not with age. In addition, participants were divided into two groups according to the years for which they were suffering from FM. Participants who had a longer duration of symptoms obtained higher theta power (p-value<0.05) in the frontal

(Fp1, F4, F7, F8, and Fz), central (C3, C4, and Cz), and parietal (P3 and Pz) areas than those who had a shorter duration of symptoms, which may be related to brain ageing.

Interpretation. This study demonstrates for the first time that the frontal, central, and parietal areas may be influenced by the years in which they were suffering from the symptoms of FM. This might indicate that the duration of these symptoms may have a higher impact on brain ageing than the actual age of the patient.

Study VI: *Influence of depressive feelings in the brain processing of women with fibromyalgia: An EEG study*

Objective. The objective of the present study was to explore the modifications of scalp EEG power spectrum in women with FM when depressive feelings are elicited in patients with and without depression. Furthermore, the study aims to compare the EEG power spectrum of patients with depression who were or not taking antidepressant medication.

Linked to objective: 2 and 2d **Linked to hypothesis**: 5

Design and participants. Twenty-eight women with FM (age=54.96 [10.43]) participated in this cross-sectional study. Moreover, they were divided into three groups according to the depression level (according to the final score of the 15-items Geriatric Depression Scale - GDS-15 -) and if they were taking antidepressant medication. Therefore:

1. FM patients with depression (GDS score > 5) who were taking antidepressant medication (n=9, age= 52.33 [9.90]).

2. FM patients with depression (GDSscore>5) who were not taking antidepressant medication (n=7, age= 53.43 [11.43]).

3. FM patients without depression (GDS score ≤ 5) and who were not taking antidepressants (n=12, age= 57.83 [10.42]).

Procedure. The participants were instructed to rest on a chair in a quiet room while responding to the GDS-15. The EEG signals were assessed by using the Enobio device, which is a wireless electrode system (Neuroelectrics, Cambridge, MA, USA). EEG was recorded from 19 scalp locations according to the International 10–20 system, namely,

from seven frontal locations (Fz, Fp1, Fp2, F3, F4, F7, and F8), three central locations (Cz, C3, and C4), four temporal locations (T3, T4, T5, and T6), three parietal locations (Pz, P3, and P4), and two occipital locations (O1 and O2). The data were banded into the theta (4–7 Hz), alpha-1 (8–10 Hz), alpha-2 (11–12 Hz), beta-1 (13–18Hz), beta-2 (19–21Hz), and beta-3 (22–30) frequency bands.

Results. FM patients with untreated depression showed a hypoactivation of the left hemisphere when compared with FM patients without depression. In addition, when compared FM patients without depression and women with both FM and depression who were taking antidepressant medications, differences in EEG power spectrum in the studied frequency bands were not found.

Interpretation. The hypoactivation of the left hemisphere while eliciting depression symptoms could be relevant in the regulation of negative emotions in women with FM.

3.3. Randomized controll trial on the effects of 24-week of exergame-based intervention

Study VII: *Benefits of 24-Week Exergame Intervention on Health-Related Quality of Life and Pain in Women with Fibromyalgia: A Single-Blind, Randomized Controlled Trial*

Objective. To evaluate the effects of 24-week exergame-based intervention on the HRQoL and the pain in people with FM as well as to analyse the effectiveness of the exergame intervention in subgroups based on the changes in the main variables (those who responded and those who did not).

Linked to objective: 3 and 3a **Linked to hypothesis**: 6

Design and participants. A total of 55 women with FM participated in this single-blinded randomised controlled trial. They were randomly allocated into two groups: Exergame group and control group.

Procedure. The exercise group completed a 24-week exergame-based intervention that focused on mobility, postural control, upper and lower limb coordination, aerobic fitness, and strength. This group received two 60-min sessions per week. The 5-level EQ-5D version (EQ-5D-5L), to assess the HRQoL, and a visual analogue scale (VAS) were administrated before and after the intervention.

Results. Significant effects on the perceived health status and pain intensity (p-value< 0.05) were found. K-means clustering procedure revealed two groups with different response to the intervention. The responding group obtained significant effects of the exergame intervention in EQ-5D-5L, pain VAS, and VAS-EQ, compared with those who did not respond.

Interpretation. Exergames-based interventions could be a useful tool to improve perceived health status and pain intensity level in women with FM with a reduced health-related quality of life.

Study VIII: *Effects of Exergames on Brain Dynamics in Women with Fibromyalgia: A Randomized Controlled Trial*

Objective. To evaluate the effects of an exergame-based intervention on the brain dynamics of women with FM via analysis of the EEG power spectrum, as well as to analyse the effectiveness of the intervention in subgroups of patients according to the number of years they had suffered from FM symptoms.

Linked to objective: 3 and 3b **Linked to hypothesis**: 7

Design and participants. A total of 55 women with FM participated in this single-blinded randomised controlled trial. They were randomly allocated into two groups: Exergame group and control group.

Procedure. The exercise group completed a 24-week exergame-based intervention that focused on mobility, postural control, upper and lower limb coordination, aerobic fitness, and strength. This group received two 60-min sessions per week. Participants were instructed to rest on a chair in a quiet room with their eyes closed. The EEG signals were assessed during a 1-minute eye closed period from 19 scalp locations according to the International 10–20 system.

Results. Significant group*time interactions (p-value<0.05) for power in the beta-3 frequency band across different EEG electrode locations (Fp2, F8, P4, P3, T6, T5, T4, O1 and O2), with all changes in favour of the exergame groups. Moreover, the subgroup analysis revealed between-group differences in the effectiveness of the exergame-based program when the duration of symptoms was included in the analysis, with differences between the EG and the CG detected in the subgroup that had suffered from FM

symptoms for fewer. In this regard, significant group*time interactions were observed in F8, T5 and T4.

Interpretation. Since previous studies have linked the EEG beta band with cerebral blood flow and reoxygenation, results of this randomised controlled trials may be related to increased cerebral blood flow after the exergame-based intervention.

Study IX: *Effects of exergames on heart rate variability of women with fibromyalgia: A randomized controlled trial.*

Objective. To evaluate the effects of 24-weeks exergame-based intervention on HRV in patients with FM.

Linked to objective: 3 and 3c **Linked to hypothesis**:7

Design and participants. A total of 55 women with FM participated in this single-blinded randomised controlled trial. They were randomly allocated into two groups: Exergame group and control group.

Procedure. The exercise group completed a 24-week exergame-based intervention that focused on mobility, postural control, upper and lower limb coordination, aerobic fitness, and strength. This group received two 60-min sessions per week. A short-term 5 min record at rest was used to assess the HRV using a heart rate monitor Polar RS800CX (Finland).

Results. Significant interaction (group*time) effects in SDNN, ln stress score, SD2, and SD1/SD2 ratio were found (p-value<0.05). Within-group analyses showed that the exergame group increased the SDNN and decreased ln stress score and SD2. In this regard, the control group showed an increased ln stress score, SD1/SD2.

Interpretation. Our results support the idea of vagal tone recovery due to exercise interventions in people with FM.

Study X: *Effect of Exergame Training and Detraining on Lower-Body Strength, Agility, and Cardiorespiratory Fitness in Women with Fibromyalgia: Single-Blinded Randomized Controlled Trial*

Objective. To analyse the effects of a 24-week exergame intervention and 24 weeks of detraining on lower-limb strength, agility, and cardiorespiratory fitness in women with FM.

Linked to objective: 3 and 3d **Linked to hypothesis**: 6

Design and participants. A total of 55 women with FM participated in this single-blinded randomised controlled trial. They were randomly allocated into two groups: Exergame group and control group.

Procedure. The exercise group completed a 24-week exergame-based intervention that focused on mobility, postural control, upper and lower limb coordination, aerobic fitness, and strength. This group received two 60-min sessions per week. A chair–stand test, 10 step stair test, and six-minute walk test were conducted to assess lower-body strength, agility, and cardiorespiratory fitness, respectively. Evaluations took place in three-time points: at the beginning, after 24-weeks of exergame-based intervention and 24-weeks after the end of the intervention.

Results. The exergame intervention significantly improved lower-limb strength and cardiorespiratory fitness. However, no significant effects on agility were observed. After the detraining period, lower-limb strength and agility returned to their baseline level, but improvements in cardiorespiratory fitness were sustained over time.

Interpretation. Exergame-based intervention is beneficial for physical fitness in people with FM. However, it should be practice regularly in order to maintain the benefits. This long-term intervention (24 weeks) may have changed the lifestyle of women with FM,

which could explain why cardiorespiratory fitness improvements remained after the detraining.

Chapter 4 | DISCUSSION

Chapter 4. DISCUSSION

Due to the lack of consensus regarding the impact of FM on the DT performance and the EEG power spectrum, this project conducted some cross-sectionals studies previously to apply the randomised controlled trial regarding these topics. Moreover, this project also aimed to study the effect of a long exergame-based intervention (24-weeks) on the quality of life, pain, autonomic modulation or EEG power spectrum of women with FM. In addition, the effects of 24-weeks of detraining after the exergame-based intervention on the physical function were analysed. Therefore, participants were monitored a total of one year since the trial started in order to address the National Institute for Health and Care Excellence (NICE) [129] recommendations to compare the effects of health treatments.

4.1. Impact of FM on DT

Results from the study ***I*** show that differences between people with FM and healthy controls. People with FM showed less performance in the handgrip, 10-step stair and arm curl test in both ST and DT conditions. These results are consistent with previous studies where differences between healthy controls and people with FM in DT conditions, during postural control tasks were reported [36,37].

Interestingly, within groups differences between DT and ST conditions in the FM group showed that only in the 10-steps stair test physical performances was significantly reduced by DT interference. The cross-domain competition model [22] (cognitive activity and physical performance compete for attentional resources) could explain this within-group difference in people with FM. Thus, when two tasks demand attention, the performance of at least one of them is reduced [22,23,130,131]. However, this was the most physically demanding test (10-steps stair test), which was analysed in this study, so that

differences could also be explained by the task prioritisation model [22]. This model hypothesised that older adults prioritised the task that they perceived to have greater relevance [34,132].

In this regard, study ***II*** showed that the DTC of the overall sway index and the anterior/posterior sway index of women with FM is negatively impacted by a cell-phone conversation, compared with healthy controls. In this study, the balance task started with a stable surface and ended with an unstable surface. This, together with the poor balance reported by women with FM [18], could make that participants would hypothetically prioritise the balance over the conversation according to the task prioritisation model [22]. This is in line with previous studies where participants with instability and risk of falling prioritised the postural control [22,34]. Moreover, in our study could be observed how in women with FM, even prioritising the motor task, the balance performance is lower than in healthy controls.

In this regard, people with FM showed and altered attention [133], which might be related to the close link between attention and pain [134]. Therefore, since women with FM may be constantly focused on pain, the attention available for other tasks would be limited (which could explain the poor performance during DT conditions). This hypothesis is supported by a previous study where Hamacher*, et al.* [135] observed that a reduction in pain reduced the DTC.

It must be noted that the motor pattern could also suffer from relevant changes as a consequence of the inclusion of a simultaneous task (not only the final score of the physical fitness test). Thus, the aim of the study ***III*** was to analyse the motor pattern changes of the upper limbs during DT conditions. In this study apart from the differences in physical performance in both ST and DT conditions between healthy and people with FM, a reduction of the elbow´s range of motion was observed between the first and the

last three repetitions, only in the DT condition. This reduction in the range of motion could be explained by the cross-domain competition model suggested by Lacour, Bernard-Demanze and Dumitrescu [22].

We hypothetically stated that the motor task, at the beginning of the task, is prioritised since the words were heard a few seconds ago. Thus, all the attention is consciously focused on the execution of the motor task (and the movement is performed with all the range of motion). However, at the end of the test when it was longer since the words were heard, the cognitive task could require more attention as well as the motor task could require less attention because some repetitions were previously performed. Moreover, the constrained action hypothesis stated that an external attentional focus may promote a more automatic motor control [136,137]. This leads to a less conscious movement execution evidenced by a more efficient or economic pattern [138-141] such as shortening the range of motion.

4.2. Impact of FM on EEG power spectrum bands

Study ***IV*** results indicated that women with FM had lower alpha-2 in the central, temporoparietal and occipital areas than healthy controls. Moreover, alpha-2 band negatively correlated with pain levels in the Cz, P4 and Pz scalp locations. Previous studies have reported abnormal EEG power spectrum in people with FM. In this regard, lower delta, theta, and alpha activity in the frontal areas [74] and greater beta activity over the right middle frontal lobe and the midcingulate gyrus [75] have been reported in people with FM. Moreover, [74] observed lower levels of alpha power spectrum in this population.

Alpha-2 oscillations are associated with tonic alertness in a network that includes the dorsal anterior cingulate cortex, the anterior insula, and the anterior prefrontal cortex

[142]. This is relevant since Vanneste, *et al.* [143] stated that the functional connectivity (in the alpha band) between the posterior and dorsal anterior cingulate cortex could indicate that the painful state has become part of the self-referential network [143]. This mechanism is known as allostatic reference resetting [144] and is hypothesised to underlie FM [145]. Allostasis can be defined as the adaptive response of the organism to maintain homeostasis to stressors. While allostasis has positive effects in the short term, excessive stress and/or inefficient management of allostasis can lead to allostatic load or overload [146]. This would prompt increases in the levels of cortisol and catecholamines, causing a structural remodelling of essential brain structures such as the hippocampus [147], the amygdala [148], or the prefrontal cortex [149,150].

These changes may relate to the learning and emotional deficits that are often observed in patients with chronic pain [151]. In the same line, the prevalence of depression in people with FM is higher in comparison with people without FM [60], and a bidirectional association between depression and FM has been observed [61]. In this regard, several studies report that traumatic events related to chronic pain diseases like FM [152-155]. These traumatic events may initiate the allostatic load and the resulting remodelling of the brain structures. This could explain the differences between people with FM and healthy controls in terms of their brain dynamics.

Depression is associated with altered brain processing patterns in the DMN and task-positive network (TPN) [156-159]. Whereas the TPN has been related to subserve active cognitive processing [160] (working memory or executive control), the DMN has been suggested to be related to self-relational processing [161] (i.e. autobiographical recall).

Study ***VI*** showed an hypoactivation of the left hemisphere when analysing the EEG power spectrum between patients with and without depression, taking the antidepressant medication into account. In this regard, women with FM with untreated depression

showed the left hemisphere hypoactivation. Previous studies in clinical populations with affective disorders [162,163] have shown that left hemisphere is important for regulation of negative emotions [164]. In our study, we used the GDS-15 [165] to elicit depressive feelings. However, other studies have used other alternatives, such as viewing images of faces expressing negative emotional states [166].

According to the mood-congruent memory, patients with depression are more likely to remember negative information [167] or create distressing memories [168]. Regarding FM, patients have shown alterations in the functional connectivity [62] and grey matter atrophy [63] in the DMN. Interestingly, a previous study reported that patients with FM have altered brain activity viewing facial expression of pain [67]. These alterations in the DMN have also been observed in patients with depression [169] during emotion processing.

The long-term consequences of pain have traditionally been of great interest in neuroscience [170]. Therefore, the effect of age and symptom duration of women with FM in EEG power spectrum frequency bands was investigated in the Study *V*. In this regard, these findings support previous research focused on chronic back pain patients where an altered brain activity and grey matter decreases correlated with the duration of the pain [171,172]. This study showed, for the first time, that theta power spectrum of frontal, central and parietal areas may be influenced by the years they were suffering from the symptoms of FM. This might indicate that the duration of these symptoms may have a higher impact on brain ageing than the actual age of the patient. It is important to consider that theta band (4-7 Hz) is of great interest because of its relationship with higher cognitive functions and induction of synaptic plasticity [78].

Regarding the alterations in theta power, previous studies have found them in Alzheimer's disease [173,174], mild cognitive impairment [175,176] or even related to brain

ageing in healthy people [177]. Authors related these alterations to hippocampus atrophy, located in frontal areas [175,178] and also in temporoparietal areas in Alzheimer's disease patients [174], which is in line with the results from the current study. Furthermore, in FM [179] and chronic pain populations [180,181], a significant reduction these important grey matter structures have been reported. In addition, FM symptoms could be partially explained by hippocampus dysfunction [182]. In our study, correlations between the age of the participant and power spectrum were not significant in any of the scalp locations. Therefore, the duration of symptoms seems to be the key variable under those alterations.

4.3. Effects of the 24-weeks exergame-based intervention

Exergames-based interventions have been previously reported improvements in the physical function and quality of life of women with FM after 8-week [127,128]. However, the effects of a longer intervention (24-week) on quality of life, physical function, autonomic modulation and EEG power spectrum were unknown.

Results from the study ***VII*** indicated that the exergame-based intervention significantly improved the perceived health status measured by the visual analogue scale of the EQ-5D-5L questionnaire and the pain level. The improvement of pain level, which also was observed in an 8-week exergame intervention [128], is relevant since pain is the main symptom of FM. Regarding the quality of life, a previous study by Collado-Mateo, Dominguez-Munoz, Adsuar, Garcia-Gordillo and Gusi [128] reported improvements of the EQ-5D-5L health utility, perceived health status using VAS and three dimensions of the EQ-5D-5L (mobility, pain and discomfort, anxiety and depression). In the same line, previous interventions based on aquatic training [183], dance [184] or stretching intervention [185] have also shown to increase the HRQoL. However, our intervention did not significantly improve the utility index of the EQ-5D-5L. As a previous one using the same program

[128], the dimensions "self-care" and "usual activities" are not improved after the intervention. This could be hypothetically attributed to the levels of pain and problems at baseline. This could partially explain why significant improvements were observed in the health VAS and not in the EQ-5D-5L utility index which employed these two unchanged dimensions to calculate the final score.

Study ***VIII*** showed that the exergame-based intervention had a significant effect on the EEG power spectrum of women with FM, increasing the beta-3 power spectrum in frontal, parietal, temporal and occipital areas. The effects of regular exercise on the brain is of great interest to the field of neuroscience since both animal [186-188] and human studies [189] have been reported benefits derived from neurogenesis and angiogenesis. In this regard, a decreased beta power spectrum is associated with reduced cerebral blood flow (because of anoxia or hypoxia) [190]. Thus, our results (an increase in beta power spectrum) is consistent with this, given that physical exercise promotes cerebral blood flow [191]. In this regard, exercise has the opposite effect to anoxia or hypoxia [192,193], and leads to an increase in the beta-band power during brain reoxygenation [194]. Interestingly, our results are also consistent with a previous study which analysed the changes in the EEG signals as a result of long-term physical exercise [192]. In this study, participants with a high level of fitness (enrolled in sports or with a minimum 3-year history of vigorous aerobic physical exercise) showed increased power in the beta band that may have been due to increased cerebral blood flow [192]. If confirmed that an increase of beta-3 is related to an increase in blood flow, this findings would be particularly relevant to people with FM since they frequently have altered cerebral blood flow variability [195] and velocity [196], as well as impaired cognitive function [197] such as memory [198] or poor performance in tests of executive functions [199]. In this regard,

previous studies have reported that exercise training can increase cerebral blood flow velocity, leading to a beneficial effect on cognitive function [200-202].

Moreover, results from study ***IX*** showed that the exergame-based intervention had a significant effect on the autonomic modulation of women with FM by a significant increase in SDNN and SD2 and a significant decrease in ln Stress Score and SD1/SD2. This is quite relevant since people with FM have shown an abnormal autonomic modulation compared with healthy controls [43,44]. Previous studies have reported HRV improvements after exercise interventions in people with FM. A 24-weeks of aerobic training [203], 16-weeks of hydrotherapy [204], 16-weeks of resistance training [205] or 12-weeks of Tai Chi intervention [206] have been reported significant improvements in HRV. However, some studies did not find significant changes on HRV after 16-weeks of strengthening [207], 8-weeks of resistance exercise [208], 12-weeks of resistance training respectively [209] and 12-weeks of moderate-intensity spinning workouts [210]. Moreover, considering both our results and the previous studies, it can be hypothesised that interventions longer than 4-months and comprising resistance or aerobic exercises are necessary to improve HRV. This hypothesis is also supported by previous studies in other populations [211,212].

Results from study ***X*** indicated that the exergame intervention improved lower-body strength and cardiorespiratory fitness. It is important to note that the study of Martin-Martinez*, et al.* [213], which corresponds to the same randomised controlled trial, showed significant improvement in physical fitness in both ST and DT conditions. In this regard, exergames have been used to improve the physical conditioning in both healthy [214] and chronic pain populations [127,215]. Furthermore, a previous study in women with FM has reported significant benefits of exergames in the physical function of women with FM

[127]. Improvements in physical fitness are relevant in women with FM since the ability to perform daily activities is conditioned by the physical fitness [216].

Moreover, in the study ***X*** the effects of six months of detraining were also reported. Previous studies showed that women with FM returned to baseline levels after a detraining period [183,217]. Consistently, our results showed that lower-body strength returned to baseline levels as previous studies have also reported. However, cardiorespiratory fitness improvements mostly remained after the six months of detraining period. A possible explanation for this result is that participants changed their lifestyle after the long-term intervention (six months). This may result in women with FM being more active even after the end of the exergame intervention. Moreover, data from the International Physical Activity Questionnaire (IPAQ) indicated that control-group participants were less physically active than exergame-group participants. On average, control-group participants were sedentary for around 45 min more per day than exergame participants were. This is quite relevant because the replacement of 30 min of sedentary time with physical activity leads to improvement in health-related quality of life, FM impact [218] or the quality of sleep [219].

In connection with that, adherence to physical exercise is often poor in women with FM [113,114]. Previous studies indicated that the introduction of VR could have a relevant impact on the motivation of participants [117,118]. Furthermore, it must be noted that the current study obtained an 89% of adherence while the previous one, involving an intervention of 8-weeks, reported a 98% of adherence in terms of the proportion of participants completing the intervention. However, the adherence in the 24-weeks intervention was reduced from 98% to 89%, which might indicate that the motivation of participants was not fully maintained when the duration of the intervention was increased. This is only hypothetical since motivation was not measured in the current study.

The study of subgroups is strongly recommended in FM [220,221] since this is a heterogeneous disease with different subgroups of patients suffering from different impact of the disease [221]. Thus, different strategies and methods have been followed in the study ***VII*** and study ***VIII*** to observe the effects in a different subgroup of patients. In the study ***VII***, two subgroups of participants were created by the K-means clustering procedure, taking into account the effects in EQ-5D-5L, pain VAS, and VAS-EQ. Participants with worse values of HRQol, pain and health perception of HRQoL at baseline are those who obtained greater effects of this intervention. This could be due to the type of exercise conducted in this intervention, where there was a high presence of mobility, postural control and coordination of the upper and lower limbs and improvements in these variables are closely related with HRQoL. In addition, considering the ceiling effect of having a full HRQoL in very healthy persons, these participants with lower scores at baseline have a wider range of potential ameliorations.

Furthermore, in the study ***VIII*** two subgroups of patients were created according to the years they had suffered from FM symptoms. The median duration of FM symptoms (17 years) was used as the threshold to divide the participants into a short-duration group and a long-duration group. Results showed that the effectiveness of the 24-weeks of exergame-based intervention was greater in the group of patients who had experienced FM symptoms for a shorter period of time. This is relevant since previous studies indicated that participants who have experienced FM symptoms for shorter periods of time might be more severely affected by the disease [222]. This is in line what we observed in the study ***VII*** where participants with worse results in pain and quality of life obtained greater benefits of this intervention.

Chapter 5 | STRENGTHS

Chapter 5. STRENGTHS

The present project has some strengths which should be highlighted:

1. The project has been addressed from a multidisciplinary approach using techniques and knowledge from a wide variety of fields such as medicine, psychology and sport sciences.
2. This thesis provides more evidence about the impact of FM on the DT performance as well as in the EEG power spectrum.
3. The impact of FM symptoms on brain electrical dynamics has been observed for the first time. This opens a new research field where the study of FM brain structures must be a priority.
4. The longest exergame-based intervention (24-weeks) has been performed in this project. Moreover, novel aspects (when compared with a previous one) have been evaluated such as the autonomic modulation, the EEG power spectrum or the effects of six months of detraining on the physical function of women with FM.
5. For the first time has been observed that the effectiveness of the exergames-based intervention could greater in those women with FM with worse HRQoL and pain level at baseline.
6. A six-month follow-up after the end of the intervention was performed, indicating that the cardiorespiratory fitness still remained higher that the participants of the control group.

Chapter 6 | LIMITATIONS

Chapter 6. LIMITATIONS

The current project has some limitations that should be addressed:

- The studies *I*, *II* and *III* did not include an ST condition of the cognitive task which had been provided interesting information about the performance model followed by women with FM [22]: the cross-domain competition model or the prioritisation model.
- The DT condition in the studies *I* and *III* seemed to be low complexity of the cognitive task used. This could limit the presence of significant differences in the DTC.
- The inclusion of a healthy control group in the studies *V* and *VI*.
- In the studies *VII, VIII, IX* and *X*, the lack of a control group who performed a traditional exercise (not based on VR) in order to isolate the effect of the exergame-based intervention.
- The relatively small sample size of the studies could make that only great differences have reached the statistical significance level in primary and secondary outcomes.
- Results from all only cannot be generalised to men with FM since only women participated in the studies.

Chapter 7 | FUTURE PERSPECTIVES

Chapter 7. FUTURE PERSPECTIVES

Based on the results and limitation of the studies, the following future perspectives emerge:

1. Due to the results of study ***V*** where the years with FM symptoms seemed to be a significant impact of theta power spectrum, the analysis of brain volumes using magnetic resonance imaging (MRI) or functional magnetic resonance imaging (fMIR) focusing on the hippocampus with pain must be developed in future studies.
2. Longitudinal studies with EEG and MRI studies are also encouraged to study the impact of FM on the brain structures.
3. Since the DT protocols are still developing, future studies test-retest are needed to standardise the procedures and study the reliability of this approach in people with FM. Moreover, the impact of different types of simultaneous task must also be studied, i.e. memory vs arithmetic-based tasks.
4. The impact of FM in the brain functioning during DT conditions through fMIR or EEG would be quite interesting for future researchers.
5. In order to explore new hypothesis related to brain and neuromotor adaptations to exercise, future studies should avoid the simple repetition of dance movements and include artistic and creative aspects of exercise intervention (also in exergame-based programs) since these aspects seem to reduce pain [223].
6. Future studies should include male participants in order to generalise the results to this population.
7. Due to the specific FM difficulties in DT conditions of women with FM, compared to healthy controls, future studies should explore the DT-based evaluations in clinical context.

Chapter 8 | CONCLUSIONS

Chapter 8. CONCLUSIONS

Based on the results, the following conclusions emerge:

1. Women with FM have lower physical fitness performance in both DT and ST compared to healthy controls. Focusing on upper limbs, the addition of a memory task led to a reduction in the elbow´s range of movement.
2. Women with FM have a more reduced physical fitness performance in DT condition compared to their performance in ST condition than healthy controls.
3. Women with FM have an altered EEG power spectrum (Alpha-2 frequency band) at rest compared with healthy controls. Moreover, the level of pain is correlated with this frequency band.
4. Years since patients were suffering from FM have a significant impact (more than the age of the patient) on EEG theta band. This could be connected to a premature brain ageing.
5. Women with FM with untreated depression showed a hypoactivation of the left hemisphere while eliciting depression symptoms.
6. A 24-week of exergame-based intervention has a significant effect on the quality of life, pain, physical function, autonomic modulation and brain electrical dynamics.
7. The exergames-based intervention has greater benefits in those women with FM with worse HRQoL and pain level at baseline as well as in those with less time suffering from FM symptoms.

Chapter 8. CONCLUSIONES

En base a los resultados obtenidos, las conclusiones que emergen de esta tesis doctoral son:

1. Las mujeres con fibromialgia tienen una condición física menor, tanto en condición simple como dual, que mujeres sin fibromialgia. Además, el rango de movimiento del codo se vio reducido cuando se añadió una tarea dual.
2. Las mujeres con fibromialgia obtuvieron valores más bajo de condición física durante tareas duales que en tarea simple, comparado con mujeres sin fibromialgia.
3. Se obtuvo una potencia espectral durante EEG (en Alpha-2) alterada en mujeres con fibromialgia en comparación con controles sanos. Además, el nivel de dolor correlacionó con los valores obtenidos en esta banda de frecuencia espectral.
4. Los años sufriendo fibromialgia correlacionaron significativamente (más que los años del paciente) en la banda espectral theta. Esto puede estar conectado con un envejecimiento cerebral prematuro.
5. Las mujeres con fibromialgia que no están siendo tratadas de depresión mostraron una hipoactivación del hemisferio izquierdo mientras le eran mencionados provocados de depresión.
6. Un programa de 24 semanas basados en una intervención de exergames mejoró significativamente la calidad de vida, dolor, función física, modulación autonómica y patrón eléctrico cerebral en mujeres con fibromialgia.
7. Aquellas personas con peor calidad de vida, mayor dolor y menor tiempo padeciendo la enfermedad obtuvieron un efecto mayor en la intervención.

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