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Patients with fibromyalgia show increased beta connectivity across distant networks and microstates alterations in resting-state electroencephalogram

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A B S T R A C T

Fibromyalgia (FM) is a chronic condition characterized by widespread pain of unknown etiology associated with alterations in the central nervous system. Although previous studies demonstrated altered patterns of brain activity during pain processing in patients with FM, alterations in spontaneous brain oscillations, in terms of functional connectivity or microstates, have been barely explored so far. Here we recorded the EEG from 43 patients with FM and 51 healthy controls during open-eyes resting-state. We analyzed the functional connectivity between different brain networks computing the phase lag index after group Independent Component Analysis, and also performed an EEG microstates analysis. Patients with FM showed increased beta band connectivity between different brain networks and alterations in some microstates parameters (specifically lower occurrence and coverage of microstate class C). We speculate that the observed alterations in spontaneous EEG may suggest the dominance of endogenous top-down influences; this could be related to limited processing of novel external events and the deterioration of flexible behavior and cognitive control frequently reported for FM. These findings provide the first evidence of alterations in long-distance phase connectivity and microstate indices at rest, and represent progress towards the understanding of the pathophysiology of fibromyalgia and the identification of novel biomarkers for its diagnosis.

1. Introduction

Fibromyalgia (FM) is a chronic disorder characterized by widespread pain and frequently accompanied by other symptoms such as fatigue, sleep disturbances or attention and memory problems (Wolfe et al., 2010). It is a disease of unknown etiology, and although abnormalities at the peripheral level have been found, FM seems to be driven by alterations in the central nervous system (Üçeyler et al., 2013; Serra et al., 2014; Clauw, 2015). In this sense, brain differences have been observed in FM, both at structural (Jensen et al., 2013; Burgmer et al., 2009; Schmidt-Wilcke et al., 2007) and functional levels. At the functional level, studies with functional Magnetic Resonance Imaging (fMRI) that applied experimental pain to patients with FM generally found higher activation in pain-related brain areas (or similar activations at lower intensity of nociceptive stimulation) in comparison with controls (Gracely et al., 2002; Pujol et al., 2009; Kim et al., 2011); reduced activation in areas related to descending pain inhibition (Jensen et al., 2009) or differences in both directions -higher and lower levels of activation- over several brain locations (Burgmer et al., 2009; Burgmer et al., 2010). In studies of electrical brain activity, increased evoked responses and reduced habituation to nociceptive stimuli are common findings (Gibson et al., 1994; de Tommaso et al., 2011; de Tommaso et al., 2014).

Given that brain indexes related with ongoing pain can be different from those associated with experimental evoked pain (Davis et al., 2017), the study of spontaneous brain activity may provide novel insights into the central alterations related with FM. In this sense, using functional neuroimaging, several abnormalities have been observed in the resting-state brain activity of patients with FM; such as altered connectivity between the insular cortex and other cortical areas (Ichesco et al., 2014), increased connectivity between the peri–aqueductal grey matter and insula, anterior cingulate cortex (ACC) and anterior prefrontal cortex (Truini et al., 2015), or several functional connectivity alterations between the default mode network and additional cortical structures (Fallon et al., 2016). EEG recordings during resting-state conditions in FM also revealed alterations in power spectral density and connectivity at several frequency bands (Fallon et al., 2018; González-Roldán et al., 2016; Lim et al., 2016; Choe et al., 2018; Hsiao et al., 2017). Nevertheless, there is still a lack of knowledge on the possible functional connectivity alterations in FM analyzing spontaneous oscillatory activity.

The spontaneous EEG also shows stable spatial distributions of the global scalp potential that vary dynamically over time in an organized manner (Koenig et al., 2002). A microstate (MS) is a time period (for around 100 ms) where the scalp potential remains stable and then

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changes to a new spatial configuration. MS are quasi-stable spatial patterns of the brain electrical activity that can be classified into a limited number of groups based on their topographical characteristics. The microstate analysis offers a method to characterize the EEG signal by the spatial configuration of the electrical fields, based on the existence of repeated topographic distributions of the EEG power in sensor space. Each MS is supposed to be related to a specific neural computation performed during that period, and thus reflecting different cognitive processes or mental states. Although there is no complete consensus about the cognitive process that can be underlying each MS, there are several works that have related the different topographical distributions with specific cognitive computations (Milz et al., 2016; Seitzman, 2017; Bréchet et al., 2019). In addition, several studies have found alterations in different parameters of the MS (like occurrence, duration and coverage) in a variety psychiatric and neurological disorders (Tomescu et al., 2014; Jia and Yu, 2018; Kikuchi et al., 2011); nevertheless, there are no previous research analyzing those patterns of scalp potentials in FM.

The aim of the present study was to explore resting state EEG patterns in patients with fibromyalgia, as compared to healthy controls. To this end, we propose two novel approaches: one, to evaluate the functional connectivity across different neural networks by computing the Phase Lag Index (PLI) (Stam et al., 2007) between components extracted using group-level Independent Component Analysis (group-ICA) (Huster and Raud, 2018); and two, assess the occurrence, duration and coverage of the microstates obtained in both groups. These analyses will provide new insights about large-scale network interactions and brain dynamics at rest in patients with FM.

2. Method

2.1. Participants

An initial sample of 46 patients with fibromyalgia (FM) and 53 healthy controls (HC) matched in sex (all women), age, and years of education participated in this study. The final sample comprised 43 FM and 51 HC (see reasons below). All FM patients were diagnosed by a physician (usually initially by a general practitioner and confirmed by a rheumatologist) and fulfilled the 1990 American College of Rheumatology criteria (Wolfe et al., 1990). The exclusion criteria for patients with FM was the presence of other disease that could explain the reported pain, generalized anxiety disorder, severe depression or other neurological and psychiatric disorders, except for low or moderate levels of depression or anxiety. The same exclusion criteria were applied for the HC group, along with the condition of having no history of chronic pain. All participants were asked not to smoke or consume coffee, alcohol, or other drugs not prescribed by a physician in the 4 h prior to evaluation. Participants were asked to keep the consumption of medication used to alleviate typical FM symptoms to the minimum necessary on the day of the evaluation.

All the experimental procedures were approved by the Ethics Committee of the University of Santiago de Compostela (Spain), in accordance with the Declaration of Helsinki. Participants were informed about the experimental protocol and all of them gave written informed consent before participation.

2.2. Sociodemographic and clinical assessment

Participants were interviewed about their sociodemographic status and the presence of symptoms related to FM. They completed a series of Visual-Analogue Scales (VAS) to evaluate their clinical status. Each scale consisted of a line of 10 cm in length in which the participants had to indicate the severity of each symptom from 0 to 10 (where 0 was “no problem at all” and 10 “maximum severity”) in the following variables: pain, health status, morning stiffness, fatigue, mood, headache, and sleep quality (all referred to the last month, except for fatigue, which referred to the last week). To further explore the presence of depressed mood, participants completed the Spanish version of Beck Depression Inventory - IA (BDI) (Sanz and Vázquez, 1998). This test has a total score ranging from 0 to 63 (higher scores indicate more severe depressive symptoms). Sleep quality was also assessed using the Spanish version of the Pittsburgh Sleep Quality Index (PSQI), a self-rated questionnaire that explores different aspects of sleep disturbance, with a total score ranging from 0 to 21 (higher scores indicate poorer sleep quality) (Buysse et al., 1989; Macías and Royuela, 1996). Quality of life and general health status were evaluated using the Spanish version of the Short-Form (Sanz and Vázquez, 1998) Health Survey (SF-36) (Alonso et al., 1995; Ware, 2000), that ranges from 0 to 100, where 0 is the worst and 100 is the best status value. Pain pressure threshold and tolerance were measured at the 18 tender point sites (Wolfe et al., 1990) using a pressure algometer (Wagner Force One, Model FDI). The results of these variables are presented in Table 1.[1]

2.3. Procedure and EEG recording

Participants were fitted with an electrode cap for EEG recording and were seated in a comfortable armchair in an electrically isolated room with low light and noise levels. They were instructed to keep their eyes open and gaze fixed (looking at a specific point on the wall, located 1.5 m in front of them) during the 10-minute registration session. They were also asked to blink when needed, but trying not to blink too often.

Brain activity was recorded with a 28- electrode cap (Electro-cap International, Inc., Eaton, OH, USA), following the 10–20 International System, and referred to the nose. An electrode placed on FPz was used as ground. The vertical and horizontal electrooculogram was recorded using 2 electrodes placed above and below the left eye and 2 electrodes attached to the outer canthus of the eyes. The EEG was recorded using a SynAmps amplifier (Neuroscan Labs, Charlotte, NC, USA) at an acquisition rate of 500 Hz. The signal was filtered online with 0.1–100 Hz bandpass filter and a 50 Hz notch filter. Electrode impedances were kept below 10 kΩ.

2.4. EEG preprocessing

EEG recordings were preprocessed using EEGLab 14.1.1 (Delorme and Makeig, 2004) and running in Matlab r2017b. Noisy electrodes were removed and reconstructed using spherical interpolation (a total of 6 electrodes were interpolated in the FM group and 7 in the HC group; making an average of < 0.15 interpolated electrodes per participant). Segments with muscular noise or bad recording of the electrodes were manually removed. Consecutive epochs of 2 s were extracted and Independent Components Analysis (ICA) for noise removal was applied using Extended Infomax ICA. Thirty independent components (ICs) were extracted from the recording of each participant. Multiple artifact rejection algorithm (MARA) software was used to automatically select ICs related to noisy activity, including eye artifacts, muscular artifacts and loose electrodes (Winkler et al., 2011). This step was reviewed by the experimenter to avoid possible misclassification of the ICs by the algorithm. During the manual steps of preprocessing, the researcher was blind to the group to which each of the EEG recordings belonged. After removing the electro-oculogram, the EEG was re-referenced to the average reference. EEG was band-pass filtered from 0.5 Hz to 40 Hz using a FIR filter. Subsequently, to homogenize the duration of the recordings among the subjects, we selected the first 219 two-second epochs of the recording, making a total of 438 s. This number of epochs was selected for showing a good ratio in keeping recordings of considerable duration without the need to eliminate too many participants. Three FM and 2 HC participants were removed for having less than 219 epochs, making a final sample of 43 FM and 51 HC.

[1] Given that there are some missing data, the number of participants evaluated in each variable is indicated.

Table 1
Demographic variables and clinical characteristics of patients and controls; standard deviations between parenthesis. Abbreviations: FM- Fibromyalgia group; HC- Healthy controls; VAS-Visual-Analogue Scale; BDI- Beck depression inventory; PSQI- Pittsburgh Sleep Quality Index; SF-36- The Short Form (Sanz and Vázquez, 1998) Health Survey; TP- Tender Points.

Variable	FM		HC		*t*-tests	*p*-value
	n	Mean (SD)	n	Mean (SD)		
Age (years)	42	47.8(8.5)	51	45.7(9.4)	1.13	0.26
Weight (Kg)	42	68.8(11.8)	51	64.6(10.3)	1.80	0.08
Height (cm)	42	159.9(5.2)	51	161.7(5.5)	−1.62	0.11
Years of education	42	12.1(3.9)	50	13.9(4.6)	−1.95	0.06
VAS Pain	42	7.0(2.0)	48	1.7(1.9)	12.73	< 0.001
VAS Health	43	7.0(2.1)	48	1.7(2.3)	11.30	< 0.001
VAS Stiffness	43	7.8(1.9)	48	2.9(2.9)	7.61	< 0.001
VAS Fatigue	43	7.8(1.9)	48	1.7(2.2)	14.07	< 0.001
VAS Mood	43	4.0(2.8)	48	1.5(1.8)	5.00	< 0.001
VAS Headache	43	5.5(3.1)	48	1.7(2.9)	6.20	< 0.001
VAS Sleep	43	7.6(2.5)	48	2.4(2.6)	9.65	< 0.001
BDI	43	18.9(8.8)	49	5.6(5.6)	8.71	< 0.001
PSQI	42	12.9(3.9)	47	5.1(3.4)	10.07	< 0.001
SF-36	40	40.7(14.2)	46	79.3(12.8)	−13.26	< 0.001
TP threshold	42	2.5(0.9)	49	5.7(0.9)	−16.39	< 0.001
TP tolerance	42	3.3(1.1)	49	6.2(1.0)	−13.61	< 0.001

2.5. Network-based connectivity

For network-based connectivity we first performed the Temporal-Concatenation Group ICA (hereinafter referred as group-ICA), that provides a powerful method to analyze functional brain networks at the multi-subject level (Raud and Huster, 2017). First, an initial Principal Components Analysis (PCA) was computed for data reduction and dimensionality estimation. To select the number of independent components (ICs) we followed the criteria suggested by Huster and Raud (2018), i.e. the first n components that altogether explain 90% of the variance of the dataset. The EEGs of all the participants were concatenated in the temporal dimension and the group-ICA decomposition was performed. Each one of the extracted ICs was defined by a common topography across subjects, and its time-course reconstructed for each participant. Group-ICA was performed using the software provided by the same authors (Huster and Raud, 2018). Subsequently, the phase lag index (PLI) was performed between all pairwise combinations of the reconstructed time series for each IC. The PLI measures the asymmetry of the distribution of phase differences between two signals (Stam et al., 2007), and returns values between 0 (no phase-locking or phase locking with zero lag) and 1 (perfect phase-locking, discarding zero-lagged phase coupling). PLI was computed from 2 Hz to 40 Hz in 1 Hz steps. The mean PLI values among all IC pairwise combinations were computed for group comparisons (see Fig. 1-Left). Afterwards, we selected the frequency band that showed significant group differences, and performed group comparisons for each pair of ICs (see Fig. 1-Right).

2.6. Microstates analysis

To obtain the microstates (MS) analyses we used the Microstate toolbox (Poulsen et al., 2018). The EEG was segmented based in the Global Field Power (GFP) and then classified in different classes according to their topographies. The datasets were normalized, and a total of 1000 peaks per subject entered the segmentation -with a minimum peak distance of 10 ms- for the extraction of the GFP peak maps. The calculation of cluster maps was done using the EEGs of both groups together. The optimal number of cluster maps was selected using the cross-validation criterion (Pascual-Marqui et al., 1995), comparing between different classifications in a range from 2 to 8 clusters. The clustering method for classifying the MS was the modified K-means algorithm (Pascual-Marqui et al., 1995). The convergence threshold was set to 10^{-6} and the maximum number of iterations was set to 1000. Given that the modified K-mean is a stochastic algorithm, we applied 50 restarts of the classification method in order to select the one with the lowest cross-validation criterion value. Once the number of MS prototypes was selected, they were back-fitted to all the recordings -ignoring their polarity, following the recommendations for the spontaneous EEG- (Poulsen et al., 2018). The back-fitting from the EEG to the MS prototypes was performed by computing the Global Map Dissimilarity index (Murray et al., 2008) Short periods of unstable EEG topographies (shorter than 30 ms) were filtered using the "small segments rejection" procedure described in (Poulsen et al., 2018). For the statistical analyses we extracted the following parameters: duration (defined as the average time a MS remains stable), occurrences (the number of times a microstate occurred per second), and coverage (the proportion of time covered by each MS).

2.7. Statistics

Group differences in sociodemographic and clinical variables, Phase Lag Index values, and microstate parameters were evaluated using independent samples *t*-test. In addition, we performed Spearman's rank correlation analysis to explore the relation between clinical variables and connectivity values. To correct for multiple comparisons we applied the False Discovery Rate correction (FDR) using the Benjamini & Hochberg method (Benjamini and Hochberg, 1995). The FDR was applied independently for global PLI and for microstates parameters. Effect sizes for PLI and microstates parameters are reported using Hedge's g_s (Lakens, 2013).

3. Results

3.1. Demographic and clinical variables

No between-groups differences were observed in demographic variables such as age, weight, height or education. Nevertheless, patients showed significant differences in symptoms related to FM, such as pain, depression, fatigue, sleep quality, or pain pressure threshold and tolerance (See Table 1).

3.2. Connectivity analyses

We first extracted 6 independent components (ICs) that explained the 92.5% of the total variance. Then, the connectivity analysis between each pair of ICs and the average of all of them were performed. We observed significantly higher global (average) PLI values for patients with FM at beta frequencies (from 17 to 34 Hz) with $p_{FDR} < 0.05$. Independent

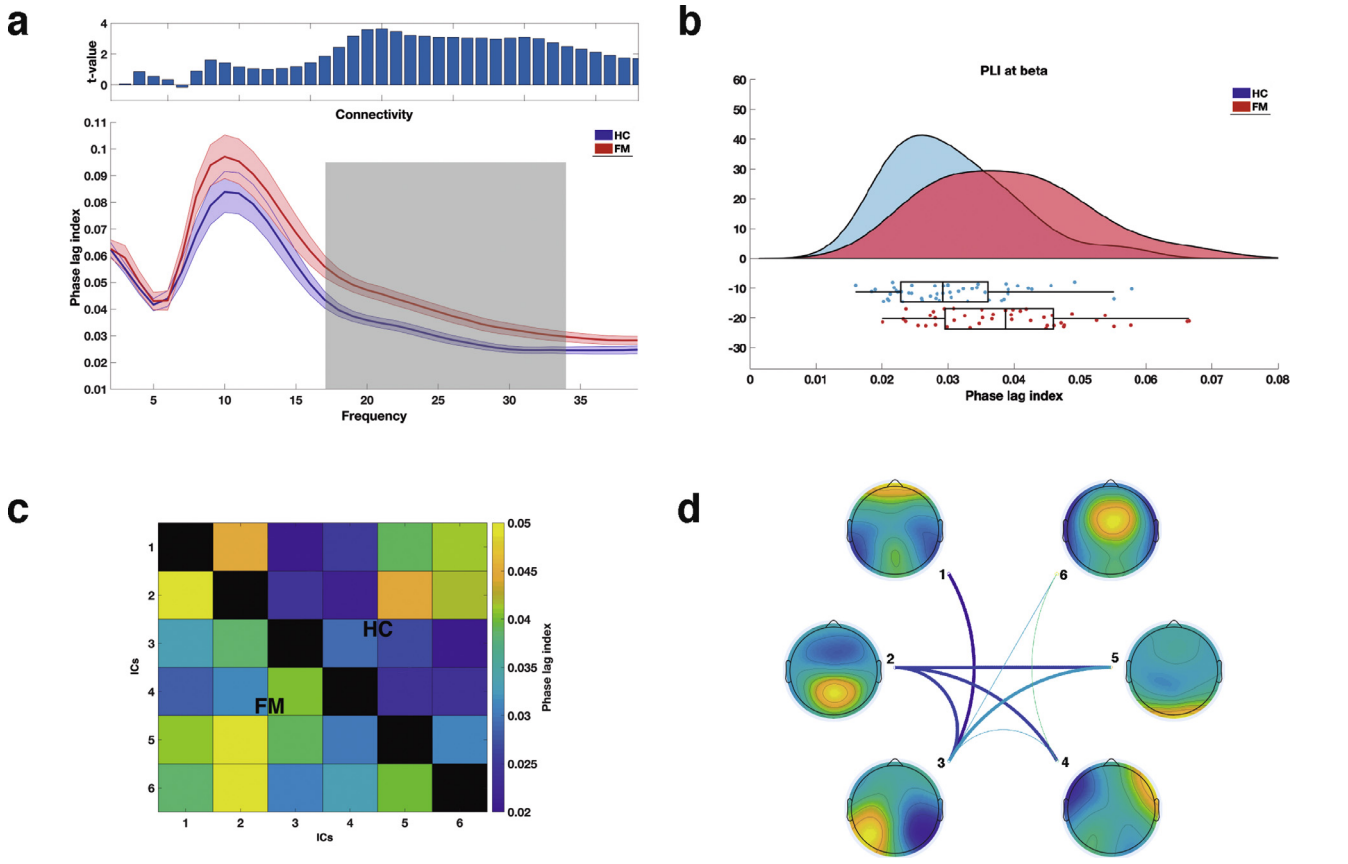

Fig. 1. *a:* Mean phase lag index (PLI) among all the independent components for patients with fibromyalgia (FM; red ink) and healthy controls (HC; blue ink) at each frequency. Red and blue shaded areas show the standard error of the mean for each group. Grey area shows the frequencies with significant group differences after false discovery rate correction. *t*-values for each frequency are shown at the top. *b*: Raincloud plot with the mean PLI values in the selected frequency window (17–34 Hz) for each group of participants. *c:* Mean phase lag index between each pair of independent components (ICs) for FM (lower triangle) and HC (upper triangle) in the frequency band with significant group differences (17–34 Hz). *d:* Topographies for each extracted IC; thick lines show significant group connectivity differences in beta -at $p_{FDR} < 0.05$ level-, while thin lines show differences at $p_{uncorrected} < 0.05$ level.

samples *t*-test of the mean PLI values in this frequency range showed a $t_{(92)} = 3.76$ and $p = 0.0011$; Hedges's $g_s = 0.77$ (mean global PLI values from 17 to 34 Hz: FM = 0.040±0.014; HC = 0.031±0.009) (See Fig. 1-a and b). Afterwards, we analyzed the differences in connectivity between all pairwise combinations of ICs. Several ICs pairs showed higher connectivity in the FM group with differences at $p_{FDR} < 0.05$ (See Fig 1-c and d). These differences involve IC 2 (in their interconnections with ICs 3, 4 and 5) and IC 3 (in their interconnections with ICs 1, 2 and 5).

To clarify the relation between long distance connectivity and the clinical measures, we correlated the mean global PLI (from 17 to 34 Hz) with the clinical variables listed in Table 1 by calculating Spearman rank-order correlation coefficient (See supplementary data). None of these variables were significantly correlated with the PLI when using the FM group or the healthy control participants separately. When gathering data from both groups of participants, we found that PLI at Beta was significantly correlated with all the clinical variables. All these correlations were in the same direction -higher PLI related to higher impairment-.

3.3. Microstate (MS) analyses

We extracted 4 microstates based on the cross-validation criterion (See Fig. 2). The four MS accounted for the 62.0% of the Global Explained Variance (GEV), although this GEV is lower than typically reported, it is a similar value to that obtained in previous research during resting state EEG (Seitzman, 2017; Britz et al., 2010); each MS contributes to GEV in each group of participant as follows: MS1: FM = 15.3% ± 9.1; HC = 20.6% ± 8.9; MS2: FM = 12.5% ± 8.1; HC = 12.2% ± 5.3; MS3: FM = 12.8% ± 8.2; HC = 11.8% ± 8.9; MS4: FM = 9.2% ± 5.3; HC = 8.5% ± 8.9. We observed that MS1 showed a similar topography to the one described in the literature as microstate Class C (Britz et al., 2010; Michel and Koenig, 2018). MS1 had significantly shorter values of Occurrence and Coverage in patients with FM than in HC, while the Duration parameter was not significant, but near to significance (See Table 2). MS2 showed a topography similar to the one described as microstate Class C', with no significant differences between groups. MS3 showed a similar topography to that described as microstate Class E, and no significant differences were observed between groups. Finally, MS4 showed a topography similar to the one usually referred as microstate Class D, again with no group differences in any of the parameters analyzed.

4. Discussion

In the present study, we investigated whether patients with fibromyalgia showed alterations in their electroencephalographic activity during open-eyes resting state. Here we pursued two novel analysis of the EEG not previously applied to data recorded in FM. First, we measured functional connectivity between different networks; second, we performed broadband microstate analysis to evaluate patterns related to spontaneous thought and neural processes that may be altered in chronic pain. We found higher global functional connectivity in the beta band for patients with FM, and also observed differences in microstate

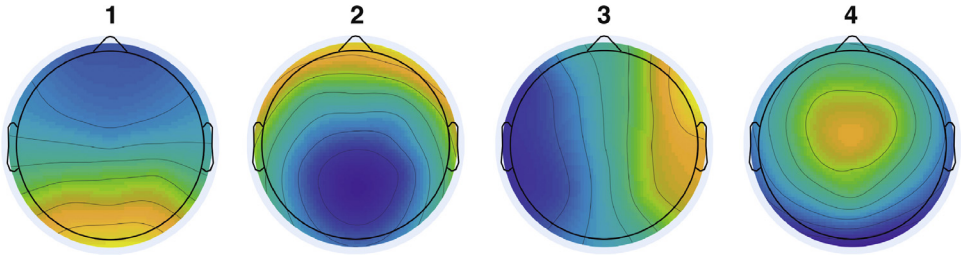

Fig. 2. Topographies of the 4 prototypes of microstates extracted.

Table 2
Mean values, standard deviations, and statistical tests for duration, occurrence and coverage for each group and microstate prototype. Abbreviations: FM – Fibromyalgia group; HC – Healthy controls group; p: p-values after False Discovery Rate (FDR) correction.

	Microstate 1	Microstate 2	Microstate 3	Microstate 4
Duration	FM = 84.412 ± 15.48; HC = 92.62 ± 16.30; $t_{(92)} = -2.46$; $p = 0.062$; Hedge's $g_s = 0.51$	FM = 88.10 ± 25.60; HC = 84.17 ± 10.37; $t_{(92)} = 0.99$; $p = 0.486$	FM = 91.59 ± 33.93; HC = 84.90 ± 16.30; $t_{(92)} = 1.32$; $p = 0.475$	FM = 83.01 ± 15.03; HC = 79.95 ± 16.30; $t_{(92)} = 1.189$; $p = 0.475$
Occurrence	FM = 2.74 ± 0.66; HC = 3.09 ± 0.46; $t_{(92)} = -3.02$; $p = 0.038$; Hedge's $g_s = 0.63$	FM = 2.87 ± 0.62; HC = 2.93 ± 0.47; $t_{(92)} = -0.47$; $p = 0.690$	FM = 2.86 ± 0.59; HC = 2.82 ± 0.46; $t_{(92)} = 0.36$; $p = 0.716$	FM = 2.67 ± 0.66; HC = 2.670 ± 0.46; $t_{(92)} = 0.55$; $p = 0.690$
Coverage	FM = 0.24 ± 0.09; HC = 0.29 ± 0.09; $t_{(92)} = -2.69$; $p = 0.048$; Hedge's $g_s = 0.65$	FM = 0.26 ± 0.12; HC = 0.25 ± 0.06; $t_{(92)} = 0.57$; $p = 0.690$	FM = 0.27 ± 0.12; HC = 0.24 ± 0.09; $t_{(92)} = 1.21$; $p = 0.475$	FM = 0.23 ± 0.08; HC = 0.21 ± 0.09; $t_{(92)} = 1.04$; $p = 0.486$

parameters between patients and controls. These results extend current knowledge on the brain activity of chronic patients during ongoing pain and provide physiological markers of altered brain function in FM.

For network connectivity analysis we first extracted six components using group-ICA decomposition, each one characterized by a different topography and time course. This group-level decomposition method is a novel and powerful tool that allows to study functional brain networks in EEG data (Huster and Raud, 2018). Subsequently we analyzed phase connectivity among components and found that patients with FM had higher global connectivity values at beta frequencies (≃17–34 Hz). We also observed group differences between pairwise PLI values, especially involving IC 2 and IC 3.

Beta-band oscillations have been classically related to the activity in motor areas (Pfurtscheller and Lopes da Silva, 1999; Pfurtscheller et al., 2005), although recently they also have been implicated in long-range communication, top-down processing, and the preservation of the current brain state (Spitzer and Haegens, 2020; Engel and Fries, 2010). These oscillations are mechanistically related to a facilitation of network-level communication (Kopell et al., 2000; Varela et al., 2001; Alavash et al., 2017; Donner and Siegel, 2011). Particularly, phase synchronization at beta frequencies are thought to regulate the communication among distant neural groups, which can be used to maintain information in working memory and facilitate the integration of distributed processing (Siebenhühner et al., 2016; Fries, 2015; Kornblith et al., 2016). This frequency band has also been related with feedback predictions in the predictive coding model (Michalareas et al., 2016; Brodski-Guerniero et al., 2017) and with the endogenous activation and reactivation of cortical content representations (Spitzer and Haegens, 2020). Our results indicate that patients with FM show a hyper-synchronization among distant distributed neural circuits. As beta activity has been also related to the continuation of the cognitive set and the dominance of endogenous top-down influences, its pathological enhancement may lead to the deterioration of flexible behavior and cognitive control (Engel and Fries, 2010). In this vein, patients with FM consistently show impairments of executive function, attention, or working memory, including poor selective and divided attention, slow information processing and vulnerability to distraction (Tesio et al., 2015; Kravitz and Katz, 2015; Glass, 2009; Teodoro et al., 2018). The observed abnormally high synchronization among long-distance networks could be a mechanism related to the impaired attention and processing of external stimuli, and the concomitant cognitive dysfunction reported by patients with fibromyalgia. Connectivity values in the beta range were significantly correlated with the measured clinical variables when using data from the whole sample (FM and HC), suggesting a positive relation between long distance beta phase connectivity and symptom severity. Nevertheless, these results should be taken with caution, since the correlations were far from significance when computed with the FM or the HC groups separately (See supplementary data). The lack of correlations in the FM group could be explained by the high heterogeneity of the disease and the existence of different profiles of patients with diverse clinical manifestations (de Souza et al., 2009; Triñanes et al., 2014). While FM symptoms are not dichotomous and everyone (either healthy controls or patients) is in a position on that continuum, distribution of scores in some clinical variables are clustered by group (See scatterplots in the supplementary data), and this may explain the significant correlations for the whole sample. Overall, these results suggest that PLI is useful in differentiating between the two groups, but shows a low correlation with specific symptoms of the FM spectrum in patients.

Contextualizing our results with recent research analyzing spontaneous magneto- and electroencephalographic activity, other previous investigations have also found alterations in beta frequencies in patients with FM. For example, González-Roldán et al. (2016) found increased beta power and increased power cross-correlation between scalp electrodes located in the left hemisphere of patients. In this vein, Lim et al. (2016) found beta power increase in FM, with the largest group differences in the anterior insular cortex, primary motor cortex, and left S1 and S2. Nevertheless, alterations were also found in other indexes like delta power (González-Roldán et al., 2016), theta power (Fallon et al., 2018; Lim et al., 2016), centroparietal theta synchronization (González-Roldán et al., 2016) and global theta connectivity (Choe et al., 2018), or gamma power (Lim et al., 2016). Although there are some common points, there is still little consistency in the electrophysiological indexes observed during resting state. These disparities may be explained by differences in the characteristics of the samples and in the types of analyses (e.g. power analysis at scalp or source level, different functional connectivity indexes).

Regarding microstate analysis, we found a reduction in occurrence and coverage of the Microstate 1, which also showed the higher global explained variance. This microstate exhibits an anterior-posterior topography, and corresponds to the described in the literature as Microstate C (Koenig et al., 1999). Similar observations were reported for patients with dementia and panic disorder, that respectively showed reduced duration and occurrence of the Microstate C (Kikuchi et al., 2011; Nishida et al., 2013). The microstate class C has been positively correlated with Blood-oxygen-level dependent (BOLD) activity in areas like the dorsal anterior cingulate cortex, the right anterior insula and the inferior frontal gyri (Britz et al., 2010). These areas are part of the so-called salience network, that is related to switching between central-executive function and the default mode. Among other functions, the salience network is supposed to contribute to self-awareness through the integration of sensory, emotional, and cognitive information. Areas that belong to this network, such as the insular cortex or the anterior cingulate cortex (ACC), are also involved in the processing of nociceptive input (Tracey and Mantyh, 2007), and brain imaging studies frequently observed functional and structural alterations over these areas in patients with FM (Ichesco et al., 2014). Therefore, the reduced duration, occurrence and coverage of this MS is consistent with the fact that FM patients show impaired performance or altered brain activity during cognitive control tasks (Bell et al., 2018; González-Villar et al., 2017b), processes that involve the activation of the insula and ACC (Swick et al., 2011; Aron, 2011).

The microstate C has also been related to the activation of brain areas involved in autonomic and interoceptive processing (Britz et al., 2010; Pipinis et al., 2017; Schiller et al., 2019). The reported data could be related to the reduced attentional focus towards the interoceptive experience in FM -as reported by Duschek et al., that found decreased interoceptive awareness in this population (Duschek et al., 2017)-, and is in line with the relation between reduced heartbeat perception and increased pain-related affect and symptom severity (Borg et al., 2018). Nevertheless, our results are inconsistent with previous reports of increased attention to body signals in those patients (Borg et al., 2015). Finally, Ceko et al. (2015) found a reduced deactivation of fMRI response over default-mode network (DMN) regions (posterior cingulate/precuneus, medial prefrontal cortex) in patients with FM during a working memory task, and also reduced modulation of DMN deactivation caused by task demands (Ceko et al., 2015). These results are also consistent with our previous observations of reduced modulation of electrophysiological indexes caused by external events in patients with FM (González-Villar et al., 2017a, 2017b; González-Villar et al., 2019). Altogether, the evidence obtained from the connectivity and microstate analysis are convergent, suggesting alterations in a neurophysiological mechanism that may be related to the diminished ability to process both interoceptive and exteroceptive information that FM patients often exhibit.

One limitation of this study is related to the consumption of medication by patients, which could not be interrupted for the study and whose effects are difficult to identify. In addition, the cross-sectional design does not allow establishing causal relations between EEG features and the clinical manifestations in FM, a complex syndrome characterized by a plethora of symptoms (mainly chronic pain, but also cognitive and affective). Furthermore, the design of the study does not allow clarifying whether the findings are FM-specific or could be common to other chronic pain diseases.

In conclusion, the present findings indicate that FM participants show increased connectivity over different brain networks at beta band, and differential microstates dynamics during resting state. Although we used two independent approaches to analyze the spontaneous EEG data (i.e. connectivity of independent components and microstate analysis), the group differences of both physiological outcomes are related to the processing of endogenous top-down information and the minimization of novel external input. These alterations could be related to the subjective complains about deficits in attentional processes and cognitive functioning commonly reported in this chronic pain disorder. The present results contribute to the understanding of the alterations in the central nervous system of patients with FM and could help in the search of EEG biomarkers for its diagnosis.

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Credit author statement

AGV was involved in data acquisition, data analysis, writing of the draft, review and editing of the manuscript. YT was involved in the conceptualization of the work, data acquisition and review of the manuscript. CGP was involved in the conceptualization of the work and data acquisition. MCP was involved in the conceptualization of the work, funding acquisition, supervision, review and editing of the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2020.117266.

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