Altered Dynamic of EEG Oscillations in Fibromyalgia Patients at Rest

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Abstract

Objective. Previous fMRI findings have shown that chronic pain patients display an altered activation and functional connectivity of the pain network. The aim of the present study was to analyze EEG dynamics in fibromyalgia patients (n = 20) and pain-free controls (n = 18) at rest.
Methods. Spectral power density, source current density, and intra- and inter-hemispheric coherence were analyzed from 64 EEG channels during 5-minutes eyes-closed rest.
Results. Results indicated that fibromyalgia patients displayed reduced power density of the delta EEG band (2-4 Hz) over right insula, right superior and middle temporal gyri as compared with pain-free controls. Fibromyalgia patients also exhibited greater power density than pain-free controls in two segments of the beta band (16-23 Hz and 23-30 Hz) over right middle frontal lobe and midcingulate gyrus. Pain duration in fibromyalgia patients was negatively correlated with delta power from right insula. Greater centro-parietal intra-hemispheric coherence was observed at the left hemisphere on theta (4-8 Hz), and beta-3 (23-30 Hz) frequency bands in fibromyalgia patients than in pain-free controls. Individual differences in depression, anxiety or negative affect did not account for these findings.
Conclusions. Fibromyalgia leads to an altered dynamic of the brain network involved in the processing of pain even at rest. Furthermore , our results provide further support for the feasibility of resting-state EEG analyses as a clinical biomarker for the characterization of chronic pain states.

Fibromyalgia, Resting-State, EEG, Source Localization, Spectral Power, Spectral Coherence

Topic:

- electroencephalography
- fibromyalgia
- pain
- brain

Issue Section:
Original Research Articles

Introduction

Fibromyalgia (FM) is a functional chronic pain syndrome [1] characterized by fatigue, sleep disturbances and affective and cognitive symptoms [2]. Previous neuroimaging and EEG studies have suggested that hyperexcitability of the central nervous system represents an important mechanism in the maintenance of chronic pain observed in these patients [2 , 3]. In accordance with this assumption, an abnormal activation in several areas involved in the processing of pain and stimulus salience [4], including thalamic nuclei, somatosensory cortex, anterior cingulate, insula, and prefrontal cortices have been reported during pain processing in FM [5–7]. In addition, significant changes in the microstructure and neurochemistry of thalamus, anterior cingulate, insula or prefrontal cortices have been also observed in FM patients associated with the persistence of pain [8 , 9] and the presence of pain-related affective symptoms [10]. Previous functional magnetic resonance imaging (fMRI) findings have also shown that FM patients display an altered activation and functional connectivity of the pain related network even when subjects are at rest [11–13]. Concretely, FM patients show strengthened connectivity of brain regions involved in pain processing, as well as significantly reduced connectivity of areas involved in pain inhibitory modulation [11]. Furthermore, changes involving the degree of connectivity between insula and other brain regions known to participate in pain modulation have been associated with the intensity of ongoing clinical pain [12 , 14].

Due to their ability to provide temporally-resolved information about brain activity, spectral and coherence EEG power have been used to analyze resting-state brain dynamics [15–18]. Spectral EEG power describes the activity of

dipole-like dendrites of cortical pyramidal cells [19 , 20], whilst EEG coherence estimates the degree of synchronization between neural activity underlying two different electrodes and is believed to reflect functional cortical connectivity on a centimeter scale [21]. Source localization analyses of EEG oscillations have been previously used to elucidate functional brain abnormalities in chronic pain patients. Thus, for instance, Stern et al. [18] found that neuropathic pain was linked to enhanced EEG power in theta and beta frequency bands localized in multiple pain-related areas as the anterior cingulate, prefrontal and somatosensory cortices. Hargrove et al. [22] observed that FM patients displayed enhanced power at high-frequency, but reduced power and interhemispheric coherence at low- to mid-frequency EEG oscillations in comparison with healthy controls. There is, however, no information about source localization of EEG oscillations in FM patients during resting conditions. This study aims to replicate and extend this prior research by using standardized low resolution brain electromagnetic tomography (sLORETA) and EEG coherence analyses to further explain altered brain dynamics in FM patients at rest. We hypothesized that FM patients would exhibit significant alterations of EEG oscillations and coherence, and that these alterations would be mainly located over brain regions involved in the processing of pain.

Methods

Participants

Twenty females with FM (mean age = 53.3; SD = 8.1) diagnosed according to the American College of Rheumatology's criteria [23], and 20 female pain-free volunteers (mean age = 52.6; SD = 10.3) with comparable sociodemographic data participated in the study (Table 1). Participants were recruited from patient support groups, outpatient pain clinics, physician referrals and media advertisements. Subjects were excluded from the study if they were pregnant, had a concurrent autoimmune or inflammatory disease that causes pain, a neurological disease or a psychiatric diagnose (e.g., current schizophrenia, major

depression with suicidal ideation, or substance abuse). A screening interview was conducted by a trained psychologist and an experienced rheumatologist reviewed each patient's chart to exclude other origins of pain.

Table 1

Mean comparison between fibromyalgia patients (FM) and pain-free controls on self-report clinical data. Mean and standard deviation (SD) as well as t-test and *P* values are reported

	Fibromyalgia patients (n = 20)	**Pain-free controls (N = 18)**	**T**
Age, years			
Mean ± SD	53.4 ± 8.1	52.7 ± 10.3	
Range	34 – 67	29 – 67	
Edinburgh Handedness Inventory			
Mean ± SD	18.2 ± 5.6	17.93 ± 4.3	
Range	11–29	10-24	
Pain duration (years)			
Mean ± SD	18.8 ± 13.7	–	
Range	3 – 55	–	
Pain intensity (10-cm VAS)			
Mean ± SD	6.0 ± 1.3	–	
Range	3.4 – 8	–	
Sleep pattern			

	Fibromyalgia patients (n = 20)	Pain-free controls (N = 18)	T
Sleep well	6	–	
Difficulty falling sleep	5	–	
Difficulty staying asleep	15	–	
Medication			
Antidepressants	13	4	
Analgesics/relaxants/NSAIDs	14	–	
Anxiolytics	8	3	
PANAS positive score			
Mean ± SD	2.5 ± 1.0	3.1 ± 0.7	T = 1,935
Range	1.0 – 4.4	1.3 – 4.3	*P* = .061
PANAS negative score			
Mean ± SD	1.9 ± 0.8	1.2 ± 0.2	T = 3,688
Range	1.0 – 4.0	1.0 – 1.7	*P* < .001
BDI score			
Mean ± SD	25.2 ± 13.3	10.4 ± 7.4	T = 4,247
Range	4 – 48	0 – 27	*P* < .001
STAI-state score			
Mean ± SD	24.2 ± 13.4	13 ± 5	T = 3,490

	Fibromyalgia patients (n = 20)	Pain-free controls (N = 18)	T
Range	4 – 48	1 – 24	*P* = .002
WHYMPI, mean ± SD (range 0-6)			
Social support	4.3 ± 1.4	–	
Affective distress	3.3 ± 1.3	–	
Pain interference	3.8 ± 1.4	–	
Pain intensity	4.1 ± 1.0	–	
Life control	3.3 ± 1.4	–	
Distracting responses	4.3 ± 1.5	–	
Solicitous responses	3.3 ± 1.7	–	
Punishing responses	0.8 ± 1.1	–	
Household chores	4.2 ± 1.3	–	
Activities away from home	2.7 ± 1.2	–	
Outdoor work	1.5 ± 1.9	–	
Social activities	2.3 ± 1.3	–	

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Participants were verbally informed about the details of the study at the time of recruitment and a written consent was obtained. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Clinical Research Ethics Committee of the Balearic Islands (Spain).

Questionnaires and Procedure

FM patients underwent a semi-standardized interview assessing their pain characteristics (pain duration, factors interfering pain, sleep pattern, etc). They also completed the West Haven–Yale Multidimensional Pain Inventory (WHYMPI) [24] to assess the impact of pain on their lives through five self-report subscales (pain severity, pain interference, affective distress, social support, life control), the responses of others to patients' pain behavior (solicitous, punishing, and distracting responses), and the extent to which patients participate in common daily activities (household chores, social and recreational activities). Finally, mood and manual preference were assessed in all participants through the following self-report questionnaires: the Beck Depression Inventory (BDI) [25], the Spielberger State Anxiety Inventory (STAI) [26], the Positive and Negative Affect Schedule (PANAS) [27] and the Edinburgh Handedness Inventory [28].

EEG Recording and Data Processing

EEG signals were collected by using a QuickAmp amplifier from 64 scalp electrodes placed according to the international 10/20 system during one 5-minutes resting period with eyes closed. Electrodes were recorded against an average reference calculated by the amplifier. An electroculogram channel was obtained by placing one electrode above and one below the left eye. Electrode impedance was kept below 10 KΩ. EEG and electroculogram signals were recorded with a sampling rate of 1000 Hz and a frequency bandpass filter of 0.05-30 Hz and a 50-Hz notch filter. Eye movement artifacts were corrected using Gratton & Coles algorithm [29]. Subjects were seated on a comfortable chair in a sound attenuated room. They were instructed to keep their eyes closed, and to avoid falling asleep during the experiment.

EEG waveforms were segmented in epochs of 1024 ms duration [30 , 31] for analyses of frequency power at delta (2–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta-1 (12–16 Hz), beta-2 (16–23 Hz) and beta-3 (23–30 Hz) [53]. In addition, an artifact rejection protocol with the following criteria was applied: maximal

allowed voltage step/sampling point 100 μV, minimal allowed amplitude -100 μV, maximal allowed amplitude 100 μV, and maximal allowed absolute difference in the epoch 50 μV. The criterion of our artifact rejection protocol for exclusion of a subject from the analysis was established in 50% of the epochs. Therefore, data from two pain-free participants were eliminated from statistical analyses because their rejection rates were above 95%.

Source Localization of EEG Oscillations

For source localization of EEG activity, sLORETA was applied to the 64-channel EEG data [32]. The mean (± SD) of rejected epochs was 15.3% ± 13.6 (range: 0–50%). The remaining 1024-ms artifact-free epochs were used for cross-spectrum calculation. Electrode coordinates were based on an extended 10/20 system template and expressed as Talairach space coordinates. Subsequently, current source densities of delta, theta, alpha, beta-1, beta-2 and beta-3 frequency bands were estimated. In order to reduce inter-subject variability, spectra values were normalized at each voxel.

Coherence of EEG Oscillations

Analyses of intra- and inter-hemispheric coherence of EEG oscillations were performed by using Brain Vision Analyzer software (Version 1.05; Brain Products GmbH, Munich, Germany). EEG coherence was computed for delta, theta, alpha, beta-1, beta-2 and beta-3 frequency bands as the cross-correlation in the frequency domain between spatially separate pairs of electrodes. For this purpose, fast-Fourier transformation (FFT) was obtained from each 1024-ms free-artifact EEG epoch for three somatomotor regions of interest (ROIs) by grouping the following electrodes: frontal (F1, F2, F3, F4, F5, F6) central (C1, C2, C3, C4, C5, C6) and parietal (P1, P2, P3, P4, P5, P6). The mean (±SD) of rejected EEG epochs was 6.7% ± 9.6 (range: 0–33%). Inter-hemispheric coherence was calculated between left and right electrodes at each ROI (frontal, central and parietal electrode locations), whereas intra-hemispheric coherence was obtained for each hemisphere by calculating coherence between pairs of ROIs (fronto-

central, centro-parietal, fronto-parietal) at right and left electrode positions. EEG coherence values were log-transformed in order to normalize their distributions.

Statistical Analyses

For clinical data and EEG coherence, statistical analyses were performed with SPSS (version 21.0). Data from self-report questionnaires (BDI, STAI, PANAS) were analyzed by using two-sample t-tests to examine group differences.

Statistical nonparametric mapping [33] was used to compare voxel-by-voxel sLORETA images obtained from source localization of EEG oscillations. This method uses a randomization strategy (5000 permutations) and is corrected for multiple comparisons [34 , 35]. The significance level was set to 0.05 (two-tailed, whole brain corrected).

In order to avoid possible volume conduction biases in our results [36–38], EEG coherence was analyzed only by comparing the effects of hemisphere and group within each ROI, thus avoiding comparisons among electrodes located at different distances over the scalp [39]. In order to control for the effects of mood, inter-hemispheric coherence values at frontal, central and parietal ROIs were separately analyzed by using ANCOVAs with the between-subject factor *group* (FM vs. pain-free controls) and *mood* (anxiety, depression, negative affect) as covariates. In addition, fronto-central, centro-parietal and fronto-parietal intra-hemispheric coherence values were separately analyzed by using ANCOVAs with the between-subject factor *group* , the within-subject factor *hemisphere* (left, right) and *mood* (anxiety, depression, negative affect) as covariates. Greenhouse-Geisser epsilon corrections were applied and post-hoc pairwise mean comparisons were corrected by using Bonferroni correction.

Finally, to investigate if the differential effects on EEG power density and coherence in FM patients were statistically associated with pain-related variables (pain intensity, pain duration, depression, anxiety and PANAS negative), Pearson’s correlations were also computed. For this purpose, log

transformed sLORETA values extracted from the single voxel nearest to the MNI coordinates (Table 2) and coherence values from those ROIs with significant group differences were used.

Table 2

Summary of significant results from whole-brain sLORETA comparisons between FM patients (N = 20) vs. pain-free controls (N = 18). Significant regions are indicated with the name of Brodmann area (BA) and MNI coordinates of the peak activation. Statistical two-tailed threshold (T) is displayed for each frequency band.

Lobe	Region	BA	Side	X	Y	Z	EEGBand	T
Pain-free controls > FM								
Temporal	Insula	13	R	50	−40	20	δ	T = 3.83, *P* = .027
	Superior gyrus	41	R	50	−35	15	δ	
	Superior gyrus	42	R	55	−35	15	δ	
	Superior gyrus	22	R	65	−40	15	δ	
	Middle gyrus	21	R	65	−55	5	δ	
FM > pain-free controls								
Frontal	Precentral gyrus	9	R	35	10	40	β2	T = 3.36, *P* = .035
	Middle gyrus	8	R	40	10	40	β2	

Lobe	Region	BA	Side	X	Y	Z	EEGBand	T
	Superior gyrus	8	R	35	15	55	β3	
	Precentral gyrus	9	R	35	10	40	β3	
	Middle gyrus	8	R	35	10	45	β3	
	Middle gyrus	6	R	35	5	50	β3	
Frontal	Medial gyrus	8	R	10	25	45	β3	T = 3.69, *P* = .004
Limbic	Midcingulate gyrus	32	R	10	20	45	β3	

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Results

Demographic and Clinical Data

Significant group differences were found on state anxiety (t(36) = 3.490, *P* = .002), depression (t(35) = 4.247, *P* < .001), and the negative affect scale of the PANAS (t(36) = 3.688, *P* < .001), indicating that chronic pain patients had higher scores than pain-free controls (Table 1).

Source Analyses of EEG Power Spectra

Differences between FM patients and pain-free controls on statistical maps of normalized source analyses of EEG power spectra are displayed in Figure 1 and Table 2 . These analyses showed that FM patients had reduced power in the delta band, as well as enhanced power in beta-2 and beta-3 bands in

comparison with pain-free controls. In particular, group differences on peak activations for delta frequency band were located within right insula (BA 13), superior temporal gyrus (BA 41, BA 42, BA 22) and middle temporal gyrus (BA 21). Differences between FM patients and pain-free controls on peak activations for beta-2 frequency were located in right precentral gyrus (primary motor area-M1) (BA 9), and right middle frontal gyrus (BA 8). Finally, group differences on peak activations for beta-3 frequency were located in right middle frontal gyrus (BA 6, BA 8), M1 (BA 9), superior frontal gyrus (BA 8), midcingulate cortex (BA 32) and right medial frontal gyrus (BA 8). No significant group differences were observed on source locations for theta, alpha, and beta-1 frequency bands.

Figure 1

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sLORETA results for 3 orthogonal brain slices (horizontal, sagittal, coronal). Red color represents increased current density in FM patients compared to pain-free controls, while blue indicates increased current density in pain-free controls compared to FM patients. Significant results were yielded for delta (BA 13, BA 21, BA 42), beta-2 (BA 8, BA 9), and beta-3 (BA 8, BA 9, BA 32) (see also Table 2). Legend: BA = Brodmann area; L = left; R = right.

Correlation analyses revealed that pain duration was negatively associated with delta power from right insula (BA 13) (r = -.495, *P* =.026). In addition, anxiety scores (STAI-state) were negatively correlated with beta-3 power from frontal medial gyrus (BA 8) (r=−.543, *P* =.013) and midcingulate cortex (BA 32) (r=−.529, *P* =.016). Finally, depression scores (BDI-state) were also negatively correlated with beta-3 power from frontal medial gyrus (BA 8) (r =-.460, *P*=.041). Scatter plots of significant correlations are displayed in Figure 2 .

Figure 2

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Significant correlations in FM patients between (A) delta power from right insula (BA 13) and pain duration, as well as, between (B) beta-3 power from frontal medial gyrus (BA 8) and (C) midcingulate cortex (BA 32)

(STAI-state) (C). Depression scores (BDI-state) were also negatively correlated with beta-3 power from frontal medial gyrus (BA 8) (D).

EEG Coherence

The ANCOVA on centro-parietal intra-hemispheric coherence yielded significant *group*hemisphere* effects at delta ($F(1,32) = 10.612$, $P = .003$), theta ($F(1,32) = 9.744$, $P = .004$), alpha ($F(1,32) = 6.320$, $P = .017$), beta-2 ($F(1,32) = 7.235$, $P = .011$) and beta-3 ($F(1,32) = 10.830$, $P = .002$) EEG frequency bands. Post-hoc analyses indicated that FM patients displayed higher coherence over the left than over the right hemisphere at delta ($P = .018$), theta ($P = .005$), alpha ($P = .012$), beta-2 ($P = .003$), and beta-3 ($P = .001$); whereas pain-free controls showed higher coherence over the right hemisphere than over the left hemisphere at delta frequency band ($P = .016$). In addition, FM patients presented higher coherence over the left hemisphere than pain-free controls at theta ($P = .037$) and beta-3 bands ($P = .027$), whereas no group differences appeared over the right hemisphere at any EEG frequency band (all ps>.05) (Figure 3). Finally, a significant interaction effect between the covariate state anxiety and the factor *hemisphere* was found at delta ($F(1,32) = 4.436$, $P = .044$) and theta EEG frequency bands ($F(1,32) = 4.816$, $P = .036$). A significant interaction between the covariate BDI and the factor *hemisphere* was also found at theta band ($F(1,32) = 4.769$, $P = .036$). No other significant main effects or interactions were found regarding the factor group in other intra or inter-hemispheric ROIs. Non-significant correlations were found between coherence values and clinical variables.

Figure 3

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Intra-hemispheric EEG coherence. FM patients showed higher left centro-parietal intra-hemispheric coherence than pain-free controls in theta and beta 3 while no differences between groups were found in right hemisphere. FM patients showed a generalized pattern of enhanced intra-hemispheric coherence in left hemisphere in comparison to the right.

Discussion

In this study, we found significant alterations in EEG oscillations during eyes-closed resting state at different brain locations of the pain network over the right hemisphere in FM patients as compared with pain-free controls. These effects were positively associated with pain duration in FM patients. In addition, we observed that FM patients had greater EEG coherence over the left than over the right hemisphere over the centro-parietal area at frequency bands ranging from 2 to 30 Hz. These findings suggest an over-activation of the pain network together with an imbalance of intra-hemispheric EEG coherence in FM patients as compared with pain-free controls, even when no stimulation was applied.

FM patients in the present study displayed reduced delta activity in right insula and temporal cortices (superior and middle temporal gyri), as well as enhanced beta activity in right frontal, midcingulate and motor areas in comparison with pain-free controls. This is in accordance with previous results obtained by Hargrove et al. [22] showing that FM patients had reduced power in low-frequency EEG oscillations, together with increased power in high-frequency EEG oscillations over frontal and central electrodes during eyes-closed resting state. Our findings are also partially in accordance with previous studies by Sarnthein et al. [40] and Stern et al. [18] showing increased EEG power over the frequency range 2-25 Hz in neuropathic pain patients during resting. The results of reduced delta and enhanced beta activity in the present study could be also interpreted as a neurophysiological marker of cortical hyperexcitability in FM patients during resting. Delta and beta EEG oscillations have been traditionally interpreted as correlates of inhibitory and excitatory brain processes, respectively [41–43]. Thus, for instance, it has been found that reduced delta EEG power in medial prefrontal cortex and in right insula during resting state is correlated with enhanced metabolic activity in frontal lobes [43]. By contrast, enhancement of beta EEG power has been interpreted as a correlate of excitatory processes generated within cortical networks during resting state [41]. Moreover, EEG oscillations in the primary motor cortex around 20-Hz

(mu-rhythm) have been associated with spontaneous activity over sensorimotor areas during resting [44]. Therefore, our results of decreased delta activity over the insular cortex and increased beta activity over prefrontal and midcingulate cortices in FM patients could be interpreted as an increase of excitatory processes in these brain regions during rest due to chronic pain. In this sense, our findings are also in agreement with previous neuroimaging studies showing that chronic pain patients might be characterized by an altered activity in several pain-related areas during both pain processing [6 , 45 , 46] and resting states [11 , 12 , 47].

Furthermore, we found that these alterations were related to clinical variables in FM patients: pain duration was significantly associated with reduced delta power in insula, and anxiety as well as depression scores were associated with beta-3 power in frontomedial regions. Anxiety scores were also associated with beta-3 power from midcingulate areas. These findings are in agreement with accumulating neuroimaging evidence showing that gray matter loss in chronic pain could be associated with pain duration [48]. Other fMRI studies have also shown that altered intrinsic brain connectivity at resting in FM was associated with spontaneous pain intensity [12]. Moreover, a recent study from our lab [11] showed that FM patients displayed a substantial alteration of the pain network connectivity with strengthened connectivity of relevant pronociceptive brain regions, together with reduced connectivity of those areas involved in pain inhibitory modulation. Taken together, all these findings provide support for the hypothesis of a dysregulation of pain-associated cortical structures as consequence of chronic pain.

We also observed that FM patients displayed a general pattern of increased intra-hemispheric coherence over the left hemisphere in centro-parietal electrodes at low (delta, theta) and high EEG frequency bands (beta-2, beta-3). Reduced EEG coherence has been traditionally related to optimal organization of cortical networks [49] and to less effective information processing [50 , 51]. Moreover, increased EEG coherence in centro-parietal brain locations at all frequency bands

has been associated with processing of pain and somatosensory information [52 , 53], as well as with an altered brain processing at rest in patients with migraine [54]. Thus, our finding that altered intra-hemispheric coherence within centro-parietal areas was increased in FM patients seem to reflect a significant change in functional cortical connectivity, probably due to the accumulated and persistent experience of pain over the time. In agreement with this interpretation, a recent study using coupled EEG-fMRI recording has shown that coherent intrinsic brain activity of the sensorimotor resting state network (SMN), which is mainly located in centro-posterior regions, was increased after 11 days of repetitive and long-lasting pain stimulation [55]. Moreover, the fact that the effects due to group on intra-hemispheric coherence were not mediated by the influence of mood as covariate further indicates that long-lasting pain may alter functional brain connectivity. In conclusion, our data provide support for the use of EEG coherence as a marker of abnormal brain function during resting state in FM patients and suggest that these alterations could be linked to an altered somatosensory processing elicited by the maintenance of pain over time.

The present study has some limitations that should be taken into account. First, the spatial resolution of EEG signals is usually low and processing of scalp EEG data by sLORETA is restricted to a solution space of 2.394 voxel within the gray matter [20]. Second, EEG signals were recorded against an average reference. Previous works [36 , 37] have shown that brain activity can be influenced by recording parameters such as the selected EEG reference or differences in volume conduction between electrodes. In the present study, we decided to use an average reference approach following previous studies using single common references [15 , 17 , 37 , 39]. According with these authors, the use of an average reference would be appropriate if the spatial EEG sampling is dense enough (we used 64 electrodes) and the signal space (that is, the closed surface containing all electrical currents within its volume) is sufficiently covered [21 , 37]. Moreover, Qin et al. [56] pointed out that the average reference would be much closer to the reference-free approach than the other commonly used single references (mastoids or Cz) in terms of spectra and coherence. Finally, it should be borne in

mind that our analyses were focused on group differences and that any influence of the reference approach on coherence values would affect both groups in a similar way. Third, since our patients were currently taking pain medication during the study, the possible effect of drugs in our results cannot be completely discarded. However, the fact that source localization differences between groups were circumscribed to specific pain-related brain areas makes unlikely that results were solely due to medication. Similarly, most of our patients (16 of 20) reported sleep disturbances such as difficulties in falling asleep or maintaining sleep. Given that these sleep alterations have been associated with pain intensity and fatigue in FM [57] and that sleep deprivation may affect resting state fMRI and EEG connectivity [58 , 59], the possible effects of sleep on the observed group differences cannot be completely discarded. Finally, our sample was only composed of women, thus preventing the generalization of the results to male patients with FM. Thus, the present study should be replicated in medication-free female and male participants.

In summary, we observed that fibromyalgia patients were characterized by abnormal delta and beta EEG power in brain regions of the pain network, as well as by an imbalance of intra-hemispheric EEG coherence in resting-state. These alterations could be related to long-lasting changes in activity and functional connectivity of the brain due to the maintenance of pain over time. These findings provide support for the hypothesis of cortical hyperexcitability in fibromyalgia and suggest that analysis of frequency-dependent EEG activity at rest could be a useful tool to characterize chronic pain states.

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