

Influence of depressive feelings in the brain processing of women with fibromyalgia

An EEG study

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Abstract

Depression is one of the most common mental health problems which affects more than 10% of the global population. The prevalence of this disorder is higher in fibromyalgia patients. However, the influence of the combination of depression and fibromyalgia in the brain processing is poorly understood.

To explore the modifications of EEG power spectrum in women with fibromyalgia when depressive feelings are elicited.

Twenty eight women with fibromyalgia participated in this cross-sectional study. They were classified as women with depression or women without depression according to the score in the Geriatric Depression Scale. This questionnaire was used to elicit depression symptoms during the EEG recording. Analyses were performed with the standardized LOw Resolution Electric Tomography (sLORETA) software. Power spectrum were compared in the following frequency bands: delta, theta, alpha-1, alpha-2, beta-1, beta-2, and beta-3.

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

The current study contributes to the understanding on the influence of the combination of fibromyalgia and depression in the brain activity patterns. Patients with untreated depression showed a hypoactivation of the left hemisphere while eliciting depression symptoms. However, further research is needed, antidepressant medication might reduce the differences between patients with depression and those who do not suffer from depression symptoms.

Abbreviations: BA = Broadmann area, DMN = default mode network, FM = fibromyalgia, GDS = Geriatric Depression Scale, GDS-15 = 15 - items Geriatric Depression Scale, ICA = independent component analysis, MNI = Montreal Neurological Institute, SSRI = selective serotonin reuptake inhibitors, TPN = task – positive network.

Keywords: antidepressant, depression, EEG, fibromyalgia, left hemisphere, mood congruent recall, sLORETA

1. Introduction

Depression is one of the most common mental health problems which affects more than 10% of the global population.^[1] It has been associated with altered brain processing patterns in the default mode network (DMN) and task-positive network (TPN)

in patients with depression.^[2–5] Whereas TPN have been related to subserve active cognitive processing^[6] (working memory or executive control), DMN has been proposed to be related with self-relational processing^[7] (autobiographical recall). Furthermore, differences in medial prefrontal, medial temporal, and

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occipital regions have been reported in patients with depression when compared with healthy controls during an autobiographical memory task.^[8]

There is growing interest in the understanding of the impact of depression on brain activity patterns when processing emotions,^[9,10] recalling fears,^[11] or during autobiographical memory.^[11] These brain functioning changes influence the behavior and cognitive functions of people with depression. Thus, the mood congruent recall emerged as a characteristic of autobiographical memory in depression,^[12] referring to a preference for remembering negative^[12] or distressing memories.^[8]

Fibromyalgia (FM) is characterized by chronic widespread pain which leads to somatic (fatigue or stiffness), psychiatric and psychological symptoms (sleep disturbance, depression, and cognitive impairment).^[13,14] In patients with FM, the prevalence of depression is higher in comparison with people without FM,^[15] and a bidirectional association between depression and FM has been observed.^[16] Regarding brain functioning, patients with FM showed alterations in the functional connectivity^[17] and gray matter atrophy in the DMN regions.^[18] In addition, FM patients showed an altered brain activity when observing negative emotions, such as facial expression of pain.^[19] Despite the scientific literature about changes in brain activity of patients with depression performing different mental tasks is rich, the influence of the combination of depression and FM is poorly understood.

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. This study also aims to compare the EEG power spectrum (in delta, theta, alpha-1, alpha-2, beta-1, beta-2, and beta-3 frequency bands) between fibromyalgia patients with and without depression. Furthermore, the study aims to compare the EEG power spectrum (in delta, theta, alpha-1, alpha-2, beta-1, beta-2, and beta-3 frequency bands) of patients with depression who were or not taking antidepressant medication. To do that, brain electrical activity was recorded while patients with FM answered the geriatric depression scale (GDS), which address depressive symptoms with a simple yes/no format.^[20]

2. Methods

2.1. Participants

The Extremadura Association of Fibromyalgia (AFIBROEX) in Cáceres (Spain) called and invited all female members to participate in the study. Consecutive patients who agreed to participate and fulfilled the inclusion and exclusion criteria were included. Twenty eight women with FM (54.96 ± 10.43 years), diagnosed according to the American College of Rheumatology's criteria,^[13] participated in this cross-sectional observational

study. All participants underwent the procedure between May and June, 2017.

The sample was divided into 3 groups:

1. FM patients with depression (GDS score > 5) who were taking antidepressant medication (n=9, 52.33 ± 9.90 years);
2. FM patients with depression (GDS score > 5) who were not taking antidepressant medication (n=7, 53.43 ± 11.43 years); and
3. FM patients without depression (GDS score ≤ 5) and who were not taking antidepressants (n=12, 57.83 ± 10.42 years).

The antidepressant medication for all 9 participants was selective serotonin reuptake inhibitors (SSRI). Characteristics of each group can be observed in Table 1. Participants with neurological diseases, psychiatric diagnose (i.e., schizophrenia or substance abuse), or neurodegenerative diseases were excluded. Participants were verbally informed about the details of the study and gave written informed consent to participate in the study. All procedures were approved by the University research ethics committee and were carried out in accordance with the updated Declaration of Helsinki (approval number: 62/2017).

2.2. Instruments

EEG data was collected using the Enobio device, a wireless electrode system (Neuroelectronics, Cambridge, MA, USA).^[21] The reliability of this instrument was demonstrated, even using dry electrodes.^[22] In order to elicit depressive feelings, the 15-items Geriatric Depression Scale (GDS-15)^[20] in the Spanish version^[23] was administered by personal interview with one of the members of the research group. This questionnaire allows researchers to classify which participants are suffering from depression. The selected cut-off was 5 in order to enhance the specificity, sensibility, and both the predictive- positive and negative values of the depression diagnosis.^[20,24] Although, this questionnaire was originally designed for geriatrics patients, it has been used in patients with FM^[25,26] since it has less focus on somatic symptoms and might therefore be a more accurate assessment of depression symptoms in patients with FM independently of their health complaints.^[26]

2.3. Procedure

EEG data was continuously registered while a researcher asked the GDS items. Participants were encouraged to response only with a yes or no, keeping in silence if more time was needed to make a decision. The experimental room was calm, and light and temperature were continuously regulated.

2.4. EEG procedure and preprocessing

EEG was recorded from 19 scalp locations, according to the International 10 to 20 system such as: frontal (Fz, Fp1, Fp2, F3,

Table 1
Sample size, age, antidepressant medication, and GDS score of the 3 groups of patients with fibromyalgia.

Participants	FM without depression and without medication Mean (SD)	FM and untreated depression Mean (SD)	FM and depression, taking antidepressants Mean (SD)	P value
Sample Size (N)	12	7	9	
Age (years)	57.83 (10.41)	53.43 (11.43)	52.33 (9.90)	.407
GDS (score)	3.17 (1.40)	7.86 (1.95)	7.89 (1.62)	<.001
SSRI antidepressant medication (N)	0	0	9	<.001

SSRI=Selective serotonin reuptake inhibitors.

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).

Electrodes placed in the mastoids served as references and impedance was kept below 10 K Ω . EEG was recorded with a sampling rate of 500Hz, 50Hz notch filter, and bandpass filtering (1–40 Hz) was employed. EEGLAB toolbox (MATLAB) was applied for pre-processing and data analysis. Rough artifacts were manually removed from EEG signals and eye movement artifacts were corrected using independent component analysis (ICA).^[27] Data were divided in 5 s epochs from the cleaned dataset.

2.5. Electrical source imaging (ESI)

To compute the intracerebral electrical sources underlying EEG activity recorded at the scalp we used the sLORETA/eLORETA software package (<http://www.uzh.ch/keyinst/loreta.htm>).^[28] This tool represents the cortex as a collection of volume elements (6239 voxels, size $5 \times 5 \times 5$ mm). sLORETA is restricted to cortical gray matter, hippocampus, and amygdala in the digitized Montreal Neurological Institute (MNI) coordinates corrected to the Talairach coordinates. Neuronal activity is computed as current density ($\mu\text{A}/\text{mm}^2$) without assuming a predefined number of active sources.^[28,29] Scalp electrode coordinates on the MNI brain were based on the international 5% system.^[30] The sLORETA algorithm solves the inverse problem by assuming related orientations and strengths of neighboring neuronal sources (represented by adjacent voxels). sLORETA has proved to be an efficient tool for functional mapping because it is consistent with physiology and is capable of correct localization.^[28] Additionally, the sLORETA localization properties have been independently validated.^[31,32]

Anatomical labels as Brodmann areas are also reported using MNI space. We calculated sLORETA images corresponding to the estimated neuronal generators of brain activity within each band.^[33] The ranges of the frequency bands were as follows: delta, 1.5 to 6 Hz; theta, 6.5 to 8 Hz; alpha-1, 8.5 to 10 Hz; alpha-2, 10.5 to 12 Hz; 8.5 to 12 Hz; beta-1, 12.5 to 18 Hz; beta-2, 18.5 to 21 Hz; beta-3, 21.5 to 30 Hz.

2.6. Statistical analysis

A Kruskal–Wallis and Chi-Squared tests, using the SPSS statistical package (version 20.0; SPSS, Inc., Chicago, Ill.), were conducted to assess differences between groups in age, GDS total score and medication.

Nonparametric randomization statistic was performed using sLORETA non-Parametric Mapping tool.^[34] This tool includes a correction for multiple comparisons and does not require any assumption of Gaussianity.^[35] In addition, a second level of non-parametric analysis, the exceedance proportion tests evaluated the significance of activity based on its spatial extent, obtaining clusters of supra-threshold voxels. In this line, in order to control Type I error cluster size were calculated^[34] within a hemisphere for single Brodmann Area (BA).

The sLORETA non-Parametric mapping tool was used to perform between-group comparisons. It allows us to obtain LORETA images (see Figs. 1–3), representing the electrical activity of each voxel in the neuroanatomic MNI space as amplitude of the computed current source density ($\mu\text{A}/\text{mm}^2$) for

each frequency band^[33] (delta, theta, alpha-1, alpha-2, beta-1, beta-2, beta-3) as well as the color bar scale which represents the log-F-ratio value for each voxel. In more detail, the sLORETA current density distribution was performed using a statistical analysis based on voxel-by-voxel log of F ratio test with 5000 randomizations. The results corresponded, for each band, to maps of log-F-ratio statistics for each voxel, for corrected $P < .05$. Significant activations at the exceedance proportion tests with a P value $< .05$, F value over 2 z-score and a minimum cluster of voxels major than calculated for each BA within a hemisphere.

All possible comparisons between groups were performed using the procedures showed above.

3. Results

The Kruskal–Wallis test did not reveal any significant difference between groups in age ($P = .407$). Moreover, Kruskal–Wallis and Chi-Squared showed significant differences between FM without depression and FM unmedicated and medicated groups (Table 1).

However, exceedance proportion test revealed significant differences between FM patients with depression who were not taking antidepressant medication and FM patients without depression (log-F-ratio threshold = 0.664, P value = .043). Specifically, the unmedicated group with depression showed reduced power in delta, theta, alpha-1, alpha-2, beta-1, beta-2, and beta-3 while answering the GDS (Table 2 and Fig. 1). These differences are located predominantly in the left hemisphere.

The sLORETA non-Parametric mapping tool allows us to obtain images (see Figs. 1–3), representing the electrical activity of each voxel in the neuroanatomic MNI space as well as a color scale bar which represents the log-F-ratio for each voxel. Figure 1a represents the EEG delta power spectrum. It shows that the maximal difference is located in the medial frontal gyrus (BA 6, MNI coordinates: $x = 5, y = -10, z = 55$). Figure 1b represents the EEG theta power spectrum. We found the maximal differences in the medial frontal gyrus (BA 9, MNI coordinates: $x = -10, y = -35, z = 35$) (see Fig. 1b). Figure 2c and 2d represents the EEG in the alpha-1 and alpha-2 power spectrums respectively. Maximal differences appeared in the cingulated gyrus (BA 32, MNI coordinates: $x = -5, y = 35, z = 30$) for alpha-1 and in the medial frontal gyrus (BA 9, MNI coordinates: $x = -5, y = -45, z = 30$) for alpha-2. Figure 3 represents the EEG power spectrum in beta-1, beta-2, and beta-3. In the beta-1, maximal differences were found in the medial frontal gyrus (BA 9, MNI coordinates: $x = -5, y = 40, z = 30$) (see Fig. 3e). In the beta-3 the maximal differences were obtained in the middle temporal gyrus (BA 19, MNI coordinates: $x = -40, y = -85, z = 20$) (see Fig. 3f). In the beta-3 the maximal difference across participant was detected in the medial frontal gyrus (BA 19, MNI coordinates: $x = -40, y = -80, z = 25$) (see Fig. 3g). Each of the previous figure is accompanied by a color bar which represents the log-F-ratio value for each voxel.

In delta power, the clusters of supra-threshold were located in left BA 6, 7, 19, 40 and right BA 6 (Table 2). Moreover, in theta power the clusters of supra-threshold were located in left and right BA 6 and in left BA 40 (see Table 2). In alpha-1 and alpha-2 were located in BA 9, 19 and 37, whereas in alpha-2 were also identified in right BA 10 (Table 2). Furthermore, beta-1 power significant clusters of supra-threshold were located in left BA 9,

Table 2
Statistical non-parametric comparisons between FM patients without depression and FM patients who have depression and were not taking antidepressants using sLORETA. The table only shows significant cluster for the delta, theta, alpha-1, alpha-2, beta-1-beta-2, and beta-3 activity.

Band	BA	Max/Min region	Lobe	MNI coordinates			Max/Min F-value	No. of voxels $P < 0.05$
				X	Y	Z		
Delta	6	Medial Frontal Gyrus	Left Frontal	0	-10	55	1.66	276
	7	Precuneus	Left Parietal	-5	-35	45	1.36	211
	18	Middle occipital gyrus	Left Occipital	-40	-90	0	1.20	173
	19	Middle temporal gyrus	Left Occipital	-55	-65	15	1.36	186
	40	Supramarginal gyrus	Left temporal	-60	-55	20	1.35	189
Theta	6	Medial-Frontal Gyrus	Right Frontal	5	-10	55	1.66	199
	6	Medial frontal gyrus	Left frontal	-10	25	40	1.29	276
	40	Supramarginal gyrus	Left temporal	-60	-55	20	1.19	189
Alpha-1	6	Superior Frontal Gyrus	Right Frontal	10	10	70	1.18	165
	9	Medial frontal gyrus	Left Frontal	-5	40	26	1.22	111
	19	Middle temporal gyrus	Left Occipital	-55	-65	15	1.13	137
	20	Inferior temporal gyrus	Left temporal	-60	-55	-20	1.03	108
	21	Middle temporal gyrus	Left temporal	-60	-60	0	1.10	105
	37	Middle temporal lobe	Left temporal	-60	-65	5	1.13	92
	40	Supramarginal gyrus	Left temporal	-60	-55	20	1.08	115
Alpha-2	47	Inferior frontal gyrus	Left frontal	-50	45	-10	0.71	107
	9	Medial frontal gyrus	Left frontal	-5	45	30	1.23	91
	10	Superior frontal gyrus	Left frontal	-5	60	30	1.16	138
	11	Orbital gyrus	Left frontal	-10	55	-20	0.70	115
	19	Middle occipital gyrus	Left Occipital	-55	-70	5	1.06	120
	20	Fusiform gyrus	Left Temporal	-40	-30	-20	0.62	96
	21	Middle temporal gyrus	Left Temporal	-60	-60	0	1.05	103
	37	Middle temporal gyrus	Left Temporal	-60	-65	5	1.07	86
Beta-1	47	Inferior frontal gyrus	Left frontal	-20	10	-20	0.76	107
	10	Superior Frontal gyrus	Right frontal	5	60	30	1.14	88
	11	Middle frontal gyrus	Right frontal	45	50	-10	0.67	124
	8	Middle frontal gyrus	Left frontal	-30	25	45	0.60	40
	9	Middle frontal gyrus	Left frontal	-35	25	40	0.60	85
	19	Precuneus	Left parietal	-25	-85	35	0.62	102
	32	Anterior cingulate	Left Limbic	-5	35	-10	0.62	37
	37	Fusiform gyrus	Left temporal	-35	-50	-20	0.61	74
	39	Inferior parietal lobule	Left parietal	-35	-65	40	0.61	75
	40	Inferior parietal lobule	Left parietal	-40	-55	40	0.67	56
Beta-2	7	Inferior parietal lobule	Left parietal	-40	-70	45	1.00	77
	9	Superior frontal gyrus	Left frontal	-20	50	40	0.66	52
	18	Middle occipital gyrus	Left occipital	-35	-90	10	1.20	121
	19	Middle temporal gyrus	Left temporal	-40	-85	20	1.24	165
	37	Middle occipital gyrus	Left occipital	-40	-70	0	1.16	94
	39	Middle temporal gyrus	Left Temporal	-45	-80	20	1.24	77
	40	Supramarginal gyrus	Left parietal	-55	-60	30	1.14	131
Beta-3	7	Inferior parietal lobule	Left parietal	-40	-70	45	1.29	145
	18	Middle occipital gyrus	Left occipital	-35	-90	10	1.43	157
	19	Superior occipital gyrus	Left occipital	-40	-80	25	1.50	186
	37	Middle temporal gyrus	Left occipital	-40	-65	5	1.39	96
	39	Middle temporal gyrus	Left temporal	-35	-75	25	1.50	77
	40	Supramarginal gyrus	Left parietal	-60	-50	35	1.44	162

BA = Brodmann area, MNI = Montreal Neurological Institute.

40, 32 and 37, while in beta-2 significant cluster of supra-threshold were identified in left BA 9, 19, 40, and 37 (Table 2). Lastly, in beta-3 were also identified significant cluster of supra-threshold in left BA 39, 7, and 19 (Table 2).

Non-parametric analyses using sLORETA showed that the FM patients who were taking antidepressant medication did not statistically differ from the FM patients who were not being treated with this medication in terms of significant voxel or clusters of supra-threshold voxels at delta, theta, alpha, or beta frequency bands. Furthermore, comparison between FM patients

with antidepressant treatment and FM women without depression was also performed. Non-significant voxel or cluster of supra-threshold voxels at delta, theta, alpha, or beta frequency bands were located.

4. Discussion

The principal aim of this study was to explore the modification of EEG power spectra induced by eliciting depressive feelings in patients with FM and to compare EEG power spectrum (in delta,

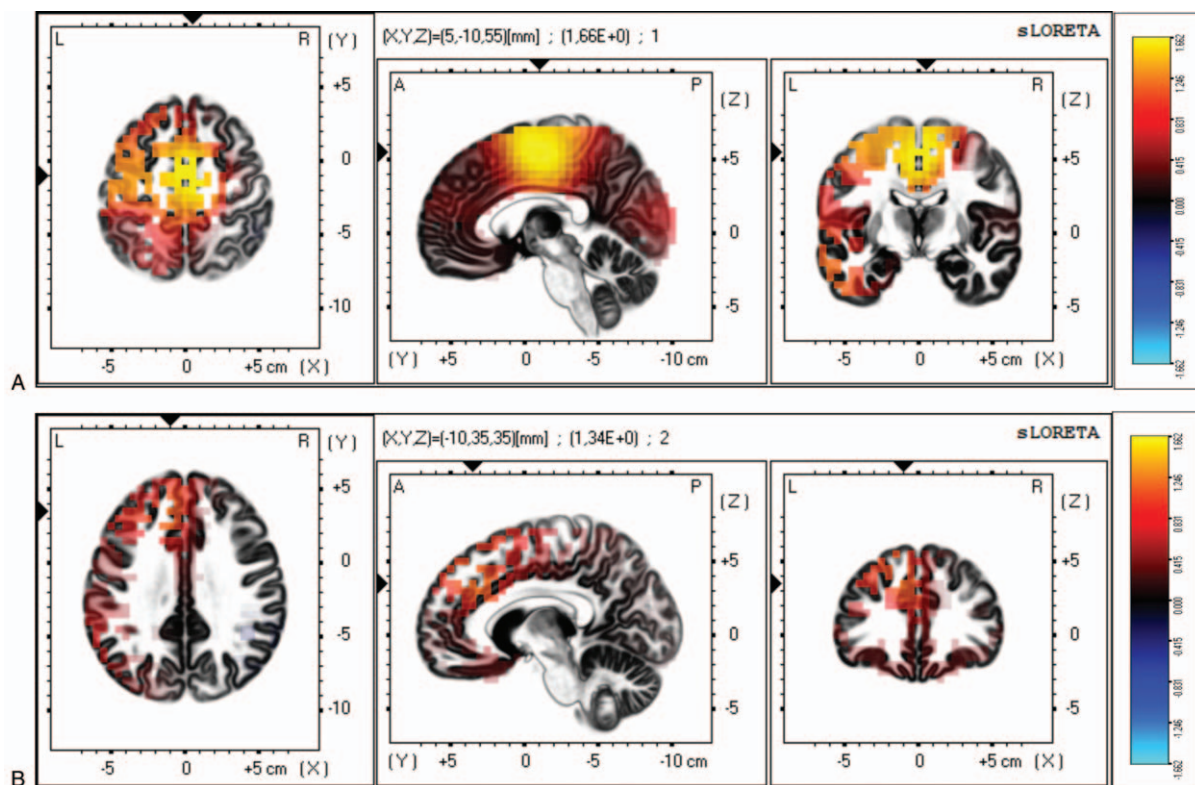


Figure 1. Differences between patients with FM with depression and patients with FM without depression on the mean current source density analyzed by sLORETA. (A) For the delta frequency, the maximal difference across patients with FM appeared in the medial frontal gyrus (BA 6, MNI coordinates: $x=5$, $y=-10$, $z=55$). (B) For the theta frequency, the maximal difference across participant was detected in the medial frontal gyrus (BA 9, MNI coordinates: $x=-10$, $y=-35$, $z=35$). The color bar shows sLORETA activation which represents the log-F-ratio value for each voxel.

theta, alpha-1, alpha-2, beta-1, beta-2, and beta-3 frequency bands) between fibromyalgia patients with and without depression, taking the antidepressant medication into account.

The main finding was that women with FM and untreated depression obtained reduced power in delta, theta, alpha-1, alpha-2, beta-1, beta-2, and beta-3 while answering GDS-15 questionnaire. Differences were found predominantly in the left hemisphere. Regarding delta power differences were located in left frontal, parieto-temporal, and occipital areas. Differences in theta power were located in frontal and parietal areas. In relation with alpha-1 and alpha-2 power, differences were located in frontal, temporal, and occipital areas. Beta-1, beta-2, and beta-3 showed differences in frontal, parieto-temporal, and occipital. However, differences were not found between patients with FM with and without depression symptoms.

Previous studies in clinical populations with affective disorders^[36,37] have showed that left hemisphere is important for regulation of negative emotions.^[38] In patients with depression, a hypoactivity in the left hemisphere has been observed,^[37] thus the alterations in left hemisphere may be related with depression symptoms, such as reduced motivation and activity^[39] or apathy.^[40] In line with these studies, Stewart and colleagues^[10] reported frontal EEG asymmetry during facial emotion task. This frontal EEG asymmetry is considered by authors as a risk major for major depression disorder. These abnormalities are consistent with our results where left hemisphere hypoactivity in power spectrum has been observed

in patients with FM and depression while depressive feelings were elicited.

Answering the GDS is other alternative to elicit depressive feelings and provide emotional stimulus and according to a previous study^[41] there is a decreased activation in prefrontal areas, hippocampus, and caudate in patients with depression when the emotional stimulus is based on viewing images of faces expressing negative emotional state, suggesting that functional impairment of fronto-limbic and fronto-subcortical brain regions may be implicated in depression. According to the mood congruent memory, these patients are more likely to remember negative information^[42] or create distressing memories.^[8] Regarding FM, patients have shown alterations in the functional connectivity^[17] and gray matter atrophy^[18] in the DMN. Interestingly, patients with FM have also reported altered brain activity viewing facial expression of pain.^[19] These alterations in the DMN have been also observed in patients with depression^[43] during emotion processing.

According to Bertolucci and de Oliveira,^[44] patients with FM have phonetic and semantic verbal fluency impairments, which may be correlated with irritability or anxiety.^[45] In this regard, voxel-based morphometric studies have shown reduced performance in non-verbal working memory and non-verbal long-term memory in a free recall condition, which is associated with changes in structural gray matter in the left dorsolateral prefrontal cortex and in the supplementary motor cortex.^[46] This may be in line with our results where we found left hemisphere hypoactivation while answering the GDS question-

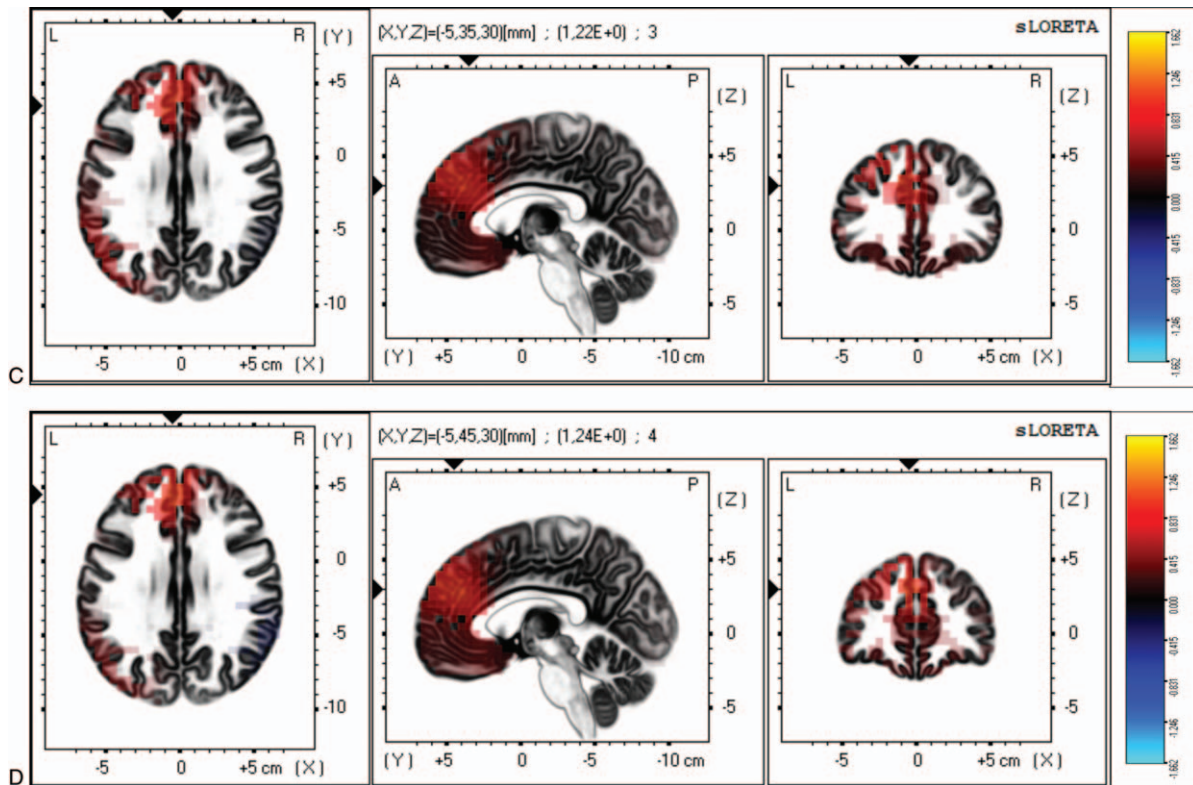


Figure 2. Differences between patients with FM with depression and patients with FM without depression on the mean current source density analyzed by sLORETA. (C) For the alpha-1 frequency, the maximal difference across patients with FM appeared in the cingulate gyrus (BA 32, MNI coordinates: $x = -5$, $y = 35$, $z = 30$). (D) For the alpha-2 frequency, the maximal difference across participant was detected in the medial frontal gyrus (BA 9, MNI coordinates: $x = -5$, $y = -45$, $z = 30$). The color bar shows sLORETA activation which represents the log-F-ratio value for each voxel.

naire, which may lead to a mentally recall of depressive feelings. In this regard, lesions in the left dorsolateral prefrontal cortex are related to increased depression symptoms, demonstrating a direct neurological contribution to depression symptoms after left hemisphere stroke.^[47] Thus, the morphology and functioning of the left hemisphere may be of great interest to investigate potential differences in brain functioning between patients with FM and pain-free subjects.

According to our results, comparing between women with FM and depression treated with SSRI and those without depression, significant differences were not found. Pharmacological treatment is widely used in order to normalize amygdala overactivation in response to negative stimuli.^[48] In this regard, in patients suffering from major depressive disorders, SSRI treatment is associated with favorable changes in brain electrical activity.^[49] In line with this study, Fales and colleagues^[50] reported that antidepressant medication increased pre-frontal cortex activity during emotional tasks.

In addition, a non-significant statistical tendency showed higher power spectrum in FM patients who were taking antidepressants when compared with those with untreated depression. Future research should study the effects of antidepressant treatment on EEG power spectrum in patients with FM when depression feelings are elicited. Furthermore, EEG neurofeedback is an alternative to other treatments such as medication,^[51] increasing the relative right frontal alpha power, and reporting positive effects on emotion, cognition, and performance in the executive function.^[52] Also, aerobic training may

have benefits in alpha power in patients with depression,^[53] supporting the effect of aerobic training on alpha activity and on depression symptoms in elderly patients. Exercise facilitates the treatment of depressive elderly adults, leading to clinical and physical improvement and protecting against a decrease in cortical activity.^[53]

One potential limitation of our study was the number of scalp EEG recordings electrodes ($n = 19$). Spatial resolution increases with the number of EEG sources reflected by sLORETA software. However, a large number of studies have been developed with the same or less number of scalp EEG recordings,^[54–56] even the reliability of sLORETA and the original validation use the original 19 electrodes.^[57–59] Lastly, the sample size ($n = 28$) was relatively small that might have caused that only great differences have reached the statistical significance level.

To summarize, the current study contributes to the understanding on the influence of the combination of FM and depression in the EEG power spectrum. Differences in EEG power spectrum were observed between FM patients with and without depression, showing in patients with untreated depression a hypoactivation of the left hemisphere compared with non-depressed FM women. Antidepressant medication seems to reduce the differences between patients with depression and those who do not suffer from depression symptoms. However, according to our results, there is not enough evidence to provide conclusions about brain dynamics changes as a consequence of the medication intake.

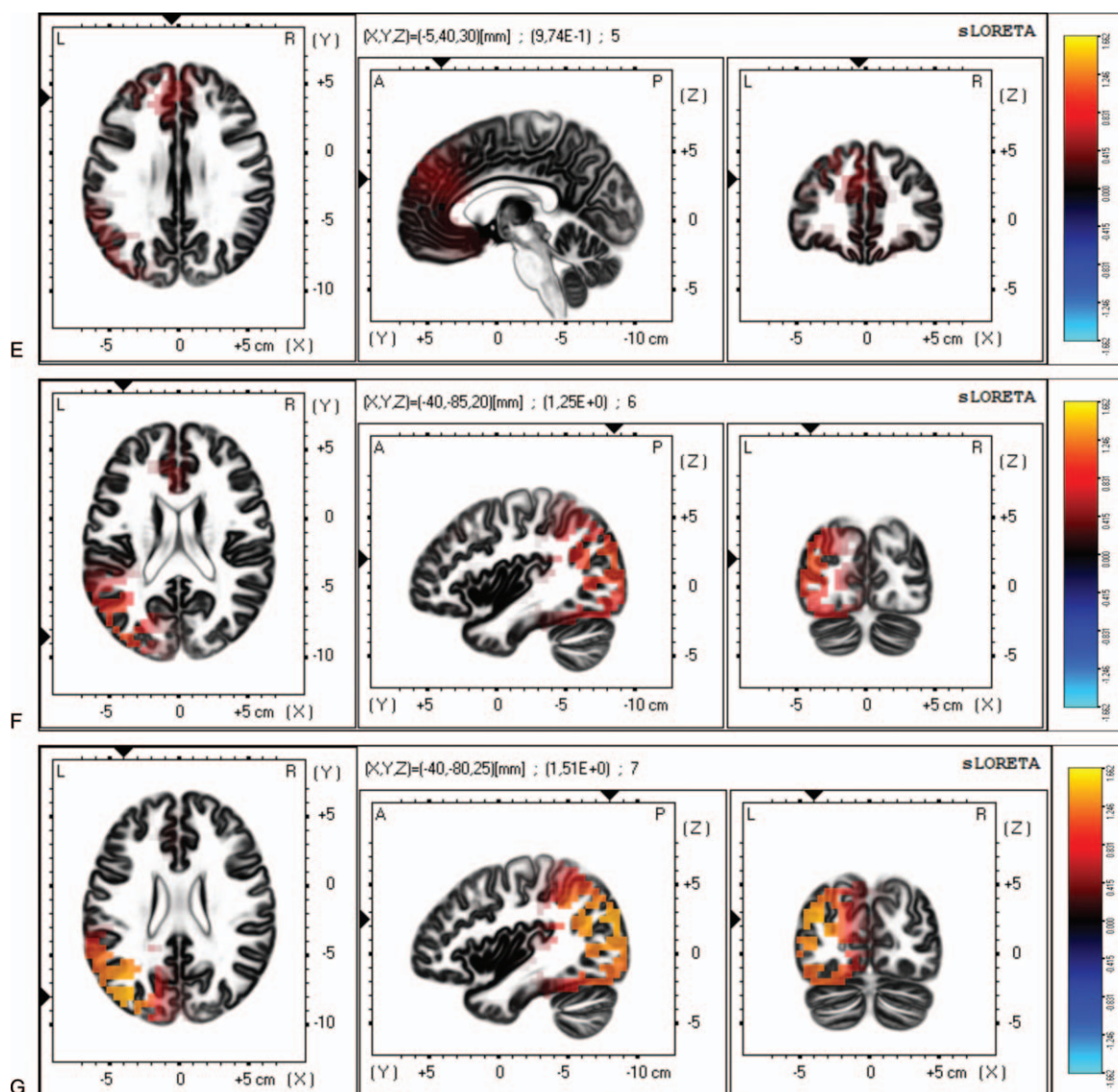


Figure 3. Differences between patients with FM with depression and patients with FM without depression on the mean current source density analyzed by sLORETA. (E) For the beta-1 frequency, the maximal difference across patients with FM appeared in the medial frontal gyrus (BA 9, MNI coordinates: $x = -5$, $y = 40$, $z = 30$). (F) For the beta-2 frequency, the maximal difference across participant was detected in the middle temporal gyrus (BA 19, MNI coordinates: $x = -40$, $y = -85$, $z = 20$). (G) For the beta-3 frequency, the maximal difference across participant was detected in the medial frontal gyrus (BA 19, MNI coordinates: $x = -40$, $y = -80$, $z = 25$). The color bar shows sLORETA activation which represents the log-F-ratio value for each voxel.

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