

# The impact of fibromyalgia symptoms on brain morphometry

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**Abstract** Fibromyalgia (FMS) is a complex clinical syndrome that includes many symptoms beyond chronic pain. The studies that have addressed brain morphometry in FMS have had very heterogeneous results. Thus, the question of which specific FMS symptoms and clinical features—pain, but also psychological distress, sleep-related problems, health status, and medication intake—impact on brain morphometry remains open. Here, we wanted to determine if brain changes in FMS are “symptom-related” more than “diagnostic-related”. We performed an observational study of 46 premenopausal women (23 FMS patients and 23 age-matched healthy participants). Magnetic resonance images were analyzed using voxel-based morphometry and subcortical segmentation. We used multiple regression models to assess the associations between total and local brain volumes and FMS clinical characteristics. Furthermore, we calculated associations between subcortical structures’ shapes and volumes and FMS clinical characteristics. Larger psychological distress, anxiety, and sleepiness, and higher analgesic consumption accounted for 38 % of FMS patients’ smaller total gray matter volume (GMV). For both groups, local

decrements of GMV in the medial orbitofrontal cortex were associated to larger psychological distress. Local increases of GMV were positively related to pain scores (superior frontal gyrus), psychological distress (cerebellum), anxiety (medial orbitofrontal cortex), and sleepiness (frontal superior medial cortex). FMS clinical characteristics were also associated to deformations in subcortical structures and volumes changes. This study reveals that total and local GMV changes in FMS go beyond the traditional “pain matrix” alterations. We demonstrated that brain morphology is altered by pain, but also by clinical characteristics that define the FMS experience.

**Keywords** Chronic pain · Fibromyalgia · Gray matter volume · MRI · Neural plasticity

## Introduction

Chronic pain is a major public health problem, due to its high prevalence and clinical challenges (Goren et al. 2014). Fibromyalgia syndrome (FMS) is one of the most common chronic pain conditions. Depending on the diagnostic criteria used, prevalence rates range from 1.1 to 6.4 % of the general population (Branco et al. 2010; Nakamura et al. 2014; Vincent et al. 2013), with middle-aged and older women having higher rates (Branco et al. 2010; Clauw 2014). FMS is primarily characterized by chronic widespread musculoskeletal pain and multiple tender points (Wolfe et al. 1990) (see Table 1). However, other non-specific symptoms, such as psychological distress and sleep disturbances, are also very common (Wolfe et al. 2011) and distressing (Shillam et al. 2011). Additionally, patients usually have multiple comorbidities (Rehm et al. 2010).

Importantly, the frequent symptoms of allodynia and hyperalgesia might express a central pain processing disturbance (Woolf 2011). Therefore, since the pathogenesis of

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**Table 1** Fibromyalgia syndrome (FMS) symptoms. Following the American College of Rheumatology (ACR) 1990 classification criteria (Wolfe et al. 1990), the defining symptoms of FMS are widespread musculoskeletal pain, affecting the left, right, upper, and lower sides of the body and the axial skeletal system for at least 3 months, and the presence of, at least, 11 out of 18 specific tender points. Other non-specific symptoms and comorbidities are highly frequent and severe. These ones have been introduced in the new 2010 ACR criteria for FMS (Wolfe et al. 1990, 2011)

Pain symptoms	Non-specific symptoms
Widespread musculoskeletal pain	Psychological distress (anxiety and depression)
Body pain (shoulders, neck, low back, hips)	Sleep complaints
Multiple tender points	Joint stiffness
Allodynia	Fatigue
Hyperalgesia	Neuropathies
	Cognitive dysfunction (“fibrofog”)
Frequent comorbidities	
Depressive disorder	Chronic fatigue syndrome
Anxiety disorder	Systemic lupus erythematosus
Sleep disorders	Rheumatoid arthritis
Headache	Temporomandibular joint dysfunction
Irritable bowel syndrome	Posttraumatic stress disorder

FMS is unknown, many efforts have been made to understand the central pain processing in these patients, as well as the brain changes in pain processing areas. Firstly, functional magnetic resonance imaging (fMRI) studies have provided evidence that FMS patients process pain differently than healthy controls (Schweinhart and Bushnell 2010; Vachon-Preseau et al. 2013). For example, they rate experimental pain stimuli as more painful and, moreover, enhanced pain-evoked neural responses are also elicited. Similarly, non-painful stimuli in healthy subjects are considered as painful by FMS patients, and they activate relevant pain-related brain areas when they are applied (Gracely et al. 2002). Secondly, voxel-based morphometry (VBM) studies have shown morphometric brain changes among FMS patients, either in total volume or in specific areas (May 2011). Although pioneering research by Kuchinad and colleagues (2007) and more recent work by Jensen and colleagues (2013) found that FMS patients had significantly lower volumes in total gray matter volume (GMV) than healthy controls, most similar studies have not found significant differences between FMS patients and healthy controls (Burgmer et al. 2009; Ceko et al. 2013; Fallon et al. 2013; Hsu et al. 2009; Robinson et al. 2011). Among VBM studies focusing on local GMV differences, decrements and increments of cortical GMV have been found among FMS patients when they are compared to healthy controls (see Table 2), with certain level of agreement

regarding a significant decrement of GMV in the anterior cingulate cortex (Burgmer et al. 2009; Ceko et al. 2013; Jensen et al. 2013; Kuchinad et al. 2007; Robinson et al. 2011; Wood et al. 2009). These heterogeneous results in VBM studies might be due to the small sample sizes assessed and some methodological inconsistencies among studies involving, for example, a high variability between participants (demographic and clinical features), as well as differences in the methods used (data acquisition and statistical analyses). Another explanation for this heterogeneity might come from the intrinsic diversity that characterizes the FMS population. Since the clinical profiles of these patients are quite variable, FMS might not constitute a single clinical entity (Rehm et al. 2010). Finally, studies showing significant morphological alterations to subcortical structures (including the bilateral basal ganglia, thalamus, hippocampus, and brainstem) in FMS patients are scarce (Fallon et al. 2013), even when it is known that subcortical structures are involved in pain processing (Bingel et al. 2002).

Despite the heterogeneity in the results from VBM studies in FMS, both in the direction of the differences and in the localization of the affected areas, it is reasonable to conclude that FMS is associated with structural alterations of the brain. Some studies agree on the presence of structural changes in areas such as the cingulate cortex or the insula—known to be involved in pain regulation (Catani et al. 2013; Gasquoin 2013). All the studies presented in Table 2 had a cross-sectional design and no statement can be made regarding the cause of this structural (re)organization. However, some longitudinal evidence showed that brain structural changes might be subsequent to pain as those changes returned to a normal state when the pain was resolved (Henry et al. 2011). Therefore, some authors suggest that this “experience-dependent” (Kolb and Gibb 2014) central nervous system (CNS) reorganization is likely to reflect a “maladaptive plasticity” (May 2008). Similar to the structural brain changes produced during sensory learning (May et al. 2007), it might be that the continuous nociceptive activation provides a similar recurring stimulus input (i.e., pain-induced plasticity). However, the FMS experience includes symptoms other than pain (Müller et al. 2007) and CNS changes might be importantly shaped by other symptoms as well (May 2011).

Insights into the CNS reorganization associated with FMS symptoms are still lacking. Among the symptoms experienced in FMS (see Table 1), psychological distress, poor sleep quality, and subsequent daytime sleepiness are highly frequent and incapacitating (Diaz-Piedra et al. 2015; Goesling et al. 2013). Pioneering research (Burgmer et al. 2009; Hsu et al. 2009; Schmidt-Wilcke et al. 2007), trying to disentangle the effect of pain and psychological distress on brain morphology in FMS patients, has shown a partial CNS reorganization which is due to depression and/or anxiety independent of pain. On the other hand, other studies have found certain brain structural changes that could not be explained by depression in



FMS (Schmidt-Wilcke et al. 2007). Additionally, despite the importance of sleep quality in relation to other FMS symptoms (Diaz-Piedra et al. 2014), the effect of sleep-related variables in altering brain structure among FMS patients has been neglected.

To summarize, although the primary symptom of FMS is pain, additional symptoms are also involved. Structural brain changes might be stimulus-dependent (Draganski et al. 2004) and, therefore, frequent FMS symptoms might have an active role in the pathophysiology of the syndrome. It is not clear, however, whether structural brain changes occur in relationship with other symptoms, other than pain, commonly reported in FMS patients and, if so, what is the specific impact of these symptoms on structural brain changes. Even when it is important to know which—and where—specific FMS symptoms alter brain structure (May 2011; Smallwood et al. 2013), the question remains open. We investigated, for the first time, the role that FMS symptoms (including pain) and clinical characteristics play in explaining changes in brain structure. We hypothesized that symptom severity other than pain intensity, such as psychological distress, anxiety, depression, sleep quality, and daytime sleepiness, as well as clinical variables (length of diagnosis and medication intake) would be related to morphological cortical and subcortical brain changes regardless of the diagnosis.

## Methods

### Participants

We performed an observational study on 48 Caucasian premenopausal women (from 74 potential participants who were interviewed for their possible inclusion in the study). This sample size is typical of MRI studies that do simple group comparisons (Table 2). The study was conducted at the Mind, Brain, and Behavior Research Center, Granada, Spain. Twenty-four FMS patients were referred from the Service of Rheumatology of the University Hospital Virgen de las Nieves (Granada, Spain). Twenty-four healthy controls were recruited from the local community by advertisements and word-of-mouth. No significant differences were observed in age, body mass index, marital status, and employment status between groups (all  $p$ -values  $> .05$ ). Inclusion criteria for patients were female gender (pain responses differ between sexes (Mogil 2012)), the diagnosis of FMS performed by an experienced rheumatologist (MAG), following the American College of Rheumatology criteria for FMS (Wolfe et al. 1990), and premenopausal status. Inclusion criteria for healthy controls were that they were premenopausal women, had no history of chronic pain, no sleep disorders, and were not taking CNS medications. Subjects were excluded from both groups if they had any of the following: severe physical impairment;

coexisting physical injury; comorbid medical illnesses (morbid obesity, autoimmune diseases, cardiopulmonary diseases, uncontrolled endocrine disorders, uncontrolled allergic disorder/asthma, cancer, and/or medical history of significant head injury or neurological disorder); existing psychopathological disorder (history of psychosis, current suicide risk—or attempt within 2 years of the study—, history of substance abuse, major depressive disorder); pregnancy; use of recreational drugs; alcohol consumption of more than 40 g per day (established as *harmful consumption* by the World Health Organization (Anderson et al. 2008)). Patients were not asked to alter or stop their medication prior to the study. One patient was excluded after the pregnancy test. The scan of one healthy control was excluded because of catastrophic artifacts in the MRI data (orthodontic brackets). The final sample was composed of 23 FMS patients and 23 healthy controls. Table 3 displays the sociodemographic descriptive statistics of the participants.

### Psychological assessment

Sociodemographic and clinical data were collected through a semi-structured interview and questionnaires. The assessment was conducted by an expert psychologist (CDP) in the evaluation of people suffering from chronic pain and/or sleep disorders. During the interview, we obtained data regarding 1) FMS and comorbid conditions: length of diagnosis, level of disability due to FMS, medication consumption (name and frequency of use of prescription medicines actually consumed with or without prescription, as well as over-the-counter medicines), current treatments other than medication (e.g., physiotherapy, alternative medicine treatments,...), pain experience (severity, localization, and quality), and other symptoms suffered; 2) lifestyle habits (e.g., tobacco use, alcohol consumption); 3) depressive disorders and other non-psychotic psychopathological disorders, assessed using an adaptation of the structured clinical interview for DSM-IV disorders (First et al. 1999), and 4) sleep disturbances, assessed using an adaptation of the Insomnia Interview Schedule (Morin and Espie 2003). Finally, to assess symptoms severity, participants were asked to complete the validated Spanish versions of several self-reports and questionnaires: A visual analogue scale to assess pain intensity (VAS), the Hospital Anxiety and Depression Scale to assess psychological distress (HADS; Herrero et al. 2003), the State-Trait Anxiety Inventory to assess anxiety (STAI; Spielberger et al. 2011), the Beck Depression Inventory to assess depression (BDI; Sanz et al. 2005), the Pittsburgh Sleep Quality Index to assess sleep quality (PSQI; Carpenter and Andrykowski 1998; Royuela and Macias 1997), the Epworth Sleepiness Scale to assess daytime sleepiness (ESS; Ferrer et al. 1999), and

**Table 3** Descriptive statistics for demographic and clinical characteristics of the fibromyalgia patients and the healthy controls

	FMS patients N=23	Healthy controls N=23
	Mean (SD), range	Mean (SD), range
Age (years) <sup>a</sup>	41.6 (4.4), 27-47	39.7 (5.4), 30-47
Body mass index (Kg/m <sup>2</sup> ) <sup>b</sup>	24.7 (4.1), 17.6-34.7	23.2 (3.5), 17.5-34.1
Time since diagnosis (months)	102.6 (75.9), 4-276 N (%)	— N (%)
Medication		
Antidepressants	13 (59.1)	—
Anxiolytics	9 (40.9)	—
Opioids	7 (31.8)	—
Aniline analgesics	9 (40.9)	—
Nonsteroidal anti-inflammatory analgesics	10 (45.4)	—
Anticonvulsants	4 (18.2)	—
Education <sup>c</sup>		
Basic education	8 (34.8)	2 (8.7)
High school	2 (8.7)	5 (21.7)
Professional instruction	9 (39.1)	3 (13.0)
University studies	4 (17.4)	13 (56.5)
Marital status <sup>d</sup>		
Single	4 (17.4)	5 (21.7)
Married	16 (69.6)	14 (60.9)
Divorced or widowed	3 (13.0)	4 (17.3)
Work status <sup>e</sup>		
Housewife	8 (34.8)	3 (13.0)
Currently employed	6 (26.1)	12 (52.2)
Unemployed	5 (21.7)	8 (34.8)
Retired	2 (8.7)	—
Disabled	2 (8.7)	—

FMS fibromyalgia syndrome group, SD standard deviation

<sup>a</sup>  $t(44) = -1.29, p = .204$

<sup>b</sup>  $t(44) = -1.31, p = .197$

<sup>c</sup>  $\chi^2(3) = 12.60, p = .005$

<sup>d</sup>  $\chi^2(2) = 0.38, p = .824$

<sup>e</sup>  $\chi^2(4) = 8.96, p = .062$

the Fibromyalgia Impact Questionnaire to assess health status (physical function, disease impact and symptoms) (FIQ; Rivera and Gonzalez 2004) (see Table 4).

### MRI procedures

MRI was performed on a 3T Phillips Achieva whole body MRI system (Philips Medical Systems, Best, The Netherlands) operating with an eight channel

phased-array head coil for reception. For each participant, a T1-weighted 3D volume was acquired using a MPRAGE sequence in sagittal orientation with  $0.94 \times 0.94 \times 1.0$  mm resolution (160 slides, FOV =  $240 \times 240$  mm<sup>2</sup>, matrix:  $256 \times 256$ , repetition time: 8 ms; echo time: 4 ms; flip angle: 8°; fat saturation band with 191 HZ/pixel). The sequence was designed to optimize the reduction of magnetic field inhomogeneities and susceptibility artifacts.

### Image processing

#### Voxel-based morphometry

T1 MRI-images were manually checked for morphological abnormalities or artifacts and aligned to the anterior-posterior commissures line. For data processing and analysis, we used SPM 8 processing pipelines (<http://www.fil.ion.ucl.ac.uk/spm/>). For the voxel-based morphometry of structural images, we used the DARTEL algorithm (Ashburner 2007). After brain tissue segmentation (Ashburner and Friston 2005), maps of gray matter (GM) and white matter (WM), were fed to DARTEL. DARTEL has proved to improve anatomical precision of alternative standard spatial normalization methods (Klein et al. 2009). Through an iterative procedure, it created optimized templates for the whole sample and the deformation field for each participant, which were later used for warping segments onto the new reference space. The GM and WM segments were resampled to 1.5 mm isotropic voxels, using trilinear interpolation and remapped onto the Montreal Neurological Institute (MNI) space using affine transformations. These volumes were scaled by the Jacobian determinants of the deformation fields, to consider the local compression and stretching inherent to warping and affine transformation processes. GM and WM maps were then smoothed by an 8 mm FWHM Gaussian kernel.

#### Subcortical segmentation and volumetric analysis

Seven subcortical structures (hippocampus, dorsal striatum [i.e., caudate nucleus and putamen], ventral striatum [i.e., accumbens nucleus], amygdala, globus pallidus, thalamus, and brainstem + 4th ventricle) were segmented for each woman's scan using a semi-automated, model-based subcortical tool (FMRIB's Integrated Registration and Segmentation Tool; FIRST v1.2) (Nugent et al. 2013; Patenaude et al. 2011) in FMRIB's Software Library (FSL) version 4.1.4 (<http://www.fmrib.ox.ac.uk/fsl>) (Smith et al. 2004). Based on manually segmented models of the Center for Morphometric Analysis, Massachusetts General Hospital (Boston, MA), FIRST computed a mesh composed by a set vertices defined by adjacent triangles. Structures can be compared across

**Table 4** Brief descriptions of the self-reports and questionnaires used to assess symptoms severity

Constructs and questionnaires/scales	Description
Pain intensity: Visual analogue scale (VAS)	Items: 1 Participants have to choose a number between 0 (no pain) and 10 (pain was “as bad as it can be”) to represent their pain experience during the last 2 weeks.
Psychological distress: Hospital Anxiety and Depression Scale (HADS)	Items: 14 (7, Anxiety and 7, Depression). Psychological Distress score is computed adding the Anxiety and Depression subscales scores. Score range: 0–21, with higher scores indicating higher psychological distress.
Anxiety: State-Trait Anxiety Inventory (STAI)	Items: 40 (20, State anxiety and 20, Trait anxiety). Subscale range: 0–60, with higher scores indicating higher levels of anxiety.
Depression: Beck Depression Inventory (BDI)	Items: 21 Score range: 0–63, with higher scores indicating higher levels of depression (scores above 25 indicate severe symptoms).
Subjective sleep quality: Pittsburgh Sleep Quality Index (PSQI)	Items: 19 Score range: 0–21, with higher scores indicating worse sleep quality. In populations with physical illnesses, scores above 8 indicate a clinically significant level of sleep disturbances, whereas in the general population the cut-off is 5.
Daytime sleepiness: Epworth Sleepiness Scale (ESS)	Items: 8 Score range: 0–24, with higher scores indicating greater sleepiness. Scores above 10 indicate excessive daytime sleepiness.
Health status: Fibromyalgia Impact Questionnaire (FIQ)	Items: 10 Score range: 0–100, with higher scores indicating higher negative impact of fibromyalgia on functioning.

subjects as the number of vertices for each structure is fixed, and the pose (rotation and translation) is removed, as they are aligned to a common space in several stages: 1) a 12° of freedom registration to the MNI152, 2) a 12° of freedom registration in which a mask is used to exclude voxels not belonging to the subcortical structure, 3) minimization of the sum-of-squares differences between subject’s vertices and average vertices (Patenaude et al. 2007). The radial distances of each vertex to the medial line of the nucleus allow for the examination of the expansions and contractions of the surface. This approach has been used both in manually and automated subcortical segmentation (Beacher et al. 2009; Becker et al. 2006; Madsen et al. 2010). Segmentations were visually checked for errors. The volume of each participant’s subcortical structures was measured in mm<sup>3</sup>, and bilateral brain volume values were used in subsequent analyses.

### Statistical analysis

Sociodemographic and clinical variables were compared between groups using chi-square and two sample *t*-tests for categorical (educational, marital, and work statuses) and quantitative variables (age and body mass index), respectively. Pearson’s correlation coefficients were computed for the association between total gray and white matter volumes and clinical variables, including length of diagnosis and medication intake (number or different medications for each category: antidepressants, anxiolytics, opioids, aniline analgesics, non-steroidal anti-inflammatory analgesics, and anticonvulsants)

in order to determine possible covariates for successive analyses. Only analgesic consumption was related to brain volumes, and served as covariate in the next analyses together with questionnaire measures. Analyses of brain volumes were done on three levels: global, voxel-by-voxel, and subcortical structures.

Total gray matter volume (T-GMV) and total white matter volume (T-WMV) from FMS and control groups were submitted to two separate between subjects ANCOVA in which analgesic consumption, pain intensity (VAS), psychological distress (HADS), anxiety (STAI-T), daytime sleepiness (ESE), and health status (FIQ) served as covariates. Multiple imputations were used for 7 missing values (information about aniline analgesics intake from one patient and HADS, STAI and FIQ scores from two controls). The significant results reported were similar for imputed and non-imputed data. All statistical analyses were done using IBM SPSS (20.0, IBM Corporation, New York, USA).

To determine whether the set of predictors of T-GMV and T-WMV were also related to voxel volumes, we analyzed smoothed volumes using the generalized linear model approach implemented in SPM 8. We compared FMS and control groups voxel-by-voxel, using analgesic consumption, pain intensity (VAS), psychological distress (HADS), anxiety (STAI-T), daytime sleepiness (ESE), and health status (FIQ) as covariates. Statistical analyses were carried out with a corrected *p*-value on the cluster level ( $p < .05$ , computed from an uncorrected voxel level  $p < .001$ , with a cluster size of 420 contiguous voxels), as estimated by AlphaSim (<http://afni>.

**Table 5** Descriptive statistics for total brain volumes of patients with fibromyalgia syndrome and healthy controls

	Fibromyalgia patients <i>N</i> = 23 Mean (SD), range	Healthy controls <i>N</i> = 23 Mean (SD), range
Total gray matter volume (mL) *	617.3 (53.1), 534.6–760.0	649.0 (43.8), 575.4–736.4
Total white matter volume (mL) *	466.4 (47.7), 395.9–556.9	485.8 (39.8), 418.1–577.3
Total intracranial volume (mL) *	1365.4 (121.2), 1171.8–1655.2	1427.2 (93.8), 1281.7–1664.6

*SD* standard deviation, *mL* milliliters

\* *p* < .05

[nimh.nih.gov/afni/doc/manual/AlphaSim](http://nimh.nih.gov/afni/doc/manual/AlphaSim)) (Ward 2000) after a Monte Carlo simulation (5000 runs), in which the brain mask included cortical, subcortical, and cerebellum gray matter.

To evaluate the association between the shape of subcortical structures and pain intensity (VAS), psychological distress (HADS), anxiety (STAI-T), daytime sleepiness (ESE), and health status (FIQ), we calculated the partial correlation between those measures from each participant and each radial distance (distances from the medial line of the structure to each surface vertex) while controlling for age, marital status, work status, and total intracranial volume (TIV). Cluster-based permutation tests were performed (10,000 permutations) using the  $r_{p-max}$  to obtain the empirical distribution of the correlation coefficients. This test was used to correct for multiple comparisons. Hierarchical forward stepwise multivariate regressions were also carried out to predict clinical measures from subcortical structures volumes. Psychological distress (HADS), anxiety (STAI-T), sleepiness (ESE), sleep quality (PSQI), pain intensity (VAS), and health status (FIQ) were used as dependent variables in those analyses. Confounders (block 1) were age, educational, marital, and work statuses, and TIV. Variables of interest (block 2) were subcortical volumes.

**Results**

**Clinical data**

FMS patients reported greater pain intensity, psychological distress, anxiety, depression, and somnolence than healthy controls, as well as poorer sleep quality and health status (all *p*-values < .05). Sample means and standard deviations for symptoms are shown in Supplementary Table 1.

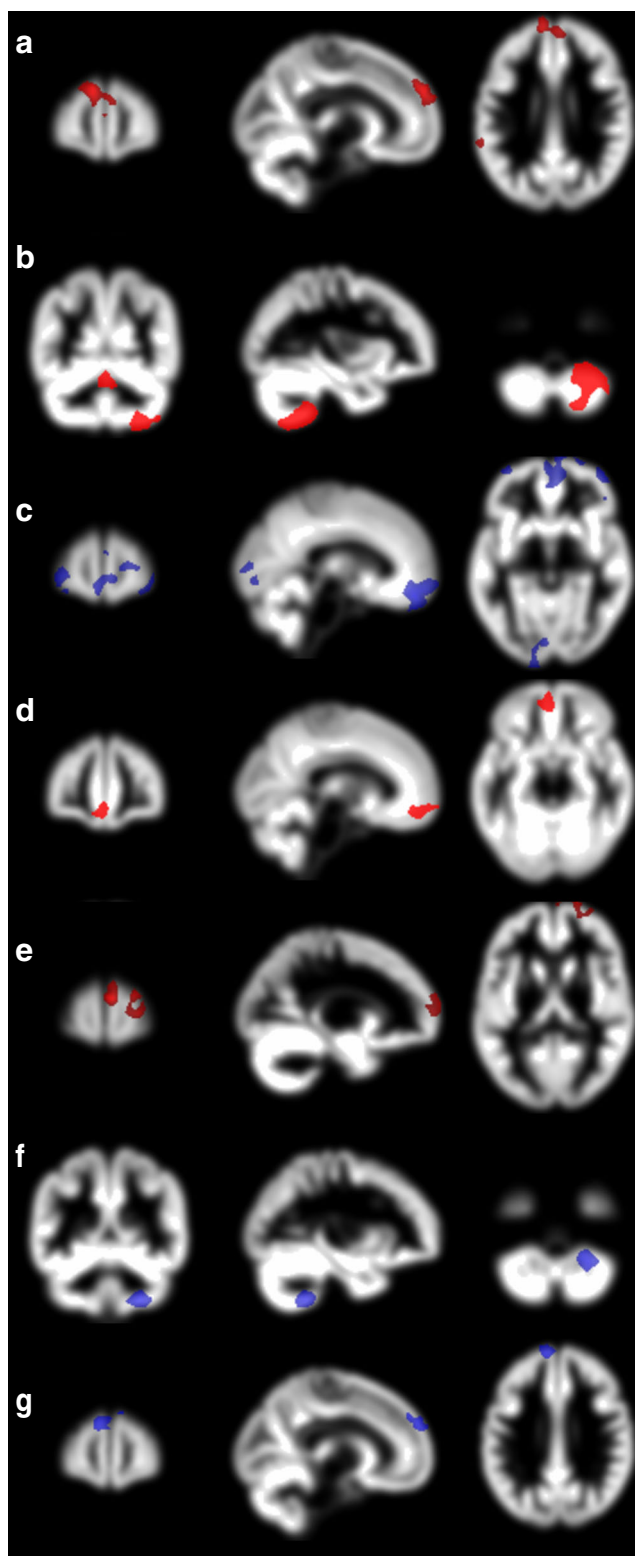
**Neuroimaging data: total volumes**

T-GMV was larger for controls than for FMS patients (see Table 5),  $F(1,37) = 5.69$ , *p* < .03, adjusted  $R^2_p = .13$ . We observed significant effects of psychological distress,  $F(1,37) = 12.10$ , *p* < .01, anxiety,  $F(1,37) = 10.62$ , *p* < .01, daytime sleepiness,  $F(1,37) = 6.14$ , *p* = .02, and analgesic consumption,  $F(1,37) = 11.96$ , *p* < .01 on T-GMV. Larger psychological distress, anxiety, daytime sleepiness, and higher consumption were associated to lower T-GMV. The whole model accounted for a significant amount of total variance in T-GMV (adjusted  $R^2_p = .38$ ). Analysis of residuals indicated they were normally distributed (minimum *p*-value for the Shapiro-Wilk estimates = .38), and

**Table 6** Relationships of local gray matter volumes with clinical measures for the whole sample (*N* = 46)

Clinical variables	Slope sign	Lobe	Area	BA	<i>k</i>	T	<i>x</i>	<i>y</i>	<i>z</i>
Analgesic consumption	–	Frontal	L frontal sup medial	9/10	462	4.25	–17	49	45
			L frontal med orb	10/11	2797	5.64	21	72	11
Psychological distress	–	Occipital	L calcarine fissure	18/17	666	4.22	–6	–87	7
			R cerebellar tonsil		1562	6.16	23	–41	–55
		Cerebellum	L declive		3256	5.69	–2	–75	–21
			L frontal med Orb	10/11	591	4.69	–2	51	–13
Anxiety	+	Frontal	R Frontal Sup Med	9/10	1354	6.65	8	67	18
			R cerebellar tonsil		842	4.76	21	–41	–55
			L/R frontal sup med	9/10	1193	5.60	–11	57	33
Sleepiness	+	Frontal	L inferior parietal	40	498	4.27	–65	–45	33

– negative, + positive, *L* left, *R* right, *Med* medial, *Sup* superior, *Orb* Orbital, *BA* Brodmann area, *k* number of voxels, *T* peak *t* values, *x*, *y*, *z* Montreal Neurological Institute coordinates (in mm)



◀ **Fig. 1** Coronal (left column), sagittal (central column), and axial (right column) brain slices showing the areas exhibiting significant local gray matter volume (GMV) increments (red areas) and decrements (blue areas) associated to **a** pain scores, **b** and **c** distress, **d** anxiety, **e** and **f** sleepiness, and **g** analgesics consumption (all corrected  $p$ -values  $< .05$ ). GMV changes are superimposed on a high-resolution T1-weighted template (generated by averaging all scans,  $N=46$ ). Table 7 shows the specific coordinates of the respective peaks

effect of psychological distress  $F(1,37)=9.61$ ,  $p < .01$ , anxiety  $F(1,37)=p < .01$ , and analgesic consumption,  $F(1,37)=8.45$ ,  $p < .01$  on T-WMV. Larger psychological distress, anxiety, and higher consumption were associated to lower T-WMV. Analysis of residuals indicated they were normally distributed (minimum Shapiro-Wilk  $p = .10$ ) and showed homogeneity of variances for the control and FMS groups (1.08 vs 1.01, respectively).

No variables were significantly associated to cerebrospinal fluid volume (all  $p$ -values  $> .05$ ), which indicated that the above effects were specific for parenchyma volumes.

#### Neuroimaging data: local volumes

Higher pain intensity was associated with an increase of the left and right superior frontal gyrus (including parts of BA9 and BA10). Higher psychological distress was significantly associated to a decrease of the right and left medial orbitofrontal cortex (BA10, BA11) and an increase of the left and right cerebellum. Higher daytime sleepiness was associated to an increase of the right frontal superior medial cortex (BA9 and BA10) and a decrement of the right cerebellum. Anxiety was also associated to increased volumes in the left medial orbitofrontal cortex (BA10, BA11). None of the variables were related to changes in local WMV (all  $p$ -values  $> .05$ ). Table 6 and Fig. 1 displays the main results observed at the voxel level in relation to symptoms. The comparison of local GMV between FMS patients and healthy controls can be found in the [supplementary material](#).

#### Neuroimaging data: subcortical structures shape and volume

Vertex analysis was performed to evaluate the relationship of the shape of the seven subcortical structures and clinical measurements. Subcortical analyses revealed surface contractions and enlargements of several subregions of those subcortical structures related to clinical measurements. Table 7 shows the specific locations and directions of those shape changes. The Video 1 shows in detail surface contractions and enlargements depending on symptoms.

Multiple regression models were performed to establish the relevance of subcortical volumes explaining clinical variables.

showed equal variance for the control and FMS groups (0.99 vs 1.08, respectively), and no outliers were detected.

We observed no significant differences in T-WMV between the FMS and control groups (see Table 5),  $F(1,37)=2.63$ ,  $p = .11$ , adjusted  $R^2_p = .07$ . However, there was a significant



**Table 7** Locations and directions of shape changes of subcortical structures related to clinical measurements for the whole sample ( $N=46$ ), after age, marital status, work status, and TIV have been partialled out

Clinical variables		Hippocampus		Caudate nucleus		Putamen		Accumbens		Amygdala		Globus Pallidus		Thalamus		Brainstem	
		L	R	L	R	L	R	L	R	L	R	L	R				
Pain intensity	A	✖	✖	✖	✖	-	-	◇	-	✖	-	-	-	✖	◇	-	◇
	V	-	-	-	-	◇	-	-	-	◇	✖	-	✖	-	-	-	-
	D	-	-	-	-	-	-	✖	◇	-	-	-	-	-	✖	-	✖
Psychological distress	A	-	-	✖	✖	-	-	-	-	-	-	-	-	✖	-	-	-
	V	-	-	-	-	◇	◇	◇	◇	◇	-	-	✖	-	✖	-	✖
	D	-	-	-	-	-	-	✖	◇	-	✖	◇	-	-	◇	-	-
Anxiety	A	✖	-	✖	✖	-	-	-	-	✖	-	-	-	-	-	-	◇
	V	-	-	-	-	◇	-	-	-	◇	-	-	✖	-	✖	-	-
	D	-	-	-	-	-	-	-	-	-	-	-	-	-	◇	-	-
Sleep quality	A	✖	✖	✖	✖	-	-	◇	-	✖	✖	-	-	-	◇	✖	✖
	V	-	-	-	-	-	-	-	-	✖	◇	◇	✖	✖	✖	-	-
	D	-	-	-	-	-	-	✖	◇	-	-	◇	◇	-	-	✖	-
Sleepiness	A	-	◇	-	✖	-	-	-	-	-	◇	-	-	◇	✖	-	✖
	V	-	◇	✖	-	-	◇	✖	-	-	-	-	✖	◇	-	-	-
	D	-	-	-	-	-	◇	-	-	-	-	◇	-	-	-	-	-
Health status	A	✖	✖	✖	✖	-	-	◇	-	✖	-	-	-	-	✖	-	◇
	V	-	-	-	-	◇	✖	-	-	◇	✖	-	✖	-	-	-	✖
	D	-	-	-	-	-	✖	✖	-	-	-	◇	-	-	✖	-	✖

◇ expansion, ✖ contraction, A anterior, D dorsal, L left, R right, V ventral

Adjusted  $R^2$  are provided. The volumes of the left caudate nucleus and the right putamen accounted for 22.2 % of the variance of pain intensity;  $\beta = -.521$ ,  $\beta = .335$ , respectively,  $F(2,43) = 7.43$ ,  $p = .002$ . The volume of the right caudate nucleus accounted for 8.1 % of the variance of sleepiness (ESE);  $\beta = -.318$ ,  $F(1,44) = 4.94$ ,  $p = .031$ . The volume of the left caudate nucleus accounted for 22.8 % of the variance of sleep quality (PSQI);  $\beta = -.495$ ,  $F(1,44) = 14.26$ ,  $p < .001$ . Anxiety scores (STAI-T) were predicted by educational status (16.7 %) and the volume of the left hippocampus (10.1 %) (whole adjusted  $R^2 = .268$ );  $\beta_1 = -.380$ ,  $\beta_2 = -.344$ ,  $F(2,43) = 9.25$ ,  $p < .001$ . FIQ scores were predicted by educational status (10.1 %) and the volume of the left caudate nucleus (7.6 %) and the right putamen (6.6 %) (whole adjusted  $R^2 = .243$ );  $\beta_1 = -.153$ ,  $\beta_2 = -.468$ ,  $\beta_3 = .313$ ,  $F(3,42) = 5.81$ ,  $p = .002$ .

## Discussion

Many human brain alterations are stimulus-dependent (Draganski et al. 2004), thus it is plausible to assume that FMS experience, beyond pain, might alter brain structure in patients. In the present study, for the first time, we used VBM to examine the specific effects of FMS clinical features on brain volumes. Our results show that psychological distress, anxiety, daytime sleepiness, and analgesic consumption account for structural brain differences in T-GMV and T-WMV

between FMS patients and healthy controls. At a local level, for both groups, decrements of GMV in the medial orbitofrontal cortex are associated to higher psychological distress. Additionally, local increases of GMV in the superior frontal gyrus, the cerebellum, the medial orbitofrontal cortex, and the frontal superior medial cortex are positively related to pain intensity, psychological distress, anxiety, and sleepiness, respectively. Shape analyses also revealed surface contractions and enlargements related to FMS symptoms in subcortical structures.

Even though an increasing number of studies have examined brain morphology in FMS (see Table 2), the interpretation of past results is limited, the significance of brain structure changes in FMS patients being still under debate. It has been suggested that brain matter volumes reflect trait rather than state characteristics of the brain (Hsu et al. 2009). However, previous studies (e.g., May 2008) have provided evidence of causal paths between FMS and brain alterations, and suggested that brain structure changes in FMS reflects “experience-dependent” plasticity. Consequently, alterations in the “pain matrix” might follow the chronicity of pain (May 2011) and could be reversible (Rodriguez-Raecke et al. 2009). Furthermore, pain processing is based on complex neural networks which involve the sensory, cognitive, and emotional dimensions of pain (Melzack 1999). Thus, in the case of chronic pain syndromes, such as FMS, understanding the pathophysiology is a challenge. Moreover, the integration

of experimental findings across studies is hard to undertake. Previous studies (see Table 2) have reported changes in brain volumes in FMS patients in a number of regions known to be critically involved in the modulation of pain experiences, but with disparate findings across studies. The very few consistencies appear in the cingulate (Burgmer et al. 2009; Ceko et al. 2013; Kuchinad et al. 2007; Robinson et al. 2011; Wood et al. 2009) and insular (Hsu et al. 2009; Kuchinad et al. 2007; Robinson et al. 2011) cortices, both of which being core “pain matrix” areas. One reason for these inconsistencies might arise at the statistical level. Many of the studies mentioned above (e.g., Burgmer et al. 2009; Hsu et al. 2009; Robinson et al. 2011; Wood et al. 2009) have selected a priori hypothesized regions. This statistical approach is useful for exploring MRI data, but it increases the probability of a type I error (Kriegeskorte et al. 2010). Therefore, we dismissed this approach. Furthermore, we controlled for menopausal status, a well-known factor that influences brain volumes (Takahashi et al. 2011) that is usually neglected.

### **FMS pathophysiology: the putative role of clinical symptoms in brain structure changes**

Our findings are relevant to understand the possible mechanisms underlying chronic pain, with complex relationships between the chronic pain experience and structural brain changes. Thus, brain changes related to chronic pain might not be just the result of a continuous nociceptive stimulation (“acute pain that it is lasting too long”), but the consequence of the chronic pain experience. In line with Schmidt-Wilcke (2015), such brain reorganization might reflect the preeminent role of various CNS levels maintaining pain (even in the absence of the original nociceptive stimulation), rather than persistent peripheral nociceptive inputs leading to a chronic stimulation of the central pain system. Therefore, central mechanisms, including cortical processing of pain and other symptoms, might play a crucial role in pain chronification. This plausible working hypothesis had already been proposed—although not proven—by a recent meta-analysis about brain alterations in a diversity of chronic pain syndromes (Smallwood et al. 2013). Our results suggest that, actually, there are relevant structural brain alterations in FMS which are “symptom-related”. Not only pain intensity, but also FMS symptoms such as psychological distress, anxiety, and sleepiness are associated with changes in GMV.

#### *Pain intensity*

FMS patients experience persistent pain, as well as altered pain processing (Gracely et al. 2002; Wolfe et al. 1990). Moreover, chronic pain patients exhibit prefrontal hyperactivity to painful stimuli (Apkarian et al. 2001). Therefore, the association between a larger frontal pole area (BA 9/10) and pain

intensity, as found in the present study, might be intrinsically related to the chronic pain experience. The prefrontal area is related to the sensory dimension of pain and receives nociceptive information from the cingulate gyrus (Treede and Apkarian 2010). Furthermore, the prefrontal area has been related to endogenous pain control (Schmahl et al. 2006), providing a decision making on stimulus value and the expected outcome (Marchand 2010). Besides, in the present study, we found an increment of GMV in parietal association areas (BA40), which is coherent with their involvement in functions related to the cognitive dimension of pain (Treede and Apkarian 2010)—pain-related memory and stimulus evaluation.

We also found subcortical contractions and enlargements related to pain intensity in multiple subcortical structures. fMRI studies support a relevant role for the basal ganglia in several aspects of pain processing in chronic pain (e.g., in FMS, Gracely et al. 2002, 2004). These aspects might include the integration of motor, emotional/affective, autonomic, and cognitive responses to pain (for a review, see Borsook and Becerra 2007; Borsook et al. 2010). Schmidt-Wilcke and colleagues (2007) already reported an increase in GMV in the striatum in FMS patients. We also found greater putamen volumes related to pain scores. These results might suggest some underlying functional alterations as a result of experiencing pain chronically. However, increments and decrements in other basal ganglia nuclei volumes, as well as their shapes, were also related to other symptoms in FMS.

#### *Psychological distress*

FMS patients suffer from repeated exposure to uncontrollable psychological distress, which is inherent to chronic pain (Weir et al. 2006). The affective dimension of pain goes beyond its immediate unpleasantness. High psychological distress usually involves an inability to effectively cope with the syndrome (Ridner 2004). This ineffective coping includes social isolation, reduced daily living and leisure activities, and the avoidance of physical activity. This absence of behavioral activation might underlie the decrements of GMV in frontal and prefrontal areas (BA10/11) described here. Additionally, although the cerebellum is not usually thought as a chronic pain-related area, our results agree with those of previous studies relating the cerebellum to the affective domain of pain processing in FMS patients (Kim et al. 2015).

#### *Anxiety*

Pain-related anxiety and fear of pain has a modulating effect on FMS severity (Wolfe et al. 1990). In the present study, the medial orbitofrontal cortex (BA 10/11) had higher volume with greater anxiety levels, which seems coherent with its associated functions. The orbitofrontal cortex is implicated

in fear extinction, specifically in expressing extinction memory and therefore reducing conditioned fear to a previously conditioned stimulus (Milad and Rauch 2007). Hence, increased activation in the orbitofrontal regions of anxiety disorder patients has been reported in symptom provocation studies (Adler et al. 2000). Moreover, recent evidence suggests a relationship between dopamine receptor availability in the orbitofrontal cortex and spontaneous pain in FMS patients (Albrecht et al. 2015).

Hippocampus volume and shape were related to anxiety scores. Previous studies already connected anterior hippocampus with anxiety, fear, and stress responses, as it receives extensive connections from the amygdala (whose shape changes are also related to anxiety scores) and hypothalamus (Fournier and Duman 2013).

### Sleepiness

FMS patients show more sleep disturbances, which impair daytime performance (Diaz-Piedra et al. 2014). This implies that patients might have to improve their alertness, overcoming sleepiness, to exhibit better performance. The ability to overcome sleepiness in task execution has been previously related to the hyperactivation of the frontal cortex, specifically in the right prefrontal cortex (Honma et al. 2010). In line with this, in the present study, greater daytime sleepiness was related to GMV increments in right frontal areas (BA 9/10).

Daytime sleepiness and poor sleep quality were also related to changes in caudate nucleus shape and volume. This nucleus might be involved in the regulation of arousal and sleep. Specifically, the dorsal striatum might enhance wakefulness (Lazarus et al. 2012). In fact, a recent fMRI study found that patients with primary insomnia presented an impaired recruitment of the head of the left caudate nucleus during an executive functioning task (Stoffers et al. 2014).

### Limitations

Although the current study sheds further light on the role played by clinical characteristics altering brain morphology in the FMS pathophysiology, there are some potential limitations to this work that should be considered. Firstly, because it is a cross-sectional study, it does not directly establish a causal relationship between FMS clinical characteristics and the brain volume changes reported. It is not clear how these changes develop over time, and whether they are reversible. Secondly, although our sample was relatively homogeneous and the matching with controls was carefully made, the generalizability of our results might be partially limited. Because our clinical sample was referred for FMS from the same rheumatologist who thoroughly checked the diagnosis criteria, our results cannot be generalized to non-referred samples (e.g., patients

who are diagnosed and treated by primary care physicians). Further longitudinal work with larger samples is needed to answer these questions.

### Conclusions

This study deepens our understanding of the brain changes associated with the chronic pain experience in FMS, and shows that those changes in total and local GMV changes are associated with pain scores, but also with distress, anxiety, sleepiness, and analgesic consumption. Therefore, many of the brain changes do not occur in the “pain matrix” areas, in which previous research has mostly focused on. This implies that altered brain morphology is associated to other frequent symptoms and clinical characteristics, and not exclusively to alterations of the ‘pain matrix’. From our results, we conclude that “maladaptive plasticity” is definitively related to continuous nociceptive activation, and as well as to continuous psychological distress and attempts to overcome daytime sleepiness. Future studies may focus on the specific therapies that may change the brain in a manner that corresponds with therapeutic effects.

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**Compliance with ethical standards** All procedures performed in studies involving human participants were in accordance with the ethical standards of the University of Granada’s Ethics Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards (Williams 2008). All participants gave written informed consent after a complete description of the study.

**Conflict of interest** The authors declare that they have no conflict of interest.

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