Nicolás Fayed[1]
Gracián García-Martí[2,3]
Roberto Sanz-Requena[2]
Luis Marti-Bonmatí[4]
Javier Garcia-Campayo[5]

Difference in Regional Brain Volume between Fibromyalgia Patients and Long-Term Meditators

[1] Radiology Department, Quirónsalud Hospital, Zaragoza, Spain
[2] Biomedical Engineering, Quirónsalud Hospital, Valencia, Spain
[3] CIBERSAM, Instituto de Salud Carlos III, Madrid, Spain
[4] Radiology Department, Quirónsalud Hospital, Valencia, Spain
[5] Deparment of Psychiatry. Miguel Servet Hospital, Zaragoza, Spain

Background. The practice of meditation has been shown to improve pain-related quality of life and also to alter brain activity. To assess brain volumetry in fibromyalgia (FM) patients, healthy meditators and healthy non-meditator control groups, and to elucidate the possible association between brain changes in meditators and years of meditation practice.

Methods. Twelve patients diagnosed with FM, eleven long-term Zen meditators and ten healthy control subjects closely matched for sex and age were recruited. A high resolution T1-3D sequence was acquired and a high-dimensional DARTEL normalization strategy was applied. Questionnaires on anxiety, depression and cognitive impairment were administered.

Results. There was a statistically significant increase in grey matter volume in the Brodmann area 20 (right and left inferior temporal gyri) in patients with fibromyalgia and a significant decrease in the meditator group as compared to controls. On the other hand, there was a significant increase in grey matter volume in fibromyalgia patients as compared to controls and meditators, to the right temporal gyrus (p=0.03, t=6.85) and left temporal gyrus (p=0.04, t=6.31). The number of months of meditation did not correlate with significant grey matter volume changes in the meditator group.

Conclusions. FM and meditation appears to be reliably associated with altered anatomical structure in the Brodmann area 20 (in both inferior temporal gyri), and these changes are associated with anxiety and depression levels. In addition, exploratory morphometric analyses for fibromyalgia patients and meditators may reveal relevant brain regions showing structural diminution in meditation practitioners. Morphologic changes might predispose toward vulnerability to develop a chronic pain state. Such structural diminutions could potentially indicate functional benefits.

Keywords: Fibromyalgia, Zen Meditators, Inferior Temporal Gyrus, Magnetic Resonance Imaging, Brain Volumetry

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Diferencias en el volumen cerebral regional entre pacientes de fibromialgia y meditadores de larga duración

Contextualización teórica/antecedentes. La práctica de la meditación ha demostrado mejorar la calidad de vida en relación con el dolor padecido, así como alterar la actividad cerebral. Se evalúa la volumetría cerebral en pacientes de fibromialgia (FM), con grupos de control de meditadores y no-meditadores sanos, para dilucidar la posible asociación entre los cambios cerebrales en meditadores y los años de práctica de la meditación.

Metodología. La muestra se compone de doce pacientes diagnosticados con FM, once meditadores Zen consolidados y diez sujetos control sanos clasificados por edad y sexo. Los sujetos se exploraron con una secuencia de Resonancia Magnética T1-3D de alta resolución y las imágenes se analizaron mediante una estrategia de normalización DARTEL *(Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra)* de alta dimensionalidad. Se administraron cuestionarios sobre ansiedad, depresión y deterioro cognitivo.

Resultados. Se observó un incremento estadísticamente significativo en el volumen de la sustancia gris en el área 20 de Brodmann (giro inferior temporal derecho e izquierdo) en los pacientes con fibromialgia y una disminución significativa en el grupo de meditadores en comparación con el grupo control. Por otra parte, se observó un incremento significativo del volumen de sustancia gris en pacientes con fibromialgia en comparación con el grupo control y el grupo

Correspondence:
Javier Garcia Campayo
Tel.: (34) 976253621
Fax: (34) 976254006
E-mail: jgarcamp@gmail.com

de meditadores en los giros temporales derechos (p=0.03, t=6.85) e izquierdos (p=0.04, t=6.31). El número de meses de práctica de la meditación no correlacionó con cambios significativos en el volumen de sustancia gris en el grupo de meditadores.

Conclusiones. La fibromialgia y la meditación parecen estar asociadas de manera fiable con alteraciones anatómicas localizadas en el área 20 de Brodmann (giro inferior y temporal), estando a su vez estos cambios asociados con los niveles de ansiedad y depresión. Además, los análisis morfológicos exploratorios en los pacientes con fibromialgia y los meditadores, pueden revelar disminuciones estructurales relevantes en regiones cerebrales en los practicantes de meditación. Los cambios morfológicos podrían suponer una mayor predisposición al desarrollo de un estado de dolor crónico, mientras que tales disminuciones estructurales podrían indicar potenciales beneficios funcionales.

Palabras clave: Fibromialgia, Meditadores Zen, Giro Temporal Inferior, Imagen por Resonancia Magnética, Volumetría Cerebral

BACKGROUND

Fibromyalgia (FM) is a chronic and disabling musculoskeletal pain disorder of unknown origin, characterized by a history of widespread pain for at least three months and patients reporting tenderness in at least 11 of 18 defined tender points when digitally palpated with about 4 kg per unit area of force. Other common accompanying symptoms are fatigue, sleep disturbance and depressed mood[1,2]. It has been suggested that prolonged nociceptive input to the brain might induce functional and morphologic maladaptive processes that in turn further exacerbate the experience of chronic pain. Alternatively, morphologic changes might predispose toward vulnerability to develop a chronic pain state[3]. Interpretation of findings from morphometric studies must also take into account genetic and experiential factors that have recently been demonstrated to influence brain morphometry and the risk of developing chronic pain[4]. Structural and functional brain abnormalities in several areas related to pain and stress response regulation (e.g., anterior cingulate cortex, insula, parahippocampal gyrus, prefrontal cortex, somatosensorial cortex) have been observed in patients with FMS. Specifically, significant grey matter reductions in the prefrontal cortex, anterior cingulate cortex and insular cortex have been reported[5]. These regions are known to be critically involved in the modulation of subjective pain experiences. The duration of pain or functional pain disability did not correlate with GM volumes. A trend of inverse correlation of GM volume reduction in the ACC with the duration of pain medication intake was detected[6]. Furthermore, reductions in GM volume were seen in the postcentral gyri, amygdala, hippocampi, superior frontal gyri and anterior cingulate gyri[7].

Zen meditation with vipassana meditation are considered typical mindfulness meditation. Mindfulness is defined as non-judgemental attention to experiences in the present moment[8]. Mindfulness is cultivated in formal meditation practices, such as sitting meditation, walking meditation and mindful movements[9]. Mindfulness meditation has beneficial effects on a number of psychiatric, functional somatic and stress-related symptoms and, therefore, has been increasingly incorporated into psychotherapeutic programmes[9,10], having reported better pain-related quality of life and are more satisfied with their life[11]. Anatomical likelihood estimation (ALE) meta-analysis found eight brain regions of GM consistently enhanced in meditators[12]. Three studies[13-15], showed an apparent pattern of structural increase in white matter (WM) of controls versus meditators.

We expected that meditators would show greater gray matter concentration in regions that are activated during meditation[16-21]. Morphometric changes of inferior temporal gyri in meditators have been previously reported in several studies[16,17]. Especially[17], have shown larger hippocampal and frontal volumes in long-term meditators than control group. Experiments using positron emission tomography or functional Magnetic Resonance Imaging (fMRI) indicated increased brain activation (compared to baseline) during mindfulness exercises on both hippocampal and parahippocampal regions[22,23]. The hippocampus also modulates amygdalar activity and its involvement in attentional and emotional processes. Furthermore, activation in the left inferior temporal gyrus and the left postcentral gyrus was found during mindfulness exercises[22]. In the present study, we performed brain morphometry on FM patients, long-term zen meditators and healthy controls to evaluate whether this neuroradiological technique would discriminate between the brain patterns of the groups and to elucidate the possible association between brain changes in meditators and years of meditation.

METHODS

Patients

Twelve patients with FM (age 43.4 ± 6.4 years) were recruited from primary health care centres in the city of Zaragoza, Spain. Patients were required to meet the following inclusion criteria: aged 18-65 years; able to understand Spanish; fulfill the criteria for FM (DSM-IV criteria); and no pharmacological treatment 1 week before the study began. FM was diagnosed according to the

American College of Rheumatology[1] by a rheumatologist. Patients were excluded if they had other Axis I psychiatric disorders, or were pregnant or lactating.

Eleven meditators (age 45.3 ± 5.1 years) were recruited from the Soto Zen Spanish Buddhist community. Individuals were required to meet the following inclusion criteria: aged 18–65 years; able to understand Spanish; long-term meditative practice (>8 years meditating for an average of 1 hour daily); no psychiatric disorder or pharmacological treatment.

Ten healthy control subjects (age 37.5 ± 8.8 years) were recruited among hospital staff (comprising 4,800 workers: 700 doctors, 2,600 non-medical healthcare professionals and 1,500 administrative and services personnel), with adjustment for gender, age (±23 years), years of education (±23 years) and ethnic group.

Sample size was calculated based on other studies to detect important differences (d=1.2)[13,24] in inferior temporal gyrus between meditation and fibromyalgia groups. The estimated sample size with a power of 80% at a significance level of 95% (p=0.05) and assuming equal variances between groups was 11 subjects per group.

The study was approved by the Ethics Committee of Aragon and conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki. All participants gave written informed consent prior to their inclusion in the study.

Clinical variables

Hospital Anxiety Depression Scale (HADS)[25]: This is a self-report scale designed to screen for the presence of depression and anxiety disorders in medically ill patients. HADS was used for the analysis of the sample of healthy people, as this questionnaire has been recommended for use in community studies and primary care settings. It contains 14 items that are rated on a 4-point Likert-type scale. Two subscales assess depression and anxiety independently (HADS-Dep and HADS-Anx, respectively)[25]. The validated Spanish version was used[26].

Mini-Mental State Examination (MMSE): This is a fully structured scale that includes the following seven categories: orientation to place, orientation to time, registration, attention and concentration, recall, language, visual construction. The validated Spanish version was used[27]. The demographic and clinical characteristics are shown in Table 1.

Table 1 Clinical and demographic data. Data is displayed as mean ± SD

	Fibromyalgia (N=12)	Meditators (N=11)	Controls (N=10)	Significance
Male/ Female	2/8	4/7	4/8	p=0.689
Age (years)	41.7; SD=7.3	43.3; SD=5.1	39.5; SD=8.8	p=0.067
HADS-Anx	6.20; SD=2.8	0.30; SD=0.48	1.70; SD=0.94	p=0.001
HADS-Dep	5.90; SD=3.8	0.30; SD=0.48	1.60; SD=0.51	p=0.001
MMSE	30.6; SD=3.3	35; SD=0	35; SD=0	p=0.001

HADS-Anx, Hospital Anxiety Depression Scale, subscale anxiety; HADS-Dep, Hospital Anxiety Depression Scale; MMSE: Mini-Mental State Examination.

Neuroimaging Techniques

Three dimensional (3D) high-resolution whole-brain gradient-echo T1-weighted images were obtained in a 1.5 Tesla clinical scanner (Sigma HD, GE Healthcare Diagnostic Imaging, Milwaukee, WI, USA) with an 8-channel phased array volume head coil. The acquisition protocol included the following parameters: 130 coronal slices, TR=9.10 ms, TE=1.72 ms, 1.5 mm slice thickness with no inter-slice gap, acquisition matrix =256 x 256, flip angle =20º and voxel size =0.86 x 0.86 x 1.5 mm. After acquisition, all images were reviewed by a radiologist and a computer engineer, who were blind to clinical subgroups in order to ensure data quality. No images were discarded after this check. Anonymized images were then transferred to a workstation for analysis and post-processing.

Image processing

Statistical Parametric Mapping software (SPM8; Wellcome Institute, London, UK) was used to perform the image processing and statistics. First, custom templates were created to minimize the bias associated with the use of predefined templates[28]. Raw images were normalized to the standard MNI template using affine transformations. The output images were then segmented and averaged using a Gaussian filter with a FWHM (Full Width at Half Maximum) of 8 mm to obtain the whole brain and tissue-specific templates.

The latest version of the voxel based morphometry method (VBM8) was used to process all the volumes. Each original T1-weighted raw image was normalized using a high-dimensional DARTEL (Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra) normalization strategy, considering the custom template as a reference. After this initial normalization, gray and white matter maps were newly aligned and used to define a new template. After six iterations, the final version of the template consistent on different tissue maps registered with DARTEL was obtained. During this step, the different images were warped to the template through a series of flow fields that encode the spatial deformations. The warped images had a voxel volume of 1.5 x 1.5 x 1.5 mm. After wards, a Jacobian modulation was applied, accounting by point-by-point contractions and expansions to preserve the total amount of tissue in the normalized images. The obtained maps were finally smoothed by a 10 mm FWHM Gaussian kernel, obtaining the final gray matter, white matter and CSF tissue-probability maps for each participant.

Statistical Analysis

Statistical models were designed and estimated according to the General Linear Model (GLM) framework[29]. The model included the GM maps for each subject and three nuisance variables (age, sex and total intracranial volume (TIV). Additionally, and only for the meditator group, each subject's meditation practice by number of months was evaluated. Estimation parameters were adjusted by performing independent Student's t-tests over the GM maps using a SPM two-tailed contrast in order to detect both increases and decreases in tissue volume between groups. The significant threshold was fixed at $p<0.05$ with a Family-Wise Error (FWE) rate correction for multiple comparisons at voxel level. Additionally, an extent threshold filter was applied to eliminate spurious findings, considering only those clusters with a minimum size of k=65 voxels (expected number of voxels per cluster provided by the SPM software). Results were labelled with self-created software adapted from the Automated Anatomical Labeling (AAL) add-on for SPM[30]. Areas identifying coordinates were determined by the maximum Student's t-value in the corresponding brain area.

RESULTS

There were no significant differences in age between the three groups of subjects (p=0.067). Psychological profiles showed the usual psychological characteristics of FM patients: high scores in anxiety (mean, 6.2; SD=2.8) and depression (mean, 5.9; SD=3.8), assessed with HADS. Ratings of anxiety and depression measured with HADS were significantly lower in the meditator group: (HADS-anx: 0.30; SD=0.48 *vs* 1.70; SD=0.94 in healthy controls, p=0.001) and (HADS-dep: 0.30; SD=0.48 *vs* 1.60; SD=0.51 in healthy controls, p=0.001). MMSE scores suggested symptoms of cognitive dysfunction in FM (mean, 30.6; SD=3.3 *vs* 35; SD=0 in meditators and healthy controls subjects p=0.001) (Table 1).

There was a statistically significant reduction in grey matter volume in the Brodmann area 20 in the meditator group as compared to controls and fibromyalgia. On the other hand, there was a significant increase in grey matter volume in fibromyalgia patients as compared to controls and meditators, to the right temporal gyrus (p=0.03, t=6.85) and left temporal gyrus (p=0.04, t=6.31). (Figures 1 and 2) (Table 2). No significant differences (in terms of increases and decreases in tissue volume) were observed in any other areas for the rest of comparisons between groups. The number of months of meditation did not correlate with significant GM volume changes in the meditator group.

DISCUSSION

To our knowledge, this is the first study comparing brain morphometry in patients with fibromyalgia and meditators. Our study revealed more gray matter in FM patients than in controls and meditators within the Brodmann area 20. Brodmann area 20, is part of the temporal cortex in the human brain. The region encompasses most of the ventral temporal cortex, a region believed to play a part in high-level visual processing and recognition memory.

This area is also known as inferior temporal area, and it refers to a subdivision of the cytoarchitecturally defined temporal region of cerebral cortex. In the human it corresponds approximately to the inferior temporal gyrus. The inferior temporal gyrus is associated with the representation of complex object features, such as global shape. It may also be involved in face perception[31], and in the recognition of numbers[32]. It can often be associated with other forms of recognition impairment, such as place, car, or emotional recognition[33] and multimodal sensory integration[34]. One part of the brain that is particularly integral to color discrimination is the inferior temporal gyrus[35]. Previous functional neuroimaging studies have shown that healthy individuals have increased activation in the inferior temporal gyrus during processing object activation, while individuals with autistic disorder tends to use more of the inferior temporal gyrus during face processing when compared to controls. This finding shows that they process faces like objects[36]. Relative to healthy subjects, the patients with chronic schizophrenia showed gray matter volume reductions in the bilateral inferior temporal gyrus (10% difference in both hemispheres)[37].

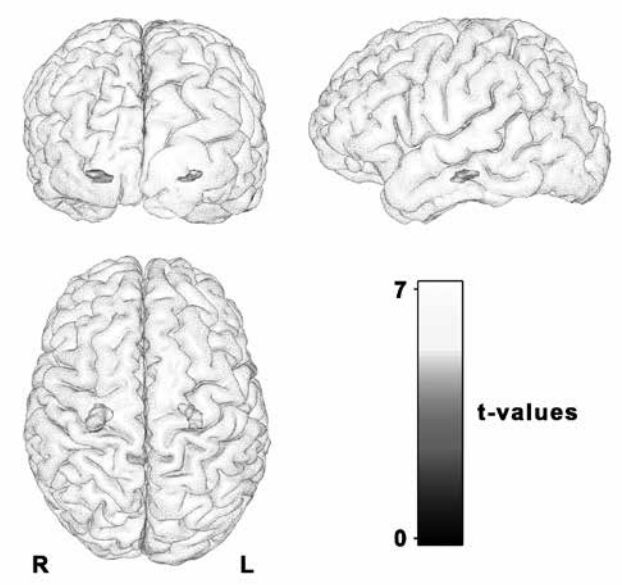

Figure 1 — *Areas of grey matter volume increases in the fibromyalgia group vs. meditators (p<0.05 FWE corrected, k=65)*

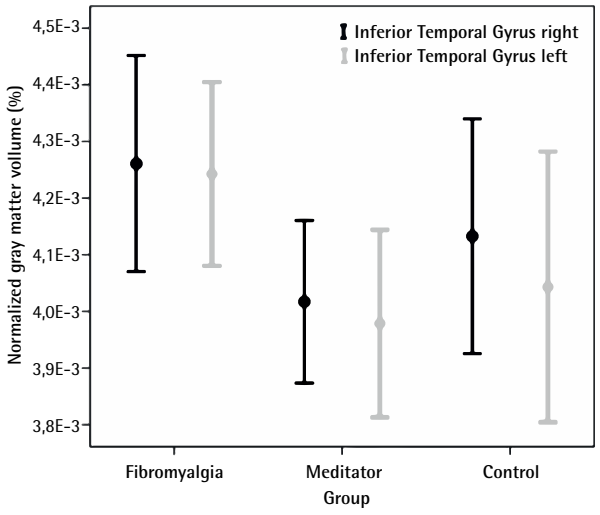

Figure 2 — *Mean plot showing differences in the normalized inferior temporal gyrus volumes (bilateral) between fibromyalgia and meditators*

Table 2 — **Areas of grey matter volume increases in fibromyalgia patients vs meditators (p<0.05 FWE corrected, k=65)**

Area	p value* (corrected)	t-value	coordinate	Brodmann area	extension (cm^3)
Hippocampus right	p=0.03	6.85 (21)	(23, -17, -17)	20	3.29
Hippocampus left	p=0.04	6.31 (21)	(-27, -20, -15)	20	2.95

Corrected p values are given at voxel level

Medically unexplained symptoms or syndromes, such as fibromyalgia (FM), might be partly caused or sustained by a mechanism involving restricted emotional processing (REP) and the subsequent attribution of emotional arousal to somatic or syndrome-consistent causes. Both at trait and at state level, FM showed restricted emotional processing[38]. The finding of brain differences between patients with FM and healthy controls in neural structures such as the hippocampus and amygdale is compatible with a possible augmented emotional processing in patients with FM, in line with the augmented pain processing proposed by some authors[39]. Meditators seem to have a higher pain tolerance. A recent review[40] described up to 17 researches in which the therapeutic potential of mindfulness in pain is analysed. Another study[41] shows that Zen meditators have pain sensitivity thresholds higher than non-meditator subjects. This is where regulation comes into play as a basic feature of meditation[42].

In the present study, ratings of anxiety and depression were significantly higher in fibromyalgia and lower in the meditators compared to healthy controls, being consistent with other studies[24,43].

With respect to clinical correlations, the patients with decreased of anxiety and depression (meditators) had significantly smaller left and right inferior temporal gyri volumes than those are increased (fibromyalgia). A study of morphometry in adolescents and young adults shows an enlarged inferior temporal gyrus in patients with depressed patients compared with healthy controls[44].

With respect to laterality of temporal lobe, gray matter volume was higher in the right inferior temporal gyrus on the left in meditating, in fibromyalgia patients and healthy controls possibly because most were skilled.

Although there are a number of studies in which mindfulness and meditation are used to treat conditions such as psychiatric relapse into depression, other forms of anxiety or addiction relapse prevention[40], there are few studies to date that also involve scanning of brain substrate. One such study[45] sought to evaluate how practicing mindfulness can prevent depression. Thus, using functional magnetic resonance imaging, show that in stressful situations, the practice of mindfulness can be protective and allow better responses to negative emotional stimuli.

Factors such as stress, excess glucocorticoids, altered gene expression of neurotrophic factors and glial transporters, and changes in extracellular levels of neurotransmitters released by neurons may modify glial cell numbers and affect the neurophysiology of depression[46].

Reducing anxiety has been associated with the emotional evaluation of external stimuli, leading one would expect that people who practice mindfulness, have the ability to reduce anxiety. There is a recently published study[47], in which participants were trained in mindfulness, achieving a reduction of anxiety in each session in which participants meditated.

Another disorder addressed through meditation is bipolar disorder, in which patients have increased levels of anxiety and poor regulation of emotions. In the first fMRI study in patients with bipolar disorder[48], patients and healthy subjects were trained in the practice of mindfulness. Their results showed that patients had a reduction in the activity of the medial prefrontal cortex and improved outcomes for anxiety and emotion regulation.

Several studies have documented the positive impact of mindfulness-based programmes on symptoms of anxiety and depression[45,49-51]. The morphological changes reported here might contribute to some of these enhancements. As for cognitive impairment, recently it has been reported that benzodiazepine use is associated with an increased risk of Alzheimer's disease. The stronger association observed for long term exposures reinforces the suspicion of a possible direct association, even if benzodiazepine use might also be an early marker of a condition associated with an increased risk of dementia[52]. Given its frequent use in patients with fibromyalgia, could be a direct relationship with the Mini-Mental decline observed in these patients.

It appears that one effect of the reduced activation of certain areas is a reduction in the connectivity between them. In the last decade, fMRI studies have progressed from only observing changes in the activation of certain areas to investigating functional relationships between them[42,53]. Connectivity has been associated with complex functions that are performed by multiple brain structures in combination[54]. The previously mentioned study showed increased activation of areas typically associated with pain, such as the insula, thalamus, ACC and prefrontal cortex[55,56]. Connectivity studies, however, show that meditation reduced the connectivity between these areas related to pain regulation. The notion that a largely mental practice, such as meditation, can produce such changes is further supported by studies showing structural differences after short-term mental training for working memory[57] and reasoning abilities[58].

The adult nervous system has the capacity for plasticity, and the structure of the brain can change in response to training[59,60]. It is generally assumed that increased GM is the result of repeated activation of a brain region[61]. However, the cellular mechanisms underlying training-induced neuroanatomical plasticity are not yet understood. A recent fMRI study shows reduced activation and functional connectivity in default mode network (DMN) regions in long-term meditation practitioners[62]. For fibromyalgia patients, spectral partitioning identified a distinct submodule with cerebellar connections to medial prefrontal and temporal and right inferior parietal lobes, whose gray matter volume was associated with the severity of depression in these patients. Volume for a submodule encompassing lateral orbitofrontal, inferior frontal, postcentral, lateral temporal, and insular cortices was correlated with evoked pain sensitivity[63]. In a study of functional magnetic resonance imaging and electrocardiography data on FM patients and healthy controls during rest (the rest phase) and during sustained mechanical pressure-induced pain over the lower leg (the pain phase), compared to the rest phase, the pain phase produced increased primary somatosensory cortex (S1) (leg) connectivity to the bilateral anterior insula in FM patients, but not in healthy controls. Moreover, in FM patients, sustained pain-altered S1 (leg) connectivity to the anterior insula was correlated with clinical/behavioral pain measures and autonomic responses[64].

There are several limitations of this study. First, this study can not answer the question whether the increased volume in patients with fibromyalgia was progressive in the peri- or post established disease course. Second, the present study also did not allow us to exclude the effect of chronic treatment with painkillers and antidepressants in alterations on inferior temporal gyrus gray matter abnormalities in patients substance (though no measure of volume correlated with doses of painkillers and antidepressants) or demonstrate the specificity of fibromyalgia. It will thus be important to investigate whether inferior temporal gyrus abnormalities

are observed or not in patients with fibromyalgia at their first visits, with minimal or no medication history. Third, as stated, the sample size in the present study is mayor drawback, it could directly influence the result. Quarter, mean age of health control is 7 more years younger than fibromyalgia patients or meditators. It may affect the results even after controlling for age. Fifth, most patients with fibromyalgia syndrome take psychiatric medications and analgesics that might alter brain morphometry. A 1-week washout period is not enough to be sure that medications were not the cause for gray matter differences. Luder et al. have shown larger volume of left inferior temporal gyrus in long-term meditators than control group[17]. The result in the current study was totally different from Luder's study. Considering field strength (1.5 T), we can not exclude the possibility that magnetic field inhomogeneity or the so-called susceptibility effects could affect the morphological accuracy, especially in regions around the skull base.

CONCLUSIONS

In conclusion, anxiety and depression scales were significantly associated with the volume of the inferior temporal gyrus. In addition, exploratory morphometric analyses for fibromyalgia patients and meditators may reveal relevant brain regions showing structural diminution in meditation practitioners. Morphologic changes might predispose toward vulnerability to develop a chronic pain state. Such structural diminutions could potentially indicate functional benefits. Future studies will be required to test whether findings extend to non-stressed individuals as well as to individuals suffering from mental disorders. Finally, the current study employed a rather small sample size and replication is necessary.

ETHIC'S APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was approved by the local ethics committee, Ethics Committee of Aragon (PI13/00131) and all participants signed a consent form indicating their willingness to participate. They were informed about the purpose of the study, and it was made clear to them that their answers would be treated confidentially.

AVAILABILITY OF DATA AND MATERIALS

The dataset supporting the conclusions of this article is included within the article.

CONFLICTS OF INTEREST

The authors have no competing interests to report.

AUTHORS' CONTRIBUTIONS

NF and JGC designed the project. GGM and RSR collected the data. LMB performed the statistical analysis. All authors interpreted the results, drafted the manuscript and read and approved the final manuscript.

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