

## No consistent difference in gray matter volume between individuals with fibromyalgia and age-matched healthy subjects when controlling for affective disorder

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### ARTICLE INFO

#### Article history:

Received 9 July 2008

Received in revised form 13 January 2009

Accepted 16 March 2009

#### Keywords:

Fibromyalgia  
Voxel-based morphometry  
MRI  
Gray matter  
Depression  
Pain

### ABSTRACT

Fibromyalgia (FM) is thought to involve abnormalities in central pain processing. Recent studies involving small samples have suggested alterations in gray matter volume (GMV) in brains of FM patients. Our objective was to verify these findings in a somewhat larger sample using voxel-based morphometry (VBM), while controlling for the presence of affective disorders (AD). T1-weighted magnetic resonance image (MRI) brain scans were obtained on 29 FM patients with AD, 29 FM patients without AD, and 29 age-matched healthy controls (HCs) using a 3T scanner. Segmentation, spatial normalization, and volumetric modulation were performed using an automated protocol within SPM5. Smoothed gray matter segments were entered into a voxel-wise one-way ANOVA, and a search for significant clusters was performed using thresholding methods published in previous studies (whole-brain threshold of  $p < .05$  correcting for multiple comparisons; region-of-interest (ROI) threshold of  $p \leq .001$  uncorrected, or  $p < .05$  small-volume corrected). The whole-brain analysis did not reveal any significant clusters. ROI-based analysis revealed a significant difference in left anterior insula GMV among the three groups ( $xyz = \{-28, 21, 9\}$ ;  $p = .026$ , corrected). However, on post-hoc testing, FM patients without AD did not differ significantly from HC with respect to mean GMV extracted from this cluster. A significant negative correlation was found between mean cluster GMV and scores of trait anxiety (State-Trait Personality Inventory, Trait Anxiety scale;  $\rho = -.470$ ,  $p < .001$ ). No other significant clusters were found on ROI-based analysis. Our results emphasize the importance of correcting for AD when carrying out VBM studies in chronic pain.

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### 1. Introduction

Fibromyalgia (FM) affects 0.5–4% of the population in developed countries [14,24], and is defined as chronic widespread pain and tenderness in at least 11 of 18 tender points [26]. Individuals with FM are more likely to also meet criteria for chronic fatigue syndrome, irritable bowel syndrome, temporomandibular joint disorder, vulvodynia, and migraine than the general population [11]. Mechanisms of central augmentation of pain and sensory processing are thought to account for the pathophysiology of FM and related conditions [15].

Evidence of abnormal CNS processing in FM can be found in a number of functional neuroimaging studies, including altered resting and stimulus-evoked regional cerebral blood flow in pain and emotional processing regions such as the thalamus, somatosensory cortex, insula, and anterior cingulate cortex [25]. In contrast to functional neuroimaging, structural neuroimaging approaches – such as voxel-based morphometry (VBM) – use differences in gray matter volume (GMV) or density to support hypotheses regarding CNS function, and may reflect trait rather than state characteristics of the brain. With recent improvements in computer processing speed, the automated process of VBM has allowed for fast, reliable calculations of GMV in large samples of subjects [2].

In recent years, VBM has been used to study differences in GMV associated with various pain conditions, including migraine [23],

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tension headache [17], chronic back pain [1,16], and FM [12,18]. The two studies published to date in FM patients reported global and/or regional GMV differences between patients and controls. However, the sample sizes were modest ( $\leq 20$  in the FM group), and there were no common regions of increased or decreased GMV between the two studies. Furthermore, while both studies addressed depression as a potential confounding variable, one study did not account for less-severe depressive disorders such as dysthymia [12], and the other study did not find any significant GMV differences at the whole-brain level after controlling for depression [18].

In the present study, we applied VBM methodology to a sample of 58 FM patients and 29 age-matched healthy controls, to look for regions of increased or decreased GMV associated with FM, and attempted to replicate the previously published findings. We used statistical thresholds identical to those published in previous studies [12,18]. We then tested whether the results changed when controlling for AD. We hypothesized that one or more regional GMV changes previously reported to be associated with FM would be replicated in this study. We also hypothesized that, even when controlling for AD, FM patients would still exhibit differences in global and/or regional GMV within pain-related brain regions relative to controls.

## 2. Methods

### 2.1. Participants

All subjects with FM who were enrolled in two ongoing non-pharmacological clinical trials were considered for the present analyses. Healthy controls were obtained from the same studies, and also from a previous cross-sectional study performed at our center. At the time of data collection, all FM patients had met 1990 American College of Rheumatology criteria for FM [26], with mean pain duration of 12.8 years ( $SD = 8.3$ ). No healthy controls had met these criteria, nor did they meet criteria for chronic regional pain (i.e., tension headaches, chronic low back pain, irritable bowel syndrome, or chronic pelvic pain). All subjects were right-handed women between ages 18 and 65. All subjects gave written informed consent, the study protocol was approved by the University of Michigan Institutional Review Board, and all procedures performed in compliance with the Helsinki Declaration.

Affective disorder (AD) was defined as current major depressive episode, bipolar disorder, dysthymia, or general anxiety disorder (according to *Diagnostic and Statistical Manual of the American Psychiatric Association IV* criteria) as determined upon subject enrollment using a structured interview [19]. Patients with a history of clinical depression according to medical records; and/or patient-reported use of antidepressants to treat depression or anxiety, were also considered to have AD. Individuals with AD were excluded from the healthy control group. Individuals with severe psychiatric illness (current schizophrenia, major depression with suicidal ideation, substance abuse within two years), were excluded from all groups.

A total of 29 FM patients with AD (FM+AD), 29 FM patients without AD (FM–AD), and 29 healthy controls were included in the analysis. The groups were individually matched by age, with an overall difference of no more than three years across each matched trio.

### 2.2. Neuroimaging and analysis

#### 2.2.1. Image acquisition

High-resolution anatomical magnetic resonance image (MRI) scans were obtained on all subjects using the same 3-Tesla scanner

(Signa LX, General Electric, Milwaukee, USA). Images were acquired by using spoiled gradient-recalled acquisition in steady state (SPGR) imaging (repetition time, 10.5 ms; echo time, 3.4 ms; flip angle, 20°; field of view 24 cm, number of contiguous images, 106; in-plane resolution .9375 × .9375 mm, slice thickness, 1.5 mm). The resulting voxel dimension was of sufficiently high resolution to permit accurate gray matter segmentation [2].

#### 2.2.2. VBM protocol

Data pre-processing and analysis were performed using SPM5 (Wellcome Department of Cognitive Neurology, London, UK) on the Matlab version 6.5 (MathWorks, Natick, MA) platform. Each image was inspected for reconstruction artifacts, and individually corrected for signal inhomogeneity using an automated Matlab protocol developed by G. Glover and K. Christoff (<http://rsl.stanford.edu/glover/>). Spatial normalization, segmentation, and volumetric modulation were performed using the automated VBM5 toolbox (C. Gaser, Structural Brain Imaging Group, Department of Psychiatry, University of Jena; <http://dbm.neuro.uni-jena.de/vbm/>) within the SPM5 environment. The toolbox employs a Hidden Markov Random Field Model in the procedure to segment each image into gray matter, white matter, and cerebrospinal fluid. The toolbox then normalizes the gray matter segment of each image to the International Consortium for Brain Mapping (ICBM) 152 template (Montreal Neurological Institute; MNI), and performs a modulation step to scale each voxel value according to the subject's total intracranial volume (TIV), as well as the regional gray matter volume (GMV) expansion/contraction that occurs during nonlinear transformation. TIV and global GMV were obtained for each image, using the "Calculate raw volumes" feature of VBM5. Gray matter image segments were inspected for segmentation artifacts, then smoothed using an isotropic Gaussian kernel of 10 mm full-width half-maximum (FWHM), to accommodate individual differences in sulcal and gyral anatomy, and to meet the distributional assumptions of the general linear models necessary for statistical analysis. This is the same smoothing kernel as was used in the previous studies ([12,18]; a comparison of methods used in the two previous studies and in the present study is shown in Table 1).

#### 2.2.3. Voxel-wise comparison of GMV between FM patients and healthy controls

The normalized, modulated, and smoothed gray matter image segments in each group were entered into a voxel-wise one-way ANOVA in SPM5, with a null hypothesis of no GMV difference among the three groups (FM+AD, FM–AD, and HC). Because the modulation step reintroduces information about the subject's TIV prior to normalization, TIV was included as a covariate. An absolute threshold mask of 0.20 was used (identical to the threshold used in the previous study [18]), to avoid possible edge effects around the border between gray and white matter. Due to the occasional presence of susceptibility artifacts at the base of the brain in our sample, an explicit mask was also used to exclude all voxels inferior to  $z = -22$  (Talairach space).

A whole brain search for significant clusters was performed using the previously published voxel-wise threshold of  $p < .05$  corrected for multiple comparisons [12,18]. In addition, an ROI-based search using all *a priori* anatomically defined ROIs from the two previously published studies (Table 2) was conducted. For the ROI-based search, all clusters with either a voxel-level  $p < .05$  (small-volume and family-wise error corrected using masks from the MarsBar ROI toolbox [6], accessible at <http://marsbar.sourceforge.net/>) or an uncorrected voxel-level  $p < .001$  were considered significant. Since post-hoc tests were not available for SPM5 at the time of these analyses, post-hoc analysis was performed using between-group contrasts on the F map to determine the peak significance value of any voxels within the cluster, and a

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