Subtle changes of gray matter volume in fibromyalgia reflect chronic musculoskeletal pain rather than disease-specific effects

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Abstract
Fibromyalgia syndrome (FMS) is a chronic pain syndrome. Neuroimaging studies provided evidence of altered gray matter volume (GMV) in FMS but, similarly, in chronic pain of other origin as well. Therefore, the purpose of this study was to evaluate the disease specificity of GMV alterations in FMS by direct comparison. Structural MRI data of the brain were acquired in 25 females with FMS and two different control groups: 21 healthy subjects and 23 patients with osteoarthritis. Regional GMVs were compared by voxel-based morphometry and additional ROI-analyses. In conclusion, we did not identify significant GMV alterations in either FMS or OA patients compared to healthy controls when adopting a conservative statistical approach with multiple comparison correction. However, even under a more liberal approach no FMS-specific GMV changes were found because both pain groups presented increased gray matter volumes in the precentral gyrus and decreased GMV in the angular gyrus/middle occipital gyrus and middle temporal gyrus in comparison with healthy controls. Since no differences between both pain groups could be detected cortical GMV changes in FMS should not be interpreted as FMS-specific but might rather reflect changes in chronic pain in general. This previously held notion is confirmed in this study by direct comparison with a control group consisting of another pain disorder.

KEYWORDS
chronic pain, fibromyalgia, gray matter volume, osteoarthritis, voxel-based morphometry

Abbreviations: ACC, anterior cingulate cortex; ACR, American college of Rheumatology; BA, Brodmann area; CTQ, childhood trauma questionnaire; FMS, fibromyalgia syndrome; FS, fibromyalgia score; FWE, family-wise error; FWHM, full width at half maximum; GM, gray matter; GMV, gray matter volume; HC, healthy controls; MNI, montreal neurological institute; MRI, magnetic resonance imaging; OA, osteoarthritis; PHQ, patient health questionnaire; ROI, region of interest; SPM, statistical parametric mapping; SSS, somatic symptom score; TIV, total intracranial volume; VBM, voxel-based morphometry; WFU, Wake Forest University; WPI, widespread pain index.

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1 | INTRODUCTION

Fibromyalgia syndrome (FMS) is characterized clinically by chronic widespread pain with additional somatic symptoms including fatigue, insomnia, and cognitive impairment (Wolfe et al., 2010). FMS affects approximately 3% of the normal population (Heidari, Afshari, & Moosazadeh, 2017) and can have a detrimental impact on these subjects’ quality of life and social functioning (Kivimaki et al., 2007). Despite numerous studies shedding light on potential genetic, biochemical, neurological, or environmental aspects of FMS etiopathogenesis, no consistent disease model of FMS could hitherto be developed (Clauw, 2014).

Subjects with FMS show a decreased threshold of pain perception (allodynia) (Desmeules et al., 2003). Therefore, the hypothesis of central sensitization is in the focus of many basic science studies in FMS. Functional neuroimaging studies both during rest and during experimental pain stimulation have provided evidence of altered cerebral activation patterns in pain-processing brain regions in FMS (Burgmer, Pogatzki-Zahn, et al., 2009, 2012; Gracely, Petzke, Wolf, & Clauw, 2002). Changes of gray matter volume (GMV) in FMS were reported in several brain regions including the cingulate cortex, the dorsolateral and medial prefrontal cortices (PFC), the superior and middle temporal gyri, amygdala, parahippocampal gyrus, precuneus, and somatosensory cortices (Burgmer, Gaubitz, et al., 2009; Jensen et al., 2013; Kim et al., 2015; Lutz et al., 2008; Puiu et al., 2016). Recent efforts to aggregate these structural findings by means of coordinate-based meta-analyses pointed toward changes of GMV in the medial PFC, cingulate cortex, parahippocampal cortex, and cerebellum (Dehghan et al., 2016; Lin, Lee, & Weng, 2016; Shi, Yuan, Dai, Ma, & Sheng, 2016). These alterations might be due to differences in pain-processing dynamics in FMS or might be part due to pre-disorder structural alterations as well. Yet it is noteworthy that almost all of these neuroimaging studies focused on differences of FMS patients compared with healthy controls.

Changes of gray matter morphology were detected in subjects with chronic pain of other origins (e.g., chronic back pain, tension-type headache, chronic joint pain, chronic fascial pain) as well. These changes involve the cingulate cortex, thalamus, prefrontal cortex, primary or secondary somatosensory cortices (S1, S2), basal ganglia, brainstem, and insula (Apkarian et al., 2004; Davis & Moayedi, 2013; Fritz et al., 2016; Gerstner, Ichesco, Quintero, & Schmidt-Wilcke, 2011; de Kruijf et al., 2016; Schmidt-Wilcke et al., 2005). Coordinate-based meta-analyses in chronic pain (migraine and chronic pain in general) depicted alterations of GMV in the frontal lobes, the cingulate cortex, superior temporal gyrus, insula, as well as the parahippocampal gyrus (Cauda et al., 2014; Jia & Yu, 2017; Smallwood et al., 2013).

In summary, GMV alterations in patients with chronic pain overlapped substantially with those observed in FMS. Because of these overlapping findings, it remains unclear whether the reported GMV alterations are truly specific to FMS or whether they rather reflect changes in chronic pain in general.

Strong commonalities of structural brain alterations in subject suffering from a wide range of conditions associated with chronic pain have been suggested, mainly based on the visual comparison of published spatial patterns from individual studies (see Apkarian, Hashmi, & Baliki, 2011 for a review). However, a direct assessment of the specificity versus generality of structural brain alterations in FMS is still lacking. Abnormalities of gray matter in chronic pain may represent pre-existing vulnerabilities or arise from disease/pain-driven plasticity or from a combination of both. Recent evidence suggests that some gray matter abnormalities in some chronic pain disorders are caused by pain itself, rather than pre-existing abnormalities (Moayedi et al., 2011) and might resolve after cessation of pain (Gwilym, Filippini, Douaud, Carr, & Tracey, 2010; Obermann et al., 2009; Rodriguez-Raecke, Niemeier, Ihle, Ruether, & May, 2009; Seminowicz et al., 2011).

In functional pain syndromes, such as fibromyalgia, in which no obvious peripheral structural or biochemical abnormality of pain exist, it is possible that gray matter abnormalities are pre-existing vulnerabilities that may contribute to the development of chronic pain (Davis, Taylor, & Anastakis, 2011). Therefore, if structural changes of gray matter in FMS exist, the disease specificity of these findings remains unclear whether they reflect plastic adaptation of chronic pain input or reflect pre-existing vulnerabilities.

The purpose of this study was to evaluate the specificity of GMV changes in FMS. Consequently, we included two separate control groups for direct comparison: one group of healthy participants and one group of patients with chronic pain caused by a distinct musculoskeletal disorder (osteoarthritis, OA). We hypothesized that both patients with FMS and OA will, compared with healthy controls, exhibit GMV similar changes and that such changes reflect chronic musculoskeletal pain in general and are thus not FMS-specific.

2 | MATERIALS AND METHODS

2.1 | Participants

A total of 27 female subjects with FMS were recruited from the surrounding community through newspaper and internet advertisements. They had to be at least 18 years old, report widespread pain longer than 6 months, have been diagnosed with FMS from a general physician or rheumatologist and were not taking any pain or central-acting medication (e.g., antidepressants, benzodiazepines, sedatives) on a regular
basis or were able to discontinue such medication 72 hr prior to the study. To confirm prior diagnosis of FMS all patients had to fulfill the revised ACR 2016 diagnostic criteria and a Fibromyalgia score (FS) of ≥12 (Wolfe, Clauw, et al., 2016). Two patients had an FS lower than 12 and were excluded from the analysis, resulting in a final sample of 25 female subjects with FMS.

Twenty-two age-matched female healthy controls (HC) were recruited from the surrounding community through newspaper and internet advertisements. Exclusion criteria for HC were a history of chronic pain or current regular intake of pain medication or central-acting medications. None of the HC fulfilled the revised 2016 ACR criteria for FMS.

Twenty-six female patients with chronic pain (over 3 months) due to osteoarthritis (OA) at one of the following joint sites (knee, hip, or shoulder) were recruited in the Department of Orthopedics of the University Hospital Münster, Germany and a local orthopedic office. Subjects with OA taking pain medication or central-acting medications on a regular basis were asked to discontinue these 72 hr before MRI data acquisition. Three of the OA patients exhibited an FS ≥12 and were subsequently excluded from the study, resulting in a final sample of 23 OA patients.

Exclusion criteria for all subjects were a history of a major psychiatric (major depression, anxiety disorder, schizophrenia, or addiction), medical (e.g., diabetes, cancer), or neurological disorder (e.g., epilepsy, dementia).

All participants provided written informed consent prior to any study procedures. The study was approved by the local ethics review board of the Medical Faculty of the University of Münster and Westphalian Chamber of Physicians (2011-030-f-S). Data acquisition comprised neuropsychological and clinical testing as well as MR imaging consisting of structural (T1-weighted and diffusion-weighted) and functional (resting state, task-based) acquisitions. This volumetric analysis is based exclusively on T1-weighted structural data.

Additionally, patients were asked to rate the intensity of their mean clinical pain during the last week on a numeric rating scale (0–10) and the interval (in years) from the start of chronic pain. Patients with FMS regularly show decrease in quality of life, increased symptoms of depression and stress or traumatization during their childhood (Häuser et al., 2013, 2015). Therefore, these variables were surveyed in each participant as well.

Quality of life was assessed with the German version of the Short-form 36-Item Health Survey (SF-36) (Bullinger, Kirchberger, & Ware, 1995). The SF-36 is a well-established and often used questionnaire assessing the health-related quality of life in the general public or patient groups. The resulting eight dimensions can be further summarized in two main components which we report: physical health (PCS) and mental health (MCS).

The German version of the Patient Health Questionnaire-9 (PHQ-9) (Löwe, Kroenke, Herzog, & Gräfe, 2004) was used to determine the amount of depressive symptoms. The PHQ-9 was developed to facilitate the detection and diagnosis of depression in primary care settings. In addition to the categorical diagnosis of depression, severity ratings are provided.

The Childhood Trauma Questionnaire (CTQ) is a well-validated and highly reliable instrument that measures the severity of different types of childhood and adolescence maltreatment (emotional, physical and sexual abuse, emotional and physical neglect). The scores of each subscale range between 5 (no abuse or neglect) and 25 (maximum abuse or neglect). Here, the German version of the CTQ (Wingenfeld et al., 2010) was used.

### 2.2 MRI data acquisition

Structural brain imaging data were acquired with a 3 Tesla Scanner (Magnem Prisma®; Siemens, Erlangen, Germany) using a 20-channel head/neck receiver coil. This included a T1-weighted magnetization prepared rapid gradient-echo (MP-RAGE) 3D sequence (field of view = 256 × 256 × 192 mm, matrix = 256 × 256 × 192, resolution = 1 × 1 × 1 mm, repetition time = 2130 ms, echo time = 2.28 ms, inversion time = 900 ms, flip angle = 8°, parallel imaging with GRAPPA [parallel imaging factor = 2]). Structural images underwent routine neuroradiological reporting in order to exclude structural lesions or relevant image artefacts.

### 2.3 Voxel-based morphometry

Regional GMVs were obtained by voxel-based morphometry (VBM) using the CAT12 toolbox (Gaser and Dahmke, dbm.neuro.uni-jena.de) in SPM12 (Wellcome Trust Centre for Neuroimaging). T1-weighted images were normalized to common standard space, the MNI template (sixth generation nonlinear International Consortium for Brain Mapping template) using linear and nonlinear transformations and subsequently segmented into gray matter (GM), white matter, and cerebrospinal fluid using the intensity distribution of the tissue probability maps. Afterward, GM segments were modulated to adjust intensity according the amount of contraction or expansion estimated by the nonlinear transformation to obtain relative volumes corrected for brain size. In addition to visual inspection, data quality was checked using sample homogeneity at this analysis stage. One HC subject had to be excluded due to substantial movement artefacts. In the final step, the modulated normalized GM maps were spatially smoothed with a Gaussian kernel (FWHM = 8 × 8 × 8 mm).

The total intracranial volume (TIV) and gray matter volume (GMV) was calculated for each subject. Correlations of GMV with the subjects height, amount of depressive symptoms (PHQ-9), trauma experience (CTQ), and duration...
of ongoing pain were tested in order to control for possible influences of these clinical parameters. Subsequently, variables with a significant correlation with GMV but without a statistically significant group difference (see below for the covariates finally included and the results/Table 1 for clinical subject characteristics) were entered into the model as additional nuisance covariates.

The resulting images were entered in a full factorial design in SPM12 with group (FMS, OA, HC) as the main factor. Age and TIV of each subject were entered as covariates to control for influence of age- or global volume-related biases. Within this design, the effect of the main factor group (F test) was tested. In case clusters with a significant main effect were detected, additional post hoc t tests for each relevant contrast combination between the three groups were performed to determine the differences between the three groups. Each analysis was performed under a statistical threshold of FWE-corrected (family-wise error) $p < .05$ (voxel level).

Because such a conservative statistical threshold is associated with a risk of type II errors and to facilitate comparability of our results with earlier studies which mostly used more liberal thresholds, the main (i.e., conservative) statistical tests were supplemented by exploratory analyses under a more liberal threshold of an uncorrected $p < .001$ (voxel level) with a cluster size greater than 30 contiguous voxels.

The correlations of GMV of significant clusters with clinical pain intensity and pain duration (Spearman Rho correlation for non-normally distributed clinical data) were tested in order to evaluate the disease relatedness of group differences in chronic pain.

Effect sizes of resulting group differences GMVs were estimated separately for each cluster by using the Marsbar toolbox for SPM. For each comparison (FMS vs. HC, OA vs. HC), the effect size $r$ was computed as $r = Z/\sqrt{n}$ ($Z =$ Mann–Whitney $U$ test, $n = $ number of subjects).

Additionally, we carried out a region of interest (ROI) analysis in order to assess the replicability of results of former systematic meta-analyses on GMV changes in FMS and chronic pain in general compared with healthy controls (Cauda et al., 2014; Dehghan et al., 2016; Jia & Yu, 2017; Lin et al., 2016; Shi et al., 2016; Smallwood et al., 2013). In summary of all results, five major pain-processing brain areas could be detected which showed changes in contrast to healthy controls. These areas were anterior cingulate gyrus (ACC), frontal gyrus (BA 10 see (Peng, Steele, Becerra, & Borsook, 2018)), insula, parahippocampal gyrus, and amygdala. Regions of interests (ROIs) corresponding to these regions were defined (separately for each hemisphere) using the WFU Pick atlas (Maldjian, Laurienti, Kraft, & Burdette, 2003). GMVs of each ROI were extracted from the unsmoothed but modulated gray matter maps using the Marsbar toolbox for SPM (Brett, Anton, Valabregue, & Poline, 2002). Resulting individual GMV estimates were entered into a one-way ANOVA with group as the main factor in SPSS 25 (IBM) and GMV differences between groups for each ROI was tested with an uncorrected $p < .05$.

### 3 | RESULTS

#### 3.1 | Subjects characteristics

After data quality assessment, one HC had to be excluded due to increased motion artefacts. Demographical and clinical characteristics of these participants are presented in Table 1. The three groups did not differ regarding age but subjects with FMS were smaller than OA subjects and HC. There was a trend toward greater overall pain levels at the

| Item                  | FMS ($n = 25$) | OA ($n = 23$) | HC ($n = 21$) | F- or T-score | p-score |
|-----------------------|----------------|--------------|--------------|---------------|---------|
| Age (years)           | 52.60 ± 11.10  | 54.09 ± 12.36| 52.24 ± 9.79 | 0.17          | .84     |
| Height (cm)           | 164.40 ± 6.28  | 168.04 ± 4.30| 168.38 ± 3.83| 4.65          | .01     |
| Clinical pain (0–10)  | 3.80 ± 2.40    | 2.39 ± 2.81  | NA           | 1.86*         | .07     |
| Pain duration (years) | 15.76 ± 10.58  | 4.61 ± 5.43  | NA           | 4.65*         | <.001   |
| SSS                   | 8.72 ± 1.57    | 3.96 ± 2.27  | 2.57 ± 2.39  | 56.73         | <.001   |
| WPI                   | 9.96 ± 3.84    | 2.09 ± 1.31  | NA           | 9.64*         | <.001   |
| FS                    | 16.68 ± 4.35   | 5.96 ± 3.05  | 2.57 ± 2.38  | 145.58        | <.001   |
| PHQ-9                 | 11.60 ± 4.26   | 5.78 ± 4.00  | 3.10 ± 2.79  | 30.87         | <.001   |
| CTQ                   | 62.96 ± 26.50  | 44.87 ± 18.62| 41.43 ± 13.43| 7.45          | .002    |
| TIV (ml)              | 1437.35 ± 106.07| 1484.22 ± 107.76| 1507.99 ± 132.92| 2.26      | .11     |
| GMV (ml)              | 626.54 ± 53.91 | 648.22 ± 57.50| 660.35 ± 55.84| 2.20          | .12     |

Abbreviations: CTQ, childhood trauma questionnaire; FS, Fibromyalgia score; FMS, fibromyalgia syndrome; GMV, gray matter volume; HC, healthy controls; NA, not applicable; OA, osteoarthritis; PHQ-9, patient health questionnaire depression; SSS, symptom severity score; TIV, total intracranial volume; WPI, widespread pain index; *, in clinical variables with data for the two pain groups: a two sample t test was performed, and the T-score is presented.
time of the examination in FMS compared with OA. Subjects with FMS reported longer duration of their chronic pain and, expectedly, greater levels specifically of widespread pain (WPI) than OA patients. Subjects with FMS reported more additional somatic symptoms as measured with the somatic symptom score (SSS) than OA and HC, OA showed a trend of greater SSS scores than HC. Regarding FS subjects with FMS had greater scores than OA and HC; subjects with OA had greater FS than HC.

Subjects with FMS reported more depressive symptoms (PHQ-9) than OA and HC, but OA and HC were not significantly different. According trauma events (CTQ), FMS subjects had higher scores than OA and HC; OA and HC were not different.

Total GMV did not differ between the three groups and was negatively correlated with age across all subjects (Spearman Rho \( r = -0.60, p < .001 \)) and the duration of chronic pain \( (r = -0.24, p = .05) \), and was positively correlated with the height of the subject \( (r = 0.35, p = .003) \). Neither traumatic childhood events \( (r = -0.02, p = .86) \) nor severity of depressive symptoms \( (r = -0.21, p = .09) \) were correlated with GMV. Because of group differences in height and duration of pain, only age and TIV were entered as covariates of possible impact on GMV in the following VBM analysis.

The fibromyalgia score (FS) was positively correlated with CTQ-score \( (r = 0.41, p = .001) \), the PHQ-9 score \( (r = 0.70, p < .001) \), the duration of pain \( (r = 0.75, p < .001) \), and the clinical pain intensity \( (r = 0.54, p < .001) \). Age, height or GMV were not correlated with FS.

### 3.2 Local gray matter volume (VBM analysis)

#### 3.2.1 Voxel-wise whole-brain analysis

No significant differences in local GMV between the three groups were observed (\( F \) test for the main effect ‘group’, \( t \) tests for comparison of groups) in the full factorial design when adopting relatively conservative FWE correction for multiple comparisons.

In the exploratory analysis adopting more liberal thresholds (and thus addressing the risk of type II errors in the main analysis), both patients groups (FMS, OA) exhibited increased GMV compared to HC in the left precentral gyrus and decreased GMV in two neighbored clusters around the left middle temporal gyrus and left angular gyrus/middle occipital gyrus (see Tables S1, S2 and Figure S1).

For the differences in the precentral cluster effect sizes were \( r = 0.28 \) (FMS vs. HC) and \( r = 0.31 \) (OA vs. HC), for the middle temporal gyrus cluster \( r = 0.62 \) and \( r = 0.58 \), for the angular gyrus \( r = 0.60 \) and \( r = 0.45 \).

In both pain groups, GMV of the left middle temporal gyrus cluster correlated negatively with clinical pain \( (r = -0.32, p = .01) \) and pain duration \( (r = -0.53, p < .001) \). Similarly, GMV of the left angular gyrus/middle occipital gyrus cluster was negatively associated with clinical pain \( (r = -0.38, p = .001) \) and pain duration \( (r = -0.45, p < .001) \). GMV of the precentral gyrus did neither correlate with clinical pain \( (r = 0.21, p > .05) \) nor pain duration \( (r = 0.14, p > .05) \).

### Region | GMV (mean ± SD ml) | ANOVA | F-score | p-score
--- | --- | --- | --- | ---
FMS | HC | OA | FMS | HC | OA | F-score | p-score
ACC | | | | | | | | |
Left | 0.49 ± 0.06 | 0.51 ± 0.07 | 0.51 ± 0.07 | 0.87 | .42
Right | 0.37 ± 0.04 | 0.39 ± 0.05 | 0.39 ± 0.06 | 1.23 | .30
Amygdala | | | | | | | | |
Left | 0.58 ± 0.06 | 0.61 ± 0.08 | 0.59 ± 0.07 | 1.15 | .32
Right | 0.52 ± 0.04 | 0.52 ± 0.06 | 0.51 ± 0.06 | 0.07 | .94
BA 10 | | | | | | | | |
Left | 0.28 ± 0.03 | 0.29 ± 0.03 | 0.29 ± 0.04 | 0.99 | .38
Right | 0.29 ± 0.04 | 0.30 ± 0.03 | 0.29 ± 0.04 | 1.04 | .36
Insula | | | | | | | | |
Left | 0.44 ± 0.05 | 0.47 ± 0.05 | 0.46 ± 0.05 | 2.24 | .11
Right | 0.49 ± 0.05 | 0.52 ± 0.05 | 0.51 ± 0.06 | 1.59 | .21
Parahippocampal gyrus | | | | | | | | |
Left | 0.39 ± 0.03 | 0.41 ± 0.04 | 0.39 ± 0.04 | 1.56 | .22
Right | 0.45 ± 0.04 | 0.48 ± 0.05 | 0.48 ± 0.05 | 2.34 | .10

Abbreviations: FMS, fibromyalgia syndrome; GMV, gray matter volume; HC, healthy controls; OA, osteoarthritis.
cluster of chronic pain in general (Cauda et al., 2014; Davis et al., 2016; Jia & Yu, 2017; Kim et al., 2008; Schmidt‐Wilcke, 2005; Wartolowska et al., 2012). This led to the assumption that different pain conditions associated with similar patterns of altered brain morphology irrespective of the underlying etiology. Studies clustering chronic pain into putative underlying mechanisms (Sugimine, Hiermeier, & Leinisch, 2010; Schmidt‐Wilcke et al., 2005; Fitzcharles, & Schweinhardt, 2013; Harper et al., 2018; Jensen et al., 2013; Lutz et al., 2008). In patients with chronic pain, irrespective of their causative etiology, share common changes in GMV due to chronic pain‐related input on the brain. This input might comprise additional sensory, cognitive, or behavioral processes such as attention, affective, or memory processing. Pain‐independent factors such as physical or psychic comorbidity might contribute to this as well.

4 | DISCUSSION
This study compared brain morphology in patients with FMS with two different relevant control groups: patients with osteoarthritis and healthy controls. The main finding is that under a stringent approach with correction for multiple testing in a whole‐brain analysis no differences between the three groups could be detected. In additional exploratory analyses, we observed similarly increased GMV in the precentral gyrus and decreased GMV in the middle temporal gyrus/temporoparietal junction in both patient groups compared to healthy controls. The finding that GMV decrease in chronic pain patients was associated with clinical pain in all of these regions except the precentral gyrus supports the relevance of these observations for clinical pain conditions in general. Therefore, the specificity of GMV alterations in FMS claimed in former studies needs to be questioned. We will therefore treat patients as one common chronic pain group (FMS + OA) in those parts of the subsequent discussion that refer to the potential relevance of individual brain regions involved.

4.1 Disease specificity versus general pain‐related GMV alterations
According to previous studies on GM morphology, patients with FMS exhibited reduced or increased GM volume or density in several brain areas with specific function in pain‐processing and pain‐independent cognitive processing like the frontal cortex, cingulate cortex, hippocampus, amygdala, insula, putamen, globus pallidus, periaqueductal gray, and cerebellum (Burgmer, Gaubitz, et al., 2009; Ceko, Bushnell, Fitzcharles, & Schweinhardt, 2013; Harper et al., 2018; Jensen et al., 2013; Lutz et al., 2008). In patients with chronic pain of other origin (e.g., chronic back pain, headache, osteoarthritis, rheumatoid arthritis), similar GMV alterations have been observed as well (Apkarian et al., 2004; Fritz et al., 2016; Jia & Yu, 2017; Kim et al., 2008; Schmidt‐Wilcke, Hiermeier, & Leinisch, 2010; Schmidt‐Wilcke et al., 2005; Wartolowska et al., 2012).

This led to the assumption that different pain conditions are associated with similar patterns of altered brain morphology irrespective of the underlying etiology. Studies clustering chronic pain into putative underlying mechanisms (Sugimine, Ogino, Kawamichi, Obata, & Saito, 2016) or in one single cluster of chronic pain in general (Cauda et al., 2014; Davis et al., 2013; Smallwood et al., 2013) were able to replicate former results of GMV alteration in single chronic pain conditions. Therefore, it seems reasonable to assume that patients with chronic pain, irrespective of their causative etiology, share common changes in GMV due to chronic pain‐related input on the brain. The finding that GMV decrease in chronic pain patients was associated with clinical pain in all of these regions except the precentral gyrus supports the relevance of these observations for clinical pain conditions in general. Therefore, the specificity of GMV alterations in FMS claimed in former studies needs to be questioned. We will therefore treat patients as one common chronic pain group (FMS + OA) in those parts of the subsequent discussion that refer to the potential relevance of individual brain regions involved.

4.2 General pain‐related GMV alterations
GMV alterations detected in both pain groups in our study differ from regions observed in former studies (ACC, frontal gyrus, insula, parahippocampal gyrus, and amygdala). They thus do not facilitate straightforward interpretation.

GMV alterations in the frontal cortex near the region of our precentral/sensorimotor cluster have been shown in FMS (Jensen et al., 2013). They have also been observed in chronic pain in general (Smallwood et al., 2013). This sensorimotor area is known to be important in pain intensity coding and repetitive painful stimulation in healthy controls leads to increased GMV due to the pain input (Teutsch, Herken, Bingel, Schoell, & May, 2008). This has been interpreted as a sign of neuronal adaptation. Recent structural MRI investigations in other chronic pain conditions have demonstrated similar increases in cortical thickness and GMV in sensorimotor areas supporting the potential relevance of long‐term overstimulation of this region as a possible cause (Labus et al., 2014; Moayedi et al., 2012). Several further areas in the frontal lobes (however with a relatively spatial variety from motor cortex, dIPFC to medial PFC) have been attributed to pain‐related functions such as anticipation of pain (Plooghaus et al., 1999) or descending pain modulation (Tracey & Mantyh, 2007). Thus, these GMV changes might also be related to affective‐cognitive dimensions of continuous expectation of pain or the attempt to downregulate the pain.

Altered GMV in the MTG was observed in patients with migraine (Coppola et al., 2017) and trigeminal neuralgia (Li et al., 2017) as well. GMV of the MTG (temporoparietal junction) was correlated with cognitive control of pain (thought suppression mediating pain intensity) in patients with low
back pain, but not in healthy controls (Chehadi et al., 2018). The MTG/TPJ might play an interface function between the salience network and the executive control network for response inhibition and interference control (Kucyi, Salomons, & Davis, 2016). It has been hypothesized to be the key region redirecting attention away from pain and attempting to keep unwanted thoughts about pain out of awareness (Kucyi et al., 2016). Therefore, abnormalities in this area may lead to dysfunctional control of pain such as an increased anxious expectation (Coppola et al., 2017) or altered affective regulation in chronic pain (Liotti et al., 2000).

4.3 Potential reasons for a failed replication of previous results and further limitations

Converging evidence suggests that several brain areas are critical components of a network that serves as central pain network and involves sensory, affective, and cognitive-attentional dimensions of pain perception and modulation (Fuchs, Peng, Boyette-Davis, & Uhelski, 2014). For example, decreased GMV in the ACC is one of the most common findings irrespective of the peripheral anatomical location, nature, or course of chronic pain (Cauda et al., 2014; Smallwood et al., 2013).

One potential reason of a failed replication results from differences in the statistical analysis approaches. Most analyses in MRI studies are based on voxel-wise statistical comparisons. This mandates correction for multiple comparisons (such as FWE or FDR correction). Unfortunately, correction comes with the risk to miss true but low-powered effects (type II error). If GMV changes in chronic pain are subtle (and therefore less powered), it is not surprising that studies with conservative statistical approaches (Chehadi et al., 2018; Coppola et al., 2017) were not able to detect GMV changes, similar as in our analysis. If changes were found in former studies, the analyses were less conservative or restricted to regions of a priori interest. Thus, comparability of different studies (and results) based on different statistical approaches is limited. However, considering that underlying morphological changes might be subtle; there might have been no chance to detect these in our medium-sized sample.

Another reason that we were not able to replicate previously reported alterations of GMV in FMS may be explained by the heterogeneity between study groups. It is well known that patients with FMS differ substantially from each other due to different comorbidities, cognitive function, disease duration, and functional impairment; they do not form a homogenous group (Bartley, Robinson, & Staud, 2018). Furthermore, individuals with OA are likely heterogeneous in terms of pain mechanisms as well, some having more “nociceptive” and others having more “centrally mediated” pain (Clauw & Hassett, 2017). Thus, small- and medium-sized studies may suffer from a selection bias. We believe that in our sample this problem was less relevant. In line with the revision of the FMS ACR criteria (Wolfe, Clauw, et al., 2016), we excluded FMS patients with a Fibromyalgia score, as a measure of “FMS-proneness,” lower than 12 and OA patients with a score greater than 12. Thus, even our medium-sized sample in this neuroimaging study was representative for a typical FMS population different from the OA subjects. But it has to be kept in mind that we included only female subjects in our study. Therefore, our results may not be generalizable to male FMS patients.

In comparison with diagnostic studies in FMS (Wolfe, Clauw, et al., 2016; Wolfe, Fitzcharles, et al., 2016; Wolfe et al., 2019), patients with FMS in our sample showed a somewhat lower clinical pain burden (pain score around 3.8 out of 10). Some former neuroimaging studies in FMS included subjects with clinical pain scores around 5–6 out of 10, for example, (Jensen et al., 2010, 2013; Kim et al., 2014), and others included subjects with pain around 3–4 out of 10 (Burgmer et al., 2010; Ceko et al., 2013; Petzke, Harris, Williams, Clauw, & Gracey, 2005; Puiu et al., 2016). Therefore, our study sample might reflect a group of less distressed and pain burdened FMS patients which might reduce the generalizability of our mainly negative results to more severely affected patients.

Furthermore, it has to be critically discussed if GMV changes in chronic pain conditions reflect neurodegeneration, which should cause changes in pain-specific anatomical regions, or might be due to other mechanisms like cerebral perfusion or neuroinflammation, which should cause more unspecific and widespread located GMV changes. Pomares et al. (2017) were able to show that neurodegeneration does not play a major role for VBM changes in chronic pain conditions as FMS. This might also explain the spatial variety of anatomical GMV changes or even the lack of GMV alterations in FMS.

5 Conclusions

In conclusion, we did not identify significant and FMS-specific GMV alterations when adopting a conservative statistical approach of multiple comparison correction. However, with a more liberal approach increased gray matter volumes in the sensorimotor cortex and decreased GMV in the temporoparietal junction in both pain groups in comparison with healthy controls were revealed. Since both pain groups showed nearly identical GMV changes in these areas, cortical GMV changes in FMS should not be interpreted as FMS-specific but might rather reflect changes in chronic pain in general.
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CONFLICTS OF INTEREST
The authors declare no conflicts of interest.

DATA AVAILABILITY
Due to German data safety regulations, the primary data are not suitable for a publicly accessibility in general. On request, primary imaging data on a level independent of the individual subject (second level in SPM) might be made accessible.

AUTHOR CONTRIBUTIONS
BS, MDN, BP, MB were responsible for concept and design of the study, acquisition, analysis and interpretation of data, drafting the article, and final approval of the version to be published. KS, LJ, LB were responsible for concept and design of the study, acquisition and interpretation of data, drafting the article, and final approval of the version to be published. RD, DL, TH were responsible for acquisition and interpretation of data, drafting the article, and final approval of the version to be published.

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REFERENCES
Apkarian, A. V., Hashmi, J. A., & Baliki, M. N. (2011). Pain and the brain: Specificity and plasticity of the brain in clinical chronic pain. Pain, 152, S49–S64.
Apkarian, A. V., Sosa, Y., Sonty, S., Levy, R. M., Harden, R. N., Parrish, T. B., & Gitelman, D. R. (2004). Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. Journal of Neuroscience, 24, 10410–10415.
Bartley, E. J., Robinson, M. E., & Staud, R. (2018). Pain and fatigue variability patterns distinguish subgroups of fibromyalgia patients. Journal of Pain, 19, 372–381.
Brett, M., Anton, J. L., Valabregue, R., & Poline, J. B. (2002). Region of interest analysis using an SPM toolbox [abstract] Presented at the 8th International Conference on Functional Mapping of the Human Brain, June 2-6, 2002, Sendai, Japan. NeuroImage, 16.
Bullinger, M., Kirchberger, I., & Ware, J. (1995). The German SF-36 health survey translation and psychometric testing of a generic instrument for the assessment of health-related quality of life. Z.f.Gesundheitswiss, 3, 21–36.
Burgmer, M., Gaubitz, M., Konrad, C., Wrenger, M., Hilgart, S., Heuft, G., & Pfeiderer, B. (2009). Decreased gray matter volumes in the cingulo-frontal cortex and the amygdala in patients with fibromyalgia. Psychosomatic Medicine, 71, 566–573.
Burgmer, M., Pfeiderer, B., Maimhöfner, C., Gaubitz, M., Wessoleck, E., Heuft, G., & Pogatzki-Zahn, E. (2012). Cerebral mechanisms of experimental hyperalgesia in fibromyalgia. European Journal of Pain, 16, 636–647.
Burgmer, M., Pogatzki-Zahn, E., Gaubitz, M., Stüber, C., Wessoleck, E., Heuft, G., & Pfeiderer, B. (2010). Fibromyalgia unique temporal brain activation during experimental pain – a controlled fMRI Study. Journal of Neural Transmission, 117, 123–131.
Burgmer, M., Pogatzki-Zahn, E., Gaubitz, M., Wessoleck, E., Heuft, G., & Pfeiderer, B. (2009). Altered brain activity during pain processing in fibromyalgia. NeuroImage, 44, 502–508.
Cauda, F., Palermo, S., Costa, T., Torta, R., Duca, S., Vercelli, U., … Torta, D. M. (2014). Gray matter alterations in chronic pain: A network-oriented meta-analytic approach. NeuroImage Clinical, 4, 676–686.
Ceko, M., Bushnell, M. C., Fitzcharles, M. A., & Schweinhardt, P. (2013). Fibromyalgia interacts with age to change the brain. NeuroImage Clinical, 3, 249–260.
Chehadi, O., Rusu, A. C., Konietzny, K., Schulz, E., Koster, O., Schmidt-Wilcke, T., & Hasenbring, M. I. (2018). Brain structural alterations associated with dysfunctional cognitive control of pain in patients with low back pain. European Journal of Pain, 22, 745–755.
Clauw, D. J. (2014). Fibromyalgia: A clinical review. JAMA, 311, 1547–1555.
Clauw, D. J., & Hassett, A. L. (2017). The role of centralised pain in osteoarthritis. Clinical and Experimental Rheumatology, 35(Suppl 107), 79–84.
Coppola, G., Petolicchio, B., Di, R. A., Tinelli, E., Di, L. C., Parisi, V., … Pierelli, F. (2017). Cerebral gray matter volume in patients with chronic migraine: Correlations with clinical features. Journal of Headache and Pain, 18, 115–0825.
Davis, K. D., & Moayedi, M. (2013). Central mechanisms of pain revealed through functional and structural MRI. Journal of Neuroimmunomodulation, 8, 518–534.
Davis, K. D., Taylor, K. S., & Anastakis, D. J. (2011). Nerve injury triggers changes in the brain. Neuroscientist, 17, 407–422.
Dehghan, M., Schmidt-Wilcke, T., Pfeiderer, B., Eickhoff, S. B., Petzke, F., Harris, R. E., … Burgmer, M. (2016). Coordinate-based (ALE) meta-analysis of brain activation in patients with fibromyalgia. Human Brain Mapping, 37, 1749–1758.
Desmeules, J. A., Cedraschi, C., Rapiti, E., Baumgartner, E., Finckh, A., Cohen, P., … Vischer, T. L. (2003). Neurophysiologic evidence for a central sensitization in patients with fibromyalgia. Arthritis and Rheumatism, 48, 1420–1429.
Fritz, H. C., McAuley, J. H., Wittfeld, K., Hegenscheid, K., Schmidt C. O., Langner, S., & Lotze, M. (2016). Chronic back pain is associated with decreased prefrontal and anterior insular gray matter: results from a population-based cohort study. Journal of Pain, 17, 111–118.
Fuchs, P. N., Peng, Y. B., Boyette-Davis, J. A., & Uhelski, M. L. (2014). The anterior cingulate cortex and pain processing. Frontiers in Integrative Neuroscience, 8, 35.
Gerstner, G., Ichesco, E., Quintero, A., & Schmidt-Wilcke, T. (2011). Changes in regional gray and white matter volume in patients with myofascial-type temporomandibular disorders: A voxel-based morphometry study. Journal of Orofacial Pain, 25, 99–106.
Gracey, R. H., Petzke, F., Wolf, J. M., & Clauw, D. J. (2002). Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthritis and Rheumatism, 46, 1333–1343.
Gwilym, S. E., Filippini, N., Douaud, G., Carr, A. J., & Tracey, I. (2010). Thalamic atrophy associated with painful osteoarthritis of the hip is reversible after arthroplasty: A longitudinal voxel-based morphometric study. *Arthritis and Rheumatism, 62*, 2930–2940.

Harper, D. E., Ichesco, E., Schrepf, A., Hampson, J. P., Clauw, D. J., Schmidt-Wilcke, T., … Harte, S. E. (2018). Resting functional connectivity of the periaqueductal gray is associated with normal inhibition and pathological facilitation in conditioned pain modulation. *Journal of Pain, 19*, 635.

Häuser, W., Galek, A., Erbsloh-Moller, B., Kolliner, V., Kuhn-Becker, H., Langhorst, J., … Glaesmer, H. (2013). Posttraumatic stress disorder in fibromyalgia syndrome: Prevalence, temporal relationship between posttraumatic stress and fibromyalgia symptoms, and impact on clinical outcome. *Pain, 154*, 1216–1223.

Häuser, W., Hoffmann, E. M., Wolfe, F., Worthing, A. B., Stahl, N., Rothenberg, R., & Walitt, B. (2015). Self-reported childhood maltreatment, lifelong traumatic events and mental disorders in fibromyalgia syndrome: A comparison of US and German outpatients. *Clinical and Experimental Rheumatology, 33*, S86–S92.

Heidari, F., Afshari, M., & Moosazadeh, M. (2017). Prevalence of fibromyalgia in general population and patients, a systematic review and meta-analysis. *Rheumatology International, 37*, 1527–1539.

Jensen, K. B., Petzke, F., Carville, S., Fransson, P., Marcus, H., Williams, S. C., … Kosek, E. (2010). Anxiety and depressive symptoms in fibromyalgia are related to poor perception of health but not to pain sensitivity or cerebral processing of pain. *Arthritis and Rheumatism, 62*, 3488–3495.

Jensen, K. B., Srinivasan, P., Spaeth, R., Tan, Y., Kosek, E., Petzke, F., … Kong, J. (2013). Overlapping structural and functional brain changes in patients with long-term exposure to fibromyalgia pain. *Arthritis and Rheumatism, 65*, 3293–3303.

Jia, Z., & Yu, S. (2017). Grey matter alterations in migraine: A systematic review and meta-analysis. *NeuroImage Clinical, 14*, 130–140.

Kim, H., Kim, J., Loggia, M. L., Cahalan, C., Garcia, R. G., Vangel, M. G., … Napadow, V. (2015). Fibromyalgia is characterized by altered frontal and cerebellar structural covariance brain networks. *NeuroImage Clinical, 7*, 667–677.

Kim, D. J., Lim, M., Kim, J. S., Son, K. M., Kim, H. A., & Chung, C. K. (2014). Altered white matter integrity in the corpus callosum in fibromyalgia patients identified by tract-based spatial statistical analysis. *Arthritis & Rheumatism, 66*, 3190–3199.

Kim, J. H., Suh, S. I., Seol, H. Y., Oh, K., Seo, W. K., Yu, S. W., … Koh, S. B. (2008). Regional grey matter changes in patients with migraine: A voxel-based morphometry study. *Cephalalgia, 28*, 598–604.

Kivimaki, M., Leino-Arjas, P., Kaila-Kangas, L., Virtanen, M., Elovaara, M., Putkonen, S., … Vahtera, J. (2007). Increased absence and presentee time in community dwelling individuals with chronic joint pain. *American Journal of Neuroradiology, 37*, 430–438.

Kucyi, A., Salomons, T. V., & Davis, K. D. (2016). Cognitive behavioral training reverses the effect of pain exposure on brain network activity. *Pain, 157*, 1895–1904.

Labus, J. S., Dinov, I. D., Jiang, Z., Ashe-McNalley, C., Zamanian, A., Shi, Y., … Mayer, E. A. (2014). Irritable bowel syndrome in female patients is associated with alterations in structural brain networks. *Pain, 155*, 137–149.

Li, M., Yan, J., Li, S., Wang, T., Zhan, W., Wen, H., … Jiang, G. (2017). Reduced volume of gray matter in patients with trigeminal neuralgia. *Brain Imaging and Behavior, 11*, 486–492.

Lin, C., Lee, S. H., & Weng, H. H. (2016). Gray matter atrophy within the default mode network of fibromyalgia: A meta-analysis of voxel-based morphometry studies. *BioMed Research International, 2016*, 7296125.

Liotti, M., Mayberg, H. S., Brannan, S. K., McGinnis, S., Jerabek, P., & Fox, P. T. (2000). Differential limbic–cortical correlates of sadness and anxiety in healthy subjects: Implications for affective disorders. *Biological Psychiatry, 48*, 30–42.

Löwe, B., Kroenke, K., Herzog, W., & Gräfe, K. (2004). Measuring depression outcome with a brief self-report instrument: Sensitivity to change of the Patient Health Questionnaire (PHQ-9). *Journal of Affective Disorder, 81*, 61–66.

Lutz, J., Lagers, J., de Quervain, D., Krauseneck, T., Padberg, F., Wichnalek, M., … Schelling, G. (2008). White and gray matter abnormalities in the brain of patients with fibromyalgia: A diffusion-tensor and volumetric imaging study. *Arthritis and Rheumatism, 58*, 3960–3969.

Maldjian, J. A., Laurienti, P. J., Kraft, R. A., & Burdette, J. H. (2003). An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *NeuroImage, 19*, 1233–1239.

Moayed, M., Weissman-Fogel, I., Crawley, A. P., Goldberg, M. B., Freeman, B. V., Tenenbaum, H. C., & Davis, K. D. (2011). Contribution of chronic pain and neuroticism to abnormal forebrain gray matter in patients with temporomandibular disorder. *NeuroImage, 55*, 277–286.

Moayed, M., Weissman-Fogel, I., Salomons, T. V., Crawley, A. P., Goldberg, M. B., Freeman, B. V., … Davis, K. D. (2012). Abnormal gray matter aging in chronic pain patients. *Brain Research, 1456*, 82–93.

Obermann, M., Nebel, K., Schumann, C., Holle, D., Gizewski, E. R., Maschke, M., … Katsarava, Z. (2009). Gray matter changes related to chronic posttraumatic headache. *Neurology, 73*, 978–983.

Peng, K., Steele, S. C., Becerra, L., & Borsook, D. (2018). Brodmann area 10: Collating, integrating and high level processing of nociception and pain. *Progress in Neurobiology, 161*, 1–22.

Petzke, F., Harris, R. E., Williams, D. A., Clauw, D. J., & Gracely, R. H. (2005). Differences in unpleasantness induced by experimental pressure pain between patients with fibromyalgia and healthy controls. *European Journal of Pain, 9*, 325–335.

Ploghaus, A., Tracey, I., Gati, J. S., Clare, S., Menon, R. S., Matthews, P. M., & Rawlins, J. N. (1999). Dissociating pain from its anticipation in the human brain. *Science, 284*, 1979–1981.

Pomares, F. B., Funck, T., Feier, N. A., Roy, S., Daigle-Martel, A., Cecko, M., … Schweinhart, P. (2017). Histological underpinnings of grey matter changes in fibromyalgia investigated using multimodal brain imaging. *Journal of Neuroscience, 37*, 1090–1101.

Puu, I., Kairyys, A. E., Pauer, L., Schmidt-Wilcke, T., Ichesco, E., Hampson, J. P., … Harris, R. E. (2016). Association of alterations in gray matter volume with reduced evoked-pain connectivity following short-term administration of pregabal in patients with fibromyalgia. *Arthritis & Rheumatology, 68*, 1511–1521.

Rodriguez-Raecke, R., Niemeier, A., Ihe, K., Ruetther, W., & May, A. (2009). Brain gray matter decrease in chronic pain is the consequence and not the cause of pain. *Journal of Neuroscience, 29*, 13746–13750.

Schmidt-Wilcke, T., Hierlemiester, S., & Leinisch, E. (2010). Altered regional brain morphology in patients with chronic facial pain. *Headache, 50*, 1278–1285.
Schmidt-Wilcke, T., Leinisch, E., Straube, A., Kampfe, N., Draganski, B., Diener, H. C., … May, A. (2005). Gray matter decrease in patients with chronic tension type headache. *Neurology*, 65, 1483–1486.
Seminowicz, D. A., Wideman, T. H., Naso, L., Hatami-Khoroushahi, Z., Fallatah, S., Ware, M. A., … Stone, L. S. (2011). Effective treatment of chronic low back pain in humans reverses abnormal brain anatomy and function. *Journal of Neuroscience*, 31, 7540–7550.
Shi, H., Yuan, C., Dai, Z., Ma, H., & Sheng, L. (2016). Gray matter abnormalities associated with fibromyalgia: A meta-analysis of voxel-based morphometric studies. *Seminars in Arthritis and Rheumatism*, 46, 330–337.
Smallwood, R. F., Laird, A. R., Ramage, A. E., Parkinson, A. L., Lewis, J., Clauw, D. J., … Robin, D. A. (2013). Structural brain anomalies and chronic pain: A quantitative meta-analysis of gray matter volume. *Journal of Pain*, 14, 663–675.
Sugimine, S., Ogino, Y., Kawamichi, H., Obata, H., & Saito, S. (2016). Brain morphological alternation in chronic pain patients with neuropathic characteristics. *Molecular Pain*, 12, 12.
Teutsch, S., Herken, W., Bingel, U., Schoell, E., & May, A. (2008). Changes in brain gray matter due to repetitive painful stimulation. *NeuroImage*, 42, 845–849.
Tracey, I., & Mantyh, P. W. (2007). The cerebral signature for pain perception and its modulation. *Neuron*, 55, 377–391.
Wartolowska, K., Hough, M. G., Jenkinson, M., Andersson, J., Wordsworth, B. P., & Tracey, I. (2012). Structural changes of the brain in rheumatoid arthritis. *Arthritis and Rheumatism*, 64, 371–379.
Wingenfeld, K., Spitzer, C., Mensebach, C., Grabe, H. J., Hill, A., Gast, U., … Driessen, M. (2010). The German version of the Childhood Trauma Questionnaire (CTQ): Preliminary psychometric properties. *Psychotherapie, Psychosomatik, Medizinische Psychologie*, 60, 442–450.
Wolfe, F., Clauw, D. J., Fitzcharles, M. A., Goldenberg, D. L., Hauser, W., Katz, R. L., … Walitt, B. (2016). 2010/2011 fibromyalgia diagnostic criteria. *Seminars in Arthritis and Rheumatism*, 46, 319–329.
Wolfe, F., Clauw, D. J., Fitzcharles, M. A., Goldenberg, D. L., Katz, R. S., Mease, P., … Yunus, M. B. (2010). The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care & Research*, 62, 600–610.
Wolfe, F., Fitzcharles, M. A., Goldenberg, D. L., Hauser, W., Katz, R. L., Mease, P. J., Russell, A. S., Jon, R. I., … Walitt, B. (2016). Comparison of physician-based and patient-based criteria for the diagnosis of fibromyalgia. *Arthritis Care & Research*, 68, 652–659.
Wolfe, F., Schmukler, J., Jamal, S., Castrejon, I., Gibson, K. A., Srinivasan, S., … Pincus, T. (2019). Diagnosis of fibromyalgia: Disagreement between fibromyalgia criteria and physician-based fibromyalgia diagnosis in a university clinic. *Arthritis Care & Research*, 71, 343–351.

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