Cross-Sectional Study

Disrupted White Matter Microstructure in Patients With Fibromyalgia Owing Predominantly to Psychological Factors: A Diffusion Tensor Imaging Study

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Background: Neuroimaging investigations have already uncovered alterations to cerebral microstructural integrity in patients with fibromyalgia (FM). In the meantime, these patients commonly suffer from depression and anxiety.

Objective: In this study, microstructure changes within white matter were examined in patients with FM with consideration of concurrent physiological factors.

Study Design: A cross-sectional case-control study.

Setting: A university hospital.

Methods: Diffusion tensor imaging was performed on 20 patients with FM and 20 healthy controls. The 4 diffusional indices, namely, fractional anisotropy (FA), mean, radial, and axial diffusivity (MD, RD, AD) were calculated using tract-based spatial statistics. The relationships between the diffusional parameters and pain scales were also examined.

Results: The patients with FM exhibited enhanced FA, reduced MD, RD, and AD in numerous white matter tracts, including the corpus callosum, corona radiata, internal capsule, corticospinal tract, posterior thalamic radiation, cerebellar peduncle, sagittal stratum, and superior fronto-occipital fasciculus. When depression and anxiety were added as covariates, most between-group diffusional difference disappeared except for AD reduction in the corona radiate, internal capsule, and cerebellar peduncle ($P < 0.05$, threshold-free cluster enhancement corrected). The diffusion tensor imaging measures were not correlated with clinical variables.

Limitation: A relatively small sample size.

Conclusion: Our results demonstrate that disrupted white matter microstructure in patients with FM is mainly restricted to tracts associated with pain sensory processing and motor control, adjusting for psychosocial factors. A considerable degree of difference in white matter characteristics may be explained by the patients with FM group's greater level of psychological distress.

Key words: Fibromyalgia, diffusion tensor imaging, tract-based spatial statistics, white matter microstructure, psychological factors

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Fibromyalgia (FM) is a chronic pain syndrome that affects a broad range of soft tissues. The prevalence of the pain syndrome varies from 2% to 8% in the general population (1). Patients with FM also typically suffer from affective symptoms such as anxiety and depression (2,3). Unfortunately, there are few efficient and satisfactory therapies available for FM so far. Therefore, it is imperative to elucidate the neuropathological mechanisms of FM to initiate new therapies.

Available evidence indicates cerebral activation is abnormal during external stimuli in patients with FM (4). Anomalies of functional connectivity at rest, regional cerebral blood flow, gray matter morphology, cortical thickness, and neurotransmitter concentration are also recognized (5-11). These findings indicate that recurrent pain sensation and comorbid conditions might have an effect on the structure, function, and neurotransmitters of the brain in patients with FM.

The cerebral areas do not function individually. They're constantly connected by short- and long-range white matter fiber bundles, thus presenting complex circuits. However, only a few of investigations have focused on the white matter property in those with FM. Lutz et al (12) reported higher fractional anisotropy (FA) in the amygdala, hippocampus and lower FA in the thalamus, thalamocortical tract, and the insular cortex in patients with FM, whereas a more restricted pattern of white matter alterations was reported by Kim et al (13). They observed FA reduction merely in the left body of the corpus callosum.

Overall, these indicate that the association between FM and white matter plasticity is intricate. The disparities may be due to a variety of factors, including demographics (such as onset of age), types or location of pain, pain severity, illness duration, or treatment. Furthermore, the presence of depression and anxiety in patients with FM leads to the emergence of more physical symptoms as well as a lowered quality of life. Increasing evidence has demonstrated that comorbid anxiety, as well as depressive disorders, are related to the brain's functional and morphological aberrations. Hence, there is an ongoing demand for investigations regarding psychosocial factors to identify white matter tracts involved in FM.

Thus, the present research was designed to analyze the white matter characteristics of patients with FM while considering the effects of psychosocial factors. Our hypothesis was that the presence of comorbid anxiety and depression would have an effect on white matter architecture in patients with FM.

Methods

Data Source

Demographic, clinical and neuroimaging data of 20 patients with FM and 20 individuals who did not have FM, hereafter called healthy controls (HC), were collected from a public dataset via OpenNeuro (https://www.openneuro.org/; accession number: ds001928). The details of the inclusion and exclusion criteria for these patients can be found in the Pando-Naude et al's study (14). We followed OpenNeuro's data use agreement regulations, which are indicated in this paper. Magnetic resonance imaging (MRI) scans and data collection were conducted in the Institute of Neurobiology, National Autonomous University of Mexico in accordance with the Declaration of Helsinki. All patients gave verbal consent and signed a written form before data collection, MRI scans, and data upload to the dataset.

On the day of the scan, patients with FM had not taken any pain medication. HC were screened to ensure that none of them experienced any pain conditions. Before the MRI scanning, all participants completed questionnaires including the Visual Analog Scale (VAS), Pain Self-Perception Scale, Pain Catastrophizing Scale, Center for Epidemiologic Studies Depression Scale , and State-Trait Anxiety Inventory . These questionnaires were designed to assess symptoms rather than to make a clinical diagnosis.

MRI Acquisition

Patients with FM and HC were scanned using a 3.0 Tesla scanner with a 32-channel head coil (General Electric Medical Systems). Fast spoiled gradient echo (FSPGR) BRAVO pulse sequence was used to acquire high-resolution T1-weighted anatomical images: plane orientation, sagittal; repetition time, 7.7 milliseconds; echo time, 3.2 milliseconds; flip angle, 12°; acquisition matrix, 256 X 256; field of view, 256 mm X 256 mm; thickness, one mm; gap, 0 mm.

Diffusion tensor imaging (DTI) scans were performed using a single-shot echo planar imaging sequence with high angular diffusion imaging. The diffusion sensitizing gradients were applied in 60 non-collinear directions ($b = 1{,}000$ s/mm^2) in conjunction with 4 diffusion-weighted acquisition (b0). Sixty consecutive axial slices with a slice thickness of 2 mm and no gap were obtained. Parameters for the sequence were: repetition time, 7000 milliseconds; echo time, 80 milliseconds; flip angle, 90°; acquisition matrix, 224 X 224; FOV, 256 mm X 256 mm.

Image Processing

The DTI data preprocessing and analysis were performed utilizing PANDA (15), mainly consisting of 3 steps: 1) strip skull: executing brain extraction and creating brain mask; 2) eddy current and motion artifact correction: co-registering each diffusion-weighted image to the b = 0 image by applying affine alignment; 3) tensor calculation: computing tensor matrix and yielding diffusion metrics of each individual, including FA, and mean, radial, and axial diffusivity (MD, RD, AD).

Tract-based spatial statistics (TBSS) analyses were performed according to the standardized pipeline. Briefly, FA data of all participants were aligned to the FMRIB58_FA target image using the nonlinear registration program FNIRT, which utilizes a b-spline representation of the registration warp field, and then transformed into the Montreal Neurologic Institute 152 standard space. After that, a mean FA skeleton depicting the centers of all white matter tracts shared by the group was generated and thinned to 0.2 to restrict the analysis to white matter voxels. Each participant's aligned FA data were then projected onto an FA skeleton. The obtained dataset was then subjected to voxel-wise permutation analysis. The same procedure was conducted for processing of MD, RD and AD.

Statistical Analysis

The age, pain score, anxiety, and depression differences across groups were determined using 2-sample t tests. For statistical analysis on white matter property, we utilized the randomize tool for nonparametric permutation inferences (5,000 permutations). Multiple comparisons were carried out utilizing threshold-free cluster enhancement correction ($P < 0.05$). First, age was introduced to the statistical model as a covariate. Second, anxiety, depression, and age were included as confounding factors. The Johns Hopkins University ICBM-DTI-81 White-Matter Labeled Atlas was used to identify the anatomical locations of white matter areas that were statistically significant. Only clusters exceeding 20 voxels per white matter region were reported.

The regions that exhibited significant between–group differences in DTI indices in the second model were defined as regions of interest. The mean values of regions of interest of each participant were extracted for subsequent analysis. Correlation analyses were conducted to investigate the potential associations between clinical profiles (such as the duration of disease, VAS scores, and pain catastrophizing scale) and DTI indices.

Results

Table 1 contains participants' demographic and clinical profiles. All participants were women. Age differences across groups were not significant ($P = 0.28$). The mean illness duration of patients with FM was 5.2 ± 5.1 years. The patients with FM who experienced severe pain in the week before their MRI scan had a mean VAS score of 7.2 ± 1.6. When compared with HC, they reported higher scores of pain catastrophizing (56.1 ± 28.7 vs 17.6 ± 23.7, $P < 0.001$), pain self-perception (27.6 ± 12.5 vs 12.0 ± 10.9, $P < 0.001$), anxious and depressive symptoms (52.8 ± 20.1 vs 26.1 ± 10.7, $P < 0.001$; 31.0 ± 13.7 vs 11.0 ± 8.6, $P < 0.001$, respectively). These findings are consistent with previous studies.

In patients with FM, TBSS analysis, controlled for age, identified enhanced FA and reduced MD, RD and AD in numerous cerebral areas when compared to HC ($P < 0.05$, corrected, Fig. 1). No brain regions exhibited reduced FA, or enhanced MD, AD or RD in patients with FM ($P > 0.05$, threshold-free cluster enhancement correction corrected). Table 2 summarizes detailed white matter tracts information (cluster sizes > 20 voxels) where FA, MD, RD, and AD showed significant variations across groups.

Furthermore, a TBSS study included anxiety, depression, and age as covariates. As shown in Fig. 1, when anxiety and depression were taken into account, the differences between patients with FM and HC regarding FA, MD, and RD were no longer present. The effect of psychological disorders on AD in patients with FM was primarily detected in the left cerebral white matter tract. In AD, differences

Table 1. *Demographic and clinical characteristics.*

	FM (n = 20)	HC (n =20)	*P* value
Age	46.4 ± 12.4	42.1 ± 12.5	0.28
Disease duration (years)	5.2 ± 5.1	-	-
VAS	7.2 ± 1.6	-	-
PCS	27.6 ± 12.5	12.0 ± 10.9	< 0.001
PSP	56.1 ± 28.7	17.6 ± 23.7	< 0.001
STAI	52.8 ± 20.1	26.1 ± 10.7	< 0.001
CES-D	31 ± 13.7	11.0 ± 8.6	< 0.001

FM, fibromyalgia; HC, healthy control; VAS, visual analog scale; PCS, pain catastrophizing scale; PSP, pain self-perception; STAI, state-trait anxiety inventory; CES-D, Center for Epidemiologic Studies Depression Scale.

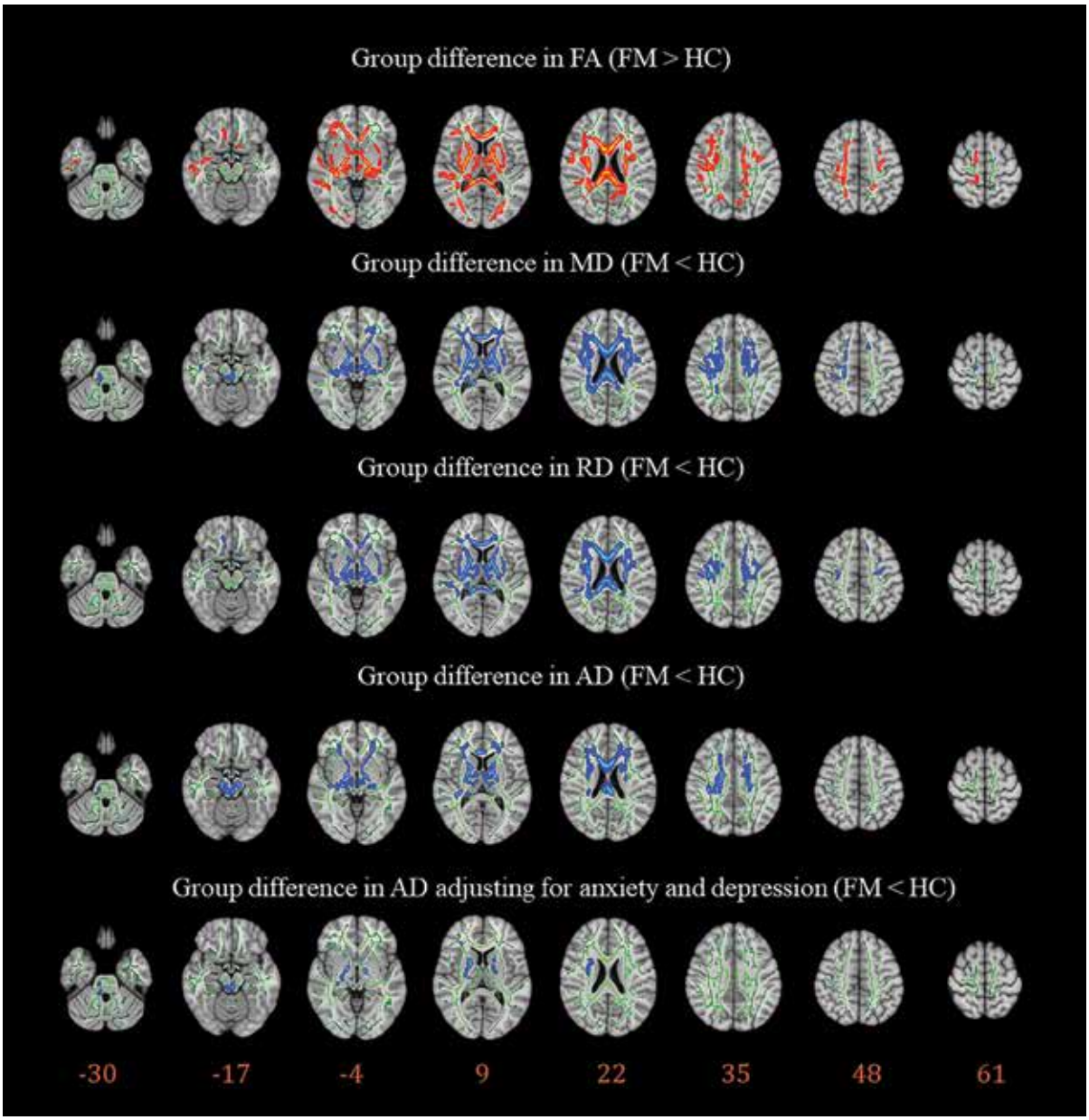

Fig. 1. *Tract-based spatial statistics (TBSS) findings with the inclusion of age as covariate. The images show white matter areas where patients with FM had higher fractional anisotropy (FA) (first row, red – yellow), lower mean diffusivity (MD) (second row, blue – light blue), lower radial diffusivity (RD) (third row, blue – light blue), and lower axial diffusivity (AD) (fourth row, blue – light blue) than healthy controls (HC). TBSS findings adjusting for age, anxiety and depression. The images show white matter tracts where patients with FM had lower AD in (fifth row, blue – light blue) than HC. The slices were overlaid on the Montreal Neurological Institute (MNI) 152 standard T1 image. White matter skeleton is shown in green. To make it easier to visualize the results, the image was thickened using the "tbss_fill" command. All images are in accordance with radiological convention. The numbers at the bottom indicate the MNI coordinates of the slices.*

between groups vanished mostly in the corpus callosum (body, genu, and splenium), left retrolenticular part of internal capsule, left anterior, superior corona radiata, and bilateral posterior corona radiate (Fig. 1 and Table 3).

There was no correlation detected between the

clinical factors and any of the DTI measurements after adjusting for age and psychological distress.

Discussion

In the present investigation, we reveal the white matter microstructural anomalies in patients with FM patients relative to HC. FA increment and MD, RD, and AD reduction were observed in widespread brain white matter tracts in FM sufferers. Specifically, the white matter bundles predominately involved in pain perception and motor control exhibited significant differences between patients with FM and HC when corrected for age, anxiety, and depression severity levels. Our results suggest that psychosocial variables have a significant effect on white matter properties in patients with FM.

Our finding of enhanced FA coupled with lower MD, RD and AD in patients with FM is inconsistent with a prior TBSS study that reported patients with FM had an FA reduction in the body subregions of the corpus callosum (13). FA increment and MD, RD, AD reduction

Table 2. *Clusters with significant DTI metrics between 2 groups adjusting for age.*

Feature	Cluster	Tract (s)	*P* value	voxels	X	Y	Z
Higher FA	1	Posterior limb of internal capsule (L)	0.014	24484	55	-19	-32
		Retrolenticular part of internal capsule (L, R)					
		Anterior corona radiata (L, R)					
		Superior corona radiata (L, R)					
		Posterior corona radiata (L, R)					
		Posterior thalamic radiation (R)					
		Sagittal stratum (L, R)					
		External capsule (L, R)					
		Fornix (L, R)					
		Superior longitudinal fasciculus (L, R)					
		Tapetum (R)					
	2	Splenium of corpus callosum					
		Posterior corona radiata (L)					
		Posterior thalamic radiation (L)					
Lower MD	1	Middle cerebellar peduncle	0.013	22112	7	-29	-33
		corpus callosum (genu, body, splenium)					
		Corticospinal tract (R)					
		Medial lemniscus (L, R)					
		Superior cerebellar peduncle (L, R)					
		Superior cerebellar peduncle (L)					
		Cerebral peduncle (L, R)					
		Anterior limb of internal capsule (L, R)					
		Posterior limb of internal capsule (L, R)					
		Retrolenticular part of internal capsule (L, R)					
		Anterior corona radiata (L, R)					
		Superior corona radiata (L, R)					
		Posterior corona radiata (L, R)					
		Posterior thalamic radiation (R)					
		Sagittal stratum (L, R)					
		External capsule (L, R)					
		Fornix (L, R)					
		Superior longitudinal fasciculus (L, R)					
		Superior fronto-occipital fasciculus (L, R)					

Table 2 cont. *Clusters with significant DTI metrics between 2 groups adjusting for age.*

Feature	Cluster	Tract (s)	*P* value	voxels	X	Y	Z
Lower RD	1	Corpus callosum (genu, body)	0.012	18041	6	31	-22
		Cerebral peduncle (L,R)					
		Anterior limb of internal capsule (L, R)					
		Posterior limb of internal capsule (L, R)					
		Retrolenticular part of internal capsule (L, R)					
		Anterior corona radiata (L, R)					
		Superior corona radiata (L, R)					
		Posterior corona radiata (L, R)					
		Sagittal stratum (L, R)					
		External capsule (L, R)					
		Fornix (L, R)					
		Superior longitudinal fasciculus (L, R)					
	2	Corpus callosum (body, splenium)					
		Retrolenticular part of internal capsule (R)					
		Posterior limb of internal capsule (L, R)					
		Posterior corona radiata (R)					
		Superior longitudinal fasciculus (R)					
Lower AD	1	Middle cerebellar peduncle	0.006	12856	9	15	22
		corpus callosum (genu, body, splenium)					
		Corticospinal tract (R)					
		Medial lemniscus (L, R)					
		Superior cerebellar peduncle (L,R)					
		Cerebral peduncle (L,R)					
		Anterior limb of internal capsule (L, R)					
		Posterior limb of internal capsule (L, R)					
		Retrolenticular part of internal capsule (L, R)					
		Anterior corona radiata (L, R)					
		Superior corona radiata (L, R)					
		Posterior corona radiata (L, R)					
		Posterior thalamic radiation (L, R)					
		Sagittal stratum (R)					
		External capsule (L,R)					
		Fornix (R)					
		Superior longitudinal fasciculus (R)					
		Superior fronto-occipital fasciculus (L, R)					
	2	Fornix	0.049	49	24	-33	5

DTI, diffusion tensor imaging; L, left; R, right; FA, fractional anisotropy; MD, mean diffusivity; RD, axial diffusivity; AD, radial diffusivity.

in patients with FM may imply greater packing of myelinated axons, which would prevent diffusion orthogonal to the white matter fibers (16). The denser packing likely stems from 1) a reduction in surrounding tissue, 2) an increase of the fiber diameter, (3) formerly extant white matter fibers with greater directionality (16).

However, inferring underlying histology and pathology from DTI parameters is a difficult task that is now the subject of research. Apart from generalized muscle pain and tenderness, the clinical symptoms of FM are greatly heterogeneous. Although patients' ages, duration of illness, and pain intensity in our study were

Table 3. *Clusters with significant DTI metrics between 2 groups for age and psychological factors.*

Feature	Cluster	Tract (s)	*P* value	voxels	X	Y	Z
Lower AD	1	Cerebral peduncle (R)	0.034	1260	14	-4	-2
		Anterior limb of internal capsule (R)					
		Posterior limb of internal capsule (R)					
		Retrolenticular part of internal capsule (R)					
		Anterior corona radiata (R)					
		Superior corona radiata (R)					
	2	Middle cerebellar peduncle	0.043	595	14	-4	2
		Corticospinal tract (R)					
		Medial lemniscus (R)					
		Medial lemniscus (L)					
		Superior cerebellar peduncle (R)					
		Superior cerebellar peduncle (L)					
		Cerebral peduncle (R)					
	3	Cerebral peduncle (L)	0.041	396	-6	-30	-22
		Anterior limb of internal capsule (L)					
		Posterior limb of internal capsule (L)					

DTI, diffusion tensor imaging; L, left; R, right; AD, radial diffusivity.

similar to Kim's study (13), variances in other comorbid symptoms such as fatigue, sleep disturbances, cognitive impairment, stiffness, anxiety and depression, and medications may account for the disparities in the TBSS results. It is necessary to categorize patients with FM into different subgroups, and specify the white matter anomalies in a subgroup analysis in the future.

The biological interpretation of diffusion characteristics remains a mystery, and therefore our results must be cautiously interpreted. The decreased AD, as Winklewski et al (17)observed, is a symptom of demyelination. Nonetheless, based on murine studies, Alexander and coworkers (18) suggested that rather than demyelination, lower AD is related to axonal damage. Sun and colleagues (19) found connections between dropped AD values and axonal degeneration, as well as between elevated RD values and myelin injury, which were corroborated using immunohistochemistry. In a human study, Pierpaoli and co-workers (20) demonstrated a reduction in AD in initial lesions and areas with subsequent white matter degeneration. This axonal loss concept is also implicated in migraine and Alzheimer disease (21,22). Given all of that, AD reduction is likely an available biomarker for axonal loss. This also suggests that FM is characterized by an extensive loss of axonal integrity.

Adjusting for psychological factors, group variations in FA, MD and RD were not found. White matter tracts with different AD across groups are mostly linked to pain processing and motor control. Our results demonstrate that most of the variation in the white matter architecture resulted from a greater degree of psychological distress in patients with FM. In our study we show that comorbid anxiety and depression symptoms have an effect on white matter architecture; this is consistent with results from earlier studies (23). We speculate that comorbid anxiety and depression, coupled with pain, is likely to recruit extra cerebral resources to enhance mission performance and strengthen pain-related mental imagery on the basis of repeated pain sensations, increasing the likelihood of FM chronification.

Patients with FM exhibited anomalies in the internal capsule. The internal capsule comprises axonal fibers linking the cortical cortex to the thalamus and the spinal cord. The anterior limbs of the internal capsule include fiber bundles that connect the prefrontal cortex and medial thalamus, a tract that presumably participates in the cognitive and attentional elements of pain perception processing (24). The ascending somatosensory and descending motor information is conveyed through the posterior limb of the internal capsule (25). This reduction in AD of the internal capsule might be related to aberrant somatosensory input processing or reduced physical exercise.

Corticospinal tracts, anterior corona radiata, and cerebral peduncles are not involved in pain perception processing. Generally, these tracts are thought to communicate motor-related information. Excessive exercise or a rapid increase in physical activity usually results

in pain exacerbation in patients with FM. Thus, it is probable that patients with FM acquire an aversion to physical exertion and subsequent avoidance behavior (26). The alterations in those white matter tracts may be indicative of pain-related behavioral changes, such as a reduction in physical activity.

Limitations

Numerous limitations should be mentioned with regard to our research. Firstly, the number enrolled in our study was relatively small; this might reduce the power of statistical significance. Secondly, since only women with FM were recruited, our results can't be generalizable to the whole FM population. Further studies with larger patient cohorts, including male patients, are required to validate these findings.

Conclusion

Our findings demonstrate the disrupted white matter microstructure in patients with FM is mainly restricted to tracts involved in pain sensory processing and motor control. Adjusting for psychosocial factors, the majority of the variance in white matter characteristics may be explained by patients with FM having a greater degree of psychological distress. These findings may help us get a better grasp of the pathogenesis of FM.

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