

An Imaging-Based Investigation of the Potential Relationship Between Trigeminal Nerve Microstructure, Paranasal Sinus Volumes, and Headache in Fibromyalgia

Ahmet Payas,¹ Fatih Çiçek,² Turgut Seber,³ Fatma Gül Ülkü Demir,⁴
Mesut Kara,⁵ İlyas Uçar⁶

¹Department of Anatomy, Amasya University, Faculty of Medicine, Amasya, Türkiye

²Department of Anatomy, Niğde Ömer Halisdemir University, Faculty of Medicine, Niğde, Türkiye

³Department of Radiology, Kayseri City Hospital, Kayseri, Türkiye

⁴Department of Physical Medicine and Rehabilitation, Kayseri City Hospital, Kayseri, Türkiye

⁵Department of Child Health and Diseases, Erciyes University, Faculty of Medicine, Kayseri, Türkiye

⁶Department of Anatomy, Erciyes University, Faculty of Medicine, Kayseri, Türkiye



Cite this article as:

Payas A, Çiçek F, Seber T, Ülkü Demir FG, Kara M, Uçar İ. An Imaging-Based Investigation of the Potential Relationship Between Trigeminal Nerve Microstructure, Paranasal Sinus Volumes, and Headache in Fibromyalgia. J Clin Pract Res 2025;47(6):0–0.

Address for correspondence:

İlyas Uçar.
Department of Anatomy, Erciyes University, Faculty of Medicine, Kayseri

Phone: +90 544 203 67 11

E-mail: ilyas.ucar@erciyes.edu.tr

Submitted: 20.06.2025

Revised: 31.10.2025

Accepted: 03.11.2025

Available Online: 21.11.2025

Erciyes University Faculty of
Medicine Publications -
Available online at www.jcprres.com

ABSTRACT

Objective: Fibromyalgia is a chronic syndrome characterized by widespread pain, fatigue, and cognitive and sleep impairments. Headache, which is highly prevalent in fibromyalgia, substantially reduces quality of life. This study aimed to investigate whether morphological features of the paranasal sinuses or microstructural alterations of the trigeminal nerve contribute to headache pathophysiology in fibromyalgia.

Materials and Methods: Twenty-five female patients with fibromyalgia and twenty-six healthy women were included. Tractographic analysis of bilateral trigeminal nerves was performed using diffusion tensor imaging (DTI), with parameters including fiber number, mean fiber length, and fractional anisotropy (FA). Paranasal sinus volumes were calculated using 3D Slicer software.

Results: No significant group differences were found in age, Body Mass Index (BMI), or paranasal sinus volumes ($p>0.05$). However, fiber number, mean fiber length, and FA values of both trigeminal nerves were significantly higher in the fibromyalgia group than in controls ($p<0.001$).

Conclusion: These findings suggest that structural alterations of the trigeminal nerve, rather than sinus anatomy, may underlie headache in fibromyalgia and could partly explain the high prevalence of migraine-like symptoms in this population.

Keywords: Diffusion tensor imaging, fibromyalgia, headache, paranasal sinus, trigeminal nerve.

INTRODUCTION

Fibromyalgia is a multifactorial syndrome affecting about 2.7% of the global population. It is characterized by chronic pain not explained by peripheral causes.^{1,2} In addition to persistent pain, patients commonly experience fatigue, sleep disturbances, cognitive dysfunction, and mood



alterations.^{3,4} Migraine and tension-type headaches are reported in approximately 70% of individuals with fibromyalgia.⁵ Among the underlying mechanisms of headache in fibromyalgia, increased central nervous system (CNS) sensitivity, also known as central sensitization, plays a significant role. Structural changes in gray matter volume have been identified in brain regions such as the primary and secondary somatosensory areas, anterior cingulate cortex, cerebellum, prefrontal cortex, and insula.^{6,7} In individuals with fibromyalgia, normally non-painful stimuli can elicit pain (allodynia), and there may be an exaggerated response to painful stimuli (hyperalgesia), which is believed to be linked to enhanced central sensitization.⁸

Both neurotransmitters and the peripheral nervous system play critical roles in the transmission of pain to the CNS. In this context, nitric oxide (NO) is a particularly noteworthy neurotransmitter. NO is synthesized in especially high concentrations in the epithelial cells of the paranasal sinuses.⁹ NO may enhance trigeminal nerve excitability through positive feedback in the trigeminovascular system, contributing to headache. Moreover, a direct relationship between NO production and paranasal sinus volume has been demonstrated.^{10,11}

The trigeminal nerve, a component of the peripheral nervous system, plays a central role in transmitting pain signals from the orofacial skin and meninges to the CNS. It conveys these signals via its three main branches (the ophthalmic, maxillary, and mandibular divisions) to the trigeminal ganglion, and from there to the spinal trigeminal nucleus and the ventral posteromedial nucleus of the thalamus. Pain is ultimately perceived and processed in the postcentral gyrus.¹²⁻¹⁴

In this study, we investigated the potential relationship between the morphological structure of the paranasal sinuses, where NO is abundantly synthesized, and the microarchitecture of the trigeminal nerve in the pathophysiology of headache among individuals with fibromyalgia. To this end, diffusion tensor imaging (DTI) was used to perform tractographic analysis of the trigeminal nerve, allowing for the evaluation of microstructural changes in the peripheral nervous system of fibromyalgia patients. Additionally, paranasal sinus volumes, known to be associated with NO production, were measured using magnetic resonance imaging (MRI), and the results were compared with those of healthy controls.

MATERIALS AND METHODS

Ethical approval for this single-center, cross-sectional cohort study was granted by Niğde Ömer Halisdemir University Non-Interventional Clinical Research Ethics Committee (approval number: 2024/18, date: 27.02.2024) in full compliance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment.

KEY MESSAGES

- Fibromyalgia causes structural changes in the peripheral nervous system.
- The trigeminal nerve may be involved in the migraine headache that occurs in fibromyalgia.
- The symptoms of fibromyalgia should be evaluated not only rheumatologically but also neurologically.

Fibromyalgia group (n=25): Twenty-five female patients diagnosed between January 2024 and December 2024 according to the 2016 fibromyalgia diagnostic criteria of the American College of Rheumatology were included.

Control Group (n=26): Twenty-six asymptomatic female volunteers without a diagnosis of fibromyalgia, neurological disease, or chronic pain condition were recruited.

Exclusion Criteria

Participants were excluded if they had a history of chronic systemic disease; inflammatory rheumatologic disorders (e.g., rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus); schizophrenia, malignancy, or other autoimmune conditions; pregnancy or lactation; chronic use of tobacco, alcohol, or illicit drugs; any chronic disease requiring neurological or psychiatric medication; any psychiatric disorder or mental health problem; depression or sleep disorders; or active smoking. These exclusion criteria were selected to minimize potential confounders that could influence nitric oxide levels or brain microstructure.

None of the participants in the fibromyalgia group had a comorbid diagnosis of trigeminal neuralgia, nor did they report a history of interventional procedures such as radiofrequency ablation, nerve blocks, or related surgeries. Furthermore, patients using medications for trigeminal neuralgia were excluded to avoid potential confounding effects on trigeminal microstructural measures.

The sample size was determined by the number of eligible participants presenting during the study period who met the above criteria, as no a priori power analysis was performed. A post hoc sensitivity analysis was later conducted to assess the adequacy of statistical power, and estimates for future studies were provided.

Image Acquisition

Imaging data were acquired using a Magnetom Skyra 3T magnetic resonance imaging system (Siemens, Erlangen, Germany). T1-weighted images were acquired in the sagittal plane to evaluate brain anatomical structures and

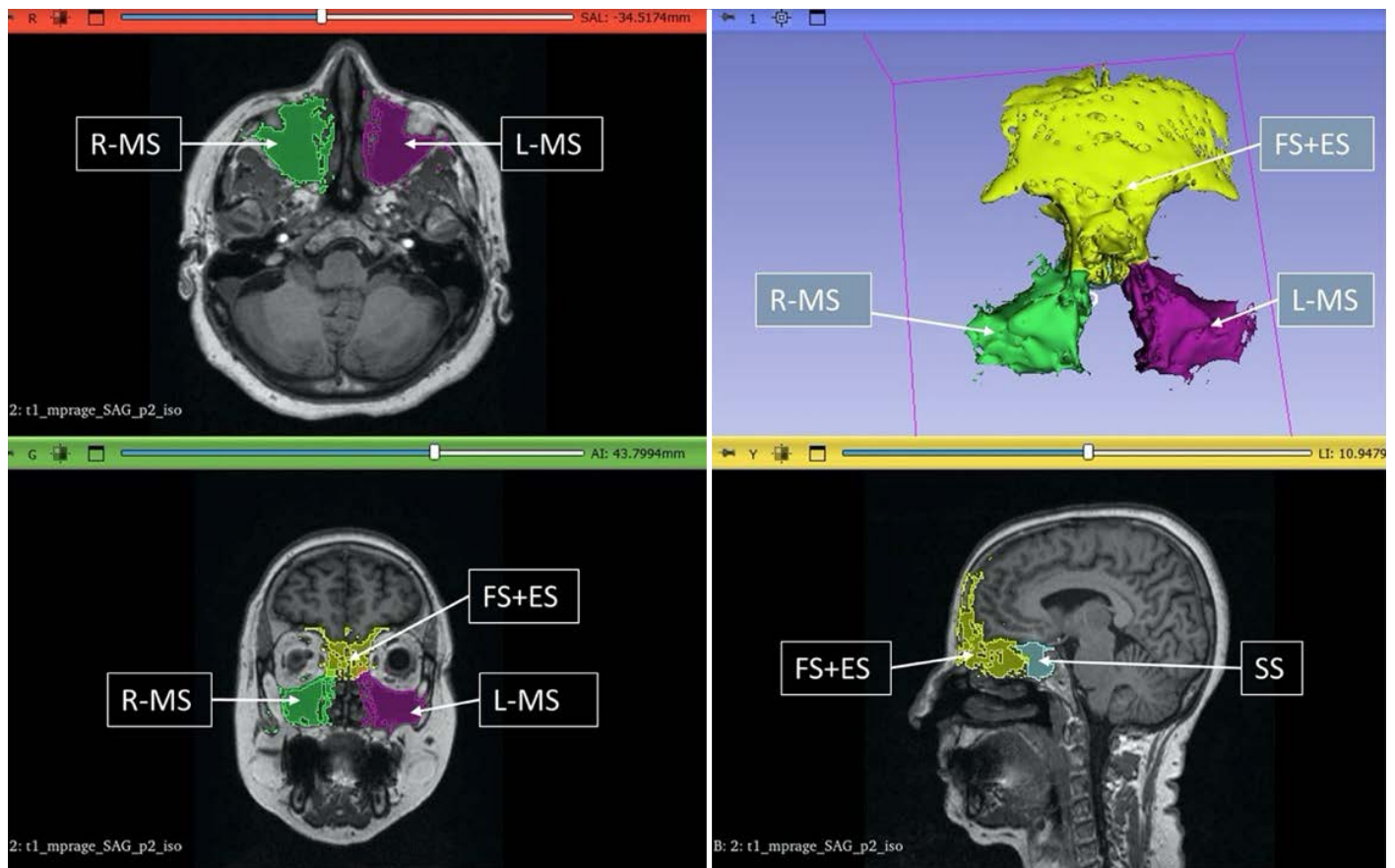


Figure 1. Calculation of paranasal sinus surface area and volume in the 3D Slicer program.

R-MS: Right maxillary sinus; L-MS: Left maxillary sinus; FS+ES: Frontal+Ethmoid sinuses; SS: Sphenoid sinus.

quantitatively measure paranasal sinus volumes. Diffusion tensor imaging data were acquired in the axial plane for tractographic analysis of the trigeminal nerve. Imaging parameters were: repetition time (TR)=4900 ms, echo time (TE)=95 ms, 36 slices, 3.5 mm slice thickness, 128 × 128 matrix, and 230 mm field of view (FOV).

DTI data were obtained using diffusion weights of $b=0$ and $b=1000 \text{ s/mm}^2$, averaged over three signals along 20 different gradient directions. DTI acquisition was performed with 20 diffusion-encoding directions at a b -value of $0,1000 \text{ s/mm}^2$. This protocol was determined by clinical scan-time limitations. Similar approaches have been reported in previous studies of small cranial nerves, including the trigeminal nerve.¹⁵

Data Processing

In this study, paranasal sinus volume calculation was performed using the semi-automatic feature of the 3D Slicer program. After the brain MRI images of the participants were loaded into the 3D Slicer program, paranasal sinus volume

calculation was initiated using the “Modules,” “Segment Editor,” and “Segmentation” tabs, respectively. Then, the “Threshold” was set on the “Threshold Range” tab, and the raw image of the paranasal sinuses was obtained using the “Apply” and “Show 3D” tabs, respectively. The anatomical borders of the paranasal sinuses to be measured on this image were checked in the axial, sagittal, and coronal planes. Any excess or deficiency detected in the anatomical borders of the paranasal sinuses was corrected using the “Paint,” “Erase,” and “Scissors” features of the program. The volume of each paranasal sinus was measured in cm^3 using the “Modules” and “Quantification,” respectively (Fig. 1).

Tractography analyses of the trigeminal nerve were performed using DSI Studio software (<http://dsi-studio.labsolver.org/>). Prior to tractography, raw DTI data underwent preprocessing, including skull stripping, eddy current correction, and motion correction using the default affine registration algorithm implemented in DSI Studio, with visual inspection of corrected images to ensure data quality.

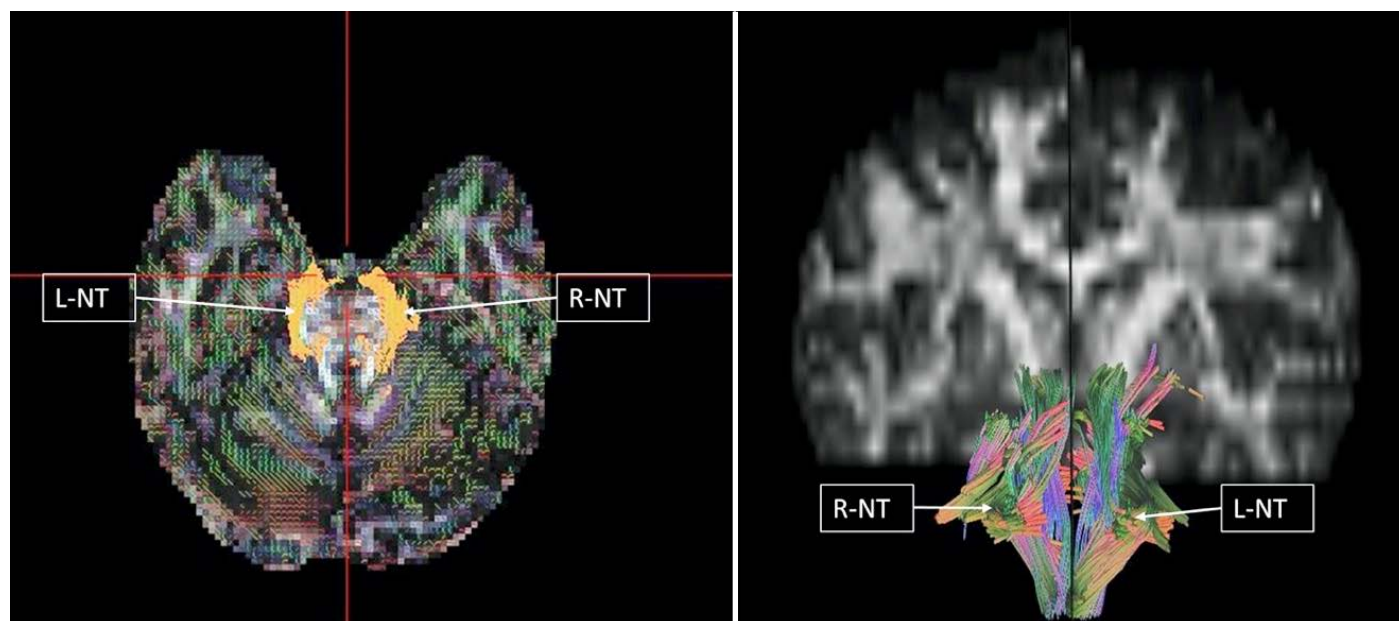


Figure 2. Tractography process of the nervus trigeminus in the DSI Studio program.

R-NT: Right trigeminal nerve; L-NT: Left trigeminal nerve.

Fiber tracking was carried out in the Fiber Tracking module of DSI Studio using a deterministic streamline tracking algorithm. The following parameters were applied uniformly to all participants: FA threshold =0.20, smoothing =0.50, angular threshold =70°, minimum fiber length =10 mm, maximum fiber length =1000 mm, and tracking was terminated at 100,000 reconstructed fibers. Bilateral trigeminal nerves were identified using the tractography atlas in DSI Studio, and region-of-interest (ROI) placement was standardized across participants.

From the reconstructed tracts, the following parameters were extracted for both the right and left trigeminal nerves:

Macrostructural metrics: total fiber count and mean fiber length (mm).

Microstructural metrics: FA, mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD), which provide insights into axonal integrity, conduction properties, and myelination (Fig. 2).

All volumetric and tractographic analyses were independently performed by two experienced evaluators: one anatomist and one neuroradiologist, each with more than 10 years of professional experience. Inter-observer and intra-observer reliability were assessed using intraclass correlation coefficients (ICC), which demonstrated excellent agreement (ICC range: 0.988–0.995). In cases of minor discrepancies, consensus was reached through joint review.

Statistical Analysis

The distribution characteristics of continuous variables were tested using the Shapiro–Wilk test, supplemented by visual inspection of Q–Q plots and histograms. Independent-samples t-tests were used for between-group comparisons. Analyses were performed using IBM SPSS Statistics software (version 22; SPSS Inc., Chicago, IL, USA), and $p < 0.05$ was accepted as the threshold for statistical significance.

To ensure transparency, a footnote was added to Table 1 specifying that all comparisons were conducted using independent-samples t-tests with $\alpha = 0.05$. As no a priori sample size calculation was performed, a post hoc sensitivity analysis was conducted to estimate achieved power and provide recommendations for future studies.

RESULTS

The overall demographic and morphometric characteristics of the study participants are summarized in Table 2. The mean age of all participants was 45.21 ± 9.21 years, with an average Body Mass Index (BMI) of 27.32 ± 4.10 kg/m², indicating a predominantly middle-aged and slightly overweight cohort. Paranasal sinus volumes demonstrated wide interindividual variability, particularly in the maxillary sinuses, where right and left mean volumes were $16.653.93 \pm 5.711.68$ mm³ and $15.719.04 \pm 5.494.56$ mm³, respectively. Among all sinus regions, the ethmoid + frontal complex showed the greatest volumetric range (12,731.60–65,740.20 mm³), reflecting marked anatomical diversity.

Table 1. Comparison of parameters between fibromyalgia and control groups

	Group	N	Mean±SD	Min–Max	p
Age (years)	Fibromyalgia	25	46.80±8.01	24.00–63.00	0.188
	Control	26	43.68±10.13	24.00–68.00	
Height (cm)	Fibromyalgia	25	163.57±8.55	150.00–183.00	0.334
	Control	26	161.58±7.35	146.00–175.00	
Weight (kg)	Fibromyalgia	25	73.27±11.06	53.00–95.00	0.644
	Control	26	71.81±13.33	48.00–103.00	
Body Mass Index (BMI)	Fibromyalgia	25	28.23±3.99	17.41–35.15	0.088
	Control	26	26.43±4.07	18.33–35.38	
Right maxillary sinus (mm ²)	Fibromyalgia	25	7110.95±2239.55	3723.27–13468.00	0.056
	Control	26	6137.35±1617.60	2309.92–8921.76	
Right maxillary sinus (mm ³)	Fibromyalgia	25	18490.22±5936.61	7878.71–34287.00	0.650
	Control	26	14876.88±4954.07	6364.13–25106.50	
Left maxillary sinus (mm ²)	Fibromyalgia	25	6694.23±1963.13	3476.67–11582.90	0.055
	Control	26	5702.29±1994.17	3012.48–13417.30	
Left maxillary sinus (mm ³)	Fibromyalgia	25	16613.87±4947.03	8304.46–29855.20	0.214
	Control	26	14853.09±5928.53	4502.76–27307.80	
Sphenoid sinus (mm ²)	Fibromyalgia	25	4495.53±1028.14	3111.65–7040.64	0.992
	Control	26	4492.72±1159.02	988.13–6564.19	
Sphenoid sinus (mm ³)	Fibromyalgia	25	11828.92±3112.97	5379.17–19198.20	0.991
	Control	26	11838.91±4165.59	1546.75–20978.10	
Ethmoid+frontal sinus (mm ²)	Fibromyalgia	25	21659.75±5057.88	12028.30–31083.80	0.362
	Control	26	19253.55±3617.98	14659.10–30655.40	
Ethmoid+frontal sinus (mm ³)	Fibromyalgia	25	37177.00±12585.19	12731.60–65740.20	0.521
	Control	26	29822.25±6977.95	16804.50–43311.80	
Left trigeminal nerve – number of tracts	Fibromyalgia	25	3971.55±1299.42	1765.00–6418.00	0.025
	Control	26	3679.07±1539.52	1414.00–9510.00	
Left trigeminal nerve – mean length (mm)	Fibromyalgia	25	29.92±5.47	20.45–46.67	0.430
	Control	26	26.85±6.10	18.33–39.53	
Left trigeminal nerve – fractional anisotropy (FA)	Fibromyalgia	25	0.39±0.04	0.31–0.44	0.020
	Control	26	0.37±0.03	0.31–0.45	
Left trigeminal nerve – mean diffusivity (MD)	Fibromyalgia	25	1.39±0.20	1.06–1.84	0.085
	Control	26	1.31±0.15	1.08–1.80	
Left trigeminal nerve – axial diffusivity (AD)	Fibromyalgia	25	1.86±0.21	1.46–2.30	0.140
	Control	26	1.79±0.15	1.57–2.28	
Left trigeminal nerve – radial diffusivity (RD)	Fibromyalgia	25	1.16±0.20	0.86–1.61	0.067
	Control	26	1.07±0.15	0.84–1.57	
Right trigeminal nerve – number of tracts	Fibromyalgia	25	4078.10±1408.53	2005.00–7478.00	0.024
	Control	26	3730.00±861.21	1474.00–5593.00	
Right trigeminal nerve – mean length (mm)	Fibromyalgia	25	32.97±7.00	22.10–51.07	0.295
	Control	26	31.27±5.51	19.59–44.13	
Right trigeminal nerve – fractional anisotropy (FA)	Fibromyalgia	25	0.42±0.03	0.33–0.45	0.040
	Control	26	0.40±0.04	0.31–0.47	
Right trigeminal nerve – mean diffusivity (MD)	Fibromyalgia	25	1.24±0.13	1.05–1.65	0.969
	Control	26	1.24±0.13	0.98–1.58	
Right trigeminal nerve – axial diffusivity (AD)	Fibromyalgia	25	1.71±0.14	1.48–2.14	0.511
	Control	26	1.73±0.13	1.49–2.02	
Right trigeminal nerve – radial diffusivity (RD)	Fibromyalgia	25	1.00±0.13	0.83–1.41	0.779
	Control	26	0.99±0.14	0.73–1.37	

SD: Standard deviation; Min: Minimum; Max: Maximum. All between-group comparisons were conducted using independent-samples t-tests; statistical significance was set at $p<0.05$.

Table 2. Descriptive statistics of the measured parameters

	N	Mean±SD	Min–Max
Age (years)	51	45.21±9.21	24.00–68.00
Height (cm)	51	162.56±7.96	146.00–183.00
Weight (kg)	51	72.52±12.18	48.00–103.00
Body Mass Index (BMI)	51	27.32±4.10	17.41–35.38
Right maxillary sinus (mm ²)	51	6616.17±1993.33	2309.92–13468.00
Right maxillary sinus (mm ³)	51	16653.93±5711.68	6364.13–34287.00
Left maxillary sinus (mm ²)	51	6190.13±2025.11	3012.48–13417.00
Left maxillary sinus (mm ³)	51	15719.04±5494.56	4502.76–29855.20
Sphenoid sinus (mm ²)	51	4494.10±1087.47	988.13–7040.64
Sphenoid sinus (mm ³)	51	11833.99±3655.12	1546.75–20978.10
Ethmoid+frontal sinus (mm ²)	51	20436.93±4514.51	12028.30–31083.80
Ethmoid+frontal sinus (mm ³)	51	33439.34±10707.21	12731.60–65740.20
Left trigeminal nerve – number of tracts	51	3827.70±1418.29	1414.00–9510.00
Left trigeminal nerve – mean length (mm)	51	28.41±5.94	18.33–46.67
Left trigeminal nerve – fractional anisotropy (FA)	51	0.38±0.04	0.31–0.45
Left trigeminal nerve – mean diffusivity (MD)	51	1.35±0.18	1.06–1.84
Left trigeminal nerve – axial diffusivity (AD)	51	1.83±0.18	1.46–2.30
Left trigeminal nerve – radial diffusivity (RD)	51	1.11±0.18	0.84–1.61
Right trigeminal nerve – number of tracts	51	3901.20±1166.43	1474.00–7478.00
Right trigeminal nerve – mean length (mm)	51	32.11±6.30	19.59–51.07
Right trigeminal nerve – fractional anisotropy (FA)	51	0.41±0.03	0.31–0.47
Right trigeminal nerve – mean diffusivity (MD)	51	1.24±0.13	0.98–1.65
Right trigeminal nerve – axial diffusivity (AD)	51	1.72±0.14	1.48–2.14
Right trigeminal nerve – radial diffusivity (RD)	51	0.99±0.13	0.73–1.41

SD: Standard deviation; Min: Minimum; Max: Maximum.

Regarding trigeminal nerve tractography, the left nerve exhibited a mean tract count of $3.827.70 \pm 1.418.29$ with an average fiber length of 28.41 ± 5.94 mm, while the right nerve showed slightly higher tract numbers ($3.901.20 \pm 1.166.43$) and longer fibers (32.11 ± 6.30 mm). Fractional anisotropy values were generally consistent between hemispheres (left= 0.38 ± 0.04 ; right= 0.41 ± 0.03), and diffusivity parameters (MD, AD, RD) remained within normal physiological ranges, suggesting preserved microstructural integrity across participants (Table 2).

When the demographic characteristics of the groups were compared, the mean age was 46.80 ± 8.01 years and the mean Body Mass Index was 28.23 ± 3.99 in the fibromyalgia group, while in the control group the mean age was 43.68 ± 10.13 years and the mean BMI was 26.43 ± 4.07 . These differences were not statistically significant ($p > 0.05$) (Table 1).

Similarly, volumetric analysis of the paranasal sinuses (maxillary, sphenoid, ethmoid + frontal) did not show any significant differences between the fibromyalgia and control groups (all $p > 0.05$) (Table 1).

In contrast, tractography analysis of the trigeminal nerve revealed significant group differences. The fibromyalgia group showed a higher number of tracts in both the left ($3.971.55 \pm 1.299.42$ vs. $3.679.07 \pm 1.539.52$, $p = 0.025$) and right trigeminal nerves ($4.078.10 \pm 1.408.53$ vs. $3.730.00 \pm 861.21$, $p = 0.024$). Fractional anisotropy values were also significantly higher in patients with fibromyalgia compared to controls in both the left (0.39 ± 0.04 vs. 0.37 ± 0.03 , $p = 0.020$) and right trigeminal nerves (0.42 ± 0.03 vs. 0.40 ± 0.04 , $p = 0.040$). Other diffusion parameters, including mean diffusivity, axial diffusivity, and radial diffusivity, did not differ significantly between the groups ($p > 0.05$) (Table 1).

DISCUSSION

In this study, we investigated whether headache in fibromyalgia is associated with alterations in paranasal sinus morphology or trigeminal nerve microstructure. Our results revealed no significant differences in paranasal sinus volumes between patients and controls but demonstrated significantly higher fiber counts and fractional anisotropy values in the trigeminal nerves of fibromyalgia patients. These findings suggest that headache in fibromyalgia may be more strongly related to peripheral nerve sensitization than to sinus anatomy.

Our observation of increased FA values in the trigeminal nerve is particularly noteworthy. FA is widely regarded as an indicator of axonal integrity and myelination.^{16,17} The higher FA values and fiber counts in our study may reflect structural reorganization or hyperactivity of the trigeminal system. Previous studies have reported that actively engaged neural pathways often display higher fiber density and FA, reflecting enhanced functional connectivity.¹⁸ In the context of fibromyalgia, this may be interpreted as a compensatory or maladaptive response of the trigeminal nerve to persistent nociceptive input, consistent with the theory of central sensitization.^{6,7}

Although an increase in FA reflects heightened neural activity or structural reorganization, DTI metrics can also be influenced by methodological factors such as crossing fibers or an insufficient number of diffusion directions. For example, reports of decreased FA in some chronic pain studies suggest that directional differences may be related to patient characteristics, disease stage, or methodological factors such as the number of diffusion directions used. Our protocol, which included 20 diffusion-encoding directions, was determined by clinical scan-time constraints and is consistent with previous studies on small cranial nerves such as the trigeminal nerve.

Our findings are also consistent with neuroimaging studies demonstrating microstructural alterations in chronic pain conditions. DTI studies in trigeminal neuralgia and migraine have reported elevated FA in trigeminal pathways, suggesting maladaptive reorganization or hyperexcitability of the nerve.^{15,19} Similarly, structural and functional MRI studies in fibromyalgia have revealed widespread brain alterations associated with central sensitization.^{6,7,20} Our results extend these observations by highlighting the trigeminal nerve itself as a site of measurable structural change. In contrast, some studies have reported reduced FA in chronic pain populations,²¹ suggesting that directional differences may depend on patient characteristics, disease stage, or methodological factors such as the number of diffusion directions used.

The clinical importance of these changes is underscored by studies showing that trigeminal nerve stimulation can alleviate pain and depressive symptoms in fibromyalgia patients.²² Moreover, the trigeminal system plays a central role in migraine pathophysiology, transmitting nociceptive signals from meningeal and vascular structures to the CNS.^{13,19} Our findings of increased FA and fiber counts provide neuroanatomical evidence supporting the high prevalence of migraine-like headaches in fibromyalgia populations.^{23,24} Recent imaging studies further highlight widespread brain alterations in fibromyalgia,²⁰ suggesting that peripheral and central mechanisms interact to exacerbate symptom severity. Headaches in fibromyalgia are often associated with migraine-like symptoms. These structural changes in the trigeminal nerve (high FA and fiber counts) suggest increased excitability of the trigeminocervical system, which is strongly linked to headache biology via trigeminal neurogenic inflammation. Therefore, our findings provide a neuroanatomical basis explaining the high prevalence of migraine-like symptoms in the fibromyalgia population, even if there is no direct correlation with headache severity or frequency.

Although nitric oxide synthesized in the paranasal sinuses has been proposed as a modulator of trigeminal excitability,^{25,26} we found no group differences in sinus volumes. This finding agrees with MRI studies showing no link between paranasal sinus size and headache prevalence in large cohorts.⁹ Thus, structural sinus variations are unlikely to play a major role in fibromyalgia-related headaches. Instead, our results highlight trigeminal nerve alterations as a more direct contributor, consistent with emerging evidence linking trigeminal neurogenic inflammation to headache biology.²⁷

Taken together, these findings support the view that fibromyalgia should not only be conceptualized as a rheumatological disorder but also as a condition involving measurable neural alterations. Structural changes in the trigeminal nerve support evidence of central sensitization and suggest that peripheral and central mechanisms act together in symptom generation. Future studies should combine tractography with biochemical markers such as NO levels and detailed clinical measures of headache severity, and explore neuromodulatory approaches like trigeminal nerve stimulation, which may hold therapeutic potential in this patient population.²⁸

Clinical Implications

Our results suggest that trigeminal nerve microstructural alterations may serve as potential imaging biomarkers for identifying fibromyalgia patients at increased risk of severe or migraine-like headaches. Recognizing these changes may encourage clinicians to integrate neuroimaging into

the diagnostic work-up of complex cases and to consider treatment approaches beyond standard pharmacotherapy. In particular, neuromodulatory strategies targeting the trigeminal system, such as transcutaneous stimulation or anti-calcitonin gene-related peptide (anti-CGRP) therapies represent promising therapeutic avenues. By highlighting the contribution of peripheral neural mechanisms, this study supports a more integrative management strategy that combines rheumatological and neurological perspectives.

Limitations

This study has several limitations. First, NO levels were not measured biochemically, limiting interpretation of the relationship between paranasal anatomy and NO-mediated trigeminal excitability. Second, the cross-sectional design prevents causal inference; whether trigeminal alterations are a cause or consequence of fibromyalgia remains unclear. Third, the sample included only female patients, which improves homogeneity but limits generalizability. Fourth, the relatively small sample size and absence of an a priori power calculation reduce statistical robustness. Finally, clinical variables such as headache frequency, pain severity, and quality of life were not directly correlated with imaging metrics. Future studies should address these limitations through larger, mixed-sex cohorts and integration of neuroimaging with biochemical and clinical measures.

CONCLUSION

Our study revealed no significant differences in paranasal sinus volumes between fibromyalgia patients and healthy controls but demonstrated significant alterations in trigeminal nerve parameters, including FA and fiber counts. These findings suggest that peripheral nerve dysfunction, rather than sinus anatomy, may play a more prominent role in the pathogenesis of headache in fibromyalgia. This study emphasizes the trigeminal system's role and highlights the importance of evaluating peripheral neural mechanisms in fibromyalgia-related headaches.

Ethics Committee Approval: The Niğde Ömer Halisdemir University Non-Interventional Clinical Research Ethics Committee granted approval for this study (date: 27.02.2024, number: 2024/18).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Use of AI for Writing Assistance: The use of AI-assisted tools were not declared by the authors.

Author Contributions: Concept – A.P., İ.U.; Design – A.P., F.Ç., İ.U.; Supervision – A.P., İ.U.; Materials – T.S., F.G.Ü.D.; Data Collection and/or Processing – T.S., F.G.Ü.D.; Analysis and/or Interpretation – F.Ç., İ.U.; Literature Review – A.P., F.Ç., M.K., İ.U.; Writing – A.P., F.Ç., İ.U.; Critical Review – A.P., F.Ç., T.S., F.G.Ü.D., M.K., İ.U.

Peer-review: Externally peer-reviewed.

REFERENCES

- Macfarlane GJ, Kronisch C, Dean LE, Atzeni F, Häuser W, Fluß E, et al. EULAR revised recommendations for the management of fibromyalgia. *Ann Rheum Dis* 2017;76(2):318-28. [\[CrossRef\]](#)
- Çiçek F, Uçar İ, Seber T, Ülkü Demir FG, Çiftçi AT. Investigation of the relationship of sleep disorder occurring in fibromyalgia with central nervous system and pineal gland volume. *Acta Neuropsychiatr* 2024;37:e17. [\[CrossRef\]](#)
- Siracusa R, Paola RD, Cuzzocrea S, Impellizzeri D. Fibromyalgia: Pathogenesis, Mechanisms, Diagnosis and Treatment Options Update. *Int J Mol Sci* 2021;22(8):3891. [\[CrossRef\]](#)
- Bhargava J, Goldin J. Fibromyalgia. Treasure Island: StatPearls Publishing; 2025.
- Jurado-Priego LN, Cueto-Ureña C, Ramírez-Expósito MJ, Martínez-Martos JM. Fibromyalgia: A Review of the Pathophysiological Mechanisms and Multidisciplinary Treatment Strategies. *Biomedicine* 2024;12(7):1543. [\[CrossRef\]](#)
- Gao Z, Xie X, Liu F, Xu T, Zhang N, Zhang X, et al. Combined Functional and Structural Imaging of White Matter Reveals Brain Connectivity Alterations in Fibromyalgia Patients. *J Pain Res* 2025;18:3361-70. [\[CrossRef\]](#)
- Xin M, Qu Y, Peng X, Zhu D, Cheng S. A systematic review and meta-analysis of voxel-based morphometric studies of fibromyalgia. *Front Neurosci* 2023;17:1164145. [\[CrossRef\]](#)
- Williams DA. Phenotypic Features of Central Sensitization. *J Appl Biobehav Res* 2018;23(2):e12135. [\[CrossRef\]](#)
- Payas A, Göktürk Ş, Göktürk Y, Koç A, Tokpınar A, Kocaman H. Could There Be a Relationship Between Paranasal Sinus and Migraine Etiology?. *Med Records* 2024;6(3):365-8. [\[CrossRef\]](#)
- Staunton CA, Barrett-Jolley R, Djouhri L, Thippeswamy T. Inducible nitric oxide synthase inhibition by 1400W limits pain hypersensitivity in a neuropathic pain rat model. *Exp Physiol* 2018;103(4):535-44. [\[CrossRef\]](#)
- Badaeva A, Maiolino L, Danilov A, Naprienko M, Danilov A, Jacob UM, et al. Neurogasobiology of migraine: Carbon monoxide, hydrogen sulfide, and nitric oxide as emerging pathophysiological tracers relevant to nociception regulation. *Open Med (Wars)* 2025;20(1):20251201. [\[CrossRef\]](#)

12. Payas A, Çiçek F, Ekinçi Y, Batin S, Göktürk Ş, Göktürk Y, et al. Tractography analysis results of the trigeminal nerve, which contains fibers responsible for proprioception sensation and motor control in Adolescent Idiopathic Scoliosis. *Eur Spine J* 2024;33(12):4702-9. [\[CrossRef\]](#)
13. Terrier LM, Hadjikhani N, Velut S, Magnain C, Amelot A, Bernard F, et al. The trigeminal system: The meningovascular complex- A review. *J Anat* 2021;239(1):1-11. [\[CrossRef\]](#)
14. Liu Q, Fan W, He H, Huang F. The role of peripheral opioid receptors in orofacial pain. *Oral Dis* 2021;27(5):1106-14. [\[CrossRef\]](#)
15. Kumaran SP, Gurram SL, Viswamitra S, Hegde V. Utility of DTI (Diffusion Tensor Imaging) Metrics to Study Microstructural Changes of Trigeminal Nerve in Patients with Trigeminal Neuralgia (TN). *Neurol India* 2022;70(1):270-4. [\[CrossRef\]](#)
16. Payas A, Çiçek F, Seber T, Ülkü Demir FG, Uçar İ. Neuroplasticity in the brain exposed to the same sensory stimulus for long periods: A fibromyalgia study. *Brain Mechanisms* 2025;145-147(6):202507. [\[CrossRef\]](#)
17. Mendez Colmenares A, Prytherch B, Thomas ML, Burzynska AZ. Within-person changes in the aging white matter microstructure and their modifiers: A meta-analysis and systematic review of longitudinal diffusion tensor imaging studies. *Imaging Neurosci (Camb)* 2023;1:imag-1-00045. [\[CrossRef\]](#)
18. Payas A, Batin S, Kurtoğlu E, Arik M, Seber T, Uçar İ, et al. Is the Integration Problem in the Sensorimotor System the Cause of Adolescent Idiopathic Scoliosis? *J Pediatr Orthop* 2023;43(2):e111-9. [\[CrossRef\]](#)
19. Huff T, Weisbrod LJ, Daly DT. *Neuroanatomy, Cranial Nerve 5 (Trigeminal)*. Treasure Island (FL): StatPearls Publishing; 2024.
20. Mosch B, Hagen V, Herpertz S, Diers M. Brain morphometric changes in fibromyalgia and the impact of psychometric and clinical factors: a volumetric and diffusion-tensor imaging study. *Arthritis Res Ther* 2023;25(1):81. Erratum in: *Arthritis Res Ther* 2023;25(1):89. [\[CrossRef\]](#)
21. Agoalikum E, Wu H, Klugah-Brown B, Maes M. Brain structural differences between fibromyalgia patients and healthy control subjects: a source-based morphometric study. *Sci Rep* 2025;15(1):17446. [\[CrossRef\]](#)
22. Powell K, Lin K, Tambo W, Saavedra AP, Sciubba D, Al Abed Y, et al. Trigeminal nerve stimulation: a current state-of-the-art review. *Bioelectron Med* 2023;9(1):30. [\[CrossRef\]](#)
23. Calandre EP, Ordoñez-Carrasco JL, Slim M, Rico-Villademoros F, Garcia-Leiva JM. Comorbidity of migraine and fibromyalgia in patients with cluster headache: psychological burden and healthcare resource utilization. A cross-sectional study. *J Oral Facial Pain Headache* 2024;38(1):32-9.
24. Sarzi-Puttini P, Giorgi V, Marotto D, Atzeni F. Fibromyalgia: an update on clinical characteristics, aetiopathogenesis and treatment. *Nat Rev Rheumatol* 2020;16(11):645-60. [\[CrossRef\]](#)
25. Gupta A, Vejapi M, Knezevic NN. The role of nitric oxide and neuroendocrine system in pain generation. *Mol Cell Endocrinol* 2024;591:112270. [\[CrossRef\]](#)
26. Spector BM, Shusterman DJ, Zhao K. Nasal nitric oxide flux from the paranasal sinuses. *Curr Opin Allergy Clin Immunol* 2023;23(1):22-8. [\[CrossRef\]](#)
27. Song X, Zhu Q, Zhang J, Yang J, Zhang X, Song Q. Trigeminal nerve-driven neurogenic inflammation linking migraine to glioblastoma invasion: a literature review. *Front Immunol* 2025;16:1632154. [\[CrossRef\]](#)
28. de Tommaso M, Scannicchio S, Paparella G, Clemente L, Libro G. Efficacy of monoclonal antibodies against CGRP in migraine patients with fibromyalgia comorbidity: a retrospective monocentric observational study. *J Headache Pain* 2025;26(1):102. [\[CrossRef\]](#)