Research Article

Pamukkale Medical Journal
doi:https://dx.doi.org/10.31362/patd.1462085

Volumetric analysis of pain centers in migraine patients

Migren hastalarında ağrı merkezlerinin volümetrik analizi

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Posted date:31.03.2024 Acceptance date:16.04.2024

Abstract

Purpose: To investigate patterns of abnormalities in pain centers among patients with chronic pain, particularly those with migraines. The study aims to explore the potential correlation with pain duration and migraine types, and to propose new interventions for managing chronic pain.

Materials and methods: Radiologic data of 32 migraine patients and 28 healthy controls underwent three-dimensional iso T1-weighted brain MRI between 2019 and 2023 at our university hospital were examined. Patients with a minimum migraine duration of three years were included and divided into two groups: patients without aura (MwoA group) and patients with aura (MwA group). Additionally, patients were categorized based on the frequency of their migraine attacks, either episodic (EM) or chronic (CM). A control group (Group C) was also established for comparison. Volumetric analysis, including cortical and subcortical pain-related structures, was performed using volBrain software.

Results: Significant differences were observed in grey matter (p=0.037), cortical grey matter (p=0.022), cerebrum grey matter (p=0.026), anterior cingulate cortex (ACC) (p=0.017), middle cingulate cortex (MCC) (p=0.014), and posterior cingulate cortex (PCC) (p=0.008) volumes among the groups. Group comparisons revealed significant differences in the ACC, MCC, and PCC between Groups C and MwoA (p=0.047, p=0.040, and p=0.047, respectively) and PCC between Groups C and MwA (p=0.026), possibly related to aura pathogenesis. Patients without aura exhibited non-significantly thinner postcentral gyrus (p=0.079), suggesting potential cortical involvement.

Conclusions: This study provides insights into pain center abnormalities in migraine patients and their potential relevance to pain duration and migraine type.

Keywords: Chronic pain, neuroimaging, voxel-based morphometry (VBM), migraine with aura, pain processing centers.

Mammadkhanli O, Yagmurlu K, Kehaya S, Sensoz E, Akinci AT, Simsek O. Volumetric analysis of pain centers in migraine patients. Pam Med J 2024;17:628-642.

Öz

Amaç: Kronik ağrısı olan, özellikle migren hastalarında ağrı merkezlerindeki anormallik paternlerini araştırmak. Çalışma, ağrı süresi ve migren tipleri ile olası korelasyonu keşfetmeyi ve kronik ağrı yönetimi için yeni müdahaleler önermeyi amaçlamaktadır.

Gereç ve yöntem: Üniversite hastanemizde 2019-2023 yılları arasında üç boyutlu izo T1 ağırlıklı beyin MRG'si çekilen 32 migren hastası ve 28 sağlıklı kontrolün radyolojik verileri incelendi. En az 3 yıllık migren süresi olan hastalar çalışmaya dahil edildi ve aura yokluğu (Grup MwoA) veya varlığına (Grup MwA) göre iki gruba ayrıldı. Ek olarak hastalar migren ataklarının sıklığına göre epizodik (EM) veya kronik (CM) olarak sınıflandırıldı. Karşılaştırma için bir kontrol grubu da (Grup C) oluşturuldu. Kortikal ve subkortikal ağrıyla ilişkili yapılar dahil olmak üzere volümetrik analiz volBrain yazılımı kullanılarak yapıldı.

Bulgular: Gruplar arasında gri madde (p=0,037), kortikal gri madde (p=0,022), serebrum gri maddesi (p=0,026), ön singulat korteks (ACC) (p=0,017), orta singulat korteks (MCC) (p=0,014) ve arka singulat korteks (PCC) (p=0,008) hacimlerinde anlamlı farklılıklar gözlendi. Grup karşılaştırmalarında ACC, MCC ve PCC'de Grup C ve MwoA arasında (sırasıyla p=0,047, p=0,040 ve p=0,047) ve PCC'de Grup C ve MwA arasında (p=0,026) muhtemelen aura patogeneziyle ilişkili anlamlı farklılıklar ortaya konuldu. Aurası olmayan hastalarda, potansiyel kortikal tutulumu düşündüren, istatistiksel olarak anlamlı olmayan (p=0,079) daha ince postcentral girus görüldü.

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Sonuç: Bu çalışma, migren hastalarında ağrı merkezi anormalliklerine ve bu durumun ağrı süresi ve migren tipi ile potansiyel ilişkisine dair anlayış sağlamaktadır.

Anahtar kelimeler: Kronik ağrı, nörogörüntüleme, voksel bazlı morfometri (VBM), auralı migren, ağrı işleme merkezleri.

Mammadkhanli O, Yağmurlu K, Kehaya S, Şensöz E, Akıncı AT, Şimşek O. Migren hastalarında ağrı merkezlerinin volümetrik analizi. Pam Tıp Derg 2024;17:628-642.

Introduction

Chronic pain persists for more than three months, occurring every day or on ≥50% of days for six months and extending beyond the expected healing period; also, unlike acute pain, it does not have a warning function [1, 2]. Patients with chronic pain have decreased quality of life that also leads to increasing costs for medical care, disability, and productivity [1, 2]. The development of imaging technologies makes a possible objective assessment of pain. These developments may provide new insight into understanding and treating chronic pain. Significantly, knowledge affecting centers in chronic pain could help better understand the central localization of pain, providing further intervention to these centers.

Migraine is a chronic neurovascular disorder with episodic headache manifestations and an enormous socioeconomic impact [3, 4]. The pathophysiology of migraine is not well understood. Despite migraine being considered a benign disease, its long-term effects are still unclear. Recent neuroimaging studies show that migraine could be associated with functional and structural brain changes. Most of the changes were researched for the altered morphology of cerebral, cerebellar, and brainstem structures [3, 4]. There is still a lack of research on pain centers.

Research on the structure of the cerebral cortex could provide more precise and reliable insights into the underlying neurophysiological mechanism associated with chronic pain. The main objective of this study was to perform a comprehensive analysis of changes in cortical morphology and limbic structures (ACC, MCC, PCC, and anterior insula) among patients with long-duration migraine (chronic pain), and explore the alteration of these centers, also the potential connection these changes with the duration of pain and type of migraine. Due to previous neuroimaging research on chronic pain, we hypothesized that pain-related regions would be altered in migraine patients [3-8]. In this article, we aimed to explore patterns of pain center abnormalities in patients with chronic pain due to long-duration migraine.

Materials and methods

This retrospective cohort study included 32 migraine patients and 28 matched healthy control subjects admitted to the Neurosurgery and Neurology Outpatient Clinics at our university hospital between 2019 and 2023. After obtaining approval from Trakya University Non-Interventional Clinical Research Ethics Committee (TÜTF-GOBAEK 2023/287), three-dimensional brain MRI was obtained using iso-T1-weighted imaging. Patients with vasculitis, previous stroke, intracranial mass, previous intracranial surgery, alcoholism, smoking, obesity (BMI >30 kg/m^2), and the presence of another headache, pregnancy, claustrophobia, or incompatible metallic devices were excluded from the study.

Questionnaires were used to gather clinical data, including age, gender, disease duration since migraine diagnosis, average pain intensity, and medication use. Patients with at least 3 years of migraine duration were included in the study. The participants were divided into two groups based on the presence or absence of aura, according to migraine phenotype: Group MwA (Migraine with aura) and Group MwoA (Migraine without aura). Their results were then compared to those of a control group (Group C) consisting of normal individuals without pain.

Moreover, patients were divided into two groups based on migraine frequency: episodic migraine (EM), with less than 15 migraine attacks per month (Group EM), and chronic migraine (CM), with more than 15 migraine attacks per month (Group CM). These groups were then compared to a normal group (Group C).

Finally, all migraine patients (MwoA and MwA groups) were compared with Group C to evaluate the effects of pain.

Brain MRI imaging was obtained using a Siemens 1.5 Tesla device in a 32-channel phased-array coil. The imaging protocol included T1-weighted, high-contrast, 3D isotropic voxel images acquired in the sagittal plane and reconstructed in the three orthogonal planes.

Volumetric analysis was conducted using volBrain software, which automatically analyzes brain MRI data and provides volumes of subcortical structures, cerebellum, brainstem, brain hemispheres, brain tissues, and the intracranial cavity (Figure 1-3).

Voxel-based morphometry (VBM) was performed for volumetric measurements, including total brain volume, cortex volume, subcortical volume, cerebral white matter volume, total gray matter volume, cortical thickness, and measures of specific regions such as the postcentral gyrus (somatosensory area), anterior insula, anterior cingulate cortex (ACC), midcingulate cortex (MCC), posterior cingulate cortex (PCC), putamen, thalamus, nucleus accumbens (n. accumbens), pallidum, hippocampus, parahippocampus (PHG), and cerebellum (Figure 4).

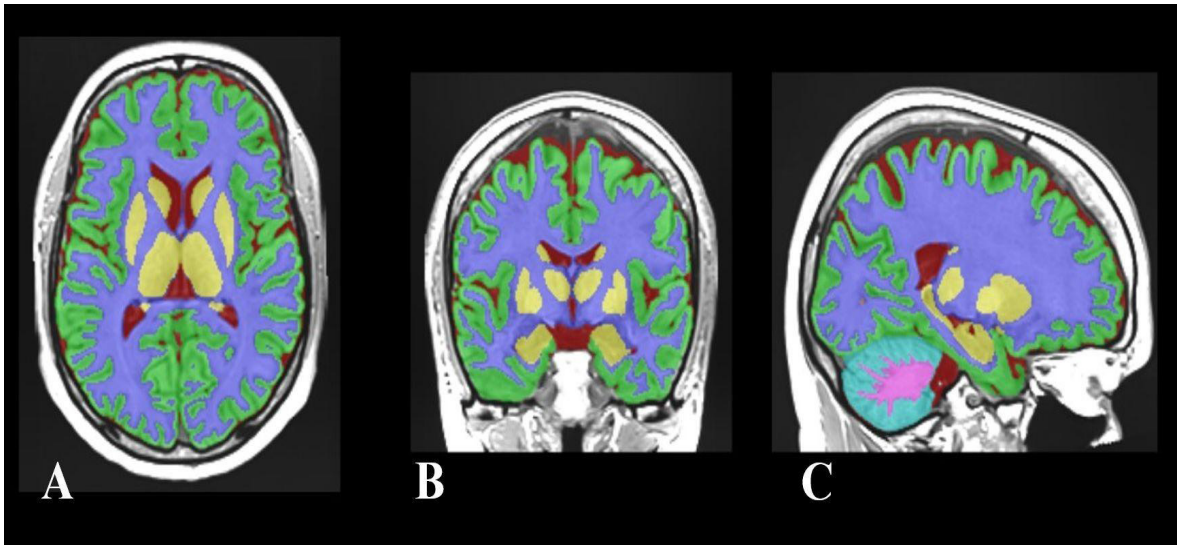

Figure 1. Tissue segmentation to cortical and subcortical structures
A. Axial view. B. Coronal view. C. Sagittal view

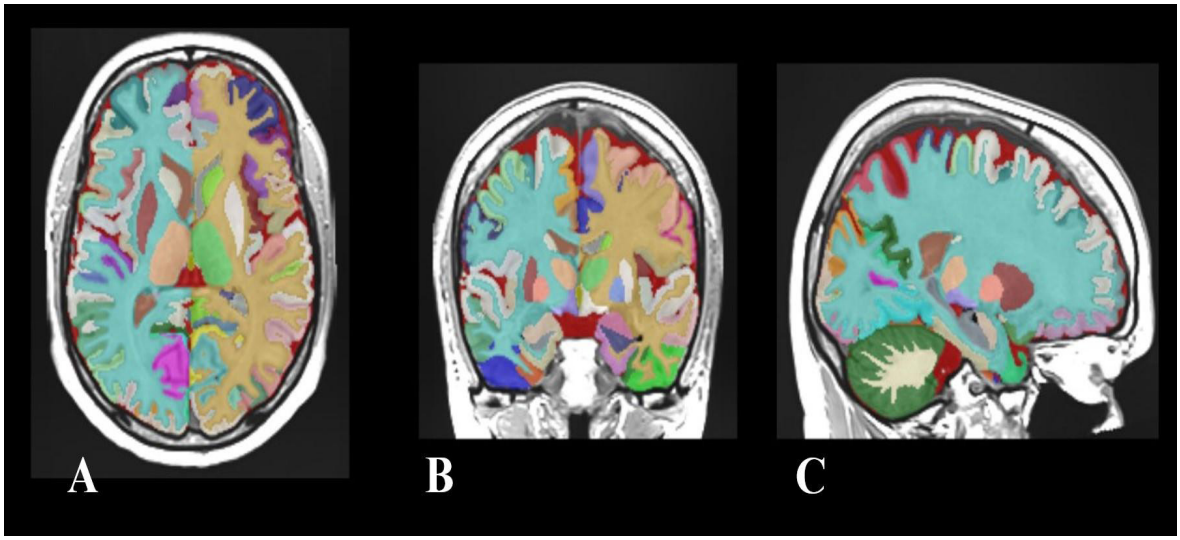

Figure 2. Structure segmentation of cortical and subcortical structures
A. Axial view. B. Coronal view. C. Sagittal view

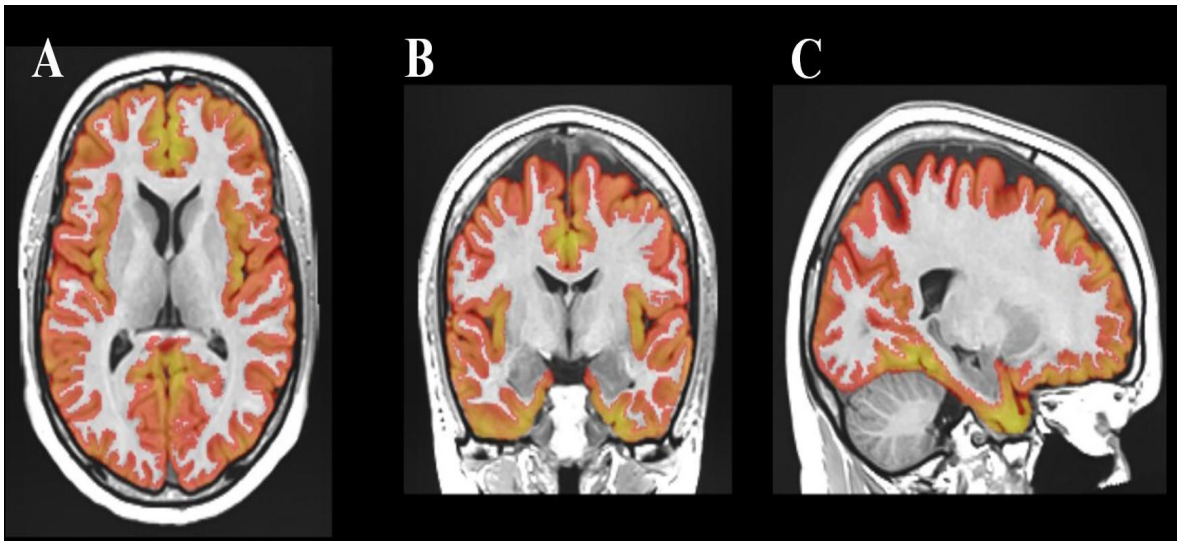

Figure 3. Cortical gray matter. A: Axial view, B: Coronal view, C: Sagittal view

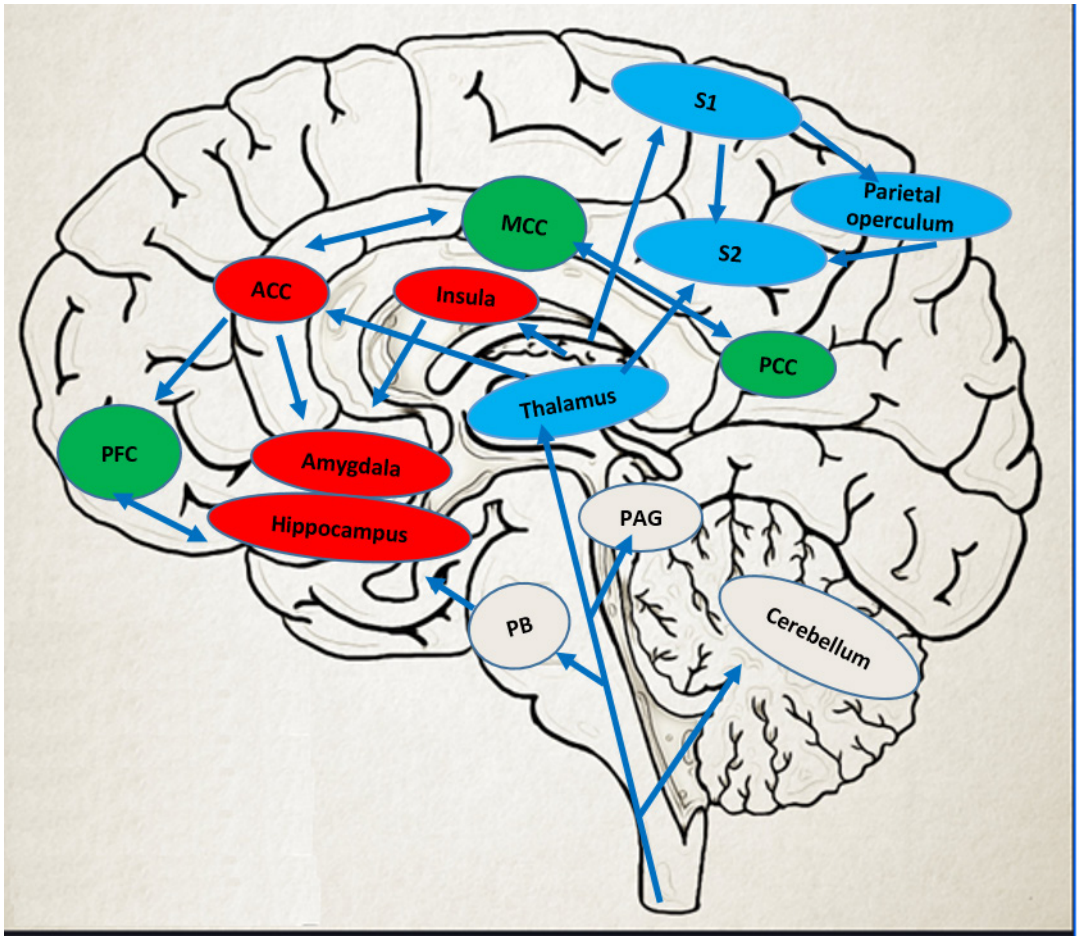

Figure 4. Schematic illustrations of neural networks associated with pain

The arrows illustrate the central connections between pain-related regions
ACC: anterior cingulate cortex, MCC: medial cingulate cortex, PCC: posterior cingulate cortex PFC: prefrontal cortex
PAG: periaqueductal gray, S1: primary somatosensory cortex, S2: secondary somatosensory cortex, PB: parabrachial nucleus
The areas involved in pain perception and location are highlighted in blue, while the red highlights indicate areas involved in the affective motivational part of pain. The green highlights indicate areas involved in the cognitive component of pain

Statistical analysis was conducted using Jamovi (version 2.3) software. The normality of the data was examined using the Shapiro-Wilk tests. Results were presented as mean ± standard deviation for parametric continuous variables and as percentages for categorical variables. Two-group comparisons were made using Mann Whitney U for numerical variables, χ^2 tests for categorical variables, and Fisher's exact test. Kruskal-Wallis tests were used to compare means or medians of continuous variables (age) between different groups, with a significance level set at $p \leq 0.05$. To conduct a post hoc pairwise comparison, a Dwass-Steel-Critchlow-Fligner test was performed to assess the volumetric differences between the groups.

Results

The study included a total of 60 participants, with 17 patients in Group MwoA, 15 in Group MwA, and 28 in Group C. Furthermore, related to the number of attacks, there were 26 patients in Group EM and 6 in Group CM, as well as 28 in Group C. The age range of the patients was between 18-45 years, and all participants were female. The mean duration since migraine diagnosis was 14.97 years.

Descriptive measurements of cortical and subcortical centers are given in Table 1. Despite no statistically significant differences, patients without aura showed thinner measurements in the n. accumbens (0.648±0.119 group MwoA, 0.709±0.095 in group MwA), hippocampus (6.93±2.39 group MwoA, 7.39±1.59 in group MwA), and thalamus (11.7±1.12 group 1, 12.5±1.03 in group MwA). In contrast, patients with aura had thinner measurements in the parahippocampus (5.82±0.486 group MwA, 5.40±1.04 in group MwoA) and anterior insula (8.12±0.92 group MwA, 7.86±1.42 in group MwoA). However, it is essential to note that these differences did not reach statistical significance.

Dwass-Steel-Critchlow-Fligner pairwise comparisons revealed statistically significant differences in cortical gray matter (p=0.041), cerebrum gray matter (p=0.047), ACC (p=0.020), MCC (p=0.020), and PCC (p=0.011) volumes among the groups (Table 1). However, no statistically significant differences were found in other variables, such as total gray matter, white matter, the volumes of total brain volume, cerebellum, n. accumbens, hippocampus, pallidum, putamen, thalamus, postcentral gyrus, parahippocampus, and anterior insula among the groups.

In comparison of Group C and MwoA, there were significant differences between ACC (p=0.047), MCC (p=0.040), and PCC (p=0.047). In comparison of Group C and MwA were noted differences between PCC (p=0.026), which probably could be involved in pathogenesis patients with aura. Moreover, despite there being no statistically significant differences, patients without aura showed thinner measurements in the postcentral gyrus (Group C-MwoA (p=0.079) compared to Group C-MwA (p=0.597)), which could be related to cortical involvement in pathogenesis patients with absence aura.

Mann Whitney U test was used for comparing all migraine patients (groups MwoA and MwA) with the Group C, were noted significant differences in structures, such as gray matter (p=0.017), cortical gray matter (p=0.012), cerebrum gray matter (p=0.013), ACC (p=0.006), MCC (p=0.005), and PCC (p=0.003) (Table 2).

Furthermore, Kruskal Wallis analyzed between groups to compare the effects of episodic and chronic migraine (Groups EM, CM, and C). Significant differences were observed in structures such as gray matter (p=0.011), cortical gray matter (p=0.007), cerebrum gray matter (p=0.008), and PCC (p=0.033). Despite this, ACC and MCC have no significant differences between all migraines and control groups (p=0.070 and 0.069), and between groups C and EM in both structures, significant differences (p=0.018 and 0.018). Also, significant differences were noted between groups EM and CM (ACC, p=0.009, MCC, p=0.005) (Table 3).

Table 1. Descriptive values and Kruskal Wallis Variance Analysis, including Dwass-Steel-Critchlow-Fligner pairwise comparisons for migraine patients with (MwA)/without aura (MwoA) and control group (C)

	Median (IQR)	Kruskal-Wallis		Dwass-Steel-Critchlow-Fligner pairwise comparisons					
				C-MwoA		C-MwA		MwoA- MwA	
	C (n=28) **MwoA** (n=17) **MwA** (n=15)	χ^2	*p*	W	*p*	W	*p*	W	*p*
GM	665 (59.6) 638 (89.9) 644 (39.3)	5.794	0.055	-3.013	0.084	-2.487	0.184	0.774	0.848
Cortical GM	523 (60.6) 495 (66.4) 504 (31.5)	**6.395**	**0.041**	-2.830	0.112	-3.063	0.077	-0.027	1.000
WM+GM	1175 (116) 1127 (84.0) 1135 (99.8)	2.146	0.342	-1.920	0.364	-1.405	0.581	0.401	0.957
WM	471 (62.0) 465 (46.0) 456 (52.8)	0.493	0.781	-0.728	0.864	-0.901	0.800	-0.080	0.998
Cerebrum GM	564 (60.6) 535 (72.8) 544 (36.3)	**6.127**	**0.047**	-2.847	0.109	-2.919	0.097	-0.027	1.000
Cerebellum	123 (10.4) 123 (9.57) 127 (12.2)	1.177	0.555	-0.066	0.999	1.406	0.581	1.308	0.625
N. Accumbens	0.690 (0.112) 0.640 (0.009) 0.680 (0.075)	3.216	0.200	-1.839	0.395	0.866	0.814	2.487	0.184
Hippocampus	7.79 (0.792) 7.80 (0.900) 7.63 (0.895)	0.975	0.614	-1.391	0.587	-.0811	0.834	0.240	0.984
Pallidum	2.73 (0.277) 2.60 (0.350) 2.81 (0.165)	2.41	0.300	-1.19	0.677	1.19	0.677	2.25	0.251
Putamen	8.29 (0.648) 8.26 (0.910) 8.68 (1.03)	1.69	0.430	-0.017	1.000	1.604	0.493	1.682	0.460
Thalamus	12.0 (1.04) 11.7 (1.58) 12.5 (1.55)	4.14	0.126	-1.97	0.345	1.50	0.541	2.64	0.148
Postcentral gyrus	18.8 (3.21) 17.7 (3.33) 18.0 (1.79)	4.54	0.103	-3.05	0.079	-1.37	0.597	1.18	0.684
ACC	10.9 (1.89) 9.77 (1.82) 9.86 (0.48)	**7.80**	**0.020**	**-3.344**	**0.047**	-3.117	0.071	0.668	0.884
MCC	10.6 (1.68) 9.45 (1.84) 9.49 (0.77)	**7.83**	**0.020**	**-3.443**	**0.040**	-3.027	0.082	0.454	0.945

Table 1. Descriptive values and Kruskal Wallis Variance Analysis, including Dwass-Steel-Critchlow-Fligner pairwise comparisons for migraine patients with (MwA)/without aura (MwoA) and control group (C) (continued)

	Median (IQR)	Kruskal-Wallis		Dwass-Steel-Critchlow-Fligner pairwise comparisons					
				C - MwoA		C-MwA		MwoA- MwA	
	C (n=28) MwoA (n=17) MwA (n=15)	**χ2**	***p***	**W**	***p***	**W**	***p***	**W**	***p***
PCC	10.6 (2.10) 9.28 (1.28) 9.37 (1.72)	**9.09**	**0.011**	**-3.344**	**0.047**	**-3.658**	**0.026**	-0.401	0.957
Parahippo-campus	5.76 (0.86) 5.91 (0.73) 5.48 (0.66)	2.88	0.237	1.738	0.436	-0.883	0.807	-2.323	0.228
Anterior insula	8.36 (1.34) 7.94 (1.53) 8.14 (1.60)	1.20	0.548	-1.424	0.573	-1.117	0.710	-0.187	0.990

GM: Gray Matter, ACC: Anterior Cingulate Cortex, MCC: Middle Cingulate Cortex, PCC: Posterior Cingulate Cortex

Table 2. Descriptive values and Mann-Whitney U test for all migraine patients (chronic pain) and control group

	Control group	All migraine patients (chronic pain)	Mann Whitney U	
	Median (SE)	**Median (SE)**	**U value**	***p***
GM	664.980 (10.905)	641.015 (11.552)	288	**0.017**
Cortical GM	522.760 (9.92)	496.810 (9.09)	278	**0.012**
WM+GM	1174.570 (16.372)	1132.190 (18.204)	351	0.154
WM	471.415 (7.422)	457.015 (9.114)	401	0.494
Cerebrum GM	563.755 (10.266)	535.640 (9.494)	281	**0.013**
Cerebellum	123.445 (2.44)	125.610 (2.212)	411	0.591
N. Accumbens	0.690 (0.016)	0.675 (0.02)	417	0.646
Hippocampus	7.790 (0.115)	7.705 (0.36)	384	0.343
Pallidum	2.730 (0.045)	2.730 (0.039)	445	0.970
Putamen	8.295 (0.14)	8.495 (0.149)	404	0.519
Thalamus	12.000 (0.161)	12.005 (0.20)	430	0.795
Postcentral gyrus	18.775 (0.471)	17.915 (0.323)	318	0.055
ACC	10.870 (0.323)	9.840 (0.289)	261	**0.006**
MCC	10.570 (0.26)	9.475 (0.222)	260	**0.005**
PCC	10.600 (0.279)	9.325 (0.218)	246	**0.003**
Parahippocampus	5.765 (0.119)	5.610 (0.143)	420	0.684
Anterior insula	8.360 (0.189)	8.040 (0.207)	374	0.276

GM: Gray Matter, WM: White Matter, ACC: Anterior Cingulate Cortex, MCC: Middle Cingulate Cortex, PCC: Posterior Cingulate Cortex

Table 3. Descriptive values and Kruskal Wallis Variance Analysis, including Dwass-Steel-Critchlow-Fligner pairwise comparisons for migraine patients with episodic migraine (Group EM) and chronic migraine (Group CM) and control group (C)

	Median (IQR)	**Kruskal-Wallis**		**Dwass-Steel-Critchlow-Fligner pairwise comparisons**					
				C - EM		**C - CM**		**EM - CM**	
	C (n=28) **EM (**n=26) **CM (**n=6)	χ^2	***p value***	**W**	***p***	**W**	***p***	**W**	***p***
GM	**665** (59.6) 644 (69.0) 614 (22.1)	**9.01**	**0.011**	-2.50	0.181	**-3.71**	**0.024**	-2.94	0.095
Cortical GM	**523** (60.6) 504 (58.3) 471 (12.1)	**9.87**	**0.007**	-2.73	0.130	**-3.77**	**0.021**	-3.07	0.076
WM+GM	1175 (116) 1141 (109) 1103 (76.3)	4.98	0.083	-1.18	0.684	-3.13	0.069	-2.39	0.209
WM	471 (62.0) 455 (65.1) 462 (61.9)	1.10	0.578	-0.514	0.930	-1.66	0.469	-0.89	0.805
Cerebrum GM	**564** (60.6) 546 (61.6) 512 (13.4)	**9.68**	**0.008**	-2.64	0.148	**-3.77**	**0.021**	-3.07	0.076
Cerebellum	123 (10.4) 126 (12.9) 120 (7.75)	3.50	0.174	1.54	0.520	-1.66	0.469	-2.46	0.191
N. Accumbens	0.690 (0.112) 0.680 (0.105) 0.640 (0.063)	2.08	0.353	0.025	1.000	-2.08	0.305	-1.78	0.420
Hippocampus	7.79 (0.792) 7.61 (1.03) 7.79 (0.650)	1.11	0.575	-1.065	0.732	-1.342	0.609	-0.546	0.921
Pallidum	2.73 (0.277) 2.77 (0.228) 2.58 (0.345)	0.056	0.972	0.037	1.000	-0.288	0.977	-0.342	0.968
Putamen	8.29 (0.648) 8.57 (0.932) 8.11 (1.00)	0.821	0.663	1.249	0.651	-0.447	0.947	-0.615	0.901
Thalamus	12.0 (1.04) 12.1 (1.53) 12.0 (1.43)	0.147	0.929	-0.269	0.980	-0.447	0.947	-0.478	0.939
Postcentral gyrus	18.8 (3.21) 17.9 (2.35) 17.5 (2.88)	4.17	0.124	-2.33	0.227	-2.24	0.254	-1.06	0.735
ACC	10.9 (1.89) 9.90 (1.66) 9.46 (0.482)	9.39	**0.009**	**-3.12**	0.070	-3.83	**0.018**	**-1.71**	0.449

Table 3. Descriptive values and Kruskal Wallis Variance Analysis, including Dwass-Steel-Critchlow-Fligner pairwise comparisons for migraine patients with episodic migraine (Group EM) and chronic migraine (Group CM) and control group (C) (continued)

	Median (IQR)	Kruskal-Wallis		Dwass-Steel-Critchlow-Fligner pairwise comparisons					
				C - EM		C - CM		EM - CM	
	C (n=28) **EM (**n=26) **CM (**n=6)	χ^2	***p* value**	**W**	***p***	**W**	***p***	**W**	***p***
MCC	10.6 (1.68) 9.69 (1.36) 8.95 (1.47)	10.67	**0.005**	**-3.13**	0.069	-3.83	**0.018**	**-2.80**	0.117
PCC	**10.6** (2.10) 9.39 (1.60) 8.45 (1.51)	**11.12**	**0.004**	-3.54	**0.033**	-3.71	0.024	**-2.46**	0.191
Parahippo-campus	5.76 (0.857) 5.74 (0.625) 5.36 (0.633)	2.99	0.224	1.26	0.646	-1.50	0.538	-2.46	0.191
Anterior insula	8.36 (1.34) 8.13 (1.46) 7.17 (1.50)	3.88	0.144	-0.759	0.853	-2.75	0.127	-2.32	0.229

GM: Gray Matter, WM: White Matter, ACC: Anterior Cingulate Cortex MCC: Middle Cingulate Cortex, PCC: Posterior Cingulate Cortex

Correlation of volume of different brain regions and pain centers

The correlation matrix showed significant positive and negative correlations between various brain regions and the duration of disease. The correlation revealed a statistically significant positive correlation of n. accumbens with several brain structures, including postcentral gyrus (p<0.001), ACC (p<0.001), MCC (p<0.001), and PCC (p<0.001), suggesting that the volume or characteristics of the n. accumbens region was related to these other brain regions. Moreover, postcentral gyrus and cerebrum gray matter demonstrated a positive correlation with ACC (p<0.001), MCC (p<0.001), and PCC (p<0.001). The parts of the cingulate cortex (ACC, PCC, MCC) demonstrated a strong positive correlation with each other (p<0.001).

Lastly, the parahippocampus and anterior insula also showed a positive correlation (p<0.001), indicating a moderate association between these structures. These findings provide valuable insights into understanding chronic pain between different brain regions in the study population.

There is a statistically significant negative correlation between duration and gray matter (p=0.003), cortical gray matter (p=0.002), total brain volume (p=0.009), cerebrum gray matter (p=0.002), postcentral gyrus (p=0.022), ACC (p=0.001), MCC (p<0.001), and PCC (p=0.001). This indicates that as the duration of migraine (chronic pain) increases, there is a tendency for a decrease in the volume of the ACC, MCC, PCC, cortical gray matter, total brain volume, cerebrum gray matter, and the postcentral gyrus (Table 4).

Table 4. Correlation matrix between duration and pain-related centers

		Duration	Gray matter	N. Accumbens	Postcentral gyrus	ACC	MCC	PCC
Duration	Pearson's r *p*-value	—-						
Gray matter	Pearson's r *p*-value	-0.375 0.003	—-					
N. Accumbens	Pearson's r *p*-value	-0.176 0.177	0.475 < .001	—-				
Postcental gyrus	Pearson's r *p*-value	-0.295 0.022	0.722 < .001	0.325 0.011	—-			
ACC	Pearson's r *p*-value	-0.402 0.001	0.851 < .001	0.397 0.002	0.606 < .001	—-		
MCC	Pearson's r *p*-value	-0.475 < .001	0.801 < .001	0.407 0.001	0.684 < .001	0.823 < .001	—-	
PCC	Pearson's r *p*-value	-0.408 0.001	0.811 < .001	0.422 < .001	0.576 < .001	0.756 < .001	0.776 < .001	—-

ACC: Anterior Cingulate Cortex MCC: Middle Cingulate Cortex, PCC: Posterior Cingulate Cortex

The correlation analysis revealed negative correlations between the duration of migraine and the volumes of specific brain regions, including the anterior insula (Pearson's r=-0.229), white matter (Pearson's r=-0.210), nucleus accumbens (Pearson's r=-0.176), hippocampus (Pearson's r=-0.106), pallidum (Pearson's r=-0.089), putamen (Pearson's r=-0.213), and thalamus (Pearson's r=-0.140). However, it is essential to note that these correlations were not statistically significant for the anterior insula (p=0.079), white matter (p=0.107), nucleus accumbens (p=0.177), hippocampus (p=0.420), pallidum (p=0.499), putamen (p=0.102), and thalamus (p=0.284).

Discussion

This retrospective cohort study provides insights into abnormalities in pain centers among patients with chronic pain, their potential relevance to pain duration and migraine type, and suggests new interventions for chronic pain management. This study has yielded significant findings based on the comprehensive analysis of cortical morphological changes in patients with chronic pain caused by long-duration migraines. The results revealed volumetric alterations in specific brain regions, particularly a decrease in the volumes of the anterior, middle, and posterior cingulate cortex, cortical gray matter, total brain volume, and the postcentral gyrus, which were all found to be negatively correlated with the duration of chronic pain. These regions play essential roles in pain processing and sensory perception, making these findings highly relevant to our understanding of the neurophysiological mechanisms related to chronic pain. Furthermore, we noticed in migraine patients without aura, there were significant differences between ACC, MCC, and PCC, compared with the presence of aura, which revealed differences in PCC, which probably could be involved in pathogenesis patients with aura. Moreover, patients without aura showed thinner measurements in the n. accumbens, hippocampus, and thalamus; conversely, patients with aura had thinner measurements in the parahippocampus and anterior insula.

The study utilized VBM to detect volumetric changes in brain tissue [8]. VBM is a computational approach that compares brain images with a template to measure differences in local brain tissue concentration at a voxel level. The observed volumetric changes showed either a decrease or increase in gray matter or white matter volumes, possibly related to the underlying pathophysiology of migraines involving recurrent ischemia due to reduced blood flow during both ictal and interictal phases [3-8]. Consistent with these findings, all migraine

patients showed thinning of gray matter, white matter, and cerebrum gray matter, which was significantly different from the control group.

Several previous studies have reported volume loss in various cortical regions in migraine patients compared to healthy controls, involving frontal/prefrontal, parietal, temporal, and occipital areas, bilateral insula, ACC, basal ganglia, and the cerebellum [3, 4, 9]. However, in this study, no significant differences were found among the basal ganglia structures (n. accumbens volume, pallidum, putamen, thalamus) among the groups [10-13]. Furthermore, correlation analysis with duration was not statistically significant for white matter (p=0.107), n. accumbens (p=0.197), hippocampus (p=0.408), pallidum (p=0.511), putamen (p=0.105), and thalamus (p=0.284), suggesting that further investigation is needed to understand their role in chronic pain.

Significant positive and negative correlations were observed in the correlation matrix between different brain regions, age, and disease duration. There is a statistically significant negative correlation between the duration of chronic pain and ACC (Pearson's r=-0.399, p=0.002), MCC (Pearson's r=-0.333, p<0.001), PCC (Pearson's r=-0.210, p=0.001), cortical gray matter (Pearson's r=-0.211, p=0.002), total brain volume (Pearson's r=-0.292, p=0.024), and the postcentral gyrus (Pearson's r=-0.290, p=0.024). These results indicate that as the duration of chronic pain increases, there is a tendency for a decrease in the ACC, MCC, PCC, cortical gray matter, total brain volume, and the postcentral gyrus.

The basal ganglia, located in the deep gray matter, are crucial in integrating various functions such as sensory, motor, motivation, cognitive, and procedural learning [10]. Previous studies have revealed changes in the volume, functional connectivity alterations, and iron deposition in the basal ganglia among migraine patients [11-13]. Furthermore, another essential structure is the thalamus, which is vital for various functions, such as pain processing, regulation of awareness, sleep-wake cycle, modulation of visual information, and cognitive behaviors [14]. Previous studies reported the volume decrease of the thalamic nuclei [15] or alterations in the microstructure of the thalamus [16] among migraine patients. These changes support the basal ganglia's role in migraine patients' pathophysiology. Like these studies, Chen et al. [17] reported enlarged right putamen and increased thalamic volume among episodic and chronic migraine patients.

Furthermore, in our study, we also measured n. accumbens and putamen. On the contrary, these studies did not find significant differences in basal ganglia structures, such as n. accumbens volume, pallidum, putamen, thalamus, and volumes among the groups [11-17]. However, we found that patients with absence aura showed thinner measurements in the n. accumbens (0.648±0.119), which suggests that further investigation is needed to understand their role in chronic pain.

Several studies explored the variation between hippocampus volume and migraine patients. Maleki et al. [18] reported that in migraine patients, the bilateral hippocampi were larger in those experiencing 1-2 headache days compared to those having 8-14 headache days per month. Furthermore, they found a negative correlation between hippocampus volumes and the estimated total number of migraine attacks. We found that patients without aura showed thinner measurements in the hippocampus volume; however, they did not reveal differences in hippocampus volumes (p=0.575), as shown in Maleki's study [18].

The ACC is known for its role in pain processing and its functions in cognition and emotion. Therefore, it is considered involved in affective pain [19]. Functional magnetic resonance imaging (fMRI) studies demonstrated activation of the ACC during pain conditions [20, 21]. In clinical studies, it has been observed that cingulotomy (surgical ablation of the ACC) or blocking the pathway to the ACC resulted in a reduction of the sensory component of pain [22, 23]. Mo et al. [24], with a mean disease duration of 5.41±4.71 years, observed significantly decreased ACC, MCC, and PCC among trigeminal neuralgia patients. In our study, with a mean pain duration of 14.98 years, significant changes were seen in ACC (p=0.006), MCC (p=0.005), and PCC (p=0.003) among migraine patients. These findings are consistent with previous research indicating that chronic pain conditions may lead to structural alterations in specific brain regions involved in pain processing and perception [8, 9]. The

observed changes in the ACC, MCC, and PCC among patients with chronic pain suggest potential long-term adaptations in chronic pain perception.

In summary, the results suggest that the duration of chronic pain, specifically long-duration migraines, may be associated with volumetric changes in specific brain regions, particularly a decrease in the volumes of the gray matter (cerebrum and cortical), MCC, ACC, and PCC. However, it is essential to note that the observed negative correlations indicate potential associations, but the lack of statistical significance suggests that these findings should be interpreted cautiously. Further research with larger sample sizes may be needed to validate and better understand the impact of duration on brain volume changes chronic pain patients.

A functional study on migraine showed increased insular activity in the insula during the interictal period, suggesting that repeated migraine attacks could modify the function of the insula throughout life [25]. Additionally, other studies have revealed increased connectivity of the anterior insula and the dorsal pons, as well as the primary visual and auditory cortices. In contrast, the posterior insula showed reduced connectivity with the thalamus and several cortical regions [25, 26]. Mammadkhanli et al. [27] reported significant differences in various insular regions, particularly the posterior insula, the parietal operculum and the whole insular cortex, when comparing chronic pain groups (migraine patients) with normal groups. The study also investigated the clinical manifestations of migraine, such as photophobia, phonophobia, and smell, through volumetric measurements This study focuses on cortical and subcortical structures. We only measured the anterior insula and did not include clinical manifestations. Patients were divided according to migraine phenotype and frequency. We did not reveal differences in anterior insula volumes (p=0.276), as shown in Tso's study [26].

When comparing with the pathophysiological mechanism and evaluation methods in the current literature:

Neumann et al. [28] conducted a study on three groups of individuals with chronic pain conditions (chronic back pain, migraine, and craniomandibular disorder) and compared them to controls. The study found significantly less gray matter volume (GMV) in clusters of the left dorsal anterior insula/temporal pole, bilateral paracingulate/ACC, left posterior insula, and the left hippocampal/PCC region in the chronic pain groups compared to the controls. Our study focused solely on patients with migraines, excluding those with chronic low back and craniomandibular pain, resulting in a more homogeneous patient group. We conducted measurements on both cortical and subcortical structures, including all gray matter measurements without separating left and right. However, we did not include measurements of the posterior insula.

Yin et al. [29] reported that gray matter structural changes in the medial inferior temporal gyrus, particularly the parahippocampus, were the crucial and initial pathological features in Migraine without aura patients. In contrast to their study, we did not observe a significant difference in PHG in our study. This may be because our patient population consisted of both migraine with aura and migraine without aura, and the sample size was smaller.

To understand the pathophysiology of migraine, Silva et al. [30] analyzed volumetric white matter lesions and concluded that aura frequency was particularly correlated with temporal lobe white matter lesions. However, our study did not investigate white matter lesions. Instead, we focused on cortical and subcortical structures.

In their systematic review and neuroimaging meta-analysis of fMRI studies based on regional homogeneity (ReHo), Chen et al. [31] revealed that the left thalamus and brainstem were significantly activated regions. However, we did not use functional MRI in our study. The focus of our study is to understand the structures involved in the chronicization of pain through volumetric measurements of the relevant structures in pain pathophysiology. Perhaps in future prospective studies, the involvement of a certain center will serve as an objective indicator of the chronicization of pain.

In their systematic review and meta-analysis of VBM, Zhang et al. [32] revealed GM alterations in multiple cortical and subcortical brain regions.

These alterations were mostly related to sensation, affection, cognition, and descending modulation aspects of pain. The study found that patients with migraines had an elevation of grey matter in the left parahippocampus and a reduction in the left insula. This was discovered using two neuroimaging meta-analysis methods: anisotropic effect size-signed differential mapping (AES-SDM) and activation likelihood estimation (ALE), which are specifically designed for analyzing functional MRI data, not structural MRI. Our study utilized volumetric analysis, excluding the use of AES-SDM and ALE methods. The results indicate that patients experiencing chronic pain, specifically prolonged migraines, had thinner GM.

Cao et al. [33] conducted a study on MwoA patients and found a correlation between changes in GM volume and altered functional connectivity in MwoA patients. These results suggest that the middle frontal cortex plays an important role in the pathophysiology of migraines. Additionally, the study found decreased functional connectivity in the left PCC and significantly increased functional connectivity in the left cerebellum lobule VI. Similar to the previous study, our study also found a significant change in PCC between the MwoA and control groups. Significant differences were observed in ACC and MCC measurements. In terms of GM volume differences, our study found significant differences between the control group and all migraine patients.

Masson et al. [34] reported that they could not detect any brain anatomical differences in migraine patients regarding GM volume, cortical surface (thickness, gyrification, and sulcus depth) as evaluated by surface-based morphometry (SBM), and WM integrity as evaluated by tract-based spatial statistics (TBSS). Diffusion tensor imaging (DTI) also demonstrated that WM volume was reduced in migraine patients in the left superior longitudinal fasciculus (SLF). Our study only used volumetric analysis and did not include surface-based morphometry (SBM), tract-based spatial statistics (TBSS), or DTI methods. Our results suggest that patients experiencing chronic pain, specifically prolonged migraines, may have thinner gray matter due to chronic cortical ischemia.

This study has limitations, such as a retrospective study, a relatively limited sample size, and the exclusion of patient groups. Therefore, further research with larger and more diverse cohorts is essential to confirm and generalize these findings. Nevertheless, the novel findings of this study may contribute to the knowledge of the pathophysiology of chronic pain in long-term migraine.

In conclusion, our study revealed significant volumetric changes in specific brain regions related to pain that are associated with long-duration migraines (chronic pain). These regions include the anterior, middle, and posterior cingulate cortex, cortical gray matter, total brain volume, postcentral gyrus, nucleus accumbens, hippocampus, thalamus, parahippocampus, and anterior insula.

The negative correlations observed indicate that longer durations of chronic pain may lead to volumetric reductions in particular brain structures involved in pain processing. This information has the potential to advance our understanding of chronic pain in long-standing migraine and could guide the development of novel treatment strategies targeting pain-related brain regions for the clinical management of chronic pain.

Conflict of interest: The authors did not declare any conflicts of interest.

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Ethics committee approval: Permission was obtained from the Trakya University Non-Interventional Clinical Research Ethical Committee approval (TÜTF-GOBAEK 2023/287).

Authors' contributions to the article

O.M. and K.Y. conceptualized the main idea and hypothesis of the study. O.M. and S.K. developed the theory and structured/edited the Materials and methods section. O.M., S.K., E.S. and A.T.A. (and/or other names) conducted the data evaluation in the Results section. The Discussion section of the article was authored by O.M. and K.Y.

O.M., K.Y., S.K. and O.S. reviewed, corrected, and approved the manuscript. Additionally, all authors contributed to the drafting or editing of parts of the manuscript and endorsed the final version.