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Gray Matter Structural Alterations in Chronic and Episodic Migraine: A Morphometric Magnetic Resonance Imaging Study

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Abstract

Objective. This study evaluates different parameters describing the gray matter structure to analyze differences between healthy controls, patients with episodic migraine, and patients with chronic migraine. **Design**. Cohort study. **Setting**. Spanish community. **Subjects**. Fifty-two healthy controls, 57 episodic migraine patients, and 57 chronic migraine patients were included in the study and underwent T1-weighted magnetic resonance imaging acquisition. **Methods**. Eighty-four cortical and subcortical gray matter regions were extracted, and gray matter volume, cortical curvature, thickness, and surface area values were computed (where applicable). Correlation analysis between clinical features and structural parameters was performed. **Results**. Statistically significant differences were found between all three groups, generally consisting of increases in cortical curvature and decreases in gray matter volume, cortical thickness, and surface area in migraineurs with respect to healthy controls. Furthermore, differences were also found between chronic and episodic migraine. Significant correlations were found between duration of migraine history and several structural parameters. **Conclusions**. Migraine is associated with structural alterations in widespread gray matter regions of the brain. Moreover, the results suggest that the pattern of differences between healthy controls and episodic migraine patients is qualitatively different from that occurring between episodic and chronic migraine patients.

Key Words: Chronic Migraine; Migraine; Magnetic Resonance Imaging; Cortical Curvature; Cortical Thickness; Gray Matter Volume; Surface Area

Introduction

Patients with chronic migraine (CMs) suffer from headache during 15 or more days per month for more than three months, with at least eight of these days of headache with migrainous characteristics, according to the third edition of the International Classification of Headache Disorders (ICHD-3) [1]. In contrast, patients with episodic migraine (EMs) suffer <15 headache days per month. Between 2% and 3% of migraine patients evolve annually from EM to CM [2]. Although some risk factors have been associated with progression from EM to CM, the pathophysiological mechanisms of this conversion remain to be elucidated. Furthermore, it is not clear whether EM and CM could represent two ranges of the same entity or, alternatively, if they are two subgroups with distinctive characteristics.

Neuroimaging, particularly magnetic resonance imaging (MRI), has revealed itself as a powerful tool for the study of migraine. Using conventional MRI, some early studies reported an increased risk of subclinical brain damage in migraine patients compared with healthy controls (HCs), including white matter hyperintensities [3, 4]. Later, more focus was devoted to the analysis of possible structural alterations in migraine patients. A recent meta-analysis found a gray matter volume decrease in migraine patients with respect to healthy controls in several regions [5]. Most of the studies included in the meta-analysis employed voxel-based morphometry (VBM) as the analysis tool. This technique automatically performs voxel-wise comparisons of the local concentration of gray matter [6].

Some studies have tried to determine whether structural differences in gray matter between EM and CM patients exist using T1-weighted magnetic resonance (MR) scans. Using VBM, one of these studies found a gray matter volume reduction in chronic vs episodic migraine patients in some regions [7]. Also employing VBM, another study reported increased and decreased gray matter volume in different regions in CM compared with EM patients [8]. Moreover, features based not only on gray matter volume, but also on cortical thickness and surface area were employed by Schwedt et al. to develop classifiers between CMs, EMs, and HCs using principal component analysis (PCA) [9]. Higher cortical thickness in high-frequency (eight to 14 attacks per month) vs low-frequency (less than two attacks per month) migraine patients was found by Maleki et al. in the inferior temporal gyrus of the right hemisphere and in the postcentral gyrus of the left hemisphere [10].

The present study compares the structural properties of the gray matter in patients with EM, CM, and healthy controls. The aims are to:

1. replicate previous findings about differences in the gray matter between EMs and CMs [7, 8] using a different analysis method that provides more information about the structure of the gray matter regions and employing a larger data set;
2. investigate structural brain differences between both subtypes of migraine patients and healthy controls;
3. examine how gray matter structural features relate to demographics and clinical characteristics of patients.

Methods

Participants

We conducted an observational analytic study with a cohort design. The target population included patients with migraine. Patients were recruited from the outpatient headache unit at the Hospital Clínico Universitario de Valladolid (Spain), a tertiary center that receives patients both from specialized care and directly from primary care. Inclusion criteria were a) diagnosis of migraine according to the ICHD-3 beta and ICHD-3 criteria [1, 11]; b) stable clinical situation in the previous six months; c) agreeing to participate and signing the informed consent. We excluded patients with a) high-frequency episodic migraine, suffering between 10 and 14 headache days per month; b) other painful conditions; c) known major psychiatric diseases (described as anamnesis or presence of depression or anxiety according to the Hospital Anxiety and Depression Scale [12]); d) other neurological diseases; e) drug or substance abuse; f) pregnancy. Patients received no preventive therapy at inclusion. Participants were asked to keep a headache diary and were classified as having episodic migraine when they had <10 headache days per month or chronic migraine (CM) according to ICHD-3 criteria. No healthy controls were included if they showed a present or past history of migraine, or if any other neurological or psychiatric condition was present. We used a nonprobabilistic sampling method by convenience sampling. Age- and sex-matched healthy controls were recruited through hospital and university colleagues and advertisements in these facilities by convenience sampling and snowball sampling.

In all patients, we collected sociodemographic and clinical data, including the duration of migraine disease (years), headache and migraine frequency (days per month), and time from onset of chronic migraine (months) when applicable.

The local Ethics Committee of Hospital Clínico Universitario de Valladolid approved the study (PI: 14–197). All participants read and signed a written consent form before their participation.

MRI Acquisition

Image acquisitions were performed for migraine patients during interictal periods (defined as at least 24 hours from last migraine attack). High-resolution 3D T1-weighted MRI data were acquired using a Philips Achieva 3T MRI unit (Philips Healthcare, Best, the Netherlands) with a 32-channel head coil in the MRI facility at the Laboratorio de Técnicas Instrumentales from the Universidad de Valladolid (Spain) between May 2014 and July 2018.

For the anatomical T1-weighted images, the following acquisition parameters were employed: Turbo Field Echo (TFE) sequence, repetition time (TR) = 8.1 ms, echo time (TE) = 3.7 ms, flip angle = 8°, 256 × 256 matrix size, 1 × 1 × 1 mm^3 of spatial resolution, and 160 slices covering the whole brain.

Image Processing

MRI images were processed to obtain cortical curvature, cortical thickness, gray matter volume, and surface area of the different gray matter regions.

From the T1 images, automatic cortical parcellation was performed using FreeSurfer (http://surfer.nmr.mgh.harvard.edu). FreeSurfer parcellation includes skull stripping, automated Talairach transformation, segmentation of subcortical gray and white matter, intensity normalization, gray-white matter boundary tessellation, and surface deformation [13–16]. The automated parcellations were manually inspected to check the quality. Afterwards, mean curvature, average thickness, gray matter volume, and surface area of all subjects were extracted from FreeSurfer and exported to MATLAB (2017b, MathWorks) for further analysis. Gray matter volume was obtained for all the 84 gray matter regions from the Desikan-Killiany atlas [17]. Also, cortical curvature, cortical thickness, and area were calculated for the 68 regions from the atlas that are cortical regions. Considering the four morphometric parameters, a total of 288 comparisons were analyzed, which correspond to 84 comparisons for the gray matter volume of cortical and subcortical regions, and 68 for each of the other three parameters: curvature, area, and thickness of cortical regions.

Statistical Analysis

We estimated sample size according Schwedt et al. [18]. We calculated in a worst possible scenario model with an estimated effect size of difference between groups of 0.04 and a variance of 0.01, a type 1 error rate of 1% and 80% power, anticipating a loss of 10% of patients; the expected sample size was 139 participants. We include a sensitivity analysis in the Supplementary Data.

The Kolmogorov-Smirnov test and Levene's test for equality of variances were used to assess normality and homogeneity of variance in age and duration of migraine in years. To test for significant differences in the ages of the three groups, a one-way analysis of variance (ANOVA) was used if the null hypothesis in the Kolmogorov-Smirnov and Levene tests was not rejected; otherwise, the Kruskal-Wallis test was employed. To test for sex-related significant differences, a chi-square test was used. To compare clinical features between migraine patients (i.e., duration of migraine history in years for both groups of patients and duration of chronic migraine in months for chronic migraine patients), a two-tailed unpaired t test was used if the null hypothesis in the Kolmogorov-Smirnov and Levene tests was not rejected; otherwise, the Mann-Whitney U test was employed.

Cortical curvature and cortical thickness data were tested for normal distribution with the Kolmogorov-Smirnov test, and homogeneity of variance was tested by the Levene test. If data met these assumptions, one-way ANOVA was performed, and if not, the Kruskal-Wallis test was performed. To control for differences in overall brain size, an analysis of covariance (ANCOVA) was performed on gray matter volume and surface area, with total intracranial volume and total surface area, respectively, as covariates. To correct for multiple comparisons, the Benjamini-Hochberg false discovery rate (FDR) procedure was used [19]. To assess differences between the two groups, the Tukey-Kramer post hoc test was applied.

After correction for multiple comparisons using FDR, the critical P value for the results was 0.0154; that is, only the tests with P values equal or lower than this critical P value survived the correction and were therefore considered to be statistically significant. In comparison to the Bonferroni correction, the cutoff P value is relatively large because the Benjamini-Hochberg method adjusts this cutoff using not only the total number of comparisons, but also the number of significant comparisons with relatively small or very small P values. In our case, there were many very small P values ($P < 0.001$) and a large amount of comparisons with small P values ($P < 0.01$), which justify the final cutoff.

Spearman correlation analysis was employed to perform correlation analysis for clinical features from the migraine patients and the structural parameters (i.e., cortical curvature, cortical thickness, gray matter volume, and surface area). To correct for multiple comparisons, the Benjamini-Hochberg procedure was also applied.

In all comparisons, the level of statistical significance was set at $P < 0.05$.

Results

During the study period, 52 healthy controls, 57 episodic migraine patients, and 57 chronic migraine patients were recruited for the study after matching the inclusion and exclusion criteria. Five patients with episodic migraine and 11 with chronic migraine were screened but excluded due to the presence of anxiety or depression according to the Hospital Anxiety and Depression Scale (HADS). Demographic and clinical data for the three groups are summarized in Table 1. Significant differences were found in duration of migraine history in years between the two migraine groups. Significant differences were also found in headache and migraine frequency between the migraine groups, as expected. No poor-quality automated parcellations were detected.

After correction for multiple comparisons, ANOVA/Kruskal-Wallis/ANCOVA results revealed significant differences between groups in cortical curvature, cortical thickness, gray matter volume, and surface area. Eighty-four cortical comparisons and five subcortical comparisons, considering all structural parameters, had significant differences. In this section, we report only 26 results with $P < 0.001$ (ANOVA, Kruskal-Wallis, or ANCOVA). The 63 remaining significant differences ($0.001 \leq P \leq 0.0154$) are reported in the Supplementary Data.

Taking into account the large number of significant results in this study, we also computed the effect size of significant results with Cohen's d in order to identify the

Table 1. Clinical and demographic characteristics of healthy controls, episodic migraine patients, and chronic migraine patients

	HCs (N = 52)	EMs (N = 57)	CMs (N = 57)	Statistical Test
Women, No. (%)	41 (79)	48 (84)	51 (89)	$\chi^2_{(2,\ N\ =\ 166)} = 2.3$, $P = 0.31$[†]
Age, y	36.4 ± 13.1	37.3 ± 8.4	38.1 ± 9.3	$\chi^2_{(2)} = 2.19$, $P = 0.33$[‡]
Duration of migraine history, y		14.3 ± 11.2	19.8 ± 10.8	$t_{(112)} = -2.7$, $P = 0.008$[§]
Duration of chronic migraine, mo			26.3 ± 34.9	
Headache frequency, d/mo		3.8 ± 2.4	23.6 ± 6.3	$U = 48.5$, $P < 0.001$[‖]
Migraine frequency, d/mo		3.8 ± 2.4	14.1 ± 7.1	$U = 145.5$, $P < 0.001$[‖]

Data are expressed as mean ± SD.
CMs = chronic migraine patients; EMs = episodic migraine patients; HCs = healthy controls.
[†]Chi-square test.
[‡]Kruskal-Wallis test.
[§]Two-tailed, unpaired Student *t* test.
[‖]Mann-Whitney *U* test.

results with the largest effect size that were least likely to be due to chance. For every comparison, the mean value of the "most pathological" group was subtracted from the mean value of the "least pathological" group.

Considering the significant differences in duration of migraine history between episodic and chronic migraine patients (Table 1), ANCOVA analysis was repeated for all the structural parameters including the duration of migraine history as a covariate. ANCOVA results showed that the regions with significant *P* values were the same regions obtained in the original analysis, except the left supramarginal gyrus, which was nonsignificant when considering the duration of migraine history as a covariate. The critical *P* value in this analysis was 0.0149. The *P* values from the ANCOVA with the duration of migraine history as a covariate were almost equal to the *P* values from the original analysis, with the difference in *P* values between both analyses close to 0.001 or 0.002 in regions where significant differences were reported in the original analysis. In the case of pairwise post hoc comparisons between EM and CM patients, every region that showed significant differences in the original analysis still had significant differences after adding duration of migraine as a covariate.

Cortical Curvature

Differences in cortical curvature with $P < 0.001$ were identified in the left posterior division of the cingulate cortex, right lateral occipital cortex, right paracentral lobule, and right precuneus cortex. For all these comparisons, both groups of migraine patients had increased curvature compared with HCs. Tukey-Kramer post hoc results for these comparisons are shown in Table 2, Figure 1, and the Supplementary Data. The results with *P* values ≥ 0.001 are shown and discussed in the Supplementary Data.

When comparing between EM and HC patients, all Cohen's *d* values (except for left cuneus cortex) were higher than 0.5, indicating a medium effect size according to the threshold established by Cohen [20]. The left posterior division of the cingulate cortex achieved a large effect (i.e., a Cohen's *d* value >0.8 [20]).

The same trend was found for the comparison between CM patients with respect to HCs, but the effect size was lower compared with EMs vs HCs. In the comparison between CM and EM patients, no value reached the medium effect size threshold, but cortical curvature values tended to be higher in EM patients. These results can be seen in the Supplementary Data.

Cortical Thickness

Differences in cortical thickness with $P < 0.001$ were identified in three regions. In the left inferior temporal gyrus and in the right fusiform gyrus, both EMs and CMs showed decreased cortical thickness compared with HCs. In the right inferior temporal gyrus, HCs and CM patients showed increased cortical thickness compared with EM patients. Tukey-Kramer post hoc results for these comparisons are shown in Table 3, Figure 1, and the Supplementary Data. The results with *P* values ≥ 0.001 are shown and discussed in the Supplementary Data.

All Cohen's *d* absolute values, except for left banks of the superior temporal sulcus, indicated a medium effect size (in this case, more negative) in the comparison between EM patients and HCs, reaching, for the right inferior temporal gyrus, a large effect size. The same trend, but with lower effect sizes (less negative), was found when comparing CM patients and HCs. Finally, no medium effect sizes were found in the comparison between CM and EM patients, although cortical thickness values were consistently higher in CM patients. These results are depicted in the Supplementary Data.

Gray Matter Volume

Differences in gray matter volume with $P < 0.001$ were found in four cortical regions and the bilateral cerebellum. In the left pars orbitalis, left pars triangularis, right insula, and bilateral cerebellum, both groups of migraine patients showed decreased gray matter volume compared

Table 2. Cortical curvature comparison between different brain regions in healthy controls, episodic migraine patients, and chronic migraine patients

Region	HC Mean Curvature	EM Mean Curvature	CM Mean Curvature	EM vs HC *P* Value	CM vs HC *P* Value	CM vs EM *P* Value
Left posterior division of the cingulate cortex	141 ± 12	151 ± 11	148 ± 10	**<0.001**	**0.004**	0.47
Right lateral occipital cortex	141 ± 8	146 ± 8	147 ± 7	**0.003**	**0.002**	0.98
Right paracentral lobule	105 ± 9	111 ± 9	111 ± 9	**0.002**	**0.003**	0.99
Right precuneus cortex	130 ± 8	135 ± 7	136 ± 7	**<0.001**	**<0.001**	0.94

The Tukey-Kramer post hoc test was used; *P* values from analysis of variance or the Kruskal-Wallis test were <0.001. Data are expressed as mean ± SD (m^{-1}).
CM = chronic migraine; EM = episodic migraine; HC = healthy control.
Significant results are shown in bold values.

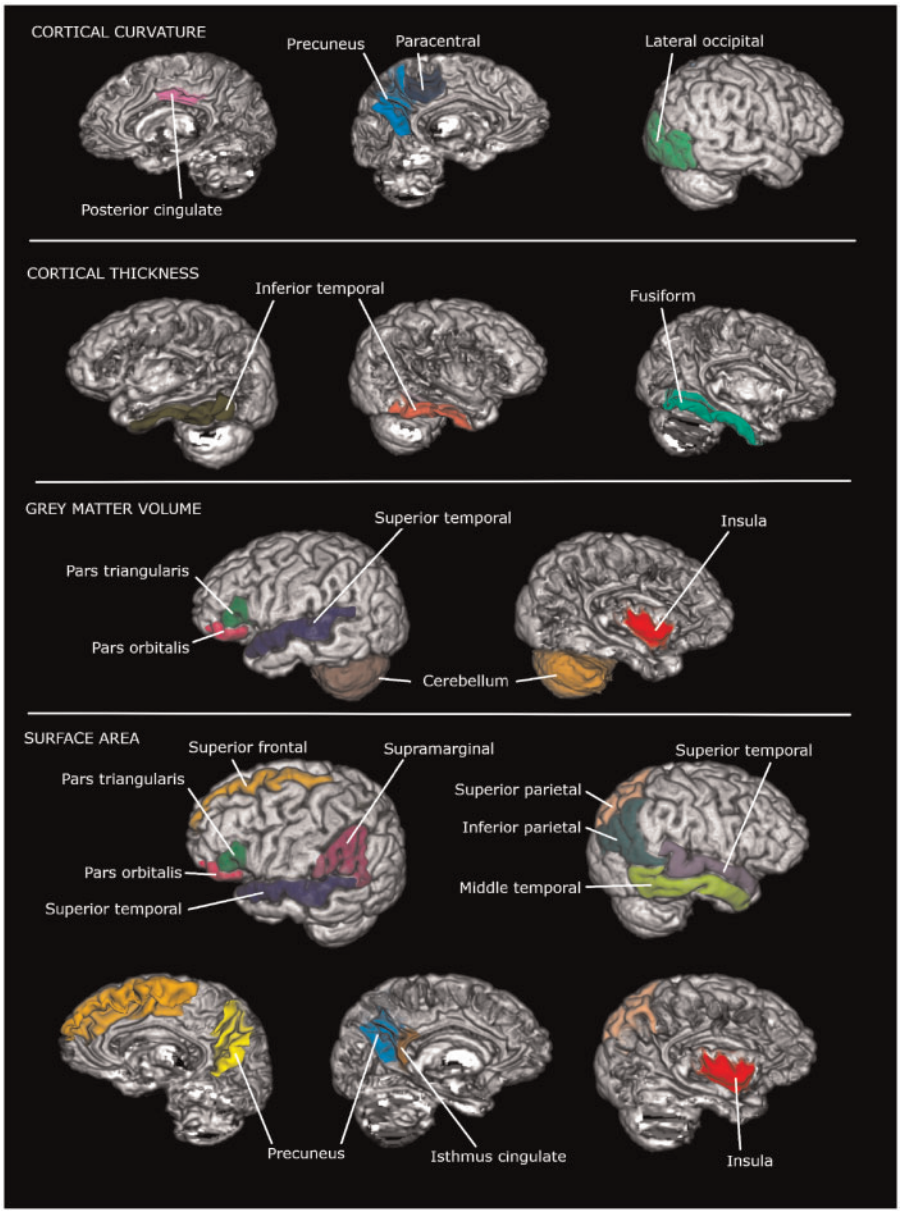

Figure 1. Regions with structural differences (all measured parameters) with *P* values of analysis of variance, Kruskal-Wallis, or analysis of covariance tests <0.001.

with HCs. In the left superior temporal gyrus, CMs showed decreased gray matter volume compared with both HCs and EMs. Tukey-Kramer post hoc results for these comparisons are shown in Table 4, Figure 1, and the Supplementary Data. The results with *P* values ≥0.001 are shown and discussed in the Supplementary

Table 3. Cortical thickness comparison between different brain regions in healthy controls, episodic migraine patients, and chronic migraine patients

Region	HC Average Thickness	EM Average Thickness	CM Average Thickness	EM vs HC *P* Value	CM vs HC *P* Value	CM vs EM *P* Value
Left inferior temporal gyrus	2.726 ± 0.151	2.611 ± 0.161	2.652 ± 0.153	**<0.001**	**0.035**	0.33
Right fusiform gyrus	2.756 ± 0.114	2.661 ± 0.126	2.686 ± 0.141	**<0.001**	**0.011**	0.56
Right inferior temporal gyrus	2.747 ± 0.152	2.613 ± 0.150	2.687 ± 0.183	**<0.001**	0.13	**0.043**

The Tukey-Kramer post hoc test was used; *P* values from analysis of variance or the Kruskal-Wallis test were <0.001. Data are expressed as mean ± SD (mm).
CM = chronic migraine; EM = episodic migraine; HC = healthy control.
Significant results are shown in bold values.

Table 4. Gray matter volume comparison between different cortical and subcortical regions in healthy controls, episodic migraine patients, and chronic migraine patients

Region	HC Gray Matter Volume	EM Gray Matter Volume	CM Gray Matter Volume	EM vs HC *P* Value	CM vs HC *P* Value	CM vs EM *P* Value
Left pars orbitalis	2,215 ± 356	1,977 ± 258	2,034 ± 330	**<0.001**	**0.001**	0.46
Left pars triangularis	3,588 ± 606	3,293 ± 537	3,161 ± 532	**0.011**	**<0.001**	0.37
Left superior temporal gyrus	11,616 ± 1,673	11,232 ± 1,462	10,560 ± 1,171	0.26	**<0.001**	**0.015**
Left cerebellum	49,756 ± 5,594	47,080 ± 5,770	45,903 ± 4,440	**0.004**	**<0.001**	0.31
Right insula	6,728 ± 899	6,279 ± 735	6,085 ± 564	**0.001**	**<0.001**	0.25
Right cerebellum	50,121 ± 5,689	47,858 ± 5,331	46,482 ± 4,142	**0.015**	**<0.001**	0.19

The Tukey-Kramer post hoc test was used; *P* values from analysis of covariance tests were <0.001. Data are expressed as mean ± SD (mm^3), and *P* values are adjusted for the effect of total intracranial volume.
CM = chronic migraine; EM = episodic migraine; HC = healthy control.
Significant results are shown in bold values.

Data. Notably, decreased volume in CMs compared with EMs was observed in five regions (Supplementary Data).

Cohen's *d* absolute values in the comparison between CM patients and HCs indicated medium effect sizes (more negative) in most regions, reaching the large effect size threshold in the right insula and having a contrary trend in subcortical regions, particularly the nucleus accumbens. The same trend, but with generally smaller effect sizes, was observed in the comparison between EM patients and HCs. In the comparison between CMs and EMs, medium effect sizes were found in the left banks of the superior temporal sulcus ($d = –0.65$), the left superior temporal gyrus ($d = –0.51$), the left transverse temporal cortex ($d \approx –0.50$), and the right isthmus cingulate gyrus. These results are illustrated in the Supplementary Data.

Cortical Surface Area

Differences in cortical surface area with $P < 0.001$ were identified in 13 regions. In the bilateral precuneus cortex, bilateral superior temporal gyrus, left superior frontal gyrus, left supramarginal gyrus, right inferior parietal cortex, and right middle temporal gyrus, CMs showed decreased surface area compared with both HCs and EMs. In the right isthmus division of the cingulate cortex and right superior parietal cortex, CMs showed decreased surface area compared only with EMs. In the left pars triangularis, CMs showed decreased surface area compared only with HCs. In the left pars orbitalis and right insula, both EMs and CMs showed decreased surface area compared with HCs. Tukey-Kramer post hoc results for these comparisons are shown in Tables 5 and 6 (showing the results for left and right hemisphere, respectively), Figure 1, and the Supplementary Data. The results with *P* values ≥0.001 are shown and discussed in the Supplementary Data. These include decreased area in CMs compared with both EMs and HCs in nine regions (Supplementary Data) and decreased area in CMs compared with EMs in eight more regions (Supplementary Data).

In the comparison between EM patients and HCs, and in the comparison between CM patients and HCs, the left pars orbitalis, the right frontal pole, and the right insula showed medium effect sizes. For the comparison between CM patients and HCs, a medium effect size was also found in the left pars triangularis. No clear trend in EM patients with respect to HCs was observed. With regard to the comparison between CM and EM patients, medium effect sizes were observed in the left banks of the superior temporal sulcus ($d = –0.66$), left transverse temporal cortex ($d = –0.58$), right banks of the superior temporal sulcus ($d = –0.51$), right inferior parietal cortex ($d = –0.64$), right isthmus cingulate gyrus ($d = –0.65$), and

Table 5. Cortical surface area comparison between different left hemisphere brain regions in healthy controls, episodic migraine patients, and chronic migraine patients

Region	HC Surface Area	EM Surface Area	CM Surface Area	EM vs HC *P* Value	CM vs HC *P* Value	CM vs EM *P* Value
Pars orbitalis	657 ± 96	611 ± 73	609 ± 89	**0.002**	**0.001**	0.99
Pars triangularis	1,296 ± 215	1,230 ± 169	1,166 ± 168	0.068	**<0.001**	0.069
Precuneus cortex	3,616 ± 491	3,598 ± 434	3,417 ± 416	0.93	**<0.001**	**<0.001**
Superior frontal gyrus	6,975 ± 1,084	6,857 ± 657	6,665 ± 666	0.27	**<0.001**	**0.029**
Superior temporal gyrus	3,677 ± 495	3,679 ± 429	3,466 ± 385	1	**<0.001**	**<0.001**
Supramarginal gyrus	3,718 ± 620	3,675 ± 525	3,447 ± 470	0.82	**<0.001**	**0.004**

The Tukey-Kramer post hoc test was used; *P* values from analysis of covariance tests were <0.001. Data are expressed as mean ± SD (mm^2), and *P* values are adjusted for the effect of total surface area.

CM = chronic migraine; EM = episodic migraine; HC = healthy control.

Significant results are shown in bold values.

Table 6. Cortical surface area comparison between different right hemisphere brain regions in healthy controls, episodic migraine patients, and chronic migraine patients

Region	HC Surface Area	EM Surface Area	CM Surface Area	EM vs HC *P* Value	CM vs HC *P* Value	CM vs EM *P* Value
Inferior parietal gyrus	5,101 ± 783	5,201 ± 693	4,812 ± 510	0.50	**0.004**	**<0.001**
Isthmus-cingulate cortex	855 ± 134	899 ± 133	817 ± 116	0.064	0.12	**<0.001**
Middle temporal gyrus	3,254 ± 450	3,281 ± 375	3,110 ± 347	0.83	**0.005**	**<0.001**
Precuneus cortex	3,753 ± 475	3,732 ± 446	3,564 ± 470	0.92	**0.002**	**0.006**
Superior parietal cortex	5,037 ± 609	5,107 ± 496	4,850 ± 479	0.55	0.15	**<0.001**
Superior temporal gyrus	3,443 ± 428	3,449 ± 352	3,290 ± 316	0.99	**0.003**	**0.001**
Insula	2,214 ± 297	2,082 ± 228	2,054 ± 212	**<0.001**	**<0.001**	0.68

The Tukey-Kramer post hoc test was used; *P* values from analysis of covariance tests were <0.001. Data are expressed as mean ± SD (mm^2), and *P* values are adjusted for the effect of total surface area.

CM = chronic migraine; EM = episodic migraine; HC = healthy control.

Significant results are shown in bold values.

right superior parietal cortex ($d = -0.53$). CM cortical surface values were lower than EM values in all regions except the right frontal pole ($d = 0.06$). These results can be seen in the Supplementary Data.

Correlation Analysis

After correction for multiple comparisons, correlation analysis showed a significant negative correlation between duration of migraine history in years in EMs and gray matter volume in the right pars opercularis ($\rho = -0.488$, $P < 0.001$), in the right superior frontal gyrus ($\rho = -0.472$, $P < 0.001$), and in the left insula ($\rho = -0.453$, $P < 0.001$). Also, a significant negative correlation between duration of migraine history in EMs and surface area was found in the left insula ($\rho = -0.457$, $P < 0.001$). All these significant results are shown in Figure 2. No significant correlations were found in CMs for duration of migraine history or duration of chronic migraine. Also, no significant correlations were found for headache and migraine frequency in either CMs or EMs.

Discussion

Gray matter volume, cortical curvature, thickness, gray matter volume, and surface area were analyzed (where applicable) for a total of 68 cortical and 16 subcortical gray matter regions. Comparisons were made between HCs, patients with low-frequency EM (<10 headache days per month), and patients with CM. A total of 89 differences out of 288 comparisons were found to be statistically significant after correction for multiple comparisons (FDR). Pairwise differences were also found to be significant in several comparisons, including not only HCs vs EMs or CMs but also, notably, comparisons between EMs and CMs. These significant findings suggest structural brain differences between subtypes of migraine and HCs, as we stated in the objectives of the study.

There are two main reasons why these results can be considered highly relevant. First, there is a high number of statistically significant differences between migraine patients and healthy controls. Many of these differences

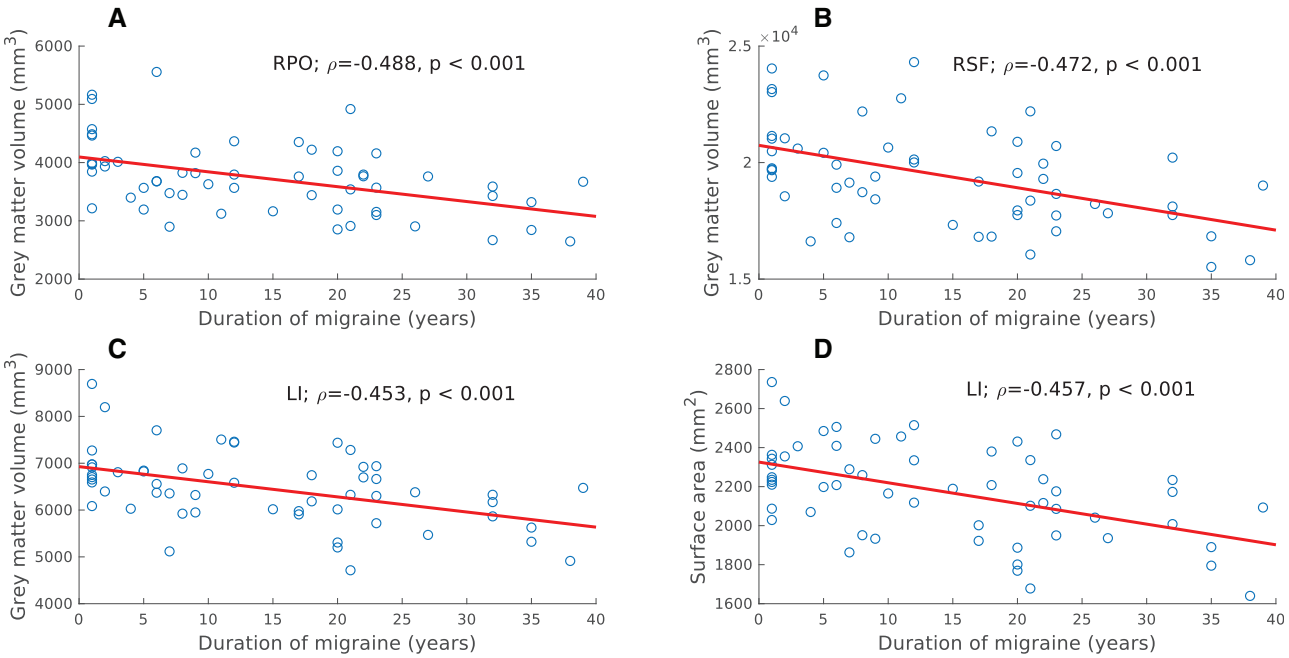

Figure 2. Association graph between duration of migraine history and gray matter volume in the (A) right pars opercularis (RPO), (B) right superior frontal gyrus (RSF), and (C) left insula (LI) of episodic migraine patients and between duration of migraine history and cortical surface area in the (D) LI of episodic migraine patients.

were found in parameters infrequently analyzed in the previous literature, such as the cortical curvature and cortical surface area [9, 18, 21, 22]. The second reason is related to the statistically significant differences between EMs and CMs. Differences between these two groups have only been previously found in a few studies [7–9], and they are important pieces of information to elucidate the neural underpinnings of the progression from EM to CM.

Compared with previous studies, a remarkably higher number of significant results was found in this work. Several factors may have contributed to this difference. First, compared with other similar studies comparing EM and CM patients in their sample, our sample size was much bigger. Neeb et al. included 21 patients from each group and 21 HCs, that is, 63 participants [8], and Valfrè et al. included 27 HCs, 16 EM patients, and 11 CM patients [7]. Neeb et al. included no high-frequency EM patients [8], as in our study, and Valfrè et al. did not provide enough information to elucidate whether they included high-frequency EM patients in their study [7]. In our study, exclusion of high-frequency EM patients may have influenced the number of significant results, as it would likely have accentuated differences between EM and CM, if the change in the brain from one state to the other is a fluid continuation. Also, in both studies, voxel-wise methods were employed for the analysis. This type of analysis is very restrictive due to the employed multiple comparison correction; that is, differences must be very profound in order to be detected as significant results. Additionally, in the case of the study by Neeb et al., the mean age of the participants was almost 50 years [8], while the mean age of the participants from our sample was <40 years. In older people, it could be more difficult to detect differences between groups due to normal cortical changes associated with age. Some other studies employed a priori selected region of interest (ROI) approaches [18, 23–25], which limits the number of possible significant results with respect to whole-brain analysis. Furthermore, we analyzed four morphometric parameters, while most studies analyzed only one parameter, commonly gray matter volume or cortical thickness. Other possible reasons for the difference in significant results in each structural parameter are explained later.

In regions where significant results were found, there were usually one or two structural parameters with differences. In nine other regions, however, there were significant differences in three or more parameters. Table 7 summarizes the findings in those regions. One of them, the left superior temporal gyrus, involved in auditory processing, was also considered to be especially relevant as a classifier between CM and EM patients in a study by Schwedt et al. [9]. In this study, and in order to distinguish migraine patients from healthy controls and EMs from CMs, the authors obtained principal components for each group of features (cortical thickness, volume, and surface area from 68 regions) and built classification models using algorithms such as diagonal quadratic discriminant analysis and decision trees. Classification accuracies of 84.2% and 86.3% were achieved at classifying between CMs and EMs and between CMs and HCs, respectively. Some of the most relevant features in the classification between CMs and HCs were cortical surface area in the *insula* (as in our study) and the temporal pole,

Table 7. Brain regions where three or more parameters have significant differences

Region	Cortical Curvature	Cortical Thickness	Gray Matter Volume	Surface Area
Left banks of the superior temporal sulcus	NS	CM < HC	CM < EM	CM < EM
Left inferior temporal gyrus	CM > HC	CM < HC	CM < HC	CM < HC
	EM > HC	EM < HC	EM < HC	EM < HC
Left lateral occipital cortex	CM > HC	NS	CM < HC	CM < HC
	EM > HC			EM < HC
Left lateral orbital frontal cortex	EM > HC	NS	CM < HC	CM < HC
Left precentral gyrus	NS	CM < HC	CM < HC	CM < HC
				EM < HC
Left superior temporal gyrus	NS	CM < HC	CM < HC	CM < HC
		EM < HC	CM < EM	EM < HC
Right fusiform gyrus	NS	CM < HC	CM < HC	CM < HC
		EM < HC		EM < HC
Right middle temporal gyrus	NS	CM < HC	CM < HC	CM < HC
		EM < HC	CM < EM	EM < HC
Right precentral gyrus	NS	CM < HC	CM < HC	CM < HC
		EM < HC		EM < HC

The significant results are shown for each case.
CM = chronic migraine; EM = episodic migraine; HC = healthy control; NS = nonsignificant.

cortical thickness in the cingulate cortex, and gray matter volume in the entorhinal cortex, cuneus cortex, and pericalcarine cortex. In the classification between CMs and EMs, the most relevant features were cortical surface area in the *superior temporal gyrus* (as in our study), cortical thickness in the medial orbital frontal cortex and anterior cingulate cortex, and gray matter volume in the pars triangularis, transverse temporal cortex, and caudal anterior cingulate cortex.

Changes in the gray matter volume in migraine have been reported in several studies in the literature. We found decreased gray matter volume in migraine patients (one or both groups) compared with HCs in several regions, a result that agrees for the most part with the studies comparing migraine patients and HCs, including a meta-analysis by Jia et al. [5]. The decreased volume in gray matter could be caused by the effect of migraine attacks. In CM, with a higher number of migraine attacks compared with EM (especially if we consider low-frequency EM patients), this reduction in cortical volume would be more pronounced. However, taking into account the correlation results, a relationship between decreased values in gray matter volume and headache frequency was not detected. The correlation analysis assessed frequencies within EMs and CMs and did not compare the effect of headache frequency from EMs to CMs, as this comparison was made in the main analysis. Moreover, the lack of significant results in the correlation analysis could also be partially due to the correction for multiple comparisons.

Future studies should consider a third patient cohort with high-frequency EM and even the use of generalized linear models considering number of headache days per month as the main independent variable of interest. The use a continuous variable (headache frequency) instead of a qualitative variable (low-frequency EM, high-frequency EM and CM) in the analysis would give us a better understanding of the effect of headache attacks on gray matter volume. In a high-frequency EM cohort, studies should consider whether high-frequency EM patients are actually closer to low-frequency EM or to CM.

In our study, gray matter volume was larger both in EMs and CMs compared with HCs in the right nucleus accumbens. Similar findings were reported by Neeb et al. [8], where increased gray matter volume in CMs compared with EMs and HCs was obtained, particularly in subcortical regions comparing CMs and HCs. The increased gray matter volume from subcortical regions may reflect structural brain plasticity as a result of permanent activation of pain-related pathways, as suggested by Neeb et al. [8]. The nucleus accumbens is located in the basal forebrain, rostral to hypothalamus, and has a role in addiction, impulsivity, fear, and sleep processing, consisting of the regulation of cognitive and behavioral processes in cortico-striatal circuits [26]. Kim et al. found an association between migraine and primary sleep disorders, particularly with insomnia [27]. Moreover, Yang and Wang reported that CM patients experience more frequent and severe insomnia symptoms that EM patients [28]. Sardi et al. showed that increased adenosinergic A_{2A} activity and decreased D_2 activity in the nucleus accumbens mediate the pronociceptive effect of REM sleep deprivation [29]. The more frequent sleep disorders in CM and the role of the nucleus accumbens in the pronociceptive effect of sleep deprivation could explain the increased gray matter volume found in CM patients.

In the comparison of the right insula between CMs and HCs, a large effect size was observed. In a previous review, Borsook et al. defined the insula as a "hub of activity" in migraine, involved in afferent pathways in migraine such as the trigeminovascular or the vestibular, and in efferent pathways such as the autonomic, and in connections with regions such as the cingulate cortex

[30]. Borsook et al. suggested that the insula is a convergence point for nociceptive inputs and that it may be involved in migraine processes like altered attention, pain during headache, dizziness, nausea, and social-emotional changes [30].

Regarding changes between both groups of migraine patients, we observed decreased gray matter volume in CMs compared with EMs in several regions. Such decreases were also observed by Valfrè et al. [7] and by Neeb et al. [8], and in high-frequency compared with low-frequency migraine patients by Maleki et al. [10]. In Valfrè et al. [7] and Neeb et al. [8], no significant differences were found using a conservative (family-wise error corrected) $P < 0.05$ threshold. In the same studies, the authors used a less conservative criterion of an uncorrected $P < 0.001$, finding significant differences with this criterion. A possible reason for the lack of significant differences using conservative criteria in the previous studies could be small sample sizes. Another reason, suggested by our effect size values (values <0.8, which correspond to a large effect size as established by Cohen), is that differences between EMs and CMs are subtle and not easily detectable. Notably, two of the significant morphometric differences between EMs and CMs observed in this study, the left transverse temporal cortex and the right superior temporal gyrus gray matter volumes, were used in Schwedt et al. [9] as parameters to accurately classify EMs vs CMs using MRI morphometry.

The other three structural parameters (cortical curvature, thickness, and surface area) have been much less studied in migraine patients. To the best of our knowledge, only one study compared cortical curvature between migraine patients and healthy controls [18], and no significant differences were reported. It is important to note, nevertheless, that only seven areas were compared between migraine patients and HCs, and cortical curvature was only assessed in one of these regions. In this study by Schwedt et al., the main objective was to compare brain structure between persistent post-traumatic headache and migraine patients. In contrast to our study, in the study by Schwedt et al., an overall cortical curvature comparison between controls and migraine patients was not performed in order to detect curvature alterations in migraine. In our case, increased cortical curvature was observed in both groups of migraineurs compared with HCs. Brain curvature provides a measure of sharper cortical folds [18]. Increased cortical curvature has previously been associated with global or gyral white matter atrophy in multiple sclerosis [31], neurodegenerative diseases [32], and mild traumatic brain injury [33]. King et al. hypothesized that increased cortical curvature could be partly caused by cortical restructuring related to tissue volume loss [33]. In a study of schizophrenia patients, a negative correlation was found between cortical curvature values and fractional anisotropy values of white matter tracts, suggesting that mean cortical curvature could be related to cortico-cortical connection integrity [34]. The cingulate cortex or precuneus, regions in which we have detected changes in cortical curvature, are included in hippocampal formation and might be involved in first stages of migraine physiopathology. They are also implicated in intrinsic control networks [35]. In the specific case of the left posterior division of the cingulate cortex, we obtained a large effect size in the comparison of EM patients and HCs.

Regarding cortical thickness, decreases were found in EMs and CMs with respect to HCs in several regions. Furthermore, we also found decreased cortical thickness in EMs compared with both CMs and HCs in the right inferior temporal gyrus. In the right inferior temporal gyrus, we obtained a large effect size in the comparison between EMs and HCs. Interestingly, a very similar result for that same region was reported by Maleki et al. [10], where the authors compared high- and low-frequency migraine patients and HCs. Also, cortical thickness in the left superior temporal gyrus was used as a feature to classify between CMs and HCs by Schwedt et al. [9]. Our results also show significant differences between both groups of migraineurs and HCs using that feature. In line with our results, Magon et al. showed generalized thinned cortex in migraine patients compared with healthy controls, particularly in the right middle temporal gyrus [36], as we obtained with EM and CM patients with respect to healthy controls. Chong et al. found decreased cortical thickness in EM patients in the right fusiform gyrus [37], a result that we also obtained (Table 3; Supplementary Data). In contrast to our results, Granziera et al. reported increased cortical thickness in the motion-processing visual areas MT+ and V3A in migraineurs (with and without aura) compared with healthy controls [23]. Similar results were reported by Gaist et al. in patients with migraine with aura (no patients with migraine without aura were included), finding increased cortical thickness in the V2 and V3A visual areas [38]. DaSilva et al. and Kim et al. reported thickening of the somatosensory cortex in patients with migraine with [24] and without aura [24, 39], but the opposite result (thinner somatosensory cortex) was obtained in patients with migraine with aura (no patients with migraine without aura were included) by Hougaard et al. [40]. Interestingly, Hougaard et al. obtained increased cortical thickness in the hemispheres contralateral to the perceived headache side in the pars opercularis, but no differences were found with regard to aura [41]. Datta et al. identified no significant differences in cortical thickness between migraine patients and healthy controls [42].

Cortical thickness is a marker of gray matter integrity, reflective of the size, density, and arrangement of cells (neurons, neuroglia, and nerve fibers) [43, 44]. Cortical thickness results from previous literature are conflicting. Differences observed between studies could be due to methodological differences (most of the studies employed a priori ROI approaches) or to sample differences. Structural abnormalities in the somatosensory cortex

could be related to clinical and demographic factors [36]. One of our results that matches previous literature was thinned cortex in the right fusiform gyrus in migraine patients with respect to healthy controls. Fusiform gyrus has been associated with pain perception and anticipation [45] and with greater pain-induced activation [46]. Another result that matches previous literature is increased cortical thickness in the right inferior temporal gyrus in CM or high-frequency migraine patients compared with low-frequency EM patients. As suggested by Maleki et al., this increased cortical thickness could imply a compensatory adaptive response of the brain to meet the increased demand for sensory processing related to a higher number of migraine attacks [10]. This hypothesis could also explain increased cortical thickness in migraine patients in visual areas from previous literature, although this increase has no clear relationship to aura due to lacking patients with migraine without aura in some studies and no differences between migraine with and without aura found by Granziera et al. [23]. In EM patients, especially in those with low-frequency headache (as in our sample) and during the initial months, the brain gray matter would not be so well adapted to migraine sensory processing.

Finally, cortical surface area seems to be an excellent biomarker to distinguish CMs from EMs. We identified 27 regions with significant differences between both groups. Among them, the surface area of the left pars triangularis, right insula, bilateral superior temporal gyrus, left postcentral gyrus, and left posterior division of the cingulate cortex were employed to classify CMs from HCs and EMs [9]. These regions are implicated in discrimination of different components of pain and sensorial processing [47]. Messina et al. obtained increased and decreased cortical surface area in patients with migraine (it is not mentioned explicitly, but it seems that no patients with CM were included) with respect to HCs [21]. We only obtained significant decreased surface area in migraine patients (EMs and especially CMs) with respect to HCs, but in EM patients we found no generalized decreased surface area in comparison with controls, as can be seen in the Supplementary Data. Petrusic et al. found no significant differences in cortical surface area between migraine with aura patients and healthy controls [22].

Cortical surface area is determined largely prenatally, in contrast to cortical thickness, which undergoes major changes postnatally [21, 48, 49]. Comparing our cortical surface area results of CM patients to EM patients or to previous literature results, it seems that generalized decreased cortical surface area, especially in regions implicated in discrimination of different components of pain and sensorial processing, is characteristic of CM patients. Decreased cortical surface area in CM patients may reflect enhanced cortical atrophy compared with EM patients and HCs, considering no brain adaptation to pain processes, as suggested before with cortical thickness. Therefore, cortical surface area could be not only a good biomarker to distinguish CM from EM, but also a possible useful feature to predict progression from EM to CM. A possible hypothesis of the surface area state in migraine would be that there might be a genetic predisposition not only to migraine, but also to CM, and area changes would be manifested throughout the migraine course and not so influenced by environmental or external factors, as may happen with cortical thickness. The findings of this study related to cortical surface area must be corroborated in future studies, and possible prediction of CM must be analyzed in longitudinal studies, including genetic data.

With respect to the comparison between both groups of patients with migraine, most of the difference between CM and EM patients was found in the temporal lobe. Previously, Maleki et al. observed diminished connectivity between the hippocampus and temporal lobe, insula, and nucleus accumbens in high-frequency with respect to low-frequency migraine [25]. The authors interpreted this result as a possible diminished interaction with brain regions involved in cognitive or associative processes in high-frequency migraine patients, contributing to the "migraine" experience [25]. The relevance of the temporal lobe in different types of migraine should be confirmed by connectivity studies.

We performed an additional analysis considering the duration of migraine history as a covariate, due to observed significant differences in this duration between both groups of migraine patients. The addition of the duration of migraine as a covariate in the ANCOVA analysis barely changed the results with respect to the analysis without covariates. In the case of the comparison between EM and CM patients, there was no reduction of the number of significant differences when adding duration of migraine as a covariate. Consequently, observed morphometric differences between EM and CM patients did not seem to be driven by differences in the duration of migraine history.

Our last objective was to examine the possible association between gray matter structural features and clinical characteristics of patients. The significant negative correlations found between duration of migraine and gray matter volume are consistent with previous studies [50, 51]. Furthermore, negative correlations between duration of migraine and gray matter volume in the left insula and in the right superior frontal gyrus have been previously reported [50]. No significant correlations in CM were found for the duration of migraine or the duration of chronic migraine, and no significant differences were found for headache and migraine frequency in either CMs or EMs.

The negative correlation between gray matter volume or cortical surface area and duration of migraine history suggests that gray matter atrophy is related to the cumulative effect of headache or migraine attacks. Considering differences between CM and EM patients, the gray matter atrophy would be related to a mixed effect of

duration and frequency of attacks, although no significant correlations were observed within the range of frequencies for CM or EM. In the case of CM patients, the nonsignificant effect of time could be produced because of a kind of steady state related to a possible "continuous ictal-like state," as suggested by Neeb et al. [8].

Significant correlations between headache frequency were previously found. Neeb et al. [8] found positive and negative correlation between headache frequency and gray matter volume, but with an uncorrected $P < 0.001$ and in all migraineurs, that is, no specific correlations for EM or CM. Valfrè et al. [7] reported that gray matter volume was negatively correlated with headache frequency in migraine patients using unmodulated images, including CM and EM patients in the same sample in the correlation analysis. Kim et al. [50] also found a negative correlation between gray matter volume and headache frequency in some regions, but no correction for multiple comparisons was performed. Kim et al. [33] reported a positive correlation between cortical thickness and lifetime headache frequency, but there was no significant correlation with headache frequency recorded in a three-month headache diary, and there was no correction for multiple comparisons. In line with our results, no significant correlation between headache frequency and cortical thickness or cortical surface area was reported by DaSilva et al. [24], Messina et al. [21], Petrusic et al. [22], or Hougaard et al. [40]. From our results and previous results, there is no clear association between headache frequency and gray matter changes, considering independently EM or CM. In this study, excluding high-frequency EM patients could have influenced the lack of significant correlations between morphometric parameters and headache frequency.

The observed pairwise significant differences and effect size values (Cohen's *d*) show interesting patterns in morphometric parameters when comparing both migraine groups with controls and also when comparing EM with CM. These patterns are summarized in Table 8. In general, as could be expected, migraine patients showed higher cortical curvature, lower cortical thickness, lower gray matter volume (except for nucleus accumbens and putamen, both subcortical structures), and lower cortical surface area compared with HCs, corresponding to, at least, medium effect size in statistically significant pairwise comparisons. However, a qualitative interpretation of these results (observing not only *P* values <0.05 in pairwise post hoc comparisons, but also *P* values <0.001 to reach a stricter level of significance) could suggest that the structural brain differences between HCs and EMs might be dominated by a cortical curvature increase, a cortical thickness decrease, and, to a lesser extent, a cortical surface area and gray matter volume decrease. These trends match the results from effect size analysis, where a medium or even large effect size was observed in almost all regions, with significant differences in cortical curvature and thickness with respect to HCs, but only in the few regions with significant differences in gray matter volume and cortical surface area. Moreover, analyzing cortical surface area, there are no significant differences between EM patients and HCs in most of the regions. Differences between EMs and CMs, on the other hand, seem to indicate that there might be no further increase in cortical curvature and that cortical thickness decreases might be slowed down (no important progression in the decline of thickness). There are even some regions where cortical thickness does not decline, but rises. These regions could be relevant in pain processing or processes related to migraine (e.g., visual areas in migraine with and without aura). Regarding differences between EMs and CMs, decreases in the gray matter volume and, especially, cortical surface area seem to be intensified. Taking all these trends into consideration, the implication could be that not only are there measurable differences in brain structure between EMs and CMs, but also that the nature of EM and CM could be qualitatively different from the differences that appear between HCs and EMs. Caution should be taken regarding this interpretation, which was previously suggested by Neeb et al. [8]. This interpretation would imply that EM and CM may be two different entities instead of one unique entity with different headache frequencies, and naturally an entity different than controls. Further longitudinal studies would be needed in order to corroborate this, especially those focusing on the temporal evolution of patients converting from EM to CM and the possible causal relationships of the diverse differences noted between the three groups.

In this study, high-frequency EM patients (10–14 headache days per month) were excluded. This decision was made in order to avoid potentially misclassified patients, which could mislead the analysis. Compared with Neeb et al. [8], CM patients from our sample had greater headache frequency and similar migraine frequency, while EM patients from our sample had lower headache and migraine frequency. This increased

Table 8. Summary of the pairwise comparisons between healthy controls, episodic migraine patients, and chronic migraine patients

Parameter	EM vs HC	CM vs HC	CM vs EM
Cortical curvature	↑ and ↑↑	↑	NS
Cortical thickness	↓↓	↓	↑
Gray matter volume	↓	↓↓	↓
Cortical surface area	↓ and ↓↓	↓↓	↓↓

The results shown are based on the most frequent results, among the significant results, with $P < 0.001$ (analysis of variance, Kruskal-Wallis, or analysis of covariance).

↑↑/↓↓ = increased/decreased measure with $P < 0.001$ in pairwise comparison; ↑/↓ = increased/decreased measure with $P < 0.05$ in pairwise comparison. If single and double arrow are present in a single cell, this means that both cases are equally frequent.

CM = chronic migraine; EM = episodic migraine; HC = healthy control; NS = nonsignificant.

difference in frequency of headache between the EM and CM groups could be a factor explaining the higher number of significant differences found in this study. However, no significant correlations were found between headache or migraine frequency and structural gray matter measures, which could mean that headache or migraine frequency does not have a relevant effect on structural gray matter parameters within the EM or CM groups. In any case, a deeper, specific analysis focusing on high-frequency EM patients would be needed to clarify whether this group of patients is closer to the low-frequency EM group or the CM group. In the latter case, gray matter changes such as an increase in the cortical thickness of several specific areas, which were observed in our analysis as well as in other previous studies [10, 24, 38], would be expected.

There are several strengths and limitations to this study. About the strengths, this is one of the few studies that has employed different structural parameters to analyze gray matter changes between HCs, EMs, and CMs. In the case of cortical curvature, this is the first study to compare whole-brain cortical curvature differences between migraine patients and healthy controls. Also, this is, to the best of our knowledge, the study with the highest number of participants from those three groups. Even though we defined no a priori regions of interest and consequently corrections for multiple comparisons had to be implemented, the high number of subjects allowed us to observe numerous and very clear differences between the groups. The effects of the lack of these a priori selections, were, however, more evident in the correlation analysis, where only four *P* values were found to be significant after multiple-comparisons correction analysis, limiting the identification of significant associations. Another limitation is that using ANCOVA for the gray matter volume and surface area analysis implies the assumption of Gaussianity in the values of those parameters, which in some comparisons could be not true. Additionally, we acquired no T2 or T2-FLAIR MRI sequences to assess white matter hyperintensities (WMHs). Migraine has been associated with an increased risk of WMHs detected on MRI [52]; also, pain in EM patients [53] and an unfavorable prognosis [54] were found to be associated with the occurrence of WMHs. Also, higher WMH load was found to be related to lower cortical thickness in the frontotemporal regions, while this load was related to higher cortical thickness in paracentral regions [55]. Moreover, anxiety and depression were not screened in all patients and not included in the analysis. Anxiety and depression are often comorbid in patients with migraine [56–58]. Gray matter volume reductions in the rostral anterior cingulate cortex in patients with major depressive disorder, and in the parahippocampal gyrus and amygdala in patients with comorbid anxiety disorders, were found [59]. Considering the relationship between depression and anxiety with morphometric parameters, not including these patients in the analysis could be a limitation of our study, but Neeb et al. did not include depression scores in their analysis as a covariate due to the positive association between depression and headache frequency [8]. Finally, important characteristics that could have affected the results, such as aura, were not considered in the analysis.

Conclusions

In this study, several parameters describing the structure of the gray matter were obtained from T1-weighted MR images in a cohort of healthy controls, patients with episodic migraine, and patients with chronic migraine and employed to investigate the differences between them.

A high number of significant differences were found between all groups, generally indicating an increase in cortical curvature and decreases in gray matter volume, cortical thickness, and cortical surface area in migraine patients compared with healthy controls. In the case of cortical curvature, increased values in regions like the cingulate cortex may reflect migraine genesis. Also, gray matter atrophy reflected in generalized cortical thickness loss or decreased gray matter volume could be potential biomarkers for the first stages of the migraine pathophysiology, that is, the first changes that can be seen on MRI.

Furthermore, significant differences were also found in chronic migraine with respect to episodic migraine, suggesting a pattern of structural changes in the brain that could be qualitatively different from those that occur between healthy controls and patients with episodic migraine. Increased cortical thickness in CM compared with EM may involve an adaptive response to meet the increased demand for sensory processing. For gray matter volume, decreased values would show an increased atrophy related to an increased number of headache attacks. Finally, in the case of cortical surface area, decreased values may reflect progression from EM to CM, making this parameter a potentially useful feature of the progression of the disease.

Further work is needed to correlate these findings with different characteristics of migraine patients (aura, allodynia, psychological disturbances) and to elucidate the implications of these findings. Specifically, longitudinal analyses are necessary, especially those focusing on the progression from EM to CM and in the first changes that appear in migraine patients.

Supplementary Data

Supplementary data are available at *Pain Medicine* online.

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