Elderly Patients with Ongoing Migraine Show Reduced Gray Matter Volume in Second Somatosensory Cortex

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Aims: To identify structural changes in gray matter in suspected migraine generators (the hypothalamus and/or brainstem nuclei) and pain pathways and to evaluate whether structural changes in migraine are definitive or resolve with age. **Methods:** Voxel-based morphometry (VBM) was used to assess differences in gray matter between 39 healthy controls (HC), 25 episodic migraine (EM) subjects, and 37 subjects with a history of migraine (HM). In addition, morphometric changes were specifically investigated in suspected migraine generators and/or pain pathways. For statistical analyses, *t* tests between the groups were performed, and a correction for multiple comparisons was used. **Results:** Whole-brain analysis did not reveal any gray or white matter changes. However, when the analysis was limited to the pain matrix, a lower gray matter volume was observed in the left second somatosensory (SII) cortex in EM subjects compared to HC subjects. This volume was significantly reduced in the EM group compared to the HC group and to the HM group, but not in the HM group compared to the HC group. **Conclusion:** Morphometric abnormalities in the SII in subjects with ongoing migraine but not in subjects with a resolved migrainous disease are likely to characterize a migrainous state rather than be a marker of brain susceptibility to migraine. *J Oral Facial Pain Headache 2018;32:67–74. doi: 10.11607/ofph.1866*

Keywords: *brain morphology, elderly, migraine, past migraine*

Migraine is a disabling primary headache characterized by repeated attacks of unilateral, pulsating headaches that may or may not be associated with aura.[1] In a recent analysis of 19 studies that used the International Classification of Headache Disorders (ICHD-II) criteria, the incidence of migraine over 12 months was 11.5% for definite migraine and 7% for probable migraine, yielding a total of 18.5% new cases of headache each year.[2] According to a nationwide population survey in France, the prevalence of definite migraine in retired subjects decreased from 11.2% to 4.7%, and of probable migraine from 10.1% to 4.9%.[3] Additionally, the female: male ratio declines from 3:1 in young and middle-aged patients to 2:1 in patients older than 60 years. The severity of migraine can be attenuated over time, with reduced frequency and severity of attacks.[4–6]

Migraine has been associated with various structural and functional brain changes,[7–10] including dysfunctions in the brainstem, diencephalic areas,[11,12] or cortical areas involved in pain processing.[13] With the development of in vivo brain imaging, a growing literature has shown increased white matter abnormalities (WMAs) and infarct-like lesions (ILLs), as well as volumetric changes in gray matter (GM) and white matter (WM),[9,10,14] in migraine patients compared to control subjects. WMAs were associated with migraine with aura,[15] especially for patients aged 70 years and older.[16] Results were more contrasted for ILLs, although migraine with aura was associated with a higher odds ratio (OR) of ILLs, especially in the posterior circulation.[17] In the case of GM, voxel-based morphometry (VBM) has shown conflicting data that show decreased and increased GM density (Table 1).[18–30] These discrepancies between studies have prevented any clear picture of GM structure being drawn in episodic migraine (EM).[31]

Table 1 Summary of Voxel-Based Morphometry Studies in Migraine (Uncorrected Results Were Not Considered as Absence of Reliable Results)

Study	No. of patients (F/M)	No. of controls (F/M)	No. of patients WA/WoA	Software	Model	Reduced areas in migraineurs	Increased areas in migraineurs	Limitations
Kim et al,[18] 2008	20 (17/3)	33 (29/4)	5/15	SPM2	Yes	Right PCG, IPL, SPG, OFC; Left ACG; Bilateral insula, motor/premotor, preFC	No increase	Use of SVC
Obermann et al,[19] 2014	17 (14/3)	17 (14/3)	NA	SPM8	Yes	Left MTG, ITG, insula, SMG, SPC; Bilateral MCG	No increase	Vestibular migraine
Schmidt-Wilcke et al,[20] 2008	35 (35/0)	31 (31/0)	0/35	SPM2	No	Right insula; ACG, PCG	No increase	19 mM No TIV, no model Use of SVC
Schmitz et al,[21] 2008	28 (28/0)	28 (28/0)	8/20	SPM2	No	No decrease	No increase	No TIV, no model Uncorrected results
Schmitz et al,[22] 2008	24 (24/0)	24 (24/0)	8/16	SPM2	No	Right MFG	No increase	No TIV, no model
Valfré et al,[23] 2008	27 (21/6)	27 (20/7)	21/6	SPM2	Yes	Right STG, ITG; Left precCG	No increase	Use of SVC
Liu et al,[24] 2013	135 (135/0)	111 (111/0)	0/135	FSL 4.1	Yes	Bilateral MFG, SFG, IPL, precuneus, SMG, ITG, MTG, STG, occipital cortices	Bilateral cerebellum, parahipp gyrus, hippocampus, amygdala, occipital cortices	
Rocca et al,[25] 2006	16 (15/1)	15 (13/2)	7/9	SPM2	Yes	Right SFG, MTG; Left ITG; Bilateral preCG, ACG, MFG	PAG	No TIV in model; Use of SVC for PAG
Matharu et al,[26] 2003	28 (26/2)	28 (26/2)	11/17	SPM99	Yes	No decrease	No increase	
Russo et al,[27] 2012	14 (7/7)	14 (7/7)	0/14	SPM8	Yes	No decrease	No increase	
Tessitore et al,[28] 2013	20 (10/10)	20 (10/10)	0/20	SPM8	Yes	No decrease	No increase	
Tessitore et al,[29] 2015	40 (24/16)	20 (12/8)	20/20	SPM8	Yes	No decrease	No increase	
Jin et al,[30] 2013	21 (16/5)	21 (16/5)	0/21	FSL 4.1	Yes	Right occipital, cerebellum, brainstem; Left MpreFC, ACG	No increase	

F = female; M = male; WA = with aura; WoA = without aura; SFG = superior frontal gyrus; preCG = precentral gyrus; preFC = prefrontal cortex; ACG = anteriocingulate gyrus; PCG = posterior cingulate gyrus; MFG = middle frontal gyrus; MTG = middle temporal gyrus; ITG = inferior temporal gyrus; PAG = periacqueductal GM; mM = menstrual migraine; TIV = total intracranial volume; STG = superior temporal gyrus; SVC = small volume correction; IPL = inferior parietal lobule; SPC = superior parietal cortex; OFC = orbitofrontal cortex; MpreFC = medial prefrontal cortex; MCG = middle cingulate gyrus; SMG = supramarginal gyrus.

All these previous VBM studies of migraine included patients younger than 65 years. Thus, whether structural abnormalities in migraine remain present in the elderly as a marker of past migraine is unknown. Migraine crises generally decrease with age and may disappear. The availability to the authors of a cohort of normal volunteers with a fixed age of 75 years presented a unique opportunity to explore the possibility of persistent structural abnormalities in elderly migraineurs. By investigating subjects with a history of migraine, the present study had the prospect of providing information on its possible long-term effects. Therefore, a VBM analysis was conducted in order to compare three groups of elderly subjects: a first group with current EM, a second group with a history of migraine that had since resolved (HM), and a third group of healthy controls without any history of headache (HC). The aims of this study were first to identify structural changes in GM in suspected generators of migraine (the hypothalamus and/or brainstem nuclei) and/or in pain pathways and to evaluate whether structural changes in migraine are definitive or resolve with age.

Materials and Methods

Population

All subjects and controls included in this study participated in the PROOF cohort, which was initiated in 2001.[32] A total of 434 volunteers aged 75 years in 2011 had a clinical follow-up and brain magnetic resonance imaging (MRI) designed for VBM analysis. Among all the collected data, the effects of gender, age, body mass index (BMI), spontaneous baroreflex (SBR), systolic/diastolic blood pressure, and obstructive apnea/hypopnea index (OAHI) were specifically analyzed.

The PROOF study was approved by the University Hospital and the Institutional Review Board/Ethics Committee (Consultative Ethical Research Committees in biomedical research; Rhône-Alpes Loire). The National Committee for Information and Liberty (CNIL) gave its consent for data collection. All subjects signed an informed consent for the study.

Of these subjects, 26 were diagnosed by a neurologist (C.C.) as having current episodic migraine (EM group). Another 41 subjects had a history of migraine (HM group) without any current headache, and another 41 healthy subjects without any history of headache or chronic pain (HC group) were gender matched to the other two groups.

Subjects were classified according to whether they presently had EM or had a history of EM. The diagnoses were made on the basis of a self-administered questionnaire that included migraine criteria as defined by the ICHD-II classification.[1] In a second step, a neurologist specialized in headache (C.C.) questioned these preselected subjects to endorse the diagnosis of EM (past or present). Only patients who fulfilled all the criteria of definite migraine (A: number of attacks over life ≥ 5; B: typical headache duration of 4 to 72 hours without treatment; C: at least two of four typical headache characteristics; and D: at least one of two types of non-pain–associated symptoms) were selected. Information on duration and frequency of migraine attacks was collected for the EM and HM groups. Migraine frequency was the number of attacks per month for the last 3 months for the EM group and the estimated lifetime attack frequency during the period of active migraine for the HM group. In order to select homogenous groups, patients with actual chronic daily headache (with a frequency of headaches ≥ 15 days per month), tension-type headache, prophylactic medications for migraine, or secondary headaches were not included. The absence of any migraine and the absence of any chronic pain that may require daily intake of analgesics were also checked in the HC group.

An experienced neuroradiologist (C.B.) also conducted a visual analysis of each MRI to exclude subjects with incidental findings (eg, pituitary adenoma, corpus callosum lesion, or brain atrophy) that may interfere with VBM analysis. Because of incidental findings and a missing image, seven subjects (2 HC, 4 HM, and 1 EM) were excluded. Finally, this study was conducted with a sample size of 25 patients in the EM group, 37 patients in the HM group, and 39 subjects in the HC group.

MRI Acquisition

MRI scans were acquired on the same whole-body 1.5 T scanner (Magnetom Avento, Siemens Healthcare). The acquisition protocol included a 3D T1-weighted Magnetization Prepared Rapid Gradient Echo (MP-RAGE) acquisition (echo time [TE] = 3.23 milliseconds; repetition time [TR] = 2,060 milliseconds; inversion time [TI] = 1,100 milliseconds; field of view [FoV] = 250 × 250; image matrix = 241 × 256; voxel size: 1 × 1 × 1 mm^3), a T2-weighted 2D turbo spin echo axial acquisition (TE = 109 milliseconds; TR = 6,270 milliseconds), and a fluid-attenuated inversion recovery (FLAIR) 2D axial acquisition (TE = 350 milliseconds; TR = 5,000 milliseconds; TI = 1,800 milliseconds) covering the whole brain.

VBM Pipeline

The VBM pipeline is used to study differences in brain volume in a given population. VBM analysis was performed in four steps: *(1)* segmentation of the original scans into GM, WM, and cerebrospinal fluid (CSF) compartments; *(2)* normalization on a reference template; *(3)* modulation according to the normalization parameters; and *(4)* smoothing. In this study, processing was done with SPM software (SPM8) on Matlab 7 for Linux. Segmentation was performed with the NewSegment algorithm.[33] GM, WM, and CSF compartments were saved, as well as pre-registered images (DARTEL imported). Registration was performed with the DARTEL toolbox[34] on the 101 images of the whole set using the RunDARTEL routine. A study-specific template based on the 101 images was thus created at this step, as well as deformation fields. Each subject was then normalized to the Montreal Neurological Institute (MNI) reference by using the "NormaliseToMNI" function. Meanwhile, modulation (which aims to preserve the total amount of GM and WM of original images) and an 8-mm full width at half maximum (FWHM) smoothing were performed. Default settings were used in these four steps.

Statistical Analyses

Statistical analyses were performed with Stata 11 for Unix. All results are given as mean ± standard deviation (SD). VBM statistical analyses were performed

Table 2 Characteristics of the Study Populations

	HC	HM	EM	Total	*P*
No. of participants	39	37	25	101	
Age (y)	75.4 (0.9)	75.4 (0.7)	75.0 (1.2)	75.3 (1.0)	.12
Sex (n), F/M	30/9	29/8	16/6	78/23	.97
Aura (n), WoA/WA	NA	30/7	19/6	88/13	.64
Frequency of headache attacks per mo	0	0	7.4 (3.4)		
Total duration (y)	NA	25.6 (12.1)	46.2 (16.4)	34.0 (17.2)	< .001
TIV (cm^3)	1500.8 (121.9)	1508.5 (135.6)	1514.2 (145.7)	1507.0 (131.9)	.92
BMI ($kg.m^{-2}$)	25.5 (3.9)	25.4 (3.6)	25.0 (4.21)	25.4 (3.8)	.90
SBR (ms/mmHg)	7.3 (3.9)	7.8 (4.0)	6.2 (2.0)	7.3 (3.6)	.36
24-H SBP	116.5 (12.9)	115.5 (13.4)	118.0 (12.7)	116.4 (12.9)	.81
24-H DBP	71.8 (8.5)	72.1 (6.7)	70.7 (6.7)	71.7 (7.3)	.81
OAHI	12.6 (10.8)	13.3 (10.0)	15.5 (9.8)	13.5 (10.1)	.71

All results are given as mean (standard deviation) unless otherwise noted. Statistical tests used were one-way analysis of variance for quantitative values and χ^2 test for qualitative values. F = female; M = male; WoA = without aura; WA = with aura; BMI = body mass index; SBR = spontaneous baroreflex; SBP = systolic blood pressure; DBP = diastolic blood pressure; OAHI = obstructive apnea/hypopnea index.

with SPM software and consisted of three *t* tests comparing HC to EM, HC to HM, and HM to EM subjects. To avoid the presence of voxels with low GM probability, an absolute threshold on image voxels of 0.2 was chosen. Because these statistical analyses were performed on hundreds of thousands of voxels, leading to hundreds of thousands of statistical tests, correction for multiple comparisons was applied. Two different corrections were used: family-wise error (FWE) correction at voxel level and FWE correction at cluster level (0.05).

Based on a priori hypotheses, two groups of brain regions that may be involved in migraine were also specifically explored: the first, described as the pain matrix,[35] consisted of the middle and anterior cingulate cortex, insula, orbitofrontal area (Broadman area 11), and parietal operculum, which was defined using Anatomy toolbox[36]; the second, described as possible generators of migraine, consisted of the thalamus, the hypothalamus, and the brainstem. Insula and thalamus regions of interest (ROI) were defined on Wake Forest University (WFU) Pickatlas,[37] while hypothalamus and brainstem ROI were extracted from the WFU Standard Atlases. Cingulate areas were extracted from the Automated Anatomical Labeling (AAL) Atlas.[38] The same thresholds used for whole-brain analyses were used in the ROI analyses. A volume-based approach was also used; clusters detected by the VBM analyses were extracted in each group, and their volumes were calculated and compared by using Kruskal-Wallis nonparametric tests with Conover-Iman test for post hoc analysis.

Results

The clinical characteristics of the three groups are summarized in Table 2. The mean age was 75 years in each group. Groups did not statistically differ for gender, total intracranial volume, BMI, SBR, OAHI, or 24-hour systolic and diastolic blood pressures. In the EM group, subjects reported a mean frequency of headache attacks that was higher than the estimated headache frequency reported by HM subjects when they were in the active period of migraine (7.4 ± 3.4 days per month vs 4.6 ± 2.5 days per month, respectively; $P < .001$). As expected, the overall duration of migraine was longer in EM subjects than in HM subjects (46.2 ± 16.4 years vs 25.6 ± 12.1 years, respectively; $P < .001$).

VBM analysis of the whole brain did not show any significant decrease or increase in GM between the three groups. When the analysis was limited to the pain matrix, GM volume was smaller in the left secondary somatosensory (SII) cortex in the EM group compared to the HC group ($P = .048$ at [MNI] x, y, and z coordinates: –52, –11, and 9 in a cluster of 58 voxels; $P = .047$ at cluster level, Fig 1). After the extraction of this cluster and the calculation of the corresponding volume on each image, Kruskal-Wallis non-parametric test showed a volume difference between these two groups ($P = .04$). Post hoc tests with Conover-Iman test confirmed a reduced volume in the left SII in the EM group compared to the HC group ($P = .03$) and to the HM group ($P = .04$), but not in the HM group compared to the HC group ($P = 1.00$, Fig 2).

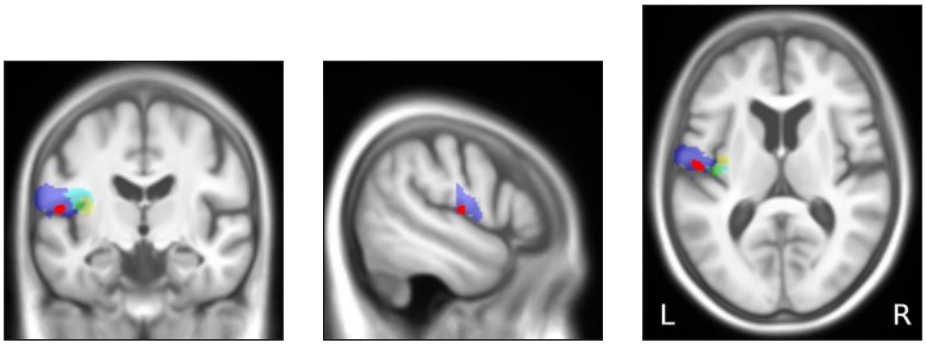

Fig 1 Decrease in gray matter (GM) in episodic migraine compared to controls (family-wise error [FEW] cluster level < .05; 58 voxels; maximum peak at MNI x, y, z coordinates −52 ,−11, and 9). Results (red) are projected onto the mean image of the 101 subjects. To indicate the borders of the secondary somatosensory cortex, light blue and blue respectively represent the OP3 and OP4 regions depicted by Eickhoff.[46] Green and yellow areas are two 5-mm radius spheres centered on the face representations depicted respectively by Mazzola[49] and Brooks.[54] L = left; R = right (neurologic convention).

When the analysis was limited to the migraine generator ROI, no difference in GM between the EM, HM, and HC groups was observed. No change in WM was observed between any of the groups.

Discussion

The whole-brain analysis did not show any difference in GM between migraineurs and controls. Previous studies have shown highly inconsistent and sometimes conflicting results, suggesting that there may be a lack of homogeneity in migraine populations, disease pathophysiology, or disease outcomes over time. Indeed, most of these studies failed to demonstrate changes in GM volume.[26–28] Hubbard et al concluded that a greater GM volume occurred in the left hippocampus of migraineurs,[39] whereas Jin et al observed a significant decrease in GM in the left medial prefrontal cortex, dorsal anterior cingulate cortex, right occipital lobe, cerebellum, and brainstem in patients with migraine lasting for 11 years.[30] Two recent meta-analyses concluded that there was GM reduction in migraine patients in the middle frontal cortex, inferior frontal cortex, pre-central cortex, sublobar insula, subgyral temporal and temporal cortex,[40] right posterior insula, left prefrontal cortex, left operculum, and left anterior cingulate.[31] However, patients with persistent migraine attacks in the present study (average duration of 46.2 years in the EM group) were thought to have more plastic changes than those observed in previous studies with younger patients.

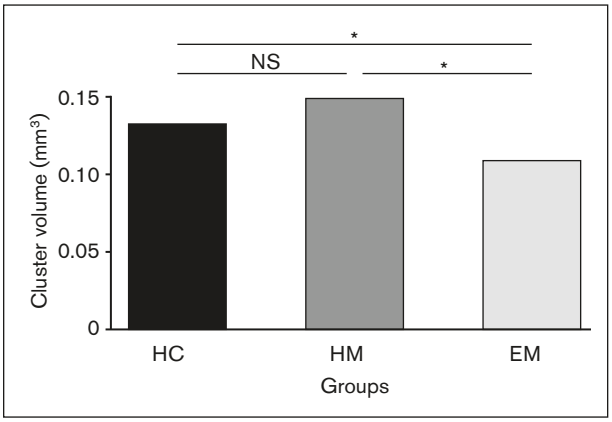

Fig 2 Volume differences in the observed cluster in the left secondary somatosensory cortex between healthy controls (HC), patients with a history of past migraine (HM), and patients with episodic migraine (EM). *P < .05 with Kruskal-Wallis test and Conover-Iman post hoc test.

The limited sensitivity related to field strength of the MRI magnet may be a limitation of the present study but seems unlikely, since negative results with higher fields strength (3 T) are as frequent as with lower fields (1.5 T, Table 1). The hypothesis of a lack of sensitivity due to analytical methods is also unlikely, since the same VBM pipeline and SPM8 software have been used previously in both positive and negative studies. Since the EM group was smaller than the HC group, a lack of sensitivity related to a limited sample size also needs to be considered. However,

the numbers of subjects in each of the three groups (EM, HC, and HM) were equivalent to those usually reported in VBM studies in migraine (Table 1). The population of the study was also highly selected, and therefore sample size is probably not an explanation for the findings. Selection modalities of volunteers and clinical specificities of the elderly were also very different features compared to the previous literature, which may have influenced the results. The PROOF cohort included volunteers recruited in the general population, and so the severity of migraine disease may be different from previous studies investigating patients from medical care settings or pain/headache centers. Since migraine severity and attack frequency are known to improve with age,[6] patients extracted from the PROOF cohort, now aged 75 years, may have a naturally dampened migraine activity compared to younger migraineurs included in previous VBM studies. In addition, pain-free intervals between attacks are likely to minimize the long-term appearance of structural lesions of GM.[41] Frontal and temporal cortices are also particularly susceptible to age-related damage.[42,43] In the PROOF cohort, frontal and temporal changes reported in migraine patients younger than those studied here may have been missed. Thus, the present study can be considered to provide information on migraineur status rather than on disease severity.

The ROI analysis showed a decrease in GM volume in the left SII, but did not show any GM difference in the supposed migraine generators. The ROI analysis was conducted precisely to increase the sensitivity of the study by taking into account the possibility of either a dysfunction in the nociceptive pain network or the existence of abnormal brainstem generators of the disease.[44–47] The SII and the adjacent posterior insular cortex are two brain regions in which decreased volume was considered to be a consistent finding in a recent meta-analysis of migraine.[31] The posterior insula and SII receive afferents from the thalamus, represent crucial areas in somatosensory and nociceptive processes,[48–50] and may encode pain intensity.[50–52] Activation of secondary somatosensory cortices is positively correlated with cutaneous allodynia[53]; thus, the structural dampening of GM in the left SII could be related to the painful nature of migraine attacks. This hypothesis is further supported by the finding that these abnormalities were restricted to the group of elderly patients with active migraine. In addition, it can also be assumed that the decrease in GM volume in ongoing migraineurs (MNI coordinates x, y, and z = −52, −11, and 9, respectively; Fig 1) is close to the subdivisions of SII representing the face area, as shown by previous functional imaging studies[54–57] (MNI x, y, and z = −39.8, −15.5, and 11.2, respectively). Similarly, the peaks of diminution of GM in migraineurs (MNI x, y, and z = 35, −7.2, and 11.6, respectively; Fig 1) were not so distant from cortical areas involved in facial pain perception after direct cortical stimulation.[58,59] These results are highly consistent with the known somatotopy of the face and orofacial somatosensory inputs in this area.

In spite of the investigations centered on the thalamus, hypothalamus, and brainstem, no evidence was found of structural abnormalities in proposed generators of migraine or in generators of the acute allodynia concomitant to the migraine crisis.[60]

In the literature, the direction to which SII volume can be influenced by migraine is controversial. Some studies using surface-based morphometry have shown either the thickening of the somatosensory cortex in migraine[11,61–63] or no structural change.[41] Conversely, others have reported a decreased cortical thickness of SII,[64] and a recent meta-analysis of morphometric studies reported decreased GM volume in the right posterior insular areas and in the left opercular regions in patients with migraine compared to controls.[31] The present results from the PROOF cohort are consistent with this latter finding and also with another study showing a progressive reduction of SII volume during a 1-year follow-up of patients with migraine.[24] If one considers that migraine activity can decrease SII volume over time, the absence of structural changes for the group in whom migraine had ceased (HM) in the present study may suggest that migraine does not cause long-term brain defects. This may argue against the proposed explanation of neurogenic inflammation and neuronal excitotoxicity[25] that may drive permanent neural damage. Conversely, reversible changes in synaptic plasticity could likely explain results changing over time and across studies. They may also reflect a migrainous state rather than traits or disease characteristics. Similar conclusions have been drawn in studies showing that changes in GM density are mainly related to migraine attacks, but not to genetic status.[65] Such results are also consistent with previous studies suggesting that structural GM changes may be reversible after pain relief with appropriate drugs.[66,67]

Conclusions

Despite the possible methodologic biases discussed above, this study is the first to assess specific morphometric changes related to migraine disease in the elderly. As the center of abnormalities was restricted to the SII cortex in patients with ongoing migraine attacks but not in subjects with a resolved migrainous disease, the morphometric abnormalities noted in the present study are likely to characterize a migrainous

state rather than be a marker of brain susceptibility to migraine disease. The absence of long-term impacts of migrainous disease on GM in elderly patients after the resolution of migraine is an important point for reassuring patients with migraine.

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