Brain Gray Matter Changes in Migraine Patients With T2-Visible Lesions : A 3-T MRI Study

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A 3-T MRI Study

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Background and Purpose—In migraine patients, functional imaging studies have shown changes in several brain gray matter (GM) regions. However, 1.5-T MRI has failed to detect any structural abnormality of these regions. We used a 3-T MRI scanner and voxel-based morphometry (VBM) to assess whether GM density abnormalities can be seen in patients with migraine with T2-visible abnormalities and to grade their extent.

Methods—In 16 migraine patients with T2-visible abnormalities and 15 matched controls, we acquired a T2-weighted and a high-resolution T1-weighted sequence. Lesion loads were measured on T2-weighted images. An optimized version of VBM analysis was used to assess regional differences in GM densities on T1-weighted scans of patients versus controls. Statistical parametric maps were thresholded at $P<0.001$, uncorrected for multiple comparisons.

Results—Compared with controls, migraine patients had areas of reduced GM density, mainly located in the frontal and temporal lobes. Conversely, patients showed increased periacqueductal GM (PAG) density. Compared with patients without aura, migraine patients with aura had increased density of the PAG and of the dorsolateral pons. In migraine patients, reduced GM density was strongly related to age, disease duration, and T2-visible lesion load (r ranging from -0.84 to -0.73).

Conclusions—Structural GM abnormalities can be detected in migraine patients with brain T2-visible lesions using VBM and a high-field MRI scanner. Such GM changes comprise areas with reduced and increased density and are likely related to the pathological substrates associated with this disease. **(*Stroke*. 2006;37:1765-1770.)**

Key Words: magnetic resonance imaging ■ migraine

Positron emission tomography and MRI studies have shown functional abnormalities in the brain stem[1,2] (in particular in the dorsal pons[2]) in migraine patients during an attack and in patients with chronic migraine,[3] as well as an altered hypothalamic function in patients with cluster headache.[4]

It is plausible that such an altered function of brain structures might be associated to structural changes. Voxel-based morphometry (VBM) is a fully automated and unbiased method[5] that is being increasingly used for the assessment of gray matter (GM) densities in several neurological conditions, including several pain conditions such as cluster headache,[6] back pain,[7] and migraine.[8] Although these studies detected disease-specific GM abnormalities in patients with cluster headache[6] and back pain,[7] no GM abnormalities have been disclosed in migraine patients with and without aura.[8] A variable that has not been considered in the latter study is the effect, if any, of the presence of macroscopic brain T2-visible lesions on GM changes in migraine patients. Brain T2-visible hyperintensities are a rather common finding in migraine patients.[9,10] Data from a population-based cross-sectional MRI study have shown that female patients with migraine have a high risk of developing white matter (WM) hyperintense lesions, independently from the presence/absence of aura.[11] It is plausible that axons passing through these lesions might undergo retrograde degeneration with secondary GM changes.

The introduction of 3-T magnetic resonance systems in the clinical arena has improved the precision of the techniques for detecting central nervous system changes thanks to an increased signal-to-noise ratio and an increased spatial resolution.[12,13] In this study, we applied VBM analysis to brain images acquired with a 3-T magnet to investigate whether changes in GM density are present in migraine patients with evidence of WM damage on conventional MRI compared with healthy controls. In case such changes were detected, additional analysis was preplanned in an attempt to provide some clues about their nature through the investigation of

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their correlation with patients' demographic characteristics (age, disease duration), clinical manifestations of the disease (presence/absence of aura), and extent of macroscopic visible lesions.

Patients and Methods

We studied 16 migraine patients (7 with aura, 9 without aura; 15 women, 1 man; mean age 42.7 years, range 28 to 58 years; mean disease duration 24.8 years, range 2 to 48 years; mean number of attacks per year 20.3, range 12 to 244; mean time elapsed from the last attack 30 days, range 15 to 45 days)[14] with ≥4 brain MRI hyperintense lesions on T2-weighted scans. The patients were recruited consecutively from the migraine population attending the outpatient clinics, Department of Neurology, Scientific Institute and University Ospedale San Raffaele, after having screened 57 patients. Patients with hypertension, hypercholesteremia, diabetes mellitus, vascular/heart diseases, and other major systemic and neurological conditions were excluded. At the time MRI was performed, 5 patients were taking a prophylactic treatment for migraine. Fifteen healthy volunteers with no familial history of migraine, no previous history of neurological dysfunction (including migraine), and a normal neurological examination served as controls (13 women and 2 men; mean age 38.6 years, range 24 to 50 years [$P=0.2$ versus migraine patients]). All subjects were assessed clinically by a single neurologist who was unaware of the MRI results. Local ethical committee approval and written informed consent from all subjects were obtained before study initiation.

Using a 3-T Philips Intera scanner (Philips Medical Systems), the following scans of the brain were obtained: (1) T2-weighted turbo-spin echo images (repetition time [TR]/echo time [TE]=3000/120 ms; flip angle [FA]=90°, matrix size=512×512; field of view [FOV]=230 mm, 28, 4 mm thick, contiguous, axial slices), (2) fluid-attenuated inversion recovery sequence (TR/TE=11 000/120 ms; inversion time=2800 ms; FA=90°; matrix size=256×256; FOV=230 mm, 28, 4 mm thick, contiguous, axial slices), and (3) high-resolution 3D T1-weighted magnetization-prepared rapid acquisition gradient echo (MP-RAGE) sequence (TR/TE=25/4.6 ms; FA=30°; matrix size=256×256; FOV=230 mm, voxel size=1×1×1 mm^3).

Lesions were identified on T2-weighted scans by consensus by 2 expert observers (M.A.R., A.F.) blinded to patient identity and marked on hardcopies. Fluid-attenuated inversion recovery scans were always used to increase confidence in lesion identification. Then, lesion volumes were measured on T2-weighted images using a local thresholding segmentation technique.[10] VBM analysis was performed on 3D T1-weighted MP-RAGE images using statistical parametric mapping (SPM2) software.[15] Before proceeding with VBM analysis, to avoid an erroneous classification of WM lesions as GM, T2-visible lesions were nulled out from the MP-RAGE scans. This procedure consisted in coregistration of the MP-RAGE images from each subject with the corresponding T2-weighted images using SPM2. Then, using MRIcro software, areas corresponding to T2-visible lesions were masked on the MP-RAGE images. The resulting MP-RAGE images were used for VBM analysis. Full details of the steps involved in the optimized method of VBM analysis have been described extensively previously.[16] In short, this procedure involves extraction of the brain from the native skull space to determine ideal stereotactic normalization parameters. The native MRI scans are stereotactically normalized and segmented into GM, WM, and cerebrospinal fluid compartments. Then, a Jacobian modulation is applied to the data to preserve the absolute regional amount of GM from distortions introduced by the stereotactic normalization.[5] The modulation step compensates for the warping effects of nonlinear normalization and preserves the variability in local tissue morphology. Finally, to improve the signal-to-noise ratio, the normalized images were smoothed with a 12-mm^3 full width at half maximum Gaussian kernel. We used a customized GM template for spatial normalization, which was created using the MP-RAGE scans of both healthy controls and migraine patients. This procedure involved spatial normalization of the original images to the standard SPM T1 template, segmentation into WM and GM, averaging of the images and smoothing with an 8-mm full width at half maximum kernel.

Anatomical localization of the cerebral areas of altered GM density has been performed using the Talairach Daemon. A 3D anatomical atlas was also used to increase confidence in the definition of the anatomical locations of these areas.[17]

The comparison of GM maps between migraine patients and controls and between migraine patients with and without aura was performed on a voxel-by-voxel basis using SPM2 and a 2-sample t test. The GM densities were compared as absolute units. Decreases and increases of densities were investigated. The statistical parametric maps were thresholded at $P<0.001$, uncorrected for multiple comparisons at a voxel level. In brain stem areas where an a priori hypothesis was available, the cutoff value for significance was set at $P<0.05$, applying a small volume correction (SVC) for multiple comparisons by using a 12-mm radius.[18] To assess the correlation of GM changes with clinical data (age and disease duration) and quantities derived from structural MRI (T2-lesion load), these metrics were entered into the SPM design matrix using basic models and linear regression analysis. To identify clusters of voxels of which GM density was related to these parameters, a threshold of $P<0.001$ uncorrected for multiple comparisons at a voxel level was used. Considering that age and disease duration are strongly inter-related, to define which of them had more influence on each these correlations, we performed a multivariate regression model including age and disease duration as independent variables using a stepwise selection procedure.

Results

All controls had normal brain MRI scans. In migraine patients, the mean number of T2-visible lesions was 26.9 (range 4 to 76; mean number of infratentorial lesions 0.1, range=0 to 3; mean number of periventricular lesions 7.7, range 1 to 34; mean number of iuxtacortical lesions 15.1, range 2 to 48; mean number of discrete lesions 2.75, range 1 to 10), the mean T2-weighted lesion load was 2.1 mL (range 0.02 to 11.2 mL). No statistically significant difference was found between patients with and without aura (mean T2-weighted lesion load: 1.5 mL, SD 2.1 mL in patients with aura versus 2.4 mL, SD 3.5 mL in patients without aura; $P=0.50$).

Compared with controls, migraine patients had several areas of reduced GM density, mainly located in the frontal and temporal lobes, bilaterally (Table 1; Figure 1). On the contrary, patients had an increased periacqueductal GM (PAG) density (SPM space coordinates: 4, −32, −22; peak Z score 3.43; $P<0.05$ after SVC; Figure 2).

The results obtained from the comparison of GM densities from the 2 groups of migraine patients (with and without aura) and controls are shown in Table 2. Compared with controls, migraine patients with aura also had an increased density of the PAG (SPM space coordinates: 0, −30, −22; peak Z score 4.17; $P<0.05$ after SVC) and the dorsolateral pons (SPM space coordinates: −3, −28, −21; peak Z score 3.40; $P<0.05$ after SVC). Compared with patients without aura, migraine patients with aura had decreased GM density of the right middle frontal gyrus (SPM space coordinates: 40, 28, 22; peak Z score 3.61; $P<0.001$ uncorrected) and increased density of the PAG (SPM space coordinates: −2, −30, −26; peak Z score 3.52; $P<0.05$ after SVC) and the dorsolateral pons (SPM space coordinates: −3, −29, −37; peak Z score 3.56; $P<0.05$ after SVC; Figure 3).

In Table 3, the correlation found between clinical (age, disease duration) and conventional MRI (T2 lesion load)

TABLE 1. Regions of Significantly Reduced GM Density in Migraine Patients Compared With Controls

Anatomical Regions	Brodmann Areas	SPM Space Coordinates *x, y, z*	Peak *Z* Scores
R SFG	6	25,12,54	4.98*
L SFG	10	−31, 64, 11	3.37
R Precentral gyrus	44	63, 13, 9	4.13*
L Precentral gyrus	44	−60, 11, 13	4.90*
R Anterior cingulated gyrus	32	1, 39, 25	3.91*
L Anterior cingulated gyrus	24	−2, 23, −2	3.95*
R MFG	10	41, 28, 32	4.23*
L MFG	10	−41, 28, 32	3.84
	10	−8, 52, −7	4.10*
	9	−25, 17, 53	3.72
R IFG	9	48, −2, 27	3.42
L IFG	...	−34, 49, 1	3.80
R STG	22	50, −49, 5	3.32
L STG	38	−47, 11, −11	3.58
R MTG	21	46, −9, −11	3.80
	39	56, −74, 22	4.29*
L MTG	21	−60, −7, −18	3.60
R ITG	37	55, −64, −18	3.66
L ITG	37	−43, −46, 27	3.70
	20	−56, −14, −34	4.44*
L Uncus	28	−18, −15, −38	4.61*

R indicates right; L, left; SFG, superior frontal gyrus; MFG, middle frontal gyrus; IFG, inferior frontal gyrus; STG, superior temporal gyrus; MTG, middle temporal gyrus; ITG, inferior temporal gyrus.

All the areas were significant at a $P<0.001$, uncorrected for multiple comparisons at a voxel level. The asterisk identifies areas significant at $P<0.05$, corrected for multiple comparisons (false discovery rate correction).

variables and regions of reduced GM density in migraine patients are shown. No correlation was found between the above-mentioned clinical and MRI variables and regions of increased GM density.

Discussion

Using VBM analysis on brain images obtained with a magnet operating at 3 T, we found that migraine patients with T2-visible hyperintense lesions have significant reductions of GM density of several brain regions when compared with healthy controls. Such changes were bilateral and mainly located in the cortex of frontal and temporal lobes and in the cingulum. In addition, such changes were similar between patients with and without aura, although there were some differences in the location of cortical areas, possibly because of the small number of subjects in each group. The role of the frontal lobe in pain processing has been underpinned by a recent morphological study,[7] which has demonstrated in subjects with chronic back pain atrophy in the prefrontal cortex. Furthermore, functional imaging studies in migraine,[1,2] cluster headache,[6,19] and capsaicin-induced pain[20] have shown an association between pain and an abnormal activation of the cingulum and insula. At least 2 factors can explain decreased GM density in migraine patients. First, GM changes might be the consequence of

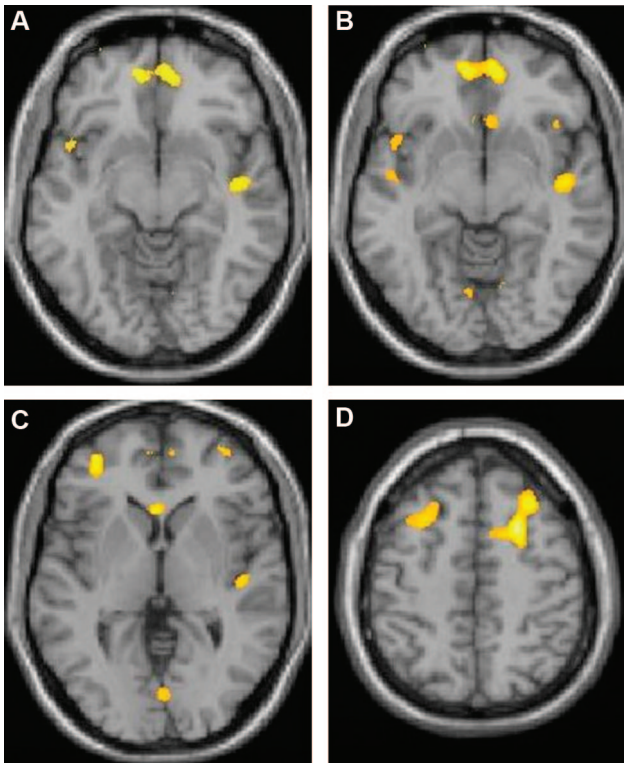

Figure 1. SPM regions superimposed on a high-resolution T1-weighted scan showing decreased GM density in migraine patients compared with controls ($P<0.001$, uncorrected at a voxel level). Several areas are visible in the frontal and temporal lobes bilaterally (neurological convention).

repeated brain insults during the migraine attacks. During the past decades, several theories have been postulated to explain the genesis of the migraine attack. Recently, the vascular theory of Wolff[21] has been confuted by accumulating evidence of mechanisms related to inflammation and excitotoxicity,[22] prompting the formulation of the so-called "neurogenic inflammation" theory. Independently of the causative mechanism, the repetition of the attacks over time might result in a damage of selected cortical structures. This notion is strengthened by the correlation found in the present study between GM density reduction of some cortical regions and disease duration. The topographical distribution of GM changes observed in our patients might be

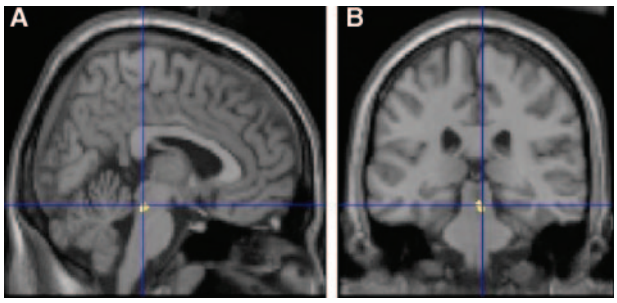

Figure 2. Sagittal (A) and coronal (B) views showing SPM regions superimposed on a high-resolution T1-weighted scan with increased GM density in migraine patients compared with healthy controls ($P<0.001$, uncorrected at a voxel level; $P<0.05$ after SVC). The PAG is visible in both sections (neurological convention).

TABLE 2. Regions of Significantly Reduced GM Density in Migraine Patients With and Without Aura Compared With Controls

		Migraine Patients With Aura		Migraine Patients Without Aura	
Anatomical Regions	Brodmann Areas	SPM Space Coordinates *x, y, z*	Peak *Z* Scores	SPM Space Coordinates *x, y, z*	Peak *Z* Scores
R SFG	6	27, 5, 55	5.05*	...	...
	9	...	...	24, 52, 37	3.50
R Precentral gyrus	6	...	...	61, −4, 32	3.52
L Precentral gyrus	44	...	...	−6, 23, −2	4.4*
L Anterior cingulated gyrus	24	...	...	−6, 23, −2	4.41*
R MFG	46	41, 29, 24	3.69	...	...
	10	39, 54, 12	3.41	38, 42, 22	5.61*
	9	...	...	2, 50, 33	4.90
L MFG	44	−61, 12, 12	4.18	...	...
	6	−26, 14, 51	3.39	...	...
	9	...	...	−42, 30, 32	4.74
	8	...	...	−23, 19, 53	3.68
R IFG	47	...	...	41, 20, −8	3.57
R STG	22	48, −18, 2	3.30	...	...
	38	...	...	42, 18, −33	3.43
L STG	38	...	...	−47, 13, 11	3.75
R MTG	21	...	...	43, −9, −12	3.58
L MTG	21	...	...	−48, −60, 9	3.75
L ITG	37	−49, −43, −22	4.17	−41, −47, −28	3.42
	20	−56, −16, −32	3.52	...	...
R Uncus	28	25, −17, −32	3.74	...	...

R indicates right; L, left; SFG, superior frontal gyrus; MFG, middle frontal gyrus; IFG, inferior frontal gyrus; STG, superior temporal gyrus; MTG, middle temporal gyrus; ITG, inferior temporal gyrus.

All the areas were significant at a $P<0.001$, uncorrected for multiple comparisons at a voxel level. The asterisk identifies areas significant at a $P<0.05$, corrected for multiple comparisons (false discovery rate correction).

explained by a different vulnerability of different cortical regions. Several cross-sectional and longitudinal studies of healthy individuals have indeed demonstrated that the frontal and the temporal cortices are particularly susceptible to age-related damage.[16,23,24] Migraine-related changes might enhance such age-related susceptibility and result in an acceleration of the physiological brain shrinkage of particular GM areas. The correlation that we found between patient age and cortical GM-reduced density supports this speculation. Second, an additional factor that might contribute to the observed GM changes is retrograde degeneration of axons passing through macroscopic

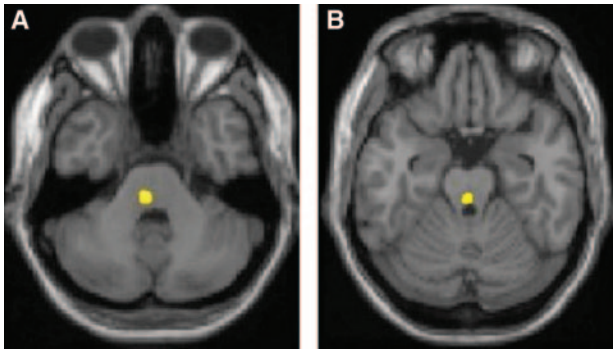

Figure 3. SPM regions superimposed on a high-resolution T1-weighted scan showing increased GM density in migraine patients with aura compared with those without aura ($P<0.001$, uncorrected at a voxel level; $P<0.05$ after SVC): A, Dorsolateral pons; B, PAG (neurological convention).

TABLE 3. Correlation Between Regions of Significantly Reduced GM Density in Migraine Patients and Clinical and MRI variables ($P<0.001$, uncorrected for multiple comparisons at a voxel level)

Anatomical Region	Age	Disease Duration	T2 Lesion Load
R SFG	r=−0.84	*r=−0.77	r=−0.71
L SFG	*r=−0.81	r=−0.77	...
R MFG	r=−0.80	*r=−0.77	...
L MFG	*r=−0.73	r=−0.81	r=−0.76
R STG	*r=−0.79	r=−0.75	NS
R MTG	NS	r=−0.79	NS
L MTG	NS	r=−0.78	NS
L ITG	r=−0.82	NS	NS

R indicates right; L, left; SFG, superior frontal gyrus; MFG, middle frontal gyrus; IFG, inferior frontal gyrus; STG, superior temporal gyrus; MTG, middle temporal gyrus; ITG, inferior temporal gyrus.

The asterisk identifies which of these variables drives the correlation for each of the areas identified (see statistical analysis for details).

T2-visible lesions of the WM, as suggested by the correlation found between GM density and T2-visible lesion load.

Our results conflict with those of a previous VBM study[8] in which no difference in GM density was found between migraine patients and controls. Because in both studies, patients were matched with appropriate control groups, this discrepancy might be attributable to the different radiological characteristics of the patients recruited. In our study, migraine patients were selected to have evidence of subcortical tissue damage on brain T2-weighted scans; this was because in the case of patients with normal MRI scans, it would have been impossible to know whether additional changes were actually not present or the technology used not sensitive enough. In addition, the higher field strength of the magnetic resonance magnet used in the present study (3 T versus 2 T) might also have resulted in an increased sensitivity for detecting subtle abnormalities and in a better segmentation of GM.

We also found an increased PAG density in migraine patients, which was more severe in migraine patients with aura. These latter patients also showed increased GM density in the dorsolateral pons. These findings fit with previous data showing an increased functional recruitment of brain stem regions of the dorsal pons[2] in a patient with migraine during an acute attack and with the results of 2 recent positron emission tomography studies showing an abnormal activation in the dorsolateral pons in a region that roughly corresponds to the one found in the present study during the migraine state in patients with and without aura.[18,25] In addition, although abnormal functional activations have been detected in migraine patients without aura,[1,2] several studies have also suggested a role of brain stem structures in the pathogenesis of migraine with aura. A case report showed functional MRI abnormalities in brain stem regions in a subject with migraine with aura.[26] These findings were subsequently confirmed in a cohort study.[27] In some of these patients, activation changes have also been detected in the dorsolateral pons and in the PAG. Finally, an abnormal iron homeostasis has been also documented in the PAG from migraine patients with and without aura,[28] possibly caused by repeated migraine attacks. All these results support the notion of PAG as a possible "generator" or "modulator" of the migraine attacks, possibly via a dysfunctional control of the trigeminovascular nociceptive system. It is indeed known that PAG stimulation modulates the activity of central trigeminal neurons that receive nociceptive input from dural and trigeminovascular afferents[29,30] and that nonheadache patients can develop migraine-like episodes after stereotactic placement of electrodes in the PAG for treatment of other pain syndromes.[31] Admittedly, we recruited a selected group of patients with migraine (ie, patients with WM hyperintense lesions) and, as a consequence, our results might not be generalized to the entire population of migraineurs. Therefore, we acknowledge the need to replicate these findings in a population of patients unselected for the presence of T2 brain abnormalities. In addition, considering the relatively small number of patients studied when considering patients with and without aura separately, the between-group comparison findings need to be replicated on larger samples of patients.

We believe that the increased GM density changes observed in our migraine patients are likely to be permanent and not related to transient increased function because all our patients were studied in a headache-free state. However, considering that definitive histopathological correlation in these patients are unlikely to ever be obtained, only a longitudinal MRI study of these patients would provide more definitive hints on this issue. At present, we can only speculate on the nature of the pathological changes underlying increased GM density in brain regions of migraine patients. First, a synaptic and neuritis size increase related to an experience-dependent plasticity can be advocated. The repetition of migraine attacks with the continuous activation of pain-related pathways might drive the formation of synapses, and these changes might lead to adaptive remodeling of neural circuits, as suggested for sensory experience[32] and learning.[33] Second, increased GM density might be the consequence of neuronal loss and secondary reactive gliosis in those brain regions that experience significant functional changes during the migraine attacks. Finally, preapoptotic osmotic changes associated to early neuronal and glial pathology secondary to the vascular changes observed during the migraine attacks might also play a role in this context.

Disclosures

None.

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