Headache
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ISSN 0017-8748
doi: 10.1111/j.1526-4610.2008.01133.x
Published by Wiley Periodicals, Inc.

Research Submission

Attack Frequency and Disease Duration as Indicators for Brain Damage in Migraine

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Objective.—The aim of this study was to pinpoint predilection sites of brain damage in migraine by quantitatively identifying morphometric and diffusion differences in migraineurs, compared with control subjects, and to assess whether migraine attack frequency and attack history are indicators for brain abnormalities in migraineurs.

Background.—Previous clinical neuroimaging investigations introduced the concept of migraine as a progressive brain disease. They reported an increased risk of white matter hyperintensities (WMH) with increasing attack frequency in migraineurs.

Methods.—We investigated 28 patients with migraine, using high-resolution T1- and diffusion-weighted magnetic resonance imaging and optimized voxel-based morphometry to localize gray and WM density, and fractional anisotropy and apparent diffusion coefficient differences.

Results.—We identified predilection sites of brain abnormalities in migraineurs in the frontal lobes, brainstem, and the cerebellum, and we show that both attack frequency and disease duration are indicators for brain damage in migraine.

Conclusion.—Our findings report an unbiased quantitative whole brain assessment of morphological abnormalities in migraine. This might help to identify indicators for migraine as a possibly progressive brain disease. In order to reveal the causes and consequences of brain damage in migraine, further neuroimaging studies have to investigate quantitative brain changes in a longitudinal design.

Key words: apparent diffusion coefficient, frontal lobe, fractional anisotropy, migraine, optimized voxel-based morphometry

Abbreviations: ANOVA analysis of variance, BA Brodman area, CSF cerebral spinal fluid, DTI diffusion tensor imaging, FDR false discovery rate, FWE family wise error, FWHM full width at half-maximum, GM gray matter, MA migraine with aura, T&T Talairach and Tournoux coordinates, MO migraine without aura, MRI magnetic resonance imaging, NABT normal appearing brain tissue, VBM voxel-based morphometry, WMH white matter hyperintensities

(*Headache* 2008;48:1044-1055)

INTRODUCTION

Migraine is a common neurovascular disorder, typically characterized by recurrent attacks of debilitating headache and associated symptoms of autonomic nervous system dysfunction (migraine without aura, MO); in up to one-third of patients, attacks are also accompanied by transient focal neurological aura symptoms (migraine with aura, MA). Adult women

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Accepted for publication March 7, 2001.

Conflict of Interest: None

are 3 times more affected than men, and on average 20% of the population will develop migraine during a lifetime. The enormous economic burden of the disease has previously been identified;[1,2] the neurobiological and pathophysiological processes underlying the disorder are, however, largely unknown. Clinical studies reported that migraine is a risk factor for ischemic stroke in younger women.[3,4] Neuroimaging findings of a large-scale population-based study showed that silent brain damage is more frequent in migraineurs, compared with control subjects.[5,6] The authors reported that migraineurs with aura have an increased risk of supra-tentorial deep white matter hyperintensities (WMH). This risk increased even further with increasing attack frequency. Therefore, the authors suggested that there is a relationship between migraine attacks and the occurrence of WMH that could lead to migraine being a progressive brain disease. The predilection sites of brain damage in migraine were, however, not specified, and only visible WMH (lesions) were investigated. Moreover, quantitative whole brain morphological differences between migraineurs and controls were not assessed. In contrast, Rocca et al,[7] using quantitative diffusion tensor imaging (DTI), reported that brain damage in migraine exists beyond WMH-visible lesions. The authors investigated widespread pathological damage of normal appearing brain tissue (NABT) in migraineurs, and reported reduced NABT mean diffusion histogram peak height in migraineurs, compared with control subjects, demonstrating the ability of quantitative imaging to reveal brain abnormalities beyond magnetic resonance (MR)-visible lesions. Also, quantitative structural whole brain voxel-based morphometry (VBM) methods have been employed to identify predilection sites of brain abnormalities in migraine; however, results are scarce and contradictory.[8-10] Rocca et al[8] reported reduced cortical gray matter (GM) density of frontal and temporal lobes, and increased periacqueductal GM density. Granziera et al[10] showed increased cortical thickness of the occipital lobes and water diffusion abnormalities of the superior colliculus and lateral geniculate nucleus; and Matharu et al[9] identified no quantitative morphological changes in migraineurs, compared with control subjects.

The aim of this study is to quantitatively identify predilection site of possible brain damage in migraineurs and to find evidence for the concept of migraine as a disease that leads to progressive brain damage. We performed a VBM analysis on high-resolution structural and DTI images in the same population of migraineurs, compared with control subjects. Additionally, we compared migraineurs with a high attack frequency to those with a low frequency of attacks, and migraineurs with a long disease duration to those with a short duration of disease, to assess the impact of attack frequency and disease duration on brain abnormalities in migraine. We furthermore assessed the volumetric extent of WMH in migraineurs and control subjects.

METHODS

Subjects.—We included 28 adult female individuals with migraine (8 with MA and 20 with MO, mean age 43.5 years, SD: 8.21), and 28 female age-matched control subjects (mean age: 42.50 years, SD: 9.31, $P < .672$) (Table 1a). Individuals with migraine were recruited through local and national magazines and newspapers, whereas controls were recruited locally by advertisement. Migraine patients were diagnosed in the department of neurology at Leiden University using International Headache Society[11] criteria. There is no conflict of interest of any of the authors.

All participants of the study gave written informed consent as approved by the local research ethics committee of Leiden University and were between 20 and 65 years of age at time of scanning. None of the participants was taking medication and all were headache-free for 7 days or more at time of scanning.

All participants underwent a structured clinical examination to exclude comorbid medical and psychiatric disorders, possibly affecting the brain. None of the participants had a history of major medical illnesses (including cardiac disease and diabetes), psychiatric or neurological disorders other than migraine (Table 1 for patient characteristics).

MRI Protocols.—All participants were scanned with a clinical 3 Tesla magnetic resonance imaging (MRI) system (Philips Medical System, Best, The

Netherlands). For each individual, all images were acquired in the same session. Prior to the neuroimaging investigation, participants were made familiar with the scanner and the scanning procedures.

1. Structural 3D T1-weighted high-resolution, gradient echo images were acquired (repetition time [TR]/echo time [TE] of 9.8/4.6 ms; axial orientation; 120 continuous [no interslice gap] slices; slice thickness 1.2 mm; flip angle 8°; 224-mm field of view (FOV); acquisition matrix 256×256; acquisition voxel size $1.20 \times 0.8 \times 0.8$ mm) to identify GM, WM density.
2. Diffusion tensor imaging was acquired using 3D multislice spin echo single shot echo-planar imaging (with: TR/TE: 8872/51 diffusion sensitivities of b = 0 and b = 1000 s/mm^2; 6 orthogonal diffusion gradients [YZ, XY, XZ, Y-Z, X-Y, and X-Z]; 48 continuous [no interslice gap] slices, slice thickness 3 mm, 224-mm FOV; acquisition matrix 112×112; acquisition voxel size $2 \times 2 \times 3$ mm). DTI data were preprocessed using in-house software[12] to create

Table 1.—Subject Characteristics
Table 1a.—Characteristics of the Study Sample (n = 48)

	Subgroups		
	Migraine (n = 28)	Controls (n = 28)	*P* value
Age (years/SD)	43.50 (8.21)	42.50 (9.31)	.672
Mean disease duration in years (SD)	30.50 (11.43)	NA	NA
Mean attack frequency per month (SD)	3.50 (1.97)	NA	NA

For continuous variables, denotation is mean (SD); for categorical variables, denotation is number (%).
NA = not applicable.

Table 1b.—Characteristics of the Study Sample, by Subdiagnosis Migraine (n = 28)

	Subgroups		
	MA (n = 8)	MO (n = 20)	*P* value
Age (years/SD)	41.25 (14.51)	44.03 (9.43)	.233
Disease duration in years (SD)	25.75 (14.49)	33.50 (8.98)	.181
Attack frequency per month (SD)	3.44 (2.13)	3.60 (2.00)	.986
Education (number of subjects in each category)			
Lowest	1	0	.381
Low	0	1	
Higher	2	7	
Highest	4	11	
Unknown	1	1	
Number of subjects with history of hypertension	0	3	.219
Smoking			
Number of smokers	3	8	.752
Pack-years (SD)	7.17 (3.01)	8.14 (7.85)	.844
Oral contraceptive			
Number of users	6 (85.7)	13 (81.3)	.795
Years of use (SD)	9.17 (4.31)	17.77 (9.60)	.015

Table 1c.—Characteristics of the Study Sample: Attack Frequency (n = 28)

	Subgroup		
	High attack frequency (hf) (n = 14)	Low attack frequency (lf) (n = 14)	*P* value
Migraine diagnosis			
MA	5	3	.421
MO	9	11	
Age (years/SD)	45.31 (10.40)	44.64 (8.51)	.866
Disease duration in years (SD)	34.46 (11.91)	26.77 (11.73)	.110
Education (number of subjects in each category)			
Lowest	0	1	.561
Low	0	1	
Higher	4	5	
Highest	9	6	
Unknown	1	1	
Number of subjects with history of hypertension	3	0	.052
Smoking			
Number of smokers	5	6	.827
Pack-years (SD)	10.08 (8.22)	5.43 (4.53)	.202
Oral contraceptive			
Number of users	10	9	.924
Years of use (SD)	16.60 (10.54)	10.33 (7.52)	.452

MA = migraine with aura; MO = migraine without aura.

Table 1d.—Characteristics of the Study Sample: Duration of Disease (n = 28)

	Subgroup		
	More than 15 years of disease (ld) (n = 18)	Less than 15 years of disease (sd) (n = 10)	*P* value
Migraine diagnosis			
MA	6	2	.149
MO	12	8	
Age (years)	46.50 (8.43)	40.33 (11.34)	.257
Attack frequency (attacks per month)	4.29 (2.25)	2.79 (2.33)	.109
Education			
Lowest	1	0	.370
Low	1	0	
Higher	5	4	
Highest	9	6	
Unknown	2	0	
Number of subjects with history of hypertension	3	0	.052
Smoking			
Number of smokers	4	7	.292
Pack-years (SD)	9.56 (10.53)	6.91 (4.09)	.657
Oral contraceptive			
Number of users	9	10	.924
Years of use (SD)	15.0 (9.41)	9.1 (6.40)	.982

Education was assessed as highest completed schooling, with lowest: primary school, low: secondary school, higher: GCSE or A-level equivalent, highest: further education (eg, college/university).
GCSE = General Certificate of Secondary Education; MA = migraine with aura; MO = migraine without aura.

apparent diffusion coefficient (ADC) and fractional anisotropy (FA) value maps. ADC maps allow the assessment of global mean brain water diffusivity and are expressed as a summary of statistical parameters representing the complex microscopic distribution and displacement of water molecules in a voxel of brain tissue. FA maps, however, are a representation of the directionality and density of WM fiber tracts. FA has an (eigen-) value between 1 (1 directional or anisotropic water diffusion) and 0 (isotropic diffusion). FA values are used as a measure of brain tissue integrity. A decrease in FA values is an indicator for WM fiber loss or water influx due to tissue damage.

3. Additionally, we acquired 3D T2-weighted turbo spin echo images (with TR/TE: 4741/80 ms; axial orientation; 48 continuous [no interslice gap] slices; slice thickness 3 mm, 224-mm FOV; acquisition matrix 448×448; acquisition voxel size $0.5 \times 0.5 \times 3$ mm), as an anatomical ADC and FA map coregistration template and to assess WMH expressed in WM lesion load in cubic centimeters (cc) of migraineurs and control subjects, using in-house software.[12]

Preprocessing of Neuroimaging Data.—All data were processed using SPM2 (Wellcome-Department of Cognitive Neurology, London, UK) modified for optimized VBM on a MATLAB platform (The MathWorks Inc., USA; version 6.5.2). Additionally, in-house software[12] was used for a fully automated assessment of ADC and FA mean histogram and normalized peak height values and the assessment of WM lesion load. For statistical comparisons, Statistical Package for Social Science (SPSS Inc., Chicago, IL, USA; version 11.0.1) was used. All images were checked for artefacts and image corruption before entering statistical analysis.

Structural T1-Weighted Images.—We used optimized VBM implemented in SPM2 to identify regional differences in WM and GM concentration (density) and cerebral spinal fluid (CSF) of individuals with migraine compared with control subjects. Optimized VBM techniques included: customized template creation, spatial normalization, tissue segmentation, and smoothing.[13-15] A participant-based template was created, using all original, nonnormalized T1-weighted images of the complete sample. Next to the customized template, prior images of GM, WM, and CSF were generated based on the existing T1-weighted template in SPM2, and smoothed with a Gaussian kernel of 8-mm full width at half-maximum (FWHM). Thereafter, automated optimizations in SPM2 (Department of Psychiatry, University of Jena, Germany) were used to spatially normalize and segment all T1-weighted images, based on the customized T1-weighted template. The prior images of GM, WM, and CSF were used for segmentation. All standard presets in SPM2 were maintained. For statistical comparison, GM, WM, and CSF segments were smoothed with a 10-mm FWHM isotropic Gaussian-kernel, which renders the data more normally distributed to achieve optimal outcome in parametric statistical comparisons.

DTI.—We used a modified optimized VBM procedure for the analysis of diffusion-weighted images.[16] This method uses a T2-weighted template to normalize $b = 0$ images. This is necessary since the subtle contrast differences between GM and WM on diffusion images rely on T2-decay. Therefore, a participant-based template was created using all original, nonnormalized T2-weighted images. We created the T2-weighted template with the same voxel-dimension as the T1-weighted template. Thereafter, a customized $b = 0$ template (DTI-template) was created using the T2-weighted anatomical information. Additionally to the DTI-template creation, spatial normalization and smoothing were carried out. Next to the customized DTI-template, prior images of WM were generated on the basis of the T2-weighted image. This T2-weighted WM mask was created to remove nonbrain tissue from the ADC and FA images. Resulting from this procedure was: 1 customized DTI template ($b = 0$ image quality), and "stripped" ADC and FA maps, containing no nonbrain tissue. The ADC and FA images were thereafter *write normalized*, using the transformation matrix of the individually spatially normalized $b = 0$ image of the corresponding subject. This procedure

ensured the quantitative nature of the FA and ADC information to stay intact. The images were then smoothed with 10-mm FWHM preceding statistical analyses.

WM Lesion Load Assessment.—T2-weighted images were used for the assessment of WM lesion load. We employed a quantitative assessment for the whole brain using in-house software.[12] The WM lesion load volume was calculated in cc for all subjects.

Statistical Analysis of Neuroimaging Data.—Analysis of variance (ANOVA) was carried out (employing the General Linear Model and the SPM platform) to investigate group differences on a voxel-by-voxel basis for GM, WM, CSF segments, ADC and FA value maps. We used ANOVA to calculate regional GM, WM, CSF, ADC, and FA differences between people with migraine and controls (Table 2). Furthermore, we compared anatomical (GM, WM, CSF) and diffusion (ADC, FA) differences in migraine subgroups of high attack frequency (more than 3 attacks a month, hf) and low attack frequency (less than 3 attacks a month, lf) (Table 1c), and long disease duration (more than 15 years of disease, ld), compared with short disease duration (less than 15 years of migraine attacks, sd) (Table 3), using 2-way ANOVA.

To reduce type 2 errors, we corrected all data for multiple comparisons. This procedure was performed in a successive order, starting at (1) at $P < .001$, uncorrected for multiple comparisons with height threshold (t) at zt = 3.27 at voxel level, with a minimal cluster size (cluster extend threshold at $P < .001$) of 50 voxels; then, (2) individual significant clusters were corrected for multiple comparisons ($P < .05$ [at cluster level, P_c]). Furthermore, (3) false discovery rate (FDR) and family wise error (FWE) corrections of multiple voxel comparisons were applied to the data. Data that do not survive correction for multiple comparisons (at a cluster level, P_c) are to be considered preliminary findings. Voxels and clusters surviving correction for multiple comparisons were localized using the Montreal Neurological Institute space and transformed into Talairach and Tournoux (T&T[17]) coordinates.[18] For results in WM and CSF segments, T&T coordinates are given as an indication of the voxel location in a standardized brain.

RESULTS

Brain Abnormalities in Migraineurs, Compared With Control Subjects.—Individuals with migraine, compared with control subjects, showed significantly (P_c, FWE/FDR < 0.0001, $Z = 5.63$) reduced FA values in the superior frontal lobe, the medial frontal lobe ($P_c < .0001$, $Z = 5.59$), the brainstem ($P_c < .0002$, $Z = 5.36$), and the cerebellum ($P_c < .0003$, $Z = 4.96$) (Table 2a). No increased FA values (Table 2b) and no significant differences in ADC values were found in our comparisons.

Additionally, migraineurs, compared with control subjects, showed preliminary (significant at $P < .001$, uncorrected) frontal, occipital, and parietal WM and frontal GM density reduction, and increased superior frontal WM density (Table 2c,d). No significant ($P < .001$, uncorrected) differences in CSF were found in migraineurs, compared with control subjects.

Brain Abnormalities Related to Attack Frequency.—Individuals with migraine with a high attack frequency (more than 3 migraine attacks per month, hf), compared with those with low attack frequency (less than 3 attacks per month, lf), show significantly ($P_c < .0002$, $Z = 4.70$) reduced left parahippocampal (Brodman area [BA] 28) GM density (and additionally, right parahippocampal [$P < .001$, not corrected, $Z = 2.7$] GM reduction), reduced left superior frontal gyrus (BA 8, $P_c < .010$, $Z = 4.53$) and the inferior parietal lobe (BA 39, $P_c < .001$, $Z = 4.34$) GM density (Fig. 1), and significantly ($P_c < .004$, $Z = 3.97$) reduced WM density in the right frontal lobe and increased density in the left parietal lobe ($P_c < .016$, $Z = 3.83$) (Fig. 1, Table 3a,b).

Fractional anisotropy and ADC values of hf and lf migraineurs did not survive correction for multiple comparisons (Table 3c).

Brain Abnormalities Related to Disease Duration in Migraineurs.—Individuals with more than 15 years of migraine attacks (long disease duration, ld), compared with those with a short disease duration (less than 15 years of migraine attacks, sd), showed significantly ($P_c < .049$) decreased GM density in the basal ganglia and the brainstem (medulla) ($P_c < .001$) (Fig. 2a, Table 3d) and significantly ($P_c < .002$, $Z = 4.63$) increased WM density in the cerebellum, bilaterally (Fig. 2a, Table 3e). Additionally, ld

Table 2.—Brain Abnormalities in Migraineurs

Brain area	BA		T&T coordinates			$P < .001$ uncorrected	Z value†‡	Corrected at $P < .05$, cluster level (P_c)	FDR/FWE corrected
(a) Decreased FA values in migraineurs									
Superior frontal lobe	WM	L	–10	18	50	.0006	5.63	.0006	0.0001/0.0008
Medial frontal lobe	WM	R	32	30	36	.0005	5.59	.0006	0.0001/0.001
Frontal lobe, precentral	WM	R	20	4	56	.0004	5.04	.0007	0.0001/0.002
Brainstem	WM	R	20	–30	–50	.0005	5.36	.0006	0.0002/0.008
Cerebellum	WM		0	–74	–34	.0009	4.96	.0008	0.0003/0.012
(b) Increased FA values in migraineurs									
(a) Decreased GM and WM density in migraineurs									
Superior frontal gyrus	BA 9	R	38	48	34	.0009	3.79	n.a.	n.a.
								n.a.	n.a.
Frontal lobe white matter, bilaterally	WM	R	56	–12	35	.0009	3.47	n.a.	n.a.
		L	–39	25	–13	.0009	3.47		
Inferior parietal lobe	BA 40	L	–40	–54	38	.0009	3.71	n.a.	n.a.
								n.a.	n.a.
Occipital lobe white matter	WM	R	37	–87	–03	.001	3.27	n.a.	n.a.
Parietal lobe white matter	WM	R	12	–36	66	.0009	3.76		
(b) Increased GM and WM density in migraineurs									
Superior frontal lobe white matter	WM	R	31	19	20	.000	3.75	n.a.	n.a.

P values at $P < .001$.
Gray matter and WM density and FA value differences in migraineurs, compared with control subjects.
†Z value is calculated for most significant voxel in a cluster of at least 50 neighboring significant ($p < .001$) voxels.
‡Z value on voxel level, P_c = significance threshold at $P < .05$, corrected for multiple comparisons at cluster level.
FDR-false discovery rate, FWE-family wise error; BA = Brodman area; FA = fractional anisotropy; FDR = false discovery rate; FEW = family wise error; GM = gray matter; n.a. = not applicable; T&T = Tailairach and Tournoux; WM = white matter.

Table 3.—Brain Abnormalities in Relation to Attack Frequency and Disease Duration

Brain area	Tissue class/BA		T&T coordinates			$P < .001$ uncorrected	Z value†	Corrected at $P < .05$, cluster level (P_c)
Attack frequency								
(a) Decreased GM and WM density								
Limbic lobe, parahippocampal gyrus	BA 28	L	–18	–12	–22	.0006	4.70	$P_c < .0002$
Superior frontal gyrus	BA 8	L	–15	35	52	.0007	4.53	$P_c < .010$
Inferior parietal lobe	BA 39	L	–41	–64	40	.0007	4.34	$P_c < .001$
Frontal lobe	WM	R	30	–26	52	.0007	3.97	$P_c < .004$
Putamen	GM	R	24	–03	–01	.0008	3.45	n.a.
Parietal lobe	WM	R	53	–21	23	.0008	3.71	n.a.
(b) Increased GM and WM density								
Superior parietal lobe	WM	L	–21	–64	38	.0008	3.83	$P_c < .016$
(c) FA value differences								
n.a.								
Disease duration								
(d) Increased GM and WM density								
Parietal lobe	WM	L	–15	–46	43	.0006	4.36	n.a.
Cerebellum, bilaterally	WM	R	33	–63	–32	.0006	4.63	$P_c < .002$
(e) Decreased GM and WM density								
Lentiform nucleus/Globus pallidus, GM	GM	R	11	–2	–1	.0006	4.02	$P_c < .049$
		R	3	–17	–40	.0006	4.20	$P_c < .001$
(f) FA value differences								
Frontal lobe	WM	R	10	30	52	.0006	4.27	$P_c < .005$
Limbic lobe	WM	L	–12	24	30	.0006	4.10	

P values at $P < .001$.
Gray matter and WM density differences in individuals with migraine with a high attack frequency compared with low attack frequency (Table 3a-c), and migraineurs with long disease duration vs short diseased duration (Table 3d-e).
†Z value on voxel level. P_c = significance threshold at $P < .05$, corrected for multiple comparisons at cluster level.
Z value is calculated for most significant voxel in a cluster of at least 50 neighboring significant ($P < .001$) voxels.
‡All individuals are age- and sex-matched in the group comparisons.
BA = Brodman area; FA = fractional anisotropy; GM = gray matter; n.a. = not applicable; T&T = Tailairach and Tournoux; WM = white matter.

migraineurs, compared with sd, had significantly ($P_c < .005$, $Z = 4.27$) decreased FA in the right frontal lobe (Fig. 2b, Table 3f). No increases in FA values and no differences in ADC values were found.

WM Lesion Load.—Whole brain WM lesion load in migraineurs did not differ from control subjects (in cc, migraineurs, mean lesion load: 0.69 cc/SD: 0.64, controls: 0.57/SD: 0.82, $P < .46$). Furthermore, WM lesion load did not differ in hf migraineurs, compared with lf (mean: hf: 0.45/SD: 0.3, lf: 0.43/SD: 0.39, $P < .31$), and SD migraineurs (0.41/SD: 0.61) compared with ld (0.43/SD: 0.56, $P < .22$).

DISCUSSION

We show that predilection sites for brain abnormalities in migraine are the frontal lobe, limbic system, parietal lobes, the basal ganglia (globus pallidus and putamen), brainstem, and the cerebellum. More importantly, we demonstrate that attack frequency and disease duration have an influence on brain structure and integrity in migraineurs. Migraineurs suffering from a high monthly frequency of migraine attacks show reduced localized GM density, compared with those with low attack frequency, in fronto-limbic and parietal regions, and WM density reductions in the frontal lobes. Furthermore, disease duration in migraineurs was associated with both brain structure and diffusion abnormalities: individuals with long compared short disease duration have reduced frontal anisotropy, and increased WM density (an indicator for the thickening of the appearance of WM fiber bundles) in the cerebellum,

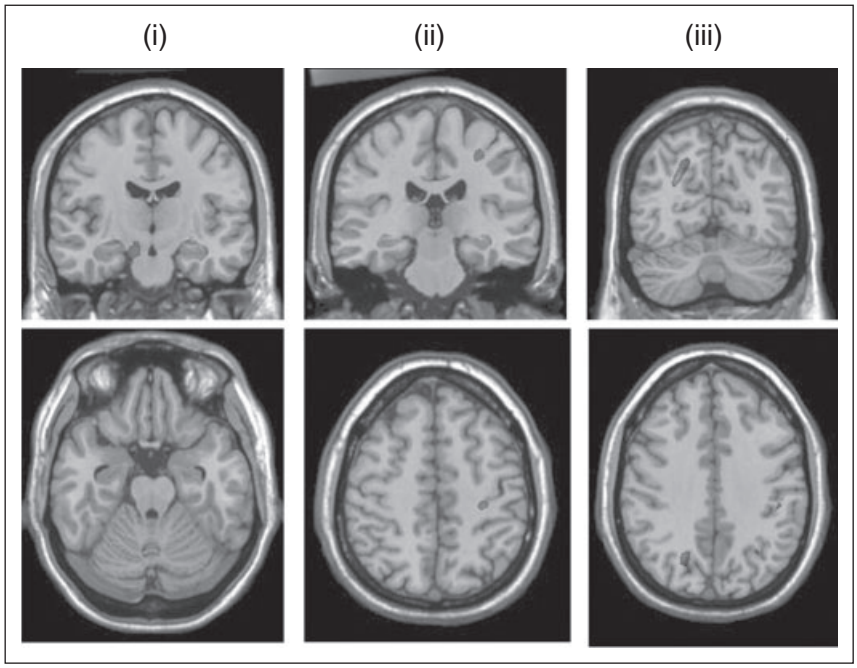

Fig. 1.—Attack frequency. Gray and white matter density differences of migraineurs with high attack frequency (hf), compared with migraineurs with low attack frequency (lf). Hf migraineurs, compared with lf migraineurs, show significantly ($P < .05$, corrected at cluster level) decreased gray matter density of the right parahippocampal gyrus (i), reduced frontal lobe (ii), and increased superior parietal lobe white matter density (iii) (see Table 3a,b).

bilaterally, and reduced GM density of the brainstem and lentiform nucleus.

We show that the frontal lobe is one of the most prominent areas of brain abnormalities in migraineurs. Morphological changes in the frontal lobes have earlier been reported in migraineurs.[8] Apkarian et al[19] attributed morphological changes in migraineurs to pathophysiological effects of pain processing. The authors investigated the neural correlates of chronic pain and reported reduced prefrontal and thalamic GM density, which was associated with atrophy of the frontal cortex. We, too, detected superior frontal gyrus and limbic lobe (parahippocampal gyrus) GM density reduction; however, we did not detect CSF changes that we could attribute to evidence of atrophy in migraineurs, compared with control subjects. Pain-related morphological changes are one possible explanation for frontal lobe-related brain differences in migraineurs. For example, during migraine attacks, Afridi et al[20] identified (among others) prefrontal and cingulate activation, using positron emission tomography. The authors speculate that pain-related processes underlying the migraine headache are associated with abnormalities of glucose metabolism in the frontal lobe, possibly causing structural damage. This could explain why we see frontal lobe abnormalities in both migraineurs suffering from high attack frequency and long-time migraine sufferers. A high frequency of migraine attacks or a long history of the disease might contribute to accumulating brain damage due to the repetitive occurrence of pain-related processes. In addition to frontal lobe differences, Afridi et al[20] and others[21,22] reported functional, pain-related activation changes in brainstem and pons during migraine attacks. We show that migraineurs with long disease duration have WM density increases, in the cerebellum, bilaterally. Cerebellar abnormalities are thought to be the underlying cause for functional[23,24] and metabolic[25] disturbances in migraine, but the relationships between the observed morphological, metabolic, and functional changes have yet to be established. Also, quantitative WM density increases in migraineurs have not been identified earlier. In contrast, local increases of GM in histological investigations of migraine models and cortical spreading depression

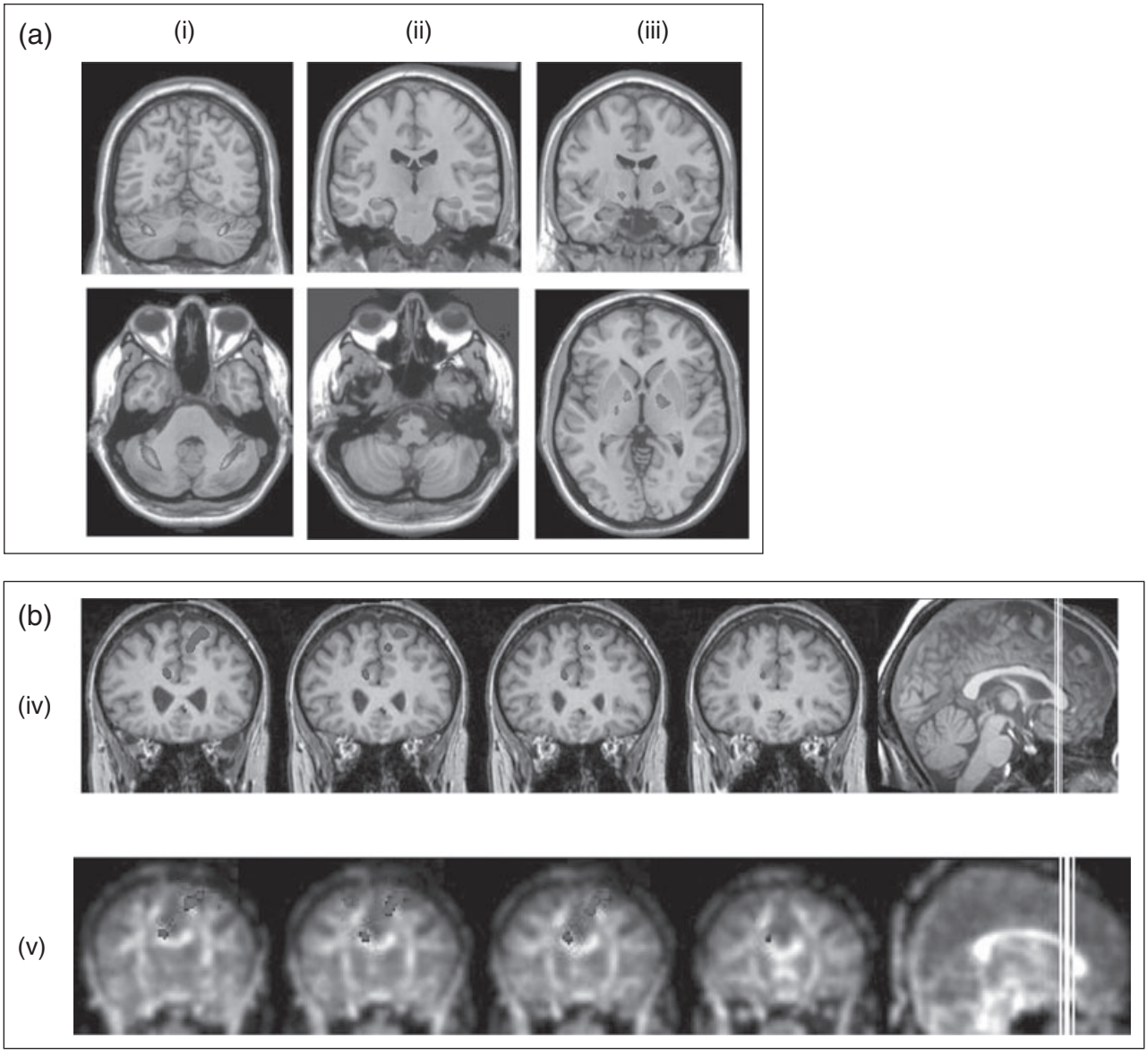

Fig. 2.—Disease duration. (a) Gray and white matter density differences of migraineurs with long disease duration (ld), compared with migraineurs with a short disease duration (sd). Ld migraineurs, compared with sd migraineurs, show significantly ($P < .05$, corrected at cluster level) increased white matter density of the cerebellum, bilaterally (i), reduced gray matter of the brainstem (ii), and basal ganglia (iii) (see Table 3c,d). (b) Fractional anisotropic (FA) differences of ld migraineurs, compared with sd migraineurs. Significantly ($P < .001$, cluster level) reduced FA in ld migraineurs overlaid on (iv) a high-resolution Montreal Neurological Institute template, (v) FA map.

(CSD) have been reported in animal studies.[26] In an induced CSD migraine model in rats, Yanamoto et al[26] reported that repetitive CSD caused generation of neuron-like cells in particularly the putamen and the cortices. The authors report that persistent neurogenesis caused cell density to increase and could therefore explain increases in GM concentration of T1- and T2-weighted images. Instead, we found decreased GM density in the basal ganglia of migraineurs (eg, in the globus pallidus of migraineurs with a long disease duration and in the putamen of migraineurs with a high attack frequency). Our findings cannot be explained by CSD-induced generation of neurons, but rather suggest a more destructive effect of migraine attack on the basal ganglia. CSD may be one of the mechanisms responsible for brain

tissue changes in migraine and it may also play a role for the anatomical correlates of disease duration and severity; however, neurogenesis is not evident from our data.

There are some limitations to the current study that need to be considered when interpreting the findings: we used an unbiased quantitative whole brain optimized VBM approach on a homogeneous sample of migraineurs. VBM, however, does not identify microstructural or cyto-architectural changes in brain; hence, the pathophysiological nature of the abnormalities found is not clear. Our results differ partly from earlier morphological assessments of the migraine brain. This could be due to data processing or subject selection: Matharu et al[9] used T1-weighted data, focusing on macroscopic structural changes in the brainstem, and in particular the hypothalamus and the pons, whereas we used an unbiased whole brain quantitative voxel-based analysis, including cortical and subcortical brain structures; Rocca et al[7] employed DTI and histogram analysis, but we used VBM to localize FA and ADC differences on a voxel-by-voxel basis, excluding the problem of histogram shifts across different brain regions. There are also differences in subject selection: Rocca et al[8] obtained images from a sample of 34 migraineurs and only 17 control subjects, who were not gender- or socioeconomically matched; and Mathura et al[9] used 10 individuals with MA, 17 with MO, and 11 control subjects. In our study, 28 female individuals with migraine and 28 age-, sex-matched control individuals were used. Furthermore, individuals with high and low attack frequency and also migraineurs with long and short disease duration were age- (and gender-) matched. This enabled us to reliably tackle the issue of progressive brain abnormalities while excluding the confounding influence of age. We included 8 individuals with MA and 20 MO individuals. The clinical prevalence of 30% of MA in the general migraine population is therefore reflected in our data; still, the population investigated in this study may not fully represent the general migraine population, as only female migraineurs were included.

Our aim was to identify predilection sites of possible brain damage in migraine and we identified morphological and diffusion abnormalities mainly in the frontal lobes, the brainstem, and the cerebellum. Furthermore, our study gives evidence for a progressive component of brain abnormalities in migraine: in line with earlier studies,[5,6] we identified GM and WM abnormalities in the brainstem and the cerebellum that were significantly more pronounced in individuals suffering from migraine for more than 15 years. Those long-time sufferers also showed diffusion abnormalities in the frontal and limbic lobes. Migraineurs with a high attack frequency showed increased brain abnormalities in the frontal and the parietal lobes. Our findings report an unbiased assessment of quantitative whole brain abnormalities in migraine. The cause of such abnormalities has not yet been identified. In order to reveal the causes and consequences of brain damage in migraineurs, further neuroimaging investigations have to quantify brain abnormalities in a longitudinal design, using interictal, ictal, and postictal assessments. The current study helps to identify indicators of predilection sites for possibly progressive brain damage in migraineurs and it provides the first step of a whole brain quantitative investigation of brain abnormalities in migraine.

Acknowledgment: This project was supported by the Hersenstichting Nederland (grant: H04/08).

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