Volumetric brain changes in migraineurs from the general population

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ABSTRACT

Objective: To assess volumetric brain changes in migraineurs from the general population compared with controls.

Methods: Structural brain changes in migraineurs from the general population-based MRI Cerebral Abnormalities in Migraine, an Epidemiologic Risk Analysis (CAMERA)-2 observational cohort study were assessed by state-of-the-art voxel-based morphometry. T1-weighted MRIs of 84 migraineurs (52 with aura, 32 without aura) and 35 headache-free controls were evaluated. Regional volumes were compared voxelwise, corrected for age, sex, and total intracranial volume, with region-of-interest and whole-brain analyses.

Results: In region-of-interest analyses, migraineurs showed decreased gray matter volume in the visual areas V3 and V5 of the right occipital cortex compared to controls ($p < 0.05$, familywise error correction). Post hoc analyses revealed that similar changes were present regardless of migraine aura status, disease activity (>1 year attack-free [inactive] vs ≥ 1 attack within the last year [active]) and attack frequency (≤ 1 [low] vs ≥ 1 attack per month [high]). In exploratory whole-brain analyses ($p < 0.001$, uncorrected for multiple comparisons), we identified additional structural differences in migraineurs in other cortical and subcortical areas, including white matter tracts, that are particularly involved in visual processing.

Conclusions: Migraineurs from the general population showed small volumetric brain changes, mainly in cortical areas involved in visual motion processing, compared to controls. The presence of morphologic changes regardless of the presence of migraine aura or disease activity suggests that migraines with and without aura share common pathophysiologic pathways and suggests that these changes are (partially) irreversible or might have been present throughout life.

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GLOSSARY

CAMERA = Cerebral Abnormalities in Migraine, an Epidemiological Risk Analysis; **DARTEL** = diffeomorphic anatomic registration exponentiated lie algebra; **MNI** = Montreal Neurological Institute; **ROI** = region of interest; **SPM** = Statistical Parametric Mapping; **VBM** = voxel-based morphometry; **WMH** = white matter hyperintensity.

Despite many studies investigating structural changes in migraine,^{1,2} it remains unclear whether, how, and to what extent migraine affects brain morphology.

Voxel-based morphometry (VBM) is an automated, unbiased method for voxel-by-voxel comparison of gray and white matter density and volume.³ Several groups have reported VBM gray matter changes in migraine, particularly volume decreases in pain-transmitting and pain-processing areas.⁴⁻¹⁰ Other groups used surface-based morphometry and found cortical thinning in areas involved in nociception¹¹ and cortical thickening in the somatosensory cortex¹² and visual motion processing areas.^{11,13} Cortical surface area was increased in regions involved in executive functioning and visual motion processing, while it was decreased in pain-processing areas.¹¹

There is, however, ongoing discussion about the relevance, specificity, and generalizability of these findings; the possible causes (e.g., changes in metabolism, neurotransmitter levels, or

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functional processing of sensory information); possible reversibility; and whether these changes are a cause or a consequence of migraine.^{1,2} The earlier study samples were relatively small and included primarily migraineurs from headache clinics who were likely to be affected more severely than average, overusing acute antiheadache medications, and with comorbid (psychiatric) diseases that may affect brain architecture.^{1,2,9,14–16} Finally, these VBM and surface-based morphometry studies did not always account for the increased risk of subclinical brain lesions that are more prevalent among migraineurs.^{17,18}

We assessed cerebral gray and white matter volumes of migraineurs from the general population by applying state-of-the-art VBM while minimizing the potential influence of the various confounders reviewed above.

METHODS **Participants.** Participants originated from the Cerebral Abnormalities in Migraine, an Epidemiologic Risk Analysis (CAMERA-2) study, a 9-year follow-up study on brain changes in participants with migraine and controls from the general population. Characteristics of the study population and the assessment of migraine have been described in detail elsewhere.¹⁸ In short, participants with migraine (diagnosed according to International Headache Society criteria¹⁹) and age- and sex-matched controls were evaluated by standardized interview, physical and neurologic examinations, and brain MRI. The brain MRI protocol included a 3-dimensional T1-weighted sequence (Maastricht research center only because of technical reasons), suitable for VBM analysis, in 128 participants. Characteristics of participants scanned with (Maastricht) and without (Doetinchem) this sequence were comparable. Nine enrolled participants were excluded because of large brain infarcts ($n = 3$) or movement artifacts ($n = 6$), leaving $n = 119$ participants (69% female; mean age 57 years; migraine with aura $n = 52$, migraine without aura $n = 32$, and controls $n = 35$) for VBM analysis. Small, punctate white matter hyperintensities (WMHs) as frequently observed in participants with migraine¹⁷ were not considered an exclusion criterion. None of the included participants had large, confluent WMHs.

Standard protocol, approvals, registrations, and patient consents. The study protocol was approved by the institutional review boards, and all participants gave written informed consent prior to participation.

Magnetic resonance imaging. Structural whole-brain 3-dimensional T1-weighted fast field echo images (repetition/echo time 8.6/4.6 milliseconds, 140 sagittal 1.0-mm continuous slices, 256-mm field of view, acquisition matrix 256, acquisition voxel size $1 \times 1 \times 1$ mm) were acquired on a 1.5T scanner (ACS-NT; Philips Medical System, Best, the Netherlands). In addition, combined proton density and T2-weighted fast spin-echo (repetition/echo time 3,000/27–120 milliseconds) and fluid-attenuated inversion recovery (repetition/echo/inversion time 8,000/100/2,000 milliseconds) sequences were acquired to check images for structural abnormalities and to assess WMHs and infarcts.

Voxel-based morphometry. One observer (M.C.K.) who was blinded to participant characteristics and diagnosis visually screened all MRIs for artifacts and gross structural abnormalities that might interfere with further postprocessing. MRIs were processed with VBM, applying diffeomorphic anatomic registration exponentiated lie algebra (DARTEL),²⁰ with default parameters in Statistical Parametric Mapping 8 (SPM8; Wellcome Department of Cognitive Neurology, London, UK; <http://www.fil.ion.ucl.ac.uk/spm>) on a MATLAB platform (The MathWorks Inc, Natick, MA; version 7.4), to localize regional differences in gray and white matter volume. The DARTEL algorithm is considered a better intersubject registration than normalization algorithms in previous SPM versions.²¹ The VBM-DARTEL procedure included checking the location of the anterior commissure in raw MRIs; segmenting into gray matter, white matter, and CSF with the standard SPM8 segmentation algorithm; creating a DARTEL template derived from nonlinear deformation fields for the aforementioned segmentation procedure; and registering all individual deformations to the DARTEL template. This registration step included modulation, which preserved the absolute amount of local gray and white matter volumes in spatially normalized images by scaling by jacobian determinants, i.e., a correction for the distance over which a voxel had to be stretched or compressed to fit into standard space. Subsequently, modulated normalized gray and white matter segments were smoothed with an 8-mm full width at half-maximum isotropic gaussian kernel for statistical comparison.

Statistical analyses. Statistical Package for Social Science (SPSS Inc, Chicago, IL; version 17.0) was used for independent-sample t tests (normally distributed continuous variables), Mann-Whitney U tests (nonnormally distributed continuous variables), and Fisher exact tests (categorical variables) to compare baseline characteristics between participants with migraine and controls. VBM analyses included region-of-interest (ROI) gray matter analyses and whole-brain gray and white matter analyses. Gray and white matter segments were compared voxelwise between (subgroups of) participants with migraine and controls by the creation of general linear models including all participants with implementation of age, sex, and total intracranial volume as covariates. To exclude false positives in nongray or nonwhite matter tissue, voxelwise comparisons were masked with explicit optimal threshold gray and white matter masks created with the SPM Masking Toolbox.²²

ROI analyses. On the basis of results from previous VBM and surface-based morphometry studies,^{2,6,11,13,23} ROI gray matter analyses were carried out in the prefrontal, insular, anterior cingulate, somatosensory and occipital cortex (visual motion processing areas V3 and V5), thalamus, and brainstem (dorsolateral pons and periaqueductal gray). For these ROIs, Montreal Neurological Institute (MNI) coordinates were extracted from the literature (supplemental material at Neurology.org). Participants with migraine were compared to controls by applying small volume corrections ($p_{FWE-SVC} < 0.05$) by centering a 10-mm sphere around these MNI coordinates. In case of significant findings, post hoc analyses were performed to assess whether these changes, found by comparing participants with migraine with controls, were similar in subgroups of participants with migraine. For these post hoc analyses, the average volume of gray matter per voxel in significant ROI clusters was obtained for each individual and compared between controls and migraine subgroups with general linear regression models correcting for main effects of age, sex, and total intracranial volume and all its possible interactions. Subgroups of migraineurs were based on aura status (with or

without aura), disease activity (>1 year free of attacks [inactive] vs at least 1 attack within the last year [active]), and attack frequency (≤ 1 [low] or >1 attack/month [high] within the past 12 months). In these post hoc analyses, values of $p < 0.05$ were considered significant.

Whole-brain analyses. For whole-brain analyses comparing gray and white matter between migraineurs and controls, statistical parametric maps were thresholded at a significance level of $p < 0.05$, corrected for multiple comparisons with random field theory (familywise error), which is the standard to control for multiple testing in neuroimaging data.²⁴ In case of significant findings, post hoc analyses similar to ROI analyses were to be performed.

Because this is the first VBM-study investigating a population-based sample of participants with migraine with a minimum of comorbid factors, we deemed it justified to perform additional exploratory whole-brain analyses at a less stringent significance level of $p < 0.001$, uncorrected for multiple comparisons and minimal cluster sizes of 20 voxels.

Localization of ROI and whole-brain VBM findings. The location of the most significant voxel in ROI and whole-brain VBM clusters of gray and white matter volume differences was determined with 2 detailed atlases in consensus.^{25,26} To ascertain whether changes in white matter between participants with migraine and controls were not due to the occurrence of WMHs, the locations of VBM changes were compared to the location of

WMHs. WMHs were segmented semiautomatically as hyperintense lesions on proton density, T2, and fluid-attenuated inversion recovery images with QBrain as described in detail elsewhere.¹⁸ Lesion maps were created per participant and registered to MNI 152 space. Probability maps, depicting the chance for participants to have a lesion in a specific area, were created for the participants with migraine and controls included in the VBM analyses. Finally, these lesion maps were registered to the study-specific DARTEL space with a 12-parameter affine linear registration.

RESULTS Participants in the migraine group were slightly older than the controls (57.8 vs 54.6 years, $p = 0.05$), particularly those with migraine with aura (58.2 vs 54.6, $p = 0.04$). No other differences were found for the demographic characteristics of participants with migraine and controls (table 1).

ROI analyses. In ROI analyses (figure 1), gray matter volumes ($p_{\text{FWE-SVC}} < 0.05$, familywise error, small volume correction) were smaller in the V3 ($p_{\text{FWE-SVC}} = 0.025$; $x\ 26/y\ -87/z\ 22$) and MT+/V5 ($p_{\text{FWE-SVC}} = 0.031$; $x\ 38/y\ -76/z\ 11$) areas of the right occipital gyrus of participants with migraine compared to controls. In post hoc analyses, migraine subgroups displayed roughly the same pattern of gray matter volume decrease in these

Table 1 Characteristics of CAMERA VBM study participants

	Total (n = 119)	Control (n = 35)	Migraineurs		
			All (n = 84)	MO (n = 32)	MA (n = 52)
Age, mean (SD), y	56.9 (8.0)	54.6 (7.8)	57.8 ^a (8.0)	57.1 (7.7)	58.3 ^a (8.2)
Female, n (%)	82 (69)	25 (71)	57 (68)	21 (66)	36 (69)
Low education, ^b n (%)	60 (50)	17 (49)	43 (51)	17 (53)	26 (50)
Body mass index, mean (SD), kg/m ²	25.5 (3.3)	26.0 (3.2)	25.2 (3.3)	24.6 (2.8)	25.6 (3.6)
Hypertension, ^c n (%)	35 (29)	9 (26)	26 (31)	8 (25)	18 (35)
History of stroke, ^c n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Current medication, n (%)					
Prophylactics	NA	NA	2 (2)	0	2 (4)
Abortive treatment	NA	NA	48 (57)	16 (50)	32 (62)
Triptans	NA	NA	12 (14)	4 (13)	8 (15)
Ergotamines	NA	NA	2 (2)	1 (3)	1 (2)
Total intracranial volume, mean (SD), L	1.12 (0.11)	1.14 (0.12)	1.12 (0.11)	1.12 (0.10)	1.11 (0.12)
DWMH volume, median (IQR), mL	0.06 (0–0.35)	0.06 (0–0.35)	0.08 (0–0.36)	0.06 (0–0.35)	0.11 (0–0.39)
Right-handed, n (%)	102 (86)	31 (89)	71 (85)	29 (91)	42 (81)
Migraine attacks per year, ^d median (IQR), n	NA	NA	9 (6–18)	10 (6–24)	9 (6–18)
Migraineurs with high attack frequency, ^d n (%)	NA	NA	32 (38)	12 (38)	20 (39)
Active disease, ^e n (%)	NA	NA	50 (60)	15 (47)	35 (67)

Abbreviations: CAMERA = Cerebral Abnormalities in Migraine, an Epidemiological Risk Analysis; DWMH = deep white matter hyperintensity; IQR = interquartile range; MA = migraine with aura; MO = migraine without aura; NA = not applicable; SE = standard error; VBM, voxel-based morphometry.

^a $p < 0.05$ (all pairs of groups tested).

^bLow education indicates primary school or lower vocational education.

^cHypertension and history of stroke were self-reported and based on a previous physician's diagnosis.

^dHigh migraine attack frequency defined as on average ≥ 1 attack per month in the last year before examination.

^eActive disease defined as ≥ 1 attack within the last year before examination.

Figure 1 Gray matter volume decreases in V3 and V5 areas in migraineurs compared to controls

Axial slices (left) and volume rendering (right) of gray matter volume decreases in (A) V3 and (B) V5 areas in region-of-interest analyses between migraineurs and controls. Color bar represent z values. Pictures depicted in radiologic convention.

areas compared to controls (table 2). However, in migraineurs with inactive disease (attack-free for >1 year), compared to controls, there was a decrease in average gray matter volume per voxel in the V3 area but not in the MT+/V5 area. Decrease of gray matter volume in the MT+/V5 area was more pronounced in migraineurs with active disease and high attack frequency; this was not the case for the V3 area. No differences were found between migraineurs and controls for the other ROIs (prefrontal, insular, anterior cingulate, and somatosensory cortex, thalamus, and brainstem).

Whole-brain analyses. In whole-brain analyses, no differences were found in gray or white matter in migraineurs compared to controls ($p < 0.05$, uncorrected for multiple comparisons).

Exploratory whole-brain analyses ($p < 0.001$, cluster extend threshold 20 voxels, uncorrected for multiple

comparisons) confirmed smaller gray matter volumes in the right occipital gyrus of patients with migraine compared to controls as already found with ROI gray matter analyses. In addition, these analyses demonstrated larger gray matter volumes in the left angular, right middle temporal, left precentral and right superior frontal gyrus, and left lateral geniculate nucleus; smaller gray matter volumes in the uvula of the left cerebellum; and smaller white matter volumes bilaterally in the occipital lobe, in the stria medullaris of the thalamus, and unilaterally in the left frontal lobe (table 3). These regional decreases in white matter volume did not correlate with deep WMHs (figure 2). Increased white matter volumes were not observed.

DISCUSSION In this population-based assessment of volumetric changes in the migraine brain, we

Table 2 Post hoc analyses based on ROI analyses comparing migraineurs, migraine subgroups and controls

	V3	p^a	p^b	V5	p^a	p^b
Controls (n = 35)	0.416 (0.074)			0.385 (0.089)		
Migraine (n = 84)	0.366 (0.063)	<0.001		0.327 (0.074)	0.001	
MA (n = 32)	0.370 (0.067)	<0.001	0.60	0.325 (0.073)	<0.001	0.84
MO (n = 52)	0.360 (0.057)	<0.001		0.330 (0.076)	0.003	
Active (n = 50)	0.359 (0.066)	<0.001	0.38	0.315 (0.068)	<0.001	0.04
Inactive (n = 34)	0.376 (0.059)	0.01		0.345 (0.078)	0.06	
HF (n = 32)	0.352 (0.061)	<0.001	0.28	0.299 (0.058)	<0.001	0.002
LF (n = 52)	0.373 (0.064)	0.003		0.344 (0.077)	0.03	

Abbreviations: HF = high migraine attack frequency; LF = low attack frequency (cutoff for high is >1 attack per month in the year before examination); MA = migraine with aura; MO = migraine without aura; ROI = region of interest. Active migraine: at least 1 attack within the last year.

Values represent the mean gray matter volume per voxel in significant ROI clusters (small volume correction [$p_{FWE} < 0.05$] comparing migraineurs and controls; denotation mean (SD).

^aThe p value for comparing migraine and migraine subgroups to controls.

^bThe p value for comparing migraine subgroups to each other.

Table 3 Increases and decreases in gray and white matter between migraineurs and controls (exploratory whole-brain analyses)

	BA	L/R	DARTEL coordinates			k _E	z Score
			x	y	z		
Gray matter increases							
Angular gyrus (1)	39	L	−50	−61	17	432	3.92
Precentral gyrus (2)	6	L	−51	−1	31	58	3.87
Middle temporal gyrus (3)	21	R	54	−32	−6	65	3.52
Superior frontal gyrus (4)	9	R	8	53	28	39	3.45
Lateral geniculate nucleus (5)	NA	L	−21	−27	−5	27	3.33
Gray matter decreases							
Occipital gyrus (6)	19	R	26	−87	22	34	3.47
Cerebellum, uvula (7)	NA	L	−14	−43	−42	68	3.44
Middle occipital gyrus (8)	19	R	38	−76	11	44	3.39
White matter increases	—	—	—	—	—	—	—
White matter decreases							
Occipital white matter (1)	NA	R	29	−78	15	173	4.48
Occipital white matter (2)	NA	R	15	−80	10	386	4.24
Stria medullaris of thalamus (3)	NA	R	5	−8	9	90	4.06
Stria medullaris of thalamus (4)	NA	L	−3	−13	5	44	3.91
Occipital white matter (5)	NA	R	42	−69	20	23	3.77
Occipital white matter	NA	R	27	−86	14	105	3.64
Occipital white matter (6)	NA	L	−22	−70	15	457	3.64
Occipital white matter (7)	NA	L	−9	−85	5	30	3.34
Frontal white matter (8)	NA	L	−34	16	19	30	3.23

Abbreviations: BA = Brodmann area; DARTEL = diffeomorphic anatomic registration exponentiated lie algebra; k_E = cluster size; NA = not applicable.

$p < 0.001$, uncorrected for multiple comparisons, cluster extend threshold 20 voxels.

Numbers 1 through 8 represent axial slices in figure 2, gray matter (A) and white matter (C).

found decreased gray matter volume in the visual areas V3 and V5 of the extrastriate cortical areas of the right occipital gyrus (Brodmann area 19) in migraineurs compared to controls. Migraine subgroups (i.e., migraine with or without aura, active or inactive disease, low or high attack frequency) displayed roughly the same pattern of differences in these areas compared to controls. In exploratory whole-brain analyses, we identified structural differences in other cortical and subcortical areas that are particularly involved in sensory processing.

Our findings of decreased gray matter volume in the visual motion processing areas V3 and V5 of the occipital gyrus are in line with previous VBM findings,⁵ although they seem to contradict the reported cortical thickening in visual processing areas in participants with migraine as assessed with surface-based morphometry.^{11,13} This apparent discrepancy might, however, be explained by the fact that local gray matter volume is defined not only by the

thickness of the cortex but also by other parameters such as cortical folding patterns and total surface area of the cortex. Structural changes in cortical visual (motion) processing areas might be related to hyperexcitability (i.e., increased cortical responses of the visual cortex to intense, repetitive, or long-lasting stimulation),²⁷ to distorted cerebral metabolic homeostasis, or to changes in local neurotransmitter compositions.^{28,29} Whether such changes are inherited, congenital, or acquired remains to be determined. Changes in cortical responsiveness might explain well-known clinical symptoms of participants with migraine such as increased sensitivity to visual (light), auditory (sound), and tactile (allodynia) stimuli. These might also relate to lack of habituation to repeated visual stimulation³⁰ and interictal deficits in visual motion processing^{31,32} in migraine with and without aura. Cortical spreading depression, the electrophysiologic correlate of migraine aura, might also be due to cortical hyperexcitability^{33,34} and may begin

Figure 2 Increases and decreases in gray and white matter between migraineurs and controls (exploratory whole-brain analyses)

(B) Volume-rendering images and (A and C) axial slices of increases (yellow) and decreases (light blue) in gray matter and of decreases (green) in white matter between migraineurs and controls ($p < 0.001$, uncorrected for multiple comparisons, cluster extend threshold 20 voxels). Axial slices correspond with numbers 1 through 8 in table 3 for gray matter (A) and white matter (C). Decreases in white matter are shown in relation to deep white matter hyperintensities in migraineurs (red) and controls (dark blue). Color bars represent z values (0–5) or probability of voxels being deep white matter hyperintensities (1%–10%). Pictures depicted in radiologic convention.

in visual motion processing areas.³⁵ We found alterations in the right visual cortex only, which may relate to asymmetries in abnormal visual function as suggested by asymmetric visual evoked potentials in interictal migraineurs with aura.^{36,37}

Participants with migraine who had not experienced migraine attacks in the year before magnetic resonance scanning (with most being attack-free for >5 years) still showed changes in the right occipital gyrus (V3 area) compared to healthy controls. Therefore, these changes appear to be irreversible, at least partially, or may have existed throughout life. Gray matter volume decrease in the visual area V5 was more pronounced in active migraineurs and those participants with a high attack frequency, which suggests that these volume decreases may (in part) be attack-related. Because no differences were found for these areas between migraineurs with and without aura, these changes appear to be independent of the presence of aura symptoms.

In exploratory whole-brain analyses, next to cortical areas involved in visual processing, we found increased gray matter volume in the lateral geniculate nucleus in migraineurs compared to controls. This thalamic structure processes visual input from the optic chiasm to the primary visual cortex³⁸ and, like the cortical areas found in ROI analyses, is associated with visual motion processing.³⁹ The lateral geniculate nucleus is also thought to attenuate light perception in the absence of visual contrast⁴⁰ and has been suggested to play a role in photophobia in migraine.⁴¹ Previous studies already described an altered structure¹³ of this nucleus and increased oxygen metabolism after visual stimulation.³³

We found a bilateral volume decrease in the occipital white matter adjacent to visual processing cortical areas. Previously, with diffusion tensor imaging,^{13,42} reduced fractional anisotropy was found in white matter tracts in the middle temporal area¹³ and optic radiation tracts of participants with migraine,⁴² possibly due to increased axonal diameter.^{13,42} However, our results of decreased white matter volume make less myelination due to abnormal maturation or axonal loss a more likely explanation.

Theoretically, white matter changes as identified with VBM might be caused by WMHs, which are known to be more prevalent in migraine.^{17,18} WMHs show a drop in magnetic resonance T1 signal resulting from gliosis and appear as relatively gray areas and therefore may be falsely classified by VBM segmentation tools as gray matter, despite their location in the deep white matter. However, the white matter decreases we found in the visual pathways did not colocalize with WMHs (figure 2).

Although previous studies notably described differences in areas known to be primarily involved in

pain processing,^{4-6,8-10,12,43} these areas were less prominent in our study. Apart from differences in image acquisition and postprocessing and statistical thresholding, the major strength of our study is that the migraineurs from the CAMERA cohort have had less frequent exposure to pain compared to the participants from headache clinics in the other studies, who tend to have more severe migraines. A recent study explicitly found no alterations in cortical structures of areas involved in visual processing in patients with migraine with visual aura.⁴ Again, differences in participant characteristics, numbers of participants, and postprocessing methods could explain the discrepancy of findings across publications. Previous studies showed that adaptive remodeling due to chronic pain might be reversible and disappear shortly after adequate therapy.^{2,44} We showed that part of (cortical) gray matter changes were still present long after the last migraine attack.

Our study also has limitations. Despite a reasonably large sample size, we were not able to find differences, corrected for multiple comparisons, in whole-brain gray or white matter when comparing migraineurs to controls. Therefore, precaution should be taken in interpreting the results of the exploratory whole-brain analyses. Moreover, we did not adjust analyses for use or even overuse of prophylactic or acute migraine medications. Only 2% of the sample used prophylactics, which did not allow robust (sub)analyses. Although half of the migraineurs used abortive treatment, the large variety in type and dose of medications precluded sensible analyses. Moreover, abortive medication strongly correlates with attack frequency, and this may have been a confounding factor for any differences related to attack frequency. Nevertheless, both participants with high and low attack frequency showed similar patterns of gray matter volume change in cortical visual motion processing areas, suggesting that acute migraine medication was not of major influence.

Furthermore, in general, it is difficult to translate VBM changes to specific alterations at the microscopic level because the technique is strongly depending on local T1 MRI signal intensity, which is influenced by local tissue composition, including number and size of neurons, configuration of the extracellular space, presence of specific compounds (e.g., iron, myelin, and neurotransmitters), homeostatic balance, and actual macrovascular and microvascular perfusion. Because whole brain T1-weighted images could be acquired only in the CAMERA-2 MRI study and not also in the 9-year earlier CAMERA-1 baseline study, we could not study changes over time. Moreover, the cross-sectional design of our study precludes analysis of whether

the observed structural brain changes are a cause or a consequence of migraine.

AUTHOR CONTRIBUTIONS

Inge H. Palm-Meinders: study concept and design, acquisition of data, analysis and interpretation of data, statistical analysis, manuscript. Enrico B. Arkink: study concept and design, analysis and interpretation of data, statistical analysis, manuscript. Hille Koppen: study concept and design, acquisition of data, analysis and interpretation of data, statistical analysis, manuscript. Souad Amlal: analysis of data. Gisela M. Terwindt, Lenore J. Launer, Mark A. van Buchem, Michel D. Ferrari, and Mark C. Kruit: study concept and design, interpretation of data, study supervision, critical revision of manuscript for intellectual content.

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