Structural brain changes in migraine and cluster headache

Arkink, E.B.

5

Volumetric brain changes in migraineurs from the general population

I.H. Palm-Meinders*

E.B. Arkink*

H. Koppen*

S. Amlal

G.M. Terwindt

L.J. Launer

M.A. van Buchem

M.D. Ferrari**

M.C. Kruit**

*shared first authors; ** shared last authors

Neurology 2017;89:2066-2074

Abstract

Objective:

To assess volumetric brain changes in migraineurs from the general population in comparison with controls.

Methods:

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

Results:

In region-of-interest analyses, migraineurs showed decreased grey matter volume in the visual areas V3 and V5 of the right occipital cortex compared to controls ($p<0.05$, family-wise error correction). Post-hoc analyses revealed that similar changes were present irrespective of migraine aura status, disease activity (>1 year attack-free [inactive] versus ≥1 attack within the last year [active] and attack frequency [≤1 [low] versus ≥1 attack/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 morphological changes irrespective of the presence of migraine aura or disease activity suggests that migraine with and without aura share common pathophysiological pathways and suggests that these changes are (partially) irreversible or might have been present throughout life.

Introduction

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 grey and white matter density and volume.[3] Several groups have reported VBM grey matter changes in migraine, particularly volume decreases in pain-transmitting and pain-processing areas.[4-10] Other groups employed surface-based morphometry and found cortical thinning in areas involved in nociception[11] and cortical thickening in the somatosensory cortex[12] 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 on: (i) the relevance, specificity and generalizability of these findings; (ii) the possible causes (e.g. changes in metabolism, neurotransmitter levels, or functional processing of sensory information); (iii) possible reversibility; and (iv) whether these changes are a cause or a consequence of migraine.[1;2] The earlier study samples were relatively small and primarily included migraineurs from headache clinics who were likely to be affected more severely than average, overusing acute anti-headache medications and suffering from comorbid (psychiatric) diseases which 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 grey 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.

Materials and methods

Participants

Participants originated from the CAMERA-2 study (Cerebral Abnormalities in Migraine, an Epidemiological Risk Analysis), a nine-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-criteria[19]) and age- and sex-matched controls were evaluated by standardized interview, physical, and neurological examination, and brain MR imaging. The brain MR imaging protocol included a 3D 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 migraine[17] 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 3D T1-weighted fast field echo images (repetition/echo time 8.6/4.6 ms; 140 sagittal 1.0 mm continuous slices; 256 mm field of view; acquisition matrix 256; acquisition voxel size 1x1x1 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 3000/27-120 ms) and fluid-attenuated inversion recovery (FLAIR; repeti-

tion/echo/inversion time 8000/100/2000 ms) sequences were acquired to check images for structural abnormalities and to assess white matter hyperintensities and infarcts.

Voxel-based morphometry

One observer (M.C.K.) who was blinded for participant characteristics and diagnosis visually screened all MRIs for artifacts and gross structural abnormalities that might interfere with further post-processing. MRIs were processed using VBM, applying diffeomorphic anatomical registration exponentiated lie algebra (DARTEL)[20], with default parameters in SPM8 (Statistical Parametric Mapping, Wellcome Department of Cognitive Neurology, London, United Kingdom, http://www.fil.ion.ucl.ac.uk/spm) on a MATLAB platform (The MathWorks Inc., Natick, Massachusetts; version 7.4), to localise regional differences in grey and white matter volume. The DARTEL algorithm is considered as a better inter-subject registration than normalisation algorithms in previous SPM versions.[21] The VBM-DARTEL procedure included (i) checking the location of the anterior commissure in raw MRIs, (ii) segmentation into grey matter, white matter, and cerebrospinal fluid using the standard SPM8 segmentation algorithm, (iii) creation of a DARTEL template derived from non-linear deformation fields for the aforementioned segmentation procedure, and (iv) registration of all individual deformations to the DARTEL template. This registration step included modulation, which preserved the absolute amount of local grey and white matter volumes in spatially normalised 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, (v) modulated normalised grey 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, USA; version 17.0) was used for independent sample t-tests (normally distributed continuous variables), Mann-Whitney U tests (non-normally distributed continuous variables) and Fisher's exact tests (categorical variables) to compare baseline characteristics between participants with migraine and controls. Voxel-based morphometry analyses included region-of-interest (ROI) grey matter analyses and whole-brain

grey and white matter analyses. Grey and white matter segments were compared voxelwise between (subgroups of) participants with migraine and controls, by creating general linear models including all participants with implementation of age, gender, and total intracranial volume as covariates. To exclude false positives in non-grey or non-white matter tissue, voxelwise comparisons were masked with explicit optimal threshold grey and white matter masks created using the SPM Masking Toolbox.[22]

Region-of-interest analyses

Based on results from previous VBM and surface-based morphometry studies,[2;6;11;13;23] ROI grey matter analyses were carried out in the prefrontal, insular, anterior cingulate, somatosensory and occipital cortex (visual motion processing areas V3 and V5), the thalamus and the brainstem (dorsolateral pons and periacqueductal gray). For these ROIs, Montreal Neurologic Institute (MNI) coordinates were extracted from the literature.[24-29] Participants with migraine were compared to controls by applying small volume corrections ($p_{FWE\text{-}SVC}<0.05$) 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, as found in comparing participants with migraine with controls, were similar in subgroups of participants with migraine. For these post-hoc analyses, the average volume of grey matter per voxel in significant ROI clusters were obtained for each individual and compared between controls and migraine subgroups using general linear regression models correcting for main effects of age, gender 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, $p<0.05$ was considered significant.

Whole brain analyses

For whole brain analyses comparing grey and white matter between migraineurs and controls, statistical parametric maps were thresholded at a significance level of $p<0.05$, corrected for multiple comparisons using random field theory (family-wise error), which is the standard to control

for multiple testing in neuroimaging data.[30] In case of significant findings, post-hoc analyses similar to ROI-analyses were to be performed.

As 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 region-of-interest and whole brain VBM findings

The location of the most significant voxel in ROI and whole brain VBM clusters of grey and white matter volume differences were determined using two detailed atlases in consensus.[31;32] 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 semi-automatically as hyperintense lesions on proton density, T2 and FLAIR images using QBrain as described in detail elsewhere.[18] Lesion maps were created per participant and registered to MNI152-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 using 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 those of controls (Table 5.1).

Region-of-interest analyses

In ROI analyses (Figure 5.1), grey matter volumes ($p_{FWE\text{-}SVC}<0.05$, family wise error, small volume correction) were smaller in the V3 ($p_{FWE\text{-}SVC}=0.025$; x 26/y -87/z 22) and MT+/V5 ($p_{FWE\text{-}SVC}=0.031$; x 38/y -76/z 11) areas of the right occipital gyrus of participants with migraine com-

pared to those of controls. In post-hoc analyses migraine subgroups displayed roughly the same pattern of grey matter volume decrease in these areas, compared to controls (Table 5.2). However, in migraineurs with inactive disease (attack-free for more than one year) , compared to controls, there was a decrease in average grey matter volume per voxel in the V3 area, but not in the MT+/V5 area . Decrease of grey matter volume in the MT+/V5 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, somatosensory and, the thalamus and the brainstem).

Table 5.1 Characteristics of CAMERA VBM study participants

			Migraineurs		
	Total (n=119)	**Control (n=35)**	**All (n=84)**	**MO (n=32)**	**MA (n=52)**
Age, mean (SD), years	56.9 (8.0)	54.6 (7.8)	57.8* (8.0)	57.1 (7.7)	58.3* (8.2)
Female, No. (%)	82 (69%)	25 (71%)	57 (68%)	21 (66%)	36 (69%)
Low education†, No. (%)	60 (50%)	17 (49%)	43 (51%)	17 (53%)	26 (50%)
Body mass index, mean (SD)	25.5 (3.3)	26.0 (3.2)	25.2 (3.3)	24.6 (2.8)	25.6 (3.6)
Hypertension‡, No. (%)	35 (29%)	9 (26%)	26 (31%)	8 (25%)	18 (35%)
History of stroke‡, No. (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Current medication, No. (%)					
Prophylactics	N/A	N/A	2 (2%)	0	2 (4%)
Abortive treatment	N/A	N/A	48 (57%)	16 (50%)	32 (62%)
Triptans	N/A	N/A	12 (14%)	4 (13%)	8 (15%)
Ergotamines	N/A	N/A	2 (2%)	1 (3%)	1 (2%)
Total intracranial volume, mean (SD), liter	1.12 (0.11)	1.14 (0.12)	1.12 (0.11)	1.12 (0.10)	1.11 (0.12)
DWMH volume, median (IQR), milliliter	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, No. (%)	102 (86%)	31 (89%)	71 (85%)	29 (91%)	42 (81%)
Migraine attacks per year#, median (IQR)	N/A	N/A	9 (6-18)	10 (6-24)	9 (6-18)
Migraineurs with high attack frequency#, No. (%)	N/A	N/A	32 (38%)	12 (38%)	20 (39%)
Active disease*, No. (%)	N/A	N/A	50 (60%)	15 (47%)	35 (67%)

MA=migraine with aura, MO=migraine without aura, DWMH=deep white matter hyperintensity, SE=standard error, IQR=interquartile range, No.=number, N/A=not applicable. *p<0.05 (all pairs of groups tested)
† Low education indicates primary school or lower vocational education
‡ Hypertension and history of stroke were self-reported, based on a previous physician's diagnosis
# High migraine attack frequency defined as on average ≥1 attack per month in the last year before examination
* Active disease defined as ≥1 attack within the last year before examination

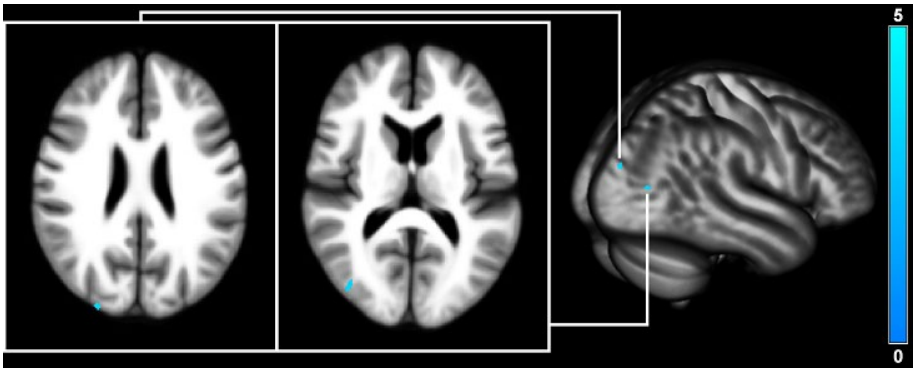

Figure 5.1 Grey matter volume decreases in V3 and V5 areas in migraineurs compared to controls. Axial slices (left) and volume rendering (right) of grey matter volume decreases in V3 (left panel) and V5 areas (right panel) in region-of-interest analyses between migraineurs and controls. Color bar represent Z-values. Pictures depicted in radiological convention.

Table 5.2 Post-hoc analyses based on region-of-interest (ROI) analyses comparing migraineurs, migraine subgroups and controls

	V3	p*	p†	V5	p*	p†
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	

Values represent the mean grey matter volume per voxel in significant ROI clusters (small volume correction [p_{FWE}<0.05]) comparing migraineurs and controls; denotation mean (standard deviation).
p*=p-value for comparing migraine and migraine subgroups to controls; p†=p-value for comparing migraine sub-groups to each other. MA=Migraine with aura; MO=Migraine without aura; active migraine= at least 1 attack within the last year; HF=High migraine attack frequency; and LF=Low attack frequency (cutoff at 'high' is >1 attack per month in the year before examination).

Whole brain analyses

In whole brain analyses, no differences were found in grey or white matter when comparing migraineurs 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 grey matter volumes in the right occipital gyrus of patients with migraine compared to controls as already found with ROI grey matter analyses. In addition, these analyses demonstrated: (i) larger grey matter volumes in the left angular, right middle temporal, left precentral and right superior frontal gyrus, and the left lateral geniculate nucleus; (ii) smaller grey matter volumes in the uvula of the left cerebellum; and (iii) smaller white matter volumes bilaterally in the occipital lobe and the stria medullaris of the thalamus, and unilaterally in the left frontal lobe (Table 5.3). These regional decreases in white matter volume did not correlate with deep white matter hyperintensities (Figure 5.2). Increased white matter volumes were not observed.

Discussion

In this population-based assessment of volumetric changes in the migraine brain, we found decreased grey 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 as 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 grey matter volume in the visual motion processing areas V3 and V5 of the occipital gyrus are in line with previous VBM findings.[5] They seem to contradict the reported cortical thickening in visual processing areas in participants with migraine as assessed with SBM, though.[11;13] This apparent discrepancy might, however, be explained by the fact that local grey matter volume is not only defined by thickness of the cortex but also by other parameters such as

Table 5.3 Increases and decreases in grey and white matter between migraineurs vs. controls (exploratory whole-brain analyses)

	BA	L/R	DARTEL coordinates			k_E	Z-score
			x	y	z		
Grey 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]	N/A	L	-21	-27	-5	27	3.33
Grey matter decreases							
Occipital gyrus[6]	19	R	26	-87	22	34	3.47
Cerebellum, uvula[7]	N/A	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]	N/A	R	29	-78	15	173	4.48
Occipital white matter[2]	N/A	R	15	-80	10	386	4.24
Stria medullaris of thalamus[3]	N/A	R	5	-8	9	90	4.06
Stria medullaris of thalamus[4]	N/A	L	-3	-13	5	44	3.91
Occipital white matter[5]	N/A	R	42	-69	20	23	3.77
Occipital white matter	N/A	R	27	-86	14	105	3.64
Occipital white matter[6]	N/A	L	-22	-70	15	457	3.64
Occipital white matter[7]	N/A	L	-9	-85	5	30	3.34
Frontal white matter[8]	N/A	L	-34	16	19	30	3.23

BA=Brodmann area, L=left, R=right, k_E=cluster size, N/A=not applicable; $p<0.001$, uncorrected for multiple comparisons, cluster extend threshold 20 voxels; number 1-8 represent axial slices in Figure 5.2, grey matter (upper two rows) and white matter (lower two rows)

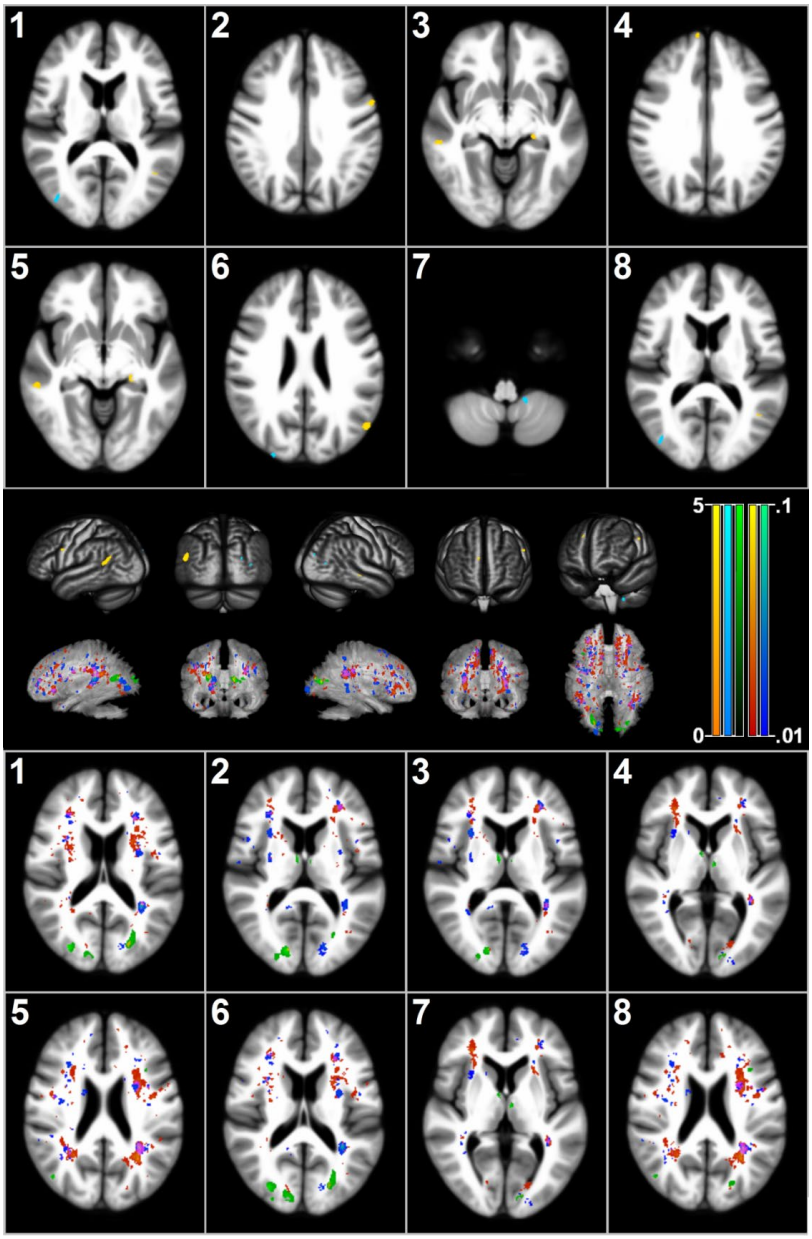

Figure 5.2 Increases and decreases in grey and white matter between migraineurs vs. controls (exploratory whole-brain analyses). Volume rendering images and axial slices of increases (yellow) and decreases (light blue) in grey matter and of decreases (green) in white matter between migraineurs vs. controls ($p<0.001$, uncorrected for multiple comparisons, cluster extend threshold 20 voxels). Axial slices correspond with numbers 1-8 in table 3 for grey matter (two upper rows) and white matter (two bottom rows). 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 radiological convention.

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 ofthe visual cortex to intense, repetitive or long-lasting stimulation),[33] to distorted cerebral metabolic homeostasis or to changes in local neurotransmitter compositions.[34;35] 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 stimuli (allodynia). These might also relate to lack of habituation to repeated visual stimulation[36] and interictal deficits in visual motion processing[37;38] in migraine with and without aura. Cortical spreading depression, the electrophysiological correlate of migraine aura, might also be due to cortical hyperexcitability[39;40] and may begin in visual motion processing areas.[41] 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.[42;43]

Participants with migraine who had not experienced migraine attacks in the year before MR scanning (with most being attack-free for over 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. Grey 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 decrease may (in part) be attack-related. As no differences were found for these areas between migraineurs with and without aura, these changes appear to be independent from presence of aura symptoms.

In exploratory whole brain analyses, next to cortical areas involved in visual processing, we found increased grey 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 cortex[44] and is, like the cortical areas found in ROI analyses, associated with visual motion processing.[45] The lateral geniculate nucleus is also thought to attenuate light perception in the absence of visual contrast[46] and has been suggested to play a role in photophobia in migraine.[47] Previous studies already described an altered structure[13] of this nucleus and increased oxygen metabolism after visual stimulation.[39]

We found bilateral volume decrease in the occipital white matter adjacent to visual processing cortical areas. Previously, with diffusion tensor imaging,[13;48] reduced fractional anisotropy was found in white matter tracts in the middle temporal area[13] and optic radiation tracts of participants with migraine,[48] possibly due to increased axonal diameter.[13;48] 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 MR T1-signal due to gliosis and appear as relatively grey areas and therefore may be falsely classified by VBM segmentation tools as grey matter, despite their location in the deep white matter. However, the white matter decreases we found in the visual pathways did not co-localize with WMHs (Figure 5.2).

Although previous studies notably described differences in areas known to be primarily involved in pain processing,[4-6;8-10;12;49] these areas were less prominent in our study. Apart from differences in image acquisition and post-processing, 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 suffer from more severe migraines. A recent study explicitly found no alterations in cortical structures of areas involved in visual processing in migraine patients with visual aura.[4] Again, differences in participant characteristics, numbers of participants, and post-processing 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;50] We showed that part of (cortical) grey 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 grey 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 prophylac-

tics, which did not allow for 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 grey matter volume change in cortical visual motion processing areas, suggesting that acute migraine medication was not of major influence.

Further, in general, it is difficult to translate VBM changes to specific alterations at microscopic level as 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 (like iron, myelin, and neurotransmitters), homeostatic balance, and actual macro- 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.

Funding

Supported by grants from the National Institutes of Health (1R01NS061382-01), the Netherlands Heart Foundation (2007B016), Netherlands Organization for Scientific Research (NOW: VICI 91856601 and Spinoza 2009) and the European Community (EC) [FP7-EUROHEADPAIN - no. 602633). The sponsors had no role in the design or conduct of the study.

References

1. Bashir A, Lipton RB, Ashina S, Ashina M. Migraine and structural changes in the brain: a systematic review and meta-analysis. Neurology 2013;81:1260-1268.
2. May A. Morphing voxels: the hype around structural imaging of headache patients. Brain 2009;132:1419-1425.
3. Ashburner J, Friston KJ. Voxel-based morphometry--the methods. Neuroimage 2000;11:805-821.
4. Hougaard A, Amin FM, Hoffmann MB et al. Structural gray matter abnormalities in migraine relate to headache lateralization, but not aura. Cephalalgia 2015;35:3-9.

5. Jin C, Yuan K, Zhao L et al. Structural and functional abnormalities in migraine patients without aura. NMR Biomed 2013;26:58-64.
6. Kim JH, Suh SI, Seol HY et al. Regional grey matter changes in patients with migraine: a voxel-based morphometry study. Cephalalgia 2008;28:598-604.
7. Rocca MA, Ceccarelli A, Falini A et al. Brain gray matter changes in migraine patients with T2-visible lesions: a 3-T MRI study. Stroke 2006;37:1765-1770.
8. Schmidt-Wilcke T, Ganssbauer S, Neuner T, Bogdahn U, May A. Subtle grey matter changes between migraine patients and healthy controls. Cephalalgia 2008;28:1-4.
9. Schmitz N, Admiraal-Behloul F, Arkink EB et al. Attack frequency and disease duration as indicators for brain damage in migraine. Headache 2008;48:1044-1055.
10. Valfre W, Rainero I, Bergui M, Pinessi L. Voxel-based morphometry reveals gray matter abnormalities in migraine. Headache 2008;48:109-117.
11. Messina R, Rocca MA, Colombo B et al. Cortical abnormalities in patients with migraine: a surface-based analysis. Radiology 2013;268:170-180.
12. DaSilva AF, Granziera C, Snyder J, Hadjikhani N. Thickening in the somatosensory cortex of patients with migraine. Neurology 2007;69:1990-1995.
13. Granziera C, DaSilva AF, Snyder J, Tuch DS, Hadjikhani N. Anatomical alterations of the visual motion processing network in migraine with and without aura. PLoS Med 2006;3:e402.
14. Gaul C, Visscher CM, Bhola R et al. Team players against headache: multidisciplinary treatment of primary headaches and medication overuse headache. J Headache Pain 2011;12:511-519.
15. Riederer F, Marti M, Luechinger R et al. Grey matter changes associated with medication-overuse headache: correlations with disease related disability and anxiety. World J Biol Psychiatry 2012;13:517-525.
16. van Tol MJ, van der Wee NJ, van den Heuvel OA et al. Regional brain volume in depression and anxiety disorders. Arch Gen Psychiatry 2010;67:1002-1011.
17. Kruit MC, van Buchem MA, Hofman PA et al. Migraine as a risk factor for subclinical brain lesions. JAMA 2004;291:427-434.
18. Palm-Meinders IH, Koppen H, Terwindt GM et al. Structural brain changes in migraine. JAMA 2012;308:1889-1897.
19. The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 2013;33:629-808.
20. Ashburner J. A fast diffeomorphic image registration algorithm. Neuroimage 2007;38:95-113.
21. Yassa MA, Stark CE. A quantitative evaluation of cross-participant registration techniques for MRI studies of the medial temporal lobe. Neuroimage 2009;44:319-327.
22. Ridgway GR, Omar R, Ourselin S, Hill DL, Warren JD, Fox NC. Issues with threshold masking in voxel-based morphometry of atrophied brains. Neuroimage 2009;44:99-111.
23. May A. Pearls and pitfalls: neuroimaging in headache. Cephalalgia 2013;33:554-565.
24. DaSilva AF, Granziera C, Snyder J, Hadjikhani N. Thickening in the somatosensory cortex of patients with migraine. Neurology 2007;69:1990-1995.
25. Georgieva S, Peeters R, Kolster H, Todd JT, Orban GA. The processing of three dimensional shape from disparity in the human brain. J Neurosci 2009;29:727-742.
26. Kim JH, Suh SI, Seol HY, et al. Regional grey matter changes in patients with migraine: a voxel-based morphometry study. Cephalalgia 2008;28:598-604.
27. Kolster H, Peeters R, Orban GA. The retinotopic organization of the human middle temporal area MT/V5 and its cortical neighbors. J Neurosci 2010;30:9801-9820.
28. Rocca MA, Ceccarelli A, Falini A, et al. Brain gray matter changes in migraine patients with T2-visible lesions: a 3-T MRI study. Stroke 2006;37:1765-1770.

29. Stankewitz A, Schulz E, May A. Neuronal correlates of impaired habituation in response to repeated trigeminonociceptive but not to olfactory input in migraineurs: an fMRI study. Cephalalgia 2013;33:256-265.
30. Nichols T, Hayasaka S. Controlling the familywise error rate in functional neuroimaging: a comparative review. Stat Methods Med Res 2003;12:419-446.
31. Mai JK, Paxinos G, Voss T. Atlas Of The Human Brain. 3rd ed. Oxford: Elsevier Science & Technology, 2007.
32. Talairach J, Tournoux P. Co-Planar Stereotaxic Atlas of the Human Brain. 3-D Proportional System: An Approach to Cerebral Imaging. Stuttgart: Georg Thieme Verlag, 1988.
33. Aurora SK, Wilkinson F. The brain is hyperexcitable in migraine. Cephalalgia 2007;27:1442-1453.
34. Reyngoudt H, Paemeleire K, Descamps B, De DY, Achten E. 31P-MRS demonstrates a reduction in high-energy phosphates in the occipital lobe of migraine without aura patients. Cephalalgia 2011;31:1243-1253.
35. Siniatchkin M, Sendacki M, Moeller F et al. Abnormal changes of synaptic excitability in migraine with aura. Cereb Cortex 2012;22:2207-2216.
36. Ambrosini A, Schoenen J. Electrophysiological response patterns of primary sensory cortices in migraine. J Headache Pain 2006;7:377-388.
37. McKendrick AM, Badcock DR. Motion processing deficits in migraine. Cephalalgia 2004;24:363-372.
38. Shepherd AJ, Beaumont HM, Hine TJ. Motion processing deficits in migraine are related to contrast sensitivity. Cephalalgia 2012;32:554-570.
39. Datta R, Aguirre GK, Hu S, Detre JA, Cucchiara B. Interictal cortical hyperresponsiveness in migraine is directly related to the presence of aura. Cephalalgia 2013;33:365-374.
40. Ferrari MD, Klever RR, Terwindt GM, Ayata C, van den Maagdenberg AM. Migraine pathophysiology: lessons from mouse models and human genetics. Lancet Neurol 2015;14:65-80.
41. Hadjikhani N, Sanchez Del RM, Wu O et al. Mechanisms of migraine aura revealed by functional MRI in human visual cortex. Proc Natl Acad Sci U S A 2001;98:4687-4692.
42. Khalil NM, Nicotra A, Wilkins AJ. Asymmetry of visual function in migraine with aura: correlation with lateralisation of headache and aura. Cephalalgia 2011;31:213-221.
43. Coppola G, Parisi V, Fiermonte G, Restuccia R, Pierelli F. Asymmetric distribution of visual evoked potentials in patients with migraine with aura during the interictal phase. Eur J Ophthalmol 2007;17:828-835.
44. Maleki N, Becerra L, Upadhyay J, Burstein R, Borsook D. Direct optic nerve pulvinar connections defined by diffusion MR tractography in humans: implications for photophobia. Hum Brain Mapp 2012;33:75-88.
45. Ungerleider LG, Desimone R, Galkin TW, Mishkin M. Subcortical projections of area MT in the macaque. J Comp Neurol 1984;223:368-386.
46. Hubel DH, Livingstone MS. Color and contrast sensitivity in the lateral geniculate body and primary visual cortex of the macaque monkey. J Neurosci 1990;10:2223-2237.
47. Boulloche N, Denuelle M, Payoux P, Fabre N, Trotter Y, Geraud G. Photophobia in migraine: an interictal PET study of cortical hyperexcitability and its modulation by pain. J Neurol Neurosurg Psychiatry 2010;81:978-984.
48. Rocca MA, Pagani E, Colombo B et al. Selective diffusion changes of the visual pathways in patients with migraine: a 3-T tractography study. Cephalalgia 2008;28:1061-1068.
49. Rocca MA, Messina R, Colombo B, Falini A, Comi G, Filippi M. Structural brain MRI abnormalities in pediatric patients with migraine. J Neurol 2014;261:350-357.
50. May A. Structural brain imaging: a window into chronic pain. Neuroscientist 2011;17:209-220.