Chapter 7  Discrete differences in brain perfusion between migraineurs and controls: a voxelwise comparison of interictal dynamic susceptibility contrast MRI measurements

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ABSTRACT

The increased cerebro- and cardiovascular risk in migraineurs may be the consequence of a basal systemic vascular susceptibility, reflected by the presence of interictal global or regional cerebral perfusion abnormalities. Whether focal perfusion changes occur during interictal migraine has not been convincingly demonstrated. In this study, we measured brain perfusion with dynamic susceptibility-contrast magnetic resonance imaging (DSC-MRI) in 30 interictal female migraineurs (13 migraine with aura (MA), 17 migraine without aura (MO)) and 17 female controls to improve our understanding of migraine pathophysiology and its potential cerebrovascular consequences. In voxelwise analyses (p<0.001, uncorrected, minimum cluster size 20 voxels), interictal hyperperfusion was observed in the left medial frontal gyrus in migraineurs and in the inferior and middle temporal gyrus in MO patients, in comparison to controls. Hypoperfusion was seen in the postcentral gyrus and in the inferior temporal gyrus in MA patients and in the inferior frontal gyrus in MO patients. Region-of-interest analyses of the pons, hypothalamus, occipital lobe and cerebellum did not show significant interictal perfusion differences between migraineurs and controls. We conclude that interictal migraine is characterized by discrete areas of hyper- and hypoperfusion unspecific for migraine pathophysiology and not explaining the increased vulnerability of particular brain regions for cerebrovascular damage.

In preparation
INTRODUCTION

Migraine is a prevalent neurovascular disorder, characterized by recurrent attacks of disabling headache accompanied by dysfunction of the autonomic nervous system. In up to a third of the patients, neurological (mostly visual) aura symptoms precede or accompany the headache phase of migraine attacks (1). Migraine, especially migraine with aura (MA), has been identified as an independent risk factor for clinical and subclinical brain infarction.(2, 3) The posterior circulation territory, notably the cerebellum, seems to be specifically vulnerable.(2, 4, 5) Further, female migraineurs both with and without aura are at increased risk of deep white matter and hyperintense brainstem lesions (2, 5, 6). Repetitive physiological and biochemical changes during migraine attacks, including changes in brain perfusion, are amongst the mechanisms proposed to explain or contribute to the increased risk of ischemic brain lesions (7).

Besides the increased risk of cerebrovascular complications in migraineurs, there is increasing evidence that migraine is also independently associated with other (ischemic) vascular disorders, including angina pectoris, myocardial infarction, claudication and retinopathy (7, 8). A direct relationship with migraine attacks is not plausible for these types of vascular disease, and therefore these associations seem to be better explained by a basal systemic susceptibility of the vasculature in migraine patients. Several lines of evidence support this concept, including interictal evidence of endothelium (dependent) dysfunction, impaired cerebrovascular reactivity, reports on ictal and interictal generalized or coronary artery vasospasm, impaired brachial artery compliance, increased aortic stiffness and hypercoagulability, which all seem to be independent of the coincidence of established cardiovascular risk factors (9).

Consequences of such basal vascular susceptibility may be reflected by the presence of interictal global or regional perfusion abnormalities in the brains of migraineurs. Earlier single photon emission computed tomography (SPECT) reported such gross differences in cerebral hemodynamics between interictal migraineurs and control subjects, but results were contradictory (10-15). More recent perfusion studies, using positron emission tomography (PET) (16-20) and dynamic susceptibility contrast magnetic resonance imaging (DSC-MRI) (21-23), concentrated on the ictal phenomena, so it has still not been convincingly proven whether in the interictal stage of migraine, differences in cerebral hemodynamics are present or absent in comparison with headache-free control subjects.

Knowledge of patterns of interictal brain perfusion will improve our understanding of the migraine pathophysiology and its potential consequences that could make certain brain areas in migraineurs more susceptible to temporary or permanent brain changes. Further, it serves as baseline measure for future analyses of brain perfusion changes during and around migraine attacks. In the current study, we investigated interictal groups of MA and migraine without aura (MO) patients vs. controls, using DSC-MRI. DSC-MRI has several advantages compared to earlier performed PET and SPECT studies, including a better spatial resolution with whole-brain coverage and a higher signal-to-noise ratio (SNR), allowing for voxelwise detection of small perfusion...
We performed unbiased whole brain voxelwise analyses of cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT) and time-to-peak (TTP) maps, but also performed region-of-interest analyses in predefined regions that have been reported to show perfusion changes during the different stages of migraine, or that have been reported to be specifically at risk for ischemic lesion development, such as the cerebellum.

METHODS

Subject population
Thirty female migraine patients (13 MA: mean age 42.9, range 28-52; 17 MO: mean age 47.6, range 38-57) and seventeen female control subjects (mean age 39.9, range 21-55) participated in this study. Migraine patients were enrolled through advertisements in newspapers and magazines. Migraineurs were diagnosed with MA or MO according to the criteria of the Headache Classification Committee of the International Headache Society (1) at the Department of Neurology (GGS); headache-free control subjects were recruited by local advertisement and enrolled in the study. None of the migraine patients were taking prophylactic medication and all were headache-free for 7 days or more at time of scanning (interictally). The study was approved by the local ethics committee and all subjects gave written and informed consent.

Neuroimaging protocol
T₂-weighted turbo spin echo images (TR/TE 4741/80 msec, echo train length 16, acquisition matrix 448x392 mm, FOV 224x180 mm², 48 slices of 3 mm thickness) and fluid-attenuated inversion recovery (FLAIR) (TR/TE 10128/120 msec, echo train length 36, acquisition matrix 224x224, FOV 224x180 mm², 48 slices of 3 mm thickness) were acquired and evaluated by an experienced neuroradiologist (MCK). Two cases showing structural brain abnormalities that could have impeded or confounded perfusion image post processing were excluded from further analyses: one control subject with a frontal cortical infarct, and one MA patient with confluent white matter lesions (WMLs). Small, punctuate deep white matter lesions were not considered an exclusion criterion.

DSC-MR imaging was performed on a 3.0 Tesla MRI system (Achieva, Philips Medical Systems, Best, The Netherlands), using an 8-channel receive array head coil; 0.2 ml/kg-bodyweight Gd-DTPA (Magnevist®, Schering) was injected intravenously at 5 ml/sec followed by a saline chaser of 25 ml (injected at 5 ml/sec (20 ml) and 2 ml/sec (5 ml)). PRESTO (PRinciples of Echo-Shifting with a Train of Observations, a 3D ultrafast gradient echo sequence combining whole brain coverage with T₂*-weighted imaging (25)) was used for the acquisition with the following parameters: data matrix 64x53 mm (zerofilled to 128x108 mm), echo time (TE)/repetition time (TR) 26/17 msec, flip angle 5°, field of view (FOV) 224x168 mm², SENSE factor of 2.4, 48 slices of
3 mm thickness, number of echoes in a echo train 21, and 60 segments per volume resulting in a dynamic scan time of 1.1 sec.

**Post-processing**

The perfusion maps of CBF, CBV, MTT and TTP were generated using validated software developed at the Massachusetts General Hospital using block-circulant singular value decomposition (26). This program requires a manual selection of the arterial input function (AIF, the passage of contrast agent through a major brain-feeding artery). At least eight voxels near the middle cerebral artery were selected to form the global AIF used in the deconvolution.

The signal drop in the $T_2^*$-weighted images resulting from the contrast agent passage was converted to the concentration contrast agent ($C(t)$) using

$$C(t) = \Delta R_2^* - \frac{1}{TE} \log \left( \frac{S(t)}{S(0)} \right)$$

The deconvolution was performed over the first and second passage of the gadolinium concentration passage with a noise threshold of 0.4 and an oscillation threshold of 0.095.

The CBF maps were used to coregister all perfusion maps spatially to the PET template in SPM5 (Wellcome Trust Centre for Neuroimaging, Institute of Neurology, UCL, London UK – [http://www.fil.ion.ucl.ac.uk/spm](http://www.fil.ion.ucl.ac.uk/spm)). To improve the spatial normalization further, an average CBF map was constructed over all subjects and the individual CBF maps were coregistered to that average CBF template together with all other perfusion maps. The relative CBF and relative CBV maps were converted to quantitative CBF and CBV maps by setting the white matter CBF to 22 ml/100g/min (27). The white matter segmentation for this quantification step was performed in SPM5 on the CBF map, since gray matter has a higher CBF than white matter; the segmentation mask consisted of all voxels with a 95% or higher certainty that the voxel is white matter.

**Statistical analyses**

All perfusion maps were smoothed using an isotropic Gaussian kernel (full width at half maximum of 8 mm). Whole brain voxelwise comparison was performed, comparing interictal scans of patients with migraine, MA, MO and controls using one-way analyses of variance implemented in SPM5, correcting for age. For statistical tests, the height threshold was set at $p<0.001$, uncorrected for multiple comparisons, with a cluster extent of minimal 20 neighbouring voxels.

Next to voxel-based comparison, regions-of-interest (ROIs) for the occipital lobe and cerebellum (constructed from the corresponding regions from the automated anatomical labeling (AAL) template for SPM5) (28), the pons and the hypothalamus (drawn manually and incorporated into the AAL template) were created to study the average distribution of perfusion parameters in these areas in the normalized, non-smoothed images. The choice of ROIs
for pons, hypothalamus and occipital lobe was based on previous reports of hemodynamic changes during migraine (16, 18-20). The cerebellum was analyzed specifically because of its suggested increased vulnerability for cerebellar infarction in migraineurs. Distributions of mean CBF, CBV, MTT and TTP were compared between migraine patients and control subjects using multivariate general linear models adjusted for age in SPSS for Windows, release 16.0.2 (Chicago, USA).

RESULTS

After exclusion of the two participants with larger brain lesions, 45 female subjects remained for analysis: 12 MA patients, 17 MO patients, and 16 control subjects for further analysis. Mean age (MA 42.9±8.2 years, MO 47.6±5.3 years, controls (39.9±12.3), p>0.05, one-way ANOVA) was not different across the groups. The results of the voxelwise whole brain comparison between interictal migraineurs and controls are shown in Table 1 and Figures 1 and 2. We found a higher CBF in a part of the left medial frontal gyrus when analyzing the whole group of migraineurs vs. controls (Figure 1A).

<table>
<thead>
<tr>
<th>Brain area</th>
<th>MNI coordinates (x y z)</th>
<th>Cluster-size</th>
<th>Z-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CBF</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Migraine vs. controls</td>
<td>L Medial frontal gyrus</td>
<td>-6 28 38</td>
<td>48</td>
</tr>
<tr>
<td>MA vs. controls</td>
<td>L Medial frontal gyrus</td>
<td>-8 26 40</td>
<td>34</td>
</tr>
<tr>
<td>MO vs. controls</td>
<td>L Medial frontal gyrus</td>
<td>-6 28 38</td>
<td>20</td>
</tr>
<tr>
<td>Decreased</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MA vs. controls</td>
<td>R Inferior temporal gyrus</td>
<td>36 0 -50</td>
<td>49</td>
</tr>
<tr>
<td>L Postcentral gyrus</td>
<td>-48 -24 32</td>
<td>24</td>
<td>3.41</td>
</tr>
<tr>
<td>MO vs. controls</td>
<td>L Inferior frontal gyrus</td>
<td>-54 20 32</td>
<td>26</td>
</tr>
<tr>
<td><strong>CBV</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MO vs. controls</td>
<td>R Middle temporal gyrus</td>
<td>48 -16 -12</td>
<td>26</td>
</tr>
<tr>
<td>R Inferior temporal gyrus</td>
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<td>3.41</td>
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<tr>
<td>58 -30 -22</td>
<td>22</td>
<td>3.34</td>
<td></td>
</tr>
<tr>
<td>No decreases</td>
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<tr>
<td>MTT</td>
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<td></td>
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<tr>
<td>No increases or decreases</td>
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<td></td>
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<tr>
<td>TTP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No increases or decreases</td>
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</tr>
</tbody>
</table>

MA=migraine with aura, MO=migraine without aura, MNI=Montreal Neurological Institute; p<0.001, uncorrected, cluster extent threshold of 20 voxels
This difference remained, also when assessing MA and MO groups separately vs. controls (not shown in figure). A lower CBF was present in a zone of the right inferior temporal gyrus (figure. 1B) and the left postcentral gyrus (figure. 1C) in MA patients and in a part of the inferior frontal gyrus in MO patients (figure. 1D). CBV was increased in a zone of the right inferior and middle temporal gyrus in MO (Figure 2). CBV reductions were not identified. In addition, no
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Voxelwise increases or decreases in MTT and TTP were observed between migraineurs and control subjects.

The results of the ROI-analyses in interictal migraineurs and controls are shown in Table 2. The CBF, CBV, MTT and TTP in pons, hypothalamus, occipital lobe and cerebellum did not differ significantly between migraine and controls, or between migraine subgroups and controls (Table 2).

### DISCUSSION AND CONCLUSIONS

To the best of our knowledge, this is the first explorative DSC-MRI study assessing brain perfusion characteristics and patterns in female migraine patients in an interictal state vs. headache-free control subjects. In this relatively large sample of migraineurs (MA and MO) and control subjects, our voxelwise comparison of perfusion maps identified some small areas of perfusion differences between migraineurs and controls, including both hyper- and hypoperfusion in frontal, parietal, and temporal regions in the interictal migraine brain. Regional analyses assessing perfusion differences in the pons, hypothalamus, occipital lobe and cerebellum between

<table>
<thead>
<tr>
<th>Region</th>
<th>CBF (ml/100g/min)</th>
<th>CBV (ml/100g)</th>
<th>MTT (s)</th>
<th>TTP (s)</th>
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<tbody>
<tr>
<td>Controls</td>
<td>Controls (n=16)</td>
<td>64.8 (9.9)</td>
<td>3.3 (0.6)</td>
<td>4.2 (0.5)</td>
</tr>
<tr>
<td></td>
<td>Migraine (n=29)</td>
<td>64.4 (8.6)</td>
<td>3.3 (0.7)</td>
<td>4.5 (0.7)</td>
</tr>
<tr>
<td></td>
<td>MA (n=12)</td>
<td>63.8 (7.2)</td>
<td>3.4 (0.6)</td>
<td>4.3 (0.7)</td>
</tr>
<tr>
<td></td>
<td>MO (n=17)</td>
<td>64.4 (9.6)</td>
<td>3.3 (0.8)</td>
<td>4.6 (0.7)</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
<td>0.172</td>
<td>0.526</td>
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<td></td>
<td>Hypothalamus</td>
<td>Controls (n=16)</td>
<td>46.1 (6.0)</td>
<td>3.7 (0.7)</td>
</tr>
<tr>
<td></td>
<td>Migraine (n=29)</td>
<td>44.2 (6.6)</td>
<td>3.8 (0.8)</td>
<td>4.4 (1.0)</td>
</tr>
<tr>
<td></td>
<td>MA (n=12)</td>
<td>41.1 (8.0)</td>
<td>3.6 (0.6)</td>
<td>4.1 (0.7)</td>
</tr>
<tr>
<td></td>
<td>MO (n=17)</td>
<td>46.3 (4.5)</td>
<td>3.9 (0.9)</td>
<td>4.6 (1.1)</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
<td>0.089</td>
<td>0.197</td>
<td>0.232</td>
</tr>
<tr>
<td></td>
<td>Occipital lobe</td>
<td>Controls (n=16)</td>
<td>60.9 (8.4)</td>
<td>3.9 (0.7)</td>
</tr>
<tr>
<td></td>
<td>Migraine (n=29)</td>
<td>59.1 (4.5)</td>
<td>4.0 (0.8)</td>
<td>4.1 (0.8)</td>
</tr>
<tr>
<td></td>
<td>MA (n=12)</td>
<td>61.0 (5.2)</td>
<td>4.0 (0.6)</td>
<td>4.0 (0.6)</td>
</tr>
<tr>
<td></td>
<td>MO (n=17)</td>
<td>57.9 (3.5)</td>
<td>4.1 (0.9)</td>
<td>4.3 (0.9)</td>
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<tr>
<td></td>
<td>p-value</td>
<td>0.362</td>
<td>0.197</td>
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<tr>
<td></td>
<td>Cerebellum</td>
<td>Controls (n=16)</td>
<td>67.5 (9.6)</td>
<td>4.6 (1.0)</td>
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<tr>
<td></td>
<td>Migraine (n=29)</td>
<td>64.7 (6.5)</td>
<td>4.7 (0.9)</td>
<td>3.7 (0.5)</td>
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<tr>
<td></td>
<td>MA (n=12)</td>
<td>66.4 (7.1)</td>
<td>4.6 (0.6)</td>
<td>3.7 (0.5)</td>
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<tr>
<td></td>
<td>MO (n=17)</td>
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<tr>
<td></td>
<td>p-value</td>
<td>0.888</td>
<td>0.316</td>
<td>0.283</td>
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</tbody>
</table>

MA=migraine with aura, MO=migraine without aura; denotation is mean (SD); p-values from linear regression models corrected for age.
interictal migraineurs and controls did not show significant differences. In general, areas with altered interictal perfusion may reflect local interictal differences in neuronal activity or density, or may point at some degree of interictal cerebrovascular dysregulation, that both might be the consequence of repetitive migraine attacks, or might be attributed to systemic vascular processes, or both.

The area of higher CBF that we identified in the left medial frontal gyrus in both MA and MO patients, seems to co-localize with a reported area of gray matter reductions in migraine patients (29). Gray matter changes in the medial frontal gyrus have been reported to correlate with pain scores in another chronic pain condition, fibromyalgia (30), suggesting a correlation between morphology and function. In MA patients, we found lower CBF in the postcentral gyrus, part of the somatosensory cortex. One earlier morphometric study described thickening of the somatosensory cortex in migraineurs, that was suggested to be an adaptation to repetitive migraine attacks (31). In MO patients, we found areas of lower CBF in the inferior frontal gyrus and higher CBV in the middle temporal gyrus. Decreases in regional CBF in these areas were seen in MO patients after administration of sumatriptan in a recently published PET study (19), and an earlier voxel based morphometry (VBM) study in migraineurs also identified gray matter reductions in these gyri (32).

Although thus seemingly altered interictal perfusion in certain brain areas in migraineurs can be co-localized with earlier reported structural or hemodynamic changes in the brains of patients with migraine and other pain conditions, we want to stress that the changes measured by DSC-MRI are small and not necessarily specific for migraine. Further, higher or lower perfusion did not consistently relate to specific structural changes; e.g. hypoperfusion seems to be related in some areas with cortical thickening, and in other areas with gray matter reduction. This makes interpretation of these changes difficult.

We found no interictal differences in CBF, CBV, MTT or TTP in the regional maps of the pons, hypothalamus and occipital lobe, although perfusion changes have previously been identified in these areas during migraine attacks (16, 18-20). Similarly, we found no interictal perfusion abnormalities in the cerebellum. These negative interictal findings may be explained e.g. by high inter- and intra-individual variance in cerebral hemodynamics, and of course do not exclude the possibility of ictal perfusion changes in these areas.

We are not aware of any PET or DSC-MRI studies that report perfusion differences in migraineurs during interictal stage in comparison with control subjects. There are however several reports on interictal CBF changes in regular migraine compared to controls, measured with SPECT, but results are contradicting. Lauritzen et al. did not find interictal CBF changes when comparing 11 migraineurs to 20 controls (14). Levine et al. reported general hypoperfusion in 15 MA and 12 MO patients in the posterior circulation territory, compared to 20 controls (15). Other studies reported single or multiple foci of interictal hypoperfusion in 43-67% of migraineurs (10, 11). However, yet another SPECT study reported interictal global hyperperfusion in 50 MO patients (mainly located in frontal regions) and global hypoperfusion in 20
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MA patients (mainly located in posterior regions), compared to control subjects (12). These contradicting results may be due to the insufficiency of visual evaluation of SPECT-derived CBF images to pick up abnormalities in interictal migraineurs (13). The small focal areas of hyper- and hypoperfusion we observed in frontal, temporal, and parietal regions in migraine patients compared to controls seem to show overlap with some of the regions found in the aforementioned SPECT studies, but comparison between these different techniques remains complicated because of differences in post-processing, which is discussed further below.

Up till now, DSC-MRI has been performed in only a few occasions in regular migraine (21-23); DSC-MRI has most often been used for studying perfusion changes during attacks of rare subforms of migraine, such as familial hemiplegic migraine or persistent migraine aura, most often only in a single case (33-40). The DSC-MRI acquisition and analysis in the current study was applied with more advanced acquisition and post-processing techniques than previously used in DSC-MRI studies in regular migraine (23). First, the 3D PREStO acquisition in combination with parallel imaging covered the entire brain at a temporal resolution of 1.1 seconds. A low dynamic scan time is important because the concentration contrast agent is monitored dynamically, and a simulation study by Knutsson et al. showed that the dynamic scan time should be below 1.5 sec (41). Second, delay-insensitive deconvolution was used. This improves the quality of the perfusion estimates, since delay effects are more present when a global AIF is used for the deconvolution (26, 42). In our analysis, a global AIF was selected close but outside the middle cerebral arteries (43). These two brain-feeding arteries supply the majority of but not the entire cortex. However, the use of a delay insensitive deconvolution technique reduced the error for tissue that is not supplied by the MCA. Third, spatial normalization was performed in two steps, first to the PET template and second to an average CBF map. This improves the accuracy of the voxelwise comparison analysis.

Next to an increased spatial resolution allowing for voxelwise comparisons, DSC-MRI has several advantages compared to other techniques used for measuring perfusion in migraine. DSC-MRI does not expose the subjects to ionizing radiation and is therefore better suited for measuring cerebral perfusion in large samples of both migraineurs as well as controls than PET or SPECT. Further, DSC-MRI is more widely available and less time consuming. SPECT only measures CBF and some SPECT techniques provide only relative values, whereas PET and DSC-MRI measure values of CBF, CBV and MTT. Furthermore, the spatial resolution of PET and SPECT is lower than DSC-MRI making it harder to detect local perfusion changes. In the SPECT studies that compared interictal migraineurs to controls, images were acquired with varying SPECT-contrast agents and were often evaluated visually or semiquantitatively leading to a substantial degree of subjectivity. To overcome this problem, our results of local hyper- and hypoperfused areas between migraine attacks were generated by an unbiased whole brain voxelwise comparison of DSC-MRI images. Besides aforementioned advantages, DSC-MRI also has a major disadvantage. Recent studies showed that the (repetitive) use of DSC-MRI contrast agents in
patients with renal failure increases the risk for attaining nephrogenic systemic fibrosis (NSF) (44, 45).

Arterial spin-labeling (ASL) likely is a good alternative technique for both DSC-MRI and PET. ASL, a relatively new MR technique, is better for perfusion estimation and has the possibility for repeated measurements to increase the sensitivity (46). Although this technique only allows for absolute quantification of CBF (and not CBV or MTT), intravenous administration of contrast agents or radioactive tracers is not necessary. The first results of ASL during migraine attacks show results comparable to those in PET studies (47, 48).

In summary, our study shows in an unbiased whole brain voxelwise approach that interictal migraineurs have discrete areas of cerebral hyper- and hypoperfusion, measured with DSC-MRI. Their specificity for migraine pathophysiology is thought to be small, and we did not find changes in hemodynamics of interictal migraineurs that likely account for subclinical cerebellar lesions found previously.
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REFERENCES


