Hypothalamus as a mediator of chronic migraine

Evidence from high-resolution fMRI

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ABSTRACT

Objective: To identify pathophysiologic mechanisms of migraine chronification using a recently standardized protocol for high-resolution brainstem imaging of trigeminal nociceptive stimulation.

Methods: Eighteen episodic migraineurs (EMs), 17 chronic migraineurs (CMs), and 19 healthy controls (HCs) underwent painful ammonia stimulation of the left nostril in a 3T MRI scanner. Functional images were acquired with a brainstem-optimized protocol for high-resolution echo-planar imaging.

Results: We detected a significantly stronger activation of the anterior right hypothalamus in CMs compared to HCs. To exclude the headache as a prime mediator of the hypothalamic activations, we compared all migraineurs with headaches (EMs and CMs) with all migraineurs without headaches (EMs and CMs) and HCs in a second analysis and found a more posterior region of the hypothalamus to be more activated bilaterally during headaches.

Conclusions: Our data corroborate the fact that the hypothalamus plays a crucial role in the pathophysiology of migraine chronification and acute pain stage of migraineurs. While the more posterior part of the hypothalamus seems to be important for the acute pain stage, the more anterior part seems to play an important role in attack generation and migraine chronification. ***Neurology*®** **2017;88:2011–2016**

GLOSSARY

CM = chronic migraineur; **EM** = episodic migraineur; **HC** = healthy control.

Chronic migraine is a disabling disorder with huge socioeconomic consequences on a patient's life.[1–8] This syndrome rarely is primarily chronic but most often evolves from episodic migraine gradually increasing in frequency and attack duration.[9,10] Consequently, prevention of migraine chronification has been outlined to be the most important step to avert all the detrimental socioeconomic consequences.[11] Although multiple factors promoting migraine chronification have been identified, the underlying pathophysiologic mechanisms leading to an increase in attack frequency and duration and ultimately to migraine chronification are still unknown. Judging from the clinical presentation of the premonitory phase of migraine attacks in general,[12–18] the hypothalamus has long been hypothesized to play an important role in migraine attack generation and sustainment of migraine pain. Neuroimaging studies have found this area to be active during the pain[19] but also the preictal phase of migraine attacks.[20,21] In chronic migraine with very frequent and sometimes even daily headache, it is very likely that the attack-generating and pain-sustaining mechanisms are constitutively activated. On these grounds, we hypothesized that the hypothalamus might be specifically involved in pain processing in chronic migraine. fMRI of standardized trigeminal nociceptive stimulation has been proven to be a useful tool for the investigation of migraine pathophysiology.[21–23] Via this technique, the brainstem could be identified as a major site of interest regarding attack generation and resolution.[24] The spatial resolution of common whole-brain fMRI, however, does not allow a detailed differentiation of certain subcortical and brainstem areas. We thus established a protocol for high-

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resolution brainstem imaging of standardized trigeminal nociceptive stimulation.[25] Using this protocol, we conducted a study investigating chronic migraineurs (CMs), episodic migraineurs (EMs), and healthy controls (HCs) via high-resolution brainstem imaging. The aim was to investigate possible mechanisms of migraine chronification and particularly to delineate the role of the hypothalamus in chronic migraine.

METHODS

Participants. Twenty-two CMs, 20 EMs, and 21 HCs were recruited from the Headache Outpatient Department of the University Medical Center Eppendorf, Hamburg, and via online advertisement. Patients fulfilling *International Classification of Headache Disorders, 3rd Edition (beta version)* criteria of episodic or chronic migraine with or without aura[26] were included in the study. HCs did not report any significant headache disorder (such as migraine, cluster headache, or frequent tension-type headache), reported to never have had a migraine attack, and did not have headaches on >10 days during the last 3 months taken together. A total of 9 patients (5 CMs, 2 EMs, 2 HCs) had to be excluded post hoc because of errors during data acquisition, leaving a total of 17 CMs (age 39.9 years, 2 men), 18 EMs (age 32.2 years, 2 men), and 19 HCs (age 37.4 years, 2 men). Neither sex distribution nor age differed significantly between groups. Patients were allowed to take acute headache medication on up to 10 d/mo. CMs were additionally allowed to take prophylactic medication if that medication was taken continually for at least 4 months without a significant change in headache days per month. Four CMs were on prophylactic treatment: 2 were on amitriptylin (dosages 60 and 75 mg, duration of intake 12 and 5 months), and 2 were on metoprolol (dosages 25 and 95 mg, duration of intake 12 and 5 months).

Exclusion criteria were the presence of any other severe neurologic or internal disease, change of prophylactic medication within the past 3 months, claustrophobia, pregnancy or lactation, and other general contraindications against MRI examination.

Standard protocol approvals, registrations, and patient consents. Written informed consent was obtained from all participants, and the study was conducted according to the Declaration of Helsinki and approved by the Ethics Committee in Hamburg, Germany (PV 4522). Data collection took place from July 2013 until March 2016.

Experimental protocol. Patients and HCs underwent one appointment of event-related fMRI of standardized trigeminal nociceptive stimulation via a well-established protocol that has been described in detail in previous publications.[25,27] In short, over the whole experiment, 4 different stimuli were each applied 15 times in a pseudorandomized order: gaseous ammonia as an activator of nociceptive fibers served as the painful stimulus, rose odor as the olfactory stimulus, air as the control condition, and a rotating checkerboard as a visual stimulus. The gaseous stimuli were delivered to the left nostril of each participant via an olfactometer with an 8-m Teflon tube. Before each scan, participants underwent a short reaction task with the instruction to press a button when a white cross turned red. After each stimulus, participants rated the intensity and unpleasantness of the stimulus. For intensity ratings, a visual numeric analog scale from 0 to 100 was used, whereas unpleasantness was rated on a bipolar scale with 0 meaning neutral, −50 representing most pleasant stimuli, and +50 representing most unpleasant stimuli. Presentation software was used for stimulus presentation, timing, logging of stimuli, ratings, reaction times, and the scanner pulse. During each scan, heart rate and breathing parameters were recorded simultaneously to the scanner pulse and later used for physiologic image denoising.

Image acquisition. All images were acquired on a 3T scanner (Siemens TRIO, Munich, Germany) using a 32-channel head coil. Participants lay supine on their backs. Special attention was paid to a straight positioning of the participants' heads within the head coil. Functional images were acquired with a previously established acquisition protocol for high-resolution echo-planar imaging of the human brainstem (38 axial slices, $1.25 \times 1.25 \times 2.5$ mm^3, repetition time 2.61 seconds, echo time 27 milliseconds, field of view 216 mm, generalized autocalibrating partially parallel acquisitions accelerated, and 2 saturation pulses to saturate areas of aliasing caused by the small field of view). High-resolution images were acquired with an magnetization-prepared rapid gradient-echo sequence.

Image processing and analysis. Functional images were analyzed with SPM12 (Wellcome Trust Centre for Neuroimaging) and Matlab version R2014b (MathWorks, Inc, Natick, MA). Image preprocessing consisted of the following steps: import and conversion to 4-dimensional NIfTI files, image denoising via the spatially adaptive nonlocal means algorithm as implemented in the CAT12 toolbox, slice time correction, and image realignment. After the first-level analysis, beta and contrast images were normalized via a segmentation-normalization sequence (consisting of coregistration of the structural T1-weighted image to the mean functional image, segmentation of the coregistered T1 image, and normalization into Montreal Neurological Institute space using the deformation field of the structural scan and a bounding box restricted approximately to the dimensions of the measured volume), upsampled to a spatial resolution of $1 \times 1 \times 1$ mm^3, and smoothed with a 4-mm full width at half-maximum isotropic gaussian kernel.

Physiologic denoising. Because the brainstem is surrounded by large blood vessels and CSF, it is susceptible to artifacts caused by changes in heart rate and breathing. We thus recorded heart rate measured via a pulse oximeter and breathing excursion measured via a respiratory belt simultaneously to the scanner pulse via an InVivo Expression Monitoring device (InVivo Corp, Orlando, FL). Physiologic signals were digitalized with a conducted energy device and Spike 2 software. The individual images could thus later be attributed to a certain phase of the respiratory and cardiac cycle with the selective averaging method proposed by Deckers et al.,[28] resulting in 18 to 20 physiologic noise regressors to be later included in the first-level general linear model.

First-level general linear model. The first-level general linear model included 4 experimental regressors, ammonia, rose odor, air, and the checkerboard, as well as 6 movement parameters and 18 to 20 physiologic noise regressors. Gaseous stimuli were modeled by convolving a delta function at event onset with the hemodynamic response function. Checkerboard stimulation was modeled as a mini-block with a duration of 4 seconds. Main effects of ammonia, rose odor, and checkerboard and the contrast ammonia > air were defined as contrasts of interest.

Group statistics. To investigate group differences, the first-level pain contrast images (ammonia > air) of the individual study participants divided into the 3 diagnosis groups (EMs, CMs, HCs) were entered into a second-level general linear model (analysis of variance). Groups were contrasted against each other.

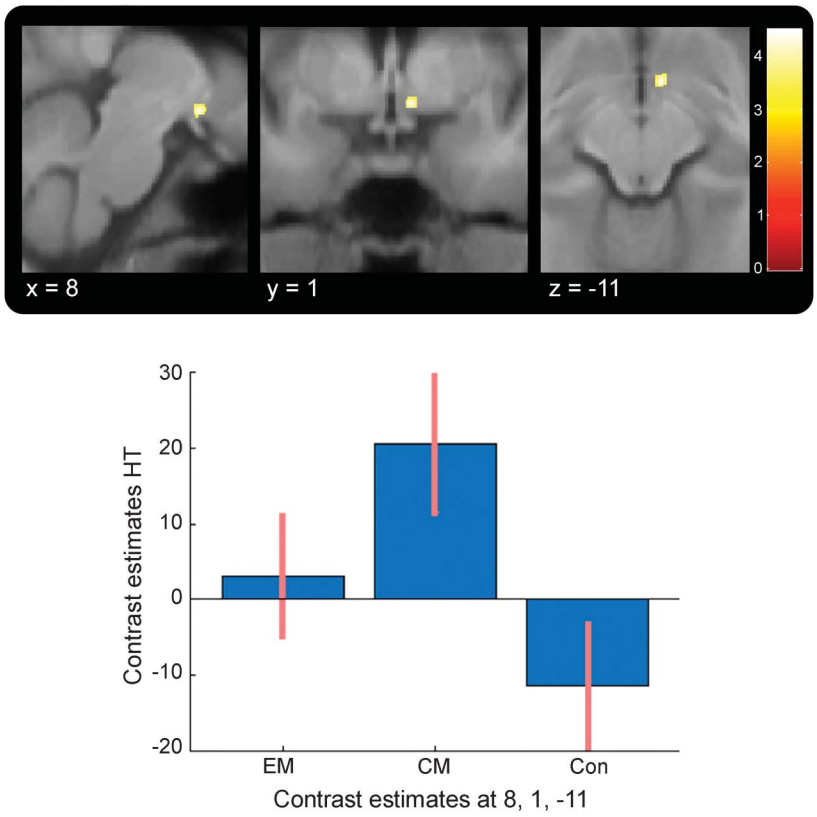
Table Demographic details of the study population

	Age, y	F/M, n	Total, n	Headaches during scanning, n	Mean headache, d/mo	Intake of acute headache medication, d/mo
EMs	32.2 (±10.6)	16, 2	18	7	7.6 (±3.1)	5.53 (±3.00)
CMs	39.9 (±11.5)	15, 2	17	12	22.7 (±6.6)	7.3 (±2.8)
HCs	37.4 (±12.1)	17, 2	19	NA	NA	NA

Abbreviations: CM = chronic migraineur; EM = episodic migraineur; HC = healthy control; NA = not applicable.

For a second analysis, which was done to elucidate the role of the hypothalamus in acute headache (regardless of whether the underlying headache pattern was chronic or episodic), patient groups were defined differently. In another second-level analysis of variance, we also contrasted all migraineurs with headache during scanning to all migraineurs without headache during scanning and against HCs. Results were regarded significant at a value of $p < 0.05$, corrected for multiple comparisons with the family-wise error rate. Because the study was specifically targeted at the hypothalamus and this region was thus our only predefined region of interest,[21] we conducted correction for multiple comparisons only for this region as defined by carefully comparing images of the Duvernoy atlas.[29] For multiple-comparisons correction, we used an 8-mm sphere around the peak coordinates of hypothalamic activation in the premonitory phase of migraine reported by Maniyar et al.[20] (x = 6, y = −6, z = −12; transformed to the left side: x = −6, y = −6, z = −12, respectively). We further extracted the contrast estimates of the individual participants. These were then further analyzed via the Pearson correlation outside SPM with SPSS (SPSS Statistics 22, IBM, Armonk, NY). The α level was set at 5%, corrected for multiple comparisons with the Bonferroni approach. To test whether the anterior hypothalamic area showed any differences in activity in a comparison of EMs (7 patients) and CMs (12 patients) with headache at the time of the scanning, we additionally conducted *t* tests between the 2 groups and searched for significant activations inside a 4-mm sphere around the peak voxel of the anterior hypothalamic activation at x = 8, y = 1, and z = −11. To further investigate whether the posterior hypothalamic area was more active during headache in all migraineurs (19 migraineurs: 7 EMs, 12 CMs) compared to migraineurs who were >24 hours away from their next attack (6 EMs, 1 CMs), we calculated a second *t* test between the 2 groups and searched using a 5-mm sphere around the peak voxels from the posterior hypothalamic activation found when all patients with headaches during the scanning were compared with all participants (migraineurs and HCs) without headaches.

Figure 1 Increased anterior hypothalamic activation in CMs compared to HCs

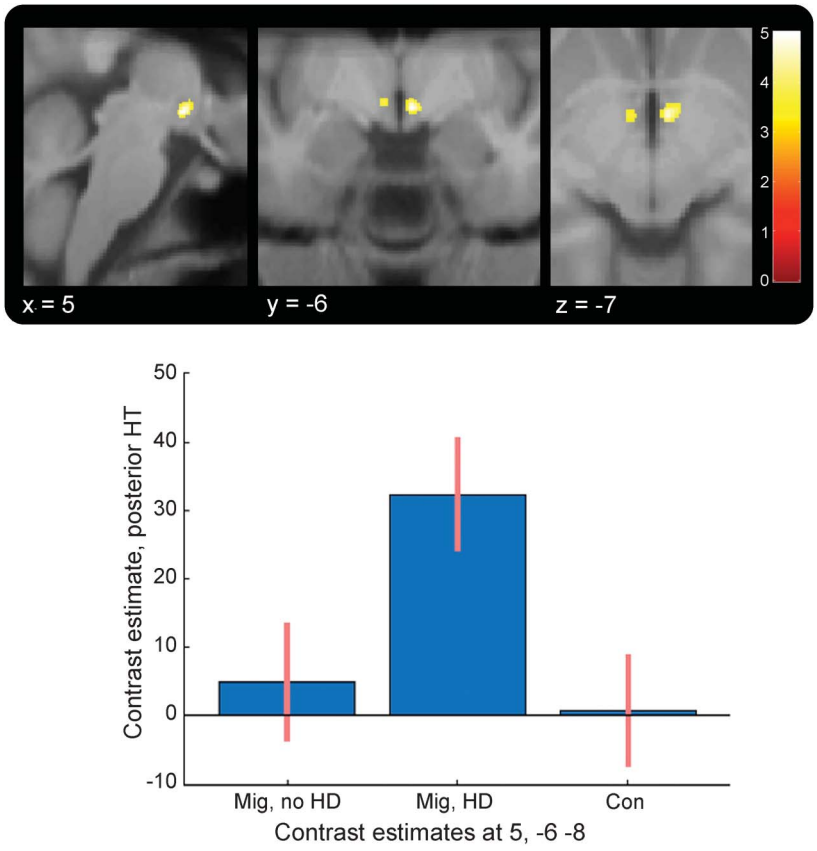


The anterior part of the hypothalamus was more activated during pain processing in CMs than in HCs. There was a positive correlation between contrast weights and diagnosis group with highest values among CMs and lowest values among HCs. Shown is a *t*-score map of the second-level analysis of variance of the first-level pain contrast images (ammonia > air) at a threshold of $p < 0.001$ laid over a mean image of participant's structural scans and a plot of contrast estimates within the peak voxel of anterior hypothalamic activation (x = 8, y = 1, z = −11, *t* = 4.33). CM = chronic migraineur; EM = episodic migraineur; HC = healthy control.

RESULTS **Epidemiologic and behavioral data.** There were no differences in age and sex distribution between groups. Among the CM group, 6 patients had daily headaches. See the table for demographic details of the study population. In addition, behavioral analysis of intensity and unpleasantness ratings of the ammonia stimulus did not yield significant results after correction for multiple comparisons.

Functional imaging data: Comparison of CMs, EMs, and HCs. In a comparison of the pain contrast ammonia > air between the groups, activity within the right anterior hypothalamus was higher among CMs than among HCs (x = 8, y = 1, z = −11, T = 4.33). The same area showed more activity in CMs with headaches at the time of the scanning compared to EMs with headaches during scanning (x = 9, y = 0, z = −9, *t* = 3.69). To test whether there was a correlation between the diagnosis and the height of the contrast estimates within the anterior hypothalamic area, we correlated the diagnosis with the contrast estimates within this area. Contrast estimates were highest in CMs and lowest in HCs, whereas in EMs, values were between those of the 2 other groups ($r = 0.5159$, $p < 0.001$). Figure 1 provides a *t*-score map of the

Figure 2 Increased posterior HT activation in migraineurs with HD compared to migraineurs without HD during scanning and HCs



The posterior part of the HT was bilaterally more activated during pain processing in migraineurs with HD compared to migraineurs without HD and HCs. Shown is a t-score map of the second-level analysis of variance of the first-level pain contrast images (ammonia > air) at a threshold of $p < 0.001$ laid over a mean image of participant's structural scans and a plot of contrast estimates within the peak voxel of posterior HT activation (right HT: x = 5, y = −6, z = −8, $t = 5.01$; left HT: x = −5, y = −6, z = −6, $t = 3.81$). HC = healthy control; HD = headache; HT = hypothalamus.

contrast CM > HC and a plot of the contrast estimates across groups for this area.

Functional imaging data: Comparison of migraineurs with headaches during the scanning with migraineurs without headaches and HCs. Because a bigger subgroup of CMs than EMs had headaches during the scanning, we conducted a second analysis to exclude that the headache was a driving force for the hypothalamic activation found. The above-mentioned anterior part was not significantly activated, but we detected a more posterior part of the hypothalamus to be more activated bilaterally in migraineurs with headache (regardless of the diagnosis chronicity) compared to migraineurs without headache and HCs (right hypothalamus: x = 5, y = −6, z = −8, $t = 5.01$; left hypothalamus: x = −5, y = −6, z = −6, $t = 3.81$). The same region was more activated in migraineurs with headaches during the scanning compared to migraineurs who were >24 hours away from their next headache attack (x = 8, y = −4, z = −9, $t = 4.33$). Figure 2 shows a *t*-score map of the contrast migraineurs with headache vs migraineurs without headache and HCs and a plot of the contrast estimates across groups for this area. Figure 3 shows the different hypothalamic activations codepicted in different colors.

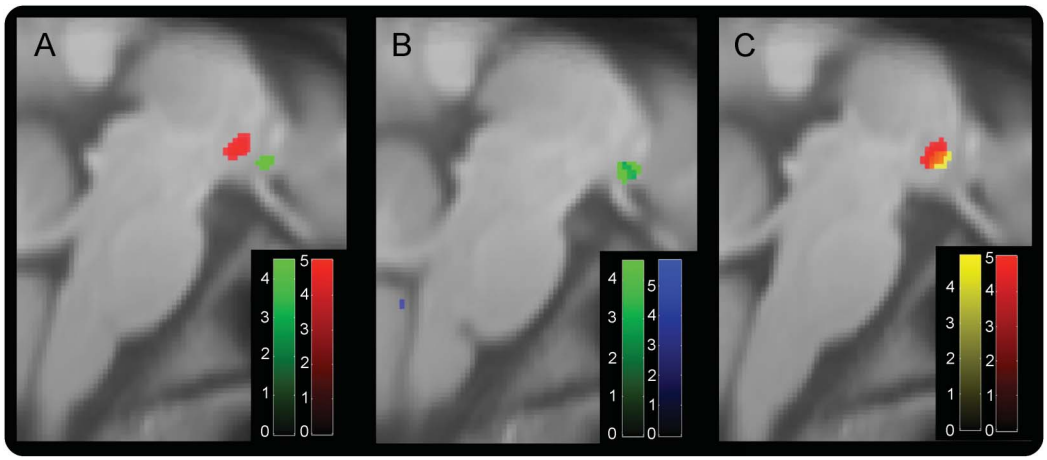
DISCUSSION Our main finding is increased hypothalamic activation as a response to painful trigeminal stimulation in CMs compared to HCs. The same area was also more activated when CMs were compared with EMs with headaches at the time of the scanning. Together, these findings point toward the hypothalamus as a key structure in chronic migraine.

Furthermore, when investigating the headache state in migraineurs (EMs and CMs) compared to the headache-free phase in migraineurs (EMs and CMs) and HCs, we found a more posterior part of the hypothalamus to be more highly activated. These data suggest an important role of 2 different parts of the hypothalamus, the anterior part playing a role in the initiation of attacks and thus (indirectly) in the pathophysiology of (chronic) migraine and the more posterior part being specifically linked to the acute pain attack itself.

The hypothalamus has long been implicated as a key modulator of the preictal phase of migraine attacks,[30] not least due to typical migraine premonitory symptoms[12–16] such as food craving and yawning. Very recently, the more anterior part of the hypothalamus has been shown to be involved in the preictal phase with functional imaging techniques.[20,21] Given that we show here that this part of the hypothalamus is more linked to chronic than to episodic migraine, the question arises, how is this region, which is involved in the initiation of attacks, involved in the process of chronification?

The hypothalamus is a part of the descending pain-modulating network.[25,31] Dysfunction of descending pain modulation due to repetitive oxidative stress resulting from frequent exposure to pain has been implicated to play an important role in migraine chronification.[11,32,33] The increased hypothalamic activation observed in chronic migraine might thus point toward a decreased threshold for attack generation in chronic migraine, which, in combination with epidemiologic factors, might lead to an enhanced susceptibility to attack generation.[2,4,10,11,34–38] The functional correlate of this process might be a constitutive activation of brain areas, namely the anterior part of the hypothalamus, typically involved in the preictal phase of episodic migraine. However, CMs are more likely to have headaches on the day of scanning than EMs. To exclude that the headache was the driving force behind the observed anterior hypothalamic activation, we contrasted all patients with headache with patients without headache

Figure 3 Codepiction of the different hypothalamic activations



(A) Main activation (red) found when all migraineurs (EMs and CMs) with headache at the time of the scanning were compared with all migraineurs (EMs and CMs) without headache and HCs. The comparison CM > HC is depicted in green. (B) Overlap between anterior hypothalamic areas more active in CMs than in HCs (green) and in ictal chronic migraine than in ictal episodic migraine (blue; only the overlap is visible in turquoise). (C) Overlap (orange) between areas more active in all participants with headaches than those without headaches during scanning (red) and areas more active in migraineurs (EMs and CMs) with headaches during scanning compared to migraineurs (EMs and CMs) without headaches during scanning (yellow). CM = chronic migraineur; EM = episodic migraineur; HC = healthy control.

and HCs. This analysis did not show the anterior but the posterior part of the hypothalamus, suggesting that the posterior hypothalamus might be involved in the pain state of migraine, whereas the anterior part seems to be important for migraine attack generation and ultimately chronicity of attacks. The anterior hypothalamus would than act as an important hub mediating between attack-precipitating factors and the descending pain-modulating system. We note that the correlation analysis showed that contrast estimates and thus activity within this region gradually increase from HCs to EMs to CMs, which might indicate that the progression from EM to CM is indeed a continuum.

The bilateral activation within the posterior hypothalamic area during the pain state in patients with migraine could be due to different effects. On the one hand, it might be due to enhanced pain-modulating processing in a state of painful trigeminal sensation (headache); on the other hand, it might indicate a primary dysfunction of the descending pain-modulating network with an enhanced hypothalamic activation to account for the deficit.

Because a key feature of chronic migraine is the very frequent headache, headache-free days are scarce and the interictal phase is no longer clearly definable. On the basis of our data, we suggest that parts of the hypothalamus that in episodic migraine are involved in the initiation of attacks[20,21] become more activated during the transition from episodic to chronic migraine, thus lowering the threshold for incoming external input to effectively initiate the next attack, which then involves the more posterior parts of the hypothalamus. This transition can evolve to a constant disposition to initiate the next attack with the consequence of nearly daily or indeed daily headache. We note that the spatial resolution of our study, although rather small, still is not high enough to identify single hypothalamic cell groups. In future studies, it will be desirable to investigate CMs in a within-subject design in the pain-free state and during the migraine headache. Furthermore, to increase the generalizability of results, future studies might also include CMs with medication-overuse headache, although this would make the study population more heterogeneous. This is nevertheless important because it is not known whether acute medication-overuse headache is mediated by the same brain regions as chronic migraine without medication overuse.

Taken together, our data suggest that the anterior hypothalamus plays a crucial role in the pathophysiology of chronic migraine, whereas the posterior parts seem to be involved in the pathophysiology of the headache phase.

AUTHOR CONTRIBUTIONS

L.H.S.: drafting of the study, data acquisition and analysis, drafting and writing of the manuscript. A.A.: data acquisition and analysis. A.M.: study concept and design, drafting and writing of the manuscript, study supervision.

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DISCLOSURE

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