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The migraine generator revisited: continuous scanning of the migraine cycle over 30 days and three spontaneous attacks

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Functional imaging using positron emission tomography and later functional magnetic resonance imaging revealed a particular brainstem area that is believed to be specifically activated in migraine during, but not outside of the attack, and consequently has been coined the 'migraine generator'. However, the pathophysiological concept behind this term is not undisputed and typical migraine premonitory symptoms such as fatigue and yawning, but also a typical association of attacks to circadian and menstrual cycles, all make the hypothalamus a possible regulating region of migraine attacks. Neuroimaging studies investigating native human migraine attacks however are scarce and for methodological but also clinical reasons there are currently no studies investigating the last 24 h before headache onset. Here we report a migraine patient who had magnetic resonance imaging every day for 30 days, always in the morning, to cover, using functional imaging, a whole month and three complete, untreated migraine attacks. We found that hypothalamic activity as a response to trigeminal nociceptive stimulation is altered during the 24 h prior to pain onset, i.e. increases towards the next migraine attack. More importantly, the hypothalamus shows altered functional coupling with the spinal trigeminal nuclei and the region of the migraine generator, i.e. the dorsal rostral pons during the preictal day and the pain phase of native human migraine attacks. These data suggest that although the brainstem is highly linked to the migraine biology, the real driver of attacks might be the functional changes in hypothalamo–brainstem connectivity.

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Introduction

Among the more than 200 headache types, migraine is the second most common headache syndrome that affects between 12 and 14% of the population. Migraine is predominantly a cycling episodic disorder that manifests in attacks of headache, photophobia, phonophobia and nausea with a certain circadian rhythmicity. Extensive research over the past 20 years has broadened our understanding of the underlying mechanisms and pathogenesis. Due to technological improvements, brain imaging techniques have gained importance in the quest to understand cycling

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headache syndromes and specific emphasis has been placed to understand neuronal activation in headache syndromes using functional MRI. Several independent functional studies have established the crucial role of the brainstem in acute and chronic migraine (Weiller *et al.*, 1995; Stankewitz *et al.*, 2011) and the hypothalamic area in trigemino-autonomic headaches (May, 2005). A recent study reinforced the specific brainstem findings in migraine by comparing brain responses during trigeminal pain processing in migraine patients with those of healthy control subjects (Stankewitz *et al.*, 2011). The main finding was that the activity of the spinal trigeminal nuclei in response to nociceptive stimulation showed a cycling behaviour over the migraine interval where the trigeminal activation level increased significantly towards the next migraine attack. However, this finding came from a cohort study, where the time towards the next attack was determined retrospectively, i.e. per telephone contact after the experiment until the next attack occurred. These data cannot answer the question of whether the trigeminal pain system is dysfunctional in itself or if other structures modulate its activity. From a clinical perspective, the hypothalamus would be the most likely 'modulator' of the trigeminal pain system as the many facets of a migraine attack, such as yawning, fatigue and craving but also circadian rhythmicity of attacks (Fox and Davis, 1998; Fox, 2005; Alstadhaug *et al.*, 2007; Nascimento *et al.*, 2014) could be best explained when considering the biological role of the limbic system. Using PET, one study reported increased cerebral blood flow bilaterally in the hypothalamus during an acute attack in migraine patients (Denuelle *et al.*, 2007) and even more recently some hypothalamic activity was reported very early in nitroglycerin-triggered attacks (Maniyar *et al.*, 2014). Based on resting state data Moulton *et al.* (2014) suggested that hypothalamic connectivity with autonomic circuits and the locus coeruleus in migraine may be altered. A problem of all the above-mentioned studies is the variance of cohort studies involving the interpretation of averaged imaging data and the fact that most studies investigate only a small space of time of the migraine cycle, i.e. the attack compared to a random day between attacks. However, just as the migraine cycle spans several days and contains up to five phases (prodromes, aura, headache, resolution, and recovery) (Blau, 1992), the trigeminal activity in migraine patients is not constant but strongly variable (Stankewitz and May, 2007; Stankewitz *et al.*, 2011). Thus the ultimate answer as to which areas of the brain and brainstem might in fact generate migraine attacks comes probably from individual data which may give us a more differentiated view as data differ from subject to subject depending on the time to the next migraine attack.

Focusing on this aspect we report an otherwise healthy migraine patient without any medication who was scanned every day for 30 days, always in the morning, with the aim to cover, using functional imaging, a whole month with three complete, untreated migraine attacks.

Materials and methods

Patient

One patient with the diagnosis of migraine without aura according to IHS criteria [Headache Classification Committee of the International Headache Society (IHS), 2013] with very regular attacks (two to three per month, lasting typically 1–2 days) underwent daily event-related functional MRI of standardized trigeminal nociceptive stimulation over a period of 31 days. Headache status (headache/no headache), headache characteristics and the presence of typical migraine premonitory and accompanying symptoms were assessed daily as well as possible use of analgesic medication or triptans, other pain symptoms and state of the menstrual cycle. The patient was otherwise completely healthy and took no regular medication. She was allowed to treat acute migraine attacks at any time but was asked to kindly refrain from taking any acute medication at least 12 h before each scan, if possible. The patient herself, however, decided to not take any medication at all although we repeatedly and explicitly offered it at least after the scan on headache days. Image acquisition took place over a continuous period of 31 days. During this period, the patient experienced three migraine attacks with typical migraine accompanying symptoms. Each attack lasted 1–2 days with a peak pain intensity of 5–7 on a visual analogue scale anchored at 0 and 10. The location was right sided except for attack number 2 with changes in pain location from left to right during the course of the attack. The functional scans from Day 22 (second day post-ictal) had to be excluded *post hoc*, due to imaging artefacts caused by a small metal clip on the participants' clothing. Behavioural data from this day however were usable and included in the analysis.

The study was approved by the local ethics committee of the chamber of physicians of Hamburg, Germany (number PV4522). The patient gave informed consent to participation in our study based on elaborate personal information and on a special information session before the actual study during which she was able to experience the experimental paradigm first hand and to make an informed decision on whether she felt able to undergo this daily. A few days later we asked her whether she was willing to participate.

Experimental paradigm

The protocol for standardized trigeminal nociceptive stimulation has been described in detail in previous publications (Stankewitz *et al.*, 2010; Kröger and May, 2015; Schulte *et al.*, 2015). In short, the paradigm consisted of three gaseous stimuli presented via a Teflon tube to the left nostril of the patient and one visual stimulus: gaseous ammonia served as standardized nociceptive stimulus, rose odour as olfactory stimulus, air as control condition and a rotating checkerboard as visual stimulus. Gaseous stimuli were presented via an olfactometer whereas visual stimuli, reaction tasks and rating procedures were presented via a mirror system using Presentation® software (version 16.4, Neurobehavioural Systems, Berkeley, California, USA). Stimuli were presented 15 times during the experiment. Stimulus-sequences were in a pseudorandomized order thus preventing direct succession of two similar stimuli. Prior to each stimulus a reaction task

was performed: the patient was asked to press a button when a white cross turned red. Following each stimulus presentation the patient rated the intensity of the stimulus on a visual numeric rating scale (0 to 100), as well as the unpleasantness of each stimulus (−50 to +50, with higher values indicating a more unpleasant experience).

Behavioural data

Intensity and unpleasantness of all stimuli were rated on a visual numeric rating scale. Behavioural data were extracted from logfiles, plotted and analysed within Matlab (R2013b, The MathWorks, Inc., Natick, Massachusets, USA) using custom scripts and basis functions. Statistical comparison of the ictal days versus the interictal days was performed by applying the function 'ttest2' of Matlab to the single data points of the respective days. For plotting behavioural data were normalized by subtracting the overall mean of the rating of each quality from each individual rating of the respective quality on every single day.

Image acquisition

Images were acquired on a 3 T MRI scanner (TIM TRIO, Siemens) using a 32-channel head coil. During the experimental paradigm ~900 to 1100 functional images were acquired using the following protocol for echoplanar imaging: voxel size: $2 \times 2 \times 2$ mm^3, 40 axial slices, repetition time = 2.62 s, echo time = 30 ms, flip angle 90°, parallel accelerated with GRAPPA. Structural images were acquired using an MPRAGE sequence (voxel size: $1 \times 1 \times 1$ mm^3, repetition time 2.3 s, echo time 2.98 ms, slice orientation: sagittal, flip angle 9°).

Preprocessing

Preprocessing of functional images consisted of the following steps: realignment, coregistration to a structural scan, and smoothing. As we expected normalization in a single subject analysis to introduce additional error, we omitted normalization of functional data into MNI space during preprocessing. Instead, functional images were transferred into the same stereotactic space by an image realignment–coregistration sequence. Functional images were smoothed using a 6 mm full-width at half maximum Gaussian kernel.

Region of interest definition and transference into single subject space

Regions of interest for small volume correction were generated via MarsBar Toolbox using the coordinates of previously reported activations within the respective brain areas as centre of spheres. Sphere diameters varied according to the anatomical properties of the brain region that the respective region of interest was located in. In general we used smaller diameters for regions of interest located within the brainstem (6–9 mm) and larger diameters for regions of interest located within supratentorial brain areas. Centre coordinates for regions of interest were obtained from the following publications: spinal trigeminal nuclei (Stankewitz *et al.*, 2011; Kröger and May, 2015; Youssef *et al.*, 2016), rostral pons (Denuelle *et al.*, 2007), hypothalamus (Denuelle *et al.*, 2007). Regions of interest of the primary and secondary visual cortex (Brodmann areas 17, 18 and 19) were defined by using the Wake Forest University Pickatlas (WFU-Pickatlas, version 3.0) (Maldjian *et al.*, 2003).

To enable small volume correction with previously reported coordinates from the literature and anatomical masks obtained from the WFU-atlas, we transferred regions of interest into subject space by a normalization procedure: first, we normalized the single subject T_1 template included in SPM12 to the already coregistered structural scan of our subject using the function 'old normalize' as implemented in SPM12. Normalization parameters were then used to transfer regions of interest to subject space.

Statistical analysis

The experimental paradigm was analysed using a general linear model (GLM) as implemented in first level models of SPM12. Herein, each day of scanning (except for Day 22 due to imaging artefacts) was included as a single session in the first level GLM. Per session, 12 regressors were included in the analysis: six experimental regressors (ammonia, rose odour, air, checkerboard, button presses, anticipation phase), and six movement regressors created during image realignment. For the three gaseous stimuli, button presses and movement parameters, a delta function at event onset was convolved with the canonical haemodynamic response function (HRF). The checkerboard stimulus and the anticipation phase were modelled by convolving box car functions of stimulus duration with the HRF. To identify changes in pain processing during different days of the migraine cycle differential contrasts were defined by attributing contrast weights of the respective size to the ammonia regressor of the days of interest. The different phases of the migraine cycle were defined as follows: interictal: at least 60 h distance from the past and to the next attack; preictal: headache onset within the next 24 h; ictal: all days with headache; postictal: headache offset within the past 24 h. As we were not only interested in categorical comparisons between the phases of the migraine cycle but also in detecting brain areas showing a linear increase of activity towards the next attack, we modelled a correlation contrast with contrast weights showing a linear increase from the fourth preictal day (in case of attack number 1 and 2) or the third preictal day (in case of attack number 3, were the fourth preictal day was also the second postictal day of the attack before and could therefore not be modelled unambiguously) on and being highest in the ictal phase. All differential contrasts were centred by subtracting the mean of all non-zero contrast weights from each individual non-zero contrast weight of a given contrast, so that the sum of contrast weights added up to (approximately) zero.

Functional connectivity

Based on a strong *a priori* hypothesis on clinical (Blau, 1992) and functional imaging grounds (Denuelle *et al.*, 2007; Maniyar *et al.*, 2014), we hypothesized the hypothalamus to play a crucial role in migraine attack generation. We thus conducted a psychophysiological interaction analysis (Friston *et al.*, 1997) using pain (ammonia) as the psychological condition and a sphere of 2-mm radius around the peak voxel of the hypothalamic activation from the correlation contrast

adjusted for effects of interest as a seed region. Three regressors were included per session and day: (i) the extracted time course from the seed region; (ii) the psychological variable (pain); and (iii) the PPI (psychophysiological interactions) interaction term. Contrast vectors for the interaction term were created and centred as described above.

Multiple comparisons correction

Although this is a single subject study, activations are assumed significant at $P < 0.05$ corrected for multiple comparisons using the family wise error rate (FWE). As we had strong *a priori* hypotheses about certain areas of the brain and brainstem regarding their involvement in migraine pathophysiology and attack generation, we defined several *a priori* regions of interest (spinal trigeminal nuclei, dorsal and middle pons, hypothalamus, visual cortex) in which small volume correction was performed. Regions of interest for small volume correction were created and transferred into subject space as described above. Outside *a priori* regions of interest activations are only reported at a threshold of $P < 0.05$, FWE corrected for all voxels.

Results

Behavioural data

A plot of behavioural data is shown in Fig. 1. When statistically comparing the ictal and the interictal state, we detected significant differences regarding intensity ratings of the pain-stimulus (ammonia, ictal mean: 63.5, interictal mean: 59.3, $P = 0.024$) and the visual stimulus (checkerboard, ictal mean: 44.7, interictal mean: 37.7, $P < 0.001$). Regarding unpleasantness ratings, significant differences were found for all of the three stimuli (ammonia: ictal mean: 26.5, interictal mean: 20.3, $P < 0.001$, rose odour: ictal mean: −2.6, interictal mean: −9.5, $P < 0.001$, checkerboard: ictal mean: 10.5, interictal mean: 1.4, $P < 0.001$).

Imaging data

When comparing the mean of the scans taken within the last 24 h before headache onset with the interictal scans, we found significant activation within the ipsilateral hypothalamus as well as bilaterally within the visual cortex (Brodmann areas 17–19). Ictally, the middle pons was significantly stronger activated than interictally, whereas the visual cortex showed significant deactivations as compared to the interictal phase. In the correlation contrast, we found the right spinal trigeminal nucleus, the middle pons, the hypothalamus and the visual cortex (Brodmann areas 18 and 19) to increase activity towards the next migraine attack. See Table 1 for further details. In the postictal phase, the visual cortex (Brodmann areas 17 and 18) was significantly stronger activated as a response to painful stimulation than in the ictal phase. No significant deactivations in any of the predefined areas of interest could be seen for the preictal or the postictal phase as compared to the interictal phase. As the hypothalamus is of interest, especially before the occurrence of migraine pain, we conducted a psychophysiological interaction analysis to determine changes in pain-related functional connectivity of the hypothalamus during the migraine cycle. During preictal days, when comparing to the interictal days, the hypothalamus showed enhanced functional coupling with the spinal trigeminal nuclei, while during the ictal days there was a significantly enhanced functional coupling between the hypothalamus and the dorsal rostral pons. When comparing the postictal with the interictal phase, functional coupling between the hypothalamus and the lower parts of the spinal trigeminal nucleus were increased at $P < 0.001$, uncorrected. This last finding however did not reach statistical significance after small volume correction. See Table 2 for further details. Figure 1 shows activations and the PPI analysis during different stages of the migraine cycle.

Discussion

The main finding of this study is that the hypothalamus, depending on the state of the migraine cycle, exhibits an altered functional coupling with the spinal trigeminal nuclei and the region of the dorsal rostral pons. More specifically, the hypothalamus is significantly more active within the last 24 h preceding the onset of migraine pain and shows the greatest functional coupling with the spinal trigeminal nuclei, whereas during the ictal state, the hypothalamus is functionally coupled with the dorsal rostral pons, an area that was previously coined ‘the migraine generator’ (Bahra *et al.*, 2001; Denuelle *et al.*, 2007).

In recent years migraine has primarily been understood and discussed as a cyclic disorder with physiological functioning and changing activity of certain areas of the brain and brainstem during different stages of the migraine cycle (Weiller *et al.*, 1995; Judit *et al.*, 2000; Stankewitz and May, 2007; Stankewitz *et al.*, 2011; Maniyar *et al.*, 2014). Increased hypothalamic activity in the hours preceding migraine pain onset has only been shown once immediately before NO-triggered migraine-like headache (Maniyar *et al.*, 2014). The authors speculated that an activation in this area in the preictal phase might represent a dysfunction that could potentially modulate the top–down inhibitory effect on the trigeminocervical complex (Maniyar *et al.*, 2014). It has to be said that activation in the hypothalamic region in this PET study was not seen, when all preictal scans were compared against baseline scans. Nevertheless, our data representing spontaneous untreated attacks suggest nitroglycerin-induced and spontaneous attacks to be very similar, including imaging data.

Scanning the same person 30 days in a row significantly reduces variance and allows monitoring common and headache-specific brain activations as a response to nociceptive stimuli throughout the migraine cycle. One way to analyse these data is to contrast different states (e.g. interictal,

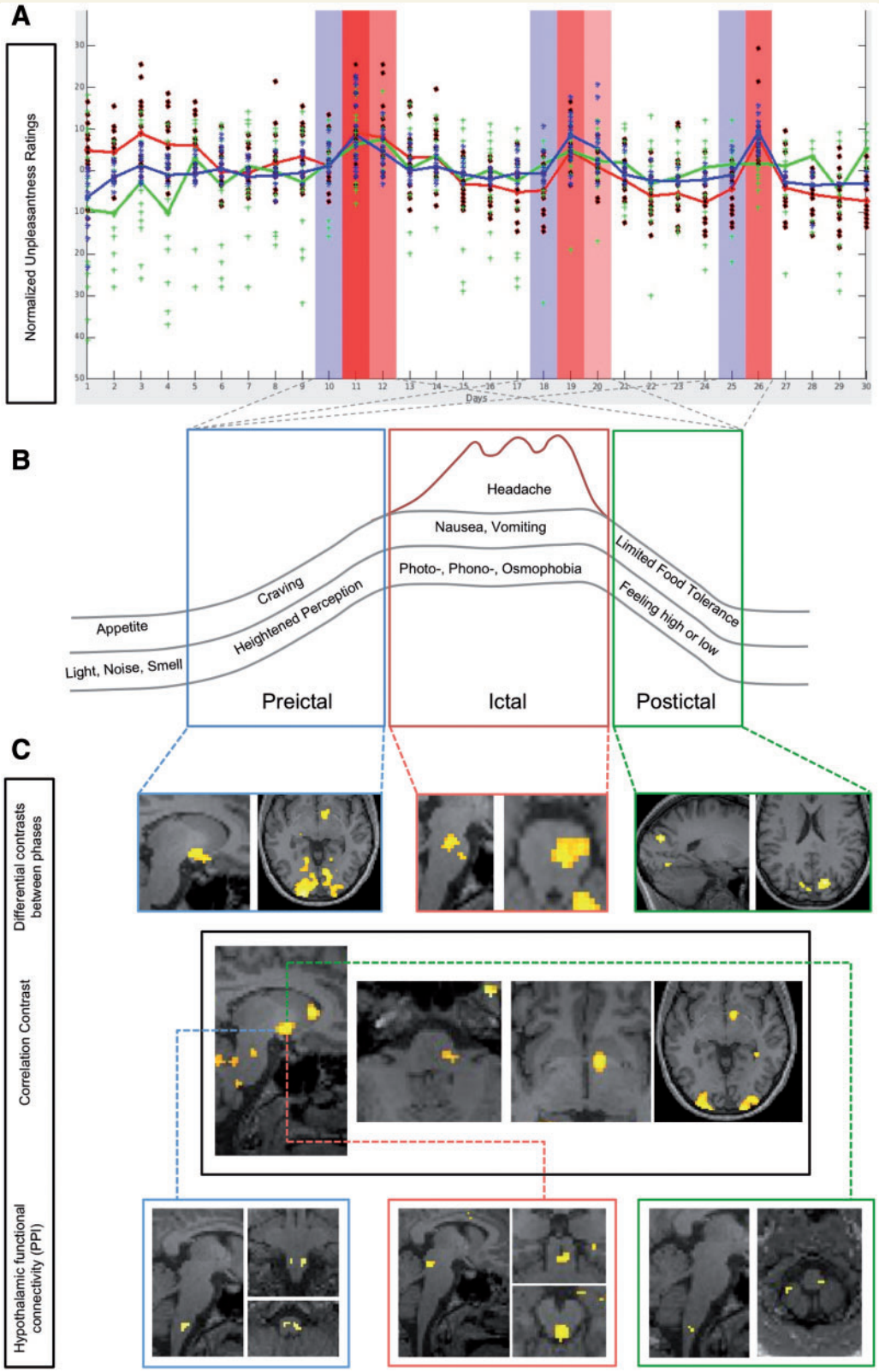

Figure 1 Changes during the migraine cycle. (**A**) Unpleasantness ratings for ammonia, rose odour and checkerboard stimulation (red line and dots: ammonia-ratings; green line and crosses: rose odour ratings; blue line and asterisks: checkerboard ratings). Data were normalized by subtracting the mean rating over all days from the individual ratings of every single day. Higher values represent a more unpleasant experience. Red areas: days of migraine pain. Varying colour intensities indicate different intensities of migraine pain. Blue areas: last scan before onset of migraine pain. (**B**) Schematic overview of the migraine cycle, modified according to Blau (1992). (**C**) Results from functional MRI.

Table 1 Changes in pain processing

Region	Centre of sphere used for small volume correction	T-score of peak voxel
Pre > interictal		
Hypothalamus right	0 2 −6 (Denuelle *et al.*, 2007)	4.09
Left visual cortex (area 17)	Anatomical mask (WFU-atlas)	4.30
Right visual cortex (area 17)	Anatomical mask (WFU-atlas)	4.57
Left visual cortex (area 18)	Anatomical mask (WFU-atlas)	4.94
Right visual cortex (area 18)	Anatomical mask (WFU-atlas)	4.46
Left visual cortex (area 19)	Anatomical mask (WFU-atlas)	4.42
Right visual cortex (area 19)	Anatomical mask (WFU-atlas)	4.40
Ictal > interictal		
Middle pons	4 −20 −20 (Denuelle *et al.*, 2007)	4.21
Post > interictal		
Right visual cortex (area 17)	Anatomical mask (WFU-atlas)	3.88
Right visual cortex (area 18)	Anatomical mask (WFU-atlas)	4.11
Correlation–contrast		
Spinal trigeminal nucleus (right)	6 −39 −45 (Stankewitz *et al.*, 2011)	3.79
Middle pons	4 −20 −20 (Denuelle *et al.*, 2007)	4.32
Hypothalamus	0 2 −6 (Denuelle *et al.*, 2007)	4.55
Right visual cortex (area 18)	Anatomical mask (WFU-atlas)	4.74
Right visual cortex (area 19)	Anatomical mask (WFU-atlas)	4.79

Main findings from the general first level model of trigeminal pain processing. As data were not normalized, we report the coordinates from the literature used as centres of spheres for small volume correction instead of peak voxel coordinates from our data. T-values are reported for the peak voxel from our data located inside the mask used for small volume correction.

Table 2 PPI analysis of the hypothalamus

Region	Centre of sphere used for small volume correction	T-score of peak voxel
Pre > Interictal		
Spinal trigeminal nucleus (right)	4 −40 −55 (Youssef *et al.*, 2016)	2.91
Spinal trigeminal nucleus (left)	−4 −40 −55 (Youssef *et al.*, 2016)	3.02
Ictal > Interictal		
Dorsal rostral pons	4 −20 −20 (Denuelle *et al.*, 2007)	3.00

Main findings from the psychophysiological interaction analysis of the right hypothalamus. As data were not normalized, we report the coordinates from the literature used as centres of spheres for small volume correction instead of peak voxel coordinates from our data. T-values are reported for the peak voxel from our data.

preictal, ictal, and postictal) with each other. Another opportunity offered by this method is to use the migraine states as a regressor and, over all 30 days, compute the activity in the brain which significantly follows this regressor. When we contrasted the ictal with the interictal state we found a strong and specific activation in the rostral pons, the region which in earlier studies has been tightly linked to attack generation (Weiller *et al.*, 1995; Bahra *et al.*, 2001; Stankewitz *et al.*, 2011). This region was not prominently activated when contrasting the preictal with the interictal state, where the hypothalamus was specifically activated. In the postictal phase, only the visual cortex showed stronger activity as a response to pain compared to the ictal phase. That the visual cortex activates as a response to pain in interictal migraineurs is well known (Boulloche *et al.*, 2010). Taken together with the findings from the preictal and ictal phase as well as the correlation contrast, this could point towards increasing multisensory integration of visual and nociceptive stimulation towards the next migraine attack with a subsequent deactivation during the pain phase of a migraine attack. This phenomenon however could also represent a baseline problem: in a situation of already increased trigeminal nociceptive input the pain-related visual cortex activity might constitutively be higher leading to lesser responses to additional painful stimulation. It appears that each region is functionally highly linked to a specific phase in the migraine cycle, a suggestion that is emphasized when weighing all states over all cycles and all days (Fig. 1).

From a biological level it is probably more important to understand whether such phase-specific activations have any functional consequences and to explore possible relationships between these areas. It is therefore highly interesting that the hypothalamic activity is not only phase-locked to the preictal phase but, in this phase, has a strong functional coupling with the trigeminal nuclei, which was not seen in the other phases. We also found that the spinal trigeminal nuclei increase activity towards

the next migraine attack and were thus able to replicate findings from a previous study from our own group (Stankewitz *et al.*, 2011). The functional coupling between the hypothalamus and the trigeminal nuclei is significantly weaker in the ictal phase, when the hypothalamus is strongly coupled to the dorsal rostral pons. This suggests that the activation in this area in the preictal phase does not represent a mere dysfunction but that the change in functional connectivity of the hypothalamus with the trigeminal nuclei and the rostral pons drives the different phases, probably by activating the top–down inhibitory effect on the trigeminocervical complex in the preictal phase and activating the dorsal pons in the ictal phase, eventually leading to the attack. The current findings thus corroborate the theory that the hypothalamus might be the true generator of migraine attacks.

In conclusion, our data suggest the hypothalamus to be the primary generator of migraine attacks which, due to specific interactions with specific areas in the higher and lower brainstem, could alter the activity levels of the key regions of migraine pathophysiology. As, however, the current study only investigated a single patient repeatedly over different stages of the migraine cycle, future investigations in a cohort of patients are needed to verify the results.

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