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Intrinsic network connectivity reflects the cyclic trajectory of migraine attacks

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ABSTRACT

Background: Episodic migraine is considered to be cyclic in nature, triggered by the hypothalamus. To assess the natural trajectory of intrinsic networks over an entire migraine cycle, we designed a longitudinal intra-individual study using functional magnetic resonance imaging (fMRI).
Methods: Intrinsic network connectivity was assessed for 12 migraineurs in 82 sessions including spontaneous, untriggered headache attacks and follow-up recordings towards the next attack.
Results: We found cyclic changes in the visual, auditory, and somatosensory networks, in limbic networks (e.g. thalamo-insular, parahippocampal), and in the salience network (anterior insula and dorsal anterior cingulate cortex). Connectivity changes also extended to further cortical networks, such as the central executive network, the default mode network, as well as subcortical networks. Almost all of these network connectivity changes followed the trajectory of a linear increase over the pain-free interval that peaked immediately prior to the headache, and "dropped" to the baseline level during the headache. These network alterations are associated with a number of cortical functions that may explain the variety of ictal and pre-ictal physiological and psychological migraine symptoms.
Conclusion: Our results suggest that migraine disease is associated with widespread cyclic alterations of intrinsic networks that develop before the headache is initiated, i.e. during the interictal and premonitory phase. The increasing magnitude of connectivity within these networks towards the next attack may reflect an increasing effort to maintain network integrity.

Introduction

Migraine is a cyclic disease that affects approximately 10% of the population. Recurring headache episodes are the most disabling symptom, but many patients also suffer from a variety of sensory and autonomous symptoms (Blau, 1992).

Migraine pathophysiology is complex and, thus far, not fully understood. Resting-state functional magnetic resonance imaging (rs-fMRI) has highlighted the presence of dysfunctional connectivities in migraineurs, particularly in somatosensory (Amin et al., 2016), dorsal attention (Coppola et al., 2019), salience (Amin et al., 2016), executive control (Coppola et al., 2019), and default mode networks (Coppola et al., 2019, 2018).

Such a broad reorganisation of brain networks is thought to influence multisensory integration processes. In particular, alterations of limbic and sensory networks may lead to an increased sensory susceptibility that might make the migraineurs' brain vulnerable to intrinsic and external factors that trigger migraine attacks. Despite the cyclic nature of the migraine disease, longitudinal studies are sparse (Schulte et al., 2020; Schulte and May 2016). The majority of neuroimaging studies have used cross-sectional designs and found deviant cortical activity (Stankewitz et al., 2011; Stankewitz and May 2011), seed-based connectivity (Schwedt and Chong, 2015), and resting-state network connectivity in migraineurs.

Here, we conducted an intra-individual rs-fMRI study to follow the trajectory of intrinsic cortical networks over the entire migraine cycle. Due to the clinical features of the disease and previous findings using neurophysiological and neuroimaging techniques (Harriott and

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Schwedt, 2014; Peng and May 2019), we hypothesised substantial alterations of sensory, limbic, and the salience networks during the migraine cycle.

Materials and Methods

Subjects

Twenty-two episodic migraine patients were included in the study; twelve of these data sets were complete and suitable for the statistical analysis (11 females and one male). Characteristics and clinical features of these 12 included participants are presented in Table 1.

Drop-outs from the initially-recruited patients resulted from incidental MRI findings (n = 2; acute mastoiditis and hydrocephalus), technical problems with the scanner hardware (e.g. broken head coil that lasted longer than four days; n = 3) or software (n = 1), illness of patients (n = 2), or taking analgesic medication due to an acute painful event (n = 1) during the scanning period. One patient decided to withdraw prematurely from the study. The exclusion of patients was required due to the within-subject design, as the inclusion of incomplete data (predefined as a period longer than 4 days between two scanning sessions) could have led to an inaccurate estimation of the patients' random effects in the statistical model. Moreover, an incomplete time series would miss mandatory data for the period immediately before the migraine attack.

Migraine patients were recruited via the interdisciplinary pain centre of the Klinikum rechts der Isar and online advertisements. Migraine diagnosis was based upon the classification criterias of the International Headache Society (Headache Classification Committee of the International Headache Society (IHS), 2018) and was confirmed by a headache expert. The patients did not report any other neurological or psychiatric disorders, were not taking preventative medication for migraine for at least six months, but were allowed to take their regular acute migraine medication immediately (within a period of 20 h to the next scan) after the recording of the headache attack (non-steroidal anti-inflammatory drugs or triptans). All patients gave their written, informed consent. The study was conducted according to the Declaration of Helsinki and approved by the Ethics Committee of the Technische Universität München, Germany. All patients were remunerated for participation.

Study design

Using a longitudinal, intra-individual study design, migraine patients were tested repeatedly over an entire migraine cycle (Figure 1). The imaging time series for each patient started with the recording of a spontaneous, untriggered and untreated headache attack within the first four hours after the beginning of the migraine headache. We only recorded headache attacks which were reported with an intensity of middle to strong, predefined as a minimum of "4" on a numerical rating scale with the endpoints zero (no pain) and 10 (extremely intense pain). Brain data were then recorded every 1–4 days at the same time of day until patients informed us by phone about the following headache attack (which was not scanned). The diagnosis of the second migraine attack was again confirmed by a headache expert. The time series was completed with the last attack-free recording. Across all patients we recorded 82 imaging sessions.

We obtained data on the first day after the attack for all patients (12/12) and for the majority of the patients (9/12) on the day before or on the same day before the subsequent attack. All patients had their final recording within 48 h before the subsequent attack.

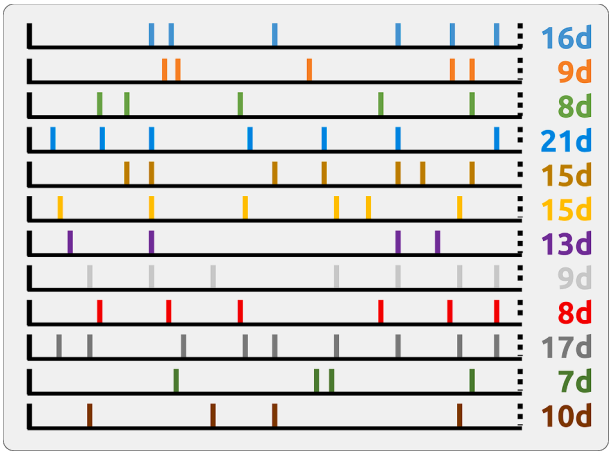

Fig. 1. Time course of individual recordings. Solid vertical blips indicate recording days. The first blip and the last blip (both in black) represent the days of migraine attacks, the colourful blips in between represent the recordings within the migraine cycle relative to the attack days. The dotted blips on the day of the last attack indicates no recording. Each patient has its own colour. The number of days between the first recorded migraine attack and the subsequent migraine attack indicates the different length of each patient's migraine cycle (7 days for patient 11 and 21 days for patient 4); each horizontal line represents an entire migraine cycle but these cycles have different lengths. The distances between blip are "normalised" and depend on the length of the cycle. The interictal recordings started the day after the migraine attack; the distance between the first blip and second blip equals to one day.

Image acquisition

MRI data were collected on a 3 Tesla scanner (Ingenia, Philips, The Netherlands) using a 32-channel head coil. Patients were instructed to remain awake and relaxed with their eyes closed. For the 300 volumes of resting state data, we used the following parameters: TR = 2000 ms; time to echo (TE) = 30 ms; FOV = 192 × 192 mm^2; flip angle = 90°; number of slices = 37; voxel size = 3 × 3 × 3 mm^3 (0.29 mm gap). For image registration, a high resolution T1-weighted anatomical image was collected with: TR = 9000 ms, TE = 4 ms, flip angle = 8°, FOV = 240 × 240 × 170 mm^3; number of slices = 170; voxel size = 1.0 × 1.0 × 1.0 mm^3). Field maps were acquired in each session to control for B0-effects; 64 slices, TR = 960 ms, FOV = 192 × 192 mm^2; voxel size = 2.0 × 2.0 × 2.0 mm^3, 0.2 mm gap between slices. TE = 6 ms / 10.55 ms, flip angle 60°.

Image preprocessing

The data were preprocessed with FSL (Jenkinson et al., 2012). The Melodic toolbox was used to execute brain extraction, high-pass filtering with a frequency cutoff of 1/100 Hz, spatial registration to the MNI template, corrections for head motion during scanning, and - due to the potential contribution of smaller subcortical structures - a spatial smoothing (5 mm FWHM). The relatively small smoothing kernel was chosen to enable the detection of nucleic connectivity in subcortical regions. A distortion correction of the images was used based on field

Table 1
Demographic characteristics and clinical migraine features.

Age (years)	Female/ male	Attacks per month	Disease duration (years)	Attack severity (0–10)	Location of headache	Visual aura
28 ± 5 range = 21–40	11f/ 1 m	3.3 ± 2.1 range = 1–10	11 ± 6 range = 2–25	6.7 ± 1 range = 5–8	right-sided = 5 left-sided = 3 bilateral = 4	Yes = 3 No = 9

Attack severity was recorded on a numerical rating scale ranging from 0 (no pain) to 10 (highest imaginable pain).

maps. The data were further semi-automatically cleaned of artefacts with ICA through Melodic (Griffanti et al., 2014). The number of components had been automatically estimated by Melodic and artefact-related components were removed from the data. Head movement during scanning did not exceed 2 mm or 2° in any direction. The movement during the migraine recording was within the range of the movement of the pre-ictal recordings (relative: 0.07 ± 0.02 vs. 0.08 ± 0.02; absolute: 0.2 ± 0.7 vs 0.19 ± 0.07).

Statistical analyses

Following preprocessing, we ran a group ICA with temporally concatenated MNI-registered data of all 82 recordings using Melodic. Sixty-one networks (components) were determined by the ICA using automatic dimensionality estimation. Seventeen of these components were identified as artefacts by visual inspection (see Supplementary File 2). Thus, we selected 44 resting-state networks. A dual regression analysis computed the individual maps for all 44 networks and each of the 82 sessions. We were running voxel-wise statistics within the boundaries of the group network maps (as defined by Melodic) for the time series of 82 recordings. We aimed to investigate whether the trajectory of the time series is following two predefined time courses. In order to do so, we created two time vectors for each patient's migraine cycle and encoded the day of the recording by assigning numbers between one and two. The numbers one or two were assigned to the measurements during the headache attack, depending on the following two possible trajectories of cortical processing (Fig. 2):

Trajectory one ("reset mode"): In this predefined model, we aimed to detect the resting-state connectivity that has its peak (or trough) just *before* the headache attack starts (during the premonitory phase) and then drops (or jumps) back to normal during the headache (Chen et al., 2009; Coppola et al., 2014). From here, we model a linear increase (or decrease) over the migraine cycle to the next attack (Fig. 2, upper part). In this hypothetical time course, the magnitude of the cortical map on the first day after the attack would be similar to the brain connectivity during the attack. This trajectory can be interpreted as a cortical "reset" mechanism and is in line with neurophysiological and imaging studies suggesting altered cortical processes in migraineurs during the interictal interval that normalise just before or during headache attacks (Chen et al., 2009; Coppola et al., 2014). For example, for five measurements over 10 days, the following vector is used to reflect trajectory one: 1 (=attack), 1.2, 1.4, 1.6, 1.8.

Trajectory two ("pain mode"): This model detects the cortical processes that have their peak (or trough) *during* the headache attack then drops (or jumps) back to normal the next day. From there, we assume a linear increase (or decrease) over the migraine cycle towards the next attack (Fig. 2, lower part). We hypothesised increased magnitude of brain connectivity in regions that contribute to the processing of migraine symptoms, e.g. pain, increased sensitivity to light, sound, and odours, and vegetative complaints. In this hypothetical time course, the brain connectivity on the day prior to the attack would be similar to the brain connectivity during the headache attack. Similar to the above-mentioned example with five measurements over 10 days, the following vector is used for trajectory two: 2 (=attack), 1.2, 1.4, 1.6, 1.8.

We explored the cyclic change of cortical rsfMRI connectivity over the migraine interval separately for each network. We computed voxel-wise linear mixed-effects models (LME) in Matlab (Version R2018a, Mathworks, USA) within the z-masks of the network map as generated by Melodic. We related the time points within the migraine cycle to the session-specific cortical map of interest:

$$(1)\ \mathrm{ICAcmp} \sim \mathrm{time} + (1|\ \mathrm{subject})$$

The statistical model is expressed in Wilkinson notation (Wilkinson and Rogers, 1973); the included fixed effect (*ICAcmp* ~ time) essentially describes the magnitudes of the population common intercept and the population common slope for the dependency of cortical data on the factor time. The added random effect (e.g. 1 | subject) is used to model the specific intercept differences for each subject. In other words, the model estimates the relationship between the cortical processes in dependence on their occurrence in the migraine cycle (fixed effect). Please note that the statistical terms of fixed effect and random effect are differently used in the common neuroimaging software package SPM as compared with the standard nomenclature in statistics that we are following here. T-values of the fixed effect were computed voxel-wise as quotients between the beta estimates and the standard errors of the equation. For a comprehensive introduction into LMEs, see Harrison et al. (Harrison et al., 2018). The statistical results were corrected for multiple testing using the false discovery rate (FDR, $p < 0.05$; Genovese et al., 2002).

Data availability

Inquiries for additional data are available upon reasonable request.

Results

Clinical characteristics

Twelve migraine patients were included in the study. Characteristics and clinical features are presented in Table 1. The time points of the attacks were equally distributed across the menstrual cycles of the female patients.

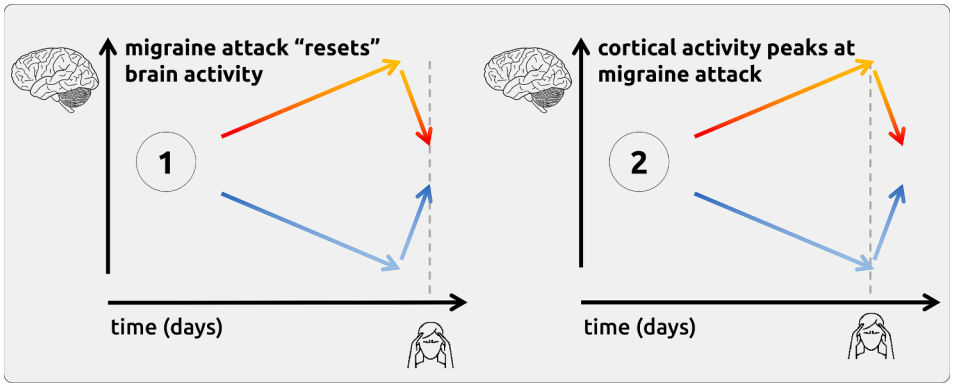

Fig. 2. Time series of migraine-related resting-state maps. Two hypothetical time series of migraine-related cortical processes were modelled in the statistical analysis. In the first time course (upper part), the cortical processes drop during the headache attacks; the brain processes would be "reset" during attacks, then would resemble the processes on the day after the attacks. In the second time course (lower part), the cortical processes would reach their climax during the attacks and are similar to the days before attacks. These processes could be used as a biomarker for an impending migraine attack. **The figure is intended to illustrate the cyclic nature of migraine attacks and the time-varying magnitude of two potential cortical processes; we recorded only one migraine cycle (grey area).**

Imaging results

We observed connectivity changes over the migraine cycle in 23 networks; 22 network changes apply to trajectory one and one network change applies to trajectory two. An overview of network changes depending on the trajectories is shown in Table 2; detailed information is given in Table 3. Maps of all networks (Supplementary NIfTI File 1) and cycle-dependent relationships for selected networks (Supplementary File 2) are included in the Supplementary Material.

Trajectory one: Changing connectivity predominantly applies to trajectory one, where 22 functional networks showed a linear increase of the magnitude of network connectivity over the interictal interval and a "drop" during the headache (Table 3a). In two of these 22 networks, we also found brain regions that showed the inverse behaviour, namely a linear decrease of the magnitude of network connectivity over the pain-free interval with peak magnitude during the headache (Table 3b). Figure 3 shows exemplary results in the visual (Fig. 3a), thalamo-insular (Fig. 3b), and the salience networks (Fig. 3c). All statistical tests were thresholded at $p < 0.05$ (FDR corrected).

Trajectory two: One limbic network followed trajectory two: the connectivity of the parahippocampal gyrus linearly decreased towards the next attack and reached its lowest magnitude during the headache (Table 3c). We did not observe any significant effect of the opposite contrast (linear increases over the pain-free interval with peak magnitude during the headache). All statistical tests were thresholded at $p < 0.05$ (FDR corrected).

Discussion

The present longitudinal fMRI study aimed to study the cyclic connectivity of intrinsic functional networks in episodic migraine. We analysed two possible network trajectories over the migraine interval.

Sensory networks. Alterations of sensory processing in migraine have been shown in various studies (de Tommaso et al., 2014; Harriott and Schwedt, 2014). Sensory thresholds have been suggested to depend on the phase within the migraine cycle, where the lowest thresholds were detected during the headache phase (Harriott and Schwedt, 2014; Peng and May 2019). Here, we mainly observed linearly increasing sensory network connectivity over the pain-free interval with a peak prior to the beginning of the headache that "dropped" to the initial level during the headache in brain regions belonging to visual (e.g. intracalcarine cortex and occipital pole), auditory (e.g. planum temporale), and somatosensory networks (e.g. postcentral gyrus). For a visual network, we also observed the inverse effect, where the connectivity of the lateral occipital cortex decreased over the pain-free interval and reached its peak during the headache. An increasing magnitude of network connectivity in sensory networks over the migraine cycle towards the attack, as observed in our study, is likely to reflect an increased sensitivity to sensory input. Additionally, it may reflect an increasing vulnerability to internal and external stressful events during the pain-free interval. External triggers for migraine attacks in some patients, such as bright or flickering light (Hougaard et al., 2013) and odours (Kelman, 2007), highlight dysfunctional sensory processing. The origin of such hypersensitivity in migraineurs is not yet understood. Genetic predispositions, such as ion channelopathies, can affect excitability thresholds making the cortex more vulnerable to diencephalic (thalamus, hypothalamus) and pontine inflow (Kullmann, 2010). Consequently, repetitive stimulation may result in an overload of cortical sensory neurons in migraine. The "drop" of network connectivity during the headache suggests a "rebooting" of cortical processes.

In the present study we found a different effect within the visual domain; there was a decrease of a lateral occipital network and an increase of two further visual networks over the migraine cycle. The increase over the migraine cycle might be considered similarly to the other affected sensory networks. The decrease of the lateral visual network may point to an impaired processing in brain regions that are related to higher-order visual functions (Jung et al., 2017; Nagy et al., 2012).

Salience networks. In line with our hypotheses, we found cyclic changes in the salience network, e.g. in the anterior cingulate cortex and the anterior insula. Similar to the sensory networks, connectivity increased over the interictal interval, reached the maximum prior to the headache, and "dropped" to the baseline level during the attack. These findings are corroborated by previous work on ictal and pre-ictal alterations of the salience network in migraine (Amin et al., 2016).

It could be speculated that the deviances in the salience network are associated with an interictally-impaired habituation in migraine, which could be explained either by reduced intra-cortical inhibition or by increased cortical excitability. Indeed, some studies report an abnormal level of both inhibitory and excitatory neurotransmitters, such as in GABA (gamma-aminobutyric acid) and glutamate (Bigal et al., 2008). Specifically, an increased amount of glutamate has been observed in migraine patients in the anterior paracingulate cortex, a region that is an essential part of the salience network (González de la Aleja et al., 2013). Numerous neurophysiological studies confirm the impaired inhibition by showing increased responsiveness to sensory stimulation in the visual, auditory, and somatosensory domain (for a comprehensive review see (de Tommaso et al., 2014)).

Limbic networks. Altered limbic connectivity is likely to be responsible for several migraine symptoms during the prodromal, ictal and postictal phases of the migraine cycle (e.g. fatigue, irritability, yawning, polyuria, and food cravings). Furthermore, many trigger factors for migraine attacks are associated with limbic circuits, e.g. psychophysical distress and emotions, homeostatic changes or circadian rhythms (Karsan et al., 2021).

Here, we revealed connectivity changes of the right DLPFC. This region is integrated in a limbic network, which also includes the hippocampus, thalamus, hypothalamus, cingulate cortex, and the insula. The DLPFC connectivity increased over the pain-free interval, reached its peak immediately prior to the headache, and "dropped" to the lowest level during the headache. The DLPFC is a key node of cognitive circuits and contributes to executive function, attention, decision-making, and emotional regulation (Carlén, 2017). The DLPFC further contributes to the top-down control of nociceptive input (Eippert et al., 2009). The increasing connectivity of the DLPFC over the pain-free interval may reflect the increasing prefrontal effort to control cognitive, emotional, and sensory processes, whereas a "drop" in DLPFC connectivity during the ictal phase is likely to reflect the altered pain and cognitive processes resulting in headache and cognitive deficits.

In a further limbic network, the connectivity of the left hippocampus (as part of a bilateral hippocampus-amygdala network) increased interictally and "dropped" during the headache. There is growing evidence showing a cortical effect of the hippocampus in migraineurs in comparison to healthy controls, e.g. a reduced volume (Chong et al., 2017) and a dependency of its connectivity on the attack frequency (Maleki et al., 2013). The amygdala-hippocampus network has been associated with the processing of mood (Kirkby et al., 2018), memory encoding (Erin, 2009), and emotion-related cognitive functions (Zheng et al., 2017). Our findings are in line with these recent studies and could reflect an increase in anxiety, decrease in mood, and pain-related

Table 2
Intrinsic networks that showed activity changes over the migraine cycle.

	Increasing cycle	Decreasing cycle
Trajectory 1	visual (basal visual areas), auditory, somatosensory, central executive, salience, cerebellar, basal ganglia, pDMN, thalamic, frontal, temporal, sensory-motor, motor, limbic, insular, and cortically distributed (occipito-parietal and fusiform-parietal) networks	visual (higher-order areas), cerebellar networks
Trajectory 2	–	limbic

Table 3a–c
Cyclic changes of intrinsic networks.

a. Trajectory 1 - linear *increasing* activity over the pain-free interval with a *"drop"* during the headache

C	Cluster sizes	t- values	MNI coordinates			Brain regions	Functional networks
			x	y	z		
4	21	4.36	−28	−80	−48	Cerebellum	Attention
	18	4.6	40	−60	42	Lateral Occipital Cortex	
5	105	4.64	14	−64	28	Precuneus Cortex	Visual
	29	4.32	−26	−62	4	Intracalcarine Cortex	
9	72	4.32	28	−90	30	Occipital Pole	Visual
13	17	4.15	46	−70	−36	Cerebellum	Cerebellar
14	96	4.41	−16	−70	28	Precuneus Cortex	Posterior DMN
	60	4.17	22	−64	32	Precuneus Cortex	
19	89	4.95	−52	−10	18	Central Opercular Cortex	Temporal
	18	4.05	64	−12	6	Planum Temporale	
20	35	5.24	−60	−36	42	Supramarginal Gyrus	Cortically distributed
21	19	3.88	4	−8	58	Juxtapositional Lobule Cortex	Motor
22	22	4.68	−36	10	−20	Temporal Pole	Auditory
25	20	4.22	−2	−30	26	Posterior Cingulate Gyrus	Posterior DMN
27	437	6.04	−2	−20	2	Thalamus	Thalamic
	34	4.5	18	−8	−6	Pallidum	
29	21	4.23	−44	−78	26	Lateral Occipital Cortex	Cortically distributed
	18	4.48	−62	−60	−6	Middle Temporal Gyrus	
30	23	4.91	–22	60	−2	Frontal Pole	Frontal
32	31	4.24	24	0	−8	Putamen	Basal ganglia
	28	4.47	−12	0	8	Caudatus	
34	136	5.04	0	34	30	Paracingulate Gyrus	Salience
	23	5.02	28	36	28	Frontal Pole	
	17	4.16	−44	–22	18	Central Opercular Cortex	
	16	4.71	40	12	−6	Insular Cortex	
35	29	4.53	56	−34	4	Superior Temporal Gyrus	Temporal
	20	4.7	30	20	−20	Frontal Orbital Cortex	
36	23	4.13	−44	−18	38	Postcentral Gyrus	Sensory-motor
37	39	4.46	48	26	0	Frontal Orbital Cortex	Fronto-angular
	18	4.01	52	−8	46	Precentral Gyrus	
	18	5.15	18	20	68	Superior Frontal Gyrus	
43	126	5.44	36	−44	−28	Temporal Occipital Fusiform Cortex	Cerebellar
	95	4.69	−52	−80	2	Lateral Occipital Cortex	
	50	4.33	−16	−60	−12	Lingual Gyrus	
	20	4.37	−50	−68	20	Lateral Occipital Cortex	
44	49	4.73	−30	−24	56	Precentral Gyrus	Sensory-motor
	48	4.21	−36	−28	40	Postcentral Gyrus	
	22	4.58	12	−52	−16	Cerebellum	
51	37	4.6	36	34	18	Dorsolateral Prefrontal Cortex	Limbic
58	152	5.52	32	−6	46	Precentral Gyrus	Sensory
	39	5.13	0	−2	52	Juxtapositional Lobule Cortex	

b. Trajectory 1 - linear *decreasing* activity over the pain-free interval with a *peak* during the headache

C	Cluster sizes	t- values	MNI coordinates			Brain regions	Functional networks
			x	y	z		
5	16	4.03	26	−90	18	Lateral Occipital Cortex	Visual
43	100	6.1	22	−90	−18	Occipital Fusiform Gyrus	Cerebellar
	21	4.6	0	−52	–22	Cerebellum	

c. Trajectory 2 - linear *decreasing* activity over the pain-free interval with a *"drop"* during the headache

C	Cluster size	t- values	MNI coordinates			Brain regions	Functional networks
			x	y	z		
54	40	4.92	−18	−4	−26	Parahippocampal Gyrus	Limbic

rumination towards the next attack. Indeed, a previous study reported growing connectivity between the amygdala and the hippocampus after stress (Ghosh et al., 2013).

In addition, a limbic network, composed of the bilateral parahippocampal gyri, hippocampi and the amygdalae, showed a linearly decreasing magnitude of connectivity of the left parahippocampal gyrus over the pain-free interval and reached its lowest level during the headache. The network that comprises these three regions has been associated predominantly with the processing of memory (Kilpatrick and Cahill, 2003) and object novelty (Kaplan et al., 2014). Further, lesions in the parahippocampal gyrus were found to cause severe memory deficits (Zola-Morgan et al., 1989) and impaired emotional responses (Gosselin et al., 2006).

The migraineurs' imperative focus on the headache is suggested to explain the low connectivity of the parahippocampus during the attack. This focus may impair cognitive functions *per se*, but can also prevent the processing of any past- or future-related memory during attacks (Gil-Gouveia et al., 2015).

Contrary to our hypothesis, we did not find any cyclic alterations of hypothalamic networks. One explanation might be that the hypothalamus is not a permanent part of the intrinsic networks, but may instead orchestrate different networks at different time points during the migraine interval as a rhythm generator.

Thalamo-insular network. There is increasing neurophysiological and neuroimaging evidence for the role of the thalamus within the migraine cycle (Younis et al., 2019). As the thalamus is connected to the sensory, salience, and limbic networks in an upstream direction, almost every stimulus that reaches the cortex is first processed and gated by the

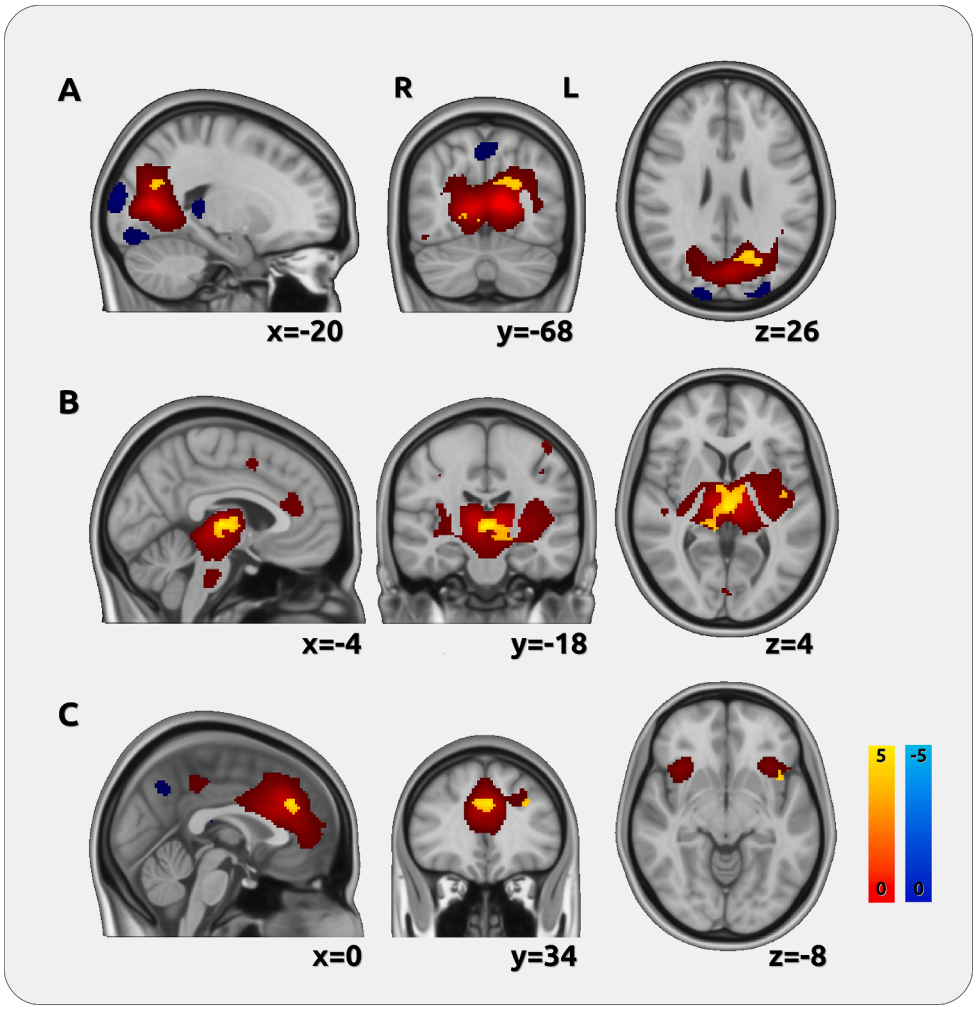

Fig. 3. Statistical analysis across the migraine cycle. The Figure shows 3 exemplary intrinsic networks (visual-sensory network, thalamo-insular network, and the salience network). The dark red and blue colours represent the entire extension of the networks. The results of the change of network connectivity throughout the migraine cycle are superimposed in lighter colours. For network 5 (A), we found a main effect in the primary visual cortex in the calcarine sulcus; for network 27 (B), we found an effect predominantly in the thalamus; and for network 34 (C), we observed an effect in the anterior insular cortex and the dorsal ACC. R = right hemisphere, L = left hemisphere. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

thalamus (LaBerge, 1997). We observed bilateral connectivity changes of the thalamus within a thalamo-insular network. Thalamic connectivity changes followed the trajectory of a linear increase over the interictal interval with a peak immediately prior to the headache and a "drop" to the baseline level during the headache. Structural (Shin et al., 2019), functional (Younis et al., 2019), and neurochemical thalamic alterations (Bathel et al., 2018) in migraine have been highlighted in recent imaging studies. During spontaneous attacks, altered functional connectivities between the thalamus and cortical regions contributing to pain processing and modulation (e.g. the insula and the orbitofrontal cortex) have been observed (Amin et al., 2018). Furthermore, using diffusion tensor MRI it has been shown that migraine patients exhibited a higher fractional anisotropy in the thalamus during the interictal interval, which normalised during the attack (Coppola et al., 2014).

Through the connections between the thalamus and the principal structures of the salience network (anterior insula, anterior cingulate cortex), the current results may suggest a maladaptive gating mechanism in the migraineurs' brain that usually prevents an overload of irrelevant and unnecessarily salient information to higher cortical areas. In migraine, internal and external input to the cortex is likely to be insufficiently filtered or inhibited by GABAerge thalamo-cortical and cortico-thalamic circuits (Peng and May 2019).

Other networks. We also found cyclic connectivity changes in various other cortical (temporal and frontal networks, as well as in cortically distributed networks) and subcortical networks (cerebellar and basal ganglia). Most of these networks followed the trajectory of a linear increase over the interictal interval with a peak prior to the headache and a "drop" to the baseline level during the headache. This applies to the posterior DMN, which has previously been shown to be altered in migraineurs (Coppola et al., 2018) and other chronic pain states (Baliki et al., 2014). DMN dysfunctions have been related to maladaptive stress responses, which seems to characterise chronic pain patients in general (Baliki et al., 2014). Similarly, we found cyclic changes of the central executive network. Although cognitive symptoms are not included as core symptoms to diagnose migraine disease, they are frequently reported by patients during the premonitory, ictal, and postdrome phases (Vuralli et al., 2018).

Limitations. There are a number of factors that could modulate the relationship between cortical connectivity and the time point within the migraine cycle, such as sex, aura, headache frequency, and disease duration. However, a proper control of the proposed factors would require a much higher number of patients equally represented for the different levels of the proposed control factors (e.g. equal or comparable number of men and women, a comparable number of patients for different headache frequency groups, etc.). This was not possible in our study, where we included only a small sample (12 patients, of which 11 were women). Nevertheless, the results can answer the basic question stated in the study. Future research is needed to explore the dependency of the cyclic processes on other factors, such as sex, attack frequency, and disease years.

In addition, the number of recordings differed across the patients. This is caused by the different length of the migraine cycles. However, a linear mixed-effects model is a suitable tool for modelling unbalanced data, so the unequal number of records for individual patients does not

reduce the quality of the model parameter estimates. A potential solution would be to include the number of recordings in the model in case there would be a systematic impact on the findings. The idea that there might be systematic differences in the pathophysiology of short vs. long cyclers does not appear plausible.

Conclusion

Our results showed that migraine disease is associated with widespread cyclic alterations of intrinsic networks including sensory, limbic and salience networks. Almost all of these network connectivity changes followed the trajectory of a linear increase over the pain-free interval that peaked immediately prior to the headache, and "dropped" to the baseline level during the headache. The increasing magnitude of connectivity within these networks towards the next attack may reflect an increasing effort to maintain network integrity. Importantly, network activity changes evolve during the pain-free migraine interval and before the headache is initiated. Therefore, our findings provide further evidence for the use of psychological approaches during the pain-free migraine interval. Cognitive-behavioural interventions, relaxation techniques, or biofeedback may prevent a recurring loss of network synchronicity that is progressing over the migraine cycle.

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CRediT authorship contribution statement

Anne Stankewitz: Conceptualization, Methodology, Data curation, Writing – original draft, Visualization, Investigation, Supervision, Validation, Writing – review & editing. **Enrico Schulz:** Conceptualization, Methodology, Data curation, Writing– original draft, Visualization, Investigation, Supervision, Validation, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ynpai.2022.100085.

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