PAIN Publish Ahead of Print
DOI: 10.1097/j.pain.0000000000001770

Temporal instability of salience network activity in migraine with aura

Dániel Veréb MD[1], Nikoletta Szabó PhD[1,2], Bernadett Tuka PhD[3], János Tajti DSc[1], András Király MD[1,2], Péter Faragó PhD[1], Krisztián Kocsis[1], Eszter Tóth MD[1], Bence Bozsik MD[1], Bálint Kincses MD[1], László Vécsei DSc[1,3], Zsigmond Tamás Kincses PhD[1,4]

[1]Department of Neurology, Albert Szent-Györgyi Clinical Center, University of Szeged, Szeged, Hungary

[2]Central European Institute of Technology, Brno, Czech Republic

[3]MTA-SZTE Neuroscience Research Group, Szeged, Hungary

[4]Department of Radiology, Albert Szent-Györgyi Clinical Center, University of Szeged, Szeged, Hungary

Corresponding author:

Zsigmond Tamás Kincses MD, PhD

Neuroimaging Research Group

Department of Neurology

Albert Szent-Györgyi Clinical Center

University of Szeged

Semmelweis u. 6

6725-Szeged

HUNGARY

e-mail: kincses.zsigmond.tamas@med.u-szeged.hu

www: www.med.u-szeged.hu/nirg

Number of pages: 24

Number of figures: 4

Number of tables: 1

Abstract

This study aims to investigate whether intra-network dynamic functional connectivity and causal interactions of the salience network is altered in the interictal term of migraine. 32 healthy controls, 37 migraineurs without aura and 20 migraineurs with aura were recruited. Participants underwent a T1-weighted scan and resting-state fMRI protocol inside a 1.5T MR scanner. We obtained average spatial maps of resting-state networks using group independent component analysis, which yielded subject-specific time series via a dual regression approach. Salience network ROIs (bilateral insulae and prefrontal cortices, dorsal anterior cingulate cortex) were obtained from the group average map via cluster-based thresholding. To describe intra-network connectivity, average and dynamic conditional correlation was calculated. Causal interactions

between the default-mode, dorsal attention and salience network were characterised by spectral Granger's causality. Time-averaged correlation was lower between the right insula and prefrontal cortex in migraine without aura vs. with aura and healthy controls ($p<0.038$, $p<0.037$). Variance of dynamic conditional correlation was higher in migraine with aura vs. healthy controls and migraine with aura vs. without aura between the right insula and dorsal anterior cingulate cortex ($p<0.011$, $p<0.026$), and in migraine with aura vs. healthy controls between the dorsal anterior cingulate and left prefrontal cortex ($p<0.021$). Causality was weaker in the <0.05 Hz frequency range between the salience and dorsal attention networks in migraine with aura ($p<0.032$). Overall, migraineurs with aura exhibit more fluctuating connections in the salience network, which also affect network interactions, and could be connected to altered cortical excitability and increased sensory gain.

Keywords: migraine; functional MRI; dynamic functional connectivity; salience network

Introduction

Migraine is associated with alterations of cortical excitability [1], more commonly in the subtype where focal neurological symptoms precede the headache, migraine with aura [15]. The effects of altered cortical excitability on brain network function are not clearly understood in migraine. In other diseases that present with this feature, e.g. epilepsy, cortical hyperexcitability induces acute and lasting changes in large-scale brain networks, impacting intra- and internetwork connections [31]. Migraine patients also exhibit altered network connectivity during and between attacks, the background of which is unclear (for a review, see [12]), though areas belonging to the default-mode, dorsal attention, salience and visual networks (DMN, DAN, SN and VN,

respectively) consistently show altered interictal connections in several studies [18; 51]. These studies, however, often investigate mixed groups, disregarding evidence that migraine with and without aura could be separate entities [18; 41; 42]. Also, stationarity of coupling between brain regions is commonly assumed, which might be an oversimplification, since functional connectivity (FC) fluctuates on different time scales [8]. Migraineurs also exhibit altered thalamocortical network dynamics [45], which means that inconsistent migraine resting state FC study results could stem from differences in methodology, heterogeneity of samples or neglecting dynamic changes in FC.

An emerging model of increased sensory gain in migraine suggests increased flexibility of network connections and altered response or adaptation to extrinsic stimuli [6], possibly more emphasized in migraine with aura due to mechanisms like cortical hyperexcitability, or cortical spreading depression [9]. Also, migraineurs show altered levels of excitatory and inhibitory neurotransmitters (e.g. glutamate and GABA, see [50] for a review). Such a neurochemical milieu would cause imbalance in network function, which might be captured by the temporal dynamics of network connections. In this model, the SN is a network of special interest: it serves as a "switch" between default-mode and task-positive networks [40; 52], flagging extrinsic stimuli as worthy or unworthy of further attentional resources. Extrinsic stimuli evoke disproportionate responses from hyperexcitable areas, making it harder to distinguish between their saliency. Accordingly, migraineurs perform less efficiently in visual tasks where relevant stimuli are to be selected from a noisy background e.g. motion detection paradigms [1]. In epilepsy - which shares pathophysiological features with migraine [29] -, cortical hyperexcitability induces lasting changes in the temporal dynamics of SN nodes [31]. Consequently, altered temporal dynamics of SN function in the interictal term might appear as a

network-level expression of altered cortical excitability, providing further grounds to differentiate between migraine subtypes.

In this study, we investigate dynamic connections of the SN in healthy participants and migraine patients with and without aura. We hypothesised that intrinsic dynamics of the SN would prove to be more variable in migraineurs and especially so in those with aura, suggesting a measure of network instability, which might influence between-network interactions. Since the SN comprises higher-order transmodal cortical areas and deals with salient stimuli of all modalities [16], we assess its function in relation to other main networks involved in higher-order stimulus processing, namely the DMN and DAN [52].

Methods

Participants

For this study, we recruited 20 migraine patients with and 37 patients without aura, and 32 healthy controls. Patients were recruited from the Headache Outpatient Clinic at the Department of Neurology, University of Szeged. Healthy controls were all recruited from the Szeged area and encompassed colleagues, their family members and students from the University of Szeged. Experienced neurologists (the authors JT and ZTK, both with over 10 years of experience) made the diagnosis of migraine based the diagnosis of migraine on the criteria outlined in the 3rd edition of the International Classification of Headache Disorders [14] and ruled out any neurological or psychiatric comorbidity during the evaluation process (further exclusion criteria included a Hamilton Depression Scale score of >8, clinical diagnosis of any anxiety disorder and abuse of alcohol or other psychoactive substances). Demographic data of the participants can be

found in Table 1. There were no differences in age, BMI or sex distribution between groups (one-way ANOVA for age and BMI: $p<0.371$, $p>0.700$ and Fisher's exact test for sex: $p<0.744$). Healthy controls did not report any chronic conditions or medication use. Migraine patients had no neuropsychiatric conditions apart from migraine, and no chronic conditions apart from a few cases of hypertension, subclinical hypothyreosis and gastrooesophageal reflux, which were treated adequately and did not cause manifest symptoms. Some of the patients took interval therapy for migraine (migraine with aura group: 1 iprazochrome, migraine without aura group: 5 iprazochrome, 1 amytriptillin, 1 topiramate). Migraineurs with aura had visual aura (symptoms included photopsia, blurry vision and scotomas), and two patients additionally had sensory aura symptoms (unilateral numbness). In the migraine with aura group, all patients predominantly had migraine attacks with preceding aura symptoms, while migraineurs without aura never experienced aura symptoms. All participants provided their written consent, as per the Helsinki declaration, and the local ethics committee approved the study (87/2009).

MR image acquisition

Participants were scanned on a 1.5T GE Signa Excite HDxt MR scanner (GE Healthcare, Milwaukee, Wisconsin, USA), at least one week after their last migraine attack, in the interictal period. We acquired 3D FSPGR (TE: 4.1 ms, TR: 10.28 ms, matrix: 256*256, flip angle: 15 degrees, FOV: 25*25 cm providing whole brain coverage) and 10 minutes of resting BOLD EPI T2*-weighted images (TE: 40 ms, TR: 3000 ms, matrix: 64*64, flip angle: 90 degrees, FOV: 30*30 cm, slice thickness: 6 mm, flip angle: 90°), resulting in 200 volumes for every participant. During the functional scan, participants were instructed to stay awake with their eyes closed.

Image pre-processing

A schematic depiction of analysis steps can be found in Figure 1. We used FEAT 6.0 to pre-process the acquired MR images, as contained in FMRIB Software Library (FSL, version 5.0.10, [39]). Steps of pre-processing included the removal of the first 2 volumes to avoid saturation effects, consequent removal of non-brain tissue via FSL's Brain Extraction Tool [37], slice-timing correction, grand mean intensity scaling and motion correction using a rigid body (6 DOF) registration to the middle volume with MCFLIRT, followed by high pass filtering with a cutoff of 0.01 Hz and removal of linear trends. We normalised the resulting volumes to standard 2 mm MNI space using a two-stage boundary-based registration process, as implemented in FSL. For the multivariate analysis, volumes were resampled to 4 mm standard space resolution. Additionally, data underwent standardization after being orthogonalized to the 6 motion parameters from the MCFLIRT output to alleviate the correlation bias introduced by head motion [20]. The three groups did not differ in terms of mean absolute or relative displacement during the scan (Kruskal-Wallis test, $p<0.425$ and $p<0.953$).

Group independent component analysis (ICA)

To acquire group-level spatial maps of resting-state brain networks, we performed group probabilistic independent component analysis with FSL's MELODIC (version 3.15, [3]), using temporal concatenation ICA. Data dimensionality was estimated automatically using the Laplace-approximation to the posterior evidence of the model order. Resulting independent components (ICs) were classified as signal or noise via visual inspection following recent guidelines [22].

Statistical analysis

In order to describe the activity of the salience network, we calculated different measures on the level of ROIs and large-scale networks. In the case of within network connectivity we calculated dynamic conditional correlation between ROIs, as a functional connectivity measure. On the network level, dynamics are more often characterized as fluid transitions between distinct patterns of node-to-node co-activations [46]. In our case, we chose an approach utilising Granger's causality to measure information flow between network activities, which provides us with a single comparable measure without the need for an a priori model.

Time series extraction

Statistical analysis was conducted using FSL tools and MATLAB (version R2012, MathWorks, Inc.). We estimated network-level time series for each subject by regressing the group level spatial maps of ICs against the subjects' fMRI data [32]. For the salience network, we investigated five major nodes: the bilateral insula, dorsal anterior cingulate cortex and bilateral anterior prefrontal cortices. ROI time series were extracted as the first temporal eigenvariate of each node in the group average salience network spatial map. Node ROIs were identified using FSL's cluster tool, as described later on.

Dynamic conditional correlation

To describe the variability of intrinsic connections in the salience network, we calculated their dynamic conditional correlation [27], a parametric, model-based dynamic functional connectivity metric that has been shown to be more accurate and reliable than the traditional sliding window method [11; 27].

Dynamic conditional correlation is calculated in two stages. To begin with, a first-order univariate generalized autoregressive conditional heteroscedasticity (GARCH (1,1)) model [4] is

fitted for each time series, which describes the conditional variance at each time point as a function of previous time point residuals and their variance:

$$\sigma^2_t = \omega + \alpha y^2_{t-1} + \beta\sigma^2_{t-1}$$

where σ represents the time-dependent variance, y is the BOLD-signal at time t, and ω, α, β are the model parameters estimated during the fitting process. This model is used to compute standardized residuals, which are then utilised to estimate framewise dynamic correlation values (see [17; 27] for the full details). This model has been evaluated for usage with fMRI data [27], and its summary measures have been subject to test-retest reliability assessment, showing fair reproducibility [11].

To get a measure similar to the static Pearson's correlation coefficient, we calculated the average of dynamic framewise correlation values across time points.

We compared this time-averaged correlation and the temporal variance of dynamic correlation coefficients between groups in a general linear model framework using a nonparametric permutation test for inference [48], similarly to the approach used in the FSLNets toolbox (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLNets). The designs we used were based on the GLM ANOVA design described in the FSL manual at https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/GLM. We set the significance threshold at p=0.05. We performed correction for multiple comparisons by controlling the family-wise error rate. To see whether the above-mentioned slight differences in medication and comorbidity between the two migraine groups had any effect on our results, we repeated the GLM analysis with dummy covariates coding for medication use and the aforementioned chronic conditions.

Granger's causality

To characterise causal interactions between the default-mode, dorsal attention and salience networks, we employed Granger's causality [21], which has been used to describe the hierarchical organization of resting-state networks in neuropsychiatric disorders before [28]. Although prone to limitations [36], the method has been shown to be viable in the analysis of fMRI data, provided certain conditions are met [47]. In this case, the time series involved do not exhibit significant zero-lag correlation, and topological differences in the hemodynamic response are averaged out during network time course estimation. Also, we investigated differences between groups, which rather means a measure of change than actual baseline causality. Here we calculated Granger's causality in the frequency domain, which can be intuitively described as the fraction of power at a certain frequency in time series X_2 that is supplied by time series X_1 [24]. In this case, the measure might be more accurate than time-domain Granger's causality, as resting-state network nodes have been shown to integrate across multiple frequency bands, with main large-scale networks having the highest power in the slow-5 and slow-4 frequency bands [19]. This is also corroborated by the fact that larger neural networks tend to be recruited during slower oscillations [7] and also the low-pass filter effect the haemodynamic response exerts on underlying neural signals (e.g. [34]).

Therefore, usually the 0.01-0.1 Hz range of network oscillations is investigated. In our case, we divided the 0.01-0.1 Hz range into two bands (0.01Hz<0.05Hz and 0.05Hz<0.1Hz), and calculated the pairwise Granger's causality of each network-network relationship in these frequency bands using the MVGC toolbox [2]. We assessed the group effect via the same approach as described in the previous section.

Results

Group ICA

The temporal concatenation ICA decomposed the data into 30 independent group average components, from which we retained those 3 that resembled the default-mode, dorsal attention and salience networks in their spatiotemporal properties [38]. Spatial maps of the selected components are depicted in Figure 2. The MELODIC group ICA analysis reported 4.5%, 3.6% and 3.4% variance explained by the DMN, DAN and SN, respectively.

Five regions usually considered as nodes of the salience network (bilateral anterior insula, dorsal anterior cingulate cortex, and bilateral anterior prefrontal cortex, similarly to [52]) were specified as regions of interest (ROI) via the following approach. The corresponding group average independent component probability map was thresholded at $p=0.9$, then we used FSL's cluster tool to obtain separate ROI maps (see Figure 3A). These ROI maps served as masks, and we extracted the principal eigenvariate of underlying voxel time courses for each participant.

Within-network connections

The variance of dynamic conditional correlation was higher in migraine with aura vs. healthy controls and migraineurs with vs. without aura between the right anterior insula and the dorsal anterior cingulate cortex, and in migraine with aura vs. healthy controls between the dorsal anterior cingulate cortex and left anterior prefrontal cortex ($p<0.011$, $p<0.026$ and $p<0.021$, corrected for multiple comparisons; see Figure 3B). The time-averaged dynamic conditional correlation was lower between the right anterior insula and right anterior prefrontal cortex in migraine without aura vs. migraine with aura and healthy controls ($p<0.038$ and $p<0.037$, corrected for multiple comparisons).

Causal network interactions

In the frequency domain, the sum of causal interaction power in the 0.01<0.05 Hz frequency range from the salience network to the dorsal attention network was significantly weaker in migraine with aura ($p<0.032$, corrected for multiple comparisons). A trend of weaker interaction from the DMN to the DAN could be observed in migraine with aura, which did not reach statistical significance (see Figure 4). No significant differences were observed in the 0.05<0.1 Hz frequency range.

The GLM analysis that contained medication use and chronic conditions as covariates yielded similar results in all comparisons.

Relation to clinical variables

Variance of dynamic conditional correlation:

Spearman's rank correlation was calculated between DCC variance and clinical parameters (attack frequency, disease duration). We found no interaction between DCC variance and clinical parameters in the aura group. In the non-aura group, variance of the bilateral PFC correlation and right anterior insula – rPFC correlation diminished moderately with increasing attack frequency ($R= -0.516$, $p<0.003$ and $R= -0.456$, $p<0.012$, p values corrected for multiple comparisons via Bonferroni).

Spectral causal interactions:

Spearman's rank correlation was calculated between causal interaction power and clinical parameters (attack frequency, disease duration). The DMN-DAN interaction diminished moderately with longer disease duration in the migraine with aura group ($R= -0.5248$, $p<0.036$, p values corrected for multiple comparisons via Bonferroni). These interactions were absent in the migraine without aura group.

Effect of intrinsic network stability on network interactions

To investigate whether the increased volatility of node correlations in the salience network affect causal network interactions (seeing as degraded network stability might exert harmful influences on internetwork dynamics), we calculated Spearman's rank correlation between causal interaction strength and node-to-node correlation variance.

The SN-DMN interaction diminished moderately with increasing variance of the dACC – rPFC correlation in the migraine with aura group ($R= -0.564$, $p<0.045$, p values corrected for multiple comparisons via Bonferroni).

Discussion

In this study, we showed that (i) migraineurs with aura exhibit more fluctuating interregional connections within the salience network, (ii) effective connectivity between the salience and dorsal attention resting-state networks is reduced in migraine with aura, (iii) that are both a function of clinical parameters and the extent of connection instability within the salience network. We used dynamic conditional correlation, a fairly novel method that has been scarcely used to investigate pain disorders. One study used it to investigate links between the salience network and multiple sclerosis-associated pain; their results show that neuropathic pain features are associated with larger fluctuations of dynamic functional connectivity between lower-order sensory cortical seeds and salience network regions [5]. Another study demonstrated that the consistency of task performance during the administration of painful stimuli correlates with variability of DCC in the salience network [10]. We aimed to describe salience network instability by the hypothetically increased variance of interregional intrinsic dynamic correlations

and then proceeded to examine whether between-network interactions are affected by the salience network's intrinsic instability. We discuss these points further below.

The physiological basis of dynamic functional connectivity has been the target of a considerable body of research in recent years, which linked it to behavioural and cognitive measures [13], the power of the EEG signal in certain frequency bands [43], and showed that its parameters differ in certain disease conditions. It has been linked to cortical hyperexcitability in the case of temporal lobe epilepsy, where the variance of dynamic functional connectivity in networks related to seizure propagation (especially the midline cingulate areas) was shown to increase with longer disease duration [31]. Our study showed that the connection between the right anterior insula and dorsal anterior cingulate cortex (areas that constitute the core regions of the salience network [40]) is more variable in migraineurs with aura. We hypothesise that this instability might come from multiple origins.

(i) Since this network deals with salient stimuli, more frequent inputs from hyperexcitable brain regions (such as the visual cortex in the case of migraine) might strengthen the structural connections between network nodes, providing a more defined link that allows a greater range of synchronization. This would be corroborated by our previous study, which showed increased fractional anisotropy, and lower mean and radial diffusivity in various white matter tracts (including the cingular white matter) in migraineurs with aura, compared to controls [41]. Such a constellation of diffusion parameters is usually interpreted as a sign of more compact and defined white matter microstructure, possibly a consequence of plastic changes in the brain [35]. Also, migraineurs without aura did not exhibit the same degree of variability in salience network integration, and in their case, a lower variance of insular connections was associated with higher attack frequency and longer disease duration.

(ii) The instability of the salience network's core connections might stem from an increased amount of glutamate in the dACC present in migraineurs [50], which might allow less salient stimuli to elicit a stronger response, making distinction between noise and stimulus harder. Furthermore, functional connectivity of the dACC has been described to strengthen with increasing glutamate levels, suggesting a higher level of synaptic efficiency in dACC connections [26]. This might, in part, represent a functional adaptation to the higher ratio of extrinsic stimuli entering the processing stream, which might be connected to the altered temporal patterns in the stimulus-processing stream migraineurs exhibit compared to healthy controls [45]. Behavioural results show that migraineurs navigate stimuli mixtures of competing features with less ease: Antal et al. showed that their judgment of motion direction in the case of coherently moving dots against an incoherent background lags behind that of healthy participants [1], which was confirmed by other studies as well (e.g. [44]). Another interesting phenomenon is that when confronted with perceptual rivalry (e.g. the Necker-cube illusion, where extended viewing of a dot within a schematic drawing of a cube will introduce two alternating visual percepts), migraineurs show increased intervals between perceptual switches in the interictal term as a function of their headache frequency [30]. Seeing as cortical spreading depression is thought to underlie the migraine aura, and arises more readily in case of a cortical excitatory/inhibitory imbalance [33], this might also show that the ability to differentiate between competing stimuli may be dependent on the extent of altered cortical excitability.

(iii) The core regions of the salience network are also involved in pain processing [25], which might imply that the network's intrinsic instability is the consequence of an increased allostatic load that migraine attacks present. This would be contradicted by our result, which shows that the intrinsic instability of the salience network differs between the two migraine groups, although

migraineurs without aura showed significantly greater attack frequency in the studied population (two-tailed Student's t-test, $p<0.01$). Considering this, still, network variability relates differently to attack frequency and disease duration in the two groups. Further investigations are required to establish the pathophysiological basis of the more variable insula-dACC connection in migraine.

The salience network has been suggested to play a role in the transition between default mode and active brain function [40; 52]. It is one of the hierarchically organized, anticorrelated networks that has been suggested to be important for cognitive functioning [23]. In migraine, the functional and effective connectivity of the salience network to other large-scale networks are altered [51]. Our study found similar differences in the information flow between the default-mode network and two networks associated with different aspects of saliency detection. We also showed that this might be explained in part by the intrinsic instability of the salience network. More variable connections in the network might lead to a larger extent of node-to-node synchronization. This might allow the generation of more frequent signals from the anterior insula, which could make further processing of attended stimuli inefficient, and result in dysfunctional large-scale network dynamics. Although it did not reach statistical significance, a tendency of diminished information flow from the DMN to the SN might suggest that the switching function of the SN is harder to evoke in migraine patients. This might be due to plastic changes in network function, which might constitute an adaptation to a lower threshold for stimulus saliency. Our results, that higher attack frequency and longer disease duration come with more hampered network interactions, may provide some basis for this hypothesis. However, more targeted studies are needed to address these possibilities, which employ paradigms that recruit saliency detection networks in a consistent and more discernible way.

Our study has several limitations. First of all, the physiological basis and methodology of dynamic functional connectivity is still an active research area, and there is a plethora of metrics in the literature, with no best one that suits every research question in the topic. Here we chose a metric that has been evaluated to be fairly accurate and reproducible, but future research might develop more prompt ways to characterize time-varying functional connections.

The temporal resolution of fMRI provides smaller space for interpreting dynamic changes, restricting observation to the scale of several seconds. Future research might aim to employ combined modalities to gain more information about the temporal reorganization of brain networks that might illuminate their functional changes in pathology more accurately.

Lastly, studying dynamic changes in the resting-state might be less informative in the case of saliency detection than targeted paradigms.

Conclusion

In this study, we found that the salience network exhibits more variability in its intrinsic connections in migraineurs with aura compared to healthy controls and migraineurs without aura, which also impacts between-network interactions. This furthers the need for distinction between the two migraine types, and adds to the current body of knowledge pertaining functional brain architecture that underlies disease phenomena in migraine with aura.

Acknowledgements

The study was supported by the Neuroscience Research Group of the Hungarian Academy of Sciences and the University of Szeged, GINOP-2.3.2-15-2016-00034 grant, EFOP-3.6.1-16-2016-00008, by a Horizon 2020 grant (H2020-MSCA-RISE-2016 734718), NAP 2.0 (2017-1.2.1-NKP-2017-00002), National Brain Research Program (KTIA_13_NAP-A-II/20) and the

Bolyai Scholarship Programme of the Hungarian Academy of Sciences. BK was supported by the UNKP-18-3 New National Excellence Program of the Ministry of Human Capacities. The authors report no disclosures.

References

[1] Antal A, Temme J, Nitsche MA, Varga ET, Lang N, Paulus W. Altered motion perception in migraineurs: evidence for interictal cortical hyperexcitability. Cephalalgia : an international journal of headache 2005;25(10):788-794.

[2] Barnett L, Seth AK. The MVGC multivariate Granger causality toolbox: a new approach to Granger-causal inference. Journal of neuroscience methods 2014;223:50-68.

[3] Beckmann CF, Smith SM. Probabilistic independent component analysis for functional magnetic resonance imaging. IEEE transactions on medical imaging 2004;23(2):137-152.

[4] Bollerslev T. Generalized autoregressive conditional heteroskedasticity. Journal of Econometrics 1986;31(3):307-327.

[5] Bosma RL, Kim JA, Cheng JC, Rogachov A, Hemington KS, Osborne NR, Oh J, Davis KD. Dynamic pain connectome functional connectivity and oscillations reflect multiple sclerosis pain. Pain 2018;159(11):2267-2276.

[6] Brennan KC, Pietrobon D. A Systems Neuroscience Approach to Migraine. Neuron 2018;97(5):1004-1021.

[7] Buzsaki G, Draguhn A. Neuronal oscillations in cortical networks. Science (New York, NY) 2004;304(5679):1926-1929.

[8] Chang C, Glover GH. Time-frequency dynamics of resting-state brain connectivity measured with fMRI. NeuroImage 2010;50(1):81-98.

[9] Charles AC, Baca SM. Cortical spreading depression and migraine. Nature reviews Neurology 2013;9(11):637-644.

[10] Cheng JC, Bosma RL, Hemington KS, Kucyi A, Lindquist MA, Davis KD. Slow-5 dynamic functional connectivity reflects the capacity to sustain cognitive performance during pain. NeuroImage 2017;157:61-68.

[11] Choe AS, Nebel MB, Barber AD, Cohen JR, Xu Y, Pekar JJ, Caffo B, Lindquist MA. Comparing test-retest reliability of dynamic functional connectivity methods. NeuroImage 2017;158:155-175.

[12] Chong CD, Schwedt TJ, Hougaard A. Brain functional connectivity in headache disorders: A narrative review of MRI investigations. Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism 2017:271678x17740794.

[13] Cohen JR. The behavioral and cognitive relevance of time-varying, dynamic changes in functional connectivity. NeuroImage 2018;180:515-525.

[14] Cohen JR. The behavioral and cognitive relevance of time-varying, dynamic changes in functional connectivity. NeuroImage 2018;180(Pt B):515-525.

[15] Coppola G, Bracaglia M, Di Lenola D, Di Lorenzo C, Serrao M, Parisi V, Di Renzo A, Martelli F, Fadda A, Schoenen J, Pierelli F. Visual evoked potentials in subgroups of migraine with aura patients. J Headache Pain 2015;16:92.

[16] Downar J, Crawley AP, Mikulis DJ, Davis KD. A cortical network sensitive to stimulus salience in a neutral behavioral context across multiple sensory modalities. Journal of neurophysiology 2002;87(1):615-620.

[17] Engle R. Dynamic Conditional Correlation. Journal of Business & Economic Statistics 2002;20(3):339-350.

[18] Farago P, Tuka B, Toth E, Szabo N, Kiraly A, Csete G, Szok D, Tajti J, Pardutz A, Vecsei L, Kincses ZT. Interictal brain activity differs in migraine with and without aura: resting state fMRI study. The journal of headache and pain 2017;18(1):8.

[19] Gohel SR, Biswal BB. Functional integration between brain regions at rest occurs in multiple-frequency bands. Brain connectivity 2015;5(1):23-34.

[20] Goto M, Abe O, Miyati T, Yamasue H, Gomi T, Takeda T. Head Motion and Correction Methods in Resting-state Functional MRI. Magnetic resonance in medical sciences : MRMS : an official journal of Japan Society of Magnetic Resonance in Medicine 2016;15(2):178-186.

[21] Granger CWJ. Investigating Causal Relations by Econometric Models and Cross-spectral Methods. Econometrica 1969;37(3):424-438.

[22] Griffanti L, Douaud G, Bijsterbosch J, Evangelisti S, Alfaro-Almagro F, Glasser MF, Duff EP, Fitzgibbon S, Westphal R, Carone D, Beckmann CF, Smith SM. Hand classification of fMRI ICA noise components. NeuroImage 2017;154:188-205.

[23] Jiang T. Brainnetome: a new -ome to understand the brain and its disorders. NeuroImage 2013;80:263-272.

[24] Kaminski M, Ding M, Truccolo WA, Bressler SL. Evaluating causal relations in neural systems: granger causality, directed transfer function and statistical assessment of significance. Biological cybernetics 2001;85(2):145-157.

[25] Legrain V, Iannetti GD, Plaghki L, Mouraux A. The pain matrix reloaded: A salience detection system for the body. Progress in Neurobiology 2011;93(1):111-124.

[26] Levar N, Van Doesum TJ, Denys D, Van Wingen GA. Anterior cingulate GABA and glutamate concentrations are associated with resting-state network connectivity. Scientific reports 2019;9(1):2116.

[27] Lindquist MA, Xu Y, Nebel MB, Caffo BS. Evaluating dynamic bivariate correlations in resting-state fMRI: a comparison study and a new approach. NeuroImage 2014;101:531-546.

[28] Liu Z, Zhang Y, Bai L, Yan H, Dai R, Zhong C, Wang H, Wei W, Xue T, Feng Y, You Y, Tian J. Investigation of the effective connectivity of resting state networks in Alzheimer's disease: a functional MRI study combining independent components analysis and multivariate Granger causality analysis. NMR in biomedicine 2012;25(12):1311-1320.

[29] Mantegazza M, Cestele S. Pathophysiological mechanisms of migraine and epilepsy: Similarities and differences. Neuroscience letters 2018;667:92-102.

[30] McKendrick AM, Battista J, Snyder JS, Carter OL. Visual and auditory perceptual rivalry in migraine. Cephalalgia : an international journal of headache 2011;31(11):1158-1169.

[31] Morgan VL, Abou-Khalil B, Rogers BP. Evolution of functional connectivity of brain networks and their dynamic interaction in temporal lobe epilepsy. Brain connectivity 2015;5(1):35-44.

[32] Nickerson LD, Smith SM, Ongur D, Beckmann CF. Using Dual Regression to Investigate Network Shape and Amplitude in Functional Connectivity Analyses. Frontiers in neuroscience 2017;11:115.

[33] Pietrobon D, Moskowitz MA. Pathophysiology of migraine. Annual review of physiology 2013;75:365-391.

[34] Sauvage A, Hubert G, Touboul J, Ribot J. The hemodynamic signal as a first-order low-pass temporal filter: Evidence and implications for neuroimaging studies. NeuroImage 2017;155:394-405.

[35] Scholz J, Klein MC, Behrens TE, Johansen-Berg H. Training induces changes in white-matter architecture. Nature neuroscience 2009;12(11):1370-1371.

[36] Seth AK, Barrett AB, Barnett L. Granger causality analysis in neuroscience and neuroimaging. The Journal of neuroscience : the official journal of the Society for Neuroscience 2015;35(8):3293-3297.

[37] Smith SM. Fast robust automated brain extraction. Human brain mapping 2002;17(3):143-155.

[38] Smith SM, Fox PT, Miller KL, Glahn DC, Fox PM, Mackay CE, Filippini N, Watkins KE, Toro R, Laird AR, Beckmann CF. Correspondence of the brain's functional architecture during activation and rest. Proceedings of the National Academy of Sciences of the United States of America 2009;106(31):13040-13045.

[39] Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, Bannister PR, De Luca M, Drobnjak I, Flitney DE, Niazy RK, Saunders J, Vickers J, Zhang Y, De Stefano N, Brady JM, Matthews PM. Advances in functional and structural MR image analysis and implementation as FSL. NeuroImage 2004;23 Suppl 1:S208-219.

[40] Sridharan D, Levitin DJ, Menon V. A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. Proceedings of the National Academy of Sciences of the United States of America 2008;105(34):12569-12574.

[41] Szabo N, Farago P, Kiraly A, Vereb D, Csete G, Toth E, Kocsis K, Kincses B, Tuka B, Pardutz A, Szok D, Tajti J, Vecsei L, Kincses ZT. Evidence for Plastic Processes in Migraine with Aura: A Diffusion Weighted MRI Study. Frontiers in neuroanatomy 2017;11:138.

[42] Szabo N, Kincses ZT, Pardutz A, Tajti J, Szok D, Tuka B, Kiraly A, Babos M, Voros E, Bomboi G, Orzi F, Vecsei L. White matter microstructural alterations in migraine: a diffusion-weighted MRI study. Pain 2012;153(3):651-656.

[43] Tagliazucchi E, von Wegner F, Morzelewski A, Brodbeck V, Laufs H. Dynamic BOLD functional connectivity in humans and its electrophysiological correlates. Frontiers in human neuroscience 2012;6:339.

[44] Tibber MS, Kelly MG, Jansari A, Dakin SC, Shepherd AJ. An inability to exclude visual noise in migraine. Investigative ophthalmology & visual science 2014;55(4):2539-2546.

[45] Tu Y, Fu Z, Zeng F, Maleki N, Lan L, Li Z, Park J, Wilson G, Gao Y, Liu M, Calhoun V, Liang F, Kong J. Abnormal thalamocortical network dynamics in migraine. Neurology 2019;92(23):e2706-e2716.

[46] Vidaurre D, Smith SM, Woolrich MW. Brain network dynamics are hierarchically organized in time. Proceedings of the National Academy of Sciences of the United States of America 2017;114(48):12827-12832.

[47] Wen X, Rangarajan G, Ding M. Is Granger causality a viable technique for analyzing fMRI data? PloS one 2013;8(7):e67428.

[48] Winkler AM, Ridgway GR, Webster MA, Smith SM, Nichols TE. Permutation inference for the general linear model. NeuroImage 2014;92:381-397.

[49] Xia M, Wang J, He Y. BrainNet Viewer: A Network Visualization Tool for Human Brain Connectomics. PLOS ONE 2013;8(7):e68910.

[50] Younis S, Hougaard A, Vestergaard MB, Larsson HBW, Ashina M. Migraine and magnetic resonance spectroscopy: a systematic review. Current opinion in neurology 2017;30(3):246-262.

[51] Yu D, Yuan K, Luo L, Zhai J, Bi Y, Xue T, Ren X, Zhang M, Ren G, Lu X. Abnormal functional integration across core brain networks in migraine without aura. Molecular pain 2017;13:1744806917737461.

[52] Zhou Y, Friston KJ, Zeidman P, Chen J, Li S, Razi A. The Hierarchical Organization of the Default, Dorsal Attention and Salience Networks in Adolescents and Young Adults. Cerebral cortex (New York, NY : 1991) 2018;28(2):726-737.

Figure legends

Figure 1.: Analysis flow chart. (A) The fMRI scans underwent preprocessing including brain extraction, motion correction, spatial smoothing, nuisance regression and temporal filtering. **(B)** Preprocessed volumes were fed into temporal concatenation ICA with FSL's MELODIC. **(C)** To characterize dynamic connections between regions of interest (ROIs) in the salience network, first we used FSL's cluster tool to segment thresholded group average component maps to obtain node spatial maps. We extracted time series from said ROIs and calculated their dynamic conditional correlation (for details see Methods). Then we compared the temporal variance and average of dynamic conditional correlation values between groups. **(D)** We characterized network interactions by calculating the spectral Granger's causality between pairs of subject-specific network time series, obtained via a dual regression approach. We compared the sum of causal interactions in the 0.01<0.5 Hz and 0.05<0.1 Hz range between groups.

Figure 2.: Spatial maps of group-level independent components. Spatial maps of the salience, default mode and dorsal attention networks, overlaid on a standard MNI brain template volume. We created three-dimensional maps using BrainNet Viewer [49]. Color bars represent Z-values

describing how a given voxel conforms to network activity as estimated by the independent component analysis. Two-dimensional maps show slices that contain the voxel with maximal Z-value. MNI-coordinates of these voxels are as follows (x, y, z):

- Salience network: 46 -2 4
- Default mode network: 10 -58 28
- Dorsal attention network: 46 -38 48

Figure 3.: Time-varying properties of intrinsic salience network connections. (A) Spatial maps of regions of interest in the salience network, overlaid on a glass brain. The correlation matrix represents the temporal average of pairwise dynamic conditional correlation between regions of interest. Abbreviations: r/lAI – right/left anterior insula, r/lPFC – right/left prefrontal cortex, dACC – dorsal anterior cingulate cortex. **(B)** Boxplots representing significant group wise differences in the temporal variance of dynamic conditional correlation between salience network regions of interest. Migraineurs with aura exhibit greater variability of correlation between right anterior insula, dorsal anterior cingulate and left prefrontal cortex activity, as demonstrated via representative subjects on **(C).**

Figure 4.: Information flow between resting state networks. (A) We calculated spectral Granger's causality between the salience, default mode and dorsal attention networks (SN, DMN and DAN, respectively). **(B)** Boxplots showing group wise differences in sub-0.5 Hz causal interactions. Migraineurs with aura show significantly decreased information flow from the salience network to the dorsal attention network, and show a tendency of decreased information flow from the DMN to the DAN. **(C)** depicts the full array of pairwise causal interaction strength between the three investigated networks.

Tables

	Healthy controls	Migraine without aura	Migraine with aura
N	32	37	20
Age (years, mean +/- SD)	35.4 +/- 11.3	35.9 +/- 9.1	32.2 +/- 7.8
Sex (male/female)	3/29	3/34	3/17
Disease duration (years, mean +/- SD)	-	15.4 +/- 11.2	15.4 +/- 8.4
Attack frequency (total attacks/year, mean +/- SD)	-	54.3 +/- 43.9	28.3 +/- 24.8
Attack duration (hours, mean +/- SD)	-	31.4 +/- 26.4	19.9 +/- 18.3
Allodynia score (mean +/- SD)	-	3.6 +/- 3.7	1.6 +/- 1.7
Pain intensity during headache (VAS, mean +/- SD)	-	8.6 +/- 1.4	7.5 +/- 1.5

Table 1.: Demographic data of the participants. Abbreviations: SD – standard deviation, VAS – visual analog scale