Impaired Effective Functional Connectivity of the Sensorimotor Network in Interictal Episodic Migraineurs Without Aura

Heng-Le Wei
Nanjing Jiangning Hospital
Jing Chen
Nanjing Jiangning Hospital
Yu-Chen Chen
Nanjing First Hospital
Yu-Sheng Yu
Nanjing Jiangning Hospital
Xi Guo
Nanjing Jiangning Hospital
Gang-Ping Zhou
Nanjing Jiangning Hospital
Qing-Qing Zhou
Nanjing Jiangning Hospital
Zhen-Zhen He
Nanjing Jiangning Hospital
Lian Yang
Nanjing Jiangning Hospital
Xindao Yin
Nanjing First Hospital
Junrong Li
Nanjing Jiangning Hospital
Hong Zhang (jnyyfsk@126.com)
Jiangning Hospital

Research article

Keywords: magnetic resonance imaging, migraine, sensorimotor network, effective functional connectivity

Posted Date: July 2nd, 2020

DOI: https://doi.org/10.21203/rs.3.rs-39331/v1

Version of Record: A version of this preprint was published on September 14th, 2020. See the published version at https://doi.org/10.1186/s10194-020-01176-5.

Abstract

Background: Resting-state functional magnetic resonance imaging (Rs-fMRI) has confirmed sensorimotor network (SMN) dysfunction in migraine without aura (MwoA). However, the underlying mechanisms of SMN causal functional connectivity in MwoA remain unclear. We aimed to explore the association between clinical characteristics and effective functional connectivity in SMN, in interictal patients who have MwoA.

Methods: We used Rs-fMRI to acquire imaging data in forty episodic patients with MwoA in the interictal phase and thirty-four healthy controls (HCs). Independent component analysis was used to profile the distribution of SMN and calculate the different SMN activity between the two groups. Subsequently, Granger causality analysis was used to analyze the effective causal connectivity between the SMN and other brain regions.

Results: Compared to the HCs, MwoA patients showed higher activity in the bilateral postcentral gyri (PoCG) and supplementary motor areas, but lower activity in left Rolandic operculum/insula. Moreover, MwoA patients showed significantly causal connectivity from the SMN to the left calcarine sulcus, left middle temporal gyrus, right angular gyrus and right precuneus. There was also significant causal connectivity from the left calcarine sulcus, left inferior orbitofrontal cortex, right cuneus, right putamen and left inferior parietal lobule to the SMN. In the interictal period, there was positive correlation between the activity of the left PoCG and headache frequency (r = 0.410, p = 0.013), but negative correlation between the activity of the right PoCG and the impact of headache (r = -0.397, p = 0.016). In addition, the disease duration was directly proportional to the connectivity strength from the left PoCG to the right angular gyrus (r = 0.418, p = 0.011), and from the right PoCG to the left calcarine sulcus (r = 0.377, p = 0.023).

Conclusions: These differential, resting-state functional activities of the SMN in episodic MwoA may contribute to the understanding of migraine-related intra- and internetwork imbalances associated with nociceptive regulation and chronification.

Introduction

Migraine is an incapacitating neurological disorder, typically characterized by unilateral, throbbing or pulsating headaches, and the second-largest contributor to global neurological disorders, after stroke[1]. Itaffects more than 10% of the general population, thus causing enormous individual and social burden. Patients with migraine often experienceanxiety, depression and sleep disturbances,which enhances the mental disorder andsignificantly impair the quality of daily life[2]. In order to exploreeffective treatment optionsfor migraine headaches, it is imperative to understand the neuropathological mechanisms of migraine.

A migraine attack is not only a somaticperturbation, but also a sensory dysfunction that amplifieslight, sound or touchperceptions in both ictal and interictal phases[3].These characteristics make migraine a somatosensory disorderthat eventually induce aberrant neuroplastic alterations in the central nervous system (CNS).In the last decades, neuroimaging has greatly contributed to the understanding of the neurological diseases involved in migraine pathophysiology. The neuroimaging data have shown that the disorder is associated with microstructural and functional alterations in various brain regions including the sensory motor network (SMN)[4]. The SMN, previously implicated in migraine, is a crucial region that is a multipurpose high-order cognitive processing center[5], which encompass the primary somatosensory cortex, primary motor cortex, premotor cortex and supplementary motor area (SMA)[6]. Previous migraine resting-state functional magnetic resonance imaging (Rs-fMRI) studieshave demonstratedfunctional alterations insome SMN subregions associated with pain and cognition[7,8].Besides, the migraine attack is a paroxysmal dysfunctional alteration or inflow-outflow dysfunctional modulation of multiple sensory systems[9].Various neuroimaging outcomes have demonstrated correlation of functional connectivity between the subregions in SMN, and the central executive network (CEN) [6], salience network(SN)[10] as well asdefault mode network (DMN)[11]in patients with MwoA. Thefunctional connectivity strength of SMN has been shown to significantly illuminatethe perception of pain intensity and therapeutic effect in MwoA[12].

Whereas many studies have found that MwoA is associated with changes in functional connectivity between the SMN and other regions, it has been difficult to discern the directionality or specificity of the disrupted connections.Here, we selected the independent component analysis (ICA) method, a data-driven method that requires no prior experience, to separate the spatiotemporal component from the whole brain and extract the distribution of the SMN in a standard template. Using the Granger causality analysis (GCA), we identified differences in the direction of the SMN functional connectivity between patients with MwoA and healthy controls (HCs).Taken together, we observe that, akin to other pain disorders, migraineurs without aura would exhibit abnormal functional alterations within the SMN and the disruptions might define thenociceptive transmission pathway related to the SMN in the interictal resting state. Moreover, the disruptions of the SMN effective connectivity would be associated with specific migraine characteristics.

Methods

Participants

All episodic patients with MwoA were screened and classifiedfollowing the criteria outlined by the third edition of the International Classification of Headache Disorders (ICHD-3; Code 1.1)[13]. By reviewing family medical history, we enrolled age- and gender-matched HCs, who were headache-free and whose family members did not suffer from any form of headache. We excluded patients who had brain organic disorders, other mental diseases, family history of mental retardation, dementia or physical disease, history of alcohol abuse, and any MRI contraindications. MwoA patients were headache-free and drug-freefor at least three days prior to and after scanning to ensure that the patients were in the interictal

periodand avoidpharmacological interferences on signal fluctuation. For female participants, the data was recorded at mid-cycle to avoid hormonal influences on cortical excitement.Clinical characteristicssuch as age at onset, frequency of attacks, pain intensity (visual analogue scale (VAS)), and headache impact (Headache Impact Test (HIT)-6) were collected. Additionally, for all the participants, psychiatric assessments including Self-rating Anxiety Scale (SAS) and Self-rating Depression Scale (SDS), were also conducted to assess depression and anxiety state. This study was approved by the Medical Ethics Committee of Nanjing Medical University. Informed written consent was obtained from all the participants.

Data acquisition

All data were acquired using a 3.0 Tesla MRI scanner (Ingenia, Philips Medical Systems, Netherlands) with an 8-channel head coil. Head motion and scanner noise were reduced bycustom-fit foam pads and earplugs. The Rs-fMRI images were obtained axially using a gradient echo-planar imaging sequence as follows: repetition time (TR) 2000 ms, echo time (TE) 30 ms, flip angle (FA) 90°, number of slices 36, field of view (FOV) 220×220 mm^2, matrix size 64×64, slice thickness 4 mm, and total 230 volumes.Structural images were acquired by a three-dimensional turbo fast echo (3D-TFE) sequence. The parameters were as follows: TR/TE8.1/3.7 ms; slices170; thickness1 mm; gap0 mm; FA8°; acquisition matrix256×256; FOV256 mm×256 mm. None of the subjects recorded any discomfort or fell asleep during scanning. No obvious structural damage was observed based on the conventional MR images.

Data preprocessing

Using an automated preprocessing pipeline, we preprocessed the data using the Rs-fMRIData Analysis Toolkit plus (RESTplus,http://restfmri.net/forum/). In the functional data pipeline, we discarded the first 10 time-point resting-state data due to the instability of the initial MRI signals. Then the remaining images were corrected for slice-timing and realigned to the middle volume using a six-parameter rigid body transformation. The generated images underwent spatial normalization into the Montreal Neurological Institute standard space at a resolution of a 3×3×$3mm^3$ and then smoothed using anisotropic Gaussian kernel (fullwidth at half maximum = 4). After removal of the linear trend of the time courses, the temporal band-pass filtering (0.01–0.08 Hz) was performed to reduce the effects of low- and high-frequency physiological noise. Besides, to further reduce the effects of confounding factors unrelated to specific regional correlation, we used linear regression to remove several sources of spurious variance. The sources include six head motion parameters and average signals from cerebrospinal fluid (CSF) and white matter (WM). To avoid the risk of obtaining spurious negative correlations, we did not remove the global signal. Subjects with maximum head translation or maximum rotation that exceeded 2 mm or 2° respectively, were excluded.

Voxel-based morphometry (VBM) analysis was performed to segment the cerebral tissues into gray matter (GM), WM or CSF using the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm), as previously described.[14]. Subsequently, GM segments were modulated (with linear components) in order to preserve

the absolute regional amount of GM from distortions. Finally, the modulated GM volumes were smoothed with a Gaussian kernel of 8 mm FWHM. We reportedsurviving clusters of voxels exceeding a voxel-level threshold of $p<0.001$ (uncorrected) or a cluster size threshold of $p<0.05$, family-wise error (FWE) correction for multiple comparisons.

ICA processing

To investigate the independent components in MwoA and HCs, the smoothed data were analyzedusing the Group ICA of fMRI Toolbox (GIFT, http://mialab.mrn.org/software/gift/). On the other hand, the preprocessed functional images for all the subjects were temporally concatenated to create a single four-dimensional data set, while the independent components were automatically estimated against consistent time-dependent functional activity. We then selected the SMN from these components as thebest-fit component as previous studies[15,16]. After estimating the group spatial maps, we performed back reconstruction of participant-specific spatial maps using the GICA method and then created output images for the components normalized with Fisher's z-transformation. One-sample *t*-tests were utilized to extract principal component images per group with the FWE correction ($p<0.001$). Subsequently, two-sample t-tests were conducted on the sensorimotor component with the false discovery rate (FDR)correction ($q< 0.001$). Age, sex, GM and education were used as covariates.

GCA processing

We used GCA to detect the effective connectivity between the reference time series of the regions of interest (ROIs) defined above in SMN and those of each voxel within the rest of the brain. GCA estimates the causal effects of the ROIsof SMN (X) on every other voxel in the brain (Y). A positive coefficient from X to Y indicates that activity in region X exerts a causal influence on the activity region Y, while, a negative coefficient from X to Y shows that the activity of region X exerts an adverse influence on the activity of region Y. The generated voxel-wise GCA model maps were transformed and normalized into z scores. For group-level comparison, clusters passing a threshold of $p< 0.001$ (uncorrected) were deemed significant ROIs with the consideration of age, sex, GM or education as covariates.

Correlation analysis

To investigate the association between abnormal activity or effective connectivity strengthof the SMN and clinical characteristics, the ICA values within the significant ROIs and the strength of connectivity were extracted and correlated with the clinical features using partial correlation analysis. Age, sex, GM and education were used as covariates. Statistical analyses were performed in SPSS 24.0 and the threshold was set at $p < 0.05$.

Results

Demographic and clinical information

Compared with the HCs, MwoA patients showed no significant differences in the age, sex, educational level or brain volumes, as shown in **Table 1**. However, migraineurs demonstrated higher scores in psychiatric tests than the HCs.

ICA findings

The SMN for all the participants was extracted and reconstructed to group-level maps by ICA. The spatial positional distribution of the resting-state SMN isshown in **Figure 1**. Inter-group comparison within the SMN revealed four significant ROIs: the bilateral postcentral gyri (PoCG) and SMAwith increased activity, and the left Rolandic operculum/insula (ROL/insula) with decreased activity (**Table2**).

GCA findings

Two-sample t-test findings of resting-state effective connectivity from the SMN to the rest of the brain are illustrated in **Figure 2** (first row, $p< 0.001$ uncorrected). Compared with the HCs, MwoA patients showed significantly increased connectivity from the left PoCG to ipsilateral middle temporal gyrus (MTG), but decreased connectivity to contralateral angular gyrus and precuneus. On the other hand, the right PoCG showed a lower causal influence onthe contralateral calcarine sulcus.

In addition, the two-sample t-test findings of resting-state effective connectivity from the whole brain to SMN is illustrated in **Figure 2** (second row, $p< 0.001$ uncorrected). Here, our data showed as significantly increased causal connectivity from left inferior orbitofrontal cortex(IOFC), left calcarine sulcus and right cuneus to the right PoCG, and from the right putamen to the left ROL/insulaas well as bilateral SMA. Furthermore, the left inferior parietal lobule (IPL) showed decreased causal influence on ipsilateral ROL/insula.

Correlation analysis results

The activity of regions in SMN significantly correlated with headache features, as shown in **Figure 3**. There was positive correlation between the activity of the left PoCG and the frequency of headache (r = 0.410, p = 0.013), but negative correlation between that of the right PoCG and headache impact intensity (r = -0.397, p = 0.016). In addition, the disease duration was positively correlated with abnormal effective connectivity from the left PoCG to the right angular gyrus (r = 0.418, p = 0.011), and from the right PoCG to the left calcarine sulcus(r = 0.377, p = 0.023).

Discussion

There are numerous challenges in discerning the directionality or specificity of the changes in functional connectivity between the SMN and other regions, especially in patients with MwoA. In this study, we extracted the distribution of SMN and identified abnormal neural activityofbilateral PoCG,left ROL/insula, and bilateral SMA unique to patients with MwoA.Specifically, the SMN in episodic patients with MwoA exhibited abnormal inflow or outflow influence on multiple functionalnetworks andheadachedysregulation related to clinical characteristics (e.g., headache impact and duration).Our

findings are in agreement with prior evidence of a disrupted SMN functional connectivity in migraineurs without aura[6], thusprovidingnew insightsinto multi-sensory modulation in migraine processing. Moreover, we demonstrate that these effective functional abnormalities are independent of structural and microstructural changes.

In the current study, we foundhigher neural activityin bilateral PoCG, decreased functional connectivity from the right PoCG to the contralateralcalcarinesulcus, as well asincreased connectivity intensity from the visual cortex (left calcarine sulcus and right cuneus)to the right PoCG.The calcarine sulcus and cuneus are core regions of the primary visual network in the brain, and therefore, the present findings suggest that functional abnormalities between the SMN and visual networkare specifically altered in patients with MwoA. Indeed, previous migraine studies have showed that altered activity within the sensory-related cortex, including SMN and visual cortex, results in dysfunction associated with affective, cognitive or pain processing[17,18].Our findings also show increased brain activity of the right PoCG, which negatively regulate the headache impact intensity, and functional deficitsthat fail to compensate recurrent endogenous and exogenous pain stimuli or inhibitnociceptive signals in the interictal period.Previous longitudinal investigation[19]showed thatthe morphological alteration of the visual cortex was significantly associated with migraine progression, especially in the calcarine sulcus and cuneus. In agreement, our results demonstratefunctional influences from the right PoCG tothe left calcarine sulcus positively correlated with disease course and prior structural plasticity.

However, Wang *et al.* reported opposite neuralactivity of the bilateral PoCG by low-frequency oscillations approach to reflect the spontaneous neural function of the brain[8]. In addition, an electroencephalography-related study[20] demonstrated higher desynchronization and power overlying the primary sensorimotor cortex in the preictal phase compared to the interictal phase, with no significant differences between interictal migraineurs and HCs. The heterogeneity of the migraineurs phase and the use of different neuroimaging methods might explain the discrepancy between the studies.Therefore, the abnormal effective functional connectivity between the SMN and visual cortex may be part of the pathological mechanismof failure to filter the unpleasant signals or lower the threshold to somatosensory stimuli in the visual pathway.Furthermore, our resting-state fMRI study also showed the abnormal effective connectivity from the left inferior OFC to the right PoCG in migraineurs without aura compared to HC. The OFC, a segment of the advanced processing center and a key function to the regulation of negative feedback[21], might constitude the cognitive function, regulation of emotions, psychiatric disorders and inhibitory control. The heightened effective connectivity might be interpreted as a dysfunctional inhibitory response to malaise signals.Our demonstration of positive functional coupling between the primary somatosensory cortex and the OFC may also infer the possible role of the OFC in migraine.

Compared with the HCs, migraineurs without aura showed changed effective connectivity from the left PoCG to many pain-related areas, such as theMTG, angular gyrus,precuneus, and IPL[5,22].These regions have been demonstrated to be crucial in the default mode network (DMN)[23]. The DMN, one of the core brain networks that is activatedwhen ata rest state, plays a pivotal role in discriminative, cognitive and

perceptive functions of pain[18,24-26].Previous studies have shownaltered functionassociated with nociceptive processing and cognitive impairment,within the angular gyrus and MTG in migraineurs[26].Moreover, the precuneus participates in thediscrimination of sensory perception of pain[27] and the brainstem-thalamus-cortex circuit which modulates pain intensity[28] in the migraineurs. Our datafound thatthe increased brain function in the left PoCG hasa negative modulatoryeffect in the frequency of headache attacks.Thus, our results indicated that the dysfunction between the primary somatosensory cortex and DMNmay disrupt the neural transmission pathway of discrimination and intensity involved in sensory perception of pain. Besides, long-term and repetitive migraine headache attacks may lead to somatosensory cortex compensatory or dysfunctional changes. These observations agree with our data which showed that influence from the left somatosensory cortex to DMN play a role in functional adaption along migraine progressing.

The current study also observed that, in resting state, there is decreased activity of the left ROL/insula, near to the limbic system, subcortical network and anterior DMN, which may trigger pain processing adjustments in multiple instinct brain networks.The insula isa component of the salient network (SN,a pivotal large-scale intrinsic network associated with perceiving) which process and integrate internal and external stimuli[29].Similarly, a resting-state fMRI study reported that insular cortex demonstrated abnormal functional connectivity to DMNencoding headache severity in migraineurs[30].Whereas, high SN function occurs when the mind is engaged in specific tasks, rise in DMN activity does not depend on external stimulation. Hence, the ROL/insula-DMN functional connectivity modulates the switching between self-monitoring and task processing.In addition, the operculum, which contains the secondary sensory cortex, is another key region involved in the processing of sensory information[31].Previous studies have shown that the secondary sensory cortex and insulacould provideinformation about the intensity, cognition and spatial discriminative pain pathways of nociceptive stimulus in migraine[8,18].The ROL/insulahas been proposed to be involved in the multi-network sensory integration of pain. It predominantly mediates the intensityand signals ascending the spinothalamic tracts of the pain processing system[32-34].Furthermore, the decreased effective connectivity from theleft IPL to the left ROL/insula may support the impaired function and lower inhibition power of DMN, and hypersensitive responses to external sensory inputs.Since the SMN and DMN are key regions of the trigeminovascular modulatory system, a pain inhibiting system, disrupted activity of these regions may lead to a dysfunctional pain inhibition pathway, thus contributing to thehypersensitivity of pain and migraine.

In addition, we observed that the SMNsubregionscould be influencedby abnormalinputs from the putamen and the caudate nucleus, components of the striatum.Literature has shownthat thestriatumaffects the neuronal pathways underlying the inhibition effect of nociceptive stimulation. These effect is mediated bythe striatal dopamine D2 receptorswhich are associated with pain inhibitory circuitry ofthe caudal trigeminal nucleus[35].The abnormal interaction of the putamen has been shown to trigger many independent components[33], justifying the hypothesis that transmission of pain is complex and multidimensional[36]. Moreover, the SMA contributes to response selection and nociceptive generation in MwoA[7,9].Furthermore, since the cortico-striato-thalamo-cortical loop affects many

neurological disorders [37], we speculated that perturbation of the striato-cortical circuit may suppress the inhibitory function on the nociceptive reflex.Together with the previous evidence, we highlight the importance of stratum and SMA in pain- and movement-related processing as well as in the regulation of migraine and other chronic pain syndromes[38,39]. The information transformation and transmission pathway corresponds toboth ventral and dorsal streams specialized in processing the intensity of painful stimuli[27]. This pattern of increased effective connectivity indicates that the putamen may influence the activity of somatosensory cortex in discriminating pain experience, thus, its potential and vitalrole in shaping of the pain perception. Our findings explain the dysregulation between the putamen and sensory cortex in migraine headaches.

Our study, however, used a small sample size. Therefore, a large sample size might be needed to enhance our data repeatability and reliability. In addition, the heterogeneity of the participants, such as the etiology, headache severity, disease duration, or neuropsychiatric comorbidity could result in neural activity biasness. Besides the functional alterations, more studies are required to investigate the possibility of structural connectivity involved in SMN.

Conclusions

In conclusion, we have explicated the abnormal interactions between the SMN and other networks in MwoA patients. Our data demonstrates that SMN plays a crucial role in pain modulation and chronification, as well as dissecting the neuropathologic mechanisms underlying episodic MwoA patients in headache-free phase.

Abbreviations

CSF: Cerebrospinal fluid; GM: Gray matter; HCs: Healthy controls; HIT: Headache impact test; ICA: Independent component analysis; IOFC: Inferior orbitofrontal cortex; IPL: Inferior parietal lobule; MwoA: Migraine without aura; MTG: Middle temporal gyrus; Rs-fMRI: Resting-state functional magnetic resonance imaging; SAS: Self-rating Anxiety Scale; SDS: Self-rating Depression Scale; SMN: Sensorimotor network (SMN); SMA: Supplementary motor area; VAS: Visual analogic scale; WM: White matter.

Declarations

Ethics approval and consent to participate

The ethical committee of Nanjing Medical University approved the study. Informed consent was obtained from each participant.

Consent for publication

Not applicable.

Availability of data and materials

Clinical, neuroimaging and statistical data will be available upon request from any qualified investigator.

Competing interests

The authors declare that they have no competing interests.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

WHL and CJ designed and drafted the manuscript. CYC, YYS and GX analyzed the data and drafted the manuscript. ZGP and ZQQ performed the experiments. HZZ and YL contributed to the acquisition of fMRI data and analyzed them. YX, LJ and ZH revised the manuscript. All authors read and approved the final manuscript.

Acknowledgements

We thank all migraineurs and controls for their participation in the study.

References

References:

1. GBD 2016 Neurology Collaborators. (2019) Global, regional, and national burden of neurological disorders, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology* 18 (5), 459-480
2. GBD 2017 DALYs and HALE Collaborators. (2018) Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet* 392 (10159), 1859-1922
3. Burstein R,Noseda R and Borsook D. (2015) Migraine: Multiple Processes, Complex Pathophysiology. *Journal of Neuroscience* 35 (17), 6619-6629
4. Tolner E A,Chen S and Eikermann-Haerter K. (2019) Current understanding of cortical structure and function in migraine. *Cephalalgia* 39 (13), 1683-1699

5. Brennan K C and Pietrobon D. (2018) A Systems Neuroscience Approach to Migraine. *Neuron* 97 (5), 1004-1021
6. Zhang J, Su J, Wang M, Zhao Y, Zhang Q, Yao Q, Lu H, Zhang H, Li G, Wu Y, Liu Y, Liu F, Zhuang M, Shi Y, Hou T, Zhao R, Qiao Y, Li J, Liu J and Du X. (2017) The sensorimotor network dysfunction in migraineurs without aura: a resting-state fMRI study. *Journal of Neurology* 264 (4), 654-663
7. Yu D, Yuan K, Zhao L, Zhao L, Dong M, Liu P, Wang G, Liu J, Sun J, Zhou G, Deneen K M, Liang F, Qin W and Tian J. (2012) Regional homogeneity abnormalities in patients with interictal migraine without aura: a resting-state study. *NMR in Biomedicine* 25 (5), 806-812
8. Wang J J, Chen X, Sah S K, Zeng C, Li Y M, Li N, Liu M Q and Du S L. (2016) Amplitude of low-frequency fluctuation (ALFF) and fractional ALFF in migraine patients: a resting-state functional MRI study. *Clinical Radiology* 71 (6), 558-564
9. Xue T, Yuan K, Zhao L, Yu D, Zhao L, Dong T, Cheng P, von Deneen K M, Qin W and Tian J. (2012) Intrinsic Brain Network Abnormalities in Migraines without Aura Revealed in Resting-State fMRI. *PLoS ONE* 7 (12), e52927
10. Zhang J, Su J, Wang M, Zhao Y, Zhang Q, Yao Q, Lu H, Zhang H, Li G, Wu Y, Liu Y, Liu F, Zhuang M, Shi Y, Hou T, Zhao R, Qiao Y, Li J, Liu J and Du X. (2017) The Posterior Insula Shows Disrupted Brain Functional Connectivity in Female Migraineurs Without Aura Based on Brainnetome Atlas. *Scientific Reports* 7 (1), 16812-16868
11. Zhang J, Su J, Wang M, Zhao Y, Yao Q, Zhang Q, Lu H, Zhang H, Wang S, Li G, Wu Y, Liu F, Shi Y, Li J, Liu J and Du X. (2016) Increased default mode network connectivity and increased regional homogeneity in migraineurs without aura. *The Journal of Headache and Pain* 17 (1), 1-9
12. Li K, Zhang Y, Ning Y, Zhang H, Liu H, Fu C, Ren Y and Zou Y. (2015) The effects of acupuncture treatment on the right frontoparietal network in migraine without aura patients. *The Journal of Headache and Pain* 16 (1), 1-10
13. Headache Classification Committee of the International Headache Society (IHS). (2013) The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia* 33 (9), 629-808
14. Good C D, Johnsrude I S, Ashburner J, Henson R N A, Friston K J and Frackowiak R S J. (2001) A Voxel-Based Morphometric Study of Ageing in 465 Normal Adult Human Brains. *NeuroImage* 14 (1), 21-36
15. Tu Y, Fu Z, Zeng F, Maleki N, Lan L, Li Z, Park J, Wilson G, Gao Y, Liu M, Calhoun V, Liang F and Kong J. (2019) Abnormal thalamocortical network dynamics in migraine. *Neurology* 92 (23), e2706-e2716
16. Hodkinson D J, Veggeberg R, Kucyi A, van Dijk K R A, Wilcox S L, Scrivani S J, Burstein R, Becerra L and Borsook D. (2016) Cortico–Cortical Connections of Primary Sensory Areas and Associated Symptoms in Migraine. *eneuro* 3 (6), 116-163
17. Eck J, Richter M, Straube T, Miltner W H R and Weiss T. (2011) Affective brain regions are activated during the processing of pain-related words in migraine patients. *Pain* 152 (5), 1104-1113

18. Lo Buono V, Bonanno L, Corallo F, Pisani L R, Lo Presti R, Grugno R, Di Lorenzo G, Bramanti P and Marino S. (2017) Functional connectivity and cognitive impairment in migraine with and without aura. *The Journal of Headache and Pain* 18 (1), 72
19. Messina R, Rocca M A, Colombo B, Pagani E, Falini A, Goadsby P J and Filippi M. (2018) Gray matter volume modifications in migraine. *Neurology* 91 (3), e280-e292
20. Mykland M S, Bjørk M H, Stjern M, Omland P M, Uglem M and Sand T. (2019) Fluctuations of sensorimotor processing in migraine: a controlled longitudinal study of beta event related desynchronization. *The Journal of Headache and Pain* 20 (1), 1-10
21. Rudebeck P H and Rich E L. (2018) Orbitofrontal cortex. *Current Biology* 28 (18), R1083-R1088
22. Zhou F, Gu L, Hong S, Liu J, Jiang J, Huang M, Zhang Y and Gong H. (2018) Altered low-frequency oscillation amplitude of resting state-fMRI in patients with discogenic low-back and leg pain. *Journal of pain research* Volume 11, 165-176
23. Raichle M E. (2015) The Brain's Default Mode Network. *Annual Review of Neuroscience* 38 (1), 433-447
24. Gao Q, Xu F, Jiang C, Chen Z, Chen H, Liao H and Zhao L. (2016) Decreased functional connectivity density in pain-related brain regions of female migraine patients without aura. *Brain Research* 1632, 73-81
25. Tessitore A, Russo A, Giordano A, Conte F, Corbo D, De Stefano M, Cirillo S, Cirillo M, Esposito F and Tedeschi G. (2013) Disrupted default mode network connectivity in migraine without aura. *The Journal of Headache and Pain* 14 (1), 89
26. Edes A E, Kozak L R, Magyar M, Zsombok T, Kokonyei G, Bagdy G and Juhasz G. (2017) Spontaneous migraine attack causes alterations in default mode network connectivity: a resting-state fMRI case report. *BMC Research Notes* 10 (1), 165
27. Oshiro Y, Quevedo A S, McHaffie J G, Kraft R A and Coghill R C. (2009) Brain Mechanisms Supporting Discrimination of Sensory Features of Pain: A New Model. *Journal of Neuroscience* 29 (47), 14924-14931
28. Schwedt T J, Larson-Prior L, Coalson R S, Nolan T, Mar S, Ances B M, Benzinger T and Schlaggar B L. (2014) Allodynia and Descending Pain Modulation in Migraine: A Resting State Functional Connectivity Analysis. *Pain Medicine* 15 (1), 154-165
29. Namkung H,Kim S and Sawa A. (2017) The Insula: An Underestimated Brain Area in Clinical Neuroscience, Psychiatry, and Neurology. *Trends in Neurosciences* 40 (4), 200-207
30. Coppola G, Di Renzo A, Tinelli E, Di Lorenzo C, Scapeccia M, Parisi V, Serrao M, Evangelista M, Ambrosini A, Colonnese C, Schoenen J and Pierelli F. (2017) Resting state connectivity between default mode network and insula encodes acute migraine headache. *Cephalalgia* 38 (5), 846-854
31. Cloutman L L, Binney R J, Drakesmith M, Parker G J M and Lambon Ralph M A. (2012) The variation of function across the human insula mirrors its patterns of structural connectivity: Evidence from in vivo probabilistic tractography. *NeuroImage* 59 (4), 3514-3521

32. Timmermann L, Ploner M, Haucke K, Schmitz F, Baltissen R and Schnitzler A. (2001) Differential Coding of Pain Intensity in the Human Primary and Secondary Somatosensory Cortex. *Journal of Neurophysiology* 86 (3), 1499-1503
33. Starr C J, Sawaki L, Wittenberg G F, Burdette J H, Oshiro Y, Quevedo A S, McHaffie J G and Coghill R C. (2011) The contribution of the putamen to sensory aspects of pain: insights from structural connectivity and brain lesions. *Brain* 134 (7), 1987-2004
34. Mouraux A and Iannetti G D. (2018) The search for pain biomarkers in the human brain. *Brain* 141 (12), 3290-3307
35. Barceló A C,Filippini B and Pazo J H. (2012) The Striatum and Pain Modulation. *Cellular and Molecular Neurobiology* 32 (1), 1-12
36. Kim J, Mawla I, Kong J, Lee J, Gerber J, Ortiz A, Kim H, Chan S, Loggia M L, Wasan A D, Edwards R R, Gollub R L, Rosen B R and Napadow V. (2019) Somatotopically specific primary somatosensory connectivity to salience and default mode networks encodes clinical pain. *PAIN* 160 (7), 1594-1605
37. Peters S K,Dunlop K and Downar J. (2016) Cortico-Striatal-Thalamic Loop Circuits of the Salience Network: A Central Pathway in Psychiatric Disease and Treatment. *Frontiers in Systems Neuroscience* 10, 104
38. Jin Y, Meng Q, Mei L, Zhou W, Zhu X, Mao Y, Xie W, Zhang X, Luo M, Tao W, Wang H, Li J, Li J, Li X and Zhang Z. (2019) A somatosensory cortex input to the caudal dorsolateral striatum controls comorbid anxiety in persistent pain. *PAIN* 161 (2), 1
39. Azqueta-Gavaldon M, Youssef A M, Storz C, Lemme J, Schulte-Göcking H, Becerra L, Azad S C, Reiners A, Ertl-Wagner B, Borsook D, Upadhyay J and Kraft E. (2020) Implications of the putamen in pain and motor deficits in complex regional pain syndrome. *PAIN* 161 (3), 595-608

Tables

Table 1 Demographic,clinical and psychiatric characteristics of the participants

	MwoA	HCs	*p* value
Age (year)[a]	35.15±10.18	35.50±8.59	0.875
Sex (male/female)	6/34	5/29	0.758
Education (year) [a]	12.15±3.02	13.41±3.16	0.084
Disease duration (year)[b]	5.5 (2,10.75)	/	/
Frequency (days/month) [b]	3 (3,5)	/	/
HIT-6 score [a]	58.45±9.32	/	/
VAS score [b]	6 (5,7)	/	/
SAS score [b]	35 (29,47)	23(22,26)	< 0.001
SDS score [b]	35 (29,50)	24(23,26)	< 0.001
Gray matter (mm^3) [a]	633.25±56.72	619.48±54.18	0.292
White matter (mm^3) [a]	492.47±44.35	499.94±55.22	0.521
Cerebrospinal fluid (mm^3) [a]	215.83±19.42	217.90±27.75	0.708
Brain parenchyma (mm^3) [a]	1125.72±92.20	1119.42±92.48	0.771

Data are presented as mean ± SD (a) or medians and interquartile ranges (25th–75th percentiles) (b). HIT-6: Headache Impact Test-6; SAS: Self-rating Anxiety Scale; SDS: Self-rating Depression Scale; VAS: visual analogue scale; MwoA: migraine without aura; HCs: healthy controls.

Table 2 Significant differences in the SMN in patients with MwoA compared with HCs

Brain regions	X	Y	Z	K	T score
R postcentral gyrus	48	-18	60	22	8.9687
L postcentral gyrus	-48	-42	60	23	9.5054
L Rolandic operculum/insula	-42	-6	15	91	-6.9314
B supplementary motor area	6	6	66	42	6.5761

Significant thresholds were corrected by false discovery rate correction (q< 0.001). SMN: sensorimotor network;MwoA: migraine without aura; HCs: healthy controls;L: left; R: right; B: bilateral.

Table 3 Altered effective connectivity between SMN and rest of brain in MwoA compared withHCs

			X	Y	Z	K	T score
From SMN							
R postcentral gyrus	→	L calcarine sulcus	-21	-60	3	16	-4.3319
L postcentral gyrus	→	L middle temporal gyrus	-63	-48	-3	11	4.7747
		R angular gyrus	54	-51	24	15	-4.2479
		R precuneus	6	-63	24	28	-3.9978
To SMN							
R postcentral gyrus	←	L calcarine sulcus	-21	-60	6	24	5.1605
		L inferior orbitofrontal cortex	-24	33	-12	24	4.6069
		R cuneus	18	-69	30	20	3.8579
L ROL/insula	←	R putamen	27	12	9	12	4.0865
		L inferior parietal lobule	-42	-36	42	10	-4.1561
B supp motor area	←	R putamen	27	9	9	10	4.1487

ROL: Rolandic operculum;SMN: sensorimotor network; supp: supplementary;MwoA: migraine without aura; HCs: healthy controls; L: left; R: right; B: bilateral; (p< 0.001, uncorrected).

Figures

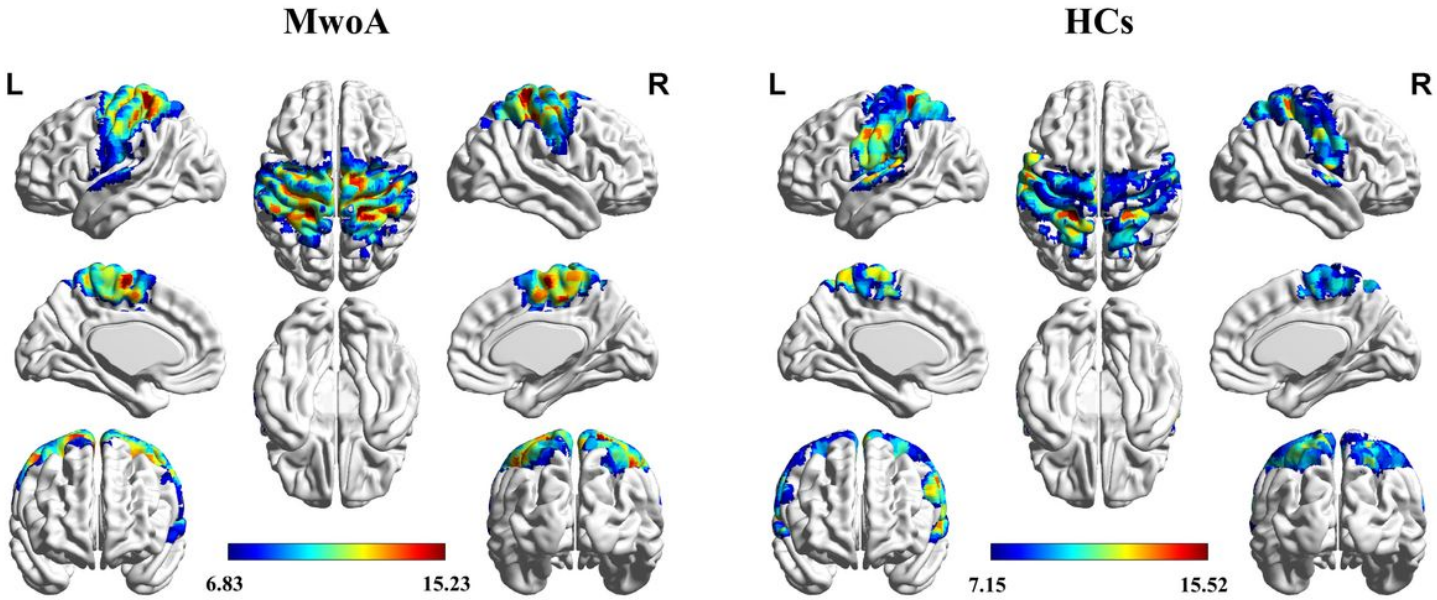

Figure 1

Group-level sensorimotor network in migraineurs without aura (MwoA) and healthy controls (HCs). Significant thresholds were corrected by family-wise error correction ($p < 0.001$).

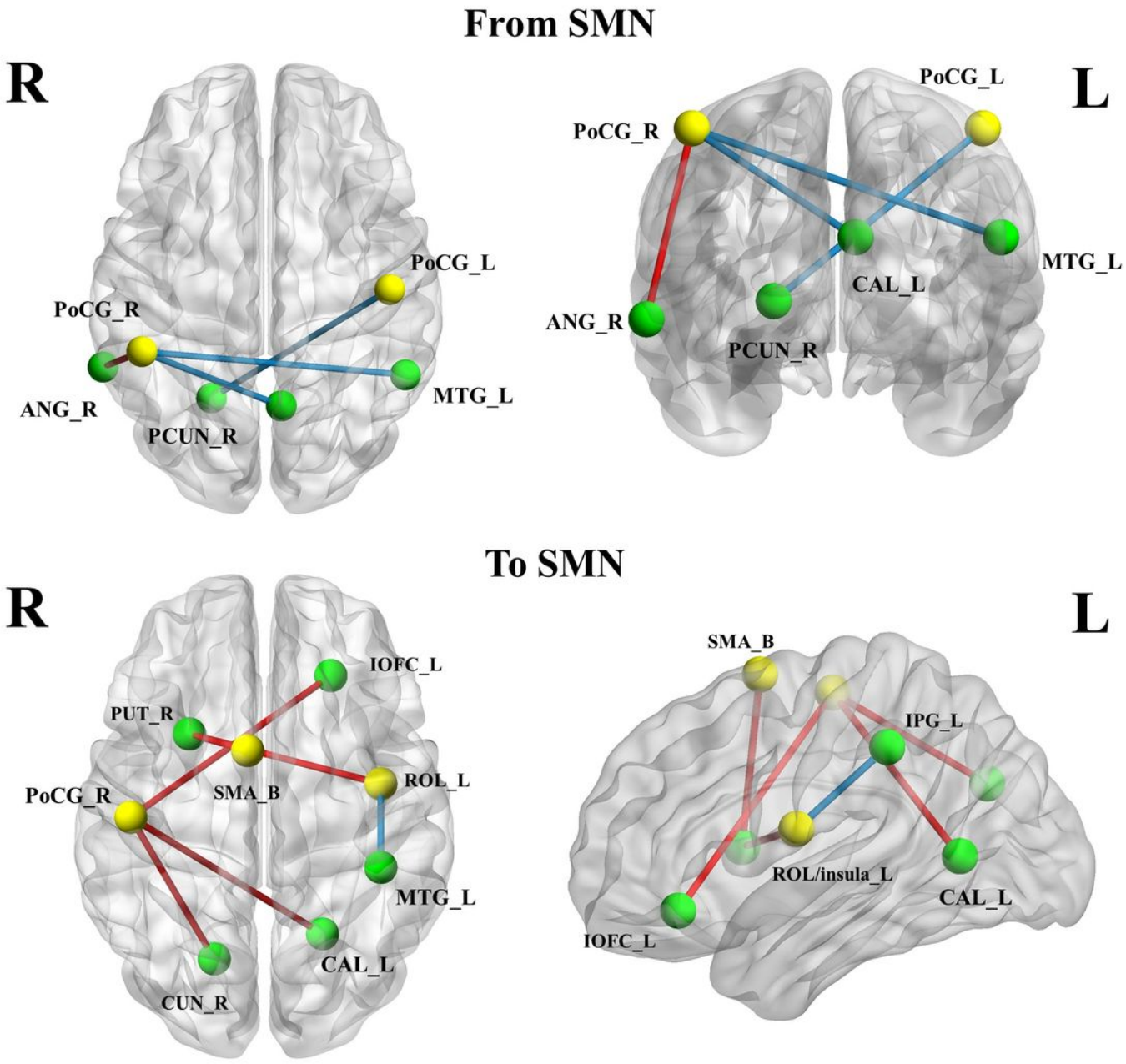

Figure 2

Altered effective connectivity from the SMN to the other brain regions and vice versa, in migraineurs without aura compared with the healthy controls. Thresholds were set at a $p<0.001$ (uncorrected). SMN: sensorimotor network; PoCG: postcentral gyrus; ANG: angular gyrus; PCUN: precuneus; MTG: middle temporal gyrus; CAL: calcarine sulcus; ROL: Rolandic operculum; SMA: supplementary motor area; PUT: putamen; IOFC: inferior orbitofrontal cortex; CUN: cuneus; L: left; R: right; B: bilateral.

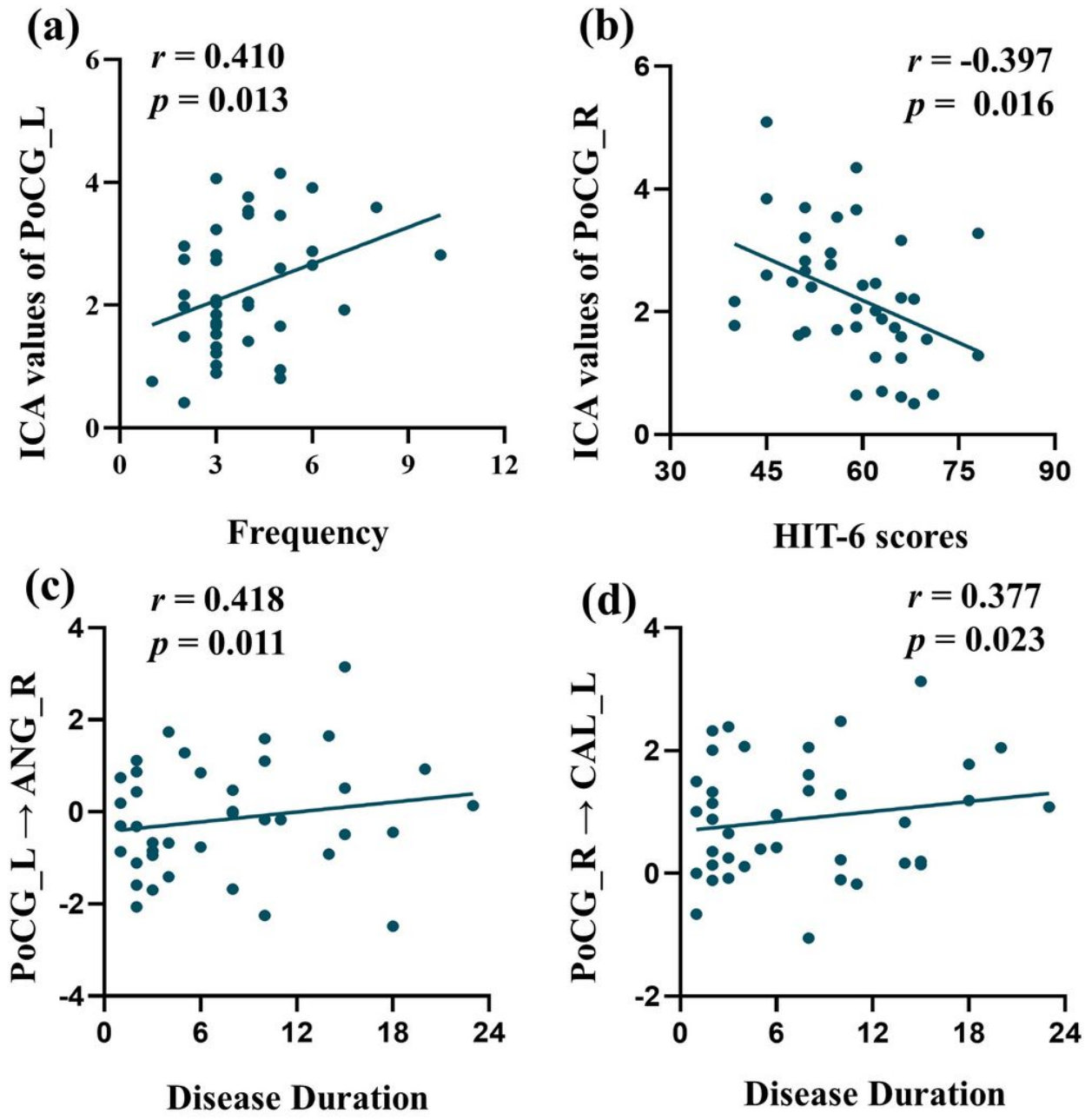

Figure 3

Significant correlations between clinical characteristics and abnormal connectivity in migraineurs. There was positive correlation between the ICA values of the left PoCG and the frequency of attacks (a); and negative correlation between the ICA values of the right PoCG and headache impact (b). There was positive correlation between the disease duration and the abnormal effective connectivity from the left PoCG to the right angular gyrus (c), as well as from the right PoCG to the left calcarine sulcus (d). ICA: independent component analysis; PoCG: postcentral gyrus; ANG: angular gyrus; CAL: calcarine sulcus; HIT: headache impact test; L: left; R: right.