Are there network differences between the ipsilateral and contralateral hemispheres of pain in patients with migraine?

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Abstract

Background

The present study aimed to investigate differences in the structural co-variance network based on structural volume and differences in the functional network based on cerebral blood flow between the ipsilateral and contralateral hemispheres of pain in patients with migraine.

Methods

We prospectively enrolled 27 patients with migraine without aura, all of whom had unilateral migraine pain that always occurred on the same side. We defined the ipsilateral hemisphere as the side of migraine pain, whereas we defined the contralateral hemisphere as that contralateral to the side of migraine pain. We obtained structural volumes using three-dimensional T1-weighted images and cerebral blood flow measurements using arterial spin labeling MRI. We then analyzed structural co-variance networks based on structural volumes and functional networks based on cerebral blood flow using graph theory.

Results

There were no significant differences in structural volume or cerebral blood flow between the ipsilateral and contralateral hemispheres. However, there were significant differences in the structural co-variance network and functional network. In the structural co-variance network, the betweenness centrality of the thalamus was lower in the ipsilateral hemisphere than in the contralateral hemisphere. In the functional network, the betweenness centrality of the anterior cingulate and paracingulate gyrus was lower, while that of the opercular part of the inferior frontal gyrus was higher, in the ipsilateral hemisphere than in the contralateral hemisphere.

Conclusion

The present findings successfully demonstrate that there are significant differences in the structural co-variance network and functional network between the ipsilateral and contralateral hemispheres of pain in patients with migraine. Such findings may be related to the pathogenesis of pain in these patients.

1. Background

Migraine is a common, disabling neurological disorder with a 1-year prevalence of approximately 12 percent, and the cumulative incidence by age 85 is approximately 18.5% in men and 44% in women.[1] Migraine pain is unilateral in 60% of patients and bilateral in 40%. Furthermore, 15.1% of patients without migraine aura and 16.9% of those with migraine aura report strictly unilateral headaches without side shifting (i.e., “side-locked” headaches).[2]

Over the last decade, advancements in neuroimaging have improved our knowledge regarding the biology of migraine, and it is now widely accepted that migraine is a complex brain network disorder.[3, 4] Functional magnetic resonance imaging (MRI) studies have consistently demonstrated that patients with migraine exhibit alterations in functional connectivity involving several areas of brain when compared to healthy controls. Migraine has also been associated with atypical brain activation in response to painful, olfactory, and visual stimuli.[4] In addition, there are significant correlations between the extent of functional abnormalities and headache frequency,[4] and accumulating evidence indicates that gray matter structure is altered in patients with migraine. One meta-analysis reported that patients with migraine exhibit concordant decreases in gray matter volume in the bilateral inferior frontal gyri, right precentral gyrus, left middle frontal gyrus, and left cingulate gyrus when compared to healthy controls.[5] Moreover, gray matter volume decreases in the right claustrum, left cingulate gyrus, right anterior cingulate, amygdala, and left parahippocampal gyrus are related to the estimated frequency of headache attacks.[5] One study involving structural co-variance network analysis based on structural volume and thickness revealed that patients with migraine exhibit weaker structural co-variance of hypothalamic regions with frontal and temporal areas relative to healthy controls.[6] However, no studies have investigated differences in the structural network between the ipsilateral and contralateral hemispheres of pain in patients with migraine.

Arterial spin labeling (ASL) is a non-invasive perfusion method that quantitatively measures cerebral blood flow in each area of brain tissue.[7, 8] Several reports have demonstrated that abnormal cerebral perfusion is associated with migraine headache using ASL perfusion MRI.[9, 10] In addition, ASL perfusion MRI can measure resting brain function directly at the voxel level using magnetically labeled arterial blood water as an endogenous diffusible tracer for quantification of regional cerebral blood flow, which is thought to be coupled to regional neural activity.[7, 8] ASL perfusion MRI can also reduce coherent noise fluctuations resulting from the combination of background suppression and time-interleaved subtraction, effectively removing the large nonfunctional background signal.[7, 8] Although the majority of functional studies rely on blood-oxygen-level dependent (BOLD) functional MRI, the BOLD signal results from overall contributions and is thus affected by significant variations in cerebral blood flow, cerebral blood volume, and cerebral metabolic rate of oxygen consumption.[11] Therefore, the functional network based on the BOLD MRI may exhibit instability over time given the presence of artifacts.[11] However, no studies have investigated the functional network based on cerebral blood flow determined using ASL perfusion MRI in patients with migraine.

Therefore, in this study, we investigated differences in the structural co-variance network based on structural volume and differences in the functional network based on ASL perfusion MRI measurements of cerebral blood flow between the ipsilateral and contralateral hemispheres of migraine pain. We hypothesized that there would be significant differences in the structural and/or functional networks between the two hemispheres.

2. Methods

2.1. Participants

This study was approved by the Institutional Review Board of our institution. We prospectively enrolled patients based on the following criteria: 1) visit to the neurology department of our hospital from August 2018 to July 2020; 2) newly diagnosed with migraine without aura at our hospital based on the International Classification of Headache Disorders[12]; 3) presence of unilateral migraine pain always occurring on the same side; 4) normal brain MRI on fluid-attenuated inversion recovery (FLAIR) imaging and T2-weighted imaging based on visual inspection; 5) no history of any other medical, neurological, or psychiatric disease.

We defined the ipsilateral hemisphere as the side of migraine pain, whereas we defined the contralateral hemisphere as that contralateral to the side of migraine pain.

2.2. MRI acquisition

All MRI scans were performed using the same 3.0-T MRI scanner (AchievaTx, Phillips Healthcare, Best, The Netherlands) equipped with a 32-channel head coil. All patients with migraine underwent the same brain MRI protocol, which included three-dimensional (3D) FLAIR imaging, coronal T2-weighted imaging, 3D T1-weighted imaging, and ASL. FLAIR and T2-weighed imaging were used to evaluate structural abnormalities in the brain. All patients were in the interictal state of headache at the time of MRI scans.

The 3D T1-weighted images were acquired using a turbo-field echo sequence with the following parameters: inversion time (TI) = 1,300 ms, repetition time (TR)/echo time (TE) = 8.6 ms/3.96 ms, flip angle (FA) = 8°, and an isotropic voxel size of 1 mm^3. ASL perfusion MR images were acquired using a pseudo-continuous ASL (pCASL) technique and a 3D gradient and spin echo (GRASE) readout. The specific imaging parameters for the pCASL experiments were as follows: TR/TE = 4,200 ms/13 ms, field-of-view (FOV) = 240 x 240 x 120 mm, voxel size = 3 x 3 x 6 mm (20 partitions), and a parallel imaging factor of 1.2.3. Dynamic scans consisting of pairs of control/label images were acquired using a label duration of 1,650 ms, a post labeling delay of 1,800 ms, and a total scan duration of 3 minutes and 46 seconds.

2.3. MRI processing to obtain structural volume and cerebral blood flow

Structural volume was obtained using the “recon-all” function in the FreeSurfer program (http://surfer.nmr.mgh.harvard.edu/). The processing stream of FreeSurfer consisted of several stages, as follows: volume registration with the Talairach atlas, bias field correction, initial volumetric labeling, non-linear alignment to the Talairach space, and final labeling of the volume. Then, the cortical surface of each hemisphere was inflated to an average spherical surface to locate both the pial surface and the white/gray matter boundary. We calculated the volumes of the cortical regions of interest (ROIs) and subcortical structures including the amygdala, caudate, hippocampus, pallidum, putamen, and thalamus using the Desikan atlas (Additional file 1). We then corrected the structural volume with total intracranial

volumes using the following equation: structural volumes (%) = (absolute structural volumes/total intracranial volumes) × 100. Cerebral blood flow was obtained using three programs based on Matlab (R2020a), SPM12 (https://www.fil.ion.ucl.ac.kr/spm/), and the ASLtbx tool box (https://www.cfn.upenn.edu/~zewang/ASLtbx.php).[13] We calculated the cerebral blood flow of the ROI according to the Automated Anatomical Labeling (AAL) atlas[14] (Additional file 2) via the following: motion correction of ASL, registration with T1-weighted imaging, smoothing, exclusion of brain voxels, mean cerebral blood flow quantification, normalization, and extraction of cerebral blood flow for each region. We excluded the vermis ROI in the AAL atlas because it could not be classified into a right and left side.

2.4. Network analysis using graph theory

We performed analysis of the structural co-variance network based on structural volumes and analysis of the functional network based on cerebral blood flow using BRAPH (http://braph.org/).[15] To combine patients with right and left migraine pain into one cohort, the regions were converted from right or left side to ipsilateral or contralateral side according to the side of migraine pain. We built a collection of nodes representing brain regions connected by edges corresponding to the connections between them. The nodes were defined using the structural volumes or cerebral blood flow of the ROI, and the edges were calculated as the partial correlation coefficients between every pair of brain regions while controlling for the effects of age and sex. For each group, an undirected and weighted connectivity matrix was built. Negative correlations were set to zero, and only positive values were used in the calculation. To detect differences between groups in the global network topology, we calculated the average degree, average strength, radius, diameter, eccentricity, characteristic path length, global efficiency, local efficiency, mean clustering coefficient, transitivity, modularity, assortative coefficient, and small-worldness index.[15, 16] To assess differences in local network topology between groups, we calculated the betweenness centrality of the ROI, which is the most commonly used measure for reflecting network centrality.[15, 16]

2.5. Statistical analysis

Differences in structural volume and cerebral blood flow between groups were analyzed using Student's t-test. Comparisons of the structural co-variance network and functional network were performed using nonparametric permutation tests with 1,000 permutations, as we obtained the network measures at the group level. Categorical variables are presented as frequencies and percentages, whereas continuous variables are presented as the mean ± the standard deviation or median and interquartile range. Statistical significance was set to $p < 0.05$. False-discovery rate correction for multiple comparisons was applied during the local structural co-variance network and functional network analysis. MedCalc® Statistical Software version 19.6 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2020) was used for the statistical analysis.

2.6. Data availability statement

The data generated in this study are available from the corresponding author upon reasonable request.

3. Results

3.1. Participants

We enrolled 27 patients with migraine without aura. Table 1 shows the clinical characteristics of the included patients with migraine. Mean patient age was 41.5 years, and four of the 27 patients were male. Fifteen patients experienced right-sided migraine pain, while 12 patients experienced left-sided migraine pain.

Table 1
Clinical characteristics of patients with migraine

	Patients with migraine
Age, years (± SD)	41.5 (± 13.8)
Male, n (%)	4 (14.8)
Age of onset, years (± SD)	30.2 (± 11.3)
Right-sided migraine pain, n (%)	15 (55.5)
Disease duration, months (interquartile range)	150 (60–294)
Attack frequency per month, n (interquartile range)	3 (2–8)
Headache intensity, visual analog scale (interquartile range)	7 (6–8)
SD: standard deviation	

3.2. Structural volume and cerebral blood flow

No significant differences in the structural volumes of ROIs were observed between the ipsilateral and contralateral hemispheres (Additional file 1). In addition, there were no significant differences in the cerebral blood flow of the ROIs between the two hemispheres (Additional file 2).

3.3. Structural co-variance network based on structural volume

The global structural co-variance network—which was determined based on average degree, average strength, radius, diameter, eccentricity, characteristic path length, global efficiency, local efficiency, mean clustering coefficient, transitivity, modularity, assortative coefficient, and small-worldness index—did not significantly differ between the ipsilateral and contralateral hemispheres (Table 2). However, there were significant differences in the local structural co-variance network. The betweenness centrality of the thalamus in the ipsilateral hemisphere was significantly decreased relative to that in the contralateral hemisphere (0.000 vs. 0.162, $p = 0.027$) (Table 3, Fig. 1, Additional file 3).

Table 2
Differences in the global structural co-variance network based on structural volume and the functional network based on cerebral blood flow between the ipsilateral and contralateral hemispheres in patients with migraine

Structural co-variance network	**Ipsilateral hemisphere**	**Contralateral hemisphere**	**Difference**	**CI lower**	**CI upper**	***p*-value**
Average degree	37.5000	38.1000	0.6000	-3.1451	2.7766	0.349
Average strength	18.2085	18.7114	0.5029	-6.3957	5.9115	0.436
Radius	3.3302	2.8584	-0.4719	-1.1290	1.1406	0.240
Diameter	5.8451	4.3864	-1.4587	-2.1246	2.0384	0.126
Eccentricity	4.2005	3.6788	-0.5217	-1.4779	1.4351	0.260
Characteristic path length	2.2858	2.2096	-0.0761	-0.6788	0.7274	0.414
Global efficiency	0.4967	0.5030	0.0063	-0.1327	0.1237	0.467
Local efficiency	1.5787	1.6155	0.0368	-0.7741	0.7873	0.479
Mean clustering coefficient	0.4468	0.4594	0.0126	-0.1498	0.1477	0.451
Transitivity	0.6798	0.6937	0.0139	-0.2238	0.2113	0.457
Modularity	0.0564	0.0585	0.0021	-0.0503	0.0500	0.467
Assortative coefficient	-0.0732	-0.0638	0.0094	-0.0492	0.0514	0.378
Small-worldness index	0.9570	0.9619	0.0050	-0.0397	0.0419	0.397
Functional network	Ipsilateral hemisphere	Contralateral hemisphere	Difference	CI lower	CI upper	*p*-value
Average degree	49.8519	50.9259	1.0741	-7.2397	7.1282	0.405
Average strength	26.7474	25.8838	-0.8635	-12.6215	13.3086	0.419
Radius	3.3167	3.1271	-0.1896	-1.4319	1.4779	0.376
Diameter	6.1212	5.2674	-0.8538	-2.4808	2.4672	0.276
Eccentricity	4.3086	3.9489	-0.3596	-2.0246	2.1458	0.359
Characteristic path length	2.1856	2.2118	0.0262	-1.1121	1.1089	0.466
Global efficiency	0.5391	0.5222	-0.0169	-0.2055	0.2035	0.396

CI: 95% confidence interval of the differences between the groups

Structural co-variance network	Ipsilateral hemisphere	Contralateral hemisphere	Difference	CI lower	CI upper	*p*-value
Local efficiency	2.2127	2.0477	-0.1650	-1.5719	1.5197	0.400
Mean clustering coefficient	0.4894	0.4642	-0.0253	-0.2324	0.2425	0.381
Transitivity	0.7491	0.7055	-0.0437	-0.3520	0.3389	0.405
Modularity	0.0576	0.0679	0.0103	-0.0837	0.0896	0.419
Assortative coefficient	-0.0610	-0.0429	0.0181	-0.1152	0.1081	0.319
Small-worldness index	0.9166	0.9315	0.0149	-0.0944	0.1006	0.408
CI: 95% confidence interval of the differences between the groups						

Table 3
Regions with significantly different local structural co-variance networks based on structural volume and functional networks based on cerebral blood flow between the ipsilateral and contralateral hemispheres in patients with migraine

	Ipsilateral hemisphere	Contralateral hemisphere	Difference	CI lower	CI upper	*p*-value
Structural co-variance network						
Thalamus	0.0000	0.0162	0.0162	-0.0121	0.0135	0.027
Functional network						
Anterior cingulate and paracingulate gyri	0.0000	0.0261	0.0261	-0.0232	0.0240	0.038
Inferior frontal gyrus (opercular part)	0.0181	0.0000	-0.0181	-0.0123	0.0113	0.019
CI: 95% confidence interval of the differences between the groups						

3.4. Functional network based on cerebral blood flow

The global functional network—which was determined based on average degree, average strength, radius, diameter, eccentricity, characteristic path length, global efficiency, local efficiency, mean clustering coefficient, transitivity, modularity, assortative coefficient, and small-worldness index—did not significantly differ between the ipsilateral and contralateral hemispheres (Table 2). However, there were significant differences in the local functional network. The betweenness centrality of the anterior cingulate and paracingulate gyrus was significantly decreased, whereas the betweenness centrality of the opercular part of the inferior frontal gyrus was significantly increased, in the ipsilateral hemisphere

relative to that in contralateral hemisphere (0.000 vs. 0.261, $p = 0.038$; 0.018 vs. 0.000, $p = 0.019$; respectively) (Table 3, Fig. 1, Additional file 4).

4. Discussion

In the present study, we investigated differences in the structural co-variance and functional networks between the ipsilateral and contralateral hemispheres of migraine pain. Our results indicated that structural volume and cerebral blood flow did not significantly differ between the ipsilateral and contralateral hemispheres. However, significant differences in the structural co-variance network and functional network were observed between the two hemispheres. In addition, we successfully demonstrated the feasibility of functional network analysis using ASL perfusion MRI in patients with migraine.

Our results demonstrated that, in the structural co-variance network, the betweenness centrality of the thalamus was significantly lower in the ipsilateral hemisphere than in the contralateral hemisphere. Alterations in the structural co-variance network may reflect alterations in dendritic complexity, changes in the number of synapses, or brain plasticity, thereby resulting in connectivity changes.[17] Betweenness centrality is a measure of centrality in a graph based on the shortest paths, a measure widely used to detect the amount of influence a node has over the flow of information in a graph.[18] The measure quantifies the number of times a node acts as a bridge along the shortest path between two other nodes.[18] Thus, the present findings suggest that the structural connectivity of the thalamus in the ipsilateral hemisphere is lower than that in the contralateral hemisphere during the interictal state. In the pathogenesis of migraine, the thalamus may play a role as a relay center for ascending nociceptive information from the brainstem to cortical regions, via the trigemino-vascular pain pathway.[19] The thalamus is therefore most likely involved in the allodynia, central sensitization, and photophobia associated with migraine.[19] Previous studies using functional MRI[20] or diffusion tensor imaging[21] have also observed abnormal thalamocortical network connectivity in patients with migraine. In addition, we recently demonstrated that patients with migraine exhibit significant alterations in thalamic nuclei volumes when compared with healthy controls, especially in the anteroventral, medial geniculate, and parafascicular nuclei.[22] Together, these findings suggest that alterations in thalamic connectivity contribute to the pathogenesis of migraine.

In the functional network analysis based on cerebral blood flow, we observed significant alterations in betweenness centrality in the anterior cingulate/paracingulate gyrus. The cingulate gyrus is involved in pain processing, modulation, and associated symptoms such as emotional disturbances in patients with migraine.[5, 23] Previous functional MRI studies have consistently reported atypical brain responses to sensory stimuli, absence of the normal habituating response between attacks, and atypical functional connectivity of sensory processing regions in patients with migraine.[4] The alterations in the betweenness centrality of the cingulate gyrus observed in our functional network analysis are in accordance with the results of previous studies, supporting the notion that sensory hypersensitivities in patients with migraine may be induced by a combination of enhanced sensory facilitation and reduced

inhibition in response to sensory stimuli.[24, 25] Furthermore, the cingulate gyrus is one of the regions of the default mode network (DMN), which plays a relevant role in adaptive behaviors other than those associated with cognitive, emotional, and attentional processes.[26] Several studies have identified disrupted DMN connectivity during the interictal period in patients with migraine.[27] Pain has a widespread impact on overall brain function, modifying brain dynamics beyond pain perception, which may produce alterations in DMN connectivity.[28] Based on the amplitude of low-frequency fluctuations, another functional MRI study demonstrated reduced DMN connectivity in the anterior cingulate cortex, prefrontal cortex, and thalamus in patients with migraine.[29] Furthermore, functional DMN changes are negatively correlated with disease duration.[29] Taken together, these results indicate that the cingulate gyrus may be involved in pain processing in patients with migraine.

In the present study, we also observed that betweenness centrality was higher in the inferior frontal gyrus of the ipsilateral hemisphere than in that of the contralateral hemisphere. The frontal cortex is one of the most important areas associated with brain abnormalities in patients with migraine. The role of the frontal lobe in pain processing has been established in previous studies, including those involving patients with chronic back pain, fibromyalgia, phantom pain syndrome, and medication overuse headache.[30, 31] A previous meta-analysis demonstrated that patients with migraine exhibited concordant decreases in gray matter volume in the inferior frontal gyrus.[5] Increased activation in the inferior frontal gyrus may reflect increased effort due to disorganization of these areas or the use of compensatory strategies involving pain processing in migraine.[5] Additionally, one functional MRI study reported increased neural activation in the frontal gyrus in response to fearful faces when compared to neutral faces in patients with migraine, relative to findings observed in healthy controls. Thus, an enhanced response to emotional stimuli may explain the triggering effect of psychosocial stressors on migraine.[32]

This is the first study to investigate differences in the structural and functional networks between the hemispheres according to the side of migraine. We successfully demonstrated significant differences in the structural/functional networks of some regions between the ipsilateral and contralateral hemispheres. Furthermore, our findings highlight the feasibility of functional network analysis based on cerebral blood flow determined using ASL MRI in patients with migraine. However, there were several limitations in this study. First, the sample size was relatively small. However, we only enrolled patients who had unilateral migraine pain that always occurred on the same side. In addition, all patients were newly diagnosed with migraine without aura and underwent MRI during the interictal state. Second, we did not obtain ASL perfusion MR images from healthy controls. Thus, we could not investigate differences in the structural and functional networks between patients with migraine and healthy controls. Third, we could not analyze the correlation between clinical factors and network measures, as we obtained network measures at the group rather than individual level. Fourth, most patients with migraine in our study were taking medications for migraine. These medications may have impacted the structural or functional networks in our patients. Further studies with larger sample sizes may be required to confirm our findings.

5. Conclusion

The present findings successfully demonstrate that there are significant differences in the structural covariance network and functional network between the ipsilateral and contralateral hemispheres of pain in patients with migraine. Such findings may be related to the pathogenesis of pain in these patients.

Declarations

Ethics approval and consent to participate

This study was conducted with the approval of our institution's institutional review board (Haeundae Paik Hospital, Busan, Korea).

Consent for publication

Not applicable.

Availability of data and materials

The datasets supporting the conclusions of this article are included within the article and its additional files.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

DA Lee, HJ Lee and KM Park conceived and designed the analysis, analyzed and interpreted the data, drafted and revised the manuscript for intellectual content. HC Kim, BS Park, JH Ko, SH Park, IH Kim, JH Park, EJ Lee and KM Park performed data acquisition, analyzed and interpreted the data, revised the manuscript for intellectual content. All authors read and approved the final manuscript.

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Figures

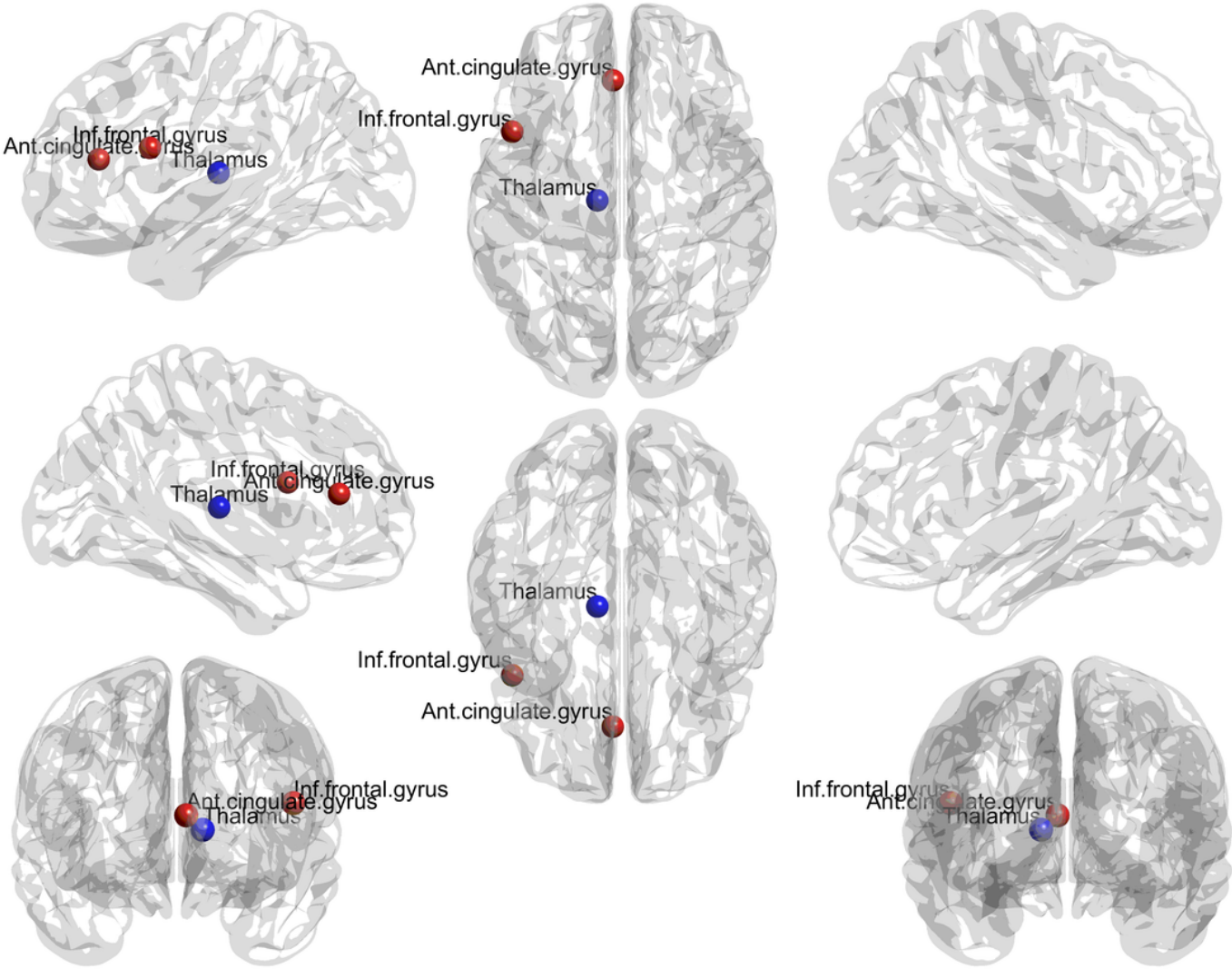

Figure 1

Regions with significantly different local structural co-variance networks and functional networks between the ipsilateral and contralateral hemispheres of pain in patients with migraine. Blue circles indicate regions with significantly different local structural co-variance networks based on structural volume. Red circles indicate regions with significantly different functional networks based on cerebral blood flow.

Supplementary Files

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