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Whole-brain functional gradients reveal cortical and subcortical alterations in patients with episodic migraine

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Abstract

Migraine is a type of headache with multiple neurological symptoms. Prior neuroimaging studies in patients with migraine based on functional magnetic resonance imaging have found regional as well as network-level alterations in brain function. Here, we expand on prior studies by establishing whole-brain functional connectivity patterns in patients with migraine using dimensionality reduction techniques. We studied functional brain connectivity in 50 patients with episodic migraine and sex- and age-matched healthy controls. Using dimensionality reduction techniques that project high-dimensional functional connectivity onto low-dimensional representations (i.e., eigenvectors), we found significant between-group differences in the eigenvectors between patients with migraine and healthy controls, particularly in the sensory/motor and limbic cortices. Furthermore, we assessed between-group differences in subcortical connectivity with subcortical weighted manifolds defined by subcortico-cortical connectivity multiplied by cortical eigenvectors and revealed significant alterations in the amygdala. Finally, leveraging supervised machine learning, we moderately predicted headache frequency using cortical and subcortical functional connectivity features, again indicating that sensory and limbic regions play a particularly important role in predicting migraine frequency. Our study confirmed that migraine is a hierarchical disease of the brain that shows alterations along the sensory-limbic axis, and therefore, the functional connectivity in these areas could be a useful marker to investigate migraine symptomatology.

KEYWORDS
functional MRI, machine learning, migraine, whole-brain connectivity

1 | INTRODUCTION

Migraine is a neurological condition characterized by episodic headaches, showing symptoms of nausea, vomiting, photophobia, and phonophobia (Silberstein, 1995). It is a prevalent disease, present in almost 6% of males and 17.6% of females in the United States (Bigal et al., 2004). As migraine is a brain disorder, the regional and network-level structural and functional characteristics of migraine have been

investigated in several studies (Ashina et al., 2021; Bashir et al., 2013; Russo et al., 2012; Tessitore et al., 2013, 2015). Advances in neuroimaging techniques, such as magnetic resonance imaging (MRI), have enabled the investigation of abnormal brain organization in patients with migraine. In particular, functional MRI (fMRI) estimates blood-oxygen-level-dependent signals, which reflect changes in the intravascular deoxyhemoglobin concentration. Thus, we can measure atypical activity in the cerebral cortex and subcortical structures in migraine using fMRI (Cutrer et al., 2019; Cutrer & Charles, 2008). To reveal the features of the migraine brain, prior studies have utilized resting-state fMRI (rs-fMRI) in patients with migraine during their interictal states. Studies have found that patients with migraine show functional alterations in primary sensory (Hodkinson et al., 2016), limbic (Chen et al., 2017; Hadjikhani et al., 2013; Messina et al., 2021), executive control, and default-mode networks (Coppola et al., 2020; Messina et al., 2020; Tessitore et al., 2013). In addition, our previous work observed that the higher-order frontoparietal network, as well as the cerebellum and brainstem, are susceptible to functional alterations associated with migraine (Lee, Park, Cho, Park, et al., 2019). Together, these studies indicate that migraine is associated with alterations in brain function across the cortical hierarchy (Mesulam, 1998), particularly in the low-level sensory and higher-order frontoparietal/limbic systems, suggesting that migraine may be a hierarchy-dependent brain disease.

Conventional approaches to identifying functional connectome alterations in diseased populations primarily adopt connectivity analysis based on graph theory (Bullmore & Sporns, 2009; Rubinov & Sporns, 2010; Sporns, 2018). Graph-theoretical approaches consider the brain as a small-world network and analyze regional and interconnectional profiles of brain structure and function by utilizing centrality and/or community measures. These techniques have been widely adopted for studying Alzheimer's disease, autism spectrum disorder, schizophrenia, and migraine (Alaerts et al., 2015; delEtoile & Adeli, 2017; Lee, Park, Cho, Kim, et al., 2019; Liu et al., 2012, 2015; Olejarczyk & Jernajczyk, 2017). These approaches mainly focus on understanding how the structure or function of a specific brain region or connection differs among different groups. The brain is organized hierarchically, where a seminal model of neural organization stratifies it into four cortical hierarchy levels (i.e., 1: idiotypic; 2: unimodal association; 3: heteromodal association; 4: paralimbic) (Mesulam, 1998). This suggests that the brain constructs an axis expanding from low-level sensory systems to higher-order association systems. A recent study introduced dimensionality reduction techniques to assess this hierarchical axis of the brain by projecting high-dimensional functional connectome data into a series of low-dimensional representations, referred to as gradients (Margulies et al., 2016). The gradients construct a new coordinate system in the low-dimensional eigenspace and establish multiple hierarchical cortical axes. This approach has been applied to microstructure (Paquola et al., 2019) and diffusion MRI studies (Park, Bethlehem, et al., 2021) to provide additional information on brain hierarchy. Such dimensionality reduction techniques can complement conventional graph-theoretical approaches by capturing the continuously changing connectivity patterns along multiple brain axes (Haak et al., 2018; Haak & Beckmann, 2020). The gradient approach has been widely applied to disease populations, such as autism spectrum disorder (Hong et al., 2019) and epilepsy (Li et al., 2021), as well as healthy populations (Vázquez-Rodríguez et al., 2019).

In this study, we examined whole-brain connectome axis alterations in migraineurs by using low-dimensional representations of functional connectivity. We then examined the reliability of the imaging features derived from functional connectivity by predicting clinical scores related to migraine using supervised machine learning.

2 | METHODS

2.1 | Participants

We recruited 50 patients with episodic migraine (mean ± standard deviation; age = 33.5 ± 9.11 years; 70% female), and sex- and age-matched healthy controls (n = 50; age = 33.5 ± 9.11 years; 70% female) from the Samsung Medical Center from August 2017 to July 2018 (Lee, Park, Cho, Park, et al., 2019). The patients with migraine were diagnosed by Mi Ji Lee according to the International Classification of Headache Disorders, third edition beta version (ICHD-3 beta). We excluded patients with chronic migraine because it has been shown that brain connectome organization and pathophysiology are different between patients with chronic and episodic migraine (Lee, Park, Cho, Kim, et al., 2019). We also excluded patients with medication-overuse headaches, chronic pain disorders other than migraine, those diagnosed with psychiatric disorders, such as bipolar affective disorder or schizophrenia, and those who used any regular medications including migraine preventive agents. The Samsung Medical Center Institutional Review Board approved this study and all participants provided written informed consent. This study is part of an ongoing longitudinal project registered at ClinicalTrials.gov (Identifier: NCT03487978).

2.2 | MRI acquisition

All participants underwent T1-weighted and rs-fMRI using a 3T scanner (Ingenia, Philips, the Netherlands). The T1-weighted data were acquired using the following parameters: repetition time (TR) = 9.9 ms; echo time (TE) = 4.6 ms; field of view (FOV) = 240 × 240 mm^2; flip angle = 8°; imaging number of slices = 180 (reconstructed to 360); slice thickness = 1 mm (reconstructed to 0.5 mm); and in-plane resolution = 1 mm × 1 mm, which was reconstructed to 0.5 mm × 0.5 mm. Acquisition parameters of the rs-fMRI data were as follows: TR = 3000 ms; TE = 30 ms; FOV = 220 × 220 mm^2; flip angle = 90°; number of slices = 33; slice thickness = 4 mm; in-plane resolution = 3 mm × 3 mm, which was reconstructed to 1.25 mm × 1.25 mm; and number of volumes = 200. All participants were instructed to keep their eyes open while looking at a fixation cross to prevent them from falling asleep during the imaging session.

2.3 | Data preprocessing

The imaging data were preprocessed using the fusion of neuroimaging preprocessing (FuNP) surface-based pipeline, which integrated AFNI, FSL, FreeSurfer, ANTs, and Workbench (https://gitlab.com/by9433/funp; Avants et al., 2011; Cox, 1996; Fischl, 2012; Jenkinson et al., 2012; Park et al., 2019). T1-weighted data preprocessing included gradient nonlinearity and b0 distortion correction, nonbrain tissue removal, and intensity normalization. White and pial surfaces were generated by following the boundaries between the different tissues (Dale et al., 1999; Fischl, 2012; Fischl, Sereno, & Dale, 1999; Fischl, Sereno, Tootell, et al., 1999). The mid-thickness surface was generated by averaging the white and pial surfaces, and was used to generate an inflated surface. The rs-fMRI data were preprocessed as follows. After re-orientation, the first four volumes were discarded to allow for magnetic field saturation, and slice timing was corrected. Volumes with large head motion (frame-wise displacement >0.5 mm) were removed (Power et al., 2012) and motion correction was performed. Skull removal and intensity normalization were applied, and nuisance variables of head motion, white matter, cerebrospinal fluid, cardiac and respiration signals, and large vein-related contributions were removed using FIX (FMRIB's independent component analysis [ICA]-based X-noiseifier; Salimi-Khorshidi et al., 2014). Thereafter, the rs-fMRI data were registered onto the preprocessed T1-weighted structural data and subsequently onto the Montreal Neurological Institute (MNI) standard space. After applying a bandpass filter with a frequency between 0.009 and 0.08 Hz, the preprocessed volumetric rs-fMRI data were mapped to the cortical surface using a cortical ribbon-constrained volume-to-surface mapping algorithm. Finally, spatial smoothing with a full width at half maximum of 5 mm was applied.

2.4 | Low-dimensional representation of functional connectivity

We constructed a functional connectivity matrix by calculating Pearson's correlation of time series between different brain regions defined using the Schaefer 7-network-based atlas with 200 parcels (Schaefer et al., 2018), and the resulting correlation coefficients were Fisher's *r*-to-*z* transformed. We generated low-dimensional representations (henceforth, eigenvectors) of functional connectivity using dimensionality reduction techniques to represent high-dimensional functional connectome data using multiple low-dimensional eigenvectors. The eigenvectors were generated using a diffusion map embedding algorithm, which is a robust and computationally efficient nonlinear dimensionality reduction technique (Coifman & Lafon, 2006; Tenenbaum et al., 2000; von Luxburg, 2007). The generated eigenvectors construct a new coordinate system on the low-dimensional eigenspace, and each eigenvector represents a different axis of the cortical organization (Margulies et al., 2016; Park, Hong, et al., 2021; Vos de Wael et al., 2020). The eigenvector generation was performed using BrainSpace (https://github.com/MICA-MNI/BrainSpace; Vos de Wael et al., 2020). We first constructed template eigenvectors using a group-averaged functional connectivity matrix with a connection density of 10% and subsequently aligned individual participants' eigenvectors to the template using Procrustes alignment (Langs et al., 2015; Vos de Wael et al., 2020).

2.5 | Between-group differences in eigenvectors

To assess perturbations in the functional connectome of patients with migraine, we conducted a statistical analysis based on multivariate linear models, which make inferences using Hotelling's T, using the BrainStat toolbox (Chung et al., 2010; Larivière et al., 2023; Worsley et al., 2009). The model assessed between-group differences in three eigenvectors (response variables) between patient and control groups (explanatory variable) after controlling for age and sex. Multiple comparisons across brain regions were corrected using a false discovery rate (FDR) < 0.05 (Benjamini & Hochberg, 1995).

2.6 | Subcortico-cortical connectivity alteration

In addition to atypical cortical connectivity, we assessed alterations in subcortical structures (i.e., accumbens, amygdala, caudate, hippocampus, pallidum, putamen, and thalamus) in patients with migraine using subcortical-weighted manifolds (Park, Hong, et al., 2021). In brief, the subcortical regions were individually defined using FSL FIRST (Jenkinson et al., 2012). For each subcortical region, we performed element-wise multiplication of the subcortico-cortical connectivity and cortical eigenvectors, resulting in subcortical-weighted manifolds. We then averaged the weights of each subcortical-weighted manifold to generate the nodal degree values. We compared the degree values between patients with migraine and healthy controls based on the univariate linear model using the BrainStat toolbox (Chung et al., 2010; Larivière et al., 2023; Worsley et al., 2009). Multiple comparisons across subcortical regions were corrected using an FDR of <0.05 (Benjamini & Hochberg, 1995).

2.7 | Prediction of a clinical variable

We adopted supervised machine learning to predict the headache frequency and disease duration using cortical eigenvectors and subcortical-weighted manifolds. Specifically, we applied the least absolute shrinkage and selection operator (LASSO) to select imaging features, and constructed a prediction model using linear regression with five-fold nested cross-validation (Cawley & Talbot, 2010; Parvandeh et al., 2020; Tenenbaum et al., 2000; Varma & Simon, 2006). Specifically, we first divided the total data into training (four out of five partitions) and test (one out of five partitions) datasets. Within the training dataset, we again divided the data into inner training and test folds. We first regressed out age and sex from the imaging features of the inner training data and constructed a linear regression model to predict the clinical variable. The model was then

applied to the inner test dataset controlled for age and sex. The model with the highest intra-class correlation (ICC) and minimum mean absolute error (MAE) across inner folds was selected. It was subsequently applied to the test partition of the outer fold and the clinical variables of the outer fold test data were predicted. This procedure was repeated 100 times with different training and test datasets to avoid subject selection bias. Prediction accuracy was assessed using ICC between actual and predicted clinical variables, where the significance was determined based on 1000 permutation tests by randomly shuffling participants. In addition, we calculated Spearman's rank correlation and MAE. The selection probability of imaging features was calculated by dividing the selection frequency by the number of repetitions.

2.8 | Sensitivity analyses

a. *Spatial scale*. To assess the robustness of our findings across different spatial scales, we repeated the analyses of generating eigenvectors and assessing between-group differences in the eigenvectors between patients with migraine and healthy controls using the Schaefer atlas with 100 and 400 parcels (Schaefer et al., 2018).
b. *Structural parcellation*. We repeated the analyses using structural parcellation with 200 parcels defined based on the Desikan–Killiany atlas (Desikan et al., 2006) to assess robustness between functional and structural parcellation schemes.
c. *Head motion*. To assess the effects of head motion, we calculated framewise displacement from rs-fMRI (Power et al., 2012), and compared it between the patient and control groups. In addition, we performed multivariate analyses to compare between-group differences in eigenvectors between patients with migraine and healthy controls after controlling for age, sex, and head motion.

3 | RESULTS

3.1 | Study participants

A total of 100 participants (50 patients with migraine and 50 healthy controls) were enrolled in this study. The healthy control subjects were recruited to match the age and sex with the patients. Detailed demographic information is summarized in Table 1.

3.2 | Cortex-wide functional connectome eigenvectors

Applying nonlinear dimensionality reduction techniques, we generated functional connectome eigenvectors, which are the low-dimensional representations of the functional connectivity data defined on the manifold space. We selected the first three eigenvectors, which explained approximately 61.3% of the affinity matrix (Figure 1a). The first eigenvector showed the sensory-transmodal axis, the second eigenvector extended from the somatomotor to visual systems, and the third eigenvector showed an axis along the multiple demand network and rest in the brain. Multivariate analysis identified significant between-group differences in the eigenvectors between patients with migraine and healthy controls in the early visual and somatomotor areas, as well as the temporal cortex and temporal pole (Figure 1b). When the effects were stratified according to the seven intrinsic functional communities (Thomas Yeo et al., 2011), dorsal attention, visual, and limbic networks showed strong effects.

3.3 | Subcortico-cortical functional connectome alterations in patients with migraine

In addition to cortical disorganization in patients with migraine, we investigated the perturbations of subcortical connectivity using subcortical-weighted manifolds (Figure 2a). Among the subcortical structures, the amygdala showed significant (FDR <0.05) between-group differences in the degree values of the subcortical-weighted manifolds (Figure 2b).

3.4 | Prediction of headache frequency

We used supervised machine learning to predict headache frequency and disease duration using cortical eigenvectors and subcortical-weighted manifolds. Across 100 repetitions, the sensory/motor cortex largely contributed to predicting headache frequency (Figure 3a), and the prediction performance was significant (ICC $= 0.33 \pm 0.13$, $p_{perm} = .001$; Spearman's $\rho = 0.38 \pm 0.12$; MAE $= 2.97 \pm 0.57$; Figure 3b). On the other hand, disease duration did not show significant prediction performance.

TABLE 1 Demographic information of study participants

Information	Patients ($N = 50$)	Controls ($N = 50$)	p
Age (years)	33.5 (9.11)	33.5 (9.11)	1
Sex (male:female)	15:35	15:35	1[a]
Headache frequency (days per month)	5.2 (3.55)	N/A	N/A
Disease duration (days)	7.4 (5.2)	N/A	N/A

Note: Mean and standard deviation are reported.
[a]Chi-square test.

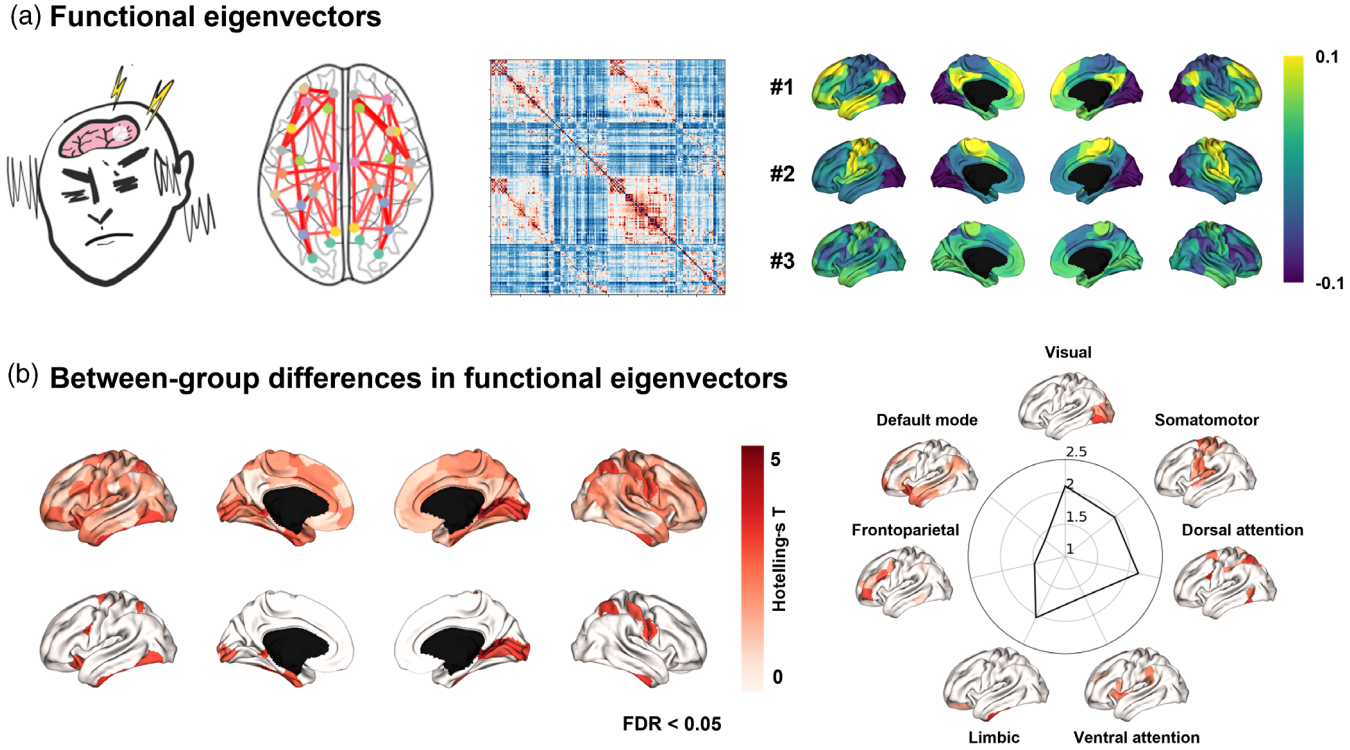

FIGURE 1 Cortex-wide functional eigenvector alterations in patients with migraine relative to healthy controls. (a) We investigated functional connectome organization in patients with migraine. A schema of migraine and brain networks is shown (left). Functional eigenvectors are generated from the group-averaged functional connectivity matrix and shown on brain surfaces (right). (b) The between-group differences in three eigenvectors between patients with migraine and healthy controls are shown on brain surfaces in the top panel, and the regions that had a false discovery rate (FDR) < 0.05 are shown in the bottom panel (left). The spider plot summarizes the effects according to seven functional networks (right)

3.5 | Sensitivity analyses

a. *Spatial scale*. When we repeated the above analysis across different spatial granularities (Schaefer et al., 2018), spatial patterns of the eigenvectors and effect sizes of between-group differences were highly consistent with the main findings (Figure S1a,b).
b. *Structural parcellation*. When we adopted structural parcellation defined based on the Desikan–Killiany atlas (Desikan et al., 2006), we observed consistent results, suggesting robustness (Figure S1c).
c. *Head motion*. The framewise displacement of patients with migraine was 0.13 ± 0.04 and 0.13 ± 0.05 for healthy controls, and did not differ between the groups ($p = .76$). After controlling for head motion effects in addition to age and sex from the eigenvectors, we found overall similar effects in between-group differences (Figure S2).

4 | DISCUSSION

Migraine is prevalent worldwide and leads to low quality of life. Recent neuroimaging studies have found network-level alterations in the brain beyond focal regional abnormalities in patients with migraine, suggesting the necessity of whole-brain investigation. In this study, we investigated perturbations in whole-brain functional connectivity in patients with migraine with respect to the hierarchical axes of the brain. Leveraging nonlinear dimensionality reduction techniques, we generated low-dimensional representations of functional connectivity and revealed that patients with migraine show atypical connectome organization in the somatosensory and limbic regions, as well as the amygdala. We adopted supervised machine learning and found that sensory regions play a particularly important role in predicting migraine frequency. Taken together, our study suggests that migraine is associated with abnormal cortical hierarchy expanding from low-level sensory systems to higher-order limbic systems as well as sensory-related subcortical connectome distortions.

The cortical hierarchy is the basis of the cortical organization (Goldman-Rakic & Rakic, 1991) and is an established model based on laminar differentiation (Mesulam, 1998). Recent advances in methodologies allow the assessment of the principal axis along the cortex (i.e., sensory-fugal axis), and this cortical axis has been found in multiple neuroimaging and histology studies based on rs-fMRI (Margulies et al., 2016), microstructure (Paquola et al., 2019), and diffusion MRI (Park, Bethlehem, et al., 2021). The key concept of this gradient approach is the projection of high-dimensional connectome data onto

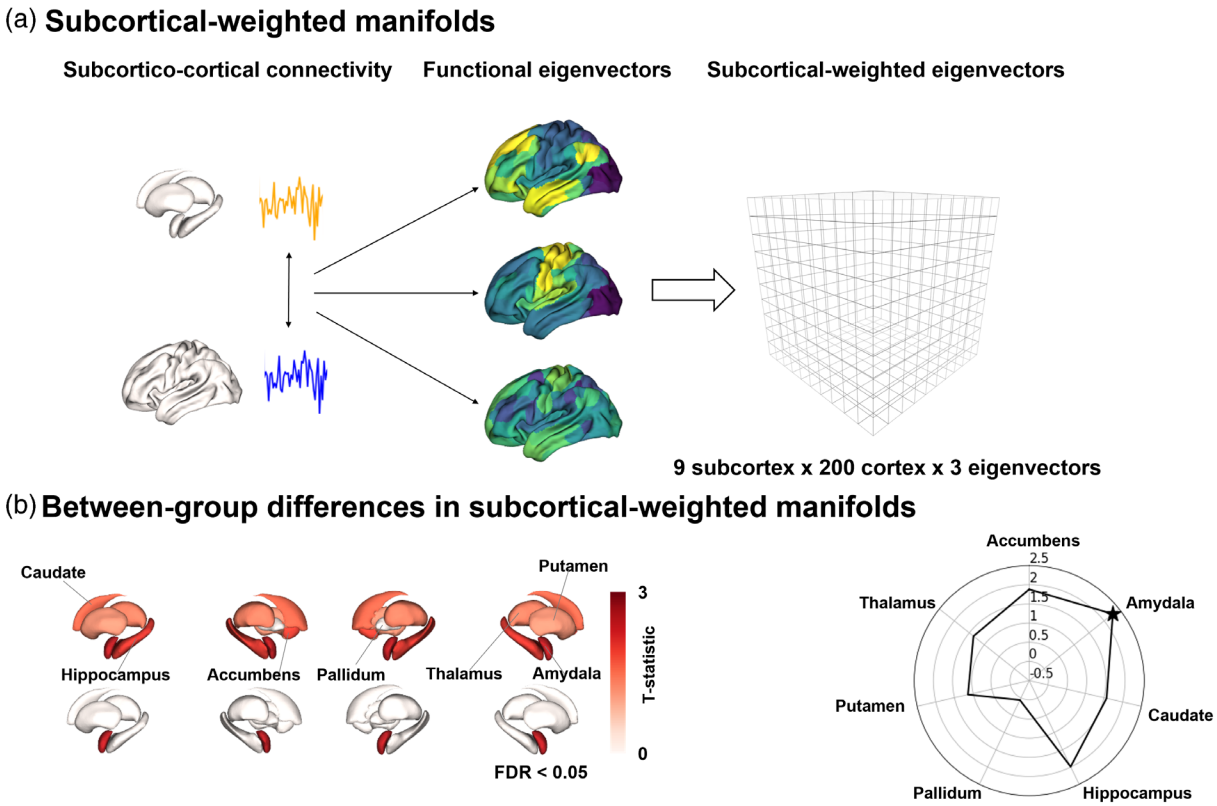

FIGURE 2 Between-group differences in subcortico-cortical connectivity. (a) A schematic of subcortical-weighted manifold calculation is shown. Subcortico-cortical connectivity matrix was computed by correlating the time series of each subcortical region and the whole cortex. We subsequently performed element-wise multiplication between the subcortico-cortical connectivity and cortical eigenvectors. (b) We compared the degree values of subcortical-weighted manifolds between the patients with migraine and healthy controls, and the effects of whole-subcortex (top panel) as well as regions with significant (FDR < 0.05) differences (bottom panel) are shown on brain surfaces. The spider plot summarizes the effects of each subcortical region, and the region which passed the significance level is marked with an asterisk. FDR, false discovery rate

the low-dimensional eigenspace. It has been shown that the estimated multiple eigenvectors represent hierarchical cortical axes of sensory-transmodal, somatomotor-visual, and multiple demand-rest patterns (Margulies et al., 2016; Park, Hong, et al., 2021; Vos de Wael et al., 2020). Prior works in migraine showed alterations in multiple brain networks from primary sensory to higher-order executive control and default-mode networks (Chen et al., 2017; Coppola et al., 2020; Hadjikhani et al., 2013; Hodkinson et al., 2016; Lee, Park, Cho, Park, et al., 2019; Messina et al., 2020, 2021; Meylakh & Henderson, 2022; Tessitore et al., 2013), providing the evidence that migraine could be considered as a cortical hierarchical brain disease. To systemically assess the hierarchical brain organization of patients with migraine, the current study expanded prior work by utilizing a nonlinear manifold learning technique to generate low-dimensional representations of functional connectivity in patients with migraine. We observed alterations in cortical eigenvectors of the patients relative to healthy controls, particularly in the sensory and limbic regions. Sensory processing abnormalities are well described in patients with migraine (Harriott & Schwedt, 2014; Meylakh & Henderson, 2022; Stankewitz & Schulz, 2022). Indeed, visual aura symptoms are frequently observed during the onset of migraine headache (Goadsby et al., 2017; Viana et al., 2019), and atypicality of other multiple sensory processes, such as auditory, olfactory, and somatosensation, are also found in patients with migraine (Harriott & Schwedt, 2014; Meylakh & Henderson, 2022), leading to their increased sensory susceptibility. Previous functional connectivity studies observed altered connection strengths in sensory systems, particularly those showing increased connectivity in somatomotor regions and decreased connectivity in visual regions (Amin et al., 2016; Stankewitz & Schulz, 2022). These studies suggested that increased vulnerability to internal and external sensory stimuli may lead to abnormal multisensory integration in sensory networks during the migraine cycle (Stankewitz & Schulz, 2022). In addition to sensory network alterations, heteromodal association and limbic systems have shown perturbed functional connectivity in patients with migraine (Amin et al., 2016; Coppola et al., 2019). Alterations in the connectivity of the limbic system are associated with migraine-related triggers, such as stress and homeostatic changes (Karsan et al., 2021). Prior studies found decreased functional connectivity during the ictal phase compared to the pain-free interval (Amin et al., 2016; Coppola et al., 2019; Stankewitz & Schulz, 2022). The decreased connectivity in the limbic systems may reflect an atypical pain regulation process as well as cognitive, emotional, and sensory processing (Stankewitz & Schulz, 2022).

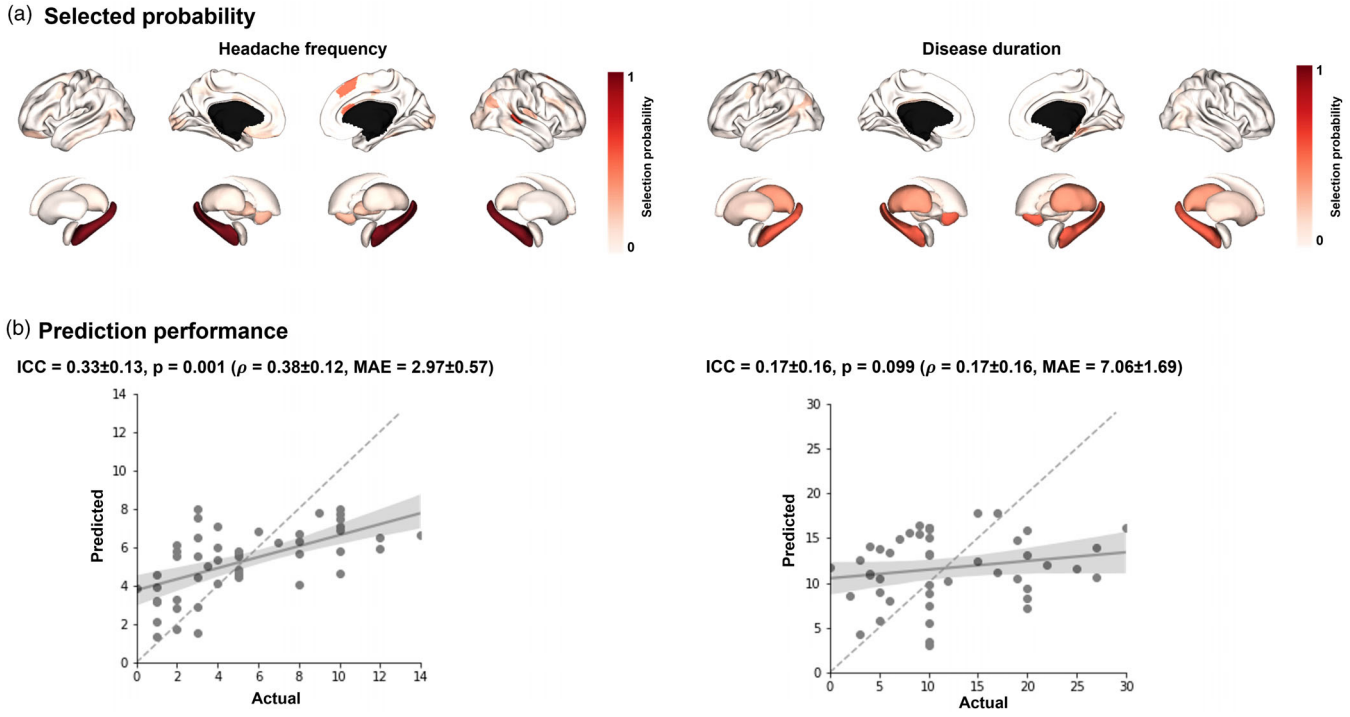

FIGURE 3 Prediction of clinical scores of headache frequency and disease duration. (a) The selection probabilities of brain regions are shown on brain surfaces. (b) Prediction performances are reported using scatter plots. The solid line indicates mean performance across 100 repetitions and the gray regions indicate 95% confidence intervals. The dotted line is an identity line. ICC, intra-class correlation; ρ, Spearman's rank correlation; MAE, mean absolute error

Our findings based on subcortical-weighted manifolds complement these findings. We observed altered connectivity in the limbic system, particularly in the amygdala. The amygdala receives sensory inputs from the limbic cortices of orbitofrontal, temporal, and cingulate regions and delivers the information to fundamental subcortical structures, such as the hypothalamus, forming a loop for information transverse (Goddard, 1964). These circuits control pain modulation, and alterations in these circuits are known to increase pain and further transform to migraine (Chen et al., 2017). Our findings were further reinforced by a machine-learning framework to predict migraine frequency using functional connectivity features. Data-driven analysis revealed that the sensory cortices could be important markers for quantifying headache frequency. Taken together, these results indicate that migraine is associated with dysfunction in brain networks, particularly in low-level sensory and higher-order limbic systems, as well as in associated subcortical structures, suggesting that migraine is a disease affecting brain hierarchy.

In this study, we examined perturbations in low-dimensional representations of functional connectivity in patients with migraine relative to healthy controls. By investigating perturbations in the whole-brain cortical hierarchy and subcortico-cortical connectivity, we expanded prior work that explored regional disruptions in connectivity. We complemented these findings by conducting a machine learning prediction analysis. Our work may provide insights for a better understanding of whole-brain alterations in patients with migraine, which could form a fertile ground for neuroimaging biomarker discovery.

AUTHOR CONTRIBUTIONS

Chae Hyeon Lee and Bo-yong Park designed the study, analyzed data, and wrote the manuscript. Mi Ji Lee designed the study, acquired and interpreted data, and revised the manuscript critically for important intellectual content. Hyunjin Park reviewed the manuscript. Mi Ji Lee and Bo-yong Park are the corresponding authors of this study and are responsible for the integrity of the data analysis. All authors reviewed and approved the final version of the paper to be published.

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CONFLICT OF INTEREST

The authors declare no competing interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author, Mi Ji Lee. The data are not publicly available due to Institutional Review Board restrictions. The codes for connectome eigenvector generation are available at https://github.com/MICA-MNI/BrainSpace; the codes for statistical analysis are available at https://github.com/MICA-MNI/BrainStat; and the codes for the whole analyses are available at https://github.com/CAMIN-neuro/caminopen/tree/master/migraine_gradient.

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SUPPORTING INFORMATION

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