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RESEARCH ARTICLE

Graph Theory

Structural brain network topology in migraine vs. healthy subjects: A graph theory study

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Abstract: There is compelling evidence that migraine is associated with a decline in grey matter in the brain. We postulate that these changes might affect the architecture of the structural brain networks and normal wiring leading to altered functioning of the brain. Therefore, our goal was to compare the global brain network topology of patients with migraines and healthy subjects using grey matter structural networks. The study involved 45 patients with migraine and 46 healthy subjects. 3D, T1-weighted brain images were obtained using a 3 Tesla MRI scanner. Images were preprocessed, and grey matter volume images were generated. Group-level structural connectivity matrices were created using Pearson correlation, and the matrices were binarized by applying a series of sparsity thresholds to compute global network topologies. According to the between-group results, patients with migraines showed increases in small-worldness and global efficiency while local efficiency and synchronization did not differ significantly between patients and healthy subjects ($p< 0.05$). Assortativity values were widely dispersed across different levels of sparsity and were significantly higher in the healthy network compared to the migraine network at sparsities of 0.4 and 0.5 ($p< 0.05$). Furthermore, as network sparsity increased, there was a noticeable trend towards a hierarchy property among patients. According to our findings, patients with migraines exhibit better integration and poorer segregation of information processing in the human brain. Graph theory-based approach provides valuable information on network topological metrics in migraine.

Keywords: Graph theory, grey matter, migraine, neuroimaging, structural networks.

INTRODUCTION

Migraine is defined as a common, disabling, primary brain disorder characterized by recurrent pulsating and throbbing pain in the head accompanied by symptoms such as nausea, sensitivity to light, sound, or scent and vomiting (Simon, 2018). Some believe that it is a neurological disorder affecting gastrointestinal and autonomic functionalities (Planchuelo-Gómez *et al.*, 2020) while others believe that it is a neurovascular disorder that is related to dilation and constriction of blood vessels in the head (Kim *et al.*, 2019). Approximately 15% of the global population suffers from migraine and statistically around 19% of females and 11% of males are affected (Vos *et al.*, 2012).

Structural neuroimaging has brought novel insights in evaluating brain changes in migraine. The findings from this approach have been used to enhance the understanding of the pathophysiology of migraine and to illustrate the potential consequences and risks linked to migraine. Several studies on magnetic resonance imaging (MRI) based neuroanatomy, conducted using voxel-based morphometry (VBM) and surface-based morphometry (SBM) techniques, reveal that repetitive migraine attacks could alter the structural volume and thickness of the brain, particularly in the grey matter (GM) regions (Jia & Yu, 2017; Zhang *et al.*, 2017).

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It is believed that abnormalities in the networks of the brain may underlie cognitive and behavioral deficits in migraine. Therefore, it is crucial to investigate how the structural network arrangement in the brains of migraine sufferers are affected by structural brain changes. Additionally, studying how the topological characteristics of the brain networks could correspond to the pathophysiology of migraine is important (Lerch *et al*., 2006; Power *et al.*, 2010).

Graph theory can visually represent the brain network architecture and provides a valuable method for assessing the architecture of large-scale brain networks. This is done by calculating a summary of connectivity matrices that describe the network's properties (Wang *et al*., 2020). The above technique sheds new light on the mechanisms of neurological disorders and helps in the discovery of new imaging biomarkers for neurological disease diagnosis.

We hypothesize that migraine could affect the amount of grey matter in the brain. This in turn may alter the structural network connection between different areas of the brain leading to changes in network topological properties in the brains of migraine sufferers. Therefore, analyzing structural brain MRI images using graph theory to identify key differences of network attributes of those with migraine could significantly benefit its diagnosis. However, these studies are largely absent.

MATERIALS AND METHODS

Subjects

This study was conducted on 45 chronic migraine patients (35 females; 39.69 ± 11.1 years) and 46 healthy controls (28 females; 37.57 ± 12.12 years). The most appropriate research design was a case - control study. The study was approved by the Ethics Review Committee of the Faculty of Medicine, General Sir John Kotelawala Defence University (KDU), Sri Lanka and in accordance with the current version of the Declaration of Helsinki (World Medical Association, 2001). The patients were chosen from the neurology and neurosurgery unit of the University Hospital, KDU, and confirmed as migraine subjects (interictal phase) by skilled consultant neurologists using the International Classification of headache disorders criteria (ICHD-3) and a neurological examination. The imaging data were obtained from the MR imaging database of the Department of Radiology, University Hospital, KDU. The control group with healthy brains were selected by an experienced radiologist from the same database who underwent MRI scans of brains and confirmed them as healthy. All subjects were above 18 years of age.

Magnetic resonance image acquisition

Brain MRI scans were performed by a 3 Tesla scanner (Ingenia, Philips Healthcare, The Netherlands), using an 8-channel head coil. The following parameters were used in a turbo field echo (TFE) sequence to obtain three-dimensional (3D), T1-weighted images: repetition time (TR) = 8.2 ms; echo time (TE) = 3.8 ms; TFE factor = 150; flip angle (FA) = 8°; the field of view (FOV) = 240 mm × 240 mm; matrix = 240 × 222; slice thickness = 1 mm; gap = 0 mm; Multi-shot mode sagittal slices and acquisition time = 329 s.

Image preprocessing

All images were examined for consistent orientation and pre-processed using the CAT12 and SPM 12 toolboxes. A Spatial Adaptive Non-Local Means filter was used to adjust bias fields, normalize intensity, and eliminate image noise. Skull stripping was done using the adaptive probability region growing (APRG) approach. The preprocessed images were then subjected to VBM analysis using CAT12.

Computing grey matter volumes using voxel-based morphometry (VBM)

Preprocessed images were spatially normalized to the same stereotactic space (Montreal Neurological Institute (MNI) space) and each brain was separated into GM, WM, and CSF tissue classes. Spatial smoothing was applied to the modulated GM volume images of each subject utilizing an isotropic Gaussian kernel with an 8-mm full-width at half-maximum width (FWHM).

Grey matter network construction

Smoothed grey matter volumes were concatenated to develop 4D volumes for each group. The GRETNA toolkit was used to develop brain structural networks and global network topology metrics. The entire brain was parcellated into 90 cortical and subcortical anatomical regions using an automated anatomical labeling (AAL) atlas excluding the cerebellum. Then the time courses were extracted from each anatomical region and averaged. Group level association matrices were then developed using Pearson correlation with a size of 90 x 90. In these matrices, nodes represent brain regions and edges represent brain connectivity.

Network metrics computation

Binary adjacency matrices were developed (undirected graph), where an edge is drawn between two regional nodes if the Pearson correlation coefficient between them exceeds the threshold. We then systematically explored the properties of the graphs over a range of thresholds based on network sparsity resulting in fully connected small world graphs. This thresholding procedure was repeated for a series of thresholds ranging from 0.05 to 0.5 with an increment step of 0.05, resulting in 10 sparsity thresholds. We used the GRETNA toolkit to compute global network topological metrics such as small-worldness, global efficiency, local efficiency, assortativity, synchronization and hierarchy. Above metrics were compared with those of random networks to determine their level non-randomness.

Statistical analysis

The gender ratio was compared using the Pearson chi-square test while the differences in age were analyzed using the two-sample t-test.

The two-sample t-test between groups was performed to detect the differences in grey matter volumes. Next, the statistical significance of between-group differences in the global network measures was determined using a non-parametric permutation test with 1000 iterations. For each randomly assigned group, an association matrix was created. The correlation matrices were then thresholded at different network sparsities to create the binary adjacency matrices. The network metrics were computed for each network at every density. A permutation distribution of differences was created under the null hypothesis. The actual between-group difference in network metrics was then placed in the corresponding permutation distribution and its percentile position was used to compute a two-tailed p value. Multiple comparisons were automatically taken into consideration by the nonparametric permutation test ($P < 0.05$) (Bruno, Hosseini, & Kesler, 2012).

Image processing steps are shown in Figure 1.

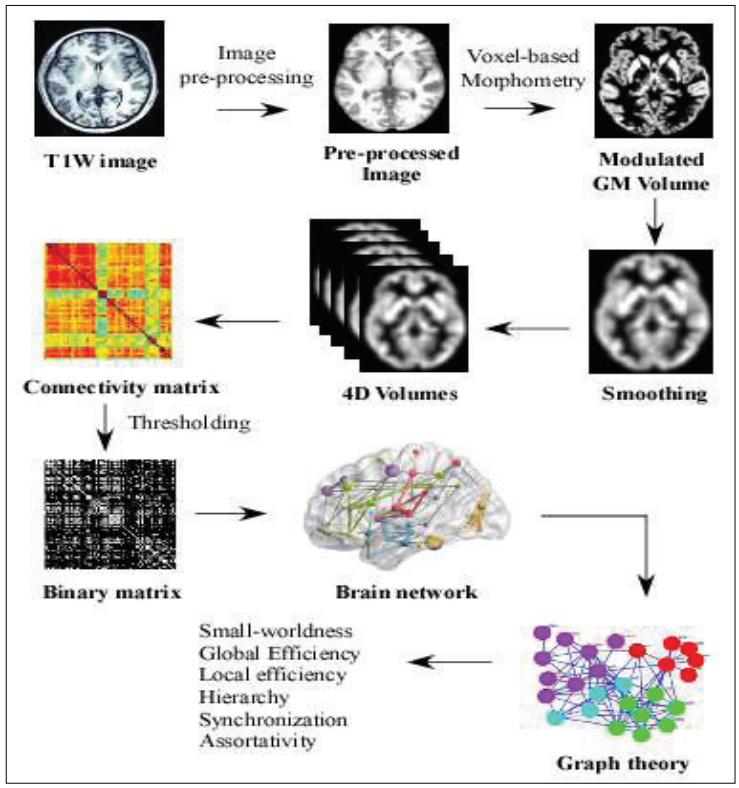

Figure 1: Schematic diagram of image pre-processing, brain network construction, and graph theoretical analysis using structural MRI data.

RESULTS AND DISCUSSION

Demographic data

No significant differences were detected in age (two sample t test, p=0.51) or gender (Chi-square test, p=0.07) between patients with migraines and healthy subjects.

Grey matter volume changes detected between patients with migraine and healthy subjects

Widespread reductions in grey matter volume were found in migraine patients compared to healthy subjects covering both hemispheres. The results are shown in Figure 2 and summarized in supplemental Table 1.

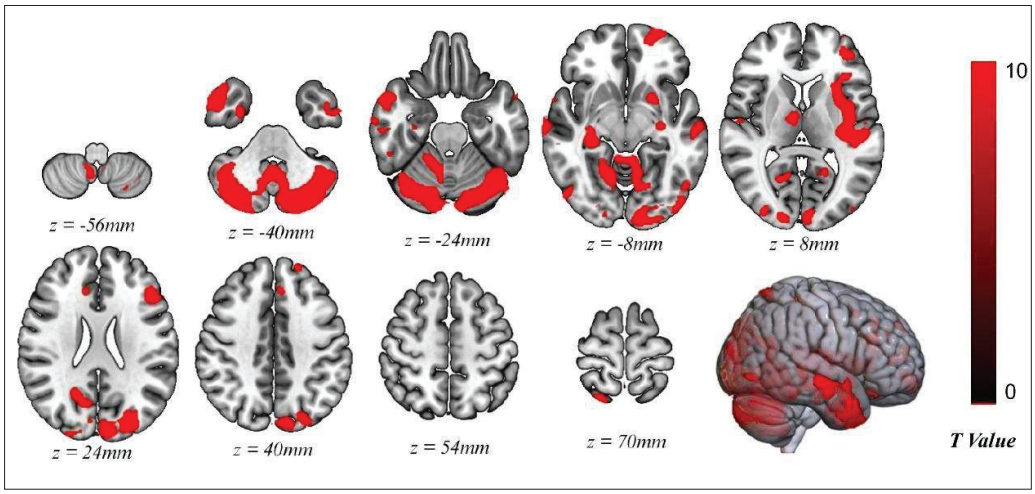

Figure 2: Regional gross volume reductions in patients with migraine compared to healthy subjects detected by Voxel-based morphometry. All detected areas, indicated in black to red (corresponding to T values obtained from two-sample t tests) had reduced volumes in patients with migraine compared with healthy subjects ($p < 0.05$, FWE corrected).

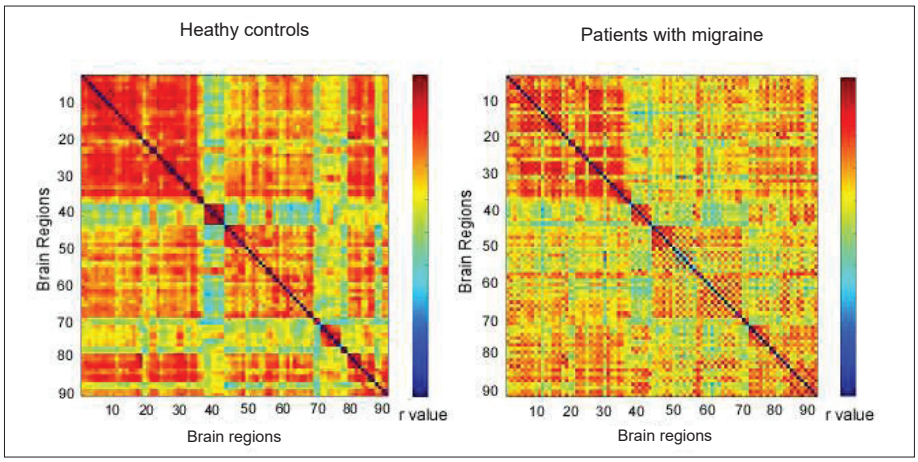

Figure 3: Pearson correlation-based association matrices of patients with migraine and healthy subjects. Each association matrix is composed of 90 x 90 edges. The grey matter (GM) regions of interest (ROIs) that were used in the research are denoted by the numbers 1 to 90 on the x- and y-axes. Correlation represents the strength of the structural connectivity (correlation coefficient, r) for each edge connection.

Bilateral reductions in grey matter volume were found in the cerebellum, middle occipital gyrus, middle temporal gyrus, superior occipital gyrus, cuneus and parahippocampus. In addition, unilateral GM reductions were found in the right fusiform, left insula, right hippocampus, and left superior frontal regions.

Comparison of structural connectivity matrices between healthy subjects and migraine patients

The association matrices within each group, without applying the threshold, are shown in Figure 3. In comparison to the correlation coefficient matrix of healthy subjects, the matrix belonging to migraineurs shows a more diverse distribution and has fewer condensed areas likely due to a lower number of edges.

Global network measures (within-group)

Figure 4 shows the analysis results of global network measures across various network sparsities. Across a wide range of sparsities, the networks of both groups were organized in a small-worldness pattern ($\sigma>1$, $\lambda\sim1$, $\gamma>1$). Compared with patients, healthy subjects exhibited less small-worldness (σ) (Figure 4a) and a less normalized clustering coefficient (γ) (Figure 4c). However, migraine patients had a decreased normalized characteristic path length (λ) (Figure 4b).

Both global efficiency (Eglob) (Figure 4d) and local efficiency (Eloc) (Figure 4e) showed a positive relationship with network sparsity threshold values. Local efficiencies of patients with migraine and healthy subjects were similar in all sparsities than global efficiencies. The assortativity values (Figure 4f) of the healthy were higher than the migraine patients from 0.25 to 0.5 network sparsity thresholds. Therefore, at high sparsities, the linking rate of nodes with similar number of edges was lower in migraine patients. Due to the indecisive data points, it was difficult to determine a relationship or clear separation between migraine patients and healthy subjects for synchronization (Figure 4g). Hierarchical organizations of migraine patients (Figure 4h) were found to be greater than those of healthy subjects at higher network sparsities and showed a positive correlation with network sparsities.

Global network measures (between-groups)

The grey matter networks of migraine brains had significantly more normalized clustering (γ) at sparsities ranging from 0.2 to 0.5 ($p< 0.05$; Figure 5c) when compared to the healthy subjects. The healthy network exhibited an overall tendency towards longer normalized path lengths (λ) with significant differences from 0.05 to 0.5, with the exception of 0.1 across the whole range of sparsities ($p< 0.05$; Figure 5b). Except 0.15 and 0.05, this pattern resulted in a substantially higher small-worldness (σ) in the migraineurs than the healthy network sparsities from 0.1 to 0.5. (Figure 5a).

Patients with migraine exhibited significantly higher global efficiency (Eglob) in their network compared to healthy controls across sparsities ranging from 0.05 to 0.5, except for 0.4. ($p< 0.05$; Figure 5d). Across the entire range of sparsities, we did not detect significant differences in migraine for local efficiency (Eloc), ($p< 0.05$; Figure 5e) and the reported differences were distributed for both reduced and increased local efficiencies.

Assortativity values were largely dispersed among their sparsities and were considerably higher in the healthy network than in the migraine network at sparsities of 0.4 and 0.5 ($p> 0.05$; Figure 5f).

There was no clear comparison in the synchronization of patients with migraine and healthy networks as the values were distributed within the confidence intervals at all levels of sparsities (Figure 5g). With increasing sparsity, the 95% CI boundaries showed a near-random behavior. This made it difficult for a reliable prediction for the identification of migraine patients based on synchronization properties.

There was a significant hierarchical network organization in migraine grey matter networks with network sparsity values ranging from 0.4 to 0.5 ($p< 0.05$; Figure 5h). Therefore, as sparsity increases, there is a strong tendency to surpass the confidence interval for the hierarchical property.

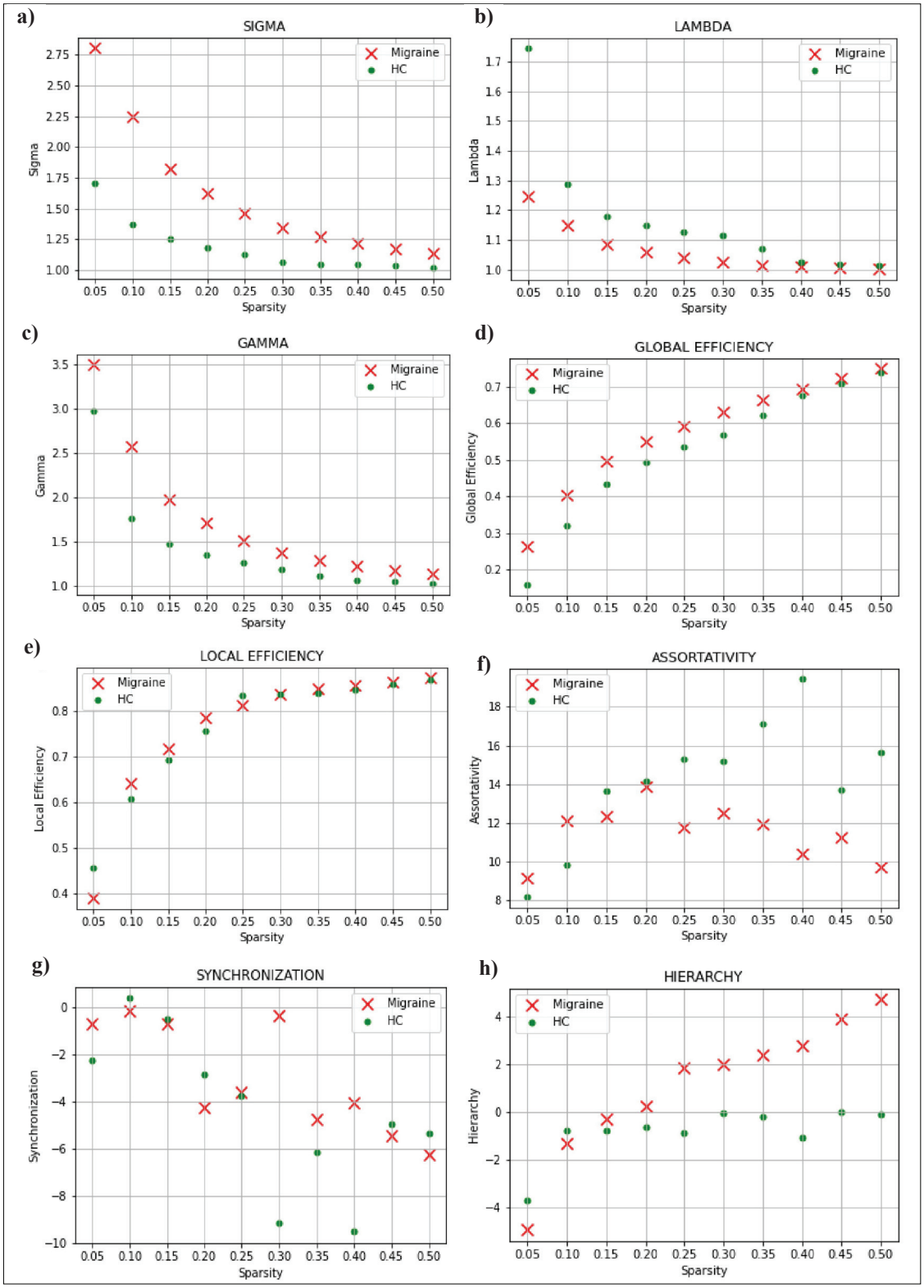

Figure 4: Changes in global network metrics of the patients with migraine and healthy subjects as a function of network density (0.05 – 0.5). (a) Small-worldness; (b) normalized path length; (c) normalized clustering coefficient; (d) global efficiency; (e) local efficiency; (f) assortativity; (g) synchronization and (h) hierarchy.

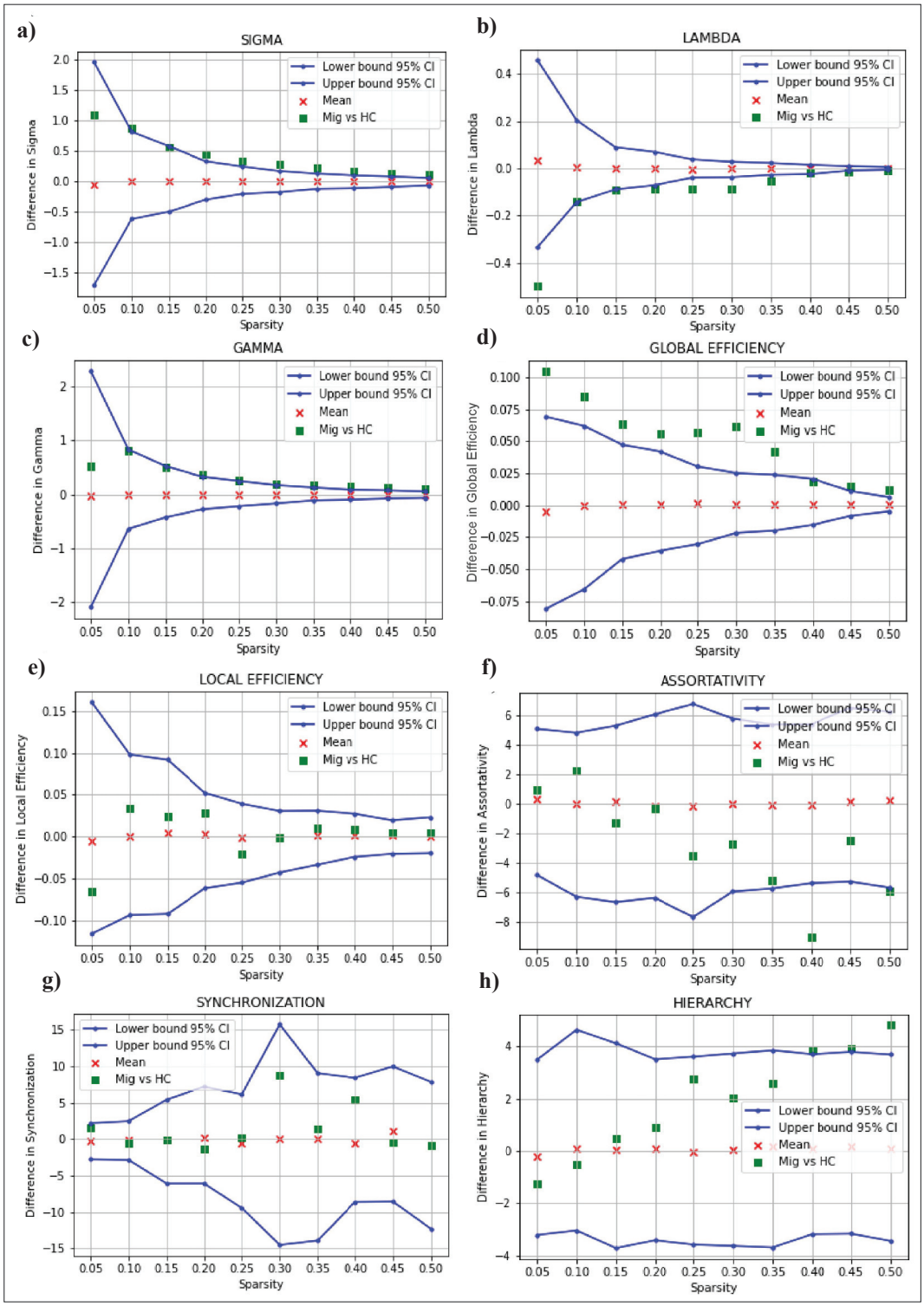

Figure 5: Differences in global network metrics between patients with migraine and healthy subjects as a function of network density (0.05 – 0.5). Between group differences are given in green squares and values that fall outside the confidence interval (blue lines, 95% confidence intervals) denote the densities at which the difference between the groups is significant. Positive numbers denote densities where patients' values are higher than healthy subjects' values, while negative values denote the reverse.

A comparison of grey matter between patients and healthy subjects revealed widespread reductions in grey matter volume. Grey matter volume reductions which were detected in our study include cerebellum, middle occipital, middle temporal, superior occipital, cuneus, and parahippocampus. These reductions have been reported in previous studies to varying extents (Valfrè *et al*., 2007, Coppola *et al*., 2017). However, compared to most of the literature our study reported several reductions in regional grey matter volume reductions unilaterally. These reductions were observed in the right fusiform, left insula, right hippocampus, right thalamus and left superior frontal regions (Cao *et al*., 2022).

To our knowledge this would be the first study to compare the highest number of brain network metrics in the same study. The small-world property provides a structural substrate for both functional segregation and functional integration, which is the ratio of normalized clustering coefficient (γ) to normalized characteristic path length (λ) (Watts & Strogatz, 1998). If a network has a higher clustering tendency, it indicates a strong connection or exchange of information between a node and its neighbours. If a network has a long path length it means that information processing is delayed.

A study has been conducted to determine hierarchical changes of brain structural and functional networks using female migraine patients (Liu *et al*., 2012). It was found that the global topology of the patients' structural and functional networks was aberrant compared to that of healthy subjects. There were greater mean clustering coefficients but no appreciable change in the shortest absolute path length. The small-world properties of grey matter volume correlation networks showed a numerically higher small-worldness in patients in, similar to our findings. In some studies migraine patients scored higher on cognitive tests than non-migraine patients (Wen *et al*., 2016).

Local efficiency, also known as segregation, measures the efficiency of information exchange between adjacent nodes. It is calculated as the average nodal efficiency of all nodes in the graph considering only the neighboring node point and always excluding the node of interest (Cohen & D'Esposito, 2016). Global efficiency, or integration, measures the brain network's ability to transfer information among all nodes (parallel information transmission). It has been found that patients with chronic migraine had altered global network properties characterized by lower global and local efficiency (DeSouza *et al*., 2020). In contrast to these findings, the global efficiency was found to be improved in migraineurs in the current study (Wen *et al*., 2016).

It has specifically considered the existence of assortative type networks, which may have a significant effect on the function of networked systems. They are internally dense and externally sparse, maintaining the segregation of information processing (Newman, 2002; Bazinet *et al*., 2023).To our knowledge, no evidence has been found to date regarding assortativity in relation to migraineurs. However, in this study, assortativity values were found to be significantly higher in the healthy network compared to the migraine network at sparsities of 0.4 and 0.5 with p-values less than 0.05. This proves that migraine disrupts the connections of nodes of similar quality in the brain network at those levels of sparsities.

Synchronization measures the likelihood of all nodes fluctuating in the same wave pattern (Xiang *et al*., 2020). It is believed that small world routes and scale-free networks can achieve synchronizability more efficiently than standard graphs, random graphs and ideal constructive schemes (Barahona & Pecora, 2002; Nishikawa *et al*., 2003). Other evidence shows that activity synchronizations between brain regions can play a critical role in cognitive integration and brain function (Varela *et al*., 2001; Vuksanović & Hövel, 2014). However, we did not find changes in synchronization in our study.

Network hierarchy is one of the fundamental characteristics of the brain that demonstrates the hierarchical network structure of the brain. The main feature of a network hierarchy is the high connectivity within a hub's network but with less clustering. This type of network arrangement helps to report relationships among nodes and reduce wiring costs (Ravasz, 2002). Our results show that the hierarchical properties of migraine patients are increased with sparsity, and the values are significant when it reaches higher sparsity values.

Many studies have reported that migraineurs are reported to have the worst cognitive performance. However, it is not surprising that other studies have reported conflicting results, particularly in the interictal phase (Vuralli *et al*., 2018). Therefore, more studies are warranted in the future to conclude on the pathophysiology of migraine at the network level.

There are three limitations to our study. First, the structural covariance network analysis was performed by correlating the grey matter volume across subjects without creating individual matrices for each subject. Second, we were unable to detect any associations between network measures and clinical parameters because we developed metrics at the group level network. Third, the study was retrospective and therefore we were unable to provide clinical data of patients.

CONCLUSION

In summary, when compared to healthy subjects, the migraine group showed an altered network topology in the brain. This was characterized by an increase in small-worldness and global efficiency (integration) as well as a decreasing assortativity (segregation). These changes may alter functional demands in the brain of migraineurs' leading to distinct profiles of cooperative and competitive connections that underlie various different aspects of sensory, cognitive, and affective comorbidities.

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