Structural Brain Network Characteristics in Patients With Episodic and Chronic Migraine

Lars Michels (lars.michels@usz.ch)
University Hospital Zurich

Nabin Koirala
Haskins Laboratories Inc https://orcid.org/0000-0002-8261-8271

Sergiu Groppa
Johannes Gutenberg University: Johannes Gutenberg Universitat Mainz

Roger Luechinger
University of Zurich

Andreas R Gantenbein
RehaClinic Bad Zurzach

Peter S Sandor
University of Zurich

Spyros Kollias
University hospital Zurich

Franz Riederer
University of Zurich

Muthuraman Muthuraman
Johannes Gutenberg University

Research article

Keywords: migraine, episodic, chronic, graph theory, connectivity

Posted Date: November 9th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-100065/v1

Version of Record: A version of this preprint was published on March 3rd, 2021. See the published version at https://doi.org/10.1186/s10194-021-01216-8.

Abstract

***Background**:* Migraine is a primary headache disorder that can be classified into an episodic (EM) and a chronic form (CM). Network analysis within the graph-theoretical framework based on connectivity patterns provides an approach to observe large-scale structural integrity. We test the hypothesis that migraineurs are characterized by a segregated network.

***Methods**:* 19 healthy controls (HC), 17 EM patients and 12 CM patients were included. Cortical thickness and subcortical volumes were computed, and topology was analyzed using a graph theory analytical framework and network-based statistics. We further used support vector machines regression (SVR) to identify whether these network measures were able to predict clinical parameters.

***Results**:* Network based statistics revealed significantly lower interregional connectivity strength between anatomical compartments including the fronto-temporal, parietal and visual areas in EM and CM when compared to HC. Higher assortativity was seen in both patients' group, with higher modularity for CM and higher transitivity for EM compared to HC. For subcortical networks, higher assortativity and transitivity were observed for both patients' group with higher modularity for CM. SVR revealed that network measures could robustly predict clinical parameters for migraineurs.

***Conclusion**:* We found global network disruption for EM and CM indicated by highly segregated network in migraine patients compared to HC. Higher modularity but lower clustering coefficient in CM is suggestive of more segregation in this group compared to EM. The presence of a segregated network could be a sign of maladaptive reorganization of headache related brain circuits, leading to migraine attacks or secondary alterations to pain.

1. Introduction

Migraine is a multifactorial neurovascular disorder which affects about 12% of the general population (1) and rates among the most disabling diseases (2, 3). In the episodic form of migraine (EM), headache occurs on average less than 15 days per month, whereas in the chronic form (CM), it occurs on 15 or more 15 days per month for at least three consecutive months. Functional neuroimaging studies identified pathophysiological changes in cortical and subcortical regions in patients with migraine (4–10). Using, resting-state functional magnetic resonance imaging (rs-fMRI) signal correlations, stronger connectivity between the periaqueductal gray matter, a known modulator of somatic pain transmission, and several brain areas within nociceptive and somatosensory processing pathways was seen in migraineurs *versus* controls (11). However, not only functional but also regional structural impairments have been reported in migraine patients in several studies (12–18). Network analysis using a graph theoretical framework has been extensively used for observing effect of various disorders in brain network integrity. This framework considers brain regions as nodes, and the interrelations between them as edges to form a network (19, 20). The network formation begins with the collection of relational data among elements of a neurobiological system, which may vary from anatomical networks of associations

between morphometry of cortical regions, inter-regional white matter projections, or multi-dimensional time series and their statistical dependencies or causal relations in behavior in social interactions. Once this data is corrected, normalized and assembled into the mathematical form of a graph or network, the common mathematical framework of graph theory is applied to obtain a set of measures to observe different alterations in the network (21). Using the anatomical networks reconstructed using the gray matter volumes (GMV) and functional network using resting-state functional magnetic resonance imaging (rs-fMRI)-correlations, Liu and colleagues demonstrated that network characteristics were disrupted in females with EM (22). From the networks from diffusion tensor imaging (DTI) and rs-fMRI it has been shown that CM exhibited altered rich club organization (higher connection density, abnormal small-world organization with increased global efficiency) compared to healthy controls (HC). It was further concluded that the higher 'bridgeness' in patients with non-rich club regions might increase the integration among pain-related brain circuits with more excitability but less inhibition for the modulation of migraine (23). In summary, the graph theory findings indicate that migraineurs lose structural network integrity, most likely seen as maladaptive integration among pain-related brain circuits, resulting in a disturbed balance of neuronal excitation and inhibition. Yet, a systematic comparison of structural morphometric measures complimented with the brain network analysis has not been performed between patients with low (EM) and high (CM) occurrence of monthly migraine attacks. We thus examined cortical and subcortical morphometric changes leading to brain network reorganization in both patients with EM and CM relative to HC. Based on extant findings, we hypothesize to see the strongest global structural network alterations, seen as dis-integrated networks in patients with CM compared to HC and EM.

2. Methods

2.1 Design and study duration.

This is the primary analysis of the reported data using a cross-sectional design. Other imaging data (MR spectroscopy and Arterial Spin Labeling MR imaging) have been collected for all participants and results are presented elsewhere (24). No statistical power calculation was conducted prior to the study. The sample size was based on the available data (during the study interval) and was similar to a recent ASL study in episodic migraine patients (25). All data was collected between December 2013 and July 2015.

2.2 Participants

19 right-handed HC, 17 right-handed patients with EM and 12 patients with CM were included for the study. The detailed demographic data are listed in Table 1. All patients fulfilled the modified ICHD-II diagnostic criteria for EM or CM (26). None of the HC demonstrated signs of EM or CM according to these criteria (family history of migraine was allowed). For all participants, exclusion criteria were severe psychiatric disorders, cardiac problems (e.g. severe hypertension) or other neurologic disorders such as epilepsy, stroke, traumatic brain injury, neck injury or cerebrovascular disease. All participants completed prospective headache diaries, the Migraine Disability Assessment (MIDAS) (27) and Hamilton Anxiety (HADS-A) and Depression (HADS-D) Score (28) questionnaires. Acute and prophylactic medication was

recorded prior to the study interval. Apart from migraine occurrence (days/month), we recorded aura occurrence. Patients were free from migraine attacks at least 48 hours before and after the scan. The study was approved by the ethics committee of canton Zurich (KEK number E-37/2007), Switzerland. All subjects provided written informed consent prior to study enrolment. Both groups received 50 Swiss Francs reimbursement for their study participation. Patients were recruited by advertisement (Intranet of the Hospital and mailing lists) and word-of-mouth.

Table 1
Demographic details of the subjects in the study. * We found no significant difference ($p > 0.05$) in age and sex between the groups: EM - HC, CM - HC and EM – CM (unpaired t-tests and Chi-Square test, respectively). MIDAS values in days. EM: episodic migraine, CM: chronic migraine, HC: healthy controls, F: female, M: male.

Group	N	Age (years)*	Sex*	MIDAS	HADS - A	HADS - D	Headache attacks / month
EM	17	32.7 ± 9.9	F = 13, M = 4	19.65 ± 20.61	5.3 ± 3.9	3.4 ± 2.6	4.0 ± 3.8
CM	12	38.19 ± 16.15	F = 8, M = 4	55.50 ± 12.76	5 ± 3.46	4.67 ± 2.96	18.50 ± 4.25
HC	19	31.7 ± 9.2	F = 10, M = 9	N/A	3.4 ± 2.3	1.3 ± 1.2	N/A
EM/CM with aura	12EM/5CM	35.68 ± 13.15	F = 12, M = 5	30.47 ± 28.32	5.11 ± 3.55	3.88 ± 2.69	8.64 ± 8.71

2.3 Data acquisition

Whole-brain magnetic resonance imaging (MRI) was performed on a 3T scanner (Philips Ingenia, Netherlands) with a 32-channel receive-only head coil at the Neuroimaging Center of the University Hospital Zurich. 3D T1-weighted magnetization prepared rapid gradient echo (MPRAGE) sequence was acquired for each subject with TE/TI/TR = 2.52/900/1900 ms, flip angle = x°, field of view (FOV) = 256 × 256 mm^2, matrix size = 256 × 256, slab thickness = 192 mm, voxel size = 1 × 1 × 1 mm^3. Subjects' scans were examined for any major anatomical abnormalities by an experienced neuroradiologist.

2.4 Data analysis

2.4.1 Cortical and subcortical morphometric analysis

Data from all subjects were analyzed using FreeSurfer version 5.3.0 (http://surfer.nmr.mgh.harvard.edu). This automated anatomic parcellation procedure enables one to extract reliable estimates of various cortical and subcortical measures including thickness, volume, area, curvature etc. (29). The procedure includes several steps: intensity normalization, skull stripping, Talairach transformation, and atlas-based assignment of neuro-anatomical labels, which are described in details in previous studies (30, 31). Here, we computed the cortical thickness (CT) and subcortical volumes for the all the subjects and used it for further network and statistical analysis.

2.4.2 Brain network analysis

Graph theoretical measures of network modularity, distance, and local information transfer was computed using the CT and subcortical volumes obtained from FreeSurfer using Brain Connectivity Toolbox (32) (https://sites.google.com/site/bctnet/). The group level correlations between the cortical regions and subcortical volumes and the differences between them were then computed in different network densities for observing the steady topological changes (33, 34). The details of the analysis have been explained elsewhere (35, 36).

Among different measures computed in the study, below is the brief overview of those relevant for the study, with simplistic illustration in Fig. 1.

a. Modularity is a measure of the degree, to which the network is subdivided into densely interconnected nodes (modules) with sparse connections to other network or modules. Louvain algorithm was used for computing the modularity which is a hierarchical clustering algorithm, that recursively merges communities into a single node and executes the modularity (37).
b. Transitivity is the ratio between the number of triangles and the number of triplets in the graph.
c. Assortativity is correlation coefficient between the degrees of all nodes on two opposite ends of a link, higher (positive) assortativity indicating the nodes tend to link to other nodes with the same or similar degree.
d. Clustering coefficient is the fraction of triangles around a node representing the node's neighbors that are also neighbors of each other.
e. Betweenness centrality of a node is the fraction of all shortest paths in the network that contain a given node. A node with higher edge-betweenness centrality participates in a large number of shortest paths.

In addition, network-based statistic (NBS) was used to assess differences in the inter-regional connectivity between the groups. NBS analysis performs the mass-univariate testing at every connection comprising the graph controlling for multiple comparisons through evaluating the null hypothesis at the level of interconnected subnetworks rather than individual connections (38). Here, the connectivity matrices obtained from the association of CT between the regions across a range of network densities were subjected to NBS analysis. The analysis primary goal was to identify the sub-network with the

regions shown to have significant difference in various network properties using graph theoretical measures. Further details regarding the procedure are mentioned elsewhere (39, 40).

2.4.3 Statistical analysis

For the graph theoretical framework analysis, we used the CT values of a network comprising 34 cortical regions in each hemisphere based on Desikan atlas (41). Subsequently, we used the sub-cortical volumes from nine regions in each hemisphere and brain stem for the sub-cortical network. For assessing the statistical significance of graph metrics between patients and HC, a nonparametric permutation tests with 5000 iterations were applied (42, 43). In each repetition, the regional data for each subject were randomly reassigned to one of the two groups and an association matrix was obtained. The network measures were then calculated for all the networks at each density. Here, density represents cost of the network computed by fraction of present connections to all possible connections. Hence, the network measures derived at each density would specify the alterations in network behavior at different levels of fragmentation (from full, partial to discontinuous connectivity). This method of thresholding ensures that all the regions (nodes) of the network are connected while discarding spurious connections (edges) (33, 44). The actual between-group difference in network measures was then placed in the corresponding permutation distribution and a two-tailed p-value (at 5% significance level, false discovery rate (FDR) corrected) was calculated based on its percentile position (45).

To assess the statistical significance for CT correlations with different clinical parameters, QDEC – a FreeSurfer statistical toolbox was used. Here, surface maps depicting regions with significant differences in the correlation with CT at each vertex were determined with general linear models (GLMs) using $p < 0.001$ as the threshold for a significant cluster. In addition, we further performed the GLM analysis to observe the association between the CT change and different clinical scores including HADS-A, HADS-D, hours of sleep and attacks per month.

To validate the significance of these network measures, we further applied support vector machine analysis to predict the clinical scores used in the diagnostic criteria for migraineurs. Here, we performed a support vector regressor (SVR) analysis – representing a machine-learning-based multiple regression method - that could associate the observed and trained values and present the regression coefficient for the accuracy of the prediction (46). The regression coefficient of 0.5 obtained after 10-fold cross validation is considered borderline significant result.

3. Results

3.1 Structural network analysis

We found no significant difference ($p > 0.05$) in age and sex between the groups : EM - HC, CM - HC and EM - CM. Comparing networks obtained using graph theoretical framework between EM and HC, we found significantly ($p < 0.05$, FDR corrected) higher transitivity and assortativity in EM (Fig. 2). We further obtained the centrality measures, namely mean node and edge-betweenness to be higher in EM. For the

contrast ‘CM – HC’, we found significantly higher modularity (and assortativity in CM. We further obtained higher centrality measures (mean node and edge-betweenness) in CM. For the comparison of the networks between two patient groups, we found significantly higher modularity but lower clustering coefficient and transitivity in CM compared to EM.

When comparing similar networks obtained using values of subcortical volumes between EM and HC, we found higher transitivity and assortativity significantly in EM. The comparison CM and HC revealed significantly higher modularity, transitivity and assortativity in CM. All sub-cortical network results are shown in Fig. 3.

Among the regions showing significant regional network difference in terms of clustering, degree and nodal edge-betweenness, NBS further revealed distinct networks with lower interregional connectivity for EM and CM when compared to HC (Fig. 4). For EM, all 20 nodes (regions) showing the graph theory differences formed a network of significantly ($p < 0.05$, corrected) reduced connectivity in comparison to HC. However, for CM, out of 22 nodes (regions) only 19 formed a network of significantly ($p < 0.05$, corrected) reduced connectivity when compared to HC.

Finally, the network measures (assortativity, transitivity and modularity) showing a significant difference between the groups, additionally yielded a significant interrelation for MIDAS and attacks per month for the migraineurs (Fig. 5). Considering all network measures together, the SVR yield MIDAS (across EM and CM) with a regression coefficient of 0.779 and attacks with 0.798. Using only assortativity as network measure, the association for MIDAS and attacks was with a regression coefficient of 0.779 and 0.812, respectively. Similarly, for transitivity – MIDAS it was 0.655 and for transitivity – attacks it was 0.649. Modularity alone could reveal the interrelation to the MIDAS and attacks with regression coefficient of 0.655 and 0.649 respectively.

3.2. CT analysis

All reported CT group-differences and correlations were observed with age and sex as nuisance variables ($p < 0.001$, uncorrected as none of them survived multiple comparison (FDR) correction). Comparing EM to HC (**supp**. Figure 1), average CT was significantly increased in EM in left lateral occipital cortex, supramarginal gyrus as well as in the right insula, lingual gyrus and precuneus. Additionally, the correlation of the average CT with HADS-A was significantly different in right precentral and inferior parietal cortex between EM and HC. Similarly, the correlation of the average CT with HADS-D was significantly different in left lingual gyrus and right supramarginal gyrus as well as the correlation of the average CT with hours of sleep in left superior parietal and right supramarginal gyrus and caudal middle frontal cortex between EM and HC.

The average CT was significantly increased in CM compared to HC in the left insula and posterior cingulate cortex (PCC) and significantly decreased in the bilateral inferior parietal and right lateral occipital cortex (**supp.** Figure 2). Additionally, the correlation of the average CT with HADS-A was significantly different in right caudal anterior cingulate and precentral cortex between CM and HC.

Similarly, the correlation of the average CT with HADS-D was significantly different in left lingual and PCC as well as the right supramarginal gyrus and precuneus between CM and HC. The correlation of the average CT with the hours of sleep differ significantly in left pars opercularis, superior parietal, insula and right lateral occipital and supramarginal gyrus.

The contrast 'EM – CM' (**supp.** Figure 3) revealed significantly decreased average CT in EM in the left insula and significantly increased in right insula-, supramarginal- and postcentral gyrus. Additionally, the correlation of the average CT with HADS-A was significantly different in the bilateral inferior parietal and left superior parietal lobule. Similarly, the correlation of the average CT with HADS-D was significantly dissimilar in left insula between EM and CM. The correlation of the average CT with hours of sleep varied significantly in left superior parietal, insula and right supramarginal, postcentral and insula between EM and CM. Moreover, the correlation of the average CT with headache attacks per month was significantly different in left insula between these groups.

4. Discussion

This study reported group differences in structural networks based on CT between HC, EM, and CM. Significant group differences were found in various graph theory measures and these measures were able to predict the clinical scores MIDAS and migraine attacks per month. Based on the results, we conclude that the impact of migraine severity leads to strong structural impairments and dysfunctional neural network configurations.

4.1 Structural network alterations in migraineurs

Previous studies have reported altered functional connectivity between various regions of the brain in migraineurs. Pituitary adenylate cyclase-activating polypeptide-38 induced migraine was associated with the altered connectivity between the regions in major resting-state networks, such as the salience, sensorimotor and default mode network (DMN) when compared with the placebo group of the patients infused with vasoactive intestinal polypeptide (47). Similarly, for patients with visual-aura during attacks when compared to attack-free state using rs-fMRI, a significant increase in functional connectivity during attacks was found between left pons and left primary somatosensory and the visual area V5 and lower middle frontal gyrus in the symptomatic hemisphere (48). Even more comprehensive analysis, using both GMV and rs-fMRI data for reconstructing structural and functional connectivity, by Liu, Zhao (22) demonstrated that EM showed abnormal global topology in both structural and functional networks, characterized by higher mean clustering coefficients. Even though these findings are noteworthy in aiding to comprehend the pathology, studies investigating structural topological changes, which might have led to these functional alterations and provide a probable explanation of symptoms in different types of migraineurs, are still distant. In our study, EM displayed higher transitivity and assortativity along with the centrality measures than HC, indicative of a shift in the hubs for information transfer in this group. Similarly, higher modularity, assortativity and centrality measures (mean node and edge-betweenness) in CM than in HC furthers indicates the network being more assortative and segregated in CM. This finding

is additionally supported by the fact that CM were found to have significantly higher modularity but lower clustering coefficient and transitivity compared to EM. As the NBS analysis yielded lower interregional connectivity in migraineurs, we conclude that migraineurs display disturbed connections not only in a localized brain area but also between regions of different anatomical compartments including the frontal, temporal, parietal and visual areas.

Importantly, as clinically relevant, we demonstrated the importance of these network measures by being able to interrelate the MIDAS scores and attacks per month for the migraineurs. The interdependence between attack frequency and network measures was highest when using assortativity followed by all network measures (assortativity, transitivity and modularity) together. For MIDAS, using all three measures or the assortativity lead to a similar association. Hence, from these and previous findings we could speculate that there might be as well a transition from episodic to chronic with the intensification of network segregation and assortativity in migraineurs.

4.2 Brain morphometric alterations in migraineurs

Some studies reported CT increases in the somatosensory cortex (49) or higher visual brain regions, including V3A and MT+ (16), whereas others reported decreased CT in migraine patents with medication overuse headache (50) or in EM (51–53). Our results indicate especially the CM showed a thicker CT compared to HC but that both EM and CM showed rather increases in CT, especially in visual brain regions (left occipital cortex, lingual gyrus). This could be related to the high presence of aura in our sample. Yet, Granziera et al., (2006) reported a CT increase in patients with and without aura in higher visual (V3A and MT+) brain regions. The CT increase could index altered excitability of the cortex in EM and even more so in CM. It has been shown that transcranial direct stimulation in EM can lead to reduced number of migraine days, indicating that neuronal excitation can be re-normalized resulting in lower migraine occurrence (54). Our novel finding of differentiating EM and CM, based on association of CT and headache attacks observed in left insula underlines (a) the validity of CT as a structural marker to differentiate migraine subgroups and (b) the role of the salience network in migraine. Recently, using rs-fMRI connectivity EM showed disturbed long-range connectivity from primary sensory regions to higher-order association areas including the DMN and the salience network (55).

5. Limitations

Our group size was moderate, especially for the group of CM patients. Yet, we found a systematic increase in impairment on structural integrity with the presence of migraine attacks, indicating that CM caused the strongest structural abnormalities compared to HC and EM. The findings from CT and subcortical volume analysis were uncorrected which might be because of the moderate sample size. Nonetheless, the results present a significant basis for the network measures observed and gives a more enhanced tool for understanding the migraine pathophysiology.

6. Conclusions

In conclusion, the level of impairment (migraine days per month) was associated with altered GVM but additionally with disturbed structural network integrity. The observation of an under-segregated network, especially in patients with CM, could be a sign of a maladaptive, elevated integration among pain-related brain circuits, leading to more excitability but less inhibition for the modulation of migraine.

List Of Abbreviations

EM Episodic Migraine

CM Chronic Migraine

HC Healthy Controls

SVR Support Vector Regressions

CT Cortical Thickness

fMRI functional magnetic resonance imaging

GMV Grey matter Volume

DTI Diffusion Tensor Imaging

MIDAS Migraine Disability Assessment

HADS-A Hamilton Anxiety Score

HADS-D Hamilton Depression Score

MPRAGE Magnetization Prepared Rapid Gradient Echo

NBS Network Based Statistics

FOV Field of View

DMN Default Mode Network

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of canton Zurich (KEK number E-37/2007), Switzerland. All subjects provided written informed consent prior to study enrolment.

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to patient consent but could be available from the corresponding author on reasonable request and would be decided upon individual basis.

Competing interests

The authors declare that they have no competing interests.

Funding

We greatly appreciate the financial support by the Swiss Headache Society (Hansruedi Isler Forschungsstipendium).

Authors' contributions

Conceived and designed the experiments: LM, FR, AG, SK, SG and PS; performed the experiments: RL, LM, and FR; analyzed the data: LM, NK, MM, FR, wrote the paper: LM, NK, SK, MM, SG, FR.

Acknowledgements

We thank all subjects for the participation in this study. We thank Catharina Fritz-Rochner for help with patient recruitment and data analysis.

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Figures

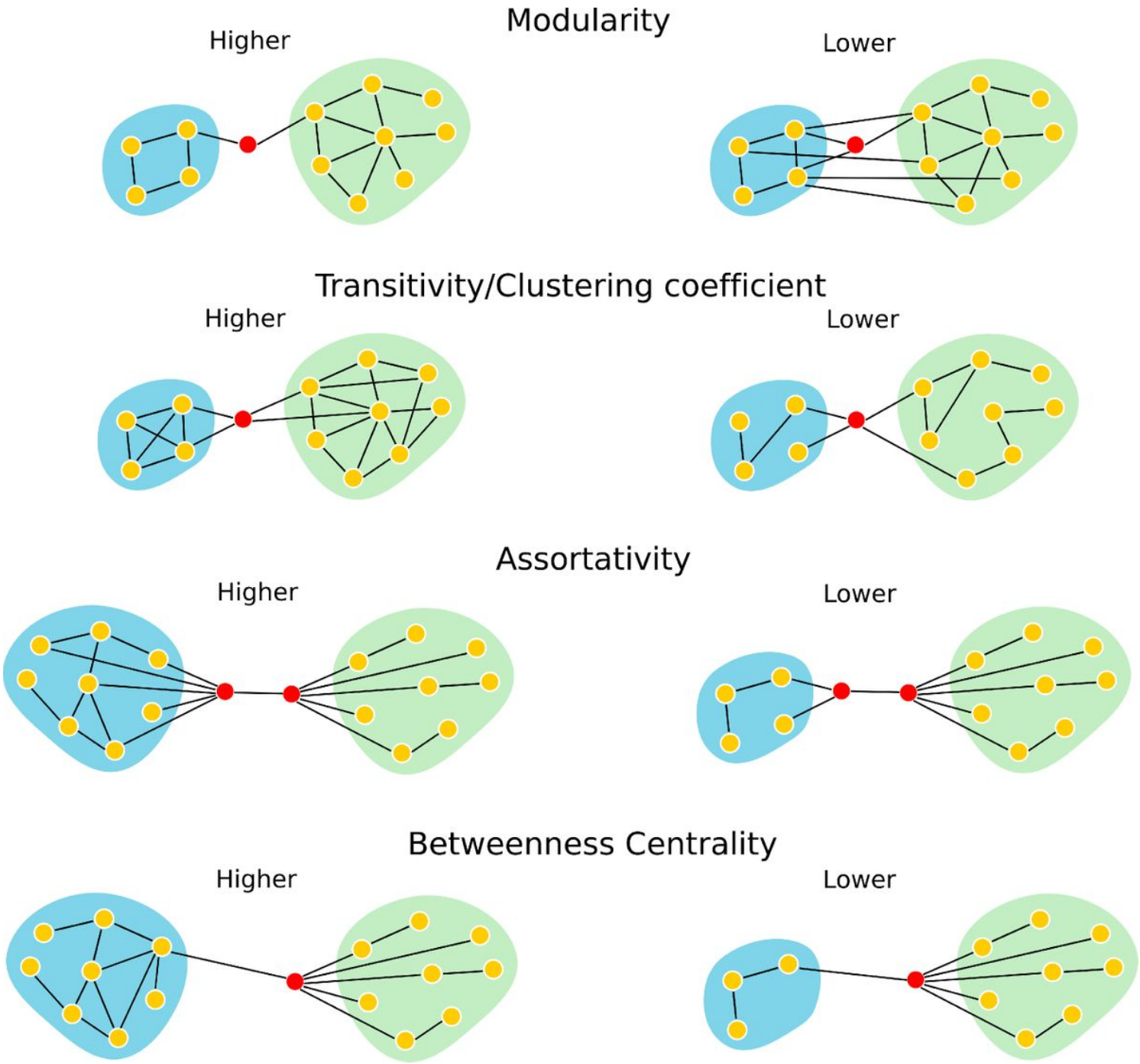

Figure 1

Simplistic illustration of the network measures used in the study. Higher assortativity illustrating the tendency of a high degree node to be connected to another higher degree node; higher transitivity shows the greater number of connections within the module (forming triangles, higher modularity illustrates the reduced inter-module connection between the network, and higher betweenness centrality displays node connecting two networks with large number of within module connections highlighting the importance of this node in the network.

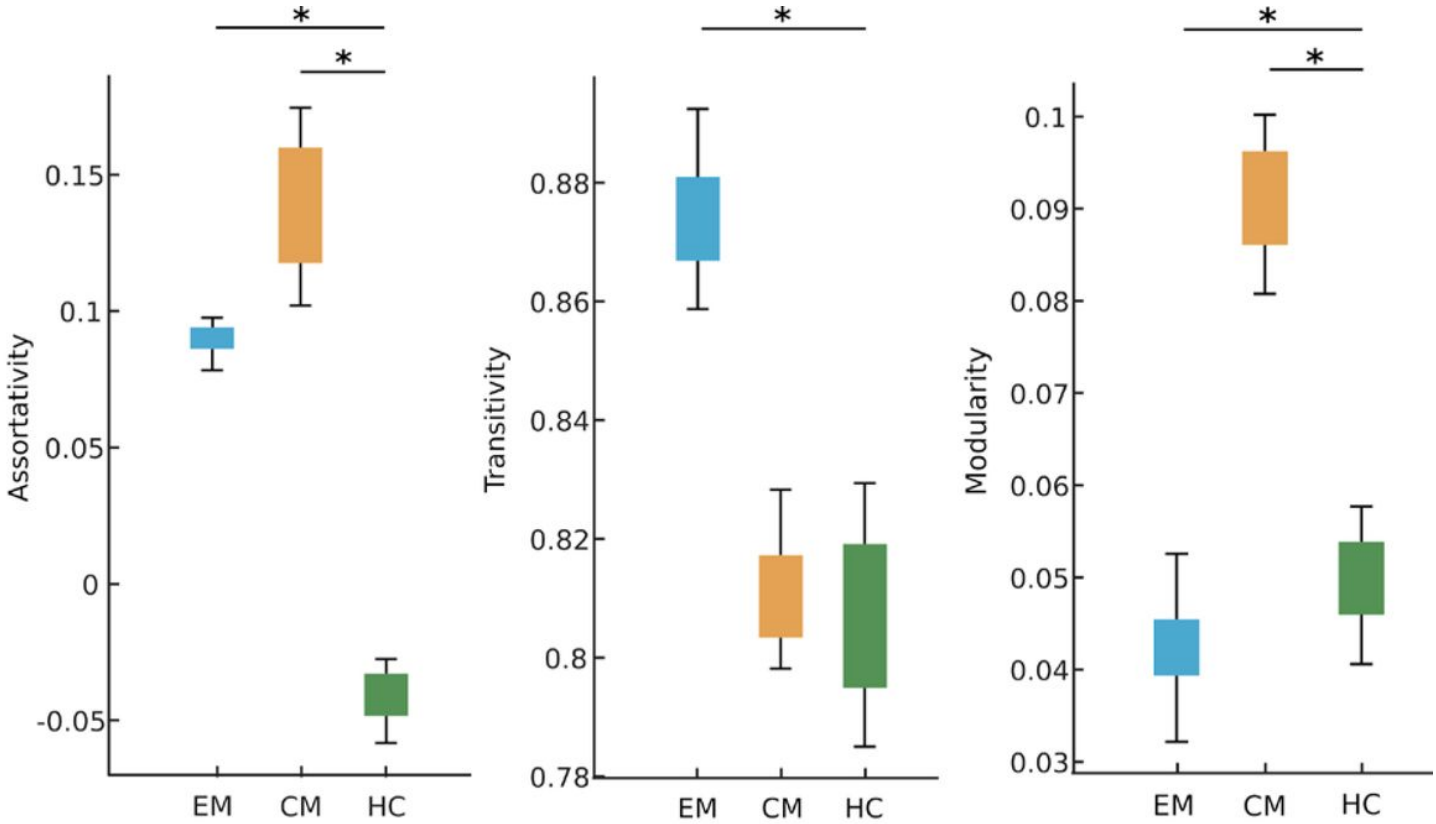

Figure 2

Figure 2

Cortical network results: Plots showing the network measures (assortativity, transitivity and modularity) significantly different between the groups: episodic migraine patients (EM), chronic migraine patients (CM) and healthy controls (HC) obtained using CT. * indicates significant group differences at $p < 0.05$ (FDR corrected).

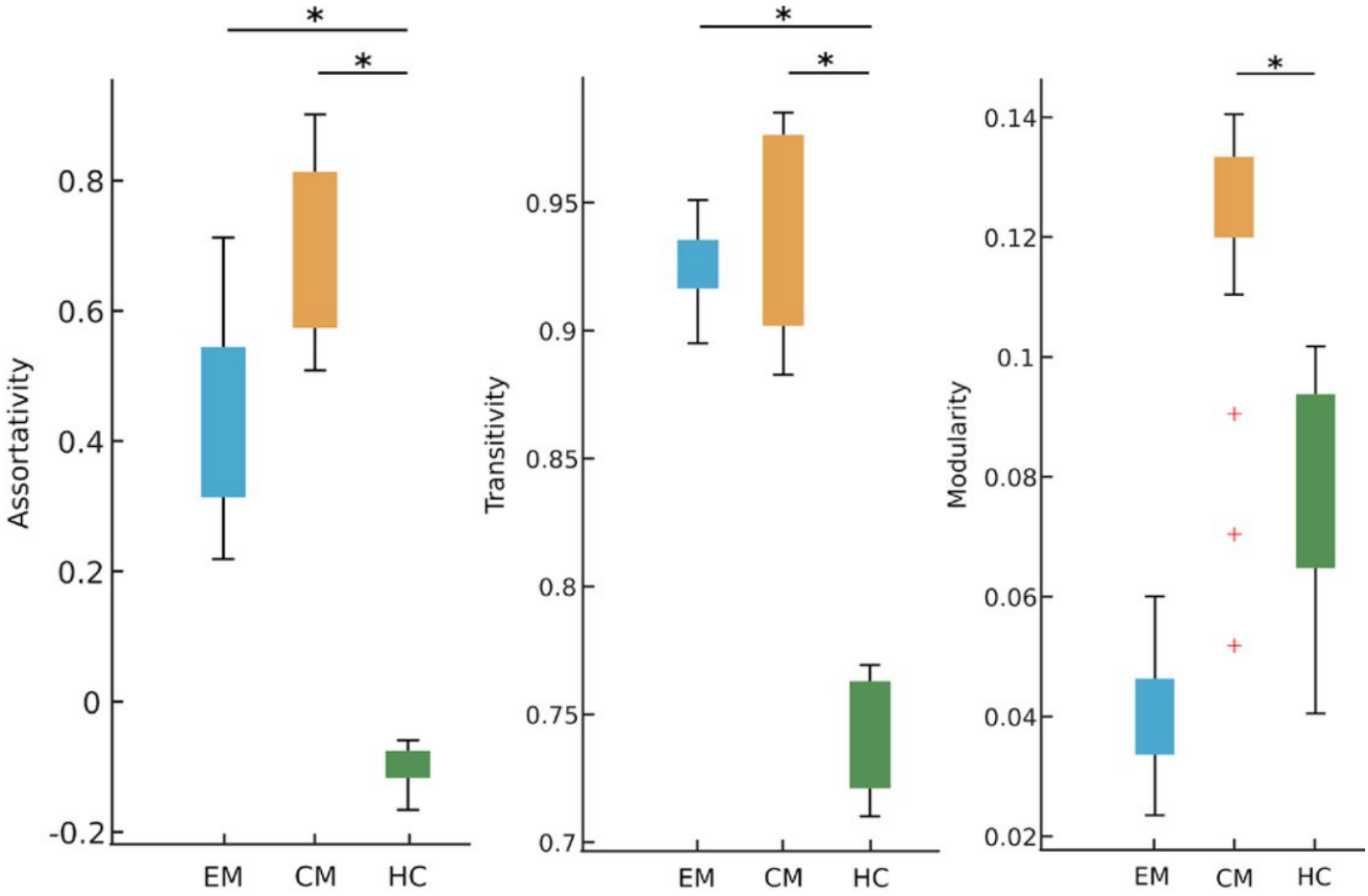

Figure 3.

Figure 3

Sub-cortical network results: Plots showing the network measures (assortativity, transitivity and modularity) significantly different between the groups: episodic migraine patients (EM), chronic migraine patients (CM) and healthy controls (HC) obtained using sub-cortical volumes. * indicates significant group differences at $p < 0.05$ (FDR corrected) and + indicates outliers (i.e. 2 standard deviations from the groups' mean).

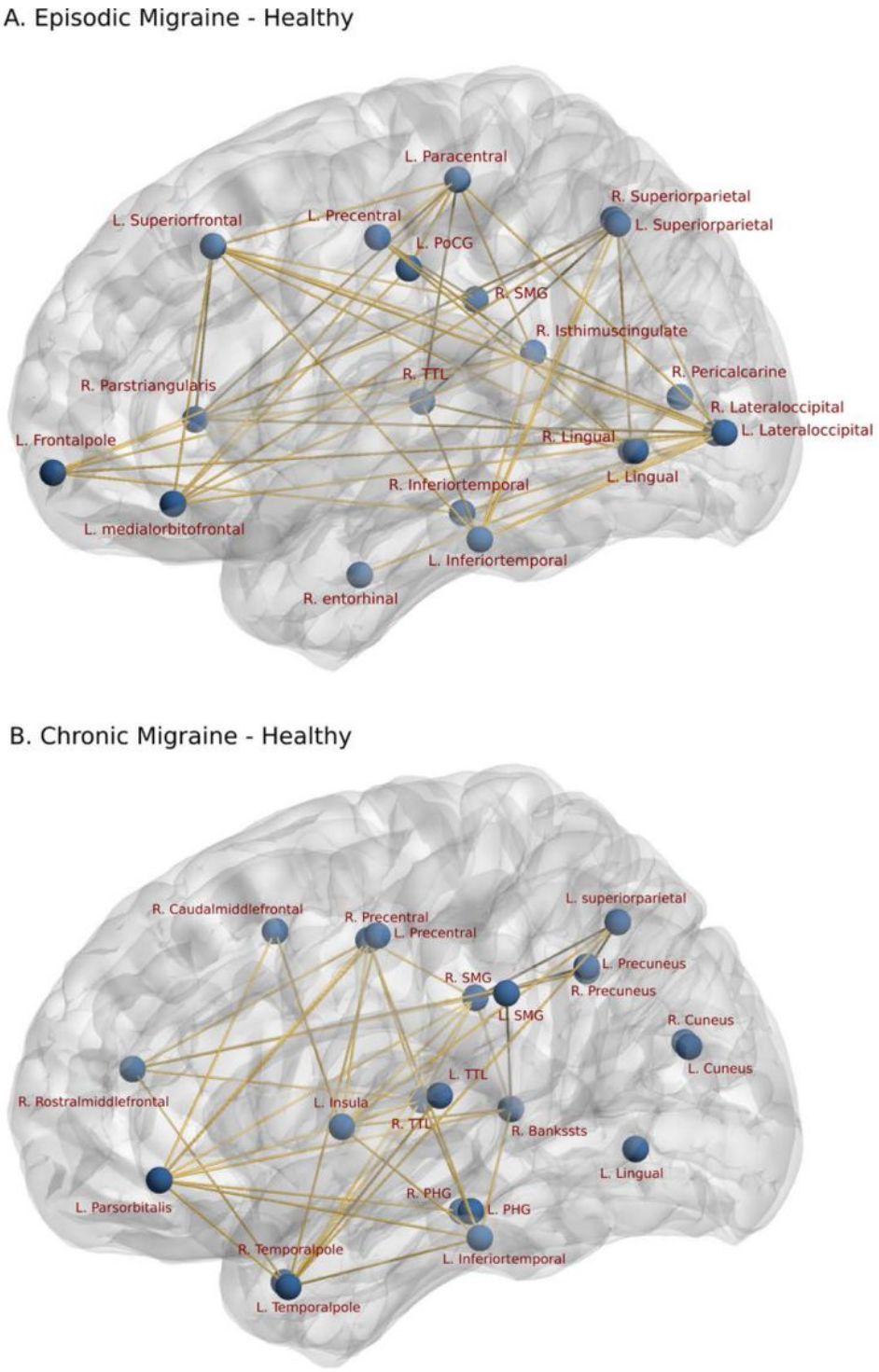

Figure 4.

Figure 4

Network showing significant ($p < 0.05$, corrected) lower structural connectivity in Episodic (A) and Chronic (B) migraine patients in comparison to HC. Abbreviations: PoCG – Posterior cingulate gyrus, TTL – Transverse temporal lobe, PHG – Parahippocampal Gyrus, SMG – Supramarginal Gyrus. L - Left and R – Right hemisphere.

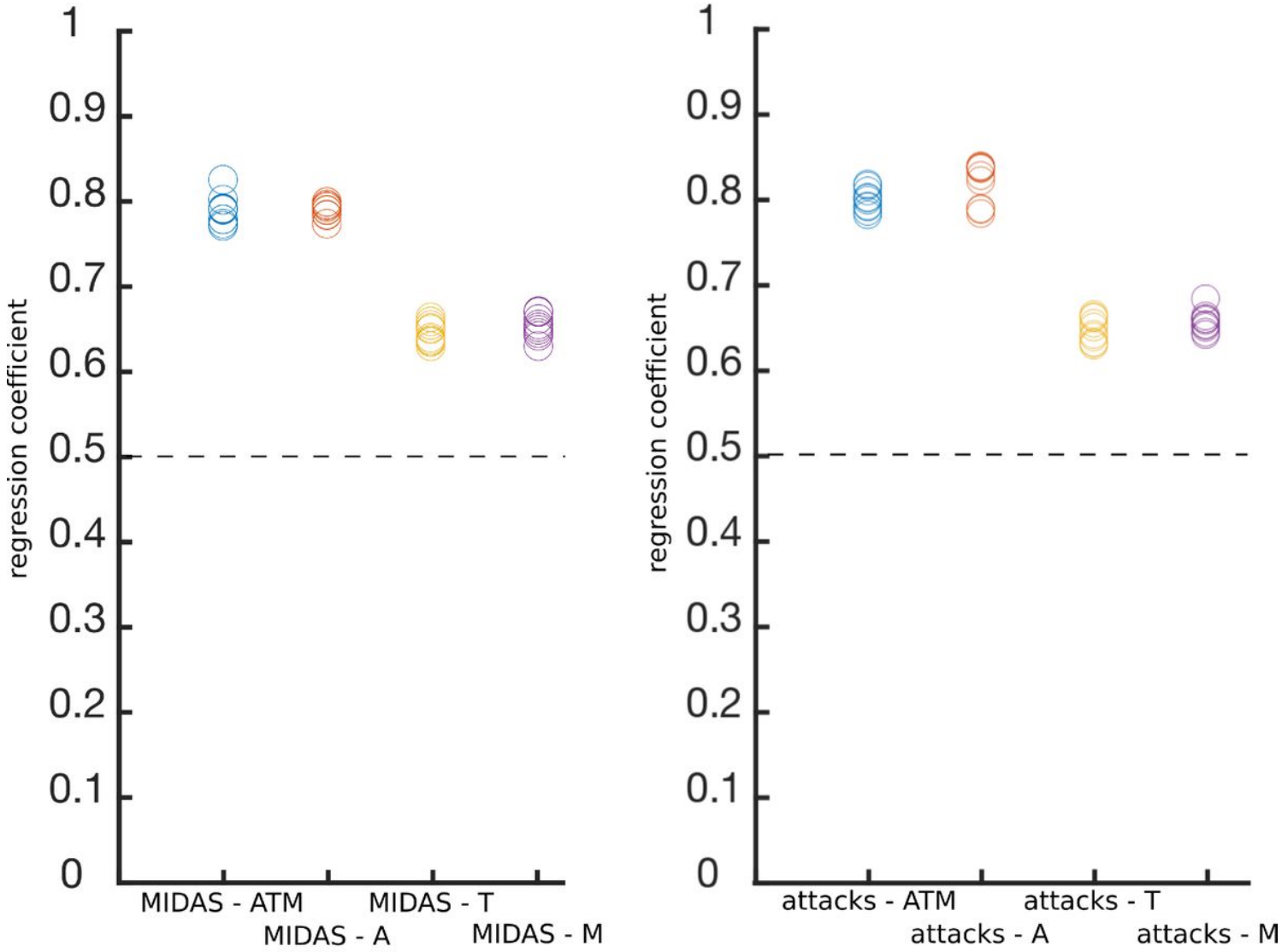

Figure 5

Plots showing the results of the SVR analysis, for predicting MIDAS (left panel) and attacks (right panel) per month using network measures assortativity (A), transitivity (T) and modularity (M). As the cross-validation was performed 10 times, each dot indicates the regression coefficient obtained for each validation. Dots above the dashed line indicate robust ($r \geq 0.5$) correlations. The combination of A, T, and M but also A alone yielded the best results.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SuppTables.docx
- Suppfigure1.pdf

- Suppfigure2.pdf
- Suppfigure3.pdf