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Title: Abnormal Network Topology in Polymicrogyric Cortex may Predispose to Seizures via Abnormal Network Topology: An fMRI Connectomics Study

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Summary

Polymicrogyria is a significant malformation of cortical development with a high incidence of epilepsy and cognitive deficits. Graph theoretic analysis is a useful approach to studying network organisation in brain disorders. In this study, we used task-free functional magnetic resonance imaging (fMRI) data from four patients with polymicrogyria and refractory epilepsy. Grey matter masks from structural MRI data were parcellated into 1024 network nodes. Functional ‘connectomes' were obtained based on fMRI time series between the parcellated network nodes; network analysis was conducted using clustering coefficient, path length, node degree and participation coefficient. These graph metrics were compared between nodes within polymicrogyric cortex and normal brain tissue in contralateral homologous cortical regions. Polymicrogyric nodes showed significantly increased clustering coefficient and characteristic path length. This is the first study using functional connectivity analysis in polymicrogyria - our results indicate a shift towards a regular network topology in polymicrogyric nodes. Regularised network topology has previously been demonstrated in patients with focal epilepsy and during focal seizures. Thus, we postulate that these network alterations predispose to seizures and may be relevant to cognitive deficits in patients with polymicrogyria.

Key Words

Polymicrogyria, Focal epilepsy, Resting state functional connectivity, Graph theory, Cortical malformations

Background

Polymicrogyria is a highly epileptogenic malformation of cortical organisation characterised by increased number of small fused cortical gyri [1] that can result from a variety of genetic and environmental insults during development [2]. Seizures and cognitive deficits are the most common consequences of polymicrogyria. Epilepsy due to polymicrogyria is frequently refractory to drug therapy and surgical treatment is challenging due to difficulty localising epileptic foci within areas of abnormal cortex that may be functionally eloquent.

Focal epilepsy is increasingly recognised as a disease of abnormal brain network organisation and function [3]. Within this framework, focal seizures are associated with engagement of brain networks beyond the conventionally recognised seizure onset zone, and there is evidence of altered connectivity of brain regions during the inter-ictal period. Graph theory is a powerful tool for analysing brain networks using a mathematical model that divides the brain into interconnected regions or nodes, and connections between these nodes are represented by edges [4]. Graph theoretical analysis has been used to characterise dynamic changes in brain networks during focal seizures [5] as well as altered inter-ictal network organisation in patients with focal epilepsy [6] when compared to normal controls.

Characterizing organisation of functional brain networks in polymicrogyric cortex is crucial to understanding its major morbidities of epilepsy and cognitive impairment. However, analysis of whole brain network organization in polymicrogyria is challenging due to statistical difficulties

in comparing brains with malformations to normal controls. In the present study, we characterise nodal functional MRI (fMRI) brain network organisation by comparing graph theoretic network properties within polymicrogyric cortex to those within normal tissue in contralateral homologous cortical regions. To control for possible hemispheric differences in network organisation, we applied the same analysis to regions in the left and right hemispheres of healthy controls. We then postulate how differences in network organization of polymicrogyric nodes might predispose to seizure generation.

Materials and methods

1. Subject characteristics

Four patients (all male, mean age 35.5 +/- 6.6yrs) with refractory focal epilepsy and polymicrogyria on a clinical magnetic resonance scan scan were recruited through the Austin Health comprehensive epilepsy program between 2012 and 2015. Three subjects had polymicrogyria limited to one hemisphere and one subject had bilateral but asymmetric involvement. Detailed information about clinical characteristics (age at onset of epilepsy, seizure type/s, frequency, electrophysiology and neuroimaging) of the patients is provided in supplementary table no 1. Four healthy control subjects (all male, mean age 32.5 +/- 9.14yrs) were also included for comparison. Ethical approval was obtained through the Austin Health Human Research Ethics Committee and written consent was provided by all subjects prior to participation in the study.

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2. Imaging parameters

All subjects were scanned on a Siemens 3T MRI system (Skyra, Siemens, Erlangen, Germany). Blood oxygen level-dependent echo planar images were obtained using the following parameters: 44 slices with 3mm thickness; TR = 3000ms, TE = 30ms, flip angle = 90°, voxel size of 3×3×3 mm and an acquisition matrix of 72×72. T1 weighted MPRAGE anatomical images were obtained using the following parameters: TR = 1900ms, TE = 2.49ms, variable flip angle, 192 sagittal slices and an acquisition matrix of 256×256.

3. Data preprocessing

10 minutes of task-free functional MRI (200 volumes) were obtained for all subjects. MATLAB R2013a (MathWorks Inc., Natick, Massachusetts, United States) implemented tools, SPM8 [7] and DPARSF [8] were used for pre-processing of the data. Acquired images were slice-timed and realigned using 24 motion parameters [9]. The data was further co-registered to structural T1 images, and segmented in to grey matter, white matter and cerebrospinal fluid using a fast diffeomorphic image registration algorithm [10]. In the next step, the data was normalised into MNI space with isomorphic voxel size of 3x3x3 mm. The signal from white matter and cerebrospinal fluid was removed from the data. All images with head movement (calculated with a framewise displacement algorithm) above 0.5mm were also removed. Moreover, fMRI data was bandpass filtered between frequencies of 0.01 and 0.08 Hz.

4. Brain graph - functional connectome

We used an in-house network analysis pipeline based on Matlab codes from the Brain Connectivity Toolbox [4] (https://sites.google.com/site/bctnet/Home). To reliably construct brain graphs in the patients with widespread structural abnormalities (Figure 1A) we used the individualised grey matter masks obtained from the fast diffeomorphic image registration algorithm segmentation (Figure 1B). The individualised grey matter masks were further segregated into 1024 randomly parcellated brain nodes, all equal in size (Figure 1C). These segregated nodes denote the modelled brain regions in our network. Pearson correlation coefficient scores were calculated between all brain nodes - these correlations represent the 'connections' or 'edges' in our network (Figure 1D). Top 10% of all connections were retained in the network before all connections were binarised. This network density threshold has been hypothesised to represent 'optimal network functioning' in medium sized functional connectomes [6].

5. Graph measures

For analysis, we chose four separate graph measures that interrogate distinct and informative aspects of nodal brain network activity (Figure 1E); *Node degree* calculates the number of connections from a node to rest of the network, giving an estimate of connectedness of a node (overall network connectivity). *Clustering coefficient* is calculated as the fraction of a node's neighbours that are also neighbours of each other. In turn, clustering coefficient represents the local 'cliquiness' or functional segregation of the network. The *path length* is characterised as number of steps (links) that separate any two nodes. A shorter average path length indicates more efficient global integration between nodes. *Participation coefficient* measures the

connectedness of a (within-module) node to a diverse set of segregated brain-wide modules. The participation coefficient therefore denotes the between-modular diversity of a node. See Rubinov and Sporns (2010) for full description and equations of all measures used in this study.

6. Region of Interest (ROI) selection

To test network differences in polymicrogyric versus normal cortex, areas of polymicrogyria were identified by an experienced neuroradiologist in all patients. Using visual inspection, nine pairs of ROIs were selected using the following criteria: 1) abnormally thickened cortical ribbon with an irregular cortico-subcortical interface, and 2) a recognisable and normal contralateral homologous cortical region. Pairs of ROI masks were generated placing equal number of voxels along the cortical ribbon in polymicrogyric and the contralateral normal region (Figure 1F - white dots). To test whether potential results among polymicrogyria patients represent a hemispheric effect, the same analysis in four healthy controls was conducted by pairing right and left hemisphere ROI masks for the above identified regions. Average nodal graph metric scores for node degree, clustering coefficient, path length and participation coefficient were calculated within these ROI masks (i.e., normal versus abnormal cortex for patients, and left versus right for controls).

7. Statistical analysis

A two-sample t-test was used to determine overall differences between normal and abnormal cortex for each of the four graph metrics used. (Figure 1G) To counteract type-1 errors, p-values were Bonferroni corrected for number of comparisons (4) at a *p*-value of 0.05, resulting in an adjusted *p*-value of 0.0125. For control subjects, the same analysis was done comparing the left and right hemisphere.

Results

Polymicrogyria vs normal nodes

Clustering coefficient and average path length was increased for all polymicrogyric nodes when compared to normal cortex (Figure 2A and B). When combining all nodes across all four subjects, this result was statistically significant (Bonferroni corrected) for clustering coefficient, p=0.009, and path length, p=0.00069 (Figure 2A-B). Degree centrality and participation coefficient were not significantly different between the polymicrogyric and normal nodes (Figure 2C-D). To further validate these findings and test the robustness of our results, we re-

analysed the data and the above results were consistent over other network density thresholds (5 and 15% top connections).

Validation analysis – left vs. right nodes in healthy controls

As a comparison, in the healthy control group, none of the graph metrics were significantly different between the hemispheres (see supplementary table 2).

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Discussion

Our results highlight differences in network organisation between polymicrogyric and normal cortex. Networks nodes within polymicrogyric cortex show higher average path length and clustering coefficient indicating increased *network segregation* and reduced *network integration*. Polymicrogyric nodes are therefore more locally 'isolated', and globally 'disintegrated', than normal homologous nodes [4].

Such a network pattern resembles a more 'regular' topology in polymicrogyria, which has previously been noted in patients with focal epilepsy using functional (scalp EEG, intracranial EEG, MEG and fMRI) and structural data [6,11,12] (see van Diessen et al [13] for meta-analysis). Electrophysiological studies using intracranial EEG data also show a transient change to a more regular network topology during focal seizures [5], and a more regular network topology has been shown to correspond to epileptogenicity in an experimental models of hippocampal sclerosis [14]. Taken together, a 'regularised' network topology appears to be associated with focal epileptogenicity.

The observed changes in network topology in polymicrogyric nodes may have a number of biological explanations. Altered cortical folding patterns, changes in neural architecture and a reduction in functional neural units likely contributes to altered connectivity. Presence of epileptogenic networks, or an adaptive response of the remaining brain networks are other possible reasons for the observed changes. The impact of epileptic transients on functional

connectivity measures cannot be tested in our study. Concurrent fMRI and EEG data could be collected in future studies. While there is no previous functional connectivity data in polymicrogyria, altered structural connectivity has been reported. Using diffusion imaging, and individual gyral topology based nodes, an analysis of white matter tracts found reduction of both short and long range U-fibre connections compared to normal controls. Network analysis of white matter connectivity revealed lower clustering, higher modularity and disrupted hub architecture in polymicrogyric areas [15]. These findings are not comparable with the current set of results due to major differences in imaging modality and network analysis, but highlight that altered network topology may be a key feature of polymicrogyria.

After seizures, developmental delay and intellectual disabilities are the most common comorbidity in patients with polymicrogyria, with the extent of the cortical malformation being a major determinant of intellectual outcome [16]. Although the patients included in the current study had no major neurologic or cognitive deficits, they all displayed subtle neuropsychological deficits. Previously, "global network efficiency" (inversely related with path length used in this study) has been shown to correlate to intellectual performance using structural and functional connectivity studies [17]. As an increase in path length in polymicrogyric nodes causes network "inefficiency" we cannot exclude that the observed network changes may contribute to the subtle cognitive deficits in our patients.

Although the observed changes in network metrics are statistically significant and consistent across the nine brain regions tested in this study, this is a modest sample size and future studies in larger cohorts of patients with polymicrogyria are needed. Elucidation of the effects of anti-epileptic drugs on resting state brain networks, and advances in data analysis techniques may also allow future studies to compare whole brain network organization of polymicrogyric and normal brains.

In summary, when compared to normal homologous cortex, polymicrogyric nodes display increased clustering coefficient and characteristic path length. This is a shift to a more regularised network topology. This effect of nodal network regularity is not attributed to any hemispheric differences in our study, as measured in healthy controls. These changes have already been described in patients with focal epilepsy [11] and during focal seizures the network also has more regular characteristics than in non-seizure periods [5]. Thus, if regularity of the network is a correlate of the hyper-synchronisation characteristic of epileptic seizures, then polymicrogyric cortex has inherent network properties that may promote seizures.

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Disclosure of Conflicts of Interest

None of the authors has any conflict of interest to disclose

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines

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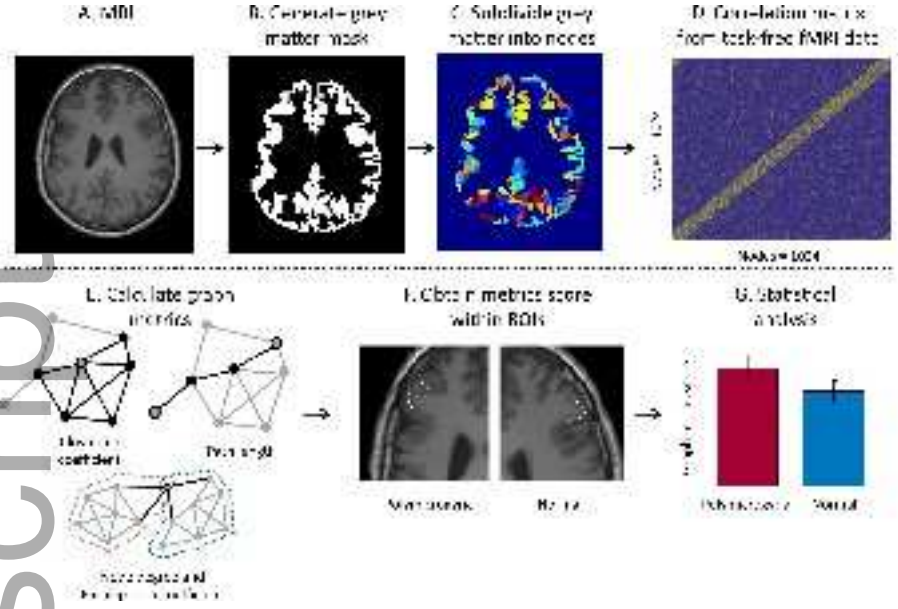

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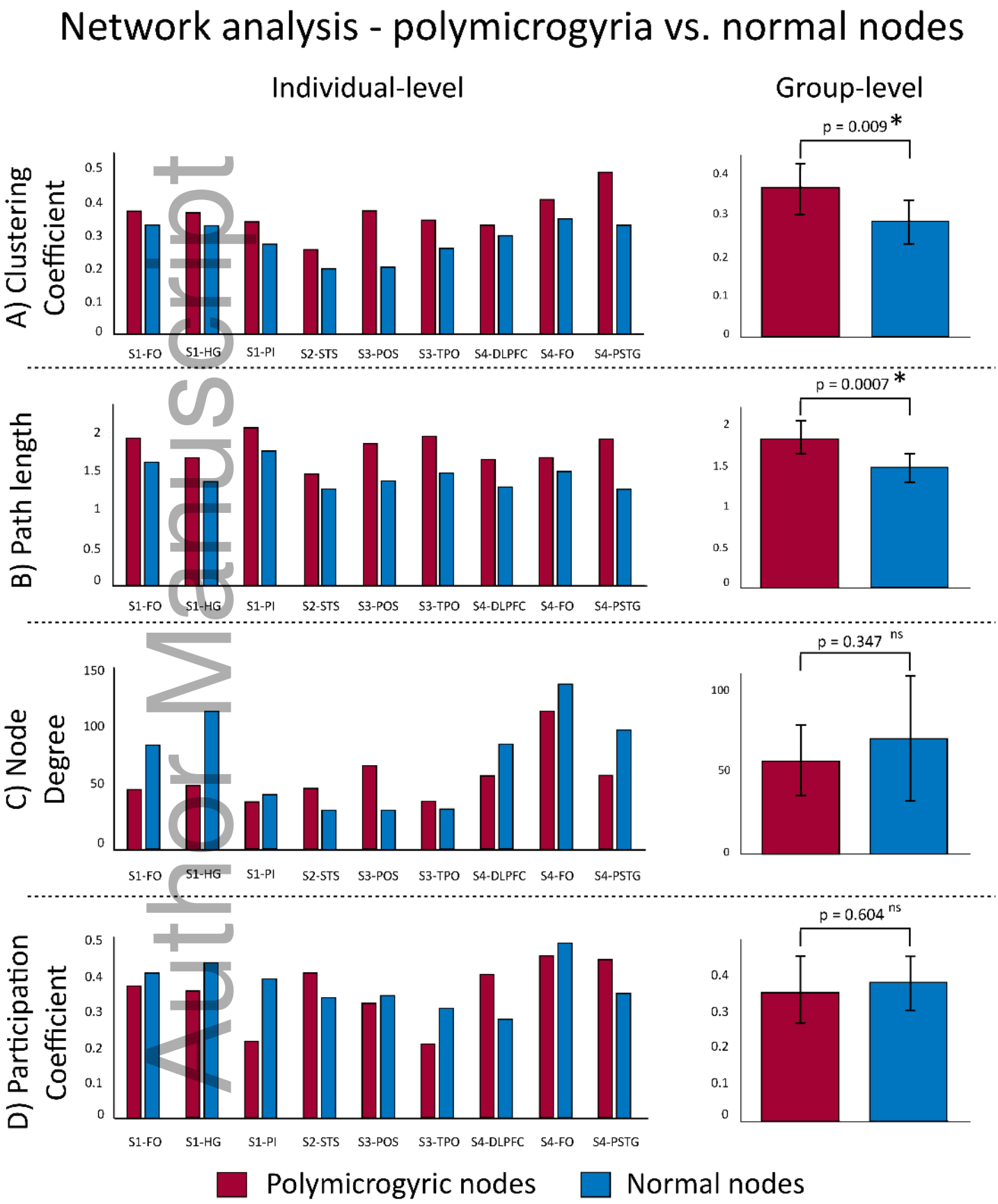

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