

# White matter connectivity and network analysis in polymicrogyria using an individual's primary gyral pattern

Kiho Im<sup>1</sup>, Michael J. Paldino<sup>1</sup>, Olaf Sporns<sup>2</sup>, and P. Ellen Grant<sup>1</sup>

<sup>1</sup>Boston Children's Hospital, Harvard Medical School, Boston, MA, United States, <sup>2</sup>Indiana University, Bloomington, IN, United States

**Purpose:** Polymicrogyria (PMG) is a malformation of cortical development in which the process of normal cortical development is disrupted during the late stages of neuronal migration; the result is the formation of multiple small gyri and altered cortical lamination. Disorganization of specific cortical layers in PMG might be associated with the altered axonal connectivity in the underlying white matter. We examined the structural connectivity and network topology of the cerebral cortex in PMG using diffusion tensor imaging (DTI). Most previous studies have employed atlas-based parcellated cortical regions for whole brain connectivity analysis. However, an atlas-based node definition at the macroscopic scale is too coarse to characterize short U-fibers connections between primary adjacent gyri. In addition, regional organization of specific pathways of axonal fiber bundles has been previously reported with subcortical U-fibers and long association fibers tending to project from and be located centrally within the gyri (1). Here we propose a novel node definition based on an individual's primary gyral pattern and topology, and performed structural connectivity and graph theoretical network analysis in PMG brains. Furthermore, we investigated whether the structural network changes were associated with regional distribution and extent of PMG involvement.

**Methods:** T1-weighted and diffusion tensor images were acquired for 25 typical ( $n$  [male/female]: 12/13, age:  $9.6 \pm 4.6$  years) and 14 PMG subjects ( $n = 9/5$ , age:  $11.0 \pm 6.0$  years) on 3 Tesla magnets with 32 channel receive only coils. For DTI, a total of 35 image sets was acquired: 5 without diffusion weighting and 30 with non-collinear diffusion-weighting gradients and a  $b$  value of  $1000 \text{ s/mm}^2$ . For each PMG patients, each lobe was categorized by visual inspection with a value of '1' indicating involvement and a value of '0' indicating no involvement. The extent of PMG involvement was scored as the sum of these values across all lobar regions. The images were processed to extract cortical surfaces using the FreeSurfer pipeline (2). To define node regions based on individual gyral patterns, we used watershed processing based on a sulcal depth map measured on the white matter surface (Fig. 1). We reconstructed whole-brain white matter fiber tracts using the Diffusion Toolkit (3). Two nodes (regions) were considered to be structurally connected by an edge, when at least the end points of 2 fiber tracts were located less than 3 mm from each of the 2 surface node regions. To weight the edge, we used the product between the connection density (number of fiber tracts per unit surface) and mean inverse ADC ( $1/\text{ADC}$ ) connecting a pair of region. We first constructed different fiber groups and networks subdivided according to individual gyral pattern and topology. We defined the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup> and 5<sup>th</sup> or more neighbors for each gyral region (short association U-fibers ~ long association fibers) (Fig. 1).

We separately measured the mean FA and ADC values and basic network measures (mean *strength* and *density* of the network) for the connections between the  $n^{\text{th}}$  neighboring gyri and between hemispheres. Furthermore, graph theoretical network analysis was carried out on whole-brain connectivity network (*clustering coefficient* and *transitivity* for network segregation measure, *characteristic path length* and *global efficiency* for network integration measure, *small-worldness*, and *betweenness centrality*). Nodes were considered as the hubs of the network if their betweenness centrality were at least one standard deviation greater than the average betweenness centrality. We identified the hubs from all individual networks on the same space and defined the regions where the hubs were constantly detected across subjects and densely clustered. Age and sex were regressed out as covariates and permutations tests were performed for all statistical analyses. Mean FA and ADC values based on gyral topology for whole brain and graph measures were compared between the typical and PMG groups. To find their relationships with the PMG extent, we performed Spearman correlation analysis in the PMG patients.

**Results:** We found significantly decreased short U-fibers connections in the PMG patients when compared to the typical control group. FA and mean strength and density of the networks between the 1<sup>st</sup> neighboring gyri were significantly lower and ADC was higher in the PMG than in the typical group (FA:  $P = 0.013$ , ADC:  $P = 0.048$ , mean strength:  $P = 0.019$ , network density:  $P = 0.003$ ). Decreased FA ( $P = 0.034$ ) and increased ADC ( $P = 0.040$ ) were found in the long association fibers for the PMG group. Significantly lower mean strength ( $P = 0.001$ ) and network density ( $P = 0.011$ ) were shown in the PMG group for the inter-hemispheric connections. Density of short connections between the 1<sup>st</sup> neighboring gyri was highly correlated with the extent of PMG involvement ( $R = -0.824$ ,  $P = 0.0005$ ). Group comparisons on network measures revealed significantly lower clustering coefficient ( $P = 0.011$ ) in the PMG patients than in the typical controls. The PMG extent score was significantly correlated with clustering coefficient ( $R = -0.618$ ,  $P = 0.021$ ) and transitivity ( $R = -0.604$ ,  $P = 0.025$ ) in PMG patients. The hub regions were predominantly identified for both groups in the medial and lateral regions of the frontal and parietal cortex (superior and middle frontal gyri, precuneus, and superior and inferior parietal gyri), and their distribution was nearly symmetric (Fig. 2). We found that the hubs in the left and right anterior prefrontal regions and left posterior inferior temporal region were detected in the typical group, but not in the PMG group. Instead, the hub region was identified in the right superior temporal region in PMG.

**Discussion and Conclusion:** We first found significantly decreased connectivity of short association fibers in PMG patients. In addition, network density of short connections significantly decreased as the severity of abnormal gyral folding increased in PMG. We also revealed significantly reduced network segregation measure, clustering coefficient. We can suppose that low clustering coefficient in PMG is caused by the disrupted short U-fibers connectivity between neighboring regions. Our gyral node-based measures of the network are good at reflecting the disease-related network characteristics in PMG. Hub nodes were not identified in the bilateral anterior prefrontal regions and left posterior inferior temporal region in PMG. Loss of network hub property in these areas seems to be closely related to delayed cognitive and language development in PMG. Our approach provides the first detailed findings and interpretations on abnormal cortical network topology in malformations of cortical development, in particular PMG, and shows the potential for an individualized method to characterize network properties and alterations in connections without having to assume normal brain structure. In addition this gyral based method allows assessment of connections in a more biological framework, with connections between primary gyri consistent with subcortical U-fibers and longer connections grouped by number of gyri traversed.

## References

1. J. D. Schmahmann, E. E. Smith, F. S. Eichler, C. M. Filley, *Ann N Y Acad Sci* **1142**, 266 (Oct, 2008).
2. A. M. Dale, B. Fischl, M. I. Sereno, *Neuroimage* **9**, 179 (Feb, 1999).
3. R. Wang, T. Beener, A. G. Sorensen, V. J. Wedeen, *Proc Intl Soc Mag Reson Med* **3720**, (2007).

