Effect of structural connectivity weightings in graph-based analysis in schizophrenia

Sara Khamseh
Department of Biomedical Engineering,
Amirkabir University of Technology,
Tehran, Iran
sara020@aut.ac.ir

Farzaneh Keyvanfard
School of Cognitive Science,
Institute for Research in Fundamental Sciences (IPM),
Tehran, Iran
f.keyvanfard@ipm.ir

Graph theory models the brain as a complex network to sets of vertices linked by connections. The connections between vertices can be determined by the structural connectivity (SC) of the brain. SC, regarding tractography, is represented through different measurements including global fractional anisotropy and fiber density. To apply graph theory, matrix thresholding is required to delete the weak connections in the data and then the graph parameters such as nodal strength are computed. In this pipeline, different metrics of representing structural connectivity and thresholding methods can be selected. Here we aim to investigate whether this selection affects the discrimination results between healthy control and schizophrenia patients. Our findings indicate that applying density-based thresholding to the global fractional anisotropy metric can identify the alternation more thoroughly, while the significant difference in graph measurements may not be detected using other approached.

Keywords—structural connectivity, schizophrenia, brain network, thresholding method, graph theory.

I. INTRODUCTION

Schizophrenia (SZ) is a chronic psychotic disorder marked by delusional beliefs, mirage, and disruptions in thought, perception, and behavior. It is linked to alterations in the structure and functionality of various brain areas. [1]. It is known that impaired brain connectivity is a major sign of schizophrenia brain [2]. Widespread white matter abnormalities have been revealed using diffusion tensor imaging (DTI) [3]. Structural connectivity reflecting the presence of white matter tracts and physically linking brain regions, has been expressed by different measurements in several studies. Global fractional anisotropy, number of fibers, and fiber density are the widely used metrics for assessing the structural connectivity.

Considering the brain as a complex network, graph theoretical analysis provides a holistic perspective to quantify the brain topological patterns in individuals with schizophrenia [4]. Graph theory models the brain network as a graph, with contributed nodes that are connected through edges. Nodes are defined by different brain parcellation and edges are the mutual connections of those nodes. The complex network analysis offers an insightful approach to characterize the brain networks by employing a small set of measures that are both relevant to brain biology and easy to compute, including clustering coefficient, small-worldness, and characteristic path length.

Dysconnectivity caused by brain disorders such as schizophrenia typically may not recognized without thresholding owing to the negligible ratio of dysconnectivity to the original connections. Thresholding instead will preserve strong connections in the brain network. Different thresholding methods, including weight-based thresholding [5] and density-based thresholding [1] have been utilized in many network studies.

In this study, we focus on four essential graph metrics—clustering coefficient (CC), characteristic path length (CPL), global efficiency (GE), and nodal strength (NS)—as our representations of brain connectivity. Previous studies have illustrated unmatched results obtained from using different graph measures. As an instance, [6] reported significant differences on the number of fibers matrix using density and GE metrics in graph theory, however, [7] showed significant differences on path length and small-world index metrics using the same matrix. We therefore aim to investigate the effect of structural connectivity metrics and thresholding methods on the determination of group differences between individuals with schizophrenia and control subjects. Here, we employ two different matrices: global fractional anisotropy (gFA), and density of fiber (DoF), and two distinct thresholding methods: weight-based and density-based thresholding. At each threshold level, we conduct t-tests to statistically assess variations in the identified graph metrics, providing a comprehensive exploration of connectivity disparities between the schizophrenia and control groups. All the tests are repeated for the two different matrices.

II. METHOD

A. Dataset

We retrospectively employed structural connectivity of 27 individuals diagnosed with schizophrenia (mean age 41 ± 9.6) and the control cohort comprised of 27 healthy participants (mean age 35 ± 6.8 years), matched across all parameters. This dataset has been previously published by Zenodo with comprehensive details available in [8]. The study participants in the SZ cohort had been sourced from the Service of General Psychiatry at the Lausanne University Hospital meeting the criteria outlined in DSM-IV for SZ and schizoaffective disorders (American Psychiatric Association, 2000). Recruited through advertisement, healthy controls had been evaluated using the Diagnostic Interview for Genetic Studies [9]. Employing the Desikan Killiany atlas [10] and extra parcellation of the cortical surface described in [11], within the MPRAGE volume, the gray matter of each subject had been segmented into 129 cortical regions of interest (ROI), which comprised of 114 cortical ROIs and 14 subcortical nuclei along with the brain stem. Deterministic tractography had been used to construct structural connectivity between each pair of brain regions. The connectivity strength was quantified in terms of two measures: density of fibers (DoF) which is defined as the number of streamlines between the two

regions, normalized by the mean of streamlines length and average surface area of the two regions [4], and the global fractional anisotropy (gFA) which is a structural indicator of white matter myelination and integrity [12].

B. Network thresholding

Two methods of network thresholding, proportional and weight-based methods were applied to evaluate their efficiency and effectiveness in detecting brain network changes of the SZ group. In addition, utilizing group-level thresholding, as opposed to node-level thresholding, was preferred due to computational efficiency [13]. In group-level thresholding a global threshold is set to affects the entire dataset or a specific set of elements as a whole. Whereas in node level thresholding individualized thresholds are set for each node or element within a system or network.

The proportional thresholding algorithm retains the strongest connections based on a specified proportion while setting others to zero. To implement this thresholding method, we initiated by calculating the density of the network's backbone (approximately 1.5%). A minimum spanning tree algorithm [14] was applied to establish this backbone, ensuring a connected network that encompassed all vertices with the smallest cumulative weights. Subsequently, the density of network (τ) gradually was increased by reintroducing previously deprecated connections, in increments of 5%, until the network reached its initial density of approximately 22% [14]. Increasing density at each step necessitated the sorting of all remaining connections.

Conversely, the weight-based algorithm involves deleting all connections below a specified threshold (w), and setting them to zero, which results in a weighted matrix with density independent of τ. This method may increases the risk of spurious connections while removing relatively strong connections below w [15]. In our study, we therefore, adopted predetermined thresholds, commencing at 0.05 and concluding at 0.2 (the maximum value observed in the SC matrices; DoF, and gFA), with increments of 0.05.

The entire analysis of network thresholding was performed using the Brain Connectivity Toolbox (brainconn 0.0.2) in Python.

C. Network measures

Four well-known graph-theoretic measures including CPL, CC, NS, and CPL were calculated on the thresholded structural brain network.

The nodal strength represented by k_i, is defined as the summation of all link weights belonging to the neighbors of node i denoted by W_{ij} as follows [1]:

$$k_i = \sum_{i \in N} W_{ij} \qquad (1)$$

The clustering coefficient (C) indicates the fraction of the node's neighbors that are connected to each other. Its calculation is as follows [1]:

$$C = \frac{1}{n} \sum_{i \in N} \frac{2t_i}{k_i(k_i - 1)} \qquad (2)$$

Where t_i is the number of triangles around the node and k_i is the nodal strength.

The average shortest path length (L), is the mean of the shortest path length among all pairs of nodes (n) in the network. It is described as [1]:

$$L = \frac{1}{n} \sum_{i \in N} \frac{\sum_{j \in N, j \neq i} d_{ij}}{n - 1} \qquad (3)$$

Where d_{ij} is path length between nodes i and j.

The average inverse shortest path length is known as the global efficiency (E) [1].

$$E = \frac{1}{n} \sum_{i \in N} \frac{\sum_{j \in N, j \neq i} (d_{ij})^{-1}}{n - 1} \qquad (4)$$

Additionally, we calculated the small-worldness denoted by σ [16] as a measure of network similarity to the human brain using the following formula (C_r and L_r are clustering coefficient and characteristic path length of an equivalent random network).

$$\sigma = \frac{\frac{c}{c_r}}{\frac{L}{L_r}} \qquad (5)$$

The entire analysis of network measures was performed using the Brain Connectivity Toolbox (brainconn 0.0.2) in Python.

D. Statistical Analysis

The unpaired two-tailed independent t-test was used to test group differences in every comparison. The difference in mean values normalized by the variances of the two groups determined the validity of the null hypothesis. A significance level was established at p < 0.05. Prior to these tests, the Levene test [17] was conducted to assess the equality of variances between the control and schizophrenia groups. Statistical analysis was carried out using the SciPy library's stats module.

III. RESULT

A. Thresholding on the density of fiber matrices

Fig. 1 shows the result of applying both methods of thresholding (density-based and weight-based thresholding) to the DoF matrices. While all mean values of schizophrenia group measures were lower than or equal to control groups during the thresholding (NS, GE, and CC), they were greater than or equal to during the thresholding of the CPL.

Our analysis detected significant differences for various chosen ranges of τ and ω except for the density-based thresholding on CC. All the τ levels and $\omega > 0.001$ retained the small-worldness characteristic of the brain network and were accepted to hold the common organization of anatomical connectivity.

B. Thresholding on the global fractional anisotropy matrix

Fig. 2 demonstrates density-based and weight-based thresholding applied to the density of gFA matrices. While all mean values of schizophrenia group measures were lower than or equal to control groups during the thresholding (e.g., NS, GE, and CC), they were greater than or equal to during the thresholding of CPL.

By increasing the thresholding level, the values of measures of the control and schizophrenia groups lessened or had small changes. By applying the density-based thresholding, all network measures illustrated significant changes in two or three τ levels. However, in the CC, thresholding failed to further detect any significant changes. In addition, all the τ levels preserved the small-worldness of the network, while only w < 0.001% disrupted the common organization of anatomical connectivity.
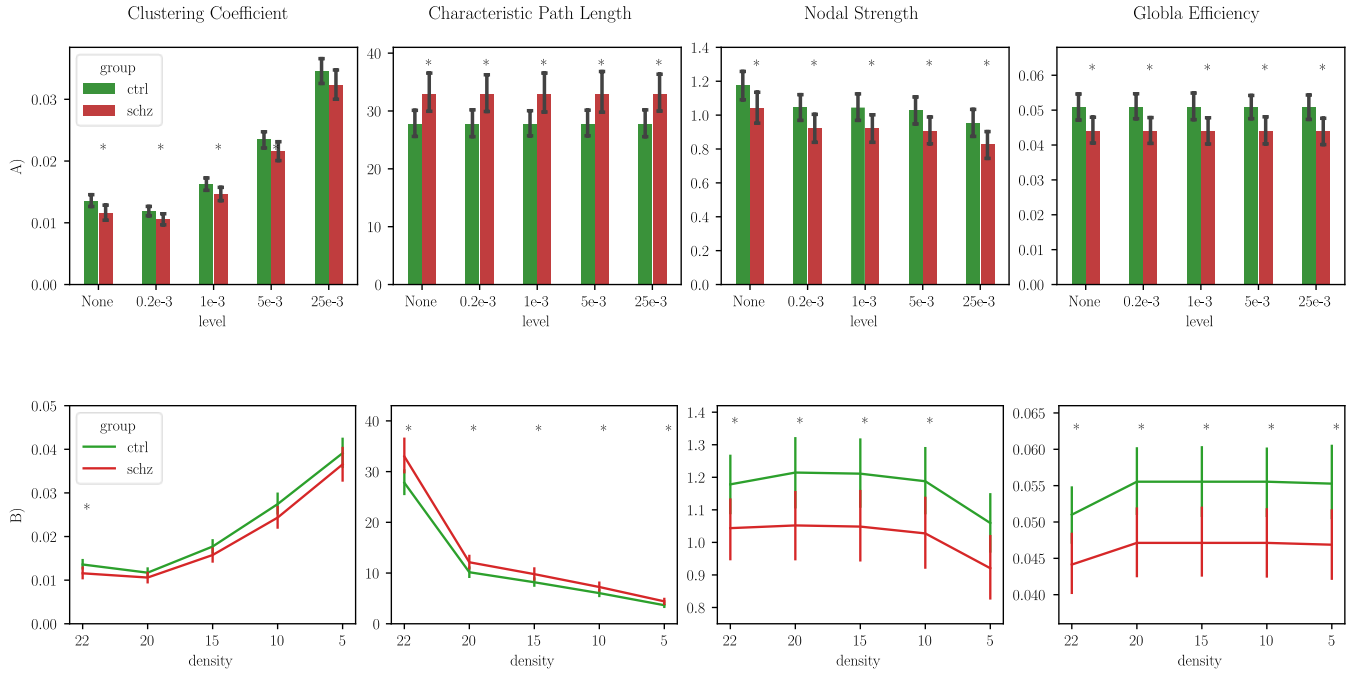

Fig. 1. Thresholding on the density of fiber matrix: a) weight-based thresholding and b) density-based thresholding were applied to the density of fiber (DoF) matrix. Graph metrics (clustering coefficient, characteristic path length, nodal strength, and global efficiency) of DoF were calculated for both the healthy control (denoted by green), and schizophrenia (denoted by red).
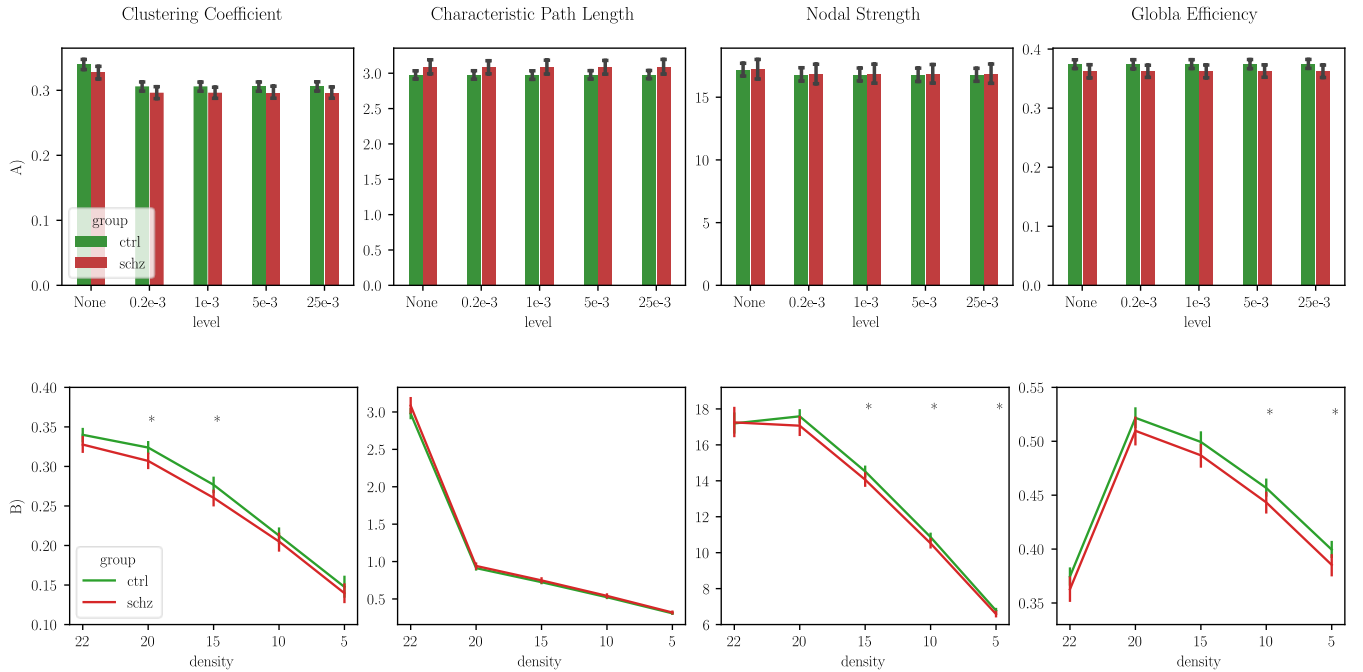

Fig. 2. Thresholding on the global fractional anisotropy matrix: a) weight-based thresholding and b) density-based thresholding were applied to the global fractional anisotropy (gFA) matrix. Graph metrics (clustering coefficient, characteristic path length, nodal strength, and global efficiency) of gFA were calculated for both the healthy control (denoted by green), and schizophrenia (denoted by red).

IV. Discussion

Here, we investigated the effect of structural connectivity metric on observing significant differences in graph measurements between HC and SZ. Using two different thresholding methods, our findings indicated that only the weight-based thresholding on the gFA failed to recognize expected anatomical changes significantly. This result suggests that an alternative weight range may be taken for the reliable detection of a significant change in patients with schizophrenia disorder. Considering previously published article, our results are in line with prior studies [5, 6], the CC, GE, and NS are higher in the control healthy group and the CPL is inferior in the schizophrenia group.

Furthermore, we examined the effect of thresholding method on the structural connectivity matrices. It has been suggested that thresholding is beneficial for deleting weak and insignificant edges. However, a bounded range of weight and density can be chosen to secure the small-world brain-like network. Another constraint was to save the backbone of the network and prevent disconnectivity during thresholding. As a result, this deletion of the connection is emphasized in sporadic networks.

In conclusion, our study demonstrated that using the density-based thresholding method is preferable to the wight-based thresholding owing to its coverage of a wider area of the weighted matrices. Furthermore, our findings shows that calculation of the network measures served as proxies for whole-brain network, is more credible when using DoF rather than gFA.

References

[1] M. Rubinov and O. Sporns, 'Complex network measures of brain connectivity: Uses and interpretations', NeuroImage, vol. 52, pp. 1059–1069, 2010.

[2] M.-E. Lynall et al., 'Functional connectivity and brain networks in schizophrenia', Journal of Neuroscience, vol. 30, no. 28, pp. 9477–9487, 2010.

[3] S. Kelly et al., 'Widespread white matter microstructural differences in schizophrenia across 4322 individuals: results from the ENIGMA Schizophrenia DTI Working Group', Molecular psychiatry, vol. 23, no. 5, pp. 1261–1269, 2018.

[4] S. R. Kay, A. Fiszbein, and L. A. Opler, 'The positive and negative syndrome scale (PANSS) for schizophrenia', Schizophrenia bulletin, vol. 13 2, pp. 261–276, 1987.

[5] P. Hagmann et al., 'Mapping Human Whole-Brain Structural Networks with Diffusion MRI', PLOS ONE, vol. 2, no. 7, pp. 1–9, 07 2007.

[6] M. Drakesmith et al., 'Schizophrenia‐like topological changes in the structural connectome of individuals with subclinical psychotic experiences', Human Brain Mapping, vol. 36, pp. 2629‑2643, 2015.

[7] J. Cabral, H. M. Fernandes, T. J. van Hartevelt, A. James, M. L. Kringelbach, and G. Deco, 'Structural connectivity in schizophrenia and its impact on the dynamics of spontaneous functional networks', Chaos, vol. 23 4, p. 046111, 2013.

[8] Jakub Vohryzek, "Structural and functional connectomes from 27 schizophrenic patients and 27 matched healthy adults". Zenodo, Apr. 23, 2020. doi: 10.5281/zenodo.3758534.

[9] M. Preisig, B. T. Fenton, M. L. Matthey, A. Berney, and F. Ferrero, 'Diagnostic interview for genetic studies (DIGS): inter-rater and test-retest reliability of the French version', Eur. Arch. Psychiatry Clin. Neurosci., vol. 249, no. 4, pp. 174–179, 1999.

[10] R. S. Desikan et al., 'An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest', Neuroimage, vol. 31, no. 3, pp. 968–980, Jul. 2006.

[11] L. Cammoun et al., 'Mapping the human connectome at multiple scales with diffusion spectrum MRI', J. Neurosci. Methods, vol. 203, no. 2, pp. 386–397, Jan. 2012.

[12] M. Porcu et al., 'Global Fractional Anisotropy: Effect on Resting-state Neural Activity and Brain Networking in Healthy Participants', Neuroscience, vol. 472, pp. 103–115, 2021.

[13] C. R. Buchanan et al., 'The effect of network thresholding and weighting on structural brain networks in the UK Biobank', NeuroImage, vol. 211, p. 116443, 2020.

[14] B. M. de Brito Robalo, N. Vlegels, J. M. Meier, A. Leemans, G. J. Biessels, and Y. D. Reijmer, 'Effect of Fixed-Density Thresholding on Structural Brain Networks: A Demonstration in Cerebral Small Vessel Disease', Brain connectivity, 2020.

[15] F. Váša, E. T. Bullmore, and A. X. Patel, 'Probabilistic thresholding of functional connectomes: Application to schizophrenia', NeuroImage, vol. 172, pp. 326–340, 2017.

[16] Z. P. Neal, 'How small is it? Comparing indices of small worldliness', Network Science, vol. 5, pp. 30–44, 2017.

[17] J. L. Gastwirth, Y. R. Gel, and W. Miao, 'The impact of Levene's test of equality of variances on statistical theory and practice', 2009.