Title: The Impact of Weighting and Thresholding Strategies on Structural Brain Network Analysis in Schizophrenia

Running Title: Network Weighting and Thresholding Effect

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Abstract

Introduction: Diffusion MRI combined with deterministic tractography enables the reconstruction of whole-brain structural networks. However, the inherent noise in measurements and probabilistic nature of fiber tracking generate an uncertain number of false white matter connections. Current limitations in network-level anatomical data make it difficult to reliably separate real connections from artifactual ones. While network thresholding methods are frequently used to filter out presumably spurious connections, their varying effects on network characteristics and subsequent statistical analyses remain almost unclear.

Method: We analyzed data from 27 schizophrenia patients and 27 demographically matched healthy controls. Five network weighting schemes (fiber density, streamline count, mean fiber length, apparent diffusion coefficient, and global fractional anisotropy) were examined under two systematic thresholding approaches (absolute and proportional) across multiple threshold levels. Network properties were quantified using three standard metrics: node degree, clustering coefficient, and global efficiency. Group comparisons were performed using independent samples t-tests.

Results: We found that lower threshold values tended to yield more significant differences in graph metrics compared to higher thresholds. Additionally, proportional thresholding produced more consistent patterns of metric reduction across all weighting methods. Among the different weightings, fiber density exhibited the greatest statistical differences between patients and healthy controls.

Conclusion: Our findings demonstrate that the choice of threshold significantly impacts graph metrics and statistical outcomes, potentially influencing study conclusions. These results highlight the need for more rigorous justification in selecting thresholding methods and suggest that researchers should consider adopting multiple analytical approaches to ensure robustness in network-based analyses.

Keywords: Brain network weighting, Diffusion MRI, Thresholding, Schizophrenia, graph metric.

Highlights:

- Threshold level has a strong impact on the statistical analysis outcomes.
- Threshold level was a stronger driver of findings variations than threshold method.
- To find significant difference in group level, chosen threshold range is important.
- Density-based weighting has higher sensitivity of graph metrics to brain alterations.

Introduction

In recent years, there has been increasing interest in constructing structural brain networks—also referred to as structural connectomes (Sporns et al., 2005) -which map the white matter pathways connecting different brain regions. These networks can be noninvasively derived on a macroscopic scale using diffusion magnetic resonance imaging (dMRI) in combination with whole-brain tractography techniques (Sotiropoulos & Zalesky, 2017). This methodological framework has proven instrumental in examining how individual differences in brain network architecture relate to behavioral outcomes and health profiles. Nevertheless, constructing a representative network model that supports both within-group and between-group comparisons presents a significant challenge (de Reus & van den Heuvel, 2013).

One core issue arises from the inherent noise and indirect nature of dMRI measurements, which frequently results in structural networks containing numerous false-positive connections (Jbabdi & Johansen-Berg, 2011; Thomas et al., 2014; Yeh et al., 2018; Zalesky & Fornito, 2009). Although substantial progress has been made in mapping major white matter tracts using tractography (Mori et al., 2009), a complete and precise anatomical reference that identifies all existing macroscale connections—encompassing thousands of tracts and millions of streamlines—remains unrealized. In response to this gap and the demand for more systematic denoising strategies (de Reus & van den Heuvel, 2013; Maier-Hein et al., 2017; van Wijk et al., 2010), researchers have developed inferential approaches to isolate and eliminate possibly spurious connections.

Some researchers believe that topological network properties are not significantly altered by the discarding of weak connections (Civier et al., 2019) and therefore they utilized the unthresholded connectivity matrices. Others have adopted thresholding techniques to reduce the possible impact of low-weight edges on the results. Absolute thresholding, which preserves only connections exceeding a fixed weight (Hagmann et al., 2007), is a commonly used approach. However, this method can lead to unequal edge counts across subjects or groups, especially problematic in clinical comparisons, as it introduces variation in network density—the ratio of actual to possible connections. This density variation is known to influence many graph-theoretical metrics, potentially confounding findings (see Van Wijk et al., 2010 for a comprehensive analysis). Despite these issues, absolute thresholding continues to be widely employed. To mitigate network density effects, an alternative approach—proportional (density- based) thresholding—has been proposed (Achard & Bullmore, 2007; Bassett et al., 2009; van den Heuvel et al., 2008). This method maintains a consistent number of connections across participants by retaining only the top PT% of strongest links, ensuring comparability across groups. In binary analyses, retained connections are set to 1 and all others to 0. This fixed-density strategy, also termed “network cost” or “network (graph) density” control (Ginestet et al., 2011; Jalili, 2016), assumes that observed group differences in network properties reflect true topological disparities rather than density-induced artifacts.

A growing body of methodological research has emphasized that the choice of thresholding strategy can substantially alter the topology of structural connectivity networks and the statistical inferences drawn from them. A recent study (Buchanan et al., 2020) has demonstrated that both the thresholding rule and edge-weighting scheme can markedly influence network density, hub structure, and group-level effects. Foundational methodological work (Fornito et al., 2016) and the sensitivity–specificity framework discussed by Zalesky et al. (Zalesky et al., 2016) further highlighted that threshold decisions can introduce variability comparable to, or even greater than, the underlying biological effects of interest. More broadly, several methodological analyses have emphasized that threshold choice can meaningfully influence network stability, reproducibility, and the interpretation of group differences.

Another complicating factor in constructing a representative structural network is the uncertainty about which connectivity weighting best explains biological structure. Structural networks derived from dMRI have used various weighting schemes to quantify connection strength, including streamline counts or densities (Hagmann et al., 2008a) and fractional anisotropy (FA) values (Robinson et al., 2010; Verstraete et al., 2011). Additional metrics such as apparent diffusion coefficient (ADC) have also been utilized to assess different characteristics of white matter microstructure (Agosta et al., 2013; Collin et al., 2014). Considering several concepts in structural network metrics in addition to different thresholding approach, motivate the present study's comparison of absolute and proportional thresholding across multiple weighting schemes.

Schizophrenia (SZ), a chronic and disabling mental disorder, affects approximately affects about 0.45% of the adult population worldwide[1] (Vos et al., 2017). It is characterized by hallucinations, delusions, and disruptions in cognition and behavior, and ranks among the top causes of disability in people aged 15 to 44 (Hany et al., 2024). A leading hypothesis posits that white matter abnormalities contribute to disrupted communication between brain regions—a hallmark of schizophrenia (Konrad & Winterer, 2007; Samartzis et al., 2014; Wang et al., 2020). Such abnormalities can be investigated using diffusion tensor imaging (DTI), which offers insight into microstructural features such as myelination and axonal density.

The present study explores the influence of two thresholding techniques—absolute and proportional—on network metrics computed from various structural connectivity weightings, including fiber density, streamline count, fiber length, ADC, and FA. We compare graph metrics across individuals diagnosed with schizophrenia and healthy controls, focusing on three commonly used measures: node degree, clustering coefficient, and global efficiency. This investigation aims to clarify how thresholding choices and weighting strategies affect the detection of network differences in schizophrenia.

Material and Methods

Dataset

In this study, we utilized structural connectivity data from 27 individuals diagnosed with schizophrenia (mean age: 41 ± 9.6 years) and a control group consisting of 27 healthy participants (mean age: 35 ± 6.8 years), matched across all relevant parameters. This dataset was previously published on Zenodo, with full methodological details provided in (Vohryzek et al., 2020). Participants in the schizophrenia group were recruited from the Service of General Psychiatry at Lausanne University Hospital and met the DSM-IV diagnostic criteria for schizophrenia and schizoaffective disorders (American Psychiatric Association, 2000). Healthy controls were recruited via public advertisement and assessed using the Diagnostic Interview for Genetic Studies (DIGS) (Preisig et al., 1999).

Cortical parcellation was performed using the Desikan-Killiany atlas (Desikan et al., 2006), along with additional surface segmentation as described in (Cammoun et al., 2012), applied to each subject's MPRAGE volume. The gray matter was segmented into 128 regions of interest (ROIs), comprising 114 cortical areas, and 14 subcortical nuclei.

[1] WHO report (https://www.who.int/news-room/fact-sheets/detail/schizophrenia).

Network thresholding and network measures

Structural connectivity between brain regions was reconstructed using whole-brain deterministic tractography. Networks were generated by identifying connections between all pairs of regions of interest (ROIs). The strength of each connection was quantified using five different network weightings:

1. **Density** – the number of streamlines between two ROIs, normalized by the mean surface area of the ROIs (Hagmann et al., 2008b);
2. **Number of Tracts (NoT)** – the total count of streamlines connecting two ROIs;
3. **Length of Fibers (LoF)** – the average length of all streamlines between a given pair of ROIs;
4. **Apparent Diffusion Coefficient (ADC)** – the mean diffusivity along the connecting streamlines, indicating the magnitude of diffusion;
5. **Global Fractional Anisotropy (gFA)** – a diffusion-based metric that reflects white matter myelination and structural integrity (Porcu et al., 2021).

For each of these five network weightings (Density, NoT, LoF, ADC, and gFA), two thresholding methods were applied: absolute thresholding and proportional (density-based) thresholding. In the absolute thresholding approach, only edges with values above a fixed threshold T (e.g., greater than 0.3) were retained, while all other connections were set to zero.

In proportional thresholding, the structural connectivity matrices were thresholded by preserving the top PT% of strongest connections, with the rest set to zero. This method yielded weighted graphs with a global network density corresponding to PT% (Buchanan et al., 2020; de Reus & van den Heuvel, 2013).

In this study we examined a range of levels T from 0.01 to 0.4 in steps of 0.02 for absolute thresholding and range of PT in proportional thresholding from 70% to 1% in steps of 5%. It should be mentioned that all five types of SC matrices were normalized to [0,1] to be able to apply similar value of thresholding.

In addition, three graph-theoretic metrics (Rubinov & Sporns, 2010) were computed to quantify the brain network variations in patients: node degree (quantifying the importance of each node), global efficiency; and network clustering coefficient (reflecting the interconnectedness of each node's neighbors).

The following formal definitions describe the graph topological characteristics used in this study for a network of N nodes.

The Node Degree, typically denoted as $\mathbf{k_i}$, is a fundamental measure of connectivity for a node within a network. It quantifies the total number of direct connections (or edges) a node has to other nodes in the network. For a node i, the degree is defined as:

$$k_{\mathrm{i}} = \Sigma_j \, a_{ij} \tag{1}$$

where $\mathbf{a_{ij}}$ is an element of the adjacency matrix.

Global efficiency (E_{global}) quantifies the degree of integration in brain networks, reflecting how efficiently information is exchanged across the entire system (Achard & Bullmore, 2007; V. Latora & Marchiori, 2003; Vito Latora & Marchiori, 2001) defined as the inverse of the average shortest path length between all pairs of nodes in the network. The formula for global efficiency is given by:

$$\boldsymbol{E_{global}} = \frac{\mathbf{1}}{\boldsymbol{N(N-1)}} \sum_{\boldsymbol{i \neq j}} \frac{\mathbf{1}}{\mathbf{min}\{\boldsymbol{L_{i,j}}\}} \tag{2}$$

where N is the total number of nodes in the network and L_{ij} is the shortest path length between node i and node j.

The absolute clustering coefficient of a node (C_i) in a weighted network measures the likelihood that its neighboring nodes are also connected to each other, taking into account the strength of the connections (Onnela et al., 2005). For a weighted graph, it is defined as the geometric mean of the intensities of triangles around a node i:

$$\boldsymbol{C_i = \frac{E_i}{\frac{k_i(k_i-1)}{2}} = \frac{2}{k_i(k_i-1)} \sum_{j,k}\left(w_{ij}, w_{ik}, w_{jk}\right)^{\frac{1}{3}}} \quad (3)$$

where k_i is the degree of node i and w_{ij} is the connection weights between nodes i and j.

Statistical Analysis

We began by calculating the average connectivity matrices and summarizing the descriptive statistics for the unthresholded networks across all five structural connectivity weightings. Subsequently, we examined how three graph-theoretical metrics varied as a function of the two thresholding methods and five types of connectivity matrices. To evaluate group differences between individuals with schizophrenia (SZ) and healthy controls (HC), independent *t*-tests were performed across the full range of thresholds, with statistical significance determined at $p < 0.05$.

Given the exploratory nature of this study and the strongly correlated structure of graph-theoretical measures across adjacent thresholds, no formal multiple-comparison correction was applied across threshold levels. Graph metrics at nearby thresholds are not statistically independent, and applying standard corrections (e.g., Bonferroni or FDR) would therefore be overly conservative and potentially obscure meaningful trends. Instead, we report uncorrected p-values across the full threshold range to provide a transparent depiction of how group differences evolve as a function of thresholding.

Results

The mean connectivity matrices and corresponding histograms of edge weights computed for each network weighting (Density, NoT, LoF, ADC and gFA) are shown in Fig.1. Before any thresholding, the mean value of network density (the proportion of nonzero-weighted elements in a connectivity matrix) across subjects was 0.238 (SD = 0.0078). We observed from the histograms of edge weights pooled across all subjects (Fig. 1) that the distribution of all network weights approximately followed a power law and involved many low weighted connections but very few high weighted connections.

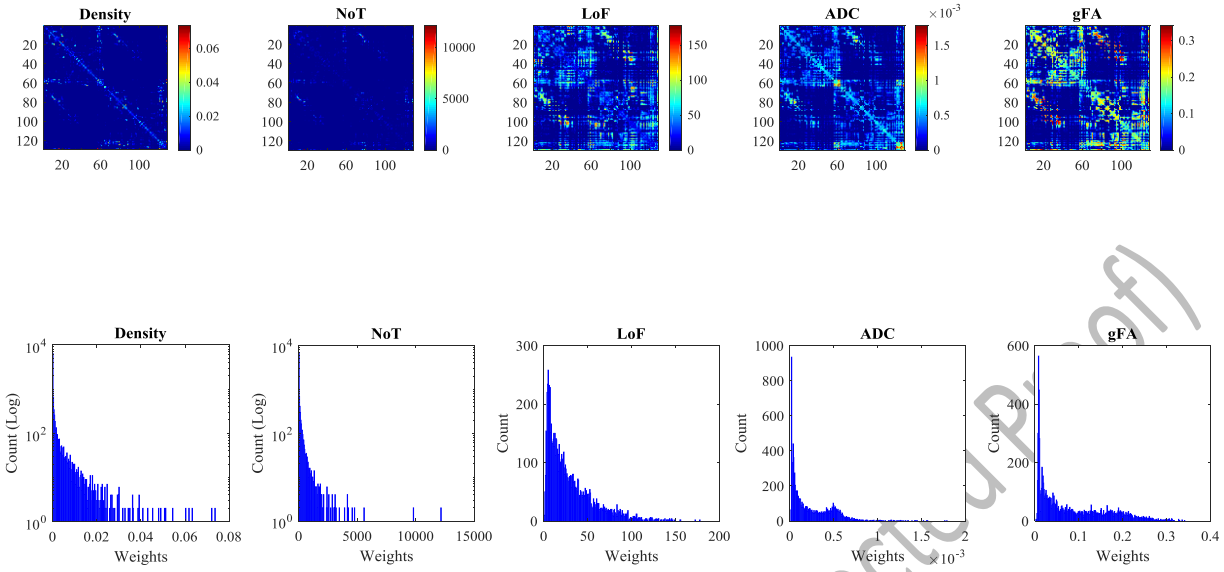

Fig. 1. Mean connectivity matrices and their distribution. Top: mean connectivity matrices (unthresholded) of connection weights between 128 regions, averaged across all healthy individuals for five network weightings. Bottom: the corresponding histograms of nonzero edge weights pooled across all healthy participants for each weighting (density and NoT is log-scaled). NoT = number of tracts; LoF = length of fiber; ADC = apparent diffusion coefficient; gFA = global fraction anisotropy.

Figures 2 and 3 present the threshold-dependent trajectories of three graph-theoretical measures under absolute and proportional thresholding schemes, respectively. In both figures, trajectories are shown for healthy controls (HC, green lines) and schizophrenia patients (SZ, red lines), with error bars indicating the standard error. For both thresholding approaches, it can be observed that the metric values of the patients' graph are lower than HC. In absolute thresholding, all graph metrics exhibit a decrease with increasing threshold values. However, the rate of reduction varies across different network weighting methods (see Fig. 2), as an instance, density-weighted networks show exponential like decay in node degree, however, LoF-weighted networks demonstrate quasi-linear reductions.

For illustration of proportional thresholding effect**,** **t**he x-axis is inverted to maintain consistent interpretation with absolute thresholding (left = denser networks). Notably, the trend of graph metric reduction relative to decreasing density percentage (proportional thresholding) remains largely consistent across different network weighting schemes (Fig. 3).

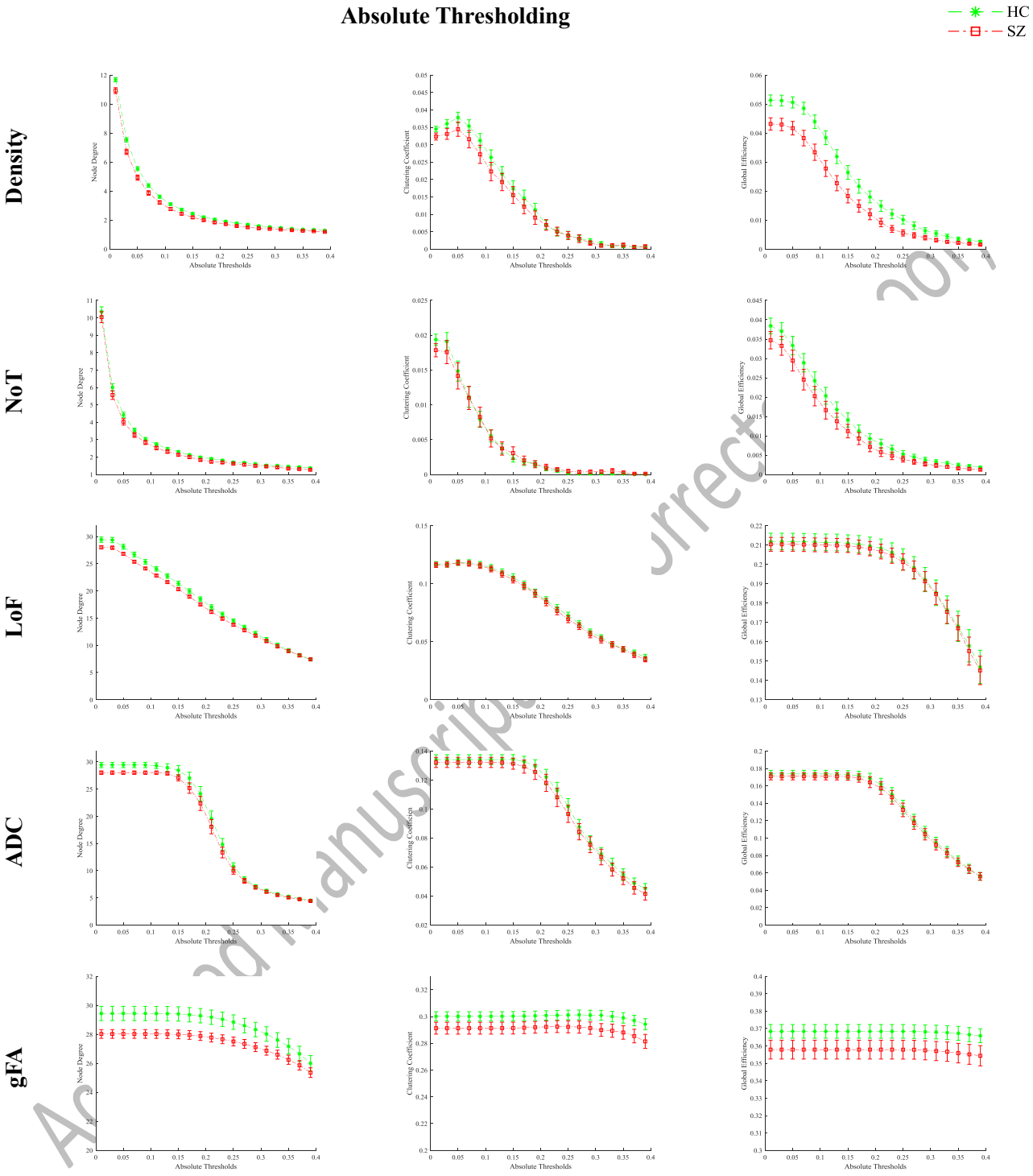

Fig. 2. Graph metric variations under absolute thresholding. Five network weightings are displayed (top-to-bottom): Density, NoT, LoF, ADC, and gFA. For each network weighting, three graph measures are shown (left-to-right): Node degree, Clustering Coefficient, global efficiency. The x-axis represents the threshold values, where higher thresholds correspond to sparser networks. The green starred line and the red squared line indicate the HC and SZ groups, respectively. Markers indicate mean and vertical error bars represent standard error.

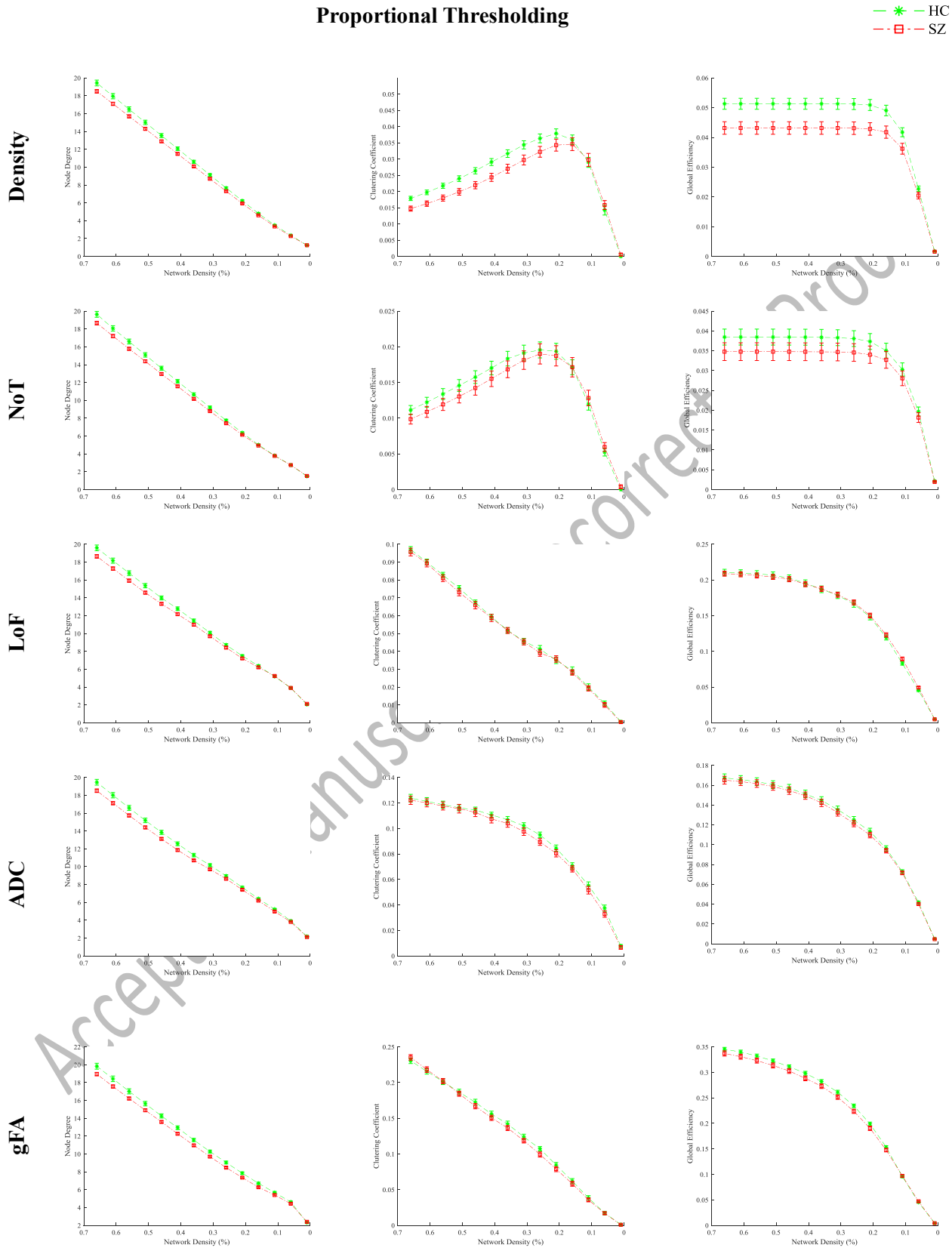

Fig. 3. Graph metric variations under proportional thresholding. Five network weightings are displayed (top-to-bottom): Density, NoT, LoF, ADC, and gFA. For each network weighting, three graph measures are presented (left-to-right): Node degree, Clustering Coefficient, global efficiency. The x-axis represents the network density (in percentage), where lower value corresponds to sparser networks. The green starred line and the red squared line indicate the HC and SZ groups, respectively. Markers indicate mean and vertical error bars represent standard error.

Figures 4 and 5 present the results of statistical comparisons between schizophrenia patients and healthy controls across threshold values for absolute and proportional thresholding, respectively. Significant intergroup differences emerge at relatively low threshold values under absolute thresholding (Fig. 4), particularly for node degree ($p < 0.05$), with a similar pattern under proportional thresholding (Fig. 5), indicating robustness across thresholding approaches. The most pronounced group differences are seen in density-weighted networks, and node degree appears to be the graph metric most affected in schizophrenia. (Fig. 4 and Fig. 5). Although mean global efficiency for NoT visually appears different between groups (Figure 3), this difference does not reach statistical significance (Figure 5), likely due to high inter-subject variability and the differing sensitivity of absolute versus proportional thresholding.

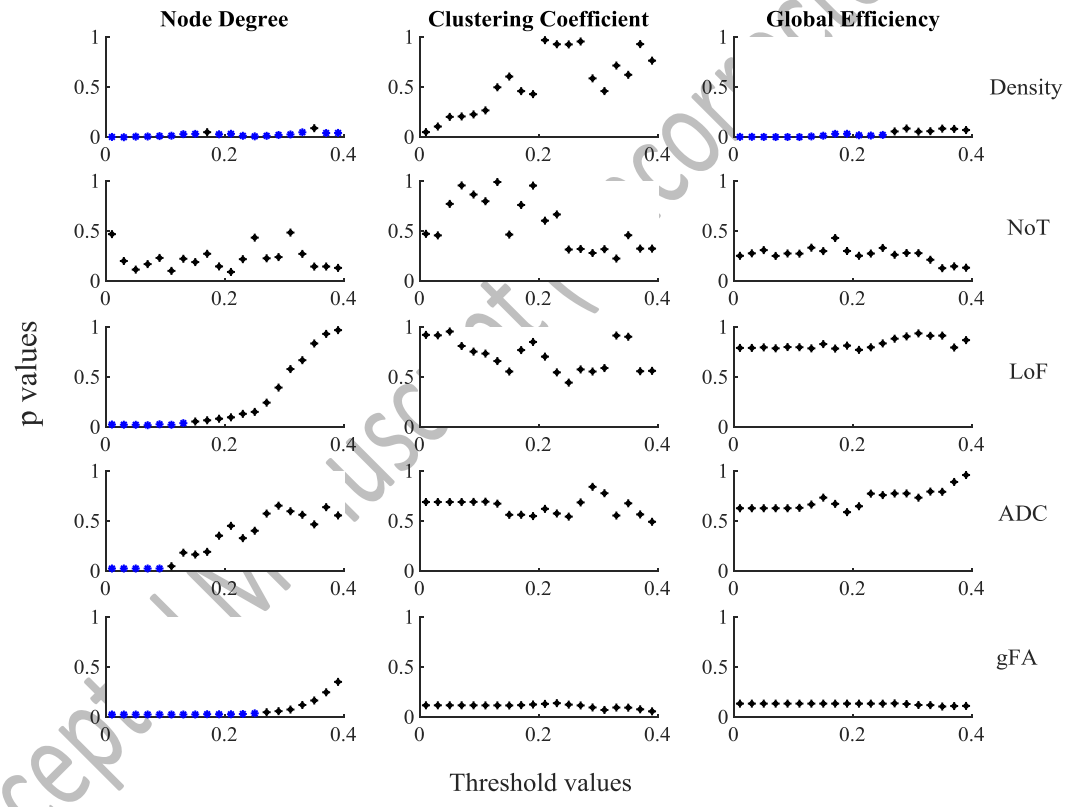

Fig. 4. Statistical test analysis for absolute thresholding approach. The blue dots represent the significant difference between SZ and HC (p-value < 0.05), the black represents the non-significant difference (p-value >= 0.05). Five network weightings are presented in the following order (top-to-bottom): Density, NoT, LoF, ADC, and gFA. For each network weighting, three measures are presented (left-to-right): Node degree, Clustering Coefficient, global efficiency.

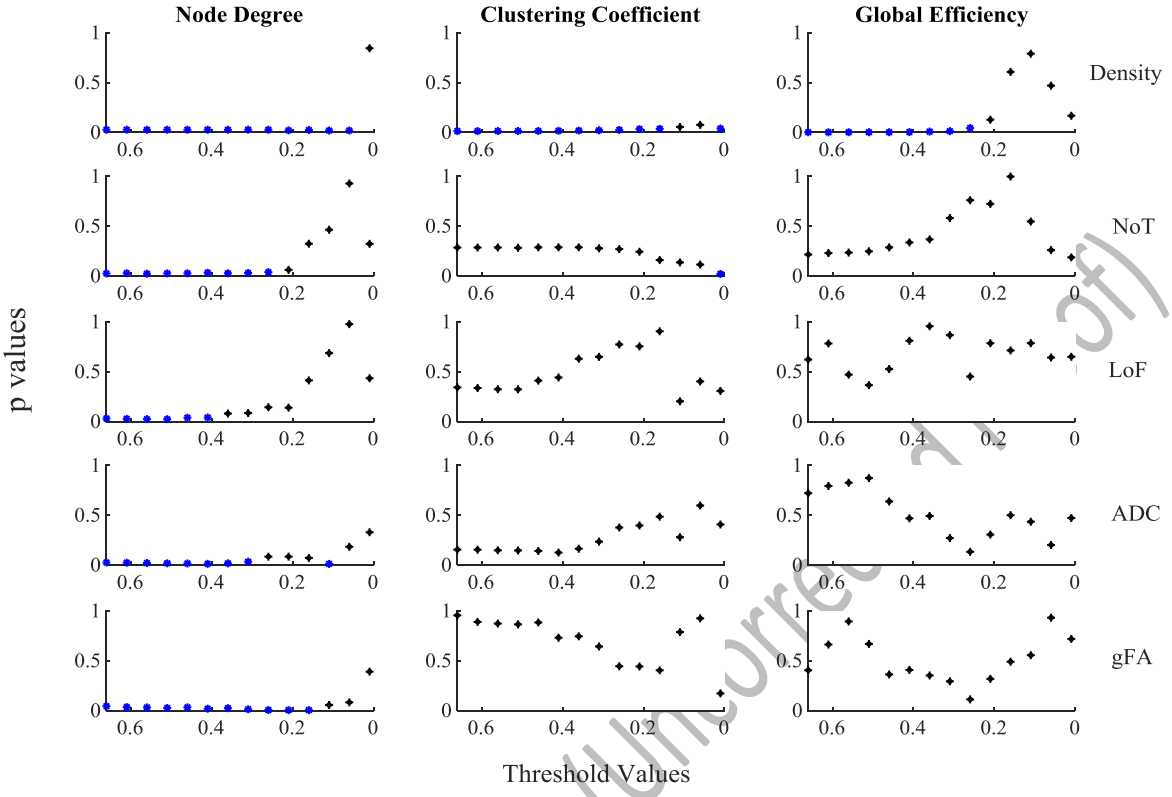

Fig. 5. Statistical test analysis for proportional thresholding approach. The blue dots represent the significant difference between SZ and HC (p-value < 0.05), the black represents the non-significant difference (p-value >= 0.05). Five network weightings are presented in the following order (top-to-bottom): Density, NoT, LoF, ADC, and gFA. For each network weighting, three measures are presented (left-to-right): Node degree, Clustering Coefficient, global efficiency.

Discussion

In this study, we investigated how different network thresholding strategies and edge-weighting schemes influence variations in graph metrics derived from structural connectivity matrices. Our findings indicate that, in the absence of thresholding, no statistically significant differences emerged between the schizophrenia group and healthy controls. However, eliminating spurious connections substantially altered the analytical outcomes.

Variations in network topology and graph-derived metrics across different threshold levels are particularly relevant in the context of the well-recognized reproducibility crisis in contemporary science, which complicates the comparability of studies employing diverse analytical pipelines (Adamovich et al., 2022; Buchanan et al., 2020). Our findings emphasize that threshold selection can substantially influence experimental outcomes, as even two closely spaced thresholds may yield divergent results. More critically, the network architecture derived at one threshold may lead to conclusions that differ from those obtained at another. While the rationale behind thresholding—removing weak edges—suggests that stable effects are most likely to be observed at higher thresholds where spurious connections are minimized, our results demonstrate that detectable effects may also arise at considerably lower thresholds. These observations highlight the necessity for a deliberate, evidence-based approach to threshold selection in network analyses.

In addition to demonstrating the general methodological impact of thresholding, our study directly examined how threshold choice influences the detection of schizophrenia-related alterations in structural connectivity. This disease–threshold interaction has rarely been assessed explicitly in prior work, where most schizophrenia connectome studies have relied on a single threshold or weighting scheme. Recent schizophrenia connectome studies and meta-analyses have consistently reported widespread dysconnectivity, including reduced global integration, altered segregation, and disruptions in large-scale structural organization (Brandl et al., 2019; Drakesmith et al., 2015; Gao et al., 2023; Keyvanfard et al., 2023; Zhu et al., 2022). Our findings are broadly aligned with prior literature in demonstrating lower values of graph-theoretical measures; such as node degree, clustering coefficient, and global efficiency; in patients with Schizophrenia. Notably, reductions in node degree and density-weighted network measures suggest impaired large-scale brain network integration, which may be clinically relevant given their established links to cognitive and functional deficits in schizophrenia. However, our results also reveal that the detectability and magnitude of these group differences depend strongly on the chosen thresholding strategy. This observation is consistent with methodological work demonstrating that graph metrics are highly sensitive to network density, pruning decisions, and weighting choices (Buchanan et al., 2020; Smucny et al., 2016; van Wijk et al., 2010; Wang et al., 2020; Zalesky et al., 2016). By integrating these two lines of evidence, our study extends existing schizophrenia findings by explicitly showing that thresholding not only shapes network topology in general but also modulates whether—and under which analytical conditions—schizophrenia-related alterations become statistically observable. These findings highlight the importance of considering threshold selection as a key analytical factor when interpreting group differences in structural connectome studies.

Our results (Figs. 2 and 3) show that node degree and global efficiency generally exhibit a smooth, gradual decline as the threshold increases. In contrast, the clustering coefficient displays a more complex and, in some cases, distinctly irregular pattern of change. Its relationship with threshold values is non-monotonic and does not consistently follow a straightforward trend, reflecting the combined influence of factors such as the underlying network topology, the specific threshold applied, and inherent random variability (Lacy & Robinson, 2020). Previous studies have reported that the clustering coefficient may exhibit a plateau at intermediate threshold levels (Adamovich et al., 2022) or present a peak within a specific range of similarity thresholds before declining (Zahoránszky-Kőhalmi et al., 2016). Based on these observations, we recommend avoiding reliance on the clustering coefficient as a sole metric for result interpretation, and instead considering it alongside other complementary network measures.

According to our results, the thresholding procedure leads to substantial variability in the data. And in overall, we have found that:

1. Global graph metrics vary as a function of threshold level. Low and high threshold values do not change these metrics in a similar way.
2. The chosen threshold may influence the outcome of the analysis (e.g., the presence or absence of the effect of group comparisons). On the other words, identifying significant difference between patient and healthy group is affected by network weighting and thresholding.
3. Finding significant difference has more robust manner in proportional thresholding.
4. Graph metric variation trend provides the evidence that proportional thresholding makes almost similar reduction trend across different network weighting.
5. Construction of SC matrix based on density weighting led to observe more significant difference between SZ and HC groups.
6. Threshold value has stronger effect on results compared to threshold approach.

7. Proportional thresholding was associated with lower standard error compared to absolute thresholding, indicating reduced variability in graph metrics.

Our study was mostly limited to the small size of dataset. Larger dataset may lead to more reliable results. Furthermore, effect of other thresholding approaches such as consistency-thresholding (Roberts et al., 2017) can also be investigated. This research can also be extended to investigate the correlation of different network weighting (and thresholding method) and demographic information such as age or clinical measure of cognitive function in a larger size of dataset.

We acknowledge that no correction for multiple comparisons across threshold levels was applied. Because threshold-dependent graph metrics are highly correlated and reflect variations of the same underlying connectivity structure, applying conventional corrections would severely reduce sensitivity. Future studies with larger samples may benefit from approaches specifically designed for dependence across thresholds (e.g., cluster-based or functional data analysis methods).

Conclusion

In conclusion, this study underscores the pivotal role of threshold selection in determining the outcomes of network-based analyses. Our results reveal that the threshold level has a more pronounced impact on graph-theoretical metrics than the specific thresholding algorithm employed. Given that threshold selection is often arbitrary and lacks strong theoretical justification, it introduces an additional layer of uncertainty into results—particularly in a field that is already characterized by considerable variability. Importantly, we also show that applying density-based network weighting enhances the sensitivity of graph metrics to alterations in brain network organization, thereby offering a more robust means of detecting connectivity changes in neuropsychiatric disorders such as schizophrenia. These insights highlight the necessity for rigorous methodological standardization and transparent reporting of thresholding parameters to improve the reproducibility and interpretability of connectome studies.

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Conflicts of interest/Competing interests the author declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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