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Research Paper

# Impact of Weighting and Thresholding Strategies on Structural Brain Network Analysis in Schizophrenia

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## ABSTRACT

**Introduction:** Diffusion magnetic resonance imaging (dMRI) 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.

**Methods:** We analyzed data from 27 schizophrenia (SZ) patients and 27 demographically matched healthy controls. Five network weighting schemes (fiber density, streamline count, mean fiber length, apparent diffusion coefficient [(ADC)], and global fractional anisotropy [gFA]) 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:** 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.

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## Highlights

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

## Plain Language Summary

The human brain functions as a complex network in which different regions communicate through "highways" formed by nerve fibers. Scientists can map these pathways using a specialized magnetic resonance imaging technique called diffusion tensor imaging (DTI). However, the resulting maps are imperfect and may contain false-positive connections that do not actually exist. To reduce these inaccuracies, researchers commonly use a procedure called thresholding, which removes the weakest connections. Nevertheless, there is currently no standardized rule regarding the appropriate threshold level. In this study, we investigated whether different approaches to thresholding brain networks influence the results, particularly when comparing individuals with schizophrenia with healthy individuals. We analyzed brain imaging data from 27 individuals with schizophrenia and 27 healthy participants. Two thresholding methods were tested across five measures of connection strength, and three key properties of brain network organization were evaluated. Our findings showed that the selected threshold level substantially influenced the results. At lower thresholds, which retained a greater number of connections, more statistically significant differences were observed between the groups. At higher thresholds, which retained only the strongest connections, many of these differences were no longer detectable. The extent of thresholding had a greater influence on the findings than the specific thresholding method used. Among the measures examined, fiber density was the most sensitive for detecting brain network differences associated with schizophrenia. Schizophrenia affects approximately 1 in 200 adults worldwide and is a major cause of disability. Understanding disruptions in brain connectivity may contribute to the development of more effective treatments. However, our findings highlight an important methodological concern: different research groups may use different thresholding approaches, potentially reaching different conclusions even when analyzing similar data. Such variability may limit the reproducibility and comparability of research findings. Therefore, standardized methods are needed to improve consistency across studies. More broadly, these results demonstrate that analytical decisions can substantially influence reported brain differences in mental health conditions and should be considered when interpreting both scientific studies and related media reports.

## 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- 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 (Van Wijk et al., 2010). 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) 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. (2016) further highlight 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 approaches, motivated the present study's comparison of absolute and proportional thresholding across multiple weighting schemes.

Schizophrenia (SZ), a chronic and disabling mental disorder, approximately affects 0.45% of the adult population worldwide (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 SZ (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 explored 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 compared graph metrics across individuals diagnosed with SZ and healthy controls, focusing on three commonly used measures: node degree, clustering coefficient, and global efficiency. This investigation aimed to clarify how thresholding choices and weighting strategies affect the detection of network differences in SZ.

## Materials and Methods

### Dataset

We utilized structural connectivity data from 27 individuals diagnosed with SZ (mean age: 41±9.6 years) and 27 healthy participants as a control group (mean age: 35±6.8 years), matched across all relevant parameters. This dataset was previously published on Zenodo, with full methodological details (Vohryzek et al., 2020). Par-

ticipants in the SZ group were recruited from the Service of General Psychiatry at Lausanne University Hospital and met the DSM-IV diagnostic criteria for SZ 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 (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.

### Network thresholding and measures

Structural connectivity between brain regions was reconstructed using whole-brain deterministic tractography. Networks were generated by identifying connections between all pairs of 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. ADC – the mean diffusivity along the connecting streamlines, indicating the magnitude of diffusion;

5. Global FA (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).

We examined a range of threshold levels T from 0.01 to 0.4 in steps of 0.02 for absolute thresholding, and a 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 enable the application of similar threshold values.

In addition, three graph-theoretic metrics (Rubinov & Sporns, 2010) were computed to quantify 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 $k_i$, 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 (Equation 1):

1.

$$k_i = \Sigma_j a_{ij}$$

Where $a_{ij}$ is an element of the adjacency matrix.

Global efficiency (Eglobal) 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. Global efficiency is calculated using Equation 2:

2.

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

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

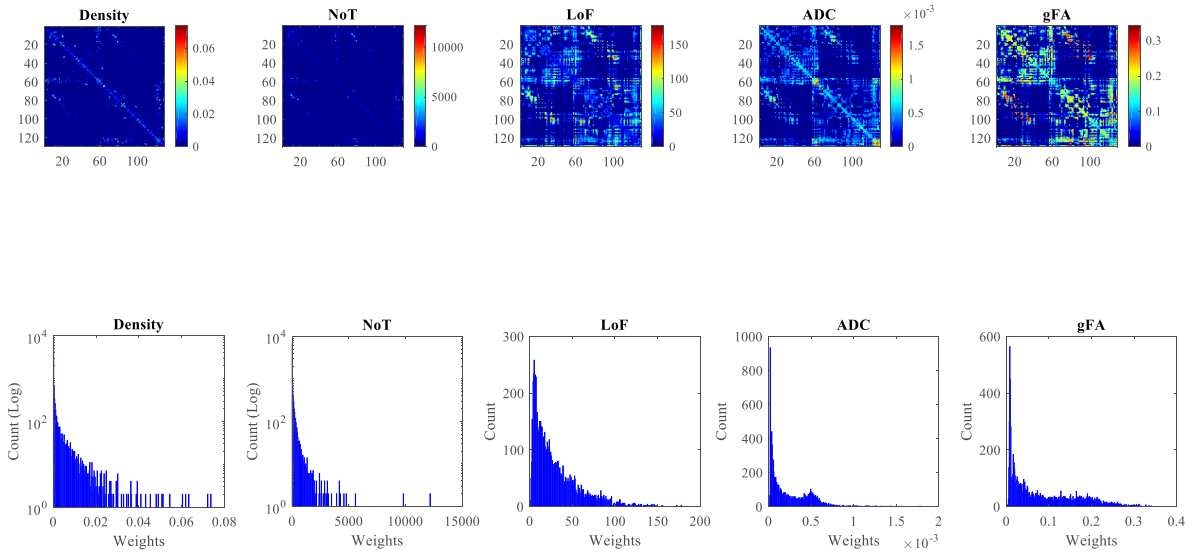


**Figure 1.** Mean connectivity matrices and their distribution

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 are log-scaled).

Abbreviations: NoT: Number of tracts; LoF: Length of fiber; ADC: Apparent diffusion coefficient; gFA: Global fraction anisotropy.

al., 2005). For a weighted graph, it is defined as the geometric mean of the intensities of triangles around a node i (Equation 3):

3.

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

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 SZ and healthy controls (HCs), 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 reported 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 Figure 1. Before any thresholding, the Mean±SD value of network density (the proportion of nonzero-weighted elements in a connectivity matrix) across subjects was 0.238±0.0078). From the histograms of edge weights pooled across all subjects (Figure 1) we observed that the distribution of all network weights approximately followed a power law, involving many low-weighted connections but very few high-weighted connections.

Figures 2 and 3 present the threshold-dependent trajectories of three graph-theoretical measures under abso-

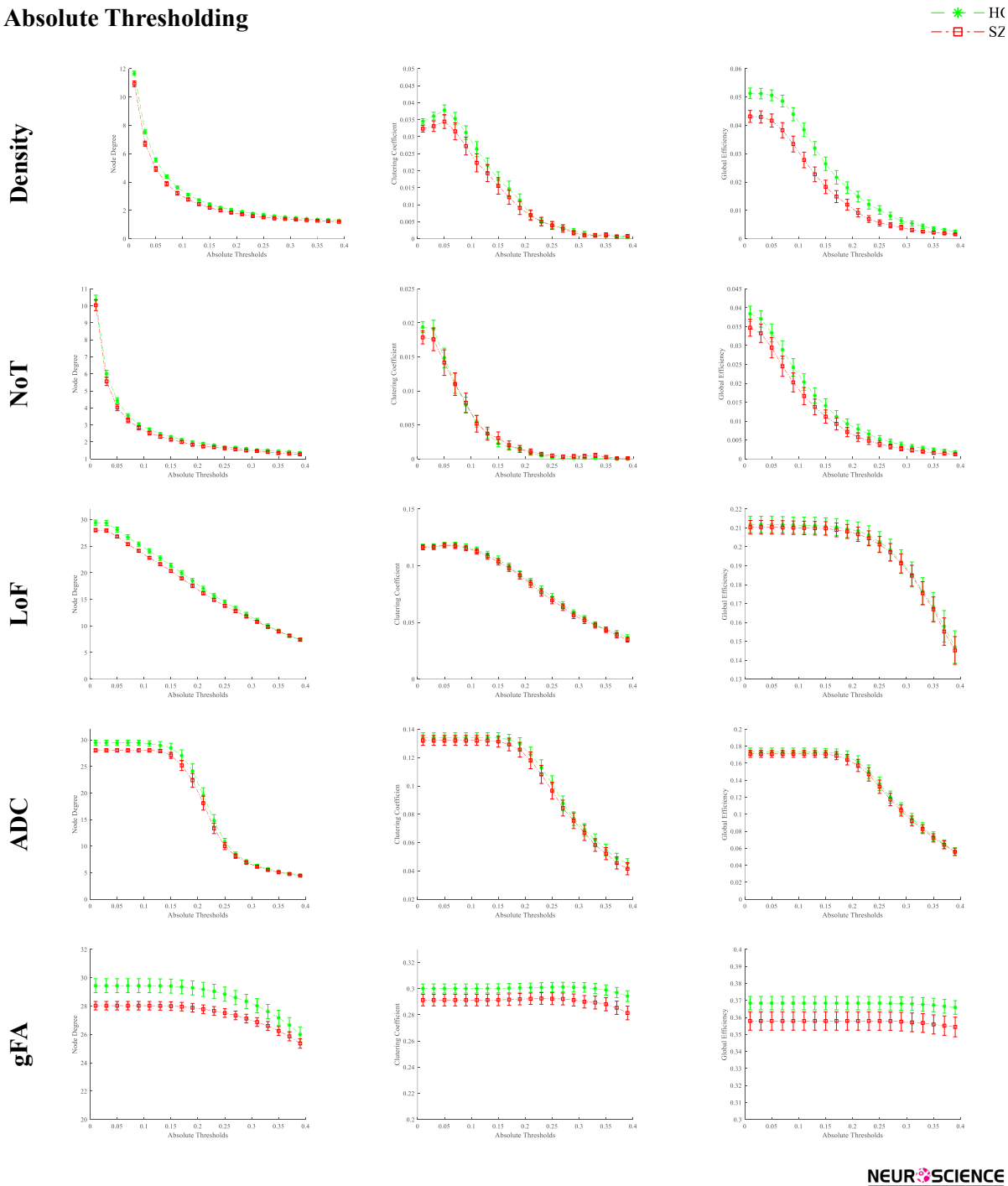


**Figure 2.** Graph metric variations under absolute thresholding

Note: 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, and 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 the mean, and vertical error bars represent the standard error.

lute and proportional thresholding schemes, respectively. In both figures, trajectories are shown for HCs (green lines) and SZ patients (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 those of HCs. In absolute thresholding, all graph metrics exhibited a decrease with increasing threshold values. However, the rate of reduction varied

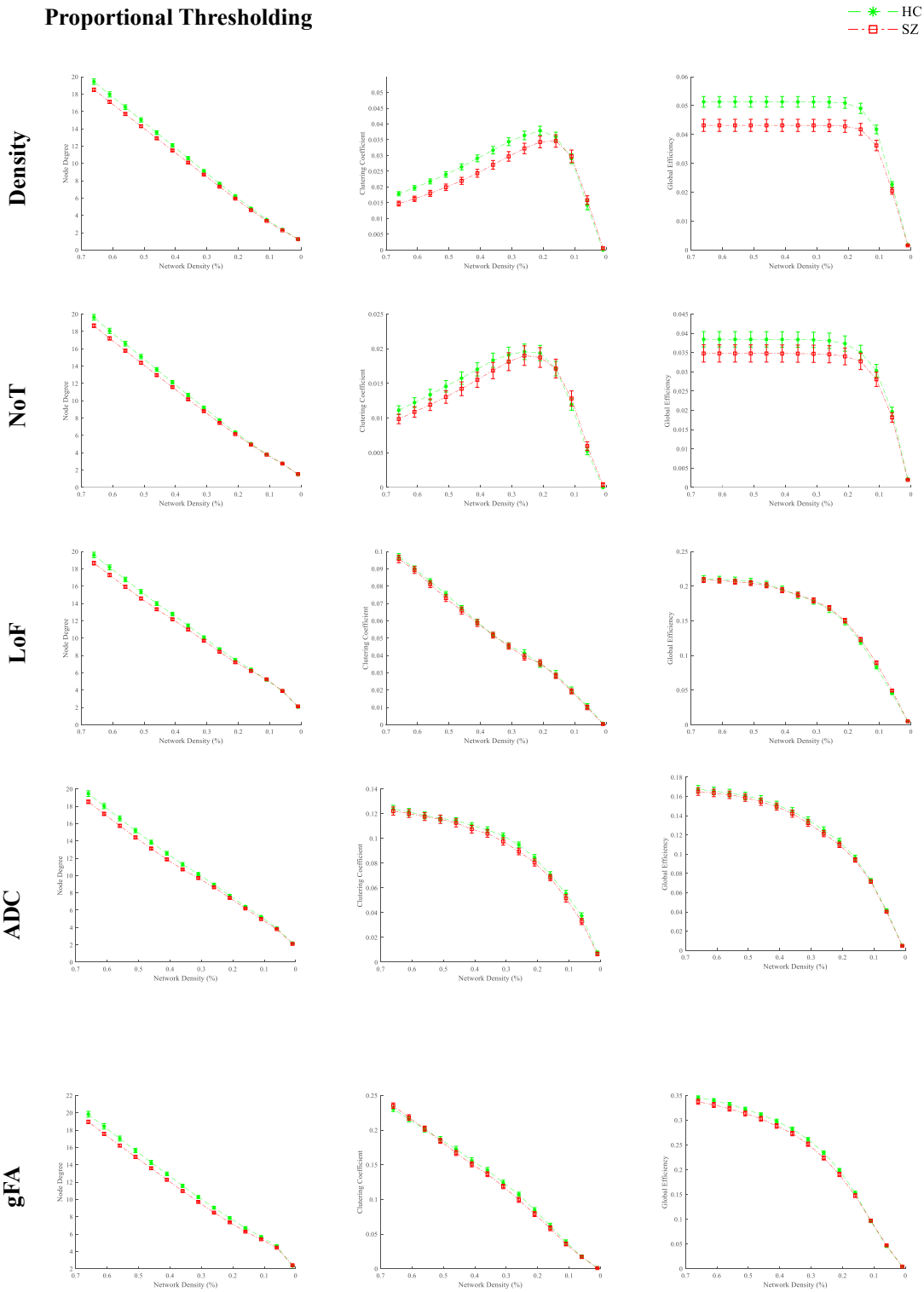


**Figure 3.** Graph metric variations under proportional thresholding

Note: 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, and global efficiency. The x-axis represents the network density (in percentage), where lower values correspond to sparser networks. The green starred line and the red squared line indicate the HC and SZ groups, respectively. Markers indicate the mean, and vertical error bars represent the standard error.

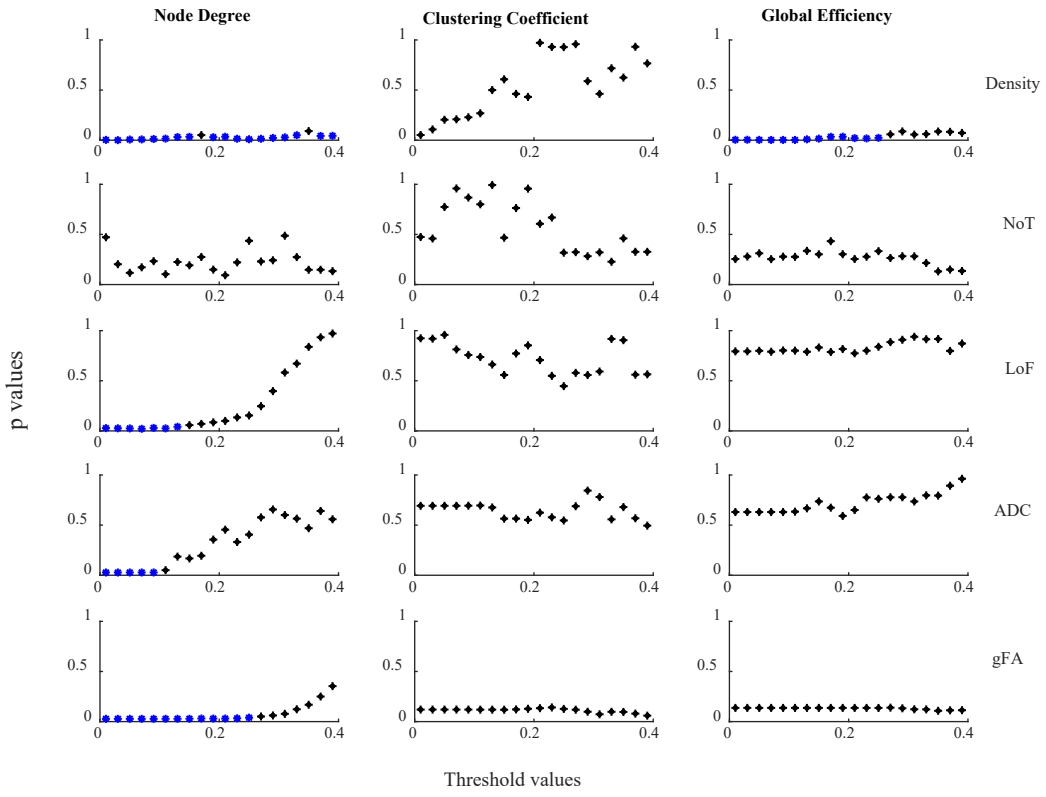


**Figure 4.** Statistical test analysis for the absolute thresholding approach

Note: Blue dots represent significant differences between SZ and HC (P<0.05), while black dots represent non-significant differences (P≥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, and global efficiency.

across different network weighting methods (Figure 2). For instance, density-weighted networks show an exponential-like decay in node degree, whereas LoF-weighted networks demonstrate quasi-linear reductions.

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

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

## Discussion

We investigated how different network thresholding strategies and edge-weighting schemes influence variations in graph metrics derived from structural connectivity matrices. Our findings indicated that in the absence of thresholding, no statistically significant differences emerged between the SZ group and HCs. However, eliminating spurious connections substantially altered the analytical outcomes.

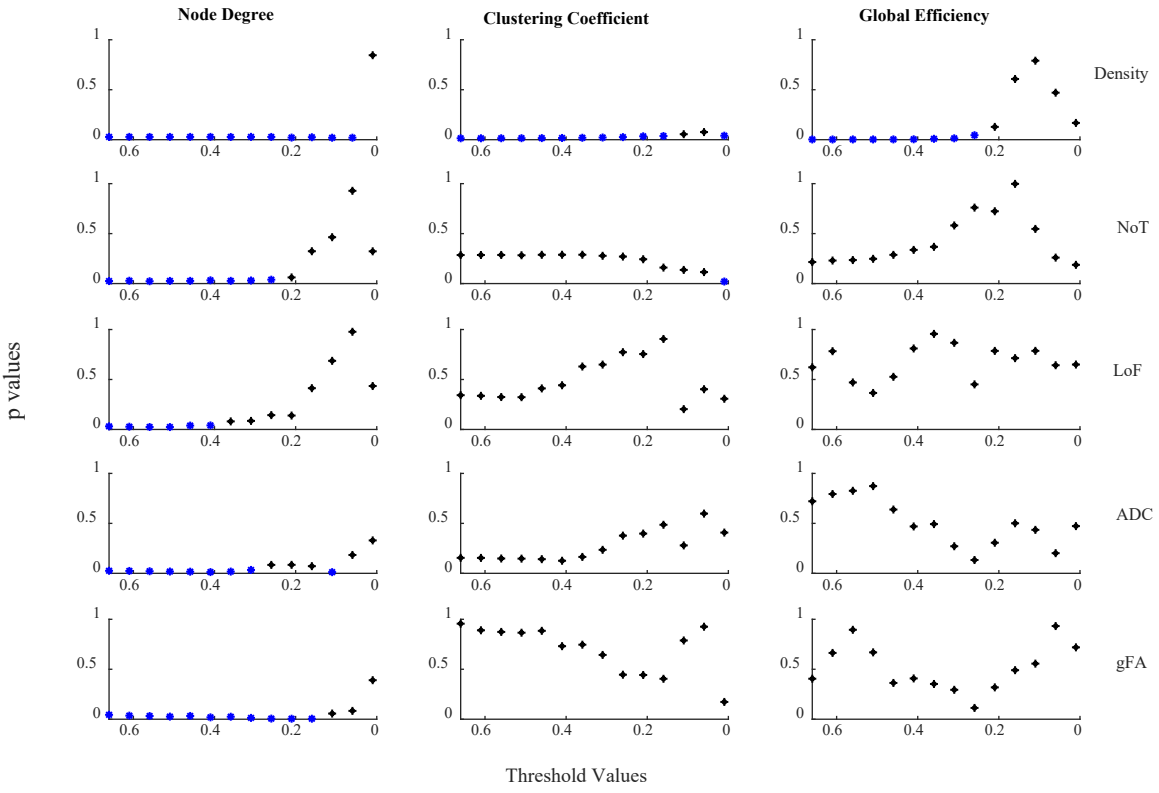


**Figure 5.** Statistical test analysis for the proportional thresholding approach

Note: Blue dots represent significant differences between SZ and HC (P<0.05), while black dots represent non-significant differences (P≥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, and global efficiency.

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 SZ-related alterations in structural connectivity. This disease–threshold interaction has rarely been assessed explicitly in prior work, where most SZ connectome studies have relied on a single threshold or weighting scheme. Recent SZ 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 SZ. 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 SZ. However, our

results also revealed 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 SZ findings by explicitly showing that thresholding not only shapes network topology in general but also modulates whether—and under which analytical conditions—SZ-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 (Figure 2 and 3) showed 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. Overall, we found that:

1. Global graph metrics vary as a function of threshold level. Low and high threshold values do not change these metrics in the same way.

2. The chosen threshold may influence the outcome of the analysis (e.g. the presence or absence of the effect of group comparisons). In other words, identifying significant differences between patient and healthy groups is affected by network weighting and thresholding.

3. Finding significant differences is more robust under proportional thresholding.

4. The trend of graph metric variation provides evidence that proportional thresholding produces a similar reduction trend across different network weightings.

5. Construction of the SC matrix based on density weighting led to the observation of more significant differences between SZ and HC groups.

6. Threshold value has a stronger effect on results compared to the 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 by the small size of the dataset. A larger dataset may lead to more reliable results. Furthermore, the 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 between different network weightings (and thresholding methods) and demographic information, such as age or clinical measures of cognitive function, in a larger 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 revealed 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 showed 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 SZ. These insights highlight the necessity for rigorous methodological standardization

and transparent reporting of thresholding parameters to improve the reproducibility and interpretability of connectome studies.

## Ethical Considerations

### Compliance with ethical guidelines

All ethical principles were considered in this study. The original data collection, which we have used, involved human participants who were informed of the research purpose and procedures, provided written consent, were assured of confidentiality, and could withdraw at any time, in accordance with the Helsinki Convention. This secondary analysis of publicly available data was approved by the Ethics Committee of Clinical Research of the Faculty of Biology and Medicine, University of Lausanne, Switzerland (Codes: #82/14, #382/11, #26.4.2005). The present article is a retrospective analysis with no direct human or animal sample.

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### Conflict of interest

The author declared no conflict of interest.

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