

Schizophrenia Biomarkers from fMRI Data Using Forman-Ricci Curvature on Hypergraphs

Eronides F. da Silva Neto, Pedro Morgado and Juliano B. Lima

Abstract—In this work, subject-level weighted 3-uniform hypergraph adjacency tensors are constructed from blood-oxygen-level-dependent (BOLD) functional MRI time series using O-information as hyperedge weights, and Forman-Ricci curvature (FRC) is computed at hyperedge and node levels. Global mean curvature and node-wise profiles are compared between schizophrenia patients and healthy controls (HC) across 90 AAL regions via Mann-Whitney U and Welch’s t -tests with Benjamini-Hochberg correction. Results reveal significantly more negative curvature in healthy controls ($p = 2.88 \times 10^{-5}$, $d \approx 0.58$) and widespread regional differences, supporting global and node-level FRC as sensitive and interpretable putative neuroimaging biomarkers for schizophrenia.

Keywords—Schizophrenia, fMRI, Functional Connectivity, Brain Network Analysis, Hypergraph, Forman-Ricci Curvature.

I. INTRODUCTION

Schizophrenia (SZ) is a severe psychiatric disorder affecting approximately 1% of the global population, characterized by disrupted thought processes, perceptual disturbances, and cognitive deficits [1]. Despite decades of research, reliable neuroimaging-based biomarkers for its diagnosis remain elusive [2], limiting early detection and objective clinical assessment. Resting-state functional MRI (rs-fMRI) captures spontaneous blood-oxygen-level-dependent (BOLD) signals and has become one of the most widely adopted noninvasive tools for studying functional brain organization, offering a promising substrate for data-driven biomarker discovery.

Classical graph-based analyses of fMRI functional connectivity networks (FCNs) model pairwise correlations between brain regions of interest (ROIs) as edges of a weighted graph [3]. While these approaches have uncovered global and local topology differences in SZ cohorts, they are inherently limited to binary interactions and cannot capture higher-order co-activation patterns simultaneously involving three or more brain regions.

Hypergraphs generalize graphs by allowing edges (hyperedges) to connect any number of vertices, and are therefore better suited to represent the polysynaptic and multi-regional coordination that characterises large-scale brain networks [4]. Recent proposals combine topological features derived from these hypergraphs, such as Hodge-decomposed gradient and solenoidal components, capture mesoscale organization and

cyclic coordination patterns not expressible in standard graph-based connectomes [5], [6]. Collectively, these approaches establish a principled topological framework for brain connectomics with potential applications in clinical biomarker discovery [7], [8].

Building on this foundation, we propose to characterize schizophrenia-related alterations in brain connectivity using Forman-Ricci curvature (FRC) computed on hypergraphs. Recently extended to hypergraph domains [9], FRC is a differential-geometry-inspired measure that captures the interplay between hyperedge weights and node participation, providing a principled description of higher-order interactions (HOIs). When applied to fMRI-derived brain hypergraphs, FRC encodes topology-driven features of functional organization, enabling the identification of topological anomalies in brain networks [10]. While prior work has demonstrated the sensitivity of graph-based FRC to psychiatric disorders, the present study extends this framework to 3-uniform hypergraphs, capturing higher-order co-activation patterns beyond pairwise models and supporting its use as a putative biomarker for distinguishing schizophrenia patients from healthy controls.

In this work, we construct subject-level weighted 3-uniform hypergraph adjacency tensors from rs-fMRI BOLD time series and compute Forman-Ricci curvature at both the hyperedge and node levels. Global mean curvature and node curvature profiles are compared between SZ patients and HC subjects via Mann-Whitney U and Welch’s t -tests with Benjamini-Hochberg false discovery rate (FDR) correction across brain regions, aiming to identify curvature-based features that reliably distinguish the two groups and serve as putative neuroimaging biomarkers for schizophrenia. This study focuses on the statistical, group-level validation of FRC as a putative neuroimaging biomarker through group and node-level analysis.

This paper is organized as follows. In Section II, we summarize the theoretical foundations of hypergraphs and Forman-Ricci Curvature for hypergraphs. Section III describes the proposed pipeline. Section IV presents the experimental results. Finally, Section V brings the conclusions.

II. PRELIMINARIES

A. Biomarkers from Functional MRI Data

The growing role of computational tools in healthcare has positioned data as a cornerstone for developing artificial intelligence (AI) solutions, particularly in neuroimaging. Among the available modalities, fMRI stands out as a prominent

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noninvasive approach for evaluating brain function, offering quantitative insights into neural activity and connectivity that can inform both diagnosis and clinical decision-making.

Resting-state fMRI measures the BOLD signal over time from a spatially discretised brain volume. To reduce the dimensionality of this high-dimensional signal and impose anatomically or functionally meaningful structure, the brain is parcellated into a set of N non-overlapping ROIs. Parcellation can be performed using either anatomical atlases, such as the Automated Anatomical Labeling (AAL) or the Desikan-Killiany atlas, or functional approaches that group voxels based on the similarity of their BOLD responses [7]. After standard preprocessing (motion correction, spatial normalization, band-pass filtering), the signal at each ROI k is represented as a time-series $x_k(t)$, $t = 1, \dots, T$.

A neuroimaging biomarker is a quantitative feature derived from rs-fMRI BOLD signals that reliably distinguishes clinical populations from healthy controls, serving as an objective indicator of psychiatric disorders [2].

B. Hypergraphs

A weighted undirected hypergraph is defined as a triple $\mathcal{H} = (\mathcal{V}, \mathcal{E}, w)$, where $\mathcal{V} = \{v_1, \dots, v_N\}$ is a finite set of vertices, $\mathcal{E} = \{e_1, \dots, e_K\}$ is a multiset of subsets $e \subseteq \mathcal{V}$ called hyperedges, and $w : \mathcal{E} \rightarrow \mathbb{R}_{>0}$ is a function that assigns a positive weight w_e to each hyperedge $e \in \mathcal{E}$. For a 3-uniform hypergraph, where each hyperedge contains exactly three vertices ($|e| = 3$), we define the adjacency tensor $\mathcal{A} \in \mathbb{R}^{N \times N \times N}$ as a third-order symmetric tensor whose entries are given by

$$\mathcal{A}[i, j, k] = \begin{cases} w_{\{i, j, k\}}, & \text{if } \{v_i, v_j, v_k\} \in \mathcal{E}, \\ 0, & \text{otherwise,} \end{cases} \quad (1)$$

for all $i, j, k \in \{1, \dots, N\}$, with symmetry under any permutation of indices. Thus, each unique vertex triplet $\{i, j, k\}$ with $i < j < k$ corresponds to a potential hyperedge, and its associated weight can be expressed as $w_{\{i, j, k\}} = \mathcal{A}[i, j, k]$. The weighted vertex degree of vertex k is defined as

$$w_k = \sum_{e' \ni k} w_{e'}, \quad (2)$$

where the sum runs over all unique hyperedges incident to k .

Hypergraphs generalize graphs by connecting more than two vertices per edge, naturally encoding HOIs in brain networks. To quantify the nature and strength of these interactions, information-theoretic measures have been proposed as a principled alternative to correlation-based metrics. Among them, O-information (OI) has emerged as a particularly compelling tool for characterizing HOIs in the brain [11]–[14], as it can distinguish between two qualitatively distinct modes of multivariate dependence: redundancy, where multiple regions convey the same information about the rest of the system, and synergy, where the collective activity of a group of regions carries information that no subset alone can provide.

Let $\{x_k(t)\}_{k=1}^N$ denote the BOLD time series extracted from N ROIs, and let $\mathbf{x}_i$ represent the random variable associated with the time series of the i -th ROI. OI metric enables a

qualitative characterization of multivariate dependencies by distinguishing whether dominant interactions among brain regions are primarily redundant or synergistic. For a triplet of ROIs $\{i, j, k\}$, OI is defined as

$$OI_{i,j,k} = H(\mathbf{x}_i) + H(\mathbf{x}_j) + H(\mathbf{x}_k) - H(\mathbf{x}_i, \mathbf{x}_j) - H(\mathbf{x}_i, \mathbf{x}_k) - H(\mathbf{x}_j, \mathbf{x}_k) + H(\mathbf{x}_i, \mathbf{x}_j, \mathbf{x}_k), \quad (3)$$

where $H(\cdot)$ is the Shannon entropy, $H(\cdot, \cdot)$, and $H(\cdot, \cdot, \cdot)$ are the joint-entropies of the arguments. Positive values of $OI_{i,j,k}$ indicate redundancy-dominated interactions, whereas negative values indicate synergy-dominated interactions.

C. Forman-Ricci Curvature for Hypergraphs

Topological properties have been increasingly explored in brain network analysis [6], with recent contributions employing the topological signal processing (TSP) framework to capture higher-order relationships among ROIs [5]. Building on this perspective, FRC offers a computationally tractable discretization of Ricci curvature applicable to hyperedges [9], making it well suited for quantifying the local geometry of hypergraph-based brain connectivity.

Since O-information values can be either positive or negative, hyperedge weights are defined as $w_e = |w_{\{i,j,k\}}|$, ensuring that both interaction regimes contribute to the hypergraph topology and that FRC captures the geometric organization of higher-order interactions regardless of their nature. For a weighted undirected hyperedge e , FRC is defined as

$$F(e) = w_e \left[\sum_{k \in e} \left(\frac{w_k}{w_e} - \sum_{e_l \sim k} \frac{w_k}{\sqrt{w_e w_{e_l}}} \right) \right], \quad (4)$$

where $e_l \sim k$ denotes all hyperedges $e_l \neq e$ incident to vertex k [9]. This expression captures the trade-off between hyperedge weight and the connectivity of its constituent vertices: strongly negative values indicate brain regions that participate in many co-activation triplets, reflecting dense integration, while near-zero or positive values characterize more segregated, locally contained interactions.

Drawing on the results of [10], Forman-Ricci curvature provides a sensitive descriptor of higher-order functional interactions by quantifying, through a differential-geometry-inspired formulation, the interplay between hyperedge weight and the participation degrees of constituent vertices, enabling the detection of subtle network alterations in brain connectivity.

III. PROPOSED METHOD

Figure 1 illustrates the overall processing pipeline of the proposed method, which consists of four sequential stages: (i) atlas-based parcellation of rs-fMRI data into normalized ROI time series, (ii) hypergraph construction using O-information as hyperedge weights, (iii) Forman-Ricci curvature computation over the resulting adjacency tensor, and (iv) global curvature analysis for schizophrenia putative biomarker extraction. All stages were implemented in Python, leveraging standard neuroimaging and scientific computing libraries.

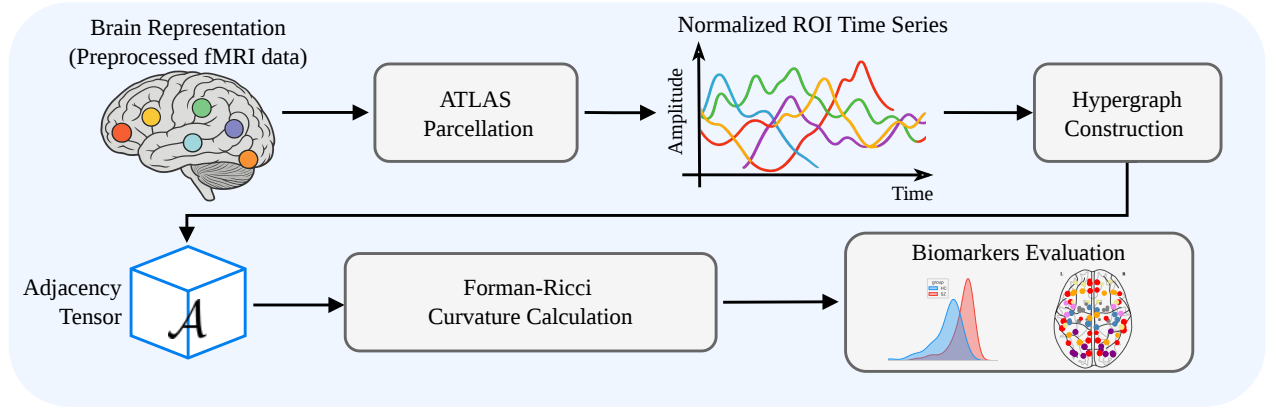


Fig. 1

OVERVIEW OF THE PROPOSED PIPELINE FOR SCHIZOPHRENIA PUTATIVE BIOMARKER IDENTIFICATION FROM fMRI DATA VIA FORMAN-RICCI CURVATURE ON HYPERGRAPHS.

Dataset and Preprocessing. Experiments were conducted using the COBRE dataset¹, obtained from the International Neuroimaging Data-sharing Initiative (INDI). The dataset comprises rs-fMRI scans from 71 subjects with schizophrenia (SZ) and 74 healthy controls (HC), aged 18–65, preprocessed using the Neuroimaging Analysis Kit (NIAC). The 4D NIfTI volumes were loaded using the Nilearn and NiBabel libraries.

Atlas parcellation and time series normalization. The raw rs-fMRI data are first parcellated into $N = 90$ ROIs using the AAL atlas, reducing the high-dimensional voxel-level BOLD signal to a set of region-level time series. To ensure comparability across regions and participants, each time series is independently normalized via z-score standardization applied per ROI.

Hypergraph construction. For each subject, the $90 \times 90 \times 90$ adjacency tensor $\mathcal{A}$ is constructed from normalized BOLD time series, where each entry $\mathcal{A}[i, j, k]$ stores the O-information of the triplet $\{i, j, k\}$, computed using the `Thoi` Python library following [15]. The hyperedge cardinality was fixed to three as a practical trade-off between capturing higher-order interactions and maintaining computational tractability. All $\binom{90}{3} = 117,480$ candidate triplets are enumerated, and a hyperedge is created whenever $w_e = |\mathcal{A}[i, j, k]| > 0$.

Forman-Ricci curvature computation. To summarize this geometric information at the region level, the node curvature of vertex k is defined as the mean FRC over all incident hyperedges, that is,

$$F(k) = \frac{1}{|\{e \in \mathcal{E} : k \in e\}|} \sum_{e \ni k} F(e), \quad (5)$$

yielding a scalar descriptor per ROI that aggregates the local geometric structure of its higher-order interactions and serves as the basis for the putative schizophrenia biomarker features proposed in this work.

The curvature $F(e)$ of each active hyperedge is computed via the direct expansion of (4):

$$F(e) = \sum_{k \in e} w_k - \sqrt{w_e} \sum_{k \in e} w_k \cdot S_k(e), \quad (6)$$

where $S_k(e) = \sum_{e_l \ni k, e_l \neq e} 1/\sqrt{w_{e_l}}$ is the neighbour sum of vertex k excluding e . This is computed efficiently using a pre-built row-sum array over the $1/\sqrt{|\mathcal{A}|}$ tensor, with per-edge self-exclusion. Node curvature profiles and a global mean $\bar{F}$ are derived for each subject.

Biomarker extraction and statistical testing. To evaluate the group-discriminating capacity of Forman-Ricci curvature as a putative schizophrenia biomarker through statistical analysis, two levels of curvature-based features are extracted per subject. The global mean curvature $\bar{F}$, defined as

$$\bar{F} = \frac{1}{|\mathcal{E}|} \sum_{e \in \mathcal{E}} F(e), \quad (7)$$

yields a single scalar descriptor summarizing the overall geometric organization of higher-order functional interactions across the brain hypergraph. The 90-dimensional node curvature vector $\mathbf{f} = [F(0), \dots, F(89)]$ provides complementary region-level descriptors, capturing local geometric properties at each AAL ROI.

IV. RESULTS AND DISCUSSION

This section presents the results of two complementary statistical analyses conducted on the COBRE dataset to evaluate the group-level separability of FRC as a putative neuroimaging biomarker for schizophrenia.

A. Global Curvature Analysis

The first experiment tests whether the global mean curvature $\bar{F}$ differs significantly between SZ and HC groups, employing the Mann-Whitney U test as a nonparametric measure robust to non-normality, Welch's t -test as a parametric complement under unequal variances, and Cohen's d to quantify the practical magnitude of group separation.

HC subjects exhibit a more negative global mean curvature ($\mu_{\text{HC}} \approx -6.23 \times 10^6$, $\sigma_{\text{HC}} \approx 3.19 \times 10^6$) than SZ patients ($\mu_{\text{SZ}} \approx -4.55 \times 10^6$, $\sigma_{\text{SZ}} \approx 2.53 \times 10^6$), a difference that is statistically significant under both Mann-Whitney U ($p = 2.88 \times 10^{-5}$) and Welch's t -test ($p = 6.35 \times 10^{-4}$), with Cohen's $d \approx 0.58$ indicating a moderate effect size. The more negative curvature observed in HC subjects suggests that healthy brain hypergraphs exhibit denser and more interconnected higher-order functional organization, whereas the less negative curvature in SZ patients may reflect a disruption

¹Available at https://fcon_1000.projects.nitrc.org/indi/retro/cobre.html

in this topology, consistent with the hypothesis of reduced functional integration in schizophrenia.

Figure 2 shows violin plots of the global mean curvature distributions for HC and SZ groups, illustrating the clear separation in central tendency and spread.

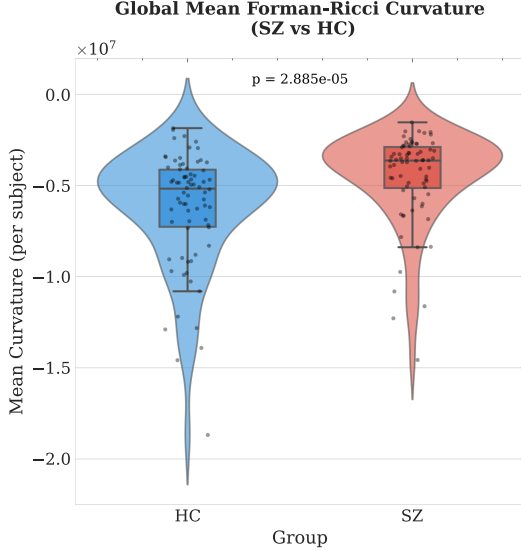


Fig. 2

VIOLIN PLOTS OF GLOBAL MEAN FORMAN-RICCI CURVATURE FOR HC AND SZ GROUPS.

B. Node-Level Curvature Analysis

The second experiment investigates whether schizophrenia-related alterations in higher-order functional connectivity are spatially localized or globally distributed across the cortex. To this end, a node-wise analysis of the node curvature $F(k)$ is performed, yielding 90 region-level descriptors per subject that capture the local geometric organization of each AAL ROI within the brain hypergraph.

Fig. 3 shows the mean node curvature $F(k)$ across all 90 AAL regions and all subjects, sorted by group label. Dashed boxes indicate the top-10 regions with the largest $|HC - SZ|$ differences. A consistent pattern is observed: HC subjects display more negative node curvatures across a broad set of regions, while SZ patients exhibit shallower curvature profiles, suggesting a widespread reduction in higher-order functional connectivity throughout the connectome.

These regions predominantly span temporal, parietal, and occipital cortices, including the lingual gyrus (LING.L), superior parietal gyrus (SPG.L), middle occipital gyrus (MOG.L), and bilateral precuneus (PCUN.L, PCUN.R), all of which are associated with visual processing, sensory integration, and higher-order cognition commonly reported as impaired in SZ.

Group differences were assessed via Mann-Whitney U and Welch's t -tests with Benjamini-Hochberg FDR correction ($\alpha = 0.05$) across all 90 AAL regions. All top-ranked ROIs, including bilateral PCUN and LING.L, remained significant after correction ($p_{\text{fdr}} < 0.05$), confirming that the observed $|HC - SZ|$ divergences reflect stable pathological signatures rather than stochastic variation. Fig. 4 illustrates the spatial distribution of FRC-based putative biomarkers across the AAL90 atlas, where the size of each bubble directly encodes the

magnitude of the node curvature $F(k)$, providing an intuitive visualization of biomarker strength per brain region. Although FDR correction confirmed significant differences across all 90 regions, discriminative strength is not uniform: the top-10 ROIs identified in Fig. 3 exhibit the largest curvature divergence and represent the most informative candidates for biomarker-driven classification, while the remaining regions reflect a weaker but statistically detectable global disruption consistent with the disconnection syndrome hypothesis.

Consistent with [10], which demonstrated the sensitivity of FRC to network anomalies in psychiatric disorders, the proposed method extends FRC to HOIs based on hypergraph structures and specifically investigates its application to schizophrenia. The resulting global curvature, defined as the mean value across subjects within each group, achieves a moderate yet statistically robust separation between HC and SZ ($d \approx 0.58$, $p = 2.88 \times 10^{-5}$) across 145 subjects, with significant differences observed across all 90 AAL regions after FDR correction.

The convergence of altered curvature across DMN, VIS, and SM regions indicates that SZ-related disruptions are globally distributed rather than spatially localized, consistent with the disconnection syndrome hypothesis [16]. Notably, several top-ranked ROIs intersect with SZ biomarkers previously identified via higher-order interaction analysis [17], further supporting node-wise FRC as a sensitive and interpretable descriptor of mesoscale functional dysconnectivity in schizophrenia.

V. CONCLUSION

This work demonstrates that Forman-Ricci curvature computed over 3-uniform hypergraphs provides a sensitive and interpretable framework for identifying schizophrenia-related alterations in higher-order functional connectivity. By modeling HOIs from resting-state fMRI BOLD time series, the proposed approach reveals consistent curvature reductions in SZ patients relative to healthy controls at both global ($d \approx 0.58$, $p = 2.88 \times 10^{-5}$) and regional levels, with significant group differences across all 90 AAL regions after FDR correction. These findings reinforce the disconnection syndrome hypothesis of schizophrenia and highlight the advantage of hypergraph-based topological representations in capturing complex brain dynamics beyond pairwise functional connectivity. Although the relatively modest sample size and the absence of cross-dataset validation limit the generalizability of these results, they nonetheless open promising avenues for future work incorporating larger, independent cohorts.

The node-wise FRC features identified in this work, particularly across DMN, visual, and somatomotor regions, represent promising candidates for putative schizophrenia biomarker discovery. The present study focuses on group-level statistical analysis rather than predictive modeling; therefore, subject-level classification remains future work. Future studies will integrate these descriptors into cross-validated classification pipelines and benchmark their discriminative capacity against pairwise and higher-order functional connectivity approaches on the COBRE dataset. If validated, node-wise Forman-Ricci curvature may support objective patient stratification and earlier clinical intervention.

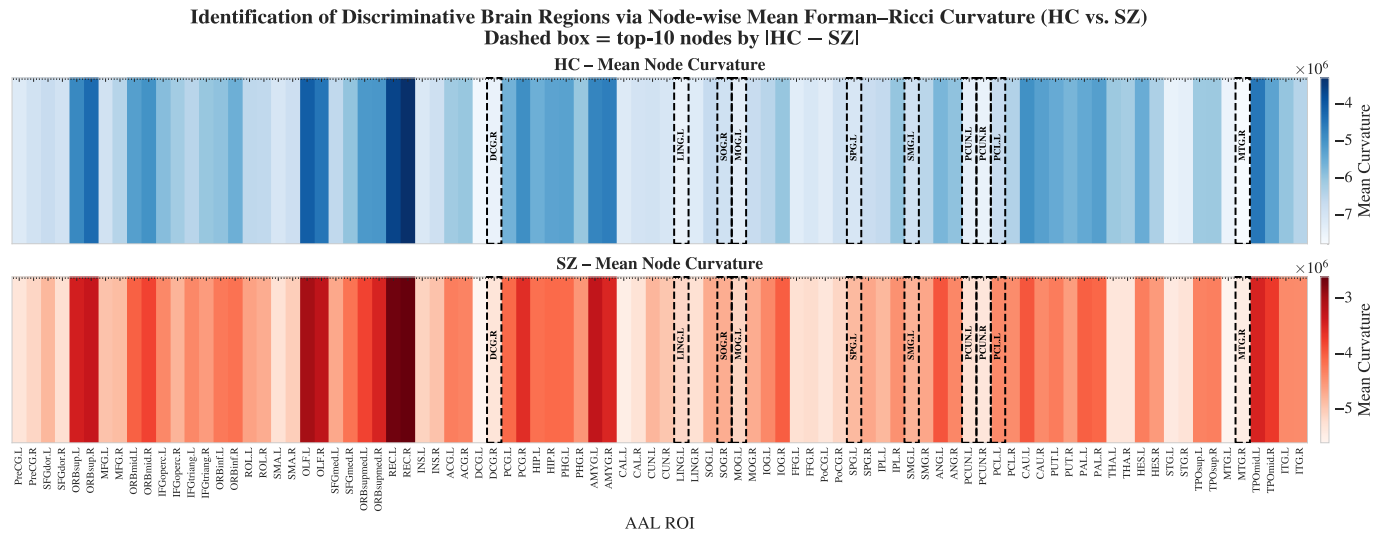


Fig. 3
GROUP-AVERAGED NODE-WISE FORMAN–RICCI CURVATURE ($F(k)$) ACROSS AAL REGIONS FOR HC AND SZ COHORTS. COLOUR INTENSITY REPRESENTS THE MEAN CURVATURE PER REGION. DASHED BOXES INDICATE THE TOP-10 REGIONS WITH THE LARGEST $|HC - SZ|$ DIFFERENCES.

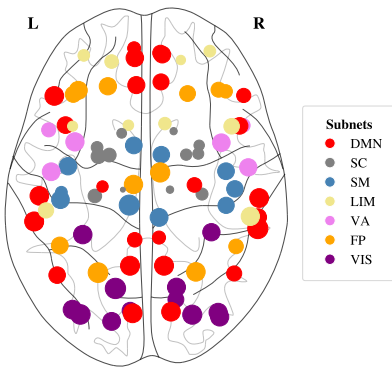


Fig. 4
SPATIAL DISTRIBUTION OF FORMAN-RICCI CURVATURE BIOMARKERS ACROSS 90 AAL ROIS. LARGER BUBBLES INDICATE REGIONS WITH GREATER HIGHER-ORDER FUNCTIONAL CONNECTIVITY STRENGTH.

DATA AVAILABILITY

The COBRE dataset is publicly available at *FCN 1000*.

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