Network Analysis of Intrinsic Functional Brain Connectivity in Alzheimer's Disease

- **Journal**: PLoS Computational Biology
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Contents

Abstract

- **Wavelet analysis** was applied to the fMRI data to compute **frequency-dependent correlation matrices**. Correlation matrices were thresholded to create 90-node undirected-graphs.
- **Small-world metrics** (characteristic path length and clustering coefficient) were computed using graph analytical methods.
- Small-world organization is characterized by a high clustering coefficient and a low characteristic path length.
- AD showed loss of small-world properties, characterized by a significantly lower clustering coefficient ($p < 0.01$).
- Network measures may be useful as an **imaging-based biomarker** to distinguish AD from healthy aging.

Introduction

- **Functional connectivity** is defined as temporal correlations between spatially distinct brain regions.
- AD patients have decreased hippocampus connectivity with prefrontal cortex and posterior cingulate cortex during memory tasks.
- **Default-mode network** includes posterior cingulate cortex, temporoparietal junction, and hippocampus.
- Although evidence is accumulating that AD disrupts functional connections between brain regions, it is not clear whether AD disrupts global functional brain organization.

- Graph metrics–the **clustering coefficient** and the **characteristic path length**—are useful measures of global organization of large-scale networks.
- The **clustering coefficient** is a measure of local network connectivity. A network with a high average clustering coefficient is characterized by densely connected local clusters.
- The **characteristic path length** is a measure of how well connected a network is. A network with a low characteristic path length is characterized by short distances between any two nodes.
- This paper examined the global functional organization of the brain in AD by
  - Creating whole-brain functional connectivity networks from task-free fMRI data
  - Characterizing the organization of these networks using small-world metrics
  - Comparing these characteristics between AD patients and age- matched controls

Author Summary

- Graph analytical methods are used to compute these measures of functional connectivity brain networks.
- The AD patients had significantly lower regional connectivity, and showed disrupted global functional organization, when compared to healthy controls.

Results

- Subjects
- Analyses of small-world metrics at different scales
- Comparison of small-world metrics in the AD and control groups
- Analysis of global efficiency of whole-brain functional connectivity network
- Specificity and sensitivity of clustering coefficient in distinguishing AD participants from controls
- Regional profile of clustering coefficient
- Regional connectivity
- Reproducibility of findings

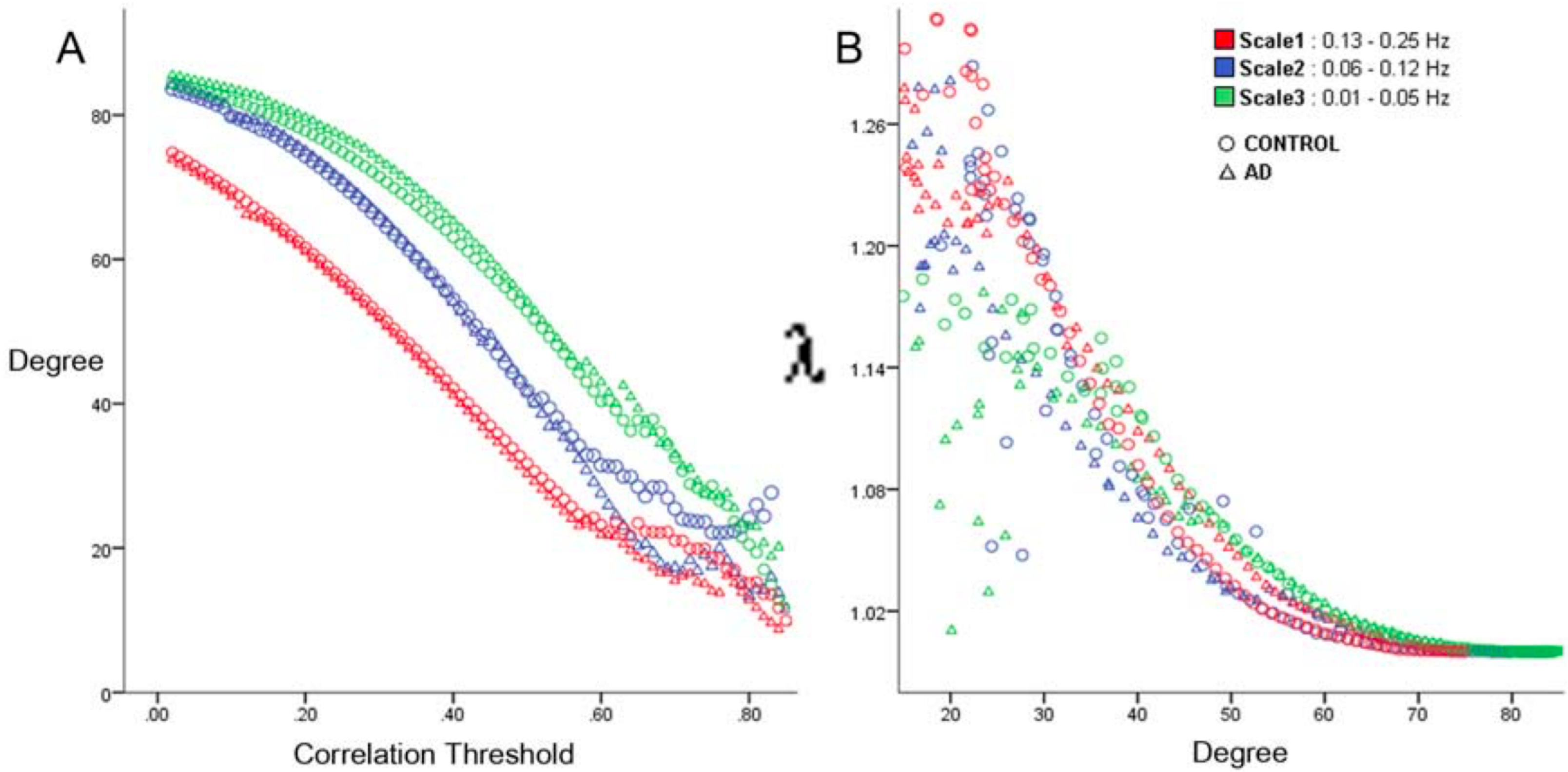
Subjects

	AD (n = 21)	Controls (n = 18)
Age	63.97 (range: 48 to 83)	62.84 (range: 37 to 77)
Sex	10 males, 11 females	10 males, 8 females
Years of Education	15.89 (range: 12 to 22)	16.53 (range: 12 to 21)
MMSE	22.14* (range: 12 to 29)	29* (range: 27 to 30)

Analyses of small-world metrics at different scales

- Functional brain networks were constructed by **thresholding** (threshold values ranged from 0.01 to 0.99 with an increment of 0.01).
- **Wavelet correlation matrix** was computed at three scales.
- The **mean degree** was highest at Scale 3.
- The **mean characteristic path length (λ)** was low ($1 < \lambda < 1.27$) for both groups.
- **Clustering coefficient (γ)** and **small-world measure σ (γ/λ)** were highest at Scale 3 for both groups.
- Functional connectivity and small-world properties were salient at lower-frequencies (0.01 to 0.05 Hz).

Figure 1. Graph metrics – degree, λ (L/L_{ran}), γ (C/C_{ran}), σ (γ/λ).



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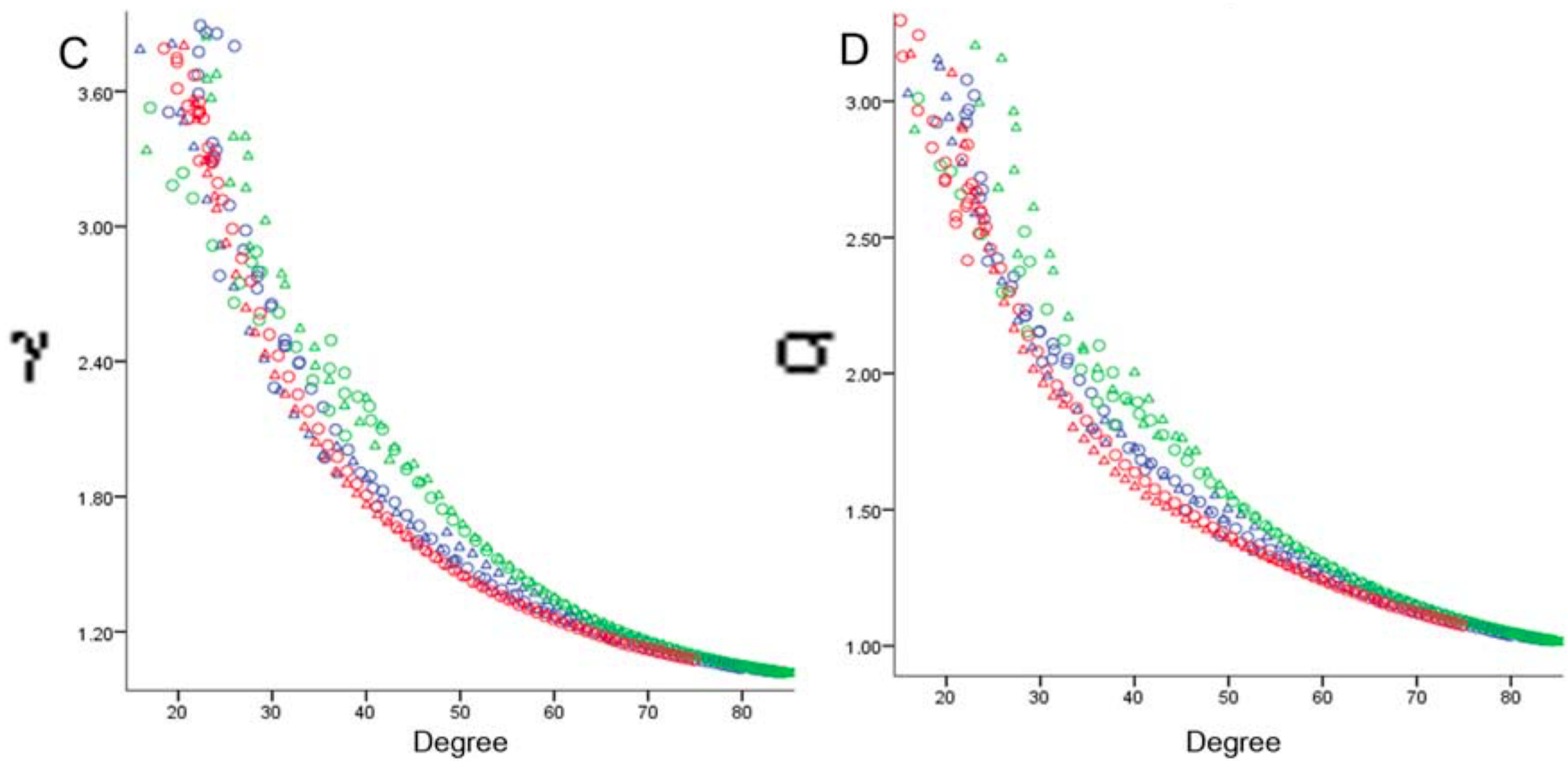
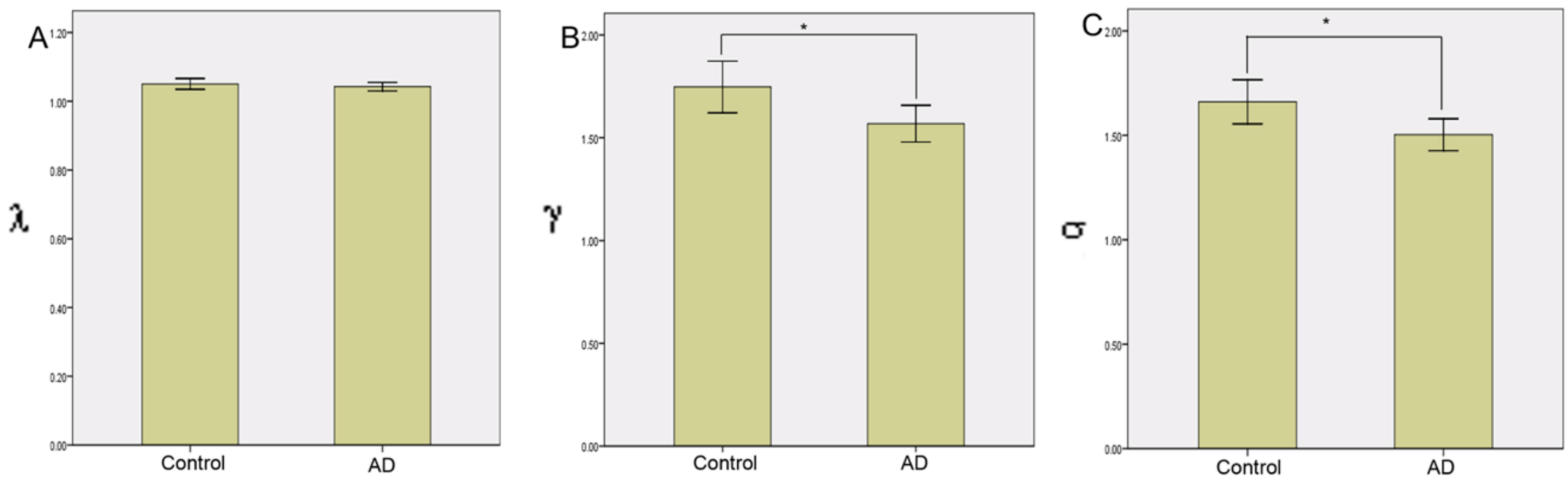


Comparison of small-world metrics in the AD and control groups

- For a given correlation threshold, the number of edges in the graph are likely to be less in AD, resulting in high λ and low γ values.
- Mean λ, mean γ, and mean σ values for the networks of the AD group and control group were derived by thresholding the correlation matrices such that the network has K' (= 40) edges.

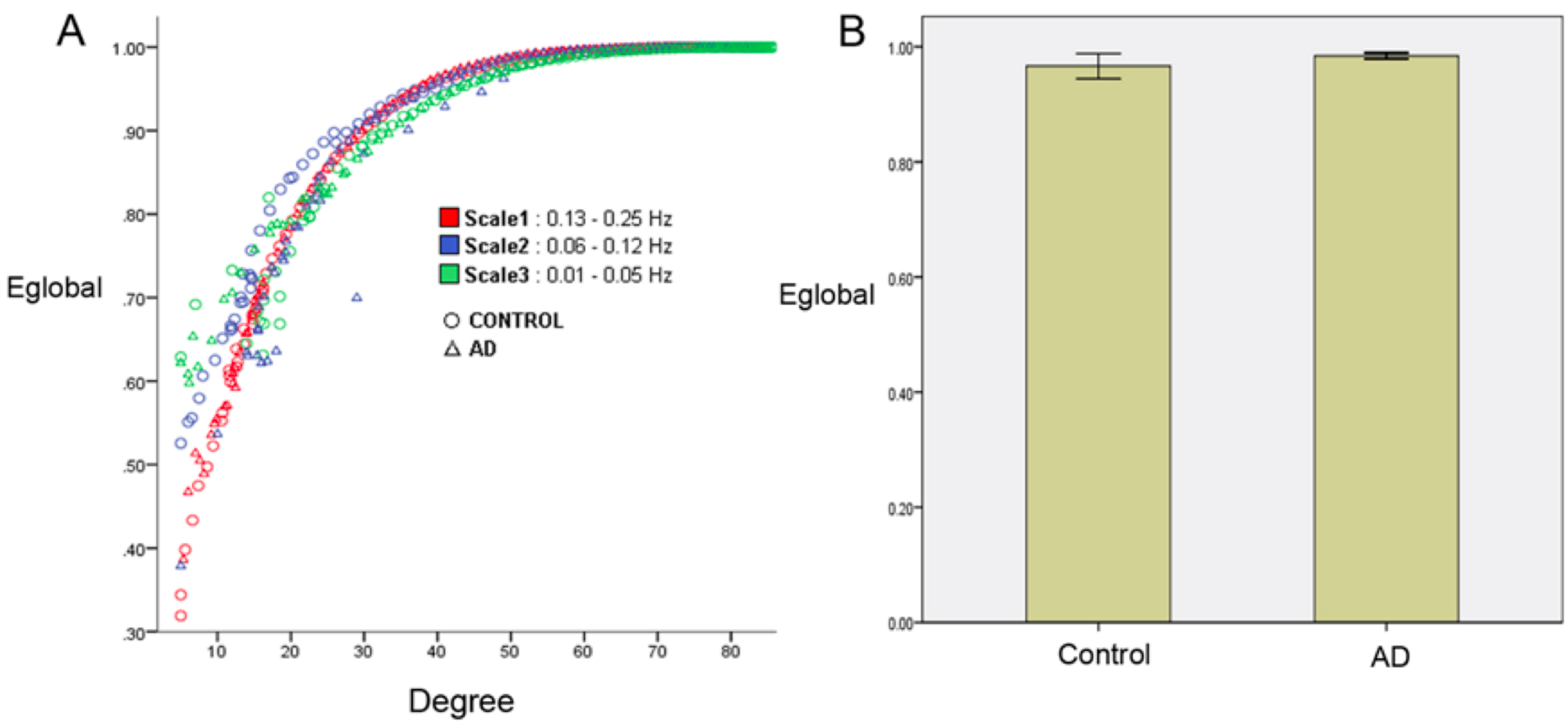
Figure 2. Small-world properties for networks derived by thresholding the correlation matrices such that the network has K' edges.



Analysis of global efficiency of whole-brain functional connectivity network

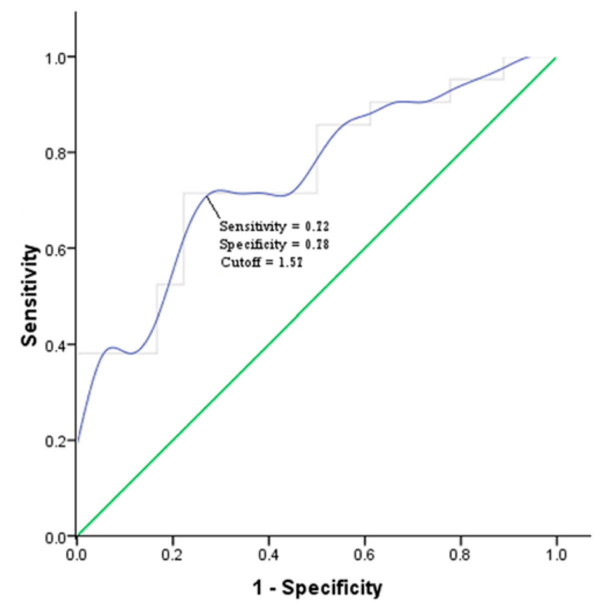
- In network science, the **efficiency** of a network is a measure of how efficiently it exchanges information. On a global scale, efficiency quantifies the exchange of information across the whole network where information is concurrently exchanged.
- No significant differences in the mean E_{global} values were observed.

Figure 3. Small-world properties for networks derived by thresholding the correlation matrices such that the network has K' edges.



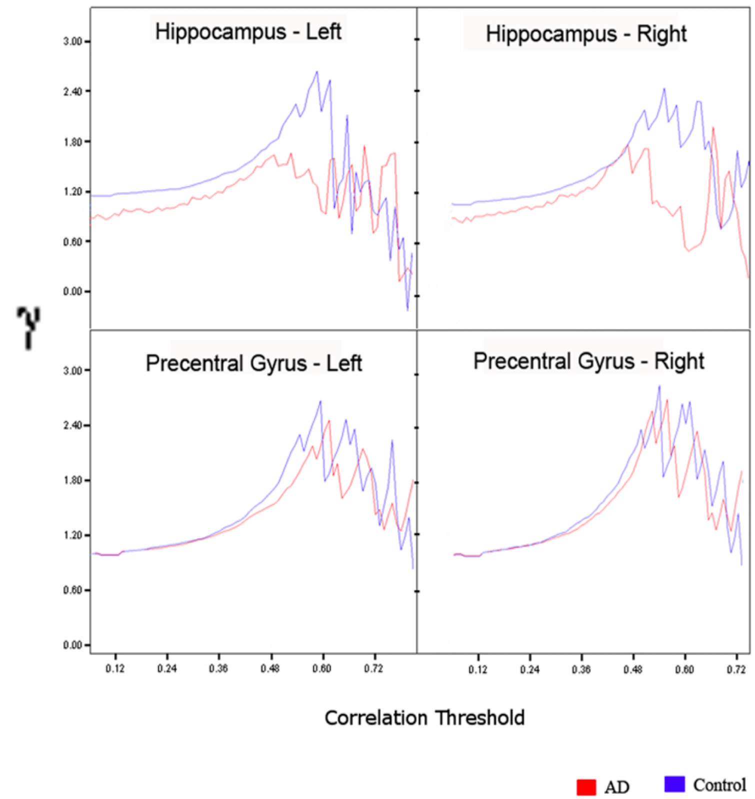
Specificity and sensitivity of clustering coefficient in distinguishing AD participants from controls

- Using the cut-off value (γ = 1.57) that maximizes sensitivity and specificity, γ correctly classified 14 out of 18 controls and 15 of 21 AD subjects, yielding 72% sensitivity and 78% specificity respectively.
- The Area Under the Curve for the ROC was 0.754 (95% CI Area 0.602 to 0.906).



Regional profile of clustering coefficient

- Figure 5 shows a plot of γ for each of the four regions, for the AD group and the control group as a function of the correlation threshold.
- Significantly lower clustering coefficient values were found in the left and right hippocampus in AD, with no significant differences in the left and right precentral gyrus.



Reproducibility of findings

- Functional brain connectivity and small-world metrics including the global efficiency were salient in the low frequency interval−0.01 to 0.05 Hz (Scale 3).
- No significant differences in the mean λ values were observed.
- Mean γ values in the AD group were significantly lower than in the control group ($p < 0.01$).
- Mean σ values in the AD group were significantly lower than that in the control group ($p < 0.01$).
- No significant differences in the mean E_{global} values were observed.
- Significantly lower clustering coefficient values were found in the left and right hippocampus in AD, with no significant differences in the left and right precentral gyrus.

Materials and Methods

- Participants
- Data acquisition
- Data preprocessing
- Anatomical parcellation
- Construction of whole-brain functional connectivity network
- Small-world analysis of the whole-brain functional connectivity network
- Analysis of global efficiency of whole-brain functional connectivity network
- Regional profile of clustering coefficient
- Regional connectivity

Data acquisition

- Rest1 scan: subjects were instructed to keep their eyes closed and try not to move for 6 minutes.
- Rest2 scan: subjects underwent another task-free scan that lasted for 6 minutes.
- Machine: 3-T General Electric Signa scanner using a standard whole-head coil.
- 28 axial slices (4 mm thick, 1mm skip) were acquired.
- T2* weighted gradient echo spiral in/out pulse sequence (TR = 2000 msec, TE = 30 msec, flip angle=80° and 1 interleave).
- T1-weighted spoiled grass gradient recalled (SPGR) 3D MRI sequence: 124 coronal slices 1.5 mm thickness, no skip, TR=11 ms, TE=2 ms, and flip angle=15°.

Data preprocessing

- Software: statistical parametric mapping (SPM2)
- The first 8 volumes were discarded to allow for stabilization.
- Preprocessing steps: realignment, normalization, and smoothing. Normalization was to the Montreal Neurological Institute (MNI) template and smoothing was done with a 4 mm full width half maximum Gaussian kernel to decrease spatial noise.

Anatomical parcellation

- Parcellated into 90 regions using anatomical templates defined by Tzourio-Mazoyer et al.
- Averaging all voxels within each region at each time point in the time series.
- Resulting in 172 time points for each of the 90 anatomical regions of interest.

Construction of whole-brain functional connectivity network

- **Wavelets** are mathematical functions that transform the input signal into different frequency components.
- **Wavelet analysis** was used to construct correlation matrices where **frequency-dependent correlations** were a measure of functional connectivity.
- A **maximum overlap discrete wavelet transform (MODWT)** was applied to each of the 90 regional time series with three frequency components: scale 1 (0.13 to 0.25 Hz), scale 2 (0.06 to 0.12 Hz), and scale 3 (0.01 to 0.05 Hz).
- Correlation matrices were then thresholded to generate a whole-brain functional connectivity network characterized in terms of its **small-world properties**.

Small-world analysis of the whole-brain functional connectivity network

- The **clustering coefficient** of every node was computed as the ratio of the number of connections between its neighbors divided by the maximum possible connections between its neighbors.
- The **clustering coefficient (C)** of the network was calculated as the mean of the clustering coefficients of all the nodes in the network.
- The **mean minimum path length** of a node was computed as the average of minimum distances from that node to all the remaining nodes in the network.
- The **characteristic path length (L)** of the network was the average of the mean minimum path lengths of all the nodes in the network.

- Coefficient and path length of nodes completely disconnected with the network were set as 0 and Inf respectively, and these nodes were excluded while computing C and L.
- **Small world networks** are characterized by high normalized clustering coefficient γ $(C/C_{ran}) > 1$ and low normalized characteristic path length λ $(L/L_{ran}) \sim 1$ compared to random networks.
- C_{ran} and L_{ran} are obtained by averaging across 1000 random networks with the same number of nodes and degree distribution.
- A cumulative metric σ – the ratio of normalized clustering coefficient (γ) to the characteristic path length (λ), a measure of small-worldness – is thus greater than 1 for small world networks.

Analysis of global efficiency of whole-brain functional connectivity network

- Only small-world metrics computed on connected graphs were considered in our analysis.
- In the node-wise clustering coefficient comparison analysis, we only considered thresholds from 0.1 to 0.6.
- It has been previously reported that efficiency as a graph metric
  - is not susceptible to disconnected nodes
  - is applicable to unweighted as well as weighted graphs
  - is a more meaningful measure of parallel information processing than path length

- **Efficiency** of a graph ($E_{global\text{-}net}$) is inverse of the harmonic mean of the minimum path length between each pair of nodes, L_{ij}, and was computed as,

$$E_{\mathrm{global-net}} = \frac{1}{N(N-1)} \sum_{i,j} \frac{1}{L_{ij}}$$

- E_{global} value was obtained by comparing the global efficiency of the network ($E_{global\text{-}net}$) with corresponding values ($E_{global\text{-}ran}$) obtained and averaged across 1000 random networks.
- A network with small-world properties is characterized by global efficiency value that is lower than the random network, namely, E_{global} ($E_{global\text{-}net}/E_{global\text{-}ran}$) < 1.