Covariance Analysis

**Preparing data for analysis**

Input data must me stored in a cell matlab variable with the following format:

- Cell element {1,1} → group title i.e. ‘Controls’

- Cell elements on the first row (excluding 1) {1,2:number of levels} labels of factor levels i.e. sex: ‘Male’ ‘Female’

- Cell elements on the first column (excluding 1) {2:number of levels,1} labels of factors i.e. age: ‘4months’ ‘6 months’ 12 months’

For each unique group, data must be stored as 2D matrices where rows correspond to regions and columns correspond to subjects.

**Building Covariance Networks**

Covariance networks for each group were computed as pairwise Pearson correlations of SUVr values across animals for each unique region pair.

**Permutation-based Thresholding of Networks**

Permutation p-values for each edge were estimated via permutation of the SUVr data 10000 times. At each iteration, each region’s SUVr values across animals in a group were randomly permuted and a null covariance network was generated via Pearson correlation. The null network set was then used to estimate edgewise permutation p-values, computed as one minus the fraction of times that the empirical correlations were stronger than the null.

**Community Detection**

Community detection was done on each groups’ covariance network using the generalized Louvain modularity maximization (1, 2), implemented in a multiresolution consensus clustering (MRCC) approach (3). MRCC generates an initial set of partition (here set to 10000), spanning a resolution parameter gamma, which impacts the size and number of communities identified. From that set, a co-classification matrix is computed, representing the probability that any region pair is assigned to the same community across spatial scale. Additionally, a consensus partition is determined, using a null model at a significance of alpha = 0.05.

**Comparing Community Partitions**

Similarity among consensus communities among groups was assess via adjusted mutual information (AMI) (4).

**Network Metrics**

Network summary metrics were computed using the Brain Connectivity Toolbox (BCT) (5).

*Density -* Number of unique connections in a network as a fraction of total possible edges.

*Degree –* Node degree is the number of edges connected to the node.

*Strength –* The sum of weights of edges connected to the node. Strength was computed separately for positive and negative weight, yielding two measures of strength per node. Total positive and negative strength values for networks were computed as sum of nodal strength values.

*Largest Connected Component –* Size of a subnetwork in which all pairs of regions are connected by a path (direct and indirect connections).

*Clustering Coefficient –* Generally described as the number of triangles around a node (cases where connected neighbors of a node are also connected). Here the signed weighted variant of the clustering coefficient was used (6). This generalization takes into account positive and negative weights together and is sensitive to sign variation in connected triangles.

**Statistics**

Where appropriate, nodal distributions of network metrics were compared with a two-sample Kolmogorov-Smirnov test.

**References**

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2. Mucha PJ, Richardson T, Macon K, Porter MA, Onnela J-P. Community Structure in Time-Dependent, Multiscale, and Multiplex Networks. Science. 2010;328(5980):876.

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4. Nguyen Xuan Vinh, Julien Epps, Bailey J. Information Theoretic Measures for Clusterings Comparison: Variants, Properties, Normalization and Correction for Chance. Journal of Machine Learning Research. 2010;11(95):2837-54.

5. Rubinov M, Sporns O. Complex network measures of brain connectivity: Uses and interpretations. NeuroImage. 2010;52(3):1059-69.

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