A MULTISCALE CONSENSUS METHOD USING FACTOR ANALYSIS TO EXTRACT MODULAR REGIONS IN THE FUNCTIONAL BRAIN NETWORK

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ABSTRACT

The brain functional connectivity network is complex, generally constructed using correlations between the regions of interest (ROIs) in the brain, corresponding to a parcellation atlas. The brain is known to exhibit a modular organization, referred to as "functional segregation." Generally, functional segregation is extracted from edge-filtered, and optionally, binarized network using community detection and clustering algorithms. Here, we propose the novel use of exploratory factor analysis (EFA) on the correlation matrix for extracting functional segregation, to avoid sparsifying the network by using a threshold for edge filtering. However, the direct usability of EFA is limited, owing to its inherent issues of replication, reliability, and generalizability. In order to avoid finding an optimal number of factors for EFA, we propose a multiscale approach using EFA for node-partitioning, and use consensus to aggregate the results of EFA across different scales. We define an appropriate scale, and discuss the influence of the "interval of scales" in the performance of our multiscale EFA. We compare our results with the state-of-the-art in our case study. Overall, we find that the multiscale consensus method using EFA performs at par with the state-of-the-art. *Clinical relevance:* Extracting modular brain regions allows practitioners to study spontaneous brain activity at resting state.

1 Introduction

The human brain is a complex network, where the statistical dependencies between specific regions or neurons uncover neurobiologically significant findings. These dependencies are the functional connections obtained from the blood-oxygenation level-dependent (BOLD) signals of functional magnetic resonance imaging (fMRI). Thus, the functional connectivity matrix is computed using pairwise Pearson's correlation coefficient measure derived from courses of the regions of interest (ROIs) of the brain, after appropriate spatio-temporal aggregation of the fMRI signals. The linear correlation has been widely used as a functional connectivity measure, which is suitable owing to the bivariate Gaussian distribution of the fMRI time series [1]. The functional connectivity network (FCN) connects nodes, i.e., ROIs, with correlation as edge weights. Here, we propose a semantics-oriented (i.e., correlation-based), multi-scale approach to identify non-overlapping node-partitions in the resting-state fNet. Resting-state networks are generated from volumetric partitions of brain regions in the fMRI data corresponding to specific functional activities in the task-free state [2]. The resting-state of the brain is widely studied, owing to more controlled data collection in resting-state than in cognitive task-based studies. The functional segregation during resting-state is given by the communities in the FCN.

Our motivation here is to understand how different ROIs in the brain get co-activated in resting-state using correlation analysis. Community detection in FCN exploits the small-world network architecture of the brain [3]. It gives node-partitions with high intra-cluster and low inter-cluster edge density, using shortest paths between any two given nodes.

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There exist several network-based and graph-theoretic methods to identify communities for functional segregation extraction, including *modularity maximization* method [4], *InfoMap* [5], and *multiresolution consensus* clustering method [6]. Some of these methods are controversial in certain aspects, such as in the use of threshold for the understanding topology of significant sub-networks, global signal regression, eyes-open versus eyes-closed studies, etc. Overall, the problem of functional segregation using data-driven methods continue to be actively solved, especially since there is no ground-truth on the number and composition of functional partitions in the brain. The difficulty in arriving at a consensus on the number of partitions is attributed to hierarchical modular organization of the functional brain [3].

Here, to avoid the need for finding a threshold for filtering edges in the correlation network, we consider the case of finding functional segregation using the completely connected network. Thus, for the weighted undirected adjacency matrix of the FCN (i.e., the correlation matrix), we propose the use of exploratory factor analysis (EFA) [7] for extracting functional segregation. The choice of EFA is owing to it being an experimental method, which is used especially on correlation, for identifying the structure of a domain [8]. The implementation depends on the number of factors, n_F, as an input, and n_F corresponds to the number of node-partitions, n_P, here. At the same time, consensus methods have been found to provide stability for the solutions of methods where a single experimental setting is not reliable [9].

Thus, in order to improve the usability of EFA for functional segregation, we impose the *number of factors* n_F in EFA as a *scale*, and use a multiscale consensus method to arrive at the functional segregation. The last step in our proposed method is intentionally scale-invariant, to allow the data to reveal its partitions automatically. Our multiscale approach thus addresses the issues with a single-scale EFA, namely, the instability of the node-partitioning, and the generalizability of the process. We run several experiments and use appropriate criteria to identify the *optimal* solution of an interval of n_F, thus addressing the issue of replication.

Our consensus method is similar to that done for complex networks [9], but the novelty here lies in the use of EFA to determine the *consensus matrix*. The consensus matrix is the weighted matrix that the correlation matrix is transformed for implementing functional segregation.

2 Materials and Methods

Here, we discuss our method and its implementation.

fMRI Data: We have used the resting-state fMRI (R-fMRI) data of Beijing Normal University, from the 1000 Functional Connectome Project[3] [10], with specific details of the subjects and data acquisition centers. A Siemens 3T scanner has been used for data acquisition, and SPM5 (Statistical Parametric Mapping) and DPARSF [11] for preprocessing. The *functional connectome* of subjects is obtained from the fMRI scans with an eyes-closed (EC) state of wakefulness.

FCN Generation: The network is computed from the fMRI data of 198 healthy right-handed volunteers in the age group 18-26 years, of whom 122 were female, and 76, male. After outlier removal, e.g., fMRI data of a subject was removed owing to rotation error, a region-based fNet[4] is generated for each subject, using a 90-node Automated Anatomical Labeling (AAL) parcellation atlas[5]. The mean time courses of the ROIs corresponding to each node are extracted, and pairwise Pearson's correlation is computed within all the nodes. Subject-wise correlation matrices are normalized using Fisher's r-to-z transformation. The one-sample t-tests on the z-score matrices across all subjects, and all connections in the network, are used to filter out the less significant connections with p-value $< 5\%$ (Bonferroni corrected significance level). The fNets are aggregated across all subjects to give the final fully connected 90×90 weighted undirected network. The ground truth here is a node-partitioning of the FCNs generated using the same fMRI data, and using the AAL atlas [13]. A network-based partitioning has been implemented in ground truth using simulated annealing for optimization for maximum modularity.

2.1 Exploratory Factor Analysis

We propose to use EFA in extracting node-partitions in FCN from correlation matrices. EFA is a statistical method that uses inter-correlated variables to find factors, i.e., patterns describing the "basic structure of a domain" [8]. We assume that the empirical knowledge of the existence of a causal model determines the *causal* labels for the factors in such a way that the factors are purely classificatory or descriptive. In factor analysis, each random variable is expressed as a linear combination of factors, as:

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[3] `https://www.nitrc.org/projects/fcon_1000/`

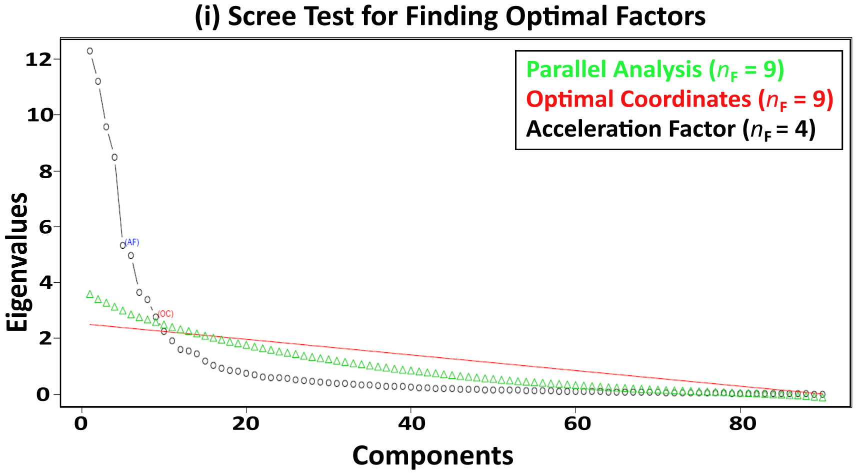
[4] The network used in our case-study has been published as a use-case for the BrainNet Viewer [11].

[5] The AAL atlas includes only the cerebrum, and excludes the cerebellum [12].

$$y_i = \lambda_{i1} f_1 + \lambda_{i2} f_2 + \ldots + \lambda_{im} f_m + \varepsilon_i$$

where $y_1, y_2, \ldots, y_p$ are the p random variables (i.e., FCN nodes), $f_1, f_2, \ldots, f_m$ are the m factors ($m < p$, always), $\lambda_{i1}, \lambda_{i2}, \cdots, \lambda_{im}$ are factor loadings of m factors and ε_i is the corresponding error term.

Need for Multiscale Approach: EFA suffers from issues of replication, generalizability, non-unique solution depending on the type of rotation, absence of a prescribed set of parameters or algorithms, and ambiguity in labels for factors [8]. That said, EFA is desirable owing to its exploratory and experimental nature. Thus, while we can use EFA, where its factors correspond to functional segregation, performing it for a specific or optimal n_F is not guaranteed to give us reliable results. Hence, we now introduce n_F as a *scale* for EFA, where EFA is performed at multiple scales, and the node-partitioning results of different scales are aggregated using a consensus method. Using n_F as the scale and running an ensemble of experiments with different values of n_F adds to the exploratory and experimental characteristic of EFA.



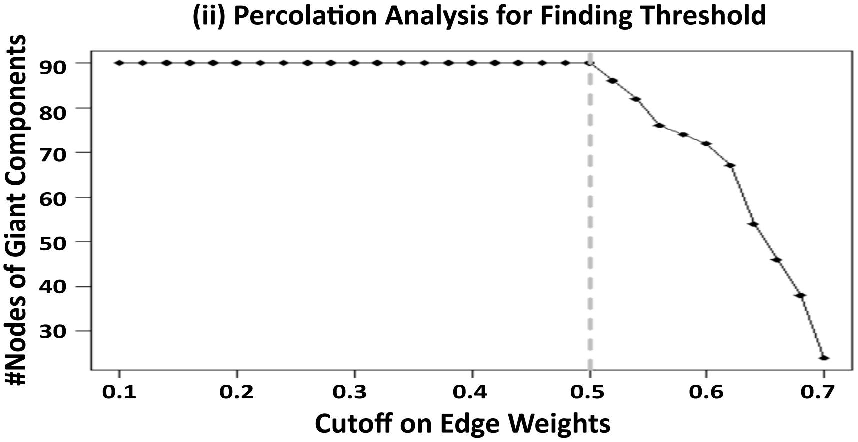


Figure 1: (i). The number of factors n_F is identified using parallel analysis and other methods, represented using scree plot. (ii). Percolation analysis is used to determine the cutoff for edge filtering of the full correlation matrix.

Selecting Appropriate Interval of n_F: For identifying appropriate scales in our multiscale method, a continuous interval[6] of values for n_F is preferred over a set of disparate values. We explore different node-partitionings of the same FCN by varying n_F from the chosen interval, for finding patterns. Thus, identifying the appropriate interval of scales becomes a crucial step. We first consider disparate *optimal* values of n_F, as suggested by theory and practice [2, 13]. After we gather as much empirical evidence of these optimal values of n_F, we pick an interval I that includes all the optimal values of n_F. As an optimal value for n_F, we use the n_P from the *ground-truth*, referred to as n_F^{gt}. We consider the number of resting-state networks (RSNs) extracted from fMRI using PICA [2] as n_F, which is referred to as n_F^{rsn}. In EFA, parallel analysis and scree test are used to identify the optimal number of factors, referred to as n_F^{pa} and n_F^{st} (§Figure 1(i)), respectively. We consider the alternative graph-theoretic methods used with FCN for community detection. For applying appropriate community detection methods in the edge-filtered network, the threshold for edge

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[6] A continuous interval $[a, b]$, where $a, b \in \mathbb{Z}^+$, refers to a set of non-negative integer values $\{a, a+1, a+2, \ldots, b-1, b\}$.

filtering is computed using percolation analysis [14] (§Figure 1(ii)). The optimal number of communities n_C in the edge-filtered network obtained from Louvain community detection [15] and Infomap algorithm [5] are used as n_F, and referred to as n_F^{lc} and n_F^{im}, respectively.

Retaining Results: After extracting factors for each scale, we use two factor retention criteria (FRC) [16] to retain factors. Firstly, we retain a factor only if at least one node belongs to the factor. Secondly, we use a criterion of the factor loading $f_s > 0.3$ for every node with respect to its corresponding factor [17]. This specific FRC can be relaxed to $f_s > 0$ in certain cases, thus making the criterion a weak one. We also apply a criterion for retaining scales, where we use only those scales for which *all* the nodes of the FCN are included in the extracted factors. Once we identify the subset of *viable* scales, I_S, i.e., $I_S \subseteq I$, and the factors in each scale to be retained using FRC, we then determine the *optimality* of the I_S by using the modularity value Q [4], and Jaccard similarity S_j of our results with the ground-truth.

Guidelines for Repeatable Implementation of EFA: Before implementing EFA, the correlation matrix is checked for its positive-definiteness to ensure non-singularity, and its *measure of sampling adequacy* (MSA) to verify the linear dependence of the variables (i.e., nodes). Singular matrices and ill-conditioned correlation matrices, which have MSA < 0.5, are not eligible for EFA. Apart from n_F, other parameters such as rotation methods must be set for implementation of EFA [17]. We check the varimax and oblimin rotation methods for every scale, and use the method which gives higher communality and simpler structure [17]. Using appropriate rotation method for each scale and aggregating results is acceptable, as we aggregate the node-partitioning results and not the factors, and also, the aggregation is done using a consensus matrix. Hence, the rationale is to use appropriate parameters for implementing EFA with a chosen n_F to get the best node-partitioning at the concerned scale.

2.2 Multiscale Aggregation Using Consensus Matrix

We use a consensus method for multiscale aggregation owing to the evidence of stability in partitions in complex network applications [9]. The node-partitioning results of an ensemble of runs, resulting from changing values of n_F, are aggregated in a *consensus* matrix D. The elements of D, which is $n \times n$, are the probabilities of any two of n nodes co-existing in a group/cluster/community, aggregated across N experimental runs [18]. Here, N is the number of scales in the interval I, e.g. [5,12] has 8 scales.

$$D_{ij} = \frac{\sum_{k=1}^{N} \delta_{ij}^{k}}{N}, \text{ where } \delta_{ij}^{k} = \begin{cases} 1 & \text{if } P_i^k = P_j^k, \\ 0 & \text{otherwise.} \end{cases}$$

where P_i^k and P_j^k are (indices of) the node-partitions containing nodes i and j in the k^{th} run, corresponding to a specific $n_F \in I$. We perform Louvain community detection [15] on the network represented by D. The consensus matrix is interestingly used to densify a sparse network usually [9], whereas, D sparsifies a dense (full) network, in our work.

3 Results and Discussion

We have observed that varimax rotation gives higher communalities than oblimin rotation at every scale. Thus, we have used varimax rotation in all scales.

One of the crucial steps for our case study is to identify I, the interval of n_F, for the multiscale implementation of EFA. As discussed in Section 2, we get the following different key optimal n_F values: $n_F^{\text{gt}} = 5$ (ground-truth [13], $n_F^{\text{rsn}} = 5$ (RSNs [2]), and $n_F^{\text{pa}} = n_F^{\text{st}} = 9$ (parallel analysis, and scree test, §Figure 1(i)). In edge-filtered network, where the cut-off was found to be 0.5 using percolation analysis (§Figure 1(ii)), we get $n_F^{\text{lc}} = 7$ (Louvain community detection) and $n_F^{\text{im}} = 12$ (Infomap). Overall, we get the interval $I = [5, 12]$. An optimal subinterval of consecutive n_F values is the one that maximizes modularity (Q), and also, Jaccard similarity (S_j) with the ground-truth [13] only when $n_P = n_F^{\text{gt}}$. To find such a subinterval, we run an ensemble of experiments with different subintervals $I_S \subseteq I$ (§Figure 2). The Q and S_j are compared across the multiscale results (the lower-right and upper-left triangles in Figure 2(i), respectively), and the Q values across single-scale EFA results (§the diagonal in Figure 2(i)). We observe that several of the runs yield $n_P = 5$ (numbers in upper-left triangle in Figure 2(i)). We observe that in single-scale EFA with $n_F = 5$ gives factor loadings $f_s < 0.3$ for two nodes, i.e., 0.22 and 0.28, due to which the I_S that include $n_F = 5$ relaxes the FRC on factor loadings to $f_s > 0$ (cases outside the red square in Figure 2(i)). Our results show that the presence of $n_F = 5$ in the subintervals used for multiscale analysis improves the Q and S_j scores. Maximizing Q gives the optimal subinterval of scales to be $I_S = [5, 6]$ for multiscale experiment and the optimal scale $n_F = 5$ for single-scale EFA, where $Q = 0.692$. Maximizing S_j gives several subintervals containing $n_F = 5, 6$. We, thus, find high values of Q and S_j co-occurring for the entire interval, $I_S = I = [5, 12]$. Overall, we conclude that the optimal number of partitions is $n_P = 5$ for this data.

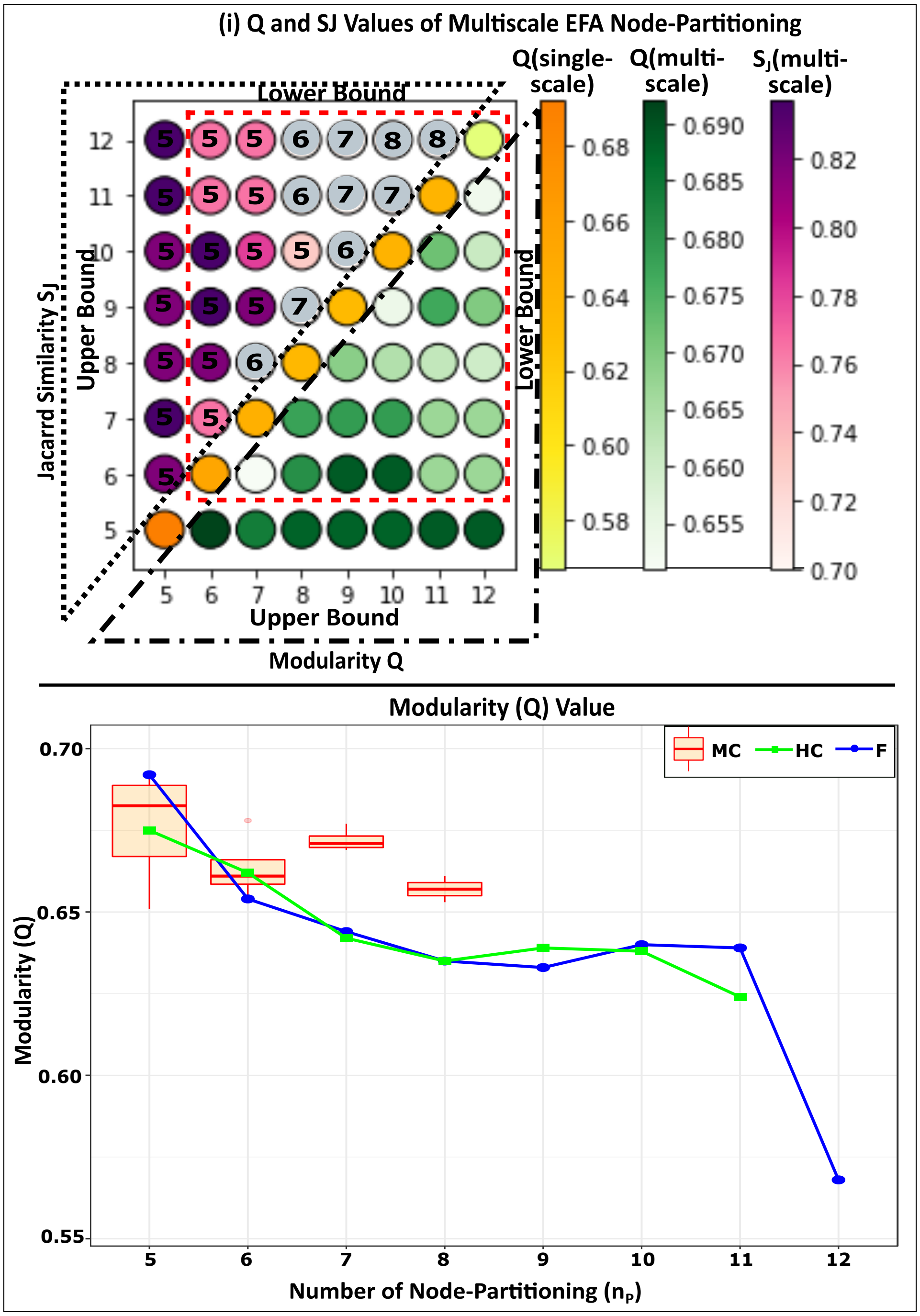
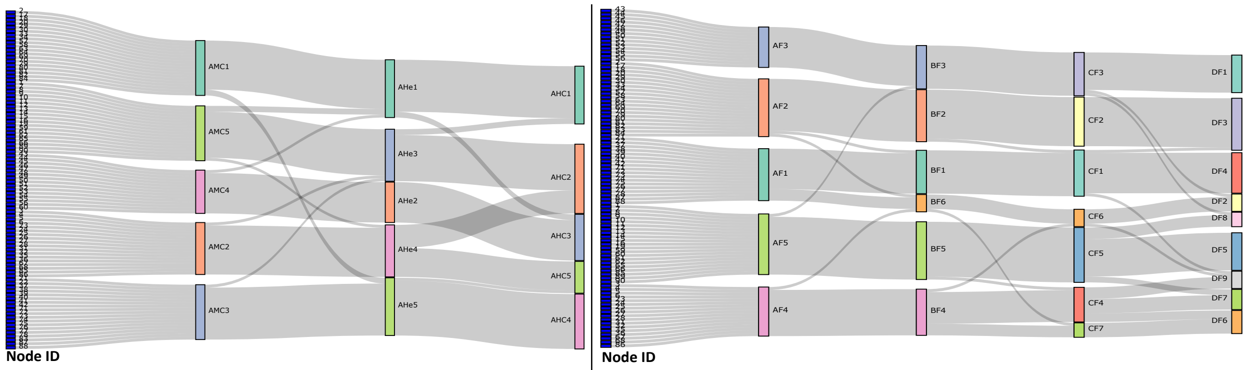


Figure 2: (i) The matrix comprehensively shows the node-partitioning results of the ensemble of experiments run with multiple consecutive scales within different intervals, specified by its bounds. The lower-right triangle compares the modularity Q of these results. The upper-left triangle compares the Jaccard similarity S_j of our results, where $n_P = 5$, with ground-truth [13]. The diagonal compares the Q of the node-partitionings from EFA with single-scale. The criterion of factor loadings $f_s>0.3$ is checked for cases within the red square, and $f_s>0$, otherwise. (ii) The plots of Q of results of hierarchical consensus clustering and EFA with both single-scale and multiscale, shows comparable performance, with higher Q being desirable.



(i) Comparison of EFA-multiscale consensus vs HC5 with ground-truth

(ii) Comparison of EFA-single scale factors (5,6,7,9)

Figure 3: (i) Sankey plot of the node-partitions from multiscale consensus method of multiscale EFA, ground truth, and hierarchical consensus (HC) clustering with 5 clusters, shows that our result is more similar to the ground truth than the HC result. (ii) Sankey plot of single-scale EFA results shows the hierarchical modular pattern, where the *flows* are subdividing with the increase in scale. The node-partitions are named in the format XY where X is $\{A, B, C, D\}$ corresponding to $\{5, 6, 7, 9\}$ node-communities, and Y is $\{MC, He, HC, F\}$ corresponding to {Multiscale Consensus using EFA, Ground-truth, Hierarchical Consensus clustering, Exploratory Factor Analysis with single-scale}.

We compare our results against the state-of-the-art consensus method, namely, the hierarchical consensus clustering (HC) method [6]. In HC, the initial clusters for consensus is identified using generalized Louvain [19] method with fixed resolution value ($\gamma = 1$). We run HC with 100 clusters and $\alpha = 0.1$, where α is a deciding parameter of co-occurrence of two nodes in the same cluster. We have compared the Q value for single-scale and multiscale EFA and HC, wherever the n_F and n_P match (Figure 2(ii)). In this case study, at the optimal $n_P = 5$, single-scale EFA has shown better modularity, $Q = 0.692$, followed by a median of multiscale EFA, $Q = 0.683$, and then HC, $Q = 0.675$. In other cases, multiscale EFA generates better Q values. The minimum height of the tree-cut in HC gives $n_P = 11$, i.e., HC can generate 5 clusters in this dataset and hierarchically divide up to 11 clusters. The visual comparison of our multiscale consensus results with HC using Sankey diagram (§Figure 3 (i)) shows the similarity between the results, i.e., 75 nodes out of 90 have similar cluster/partition co-membership by both the methods. Comparing our results with the ground-truth, we get $S_j = 83.7\%$ for EFA-multiscale at optimal $I_S = I = [5, 12]$, with 82 out of 90 nodes with matching co-membership. Comparing HC results with the ground truth, $S_j = 74.8\%$, with 77 out of 90 nodes with matching co-membership. Thus, the node-partitioning of EFA-multiscale has a higher relative likeness to the ground-truth, than that of HC, for this dataset.

Hierarchical Modularity and Hemispheric Symmetry: The Sankey plot of node-partitions of single-scale EFA with $n_F = \{5, 6, 7, 9\}$ reveals hierarchical grouping (Figure 3 (ii)). The hierarchical modular organization of the brain has been widely studied [3], and single-scale EFA interestingly confirms this behavior in this dataset. Since there is no unique hierarchical grouping in FCN at resting-state, this result is not generalizable. Hence, this pattern in single-scale EFA is specific to this dataset.

At the optimal $n_P = 5$ of multiscale EFA, we observe that the partitions show hemispheric symmetry and spatial clustering (§Figure 4), as expected [13]. Similar to the ground-truth results, nodes of the module I mostly belong to the motor and auditory related regions of the brain. Module II nodes are the default network regions. Nodes of module III are components of limbic and subcortical areas of the brain. Major nodes of module IV are visual processing regions, and module V is predominantly with the nodes of attention processing regions, including the fronto-parietal cortices.

Methodology Comparisons: Both the methodology used in the ground-truth [13] and HC [6] are similar, where optimizing modularity of the network Q is the governing model. Yet, the method HC show lower similarity value, $S_j = 74.8\%$, and only 77 of 90 nodes have matching co-membership in the node-partitioning. The reason why our method gives a similar output as the ground-truth methodology is owing to the deterministic approach, unlike the stochastic approach in HC. In our method, for a given N, we run EFA N times, compute the consensus matrix, and generate node-partitioning using one run of generalized Louvain method. On the other hand, HC performs ~ 1000 runs of generalized Louvain method to improve the outcome of the consensus matrix. Since generalized Louvain method is of $O(m)$ computational complexity, where m is the number of positive values in D, our method is more efficient than HC.

The limitation of our method is in identifying an appropriate interval for n_F for the multiscale method. The results from state-of-the-art node-partitioning methods and EFA, which is usually not used for FCN data, need not yield

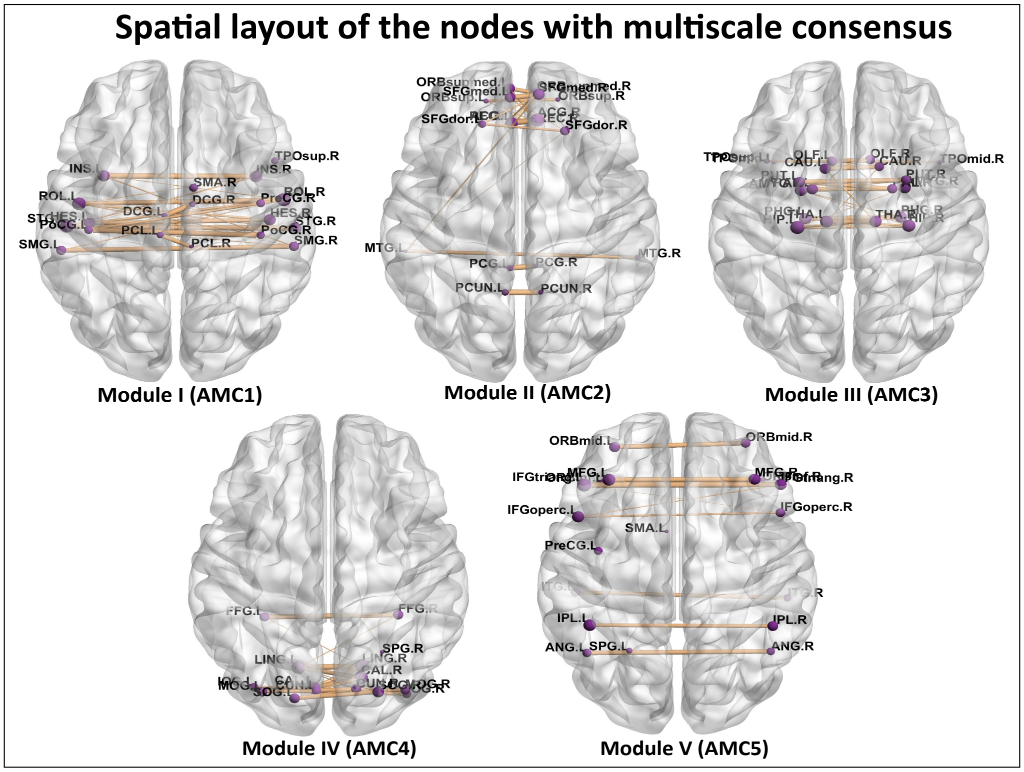


Figure 4: The spatial layout of the nodes of our optimal node-partitioning from our multiscale consensus method using exploratory factor analysis, using all scales between 5 and 12, demonstrate hemispherical symmetry. These superior views have been generated using the BrainNet viewer [11]. The labels (AMC*) correspond to the clusters in Figure 3(i).

matching results owing to the difference in the objective function in the methods. For instance, network-based methods, distance-based methods, and EFA maximize modularity, inter-cluster distances, and inter-factor variances of correlation values, respectively. The cross-impact of variables in such objective functions is dependent on the dataset, owing to which there are possibilities of missing out values of n_F, which may be critical for correlation analysis. Thus, the overdependence of multiscale EFA on the empirical values of n_F for determining I affects the results. For example, in this dataset, if $n_F = 5, 6$ are absent, we will not be able to observe the hierarchical behavior. This may be alleviated by the conservative choice of n_F in I with a trade-off against efficiency. Hence, overall, our method is exploratory, and this work demonstrates an effective correlation analysis using multiscale EFA with appropriate I.

4 Conclusions

We have demonstrated that EFA can be used for extracting functional segregation of the human brain. We have proposed a multiscale approach, where the number of factors n_F is treated as a scale to mitigate the replication and generalizability issues of using EFA. Our method exploits the classificatory solutions that EFA provides, and aggregates them using a consensus method, used for complex networks. We have implemented it with varying intervals of n_F, thus giving an ensemble of experiments. We have determined the optimal interval of factors, which gives high Q, and high S_j values with the ground-truth [13]. We find that multiscale EFA is comparable to the state-of-the-art hierarchical consensus clustering [6]. We also find that using the entire interval of n_F that includes all optimal values of n_P found empirically gives us optimal node-partitioning using multiscale EFA.

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