Network biomarkers of schizophrenia by graph theoretical investigations of Brain Functional Networks

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Abstract—Brain Functional Networks (BFNs), graph theoretical models of brain activity data, provide a systems perspective of complex functional connectivity within the brain. Neurological disorders are known to have basis in abnormal functional activities, that could be captured in terms of network markers. Schizophrenia is a pathological condition characterized with altered brain functional state. We created weighted and binary BFN models of schizophrenia patients as well as healthy subjects starting from fMRI data in an effort to search for network biomarkers of the disease. We investigated 45 topological features of BFNs and their 27325 higher order combinations (pairs, triads and tetrads). We find that network features embodying closeness, betweenness, assortativity and edge density emerge as key markers of schizophrenia. Also, features derived from weighted BFNs were observed to be more effective in disease classification as compared to those from binary BFNs. These topological markers provide insights into mechanisms of functional activity underlying disease phenotype and could further be used for designing algorithms for clinical diagnosis of schizophrenia as well as its early detection. Thus results from our study could be leveraged for effective treatment of schizophrenia at reduced cost.

Index Terms—Brain functional networks (BFNs), fMRI, network features, schizophrenia.

I. INTRODUCTION

NEURONAL disorders are known to have basis in abnormal brain functional activities. Brain imaging data have been used to investigate underlying structure and function of a healthy brain and also to pin down differences in functional activity under pathological conditions such as schizophrenia, Alzheimers and autism. Beyond identification of neuronal correlates of these disorders, the need to identify patterns in functional activity has paved way for systems modeling of brain activity data and search for higher order features.

Amongst several neuro-imaging techniques, fMRI has gained widespread popularity for scrutinizing brain activity, owing to its high spatial and temporal resolutions. fMRI is a blood oxygen level signal which is indirectly dependent on the neuronal activity. It captures the hemodynamic response function of the brain neuronal activities giving indirect indications of temporal and spatial neuronal changes. The fMRI data is collected in terms of voxels where each voxel corresponds to hemodynamic response of the neural activity. This four-dimensional spatio-temporal fMRI data could be used to create systems-level models of brain activities using graph theoretic (complex networks) approach [1]–[3].

Brain functional networks (BFNs) are graph theoretical models of functional activities that provide a deep visual insight into connectivity patterns within the brain. BFNs could be utilized to measure anatomical or functional connectivity between different brain regions and hence to probe network characteristics of functional connectivity under brain disorders with the help of graph theoretical metrics. There is a growing interest in application of BFN models for studying various cognitive states as well as pathological conditions and development of methods for the same. In last decade, several advances have happened towards application of network theory for investigation of fMRI data [4]. This approach has been used to understand the organization of brain at macro-level using BFN models [5]–[7]. A variety of network modelling approaches have been implemented for this purpose [8], [9]. These studies have provided insights into the systems architecture of the brain and have highlighted salient features such as presence of default mode network in resting state of brain [10], small-world architecture [11], [12], modularity and hierarchical organization [13]–[15].

Significant structural and functional neuronal abnormalities are known to happen under pathological conditions such as schizophrenia [16]–[18], autism [19], [20], and Alzheimers [21]. There is an increased focus in finding potential network biomarkers for brain disorders. This will not only assist clinical diagnosis but could eventually help in early diagnosis and effective treatment at reduced cost.

Schizophrenia, known for altered functional brain state, has been studied with the help of BFN models and machine learning techniques for its classification from healthy brain states. Anderson et al. [22] classified schizophrenia patients from healthy under resting and tasked activities using distance matrices modeled from ICAs of fMRI scans with classification accuracies up to 90%. Yang et al. [23] demonstrated hybrid machine learning method using fMRI and genetic data of schizophrenic patients for their classification with high accuracies. Similar studies were performed using features extracted from default mode network and motor temporal ICA components employing two level feature detection technique [24].

Using linear and non-linear discriminative methods, Arbabshi-
TABLE I  
DEMOGRAPHIC PROFILE OF SUBJECTS IN COBRE DATASET.

| Parameter          | Healthy Subjects | Schizophrenic Patients |
|--------------------|------------------|------------------------|
| Age                | 35.8±11.58       | 38.1±13.89             |
| Female (%)         | 31               | 19                     |
| Right Handedness (%) | 96              | 83                     |

...ran et al. [25] examined resting state functional connectivity features for disease classification to achieve up to 96% accuracy using non-linear classifiers. Multiple kernel learning was further used by Castro et al. [25] to modify the feature selection method thereby achieving improved accuracies. Chyzhyk et al. [27] used extreme learning machines to build a computer aided diagnostic system employing features derived from fMRI data. Beyond these key studies, many efforts have gone into application of machine learning techniques on fMRI derived brain network parameters for classification of schizophrenia with higher accuracy [28]-[33].

In this study we investigated BFNs constructed from fMRI data of schizophrenia subjects and healthy subjects so as to identify higher order topological features that characterize the disease. Starting with COBRE data set, we implemented the protocol established by Anderson and Cohen [22] for creating BFN models and for their graph theoretical investigations. Towards identification of key distinguishing network features of schizophrenia, we exhaustively investigated 17 and 28 first order derived network features of binary (unweighted) and weighted BFNs, as well as their higher (second, third and fourth) order tuples. We believe that features thus identified could be effectively used for semi-automated diagnosis of schizophrenia, and may further be used for early detection protocol.

II. MATERIALS AND METHODS

For investigating systems-level differences in brain activity of healthy subjects and pre-diagnosed schizophrenic patients we used the COBRE dataset. This dataset, obtained from International Neuroimaging Data-Sharing Initiative under 1000 Functional Connectomes Project, comprised of fMRI data of 74 healthy subjects (controls) and 72 patients of schizophrenia with varying ages ranging from 18 to 65 years in both classes. The patients were pre-diagnosed with schizophrenia based on ‘structured clinical interview’ used for DSM disorders. Echo-planar imaging was used for resting state fMRI data collection with (Repetition Time) TR=2s, (Echo Time) TE=29ms, matrix size: 64×64, slices=32, voxel size=3×3×4 mm³. Table I depicts the demographic profile of the subjects. Detailed profiles of all subjects are provided in Table S1 of Supplementary Material.

The fMRI data is a 4-Dimensional metadata comprising of information from spatial and temporal dimensions of blood oxygen-level dependent activities under resting state of the brain, along with some additional information about the dataset such as its size, dimensions and details of voxels. We implemented a protocol for transforming fMRI data into their functional network representation described by Anderson and Cohen [22]. This protocol involves a series of steps including pre-processing of the raw fMRI data, decomposing 4-D data into spatial and time series components using ICA, creating functional graphs from the components thus extracted, and finally evaluating graph theoretical properties of brain functional networks. Following are details of each of these steps of the protocol implemented.

A. Preprocessing

The COBRE data needs to be processed before further analysis. The preprocessing step is aimed at removal of artifacts and standardizing locations of brain regions across all subjects. As a first step of pre-processing, motion correction was implemented for each subject by synchronizing signals recorded in each voxel across all slices. This step corrects any misrepresentation of data from individual voxels due to subject’s head motion. The corrected recording from each voxel was obtained by shifting images from each slice with respect to the reference image. This step was then followed by filtering steps, which include spatial and temporal filtering as well as noise reduction. We obtained filtered 4-D fMRI data for each subject at the end of pre-processing steps, which were performed using fMRI Software Library (FSL) [34].

B. Independent Component Analysis (ICA)

 Extracting meaningful features from this high dimensional fMRI data is expected to reduce the redundancy and noise that is not removed at the pre-processing stage. Towards this end ICA was implemented to bring down the complexity of this high dimensional data to a manageable level [35], [36]. The four dimensional space-time fMRI data was represented in terms of an array of dimension (T, X * Y * Z) such that the fMRI scan of time length T and space S can be represented by a linear combination of M < T components and corresponding time series:

\[ X_{ts} = \sum_{\mu=1}^{M} A_{\mu s} C_{\mu s} \]  

(1)

where \( X_{ts} \) represents raw scan intensity at time \( t \) and space point \( s \), \( A_{\mu s} \) is the amplitude of component \( \mu \) at time \( t \), \( C_{\mu s} \) is the magnitude of component \( \mu \) at space point \( s \) and \( M \) stands for total number of components. For the COBRE data the time points \( T \) in the signal were 150 and \( X, Y \) and \( Z \) were 64, 64 and 32 where \( X \) and \( Y \) are number of points in two dimensional space and \( Z \) is the slice number.

In ICA, data is assumed to be a linear combination of signals and fMRI data complies with this assumption. Spatial ICA was employed to decompose fMRI data into a set of maximally spatially independent maps and their corresponding time-courses. These time-courses show considerable amount of time-dependencies between distinct functional activities captured in various components, indicating their potential for use in functional network connectivity analysis. The time-courses, that measure time-varying activity of components, were used for further analysis. These components represent spatially independent time-varying functional activities of the brain under resting state. The ICA of fMRI data was implemented using FSL.
C. Brain Functional Networks and enumeration of network parameters

Brain functional network is a complex networks model of brain where a node represents ‘spatially’ independent functional activity extracted with ICA and an edge specifies the ‘extent’ of temporal dependency between the nodes. Temporal dependencies between functional activities were measured by finding correlations between them. Dependencies were computed using a correlation based distance metric that is a transformation of the maximal absolute cross-correlation between two time-series. For every pair of nodes cross-correlation function (CCF) was calculated over a range of temporal lags, $CCF(X_{\mu_i}, X_{\mu_j}, l) = \frac{E[(x_{\mu_i,t} - X_{\mu_i})(x_{\mu_j,t} - X_{\mu_j})]}{\sqrt{E[(x_{\mu_i,t} - X_{\mu_i})^2]E[(x_{\mu_j,t} - X_{\mu_j})^2]}}$ (2)

where, $X_{\mu_i}, X_{\mu_j}$ are time series of $i^{th}$ and $j^{th}$ components, l is the temporal lag between them and varied from 0 to 3 points (total 6 seconds with an interval of 2 seconds). The distance matrix dist($X_{\mu_i}, X_{\mu_j}$) was determined by subtracting maximal absolute CCF from 1 and is given by,

d($X_{\mu_i}, X_{\mu_j}) = 1 - max[|CCF(X_{\mu_i}, X_{\mu_j}, l)|]$ (3)

This distance signifies temporal similarity between two components; the higher the distance lesser the correlation. The distance matrix, thus calculated, represents the weighted brain functional network of a subject.

The weighted BFN was further pruned to remove weak connections on the basis of k-nearest neighbor approach where k was chosen as 10% of total components of the subject or 2, whichever was maximum. This pruned BFN was used for computation of graph theoretical parameters. While the graph creation was implemented by R programming language [37], computation of graph theoretical metric was done in MATLAB. Fig. 1 shows the strategy implemented to obtain BFN of each subject and for its graph theoretical characterization.

Binary BFNs were obtained by thresholding the weighted BFNs. The threshold was chosen on trial and error basis such that a single component network is maintained. Following network parameters were computed on both the binary as well as weighted BFNs for each subject: degree, edge density, node betweenness, edge betweenness; clustering coefficient, characteristic pathlength, efficiency, modularity, closeness, coreness, eccentricity and weak ties. This study was aimed at identification of network parameters that play crucial role in discriminating BFNs of schizophrenia subjects from those of controls. Towards this end we computed higher order statistics (mean, median and standard deviation) for the above mentioned network parameters. We obtained 28 and 17 such statistical features for weighted and binary BFNs, respectively. Table S2 in Supplementary Material provides an exhaustive list of all network derived features.

D. Feature Classification

The BFNs were classified into schizophrenic and control subjects on the basis of the network features derived from weighted as well as binary BFNs. Support Vector Machine (SVM) was used as a classifier with radial basis function as its kernel function. When trained with features of BFNs along with their predefined classes, SVM can classify test cases of BFNs. The performance of SVM classification was assessed with 10-fold cross validation statistics.

We investigated the feature set consisting of individual network features (of weighted and binary BFNs) as well as their pairwise, triad and tetrad combinations with a total of 146 subjects. Combinations with more than four features were not only computationally challenging but were also found to be redundant towards identification of optimal feature set. Our study identified topological features of BFNs with potential for accurate classification between schizophrenia and healthy subjects by an exhaustive search of network features and their higher combinations without using feature selection approach.

III. RESULTS

A. Brain Functional Networks

Brain Functional Networks represent systems model of brain functional activities. Fig. 2 depicts detailed process used for creation of BFNs starting from raw fMRI data. The raw fMRI data was pre-processed to obtain a filtered fMRI signal which was further decomposed into spatially independent components to fetch time-series for each component using ICA. Using time-series data in components, correlation based normalized distance matrix was calculated. This matrix was transformed into weighted and binary adjacency matrices, which represent the network of independent components. Various graph theoretical properties of BFNs were then computed so as to generate a unique feature set to be used for classification (Table S2 of Supplementary Material). The final features set comprised of pairwise, triad and tetrad combinations of individual features derived from both binary as well as weighted BFNs. The classification between healthy and schizophrenic subjects was performed with the help of these features.
B. Topological biomarkers of schizophrenia

Towards identification of topological biomarkers of schizophrenia, we investigated network features derived from BFNs of patients and healthy controls. Fig. 3 illustrate apparent differences between (weighted) BFNs and their topological properties of healthy and schizophrenia subjects. The differences that are almost indiscernible at the level of BFN adjacency matrices, become more apparent when seen through the lens of topological features.

Closeness was among the few topological features that contributed significantly to classification accuracy. It reflects proximity of a node to the core of the network. Lower values of closeness represent longer distance to travel between two nodes. The difference in networks belonging to two categories support the hypothesis that recognizes schizophrenia as a disorder of dysfunctional integration between distant brain regions [39], [40]. While the ability to consistently classify schizophrenia BFNs from that of healthy subject may be limited with single features, we anticipated better efficacy for higher order (pairwise, triad and tetrad combinations) features. We present our results on ability to segregate between BFNs of healthy and schizophrenia subjects in the following sections.

C. Individual parameters

First, we created a feature set using individual parameters. For weighted and binary BFNs 28 and 17 such parameters were independently trained and tested in the classifier. Fig. 4 (a) and Fig. 4 (b) show highlights of our studies with individual parameters with best classification ability (>55% accuracy; arbitrarily chosen), for weighted and binary BFNs respectively. The accuracy obtained by random sampling
Fig. 4. Average accuracy of best individual network features with their standard errors for (a) weighted, and (b) binary BFNs. Horizontal line shows random classification rate of 50.6%.

stands at 50.6% (shown with a horizontal line in figures) for this dataset. The classification results for all parameters are listed in Table S3 and Table S4 of Supplementary Material. Following were the best individual parameters obtained with weighted BFNs (Fig. 4 (a)): 1. Optimal community structure, 2. Std. deviation of closeness, 3. Longest distance between two vertices, 4. Max. of vertex eccentricity, 5. Sum of product of degrees across all edges, 6. Median closeness, 7. Mean closeness, 8. Median degree, and 9. Maximum degree. Similarly, following were the best individual parameters obtained with binary BFNs (Fig. 4 (b)): 1. Maximum edge overlap, 2. Maximum matching index between two vertices, 3. Number of weak ties, 4. Global efficiency, 5. Edge density, and 6. Maximum edge betweenness.

In weighted networks, the ‘community structure’ underlying the subject’s network provides the best performance individually. On the other hand, the ‘maximum of edge overlap between the two nodes’ in the binary network yielded the highest accuracy.

D. Pairwise Features

Motivated with the idea of creating a better feature set that could potentially enhance the ability to distinguish between correlations across the BFNs, we created pairwise combination of features set using individual features. The pairwise feature set had 378 and 136 combinations for weighted and binary BFNs, respectively. Interestingly, the classification performance for pairwise features was much better than that of individual features. Fig. 5 (a) and Fig. 5 (b) depict the combinations with accuracies were better than 60% for weighted and binary BFNs, respectively. A more detailed list of top ten pairwise combinations, along with their accuracies and standard deviations, are provided in Table S5 and Table S6 of Supplementary Material.

Optimum community structure emerged as the best feature which when paired with other features yielded among the best classification accuracies. Following were among the best pairwise features (accuracy>60%; chosen arbitrarily) when coupled with ‘optimum community structure’: 1. Std. deviation of closeness, 2. Median closeness, 3. Mean closeness, 4. Assortativity and 6. Max. of vertex eccentricity. Combination 5 in Fig. 5 refers to Characteristic pathlength and Transitivity. Following were the three best pairwise features (accuracy>60%) obtained with binary BFNs (Fig. 5 (b)):
Triad Combinations

Average Accuracy (10-cross fold validation)

Classification accuracy of triad features

65.78%
65.53%
65.35%

Fig. 6. Average accuracies of top three triad combinations of network features for (a) weighted, (b) binary BFNs.

1. Edge count and Transitivity, 2. Transitivity and Mean closeness and 3. Maximum edge overlap and No. of weak ties. The improved performance of pairwise features compared to that of individual indicates at synergistic effect of multiple topological features extracted from the BFNs leading to better classification accuracy. To test the efficacy of such synergistic effect for higher order of feature combinations, we further created triad features.

E. Triad Features

Creating triad features yields 3276 and 680 such combinations respectively for weighted and binary BFNs. Fig. 6 depicts the classification accuracies of three best triadic features. Detailed results of top ten combinations are provided in Table S7 and Table S8 of Supplementary Material.

The pair ‘Standard deviation of closeness’ and ‘Maximized modularity’ were consistently present among the best three triads of weighted BFNs. When used with 1. Assortativity, 2. Std. deviation of degrees and 3. Maximum matching index, these yielded best classification of schizophrenia BFNs. In binary BFNs, ‘Transitivity’ and ‘Mean closeness’ were consistently present among the best three triadic combinations along with, 1. No. of weak ties, 2. Edge density, and 3. Characteristic pathlength. The improved accuracy with triadic combinations motivated us to examine further higher order combinations.

F. Tetrad Features

We observed that increasing the order of feature combination did not yield any significant improvement above the triads for binary BFNs. Marginal improvement was observed for tetrad features of weighted BFNs. A total of 2380 and 20475 tetrad combinations were investigated for binary and weighted BFNs, respectively. The details of top ten tetrad feature combinations are shown in Table S9 and Table S10 in Supplementary Material.

Fig. 7 summarizes the effectiveness of higher order combinations of network features. The figure shows the trend in highest average accuracy with increasing number of features in the feature set. Improved classification accuracy was observed with increased order of features up to triad combinations. Interestingly, features extracted from weighted BFNs yielded better classification accuracy than those from binary BFNs. With increased complexity of features the accuracy, after initial increase, plateaued. Increased redundancy was observed among the top features obtained.

IV. DISCUSSION

Brain functional networks, graph theoretical models of brain activity data, provide macro-level understanding of complex functional connectivity in the brain [1], [2], [4], [41]. Functional networks of brains ink pathological conditions, such as schizophrenia, have been reported to have altered properties quantifiable in terms of topological features (For eg.: low average clustering, long characteristic pathlength, lower degree of connectivity, lower strength of connectivity and reduced modularity) [16], [42]-[45]. Such disruptions of topological features are understood to be an indication of dysfunctionality in schizophrenic BFNs as studied in fMRI scans of dorsal and ventral prefrontal, anterior cingulate, and posterior cortical regions [46], [47].
Here, we performed an exhaustive investigation of graph theoretical features of binary and weighted BFNs and their higher order combinations towards classification of BFNs of schizophrenic and healthy subjects. One of the objectives of our study was to assess the utility of increased order of features on classification accuracy. Other than that we aimed to identify network metrics and their possible implication for altered brain functional patterns.

Our study provides some of the key features that can play an important role in characterizing schizophrenia. Liu et al. [16] had shown that small-world organization in brain networks of schizophrenic patients are significantly altered in many brain regions with decreased clustering and increased characteristic path length. Beyond disrupted small world nature, our study presents other properties that may be associated with BFNs of dysfunctional schizophrenic phenotype. Weighted BFNs of schizophrenia subjects were distinct in terms of closeness, sum of product of degrees across all edges, vertex eccentricity, maximized modularity, assortativity and transitivity. On the other hand, binary BFNs presented transitivity, node betweenness, edge density, number of weak ties, characteristic pathlength and matching index between nodes among the best features that could be used for classification of schizophrenia patients from healthy subjects. Broadly these properties reflect on connectivity, modularity and hierarchical organization of the network.

One of the highest accuracies reported with BFN-based models exceeds 65% as reported by Anderson and Cohen [22]. Although, the classification accuracies achieved in our study were not exemplary, our study highlights the role of topological features derived from weighted BFNs for classification of schizophrenia (MRI) data. Few key network features (such as closeness, node betweenness, assortativity and edge density) emerged as potential network biomarkers of schizophrenia. The study also underlines limits on higher order feature combinations indicating saturation of classification accuracy. Specific network features obtained from our study could further be used for designing better disease classification algorithms as well as early detection systems.

Our study suggests that instead of exhaustive search for features through higher order combinations of features (ntuples) appropriate use of feature selection methods could be the way forward. The insights gained from our study into network biomarkers and limitations of higher order features could be used for efficient design of computational protocols for diagnosis of schizophrenia at an early stage.

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| ID    | Current Age | Gender | Handedness | Subject Type | Diagnosis     |
|-------|-------------|--------|------------|--------------|---------------|
| 40000 | 20          | Female | Right      | Patient      | 295.9         |
| 40001 | 27          | Male   | Right      | Patient      | 295.3         |
| 40002 | 19          | Male   | Right      | Patient      | 295.3         |
| 40003 | 28          | Male   | Right      | Patient      | 295.1         |
| 40004 | 55          | Male   | Right      | Patient      | 295.3         |
| 40005 | 48          | Female | Right      | Patient      | 295.3         |
| 40006 | 53          | Male   | Right      | Patient      | 295.6         |
| 40007 | 65          | Female | Right      | Patient      | 295.3         |
| 40008 | 28          | Male   | Right      | Patient      | 295.9         |
| 40009 | 31          | Female | Right      | Patient      | 295.3         |
| 40010 | 52          | Male   | Right      | Patient      | 295.3         |
| 40011 | 28          | Male   | Left       | Patient      | 295.6         |
| 40012 | 32          | Female | Right      | Patient      | 295.3         |
| 40013 | 34          | Male   | Right      | Control      | None          |
| 40014 | 31          | Male   | Right      | Control      | None          |
| 40015 | 47          | Male   | Right      | Patient      | 295.3         |
| 40016 | 49          | Male   | Both       | Patient      | 295.3         |
| 40017 | 30          | Female | Right      | Control      | None          |
| 40018 | 47          | Male   | Right      | Control      | None          |
| 40019 | 44          | Male   | Right      | Control      | None          |
| 40020 | 22          | Male   | Right      | Control      | None          |
| 40021 | 21          | Female | Right      | Patient      | 295.3         |
| 40022 | 23          | Male   | Left       | Patient      | 295.6         |
| 40023 | 48          | Male   | Right      | Control      | None          |
| 40024 | 42          | Male   | Right      | Control      | None          |
| 40025 | 33          | Male   | Right      | Patient      | 295.3         |
| 40026 | 44          | Male   | Right      | Control      | None          |
| 40027 | 48          | Male   | Right      | Control      | None          |
| 40028 | 64          | Male   | Right      | Patient      | 295.3         |
| 40029 | 20          | Male   | Right      | Patient      | 295.6         |
| 40030 | 43          | Male   | Right      | Control      | None          |
| 40031 | 43          | Female | Right      | Control      | None          |
| 40032 | 31          | Female | Right      | Patient      | 295.3         |
| 40033 | 31          | Female | Right      | Control      | None          |
| 40034 | 29          | Male   | Left       | Patient      | 295.3         |
| 40035 | 30          | Male   | Right      | Control      | None          |
| 40036 | 26          | Male   | Both       | Control      | None          |
| 40037 | 24          | Male   | Right      | Patient      | 295.3         |
| 40038 | 53          | Female | Right      | Control      | None          |
| 40039 | 51          | Female | Left       | Patient      | 295.7         |
| 40040 | 63          | Male   | Right      | Patient      | 295.3         |
| 40041 | 62          | Male   | Right      | Patient      | 295.3         |
| 40042 | 40          | Female | Right      | Patient      | 295.3         |
| 40043 | 38          | Male   | Right      | Control      | None          |
| 40044 | 48          | Male   | Left       | Patient      | 290.3         |
| 40045 | 30          | Male   | Right      | Control      | None          |
| 40046 | 18          | Male   | Left       | Patient      | 295.70 depressed type |
| 40047 | 37          | Male   | Right      | Patient      | 295.3         |
| 40048 | 31          | Male   | Right      | Control      | None          |
| 40049 | 44          | Male   | Right      | Patient      | 295.3         |
| 40050 | 36          | Male   | Right      | Control      | None          |
| 40051 | 23          | Male   | Right      | Control      | None          |
| 40052 | 22          | Female | Right      | Control      | None          |
| 40053 | 24          | Female | Right      | Control      | None          |
| 40054 | 52          | Male   | Right      | Control      | None          |
| ID   | Age | Gender | Side   | Status  | Diagnosis |
|------|-----|--------|--------|---------|------------|
| 40055| 30  | Female | Right  | Control | None       |
| 40056| 27  | Male   | Right  | Control | None       |
| 40057| 36  | Male   | Right  | Control | None       |
| 40058| 27  | Female | Right  | Control | None       |
| 40059| 25  | Male   | Right  | Patient | 295.3     |
| 40060| 41  | Male   | Right  | Patient | 295.3     |
| 40061| 18  | Male   | Right  | Control | None       |
| 40062| 50  | Male   | Right  | Control | None       |
| 40063| 37  | Male   | Right  | Control | None       |
| 40064| 56  | Female | Both   | Patient | 295.6     |
| 40065| 22  | Male   | Right  | Control | None       |
| 40066| 62  | Male   | Left   | Control | None       |
| 40067| 33  | Male   | Right  | Control | None       |
| 40068| 24  | Female | Right  | Control | None       |
| 40069| 58  | Male   | Right  | Control | None       |
| 40070|     |        |        | Disenrolled | Disenrolled |
| 40071| 51  | Female | Right  | Patient | 295.6     |
| 40072| 25  | Male   | Right  | Patient | 295.3     |
| 40073| 23  | Male   | Right  | Patient | 295.7     |
| 40074| 34  | Female | Right  | Control | 311        |
| 40075| 40  | Male   | Right  | Patient | 295.1     |
| 40076| 52  | Male   | Right  | Control | None       |
| 40077| 28  | Male   | Right  | Patient | 295.6     |
| 40078| 57  | Male   | Right  | Patient | 295.6     |
| 40079| 26  | Male   | Right  | Patient | 295.6     |
| 40080| 26  | Male   | Right  | Patient | 295.6     |
| 40081| 43  | Male   | Right  | Patient | 295.7     |
| 40082| 50  | Male   | Right  | Patient | 295.3     |
| 40083|     |        |        | Disenrolled | Disenrolled |
| 40084| 60  | Male   | Right  | Patient | 295.1     |
| 40085| 22  | Male   | Right  | Patient | 295.3     |
| 40086| 65  | Male   | Right  | Control | None       |
| 40087| 27  | Male   | Right  | Control | None       |
| 40088| 33  | Female | Right  | Patient | 295.9     |
| 40089| 62  | Male   | Right  | Patient | 295.3     |
| 40090| 18  | Female | Right  | Control | None       |
| 40091| 24  | Male   | Right  | Control | None       |
| 40092| 49  | Male   | Right  | Patient | 295.3     |
| 40093| 25  | Male   | Right  | Control | None       |
| 40094| 57  | Male   | Left   | Patient | 295.92    |
| 40095| 40  | Female | Right  | Control | None       |
| 40096| 22  | Male   | Right  | Patient | 295.9     |
| 40097| 52  | Female | Right  | Patient | 296.4     |
| 40098| 35  | Male   | Right  | Patient | 295.3     |
| 40099| 38  | Male   | Right  | Patient | 295.70 bipolar type |
| 40100| 35  | Male   | Right  | Patient | 295.3     |
| 40101| 50  | Male   | Right  | Patient | 295.3     |
| 40102| 40  | Female | Right  | Control | None       |
| 40103| 40  | Male   | Right  | Patient | 295.3     |
| 40104| 26  | Male   | Right  | Control | None       |
| 40105| 52  | Male   | Right  | Patient | 295.3     |
| 40106| 46  | Male   | Right  | Patient | 295.6     |
| 40107| 33  | Female | Right  | Control | None       |
| 40108| 29  | Male   | Right  | Patient | 295.3     |
| 40109| 33  | Male   | Right  | Patient | 295.3     |
| 40110| 43  | Male   | Left   | Patient | 295.7     |
| 40111| 58  | Female | Both   | Control | None       |
| 40112| 42  | Male   | Right  | Patient | 295.3     |
|    |   |     |    |    |          |
|----|---|-----|----|----|----------|
| 40113 | 20 | Male | Right | Control | None |
| 40114 | 23 | Male | Right | Control | None |
| 40115 | 27 | Male | Right | Control | None |
| 40116 | 47 | Male | Right | Control | None |
| 40117 | 19 | Male | Right | Patient | 295.3 |
| 40118 | 34 | Female | Right | Control | 296.26 |
| 40119 | 44 | Female | Right | Control | None |
| 40120 | 26 | Male | Right | Control | None |
| 40121 | 21 | Female | Right | Control | None |
| 40122 | 22 | Male | Right | Patient | 295.3 |
| 40123 | 48 | Male | Right | Control | None |
| 40124 | 35 | Male | Right | Control | None |
| 40125 | 48 | Male | Right | Control | None |
| 40126 | 41 | Female | Right | Patient | 295.3 |
| 40127 | 26 | Male | Right | Control | None |
| 40128 | 22 | Male | Right | Control | None |
| 40129 | 23 | Male | Right | Control | None |
| 40130 | 47 | Female | Right | Control | None |
| 40131 | 47 | Male | Right | Control | None |
| 40132 | 50 | Male | Right | Patient | 295.7 |
| 40133 | 20 | Male | Right | Patient | 295.3 |
| 40134 | 42 | Male | Right | Control | None |
| 40135 | 24 | Female | Right | Control | None |
| 40136 | 38 | Male | Right | Control | None |
| 40137 | 21 | Male | Left | Patient | 295.2 |
| 40138 | 28 | Male | Right | Control | None |
| 40139 | 28 | Female | Right | Control | None |
| 40140 | 53 | Female | Right | Control | None |
| 40141 | 35 | Female | Right | Control | None |
| 40142 | 23 | Male | Left | Patient | 295.9 |
| 40143 | 52 | Male | Right | Patient | 295.3 |
| 40144 | 54 | Male | Right | Control | None |
| 40145 | 19 | Male | Right | Patient | 295.6 |
| 40146 | 39 | Male | Right | Control | None |
| 40147 | 34 | Male | Right | Control | None |

**TABLE S1: Detailed profiles of all subjects.**
| S.No. | Weighted Network Property | S.No. | Binary Network Property |
|-------|---------------------------|-------|-------------------------|
| 1.    | Node count                | 1.    | Edge count              |
| 2.    | Minimum degree            | 2.    | Edge density            |
| 3.    | Maximum degree            | 3.    | Assortativity           |
| 4.    | Mean degree               | 4.    | Mean node betweenness   |
| 5.    | Median degree             | 5.    | Maximum node betweenness|
| 6.    | Standard deviation of degrees | 6.    | Standard deviation of node betweenness |
| 7.    | Edge density with threshold| 7.    | Maximum edge betweenness|
| 8.    | Assortativity             | 8.    | Longest distance between two vertices |
| 9.    | Mean node betweenness     | 9.    | Global efficiency       |
| 10.   | Maximum node betweenness  | 10.   | Average clustering coefficient |
| 11.   | Minimum node betweenness  | 11.   | Transitivity            |
| 12.   | Standard deviation of node betweenness | 12.   | Maximum edge overlap    |
| 13.   | Maximum edge betweenness  | 13.   | Maximum matching index between two vertices |
| 14.   | Shortest distance between two vertices | 14.   | Mean closeness          |
| 15.   | Global efficiency         | 15.   | Characteristic pathlength|
| 16.   | Average clustering coefficient | 16.   | Number of weak ties     |
| 17.   | Transitivity              | 17.   | Minimum node betweenness|
| 18.   | Optimal community structure |       |                         |
| 19.   | Maximized modularity      |       |                         |
| 20.   | Maximum of matching index between two vertices |       |                         |
| 21.   | Median coreness           |       |                         |
| 22.   | Mean closeness            |       |                         |
| 23.   | Median closeness          |       |                         |
| 24.   | Standard deviation of closeness |       |                         |
| 25.   | Sum of product of degrees across all edges |       |                         |
| 26.   | Mean Vertex eccentricity  |       |                         |
| 27.   | Standard deviation of node betweenness |       |                         |
| 28.   | Longest distance between two vertices |       |                         |

**Table S2**
Network based features of each subject that were used for classification between two classes.

| S.No. | Name of the Parameter                      | Accuracy | Std. Error |
|-------|--------------------------------------------|----------|------------|
| 1.    | Optimal community structure                | 60.17    | 0.0134     |
| 2.    | Std. deviation of closeness                | 57.97    | 0.0108     |
| 3.    | Longest distance between two vertices       | 57.36    | 0.0130     |
| 4.    | Max. of vertex eccentricity                | 56.77    | 0.0178     |
| 5.    | Sum of product of degrees across all edges  | 56.53    | 0.0158     |
| 6.    | Median closeness                           | 56.13    | 0.0117     |
| 7.    | Mean closeness                             | 55.73    | 0.0166     |
| 8.    | Median degree                              | 55.27    | 0.0204     |
| 9.    | Max. degree                                | 55.17    | 0.0206     |
| 10.   | Characteristic pathlength                  | 54.12    | 0.0213     |
| 11.   | Global efficiency of the network           | 53.36    | 0.0224     |
| 12.   | Mean degree                                | 52.12    | 0.0213     |
| 13.   | Avg. clustering coefficient                | 51.90    | 0.0191     |
| 14.   | Shortest distance between two vertices      | 51.82    | 0.0270     |
| 15.   | Transitivity                               | 51.72    | 0.0173     |
| 16.   | Node count                                 | 51.68    | 0.0241     |
| 17.   | Standard deviation of node betweenness     | 50.46    | 0.0222     |
| 18.   | Max. edge betweenness                      | 50.10    | 0.0201     |
| 19.   | Maximized modularity                       | 50.03    | 0.0192     |
| 20.   | Median coreness                            | 49.20    | 0.0244     |
| 21.   | Minimum degree                             | 49.09    | 0.0216     |
| 22.   | Edge density with threshold                | 49.04    | 0.0234     |
| 23.   | Maxi. maximal matching between two vertices| 48.18    | 0.0283     |
| 24.   | Std. deviation of degrees                  | 47.21    | 0.0335     |
| 25.   | Assortativity                              | 45.74    | 0.0263     |
| 26.   | Min. node betweenness                      | 44.25    | 0.0143     |
| 27.   | Max. node betweenness                      | 41.47    | 0.0317     |
| 28.   | Mean node betweenness                      | 41.38    | 0.0301     |

**Table S3**
Average accuracies with their standard error for all binary network properties.
| S.No. | Name of the Parameter                                      | Accuracy | Std. Error |
|-------|-----------------------------------------------------------|----------|------------|
| 1.    | Maximum edge overlap                                      | 59.06    | 0.0129     |
| 2.    | Maximum matching index between two vertices               | 57.44    | 0.0139     |
| 3.    | Number of weak ties                                       | 57.15    | 0.0143     |
| 4.    | Global efficiency                                         | 55.54    | 0.0137     |
| 5.    | Edge density                                              | 55.43    | 0.0211     |
| 6.    | Maximum edge betweenness                                  | 55.24    | 0.0161     |
| 7.    | Minimum node betweenness                                  | 55.21    | 0.0139     |
| 8.    | Characteristic pathlength                                 | 54.84    | 0.0231     |
| 9.    | Longest distance between two vertices                     | 54.78    | 0.0114     |
| 10.   | Assortativity                                             | 54.43    | 0.0199     |
| 11.   | Edge count                                                | 52.06    | 0.0163     |
| 12.   | Mean closeness                                            | 50.23    | 0.0247     |
| 13.   | Transitivity                                              | 49.29    | 0.0270     |
| 14.   | Standard deviation of node betweenness                    | 46.93    | 0.0251     |
| 15.   | Average clustering coefficient                            | 43.87    | 0.0284     |
| 16.   | Maximum node betweenness                                  | 42.95    | 0.0306     |
| 17.   | Mean node betweenness                                     | 42.86    | 0.0337     |

**TABLE S4**
AVERAGE ACCURACIES WITH THEIR STANDARD ERROR FOR ALL BINARY NETWORK PROPERTIES.

| S.No. | Name of the Parameter                                      | Accuracy | Std. Error |
|-------|-----------------------------------------------------------|----------|------------|
| 1.    | Optimal community structure & Std. deviation of closeness  | 64.74    | 0.0138     |
| 2.    | Optimal community structure & Median closeness             | 63.32    | 0.0140     |
| 3.    | Optimal community structure & Mean closeness               | 62.28    | 0.0171     |
| 4.    | Optimal community structure & Mean closeness               | 62.03    | 0.0146     |
| 5.    | Characteristic pathlength & Transitivity                   | 61.89    | 0.0198     |
| 6.    | Optimal community structure & Max. of vertex eccentricity  | 61.79    | 0.0138     |
| 7.    | Optimal community structure & Max. edge betweenness        | 60.85    | 0.0157     |
| 8.    | Optimal community structure & Sum of product of degrees across all edges | 60.62 | 0.0158 |
| 9.    | Optimal community structure & Longest distance between two vertices | 60.42 | 0.0141 |
| 10.   | Optimal community structure & Median degree                | 60.32    | 0.0170     |

**TABLE S5**
AVERAGE ACCURACIES WITH STANDARD ERROR FOR TOP TEN PAIRWISE COMBINATIONS OF WEIGHTED NETWORK FEATURES.

| S.No. | Name of the Parameter                                      | Accuracy | Std. Error |
|-------|-----------------------------------------------------------|----------|------------|
| 1.    | Edge Count & Transitivity                                 | 61.79    | 0.0157     |
| 2.    | Transitivity & Mean closeness                             | 60.71    | 0.0177     |
| 3.    | Maximum edge overlap & Number of weak ties                | 60.46    | 0.0176     |
| 4.    | Minimum node betweenness & Mean closeness                 | 59.38    | 0.0191     |
| 5.    | Transitivity & Number of weak ties                        | 59.37    | 0.0177     |
| 6.    | Maximum matching index between two vertices & Number of weak ties | 59.33 | 0.0184 |
| 7.    | Longest distance between two vertices & Transitivity      | 58.52    | 0.0147     |
| 8.    | Maximum matching index between two vertices & Mean closeness | 57.89 | 0.0216 |
| 9.    | Maximum edge overlap & Maximum matching index between two vertices | 57.83 | 0.0223 |
| 10.   | Minimum node Betweenness & Transitivity                   | 57.66    | 0.0206     |

**TABLE S6**
AVERAGE ACCURACIES WITH STANDARD ERROR FOR TOP TEN PAIRWISE COMBINATIONS OF BINARY NETWORK FEATURES.

| S.No. | Name of the Parameter                                      | Accuracy | Std. Error |
|-------|-----------------------------------------------------------|----------|------------|
| 1.    | Std. deviation of closeness, Maximized modularity & Assortativity | 65.78 | 0.0131 |
| 2.    | Std. deviation of closeness, Maximized modularity & Std. deviation of degrees | 65.53 | 0.0212 |
| 3.    | Std. deviation of closeness, Maximized modularity & Max. Matching index between two vertices | 65.34 | 0.0141 |
| 4.    | Std. deviation of closeness, Maximized modularity & Max. of vertex eccentricity | 64.47 | 0.0153 |
| 5.    | Maximized modularity, Median closeness & Assortativity     | 64.41    | 0.0148     |
| 6.    | Std. deviation of closeness, Maximized modularity & Max. degree | 64.20 | 0.0149 |
| 7.    | Std. deviation of closeness, Maximized modularity & Mean degree | 64.19 | 0.0134 |
| 8.    | Std. deviation of closeness, Maximized modularity & Optimal community structure | 64.08 | 0.0145 |
| 9.    | Std. deviation of closeness, Maximized modularity & Global efficiency of the network | 64.05 | 0.0148 |
| 10.   | Maximized modularity, Mean closeness & Assortativity       | 64.01    | 0.0166     |

**TABLE S7**
AVERAGE ACCURACIES WITH STANDARD ERROR FOR TOP TEN THREE FEATURE COMBINATIONS OF WEIGHTED NETWORK FEATURES.
| S. No. | Name of the Parameter                                                                 | Accuracy | Std. Error |
|--------|----------------------------------------------------------------------------------------|----------|------------|
| 1.     | Transitivity, Number of weak ties & Mean closeness                                      | 64.44    | 0.0168     |
| 2.     | Transitivity, Mean closeness & Edge density                                            | 62.76    | 0.0200     |
| 3.     | Transitivity, Mean closeness & Characteristic pathlength                                | 62.62    | 0.0218     |
| 4.     | Transitivity, Mean closeness & Edge count                                              | 61.96    | 0.0178     |
| 5.     | Transitivity, Edge count & Average clustering coefficient                                | 61.82    | 0.0186     |
| 6.     | Transitivity, Edge count & Standard deviation of node betweenness                       | 61.56    | 0.0218     |
| 7.     | Transitivity, Number of weak ties & Maximum matching index between two vertices         | 61.32    | 0.0202     |
| 8.     | Transitivity, Mean closeness & Minimum node betweenness                                 | 61.17    | 0.0203     |
| 9.     | Transitivity, Number of weak ties & Standard deviation of node betweenness              | 61.16    | 0.0215     |
| 10.    | Transitivity, Number of weak ties & Edge count                                         | 61.07    | 0.0167     |

**TABLE S8**
AVERAGE ACCURACIES WITH STANDARD ERROR FOR TOP TEN THREE FEATURE COMBINATIONS OF BINARY NETWORK FEATURES.

| S. No. | Name of the Parameter                                                                 | Accuracy | Std. Error |
|--------|----------------------------------------------------------------------------------------|----------|------------|
| 1.     | Global efficiency, Transitivity, Maximized modularity & Median closeness               | 65.90    | 0.0196     |
| 2.     | Global efficiency, Transitivity, Maximized modularity & Mean closeness                 | 65.51    | 0.0184     |
| 3.     | Mean degree, Assortativity, Maximized modularity & Mean closeness                      | 65.49    | 0.0179     |
| 4.     | Assortativity, Global efficiency, Maximized modularity & Std. deviation of closeness   | 65.29    | 0.0160     |
| 5.     | Mean degree, Maximized modularity, Mean closeness & Assortativity                      | 65.27    | 0.0171     |
| 6.     | Assortativity, Median Coreness, Maximized modularity & Median closeness                | 65.21    | 0.0185     |
| 7.     | Node Count, Assortativity, Median closeness & Maximized modularity                    | 65.10    | 0.0206     |
| 8.     | Mean node betweenness, Standard deviation of node betweenness, Median closeness & Maximized modularity | 64.97    | 0.0167     |
| 9.     | Minimum degree, Assortativity, Median closeness & Maximized modularity                | 64.86    | 0.0193     |
| 10.    | Median degree, Maximized modularity, Mean closeness & Assortativity                   | 64.84    | 0.0182     |

**TABLE S9**
AVERAGE ACCURACIES WITH STANDARD ERROR FOR TOP TEN FOUR FEATURE COMBINATIONS OF WEIGHTED NETWORK FEATURES.

| S. No. | Name of the Parameter                                                                 | Accuracy | Std. Error |
|--------|----------------------------------------------------------------------------------------|----------|------------|
| 1.     | Transitivity, Characteristic pathlength, Mean node betweenness & Standard deviation of node betweenness | 63.71    | 0.0196     |
| 2.     | Transitivity, Edge density, Characteristic pathlength & Mean node betweenness          | 63.64    | 0.0197     |
| 3.     | Transitivity, Edge count, Mean closeness & Standard deviation of node betweenness      | 63.11    | 0.0229     |
| 4.     | Transitivity, Mean closeness, Characteristic pathlength & Standard deviation of node betweenness | 62.87    | 0.0208     |
| 5.     | Edge density, Maximum matching index between two vertices, Characteristic pathlength & Number of weak ties | 62.86    | 0.0188     |
| 6.     | Transitivity, Edge density, Mean closeness & Standard deviation of node betweenness    | 62.79    | 0.0206     |
| 7.     | Transitivity, Characteristic pathlength, Mean node betweenness & Edge count           | 62.71    | 0.0195     |
| 8.     | Transitivity, Number of weak ties, Maximum matching index between two vertices & Number of weak ties | 62.32    | 0.0178     |
| 9.     | Transitivity, Number of weak ties, Maximum matching index between two vertices & Edge density | 62.24    | 0.0200     |
| 10.    | Transitivity, Mean closeness, Global efficiency & Standard deviation of node betweenness | 62.16    | 0.0175     |

**TABLE S10**
AVERAGE ACCURACIES WITH STANDARD ERROR FOR TOP TEN FOUR FEATURE COMBINATIONS OF BINARY NETWORK FEATURES.