

A Comparative Study of the Effect of Weighted or Binary Functional Brain Networks in fMRI Data Analysis

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Abstract

Purpose: Graph theory is a widely used and reliable tool to quantify brain connectivity. Brain functional connectivity is modeled as graph edges employing correlation coefficients. The correlation coefficients can be used as the weight that shows the power of connectivity between two nodes or can be binarized to show the existence of a connection regardless of its strength. To binarize the brain graph two approaches, namely fixed threshold and fixed density are often used.

Materials and Methods: This paper aims to investigate the difference between weighted or binarized graphs in brain functional connectivity analysis. To achieve this goal, the brain connectivity matrices are generated employing the functional Magnetic Resonance Imaging (fMRI) data of Alzheimer's Disease (AD). After preprocessing the data, weighted and binarized connectivity matrices are constructed using a fixed threshold and fixed density techniques. Graph global features are extracted and a non-parametric statistical test is performed to analyze the performance of the methods.

Results: Results show that all three methods are powerful in distinguishing the healthy group from AD subjects. The P-Values of the weighted graph is close to the fixed threshold method.

Conclusion: Also, it is worthwhile mentioning that the fixed threshold method is robust in changing the threshold while the fixed density method is very sensitive. On the other hand, graph global measures such as clustering coefficient and transitivity, regardless of the method, show significant differences between the control and AD groups. Furthermore, the P-Values of modularity measure are very varied according to the method and the selected threshold.

Keywords: Functional Connectivity; Correlation; Binary Graph; Weighted Graph; Functional Magnetic Resonance Imaging; Alzheimer's Disease.

1. Introduction

One of the main approaches in brain studies is to investigate the connectivities in the brain. In this regard, there are three different types of connectivities. Structural connectivity that emphasizes the anatomical connection in the brain, functional connectivity which studies the brain functions regardless of the order of communication, and effective connectivity that investigates brain function but pays attention to the causality of the connections [1]. In functional and effective connectivity analysis the communication among brain voxels is investigated. Also, it is possible to facilitate the time and computational cost by brain parcellation into Regions of Interests (ROI) based on different atlases [2].

Functional Magnetic Resonance Imaging (fMRI) is a prevalent and non-invasive method that provides functional data of the brain. In an fMRI exam, the Blood Oxygen Level Dependent (BOLD) signals are recorded and they show the brain function based on Oxygen consumption [3]. The mathematical approach to assess the functional connectivity is to evaluate the correlation coefficient between the time-series of different ROIs or voxels. The most commonly used method is the Pearson Correlation Coefficient (PCC) [4].

Functional connectivity analysis employing fMRI data is very common in literature [5]. Evaluation of the alterations of functional connectivity in Parkinson [6], Autism [7], Attention Deficit Hyperactivity Disorder (ADHD) [8] and, Bipolar [9] disorders are very prevalent in the literature. One of the most common disruptive illnesses of the nervous system is Alzheimer's Disease (AD) and it is the sixth leading cause of death in the United States. Although in the range of 2000 to 2017, deaths occur due to stroke, coronary illness, and prostate cancer growth diminished, revealed deaths from AD expanded by 145% [10]. Studies show that the functional connectivity in dorsal and ventral systems is decreased by AD [11]. Also, the pattern of functional connectivity in insular regions changes [12]. On the other hand, a recent study reported increased functional connectivity after listening to music [13]. Several studies utilize functional connectivity to distinguish patients from healthy subjects [14-16].

Furthermore, a comparison of functional connectivity modification between normal aging and AD has been done [17]. Some studies employed other data such as structural medical images and combined the functional information to analyze AD [18]. Investigating the stages before AD called Mild Cognitive Impairment (MCI) is another field of research that is very common in the literature [19-21].

While the functional connectivity is measured as PCC the results are numbers between -1 to 1. The magnitude shows the weight of connection and the sign corresponds to the direction [22]. Some of the results are fake due to the artifacts and noises. Furthermore, the weak connectivities are not reliable and cannot be considered as the real functional connectivity between two ROIs or voxels [23, 24]. Due to these reasons, some studies perform a sparsification process to eliminate weak and spurious correlations. There are two main approaches for implementing a sparsification process, including fixed threshold and fixed density. The main disadvantage of these techniques is that they use trial and error and are operator based [24]. Although there are lots of studies on functional connectivity analysis, the need for a practical comparison between different common methods for generating brain networks is felt. This study aims to evaluate the performance and the difference of fixed threshold, fixed density, and the weighted graphs in functional connectivity analysis. The brain graphs are made utilizing fMRI signals of AD patients through the aforementioned methods and compared by graph global measures and non-parametric statistical test.

The rest of the paper is organized as follows: in the materials and methods section, graph theory and brain functional network are introduced. Also, the binary and weighted graphs are presented. Then graph global measures are explained and finally the database and data preprocessing step are given. In the results section, the outcomes of non-parametric statistical tests are presented and the methods are compared. In the last section entitled 'discussion' the results are analyzed and the research is concluded.

2. Materials and Methods

In this section, the data and tools are presented. The summary of the study is shown in Figure 1 as a flowchart.

2.1. Data and Preprocessing

The Alzheimer's Disease Neuroimaging Initiative (ADNI) database is used in this research [25]. A 3 Tesla Siemens machine is used to collect the images [26]. The parameters of the functional recording data are the flip angle of 80 degrees, 3.3125 mm of slice thickness, 48 slices, and TR/TE of 3000/30 msec. Also, there are 140 functional volumes. Table 1 shows the demographic information. ADNI database assesses two scores, including Mini-Mental State Examination (MMSE) and Clinical Dementia Rating (CDR). They are two clinical examinations performed on all of the subjects (both healthy ones and AD subjects). They were performed for analysis and to assess the mental health of people.

The preprocessing was performed through the Data Processing Assistant for Rs-fMRI (DPARSF) toolbox and Resting-State fMRI Data Analysis Toolbox (REST) [27].

First of all, slice timing correction is performed. The last slice is used as the reference. Second, to correct head motion realignment is implemented. Employing the Montreal Neurological Institute (MNI) atlas the data are normalized. The smoothing is performed by employing a Gaussian filter with the Full Width at Half Maximum (FWHM) of 4 mm. Then voxel signals are passed through a bandpass filter (0.01-0.08 Hz). The Automated Anatomical Labeling (AAL) atlas [28] was used to extract the Regions of Interest (ROIs). AAL divides the brain into 116 distinct ROIs. The average signal over all the voxels in an ROI makes the fMRI signals.

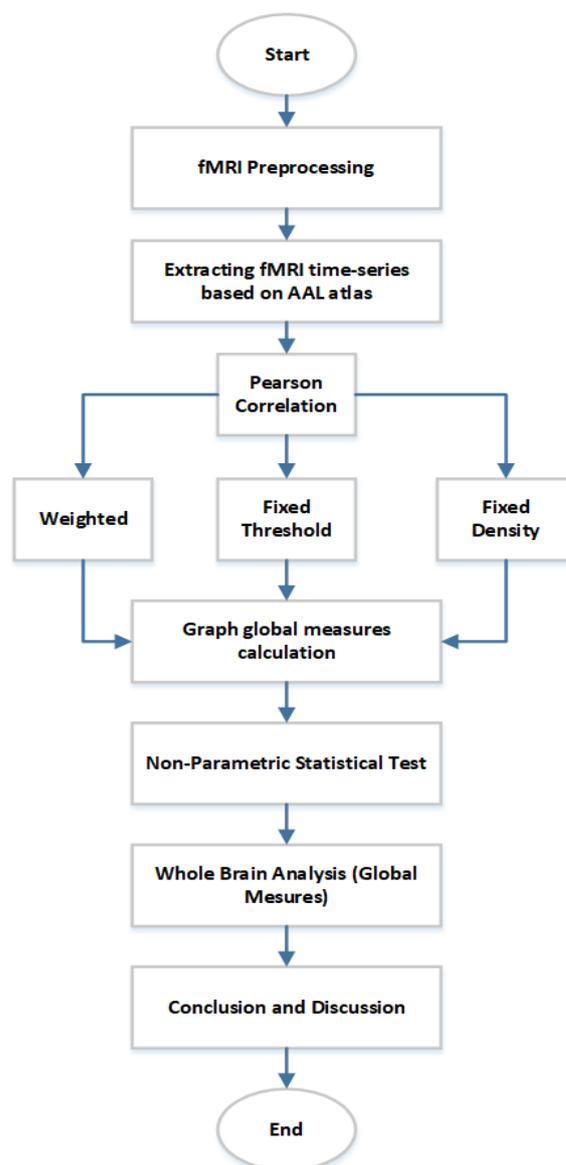


Figure 1. The flowchart of the study

2.2. Graph Theory and Brain Functional Networks

In mathematics, graph theory is used to model complex networks. $G = (V, E)$ is the symbol of a graph where V indicates the vertices (nodes) and E demonstrates the edges of the graph. In brain networks

Table 1. The demographic information of the data

Group	No. (Male/Female)	Age	Head Motion	MMSE Score	CDR Score
AD	(14/14)	74.9±4.9	0.32±0.09 mm	20.35±0.54	1.03±0.54
CN	(14/20)	74.1±4.3	0.22±0.14 mm	29.11±1.24	0.16±0.05

analysis the voxels or ROIs are nodes of the graph and functional connectivity is modeled as edges. PCC analysis is the most prevalent technique to compute functional connectivity [29]. The PCC is computed as follows:

$$\rho_{x,y} = \frac{cov(x,y)}{\sigma_x\sigma_y} \quad (1)$$

Where σ_x and σ_y correspond to the standard deviation of the variable (signal) x and y , respectively.

In the weighted graphs, the magnitude of the correlation is considered but in the binary graph, the availability of links is considered. There are two main approaches to binarize a graph, one of which is thresholding. In this method, the operator sets a threshold manually, the correlations below the threshold turn into zero and the other ones turn into one. Evidently, the result relies on the threshold and varies as the threshold changes. Finding the optimal threshold is usually done by trial and error. Another approach to binarize a graph is fixed density. In this method, a determined fraction of edges remain connected and the others are eliminated [24, 30, 31].

This study aims to generate the brain graphs based on the three mentioned methods (weighted, fixed density, and fixed threshold) and evaluate them by graph measures and a statistical test in fMRI signals. In Figure 2, three types of functional connectivity matrix are illustrated.

As it is demonstrated in Figure 2, the elements of a weighted matrix are between 0 to 1 but in binary matrices, they can be only zero and one. Also, if a weighted matrix is binarized by fixed threshold or fixed density method the result is varied. Besides changing the threshold or density, it changes the results again.

2.3. Graph Measures

After constructing brain networks, there is a feature extraction step. The definition and formula of extracted features are listed below. The brain functional integration and segregation are demonstrated in the features below.



Figure 2. A functional connectivity matrix. A weighted matrix (up). A binary matrix which is sparsified by threshold 0.5 (Middle) and a binary matrix which is sparse by density 50% (bottom)

2.3.1. Degree

The total number of the edges related to a hub shows the degree of that node.

2.3.2. Efficiency (EFF)

The shortest path length is the minimum distance between the vertices. The average efficiency of a graph is $E(G) = \frac{1}{n(n-1)} \sum_{x \neq y \in G} \frac{1}{p(x,y)}$ where $p(x,y)$ is the shortest path length between x and y . The global

efficiency is defined as the average of the inverse shortest path length:

$$E_{glob}(G) = \frac{E(G)}{E(G^{ideal})} \quad (2)$$

Where G^{ideal} corresponds to a fully connected graph of n hubs. The local efficiency is an efficiency that is computed on a subgraph of the neighbors. The formula is [32]:

$$E_{loc}(G) = \frac{1}{n} \sum_{x \in G} E(G_x) \quad (3)$$

2.3.3. Clustering Coefficient (CC)

It is computed according to the triangles around vertices. This measure quantifies the tendency of the hubs to make the clusters. In the graph theory, triples are three nodes connected by two or three edges which are called closed or open, respectively. Three closed triplets make a triangle. The CC formula is as follows [33]:

$$C = \frac{\text{Number of closed triplets}}{\text{number of all triplets}} \quad (4)$$

2.3.4. Modularity

The tendency of a graph to be divided into communities is called modularity. It can be calculated as:

$$M = \frac{1}{l} \sum_{x,y} \left[A_{x,y} - \frac{k_x k_y}{l} \right] \delta_{x,y} \quad (5)$$

Where, l is the number of links. $A_{x,y}$ is the connectivity matrix and if the two nodes are from one subgraph the $\delta_{x,y}$ is zero otherwise, it is equal to one. Also, K_x and K_y show the degree of vertices x and y , respectively [34].

2.3.5. Transitivity

Transitivity is similar to the CC. It is defined according to the relative triangles. The relation is [34]:

$$T = \frac{3 * \text{number of triangles}}{\text{number of connected triples of nodes}} \quad (6)$$

It is worthwhile to mention that all the processings were implemented in Matlab 2018a software. The preprocessing step was performed employing the

DPARSF toolbox. For graph measures computations the Braph toolbox [35] was utilized and for the rest of the analysis, several scripts have been written. Please note that the Braph toolbox computations are based on the above-mentioned formulas.

2.4. Statistical Test

After evaluating the graph measures the comparison between groups has to be done. In order to perform this issue, the non-parametric permutation test has been employed. Note that this statistical test was considered no hypotheses about the distribution of data and is very common and reliable in neuroscience studies [36]. In the permutation test, subsets of the data were selected randomly and the statistical test was performed in every subset (bootstrapping). The resampling was performed 1000 times to make the results more reliable.

3. Results

Based on the fMRI time series the functional connectivity matrices are generated. First of all, the weighted matrices are calculated. Secondly, the matrices are sparsed by fixed threshold and fixed density methods. In order to evaluate the effects of the threshold, different thresholds are investigated. Table 2 shows the results of the non-parametric permutation test of the weighted graphs between the two groups (AD group vs. healthy subjects).

Table 2. Results of the statistical test in the form of P-Values. The significance level is 1%. The boldface P-Values are significantly different

Feature	P-Values
Degree	0.0223
Global Eff.	0.0020
Local Eff.	0.0021
Clustering	0.0026
Transitivity	0.0032
Modularity	0.0283

As it is shown in Table 2, based on weighted graphs, all features except modularity and degree demonstrate

significant changes between the AD group and the control group. Although the weighted graphs consist of strong and low correlations (signals and noises) together, based on the graph measures and non-parametric permutation test's result (Table 2), weighted graphs are appropriate tools to discriminate against the groups. As they are very crowded graphs they are not efficient in visualizing the brain functional connectivity (only visualizing). In comparison between a weighted graph and a sparse graph, the weighted one has more number of links while a sparse one has lost several links (based on the selected threshold). Accordingly, the computational cost of a weighted graph is high due to the full connected nature of the graphs.

The weighted graphs are sparsed with different thresholds from 0.3 to 0.7. Table 3 shows the results of the statistical analysis of the fixed threshold method. The results are in the form of P-Values and the numbers below the significance level (1%) are bold.

As illustrated in Table 3, based on different thresholds, the results of statistical tests vary considerably. Only the clustering feature shows significant changes in both groups in every threshold.

Among the different thresholds, the 0.4 has the best result and all of the features are significantly different between the AD and control groups. Also, it can be concluded from Table 2 that there is no stable pattern in P-Values variation while the threshold is changed. In comparison between the fixed threshold method

and weighted graphs, it can be concluded that the threshold makes some features, including degree and modularity significantly different. Other studies such as [37] reported that the modularity feature is diminished in AD patients and is significantly different from healthy subjects. According to this research, the fixed threshold method may provide more reliable results and also the computation cost is less due to less crowded graphs. For instance, the variation of clustering features in both groups based on different thresholds is demonstrated in Figure 3. The variation pattern of other features is almost the same. As Figure 3 depicts, the variation pattern in both groups is approximately similar and there is no threshold where the results are significantly different.

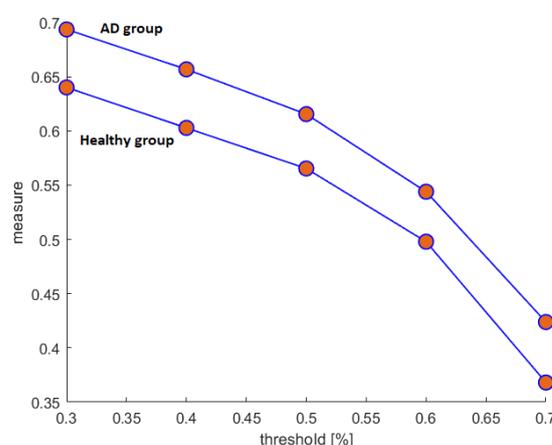


Figure 3. Variation of clustering feature (average) in both groups as the threshold changes from 0.3 to 0.7

According to Table 4, regardless of the density, clustering, and transitivity features are significantly

Table 3. Results of the non-parametric statistical test in terms of P-Values. Each column corresponds to a specific threshold (graph sparsification threshold). The significance level is 1%. The boldface P-Values show significant differences (P-Values≤0.01)

Features	Threshold				
	0.3	0.4	0.5	0.6	0.7
Degree	0.0111	0.0049	0.0018	0.0007	0.0004
Global Eff.	0.0105	0.0082	0.0108	0.0157	0.0084
Local Eff.	0.006	0.0065	0.0138	0.0342	0.0081
Clustering	0.0046	0.0017	0.0016	0.0054	0.0090
Transitivity	0.0019	0.001	0.0008	0.0017	0.0212
Modularity	0.0191	0.0057	0.0042	0.0012	0.0035

different. Among the different densities, 40% and 50% have a better performance. In order to compare the fixed threshold and fixed density methods, the variation of the clustering measure is plotted in Figure 4. As depicted in Figure 4, the trend of variation is almost the same as the fixed threshold. As the density grows (fewer sparsifications) the feature increases. The modularity feature shows no significant changes as the density varies. The trend of modularity feature is also demonstrated in Figure 5. The average value of both groups is too close, therefore based on the statistical test there are no significant changes. Besides, as density grows, the distance between groups becomes less and the P-Value of the statistical test becomes larger according to Table 4. The fixed density result is almost the same as weighted graphs. No significant changes in modularity and only in a specific density does the degree feature show significant changes.

To compare the fixed threshold and fixed density results, the boxplot of P-Values is depicted in Figure 6. As Figure 6 shows, the variation of P-Values in the fixed density method is much greater than the fixed density threshold method and it can be concluded that the fixed density method is more sensitive to the selection of density.

Only in clustering and transitivity measures, are the results of two methods similar and it can be concluded that regardless of the method and the selected borders these features are significantly different in the AD group and healthy subjects. In other words, they are

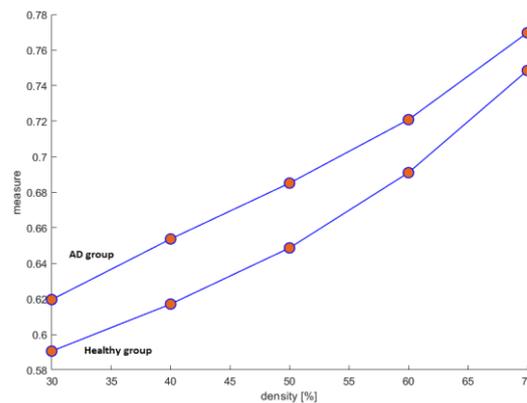


Figure 4. Variation of clustering feature (average) in both groups as the density changes from 30% to 70%

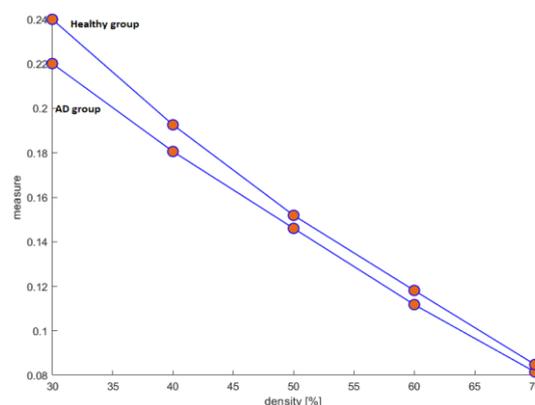


Figure 5. Variation of modularity feature (average) in both groups as the density changes from 30% to 70%

proper measures to discriminate amongst the groups. Also, the P-Values of weighted graphs are illustrated in Figure 6 and they are closer to the fixed threshold method. Some measures, including clustering and transitivity in all three methods show significant

Table 4. Results of the statistical test. Each column corresponds to a specific density. The numbers of P-Values (graph sparsification threshold). The significance level is 1%. The boldface P-Values show significant differences (P-Values≤0.01)

P-Value	Remain Density				
	70%	60%	50%	40%	30%
Degree	0.1560	0.2530	0.0978	0.0034	0.0586
Global Eff.	0.2005	0.0791	0.0003	0.0005	0.0001
Local Eff.	0.001	0.0015	0.0038	0.0184	0.4487
Clustering	0.0015	0.0014	0.0017	0.0031	0.0064
Transitivity	0.0008	0.0008	0.0011	0.0014	0.0030
Modularity	0.1798	0.0963	0.1911	0.0954	0.0446

changes but the rest of the features depend on the method and the selected threshold.

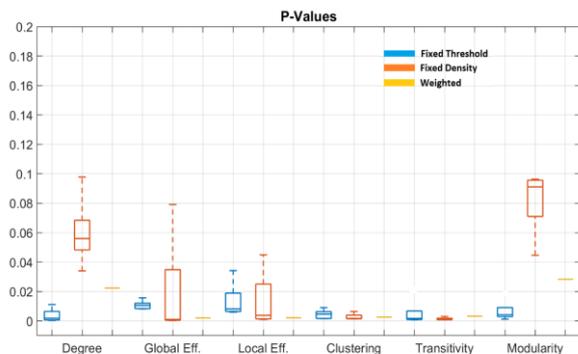


Figure 6. P-Values variation based on selected thresholds and densities

4. Discussion

In brain function studies, connectivity graphs are often generated, employing the Pearson correlation coefficient. Then, there is an option to utilize them as weighted matrices or make them binary by sparsifications. The common approaches to have sparse graphs are fixed threshold and fixed density techniques. When the existence of an edge is considered the binary graphs are used and when the weight of the edges is of importance the weighted graph is considered. This paper aims to compare the weighted and binary graphs and also evaluate the fixed density and fixed threshold techniques. Accordingly, the fMRI data from the ADNI database is used. fMRI signals correspond to age-matched healthy subjects and AD patients. After performing the preprocessing step, the functional connectivity graphs are created employing the Pearson method. The graphs are weighted graphs and are also sparse due to the above-mentioned methods utilizing different thresholds. Subsequently, graph global measures are computed and a non-parametric permutation test is performed as statistical analysis. In the weighted analysis, the degree and modularity measures show no significant changes. As the weighted graphs are often fully connected matrices the average degree in both groups is the same and, apparently, there are no significant changes. Measures such as clustering, transitivity, and efficiency show a significant difference and match previous studies in the literature [38]. In fixed threshold graphs, unlike the weighted graphs, the

modularity measure shows significant changes. Since AD disrupts brain functional integration it is expected that the modularity is different with respect to healthy subjects and AD patients. In fixed density analysis the modularity shows no significant changes. The results of the weighted graphs and fixed density techniques are similar. In all three methods, the clustering coefficient and transitivity show significant differences in all thresholds. It can be concluded that AD affects these features enormously because regardless of the methods they demonstrate significant changes. On the other hand, the modularity measure is very sensitive to the method of analysis. Among the different thresholds, the result of the fixed threshold method is robust and approximately the same but the fixed density is very sensitive to the selected threshold. Consequently, if the goal of a study is to discriminate against some groups, different methods and different thresholds should be examined to find a better method and the optimal threshold. It is worthwhile mentioning that, the binary methods are faster and have less computational costs because the graphs are more sparse in comparison to weighted graphs. On the other hand, in neuroscience studies, these methods are not very suitable because the procedure does not consider the physiological and pathological conditions of the brain.

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