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Region Role Detection in Autism Spectrum Disorder using Graph Theoretical Approaches

Geetha Ramani R, Sivaselvi K

Department of Information Science and Technology, Anna University, Chennai, Tamilnadu, India

ABSTRACT

Connectome analysis has received increased attention in the field of neurological research. Graph theoretical measures are extensively applied to understand the intricate structure of the brain. In this work, resting state functional connectome of Autism Spectrum Disorder and Typically Developing brain are investigated to reveal the influential regions in the brain. Centrality measures are involved in the detection of global region role identification and they are compared against functional cartography. Then, the modular region role is determined from both individual functional connectome and group averaged connectome of both Autism Spectrum Disorder and Typically Developing subjects. The modular roles are compared using supervised association rule mining. The major alterations are identified mostly in visual and frontal regions of Autism Spectrum Disorder functional connectome.

Keywords: Autism Spectrum Disorder, Connectome, Magnetic Resonance Imaging, Centrality

I. INTRODUCTION

One of the most common neurodisorder in the present world is Autism Spectrum Disorder (ASD) which includes disorders namely Asperger's syndrome and pervasive developmental disorders. ASD develops in childhood and persisting throughout the life [1]. Children with ASD of age 2-3 show behavioural changes on comparison with typically developing (TD) children [2]. ASD children reveal behavioural issues, improper communication, attentional problems, reasoning challenges, comprehension issues, etc. [3,4]. But these challenges are similar to other neurodisorders namely Attention Deficit Hyperactive Disorder (ADHD), depression etc. To differentiate the problems, skills related to reasoning, language, attention, etc. are evaluated [5].

Autism Spectrum Disorder (ASD) has received increased notice since considerable number of children is affected by the spectrum of developmental disorders. Researchers make great efforts to detect the causes of the disorder and alterations in the brain region to provide better therauptic treatment. During the growth of child, ASD should be diagnosed at their early age for reducing the severity of the disorder. Individuals affected by ASD exhibit the repeated behaviour, loss of interaction with other people, loss of concentration, poor communication, loss of eye contact, unusual response, echolalia, high sensitivity and extreme interest in few details like numbers, pictures, movements etc [7,8].

The analysis on the ASD is performed either through images or network constructed from the images. These brain networks are known as connectome. Connectome can be formed from the structural or functional MR images[8]. Generally, the nodes in the network are region of interest or voxel and the edges between the nodes indicate structural or functional connectivity. Few researches related to the identification of abnormalities in ASD affected brain is presented here.

Libero et al. (2015) have used multiple modalities namely structural MRI which depicts cortical information, Diffusion Tensor Imaging which provides white matter connections, proton magnetic resonance spectroscopy which reveals neurochemical concentration are used to differentiate between ASD and TD subjects. They acquired images from 19 ASD and 18 TD individuals. It can be understood from the analysis that the brain regions namely left cingulum, left

inferior temporal cortex, right precuneus part of left inferior frontal gyrus region have increased cortical thickness some other regions namely right cuneus and right precentral gyrus show decreased cortical thickness in ASD individuals compared to TD individuals. Similarly, other modalities also reveal some anatomical alterations in the ASD subjects [9].

Deshpande et al. (2013) acquired task based fMRI from 15 ASD and 15 TD individuals. The subjects are provided with comic series and they were asked choose the conclusion from three options. Eighteen regions are found to be activated from the peprocessed images. Fusiform gyrus and middle temporal gyrus show altered connections. These regions are mainly involved in social communication [10].

Ecker et al. (2010a) acquired structural MRI obtained from the 22 ASD and 22 TD individuals. On analysis, it is detected that the networks of ASD and TD are differentiated especially in the following regions fronto-temporal, limbic, cerebellar, fronto-parietal and frontal-striatal systems[11].

Plitt et al (2014) obtained resting state fmri from 59 ASD and 59 TD male subjects and data of 89 ASD and TD were obtained from the Autism Brain Imaging Data Exchange (ABIDE). Brain regions involved in information processing function reveals significant alterations in the connections [12].

Zhou et al.(2014) obtained structural and resting state functional MRI from 127 ASD and 153 TD individuals. Through analysis, it has been found that the increased cortical thickness of cerebellum region, decreased white matter in frontal and temporal regions and altered functional connectivity in default mode network [13].

With the introduction on ASD and the recent works in the identification of alterations in brain regions, remaining sections are arranged as follows. Section 2 describes about the dataset utilised for experiments and the methodology adopted. Section 3 elaborates on the research outcomes and analysis on the results. Section 4 presents conclusion and future directions in the research.

II. METHODS AND MATERIAL

This section explains the dataset used for experiments followed with methodology involved in the identification of changes in brain regions of ASD affected subjects.

A. Dataset description

Dataset consists of information obtained from the ASD and TD adults and children through UCLA's Center for Autism Research and Treatment (CART) [14] which exempts the individuals with neurological complaints. Informed consent is received from the subjects as approved by UCLA Institutional Review Board (IRB). Wechsler Abbreviated Scale of Intelligence [15] and full Wechsler Intelligence Scale for Children [16] is used to assess the intelligence factor of adults and children respectively. Diagnostic and Statistical Manual of Mental Disorders is employed to diagnose ASD children [17].

Diffusion Tensor Imaging and functional Resting State functional Magnetic Resonance Imaging is acquired from 60 ASD (52 - males and 8 – females) and 45 TD subjects (38 - males and 7 – females) [14]. For experiments, 42 ASD and 37 TD subjects were utilised after elimination of improper acquisitions. The subjects are gender-matched, age-matched and no significant difference found between medicated and unmedicated. The resting state images are acquired using the Siemens 3 T Trio scanner located at UCLA.

B. RS-fMRI Pre-processing

The images are processed using the FSL version 4.1.4 (FSL Analysis) [18,19] and AFNI [20] to form the functional network (connectivity matrix). Initially, extra-cranial tissues in the images are removed followed by head motion correction and smoothening. Then, the unwanted signals are eliminated through filteration. Then, abnormal global intensity changes are removed using regressors. It is followed by parcellation that specifies the brain regions. Functional regions are identified through voxel approaches and atlas based approaches (Power et al. 2012). Functional connectivity matrix of size 264×264 is obtained by determining correlation between the regions. UCLA multimodal connectivity database provides the connectivity matrices (Brown et al. 2012). The weighted functional connectivity matrix is thresholded using sparsity method which is explained in next sub-section. The 264 regions are listed in Table 6.1.

TABLE I. BRAIN REGION NAMES (LIST OF ABBREVIATIONS AND FULL FORM OF REGIONS PARCELLATED THROUGH POWER NEURON)

S.No.	Abbreviated Region Name	Full Form of Region Name
R1	ROP1	Right Occipital Pole
R2	ROP2	Right Occipital Pole
R3	LPC1	Left Precuneous Cortex
R4	RPC1	Right Precuneous Cortex
....	...	....
....	...	....
R262	LPC3	Left Precuneous Cortex
R263	LPC4	Left Precuneous Cortex
R264	LTP	Left Temporal Pole

C. Sparsity thresholding

Generally, thresholding is performed to convert weighted functional connectivity matrix into binary matrix. Sparsity can be defined as the ratio of the actual edge number (K) to the maximum possible edge number in a network [i.e. N(N-1)/2]. The value of sparsity is not constant and no specific conditions.

Centrality measures are determined from the thresholded matrix is detailed in next sub-section.

D. Centrality estimation

Complex network analysis has been used to understand the modifications occurred in human brain due to neurological disorders. They include many measures namely measures of segregation, measures of integration, centrality measures, etc. In the detection of abnormal regions globally, centrality measures are employed. Degree, betweenness, eigenvector, leverage and weighted leverage variants are estimated from the sparsity based thresholded matrix, which could be utilised for discriminating the ASD and TD subjects.

Degree centrality [21] indicates the number of immediate neighbours of a particular node as defined in Equation 1.

$$N_{dc}(i) = \sum_{j \in N} a_{ij} \quad (1)$$

Where, i and j indicates node and the neighbours respectively, a_{ij} represents the i^{th} and j^{th} node connection, if a_{ij} = 1 nodes are connected, else nodes are not connected, N is the total number of nodes, $N_{dc}(i)$ is the degree centrality of node i.

Betweenness centrality [22] determines the bridging node i.e. node mostly present in the connection between two nodes is defined as in Equation 2.

$$N_{bc}(i) = \frac{1}{(n-1)(n-2)} \sum_{h,j \in N, h \neq j, h \neq i, i \neq j} \frac{p_{hj}(i)}{p_{hj}} \quad (2)$$

where, h, i and j indicates start, middle and end node, $N_{bc}(i)$ is the betweenness centrality of node i, p_{hi} and $p_{hj}(i)$ represents the number of geodesic paths between h and j and between h and j that pass through i respectively.

Eigenvector measure [23] estimates the significance of node based on connections with neighbours as defined as in Equation 3.

$$N_{ec}(i) = \frac{1}{\lambda} \sum_{j \in N} (a_{ij} e_j) \quad (3)$$

where, λ is the largest eigenvalue and e is the corresponding eigenvector, $N_{ec}(i)$ is the eigenvector centrality of the node i.

Leverage centrality [24] determines the influential node based on the connections of immediate neighbours is estimated as shown in Equation 4.

$$N_{lc}(i) = \frac{1}{N_{dc}(i)} \sum_{n_i} \frac{N_{dc}(i) - N_{dc}(j)}{N_{dc}(i) + N_{dc}(j)} \quad (4)$$

where, $N_{dc}(i)$ and $N_{dc}(j)$ is a degree of a node i and j respectively, n_i is the total number of neighbours of node i. The measure may have positive and negative value indicating the influence of the node on the neighbours and the influence of neighbours on the node respectively.

Weighted leverage centrality measure estimates the node influence based on the neighbour node's influence in the network. It is a hybrid measure which includes

the concept of eigenvector and leverage centrality. Two variants of leverage centrality are developed. Eigenvector measure is included as weight factor in the leverage measure to enhance the node role identification in the network.

Initially, the eigenvector value of node is included as weightage factor to the degree of the node which is called as weighted leverage variant-1. To further improve the measure, weighted leverage variant-2 is introduced which includes the probability of particular node eigenvector's as weightage to the degree of the node. The eigenvector value of the node and its neighbours has been added and the weightage factor is calculated as shown in Equation 5. Then, the weightage is multiplied to the degree as depicted in Equation 6.

$$N_{wl}(i) = \frac{1}{N_{dc}(i)} \sum_{n_i} \frac{W(i) * N_{dc}(i) - W(j) * N_{dc}(j)}{W(i) * N_{dc}(i) + W(j) * N_{dc}(j)} \quad (5)$$

$$W(i) = \frac{\mathrm{N_{ec}(i)}}{\mathrm{N_{ec}(i)} + \sum_{n_i} \mathrm{N_{ec}(j)} * \mathrm{a_{ij}}} \quad (6)$$

where, $N_{dc}(i)$ and $N_{dc}(j)$ is degree of node i and immediate neighbour node j respectively and n_i is the total number of neighbours of node i. $N_{ec}(i)$ and $N_{ec}(j)$ is a eigenvector measure of a neighbours of node i and j respectively, W(i) is the weight factor of the node i. The positive value indicates the influence of node on its neighbours and negative value indicates the influence of neighbours on the node. After estimating the centrality measures for each ASD and TD subjects, globally influential regions (hub) in brain can be determined.

The methodology applied to determine the global region role is discussed in next sub-section.

E. Methodology for Global Region Role Determination in Autism Spectrum Disorder and Typically Developing Brain

Generally, in the network structure, the central nodes are identified using centrality measures. The node, which is central according to one measure, may not be central according to another measure. Each measure attempts to define the influence of nodes in different perspectives of the network. Inspite of all these, there are some nodes that could be very significant in all aspects. The central nodes in the global network are known as hub and others as non-hub. The methodology for detecting the possible hubs in the brain network is shown in Figure 1.

To detect the hubs in the network, graph measures are engaged in the process of analysing the functional connectivity matrix constructed from the neuroimages. The functional connectome data is generally binarized to convert it into thresholded matrix, which could avoid spurious connections in the network. The weighted functional connectivity matrices are averaged for each group. Both the individual and group averaged matrices are thresholded using sparsity method.

Sparsity based thresholding is widely used for binarization of the matrix. In this study, Sparsity value of 10% to 50% is analysed and found that 20% thresholded brain network could have reasonable number of connections and without any isolated nodes in the network. Hence 20% sparsity thresholded matrix is used for further analysis.

Input: Functional Connectivity Matrix FC_i
Output: $Cent\_GRR_i$ = { Hub, Non-Hub}, $Clus\_GRR_i$ = { Hub, Non-Hub}

Methodology:
1. Read functional connectome data FC from ASD and TD
2. Average the functional connectome of ASD group (GFC_{ASD}) and TD group (GFC_{TD})
2. for each group S
2a. Binarize the matrix BFC_i = Sparsity thresholding(GFCi, Svalue)
2b. Calculate centrality measures Degree (Deg), Betweenness (Bet) Eigenvector (Eig), Leverage (lev) and weighted leverage variants (wl1 and wl2)
3. for each group determine global region role through individual centrality measures
. 3a. If (deg_i > mean(deg)+std(deg))
$Cent\_GRR_i$ = Hub
Else $Cent\_GRR_i$ = Non-hub
3b. Repeat Step 3a for all 264 brain regions.
3c. Repeat the steps 3a and 3b for other centrality measures
4. Construct feature vector FV with the centrality measures
5. Apply clustering on the centrality measures
$Cluster_i$ = K-Means Clustering(FV)
6. Determine global region role using clustering
6a. If (Cardinality(Class1)<Cardinality(Class2))
Cluster1 = Hub and Cluster2 = Non-hub
6b. Else
Cluster2 = Hub and Cluster1 = Non-hub
7. Assign $Clus\_GRR_i$ to hub or non-hub based on the Cluster it belongs to
8. Determine functional cartography for hub detection and compare the outcomes of individual measures and clustering of measures

Figure 1: Methodology for Global Region Role Identification in Autism Spectrum Disorder and Typically Developing

Then, the common centrality measures namely degree, betweenness, eigenvector, leverage and weighted leverage variant - 2 are estimated from the binarized functional connectivity matrix. If the computed value of centrality measure of a region is greater than the sum of mean and standard deviation of particular centrality measure, then the region is said to be hub. Otherwise, it is considered as non-hub.

To enhance the detection of hubs in the brain network, unsupervised learning is utilised that has been detailed in next subsection.

F. Clustering of Centrality Measures

Further, for better prediction of the hub regions in the brain network, unsupervised learning model, clustering is adopted [25]. Those techniques group the regions into two clusters i.e. either hub or non-hub. The centrality measures computed are used as features to be fed as input to the clustering process. In this case, centrality measures are considered as features and each region is regarded as instances. Depending upon the dataset, the number of instances in the feature vector may vary. The number of features is constant as they include the estimated centrality measures. K-means clustering, farthest first and density based cluster are adopted for grouping the regions into two categories. K-Means clustering is well known grouping methodology that employs the divisive technique for construction of clusters in the dataset. It requires the prior information about the probable number of clusters in the group. Figure 2 depicts the algorithm of K-Means clustering.

Step 1: Randomly choose k instances as cluster centers from the given data of size N.
Step 2: Assign each instance to the cluster
For each i, from 1 to N do
$\text{cluster(i)} = \min(\text{dist}(x_i, c_j))$
where ,

j indicates the number of clusters defined by user
x_i is the i^{th}instance from the data
$\text{dist}(x_i, c_j) =$
Manhatten distance between two instances calculated as $|x_{i_1} - c_{j_1}| + \cdots + |x_{i_m} - c_{j_m}|$
m is the number of attributes
Step 3: Update the cluster means
For all clusters

$\text{Avg}_j = \text{Mean}(x_i \text{ which belongs to cluster j})$
Step 4: For all j
$\text{prevAvg}_j = \text{Avg}_j$
Step 5: Repeat the process until the there is no cluster member changes in each cluster

Figure 2: Algorithm of K-Means Clustering

In K-Means clustering, depending upon the number of clusters, instances are randomly chosen and assigned to each cluster. Then, the mean of the cluster is determined for each cluster and the difference between the each instance value and the mean of each cluster is estimated. If the difference between the mean of another cluster is minimum when compared to current cluster, then the instance is reassigned to the cluster. The process is repeated until it reaches the condition that the instance stay in the same cluster. K-Means clustering is robust and has achieved better results in the identification of global region role from the functional connectome of ASD and TD. The two groups are identified through the clustering technique. Group with lesser number of regions are considered to be hub and another group is considered as non-hub. Generally, it is hypothesized that the hub regions are comparatively less than the non-hub regions in the brain. With that information, hub and non-hub regions are determined from the clustering procedure.

To evaluate the outcome of the centrality computations in the identification of influential nodes in the brain network, the utilization of functional cartography is generally exploited. The community structure is used for the calculation of two metrics namely within-module degree and participation coefficient which is involved in the estimation of central nodes in the network. These nodes are regarded as gold standard and the outcome of the centrality measures are evaluated through this technique and details are presented in results section. In addition to the identification of global region role, modular region role is also determined to understand the changes at the modular level. The methodology involved in the identification of modular region role is discussed in next sub-section.

Functional Connectome Analysis for Modular Region Role Identification

Human brain networks exhibit the modular organization and they can be identified through the graph theoretical approaches. The resting state functional brain network of ASD and TD are utilised to extract the changes happened in the brain at the modular level in the perspective functional connectivity. The identification of the modular roles of the regions and the alterations occurred due to disorder is detailed in this sub-section.

The regions in the human brain may either have a role of importance or not depending upon the condition of the subject. The region may be highly influential when the subject performs some task or when it is disordered. The methodology involved in the identification of the modular roles of the regions is depicted in Figure 3.

The resting state functional connectome data is obtained for AD and TD. These weighted functional connectivity matrices are averaged for each group. Then, the binarization is applied based on the sparsity level. In this research, sparsity value of 20% is utilised for the matrix binarization.

Input: Functional Connectivity Matrix FC_i
Output: MRR_i = {Hub, Non-Hub}, S_MRR_i={Provincial hub, Connector hub, Kinless hub, Ultra-peripheral node, Peripheral node, Non-hub connector, Kinless node}

Methodology:
1. Read functional connectome data FC from individual and group averaged ASD and TD
2. for each subject S
2a. Binarize the matrix BFC_i = Sparsity thresholding(FC_i, Svalue)
2b. Detect modules mod_i = Spectral_part(FC)
2c. Calculate within module degree z-score(Z_i) and participation coefficient(PC_i)
3. for each subject determine modular region role through Functional catography
3a. If (Z_i >1)
MRR_i = Hub
If(PC_i >0.32)
S_MRR_i = Provincial hub
ElseIf(0.32<PC_i <=0.75)
S_MRR_i = Connector hub
Else
S_MRR_i = Kinless hub
Else MRR_i = Non-Hub
If(PC_i >0.05)
S_MRR_i = Ultra-peripheral node
ElseIf(0.05<PC_i <=0.6)
S_MRR_i = Peripheral nod
ElseIf(0.6<PC_i <=0.8)
S_MRR_i = Non-hub connector
Else
S_MRR_i = Kinless node
3b.Repeat Step 3a for all 264 brain regions.
4. Apply supervised association rule mining on individual matrices of ASD and TD and obtain aggregated role
5. Compare the predicted roles and report the region role alterations

Figure 3: Methodology for Modular region Role Identification in Autism Spectrum Disorder and Typically Developing

Then, the modules in the ASD and TD network are determined through modularity detection algorithm. Spectral partitioning algorithm is employed for modularity detection [26]. Then, the module degree z-score and participation coefficient are used to detect the modular role of each region in the brain network. The modularity is detected for both group averaged matrices and individual subject matrices. To analyse the depth of matching between the group averaged and individual matrices, the modular hub and non-hub roles are matched between them. To perform the comparison, the individual modular hub and non-hub roles are applied to the supervised association rule mining algorithm and roles are predicted. Further, the changes in the roles of region between the ASD and TD individuals are investigated. The methods involved are explained in further subsections.

Community detection is an optimization problem where the number of connections between the nodes in a single module should be higher when compared to the connections of those regions with other modular regions [27,28] The optimal number of communities is determined based on the partition parameter [29].

Within-module degree z-score determines the modular region i.e. either it plays a role of hub or non-hub in the network. If the z value of a nodeis higher, it is said to be highly influential with increased intra-modular connections in the network. Node with Z value greater than one are considered as modular hubs and node with Z value lesser than or equal to one are considered as modular non-hubs in this investigation [30,31]

Further, the role can be sub divided based on participation coefficient which evaluates the connections of a node between modules in the network. The hub nodes can be classified into kinless, provincial and connector if they are equally connected, high intramodule connections and high intermodule connections respectively. Similarly, the non-hub nodes are classified as ultra-peripheral, peripheral, non-hub connector nodes. The thresholds for participation coefficient defined in the functional cartography technique are followed to define the regional roles for each node.

The modular hub and non-hub roles are determined for each region of group average functional connectivity matrix of ASD and TD. Similarly, roles are determined for individual functional connectivity matrices. Then the individual roles are aggregated through the rules derived through supervised association rule mining.

Supervised association rule mining is used to identify the frequent items based on the sample. The roles for each brain region of all individuals in ASD and TD group are given as input for supervised association rule mining. It is compared with the roles determined from the group averaged functional network of ASD and TD. The outcomes are discussed in next section.

III. RESULTS AND DISCUSSION

The network representation of brain could be analysed exhaustively to discover unknown information. In this research, resting state functional MRI of the ASD and TD provided in the UCLA_Autism study has been considered. The functional connectome of the subjects are obtained from the public repository of connectome data i.e. UCLA Multimodal Connectivity Database. The functional connectivity matrix is constructed from the resting state fMR images with the parcellation of 264 regions defined as Power Neuron. This forms the weighted connectivity matrix of size 264*264. The weighted connectome has been acquired from the dataset and then, the functional connectome is thresholded with different sparsity levels from 10% to 50% and form binarized network structure. The analysis on the network at different levels is performed.

G. Analysis on Global Role determined through Centrality Measure

After thresholding, various centrality metrics namely degree, betweenness, eigenvector, leverage and the weighted leverage variants have been calculated from the binarized functional connectivity matrix. To understand and evaluate the regional role identification in the brain network, functional cartography is employed. The thresholded network is involved in the clustering of regions into modules. Spectral partitioning algorithm is utilized to form the modules which enable to calculate within-module degree z-score. The regions which have within-module degree z-score greater than one are considered as hubs and other regions as non-hubs.

In addition to the common centrality measures, leverage centrality to determine hubs in the brain network is also calculated. Leverage has lower value if the nodes are highly interconnected in comparison with other measures. It involves the degree of the node and its immediate neighbours. The two variants of weighted leverage measure have been devised for enhancement of the measure. Initially, the eigenvector is utilised as weight to the degree of the nodes that has resulted in weighted leverage variant-1. Then, instead of utilising the direct value, the contribution of the node in eigenvector measure is determined through the probability score of the node with its neighbours which is known as weighted leverage variant-2. The performance of weighted leverage variant-1 is not significant as compared to weighted leverage variant-2. However, leverage is computationally easier as they involve only simple calculation from the degree measure whereas eigenvector involves intensive computation. In the aspect of identifying hubs, the appropriate determination of region role especially hub regions is very essential rather than complexity. In this study, the regions which have value greater than the threshold are considered as hubs and others as non-hubs. The threshold value is assigned to sum of the average value and the standard deviation of the measure. The regions identified as hubs are compared to the hubs determined by the functional cartography [30,31].

The analysis on the resting state functional connectome of autism spectrum disorder and typically developing individuals are performed. The weighted functional connectivity matrix of 42 ASD individuals is averaged. Similarly, the functional connectivity matrix of 37 TD individuals is also averaged. Thus, it results in 2 group averaged functional connectivity matrices. Then, the centrality measures are calculated and results are presented. The mean sensitivity (%) in determination of global hubs of each measure of the 10% to 50% sparsity level of the group averaged ASD and TD subjects are presented in the Table II.

TABLE III. AVERAGE PERFORMANCE EVALUATION METRICS OF THE CENTRALITY MEASURES IN GROUP AVERAGED ASD AND TD

Centrality	ASD	TD
Degree	66.94	71.13
Betweenness	64.96	60.93
Eigenvector	60.66	67.31
Leverage	65.74	72.16
Weighted Leverage variant-1	59.76	66.33
Weighted Leverage variant-2	68.68	73.80

From the Table 6.4, it can be found that the performance of weighted leverage variant is appreciable in identifying the global region role in group averaged

subjects of ASD and TD. As the performance of weighted leverage variant-1 is not found to be appreciable. Hence, it has not been considered in further analysis. The mean accuracy of identifying the hub and non-hub in the group averaged matrix of ASD and TD of 10% to 50% sparsity level is shown in Figure 4.

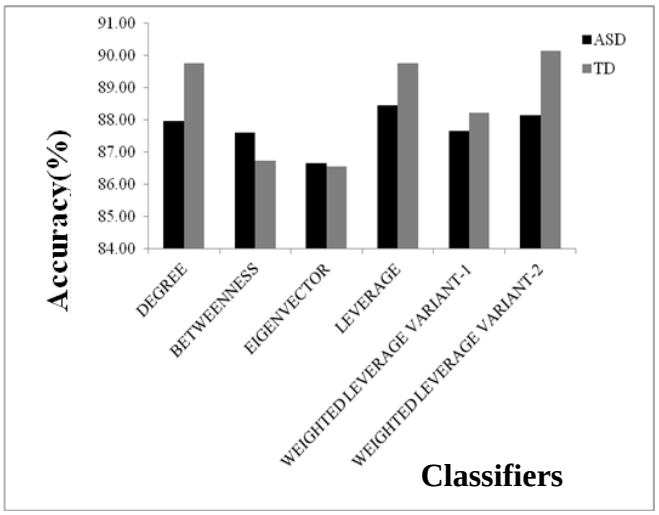

Figure 4: Performance of centrality measures in global region role identification in group averaged ASD and TD

From the Figure 4, it could be found that the accuracy value has increased significantly by the weighted leverage variant-2 measure which indicates that the hubs and non-hubs are identified appropriately on comparison with other measures. The statistical test has been performed on the accuracy values of each centrality measure. Pairwise T-test has been applied on the proposed measure with leverage measure and significant difference is found in the performance. The analysis of the centrality measures are also performed on the individual subjects and better performance is obtained by the weighted leverage variant-2 on comparison with other measures. Through the experimental results, it can be found that 20% sparsity could form the network structure that does not disturb the underlying structure of the brain organization. Hence, for further analysis, 20% sparsity thresholded matrix is utilised in this study.

In the binarized group averaged matrix of ASD at the sparsity level of 20%, the degree and betweenness measure has identified 44 regions as hubs correctly whereas eigenvector has identified 45 regions. Then, leverage and weighted leverage variant-2 predicted 41 and 46 regions as hubs in ASD group.

In TD group, the degree measure has identified 41 regions as hubs, betweenness has detected 43, eigenvector has found 51 as hub regions in the brain network. The leverage has detected 48 regions as hubs and the weighted leverage variant-2 has found 45 regions as important in the brain network of TD subjects. It is clearly evident that weighted leverage variant-2 could able to find the influential regions in the brain network better than other measures.

On analysis of the regions identified by the measures, the global region role can be determined. The region can either take a role as hub or non-hub. Mostly, it has been found that left lateral occipital cortex, left angular gyrus, superior and middle frontal region, right precuneous and right cingulated regions are some of the regions found to acquire the top positions in the global network in the autism spectrum disorder. In typically developing individuals, the right lateral occipital, superior frontal, left precuneous and right paracingulate are some of the regions which possess influential role in the brain network.

The role of region are determined through the examination of various centrality measures namely degree, betweenness, eigenvector, leverage centrality and weighted leverage variant-2. The number of hub nodes identified by weighted leverage variant-2 is higher when compared to other measures in both ASD brain network.

In terms of degree measure, higher degree node has high importance in the brain network. The degree value of regions which is greater than the sum of mean and standard deviation of degree of all nodes were differentiated as global hubs. On comparison with TD network, ASD has found to have decreased number of connection with the following regions LCGad4, LCGad5, LPG19, RCGad3, RFMC2, RFP8, RMTGpd2 and RMTGpd4 and RPG4 and thus these regions are found to be non-hub in ASD. The following regions have gained more connections in ASD when compared to TD as it has changed its role from non-hub in TD to hub in ASD LLOCsd2, LPG16, LSGpd, LSPL2, RAG1, RCI3, RLOCsd5, RLOCsd3, RLOCsd8, RSGad, RSPL2 and RSPL3. The degree of each region for both ASD and TD network is depicted in Figure 5 and Figure 6 respectively.

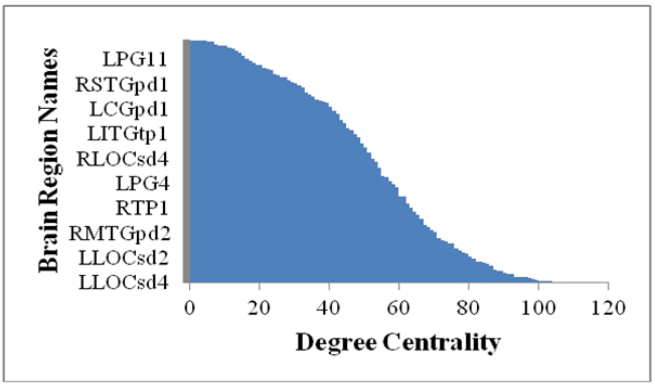

Figure 5: Degree Centrality of Autism Spectrum Disorder

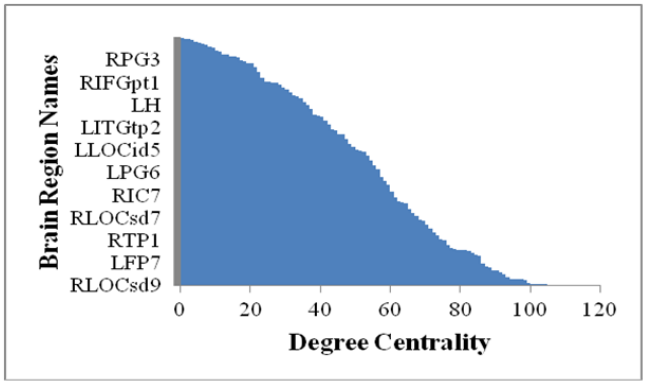

Figure 6: Degree Centrality of Typically Developing

From the figures 5 and 6, it can be inferred that, in overall view, the values of degree centrality for regions in ASD are comparatively higher than TD. It can be seen that the value of region is different in ASD and TD eventhough they have similar region role.

Betweenness centrality has also found to have the hub regions which are similar to degree measure. The central region that stands in between the path of two regions can be known through this measure. The region which have taken central role in ASD but not in TD are LFP7, LLG3, LLOCsd2, LPC2, LSGpd, LSPL1, LSPL2, RAG1, RCI3, RFP11, RFP12, RLOCsd3, RPC1,RPC2,RPC4, RPG3, RSGpd2 and RSPL1. This shows that these regions have obtained new connections and found to be important the path of information transfer and hence play a role of hub in ASD. Few regions have lost their importance in the communication path of two regions and hence they are said to be non-hub in ASD but they act as hub in TD network. The regions with lost connections are LCGad4, LCGpd2, LFP2, LFP4, LFP10, LOP4, LPG1, LPG3, LSFG2, LSFG4, RCGad3, RFP5, RFP8, RLOCsd6, RLOCsd7, RPG2 and RTP1. The betweenness centrality measure of each region for both ASD and TD network is depicted in Figure 7 and Figure 8 respectively.

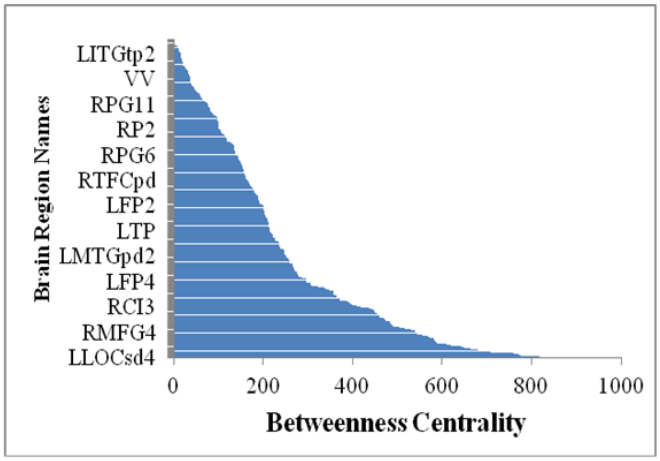

Figure 7: Betweenness Centrality of Autism Spectrum Disorder

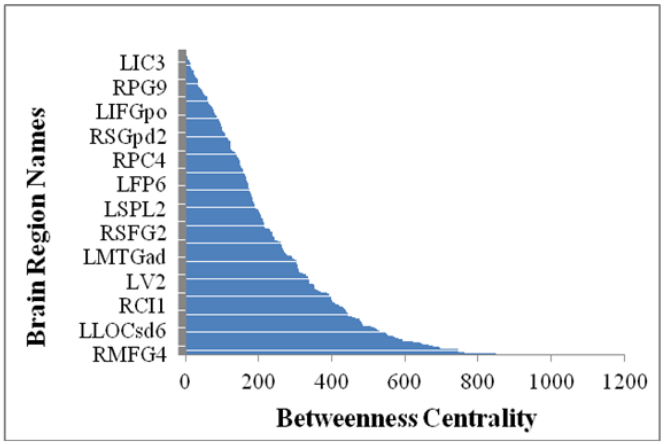

Figure 8: Betweenness Centrality of Typically Developing

From the figures 7 and 8, it can be understood that the betweenness centrality value of regions in ASD is higher than TD.

Similarly, eigenvector centrality found few regions as hub in ASD which deviates from the TD network are LSPL2, RAG1, RCI1, RCI3, RCOC1, RLOCsd5, RLOCsd8, RSF1 and RSPL2. The hub regions in TD network and have not been found in ASD network as hubs are LCGad4, LCGad5, LCOC3, LLOCsd1, LPC4, LPG19, LV1, RFMC2, RFP8, RMFG3, RMTGpd4, RPG4, RSFG2 and RSPL3. The eigenvector centrality measure of each region for both ASD and TD network is depicted in Figure 9 and Figure 10 respectively.

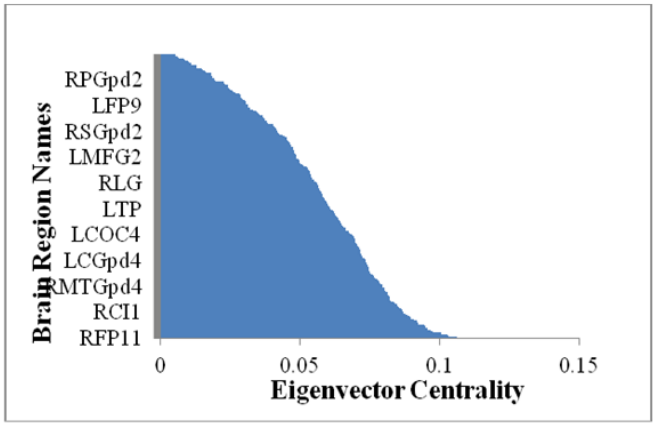

Figure 9: Eigenvector Centrality of Autism Spectrum Disorder

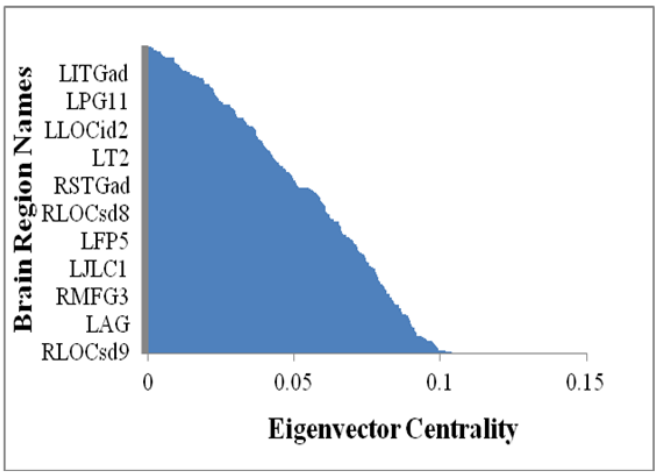

Figure 10: Eigenvector Centrality of Typically Developing

From the figures 9 and 10, it can be inferred that the increase in eigenvector centrality value of regions is steady in TD compared to ASD. The highest value of TD is lesser than 0.1 when compared to ASD which is higher than 0.1.

Leverage measure determines the region through the connections with neighbours. The hub regions in ASD but not in TD in the perspective leverage measure are RSPL1, RLOCsd3, LLOCsd2, RLOCsd5, LSGpd, RAG1 and RCI3. The regions which have been found as hubs in TD but not in ASD are LSFG2, RFP5, RCGad3, LCGad4, LCGad5, RFP8, LPG19, RMTGpd2, RPG4, LMTGpd4, LPG21, RFMC2, RTP1, and RMTGpd4. The leverage centrality measure of each region for both ASD and TD network is depicted in Figure 11 and Figure 12 respectively.

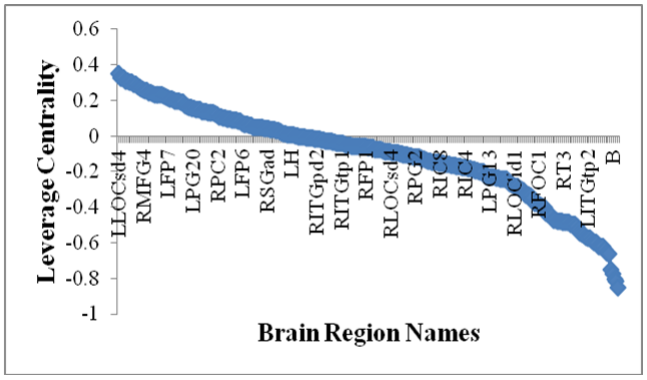

Figure 11: Leverage Centrality of Autism Spectrum Disorder

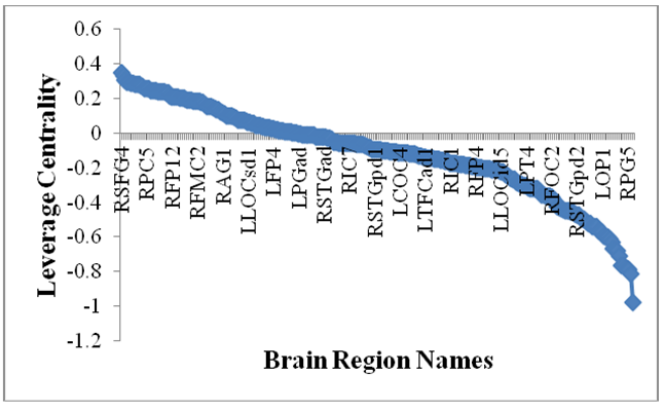

Figure 12: Leverage Centrality of Typically Developing

From the figures 11 and 12, it can be observed that the leverage value of regions in ASD is higher than TD. The order of regions in ASD and TD are different. Weighted leverage variants utilise the influence on the region by the immediate neighbours along with the indirect neighbours. The number of connections with the neighbours play key role in this measure. Some of the regions which have been identified as hubs by these measures are similar to the leverage and eigenvector measure.

Weighted leverage variant-2 performs better than the weighted leverage variant-1 and hence, weighted leverage variant-2 is taken for analysis. In addition, it could also find few other regions that could have a hub role which have not been detected through those measures. Some of those regions act as influential region in ASD but not in TD are LSPL2, RAG1, RLOCsd3, RLOCsd5, LPC1, RSPL1, RSPL3, LSGpd, LLOCsd2 and RCI3. Similarly, the regions that act as hubs in TD but not in ASD are LCGad4, LCGad5, LPG19, RFMC2, RFP8, RMTGpd2, RPG4, RCGad3, RMTGpd2 and RTP1. The weighted leverage variant-2 centrality measure of each region for both ASD and TD network is depicted in Figure 13 and Figure 14 respectively.

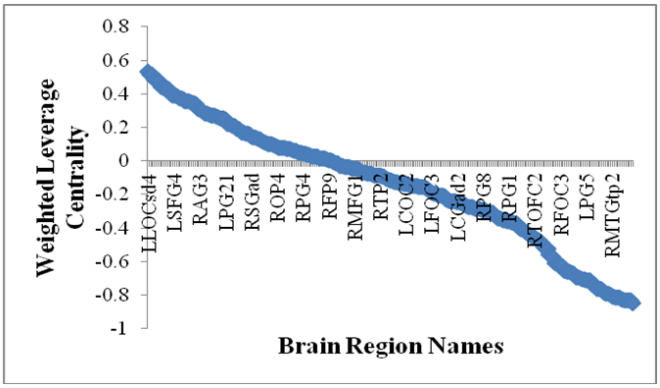

Figure 13: Weighted Leverage Variant-2 Centrality of Autism Spectrum Disorder

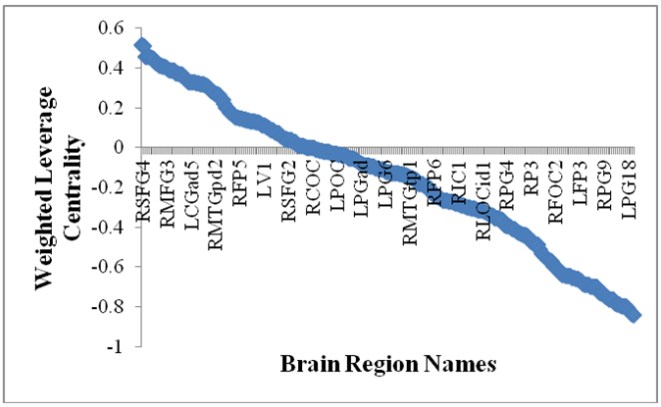

Figure 14: Weighted Leverage Variant-2 Centrality of Typically Developing

From the figures 13 and 14, weighted leverage variant-2 generally regarded as weighted leverage that have higher values in TD than ASD. On the whole, the number of regions that have gained connections are relatively lower when compared to the regions that have lost its connections. Frequently identified hub regions by the measures in the ASD individuals are Right superior parietal lobe, right crus, left superior parietal lobe and right central opercular cortex. The part of right lateral occipital cortex superior division and right temporal gyrus posterior division have shown increased connections while some parts of those regions have decreased connections. The commonly occurred hub regions in typically developing but have not found in ASD network are Left cingulated gyrus, left lateral occipital cortex superior division, right paracingulate gyrus, right temporal pole, right frontal pole, left paracingulate gyrus, right cingulated gyrus anterior division, left precuneous and right superior parietal lobe. The increased and decreased connections are associated with the abnormalities shown by autistic people.

H. Analysis on Global Role determined through Clustering of Centrality Measures

Further, in the view of aggregating the hubs detected in the network, unsupervised learning model is attempted on the set of centrality measures. As the exact role of brain region would be unknown, no training data is available for constructing the supervised learning model. Hence, the clustering technique is employed on the feature vector consisting of different centrality measures. Different clustering algorithms are employed on the feature set. K-Means, farthest first and density based cluster [32] are attempted to identify the hub and non-hub clusters in the network of ASD and TD subjects. K-Means clustering with two clusters could segregate the regions in the brain network in a better way. From the Table III, it can be found that the sensitivity (%) value is quite higher with clustering as they detect more number of hubs but this in turn affect the identification non-hubs to some extent.

TABLE IIIII
IMPACT OF CLUSTERING OF CENTRALITY MEASURES IN GROUP AVERAGED ASD AND TD

Clustering	Without Weighted Leverage Measure		With Weighted Leverage Measure	
	ASD	TD	ASD	TD
K-Means Clustering	95.45	100	97.77	100
Farthest first	88.63	100	90.90	100
Density based Clustering	95.45	100	97.77	100

From the Table III, it can be inferred that the inclusion of the weighted leverage variant-2 measure helps in identification of the hubs in ASD subjects. In TD subjects, the hubs are determined completely with or without the inclusion of the measure. Clustering can aid in the determination of hubs and it can result in aggregation of the centrality measures in hub identification. With the overview on the global region role detected in ASD and TD through the centrality measures, identification of modular region role is explained in next section.

I. Analysis on Modular Region Role Identification

Modularity is a fundamental property of biological networks [33]. Module in a network is defined as set of nodes with tighter connections within themselves and

sparser with nodes of other group. Modularity of a network will decrease with increasing sparsity. Thus, to maximize modularity (Q) value, low sparsity is set as threshold. Sparsity is set in such a way that it does not disturb the underlying backbone structure of a network and all the nodes are connected to the network. In this study, sparsity level of 20% was employed and spectral partitioning algorithm was used to form the modules from the brain network. The identified modules and the roles of region in the brain network of ASD are explained in subsequent subsection.

1) Regions and their modular roles in autism spectrum disorder subjects: Autism Spectrum Disorder network consists of four modules with varying number of regions in each group. Module 1, 2, 3 and 4 consists of 46, 82, 53 and 83 brain regions which belongs to various anatomical classes namely primary, association, visual, paralimbic cortex and sub-cortical areas. There are 9 regions which seem to be influential in the module 1. All these hub regions are found to be connector nodes as they have equal connections with other modules in the network. Module 1 contains 37 non-hub regions; all of them play a role of non-hub connector as they have equal participation inside and between the modules. There are 82 regions in module 2, out of which 15 were connector hubs and the remaining 67 regions were non-hubs. In those 67 regions, 8 regions acts as peripheral node which have high intra-mocule connections and remaining act as non-hub connectors with high inter-modular connections. Module 3 consists of 83 regions, out of which 10 regions are modular hubs and all of them are connector hubs. The remaining regions are non-hub connector nodes. Module 4 includes 53 regions totally, out of which 10 regions are modular hubs which found to be connector. Remaining regions are modular non-hub. Among those, modular non-hubs, 15 are peripheral nodes with high intra-module connections and other regions in modular non-hubs are connector. The TD brain network and the modules are presented in next subsection.

2) Regions and their modular roles in autism spectrum disorder subjects: Typically developing network contains three modules with different number of regions in each module. Module 1, 2 and 3 includes 78, 133 and 53 respectively brain regions which belong to various anatomical classes namely primary, visual, auditory, association, visual, paralimbic cortex and sub-cortical areas. Module 1 contains 78 regions, out of which 12 regions are nodule hubs which also found to connector hub as they possess high number of connections within and between modules. The non-hub regions are 66, out of which 13 regions are peripheral nodes and remaining regions are non-hub connectors. Module 2 includes 133 regions out of which 25 regions are modular hub. In the modular hubs, all are found to be connector hubs. There are 108 non-hub regions in the module 2. In those non-hub regions, 1 region is ultra-peripheral node, (ROP1), 90 regions are peripheral nodes and left over regions are non-hub connectors. Module 3 contains 52 regions, 9 regions are connector hubs and remaining regions are modular non-hubs. Among modular non-hubs, 3 regions are peripheral nodes and 40 regions are non-hub connectors.

3) Comparison of roles of nodes: To analyse the outcomes of group averaged functional connectivity matrix are compared with the role determined through individual functional connectivity matrices. Within module degree z-score is estimated for each region. Then, the hubs and non-hubs in each group are determined. The modular roles are identified for both individual and group functional connectivity matrix. To derive single role from the individual functional connectivity matrices of each group, a feature vector is formed and supervised association rule mining is applied. In the feature vector, roles of each region are attributes and the last column is target class. Each subject is the instance of the feature vector and rule mining is applied to obtain rules specific to a group. Brain region and its role form antecedent part and the target (ASD or TD) form consequent part. Association rules are obtained based on the repetitive presence of particular for a region of a particular group. In this study, role frequency is determined if it satisfies at least 20% support i.e. the role of region should be present in atleast 20% of instances in the feature vector. Rules are constructed only if 50% of instances contain the same region role for specific target class. For example, For example, brain stem act as non-hub in group averaged matrix of ASD and the rule mining derived role from the individual matrices also seem to have non-hub role. Similarly, it has been obtained for other regions of ASD and TD functional connectivity matrices and the outcomes are shown in Figure 6.22 and Figure 6.23 respectively. The value A represents hub and B indicates non-hub roles and '–' no role can be obtained through the given set of information.

With the limited dataset, the role of few regions may not have occurred as frequent as possible to construct the rule and so they could not form the association rule. On comparison of the group averaged and individual matrices, it can be known that 70% of role determined by ASD group averaged matrix matches with individual matrix roles and 30% have mismatched between them. In TD group 56% of roles have matched, 2% roles have not been derived and 42% have mismatched between the group averaged and individual matrices.

To examine the random grouping of individual functional connectivity matrices by blinding the information of target group, the matrices have been randomly selected and averaged to form group matrix. Then, the region roles are identified between these two

groups and roles are determined. The region roles of both groups are similar and no difference could be found. Hence, it does not provide any valuable information about the modular organization changes in the functional brain network.

4) Nodal role alterations in autism spectrum disorder: The existence of modular organization can be comprehended through the resting state functional network through the formation of functional connectivity. Spectral partitioning algorithm is applied to divide the regions into community or modules. The algorithm managed to determine 4 modules in ASD and 3 modules in TD group. This study utilised spectral partitioning to obtain major functional modules. The parcellation has derived 264 regions and they are grouped into modules. Since, the single regions have multiple divisions within them, based upon the connections; their presence can be found in different groups. So, modules have regions which are mixture of different networks namely default mode network (DMN), visual network, sensorimotor network, subcortical regions in ASD and TD group. But, 4 modules could be identified in ASD whereas only 3 modules are obtained in TD group. In TD group, module 2 consists of most of the regions from DMN, visual network, sensorimotor network and regions from other networks also. The dysconnectivity has lead to divide the regions into 4 modules in ASD group. With comparison to TD group, it can be observed that connectivity variations are significantly higher in the ASD group. Hence, the grouping of regions in the modules is considerably varied. The alterations in the modular organization in the ASD group have resulted in the modular role played by the regions. The modular hubs in ASD are found to be connector hubs and no provincial and kinless hubs are determined.

Similarly, regions in TD group are connector hubs. No role in the perspective of participation within and between modules has been found between ASD and TD. But, many hub regions in TD have changed it activities and formed into non-hub in ASD. Fifteen regions which act as connector hub in TD have changed into non-hub connector in ASD. One region (LLOCsd7) has changed its role from connector hub to peripheral node in ASD. Left lateral occipital cortex superior division has lost many of its connections between other modules and thus major alteration is created. Right occipital pole has changed its condition from ultra peripheral node in TD to non-hub connector in ASD with increased number of connections between the modules. Four superior divisions of right lateral occipital cortical region has gained more number of connections and changed its role from non-hub connector in TD to connector hub in ASD. Other than occipital region, few regions in frontal lobe (right frontal pole and left frontal operculum) and right paracingulate regions has changed its role from non-hub connector in TD to connector hub in ASD with increased number of inter- module connections. Left cuneal and right cuneal region, along with the few regions in right frontal pole, right precuneous, right superior temporal gyrus region, right superior frontal region has altered its role from peripheral node to connector hub since it has high number of connections in ASD than TD

The thirteen regions that have played a role of non-hub connector in TD have changed to peripheral node in ASD and most of them have lost their connections and few of them retained the same role. Forty six percent of region that holds the role of peripheral node in TD has varied its role to non-hub connector in ASD due to decrease in the number of connections. The outcomes reveal that the alterations in ASD group are extremely evident from the analysis of the resting state functional brain network.

Major changes are identified in the occipital and frontal regions of the brain which is in accordance with earlier studies [34]. From the literature, it can be understood that the reduction in the volume of white matter in the left occipital region [35]. In another study, it shows that hyperconnectivity is present between the frontal and occipital regions, frontal and parietal and temporal and parietal lobes. It is very well known that the visual related functionalities are performed by the regions in the occipital cortex. The local over connectivity is evident in temporo-occipital regions in the previous studies. In this study also, it has been observed that the occipital region has lost its connection with other modules and highly connected within the modules. The changes in the functional connectivity of those regions results in the abnormalities of visual processing of ASD subject [36]. Changes in the cuneus region are also exhibited in the study which is greatly involved in the visual processing in the human.

The superior temporal gyrus is an important region as they involve in acoustic processing which is primarily required for language production and comprehension [37]. It will also indulge in non-social cognition and these regions have shown abnormalities in the existing works. In this study also, it has been observed that the

region has gained higher number of connections and changed its natural connectivity with other regions [38].

The alterations in frontal region of the ASD subjects can be inferred from this study which is inline with the previous works. It has been observed that the frontal regions have increased functional connectivity [39]. Frontal regions are mostly related to the social cognition and it is also known that the autistic people have very poor social communication when compared to typically developing people. Similarly, the other regions also exhibit the hypo and hyper-connectivity between various brain regions in the literature.

IV.CONCLUSION

The global region role of the ASD and TD subjects are analysed based on the binarized resting state functional connectivity matrices. The connectivity matrices of ASD and TD subjects are averaged and utilised for the analysis of global region role in the brain network. Different sparsity values from 10% to 50% are utilised for thresholding the matrix and the thresholded network of 20% sparsity value is considered for further analysis as all regions in the network are connected To identify the global hubs in the brain network, different centrality measures are utilised along with the weighted leverage variants. Weighted leverage variant-2 show significant improvement in the detection hubs in ASD and TD. In the higher prediction of global hubs, clustering is applied on the centrality measure. As expected, it determines increased number of hubs whereas non-hub regions are also considered as hubs which resulted in lower accuracy. Thus, the weighted leverage variant-2 determines the hub and non-hub regions in the brain network of ASD and TD appropriately than other measures. The comparison is performed with the hubs identified through functional cartography technique.

Further, the modular region role and the alterations in the region role of ASD and TD are determined through the thresholded group averaged matrices of ASD and TD. The modular role is determined through functional cartography technique in group averaged and individual matrices. Then, the role of each in individual matrices is aggregated through supervised association rule mining and compared with the group averaged role to understand the reliability of group averaged matrices in the analysis of functional connectome. Then, the role changes are discussed and it has been found that major alterations are present in occipital and frontal regions of the brain in the ASD subjects. The outcomes are strongly supported by the existing literature.

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