

# Graph-Theoretic Characterization on Differentiation between Normal Healthy and Autism Spectrum Disorder (ASD) Subjects

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## Abstract

With the growing exercises of structurofunctional network attributes as potential indicators for disease brains, an effective representation and assessments have become important. Eigenvector centrality characterization of functional *MRI* (*fMRI*) networks permits node wise graph theoretical representations as brain diagnostic charts. This article analyses adequacy of node centrality measures to perform group difference studies in neuroimaging data.

**Keywords:** *fMRI*, regions-of-interests, eigenvector centrality, autism spectrum disorder

## 1. Introduction

Graph theoretic characterization of a network had long been exercised to illustrate complex phenomenon in several ways, ranging from a typical weather forecasting to biological exchanges. In large-scale constitution of cortical connectivity data, graph centrality measures played a fundamental role. For instance, by means of *fMRI* data, Achard et al. [1] verified that brains were largely influenced by neo-cortical core of immensely coupled hubs that had long-distance associations to other brain regional nodes. These hubs were related through network robustness as cortical networks exposed to be further resilient to targeted attacks on their hubs compared to an analogous scale-free network. Therefore, network central nodes

play an elemental role in brain working. There are many metrics to quantify node centrality in network data, as given by:

- number of links of any node (degree centrality)
- number of occurrences a particular node occurs on shortest path among two different nodes in a network (betweenness centrality).
- the reciprocal of sum of length of the shortest distances between a node and rest of the network (closeness centrality).

In many other cases, a relation to a well-known node may further be considered significant compared to a connection to an isolated node. The eigenvector centrality measures of any network considered not only how different connections a particular node had (i.e., its degree), but also taken into consideration the centrality of nodes that it has been connected with. Voxel wise evaluation of eigenvector centrality measures [2] had shown to quantify functional brain network analysis, which is robust in accordance with physiological and scientific astonishing elements and susceptible to small changes related with clinical pathology. Consequently, the eigenvector centrality measures had been applied to categorize functional brain node differences in typical subjects like Alzheimer's and dementia [3], Parkinsons, multiple sclerosis [4] and also in other healthy subject groups at menace to neurological disorders [5].

*Autism Spectrum Disorder* (ASD) is a neurodevelopment disorder regarded as constant deficits in societal communication and restricted repetitive behaviours (RRBs) affecting about one out of every 68 children. The worldwide surveillance of ASD had speedily progressed over time; though, etiology of ASD types had been poorly unstated [6, 7]. According to *The Diagnostic and Statistical Manual of Mental Disorders* (DSM)-5 (American Psychiatric Association, 2013), three distinctive criteria of ASD namely (1) qualitative degradation in societal interface, (2) communication and (3) restricted repetitive or stereotyped patterns in interests, behaviour and activities had been reconstructed with continual deficits in societal communication and interaction thereof.

The present study aimed at explicitly assess the association between the node centrality and functions of *fMRI* data, and individual difference in inclination to perceive ASD and typically developing control (TDC) characteristics. To further elucidate the implications of the typical *Regions of Interest* (ROIs) in susceptibility to brain disorder, we consider statistical analysis of respective node activations, while participants from different subject groups were considered a dependent case. This task also recruited both female and male *fMRI* network data and *x-y-z* coordinates of respective nodes. Based on the limited existing literature, we also tentatively hypothesised that *Left Cuneal Cortex*, *Left Insular Cortex*, *Left Lingual Gyrus*, *Right Superior Parietal Lobule*, *Left Hippocampus*, *Right Frontal Pole*, *Right Precuneous Cortex* and *Right Lateral Occipital Cortex* would exhibit changed activities and improved functional connectivity in relation to ASD compared to healthy control.

## 2. Materials and Methods

### 2.1 Network Construction

Imaging data were downloaded from a well-known web-based repository named USC Multimodal Connectivity Database (UMCD) (<http://umcd.humanconnectomeproject.org/>). The UMCD data set included 2354 publicly shared brain networks, rs-fMRI time series of 95 ASD subjects. Brain connectivity information was then studied with graph theoretic structures representing vertices as nodes and edges as connectivity values [8, 9], considering 264 unique ROIs that represented as nodes. Nodes were labelled by names along with their coordinate positions (i.e., MNI coordinates). The correlation matrix was then graph-transformed with *R igraph* library. Network construction and following analysis was subsequently performed using *R* packages (Mathworks Inc., USA).

### 2.2 Connectivity Analysis

We adopted eigenvector centrality measure which seemed to be important for a particular node that is attached to other essential nodes. Therefore, if the “importance” has quantified by a vector  $a$ , then importance of  $k$  can be represented as

$$a_k = \frac{1}{\lambda} \sum_{i=1}^n A_{k,i} a_i, \quad (1)$$

where  $\lambda \neq 0$  is a constant. This could be further reduced to a matrix form as given by

$$\lambda a = aA \quad (2)$$

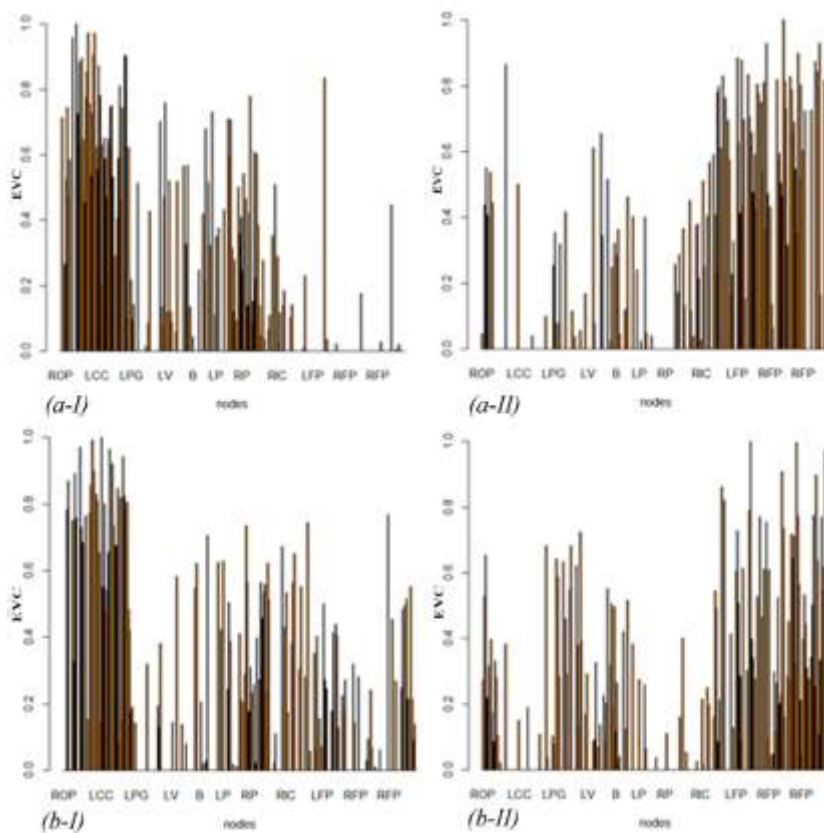
Thus, the “importance” of a node  $k$  may be represented with the eigenvector with eigenvalue  $\lambda$  of corresponding adjacency matrix  $A$ . Due to *Perron-Frobenius* hypothesis, if matrix  $A$  is not further reducible then  $a$  will become unique and positive. The basic logic behind eigenvector centrality was that associations with essential nodes increases nodes impact over the network. Nodes residing at the centre of a network with highest values of eigenvector centrality considered to play a significant function in network analysis [8, 9].

### 2.3 Statistical Analysis

Present work considered statistical approach to classify brain network data that showed significant variations of gender (female and male) and different symptoms of ASD brains. Eigenvector centrality measures of brain network were dependent variable and gender, symptom, node name and positions were respectively the independent variables. It became easier to find more information than the measures of central tendency (median, mean, and mode) using *R boxplot* method. Boxplots were a uniform way of portraying data distribution between many groups or datasets based on a five-number summary (“minimum”, “first quartile”, “median”, “third quartile”, and “maximum”). Brain networks with significant non-overlapping regions were regarded as candidate nodes affected by both gender and symptoms concerned.

### 3. Results and Discussions

The measures of eigenvector centrality (EVC) for each node in *fMRI* representation were depicted in fig. 1. Several cortical regions were noticed including left cerebellum, brain-stem, pallidum, putamen, left postcentral gyrus, occipital, frontal pole, etc. Higher eigenvalues of brain networks correspond to visual region (TDC) and frontal pole (ASD). However, no specific marker was identified to differentiate the TDC with respect to ASD subject groups only upon considering the bar-diagram plots of the corresponding functional network.



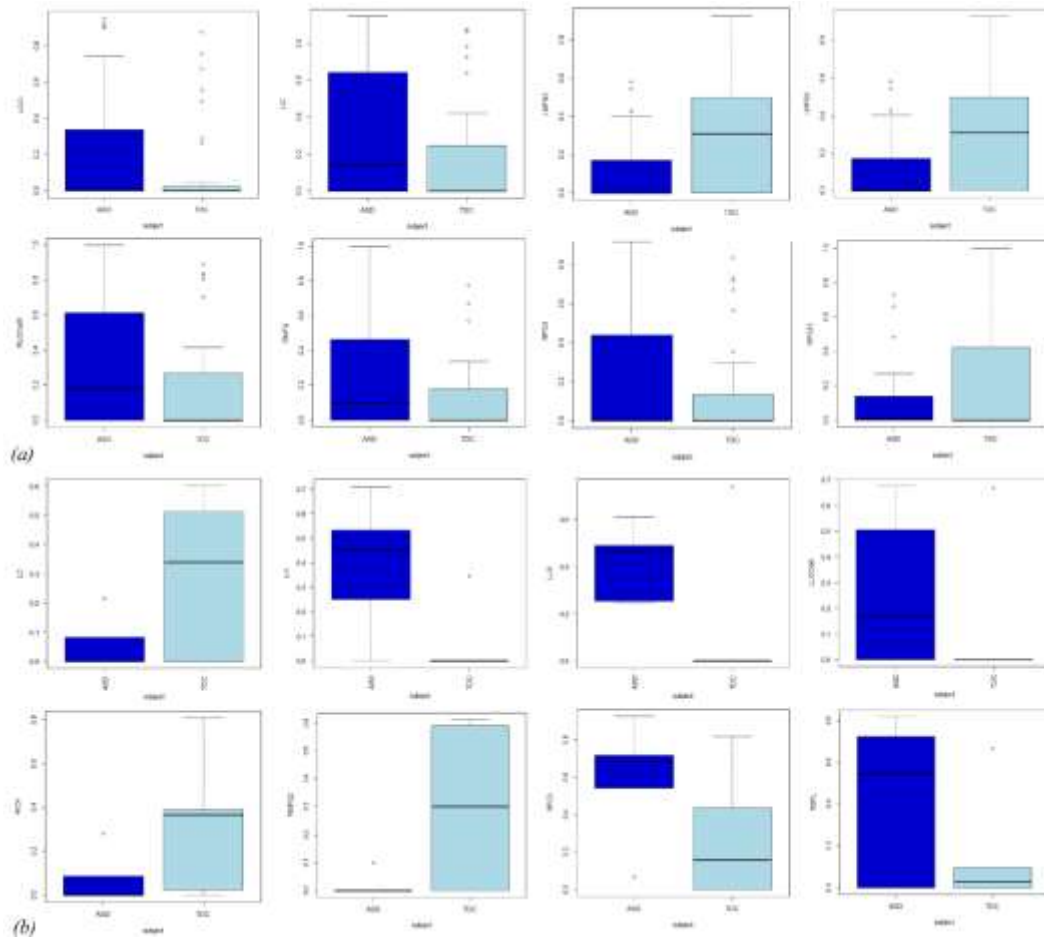
**Figure 1.** Eigenvector centrality representation of ASD brain networks for (a) female and (b) male subject groups under (I) TDC and (II) ASD.

In the following, a general boxplot formalism is used in finding differentiating ASD nodes which are significantly non-overlapping with the normal healthy subjects. We have tried to isolate the marker nodes based on the relatively high range of EVC values. The manually identified marker nodes for both genders, their MNI coordinate positions, respective network, and the target group are listed in table 1. The male TDC subjects may be correctly identified based on the high EVC values of the two nodes located at the left middle frontal gyrus in the frontoparietal net-

work, and right postcentral gyrus in the somatomotor area. At these nodes, the EVC of the control group was always higher than 0.42. The number of TDC identifying nodes selected was higher (= 4) for the female group. In contrary, the list includes nodes from the frontoparietal, basal ganglia, ventral attention and default mode networks. For the ASD subject groups, marker nodes for the male group majorly belong to the ventral attention, limbic, frontoparietal, visual and default mode networks. Additionally, a marker node at the dorsal attention network has also been identified for the female subject group. The detailed boxplots of EVC distribution for each marker nodes are illustrated in fig. 2.

**Table 1.** Potential non-overlapping candidate markers to differentiate ASD subject from TDC groups.

Sl. no.	Node names	Regions full names	MNI coordinates	Network	Target category
<b>MALE</b>					
1.	LCC1	Left Cuneal Cortex	<-3, -81, 21>	visual	ASD
2.	LIC	Left Insular Cortex	<-35, 20, 0>	ventral attention	ASD
3.	LMFG3	Left Middle Frontal Gyrus	<-32, -1, 54>	frontoparietal	TDC
4.	RFP9	Right Frontal Pole	<38, 43, 15>	limbic	ASD
5.	RLOCsd6	Right Lateral Occipital Cortex superior division	<37, -65, 40>	visual	ASD
6.	RMFG	Right Middle Frontal Gyrus	<31, 33, 26>	frontoparietal	ASD
7.	RPC4	Right Precuneous Cortex	<11, -39, 50>	default mode	ASD
8.	RPG13	Right Postcentral Gyrus	<42, -20, 55>	somatomotor	TDC
<b>FEMALE</b>					
9.	LC	Left Caudate	<-15, 4, 8>	basal ganglia	TDC
10.	LH	Left Hippocampus	<-13, -40, 1>	limbic	ASD
11.	LLG	Left Lingual Gyrus	<-26, -40, -8>	visual	ASD
12.	LLOCid4	Left Lateral Occipital Cortex inferior division	<-26, -90, 3>	visual	ASD
13.	RIC4	Right Insular Cortex	<34, 16, -8>	ventral attention	TDC
14.	RMFG2	Right Middle Frontal Gyrus	<40, 18, 40>	frontoparietal	TDC
15.	RPC3	Right Precuneous Cortex	<11, -54, 17>	default mode	TDC
16.	RSPL	Right Superior Parietal Lobule	<22, -42, 69>	dorsal attention	ASD



**Figure 2.** The EVC boxplots of the candidate neural marker nodes for TDC and ASD subjects: (a) male and (b) female groups.

In summary, in the high EVC ratings of the visual cortex, the control groups corroborate with the observed behavioural traits of ASD. It has also been established that activation of ventral occipitotemporal cortex, including lingual gyrus, is associated with processing of visual data about sections of human faces. Accordingly, the left lingual gyrus is seemed to be a viable candidate marker for ASD female groups. In addition to its usual role as a site for visual processing, the grey matter volume in cuneus that associated with more inhibitory mechanism was subsequently found to be highest for ASD male subjects ( $LCC_{-3-81\ 21}$ ). The superior parietal lobule has close links with occipital lobule and is involved in attention and visuospatial insight, including representation and manoeuvring of objects. It reaches at its maximum ranges under ASD female groups. It is well known that frontal lobes are mostly involved in problem solving, motor function, impulse control, language, memory, judgement and social behaviour. Highest EVC variations was observed for ASD male subject groups. Recent development in functional neuroimaging studies established that precuneous cortex played an

essential function between task and rest states within default mode and frontoparietal networks across typical development that allowed integration of repeated recovery in *default mode network* with goal-oriented cognition [10]. Alongside, it was found to be highest for TDC female and ASD male subject groups. One finding also assist the hypothesis that left hippocampus played a critical *task* in episodic verbal memory [11], and consequently shown highest EVC for ASD female subjects. One of the nodes from the left caudate which played essential roles in many other non-motor functions, such as procedural and associative learning, restrictive control of actions, etc., in the basal ganglia network was also identified as a TDC marker. In summary, the presence of multiple differentiating nodes from visual, frontoparietal, limbic, basal ganglia, ventral attention and default mode networks strongly vouch for the established hypothesis of ASD-specific neuronal dysfunction.

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