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Resting-State Functional Connectivity in Popular Targets for Deep Brain Stimulation in the Treatment of Major Depression: An Application of a Graph Theory

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***Abstract*— We examined the functional connectivity of subcallosal cingulate gyrus (SCG), nucleus accumbens (NAc), and ventral caudate (VCa), the main target areas for the treatment of major depression disorder (MDD), using deep brain stimulation (DBS). MDD is one of the most common diseases in the world, and approximately 30% of MDD patients do not respond to common therapies, including psychotherapy and antidepressant medications. Alternatively, DBS has been recently used to treat MDD. Resting state fMRI was obtained from seventeen healthy subjects and seven MDD patients. The functional connectivity network of the brain was constructed for all subjects and measured by the 'degree' value for each SCG, NAc, and VCa regions using the graph theory analysis. The results show that the degree values of VCa and the left SCG are higher in the MDD group than the healthy group. Furthermore, the patterns of the degree values were different for the right and left hemispheres in MDD patients. Our findings suggest that degree values and their patterns have a potential to be used as diagnosis tools to detect the brain areas with abnormal functional connectivity.**

Keywords- Major depression, resting state Functional connectivity, Graph theory analysis, Deep brain stimulation.

I. INTRODUCTION

Major depression disorder (MDD) is one of the most common diseases that has affected 4.7% of people worldwide [1].Common therapies for MDD are the use of psychotherapy as antidepressant medications [2]. However, approximately 30% of MDD patients have treatment resistant depression (TRD)[3].

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Recently, with the development of advanced technology, the direct deep stimulation of the brain has become viable, and consequently deep brain stimulation (DBS) has been developed and used to treat TRD [4][5][6][7] . However, the effectiveness of DBS in the treatment of TRD is strongly dependent on the best effective target areas of TRD, which is still undetermined due to the complexity of these diseases[3]. To address this issue, DTI and fMRI imaging have been used to select the target area for DBS[8] [9][10] .
In earlier studies, based on PET-scan images, areas such as subcallosal cingulate gyrus (SCG) and nucleus accumbens (NAc) have been introduced and used as a DBS target area for the treatment of TRD, but about 40% of patients did not respond to the stimulation of these areas[11][6][12][4]. Later studies have focused on functional and structural networks, and the interactions of the nodes of these networks to determine the appropriate DBS target area and set the DBS stimulation parameters. Recent investigations have suggested that graph based network analysis is a strong method that allows us to determine the organization of brain connectivity and characterize topological properties of brain networks by mapping the brain as functional or structural networks consisting of nodes (brain regions) and edges (functional or structural connectivity between regions)[13][14]. In this study, for the first time, we investigated resting-state functional connectivity for the selected areas in both health subjects and MDD patients using graph theory analysis. These areas include SCG, NAc, and Ventral caudate (VCa), which are the most commonly used DBS target areas for TRD treatment.

II. MATERIAL AND METHOD

A. Subjects

Twenty-four subjects were selected, including 7 MDD patients (mean age41± 7.1 years,2male) and 17 healthy controls (mean age39±8.2,10male). The diagnosis of MDD was made according to the Hamilton Depression Rating Scale (HAMD) (mean 31± 6.3) by an experienced psychiatrist.

B. Image Acquisition

All subjects were scanned with a Siemens magnetom Prisma MRI at 3T system. Resting state functional imaging (echo-planar imaging sequence) parameters were as follows: 240 volumes, 32 slices with 3.5 mm thickness, TR = 2000 ms, TE = 30 ms, flip angle = 90°, voxel size: 3.1×3.1×3.5 mm, field of view =200×200 mm and an acquisition matrix of 64 × 64.

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T1 weighted images were also acquired for co-registration of functional images. During the whole scanning process, the subjects were asked to keep their eyes open.

The analyses included preprocessing, functional connectivity, thresholding for binary matrix, and graph theory and statistical analyses, shown in Fig.1.

C. Data Analysis

- *Preprocessing*

The most important step in the resting state fMRI analysis is the pre-processing stage. The resting state fMRI data includes a weak signal with a complex noise structure. To increase the signal to noise ratio and reduce the noise of psychological and instrumental sources, we used DPABI toolboxes in MATLAB R2016a (MathWorks Inc., Natick, MA,United States)[15]. Thus, a series of standard pre-processing was performed on data fMRI, including (i) the first ten volumes of each functional time course was removed to allow for T1 equilibrium and the participants to adapt. (ii) The remaining volumes were corrected for the intra-volume acquisition time delay using slice-timing, and were realigned to the first volume using the six-parameter (rigid body) spatial transformation. (iii) The high-resolution T1 weighted image was reoriented to the mean functional image. (iv) Skull stripping was performed for better registration and registration T1 image to functional space. (vi) The T1 images were segmented into grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF). (vii) WM, CSF, and global signals were regressed on the fMRI data. (viii) the images were spatially normalized to the standard Montreal Neurological Institute (MNI) space. Spatial smoothing was performed using a 4-mm full-width at half-maximum (FWHM) Gaussian kernel. (ix) Finally, a temporal band-pass filter ($0.01 < f < 0.1$ Hz) was applied to reduce the influence of low-frequency drift and high frequency respiratory and cardiac noise.

The graph theory analysis was used to construct a functional brain network [16], utilizing BRAPH toolboxes in MATLAB R2016a (MathWork Inc., Natick, MA,United States).

- *Functional connectivity*

Functional connectivity was performed as follows: The seed regions were obtained from the Brainnetome atlas (BN_atlas) which divided the whole brain into 246 regions [17]. The time course (series) of the seed regions were extracted, and Pearson correlation was used to calculate functional connectivity between the extracted time course of the whole brain regions.

- *Thresholding*

In the previous step, the weighted connectivity matrix (matrix size 246×246) was measured for each subject and negative correlation values were discarded. The density thresholding method was used to construct a binary connectivity matrix.

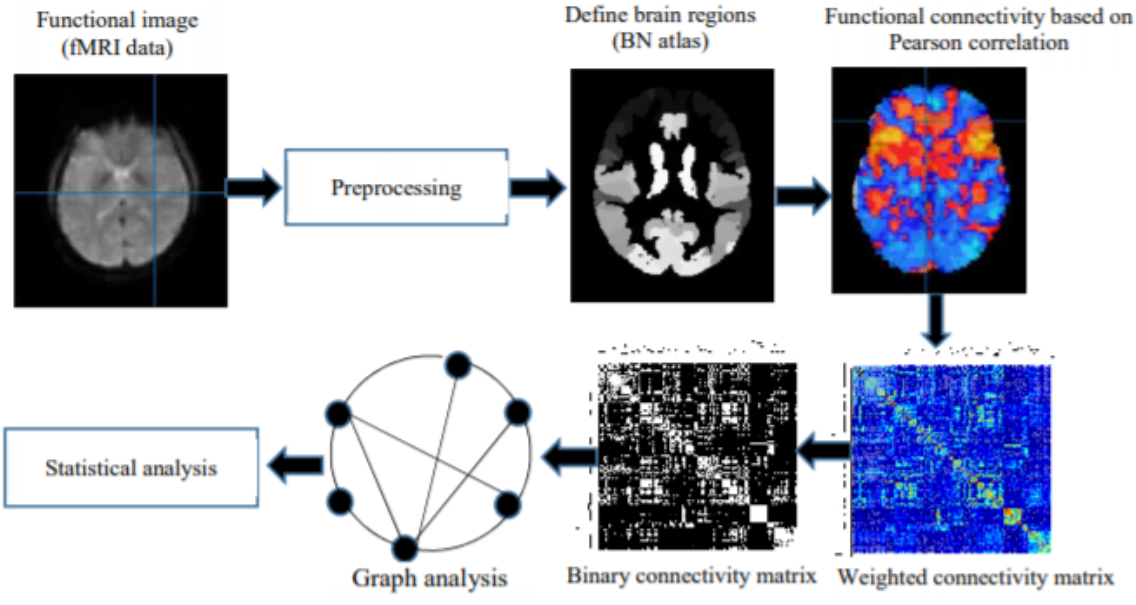

Figure1. A schematic data analysis overview

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This approach includes the choice of the strongest D% of connections in each individual network, placing all remaining connections to 1 and other connections to 0 [18]. Here, there is a network density of 0-100%; the strongest correlation was preserved with a 1% edge increase for each threshold step.

- *Graph theory analysis*

The graph consists of a series of nodes that are connected by edges. For the graph analysis, the graph was first constructed from the binary connectivity matrix (nodes: brain regions and edges: correlation value between brain regions), then the 'degree' for each node was calculated based on the following formula. The degree of each node equals the total number of edges that are connected to a node.

$$(Degree)_i = \sum_{j \in N} a_{ij}$$

N: number of all nodes

a_{ij}: connection value between node i,j that a_{ij}=1 when a connection between (i,j) exists and equals 0 otherwise .

D. Statistical analysis

The non-parametric permutation test was used to evaluate the significance of differences between healthy and MDD patient groups [19]. The permutation test evaluates whether the null hypothesis (the null hypothesis is the statement that an observed effect is due to randomness) can be rejected by calculating the associated p-value and comparing it to a predetermined threshold (p = 0.05).

III. RESULT

The degree value was calculated in the range of density (0-100) for three regions including SCG, VCa, and NAc in healthy and MDD patient groups. The trends of the group average results for the degree values as a function of density networks for healthy and MDD subjects are shown in Fig.2.

The results showed three major differences:

1- The degree value of SCG was higher in the healthy groups than the MDD groups within the density range of 0-25, but was lower for densities of 25 degrees or higher.

2- The patterns and values of degrees were slightly different for SCG and VCa within the density range of 0-45% between the two groups; they increased linearly as a function of density and were slightly higher in the MDD group as compared to the healthy control group.

3- The degree values were saturated for the density of 45% for all three areas in both groups, and were higher in the MDD group than the control group for the SCG and VCa areas.

Figure 3 shows the non-parametric permutation test results for all three regions SCG, VCa, NAc. Dark-blue points show the difference in degree values between the healthy and MDD groups (HC-MDD), and within the purple zone lies the confidence intervals. The actual difference value (dark blue color points) is significant if it falls outside the confidence intervals (purple zone).

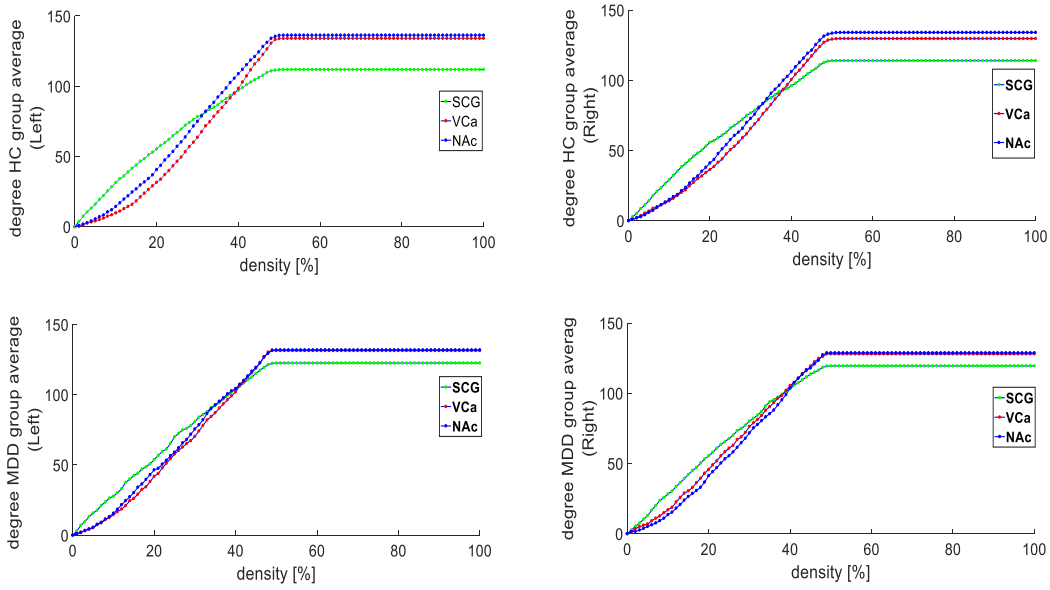

Figure 2. The group average results of the 'degree' value of the left and right SCG (green color) ,VCa (red color) and NAc (blue color) as a function of network density for the healthy (top) groups and the MDD (bottom) groups

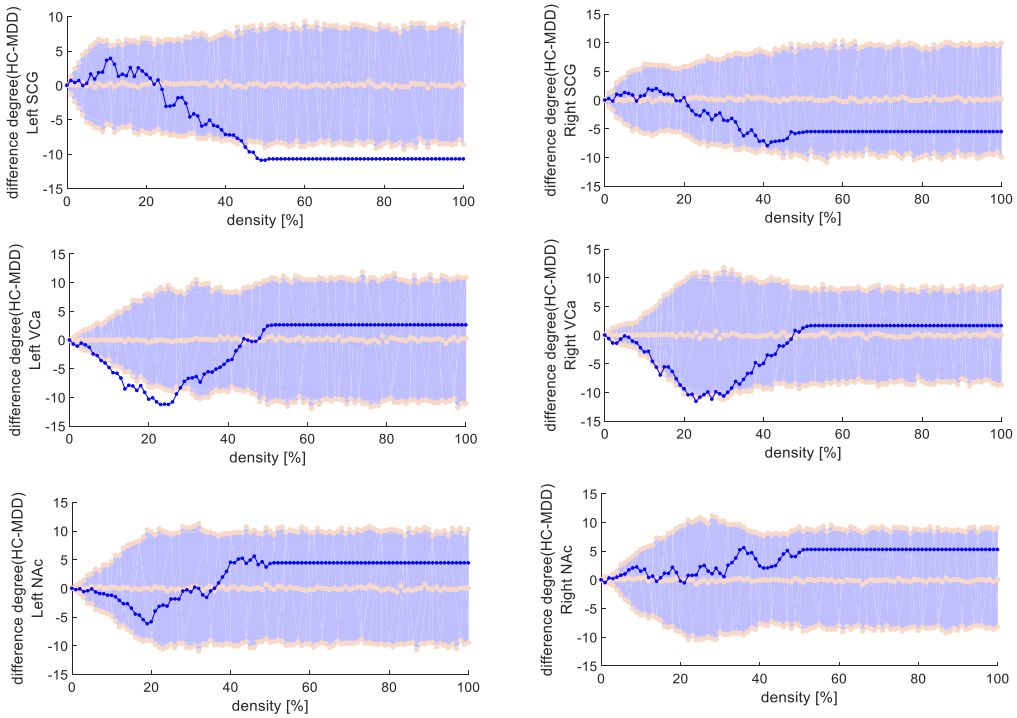

Figure 3. The significance of the differences between healthy and MDD patient groups for three regions SCG,VCa,NAc . From top to bottom, respectively. The dark blue points represent the actual difference between the degree of healthy and MDD group. the actual difference value (blue color points) is significant if falls outside the confidence intervals (purple zone).

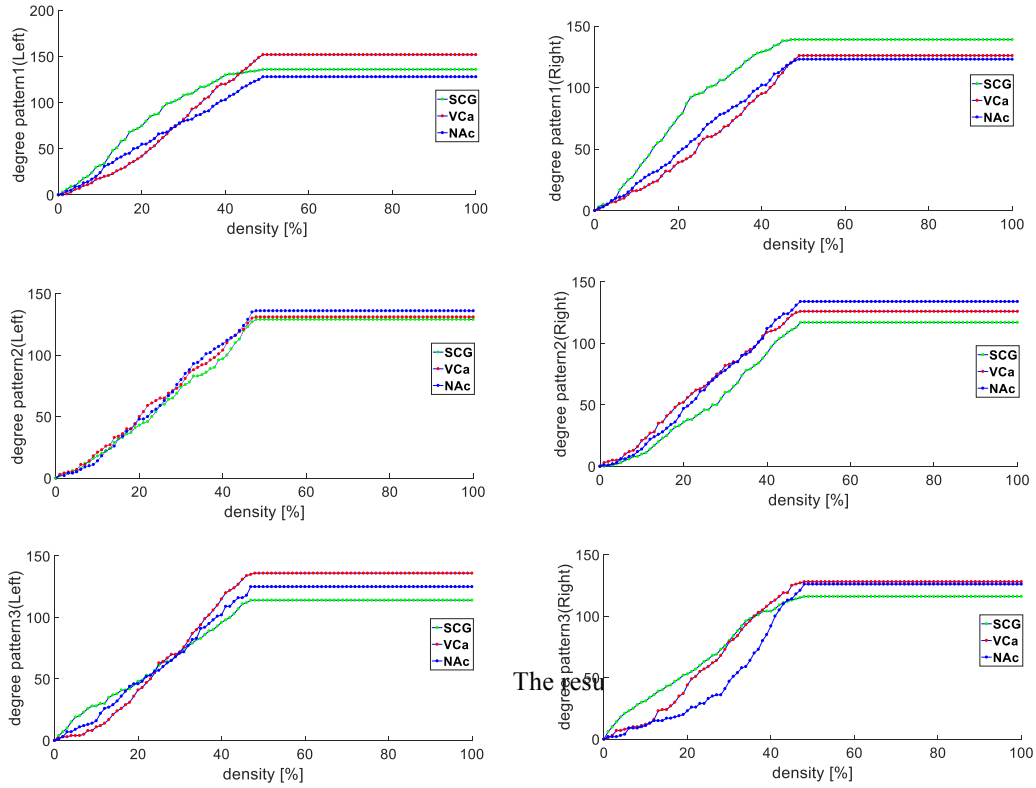

Figure 4. From top to bottom, three different patterns of the 'degree' values as a function of network density in MDD subjects are shown. SCG (green color), VCa (red color) and NAc (blue color).

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Fig. 3 presents two major important points:

1- The degree values were significantly higher in MDD subjects than in healthy subjects over a range of 5-30% intensity for VCa and for a density of 45 or higher for the left SCG.

2- There was no significant difference in the degree value between the two groups in the areas of the right SCG and the left and right NAc.

Fig.4 shows the patterns of the degree values vs. network density for three MDD patients. The values and patterns of the degree vs. network density were different in the two hemispheres in each patient and in SCG, VCa, and Nac areas Thus, unlike healthy subjects, MDD patients presented a high intersubject variability in both the value and pattern of degree.

IV. DISCUSSION

The aim of this study was to examine the functional connectivity of the three SCG, VCa, and NAc regions, which are popular DBS target regions for the treatment of MDD patients. Determining the best DBS target for each MDD patient is the major challenge for DBS treatment. Investigating the structural and functional connectivities of the brain can help determine the most appropriate DBS to address this clinical challenge.

Our results showed that the degree values were higher in the VCa and left SCG regions in MDD patients than in healthy subjects. In the theory graph, the higher degree of each region indicates the higher local processing ability, more interaction with other areas within the brain and greater functional connectivity. Thus, our findings may imply that the VCa and left SCG regions can be considered as appropriate DBS targets.

Our findings also indicated that the patterns of the functional connectivities were different in the left and right hemispheres in MDD patients. Also, the patterns of the degree values for SCG, VCa and NAc regions were different among MDD subjects. These findings demonstrate the high intersubject variability in functional connectivities of the brain. The clinical implication is that the appropriate DBS target is different for each MDD patient and must be individualized for each case.

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