

# Abnormal structural connectivity networks of patients with major depressive disorder: graph theoretical and network-based statistic analyses

Hao Hu<sup>1</sup>, Vincent Chin-Hung Chen<sup>2</sup>, Ming-Chou Ho<sup>3</sup>, Yeu-Sheng Tyan<sup>4,5</sup>, and Jun-Cheng Weng<sup>4,5</sup>

<sup>1</sup>Department of Radiology, First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu Province, China, <sup>2</sup>Department of Psychiatry, Chung Shan Medical University Hospital, Taichung, Taiwan, <sup>3</sup>Department of Psychology, Chung Shan Medical University, Taichung, Taiwan, <sup>4</sup>School of Medical Imaging and Radiological Sciences, Chung Shan Medical University, Taichung, Taiwan, <sup>5</sup>Department of Medical Imaging, Chung Shan Medical University Hospital, Taichung, Taiwan

## Introduction

Previously disrupted topological organization of major depressive disorder (MDD) patients regarding functional brain network has been declared by several studies [1-3]. However, only few studies mentioned about the particular structural brain network changes of this patient group [4, 5]. Diffusion tensor imaging (DTI) enables comprehensive whole brain mapping of the white matter tracts that link regions throughout the entire brain. Thus, our study aims to map the structural connectomic changes over MDDs based on DTI tractography using graph theoretical and network-based statistic analyses.

## Materials and Methods

The structural connectivity of 4 MDD patients and 3 healthy controls (HC) was obtained by DTI tractography. All patients were arranged for a brain MRI examination on a 1.5T imaging system (Signa HDxt, GE Medical System, USA) with an 8-channel head coil. DTI parameters included 37 axial contiguous slices; 128 x 128 matrix; 250 x 250 mm<sup>2</sup> FOV; 4 mm slice thickness; repetition time = 10500 ms; echo time = 120 ms; 25 diffusion orientations; and b-values of 0, 1000, 1500 and 2000 s/mm<sup>2</sup>.

Each participant's echo planar image was spatially normalized to the Montreal Neurological Institute (MNI) T2W template using parameters determined from the normalization of the diffusion null image to T2 template using SPM8 (<http://www.fil.ion.ucl.ac.uk/spm>). Images were resampled with a final voxel size of 2 x 2 x 2 mm<sup>3</sup>. DSI Studio (<http://dsi-studio.labsolver.org>) was employed for whole-brain tractography with FA threshold of 0.15 and max angle of 70°. Then the individual structural connectivity matrix (fiber number based weighted undirected networks) of each participant with size of 90 x 90 could be output followed by importation of ROIs based on the Automated Anatomical labeling (AAL).

Graph theoretical and network-based statistic (NBS) analyses were then applied to investigate systematical alteration of whole brain structural topological organization and structural connectivity in MDDs. Graph theoretical analysis was performed on the interregional connectivity matrix by using Graph Analysis Toolbox (GAT) (<http://ncnl.stanford.edu/tools.html>). A user-defined sparsity (S%) of 8% to 25% in steps of 1% was applied. The topological measures of structural brain networks were calculated, including clustering coefficient (C), characteristic path length (L), normalized clustering coefficient ( $\gamma$ ), normalized characteristic path length ( $\lambda$ ), small-worldness index ( $\sigma$ ), local efficiency ( $E_{local}$ ), global efficiency ( $E_{global}$ ), assortativity, transitivity, and modularity. Both P value < 0.05 for the permutation test in graph theoretical analyses and the two-sample t test in NBS were considered to indicate statistical significance. The BrainNet viewer (<http://www.nitrc.org/projects/bnv/>) was applied to visualize the significant sub-networks revealed from NBS.

## Results and Discussions

Small world topology was observed in both HC and MDD groups. Significantly altered topological measures were further revealed in MDD patients using the permutation test. In particular, higher L,  $\gamma$ ,  $\lambda$ ,  $\sigma$ , modularity (P<0.05) and lower  $E_{global}$ , assortativity (P<0.05) were obtained in MDDs compared to HCs, while no significant difference of C,  $E_{local}$  and transitivity between groups was found (P>0.05) (Fig. 1). A disrupted sub-network consisted of 21 regions and 24 edges was identified by the NBS (P=0.023, corrected). The edges included the connections from the left insula and left putamen to left rolandic operculum, left heschl, left superior temporal gyrus and left supramarginal gyrus; from left inferior parietal lobule to bilateral thalamus and left postcentral gyrus; from right thalamus to left thalamus, left putamen and right amygdala; from right middle cingulate cortex to left caudate and right pallidum; from left anterior cingulate cortex to right caudate and right medial orbitofrontal cortex; from left caudate to right anterior cingulate cortex and right medial orbitofrontal cortex; and from left olfactory to left caudate, left putamen, left pallidum and left amygdala (Fig. 2). Notably, the sub-network exhibited all decreased connections in MDD patients compared to HCs.

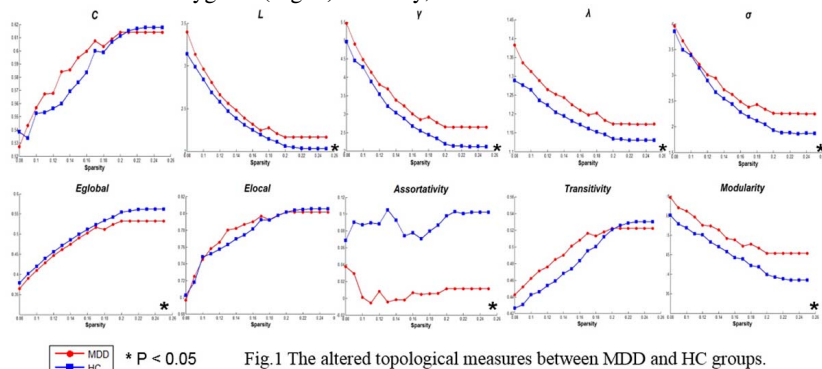


Fig.1 The altered topological measures between MDD and HC groups.

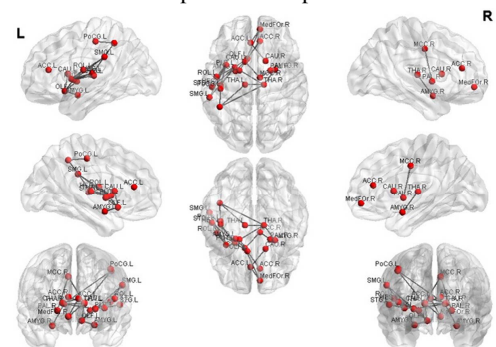


Fig.2 The disrupted sub-network identified by the NBS

The first major finding of present study was the altered whole-brain structural topological organization in MDD patients. The detected higher L and lower  $E_{global}$  among patient group indicated lower global integration of structural brain network of MDD patients, while no definite change over local segregation might be considered due to the non-significant between-group measures of C,  $E_{local}$  and transitivity. Meanwhile, the especially decreased and negative assortativity coefficient of patient group further indicated the poorer network resilience as compared to HCs. The second major finding in our study was the altered structural connectivity mainly regarding bilateral default mode network (DMN) and frontal-limbic regions, both of which were considered as core regions associated with MDD [4, 5]. The decreased structural connectivity among these regions causing possibly local dysfunction might reflect the underlying mechanism in MDD patients.

## Conclusions

Meaningfully altered topological organization of structural connectivity network could be achieved based on DTI tractography, indicating disturbance of the optimal balance between local segregation and global integration in MDD patients. Meanwhile, decreased structural connectivity regarding areas of default mode network and frontal-limbic regions might facilitate understanding of the underlying mechanism in the disorder.

## References

- [1] Guo H, et al., Neural Regen Res. 2014; 9: 153-63.
- [2] Zhu X, et al., Bio Psychiatry. 2012; 71: 611-7.
- [3] Ma C, et al., PLoS One. 2012; 7: e45263.
- [4] Korgaonkar MS, et al., Biol Psychiatry. 2014; 76: 567-74.
- [5] Long Z, et al., Prog Neuropsychopharmacol Biol Psychiatry. 2014; 56: 18-26.