PIBB 生物化学与生物物理进展
Progress in Biochemistry and Biophysics
2018, 45(1): 43~50
www.pibb.ac.cn

The Changes of Brain Network Efficiency in Patients With Major Depressive Disorder Estimated by Intrinsic Functional Connectivity*

LI Huai-Zhou[1, 2, 3, 4)], ZHOU Hai-Yan[1, 3, 4)], YANG Yang[2, 3, 4, 5)], YANG Xiao-Jing[1, 2, 3, 4)],
WANG Hai-Yuan[1, 2, 3, 4)], ZHONG Ning[1, 2, 3, 4, 5)**]

([1)] *Faculty of Information Technology, Beijing University of Technology, Beijing* 100124, China;
[2)] *Beijing Advanced Innovation Center for Future Internet Technology, Beijing University of Technology, Beijing* 100124, China;
[3)] *Beijing International Collaboration Base on Brain Informatics and Wisdom Services, Beijing* 100124, China;
[4)] *Beijing Key Laboratory of MRI and Brain Informatics, Beijing* 100124, China;
[5)] *Department of Life Science and Informatics, Maebashi Institute of Technology, Maebashi* 371-0816, *Gunma*, Japan)

Abstract This study focused on the changes of network topological efficiency under the condition of maximizing the intrinsic functional connectivity, and explored the relationships between altered topological efficiency and depressive psychopathology. For this purpose, we collected the resting-state functional MRI data from 20 major depressive disorder (MDD) patients and 20 healthy control (HC) individuals with matching of age, gender and education level. Graph theory analysis showed that the patients with MDD exhibited significantly reduced nodal efficiency in the left parahippocampal gyrus, right amygdala, left heschl and left temporal pole (middle temporal gyrus) compared with the HC group. The reduced nodal efficiency indicated that the function of transmitting information to other regions was weakened in MDD patients. The local efficiency of the left medial superior frontal gyrus, left orbital superior frontal gyrus, right rectus, left amygdala, right superior parietal gyrus, left thalamus, and left temporal pole (middle temporal gyrus) were also significantly reduced. And the local efficiency of the left medial superior frontal gyrus, left amygdala, left thalamus had negative correlation with PHQ-9. The reduced local efficiency implied that the ability of information transmission at the local level was damaged in the depressed brain network. These results suggested that the prefrontal-thalamo-limbic system involving affective processing was damaged in MDD patients. Our findings might provide a potential biomarker for the clinical diagnosis of depressed patients.

Key words major depressive disorder, resting state functional magnetic resonance imaging, network efficiency, graph theory
DOI: 10.16476/j.pibb.2017.0166

Major depressive disorder (MDD) is a mental disorder that results from abnormal interactions among brain regions engaged in regulating both emotion and cognition [1-2]. Recently, the different methodologies have been used to reveal the neural mechanisms in MDD patients. In particular, the graph theory provides a conceptual framework for identifying the characteristics of complex network such as functional or structural brain networks[3].

The abnormal nodal properties were found in many brain regions including the frontal lobe (orbital part of superior frontal gyrus, middle frontal gyrus,

*This work was supported by grants from The National Basic Research Program of China (2014CB744600), The National Natural Science Foundation of China (61420106005, 61272345), Open Research Fund of Beijing Key Laboratory of Magnetic Resonance Imaging and Brain Informatics (2014CGZC03), Beijing Municipal Natural Science Foundation (4164080), and International Science & Technology Cooperation Program of China (2013DFA32180).
**Corresponding author.
Tel: 86-27-265-7366, E-mail: zhong@maebashi-it.ac.jp
Received: May 1, 2017 Accepted: August 30, 2017

dorsolateral prefrontal cortex, parietal lobe (inferior parietal lobule), temporal lobe (hippocampus, middle temporal gyrus, fusiform gyrus), occipital lobe (lingual gyrus, calcarine fissure, precuneus) and subcutaneous region (amygdala, putamen, insula, thalamus, striatum) in the functional brain networks of MDD patients[4-5]. The profound insights about the neural mechanisms in depression were provided, highlighting aberrant function and interaction of cortical and subcortical to convey cognitive and emotional information. However, the results were not entirely inconsistent. One possible reason was the difference in the definition of edges by partial correlation coefficient or Pearson correlation coefficient[4, 6]. And the number of edges in the MDD group and control group was strictly equal by the threshold of the descending order correlation coefficients [7-8]. This method partially ignored the differences in the intrinsic functional connectivity network between the two groups. The altered functional connectivity has been found in the default mode network, salience network, affective network and limbic brain regions in MDD patients[1].

Here, we used the statistical values of Pearson correlation as the threshold of the binary network to maximize the intrinsic functional connectivity in the MDD and healthy cohorts. The differences of network efficiency were examined between the two groups. We hypothesized that both nodal efficiency and local efficiency were reduced in the network of MDD patients due to the impairment transmission of cognitive or emotion information in these areas. This provides a new perspective for understanding the pathologic mechanism of depression.

1　Materials and methods

1.1　Subjects

This study recruited 22 patients with MDD aged 21–58 years among outpatients from Beijing Anding Hospital, Capital Medical University. Two patients were excluded because of excessive head displacement and claustrophobia (see Data preprocessing). Hamilton Depression Rating Scale 17 Items (HAMD-17) was used to assess the depression severity in depressive disorders. Twenty healthy control (HC) individuals aged 21–57 years with matching of age, gender and education level were recruited from the surrounding community. The Mini International Neuropsychiatric Interview 6.0 (MINI 6.0) was used for clinical diagnosis. All MDD patients met the major depression criteria determined by Diagnostic and Statistical Manual of Mental Disorder, 4th ed. (DSM-IV) [9]. Common criteria for inclusion: (1) right handedness; (2) age of 18–65 years; (3) primary school or higher education; (4) no history of alcohol and drug abuse. Before scanning, the Patient Health Questionnaire 9 Items (PHQ-9) and Trait Anxiety Inventory (T-AI) were used in both groups to assess the level of depression and anxiety respectively. The demographic and clinical status information of individuals are listed in Table 1. This study was approved by Ethics Committee of Beijing Anding Hospital and Xuanwu Hospital of Captial Medical University, and the informed consent was signed by each subject.

Table 1　Demographic data and clinical characteristics of participants

	MDD(n=20)		HC(n=20)		Analysis	
	Mean	*SD*	Mean	*SD*	t	P
Age(years)	35.35	10.73	34.30	10.11	1.63	0.119
Sex(Male/Female)	8/12	–	8/12	–	–	–
Education(years)	13.10	3.21	13.30	3.45	–0.354	0.727
HAMD-17	15.55	7.15	–	–	–	–
PHQ-9	20.35	5.84	12.60	3.15	4.68	< 0.001
T-AI	51.75	9.32	37.20	9.32	4.94	< 0.001

MDD: Major depressive disorder, HC: Healthy controls, SD: Standard deviation, HAMD-17: Hamilton Depression Rating Scale 17 Items, PHQ-9: Patient Health Questionnaire 9 Items, T-AI : Trait Anxiety Inventory. Significance was evaluated using two-tailed paired t-test (P < 0.05).

1.2　MRI data acquisition

The brain images were acquired using Siemens Trio 3.0T MRI scanner (Siemens Medical System, Erlanger, Germany) with a standard head coil at the

Xuanwu Hospital of Captial Medical University. In order to limit the head displacement and scanning noise, the headphones and foam pads were used separately during the MRI data acquisition process. Meanwhile, all subjects were required to lie quietly and keep their eyes open, without thinking any specific problems. First, the brain structural images were acquired by T1-weighted 3D magnetization prepared rapid gradient echo sequence with the following scan parameters: repetition time (TR) = 1 600 ms, echo time (TE) = 3.28 ms, inversion time (TI) = 800 ms, field of view (FOV) = 256×256 mm^2, flip angle = 9°, slice thickness = 1 mm, inter-slice gap = 0 mm, total number of slices = 192, resolution = 1×1×1 mm^3. After serious examination, the radiologist confirmed that the brain structure and image quality were excellent. The echo-planar imaging sequence was used to scan the rs-fMRI data, and the parameters are as follows: TR = 2 000 ms, TE = 31 ms, FOV = 240 × 240 mm^2, flip angle = 90°, slice thickness = 4 mm, inter-slice gap = 0.8 mm, total number of slices = 30, resolution = 3.75× 3.75×4 mm^3. A total of 152 volumes were obtained in 5 min and 10 s. After strict examinations, the radiologist confirmed that the quality of the collected structural and functional brain images was suitable for the following analyses.

1.3 Data preprocessing

All the image data were preprocessed using SPM8 package (Wellcome Trust Centre for Neuroimaging, University College London, United Kingdom, http://www.fil.ion.ucl.ac.uk/spm) and Data Processing Assistant for Resting-State fMRI(http://www.rfmri.org/DPARSF)[10]. The first 10 time-points were discarded to achieve the dynamic equilibrium. The slice timing differences were corrected for the remaining 142 volumes. And the six parameter rigid body model was used to correct the head motion to align them with their median volume of the run. If the head movement exceeded 2 mm or the rotation greater than 2° in any direction, the image data of this subject would be excluded. Then the images were spatially normalized into standard Montreal Neurological Institute (MNI) space, and were resampled to 3×3×3 mm^3. After that, a 6 mm full-width at half-maximum Gaussian kernel was used for spatial smoothing. Considering the low-frequency drift and high-frequency noise, the time domain bandpass filtering ($0.01 < f < 0.08$ Hz) was applied[11-12]. Due to the long time scanning, the linear trend was also removed. Finally, the six motion parameters, cerebrospinal fluid signals and white matter were regressed out to reduce confounding factors.

1.4 Construction and analysis of functional brain network

A total of 90 nodes (45 in each hemisphere) of the functional brain network are determined by the Automated Anatomical Labeling (AAL) template provided by Montreal Neurological Institute[13]. After data preprocessing, the signal for each nodal region was calculated by averaging the time series of all voxels within the AAL region. By calculating the Pearson correlation coefficient of all pairs of nodal region signals, a 90-by-90 functional connectivity matrix was generated for each individual[14]. Then the maximized intrinsic functional connectivity of all subjects were obtained by threshold at $P < 0.05$ (Bonferroni corrected). Finally, the graph theoretical network analysis tool box (http://www.nitrc.org/projects/gretna) implemented in MATLAB was used to calculate the network properties including nodal and local efficiency[15].

Local efficiency was used to measure the ability to special information processing in the functional brain network[16-17]. The local efficiency of any node i is given by Equation (1). The local efficiency of the whole network is obtained by Equation (2), which is an indicator of the segregated or professional information processing of the whole brain,

$$E_{\mathrm{loc}}(i)=\frac{1}{N_{G_{\mathrm{sub}}(i)}(N_{G_{\mathrm{sub}}(i)}-1)}\sum_{m\neq n\in G_{\mathrm{sub}}(i)}\frac{1}{D_{\min}(m,\ n)} \quad (1)$$

$$E_{\mathrm{loc}}=\frac{1}{N}\sum_{i\in G}E_{\mathrm{loc}}(i) \quad (2)$$

where $G_{\mathrm{sub}}(i)$ is the subgraph of neighbors of node i; $N_{G_{\mathrm{sub}}(i)}$ is the total number of nodes in the subgraph; $D_{\min}(m,\ n)$ is the shortest path length that is the minimum number of edges traversed to get from a node m to another node n.

Nodal efficiency measures the ability of a given node i to transmit information with all other nodes in a network. The larger node efficiency indicates higher integrity in the brain[18]. The nodal efficiency and global efficiency are given by Equation (3) and Equation (4) respectively

$$E_{\mathrm{node}}(i)=\frac{1}{N-1}\sum_{i\neq j\in G}\frac{1}{D_{\min}(i,\ j)} \quad (3)$$

$$E_{\mathrm{glob}}=\frac{1}{N}\sum_{i\in G}E_{\mathrm{node}}(i) \quad (4)$$

which play key roles in the measures of information transmission of the whole network.

In order to investigate whether significant intergroup differences existed in the network efficiency, the statistical comparisons of nodal and global properties were conducted by using two-tailed paired *t*-test and the statistical threshold was set at $P < 0.05$. Moreover, using Pearson correlation coefficient, we assessed the relationships between these differences of network attributes and clinical characteristics including HAMD-17, PHQ-9, and T-AI scores.

2 Results

The demographic and neuropsychological data of the two groups were summarized in Table 1. No significant differences were found in age, gender and education level between the MDD and HC groups ($P > 0.05$). Compared with HC group, the MDD group showed significantly higher scores in PHQ-9 and T-AI respectively ($P < 0.05$).

Compared with the HC group, the patients with MDD exhibited significantly reduced nodal efficiency in the left parahippocampal gyrus, right amygdala, left heschl and left temporal pole (middle temporal gyrus) as shown in Figure 1 ($P < 0.05$). Nodal efficiency measures the ability of information propagation between a given node and the rest of the nodes in a network. Higher nodal efficiency is indicative of higher integration in the brain. This reduced nodal efficiency indicates that the function of transmitting information to other regions is weakened in MDD. Last, there was no significant difference in the global efficiency between the two groups.

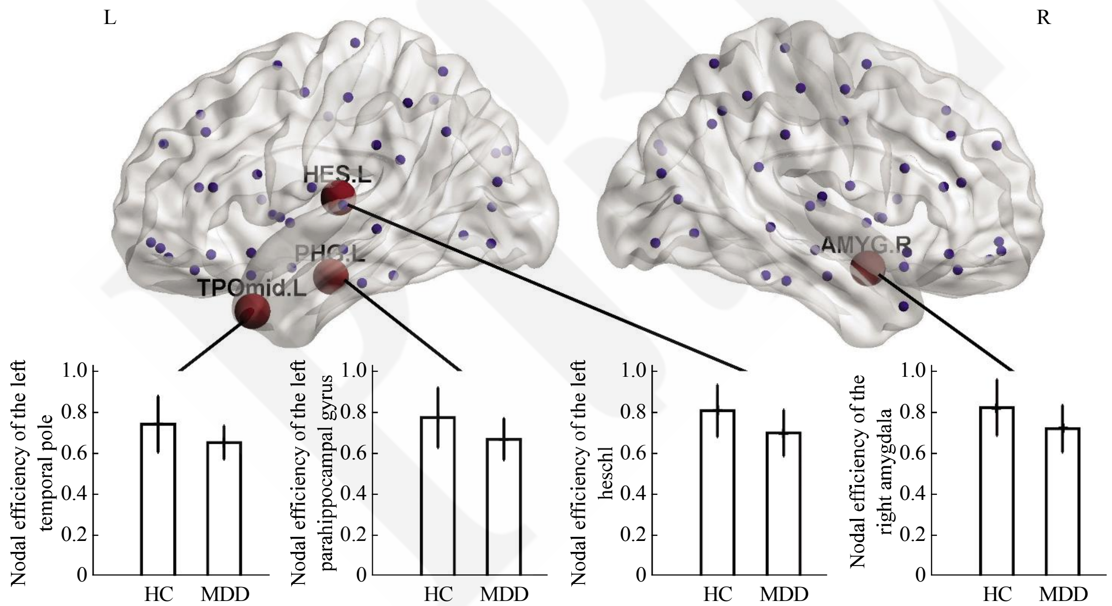

Fig. 1　Regions showing a significant difference in nodal efficiency between major depressive disorder (MDD) patients and healthy controls (HC)

HES.L: Left heschl; PHC.L: Left parahippocampal gyrus; TPOmid.L: Left temporal pole (middle temporal gyrus); AMG.R: Right amygdala.

As shown in Figure 2, the local efficiency of the left medial superior frontal gyrus, left orbital superior frontal gyrus, right rectus, left amygdala, right superior parietal gyrus, left thalamus, and left temporal pole (middle temporal gyrus) were also significantly reduced ($P < 0.05$). The local efficiency measures the ability of information transmission of a network at the local level. And there was no significant difference in the local efficiency of the whole brain network between the two groups.

The correlation analysis showed that the local efficiency of the left medial superior frontal gyrus, left amygdala, left thalamus had significantly negative correlation with PHQ-9 scores(Figure 3)($P < 0.05$). No other significantly correlation was found in this study.

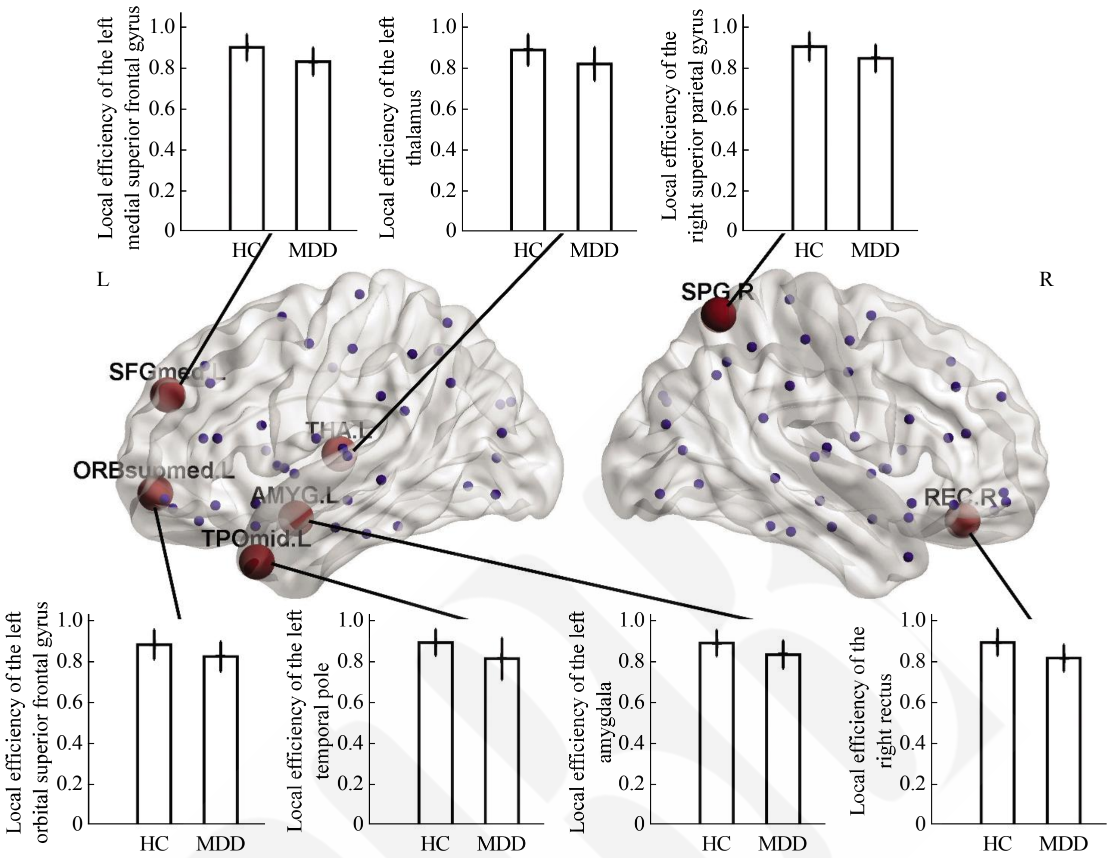

Fig. 2 Regions showing a significant difference in local efficiency between major depressive disorder (MDD) patients and healthy controls (HC)

SPGmed.L: Left medial superior frontal gyrus; THA.L: Left thalamus; ORBsupmed.L: Left orbital superior frontal gyrus; AMG.L: Left amygdala; TPOmid.L: Left temporal pole (middle temporal gyrus); SPG.R: Right superior parietal gyrus; REC.R: Right rectus.

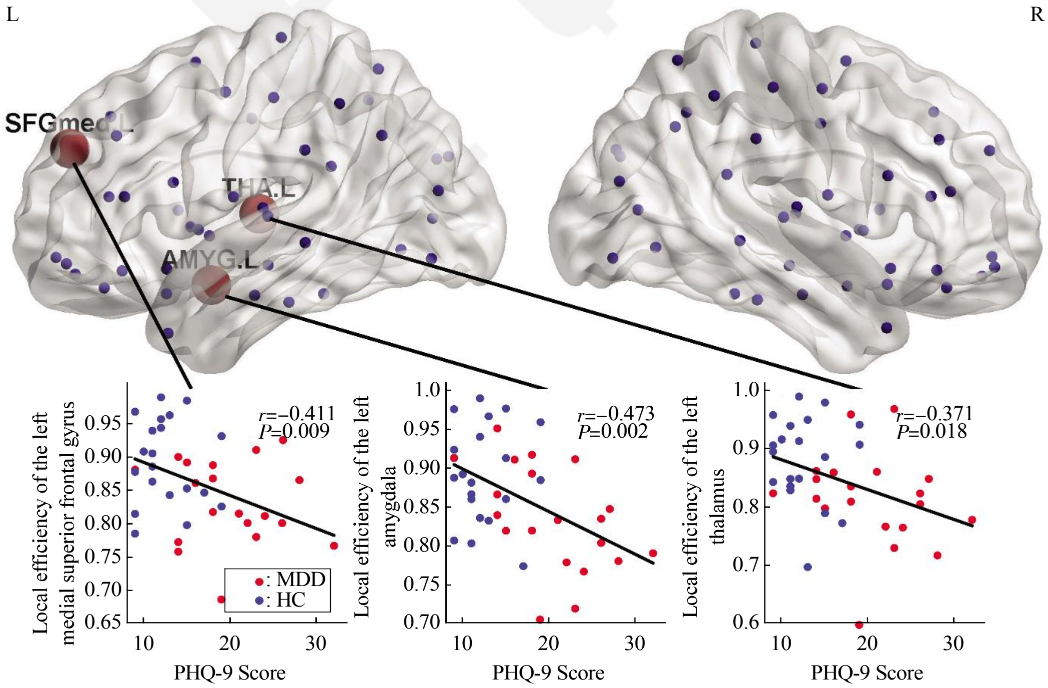

Fig. 3 Regions showing significant correlation between local efficiency and the scores of Patient Health Questionnaire 9-Item (PHQ-9)

SPGmed.L: Left medial superior frontal gyrus; AMYG.L: Left amygdala; THA.L: Left thalamus.

3 Discussion

The present study examined the network efficiency of functional brain networks in MDD patients and healthy controls. The results revealed that MDD decreased nodal efficiency or local efficiency in limbic regions including the right amygdala, left parahippocampal gyrus, left amygdala, left temporal pole (middle temporal gyrus) and left orbital superior frontal gyrus, implying the transmission of affective and cognitive information was disturbed. Most of the changes in the regional properties are consistent with previous findings [19-21]. However, inconsistent with previous studies was that higher node efficiency or local efficiency in MDD patients was not found. It is likely because of the difference in the threshold method of the binary matrix. These results demonstrated that the binary matrices based on the threshold of statistical values are more realistic to reflect the difference in the intrinsic functional network between the two groups.

It is well known that the human brain tends to maximize efficiency at a minimal cost to perform effective information processing. However, the network efficiency in MDD patients was lower in some regions involving affective and cognitive processing compared with the healthy controls. The amygdala was a center for emotional processing, fear and motivation[3]. Nevertheless, the nodal efficiency in left amygdala and local efficiency in right amygdala decreased in MDD patients respectively. The nodal efficiency indicted the importance of node in the whole network. And the local efficiency measured the ability of special information processing. This indicated that the amygdala has been subjected to pathological attack in MDD patients. As previous studies suggested that emotional stimuli was projected to amygdala through the transfer of thalamus [22]. The decrease in the nodal efficiency of left parahippocampal gyrus might be supported by reduced ALFF, fALFF and ReHo in previous studies [23-25], indicative of a longer average path length between the parahippocampal gyrus and the rest of the network. The medial superior frontal gyrus and orbital superior frontal gyrus are key structures in reward circuit. The links between the superior and medial regions of the orbitofrontal cortex in the emotion and reward circuit significantly altered in depressed patients[5]. To verify the differences in these regions, we made correlation analysis between network efficiency and clinical features. The results demonstrated that the local efficiency of the left medial superior frontal gyrus, left amygdala and left thalamus were significantly negative correlation with the PHQ-9 scores. Our finding further shed light on the abnormality of the affective processing system of MDD from the perspective of network.

In conclusion, our findings support the hypothesis that the nodal efficiency and local efficiency had reduced in prefrontal-thalamo-limbic systems involving affective processing [26]. These results provided new evidences for a better understanding of the underlying pathophysiology of depression.

Acknowledgements The data was collected in the Xuanwu Hospital and Beijing Anding Hospital of Captial Medical University. We thank Dr. ZHANG Mo and Dr. TIAN Teng-Fei for support in data acquisition.

References

[1] Dichter G S, Gibbs D, Smoski M J. A systematic review of relations between resting-state functional-MRI and treatment response in major depressive disorder. Journal of Affective Disorders, 2015, **172**: 8-17

[2] Smith D F. Systematic review of an emerging trend in china: resting-state functional connectivity in major depressive disorder. The Journal of Neuropsychiatry and Clinical Neurosciences, 2015, **27**(2): 104-111

[3] Mears D, Pollard H B. Network science and the human brain: Using graph theory to understand the brain and one of its hubs, the amygdala, in health and disease. Journal of Neuroscience Research, 2016, **94**(6): 590-605

[4] Zhang J, Wang J, Wu Q, *et al*. Disrupted brain connectivity networks in drug-naive, first-episode major depressive disorder. Biological Psychiatry, 2011, **70**(4): 334-342

[5] Tao H, Guo S, Ge T, *et al*. Depression uncouples brain hate circuit. Molecular Psychiatry, 2013, **18**(1): 101-111

[6] Lord A, Horn D, Breakspear M, *et al*. Changes in community structure of resting state functional connectivity in unipolar depression. PloS One, 2012, **7**(8): e41282

[7] Peng D, Shi F, Shen T, *et al*. Altered brain network modules induce helplessness in major depressive disorder. Journal of Affective Disorders, 2014, **168**: 21-29

[8] Jin C, Gao C, Chen C, *et al*. A preliminary study of the dysregulation of the resting networks in first-episode medication-naive adolescent depression. Neuroscience Letters, 2011, **503**(2): 105-109

[9] Sheehan D V, Sheehan K H, Shytle R D, *et al*. Reliability and validity of the mini international neuropsychiatric interview for children and adolescents (MINI-KID). J Clin Psychiatry, 2010,

71(3): 313−326

[10] Yan C, Zang Y. DPARSF: A MATLAB toolbox for "pipeline" data analysis of resting-state fMRI. Frontiers in Systems Neuroscience, 2010, **4**(13): 13

[11] Lowe M J, Mock B J, Sorenson J A. Functional connectivity in single and multislice echoplanar imaging using resting-state fluctuations. NeuroImage, 1998, **7**(2): 119−132

[12] Birn R M, Murphy K, Bandettini P A. The effect of respiration variations on independent component analysis results of resting state functional connectivity. Human Brain Mapping, 2008, **29**(7): 740−750

[13] Tzourio-Mazoyer N, Landeau B, Papathanassiou D, *et al*. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. NeuroImage, 2002, **15**(1): 273−289

[14] Ye M, Yang T, Qing P, *et al*. Changes of functional brain networks in major depressive disorder: a graph theoretical analysis of resting-state fMRI. PloS One, 2015, **10**(9): e0133775

[15] Wang J, Wang X, Xia M, *et al*. GRETNA: a graph theoretical network analysis toolbox for imaging connectomics. Frontiers in Human Neuroscience, 2015, **9**(386): 386

[16] Latora V, Marchiori M. Economic small-world behavior in weighted networks. The European Physical Journal B - Condensed Matter and Complex Systems, 2003, **32**(2): 249−263

[17] Achard S, Bullmore E. Efficiency and cost of economical brain functional networks. PLoS Computational Biology, 2007, **3**(2): e17

[18] Onoda K, Yamaguchi S. Dissociative contributions of the anterior cingulate cortex to apathy and depression: Topological evidence from resting-state functional MRI. Neuropsychologia, 2015, **77**: 10−18

[19] Guo H, Cheng C, Cao X, *et al*. Resting-state functional connectivity abnormalities in first-onset unmedicated depression. Neural Regeneration Research, 2014, **9**(2): 153−163

[20] Ye M, Qing P, Zhang K, *et al*. Altered network efficiency in major depressive disorder. BMC Psychiatry, 2016, **16**(1): 450

[21] Meng C, Brandl F, Tahmasian M, *et al*. Aberrant topology of striatum's connectivity is associated with the number of episodes in depression. Brain: A Journal of Neurology, 2014, **137** (Pt 2): 598−609

[22] Drevets W C. Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features of mood disorders. Current Opinion in Neurobiology, 2001, **11** (2): 240−249

[23] Guo W B, Liu F, Xue Z M, *et al*. Abnormal neural activities in first-episode, treatment-naive, short-illness-duration, and treatment-response patients with major depressive disorder: a resting-state fMRI study. Journal of Affective Disorders, 2011, **135**(1−3): 326−331

[24] Guo W, Liu F, Zhang J, *et al*. Dissociation of regional activity in the default mode network in first-episode, drug-naive major depressive disorder at rest. Journal of Affective Disorders, 2013, **151** (3): 1097−1101

[25] Liu F, Guo W, Liu L, *et al*. Abnormal amplitude low-frequency oscillations in medication-naive, first-episode patients with major depressive disorder: a resting-state fMRI study. Journal of Affective Disorders, 2013, **146**(3): 401−406

[26] Lui S, Wu Q, Qiu L, *et al*. Resting-state functional connectivity in treatment-resistant depression. The American Journal of Psychiatry, 2011, **168**(6): 642−648

基于内在功能连接推定抑郁症脑网络效率的改变 *

李淮周 [1,2,3,4]　周海燕 [1,3,4]　杨　阳 [2,3,4,5]　杨孝敬 [1,2,3,4]
王海渊 [1,2,3,4]　钟　宁 [1,2,3,4,5]**

([1] 北京工业大学信息学部，北京 100124；[2] 北京工业大学未来网络科技高精尖创新中心，北京 100124；
[3] 脑信息智慧服务北京市国际科技合作基地，北京 100124；[4] 磁共振成像脑信息学北京市重点实验室，北京 100124；
[5] *Department of Life Science and Informatics*, *Maebashi Institute of Technology*, *Maebashi* 371-0816, *Gunma*, Japan)

摘要　本文研究了在保留最大化内在功能连接条件下抑郁症患者脑网络效率的改变，并探索了改变的拓扑效率和抑郁症病理学之间的关系．为此，我们收集了 20 例抑郁症患者和 20 例在年龄、性别和教育水平相匹配的健康被试的静息态功能磁共振图像数据．图论分析显示，与健康对照组比较，抑郁症患者的节点效率减少在左海马旁回、右杏仁核，左颞横回和左颞极(颞中回)减少．减少的节点效率表明，在抑郁症患者脑网络中这些区域传送信息到其他区域的能力减弱．此外，发现局部效率降低在左内侧额上回、左眶部额上回、右回直肌、左杏仁核、右顶上回、左丘脑和左颞极(颞中回)．并且发现左内侧额上回、左杏仁核、左丘脑与 PHQ-9 得分呈负相关．降低的局部效率表明抑郁症患者脑网络中这些区域的局部网络信息传送能力受到抑制．这些结果进一步确认在抑郁症患者中涉及情感信息处理的前额 - 丘脑 - 边缘区域被破坏．我们的发现为抑郁症病人的辅助诊断提供了新的潜在生物学标记物．

关键词　抑郁症，静息态功能磁共振，网络效率，图论
学科分类号　R445.2，O231.5　　**DOI**: 10.16476/j.pibb.2017.0166

* 国家重点基础研究发展计划资助(2014CB744600), 国家自然科学基金资助项目(61420106005, 61272345), 磁共振成像脑信息学北京市重点实验室资助(2014CGZC03), 北京市自然科学基金(4164080)和国家国际科技合作专项资助(2013DFA32180).

** 通讯联系人.
Tel: 027-265-7366, E-mail: zhong@maebashi-it.ac.jp

收稿日期：2017-05-01，接受日期：2017-08-30