Peripheral Interleukin-18 Is Negatively Correlated With Abnormal Brain Activity In Patients With Depression: A Resting-State fMRI Study

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Abstract

Background: Interleukin-18 (IL-18) may participate in the development of major depressive disorder, but the specific mechanism remains unclear. This study aimed to explore whether IL-18 correlates with areas of the brain associated with depression.

Methods: Using a case-control design, 68 subjects (34 patients and 34 healthy controls) underwent clinical assessment, blood sampling, and resting-state functional Magnetic Resonance Imaging (fMRI). The total Hamilton depression-17 (HAMD-17) score was used to assess depression severity. Enzyme-linked immunosorbent assay (ELISA) was used to detect IL-18 levels. Rest-state fMRI was conducted to explore the spontaneous brain activity.

Results: The level of IL-18 was higher in patients with depression in comparison with health controls. IL-18 and degree centrality (DC) were negatively correlated with the left posterior cingulate gyrus in the depression patient group, but no correlation was found in the healthy control group.

Conclusion: This study suggests the involvement of IL-18 in the pathophysiological mechanism for depression and interference with brain activity.

1. Introduction

Depression is a very common disease with a global prevalence of 4% [1] and lifetime prevalence in China of 6.8% [2]. Although the exact mechanism of depression remains unknown, the classic monoamine, glutamate, hypothalamic-pituitary-adrenal axis, and neurotrophic hypotheses propose several pathophysiological etiologies. However, these theories have not fully revealed the pathogenesis of depression. Several studies suggest the important role of inflammatory immune factors in depression development.

Interleukin-18 (IL-18) is an inflammatory factor involved in immune function regulation. Prior studies suggest the involvement of IL-18 in depression-like behaviors in mice [3]. Additionally, several clinical studies report increased IL-18 peripheral blood levels in patients with depression in comparison to healthy individuals [4-7]. Furthermore, our prior study demonstrated the involvement of IL-18 in the mechanism for post-stroke depression (Wu et al., 2020). However, the role of IL-18 remains unclear in depressive behaviors and warrants further investigation.

Resting-state brain imaging can be used to indirectly analyze spontaneous brain activity changes during non-task activities through detection of the blood oxygen concentration – a method used widely in exploring depression etiologies. Degree centrality (DC) is a metric that reflects the importance of specific brain node or area relative to the whole brain network [8, 9]. In recent years, DC has been used to study characteristics of brain imaging in depression. Several resting-state imaging studies have demonstrated DC abnormalities in patients with depression [10, 11]. However in these studies, the association between IL-18 and the functional activity of depression-related brain areas was not explored.

In the current study, we measured serum IL-18 levels and analyzed its relationship with depression-related brain region activity in patients and healthy controls. To our knowledge, this is the first study to explore the correlation between IL-18 and DC.

2. Methods

2.1. Patients and controls

A case-control study was conducted from June 2019 to November 2020 in the Guangji Hospital affiliated with Soochow University (Suzhou City, China). Recruited patients met the following inclusion criteria: (1) inpatient adults (20 to 65 years-old) and (2) depressive diagnosis meeting DSM-5 criteria. Subjects were excluded if they were: (1) unable to undergo MRI scanning, (2) left-handed, (3) pregnant females, (4) febrile within 2 weeks, (5) subjects with immune dysfunction, or (5) subjects with organic psychosis.

Healthy volunteers were recruited as controls through matching demographic data on enrolled patients. These volunteers were (1) adults (20 to 65 years old) who did not meet any DSM-5 diagnostic criteria and (2) of normal intelligence. Subjects were excluded if they were: (1) unable to undergo MRI scanning, (2) left-handed, (3) pregnant females, (4) febrile within 2 weeks, (5) subjects with immune dysfunction, or (5) subjects with substance abuse or dependence history within one year, (6) subjects with a HAMD-17 score greater than or equal to 8 points, or (7) subjects with mental or genetic neurological disorders in first-degree relatives.

This study was approved by the ethics committee of the Guangji Hospital affiliated to Soochow University (ethics number 2017YFE0103700). All participants provided the written informed consent. All study procedures were in compliance with the Declaration of Helsinki.

2.2. Blood sampling and ELISA test

Fasting peripheral blood was collected from the enrolled patients and controls. After centrifugation at 3000 rpm for 10 minutes, the supernatant was stored at -80 °C and the ELISA test was performed according to the kit manual to obtain the IL-18 concentration.

2.3. Clinical assessment

The Chinese HAMD-17 Depression Rating Scale was used to assess depression due to good reliability and validity [12]. Subjects with depressive disorders were defined as having a HAMD-17 score no less than 8 points. Clinical assessments were completed by the same psychiatrist.

2.4. Image data collection

Resting-state imaging data was collected using Siemens SKYPE 3.0T MRI equipment. Prior to resting-state imaging, patients were scanned for anatomical positioning using parameters of 192 slices, 1 mm slice thickness, TR of 2530.0 ms, TE of 2.98 ms, FOV of 256 mm x 256 mm, and an element size of 1.0

mm x 1.0 mm x 1.0 mm. EPI sequence was used to acquire rs-MRI BOLD signal with parameters of 32 layers, 3.5 mm layer thickness, TR 2000.0 ms, TE 30.0 ms, FOV 224 mm x 224 mm, 64 x 64 matrix, 90° flip angle, and voxel size of 3.5 mm x 3.5 mm x 3.5 mm.

2.5. Image data pre-processing

Data was pre-processed by the cortex-based resting-state fMRI data analysis package DPABISurf developed by DPABI/DPABISurf. DPABISurf calls fMRIPrep to pre-process the structural and functional magnetic resonance data and provides a series of statistical and visualization tools through fMRIPrep.

The process involved: (1) removing the first 10 time points to ensure the magnetic field signal uniformity, (2) converting the data to BIDS format and call fmrip1.5.0 docker, (3) pre-processing of structural image data, (4) pre-processing of functional image data, (5) nuisance regression, and (6) filtering and smoothing.

Pre-processed image results were processed through online quality control to eliminate subjects with large T1 structural image translations and fuzzy functional images with poor quality or incomplete functional image coverage. Subject data with head movements greater than 3 mm and 3 degrees was excluded and the remaining data was retained for statistical analysis.

2.6. Statistical analysis

The differences between groups of normally distributed continuous, non-normally distributed continuous, and categorical variables used two independent sample t-tests, the Mann-Whitney-rank sum test, and chi-square analysis, respectively. Using SPSS 24.0, data was statistically analyzed with a two-tailed statistical significance set at $p < 0.05$.

The relationship between resting-state fMRI data and serum IL-18 levels was analyzed with DPABISurf statistical analysis using Matlab 2017b software. Pearson correlation was performed and corrected through threshold-free cluster enhancement (TFCE) to determine whether brain region differences between groups were present at the whole brain level. The false positive rate (family wise error rate) level was controlled at $p < 0.025$ and the Bonferroni correction was performed on the two brain hemispheres.

3. Results

A total of 37 depression patients (10 men and 27 women) and 35 demographic-matched healthy controls (8 men and 27 women) were recruited for the study. The following subjects were excluded from the study: one male patient diagnosed with bipolar disorder during the study, one male and one female patient who were unable to undergo MRI scan due to discomfort, and one healthy female with head movement exceeding 3 mm. Thus, a total of 68 patients (34 depression patients and 34 healthy controls) were included in the study (Table 1). Pearson correlation analysis showed a positive correlation between IL-18 and age in patients with depression ($r = 0.403$, $P = 0.018$). The serum levels of IL-18 in patients with depression and healthy people can be seen in the

Figure 1 and serum IL-18 levels were statistically increased in patients with depression compared to healthy controls ($Z=-4.729$, $P<0.001$). Similarly, the HAMD-17 score were also significantly higher in patients with depressions ($P<0.001$).

Pearson correlation analysis of serum IL-18 level and resting-state fMRI imaging using covariates of patient age, gender, and years of education was completed to determine differences at the whole brain level between depression patients and healthy controls. Correction was made by the replacement test processed by TFCE. The false positive rate was controlled at $p<0.025$ and Bonferroni correction was performed on both hemispheres of the brain. DC of the left posterior cingulate gyrus was negatively correlated with IL-18 in patients with depression ($p<0.05$). However, there was no correlation between DC and the HAMD-17 score. Further results and specific correlations can be seen in Figures 2 and 3.

4. Discussion

To the best of our knowledge, this is the first study to investigate the correlation between the IL-18 and DC. Furthermore, we explored the possible mechanism of IL-18-mediated depression and interference with depression-related brain activity. In patients with depression, DC of the left posterior cingulate gyrus was significantly and negatively correlated with serum IL-18 levels. This association may be related to the neuronal activity of the left cingulate gyrus. Furthermore, a correlation was not found in healthy controls.

As a pro-inflammatory cytokine of the IL-1 superfamily, IL-18 can synthesize several other cytokines including TNF- α and IL-1 β [13]. Additionally, IL-18 plays a vital role in the regulation of innate and adaptive immunity, where abnormal regulation may cause various autoimmune diseases [14, 15]. As an important regulator of immune activity, IL-18 has been found that it may be related to the occurrence of schizophrenia [16], and may also be involved in the pathogenesis of depression.

Peripheral inflammation is highly associated with depressive symptoms, increasing the risk for major depressive disorder. However, the exact mechanism of inflammation-induced depression remains unclear. One prior study showed that elevated levels of IL-6, a pro-inflammatory cytokine, were negatively correlated with changes in the sub-genual anterior cingulate cortex (sgACC) and may suggest depressive changes [17]. This suggests that IL-6 may interfere with central nervous system function. As IL-6 acts as a cytokine downstream of IL-1, it may be positively correlated with serum IL-18 levels – suggesting that IL-18 may also cause abnormal changes in brain activity.

The posterior cingulate gyrus is highly connected and metabolically active [18] component of the default network [19]. As the default network is closely related to cognitive function, the posterior cingulate gyrus is involved with attention, executive, and cognitive function [20-23]. It is hypothesized that the posterior cingulate gyrus plays a pivotal role in supporting internally directed cognition [19, 24]. Several studies have shown periods of “cognitive freedom” with increase cingulate gyrus cortex activity during periods of autobiographical memory recall and non-controlled brain activity [25-27]. However, other studies suggest that the posterior cingulate gyrus plays a more direct role in adjusting attention focus – internal idea retrieval, episodic and semantic memory, and behavioral responses to external environments [28, 29]. The

posterior cingulate gyrus has been proposed to regulate the metastable state of the whole brain internal network, adjust brain activity stability, and control the degree of change in neural activities – all of which affect attention [30]. Additionally, changes in posterior cingulate cortex (PCC) activity with arousal and its interaction with other neural networks may suggest an important role in conscious awareness [31].

Prior imaging studies have suggested that patients with depression have abnormalities in the structure and function of the posterior cingulate gyrus. One study highlighted the reduction in functional connectivity from the posterior cingulate back to the caudate body in patients with depression [32]. In depression, enhanced PCC and sgACC activity is associated with excessive ruminant thinking, a behavioral characteristic of the disorder [33]. Several studies have shown that ruminative thinking is a risk factor for the development and maintenance of depression [34-36].

One widely accepted hypothesis is the interference of inflammation on neurotransmitters (serotonin, dopamine, and norepinephrine) within brain neural circuits that induce emotional responses. This is suggested to be due to the activity of pro-inflammatory cytokines (including IL-18) on indoleamine-2,3-dioxygenase in reducing extracellular serotonin (5-HT) [37]. Studies show that 5-HT subtypes (5-HT1A and 5-HT2A) both affect the default mode network (DMN) – suggesting its close relationship with clinical manifestations of depression [38, 39]. While the DMN is known to be closely related to rumination and depression, the core component involves the posterior cingulate gyrus [19]. Thus, serotonin may also affect the posterior cingulate gyrus. Furthermore, recent studies have demonstrated an interaction between IL-18 and 5-HT may cause alexithymia [40]. Thus, IL-18, a peripheral pro-inflammatory cytokine, may affected individual brain neurons through 5-HT modulation inducing corresponding changes in brain activity and manifestation of affective disorders.

The current study found that IL-18 showed a significant and negative correlation with DC values in the left posterior cingulate gyrus. This suggests that elevated IL-18 may affect 5-HT to cause neural circuit modulation in the left cingulate gyrus and interference in the back left cingulate region. Furthermore, abnormal levels of IL-18 may also be related to the pathogenesis of depression. The DC level in the left posterior cingulate gyrus showed a significant and negative correlation with IL-18 in depression patients. This suggests that abnormal levels of IL-18 in the peripheral blood may interfere with functional brain activity – suggesting a relationship between depression onset and IL-18. As the brain is highly connected with surrounding regions, these changes suggest a decrease in signal and hub function in the primary affected neural region and its surrounding connected brain areas. These brain activity changes may be related to an individual's attention, executive, memory, and emotional function. These decreases in regulatory functions may be related to depression-like manifestations – suggesting that IL-18 mediates the pathogenesis of depression through an inflammatory response.

5. Limitations And Conclusion

The negative correlation between IL-18 and DC in the left cingulate gyrus suggests that IL-18 cause regional interference and dysfunction, resulting in depression-like manifestations such as low mood and

reduced executive function. This may suggest that IL-18 mediates the pathophysiological mechanism of depression and interferes with brain activity. However, resting-state fMRI can't reflect brain activity during emotional and cognitive tasks. To further verify functions of various brain regions, a combination of task-state and resting-state fMRI should be used for future studies.

6. Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committees of the Guangji Hospital affiliated to Soochow University, and signed informed consent was obtained from all participants.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available and may be obtained from the corresponding author on request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Xiangdong Du and Siyun Zou: Contributed equally to this work. Conceptualization, Data curation, Writing original draft. **Yan Yue, Xiaojia Fang, Yuxuan Wu, Siqi Wu, Haitao Wang, Zhe Li, Xueli Zhao, Ming Yin, Gang Ye, Hongyan Sun, Xiaochu Gu, Xiaobin Zhang, Zhigang Miao:** Conceptualization, Data curation, Supervision. **Jeff Wang Jin, Hanjing Wu:** Conceptualization, Data Interpretation, Critical revision of the manuscript. **Yansong Liu, Xingshun Xu:** Conceptualization, Data curation, Critical revision of the manuscript. The author(s) read and approved the final manuscript.

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Declarations of interest

None.

Abbreviations

DC: Degree Centrality; MDD: major depressive disorder; IL-18: Interleukin-18; IL-6: Interleukin-6; MRI: Magnetic Resonance Imaging; fMRI: functional Magnetic Resonance Imaging (fMRI) HAMD-17: Hamilton depression-17 (HAMD-17); ELISA: Enzyme-linked immunosorbent assay

References

1. Ferrari AJ, Charlson FJ, Norman RE, Patten SB, Freedman G, Murray CJ, Vos T, Whiteford HA: **Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010.** *PLoS Med* 2013, **10**(11):e1001547.
2. Huang Y, Wang Y, Wang H, Liu Z, Yu X, Yan J, Yu Y, Kou C, Xu X, Lu J *et al*: **Prevalence of mental disorders in China: a cross-sectional epidemiological study.** *Lancet Psychiatry* 2019, **6**(3):211–224.
3. Yamanishi K, Doe N, Mukai K, Ikubo K, Hashimoto T, Uwa N, Sumida M, El-Darawish Y, Gamachi N, Li W *et al*: **Interleukin-18-deficient mice develop hippocampal abnormalities related to possible depressive-like behaviors.** *Neuroscience* 2019, **408**:147–160.

4. Merendino RA, Di Rosa AE, Di Pasquale G, Minciullo PL, Mangraviti C, Costantino A, Ruello A, Gangemi S: **Interleukin-18 and CD30 serum levels in patients with moderate-severe depression.** *Mediators Inflamm* 2002, **11**(4):265–267.
5. Alcocer-Gomez E, de Miguel M, Casas-Barquero N, Nunez-Vasco J, Sanchez-Alcazar JA, Fernandez-Rodriguez A, Cordero MD: **NLRP3 inflammasome is activated in mononuclear blood cells from patients with major depressive disorder.** *Brain Behav Immun* 2014, **36**:111–117.
6. Al-Hakeim HK, Al-Rammahi DA, Al-Dujaili AH: **IL-6, IL-18, sIL-2R, and TNFalpha proinflammatory markers in depression and schizophrenia patients who are free of overt inflammation.** *J Affect Disord* 2015, **182**:106–114.
7. Al-Hakeim HK, Twayej AJ, Al-Dujaili AH: **Reduction in serum IL-1 β , IL-6, and IL-18 levels and Beck Depression Inventory-II score by combined sertraline and ketoprofen administration in major depressive disorder: A clinical trial.** *Neurology, Psychiatry and Brain Research* 2018, **30**:148–153.
8. Buckner RL, Sepulcre J, Talukdar T, Krienen FM, Liu H, Hedden T, Andrews-Hanna JR, Sperling RA, Johnson KA: **Cortical hubs revealed by intrinsic functional connectivity: mapping, assessment of stability, and relation to Alzheimer's disease.** *J Neurosci* 2009, **29**(6):1860–1873.
9. Zuo XN, Ehmke R, Mennes M, Imperati D, Castellanos FX, Sporns O, Milham MP: **Network centrality in the human functional connectome.** *Cereb Cortex* 2012, **22**(8):1862–1875.
10. Liao H, Yi J, Cai S, Shen Q, Liu Q, Zhang L, Li J, Mao Z, Wang T, Zi Y *et al*: **Changes in Degree Centrality of Network Nodes in Different Frequency Bands in Parkinson's Disease With Depression and Without Depression.** *Front Neurosci* 2021, **15**:638554.
11. Li J, Gong H, Xu H, Ding Q, He N, Huang Y, Jin Y, Zhang C, Voon V, Sun B *et al*: **Abnormal Voxel-Wise Degree Centrality in Patients With Late-Life Depression: A Resting-State Functional Magnetic Resonance Imaging Study.** *Front Psychiatry* 2019, **10**:1024.
12. Zheng YP, Zhao JP, Phillips M, Liu JB, Cai MF, Sun SQ, Huang MF: **Validity and reliability of the Chinese Hamilton Depression Rating Scale.** *Br J Psychiatry* 1988, **152**:660–664.
13. Baker KJ, Houston A, Brint E: **IL-1 Family Members in Cancer; Two Sides to Every Story.** *Front Immunol* 2019, **10**:1197.
14. Sutinen EM, Pirttila T, Anderson G, Salminen A, Ojala JO: **Pro-inflammatory interleukin-18 increases Alzheimer's disease-associated amyloid-beta production in human neuron-like cells.** *J Neuroinflammation* 2012, **9**:199.
15. Zhu H, Wang Z, Yu J, Yang X, He F, Liu Z, Che F, Chen X, Ren H, Hong M *et al*: **Role and mechanisms of cytokines in the secondary brain injury after intracerebral hemorrhage.** *Prog Neurobiol* 2019, **178**:101610.
16. Xu Y, Yue W, Shugart YY, Yuan J, Wang G, Wang HZ, Lehrman B, Zhang F, Zhang D: **Potential involvement of the interleukin-18 pathway in schizophrenia.** *J Psychiatr Res* 2016, **74**:10–16.
17. Harrison NA, Brydon L, Walker C, Gray MA, Steptoe A, Critchley HD: **Inflammation causes mood changes through alterations in subgenual cingulate activity and mesolimbic connectivity.** *Biol Psychiatry* 2009, **66**(5):407–414.

18. Hagmann P, Cammoun L, Gigandet X, Meuli R, Honey CJ, Wedeen VJ, Sporns O: **Mapping the structural core of human cerebral cortex.** *PLoS Biol* 2008, **6**(7):e159.
19. Buckner RL, Andrews-Hanna JR, Schacter DL: **The brain's default network: anatomy, function, and relevance to disease.** *Ann N Y Acad Sci* 2008, **1124**:1–38.
20. Vincent JL, Kahn I, Snyder AZ, Raichle ME, Buckner RL: **Evidence for a frontoparietal control system revealed by intrinsic functional connectivity.** *J Neurophysiol* 2008, **100**(6):3328–3342.
21. Leech R, Kamourieh S, Beckmann CF, Sharp DJ: **Fractionating the default mode network: distinct contributions of the ventral and dorsal posterior cingulate cortex to cognitive control.** *J Neurosci* 2011, **31**(9):3217–3224.
22. Leech R, Braga R, Sharp DJ: **Echoes of the brain within the posterior cingulate cortex.** *J Neurosci* 2012, **32**(1):215–222.
23. Spreng RN: **The fallacy of a "task-negative" network.** *Front Psychol* 2012, **3**:145.
24. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL: **A default mode of brain function.** *Proc Natl Acad Sci U S A* 2001, **98**(2):676–682.
25. Gusnard DA, Akbudak E, Shulman GL, Raichle ME: **Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function.** *Proc Natl Acad Sci U S A* 2001, **98**(7):4259–4264.
26. Addis DR, Wong AT, Schacter DL: **Remembering the past and imagining the future: common and distinct neural substrates during event construction and elaboration.** *Neuropsychologia* 2007, **45**(7):1363–1377.
27. Mason MF, Norton MI, Van Horn JD, Wegner DM, Grafton ST, Macrae CN: **Wandering minds: the default network and stimulus-independent thought.** *Science* 2007, **315**(5810):393–395.
28. Gusnard DA, Raichle ME, Raichle ME: **Searching for a baseline: functional imaging and the resting human brain.** *Nat Rev Neurosci* 2001, **2**(10):685–694.
29. Hampson M, Driesen NR, Skudlarski P, Gore JC, Constable RT: **Brain connectivity related to working memory performance.** *J Neurosci* 2006, **26**(51):13338–13343.
30. Leech R, Sharp DJ: **The role of the posterior cingulate cortex in cognition and disease.** *Brain* 2014, **137**(Pt 1):12–32.
31. Vogt BA, Laureys S: **Posterior cingulate, precuneal and retrosplenial cortices: cytology and components of the neural network correlates of consciousness.** *Prog Brain Res* 2005, **150**:205–217.
32. Bluhm R, Williamson P, Lanius R, Theberge J, Densmore M, Bartha R, Neufeld R, Osuch E: **Resting state default-mode network connectivity in early depression using a seed region-of-interest analysis: decreased connectivity with caudate nucleus.** *Psychiatry Clin Neurosci* 2009, **63**(6):754–761.
33. Berman MG, Peltier S, Nee DE, Kross E, Deldin PJ, Jonides J: **Depression, rumination and the default network.** *Soc Cogn Affect Neurosci* 2011, **6**(5):548–555.
34. Huffziger S, Kuehner C: **Rumination, distraction, and mindful self-focus in depressed patients.** *Behav Res Ther* 2009, **47**(3):224–230.

35. Morrow J, Nolen-Hoeksema S: **Effects of responses to depression on the remediation of depressive affect.** *J Pers Soc Psychol* 1990, **58**(3):519–527.
36. Rebstock L, Schafer LN, Kube T, Ehmke V, Rief W: **Placebo prevents rumination: An experimental study.** *J Affect Disord* 2020, **274**:1152–1160.
37. Heyes MP, Saito K, Crowley JS, Davis LE, Demitrack MA, Der M, Dilling LA, Elia J, Kruesi MJ, Lackner A *et al*: **Quinolinic acid and kynurenine pathway metabolism in inflammatory and non-inflammatory neurological disease.** *Brain* 1992, **115** (Pt 5):1249–1273.
38. Hahn A, Wadsak W, Windischberger C, Baldinger P, Hoflich AS, Losak J, Nics L, Philippe C, Kranz GS, Kraus C *et al*: **Differential modulation of the default mode network via serotonin-1A receptors.** *Proc Natl Acad Sci U S A* 2012, **109**(7):2619–2624.
39. Miller MW, Sperbeck E, Robinson ME, Sadeh N, Wolf EJ, Hayes JP, Logue M, Schichman SA, Stone A, Milberg W *et al*: **5-HT2A Gene Variants Moderate the Association between PTSD and Reduced Default Mode Network Connectivity.** *Front Neurosci* 2016, **10**:299.
40. Sacchinelli E, Piras F, Orfei MD, Banaj N, Salani F, Ciaramella A, Caltagirone C, Spalletta G, Bossu P: **IL-18 Serum Levels and Variants of the Serotonin Transporter Gene Are Related to Awareness of Emotions in Healthy Subjects: A Preliminary Study.** *Neuroimmunomodulation* 2018, **25**(3):129–137.

Table

Table 1 General demographic data and clinical characteristics of the patient and the normal control

variable	MDD	HC	χ^2 / Z	P
Gender(M/F)	8/26	8/26	0.000	1.000
Age	43.74±14.09	41.09±12.44	-0.890	0.373
Education(years)	10.41±5.48	11.12±4.42	-0.316	0.752
HAMD-17	18.41±7.82	1.18±1.83	-7.184	<0.001
IL-18	100.54 ±61.24	47.48±78.76	-4.729	<0.001

Figures

Figure 2

Correlation between IL-18 levels and DC in patients with depression and healthy people in the whole brain. Blue clusters are the brain area with negative correlation. MDD: major depressive disorder, HC: healthy control; L: left hemisphere; R: right hemisphere.

Figure 3

IL-18 and DC in brain imaging of patients with depression.