Complementary Therapies in Medicine 42 (2019) 292–297

Contents lists available at ScienceDirect

Complementary Therapies in Medicine

journal homepage: www.elsevier.com/locate/ctim

Brain activity in patients with deficiency versus excess patterns of major depression: A task fMRI study

Yong-zhi Wang[a], Yu Han[b], Jing-jie Zhao[a], Yi Du[a], Yuan Zhou[c], Yan Liu[d], Yin-feng Zhang[a], Li Li[a,*]

[a] Beijing Friendship Hospital, Capital Medical University, Beijing 100050, China
[b] Your health & Wellness International Medical Clinic, Beijing 100005, China
[c] Institute of Psychology, Chinese Academy of Sciences, Beijing 100101, China
[d] School of Community Health Sciences, University of Nevada, Reno, 89557, USA

ARTICLE INFO

Keywords:
Major depressive disorder
Syndrome differentiation of TCM
Task fMRI
Brain activation
Negativity bias

ABSTRACT

Objective:Patients with major depressive disorder (MDD) may experience a series of emotional and mental problems accompanied by characteristic clinical symptoms. Depressive patients often have emotional recognition disorders, but the reasons remain unclear. Though a great many functional abnormalities have been observed in the brains of depressed patients, such abnormalities are not often related to clinical symptoms. Currently in Traditional Chinese Medicine (TCM), syndrome differentiation for the MDD mainly consists of excess pattern (EP), and deficiency pattern (DP). EP and DP emphasize balance-regulation thought processes, and are widely used in diagnosis of diseases including depression, anxiety, insomnia, and other emotional disorders. We hope that syndrome differentiation in TCM can combine clinical symptoms and brain function more effectively. The present study investigated altered patterns and different association of brain activation in MDD patients with EP and DP during a facial emotion discrimination task with fMRI.

Methods:A total of 45 patients (20 with EP and 25 with DP) and 18 normal controls participated in this study. Whole-brain functional scans were collected for each subject. Different patterns of brain activation and association during the facial emotion discrimination task were analyzed statistically.

Results:Comparing all the MDD patients with the normal controls, there were no significant differences for sad vs. neutral condition or for happy vs. neutral condition (corrected $p > 0.05$). One-way ANCOVA showed significant differences in the left inferior frontal gyrus, the left insula, and the left caudate for sad vs. neutral condition across the DP, EP and NC groups (corrected $p < 0.05$). The whole brain activation comparison for sad vs. neutral condition between the EP MDD subtype and the DP MDD subtype further verified these differences in the left insula and left inferior frontal gyrus, discovering that these regions showed increased activation in EP MDD subtype compared with the DP MDD subtype (corrected $p < 0.05$). There were no significant differences in brain activation between each MDD subtype and the normal controls.

Conclusion:Disparities in sad face processing exist between MDD patients with different TCM syndrome types, suggesting that TCM syndrome differentiation may provide a biological basis for negativity bias in depression, and may determine both symptom formation and social dysfunction.

1. Introduction

Major depressive disorder (MDD) is a mental disorder characterized by a pervasive and persistent low mood that is accompanied by low self-esteem and by a loss of interest or pleasure in normally enjoyable activities.[1] Because depressive patients have emotional recognition disorder, studying the effects of MDD and its correlation with facial stimuli within the field of neurobiology is particularly valuable.[2] When testing patients with MDD, neural activation within the common face-processing network showed various abnormalities.[3] Patients displayed hyperactivation to negative stimuli, and hypoactivation to positive stimuli.[4] Researches suggest that the amygdala, insula, parahippocampal gyrus, fusiform area and putamen, were the main areas that exhibited mood-congruent processing bias.[5] However, abnormal activation patterns were also detected in regions of the cingulate gyrus and the orbitofrontal cortex.[6] What caused the inconsistency in the activation of brain regions remains unclear within modern medicine. Since phenotypic characteristics, genetic data, and other biological

* Corresponding author at: Beijing Friendship Hospital, Capital Medical University, 95 Yong-An Road, Xicheng District, Beijing 100050, China.
E-mail address: lili@ccmu.edu.cn (L. Li).

https://doi.org/10.1016/j.ctim.2018.12.006
Received 11 September 2018; Received in revised form 2 December 2018; Accepted 8 December 2018
Available online 11 December 2018
0965-2299/

Table 1
General information of MDD patients with Excess/ Deficiency pattern and normal participants.

Category	NC	EP	DP
Cases	18	20	25
Male/female	4/14	5/15	2/23
Age, Mean years (SD)	45.4 ± 11.69	43.51 ± 11.23	44.37 ± 12.13
Typical Traditional Chinese Medicine Syndromes	N/A	restlessness rib-side pain hoarse breathing dull tongue yellow-greasy coating excess pulse	fatigue slow speech shortness of breath pale tongue white-greasy coating weak pulse

Note: NC, normal controls; EP, depressed patients with excess pattern; DP, depressed patients with deficiency pattern; SD, standard deviation; NA, not available. Values given are mean (standard deviation) of proportion.

markers are still not used as methods for the diagnostic classification of MDD,[7] this inconsistency may be related to the heterogeneity of populations with diverse symptom clusters.[8] The clinical symptoms of the depressed patient need to be studied further, and new avenues and methodology for research considered, such as Traditional Chinese Medicine (TCM), which groups symptoms with greater complexity.

Generally, patients with MDD exhibit low moods and multiple physical symptoms such as fatigue, insomnia, headaches, forgetfulness or digestive problems.[9] The physical symptoms can be grouped by Zheng (meaning “Syndrome” or “Pattern”) differentiation, which is one of most important concepts in the practice of TCM that consists of a series of diagnostic procedures.[10] Syndrome differentiation is the overall physiological or pathological pattern of the human body in response to a given internal and external condition.[11] Currently, syndrome differentiation for the MDD in TCM mainly includes excess pattern (EP), and deficiency pattern (DP). EP and DP are two key conditions of the TCM syndrome that emphasize balance-regulation thought processes,[12] and are widely used in diagnosis of diseases including depression, anxiety, stress, and other emotional disorders. The typical syndromes of the two types for depression are listed in Table 1.

There is no laboratory test for MDD, although doctors generally request examinations for physical conditions that may cause similar symptoms.[13] Recent advances in functional magnetic resonance imaging (fMRI) have made it possible to measure the effects of MDD, by investigating brain structures and functions in vivo.[14] Depending on the paramagnetic properties of oxygenated and deoxygenated hemoglobin, fMRI can see images of changing blood flow in the brain associated with neural activity. This permits images to be generated that show which brain regions are activated during performance of different tasks or during resting states, providing helpful feedback for further study and diagnosis.[15]

Previous studies have found that different symptomatic aspects of depression (e.g. affective, somatic, and interpersonal symptoms) have distinct associations with cognitive functioning, brain structure, and clinical outcomes.[16] However, the information obtained from syndrome differentiation in TCM for major depression, (including symptoms such as pulse rate and tongue appearance) are not often related to functional abnormalities in the brain.[17] Accurate method procedures for discovering the biological basis for MDD through the process of TCM, require further development. TCM is a differentiating classification system from clinical diagnosis. For instance, our previous study confirmed that the disruption patterns of functional connectivity in resting-state fMRI differed between depressed patient groups separated according to TCM-defined syndromes.[18] It is possible to integrate TCM syndrome differentiation and biomedical diagnosis in modern clinical practice. The identification of brain activation patterns in MDD could enhance our understanding of cognitive dysfunctions in MDD, which are associated with functional brain activity in the default mode network.

To our knowledge, there are few publications about brain activity alterations in MDD patients under different TCM syndromes. We hypothesized that depressive patients with EP and DP would exhibit altered patterns of brain activation and show different association during a facial emotion discrimination task with fMRI.

2. Materials and methods

2.1. Subjects

The patients in this study were recruited from the Beijing Friendship Hospital and Beijing Anding Hospital. Normal controls (NC) were recruited from the local community by advertisement. A total of 45 patients (20 with EP and 25 with DP) and 18 normal controls were included in this study. The normal controls consisted of volunteers without any emotional disorders. All patient-involved activities were pre-approved by the Medical Research Ethics Committee of Beijing Friendship Hospital Affiliated with Capital Medical University. Written informed consent was obtained from each participant. All participants were right handed and had normal or corrected-to-normal vision.

A psychiatric evaluation was conducted before patients were recruited. The psychiatrists diagnosed participants under the criteria of MDD according to the Structured Clinical Interview for the DSM-IV (SCID).[19]. Patients with a history of neurologic illness, substance or alcohol abuse, electro convulsive therapy, or transcranial magnetic stimulation within the last 2 years, were excluded from the current study. The subjects were assessed using the Hamilton Rating Scale for Depression (HAMD-21), and the additional criterion for normal controls was a HAMD score < 8. Meanwhile, exclusion criteria for patients with depression included severe learning disabilities, color blindness, head trauma, psychotic symptoms, current panic disorder, and alcohol or substance abuse within the past 6 months.

TCM syndrome differentiation was judged by two experienced chief TCM physicians. The clinical characteristics of these patients were also evaluated according to the “Criteria for diagnosis and therapeutic effects of diseases and syndromes in TCM”, published by the China State Administration of TCM.[20] Only patients diagnosed as EP or DP who experienced typical manifestations of the pattern, were enrolled in this study. The main clinical features of patients with EP and DP are shown in Table 1.

2.2. Stimulus presentation

The images used were from a standardized series of Chinese faces.[21] Happy, sad and neutral faces were selected as the experimental faces. All participants reported that they had never seen such faces before. The set of stimuli presented to the subjects was weighted equally with each affective condition, such that it included equal numbers of negative, neutral and positive pictures.

The picture presented to the participants consists of a pair of faces from the same person or different persons. Subjects viewed each image for 2 s and determined whether the face was the same or different by pressing a button (1 for the same face, and 2 for the different face). The inter-stimulus interval lasted 0.5 s. The design makes sure that subjects will see the image and are concerned about the emotional changes in the images. There were in total 180 pairs of pictures with happy, sad and neutral faces. Sixty paired pictures of each emotion with the same or different person’s face were provided. The total duration of the study lasted 480 s (8 min), including the instruction before the scan and the fixation time of the fMRI (Fig. 1). Before scanning, the subjects were instructed not to move and to fixate on the faces presented (i.e., passive viewing).

Behavioral performance (number of correct responses or accuracy and reaction time) of the subjects was determined separately by

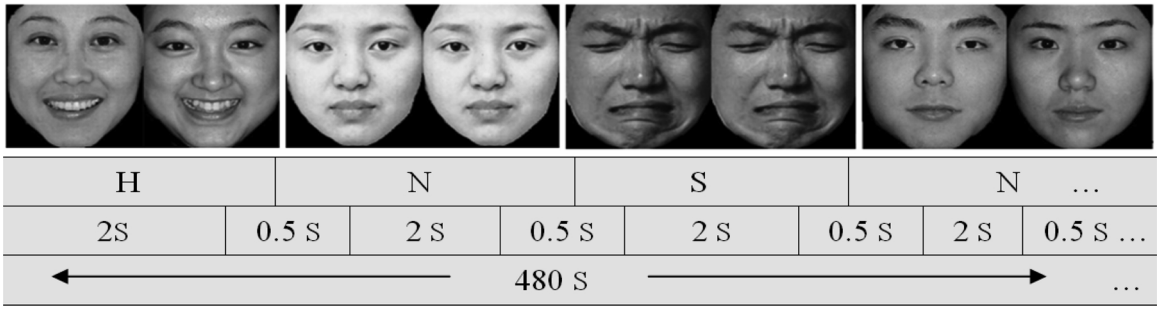

Fig. 1. Examples of facial stimuli used in fMRI procedure. The study used a block design. The procedure of the facial stimuli is H-N-S-N-S-H-S-N-H-N-H-S-H-S-N-S-H-N which takes 45 s and repeated ten times. During the facial trials, subjects indicated whether the face was the same or different. H = happy faces; N = neutral faces; S = sad faces.

calculating reaction time and errors.

2.3. MRI data acquisition

Images were acquired with a 3.0 T GE MRI scanner. Whole-brain functional scans were collected in 34 axial slices using an echo-planar imaging (EPI) sequence (repetition time = 2000 ms, echo time = 30 ms; matrix = 64 × 64; field of view = 220 × 220 mm^2; slice thickness = 4 mm; slice gap = 0.5 mm). Stimuli were projected onto a screen approximately 55 cm from the participants with a rear screen projector. High-resolution T1-weighted magnetization prepared rapid gradient echo (MP-RAGE) structural images were acquired (repetition time: 1630 ms; echo time: 2.48 ms; flip angle = 20 °; slice thickness = 1 mm, no gap; 160 slices).

2.4. fMRI preprocessing and data analysis

Prior to preprocessing, the first 5 frames were discarded to allow for signal stabilization. Data preprocessing and statistical analyses were performed using SPM8 software (Well come Department of Imaging Neuroscience, London, UK). All volumes acquired from each subject were corrected for different slice acquisition times. The resultant images were then realigned to correct for small movements occurring between scans. This process generated an aligned set of images and a mean image for each subject. Each participant's T1-weighted structural MRI was co-registered to the mean of the realigned EPI images and segmented to separate out the gray matter, which was normalized to the gray matter in a template image based on the Montreal Neurological Institute (MNI) reference brain. Using the parameters from this normalization process, the EPI images were also normalized to the MNI template (re-sampled voxel size 3 mm × 3 mm × 3 mm) and smoothed with an 8 mm full-width at half-maximum Gaussian kernel. Based on their recorded motion correction estimates, subjects who had more than 3 mm maximum displacement in any of the x, y or z directions or more than 3° of angular rotation about any axis were excluded from this study.

During image processing, 9 subjects (5 DP, 3 EP, and 1 NC) were excluded due to excessive head movement. For each participant, data analysis was first conducted in a voxel-wise way. All instances of a particular event type at the time of the participants' responses were modeled through convolution with a canonical hemodynamic response function. There were a total of three experimental conditions: sad, happy, and neural condition. Additionally, six motion parameters obtained by realignment were used as nuisance variables. The parameter estimates (betas) for each condition were calculated for all brain voxels, and the relevant contrasts of parameter estimates were computed. A high-pass filter of 1/128 Hz was used to remove low-frequency noise, and an AR (1) model was used to correct for temporal auto correlations. Each task condition (sad and happy) was then contrasted against the baseline condition (neutral).

The contrast images for all participants were then entered into the second-level analysis. At the second-level analysis (group analysis), several group-comparisons were conducted. We first tested whether there were significant differences between MDD patients by combining EP and DP subgroups and normal controls using two-sample tests for interested contrasts. Then one-way ANCOVA analyses were conducted to test whether there were any group differences across the DP, EP and NC group, while taking age, gender and education level as no interests of covariates. Finally, the whole brain activation comparison between each paired groups was conducted using two-sample tests in order to determine group differences.

In order to reduce multiple comparisons, a grey matter mask generated by the segmented grey matter of each participant was used. The statistical significance was determined by Monte Carlo simulations with the Alphasim software to obtain a p-corrected < 0.05 after correcting for multiple comparisons (with 5000 permutations). The corrected threshold corresponds to a p-uncorrected < 0.005 with a minimum cluster size that is dependent on the mask size (52,300 voxels) and the FWHM estimated by the statistical map.

3. Results

3.1. Behavioral results

The demographic characteristics of the depressed groups and comparison group were similar (Table 2). There were no significant differences between the groups in mean age, gender distribution, education level and button-pressing accuracy (›0.05). In the depressed groups, the mean total score on the HAMD was moderately severe. The mean score on the HAMD in the EP group was 26.76 (SD = 7.23) and the mean score for the DP group was 28.15 (SD = 7.81) and there were no significant differences between them (p ›0.05).

Table 2
Demographic characteristics and behavioral results.

Variables	NC(n = 17)	EP(n = 17)	DP(n = 20)	p value
Age (years)	45.24 ± 12.69	42.71 ± 10.63	44.65 ± 11.20	0.67[a]
Gender (male/female)	4/13	5/12	1/19	0.10[b]
Education (years)	12.63 ± 3.79	11.47 ± 2.79	11.45 ± 2.78	0.35[a]
HAMD score	–	26.76 ± 7.23	28.15 ± 7.81	0.38[c]
Button-pressing accuracy (%)	79.53 ± 7.18	79.20 ± 6.10	76.68 ± 5.85	0.27[a]

Note: Data are presented as the (mean ± SD). NC, normal controls; EP, depressed patients with excess pattern; DP, depressed patients with deficiency pattern; HAMD, 21-item Hamilton Depression Rating scale.
[a] one-way analysis of variance (SNK-q test).
[b] chi-square test.
[c] two-sample t-test.

Table 3
Regions showing significant differences in evoked-activity by the sad faces compared to the neutral faces across all three groups.

Region	BA	Cluster Size	MNI	peak F
		(number of voxels)	(x, y, z)	
left caudate		33	−9,15, 9	10.18
left insula	13	54	−27,18,-3	9.54
left IFG	10/46	99	−48,21,36	9.03

Note: BA, Brodmann area; MNI, Montreal Neurological Institute coordinates; IFG, inferior frontal gyrus.

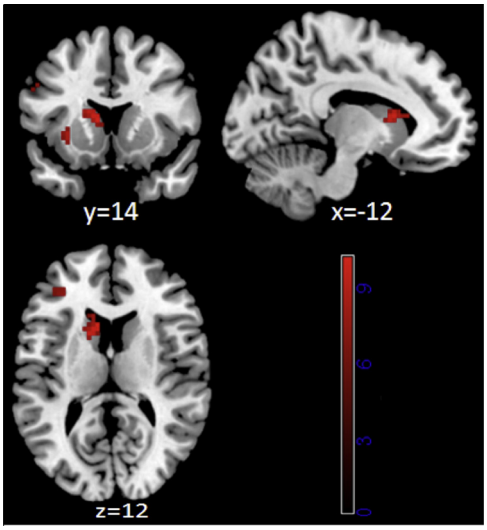

Fig. 2. Brain regions showing the main effect of diagnosis for sad vs. neutral condition. The figure shows brain activations in response to sad vs. neutral condition across all three groups, including activations in left caudate, left insula and left IFG.

3.2. fMRI results

Comparing all the MDD patients with the normal controls, there were no significant differences for sad vs. neutral condition or for happy vs. neutral condition (corrected $p > 0.05$). One-way ANCOVA showed significant differences in the left inferior frontal gyrus (IFG), the left insula, and the left caudate for sad vs. neutral condition when brain activation was compared across the DP, EP and NC groups (corrected $p < 0.05$; Table 3, Fig. 2). No significant differences for happy vs. neutral condition were found across the three groups (corrected $p < 0.05$). As to sad vs. neutral condition, the whole brain activation comparisons between groups were conducted to have a closer look on the group differences. When comparing the EP MDD subtype with the DP MDD subtype, we found that the brain activation in the left insula and left inferior frontal gyrus were increased in the EP MDD subtype. And we also found that the right insula, the bilateral superior temporal gyri, the right medial frontal gyrus, and the left inferior parietal lobule showed increased activation for sad vs. neural condition in EP MDD subtype compared with the DP MDD subtype (corrected $p < 0.05$; Table 4, Fig. 3). While comparing each MDD subtype with NC, no significant differences in brain activation were found (corrected $p < 0.05$).

All of these results suggest that the EP MDD patients process sad faces in a way different from the DP MDD patients.

4. Discussion

TCM is an important part of the healthcare system in some Asian countries, and is considered a complementary or alternative medical system in most Western countries.[22] Establishing a biological basis for TCM, especially the core diagnostic and therapeutic concept of syndromes, is a critical step in the modernization of TCM. In clinic, both the biomedical diagnosis for the condition and TCM Syndrome differentiation are combined in China, and measuring the correlation between the biomedical condition and TCM pattern is considered a key approach to modern TCM diagnosis research.[23] In TCM, EP or DP is a reflection of the body's imbalance. EP reflects the hyperfunction of the body manifesting itself in an anxious, irritable or restlessness state.

The hyperactivation in EP from the aspect of TCM refers to a kind of pathological change in which the pathogenic factors are prosperous while the vital Qi is not yet fading. The excess of the pathogenic factors is the main contradiction, under such contradiction the excess pulse, yellow-greasy coating, and rib-side pain are just the manifestations of TCM excess pattern from the patient's different body parts which means excessive cardiovascular activity, heat and thick tongue coating, exaggerated flank pain respectively. To some extent, we can think of these hyperactive somatic symptoms as physical manifestations of depression. DP reflects the hypofunction of the body, which involves fatigue, slow speech, shortness of breath and weak pulse, etc. The current fMRI results showed that EP or DP for depression not only manifested in TCM symptoms, but also associated with activation in different brain regions.

Neuroimaging techniques such as fMRI can precisely localize and measure sustained cognitive processing within networked neural structure. In addition, facial affect processing is an important component of interpersonal relationships and particularly relevant to models of depression.[24,25] Some studies have confirmed that there is significant negativity bias in depression.[26]

Our previous resting-state fMRI test demonstrated that TCM diagnosis of MDD syndrome in DP and EP groups correlated with differing cerebral functional activity. Thus, functional connectivity changes differed between MDD patients with different TCM syndrome types.[18] Significant differences were detected in the left IFG, the left insula and the left caudate in sad vs. neutral condition when brain activation was compared across all three groups. The whole brain activation comparison for sad vs. neutral condition between the EP MDD subtype and the DP MDD subtype further verified these differences in the left insula and left IFG, discovering that these regions showed increased activation in EP MDD subtype compared with the DP MDD subtype. Under the happy vs. neutral condition, the three groups did not differ significantly in the above mentioned regional brain activation. All of these results suggest discrepancies in sad face processing between MD subtypes.

A meta-analytic study of changes in depressed brain activation indicated that the most consistently identified regions included areas of the IFG, insula, anterior cingulate, dorsolateral, medial and superior temporal gyrus, basal ganglia and cerebellum. The IFG is thought to play a key role both in terms of basal activity and responses to affective stimuli.[27] Left IFG is critical for the cerebral cortical network to support visual word recognition and reading.[28] Patients with damage in the left IFG and the insula were tested in a Go/NoGo response inhibition task. Researchers found that the left IFG injury patients had higher error rates than normal controls. In the current study, the left IFG and insula showed increased brain activation in the EP group compared with the DP group. These results are in accordance with the TCM syndrome differentiation.

MDD is characterized by a stable negative bias toward emotional stimuli, which is the result of a dysregulated fronto-limbic network.[29] The insula is a small region of the cerebral cortex folded deep within the lateral sulcus.[30] With its extensive connections to the fronto-limbic network, the insula has been implicated in stimulus-independent thought and believed to be a primary node in the default mode network.[31] The hyperactivation of the fronto-limbic network leads to enhanced attention and processing of emotional information, with a bias toward negative stimuli. We speculated that, hyperactivation in the insular in the EP depressed patients compared with the DP group may reflect an increased ntegration of emotional, autonomic, and

Table 4
Regions activated in whole brain analyses between EP and DP for sad vs. neutral condition.

Region	BA	Cluster Size (number of voxels)	MNI (x, y, z)	peak T
right insula / inferior frontal gyrus	13/45	235	36 21 -6	4.60
left insula	13	120	−27 18 -3	4.32
left middle / inferior frontal gyrus	9/46	376	−48 21 36	4.25
left inferior parietal lobule	40/7	96	−45 -57 54	4.06
left superior temporal gyrus / supramarginal gyrus	22/40/41/42	174	−54 -39 12	3.51
right superior temporal gyrus / supramarginal gyrus	22/40/41/42	285	60 -30 15	3.48
right medial prefrontal gyrus	9/32	84	6 45 36	3.45

Note: BA, Brodmann area; MNI, Montreal Neurological Institute coordinates.

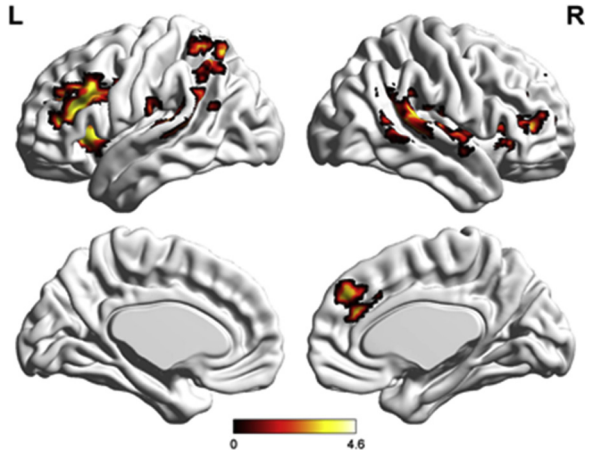

Fig. 3. Whole brain activation in ES patients compared with DS patients while viewing sad and neutral facial expressions. Regions showing significant differences between ES and DS patients for sad vs. neutral condition. Color bar indicates *t* value.

interoceptive information by the insula.

In addition to these brain regions, the caudate nucleus has been suggested to play a vital role in depression. The caudate is also part of the reward system and it integrates data from many brain regions, including the cerebral cortex. Researchers speculate that thoughts, feelings and motivations associated with positive emotions may assemble in the caudate. A 77-year-old man without any previous psychiatric disorder developed a new onset of psychotic symptoms following left caudate infarction, damage of the structure indicated change in normal functioning, and a decrease in caudate activity.[32] The activation likelihood estimation (ALE) analyses indicated the brain metabolism in right caudate were significantly decreased in MDD patients.[33] In our study, significant differences were detected in the left caudate in sad vs. neutral condition when brain activation was compared across all three groups. However, we didn't find any significant differences in the left caudate for the whole brain activation comparison in sad vs. neutral condition between MDD subtype and NC. In addition, researches in fMRI showed that there were obvious gender differences in activation of caudate nucleus for emotion memory enhancement effect in depressed patients, which was related with function of caudate nucleus head.[34] In our study, the gender distribution of the participants was unbalanced and we have more female participants in each group. Further studies with balanced gender distribution are needed to investigate the role of caudate nucleus in MDD subgroups of EP and DP.

A voxel-by-voxel comparison for sad vs. neutral condition in our study found that the right insula, the bilateral superior temporal gyri, the right medial frontal gyrus, and the left inferior parietal lobule also showed increased activation in EP MDD subtype compared with the DP MDD subtype. However, we do not find significant differences in these areas for happy vs. neutral condition. Further investigation is needed to verify the result in the future. In addition, in our study, the sample size is small and the statistical significance was determined by Monte Carlo simulations with the Alphasim software with a relative looser threshold. Future studies with larger sample sizes and strict correction method are needed to verify the current findings.

In summary, negativity bias in EP MDD group correlated with hyperactivity in the IFG and the left insula – areas associated with negative emotions and thoughts. The increased activation in these regions suggests that negative perception prevails over positive perception of sad facial expressions in individuals with EP depression and that perception differs between the MDD subgroups of EP and DP. The difference in MDD subgroup brain activity based on TCM depression subtypes may provide a basis for negativity bias in depression, and may determine both symptom formation and social dysfunction. The current finding that the EP MDD and DP MDD do not have the same fMRI activation suggests that TCM syndrome differentiation may be an appropriate tool for the future investigation of the pathogenesis of major depression.

Conflicts of interest

The authors declare there are no conflicts of interest regarding the publication of this paper.

Acknowledgments

This study was supported by grants from National Natural Science Foundation of China (grant No.81673737); the Beijing Natural Science Foundation (grant No. 7172063), the Beijing Administration of Traditional Chinese Medicine (grant JJ2018-51); the Beijing Health System Training Program for High Level Technique Talents (grant No. 2014-3-001) and the Beijing Municipal Administration of Hospitals Incubating Program (grant Code: PZ2017024).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ctim.2018.12.006.

References

1. Pang X, Xu J, Chang Y, et al. Mismatch negativity of sad syllables is absent in patients with major depressive disorder. *Plos One.* 2014;9(3):e91995.
2. Jin C, Zhang M, Li D, Ma S, Wang Y. Meta-analysis of brain activation in depressive patients with emotional perception disorders. *Neural Regen Res.* 2011;06(31):2429–2434.
3. Li L, Ding N, Xue F, Mei L, Dong Q. Correlation between clinical symptoms and brain function change in unipolar depression: an fMRI study. *J Cap Med Univ.* 2009;30(1):32–36.
4. Zhong M, Wang X, Xiao J, Yi J, Zhu X. Amygdala hyperactivation and prefrontal hypoactivation in subjects with cognitive vulnerability to depression. *Biol Psychol.* 2011;88(2):233–242.
5. Berntson GG, Norman GJ, Bechara A, Tranel D, Bruss J. The insula, the amygdala and evaluative processes. *Psychol Sci.* 2011;22(1):80–86.
6. Shibata K, Watanabe T, Kawato M, Sasaki Y. Differential activation patterns in the same brain region led to opposite emotional states. *Plos Biol.* 2016;14(9):e1002546.
7. Verduijn J, Milaneschi Y, Peyrot WJ, Hottenga JJ, Abdellaoui A. Using clinical

characteristics to identify which patients with major depressive disorder have a higher genetic load for three psychiatric disorders. *Biol Psychiatry.* 2016;81(4):316–324.
8. Demyttenaere K, Desaiah D, Petit C, Croenlein J, Brecht S. Time course of improvement of different symptom clusters in patients with major depression and pain treated with duloxetine or placebo. *Cur Med Res Opin.* 2012;28(1):41–48.
9. Yamamoto K, Shiota S, Ohno S, Kuroda A, Yoshiiwa A. A diagnosis of depression should be considered in patients with multiple physical symptoms in primary care clinics. *Tohoku J Exp Med.* 2013;229(4):279–285.
10. Yang S, Chen H, Lin Y, Chen Y. The exploration of disease pattern, zheng, for differentiation of allergic rhinitis in traditional Chinese medicine. *Evid Based Complem Altern Med.* 2012:e521780.
11. Jiang M, Lu C, Zhang C, Yang J, Tan Y. Syndrome differentiation in modern research of traditional Chinese medicine. *J Ethnopharmacol.* 2012;140(3):634–642.
12. Zhang X, Li L, Chen T, Sun Z, Tang W. Research progress in the effect of traditional Chinese medicine for invigoration on neurotransmitter related diseases. *Evid Based Comp Altern Med.* 2018;2018(4):1–14.
13. Chen JJ, Zhou CJ, Zheng P, Cheng K, Wang HY. Differential urinary metabolites related with the severity of major depressive disorder. *Behav Brain Res.* 2017;332:280–287.
14. Hall LM, Klimes-Dougan B, Hunt RH, et al. An fMRI study of emotional face processing in adolescent major depression. *J Affect Disorders.* 2014;168:44–50.
15. Smoski MJ, Felder J, Bizzell J, Green SR, Ernst M. fMRI of alterations in reward selection, anticipation, and feedback in major depressive disorder. *J Affect Disorders.* 2009;118(1):69–78.
16. Kirton JW, Resnick SM, Davatzikos C, et al. Depressive symptoms, symptom dimensions, and white matter lesion volume in older adults: a longitudinal study. *Am J Geriatr Psychiatry.* 2014;22(12):1469–1477.
17. Tang C, Ye Y, Feng Y, Quinn RJ. Tcm, brain function and drug space. *Nat Prod Rep.* 2015;33(1):6.
18. Zhang YF, Han Y, Wang YZ, Zhang YF, Jia HX. Characterization of resting-state fMRI-derived functional connectivity in patients with deficiency versus excess patterns of major depression. *Complement Ther Med.* 2015;23(1):7–13.
19. First MB, Spitzer RL, Miriam G, Williams JBW. *Structured clinical interview for DSM-IV axis I disorders: SCID-I: clinical version: administration booklet.* American Psychiatric Press; 1997.
20. *State administration of traditional Chinese medicine. Standards for diagnosis and curative effect of Chinese medical symptom.* Nanjing: Nanjing University Press; 1994:78.
21. Wang Y. Standardization and assessment of College students' facial expression of emotion. *Chin J Clinical Psychol.* 2005;13(4):396–398.
23. Tang JL, Liu BY, Ma KW. Traditional Chinese medicine. *Lancet.* 2008;372(9654):1938–1940.
24. Bistricky L, Ingram RE, Atchley RA. Facial affect processing and depression susceptibility: cognitive biases and cognitive neuroscience. *Psycho Bull.* 2011;137(6):998–1028.
25. Ito T, Yokokawa K, Yahata N, Isato A, Suhara T, Yamada M. Neural basis of negativity bias in the perception of ambiguous facial expression. *Sci Rep.* 2017;7(1):420.
26. Dai Q, Wei J, Shu X, Feng Z. Negativity bias for sad faces in depression: an event-related potential study. *Clin Neurophysiol.* 2016;127(12):3552–3560.
27. Fitzgerald PB, Laird AR, Maller J, Daskalakis ZJ. A meta analytic study of changes in brain activation in depression. *Acta Neuropsychiatrica.* 2010;18(6):286–287.
28. Cornelissen PL, Kringelbach ML, Ellis A, Whitney C, Holliday IE. Activation of the left inferior frontal gyrus in the first 200 ms of reading: evidence from magnetoencephalography (MEG). *Plos One.* 2009;4(4):e5359.
29. Liao C, Feng Z, Zhou D, Dai Q, Xie B. Dysfunction of fronto-limbic brain circuitry in depression. *Neuroscience.* 2012;201(1):231–238.
30. Alcauter S, Lin W, Smith JK, Gilmore JH, Gao W. Consistent anterior–posterior segregation of the insula during the first 2 years of life. *Cereb Cortex.* 2013;25(5):1176.
31. Sliz D, Hayley S. Major depressive disorder and alterations in insular cortical activity: a review of current functional magnetic imaging research. *Front Hum Neurosci.* 2012;6(2):323.
32. Cheng YC, Liu HC. Psychotic symptoms associated with left caudate infarction. *Int J Gerontol.* 2015;9(3):180–182.
33. Su L, Cai Y, Xu Y, Dutt A, Shi S, Bramon E. Cerebral metabolism in major depressive disorder: a voxel-based meta-analysis of positron emission tomography studies. *BMC Psychiatry.* 2014;19(14):321.
34. Huang G, Wang H, Xu L, Wang J, Li X, Yu Y. Functional MRI study on gender-related differences of caudate nucleus activation for emotional memory in major depression disorder. *Chin J Interv Imaging Ther.* 2014;11(9):582–586.