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Xin Chen
First Affiliated Hospital of Anhui Medical University
Wei Gui
The First Affiliated Hospital of USTC: Anhui Provincial Hospital
Mei Dan Zu
First Affiliated Hospital of Anhui Medical University
Juan Zhang
First Affiliated Hospital of Anhui Medical University
Han Li Li
First Affiliated Hospital of Anhui Medical University
Zi Ru Deng
First Affiliated Hospital of Anhui Medical University
Long Wang
First Affiliated Hospital of Anhui Medical University
Ben Sheng Qiu
USTC: University of Science and Technology of China
Jin Ying Yang
USTC: University of Science and Technology of China
Yu Wang (yw4d@hotmail.com)
The First Affiliated Hospital of Anhui Medical University https://orcid.org/0000-0002-9454-9699

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Alterations of amygdala volume and functional connectivity in patients with migraine comorbid depression

Xin Chen [1, 2], Wei Gui[3], Mei-Dan Zu[1], Juan Zhang [1], Han-Li Li [1], Zi-Ru Deng [1], Long Wang [1], Ben-Sheng Qiu[4], Jin-Ying Yang[5] and Yu Wang [1]*

1. Department of Neurology, Epilepsy and Headache Group, the First Affiliated Hospital of Anhui Medical University, Jixi Road 218, Hefei 230022, China
2. Department of Neurology, the Fourth Affiliated Hospital of Anhui Medical University, Huaihai Avenue 100, Hefei 230000, China
3. Department of Neurology, the First Affiliated Hospital of University of Science and Technology of China, Lujiang Road 17, Hefei 230000, China
4. Hefei National Lab for Physical Sciences at the Microscale and the Centers for Biomedical Engneering, University of Science and Technology of China, Hefei, China.
5. Laboratory Center for Information Science, University of Science and technology of China, Hefei, China.

Email addresses:

Xin Chen, xinchen_n@163.com

Wei Gui, hahagw@163.com

Mei-Dan Zu, 18355180890@163.com

Juan Zhang, 1296576130@qq.com

Han-Li Li, 18715114907@163.com

Zi-Ru Deng, 1518536046@qq.com

Long Wang, guxindao606@163.com

Ben-Sheng Qiu, bqiu@ustc.edu.cn

Jin-Ying Yang, jinying@ustc.edu.cn

Yu Wang, yw4d@hotmail.com

* Corresponding author

Yu Wang,

Department of Neurology, Epilepsy and Headache Group, the First Affiliated Hospital of Anhui Medical University, Jixi Road 218, Hefei 230022, China

Email, yw4d@hotmail.com

Telephone, 86 551 65908480

ABSTRACT

Objective: The comorbidity of migraine and depressive has been recognized, but the pathophysiology remains unknown. Here, we aimed to explore the structural change of amygdala(AMY) and abnormal function in the centromedial amygdala(CMA) among migraineurs with depression.

Methods: High-resolution T1-weighted and functional magnetic resonance images were acquired from subjects of 22 migraine comorbid with depression(EMwD), 22 episodic migraine (EM), 20 major depressive disorder (MDD), respectively, and 18 healthy controls(HC). Apply voxel-based morphometry (VBM) and resting state functional connectivity (rsFC) to examing inter-group differences in brain structure and function.

Results: The volume of bilateral AMY increased in EMwD and EM compared to HC. EMwD showed larger volume than MDD. And the volume of AMY showed positive correlation with duration of illness in patient groups. Compared with EM, EMwD exhibited decreased rsFC between the right CMA and left cerebellum, left dorsolateral prefrontal cortex (DLPFC), left precuneus(PCC). In addition, rsFC between the left CMA and left DLPFC was negatively correlated with Hamilton Anxiety Scale (HAMA), Hamilton Depression Scale (HAMD).

Conclusions: According to our findings, the larger volume of amygdala and the abnormal functional connectivity may help to determining the common symptoms in migraine with depression, and may be a treatment target for migraine and depression comorbidities.

Keywords: Migraine, Depression, Amygdala, Centromedial amygdala, Voxel-based Morphometry, Functional connectivity.

INTRODUCTION

Migraine is a common brain disease characterized with a recurrent headache and afflicts nearly 10% of adults worldwide[1, 2]. Many migraineurs suffer from depression and other comorbidities. A 2018 review of the correlation between migraine and psychiatric comorbidities showed that patients with migraine are two to four times more likely to have depression than healthy people[3]. Migraine and depression usually coexist, and their comorbidity may be caused by a common cause. Therefore, a better understanding of the neurophysiological mechanisms associated with migraine and depression comorbidities deserves further attention.

In addition to the neurovascular model, a dysfunctional neural limbic pain network model also expands the traditional concept of migraine, which can help clarify migraine attacks, chronicity and refractory[4].The limbic system is involved in pain modulation, memory consolidation and physiological stress response[5]. The amygdala is an essential element of the limbic system, well-known to be relevant to fear, learning, anxiety and pain[6, 7]. It is also the brain area that processes negative emotions[8], often shows abnormal structure and function in MDD patients[9, 10].The amygdala is divided into three independent but interconnected subregions: later basal amygdala(LBA), centromedial amygdala (CMA), and superficial amygdala[11].Recent studies have shown the abnormal structure and function of different areas of the amygdala are also observed in patients with depression[12, 13]. The CMA, referred to as the 'nociceptive amygdala', serves as the main output nucleus for amygdala functions[6].The CMA forms widespread connections with forebrain areas and the brainstem, which have been implicated in mediating fear and mood disorders[14, 15]. A resting state fMRI data showed that when comparing all migraineurs with controls, there was increased connectivity between the left and the right amygdala and the anterior insula[16].The functional connectivity of the left amygdala indicated increased connectivity in episodic migraine and is related to sleep quality[17]. Functional connectivity between the CMA and the dorsal raphe nucleus was reduced in patients with chronic pain and depressive symptoms but not in patients in chronic pain without depression[18]. A structural MRI study showed that life stress within the last six months was associated with smaller left amygdala volume[19].

Migraine combined with depression is different from patients who have only migraine or only depression. The brain volume caused by the combination of migraine and depression is smaller than that of patients with or without these conditions[20].Previous neuroimaging studies of migraine had explored changes in the brain, identified abnormal functions in specific brain regions, and speculated that these regions may help determine the depressive symptoms of migraine without aura[21-23].In view of the important role of amygdala in migraine and depression, the motivation of this study is to study the changes in the structural and functional connectivity of the amygdala in comorbidity of migraine and depression. We used a seedbased method to compare amygdala volume and intrinsic functional connectivity between episodic migraine with depression (EMwD), episodic migraine (EM), patients with major depressive disorder (MDD) and healthy controls (HC).

METHODS

Subjects

All patients were recruited from the Department of Neurology of the First Affiliated Hospital of Anhui Medical University and the First Affiliated Hospital of Science and Technology University of China between March 2019 and October 2020.They were received evaluation by two neurologists and two psychiatrists. Diagnosis of migraine without aura is based on the third edition (beta) of the International Classification of Headache Disorders (ICHD-3 beta)[24].Depression was diagnosed by two experienced psychiatrists using Diagnostic and Statistical Manual of Mental Disorders for 5th Edition (DSM-5) criteria[25]. The selection criteria for all subjects were (1) Han nationality (the main ethnicity in China), (2) 18-55 years old, (3) right-handed. The exclusion criteria were (1) a history of systemic diseases and severe neurological diseases, (2) migraine preventive medication used in the past 3 months or overuse of painkillers, (3) intracranial lesions found on previous MRI or CT scans, (4) contraindications for MRI scans, including metal implants or mental illnesses. Before MR scanning, all participants provided written informed consent.

The EMwD group

According to the criteria of ICHD-3 beta and DSM-5, 22 patients were diagnosed with episodic migraine without aura and depression. They were in the stage of depressive episodes. They did not use any antidepressants or drugs to prevent migraine in the past 3months. All migraineurs were migraine-free for at least 3 days prior to examination and were followed-up 3 days after the scanning to ensure that they had remained migraine-free to avoid any possible interference from headache pain on the imaging results.

The EM group

22 patients were diagnosed with episodic migraine without aura and without any history of mental illness (including MDD or depressive mood). They had no other medical condition than migraine, no history of medications overuse, and without any prophylactic or chronic medication for at least 3 months prior to study entry. This group also had no migraine at least 3 days before the examination, and followed up 3 days after the scan.

The MDD group

20 patients in the MDD group were received the clinical diagnosis of depression

based on the DSM-V. They were clinically interviewed by two qualified psychiatrists and in the current stage of depressive episodes. They had no history of headache.

The HC group

18 right-handed healthy participants were involved. All subjects underwent routine physical examinations and neurological examinations, and were normotensive (≤140/90 mmHg), and had no cardiovascular, metabolic or mental diseases.

All subjects underwent a neurological examination and completed a standardized questionnaire to ascertain demographics including age, sex, and educational level. The clinical characteristics of patients were obtained, including migraine duration, attack frequency and attack duration of migraine, headache degree, Visual Analogue Scale(VAS),The Migraine Disability Assessment questionnaire (MIDAS), the Headache Impact Test-6 (HIT-6), Hamilton Anxiety Scale (HAMA), Hamilton Depression Scale (HAMD) and Mini-mental State Examination(MMSE). Of all the MDD patients were treated with monotherapy or combination therapy. The study was approved by the Anhui Medical University Ethics Committee.

MRI data acquisition

All images were acquired on a 3.0-T MRI scanning system (Discovery GE750w; GE Healthcare, Buckinghamshire, United Kingdom) at University of Science and Technology of China, Hefei, Anhui Province. 8-channel head coil. High-resolution 3D T1-weighted structural images were acquired using a brain volume (BRAVO) sequence with the following parameters: repetition time (TR) = 8.16 ms; echo time (TE) = 3.18 ms; flip angle (FA) = 12°; field of view (FOV) = 256 mm × 256 mm; matrix = 256 × 256; slice thickness = 1 mm, no gap; 188 sagittal slices; Resting-state BOLD data were obtained by using a gradient echo planar imaging (EPI) sequence(TR = 2400 ms; TE = 30 ms; FA = 90°; FOV = 192 mm × 192 mm; matrix = 64 × 64; slice thickness = 3 mm, slice gap = 1 mm). Before the scanning, all participants were instructed to keep their eyes closed, to let their minds wander, and to avoid falling asleep.

Brain volume quantification

The 3D T1-weighted structural images were processed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm) and VBM8 (http://dbm.neuro.uni-jena.de/ vbm) under MATLAB R2013b (The Mathworks, Natick, MA, USA), involving spatial normalization, segmentation, modulation, and smoothing. The software package's segmentation algorithm was used to partition images into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). Total intracranial volume (TIV) was

assessed by combining the totality of GM, WM, and CSF volumes. With respect to ROI volume, the bilateral amygdala were defined using WFU PickAtlas software (http://www.ansir.wfubmc.edu) (Fig. 1a).

fMRI data preprocessing and functional connectivity analysis

Functional images were conducted using the software Data Processing and Analysis for Brain Imaging (DPARSFA, http://rfmri.org/DPARSF) in MATLAB R2013b. The first 10 volumes were discarded for each subject. The remaining images were corrected by the following steps: slicing time, realignment for head motion correction (all head movements exceeding 2.0mm were excluded), spatial normalization to Montreal Neurological Institute (MNI) (coordinate space with 3 × 3 × 3mm), smoothing with an 8 × 8 × 8 mm^3 full width at half-maximum kernel(FWHM), detrending and filtered using a frequency range of 0.01–0.1 Hz.

The functional connectivity analysis was performed as follows: 1) The centromedial amygdala (CMA) ROI mask was created from a data-driven characterization using coactivation-based parcellation[11] (Fig. 1b). 2) Functional connectivity computation of the left and right CMA were performed using DPARSFA. The averaged time courses of ROI were extracted and then Pearson's correlations were used to calculate the functional connectivity between the extracted time courses and the averaged time courses of each voxel in the whole brain. Fisher's Z transform was conducted to normalize the correlation coefficient.

Statistical analysis

Demographic variables(the age, sex, education years, TIV) and clinical features (HAMA, HAMD) were performed with one-way analysis of variance (ANOVA). VAS, MIDAS, HIT-6 were performed with two-sample t test. Post Hoc multiple comparisons were performed by LSD methods with equal variances. The amygdala volumes were compared using ANOVA among the four groups. Pearson correlation analyses were used to examine the relationship between clinical features and amygdala volume. These statistics were performed by using IBM SPSS 24.0 (version 24.0;SPSS, Chicago, IL, USA), and the $P < 0.05$ was considered to be a statistically significant difference. To obtain rsFC differences between the four groups, ANOVA tests were performed using dpabi software[26]. We put the age, sex, education years as the covariates in the calculates. All statistical maps were corrected with a Gaussian Random Field(GRF) method. The threshold was set at $p < 0.001$ at the voxel level, $p < 0.05$ at the cluster level, two-tailed. Pearson correlation analyses between the RSFC and each clinical

indicator was calculated using SPSS 24.0.

RESULTS

Demographic and clinical characteristics

Subject demographics and neurophysiological characteristics are shown in Table 1. There were no significant differences observed among the four groups in regards to age, sex, education years, total intracranial volume (TIV).

Intergroup differences in amygdala volume

The volume of the amygdala, grey matter, white matter and the total intracranial are shown in Table 2. Figrue 2 showed that the left and right AMY volume of the four groups. The comparisons of bilateral amygdala volume among the four groups presented in Table 3. The results showed that there were significant differences in the volume between EMwD and MDD, EMwD and HC, EM and HC,($P<0.05$). Compared to HC group, the volume of amygdala increased in EMwD group and EM group. EMwD group showed larger volume than MDD group. There was no significant difference between the EMwD group and EM group.

Correlation analysis between clinical variables and AMY volume

As illustrated in Figure 3, in both right and left amygdala, the volume was positively correlated with the duration of illness in patient groups. Other clinical indicators showed no significant correlation with AMY volume.

Intergroup differences in functional connectivity of CMA

Compared with the EM group, EMwD group showed a decreased rsFC between the left CMA and the left pallidum. For the right CMA, the decreased rsFC located in left cerebelum8, the left dorsolateral prefrontal cortex (DLPFC), the left precuneus cortex (PCC) (Fig. 3; Table 4). Compared with HC, patients in EM showed a significant increased rsFC between the right CMA and the right pallidum, the left and right dorsolateral prefrontal cortex (DLPFC), the right cingulum gyrus (Fig. 4; Table 4).

Correlation analysis between clinical variables and FC

A significantly negative correlation between FC and HAMD($r=-0.654$,$p<0.001$), HAMA($r=-0.368$,$p=0.01$) scores was demonstrated between the right CMA and left DLPFC, where FC is lower in this loop of patients had greater HAMD, HAMA scores (Fig. 5).

DISCUSSION

In this study, the individual AMY was created by applying the deformation field[27] to the AMY template, and it could be used to compute the true AMY volume. We demonstrated that amygdala volumetric differences between patients and HC. EMwD had the largest amygdala volume, and it was significantly larger than that of MDD and NC. The AMY volume of EM also larger than HC. Specifically, we found increased volume of amygdala was positively correlated with the duration of illness. Although there was no significant difference of AMY volume within EMwD and EM groups, the AMY volume of EMwD showed a slightly increased tendency compared with EM. We also did not detect any differences between MDD and HC groups.

Some previous studies either in animal models[28] or human subjects[29] reported that the increased volume of the amygdala can be seen in the neuropathic pain. Some reported that altered volume of the amygdala in migraine patients. A VBM data established that the GMV was decreased in several brain regions involved in central pain processing, such as insula, amygdala, parietal operculum, middle and inferior frontal gyrus. The amygdala volume of chronic migraine was smaller than that of episodic migraine[30].A previous study showed that amygdala volume changed with headache frequency and the volume was correlated with frequency in specific ranges[31].Our findings showed some inconsistent of the AMY volume could possibly due to heterogeneity in patients, differences in attack frequency and MRI data processing approaches.

The AMY volume showed a increased tendency in EMwD and EM with the length of illness. The volume of comorbidity showed significantly larger than HC. Therefore, it could be considered that AMY structural change might be the cause of the comorbidity, and AMY volume expansion might be the result of disrupted AMY network in migraine. Given the established role of the amygdala in emotional behaviour, we propose that these neuroplastic changes might contribute for the development of depressive symptoms.

Many previous studies had shown some associations between migraine and depression, but most of them were based on case studies, clinical observations, and genetic epidemiology. Resting-state functional connectivity(rsFC) is often used for explore regional cooperation between a predefined seed region and functionally related regions[32], and had been used to study various disorders. Previous studies had shown that the CMA might be devoted to influencing motor movement, visceral responses, attentional reallocation, and related to its coactivation areas such as the posterior mid-

cingulate cortex (pMCC), primary motor cortex, supplementary motor area, basal ganglia, primary somatosensory cortex, insula, and thalamus[11]. Our current study showed that patients with EMwD had disrupted resting-state CMA FC with a set of brain regions including diverse functional areas.

There was a significant decreased rsFC of right CMA in EMwD compared with EM in our study, involving left cerebellum, left dorsolateral prefrontal cortex (DLPFC) and left precuneus cortex (PCC). For the left CMA, we found decreased rsFC in the left pallidum. The changes in rsFC pattern of left and right CMA may be related to different functions of bilateral amygdala. The left amygdala mainly induced either pleasant (happiness) or unpleasant (fear, anxiety, sadness) emotions, while the right amygdala mainly induced negative emotions such as fear and sadness[33].

The dorsolateral prefrontal cortex (DLPFC), also known as Brodmann's areas 9 and 46, regulates cognitive and executive functions. It plays a vital role in MDD[34].Previous studies reported that in patients with MDD, the DLPFC had been found to exhibit abnormal metabolism[34], blood flow reduction [35], and gray matter volume reduction[36]. In post-mortem MDD patients, the density of neurons and glial in DLPFC were reduced[37]. Therefore, DLPFC is considered to be a key area in the neuronal circuit underlying the pathophysiology of MDD. Prefrontal dysfunction in the form of impaired neuropsychological tests of prefrontal function has been reported in patients with chronic migraine[38]. In addition, a study involving healthy volunteers reported that reduced capsaicin induced pain on the dorsum of both the hands on left DLPFC stimulation, with no such effect on right DLPFC stimulation[39].In the comorbidity of migraine with depression patients, a previous magnetic resonance spectroscopy (MRS) study found an increased myo-inositol/ total creatine(mI/tCr) ratio in the DLPFC[40].A previous research conducted high frequency repetitive transcranial magnetic stimulation(HF-rTMS) over left DLPFC in migraine comorbid with depression, and showed significantly reduced in headache frequency, severity and functional disability at the end of treatment as compared to baseline[41].Our study suggested that decreased rsFC of right CMA and left DLPFC in EMwD compared with EM, and a significant negative correlation between the values of FC and HAMD and HAMA scores. Compared with HC, EM showed increased rsFC. However, we did not detect any alter regions between MDD and HC, perhaps due to the use of antidepressant medication in MDD patients. Thus, our work suggested that the DLPFC might be the target impaired brain region in the disrupted CMA dysfunction network. We speculated that left DLPFC

is associated with the onset of migraine and may contribute to the comorbidity of migraine with depression patients and associated with the depressive tendency.

In recent years, the cerebellum is implicated in several neurological and psychiatric disorders, mounting evidence has shown that the cerebellum is not only involved in motor and coordinative functions, but also involved in memory, associative learning, cognition, somatosensory processing, including nociception[42]. Earlier structural MRI studies of migraine demonstrated that decreased gray matter volume in cerebellum[43]. FC also changed between the cerebellum and other brain regions, such as thalamus, occipital areas, prefrontal cortex and fusiformis gyrus[44]. Recent study showed patients with MDD had decreased cerebellar-cerebral dynamic FC of the cerebellar subregions connecting with the executive, default-mode and affective-limbic networks. The dynamic FC of the cerebellar subregion connecting with the affective-limbic network was related to severity of depression and anxiety symptoms in MDD patients[45].Our findings proved that migraine patients comorbid depression had decreased FC of cerebellum compared migraineurs. Thus we can consider cerebellum not only involve the processing of migraine pain but also plays a role in contribute to modulate cortical excitability in migraineurs with depression.

The precuneus cortex (PCC) is the key core of default mode network(DMN), which is one of the main networks that are consistently identified when an individual is at wakeful rest and not performing an attention-demanding task. In MDD patients, the disrupted connectivities of PCC had been found, including areas such as the dorsolateral prefrontal cortex, temporal cortex, and angular and supramarginal areas[46].A previous study showed abnormalities of the PCC in migraine without aura, suggested that information transfer and multimodal integration dysfunction and pain sensitivity and pain processing may also be affected[47]. A comorbidity research found that the altered activity of PCC in migraine might be related to the depressive tendency[22]. In our study, the rsFC between right CMA and left precuneus was reduced, and this connectivity pattern suggested the amygdala modulation network had a vital role in the migraine and depression.

Our results revealed that migraine with depression exhibit significantly decreased rsFC in the amygdala compared with EM while EM showed enhanced rsFC compared with HC. We speculate that these changes are related to different symptoms. This finding emphasizes the abnormal developmental patterns of brain activity inherent in migraine with depression comorbidity, rather than migraine or depression alone. Our

findings suggested that the reduced connection between CMA and DLPFC may be a potential neural substrate for the coexistence of migraine and depression. A better understanding of the neural mechanisms in the comorbidity may facilitate further classification diagnosis and help optimize clinical treatment. For example, increasing the connection between the CMA and DLPFC through deep target stimulation can provide a treatment in migraine patients with depression.

The current research has several limitations. First, the number of patients with EMwD, EM, MDD was relatively small, and future studies will require a large number of sample studies. Second, this study was a cross-sectional study, and the longitudinal observation should be conducted to investigate the disease development. Third, the HAMD score of the EMwD group is lower than that of the MDD group, and antidepressants may change the functional connections of brain regions related to depression[48].

CONCLUSIONS

This study explored the amygdala volume and functional connectivity of migraine comorbid depression in four groups. Our research is the first to investigate the roles of amygdala in the neurolimbic modulating in the migraine comorbid depression pathogenesis. The increased volume of bilateral amygdala gave a direct evidence to migraine with depression and migraine. And the decreased rsFC of right CMA and cerebellum, dorsolateral prefrontal cortex (DLPFC) and precuneus cortex(PCC) enlightened the neural mechanism of the comorbidity. Our results indicate that the comorbidity is produced through a specific mechanism, rather than a simple superposition of migraine and depression. In the future, migraine research may need to consider depression when interpreting fMRI data.

Abbreviations

EM: episodic migraine; EMwD: migraine comorbid with depression; MDD: major depressive disorder; HC: healthy controls; AMY: amygdala; CMA: centromedial amygdala; VBM: voxel-based morphometry; rsFC: resting state functional connectivity; DLPFC: dorsolateral prefrontal cortex; PCC: precuneus cortex.

References

[1] Lj S, Hagen K, Jensen R, et al. The global burden of headache: a documentation of headache prevalence and disability worldwide. Cephalalgia. 2007. 27(3): 193-210.

[2] GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016. 388(10053): 1545-1602.

[3] Bergman-Bock S. Associations Between Migraine and the Most Common Psychiatric Co-Morbidities. Headache. 2018. 58(2): 346-353.

[4] Maizels M, Aurora S, Heinricher M. Beyond neurovascular: migraine as a dysfunctional neurolimbic pain network. Headache. 2012. 52(10): 1553-65.

[5] Herman JP, Ostrander MM, Mueller NK, Figueiredo H. Limbic system mechanisms of stress regulation: hypothalamo-pituitary-adrenocortical axis. Prog Neuropsychopharmacol Biol Psychiatry. 2005. 29(8): 1201-13.

[6] Neugebauer V, Li W, Bird GC, Han JS. The amygdala and persistent pain. Neuroscientist. 2004. 10(3): 221-34.

[7] Tye KM, Prakash R, Kim SY, et al. Amygdala circuitry mediating reversible and bidirectional control of anxiety. Nature. 2011. 471(7338): 358-62.

[8] Morris JS, Frith CD, Perrett DI, et al. A differential neural response in the human amygdala to fearful and happy facial expressions. Nature. 1996. 383(6603): 812-5.

[9] Cullen KR, Westlund MK, Klimes-Dougan B, et al. Abnormal amygdala resting-state functional connectivity in adolescent depression. JAMA Psychiatry. 2014. 71(10): 1138-47.

[10] Nolan M, Roman E, Nasa A, et al. Hippocampal and Amygdalar Volume Changes in Major Depressive Disorder: A Targeted Review and Focus on Stress. Chronic Stress (Thousand Oaks). 2020. 4: 2470547020944553.

[11] Bzdok D, Laird AR, Zilles K, Fox PT, Eickhoff SB. An investigation of the structural, connectional, and functional subspecialization in the human amygdala. Hum Brain Mapp. 2013. 34(12): 3247-66.

[12] Leaver AM, Yang H, Siddarth P, et al. Resilience and amygdala function in older healthy and depressed adults. J Affect Disord. 2018. 237: 27-34.

[13] Qiu L, Xia M, Cheng B, et al. Abnormal dynamic functional connectivity of amygdalar subregions in untreated patients with first-episode major depressive disorder. J Psychiatry Neurosci. 2018. 43(4): 262-272.

[14] Han S, Soleiman MT, Soden ME, Zweifel LS, Palmiter RD. Elucidating an Affective Pain Circuit that Creates a Threat Memory. Cell. 2015. 162(2): 363-374.

[15] Penzo MA, Robert V, Tucciarone J, et al. The paraventricular thalamus controls a central amygdala fear circuit. Nature. 2015. 519(7544): 455-9.

[16] Hadjikhani N, Ward N, Boshyan J, et al. The missing link: enhanced functional connectivity between amygdala and visceroceptive cortex in migraine. Cephalalgia. 2013. 33(15): 1264-8.

[17] Chen Z, Chen X, Liu M, Dong Z, Ma L, Yu S. Altered functional connectivity of amygdala underlying the neuromechanism of migraine pathogenesis. J Headache Pain. 2017. 18(1): 7.

[18] Zhou W, Jin Y, Meng Q, et al. A neural circuit for comorbid depressive symptoms in chronic pain. Nat Neurosci. 2019. 22(10): 1649-1658.

[19] Sublette ME, Galfalvy HC, Oquendo MA, et al. Relationship of recent stress to amygdala volume in depressed and healthy adults. J Affect Disord. 2016. 203: 136-142.

[20] Gudmundsson LS, Scher AI, Sigurdsson S, et al. Migraine, depression, and brain volume: the AGES-Reykjavik Study. Neurology. 2013. 80(23): 2138-44.

[21] Li XL, Fang YN, Gao QC, et al. A diffusion tensor magnetic resonance imaging study of corpus callosum from adult patients with migraine complicated with depressive/anxious disorder. Headache. 2011. 51(2): 237-45.

[22] Ma M, Zhang J, Chen N, Guo J, Zhang Y, He L. Exploration of intrinsic brain activity in migraine with and without comorbid depression. J Headache Pain. 2018. 19(1): 48.

[23] Tietjen GE, Buse DC, Fanning KM, Serrano D, Reed ML, Lipton RB. Recalled maltreatment, migraine, and tension-type headache: results of the AMPP study. Neurology. 2015. 84(2): 132-40.

[24] Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia. 2013. 33(9): 629-808.

[25] Regier DA, Kuhl EA, Kupfer DJ. The DSM-5: Classification and criteria changes. World Psychiatry. 2013. 12(2): 92-8.

[26] Yan CG, Wang XD, Zuo XN, Zang YF. DPABI: Data Processing & Analysis for (Resting-State) Brain Imaging. Neuroinformatics. 2016. 14(3): 339-51.

[27] Ashburner J. A fast diffeomorphic image registration algorithm. Neuroimage. 2007. 38(1): 95-113.

[28] Gonçalves L, Silva R, Pinto-Ribeiro F, et al. Neuropathic pain is associated with depressive behaviour and induces neuroplasticity in the amygdala of the rat. Exp Neurol. 2008. 213(1): 48-56.

[29] Mao C, Wei L, Zhang Q, Liao X, Yang X, Zhang M. Differences in brain structure in patients with distinct sites of chronic pain: A voxel-based morphometric analysis. Neural Regen Res. 2013. 8(32): 2981-90.

[30] Valfrè W, Rainero I, Bergui M, Pinessi L. Voxel-based morphometry reveals gray matter abnormalities in migraine. Headache. 2008. 48(1): 109-17.

[31] Liu HY, Chou KH, Lee PL, et al. Hippocampus and amygdala volume in relation to migraine frequency and prognosis. Cephalalgia. 2017. 37(14): 1329-1336.

[32] Lee MH, Smyser CD, Shimony JS. Resting-state fMRI: a review of methods and clinical applications. AJNR Am J Neuroradiol. 2013. 34(10): 1866-72.

[33] Lanteaume L, Khalfa S, Régis J, Marquis P, Chauvel P, Bartolomei F. Emotion induction after direct intracerebral stimulations of human amygdala. Cereb Cortex. 2007. 17(6): 1307-13.

[34] Koenigs M, Grafman J. The functional neuroanatomy of depression: distinct roles for ventromedial and dorsolateral prefrontal cortex. Behav Brain Res. 2009. 201(2): 239-43.

[35] Caetano SC, Fonseca M, Olvera RL, et al. Proton spectroscopy study of the left dorsolateral prefrontal cortex in pediatric depressed patients. Neurosci Lett. 2005. 384(3): 321-6.

[36] Chang CC, Yu SC, McQuoid DR, et al. Reduction of dorsolateral prefrontal cortex gray matter in late-life depression. Psychiatry Res. 2011. 193(1): 1-6.

[37] Si X, Miguel-Hidalgo JJ, O'Dwyer G, Stockmeier CA, Rajkowska G. Age-dependent reductions in the level of glial fibrillary acidic protein in the prefrontal cortex in major depression. Neuropsychopharmacology. 2004. 29(11): 2088-96.

[38] Mongini F, Keller R, Deregibus A, Barbalonga E, Mongini T. Frontal lobe dysfunction in patients with chronic migraine: a clinical-neuropsychological study. Psychiatry Res. 2005. 133(1): 101-6.

[39] Brighina F, Cosentino G, Vigneri S, et al. Abnormal facilitatory mechanisms in motor cortex of migraine with aura. Eur J Pain. 2011. 15(9): 928-35.

[40] Lirng JF, Chen HC, Fuh JL, Tsai CF, Liang JF, Wang SJ. Increased myo-inositol level in dorsolateral prefrontal cortex in migraine patients with major depression. Cephalalgia. 2015. 35(8): 702-9.

[41] Kumar S, Singh S, Kumar N, Verma R. The Effects of Repetitive Transcranial Magnetic Stimulation at

Dorsolateral Prefrontal Cortex in the Treatment of Migraine Comorbid with Depression: A Retrospective Open Study. Clin Psychopharmacol Neurosci. 2018. 16(1): 62-66.

[42] Moulton EA, Schmahmann JD, Becerra L, Borsook D. The cerebellum and pain: passive integrator or active participator. Brain Res Rev. 2010. 65(1): 14-27.

[43] Jin C, Yuan K, Zhao L, et al. Structural and functional abnormalities in migraine patients without aura. NMR Biomed. 2013. 26(1): 58-64.

[44] Mehnert J, May A. Functional and structural alterations in the migraine cerebellum. J Cereb Blood Flow Metab. 2019. 39(4): 730-739.

[45] Zhu DM, Yang Y, Zhang Y, et al. Cerebellar-cerebral dynamic functional connectivity alterations in major depressive disorder. J Affect Disord. 2020. 275: 319-328.

[46] Cheng W, Rolls ET, Qiu J, et al. Functional Connectivity of the Precuneus in Unmedicated Patients With Depression. Biol Psychiatry Cogn Neurosci Neuroimaging. 2018. 3(12): 1040-1049.

[47] Zhang J, Su J, Wang M, et al. Increased default mode network connectivity and increased regional homogeneity in migraineurs without aura. J Headache Pain. 2016. 17(1): 98.

[48] van Marle HJ, Tendolkar I, Urner M, Verkes RJ, Fernández G, van Wingen G. Subchronic duloxetine administration alters the extended amygdala circuitry in healthy individuals. Neuroimage. 2011. 55(2): 825-31.

Declarations

Ethics approval and consent to participate

The studies involving human participants were reviewed and approved by the Ethics Committee of The First Affiliated Hospital of Anhui Medical University. The patients/participants provided their written informed consent to participate in this study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated for this study are available on request to the corresponding author.

Competing interests

The authors declare that there is no conflict of interest.

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Author contributions

Yu Wang designed the study and revised the final manuscript. Xin Chen performed the experiments and data analysis, and wrote the draft manuscript. Wei Gui, Mei-Dan Zu, Long Wang and Juan Zhang contributed clinical data collection and assessment. Ben-Sheng Qiu and Jin-Ying Yang conducted acquisition of neuroimaging data. All authors read and approved the final version of the manuscript.

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Table 1 The demographic and clinical characteristics of Participants

	EMwD	EM	MDD	HC	P value
Demographic and Clinical data					
Num(F/M)	22(18/4)	22(18/4)	20(16/4)	18(14/4)	0.987[a]
Age(years)	30.8(6.8)	32(7.7)	35.5(11.1)	31.3(8.8)	0.359[b]
EduYears	12.4(4.6)	14.1(3.5)	11.6(4.9)	14.3(4.2)	0.13[b]
TIV (cm3)	1369.1(127.3)	1418.4(115)	1442.4(137.7)	1421.1(118.6)	0.275[b]
Duration of illness(years)	8.2(5.5)	8.8(5.1)	4.9(7.2)	/	0.086[b]
VAS	6.2(1.2)	6.3(1.5)	/	/	0.821[c]
MIDAS	23.5(20.1)	16.6(11.4)	/	/	0.43[c]
HIT-6	60.7(4.8)	59.5(5.4)	/	/	0.171[c]
17-HAMD	17.3(3.9)	3.8(4)	27.2(3.9)	1.7(2)	<0.001[b]
14-HAMA	9.99(5)	3.8(1.9)	24.5(6.4)	2.3(2.5)	<0.001[b]
Antidepressant Medication (Number Of Patients)					
SSRIs			13		
SNRIs			5		
NaSSA			5		

The data are shown as the mean (SD).[a] The P-value was obtained by Pearson Chi-square test.[b] The P-value

was separate one-way ANCOVA tests.[c]The P-values were obtained by two-sample t-tests. TIV, total intracranial volume; VAS visual analogue scale; HIT-6 Headache Impact Test; MIDAS Migraine Disability Assessment questionnaire ; HAMD, Hamilton Rating Scale for Depression; HAMA, Hamilton Rating Scale for Anxiety; SSRIs = selective serotonin reuptake inhibitors; SNRIs = serotonin–norepinephrine reuptake inhibitors; SARIs = serotonin antagonist and reuptake inhibitors; NaSSA = norepinephrine and specific serotonergic antidepressants.

Table 2 volumes of patients and healthy controls

Volumes (cm3)	EMwD(n = 22)	EM(n = 22)	MDD(n = 20)	HC(n = 18)
L-amygdala	1.28±.0.1	1.22±0.2	1.17±0.16	1.11±0.16
R-amygdala	1.34±0.1	1.29±0.21	1.24±0.17	1.17±0.17
Gray matter	634.05±53.33	657.09±52.5	655.1±49.66	661.87±57
White matter	527.08±58.55	542.4±52.82	552.83±70.61	540.06±50.54
TIV	1369.09±127.29	1418.39±115.04	1442.43±136.68	1421.08±118.63

Data are presented as mean±SD; L Left, R Right

EMwD episodic migraine with depression; EM episodic migraine; MDD patients with major depressive disorder; HC healthy controls. TIV total intracranial volume.

Table 3 The comparison of amygdala volume among groups using one-way ANOVA

	Mean difference (95% CI)*	Std. Error.	Sig.[a]
EMwD vs.EM （left/right）	0.05914/0.06182	0.04709/0.04935	0.213/0.214
EMwD vs. MDD （left/right）	0.10501/0.10483	0.04825/0.05057	0.033/0.041
EMwD vs. HC （left/right）	0.17174/0.17812	0.04964/0.05202	0.001/0.001
EM vs. MDD （left/right）	0.04587/0.04301	0.04825/0.05057	0.345/0.398
EM vs. HC （left/right）	0.11261/0.1163	0.04964/0.05202	0.026/0.028
MDD vs. HC （left/right）	0.04587/0.07329	0.05074/0.05318	0.192/0.172

** The mean difference is significant at the 0.05 level*

[a] Adjustment for multiple comparisons: Least Significant Difference (equivalent to no adjustments)

Table 4 Abnormal functional connectivity of bilateral centromedial amygdala in patients compared with healthy controls

Group	seed	Region(AAL)	Region(BA)	MNI			Voxel Size	Peak t
				x	y	z		
EMwDvsEM	L_CMA R_CMA	Pallidum_L	48	-24	-9	-6	36	-4.47
EMwDvsEM		L cerebelum_8	-	-15	-66	-48	47	-4.08
		L middle frontal	9，46	-27	36	36	123	-5.04
		L precuneus	7	-12	-78	51	66	-4.45
EMvsHC		Pallidum_R	20	27	-9	-6	29	5.63
		Frontal_Mid_R	45，46	30	45	33	107	4.4
		Frontal_Mid_L	9，46	-27	39	33	122	4.84

Cingulum_Mid_R	24, 32	9	12	33	82	4.71

voxel level set at p < 0.001, cluster level set at p <0.05 (GRF correction) ;BA Brodmann Area
MNI Montreal Neurological Institute, L left, R right

Figure legend

Fig.1 (a) the mask of the bilateral AMY; (b) the mask of the left and right CMA

Fig. 2 AMY volume of the four groups.

Fig. 3 The duration of illness in patients groups was positively correlated with both the left and right amygdala.

Fig. 4 Altered effective connectivities between the CMA and whole brain regions in EMwD compared with EM. (a) a decreased rsFC between the left CMA and the left pallidum; (b),(c),(d) for the right CMA, decreased rsFC in the left cerebelum_8, the left middle frontal gyrus, the left precuneus gyrus.

Fig. 5 Compared EM with HC, increased rsFC between the right CMA and the right pallidum, the left and right middle frontal gyrus, the right cingulum gyrus.

Fig. 6 The relationship between right CMA-left DLPFC FC and HAMD,HAMA score. A significant negative correlation ($r = -0.654/-0.386$, $p<0.001/P=0.01$) was observed in EMwD and EM patients between the value of rsFC and HAMD/HAMA score.

Figures

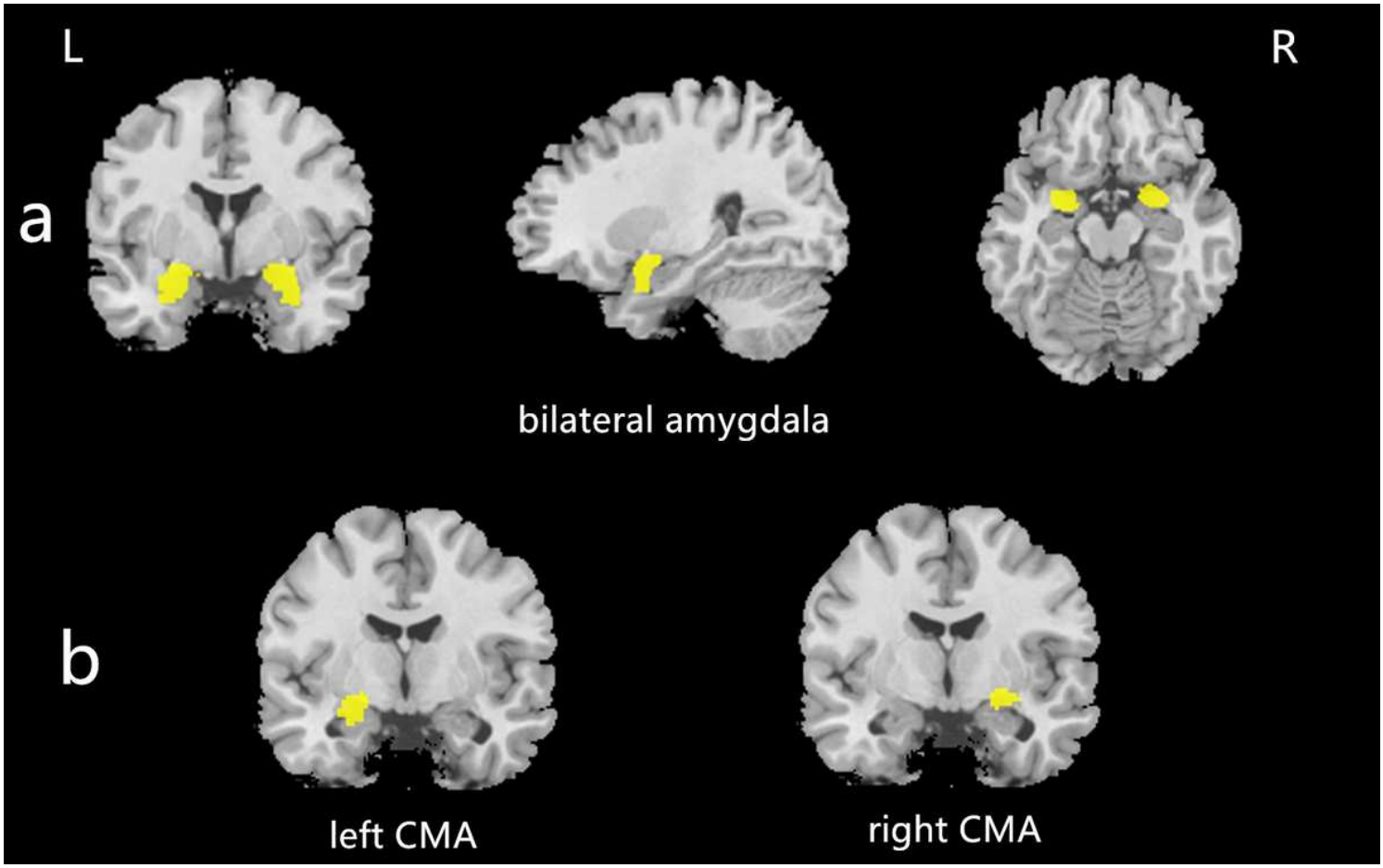

Figure 1

(a) the mask of the bilateral AMY; (b) the mask of the left and right CMA

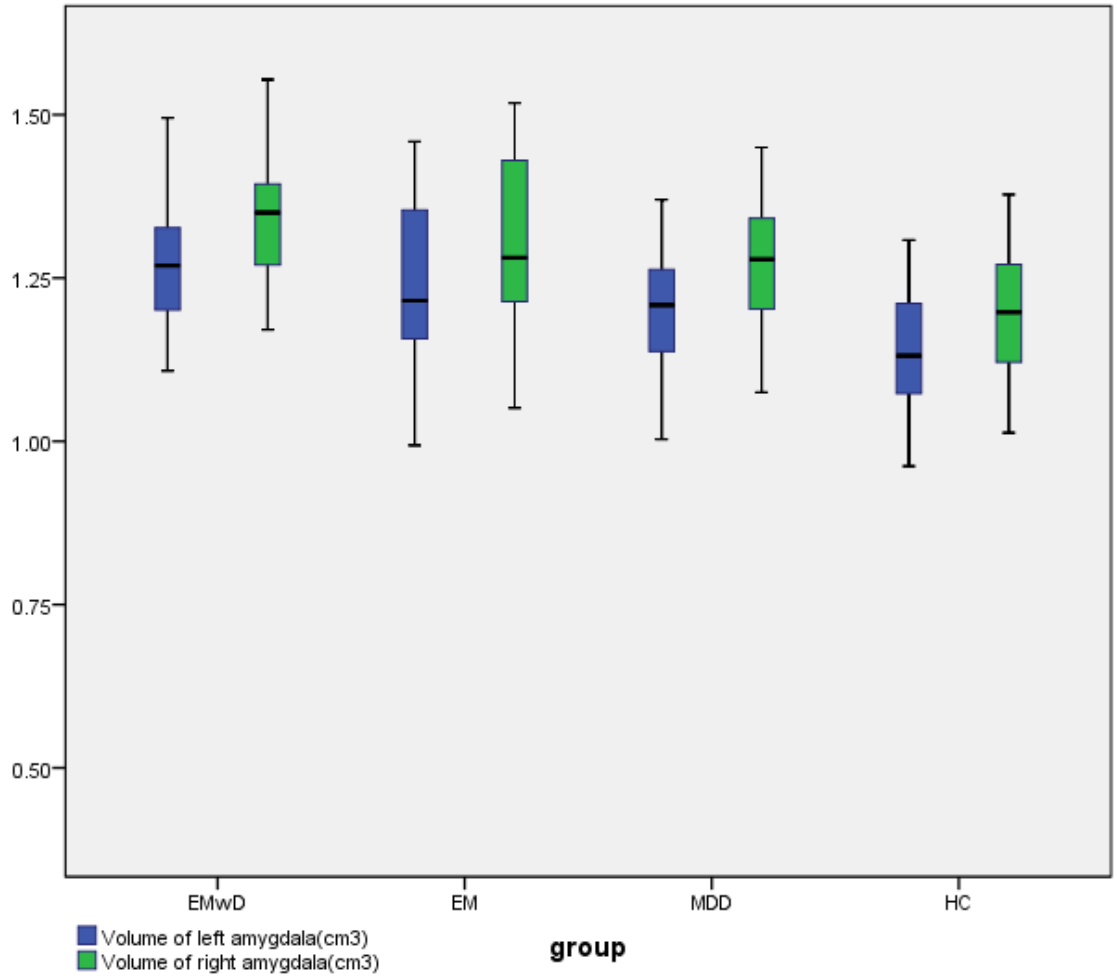

Figure 2

AMY volume of the four groups.

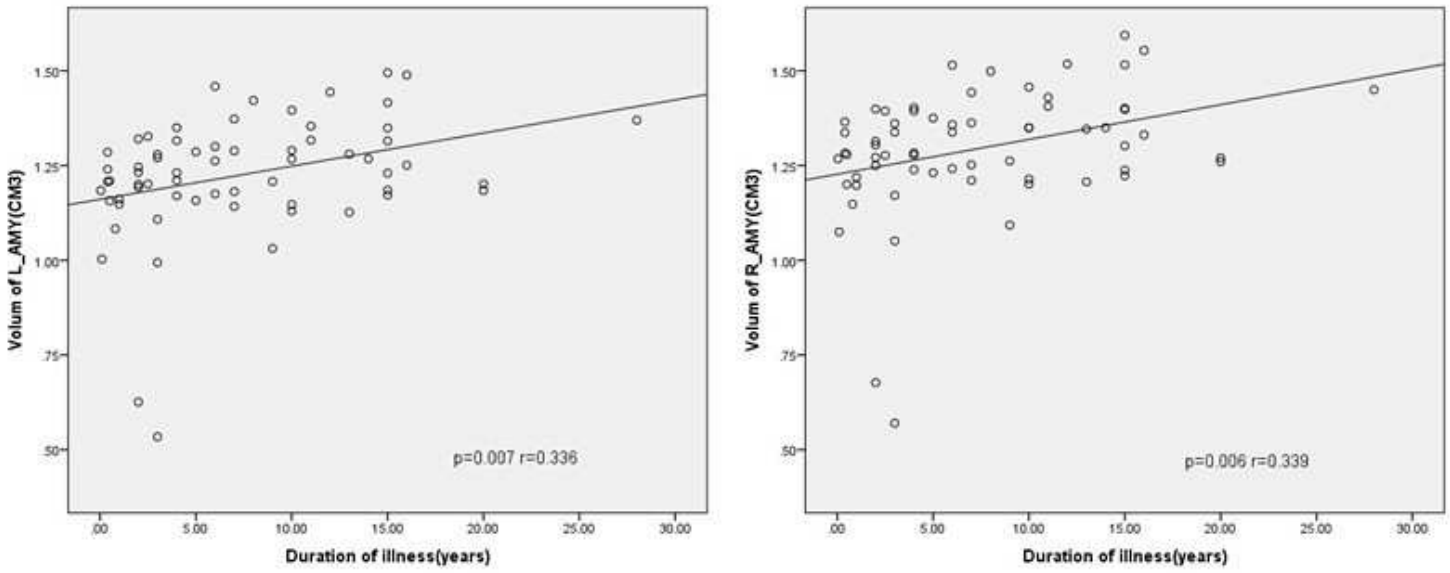

Figure 3

The duration of illness in patients groups was positively correlated with both the left and right amygdala.

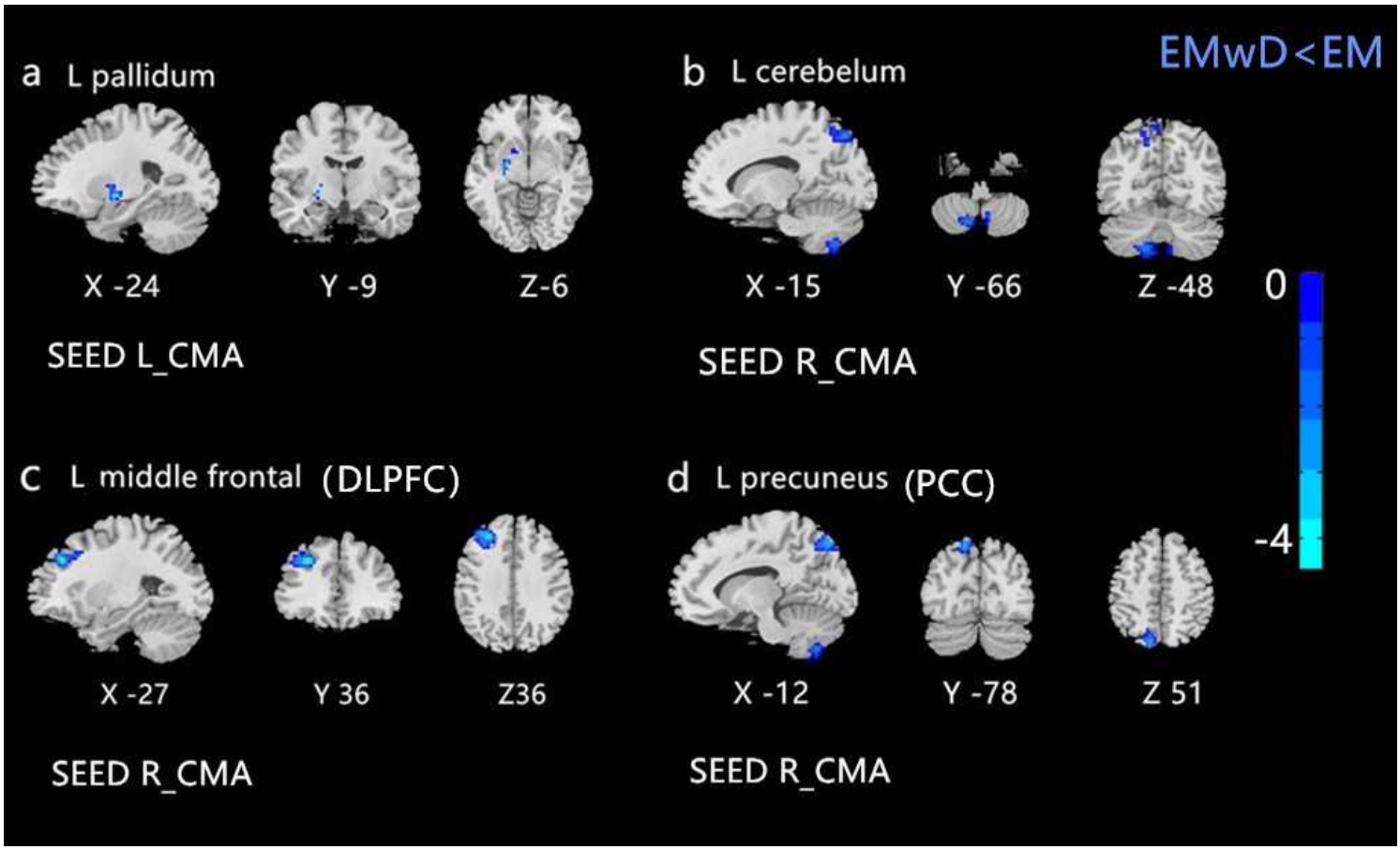

Figure 4

Altered effective connectivities between the CMA and whole brain regions in EMwD compared with EM. (a) a decreased rsFC between the left CMA and the left pallidum; (b),(c),(d) for the right CMA, decreased rsFC in the left cerebelum_8, the left middle frontal gyrus, the left precuneus gyrus.

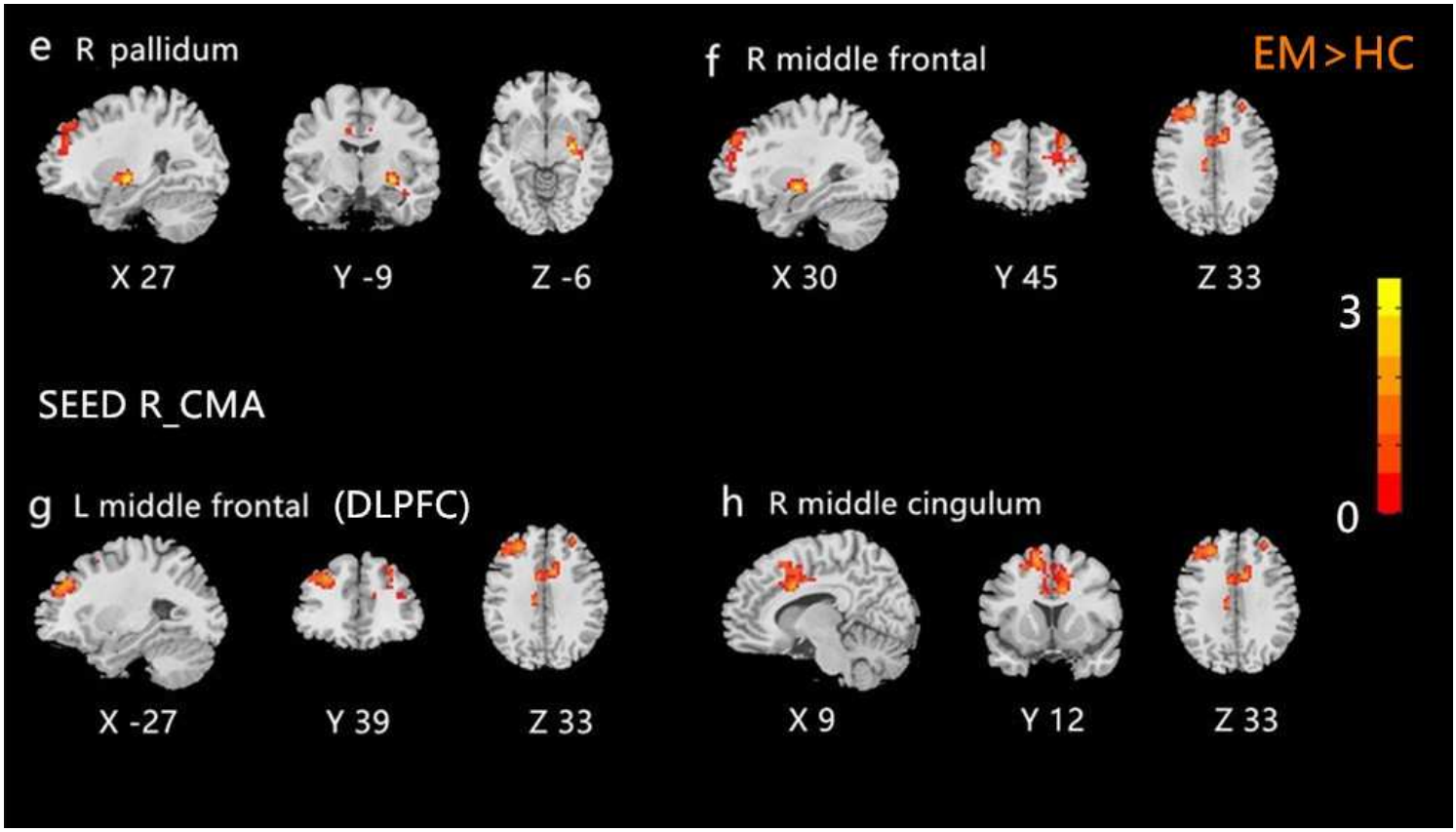

Figure 5

Compared EM with HC, increased rsFC between the right CMA and the right pallidum, the left and right middle frontal gyrus, the right cingulum gyrus.

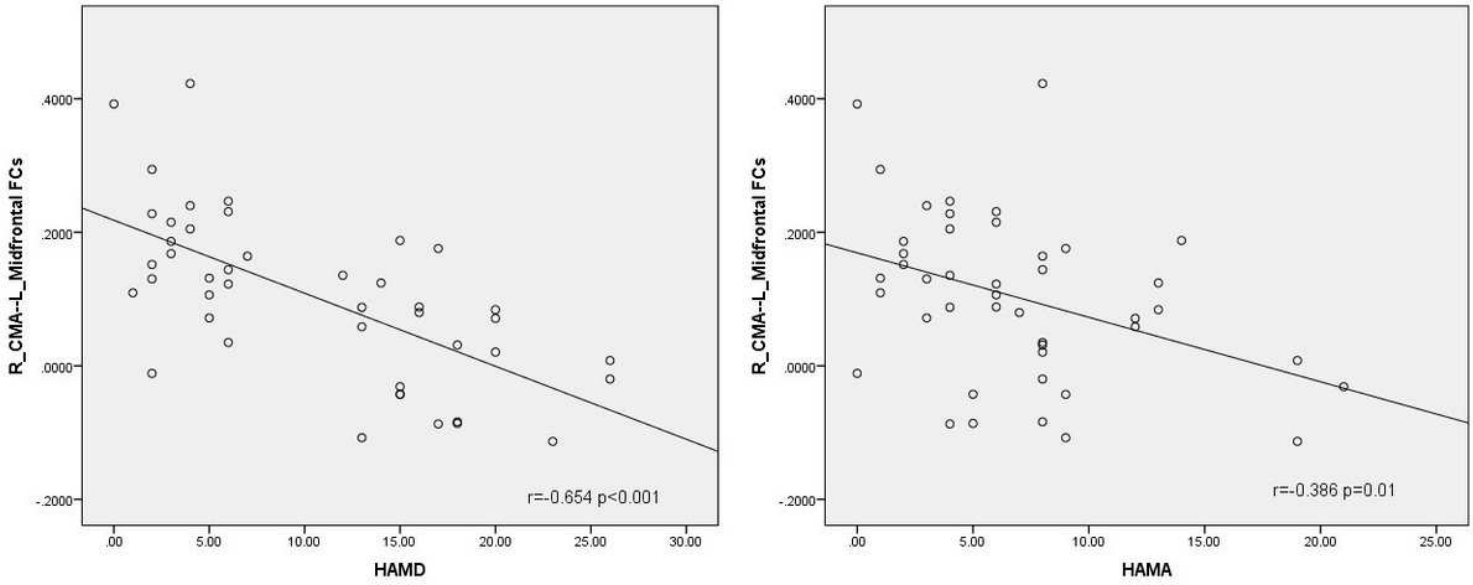

Figure 6

The relationship between right CMA-left DLPFC FC and HAMD,HAMA score. A significant negative correlation (r =-0.654/−0.386, p<0.001/P=0.01) was observed in EMwD and EM patients between the

value of rsFC and HAMD/HAMA score