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Functional network changes in the hippocampus contribute to depressive symptoms in epilepsy

Weifeng Peng[a], Lingyan Mao[a], Dazhi Yin[b], Wei Sun[c], He Wang[d], Qianqian Zhang[a], Jing Wang[a], Caizhong Chen[c], Mengsu Zeng[c], Jing Ding[a,*], Xin Wang[a,e,*]

[a] Department of Neurology, Zhongshan Hospital, Fudan University, Shanghai, China
[b] Institute of Neuroscience, Key Laboratory of Primate Neurobiology, CAS Center for Excellence in Brain Science and Intelligence Technology, Shanghai Institute for Biological Sciences, Chinese Academy of Sciences, Shanghai, 200031, China
[c] Department of Radiology, Zhongshan Hospital, Fudan University, Shanghai, 200031, China
[d] Institute of Science and Technology for Brain-Inspired Intelligence, Fudan University, Shanghai, 200433, China
[e] The State Key Laboratory of Medical Neurobiology, The Institutes of Brain Science and the Collaborative Innovation Center for Brain Science, Fudan University, Shanghai, China

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ABSTRACT

Purpose: Our study aimed to investigate the functional connectivity (FC) between the hippocampus and other brain regions in epilepsy patients with depressive symptoms.

Methods: Epilepsy patients with and without depressive symptoms, assessed using the 17-item Hamilton Depression Rating Scale scores, were enrolled. Healthy volunteers were recruited as the control group. Resting state functional magnetic resonance imaging was performed, and the data were processed using Resting-State fMRI (DPARSFA2.0) software. The regional homogeneity (ReHo) values and the FC between the right hippocampus and other brain regions were analysed.

Results: The ReHo value of the cerebellum (particularly the left cerebellar hemisphere) was significantly lower in epilepsy patients than in healthy controls, and was lower in epilepsy patients with depressive symptoms (EP + DS group) than in those without depressive symptoms (EP-DS group, $p < 0.05$). Additionally, the FC between the right hippocampus and the bilateral cerebellum was significantly greater in the EP + DS group than in the EP-DS group ($p < 0.05$). Moreover, abnormal ReHo values in the bilateral frontal lobes, including the right anterior cingulate cortex, and changes in the FC between the right hippocampus and the bilateral frontal lobes were found in the EP + DS group. Minor changes in the FC between the temporal and parietal lobes were also found in the epilepsy patients.

Conclusion: The functional right hippocampus–cerebellum circuit might contribute to the pathogenesis of depressive symptoms in epilepsy, with the exception of brain areas associated with emotion such as the frontal and temporal lobes. Modulating the hippocampus–cerebellum circuit is a potential therapeutic strategy for epilepsy patients with depressive symptoms.

1. Introduction

Depression is highly common in patients with epilepsy, with a prevalence of approximately 30% in patients with recurrent seizures [1]. Depression not only negatively affects patient quality of life but is also correlated with cognitive functioning in patients with epilepsy [2,3]. However, the mechanisms underlying the comorbidity of epilepsy and depression remain unclear. Evidence from clinical and laboratory research indicates that there are common pathogenic mechanisms associated with epilepsy and depression [4].

The hippocampus is an important brain region involved in emotional processing and likely contributes to the comorbidity of epilepsy

Abbreviation: ACC, anterior cingulate cortex; AEDs, ntiepileptic drugs; BPRS, Brief Psychiatric Rating Scale; CBZ, carbamazepine; CZP, clonazepam; EP + DS, epilepsy patients with depressive symptoms; EP-DS, epilepsy patients without depressive symptoms; FC, functional connectivity; fMRI, functional magnetic resonance imaging; FS, focal seizure; FS to GTCS, focal to generalised tonic–clonic seizure; Glx/Cr, glutamate and glutamine/creatine; GTCS, generalised tonic–clonic seizure; HAMD-17, 17-item Hamilton Depression Rating Scale; HC, healthy controls; ^{1}H-MRS, single proton magnetic resonance spectroscopy; LTG, lamotrigine; MDD, major depressive disorder; MMSE, the Mini-Mental State Examination; MRI, magnetic resonance imaging; NHS3, the National Hospital Seizure Severity Scale; OXC, oxcarbazepine; PB, phenobarbital; PET, positron emission tomography; PHT, phenytoin; ReHo, regional homogeneity; SD, standard deviation; SE, status epilepticus; TLE, temporal lobe epilepsy; TPM, topiramate; VPA, valproate; ROI, region of interest

* Corresponding authors.
E-mail addresses: ding.jing@zs-hospital.sh.cn (J. Ding), wang.xin@zs-hospital.sh.cn (X. Wang).

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and depression, as both of these conditions are associated with reduced hippocampal volumes [5,6]. Shamim et al. found that contralateral hippocampal atrophy is correlated with depression in patients with temporal lobe epilepsy (TLE) [7]. A single proton magnetic resonance spectroscopy (^{1}H-MRS) study by Gilliam et al. reported that the severity of depressive symptoms was positively correlated with the abnormality of the creatine/N-acetylaspartate ratio in the hippocampus of patients with TLE, indicating that depression is associated with hippocampal dysfunction [8]. Two positron emission tomography (PET) imaging studies by Savic et al. and Hasler et al. demonstrated that patients with comorbid TLE and depression exhibited a significantly more pronounced reduction in 5-HT_{1A} receptor binding in the hippocampus than did those without depression [9,10]. Our previous ^{1}H-MRS study also indicated that an increased glutamate and glutamine/creatine (Glx/Cr) ratio in the right hippocampus is an independent risk factor for depressive symptoms in patients with epilepsy [11]. These pieces of evidence indicate that the hippocampus is an essential area that not only mediates epileptic discharges but also regulates emotion. The changes in the functional connectivity (FC) between the hippocampus and other specific brain regions in patients with comorbid epilepsy and depression remain to be investigated.

Resting state functional magnetic resonance imaging (fMRI) can detect regional neuronal activity alterations and FC between different areas of the brain, and has been widely used to study the mechanisms underlying neurological and psychiatric diseases [12,13]. Regional homogeneity (ReHo) analysis evaluates the degree of synchronization between the time-series of a voxel and its neighbouring voxels, and the ReHo value represents the local neuronal activity [14]. In this study, we employed the resting state fMRI technique to observe the ReHo values in different brain regions and the FC between the hippocampus and other brain regions in epilepsy patients with and without depressive symptoms.

As many factors, such as antiepileptic drugs (AEDs), may affect functional networks in the brain, previous studies predominantly recruited patients with TLE who had not been prescribed AEDs [15,16]. However, in the real world, > 90% of patients with epilepsy are prescribed AEDs as a first line treatment for an extended period. In such patients, changes in brain functional networks may occur owing to the complicated combined effects of epilepsy, comorbidities, and AEDs. Therefore, in this study, we enrolled a group of epilepsy patients with depressive symptoms, a group of epilepsy patients without depressive symptoms, and a group of healthy volunteers (control group). We examined the ReHo values in different brain regions and the FC between the right hippocampus and other brain regions in the three groups.

2. Methods

2.1. Participants

Patients with epilepsy who met the following criteria were included as the group of patients with comorbid epilepsy and depressive symptoms (EP + DS group) in our study: 1) are 18–50 years old, no gender limitation; 2) have experienced epilepsy for ≥6 months; 3) have a score of ≥7 on the 17-item Hamilton Depression Rating Scale (HAMD-17); 4) have not been under treatment with any medication other than AEDs in the past 2 weeks; and 5) have no abnormal findings on magnetic resonance imaging (MRI) with T1, T2, and fluid-attenuated inversion recovery (FLAIR) sequences. The exclusion criteria were as follows: 1) a history of psychiatric diseases or psychiatric symptoms as evaluated by the Brief Psychiatric Rating Scale (BPRS); 2) a score of < 24 on the Mini-Mental State Examination (MMSE); and 3) severe organ failure and malignant tumours. The epilepsy patients without depressive symptoms (EP-DS group) were recruited based on the above inclusion and exclusion criteria, but the HAMD-17 score cut-off was < 7. Age-, gender-, and education-matched healthy volunteers were recruited as the healthy control (HC) group.

Basic demographic data including age, gender, marital state, and education level were collected from all participants. The seizure-related parameters such as seizure type, frequency, severity, aetiology, history of status epilepticus (SE), and AED use in the patients with epilepsy were recorded by a neurologist. All participants were fully informed of the aim of this study and provided written informed consent. The local ethics committee approved this study.

2.2. Neuropsychological evaluation

All participants were assessed with the HAMD-17 to evaluate the presence and severity of depressive symptoms. The Chinese version of the HAMD-17 has been proven to have good reliability, and a HAMD-17 score of ≥7 is considered to indicate depressive symptoms based on the generally acknowledged standard [17,18]. The MMSE and BPRS were used to exclude patients with cognitive disorders or psychiatric symptoms that might be confused with depressive symptoms. Participants with a MMSE score of ≤24 or a BPRS score of > 35 were excluded [19]. The Chinese versions of the MMSE and BPRS have both been tested for reliability [20,21].

3. fMRI data acquisition and processing

3.1. Image acquisition

fMRI was performed using a 3.0-T clinical scanner with an eight-channel phased array head coil (SignaHDx, GE Medical System, Milwaukee, WI, USA). The participants were provided with a pair of earplugs to reduce noise disturbance. They were instructed to lie still in the GE quadrature radiofrequency head coil with foam cushioning for motion stability, keep their eyes closed, and remain calm during scanning. After verifying patient position, image quality, and voxel positioning, high-resolution T1-weighted images were acquired using a 3D magnetic prepared rapid gradient echo pulse sequence, with slice thickness = 1 mm, echo time (TE) = 12 ms, repetition time (TR) = 500 ms, field of view (FOV) = 256 × 256 mm, matrix size = 256 × 256 mm, 192 slices in the axial plane, voxel size = 1 × 1 × 1 mm. The resting state fMRI scans of the whole brain were acquired using a T2*-weighted echo-planar imaging sequence: TR = 2000 ms, TE = 30 ms, number of excitations (NEX) = 1, matrix size = 128 × 128, FOV = 256 × 256 mm, flip angle = 90. Further T2-weighted (TR = 4500 ms, TE = 99 ms, NEX = 1) and FLAIR (TR = 10,002 ms, TE = 133 ms, inversion time = 2200 ms, NEX = 1) images were acquired to screen for incidental neuroradiological abnormalities.

3.2. fMRI data processing

In this study, the Data Processing Assistant for Resting-State fMRI 2.0 (DPARSFA2.0, http://restfmri.net/forum/) developed by the State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University was used to process the resting state fMRI data [21]. As described previously [22], DICOM images were converted into the NIFTI format. To maintain the magnetization equilibrium, the images from the first ten time points were removed. Slice timing correction and realignment were performed. Excessive motion was defined as parallel movement in any direction of > 2.5 mm or rotation of > 2.5°. The functional images were then spatially normalised to the Montreal Neurological Institute space and the resampled voxel size was 3 × 3 × 3 mm. The images were then subjected to detrending and filtering (0.01 Hz < f < 0.08 Hz) to reduce low-frequency drift and filter high-frequency physiological noise. Finally, a multiple linear regression analysis was performed to remove covariates.