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Brain network alteration in patients with temporal lobe epilepsy with cognitive impairment

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ABSTRACT

The aims of this study were to investigate the brain network alternation in patients with temporal lobe epilepsy (TLE) with and without cognitive impairment (CI) using functional magnetic resonance imaging (fMRI) and to further explore the potential mechanisms of epilepsy-induced CI. Forty patients with TLE and nineteen healthy controls (HCs) were recruited for this study. All participants received the Montreal Cognitive Assessment (MoCA) test, and the patients were divided into CI (n = 21) and cognitive nonimpairment (CNI) groups (n = 19) according to MoCA performance. Functional connectivity (FC) differences of resting state networks (RSNs) were compared among the CI, CNI, and HC groups. Correlation between FC and MoCA scores was also observed. When compared with the HC group, significantly decreased FC between medial visual network (mVN) and left frontoparietal network (lFPN) as well as between visuospatial network (VSN) and the anterior default mode network (aDMN) were revealed in both CI and CNI groups. In addition, significantly decreased FC between lFPN and executive control network (ECN) and increased FC between ECN and sensorimotor-related network (SMN) were found in CNI and CI groups, respectively. When compared with the CNI group, the CI group exhibited significant increased FC between ECN and lFPN as well as between ECN and SMN. Moreover, in the CI group, FC between ECN and lFPN showed negative correlation with attention scores. Our findings suggested that cognitive networks are different from epileptic networks, and the increased FC between RSNs closely related to cognitive function changes may help us to further understand the mechanism of CI in TLE.

1. Introduction

Temporal lobe epilepsy (TLE) is a common type of pharmacoresistant epilepsy [1,2]. Cognitive impairment (CI) is the most common complication of TLE that seriously affects the physical and mental health of patients, and the associated harm is perhaps equivalent to or greater than the epileptic seizure itself. Although surgical resection of the epileptogenic focus is an effective treatment for seizures [3], CI may not be alleviated and may progress regardless of seizure-free status after surgery in a certain proportion of patients [4–6]. At present, the pathological mechanism of CI in TLE is still poorly understood. Synaptic-connection damage caused by epileptiform discharges [7,8], abnormal 5-hydroxytryptamine1A (5HT1A)-receptor in the hippocampus of patients with TLE [9], and the adverse effects of antiepileptic drugs on neuronal excitability [10], are usually considered as the possible mechanism of CI in patients with epilepsy.

The prominent pathologic feature of TLE is neuronal loss and gliosis in the hippocampus and amygdala [11]. In recent years, various magnetic resonance imaging (MRI) techniques have been widely applied to the study of TLE with CI. Diffusion tensor imaging (DTI) studies on

Abbreviations: aDMN, anterior default mode network; BOLD, blood oxygen level-dependent; CI, cognitive impairment; CNI, cognitive nonimpairment; CC, corpus callosum; DMN, default mode network; DLPFC, dorsolateral prefrontal cortex; DPABI, Data Processing & Analysis for (Resting-State) Brain Imaging; ECN, executive control network; EEG, electroencephalography; FC, functional connectivity; FWHM, full width at half maximum; FA, fractional anisotropy; FD, framewise displacement; GIG-ICA, group-information-guided independent component analysis; GLM, general linear model; HC, healthy control; ICA, independent component analysis; ICs, independent components; IPC, inferior parietal cortex; lFPN, left frontoparietal network; MD, mean diffusivity; MoCA, Montreal Cognitive Assessment; mVN, medial visual network; MEG, magnetoencephalography; MDL, minimum description length; PCC, posterior cingulate cortex; pDMN, posterior default mode network; RSN, resting state network; REST, resting state fMRI data analysis toolkit; SMA, supplementary motor areas; SMN, sensorimotor-related network; SPM, statistical parametric mapping; SLF, superior longitudinal fasciculus; SEEG, stereotactic electroencephalography; PFC, prefrontal cortex; TLE, temporal lobe epilepsy; VBM, voxel-based morphometry; VN, visual network; VSN, visuospatial network; vmPFC, ventromedial prefrontal cortex.

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TLE have revealed abnormalities of gray and white matter [12]. Changed mean diffusivity (MD) of the uncinate fasciculus, fronto-occipital fasciculus, and areas of the hippocampus and cingulate may be associated with memory decline [13,14], altered fractional anisotropy (FA) of superior longitudinal fasciculus (SLF), uncinate, and corpus callosum (CC) related to language dysfunction [15]. A longitudinal study conducted before and after surgery indicated that altered FA and MD in the ventromedial language network correlated with a change in verbal fluency after surgery [16]. In addition, by means of voxel-based morphometry (VBM) [17] and cortical thickness analysis [18], abnormalities of the brain structure beyond the area of the mesial temporal lobe have been reported wherein the decreased white matter volume and subtle gray matter atrophy were associated with CI in epilepsy [19,20]. However, these findings are inconsistent and cannot completely explain the mechanism of CI [21,22].

At present, resting state functional magnetic resonance imaging (fMRI) is widely utilized to observe task-free intraregional neuronal activities and interregional signal correlation in many neuropsychiatric disorders [23–25]. Functional connectivity (FC) is defined as the spatial domain correlation between spatially distant brain regions [26], and altered FC of networks can reflect brain reorganization and abnormal functional interactions [27,28]. Epileptic seizure is not only closely related to the epileptogenic foci but also significantly correlated with abnormal FC of resting state networks (RSNs); altered FC of RSNs can explain some seizure semiology and noninvasively identify seizure lateralization [29,30]. Alteration of multiple RSNs has been detected in TLE and is significantly related to CI; alteration of alertness-related network, visuospatial working memory-related network, executive control network (ECN), and language network potentially explained CI including alertness, visuospatial working memory, executive and language function [31–33]. However, because of differences in study populations and the method of data analysis, whether abnormal FC represents the underlying neuronal substrate for cognitive decline is still debatable [6].

As mentioned above, RSNs play a major role in studying the pathophysiology of epilepsy and the associated cognitive dysfunction [34,35]. The majority of previous fMRI studies have focused on differences in RSNs between healthy controls (HCs) and patients with epilepsy or patients with cognitive dysfunction, but few studies have compared the RSNs between patients with TLE with and without CI. Nevertheless, in patients, the physiological basis of CI is distinct from the pathophysiological processes that cause seizures [34]. We hypothesized that the foundation of epileptic networks as well as cognitive networks may also be different. Thus, we utilized fMRI to investigate whether patients with TLE with CI have different alteration of RSNs as compared with patients without CI to further differentiate cognitive networks and epileptic networks and highlighted our insights on the mechanism of CI in patients with TLE.

The Montreal Cognitive Assessment (MoCA) is a brief cognitive screening tool with high specificity and sensitivity for detecting CI [36]. It is more sensitive than other cognitive scales with respect to abnormal performance across multiple domains and is widely used in various neuropsychiatric disorders [37,38]. Several researchers have suggested using MoCA as a screening test for patients with epilepsy [39,40].

2. Materials and methods

The study protocol was approved by the Ethics Committee of Xuanwu Hospital of Capital Medical University, Beijing, China. Written informed consent was obtained from each participant in accordance with the Declaration of Helsinki.

Forty right-handed patients with intractable mesial TLE (22 male, 18 female; mean age, 26.88 ± 7.6 years; range, 13–43 years; mean education, 9.55 ± 2.7 years; range, 5–18 years; mean duration of disease, 12.36 ± 7.6 years; range, 1–34 years) were recruited from our hospital. All patients underwent comprehensive assessment including clinical symptoms, medication, MRI manifestations, magnetoencephalography (MEG) findings, and electroencephalography (EEG) and stereotactic electroencephalography (SEEG) examinations. The patients showed either no abnormalities or only hippocampal sclerosis on MRI; intracranial electrode implantation confirmed that the epileptogenic focus was located in the medial temporal lobe. All patients underwent anterior temporal lobectomy, and the pathological findings confirmed hippocampal sclerosis. The control (HC) group included 19 healthy volunteers (11 male, 8 female; age, 27.41 ± 3.9 years; range, 23–35 years; mean education, 8.94 ± 3.2 years; range, 5–17 years). None of the control subjects had any previous neurological disease; additionally, no structural abnormality was evident on conventional MRI.

All the participants underwent a comprehensive MoCA evaluation including tests for visuospatial/executive function, naming, memory, delayed recall, attention (including forward and backward digit span, number 1 tapping test, serial 7 subtractions), language ability (including sentence repetition and verbal fluency), abstraction, and orientation. A score of ≥26 was considered normal [41,42]. According to MoCA results, the patients were divided into the following two groups: cognitive nonimpairment (CNI) group (n = 19; 11 male and 8 female; mean age, 28.47 ± 6.9 years; range, 16–43 years; mean education, 9.79 ± 2.5 years; range, 5–15 years; mean duration of disease, 12.42 ± 6.00 years; range, 5–24 years) and CI group (n = 21; 11 male and 10 female; mean age, 25.42 ± 8.0; range, 13–42 years; mean education, 9.19 ± 2.4; range, 5–15 years; mean duration of disease, 12.33 ± 8.91; range, 1–34 years). There were no significant intergroup differences with respect to age, sex, and years of education.

2.1. MRI data acquisition

We used a 3.0-T MRI system (Trio Tim, Siemens, Erlangen, Germany) with a 32-channel phase array head coil to obtain images. Comfortable foam padding and earplugs were used to minimize the head motion and reduce imaging noise, respectively. The participants were asked to close their eyes, breathe evenly, stay calm, and refrain from specific thoughts. T1-weighted image (T1WI) were acquired using a three dimensional magnetization prepared rapid acquisition gradient echo sequences (3D-MP-RAGE), providing isotropic voxels of 1 mm × 1 mm × 1 mm. The resting-state blood oxygen level-dependent (BOLD) images were acquired with echo-planar imaging sequence with the following parameters: repetition time (TR)/echo time (TE) = 2000/30 ms; Field of view (FOV) = 220 mm × 220 mm, Generalized Autocalibrating Partially Parallel Acquisitions (GRAPPA) (phase encoding (PE)) 2; slice thickness = 3 mm, voxel size = 3.4 mm × 3.4 mm × 3.0 mm, 35 slices, flip angle = 90°; total scan time = 6 min, and 180 volumes. Conventional whole brain axial fluid attenuated inverse recovery (FLAIR) sequence was scanned to exclude other abnormalities in the brain.

2.2. Data preprocessing

The resting-state fMRI data of all subjects were preprocessed using Data Processing & Analysis for (Resting-State) Brain Imaging (DPABI) [43]. The first 10 volumes of each functional time series were discarded owing to the signals reaching equilibrium and the participants adapting to the scanning noise. Slice timing performance on the remaining 170 volumes was done to correct the time difference between all slices, following which, the other volumes were realigned to the first one. Head motion parameters were evaluated on each subject by using the Friston-24 model, wherein a maximum displacement of >2 mm, maximum rotation of >2.0°, or mean framewise displacement (FD) of >0.3 was excluded [44]. After that, we normalized the fMRI data to standard echo planar imaging template, and then resampled them to 3-mm cubic voxels. Finally, all fMRI data were smoothed (6-mm full width at half maximum (FWHM)) [45].