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Research article

Mapping the convergent temporal epileptic network in left and right temporal lobe epilepsy

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HIGHLIGHTS

- Left and right temporal lobe epilepsy share a decreased convergent circuit.
- The circuit locates in prefrontal-limbic network and temporo-occipital network.
- The circuit accounts for the mood and emotional deficits in temporal lobe epilepsy.

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ABSTRACT

Left and right mesial temporal lobe epilepsy (mTLE) with hippocampal sclerosis (HS) exhibits similar functional and clinical dysfunctions, such as depressive mood and emotional dysregulation, implying that the left and right mTLE may share a common network substrate. However, the convergent anatomical network disruption between the left and right HS remains largely uncharacterized. This study aimed to investigate whether the left and right mTLE share a similar anatomical network.

We examined 43 (22 left, 21 right) mTLE patients with HS and 39 healthy controls using diffusion tensor imaging. Machine learning approaches were applied to extract the abnormal anatomical connectivity patterns in both the left and right mTLE.

The left and right mTLE showed that 28 discriminating connections were exactly the same when compared to the controls. The same 28 connections showed high discriminating power in comparisons of the left mTLE versus controls (91.7%) and the right mTLE versus controls (90.0%); however, these connections failed to discriminate the left from the right mTLE. These discriminating connections, which were diminished both in the left and right mTLE, were primarily located in the limbic-frontal network, partially agreeing with the limbic-frontal dysregulation model of depression.

These findings suggest that left and right mTLE share a convergent circuit, which may account for the mood and emotional deficits in mTLE and may suggest the neuropathological mechanisms underlying the comorbidity of depression and mTLE.

1. Introduction

Mesial temporal lobe epilepsy (mTLE) with hippocampal sclerosis (HS), which is often associated with cognitive impairment [1], has been considered as a focal disease centered on a lateralized focus for a long time [2]. However, previous magnetic resonance imaging (MRI) studies have demonstrated widespread abnormalities in various cortical regions and networks [3–6], suggesting that mTLE is a brain disease that involves network dysfunction [7,8].

Pioneering studies indicated that the left and right mTLE involved distinct underlying pathological and etiological substrates [9]. In our last study, we found that the left mTLE could be distinguished from the right mTLE. However, the left mTLE partly exhibited a comparable connectivity pattern to the right mTLE [10]. Furthermore, similar functional connectivity reductions were found in both left and right mTLE [11]. Left mTLE patients even exhibit similar clinical dysfunctions to right mTLE patients, such as

Abbreviations: MRI, magnetic resonance imaging; TLE, temporal lobe epilepsy; HS, hippocampal sclerosis; DTI, diffusion tensor imaging; LOOCV, leave-one-out cross-validation; ROI, region of interest; SVM, support vector machine; GR, generalization rate; SC, specificity; SS, sensitivity; ROC, receiver operating characteristic; FA, fractional anisotropy; dlPFC, prefrontal cortex; OFC, orbitofrontal cortex.

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depressive mood, emotional dysregulation, memory deficits [12] and even major depression [13]. More importantly, some studies failed to detect significant white matter differences in direct comparisons between left and right mTLE [14]. The neuropathology underlying these phenomena remains unclear. One hypothesis is that white matter abnormalities reflect a secondary effect of ongoing seizure activity, representing downstream axonal degeneration [15], such that left and right mTLE may share a common extra-temporal network disruption.

In the current study, we investigated whether left and right mTLE share a common disrupted anatomical network; to address this question, we aimed to characterize the convergent disruptions of the anatomical networks in left and right mTLE using machine learning approaches. Whereas mass-univariate methods consider each individual variable separately, machine learning approaches take into account patterns of information that may be presented across multiple variables [16]. Thus, machine learning approaches may provide increased sensitivity for extracting stable patterns from neuroimaging data and for detecting subtle and spatially distributed differences in the brain [17]. First, we performed diffusion tensor imaging (DTI) probabilistic tractography to extract whole-brain anatomical networks. Then, machine learning approaches were used to extract the most discriminating connections and to investigate the convergent anatomical network disruptions between left and right mTLE.

2. Methods

This study was approved by the Research Ethics Review Board of the Institute of Mental Health of Southern Medical University. Each participant was informed of the details of the project, and written informed consent was obtained from all participants in accord with the standards of the Declaration of Helsinki. We confirmed that all potential participants who declined to participate or otherwise did not participate were eligible for treatment (if applicable) and were not disadvantaged in any way by not participating in this study.

2.1. Participants

We enrolled 43 consecutive right-handed patients suffering from unilateral HS and mTLE who received a presurgical evaluation at the Guangdong 999 Brain Hospital. The diagnosis and lateralization of the seizure focus to the left mTLE (n = 22) or the right mTLE (n = 21) were determined based on a comprehensive evaluation, including a detailed history, video-EEG telemetry and neuroimaging. An increase in the T2 fluid-attenuated inverted recovery signal in the hippocampus was used as the diagnostic criterion for HS, and the site of HS was concordant with the epileptogenic site in all patients. None of the patients had a mass lesion (including tumor, vascular malformation or malformations of cortical development) or suffered from traumatic brain injury or a psychiatric disorder, but all patients experienced degeneralized seizures. After MRI acquisition, all patients received anterior temporal lobectomy. Following qualitative histopathological analysis, HS was detected in all patients. Thirty-nine age-, gender- and education-matched right-handed healthy control participants were recruited for this study. The demographic and clinical data are displayed in Table 1.

2.2. Imaging protocol

All participants were scanned using a 1.5 T Philips Intera MR scanner. During scanning, foam pads were used to reduce head motion and scanner noise. Diffusion-weighted images were obtained using a single-shot echo-planar imaging sequence according to the following parameters: repetition time (TR) = 11,000 ms; echo time (TE) = 71.6 ms; field of view (FOV) = 230 mm × 230 mm; matrix size = 144 × 144; voxel dimensions = 1.6 × 1.6 × 2 mm; slice thickness = 2 mm; 32 non-collinear diffusion directions with a b-value of 800 s/mm^2 and one additional volume without diffusion weighting (b = 0 s/mm^2); and 73 transverse slices without gaps, covering the entire brain. We also acquired high-resolution 3D brain anatomical images using a T1-weighted MP-RAGE sequence according to the following parameters: TR = 25 ms, TE = 4.6 ms, FOV = 240 mm × 240 mm, matrix size = 256 × 256, and 140 contiguous axial slices with slice thickness = 1 mm.

2.3. DTI data processing

Diffusion tensor images were corrected for distortions caused by head motion and eddy currents using affine registration in Eddy Current Correction [18]. Then, the resulting images were brain extracted using the Brain Extraction Tool [19], and a diffusion tensor model was fit to each voxel using DTIFit to generate images of FA and other parameters. Here, we adopted an automated anatomical labeling (AAL) parcellation method to parcellate the cortex into 116 regions of interest (ROIs) [20]. Then, the local probability distribution of the fiber directions was estimated for each voxel using BedpostX. We adopted ProbtrackX for probabilistic tractography, which tracked fibers between each pair of ROIs by sampling 5000 streamline fibers per voxel using a turning threshold of 60°. The ROI associated with node v is denoted as $ROI(v)$. If $ROI(v)$ contained n voxels, the total number of fibers connecting to $ROI(v)$ was $5000 \times n$. Given the number of fibers from $ROI(v)$ to $ROI(u)$ was m, the connections between the nodes $ROI(v)$ and $ROI(u)$ were defined as edge $e(v, u) = \frac{m}{5000 \times n}$. The connectivity strength between $ROI(v)$ and $ROI(u)$ was defined as $E(v, u) = \frac{e(v,u) + e(u,v)}{2}$ [21].

2.4. Feature selection and classification

We applied a two-sample t-test to identify the connections that were significantly different between groups, which were the most discriminating features. Then, we adopted a locally linear embedding algorithm (LLE) to reduce the feature space dimensionality to a more manageable level. Finally, a support vector machine (SVM) with the default Gaussian radial basis function kernel was applied for classification. Here, we performed two classifications of left mTLE versus controls and right mTLE versus controls with whole brain connections. We extracted exactly the same features from these two classifications as the convergent features. Two-way group classifications using the convergent features of the left mTLE, right mTLE and controls were performed to assess these features.

Because the sample size was limited in this study, we adopted a leave-one-outcross-validation (LOOCV) strategy to estimate the generalization rate (GR) of the SVM classifier [17]. One sample was used as the test sample in one loop of LOOCV, and the remaining samples were used to train the SVM classifier. First, we adopted two-sample t test (TSTT) to extract the most significantly different features from the remaining samples, then, the features were projected to a more manageable feature space by Local Linear Embedding (LLE). At the last, the features were used to train the SVM and the test sample were used to evaluate the classifier. As we adopted the LOOCV strategy and there are N sample, we trained and tested the classifier N times. The performance of each classifier was quantified for its Sensitivity (SS), Specificity (SC) and Generalization Rate (GR) based on the results of LOOCV. The SS indicated the proportion of patients correctly classified, and the SC represented the proportion of controls that were correctly classified. The overall proportion of samples correctly classified was represented by GR. We applied permutation tests and receiver operating characteristic (ROC) curves to assess the statistical significance of the observed classification accuracy values.