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Multivariate pattern analysis reveals anatomical connectivity differences between the left and right mesial temporal lobe epilepsy

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ABSTRACT

Previous studies have demonstrated differences of clinical signs and functional brain network organizations between the left and right mesial temporal lobe epilepsy (mTLE), but the anatomical connectivity differences underlying functional variance between the left and right mTLE remain uncharacterized. We examined 43 (22 left, 21 right) mTLE patients with hippocampal sclerosis and 39 healthy controls using diffusion tensor imaging. After the whole-brain anatomical networks were constructed for each subject, multivariate pattern analysis was applied to classify the left mTLE from the right mTLE and extract the anatomical connectivity differences between the left and right mTLE patients. The classification results reveal 93.0% accuracy for the left mTLE versus the right mTLE, 93.4% accuracy for the left mTLE versus controls and 90.0% accuracy for the right mTLE versus controls. Compared with the right mTLE, the left mTLE exhibited a different connectivity pattern in the cortical-limbic network and cerebellum. The majority of the most discriminating anatomical connections were located within or across the cortical-limbic network and cerebellum, thereby indicating that these disease-related anatomical network alterations may give rise to a portion of the complex of emotional and memory deficit between the left and right mTLE. Moreover, the orbitofrontal gyrus, cingulate cortex, hippocampus and parahippocampal gyrus, which exhibit high discriminative power in classification, may play critical roles in the pathophysiology of mTLE. The current study demonstrated that anatomical connectivity differences between the left mTLE and the right mTLE may have the potential to serve as a neuroimaging biomarker to guide personalized diagnosis of the left and right mTLE.

1. Introduction

Epilepsy is a chronic brain disorder affecting about 1% of the population worldwide, while mesial temporal lobe epilepsy (mTLE) is the most common type of intractable epilepsy (Almeida et al., 2012)

Recent studies have reported default mode (Liao et al., 2011; McCormick et al., 2013), language (Waites et al., 2006) and sensorimotor network (Voets et al., 2012) disturbances in mTLE, suggesting that mTLE is referred to as a system disorder involving network dysfunctions (Bernhardt et al., 2011; Engel, 2001; Riederer et al., 2008; Waites et al., 2006). The left and the right mTLE are reported to exhibit different clinical performances in emotion, cognition and verbal memory (Hermann et al., 2008). Resting-state fMRI studies showed that the left and right mTLE differed in default mode network (Voets et al., 2012), memory and cognitive network organization (Doucet et al., 2013). Generally, it is reported that left TLE patients have more marked cognitive disorders and impaired executive functions than right TLE patients (Pereira et al., 2010). However, anatomical connectivity, underlying functional variance between the left and right mTLE, is seldom adopted to investigate the direct anatomical differences between the left and right mTLE. As the left and the right mTLE with HS have visually the same brain lesion, only the side matters, the anatomical differences in the left and right mTLE may reveal the variation in neuropathology between them.

Besson et al. demonstrated the anatomical connectivity variance between mTLE and controls, however, no significant connectivity differences were observed in direct univariate statistical comparison of the left mTLE versus the right mTLE (Besson et al., 2014). The difficulty in investigating the direct anatomical connectivity differences between the left and right mTLE is possibly due to the limitations of conventional univariate statistical analysis, which consider the connections independently. Because of the complexity of neuronal networks, the anatomical connectivity differences between the left and right mTLE are encoded by multiple connections which could likely be detected by multivariate pattern analysis (Walther et al., 2009). Multivariate pattern analysis takes inter-regional correlations into account (Shen et al., 2010) and is therefore may have increased sensitivity in extracting stable patterns

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from neuroimaging data and detecting subtle and spatially distributed differences in the brain (Pereira et al., 2009b); as such, multivariate pattern analysis provides a promising approach for investigating mTLE that is likely to affect networks of the brain (Gong et al., 2011). Compared with group analysis, multivariate pattern analysis is capable of extracting stable structural or functional patterns from neuroimaging data, and can identify potential neuroimaging-based biomarkers to differentiate patients from controls at an individual subject level (Pereira et al., 2009a; Zhu et al., 2008). In fact, there has been increasing interest in multivariate pattern analysis methods to investigate network disturbances in brain-network diseases such as depression (Zeng et al., 2012), schizophrenia (Shen et al., 2010) and Alzheimer's disease (Zhou et al., 2010). Therefore, multivariate pattern analysis should be well suited to explore the direct anatomical connectivity differences between the left and right mTLE.

Clinically speaking, to study the variation of neuropathology between the left and right mTLE and to provide a biomarker for identification of them, it would be valuable to investigate the direct differences between the left and right mTLE from connectivity perspective. In the current study, we therefore adopted multivariate pattern analysis to characterize the direct anatomical network differences between the left and right mTLE.

2. Materials and methods

2.1. Ethics statement

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. We certify that we have participated sufficiently in the work to take public responsibility for the appropriateness of the experimental design and method, and the collection, analysis, and interpretation of the data. We have reviewed the final version of the manuscript and approve it for publication. We certify that this manuscript has not been published in whole or in part nor is it being considered for publication elsewhere. In addition, the authors of this manuscript have no conflicts of interest.

2.2. 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 ($n = 21$) that 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 any psychiatric disorders, but all patients experienced secondary generalized seizures. After MRI acquisition, all patients received anterior temporal lobectomy. Following qualitative histopathological analysis, HS was detected in all patients. So far, there is no seizure recurrence in post-operation patients. Thirty-nine age-, gender- and education-matched right-handed healthy control participants were recruited for this study. All controls were healthy and free of neurological or psychiatric disorders at the time of the study. The demographic and clinical data are presented in Table 1.

Table 1
Demographic and clinical data.

Variable	Left mTLE	Right mTLE	Control	*p*-Value
Sample size	22	21	39	
Gender (M/F)	14/8	11/10	22/17	0.45[a]*
Age (median, range in years)	26.2 ± 7.4 (18–42)	28.33 ± 7.8 (18–43)	26.11 ± 7 (18–44)	0.97[a]*
Education (years)	11.1 ± 2	11.5 ± 2.3	11.4 ± 2.28	0.82[a]*
Duration of episode (years)	12.2 ± 7	12.9 ± 7.4		0.74[b]*
Onset of epilepsy (years)	14 ± 9.9	15.6 ± 9.8		0.59[b]*

mTLE = mesial temporal lobe epilepsy; M = male; F = female.
[a] Pearson's chi-square test.
[b] Two-sample *t*-test.
* No significant difference between groups (significance defined as $p < 0.05$).

2.3. 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 × 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 × 240 mm, matrix size = 256 × 256, and 140 contiguous axial slices with slice thickness = 1 mm.

2.4. DTI data processing

Images obtained in DICOM format were initially converted to ANALYZE format. Subsequently, the diffusion tensor images were corrected for distortions caused by head motion and eddy currents using affine registration in Eddy Current Correction. After completing these preprocesses, the resulting images were brain extracted using the Brain Extraction Tool (Smith, 2002), and a diffusion tensor model was fit to each voxel using DTIFit to generate images of FA and other parameters.

2.4.1. Cortical parcellation

One critical step in network construction was the parcellation of the cortex into regions of interest (ROIs) (Li et al., 2012). Here, we adopted an automatic ROI parcellation method to parcellate the cortex into 116 ROIs, which comprised the nodes in the network (Fang et al., 2012). First, we registered the b0 images to T1-weighted images. Then, we registered the transformed T1-weighted images to the T1-ICBM152 template in MNI space (Andersson et al., 2007). Finally, the resulting transformation matrix was inverted to warp the automated anatomical labeling atlas to the diffusion-MRI native space.

2.4.2. White matter probabilistic tractography

For each DTI set, the Gaussian kernel size was set to 6 for smoothing prior to reconstruction. Then, the local probability distribution of the fiber directions was estimated for each voxel using BedpostX (Behrens et al., 2003b). Here, we selected a computational model that enabled the automatic estimation of two fiber directions within each voxel, which helped to alleviate the fiber-crossing problem and improved the fiber tracking sensitivity in the brain. We adopted ProbtrackX for probabilistic tractography, which tracked fibers between each pair of ROIs by sampling 5000 streamline fibers per voxel using a turning