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Reduced local diffusion homogeneity as a biomarker for temporal lobe epilepsy

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Abstract

In the present study, we adopted a novel method—local diffusion homogeneity (LDH)—to characterize the structure feature in mesial temporal lobe epilepsy (MTLE). Diffusion-weighted images were acquired from 11 left MTLE patients, 16 right MTLE patients, and 20 healthy controls from May 2014 to January 2015. Local diffusion homogeneity was compared among patient groups and controls by 2 sample *t* test. The discriminative value of LDH abnormalities was examined by receiver operating characteristic (ROC) curve analysis. Correlations with disease duration and onset age in both patient groups were assessed using Pearson's coefficient. Both patient groups exhibited lower LDH in the anterior corpus callosum ($P < 0.05$, corrected), and this regional anomaly exhibited excellent classification performance in left MTLE patients (sensitivity = 82%, specificity = 100%), right MTLE patients (sensitivity = 81%, specificity = 90%), and the entire patient cohort (sensitivity = 82%, specificity = 95%). In summary, left and right MTLE patients show common pathological changes in the anterior corpus callosum. This regional LDH abnormality is a potential quantitative biomarker for MTLE.

Abbreviations: DTI = diffusion tensor imaging, DWI = diffusion-weighted imaging, FA = fractional anisotropy, HS = hippocampus sclerosis, LDH = local diffusion homogeneity, LMTLE = left mesial temporal lobe epilepsy, MD = mean diffusivity, MNI = Montreal Neurological Institute, MTLE = mesial temporal lobe epilepsy, RMTLE = right mesial temporal lobe epilepsy, ROC = receiver operating characteristic, ROIs = regions-of-interest, TBSS = tract-based spatial statistics.

Keywords: diffusion MRI, local diffusion homogeneity, mesial temporal lobe epilepsy, receiver operating characteristic

1. Introduction

Mesial temporal lobe epilepsy (MTLE) is the most common type of focal epilepsy, and mostly characterized by hippocampus sclerosis (HS).[1] Epileptic discharges originating in pathological mesial temporal lobe can spread to widely distributed brain regions and disrupt a multitude of brain functions.[2,3] Anatomical tracts connecting bilateral hemispheres have been implicated in the spread of these epileptic discharges.[4]

Diffusion-weighted imaging (DWI) allows for noninvasive estimation of microstructural features in discrete white matter fiber bundles. The 2 most common diffusion measures in DWI are fractional anisotropy (FA), a measure of the preferred directionality of diffusion, and mean diffusivity (MD), a measure of total magnitude of diffusion.[5] These measures have been widely applied in MTLE to characterize pathological changes in fiber bundles. A recent meta-analysis of 13 cross-sectional studies for MTLE patients found decreased FA and increased MD in anterior corpus callosum, cingulum, and uncinate fasciculus.[6] Structural connectome studies combining diffusion tensor imaging (DTI) and graph theory have also found widespread fiber bundle changes in MTLE patients,[7–11] with distinct topological features between left and right MTLE patients.[12] Moreover, these findings are consistent with functional connectome studies on MTLE patients.[2,13]

To the best of our knowledge, most DWI indices applied to epilepsy (e.g., FA and MD) reflect diffusion properties solely within voxels, whereas intervoxel diffusion characteristics are still largely unknown in MTLE patients. Only a few intervoxel measures have been developed,[14,15] and all are based on the diffusion tensor model. Hence, these studies are all limited by the problematic assumption that a simple Gaussian profile can be applied to water diffusion in complex anatomical structures.[16] Recently, a novel measure, local diffusion homogeneity (LDH), has been proposed to investigate intervoxel features by capturing the overall coherence of water molecule diffusion within a voxel and its neighbors. LDH is independent of the tensor model and showed unique intersubject variability and age-related alteration in specific WM regions distinct to FA and MD.[17] Thus, LDH, reflecting the microstructural coherence of white matter fiber tracts, provides important information complementary to conventional DWI markers.[17]

In the current study, we aim to characterize the microstructural coherence feature in left and right MTLE patients based on diffusion data. More importantly, we examine whether the

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coherence feature could be a quantitative biomarker for diagnosing MTLE, complementary to the conventional qualitative criteria.

1.1. Materials and methods

This prospective study was approved by the local institutional review board and conducted in compliance with the Health Insurance Portability and Accountability Act of 1996. All participants provided written informed consent before magnetic resonance imaging (MRI) and neurologic evaluations.

1.2. Subjects

Eleven left MTLE (LMTLE) and 16 right MTLE (RMTLE) patients were recruited from the Epilepsy Clinic of the First Affiliated Hospital of Guangxi Medical University, from May 2014 to January 2015. Two experienced neurologists (HHL and JZ with 14 and 36 years of experience with clinical epilepsy examinations, respectively) screened the patients and inspected their EEG data, independently. If discrepancy occurred, they would discuss until achieving consent or the case would be abandoned. All patients (right-handed) underwent a comprehensive clinical evaluation, including medical history, neurological examination, diagnostic MRI, and EEG records, and diagnosed according to the International League Against Epilepsy 2001 classification. All patients have complex partial seizures, and 11 patients additionally have secondary generalized tonic-clinic seizures (7 RMTLE and 4 LMTLE). Each patient presented 1 or more typical MTLE symptoms, such as abnormal emotional experiences, psychiatric symptoms, epigastric rising, automatisms, or dystonic posturing of the limbs. LMTLE and RMTLE patients exhibited left and right hippocampal sclerosis without other imaging abnormalities, respectively; demonstrated epileptic spikes in the left and right frontotemporal/temporal lobes on interictal/ictal scalp electroencephalography, respectively. After medical treatment, all patients were in similar level of epilepsy control (seizure frequency $<1/3$ months). Twenty age- and sex-matched healthy volunteers (right-handed) were recruited as controls from May 2014 to January 2015 in local community. They had no history of neurological illness or psychiatric disorder, and no identifiable focal abnormalities in structural MR, such as cortical dysplasia, vascular malformation, and tumors.

1.3. Data acquisition

We performed MRI scanning of all participants using a 3.0 T Philips scanner (Philips, The Netherlands) at the First Affiliated Hospital of Guangxi Medical University. Diffusion-weighted imaging data from the whole brain were obtained by spin-echo echo-planar imaging. Image acquisition included 30 volumes with diffusion gradients applied along 17 noncollinear directions ($b=1000\,s/mm^2$) and 1 volume without diffusion weighting ($b=0\,s/mm^2$). Each volume consisted of 64 contiguous axial sections (repetition time/ehco time, 6900/68; flip angle, 90 degrees; field of view, $224\times224\,mm^2$ matrix size, 112×112; voxel size, $2\times2\times2\,mm^3$).

1.4. Data processing

Data were preprocessed and analyzed using the Pipeline for Analyzing Brain Diffusion Images toolkit (PANDA; http://www.nitrc.org/projects/panda)[18] and FSL (http://fsl.fmrib.ox.ac.uk/fsl). For each subject, diffusion images were geometrically corrected using an unweighted B0 image ($b=0\,s/mm^2$) and coregistered to the B0 image by affine transformations to minimize the effects of head movement. Then, an LDH map was computed for each participant according to a previous study.[17] In DWI, each voxel has multiple diffusivity values corresponding to different gradient directions. These diffusivity values yield a vector for each voxel. Local diffusion homogeneity measures adopt Kendall's coefficient of concordance to quantify the similarity of each voxel diffusivity vector to those of the 26 nearest voxels. We computed the LDH map for each participant in diffusion space. For between-subject comparisons, the framework of Tract-Based Spatial Statistics (TBSS) was used to establish the white matter (WM) correspondence between subjects.[19] Specifically, fractional anisotropy (FA) and mean diffusivity (MD) values were generated using the DTIfit algorithm, and then nonlinearly transformed to Montreal Neurological Institute (MNI) space and projected onto the WM skeleton. Finally, these nonlinear warps and skeleton projections were applied to FA, MD, and LDH maps. All the procedures described above were implemented by the PANDA toolbox.[18]

1.5. Receiver operating characteristic curve

To examine whether LDH is sufficiently sensitive and specific to serve as a biomarker for differentiating patients from healthy controls, we performed receiver operating characteristic (ROC) analysis using the public MATLAB codes (http://www.mathworks.cn/matlabcentral/fileexchange/19950-rocout=roc-varargin-; Giuseppe Cardillo, Naples, Italy). ROC analyses were based on LDH in 3 regions-of-interest (ROIs). The first is the region showing abnormal LDH in LMTLE; it was used to discriminate LMTLE patients from controls. The second is the region showing abnormal LDH in RMTLE; it was used to discriminate RMTLE patients from controls. The third is an overlapping of the first 2; it was used to discriminate all patients (no matter RMTLE or LMTLR) from controls.

1.6. Statistical analysis

The skeletonized LDH maps in the 2 patient groups were compared to controls using a voxel-wise analysis. Threshold-free cluster enhancement was applied to obtain cluster-wise statistics corrected for multiple comparisons (5000 permutations, $P<0.05$).[20] Significant results were localized to anatomical locations using the Johns Hopkins University–ICBM-DTI-81 white matter labels atlas [21] and the white matter tractography atlas.[22] Tracts showing abnormalities in patients were tested for correlation to disease duration using Pearson's coefficient ($P<0.05$).

To determine if discriminative performance occurred by chance, we employed a nonparametric permutation test. Briefly, we randomly reallocated all participants into 2 groups (i.e., patients and controls) and recomputed the area under curve (AUC) based on these 2 randomized groups with 10,000 permutations. This procedure built an empirical distribution of the AUC. The 95th percentile points of these distributions were used as critical values to estimate statistical probabilities (P values) that indicate the deviation of the observed discriminative performance from those expected by chance.

Given the relatively small sample size in the current study, we also performed a bootstrap resample procedure to test the

Table 1

Demographic and clinical characteristics of patients and controls.

Characteristic	LMTLE	RMTLE	NC	*t* or x^2 (*P*)		
				LMTLE vs NC	RMTLE vs NC	LMTLE vs RMTLE
Age, y	24.3±1.2	26.8±1.8	26.0±1.7	0.70 (0.49*)	0.33 (0.75*)	1.04 (0.31*)
Sex, F/M	6/5	8/8	11/9	1†	1†	1†
Onset age, y	18.4±1.5	17.9±2.6	NA	NA	NA	0.17 (0.87*)
Duration, y	5.9±3.6	9.0±8.1	NA	NA	NA	1.20 (0.24*)

F = female, LMTLE = left mesial temporal lobe epilepsy, M = male, NA = nonavailable, NC = normal control, RMTLE = right mesial temporal lobe epilepsy.
* Two-sample *t* test.
† χ^2 test.
NA = not available.

robustness of our discriminative results against small data fluctuations. Specifically, we generated 10,000 bootstrap samples by resampling without replacement from all 47 participants. Of note, we ensured that the same proportion (80%) for both controls and patients were included in each bootstrap sample (e.g., including 16 of the 20 controls each time). ROC was computed for each bootstrap sample, producing a distribution of the AUC. The 95th percentile points were used to determine whether the observed discriminative performance fell within those derived from the bootstrap samples.

We further evaluated the classification ability using half-split cross-validation. All the subjects were randomly assigned to either the training (13 patients and 10 controls) or test set (14 patients and 10 controls). A classification model was computed based on the LDH values of the third ROI in the training set, and then applied to the test set to estimate its discriminating sensitivity, specificity, and the area under the curve (AUC). The significance of these measures was determined by the aforementioned nonparametric permutation test.

2. Results

The demographic and clinical characteristics of the participants are summarized in Table 1. Mean age and sex ratio did not differ significantly between patients and controls ($P > 0.05$). The disease duration and onset age did not differ significantly between LMTLE and RMTLE patients ($P > 0.05$).

Local diffusion homogeneity maps of both controls (Fig. 1) and patients (Fig. 2) are characterized by sharp contrasts between white matter, grey matter, and cerebrospinal fluid, in accord with a previous study.[15] Compared to controls, both LMTLE and RMTLE patients showed significantly lower LDH in the anterior part of the corpus callosum ($P < 0.05$, corrected; Fig. 2); effect size are 2.21 and 2.36 according to Cohen's *d*, respectively. RMTLE patients showed decreased FA in right hemisphere (internal and external capsule, posterior thalamic radiation, and inferior/superior longitudinal fasciculus), left anterior thalamic radiation, and corpus callosum (body and genu part), but nonsignificant alteration in MD (see Supplementary Fig. E1, http://links.lww.com/MD/B97). LMTLE patients showed increased MD in left hemisphere (internal and external capsule, posterior thalamic radiation, superior longitudinal fasciculus,

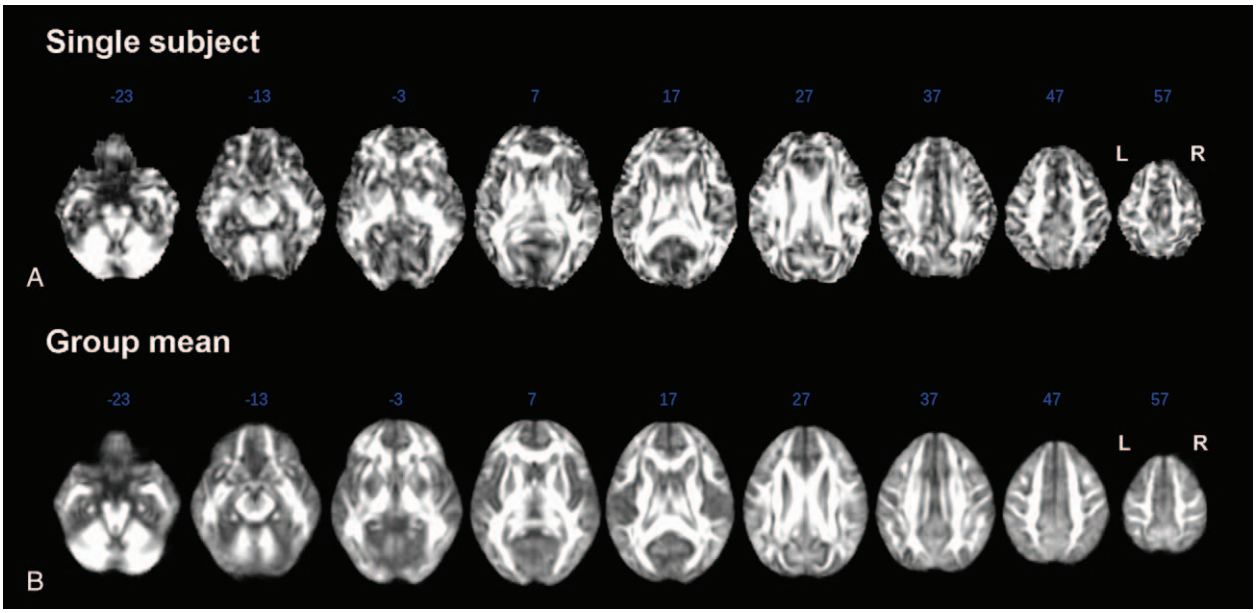

Figure 1. Local diffusion homogeneity across the entire healthy brain. (A) Representative LDH images from a healthy subject in the native space. (B) The corresponding average LDH images across the 20 normal controls. L = left hemisphere, LDH = local diffusion homogeneity, R = right hemisphere.

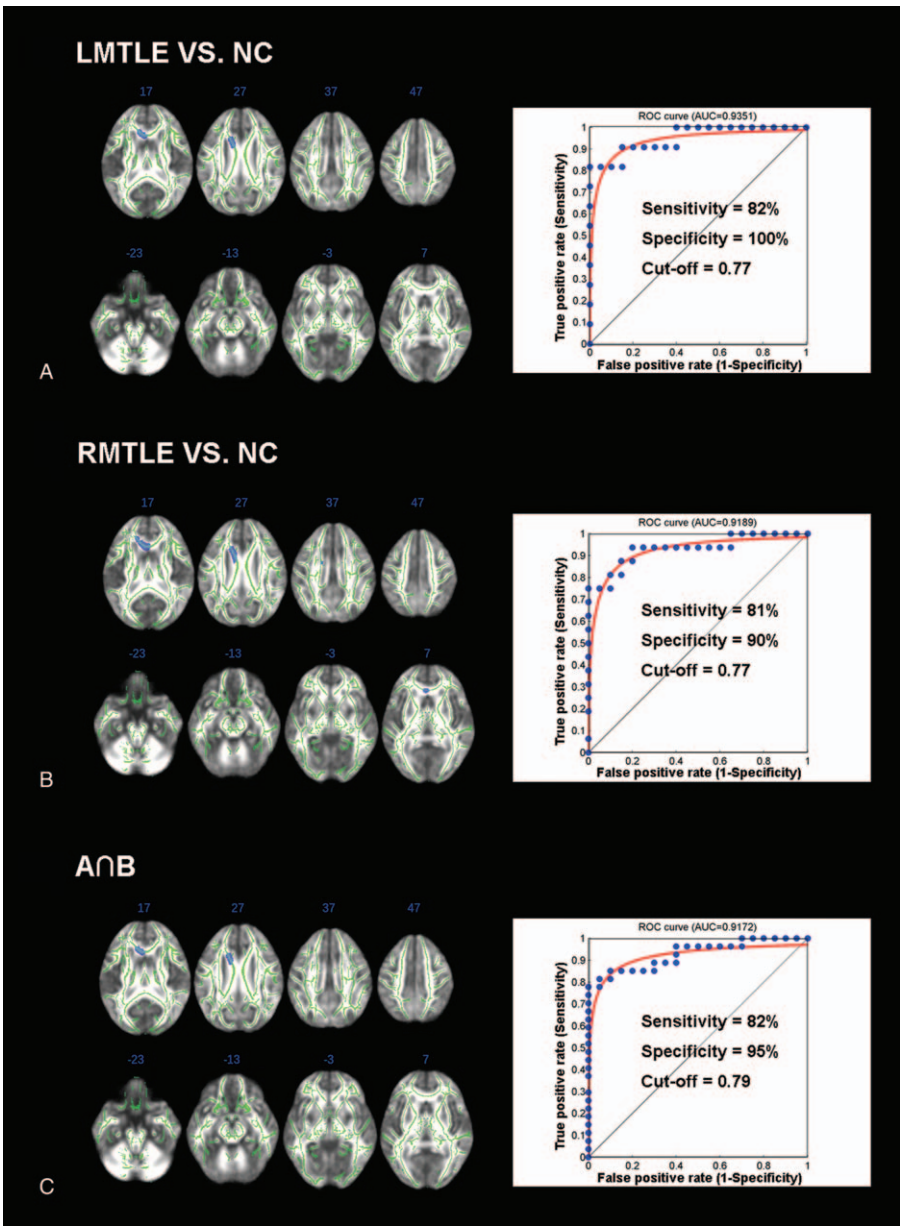

Figure 2. Regions showing abnormal LDH in patients and their discriminating performance. Both LMTLE (A) and RMTLE (B) patients exhibited lower LDH in the anterior corpus callosum. Line graphs (right) indicate the performance of the abnormal area for discriminating the corresponding patient cohort from normal controls (NC). (C) The overlap of the abnormal areas in LMTLE and RMTLE (A∩B) and its discrimination performance (line graph in the bottom-right corner). LDH = local diffusion homogeneity, LMTLE = left mesial temporal lobe epilepsy, RMTLE = right mesial temporal lobe epilepsy.

cingulum, and, corticospinal tracts) and corpus callosum (body and splenium part), but nonsignificant alteration in FA (see Supplementary Fig. E1, http://links.lww.com/MD/B97).

ROC analyses revealed that the mean LDH values of the abnormal clusters in the anterior corpus callosum of patients (those specific to LMTLE and RMTLE and that of the region of overlap) exhibited excellent performance for discriminating MTLE patients from controls (all sensitivity $> 80\%$, specificity $> 90\%$, and AUC > 0.91) (Fig. 2). The AUCs were significantly higher than expected by chance (all $P < 10^{-3}$, permutation test) but comparable to those from bootstrap samples (all $P > 0.05$). Half-split cross-validation indicated that applying the discrimination model obtained from the training group to the test group yielded good classification specificity (70%), sensitivity (92%), and AUC (82.63%) (all $P < 10^{-3}$, permutation test, Fig. 3).

In both patient groups, disease duration was not significantly correlated with abnormal LDH value across subjects (LTLE: $r = -0.33$, $P = 0.32$; RTLE: $r = 0.15$, $P = 0.57$). In contrast, onset age positively correlated with LDH in LMTLE patients ($r = 0.67$, $P = 0.03$; Fig. 4), but not RMTLE patients ($r = 0.23$, $P = 0.39$).

3. Discussion

In the current study, we estimated the diffusion coherence in MTLE patients using a novel diffusion parameter, local diffusion heterogeneity. Both LMTLE and RMTLE patients showed lower

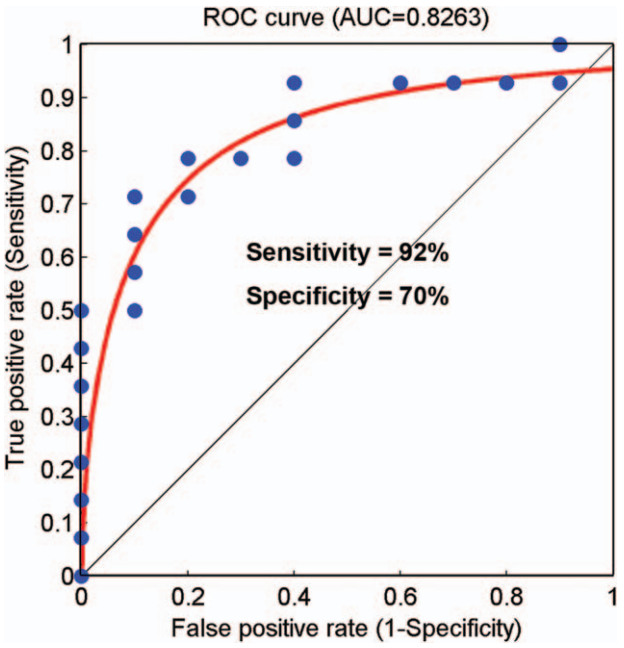

Figure 3. Receiver operating characteristic curve for the independent test group. The area under the curve (= 0.8263) indicating good discriminating ability. Blue dots represent subjects in the test group (13 patients and 10 controls).

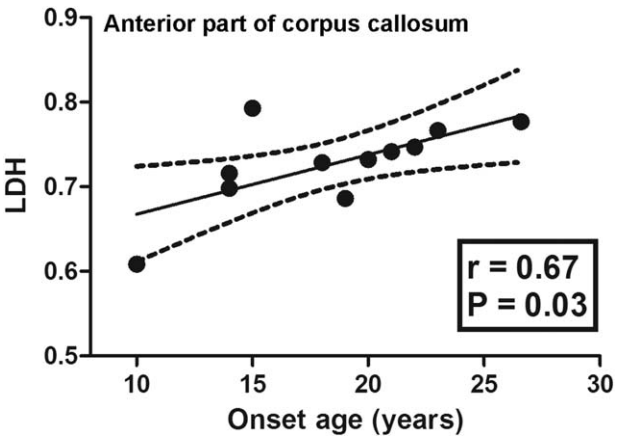

Figure 4. Scatter plot showing the significant positive correlation between LDH of the anterior corpus callosum and age of onset in LMTLE patients. LDH = local diffusion homogeneity, LMTLE = left mesial temporal lobe epilepsy.

LDH in partially overlapping regions of the anterior corpus callosum. Importantly, the LDH feature demonstrated good performance for discriminating MTLE patients from controls, suggesting potential use as an objective marker to dignose MTLE.

There are numerous DWI studies investigating anatomical connectivity changes in MTLE. A meta-analysis concluded that microstructure was abnormal in multiple tracts of MTLE patients, including the anterior/posterior corpus callosum, cingulum, external capsule, and uncinate fasciculus.[6] The abnormality of these structures was also demenstrated in the current study. Interestingly, RMTLE patients showed abnormal FA but not MD, whereas LMTLE patients showed abnormal MD but not FA. According to the physiological representation of FA and MD, these fingdings implicated that myelin and axonal intact were destoried in MTLE patients, and the abnormalities in LMTLE and RMTLE patients were more sensitvie to FA and MD, respectively. Importantly, we found that both LMTLE and RMTLE patients showed decreased LDH uniqly in the anterior part of corpus callosum. Unlike the observation from conventional microstrcture measures, abnormalities in the pathological temporal lobe were not identified by LDH. This difference is accordance with the poineer study of LDH, which suggested that LDH is an intervoxel diffusion measure and could provide complementary information to the conventional measures.[17] Corpus callosum contains commissural fibers topologically arranged as their origin in neocrotices. Adjacent voxels may connect neocortices with quite different functions. Thus, it is possible that 1 voxel in corpus callosum is disrupted, whereas its neighbors are normal. In this condition, the abnormality in corpus callosum may be quite sensitive to LDH, which estimates the overall coherence of water molecule diffusion within a voxel and its neighbors.[17] On the contrary, the pathological changes in temporal lobe may be quite diffusion and the transition from normal to abnormal areas is not as abrupt as corpus callosum. Thus, the abnormality in mesial temporal lobe may be not sensitive to the LDH. Both LMTLE and RMTLE patients exhibited lower LDH in anterior corpus callosum, suggesting a common pathological feature in both subsydromes. As suggested by a recent structure–function study, this abnormality of the anterior corpus callosum in MTLE may be related to cognitive dysfunction.[23] Consistent with a previous Tract-Based Spatial Statistics (TBSS) study,[24] we found a significant correlation between onset age and decreased LDH in LMTLE patients, suggesting that earlier age at onset of LMTLE may be associated with greater disruption in temporal–frontal lobe communication and thus more severe deficits in the cognitive functions dependent on this pathway. However, this correlation was not significant for RMTLE patients, implicated that these 2 subsyndromes have different structural connectivity features.[25] Addtionally, we did not find significant correlation between LDH and disease duration. This may be attributed to the relatively short duration of our samples, as previous studies sugested that linear correlation of duration is more likely to be significant after 10 years duration.[26,27]

Along with advances in neuroimaging techniques, much effort has been expended identifying quantitative measures that can discriminate MTLE patients from heathy subjects.[28,29] Using resting-state functional MRI, a recent study suggested the a combination of local activity and functional connectivity density may differentiate patients from controls.[29] To assess the clinical potential of local differences in LDH for diagnosis of MTLE, we performed ROC analysis for both patient groups and the total patient sample. In all 3 cohorts, reduced LDH in anterior corpus callusom exhibited excellent performance for group classification. Consistent with a previous study,[30] our findings suggest that advanced diffusion data and classification methods may provide promising information for dignosing MTLE.

Although the results of present study are encouraging, some limitations should be mentioned. The relative small sample size limits the statistical power for revealing subtle pathological changes and challenges the generalizability of our findings. Additionally, whether the conclusion are suitable for the bilateral MTLE patients need further investigation. Second, there was substantial patient heterogeneity due to medication effects, as all patients had received various medical treatments for several months before recruitment. Thus, it is necessary to demonstrate if

these findings are also applicable to drug-naive patients. The third limitation is that this study does not provide specific information on the underlying neurobiological causes of the abnormally low LDH or how it relates to patient symptoms, such as frontal lobe dysfunction.[23] Thus, future studies should perform a comprehensive cognition examination to investigate the possible correlation between reduced regional LDH and frontal deficits.

4. Conclusion

Our findings indicated decreased LDH in the anterior corpus callosum of both left and right MTLE patients. This local WM anomaly distinguished patients from matched controls with high sensitivity and specificity, and thus could be a potential biomarker for the dignosis of MTLE.

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