

RESEARCH ARTICLE

Magnetic resonance fingerprinting of temporal lobe white matter in mesial temporal lobe epilepsy

Kang Wang¹, Xiaozhi Cao², Dengchang Wu¹, Congyu Liao², Jianfang Zhang¹, Caihong Ji¹, Jianhui Zhong^{2,3}, Hongjian He² & Yanxing Chen⁴ 

¹Department of Neurology, the First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China

²Center for Brain Imaging Science and Technology, Key Laboratory for Biomedical Engineering of Ministry of Education, College of Biomedical Engineering and Instrumental Science, Zhejiang University, Hangzhou, China

³Department of Imaging Sciences, University of Rochester, Rochester, New York

⁴Department of Neurology, the Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China

Correspondence

Yanxing Chen, Department of Neurology, the Second Affiliated Hospital, School of Medicine, Zhejiang University, 88 Jiefang Rd, Hangzhou 310009, China. Tel: +86-571-87784779; Fax: +86-571-87784752; E-mail: chenyanxing@zju.edu.cn

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Abstract

Objective: Mesial temporal lobe epilepsy (MTLE) is a network disorder. We aimed to quantify the white matter alterations in the temporal lobe of MTLE patients with hippocampal sclerosis (MTLE-HS) by using magnetic resonance fingerprinting (MRF), a novel imaging technique, which allows simultaneous measurements of multiple parameters with a single acquisition. **Methods:** We consecutively recruited 27 unilateral MTLE-HS patients and 22 healthy controls. Measurements including T1, T2, and PD values in the temporopolar white matter and temporal stem were recorded and analyzed. **Results:** We found increased T2 value in both sides, and increased T1 value in the ipsilateral temporopolar white matter of MTLE-HS patients, as compared with healthy controls. The T1 and T2 values were higher in the ipsilateral than the contralateral side. In the temporal stem, increased T1 and T2 values in the ipsilateral side of the MTLE-HS patients were also observed. Only increased T2 values were observed in the contralateral temporal stem. No significant differences in PD values were observed in either the temporopolar white matter or temporal stem of the MTLE-HS patients. Correlation analysis revealed that T1 and T2 values in the ipsilateral temporopolar white matter were negatively correlated with the age at epilepsy onset. **Interpretation:** By using MRF, we were able to assess the alterations of T1 and T2 in the temporal lobe white matter of MTLE-HS patients. MRF could be a promising imaging technique in identifying mild changes in MTLE patients, which might optimize the pre-surgical evaluation and therapeutic interventions in these patients.

Introduction

Hippocampal sclerosis (HS) is the most common pathology underlying mesial temporal lobe epilepsy (MTLE).¹ It has been noted for decades that more extensive structural abnormalities within and beyond the temporal lobe exist, accompanying HS. These changes, involving temporal and extratemporal cortex and white matter, can be located both ipsilateral and contralateral to the hippocampus.^{2,3} Therefore, MTLE is thought to be a network disorder.

Abnormalities on conventional magnetic resonance imaging (MRI) are characterized by signal changes,

volume loss, and loss of gray-white matter differentiation, namely gray-white matter blurring. The diagnosis accuracy of structural abnormalities on MRI depends highly on the expertise of the observers. Visual observation of MRI images can only detect obvious gray/whiter matter atrophy or signal intensity changes. Efforts have been made to improve the accurate diagnosis by using quantitative MRI, which can increase the reliability, comparability, and sensitivity of the data obtained compared to the T1- and T2-weighted images.⁴ As to the diagnosis of MTLE-HS, quantitative MRI was reported to increase the detection of HS by 28%.^{5,6} However, given that only a

single parameter can be acquired at a time, this technique is quite time-consuming and impractical, resulting in limited clinical application.^{7,8}

Magnetic resonance fingerprinting (MRF), a novel approach for MRI quantification mapping, allows simultaneous measurements of multiple parameters with a single acquisition.^{7–9} Quantitative measurement of T1, T2, and proton density (PD) values by MRF may enable the identification of subtle changes that were usually not recognized by vision inspection with conventional weighted MR images, resulting in improvement of the accuracy and sensitivity of lesion detection.

In this study, we mainly focused on the analysis of T1, T2, and PD values in the temporal pole and temporal stem of MTLE patients. Because white matter abnormalities in the temporal pole are frequently observed in HS patients, and temporal stem is composed of white matter tract fibers that connect the temporal lobe to the rest of the brain, investigation of these two structures is of great interests to help better understanding of the structural changes in MTLE.

Methods

Participants

This was a prospective study of patients consecutively recruited from the epilepsy clinic of the First Affiliated Hospital, School of Medicine, Zhejiang University (Hangzhou, Zhejiang Province, China) between April 1, 2016 and November 30, 2016. The diagnosis of probable drug-resistant MTLE was made based on the detailed medical history, seizure semiology, and interictal scalp electroencephalography by two experienced epileptologists (K.W. and D.W.). The inclusion and exclusion criteria were as previously described.¹⁰ The diagnosis of HS was in accordance with previously described method.¹⁰ Twenty-seven unilateral MTLE-HS patients (20 left sided, 7 right sided; 20 female, 7 male; mean age, 32.85 years; range, 16–60 years) were included in this study (Fig. 1). Twenty-two healthy controls (9 female, 13 male; mean age, 27.82 years; range, 23–41 years) with no history of neurological or psychiatric disorders were recruited from the local community. The clinical and demographic features of the participants were summarized in Table 1. All the patients and controls underwent the same imaging protocol.

This study was approved by the Medical Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine (Study No. MER2015006), written informed consent was obtained from each participant or from a legal representative.

MR imaging and data acquisition

MR measurements were performed on a 3T scanner (Magnetom Prisma; Siemens Healthineers, Erlangen, Germany) with a 20-channel head coil. The total acquisition time for each subject was about 18 min. The imaging protocol was as previous described, which included conventional fluid-attenuated inversion recovery, T1- and T2- weighted imaging, and two-dimensional (2D) MRF.¹⁰ A multi-slice 2D MRF acquisition was implemented based on the fast imaging with steady-state precession (FISP) sequence.¹¹ For FISP-MRF acquisition in each slice, a total of 600 time-points were acquired. The time repetitions (TRs) of the acquisition varied between 12 and 15 ms with a Perlin noise pattern, and the flip angles (FAs) varied sinusoidally from 5° to 78°. Variable density spiral sampling trajectory with zero-moment nulling was utilized for the acquisition. A total of 20 slices with 3-mm slice thickness were acquired to achieve the temporal lobe coverage, and the total acquisition time of MRF was about 5 min. After the acquisition, a sliding-window reconstruction process^{12,13} was performed on the highly accelerated data to obtain high-quality MRF image frames. Finally, the T1, T2, and Proton density maps were generated by template matching with a pre-calculated dictionary and selecting the best matched dictionary entry, voxel by voxel.

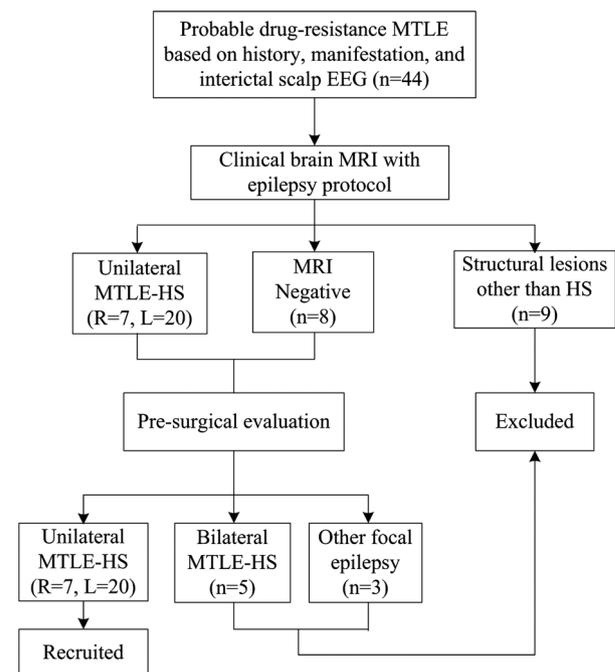


Figure 1. Flow diagram for patient selection. MTLE-HS, mesial temporal lobe epilepsy patients with hippocampal sclerosis; EEG, electroencephalography; R, right; L, left.

Table 1. Clinical and demographic features of the participants.

	MTLE-HS	Controls
Gender	20 female/7 male	9 female/13 male
Age (mean \pm SD, years)	32.85 \pm 10.58 Range: 16–60	27.82 \pm 4.86 Range: 23–41
Epilepsy duration (mean \pm SD, years)	6.3 \pm 4.3	–
Laterality	20 left/7 right	–

MTLE-HS, mesial temporal lobe epilepsy patients with hippocampal sclerosis; SD, standard deviation.

Region of interest (ROI) analysis

The analysis of ROIs was performed independently by two separate neurologists (K.W. and Y.C.) who were blinded to the subject's clinical information. The data processing was performed on MATLAB 2018a (The MathWorks, Inc., Natick, MA). The anatomical boundaries of the temporal pole on MR were defined according to a previously describe criteria.¹⁴ Briefly, the posterior limit of the temporal pole was defined by the first coronal section with the appearance of uncinata bundle. The ROI for measurement of temporopolar white matter measurement was placed at the white matter of the superior temporal gyrus (Fig. 2). The temporal stem on sequential coronal images extends from the level of amygdala anteriorly to

the level of the lateral geniculate body posteriorly. The ROI for measurement was placed between the white matter directly inferior to the circular sulcus of the insula and the lateral superior margin of the temporal horn (Fig. 2).¹⁵ The mean of values from three coronal sections was calculated as the final measurement. Interobserver reliability was assessed using the intraclass correlation coefficient (ICC), which was excellent for the measurement of both temporal pole (ICCs = 0.935, 0.973, 0.996 for T1, T2, and PD values, respectively) and temporal stem (ICCs = 0.971, 0.977, 0.984 for T1, T2, and PD values, respectively). Only ROI output from one investigator was used for all statistical analysis. The volume of bilateral hippocampi (normalized by intracranial volume and adjusted by age) was automatically segmented and measured by MAP18.¹⁶

Statistical analysis

Comparison of parameters between the MTLE patients and controls were assessed by using Student's *t*-test. Paired *t*-test was used for the comparison of parameters between ipsilateral and contralateral side. Pearson's correlation analysis was used for the assessment of association between two variables. All statistical analyses were performed by using IBM SPSS Statistics version 23.0. A $P < 0.05$ was considered statistically significant.

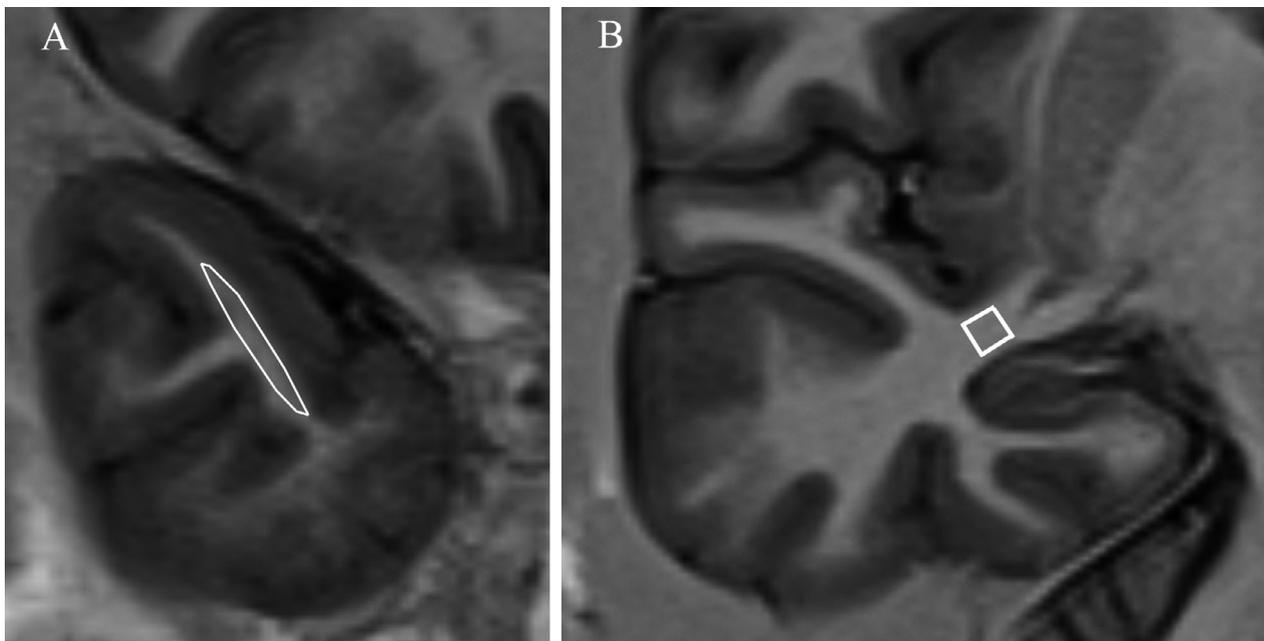


Figure 2. Coronal T1-weighted image showing selection of the region of interest (ROI) for the measurement of MRF based quantitative parameters in the temporopolar white matter (A) and temporal stem (B).

Results

Quantification of temporopolar white matter

As shown in Figure 3, both T1 (mean value, 802.2 ± 55.11 ms) and T2 values (mean value, 95.69 ± 11.37 ms) of the temporopolar white matter ipsilateral to the HS side in MTLE patients were significantly higher than the T1 (mean value, 744.3 ± 54.12 ms) and T2 values (mean value, 80.86 ± 9.259 ms) in healthy controls ($P = 0.0005$ for T1 comparison; $P < 0.0001$ for T2 comparison). Besides, the white matter changes were not just

limited to the ipsilateral temporal pole, the contralateral temporopolar white matter also showed significantly increased T2 values (mean value, 91.62 ± 11.25 ms; $P = 0.0008$) compared to controls. The ipsilateral temporopolar white matter exhibited significantly higher T1 ($P = 0.0289$), and T2 ($P = 0.0372$) values than the contralateral side. Whereas, T1 and T2 values between the left and right temporopolar white matter were of no significant differences in healthy controls. As for PD values, no significant differences were observed either between MTLE patients and healthy controls, or between ipsilateral and contralateral side of the patients.

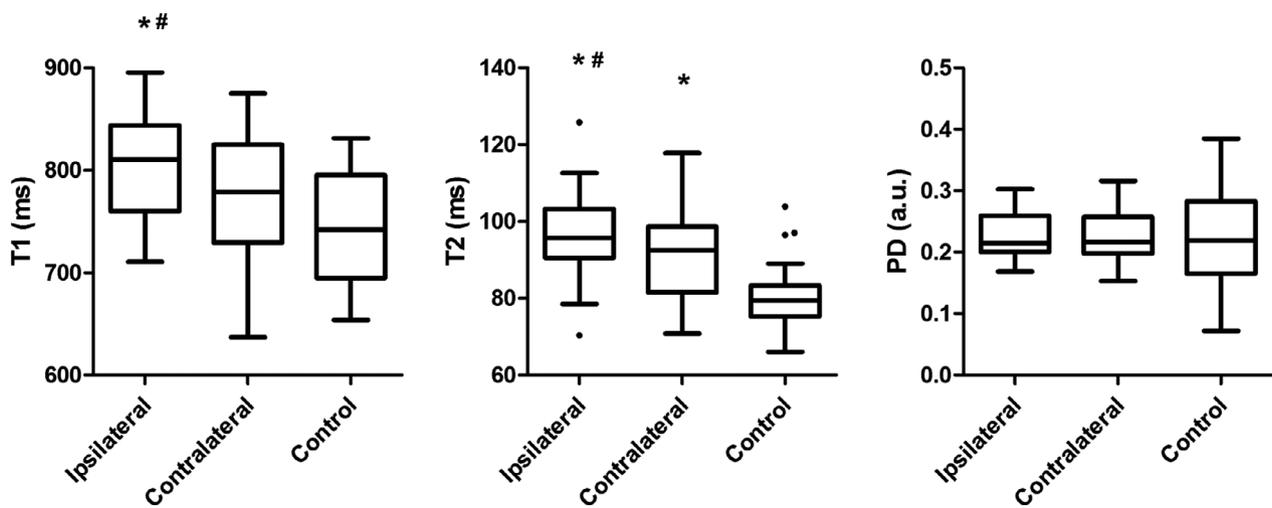


Figure 3. Box-and-whisker plots of T1, T2, and PD values of the temporopolar white matter. The boxes represent the median, the 25th, and 75th percentiles. The whiskers go 1.5 times the interquartile distance (the difference between the 25th and 75th percentiles) or to the highest or lowest point, whichever is shorter. * $P < 0.05$ versus control; # $P < 0.05$ versus contralateral.

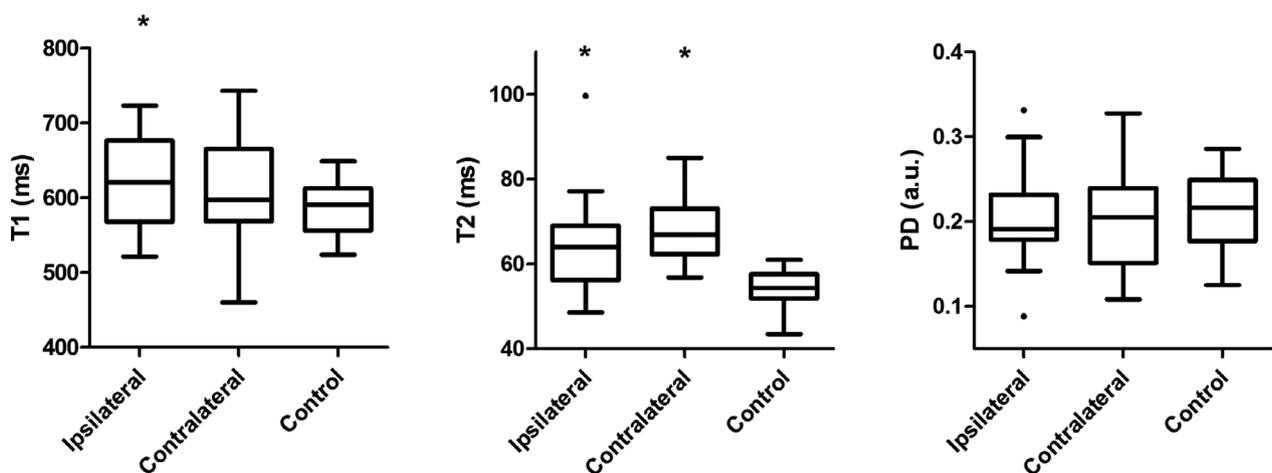


Figure 4. Box-and-whisker plots of T1, T2, and PD values of the temporal stem. The boxes represent the median, the 25th, and 75th percentiles. The whiskers go 1.5 times the interquartile distance (the difference between the 25th and 75th percentiles) or to the highest or lowest point, whichever is shorter. * $P < 0.05$ versus control.

Table 2. Receiver operating characteristic curve analyses.

Variable	AUC	Cutoff (ms)	Sensitivity (%)	Specificity (%)	Youden Index
Temporal pole T2	0.843	85.5	85.19	81.82	0.670
Temporal stem T2	0.813	61.0561	62.96	100	0.630
Temporal pole T1	0.771	779.4118	70.37	72.73	0.431
Temporal stem T1	0.670	650.1008	40.74	100	0.407

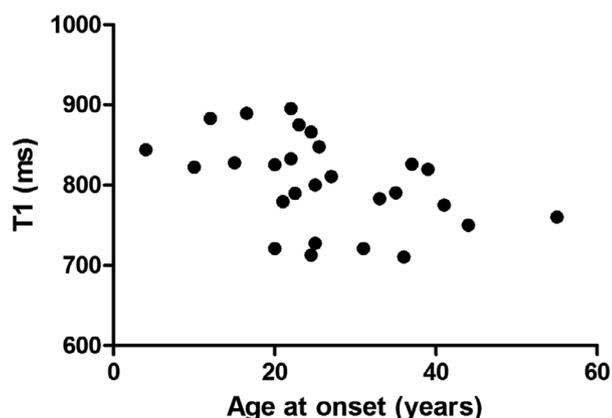
AUC, area under the receiver operating characteristic curve; Temporal pole T2, T2 relaxation time of the temporopolar white matter; Temporal pole T1, T1 relaxation time of the temporopolar white matter.

Quantification of temporal stem

We also measured T1 and T2 values in the temporal stem (Fig. 4). The MTLE patients had higher T1 (mean value, 623.1 ± 59.23 ms; $P = 0.0175$) and T2 values (mean value, 64.45 ± 10.54 ms; $P < 0.0001$) in the temporal stem ipsilateral to the HS side than the controls (mean value, 589.2 ± 35.59 ms for T1; 54.23 ± 4.349 for T2). The contralateral temporal stem of the patients also showed higher T2 (mean value, 69.05 ± 7.759 ms; $P < 0.0001$), but not T1 (mean value, 610.1 ± 71.53 ms; $P = 0.1916$) values than the controls. No significant differences were observed in T1 and T2 values between ipsilateral and contralateral temporal stem of the patients. Similar to the measurements in the temporopolar white matter, no significant differences in PD values were observed either side of the temporal stem.

Receiver operating characteristic curve analysis

The receiver operating characteristic (ROC) curves analysis was used to evaluate the diagnostic accuracy



of these MRF parameters. The performance of ipsilateral temporopolar white matter and temporal stem T1/T2 values are shown in Table 2. T2 of the temporopolar white matter (AUC = 0.843) and temporal stem (AUC = 0.813) had much higher area under the curve (AUC) than T1 (AUC = 0.771 for temporal pole; AUC = 0.670 for temporal stem). The sensitivity and specificity (85.19% sensitivity and 81.82% specificity for T2 of the temporopolar white matter; 62.96% sensitivity and 100% specificity for T2 of temporal stem) at the optimal cut-off point, which was defined according to the Youden index, are also listed in Table 2.

Correlation analysis

Correlation analysis revealed that the T1 and T2 values of the ipsilateral temporopolar white matter were negatively correlated with age at epilepsy onset ($r = -0.48$, $P = 0.019$ for T1; $r = -0.488$, $P = 0.01$ for T2) (Fig. 5), but were not correlated with disease duration, age at imaging acquisition, or T1/T2 values of the ipsilateral hippocampus. No correlations were found between T1/T2 values of the temporal stem and clinical parameters (disease duration and age at imaging acquisition) or T1/T2 values of the hippocampus. We also measured the ipsilateral hippocampal volume, which correlated negatively with the corresponding T1 ($r = -0.554$, $P = 0.003$) and T2 ($r = -0.511$, $P = 0.006$) values. However, we did not observe correlations between the hippocampal volume and any of the MRF parameters.

Discussion

In this study, by using MRF, we performed T1, T2, and PD mapping simultaneously on the temporal lobe in MTLE-HS patients, with focus on its myelin

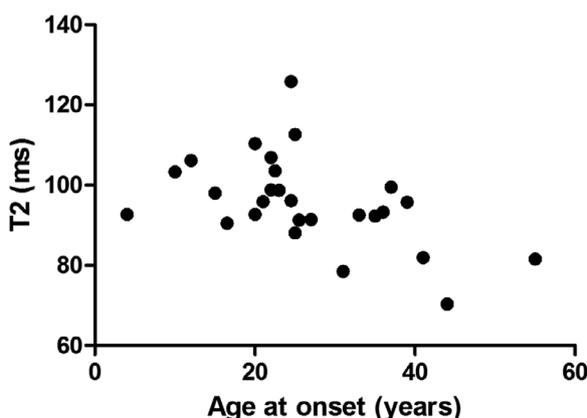


Figure 5. Scatterplots showing the correlation of T1 ($r = -0.48$, $P = 0.019$) and T2 ($r = -0.488$, $P = 0.01$) relaxation times in the temporopolar white matter with age at epilepsy onset.

components, which has not been explored by conventional quantitative methods, such as inversion-recovery sequences (for T1 mapping) and spin-echo sequences (for T2 mapping) due to their long acquisition time. We found longer T1 and T2 in both the ipsilateral and the contralateral temporopolar white matter, and the T1 and T2 values were significantly higher in the ipsilateral than the contralateral side. Significantly increased T1 and T2 values were observed in the ipsilateral temporal stem, but only T2 values were increased in the contralateral temporal stem. The prolonged relaxation time in the ipsilateral temporopolar white matter was negatively correlated with the age of epilepsy onset.

MRF is a new imaging technique, allowing for simultaneous measurements of T1 and T2 relaxation time with high repeatability and accuracy.¹⁷ The total acquisition time of 2D-MRF covering bilateral temporal lobes for each participant is 5 min, which is much shorter than conventional quantitative MRI approaches, and is robust to movement artifacts.¹⁰ We have previously demonstrated high accuracy and sensitivity of MRF in HS diagnosis (96.9%).¹⁰ Significantly increased T1 and T2 values were found in the HS lesions compared to the values of the hippocampus from healthy controls, though with some variation.¹⁰ Previous studies using conventional T2 relaxometry for quantitative analysis were mainly on hippocampus or temporal stem, with efforts to assist the lateralization of the epileptic focus.^{5,18,19} To the best of our knowledge, this is the first study that performed T1, T2, and PD mapping on the two most representative white matter regions (temporal pole and temporal stem) in MTLE patients. Our study further demonstrated that quantification of the T1 and T2 relaxation times by MRF allows identification of invisible structural abnormalities in white matter.

It has been shown that temporopolar abnormalities, mostly T2-weighted intensity increases in the white matter with gray-white matter blurring or atrophy, can be observed visually on MRI in more than half of patients with HS, but also in those without HS. These abnormalities were always on the ipsilateral side to HS.^{20–23} However, in our study, by using MRF, we also found higher T2 relaxation times in the white matter of the contralateral temporal pole. This discrepancy maybe because those reported studies defined temporopolar abnormalities based on visual detection. By using MRF, we were able to detect relatively mild, invisible contralateral structure changes. The histopathological changes concerning the temporopolar abnormalities are not clear. It was previously assumed by various authors that these abnormalities were either gliosis of the white matter or ectopic neurons due to developmental abnormalities.^{5,22,24} However,

ectopic neurons can also be found in the temporal lobe of the normal adult controls.²⁵ Besides, some studies failed to observe differential gliosis numbers in patients with or without blurring.²² Thus myelin abnormalities were suspected. This was later confirmed by Garbelli *et al.*²¹ who observed similar extent of white matter gliosis and ectopic neurons in the temporal pole of all the MTLE cases, regardless of the presence/absence of blurring. But they found dishomogeneous staining of the white matter in patients with blurring by myelin staining. Electron microscopy revealed axonal degeneration and loss of axon numbers and axonal density,²¹ indicating that degeneration of fiber bundles might cause the visible gray-white matter blurring.

Epilepsy onset at a younger age has been found to be independently associated with the occurrence of temporopolar abnormalities. Similarly, we also found a negative correlation between T1/T2 values and the age at epilepsy onset. This correlation indicates that seizure-related insults during the first years of life, which might affect cerebral myelination, were critical.^{21,26} Studies concerning the correlation between the temporopolar abnormalities and duration of epilepsy were controversial. Some found longer duration of epilepsy in patients with temporal pole blurring or atrophy,^{21,27} suggesting cumulative damage due to chronic seizures, while some could not find such correlation.²³ In our study, we did not observe the correlation between the disease duration and T1/T2 values of the temporopolar white matter. Surprisingly, the temporopolar T1/T2 values did not correlate with hippocampal volume either. Thus, we believe some other factors, like seizure frequency, and non-epileptic insults occurred during the early critical developmental stage like the history of birth complications, may be involved in the development of temporal lobe white matter abnormalities.

Temporal stem is comprised of major projection fiber tracts that connect the temporal lobe to the rest of the brain, including frontal lobe, corpus striatum, thalamus, hypothalamus, contralateral temporal lobe, and septal region.²⁸ Alteration in certain fiber tracts, like the fimbria-fornix, parahippocampal white matter bundle, and uncinate fasciculus, are suggested to play an important role in the generation and propagation of temporal lobe seizures.²⁹ Studies specifically focusing on the white matter changes in the temporal stem are limited. An earlier study indicated that a proportion of MTLE-HS patients had increased T2 signal in the white matter of the ipsilateral or both sides of anterior temporal lobes.³⁰ Another study also revealed prolonged T2 relaxation time in the temporal stem in about 70% of the MTLE patients by using T2 relaxometry. The increase in T2 relaxation time was bilateral and symmetrical in about half of the patients.⁵ Consistently, we also

observed higher T1 and T2 relaxation times in the ipsilateral temporal stem and higher T2 relaxation times in the contralateral temporal stem by using MRF. Correlation analysis of T1 and T2 relaxation times between the ipsilateral hippocampus and the temporal stem failed to show any significant correlations, suggesting that the extent of hippocampus structural changes cannot predict the white matter changes in the temporal stem.

Our study demonstrated that both T1 mapping and T2 mapping in temporal lobe could accurately discriminate white matter changes but PD mapping failed, and T2 mapping was more sensitive than T1 mapping. T1 relaxation time is believed to be linked to myelin maturation while long T2 relaxation time reflects increased water content in the tissue. This might account for why white matter gliosis and fiber degeneration in MTLE can be sensitively reflected by T1 and T2 relaxometry. PD map mirrors the concentration of hydrogen nuclei which is uniformly and sparsely distributed in the brain, thus PD appears not a suitable quantitative parameter for MTLE.

This study has several limitations. Firstly, the major methodological limitation is that the spatial resolution of 2D-MRF is 1.2×1.2 mm with 3-mm thickness, which is not good enough for subtle structure imaging. We only covered temporal lobes in this study, but MTLE is well-recognized as a network disease extending beyond temporal lobe. The newly developed 3D-MRF technique with higher resolution covering the whole brain may overcome these shortcomings, providing extra information with more accurate T1, T2, and PD estimation.^{13,31} Secondly, although we prospectively collected all the data, our study design was cross-sectional. Longitudinal studies are needed to explore the association between white matter alterations and seizure frequency, the contribution of white matter changes to the long-term seizure outcome. Thirdly, the sample size is relatively small. The subjects included in this study comprised mainly of patients with left MTLE. Therefore, we were unable to compare between left and right MTLE. Some studies using DTI have shown a different pattern of connectivity changes in left MTLE compared to right MTLE.^{32,33} But a more recent study failed to observe such lateralized differences. Widespread white matter alterations were observed in MTLE patients, independent of the disease side.³⁴ The aim of the present study was to investigate epilepsy-related white matter changes regardless of the epileptogenic side. Therefore, further studies are needed to compare side-specific differences in the temporal lobe white matter with a larger sample size. Finally, the histopathological abnormalities underlying these white matter relaxation time changes have not been fully elucidated, further studies focusing on the correlation between these changes and

the related histopathological findings would enrich our understanding of MTLE.

In conclusion, by using MRF, we were able to quantify the abnormalities in the white matter of temporal lobe in MTLE-HS patients. Prolonged T2 relaxation times were observed in the bilateral temporopolar white matter and temporal stem in MTLE patients, while T1 relaxation times were increased only in the ipsilateral white matter, indicating that T2 mapping was more sensitive in discriminating the white matter abnormalities than T1 or PD mapping. This study might improve our knowledge about the clinical manifestations and prompt the optimization of surgical interventions. The clinical implications and its relationship to surgical outcomes remain to be further investigated.

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Author Contribution

Study concept and design, K.W. and Y.C.; Data acquisition and analysis, K.W., X.C., D.W., Y.L., J.Z., C.J., J.Z., H.H., and Y.C.; Drafting and critical analysis of manuscript, K.W., X.C., and Y.C.

Conflicts of Interests

The authors have no financial conflicts of interest.

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