Application of Magnetic Resonance Fingerprinting in Epilepsy

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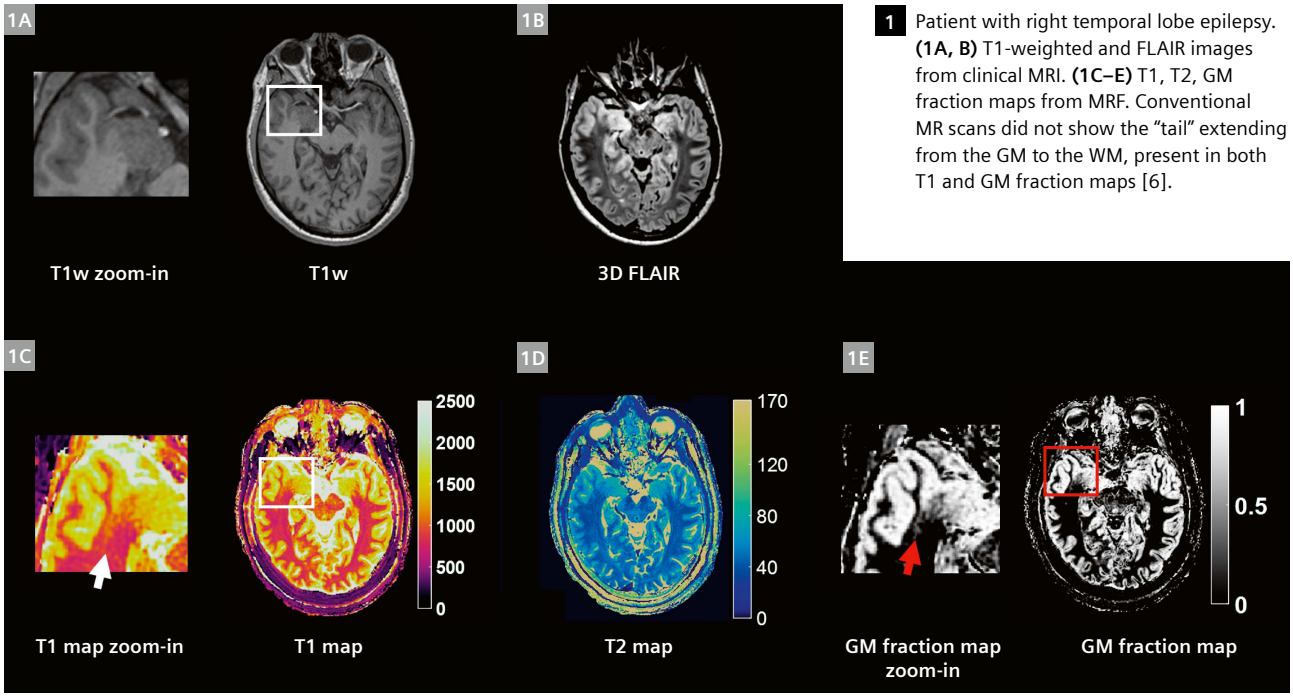
Introduction

Afflicting 3.4 million patients, epilepsy is one of the most common neurological diseases in the US [1]. Presurgical evaluation of epilepsy strongly relies on diagnostic magnetic resonance imaging (MRI) for accurate identification of epileptogenic lesions. In particular, it is crucial to visualize and detect subtle lesions such as small focal cortical dysplasias (FCDs). The diagnosis of mesial temporal lobe epilepsy (MTLE) benefits from precise evaluation of the hippocampal volume and contrast for detection of hippocampal sclerosis (HS). In cases where multifocal and widespread lesions exist, such as periventricular nodular heterotopias (PVN) and tuberous sclerosis complexes (TSC) [2], characterization of each lesion also provides helpful information for surgical planning. However, there is much room for improvement for the routine MRI scans currently implemented in most clinical settings to reach the above expectations [3]. Over the past year, several studies have proposed magnetic resonance fingerprinting (MRF) as an alternative imaging method. This quantitative MR imaging technique has shown promising efficacy to provide additional, clinically relevant information as compared to conventional MRI for patients with epilepsy [4–6].

Here we present a review of previous studies on the application of MRF in epilepsy. Discussion will first start with conventional MRI methods as well as the challenges of these methods in epilepsy. Then we will briefly introduce the basic concept and implementation of MRF, followed by an explanation of its benefits and advantages compared to standard MRI protocol. Lastly, improvements of epilepsy diagnosis by using MRF will be described in sections for FCD, PVN/TSC, and MTLE.



1 Patient with right temporal lobe epilepsy. **(1A, B)** T1-weighted and FLAIR images from clinical MRI. **(1C–E)** T1, T2, GM fraction maps from MRF. Conventional MR scans did not show the "tail" extending from the GM to the WM, present in both T1 and GM fraction maps [6].

Challenges of conventional MRI methods

MR imaging for epilepsy can be challenging and time consuming. Firstly, the structural and morphological changes of epileptogenic lesions can be as subtle as in the scale of millimeters, and these lesions can occur in any cerebral lobe or spread across different lobes. This requires the epilepsy MRI protocol to have high image resolution (submillimeter) and whole brain coverage. Secondly, for detection of subtle lesions, images with multiple contrasts are typically acquired. A typical epilepsy MRI protocol consists of multiple scans running a series of multislice imaging sequences, including fluid-attenuated inversion recovery (FLAIR), T1- and T2-weighted imaging [7], which altogether usually takes more than half an hour.

More importantly, conventional MR scans generate qualitative images, in which visualization of tissue abnormalities is highly dependent on image contrast. Take the T1- and T2-weighted images for example, these two contrasts are mostly but not completely governed by T1 or T2 values. As a result, signal intensities and contrasts of MR images are the product of mixture of multiple underlying tissue properties, which could cancel out contrast signatures and obscure lesion features in images. This may explain why some subtle FCD and HS lesions were not detectable by conventional MRI. The qualitative nature also confines its abilities in multicenter/longitudinal studies, since signal contrast may vary due to the type and setup of scanners. In the case of multifocal lesions such as PVN and TSC, although conventional MRI could visualize them well, it is not capable of recognizing which one of the lesions is the most relevant to the epilepsy. Additionally, diagnosis of lesions based on qualitative MRI adopts comparative strategies; thus the accuracy of such approach strongly depends on the expertise of the reviewing neuroradiologist. For example, routine MRI examines bilateral MTLE by comparing volume and signal of both hippocampi, assuming that the contralateral hippocampus is healthy. Erroneous conclusions are likely made for patients with bilateral volume loss/signal changes, and patients with subtle unilateral signal variations [4].

Quantitative MRI, by providing tissue property maps such as T1, T2 maps, could inherently detect subtle tissue changes with enhanced sensitivity and specificity. Quantitative maps depict pure tissue properties, which avoids mixing of contrast as in the case of weighted signals and helps clearly present lesion signatures. Since absolute values are measured, the resulting maps are immune to the impact of variations in scanner setup. These advantages make the T1 and T2 maps more reliable and objective for clinical diagnosis, as compared to the weighted images. Previous studies have shown both T1 and T2 values of epileptogenic foci are longer than in healthy tissue controls, which is relevant to cytological abnormalities, gliosis and neuronal cell loss [8–10].

Despite its advantages, conventional quantitative MRI is rarely adopted in a clincial setting, due to its great consumption of time, low spatial resolution and low robustness.

MR Fingerprinting scan

As a state-of-the-art quantitative MR imaging method, MRF provides multiple tissue property maps from a single scan within clinical tolerable time. The underlying concept of MRF is that different tissues could generate unique signal evolutions under appropriate data acquisition schemes, which are achieved by pseudo-randomly varying acquisition parameters. By incorporating possible tissue property values, a dictionary containing all foreseeable signal evolutions is constructed, signals from each pixel can be assigned to an entry of the dictionary by signal pattern recognition. This scenario is analogous to matching unique human fingerprints with existing records, in order to retrieve information from a database. Similarly, once an entry of signal vectors is selected, information such as tissue types, T1 and T2 values in a pixel could be retrieved from the dictionary altogether [11].

MRF yields many benefits allowing it to overcome limitations in clinical applications. For example, results of MRF are highly repeatable and reproducible in human brain imaging [12]. Although signal fingerprints could be influenced by imperfections in scanning systems, the processing algorithms could account and compensate for it during dictionary construction. T1 and T2 relaxation times measured by MRF using different scanners are consistent, especially for solid compartments of brain [12]. Another significant advantage of MRF is its ability to fully extract multiple tissue property values from one scan within clinically feasible time [11]. This process is highly efficient, as it substantially shortens scanning time while examining more tissue parameters than traditional quantitative imaging methods. These quantitative maps can also be used to synthesize clinical standard MR images, such as T1-weighted, T2-weighted and FLAIR, without additional scan time.

Moreover, maps are perfectly coregistered, which facilitates multiparametric analysis of tissue maps. Comprehensive analysis across multiple of MR parameters could expose complex morphological tissue changes with increased sensitivity and specificity in previous studies. For example, T1 and T2 maps generated from MRF was reported to distinguish different types of intra-axial brain tumors [13]. In prostate cancer applications, multiparametric analysis combining T1, T2 maps and apparent diffusion coefficient (ADC) mapping has been proven to differentiate normal peripheral zone from transition zone [14, 15].

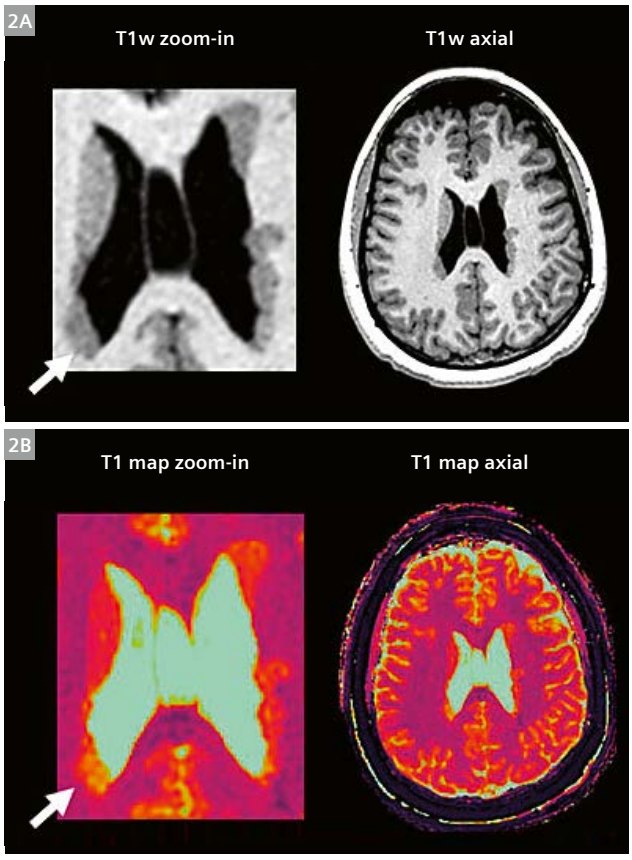
MRF is robust in rejecting acquisition and motion errors due to its pattern matching algorithm. Acquisition and reconstruction artifacts are suppressed in MRF images due to spatial and temporal incoherence between measurement errors and predicted signals. Images obtained from a motion-corrupted scan with random motion happened during the last ¼ of the scan time demonstrate almost the same quality and anatomical structure as motion-free images [11]. Advanced image reconstruction algorithms, such as Motion insensitive MRF (MORF)[1] is able to recover maps while tolerating 54% of motion corruption in data [16]. Besides, strategies have been developed in many aspects to further avoid image and map corruption of MRF with reduced scan time, such as incorporating more efficient sequences [17–19], and advanced reconstruction algorithms before pattern matching [20, 21].

MRF in epilepsy

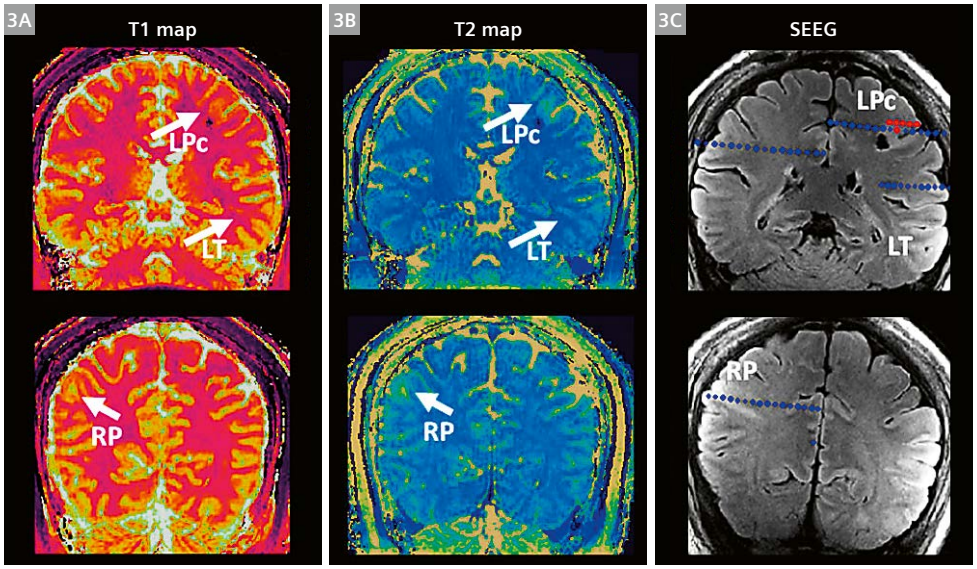
In a number of studies, MRF scans and conventional MR images were reviewed separately and independently for diagnosis of different types of epileptogenic lesions. These studies provided encouraging data that MRF could provide additional findings in detection and characterization of epileptogenic lesions, assisting presurgical evaluation.

Focal cortical dysplasia (FCD)

MRF was shown to be able to reveal subtle FCD lesions that were not obvious when reviewing clinical MR scans. Since T1 and T2 maps particularly reflect cell structure, myelin/water content and microenvironment, they are in principle more sensitive to tissue malformation than the weighted

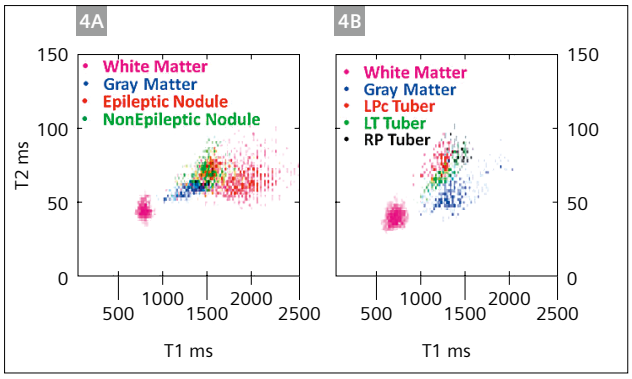


2 Patient with bilateral PVN. **(2A)** Axial T1-weighted image from the conventional scan. **(2B)** T1 map from MRF. T1 map showed increased values of the nodules at the right occipital horn, where signal intensity was uniform among all the nodules on the T1-weighted scan [6].



3 Patient with multiple TSC tubers (three lesions shown). **(3A, B)** T1 and T2 maps from MRF. **(3C)** Invasive stereo-EEG electrode locations (blue spheres) shown on T2-weighted FLAIR image, with red spheres showing ictal onset. Characterization from T1 and T2 maps were consistent with the invasive evaluation results of the three lesion areas [6].

[1] *Work in progress: the application is currently under development and is not for sale in the U.S. and in other countries. Its future availability cannot be ensured.*



4 ROI analysis of **(4A)** the PVN patient in Figure 2 and **(4B)** the TSC patient in Figure 3. Lesions, normal gray matter and normal white matter form distinct clusters [6].

measures provided by clinical MRI [6]. Also, GM and WM fraction maps which segment brain tissue structures are useful in lesion detection at the GM/WM boundary.

Figure 1 illustrated an examplary patient with right temporal lobe epilepsy [6]. Conventional MRI (Fig. 1A, B) showed hyperintensity of the right amygdala in the FLAIR scan, and no noticeable abnormalities in the temporal lobes otherwise. MRF maps (Figs. 1C–E) visualized an additional tail-like tissue alternation on the right temporal lobe besides the amygdala hyperintensity. This "tail" had an increased T1 value and higher GM fraction implying a potential epileptic abnormality. Subsequent interictal and ictal EEG monitoring was consistent with the location of the abnormality. Resective surgery completely included the abnormality. Histopathology revealed mild malformation of cortical development. The patient remained seizure-free after surgery.

Periventricular nodular heterotopias (PVN)/ tuberous sclerosis complexes (TSC)

For multifocal lesions such as PVN and TSC, clinical MRI scans were able to map their distribution and boundaries, but no signal differences manifested to distinguish one lesion from another. Through multiparametric quantitative ROI analyses, quantitative T1 and T2 maps from MRF could enable the characterization of these lesions [6]. This was illustrated in Figure 2, which showed a patient diagnosed with bilateral PVN. T1 map highlighted an extraordinary increase of T1 value from the nodules at the right occipital horn, which exhibited little signal differences with other heterotopias on conventional T1-weighted scan. The ROI analysis (Fig. 4A) demonstrated a significant shift of T1 values in the right occipital horn as compared to the left-sided nonepileptic nodules. This patient underwent stereo-EEG (SEEG) monitoring to verify the epileptogenic zone, and the separation of lesion clusters was concordant with their individual epileptogenicity [6].

Figure 3 was an example of a patient with three TSC lesions, located in the left precentral (LPc), right parietal (RP) and left temporal (LT) lobes of the brain respectively. MRF maps indicated variations of quantitative T1 and T2 values among these TSC lesions. In the ROI analysis (Fig. 4B), the LPc tuber formed a distinct cluster with a significantly different T2 value from the other clusters. The following SEEG evaluation targeting all the tubers proved the highest epileptogenicity was indeed from the LPc tuber.

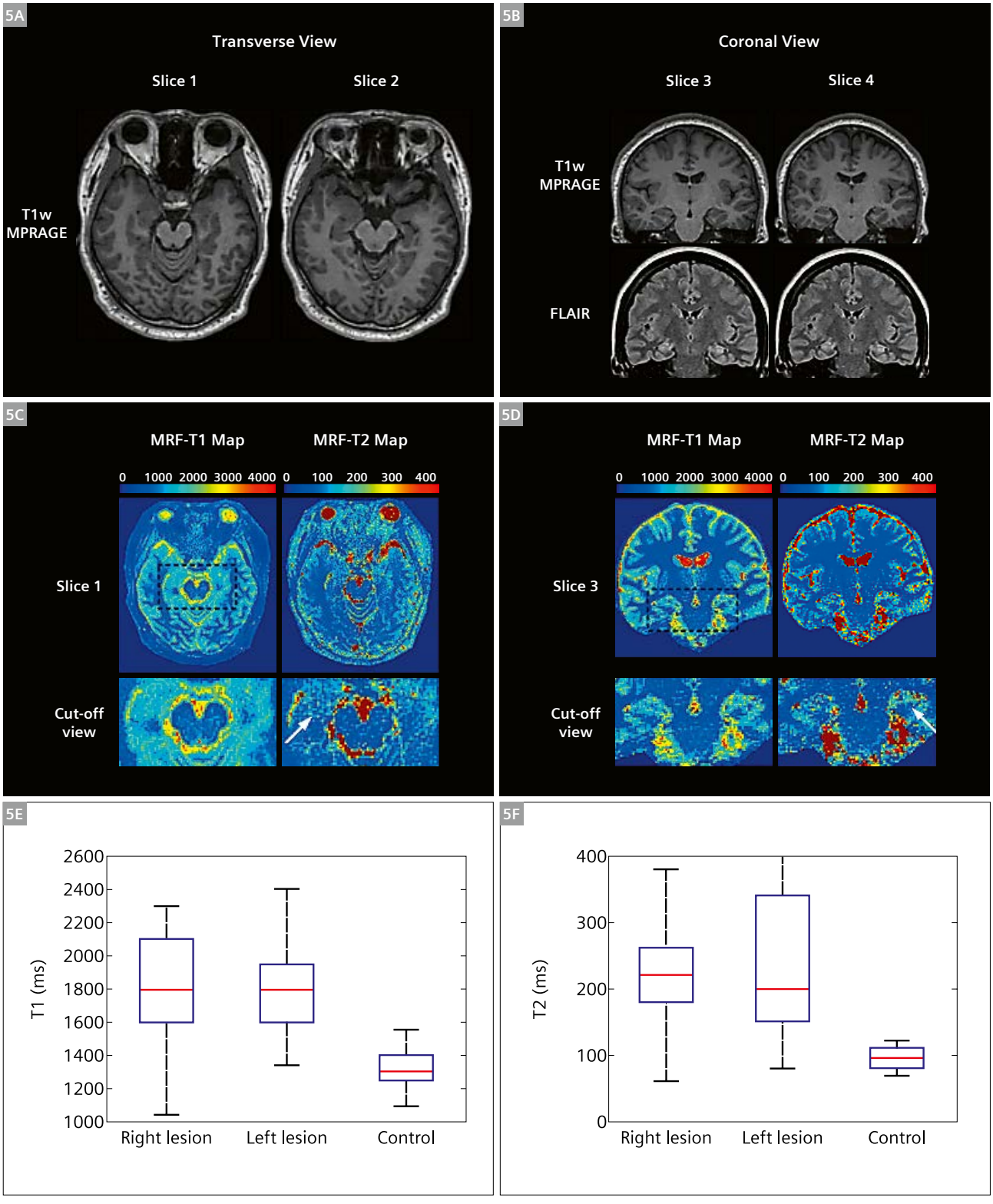
Mesial temporal lobe epilepsy (MTLE)

Accuracy of MTLE diagnosis could be further improved by MRF through quantitative comparison of T1 and T2 values in the hippocampus between patients and healthy controls. HS lesions showed higher values of both T1 and T2 than normal contralateral hippocampus and healthy control groups [4]. For unilateral MTLE patients who received negative MRI results on conventional scans (due to the very subtle T1/T2 signal changes in the HS lesions), MRF maps were sensitive and effective in detecting such tiny differences via statistical analysis. MRF also facilitated quantitative comparison among both sides of hippocampus and healthy controls, which reduced incorrect diagnosis of bilateral HS as unilateral and elevated diagnosis rate of MTLE from 69.7% to 96.9% [4].

Table 1 listed the statistics of average T1 and T2 values for unilateral MTLE patient group and healthy control group. Tissue properties of atrophic hippocampus were compared against both healthy controls and the contralateral regions. Mean T1 and T2 values of HS lesions were at least one standard deviation higher than the other two reference groups, which confirmed the existence of unilateral HS. No difference was seen between contralateral hippocampus regions and healthy controls.

Figure 5 illustrated the clinical images and MRF maps in coronal and axial views from a patient with bilateral HS. While lesion signatures were vague on conventional scans, MRF demonstrated significantly higher T1 and T2 values of the hippocampi on both sides, as compared to healthy controls, which supported the diagnosis of this patient as bilateral HS. In this case, the quantitative nature of MRF allowed for lesion recognition in MTLE, independent of the condition (normal or pathologic) of the contralateral side, which had been impossible with conventional MRI [4].

Besides diagnosis purposes, MRF was also useful in investigating the structural changes outside of the hippocampus caused by MTLE, such as temporal lobe white matter. Longer T2 values were detected in temporopolar white matter and temporal stem on both sides of unilateral MTLE-HS patients, but only ipsilateral white matter had higher T1 value [5]. This finding might extend our understandings of the pathology, neuronal malformation, and microstructure alternation in MTLE.



5 Patient with bilateral HS-MTLE. **(5A, B)** T1-weighted and FLAIR scans in axial views and coronal views. **(5C, D)** T1 and T2 maps (axial and coronal views) from MRF **(5E, F)** Box-and-whisker plots of both sides of HS lesions as compared to healthy hippocampi [4].

Participant	T1 (msec)	T2 (msec)
Atrophic hippocampus (n = 28)*	1361 ± 85	135 ± 15
Contralateral hippocampus (n = 28)*	1255 ± 68	103 ± 11
Healthy control participants (n = 30)	1249 ± 59	104 ± 9

*Patients with unilateral mesial temporal lobe epilepsy.

Table 1: T1 and T2 values of HS lesions and contralateral hippocampus.

Conclusion

In epilepsy applications, MRF has been shown to provide additional information to improve diagnosis accuracy and assist surgical planning. It has the potential to detect subtle tissue abnormalities that is invisible on clinical MR scans with high sensitivity and specificity. Lesion characterization based on epileptogenicity could benefit from multiparametric analysis of tissue properties maps. The diagnosis could thus become more objective and less biased because no contrast comparison from apparent health tissue is needed. With enhanced efficiency and reliability, MRF offers great opportunities of improving the current clinical MRI examination for epilepsy patients.

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