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Review

# Neuroimaging in refractory epilepsy. Current practice and evolving trends

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ABSTRACT

Identification of the epileptogenic zone is of paramount importance in refractory epilepsy as the success of surgical treatment depends on complete resection of the epileptogenic zone. Imaging plays an important role in the locating and defining anatomic epileptogenic abnormalities in patients with medically refractory epilepsy. The aim of this article is to present an overview of the current MRI sequences used in epilepsy imaging with special emphasis of lesion seen in our practices. Optimisation of epilepsy imaging protocols are addressed and current trends in functional MRI sequences including MR spectroscopy, diffusion tensor imaging and fusion MR with PET and SPECT are discussed.



## 1. Introduction

About a 15–30% of patients with epilepsy are refractory to medical therapy, and surgery is the most effective method for controlling seizures in this group of individuals [1–3]. Pre-surgical evaluation aims to delineate the epileptogenic zone, which is a theoretical concept of a cortical area that is indispensible for the generation of epileptic seizure [4]. The extent of epileptogenic zone cannot be measured directly but the hypothesis of the localisation of the epileptogenic zone can be generated by localisation of other cortical zones including ictal onset zone, irritative zone (the area occupied by interictal discharges in EEG), epileptogenic lesion, symptomatogenic zone, and functional deficit zone. Neuroimaging is essential and mandatory in the pre-surgical work-up of the localisation and lateralisation of epileptogenic zone. CT scan of the head has the advantages of easier access, quicker scanning time, and lower cost. It is thus particularly useful in acute symptomatic seizures and status epilepticus, and when MRI is less accessible. CT is also able to better demonstrate bone pathology, calcification and haemorrhage. During epilepsy pre-surgical evaluation, CT is also useful to co-register invasive electrodes with the magnetic resonance imaging (MRI).

Surgery has become an invaluable treatment modality of refractory epilepsy. The role of neuroimaging is in particular to delineate discrete lesions amenable to surgical resection, such as mesial temporal sclerosis, focal cortical dysplasia, or hypothalamic hamartoma. MRI has become the method of choice due to its superior soft tissue contrast, multiplanar imaging capability and lack of beam hardening artifacts. MRI of the brain should be the investigation of choice in children and adults with epilepsy to screen for structural abnormalities as recommended by the National Institute of Health and Clinical Excellence (NICE) guidelines [5]. In particular, MRI is indicated in those individuals who develop epilepsy before the age of 2 years or in adulthood, suggestion of focal onset based on history, examination or EEG (unless clear evidence of benign focal epilepsy) and refractory to anti-epileptic medications.

In this article, we first review the applications of MRI in refractory epilepsy with use of conventional imaging protocols with regards to the common cortical abnormalities associated with refractory epilepsies that are surgically remediable. The second part of this review focuses on the role of EEG and integrated MRI and EEG. The final part looks at other neuroimaging modalities including CT and nuclear imaging techniques.

## 2. Conventional MRI imaging protocols in epilepsy

The recommended epilepsy protocol MRI at 1.5 T or 3.0 T includes the entire brain from nasion to inion, T1-weighted magnetisation prepared rapid gradient echo (MPRAGE), or spoiled gradient recalled (FSPGR) Images 1.5-mm slice thickness with no

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intervening gap obtained in the coronal oblique plane (if TLE is suspected), coronal, and axial FLAIR sequences with 2–3-mm slice thickness and 0–1-mm interslice gap. These images are acquired as a 3D volume, 'thereby allowing post-processing to correct for head misalignment and for reformatting images into multiple planes to confirm a subtle malformation of cortical development [6–9]. It has been reported that the overall specificity for finding of focal lesion in standard MRI was 22%, if re-assessed by experts 40%, and of dedicated MRI epilepsy protocol is 89%. The use of standard MRI in epilepsy should be limited to exclusion of abnormalities, which have to be treated irrespective of seizure considerations at the onset of the disorder like stroke or malignant brain tumours [10]. In order to optimise a dedicated epilepsy MRI imaging protocol; increasing field strength, hard ware and sequences contributions are required.

### 2.1. The role of MRI field strength in epilepsy imaging

High field 3 T when compared to the 1.5 T is found to increase detection of new lesions, providing additional relevant clinical information and detection of lesion in 65% of cases referred with a normal routine epilepsy 1.5 T MRI studies [11]. The high field 3 T with the presence of strong gradients allows the use of 3D sequences of greater signal-to-noise ratio than on the 1.5 T MRI, which are very useful for small lesions with an advantage of reduced acquisition time. A recent study on focal epilepsy found that 3 T scans offer better performance than 1.5 T scans in terms of better characterisation of atrophy and gliosis. Focal cortical dysplasia (FCD) was detected in 11% of patients using 3 T, majority of whom were tested to be negative on 1.5 T MR [12]. A study on the detection of transmantle sign in type 2 focal cortical dysplasia (FCD2) showed that 3 T MRI allowed a high spatial resolution in a given acquisition time with isotropic millimetric voxels. The authors stated that the detection and characterisation of FCD2 was better at 3 T than at 1.5 T with similar head coils and acquisition time, owing to greater ability at 3 T to detect the transmantle sign [13].

### 2.2. Hardware requirement in epilepsy imaging

The hard ware required, is a phased array (PA) surface coil instead of a quadrature head-coil to increase signal to noise ratio (SNR) dependence. PA improves SNR up to fivefold in the cortex which inturns results in an increased lesion detection and diagnosis in 64% of patients with focal epilepsy [14]. PA imaging at 3 T significantly improves image quality compared with that in routine 1.5 T head coil studies that will also significantly increase lesion detection in patients with focal epilepsy. In previous study on children with intractable epilepsy, high-resolution MRI identified lesions not detected by standard MRI in more than half the children (56%). Technical advances such as four-coil phased surface array MRI can help identify and better delineate lesions, improving the diagnosis of patients who are candidates for surgical treatment of refractory epilepsy [15]

Increasing the number of channels within the coil has the effect to provide improved signal-to-noise ratio (SNR) in the periphery field of view as well as providing accelerated imaging. For example, 64-channel array provides similar SNR in the brain centre as the 32-channel array but a 1.3-fold more SNR in the brain cortex [16]. This plays an important role in optimizing grey and white matter differentiation on epilepsy imaging.

High resolution MRI including thin coronal slices, in addition to a "dynamic" analysis in a workstation with MPR allows a significative improvement in lesion detection compared to the traditional analysis with radiographic films (94% versus 80%). Patients with focal epilepsy and "normal" MRI need to be investigated further with thin slices and post-processing techniques such as volume acquisitions that allow adequate multi-planar re-slicing [17]. Semi-automated image-analysis techniques have the potential to improve lesion detection, assess lesion burden more accurately, characterise cortical abnormalities, and determine the location and extent of associated cortical and deep grey nuclei involvement. [11]

**Table 1**
Standard brain Epilepsy protocol on 3T MRI at our institution.

| Sequence | TR/TE | Plane | Time (min) | Slice thickness (mm) |
|---|---|---|---|---|
| T1 FSPGR | 6.7/1.8 | Coronal | 3.5 | 1.2 (0.6 overlap) |
| or BRAVO(optional) | 7.4/2.9 | Coronal | 4:0 | 0.8–1.0 |
| FLAIR | 8000/120 | TL Coronal | 7:0 | 3.0 |
| T2 FSE | 3760/102 | Axial | 2:2 | 5.0 |
| T2 FRFSE | 7400/102 | TL Coronal | 3:2 | 3.0 |
| FSEIR | 8000/50 | TL Coronal | 6:0 | 3.0 |
| GE | 655/20 | Coronal | 2.19 | 5.0 |

FSPGR, Fast Spoiled Gradient Echo; BRAVO, brain volume 3D isotropic FSPGR; FLAIR, fluid-attenuated inversion recovery; FSEIR, fast spin echo inversion recovery GE, gradient echo; TL, temporal lobe angulation.

### 2.3. Sequence contribution

At our institution routine scanning protocol for a patient with epilepsy includes: T1 Volumetric 3D spoiled gradient echo sequence, T2 W Axial fast spin echo (FSE), Coronal white matter inversion recovery (WMIR), Coronal T2 fluid attenuation inversion recovery (FLAIR), coronal gradient echo (GE) and high resolution T2 W FSE (Table 1) 2-plane post-contrast images and spectroscopy are required when there is a need to evaluate for suspected conditions such as neoplastic, inflammatory or infectious process. These sequences are used with three main aims: (1) to optimise grey and white matter differentiation, (2) delineate detail of small structures and volumetric assessment, and (3) enhance lesion conspicuity. The total scan time for routine epilepsy protocol is approximately 30–35 min (Table 1)

#### 2.3.1. Optimisation of grey and white matter differentiation

Optimisation in the grey and white matter differentiation assists in localisation and identification of the various types of grey matter heterotopia, delineation of malformation of cortical development [6] and mesial temporal sclerosis (MTS) [18]. MCD has been increasingly recognised as a cause for uncontrolled epilepsy, with the improvement and utilisation of high-resolution MRI techniques. MCD contributes to 25–45% of medically refractory childhood epilepsy [19]. The sequence for optimisation of grey and white matter differentiation is high resolution fast inversion recovery T2-weighted sequence, which is done in near coronal oblique with slice thickness of 3 mm, slice interval of 0.5 mm and scan time of approximately 6 min 9 s. This sequence utilises T2-based sequence with modification of inversion time that will increase the contrast between grey and white matter (Figs. 1 and 2). T2W Images are then inverted at the review console to appear like a T1W. It is also referred to as white matter inversion recovery (WMIR). There is improved sensitivity of high-resolution protocols compared to standard MRI as a result of improved signal to noise ratio and superior anatomical detail [20]. New high-resolution sequence such as 3D double inversion recovery (DIR) has been shown to be more sensitive than FLAIR and T2W in the detection of seizure laterality in temporal lobe epilepsy [21]. Overall, the largest consecutive analysis investigating 2000 patients referred for MRI after a seizure reported epilepsy related abnormalities in roughly 20% of the cases. In patients with refractory epilepsy, structural lesions can be depicted in up to 82–86% of imaging studies by visual inspection [22].

Volumetric 3D spoiled gradient echo sequence (SPGR) or Fast Spoiled Gradient Echo (FSPGR) should be performed using