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## **Malformations of cortical development: the role of 7 Tesla magnetic resonance imaging in diagnosis**

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## ***Abstract***

Comparison studies between 7T and 1.5 or 3T magnetic resonance imaging (MRI) have demonstrated the added value of ultra-high field (UHF) MRI to better identify, delineate and characterize malformations of cortical development (MCD), and to disambiguate doubtful findings observed at lower field strengths. High-resolution structural sequences such as magnetization-prepared two rapid acquisition gradient echoes (MP2RAGE), fluid and white matter suppression MP2RAGE (FLAWS), and susceptibility-weighted imaging (SWI) appear to be key to the improvement of MCD diagnosis in clinical practice.

7T MRI offers not only images of high resolution and contrast but also provides many quantitative approaches capable of acting as more efficient probes of microstructure and ameliorating the categorization of MCDs. Postprocessing of multiparametric ultra-high resolution and quantitative data may also be used to improve automated detection of MCD via machine learning.

Therefore, 7T MRI can be considered as a useful tool in the presurgical evaluation of drug-resistant partial epilepsies, particularly, but not exclusively, in cases of normal appearing conventional MRI. It also opens many perspectives in the fields of *in vivo* histology and computational anatomy.

### **Key words:**

7 Tesla MRI, Ultra-high field MRI, Malformation of cortical development, Focal cortical dysplasia, Polymicrogyria, Periventricular nodular heterotopia.

## Introduction

Magnetic resonance imaging (MRI) is tightly linked to the history and classification of malformations of cortical development (MCD). Depicting, characterizing, and accurately delineating MCDs is particularly crucial in drug-resistant partial epilepsies (DRPE) in which MCD are common causes of epileptogenic lesions, particularly in children. Currently, using optimal protocols, conventional MRI at 1.5 or 3T allows for identification and classification of most MCDs [1].

However, in those patients presenting with refractory epilepsy, from 15 to 40% are still MRI-negative even with adapted protocols, and a normal appearing MRI has been identified as a negative predictive factor for surgery in several studies [1][2][3][4]. Conversely, identification of focal cortical dysplasia, particularly type II, has been demonstrated to be a positive factor for surgical outcome [5][6]. In addition, complete resection of malformations has been consistently associated with better outcomes [7][8]. In a retrospective study, Fois et al. analyzed 612 patients admitted for presurgical assessment in a tertiary center [9]. Using a multivariate regression model, non-lesional MRI was one of the three factors (with bilateral lesions and extra-temporal epilepsy) that significantly decreased the probability of being operated on. It is actually very likely that many patients are referred to surgery or to specialized centers only when a visible lesion is present on MRI, even if effective surgery is possible in patients with a normal appearing MRI [4].

As such, although the surgical management of patients with negative MRI has been improved over in recent years [10], the yield of MRI in the definition and delimitation of MCD responsible for DRPE is still a key factor in presurgical assessment. In this context, ultra-high field (UHF) MRI – particularly at 7T – can play a major role. In this paper we will review the literature and show an illustrative case, demonstrating the added value of UHF as well as the perspectives it offers in the diagnosis of MCD.

## 1. Principal MCD responsible for DRPE and usual radiological features

### 1.1. Focal cortical dysplasia

Within the broad spectrum of MCDs, focal cortical dysplasias (FCDs) represent the vast majority of malformations responsible for DRPE considered for surgery. FCDs are localized cortical malformations encompassing a large spectrum of histopathological types [11]. Type I FCDs are characterized by localized radial (type Ia) or tangential (type Ib) cortical lamination abnormalities (type Ic referring to lesions with both lamination anomalies). Type II are characterized by disrupted cortical lamination and cytological abnormalities which differentiate type IIa (presenting with dysmorphic neurons) from type IIb (presenting with dysmorphic neurons associated with balloon cells). Type III are characterized by cortical lamination abnormalities associated with another principal lesion generally located in the same cortical region or lobe. Depending on the associated lesion, four subtypes are identified: type IIIa is associated with hippocampal sclerosis, type IIIb is associated with

tumors, type IIIc is associated with vascular malformations and type IIId is associated with another type of lesion.

MRI has contributed greatly to the definition of FCDs, particularly in type II FCDs which exhibit a typical radiological semiology including: cortical thickness alterations, signal intensity changes (mainly hypersignal on T<sub>2</sub>-weighted images and usually better depicted in fluid-attenuated inversion recovery (FLAIR) sequences), grey/white matter interface blurring (better seen on T<sub>1</sub>-weighted images), gyration and sulcation (sulcal depth and shape) anomalies [12]. Signal hyperintensity can involve both cortical and subcortical regions, the hypersignal traversing white matter from the periventricular region to the abnormal cortex (“transmantle sign”) being prototypical of FCD type IIb. Type I FCDs are more often MRI-negative and present with more subtle abnormalities compared to type II. Type III presentation depends on the associated lesion. Type IIIa is more often identified by a blurred grey-white matter interface than signal intensity or gyration abnormalities [2].

### **1.2. Polymicrogyria with or without schizencephaly**

Polymicrogyria (PMG) is a malformation characterized by excessive folding of small convolutions. These microgyri surround the cleft when associated with schizencephaly.

With a sufficiently high resolution, MRI may provide evidence of cortical overfolding (better seen on T<sub>1</sub>-weighted images). Signal in the cortex is usually not modified on T<sub>2</sub>-weighted images [1].

However, PMG often appears as a slight cortical thickening and is sometimes misdiagnosed as pachygyria. The classical location of PMG in the perisylvian region(s) can extend to other regions, and is often bilateral (either symmetrical or asymmetrical), but can be unilateral. Other forms, generally symmetrical and bilateral, involve the frontal lobes, posterior regions, parasagittal regions or are generalized. This MCD, often broader than FCD and often involving eloquent cortex, can be considered for surgery with a careful presurgical evaluation [13]. A fine delineation of the entire abnormal cortex for potential complete resection is useful [8] even if good results may be obtained with partial resection when guided by stereo-electroencephalography (SEEG) [13].

### **1.3. Periventricular nodular heterotopia**

Periventricular nodular heterotopias (PNHs) are characterized by single or multiple agglomerates of normal neurons in ectopic position lining the ventricular wall and protruding into the ventricle.

MRI can identify grey matter nodules located bilaterally in its typical form or in posterior regions.

Association with other malformations including PMGs has also been reported [1].

PNHs are difficult cases for surgery and require invasive recordings with sampling of both relevant nodules and adjacent cortex [14]. Recent conservative approaches such as radio-frequency thermo-coagulation of selected nodules during SEEG procedures have been proposed as potential efficient alternatives [15]. Therefore, depiction of nodules is a prerequisite for optimal presurgical assessment.

## 2. Key sequences of structural 7T MRI for MCD diagnosis

Given higher signal-to-noise ratio (SNR) – with a 2 to 6-fold increase in the brain – and higher contrast-to-noise ratio (CNR), UHF significantly improves image resolution and sensitivity compared to 1.5 and 3T [16]. However, UHF also suffers from drawbacks, particularly transmit field ( $B_1$ ) inhomogeneities in structural MRI. In order to both overcome the drawbacks of UHF and to take advantage of signal and contrast increases, several sequences have been developed and implemented at 7T. Of particular interest for structural imaging,  $T_1$ -weighted double-inversion recovery sequences such as Magnetization Prepared with 2 Rapidly Acquired Gradient Echos (MP2RAGE) [17] and fluid and white matter suppression MP2RAGE (FLAWS) [18] allow for high-resolution images while mitigating transmit field inhomogeneities responsible for signal loss in some regions of the brain. The MP2RAGE sequence offers  $T_1$ -weighted images, quantitative  $T_1$  mapping, and a set of images obtained with a specific inversion time for which grey and white matter have the same longitudinal magnetization magnitude but with opposite signs (Fig.1). This results in a null signal in the voxels where the same amount of grey and white matter is present. Thus, grey/white matter interfaces appear as hyposignal, clearly delineating grey/white matter transitions. The use of this kind of inversion time as also been called tissue-border-enhancement (TBE) and may be used in other types of sequences [19]. Both FCD depiction (Fig.1) as well as PMG delineation [19] can be aided/improved by this kind of protocol.

The FLAWS sequence uses two inversion times selected for the suppression of both cerebrospinal fluid (CSF) and white matter, resulting in ‘pure’ grey matter images. The use of this sequence in MCD diagnosis has yet to be published. We propose to use FLAWS in case(s) of suspected FCD, as it can identify the “transmantle sign” more accurately (Fig.1). FLAWS is also likely to detect heterotopic neurons outside the cortex.

Susceptibility-weighted imaging (SWI) is a technique using susceptibility differences between tissues to enhance contrasts between brain structures such as grey/white matter or between different subcortical or cortical structures. SWI images are  $T_2^*$ -weighted images created from both magnitude and phase in gradient echo data and are sensitive to both paramagnetic and diamagnetic compounds. These images can also be reconstructed as a minimum intensity projection (MIP) to provide high-resolution angiograms. Both SWI and angiograms have been found to be useful in FCD and PMG diagnosis [20][19].

The high-resolution of these sequences (0.6mm isotropic voxels for  $\approx 10$ min acquisition in our protocol) is also an asset for MCD diagnosis.

## 3. Demonstrated added value of structural 7T MRI in MCD diagnosis

Since the earliest experience, 7T MRI seems to provide gains for better characterizing the localized forms of MCDs such as FCD or PMG [1]. More recent studies have now demonstrated the added

value of UHF by comparing images obtained at 7T to those obtained at 1.5 and 3T MRI in several neurological diseases (n=40 and n=104 respectively) [21][22]. These studies found both better conspicuity and unambiguity on images obtained at 7T. In the first study, among the 55 epileptic patients included, 22 presented with MCD (13 FCD, 6 FCD type IIIa, 2 PNH and 1 PMG) [21]. In all of those, 7T exhibited better conspicuity and delineation based on inter-rater agreement among 10 experienced radiologists. Interestingly, 25 patients with ambiguous images at lower field had no abnormality at 7T. The second study included nine patients with epilepsy (5 MRI-negative) [22]. Using a semi-quantitative diagnostic confidence score between two experienced neuroradiologists, MCDs were found to be better defined or excluded but differences between 3T and 7T did not reach statistical significance.

The yield of 7T MRI in the diagnosis of subtle lesions in patients presenting with DRPE and negative-MRI at lower field has been specifically addressed in two other recent studies [20][23]. De Ciantis et al. studied 21 patients with normal appearing MRI at 1.5 or 3T [20]. They found structural lesions compatible with FCD in 6 (28%) on T2\*-weighted and FLAIR images at 7T. Among those six lesional patients, four had resective surgery and histopathology revealed FCD type II in three and type IIIa in one, demonstrating higher sensitivity than at lower field strength. In the 15 patients remaining apparently non-lesional at 7T, four were operated-on and histopathology showed only gliosis, suggesting UHF also has higher specificity than examinations at lower field strengths.

Veersema et al. studied a series of 38 patients presenting with DRPE and normal appearing MRI at 3T (88%), 1.5 (10%) or 1T (one patient only) [23]. They found structural lesions compatible with FCD in eight patients at 7T. Among those eight lesional patients, six had resective surgery, with histopathology revealing FCD type II in five and proliferative oligodendroglial hyperplasia with mild MCD in one. In the 30 patients remaining non-lesional at 7T, six were operated on and histopathology showed gliosis in three and FCD type II in three. Two other patients had suspicion of dual pathology at 3T. 7-Tesla showed an additional lesion in one patient with confirmed FCD type II and no hippocampal sclerosis, but no additional lesion in the second patient despite the presence of FCD type IIIa in the pathological specimen.

7-Tesla MRI has demonstrated the ability to depict finer anatomic detail compared to 3T in 10 patients presenting with PMG [19]. Interestingly, the additional details revealed at 7T could have implications for diagnosis and surgical management. Among the six patients diagnosed as bilateral at 7T, four were considered as unilateral at 3T. Susceptibility-weighted angiography also depicted dilated superficial veins suggesting a potential role of vascular dysgenesis.

Several case series have also illustrated the added value of UHF in the diagnosis of other types of localized epileptogenic lesions such as ganglioglioma, dysembryoplastic neuroepithelial tumor (DNET), cavernomas or subtle lesions associated with tuberous sclerosis complex [24][25][26].

#### 4. Perspectives for quantitative and functional 7T MRI in MCD

#### **4.1. Quantitative MRI – towards *in vivo* histology**

Quantitative MRI provides measures of biophysical properties acting on signal intensity. With high SNR and CNR, 7T enables wider application of qMRI and broader use of quantitative images to probe the microstructure of MCDs. This could help in the identification of subtypes depending on histopathology [27].

Zucca et al. explored 13 surgical specimens with FCD type II at 7T [28]. They quantified  $T_2$  signal intensities in regions of interest (ROI) within the lesion and in the perilesional grey and white matter. Different patterns could help to differentiate type IIa and IIb even in MRI-negative patients. In FCD type IIb,  $T_2$  hyperintensity of the white matter was related to dysmyelination, severe fiber loss and abnormal cells. The mild alteration in MRI was in line with less severe histopathological findings in Type IIa.

Reeves et al. combined 9.4T MRI and immunohistochemistry in 13 surgical resections with confirmed FCD (in five cases) and in normal cortex [29].  $T_1$ ,  $T_2$ ,  $T_2^*$  and magnetization transfer ratio (MTR) signal intensities were quantified in 43 ROI and compared to quantitative immunohistochemistry for myelination, neuronal populations, glia and blood-brain-barrier. Significant correlations were found between quantitative signal measures and myelin and neuronal contents in all ROI, additionally demonstrating the ability of UFH MRI to quantify pathological changes in FCD with altered cortical lamination and myelination. As in Zucca et al., significant MRI alterations were observed even in normal appearing cortex on *in vivo* preoperative MRI at lower field. This semi-quantitative approach compared to histological findings in FCD opened a perspective towards a better phenotyping of MCD using qMRI *in vivo*.

By quantifying the sources of magnetic field distortions that generate different phase shifts in SWI, the quantitative susceptibility mapping (QSM) technique can theoretically differentiate paramagnetic (iron) from diamagnetic (calcified) substances and interrogate microstructure and molecular content [30]. Although QSM at 7T has been demonstrated to be useful for lesion characterization in several brain diseases, the method has not yet been applied in the diagnosis of MCD [31][32].

Diffusion MRI (dMRI) can probe microstructural changes by quantifying the self-diffusion of water molecules constrained by cell membranes in intra and extracellular spaces. Using specific sequence schemes and models, dMRI provides several parameters capable of quantifying histological changes. So far, even though diffusion parameter changes have been observed in MCD, dMRI has not been demonstrated to be specific of malformations [27]. At 7T, dMRI suffers from many technical challenges. However, it is also very promising since it can be performed at high-spatial and high-angular resolution not only for microstructure analyses but also for reconstruction of whole-brain high-resolution structural connectivity using tractography [33].

#### **4.2. Ultra-high resolution and quantitative data for computational neuroanatomy**



MR image postprocessing is a very active and fruitful domain in constant evolution that is entering a new era thanks to artificial intelligence (AI) methods [34]. At 7T, higher contrast and resolution will also improve this field of computational anatomy by increasing the range of image features that can be used as inputs. Automated methods for detecting FCD, using machine learning and deep learning mainly applied to  $T_1$ -weighted or/and FLAIR volumetric sequences, have been proposed and proven to be effective in MRI-negative patients with histologically confirmed FCD [35]. Many features have been analyzed, including cortical thickness, gray-white matter intensity contrast (gradient), curvature, sulcal depth, local cortical deformation, and found to be efficient in detecting FCD [27]. Thus, high-resolution morphological images offered by 7T MRI are of particular interest for these approaches, most especially using multiparametric approaches as have been successfully applied at lower field [27].

### **4.3. Functional MRI**

At 7T, task-related functional MRI (fMRI) used for presurgical mapping has higher specificity, sensitivity, and reliability of localization in addition to decreased scan time compared to 3T [16]. However, fMRI at 7T also suffers more from artifacts, particularly movements and static magnetic field inhomogeneities, as is the case for dMRI. Nevertheless, many solutions are now available to overcome these pitfalls.

High-resolution resting-state fMRI may also be used for whole-brain high-resolution functional connectivity in order to better understand the interrelation between MCD and the rest of the brain [36].

## **5. Limitations of 7T MRI**

The dramatic increased SNR and gain in resolution is accompanied by several limitations. The first is the increase number of contraindications principally due to implants or implanted medical devices not tested yet at UHF. The second is the highest sensitivity to patients' movements as a side effect of increased resolution. The advantages of increased magnetic field strength come also with drawbacks such as principal magnetic field ( $B_0$ ) and  $B_1$  field inhomogeneities leading to potential artifacts and signal inhomogeneities that need to be corrected or mitigated. In addition, considering the higher energy of the radio-frequency (RF) at UHF the regulatory limitation of energy absorption imposed in MRI – that is the same for every field strength – obliges to use specific and often complex RF pulse design and a difficult adaptation of several sequences usually used at lower field strengths. Nevertheless, improvement of acquisition schemes and optimization of RF pulses allow today clinically compatible protocols able to explore FCDs efficiently.

## **Conclusion**

7T MRI is of major interest in patients presenting with DRPE and normal appearing MRI at lower field. UHF MRI is also very useful for better delineating lesions in patients with visible MCDs in the perspective of surgery. It is also likely that in the near future, 7T MRI will provide valuable quantitative multiparametric measures capable of probing histopathological features, as well as high-resolution images for application with AI approaches for automated detection of MCDs. Thus, despite the technical challenges and the higher number of contraindications, 7T MRI is clearly emerging as a key tool in the presurgical evaluation of difficult cases. The FDA and CE approval of 7T systems for clinical use will likely further open up access to UHF MRI, a prerequisite for large cohort studies and formal validation.

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### Declarations of interest

The author declare that they no conflict of interest concerning this article.

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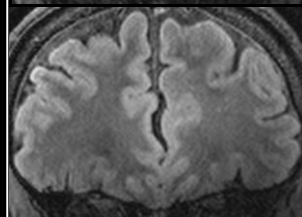
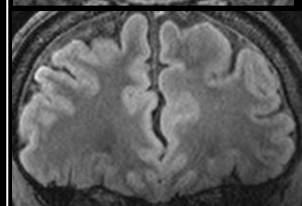
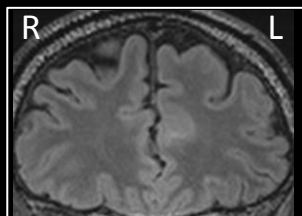
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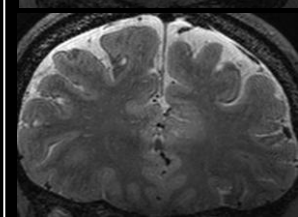
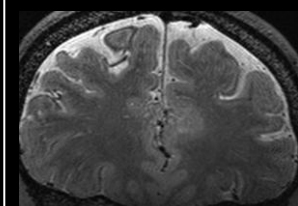
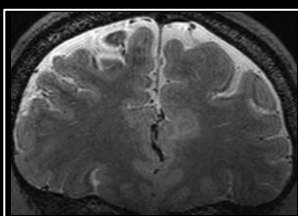
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## Figure legend

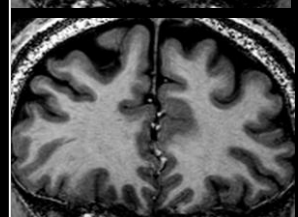
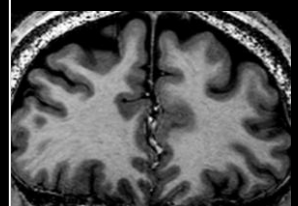
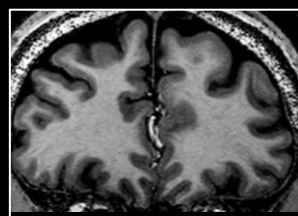
Fig. 1. Structural 7T MRI in a patient presenting with a focal cortical dysplasia (FCD) type IIb confirmed by histopathology, not diagnosed on 3T MRI. The malformation located in the anterior part of the left cingulate gyrus is visible on the three contiguous images of all the 3D high-resolution sequences (i.e. FLAIR, T<sub>2</sub> SPACE, MP2RAGE and FLAWS). Note the clear modification of the grey/white matter interface particularly well depicted using a specific inversion time providing “tissue border enhancement” (white arrow). Note also the “transmantle sign”, typical of FCD type II, identified by the FLAWS sequence only (dashed white arrow).



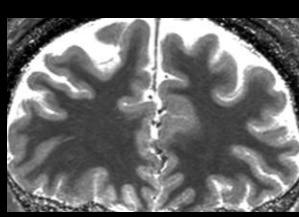
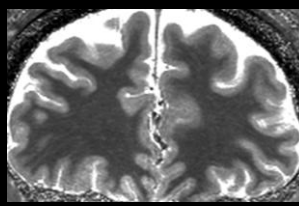
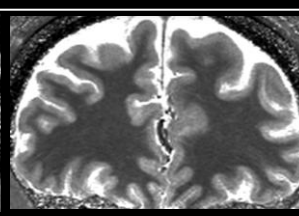
**FLAIR** (0.8mm)<sup>3</sup>



**T<sub>2</sub> SPACE** (0.6mm)<sup>3</sup>

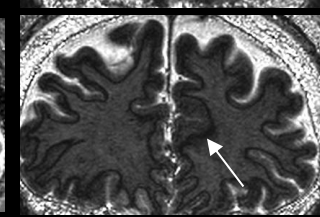
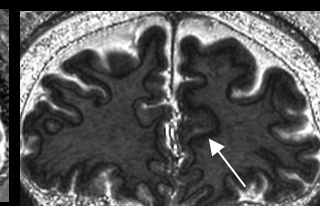
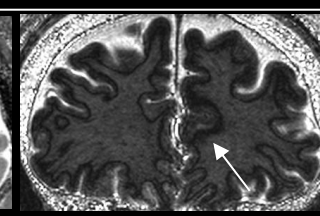


**T<sub>1</sub>-weighted**

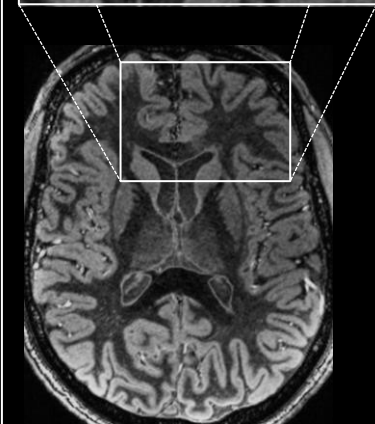
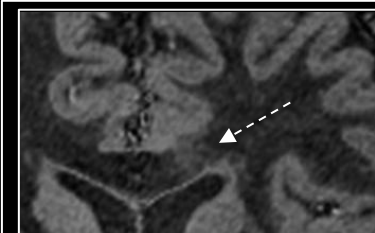


**T<sub>1</sub> mapping**

**MP2RAGE** (0.6mm)<sup>3</sup>



**Tissue border  
enhancement**



**FLAWS** (0.6mm)<sup>3</sup>