Chapter 6
Epilepsy Imaging

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Introduction

Epilepsy is one of the most frequent chronic neurological disorders and is characterized by the recurrence of spontaneous seizures. Epilepsy imaging is considered in different situations:

- In patients without known epilepsy presenting with a first episode of acute seizure. In this case, the role of imaging is to detect and characterize a causal lesion and refer the patient for a specific treatment.
- In approximatively one third of patients with chronic focal epilepsy becoming drug-resistant and referred for presurgical evaluation. In this case, and especially if previous MRIs were negative, an optimized MR protocol and advanced imaging techniques are required in order to help in delineating the epileptogenic zone, one of the main conditions for an efficient surgery.
- In candidates for epilepsy surgery, neuroimaging is required before surgery to predict the functional outcome, including mapping of eloquent areas with fMRI; and, postoperatively, to evaluate the extent of the resection.

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- In the research field, imaging helps in finding diagnostic and prognostic biomarkers in order to refine individually tailored treatment of epilepsy [1].

For all the above indications, MRI outperforms CT scanner, which may be limited to emergencies and will not be considered in this chapter. However, MRI is not needed in several typical syndromic epilepsies (such as absence epilepsy, juvenile myoclonic epilepsy, benign partial epilepsy of childhood with centrotemporal spikes, idiopathic generalized epilepsy) [2].

Despite advances in antiepileptic drugs treatment in the past 20 years, seizure freedom is not always reached and side effects can be difficult to tolerate. Intractability of epilepsy is defined as persistence of seizures in spite of two tolerated, appropriately chosen and used antiepileptic drugs, whether as monotherapies or in combination [3]. Uncontrolled epilepsy alters quality of life and cognitive function and increases the risks of sudden death. For these reasons, patients should be referred as early as possible for presurgical investigations. The role of neuroimaging is crucial in identifying the causal lesion, as its characterization may play a major role for referring the patients to surgery. In addition, identifying a lesional epilepsy is associated with a better prognosis after surgery [4, 5].

This chapter will review the role of neuroimaging and especially MRI in epilepsy, with a special focus on focal intractable epilepsies.

Which Protocol in MRI?

Choice of the Sequences

Epileptogenic lesions, especially malformations of the cortical development, may be small and subtle, hidden in the normal cortex. Therefore, a "standard" MR protocol early is ineffective for epilepsy [6]. By contrast, it is now clearly established that the seek for a causal lesion with brain MRI is improved when carried out by a neuroradiologist experienced in epilepsy imaging and when guided by clinical and electroclinical data [2, 7]. Moreover, an optimized protocol combining volumetric acquisition is required, with high spatial resolution allowing multiplanar reformat and gyral structures delineation and sequences with high contrast resolution in order to identify subtle cortical lesions [8]. This "minimal" optimized protocol is detailed in Table 6.1. Advanced sequences developed in the recent years can be added. Their selection is however subject to imaging duration and patient tolerance and should be chosen depending on the clinical data and the type of lesion expected. For example, when a focal cortical dysplasia (FCD) is suspected, 3D FLAIR [9] and/or 3D T2 double inversion recovery [10, 11] weighted sequences help in enhancing cortical contrast/noise ratio. For mesial temporal lobe epilepsy (TLE), other sequences are also important: thin coronal MRI slices, perpendicular to the long axis of the

Table 6.1 Imaging protocol for patients referred for epilepsy: basic sequences and additional/optional sequences

	Characteristic	Advantages
Volumetric FLAIR	Slice thickness <1.5 mm	Multiplanar reformat Excellent contrast resolution of subcortical anomalies Detect abnormal cells, inflammation, edema, gliosis (especially in hippocampal sclerosis), scar
Coronal spin echo T2	Slice thickness <3 mm If temporal lobe epilepsy: Oriented in the axis perpendicular to hippocampus In intercommissural axis otherwise	Excellent delineation resolution of the cortex and especially of hippocampus (digitations loss, dedifferentiation)
Axial T2 gradient echo (or susceptibility weighted imaging)		Hemosiderin/calcification sensitive sequences (trauma/scar, vascular malformations/cavernomas, tumor with calcifications)
Volumetric T1-weighted sequence	Slice thickness <1 mm isotropic (inversion recovery may optimize the gray-white matter contrast) and isotropic voxels <1 mm. Multiplanar reformats	Excellent spatial resolution Multiplanar/curvilinear/volumetric reformat May detect subtle sulco-gyral and cortical abnormalities Especially useful for malformation of cortical development
Additional/optional sequences		
Volumetric T2 with double inversion recovery	Suppression of the signal from both white matter and CSF Slice thickness <2 mm	May provide better contrast for cortical lesion detection such as focal cortical dysplasia
Arterial spin labeling	Post labeling delay depending on the age of the patient (1–1.5 s in children/>1.5 s in adults)	Quantitative maps of cortical perfusion Postictal hyperperfusion Interictal hypoperfusion of several cortical lesions
Volumetric T1-weighted sequence With contrast media injection		Rarely necessary, not systematic Helps characterization of epilepsy related tumors and vascular malformations
Functional MRI and diffusion tensor imaging	Paradigms depend on the location of the lesion	Surgery planning and prediction of the risk of corticectomy
T2 relaxometry		Quantitative MRI technique Detection of hippocampal sclerosis

hippocampus, T2-weighted, FLAIR, and T1-weighted with inversion recovery. Injection of a contrast media (Gadolinium) is in most cases not required except when tumor or vascular malformations are suspected, based on a high clinical hypothesis or on other sequences.

Choice of Magnetic Field and Head Coil

Higher field magnet is associated with higher signal-to-noise ratio and spatial resolution and could therefore benefit to brain MRIs in epilepsy, especially when a subtle cortical lesion is suspected. However, distortion and artifacts are more prominent. Studies comparing 3 T with 1.5 T MRI in patients with epilepsy suggested that even if the rate of lesion detected at 3 T is not significantly higher than at 1.5 T, increasing field is clearly associated with an improvement of lesion characterization an delineation [12–15]. Similarly, a few authors analyzed the benefit of 7 T magnets in epilepsy imaging, including a better delineation of anatomical details such as hippocampal subfields [16]. However, the clinical relevance of these findings is not established yet.

Increasing the number of channels in phased array coil increases the quality of images [17] but also increases the risk of inhomogeneity, with a low SNR in central deep cerebral region, distant to the peripheral head coils.

Overview of the Principle Causes of Refractory Epilepsy

Hippocampal Sclerosis (HS)

Hippocampal sclerosis (HS) is the most frequent lesion found in intractable temporal lobe epilepsy in adults. The MRI signature of HS relies on a simple pattern, combining volume loss of hippocampal formation better visualized on coronal T2w images and 3D T1 increased signal intensity on FLAIR sequences and loss of the internal hippocampal architecture better found on coronal T2 (Fig. 6.1). These features refer to the pathology, displaying, respectively, neuronal loss and gliosis, mainly located in the hilus of the dentate gyrus and in the CA1 and CA3 pyramidal cell layers.

In doubtful or unclear lesions, a loss of hippocampal head digitation, best identified in thin T2w slices perpendicular to the axis of the hippocampus

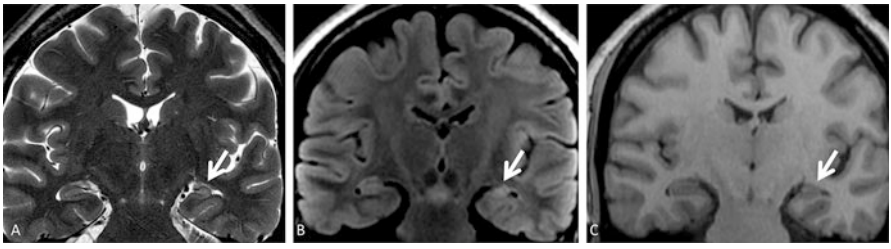

Fig. 6.1 Patient with left temporal lobe epilepsy. Coronal view perpendicular to the hippocampus long axis in T2 (**a**), FLAIR (**b**), and T1 (**c**) shows a left hippocampal atrophy, loss of the global architecture, and increased FLAIR signal in comparison to the right side, typical of HS

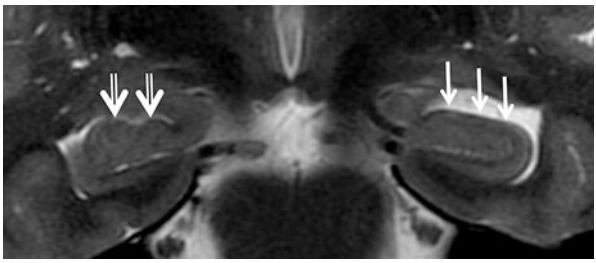

Fig. 6.2 Loss of the digitations of the left hippocampal head (arrows) on a T2w coronal view perpendicular to the hippocampal long axis in a case of left HS, in comparison to normal hippocampal digitations on the right side (double arrows)

(Fig. 6.2), can also support the diagnosis [18]. Associated with these anomalies limited to the hippocampus, modification of the architecture and MR signal can spread to other temporal and limbic region. Thus, FLAIR hyperintensity can also affect the ipsilateral lobe associated with a blurring of the temporal cortex. The atrophy can also affect the ipsilateral fornix, mammillary body, amygdala, cingulate gyrus, pulvinar, and contralateral cerebellum. The comparison between both hippocampi is an important tool to detect asymmetries, although one must keep in mind that about 10–20% of patients may have visually bilateral HS (Fig. 6.3).

When an extra-hippocampal cause of epileptogenic lesion is found, careful screening of the hippocampi is important. Indeed, a "dual pathology" [19, 20] can be found in up to 15% in association of HS and another temporal or extratemporal epileptogenic lesion (such as cortical dysplasia, developmental tumors, perinatal injury, etc.). Explanations for the coexistence of both lesions are controversial but may include the secondary development of HS from the symptomatic and prolonged seizures originating from another neocortical lesion.

Advanced Imaging and Temporal Lobe Epilepsy

When conventional MRI is considered normal, but clinical and electroclinical evaluations suggest a temporal lobe epilepsy, advanced MR techniques of imaging can be useful for lateralization, localization, and characterization of the epileptogenic zone.

Among the proposed advanced MR tools, quantitative analysis offers an objective and automated evaluation of the atrophy (volumetry) and of the altered signal (relaxometry) within the hippocampus formation and temporal lobe. These two techniques were recently enriched by the new robust techniques of automated segmentation of temporo-mesial structures. Thus, volumetry and morphometry, based on statistical parametric mapping to compare voxels against corresponding voxels derived from a normative database, help to detect volume loss and shape changes in patients with MR negative TLE [21]. T2 relaxometry provides a

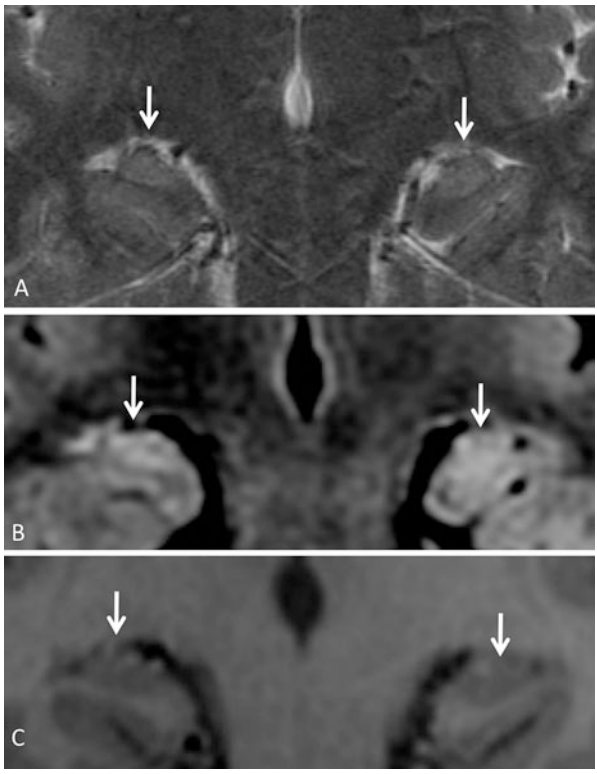

Fig. 6.3 Coronal view perpendicular to the hippocampus long axis in T2 (**a**), FLAIR (**b**), and T1 (**c**) shows a bilateral hippocampal atrophy and increased FLAIR signal. Even if pronounced, this HS case might be difficult to diagnose because of the absence of asymmetry

quantitative assessment of T2 relaxation time using a multi-echo sequence which can be performed on single subjects with TLE and may be a clinically useful tool for the detection of the seizure focus [22]. It provides quantitative data within extra-hippocampal adjacent structures in the temporal lobe and amygdala that are difficult to assess in conventional visualization only.

Arterial spin labeling (ASL) is now routinely used in MR protocols. This sequence uses magnetically labeled arterial blood water molecules as an endogenous contrast agent and provides, noninvasively and without any contrast media injection, a cartography of cerebral blood flow, related to cortical perfusion. In epilepsy protocols, ASL is now moving toward a "conventional" and is no longer an "advanced" MR sequence. Thus, it can also help localizing and defining the epileptic zone by showing, without any contrast media, an interictal mesial temporal hypoperfusion, with a good correlation, when present, to the hypometabolism found on interictal PET [23–25]. If the ASL sequence is acquired during or just after seizure (rarely observed in clinical practice), the injured hippocampus will be highly hyper-perfused (Fig. 6.4).

Proton MR spectroscopy, another quantitative analysis of cerebral structures, can be used to measure NAA/Cr in temporal lobes, with a poor diagnosis value related to a non-specific reduced NAA secondary to neural loss. However, a low prognosis

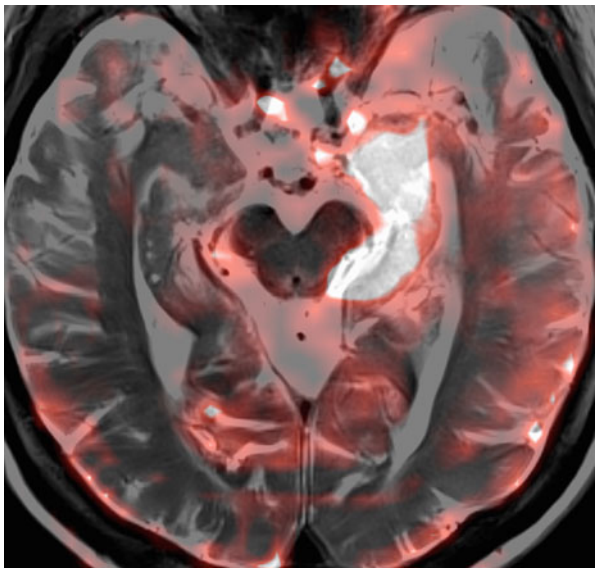

Fig. 6.4 Axial T2-weighted image in the hippocampal axis co-registered with ASL cerebral blood flow map (red-white scale) in a patient with left HS, 15 min after a temporal seizure, shows an increase of the blood flow within the injured hippocampus

value can be related to the widespread of abnormal spectrum in extra-hippocampal region and in contralateral temporal lobe [26].

Focal Cortical Dysplasia

Focal cortical dysplasia (FCD) is one of the main causes of extratemporal, drug-resistant partial epilepsy that is surgically curable in adults and the first cause in children. It designates a spectrum of histological abnormalities in the structure of the laminar cortex associated with the presence of abnormal cells, such as dysmorphic neurons and/or balloon cells. The latest classification subdivides FCD in three categories: Type I (abnormal lamination without abnormal cells), Type II (major cortical disorganization, presence of dysmorphic neurons with or without balloon cells), and Type III (Type I associated with another epileptic lesion) [27]. The major predictor of a favorable surgical outcome is complete removal of the dysplastic cortex, especially for FCD Type II. Therefore, accurate MR assessment of the lesion location and extent is critical for the outcome.

Typical MR features (Fig. 6.5) include abnormalities of the cortex and of the underlying white matter, for which isotropic volumetric with a high contrast resolution is essential.

- Cortical thickening and blurring of the gray-white matter interface, best seen on T1 wi, correspond to the presence of dysmorphic neurons and balloon cells in the cortex and the subcortical junction, ectopic neurons, or axonal loss in underlying white matter. This sign can be very subtle and needs to be observed in at least two

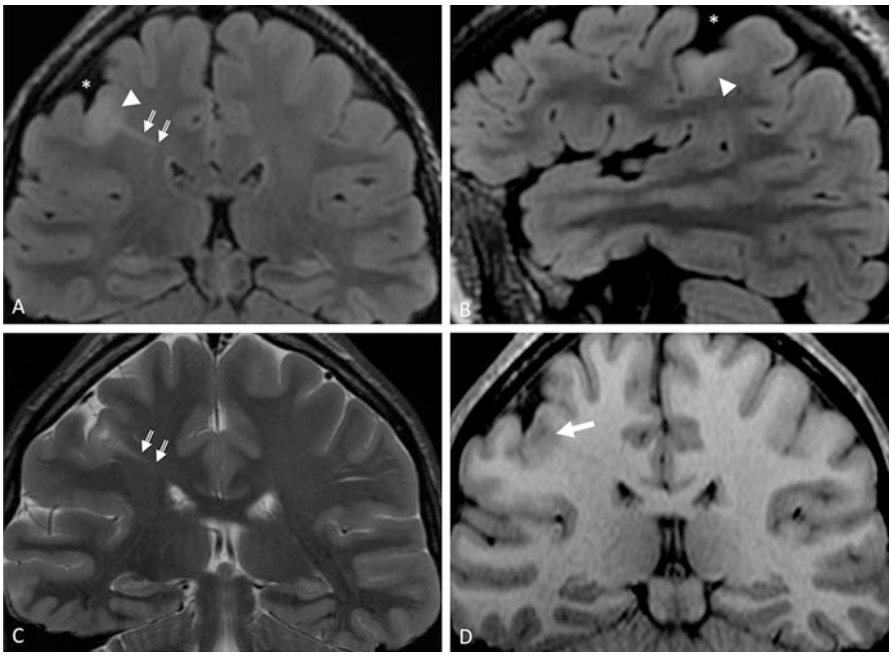

Fig. 6.5 Coronal and axial reformats of a 3D FLAIR (**a**, **b**), coronal T2 (**c**), and T1 (**d**) in a patient with right frontal lobe epilepsy show the typical pattern of a FCD: Cortical thickening and blurring (arrow), cortical and subcortical hypersignal (arrow head) tapering to the ventricle wall ("transmantle sign" – double arrow), and sulcal abnormality with enlarged sulcus (asterisk)

adjacent sections and in at least two different axes (Fig. 6.6) in order to avoid being confounded with pseudo-thickening [28].

- T2/FLAIR signal increase of cortical and more frequently of subcortical underlying white matter [29] and related to a high density of balloon cells in the cortex [30]. Sequences with an increased gray-white matter contrast, such as T2 double inversion recovery (DIR) imaging, that suppresses signal from both CSF and white matter, can be of interest for the detection of these cortical abnormalities [11].
- Transmantle sign, best visible in FLAIR, is a linear extent of the subcortical signal increase to the ventricle surface, reproducing the path of migrating neuroblasts. This typical feature, a MR "signature" of FCD, is associated with a good postoperative prognostic [31]. Being better visible at 3 T [12], this sign does not systematically taper an orthogonal plane and highly benefits from 3D FLAIR multiplanar reformats (Fig. 6.7) [9].
- Sulco-gyral abnormalities might be the more subtle, difficult to assess and thus are underestimated in FCD. Yet, these subtle features might be the only detectable abnormality, all other signs being absent, in the so-called negative MRI FCD [29, 32] and have thus to be carefully searched. They are defined as unusual depth, angulation, or shape of a sulcus (Fig. 6.7). In central region, which is

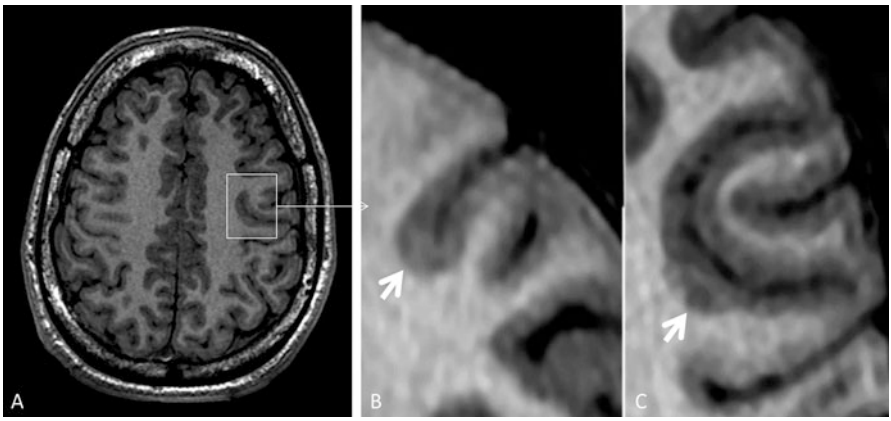

Fig. 6.6 Left precentral FCD with subtle cortical thickening and blurring if the gray-white matter interface in axial T1 (**a**). Reformat in two other axis (**b**, **c**) confirms that it does not correspond to a partial volume effect ("pseudo-thickening"). Of note, the unusual depth of the sulcus also helps to define the location of the FCD

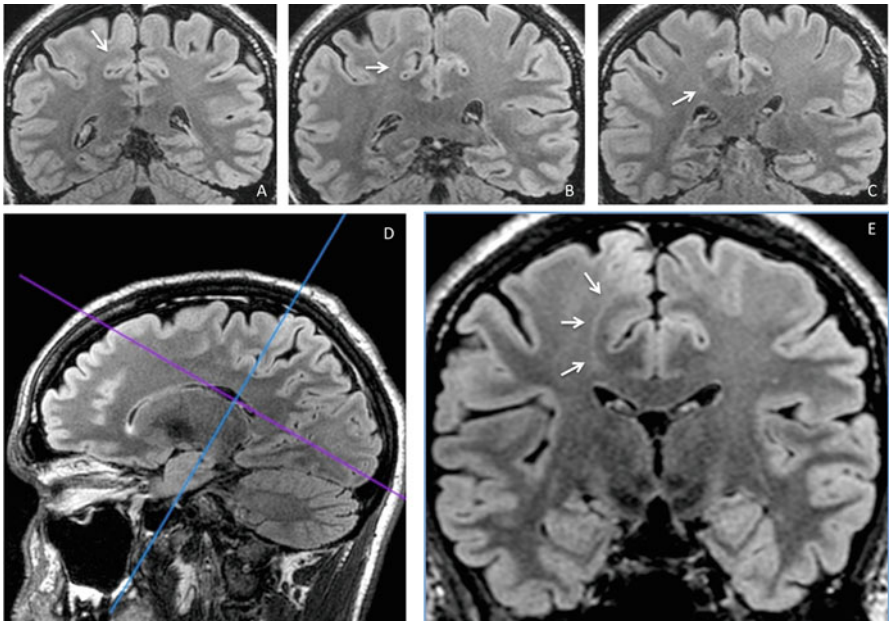

Fig. 6.7 Orthogonal coronal view (**a**–**c**) of a 3D FLAIR in a patient with a FCD Type II of the paracentral lobule: the transmantle sign is hardly visible, limited to a thin linear hyper signal. When reformatted in the axis of the dysplastic sulcus (**d**, **e**), the transmantle sign is much more obvious, tapering from the cortex to the ventricle wall

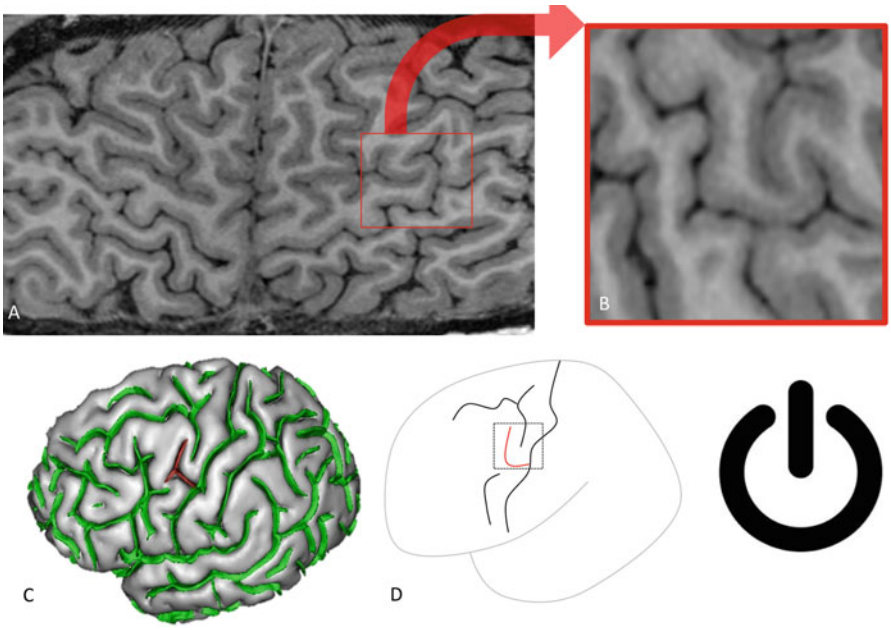

Fig. 6.8 Curvilinear reformat of the left and right central sulci (**a**) with magnification and rotation of the left central sulcus (**b**) corresponding to the "power button sign." 3D view of the left hemisphere surface (**c**) and schematic representation (**d**) of this pattern typical of the presence of a FCD in the homolateral central region

known to display a low interindividual variability, FCD might be associated in up to 62% of the case with a specific particular sulcal pattern reproducing the "power button" symbol (Fig. 6.8), even when all other previously described signs are absent [33].

Recent studies reveal that 20–40% of patients with proven FCD have negative MRI [29, 30, 34, 35], while other studies report that up to 60% of patients referred for epilepsy and negative MRI may present FCD [36, 37].

A negative MRI is known to be associated with a late referral to surgery and a reduced prognosis [5], suggesting that conventional MRI is not sufficient for evaluation of patients with a clinically suspected FCD. Thereby, multimodal advanced techniques present a special interest in this epileptogenic lesion.

A promising advanced processing is the morphometric analysis. Diffusion tensor imaging in the subcortical white matter helps in visualizing white matter alterations that are associated with FCD [38]. A reduction in the fractional anisotropy near the seizure focus as compared with the contralateral side can thus increase sensitivity for the detection of FCD. This feature is, however, not specific of any epileptogenic lesion.

Arterial spin labeling provides a cartography of the cerebral blood flow that is physiologically comparable to cortical metabolism obtained with PET, even if less sensitive. This technique can be easily added to the routine MRI evaluation, and, in

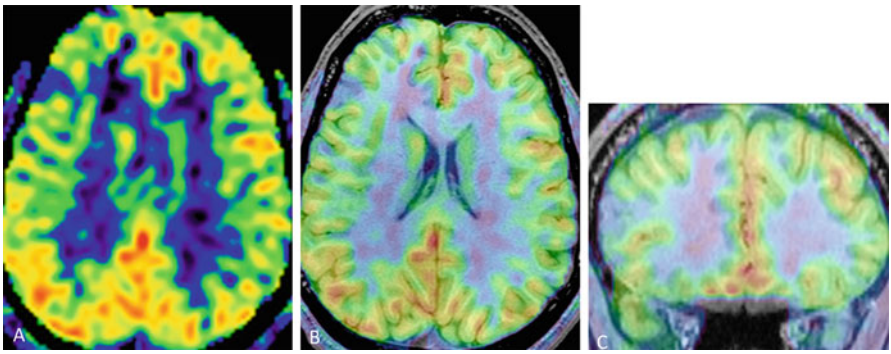

Fig. 6.9 Patient with a right frontal DCF. Interictal ASL with cerebral blood flow cartography in axial view (**a**). This CBF map is registered to T1 in axial (**b**) and coronal view (**c**) in order to better identify a cortical hypoperfusion in the right frontal lobe, matching with an underlying FCD

order to provide efficient data on cortical perfusion, this cartography needs to be overlapped with the anatomical 3D T1 or 3D FLAIR, acquired during the same MR session. As in HS, if the ASL sequence is acquired during or just after seizure, the epileptogenic focus will be highly hyper-perfused [39]. This latter condition is however rarely observed in clinical practice. Thus, the relevance of ASL relies during the interictal phase with the observation of a focal zone of cortex on structural MRI that is hypoperfused compared to the adjacent cortex (Fig. 6.9). This hypoperfusion, co-localized with FCD, can also give an additional clue on the location of subtle lesion [24]. However, as for DTI, this hypoperfusion can also be observed in other epileptogenic lesions [40].

Voxel-based morphometry (VBM) can also decrease the amount of negative MRI in FCD [41]. Morphometric analysis procedure methods produce a junction map to detect gray-white matter abnormal features and sulcal increased depth and direct the attention to suspicious regions of interest. Associated with conventional reading, these techniques may improve detection of subtle lesions [42]. However, these techniques have not entered to routine, yet. As for temporal lobe epilepsy, T2 relaxometry maps can also increase sensitivity for detection of FCD [43].

Gyral and sulcal abnormal patterns can also benefit from surface-based morphometry techniques that allow features such as cortical thickness to be measured [32] but also abnormal sulcal patterns to be recognized [44].

Epileptogenic Tumors

All different histological types of tumor can provide seizures as they involve the cortex. However, two developmental neoplasms that are part of the wide range of malformations of the cortical development, gangliogliomas and dysembryoplastic neuroepithelial tumors, are highly associated with intractable seizures in children

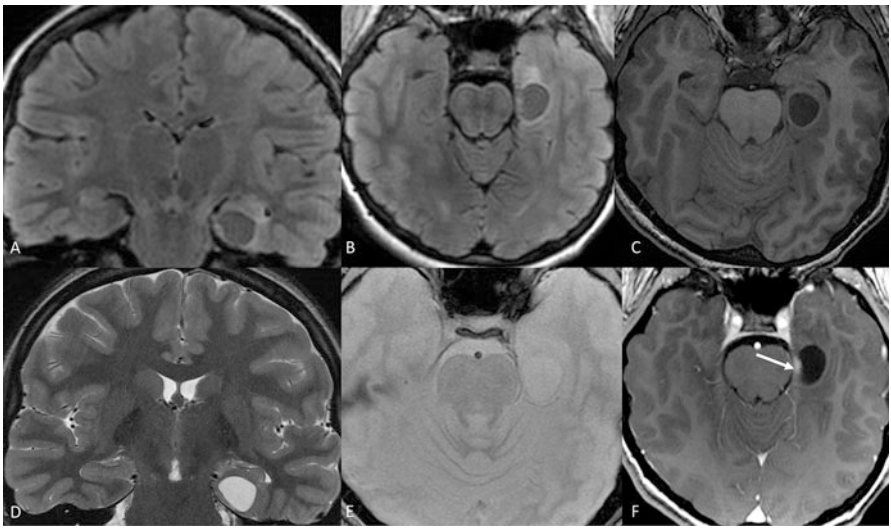

Fig 6.10 A 22-year-old male patient with intractable left temporal epilepsy. Coronal and axial FLAIR (**a**, **b**), axial T1 (**c**), coronal T2 (**d**), T2* (**e**), and axial T1 with contrast media (**f**) show a mixed cystic and solid cortical mass. The nodular portion presents with mild enhancement (arrow)

and young adults. These low-grade tumors are composed of neural and glial elements. They are usually slow growing, and their main clinical feature is epilepsy.

Surgery is the treatment of choice for glioneuronal tumors in most of the cases, providing good results even in eloquent areas [45]. Complete tumor resection is crucial for long-term favorable outcome.

Gangliogliomas

Gangliogliomas are glioneuronal tumors defined by the presence of large binuclear neurons within a glial component comprising inflammatory infiltrates. The association with other dysplastic cortical abnormalities is frequent.

Gangliogliomas are mainly supratentorial with a clear temporal predominance, although they can be found in all the lobes, always located within the cortex. The classical aspect (Fig. 6.10) consists in a mixed cystic and solid cortical mass, either mainly nodular with a poorly defined limit or mainly cystic with a mural nodule. The nodular portion presents with a moderate hyper T2 and FLAIR and is generally slightly and nonhomogeneously enhanced. The cystic portion, on the other hand, is homogeneous in highly hypo T1 and hyper T2 without enhancement [46]. Small calcifications can be found in up to 40% of the cases. Of note, surrounding edema and mass effect are rare due to the developmental origin of these tumors. Hemorrhagic forms are extremely rare. Malignant transformation may rarely occur and lead to anaplastic ganglioglioma. For this reason, a prolonged and systematic MR follow-up is required, especially in cases of surgical abstention or incomplete resection.

In diffusion, the ADC within gangliogliomas is high, reflecting a low tumor cellularity, contrary to purely glial tumors such as astrocytoma [47]. In spectroscopy, low NAA and variable choline are nondiscriminating [46]. In gradient echo perfusion, a small increase in relative cerebral blood volume can be observed without impairment of the permeability [48].

Dysembryoplastic Neuroepithelial Tumors

Dysembryoplastic neuroepithelial tumors (DNETs) are benign tumors, also classified in glioneuronal tumors, predominantly located in the temporal lobe and mostly revealed by partial seizures in children and young adults. DNETs are characterized by a specific glioneuronal component which is isolated (simple forms) or associated with multinodular glial proliferation as well as cortical disorganization (complex forms). A third subtype (non-specific) is composed by various types of glial proliferation: oligodendroglial, astrocytic, or mixed. As previously mentioned, DNET can be associated with other epileptogenic lesions such as hippocampal sclerosis ("dual pathology") or FCDs (Type III).

A recent study proposed an MRI-based scheme with three main features, associated with the optimal surgical resection strategy and well correlated with each histological subtype [49]:

- DNET type 1 ("cystic or polycystic-like") consists of a well-delineated mass with a liquid signal similar to that of the CSF, giving it a cystic (Fig. 6.11) or polycystic "bubbly" appearance (Fig. 6.12) within the cortex [50]. This subtype is very characteristic and easy to diagnose in most cases. When close to the skull inner table, a smooth bone remodeling can be observed.
- DNET type 2 ("nodular-like") is characterized by a heterogeneous and variable signal within a partially delineated nodular or multinodular appearance in the cortex. Calcifications are present in 60% of the cases (Fig. 6.13).
- DNET type 3 ("dysplastic-like") presents with a poorly delineated homogeneous infiltration with a very slight hypersignal on T2 FLAIR, sometimes limited to a poor gray-white matter demarcation (Fig. 6.14), and is thus more difficult to distinguish from other glial neoplasms. One of its characteristic patterns is the very strong predominance in mesial areas, especially in amygdalo-hippocampal complex.

Contrast enhancement is rare (10–20%), often partial and nodular, and equally found in each MRI subtype.

Type 1 are always associated with simple and complex subtypes; the cystic appearance is correlated to the high-water content of the specific glioneuronal component. However, types 2 and 3 correspond to non-specific forms. This classification may help to determine the extent of the resection as a strong relationship between the MRI feature, the pathological structure, and the extent of the epileptogenic zone has been demonstrated [51].

Tumor recurrence and malignant transformation are uncommon.

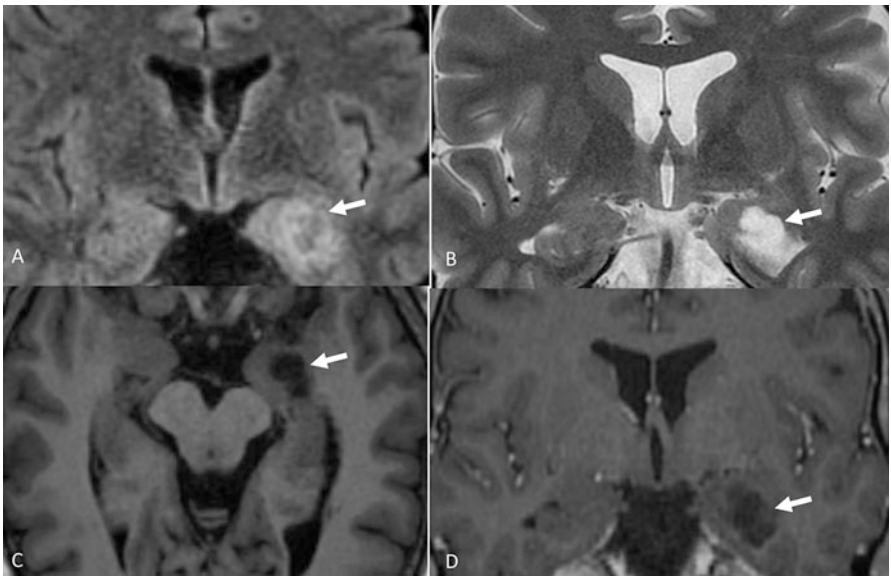

Fig. 6.11 Coronal view in FLAIR (**a**) and in T2 (**b**), axial T1 (**c**), and coronal T1 with contrast media (**d**) in a patient with left temporal drug-resistant epilepsy. Pseudocystic lesion of the left amygdalo-hippocampal complex without any mass effect. The signal in all sequence is similar to the CSF. Note the thin rim in hyper FLAIR. No enhancement is observed after gadolinium. This aspect is typical of DNET type 1

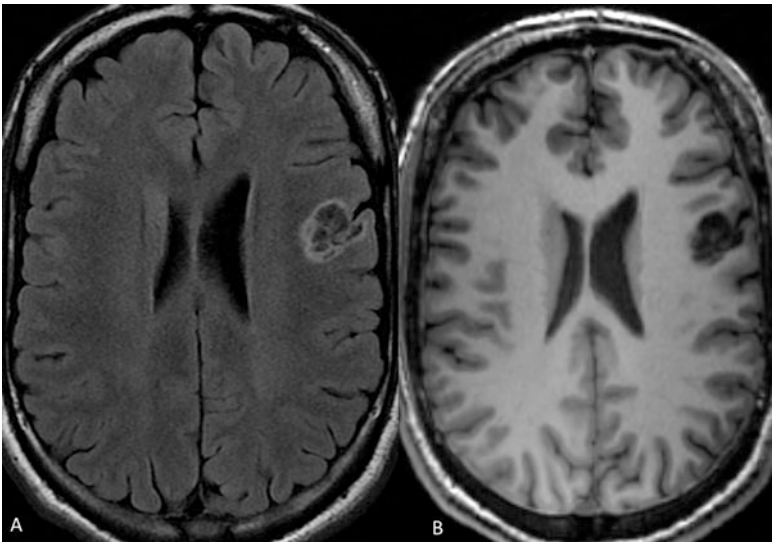

Fig. 6.12 Pseudo-polycystic "bubbly" appearance of a left frontal type 1 DNET in axial FLAIR (**a**) and T1 (**b**)

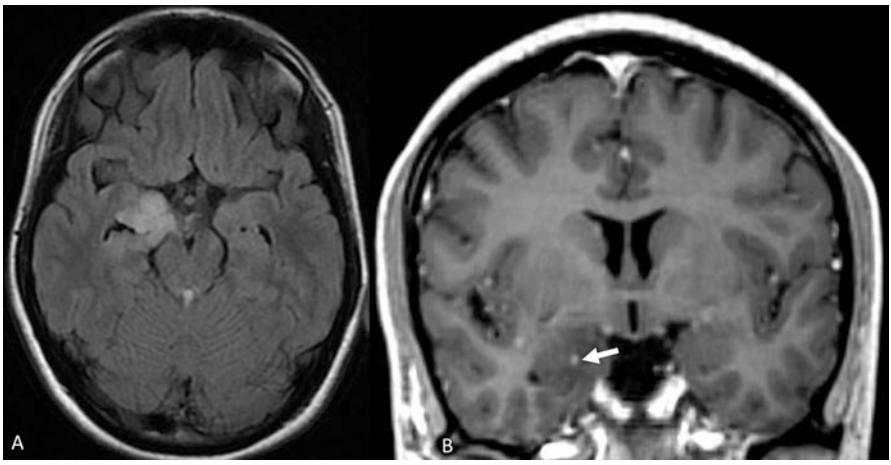

Fig. 6.13 Partially delineated nodular appearance of a type 2 DNT with signal increase in axial FLAIR (**a**) and hyposignal in T1 with a small punctate contrast enhancement after gadolinium infusion (**b** arrow)

Advanced imaging can help characterize DNETs, but as for conventional visualization [52], the more specific patterns are observed in type 1 forms rather than in non-specific subtypes. In diffusion, the ADC is very high due to the importance of water content in the extracellular space and superior to that observed in gliomas. In spectroscopy, a low increase or normal choline allows the differential diagnosis with a glioma. In perfusion (gradient echo or ASL), the decrease of local perfusion also distinguishes from an ordinary glioma (Fig. 6.15).

Other Malformations of Cortical Development

Classifications for malformations of cortical development (MCD) are numerous and complex. Several classifications are based on chronological elements (referring to the supposed stages of each developmental disorder) and/or morphological considerations. These classifications have the advantage to provide an approach of the pathogenic mechanisms affecting the normal development of the cerebral cortex at each stage from neuronal proliferation (focal cortical dysplasia, DNET and gangliogliomas, tuberous sclerosis. . .), to migration (heterotopia, lissencephaly. . .) and subsequent cortical organization (polymicrogyria, schizencephalia. . .) [53].

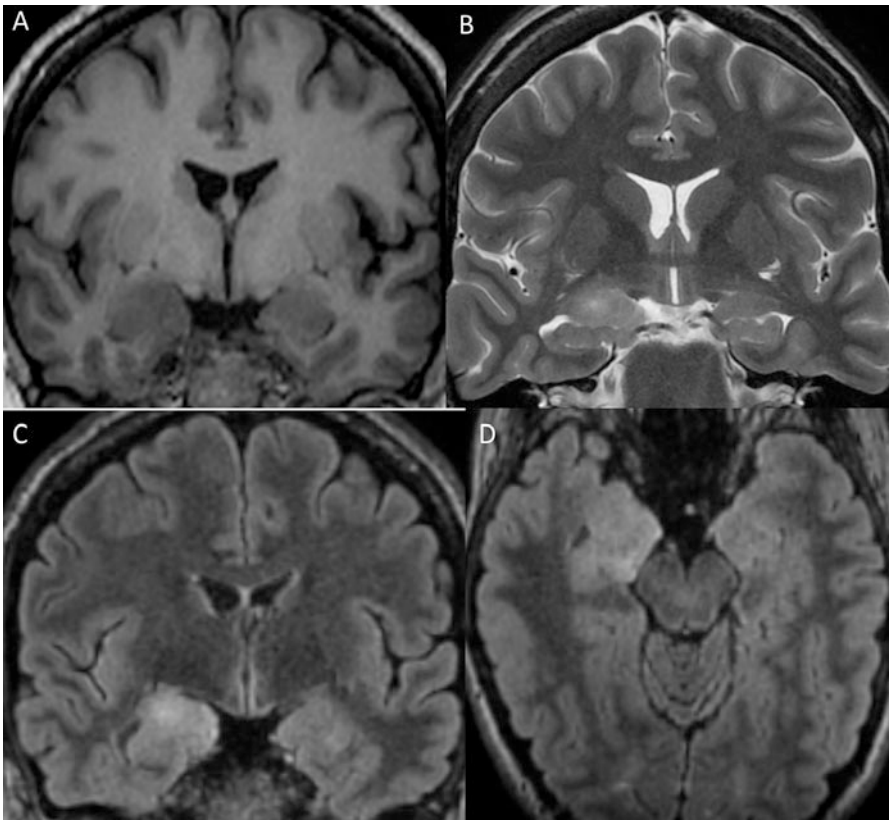

Fig 6.14 "Dysplastic" form of a right amygdalo-hippocampal DNET, hardly visible on coronal T1 (**a**), with a simple gray-white matter smoothing, in slight hyper signal on coronal T2 (**b**), coronal (**c**), and axial (**d**) FLAIR

Polymicrogyria

Polymicrogyria (PMG) is a common malformation of cortical development, characterized by numerous excessive small convolutions separated by shallow sulci, leading to a scalloped aspect of the cortex. This lesion can be multifocal or limited to a cortical region. The perisylvian location is classical (Fig. 6.16), often bilateral. It may be associated with other developmental lesions such as schizencephaly, callosum agenesis, or nodular heterotopia. Other neurological disorders may be associated to epilepsy such as cognitive deficiency and focal impairment. The severity of these neurological disorders depends on the extent and topography of the PMG as well as the associated abnormalities.

As polymicrogyria is the result of an abnormal cortical organization of "normal" neurons, there is no signal anomaly on conventional sequences. Three-dimensional and curvilinear reformatting from a volumetric T1 sequence helps characterize PMG

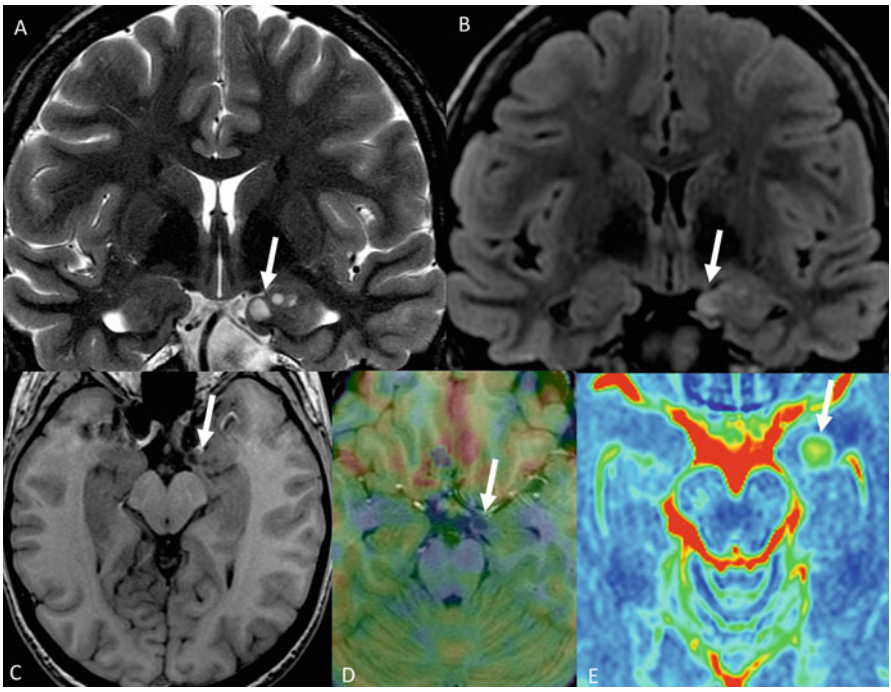

Fig. 6.15 Advanced imaging in a case of pseudocystic type 1 DNET of the left cerebral amygdala (arrow) on coronal T2 (**a**) and FLAIR (**b**) slices, axial T1 (**c**), ASL with co-registration of cerebral blood flow map on a T1 slice (**d**) showing a decrease of the local cerebral blood flow of the DNET in comparison to the right amygdala. Finally, the apparent diffusion coefficient map (**e**) shows an increased ADC of the DNET in comparison to adjacent cortex

MR features (irregular, scalloped, and discretely thickened cortex) and their extent, as well as associated anomalies of sulcal depth and orientation. In perisylvian polymicrogyria, for example, the lateral fissure may be in continuity with the central sulcus (Fig. 6.17).

The diffusion/spectral/perfusion parameters of the abnormal cortex are identical to those of the adjacent normal cortex during interictal period.

Gray Matter Heterotopias

Gray matter heterotopias correspond to unique or multiple clusters of normal neurons in an inappropriate position. They are the consequence of the disruption of neuronal migration and often associated with genetic anomalies. There are three types of gray matter heterotopia corresponding to different positions on the neuronal migration pathway during the fetal period [53] from the germinal (subependymal) zones to the cortex: periventricular nodular heterotopia, the most frequent, laminar

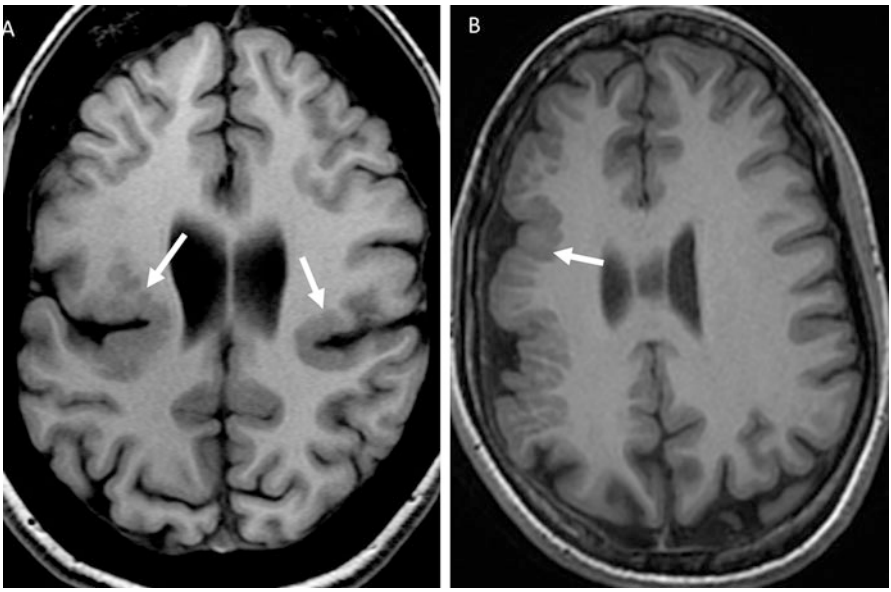

Fig. 6.16 Bilateral perisylvian polymicrogyria (**a**) and frontoparietal polymicrogyria in another patient (**b**) with a scalloped aspect of the cortex composed by numerous excessive small convolutions

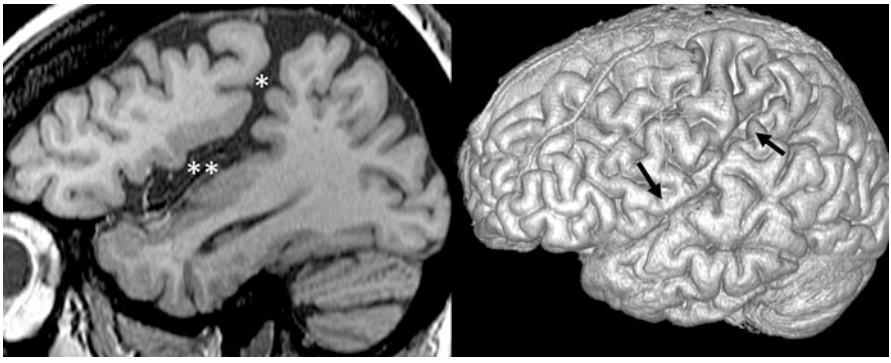

Fig. 6.17 Abnormal sulcal pattern in a patient with left perisylvian polymicrogyria. The lateral fissure (double asterisk) is in continuity with the central sulcus (asterisk)

heterotopia, and nodular subcortical heterotopia. There is a continuum between laminar heterotopia and lissencephaly (absence or decrease of cortical convolutions).

Periventricular nodular heterotopias can be found on the entire surface of the lateral ventricles. They are isolated or multiple, sometimes bilateral, and can be confluent with a scalloped appearance of the ventricle wall. The subcortical nodular heterotopia can be directly in contact with the cortex, with a pseudo-thickening of the gyrus.

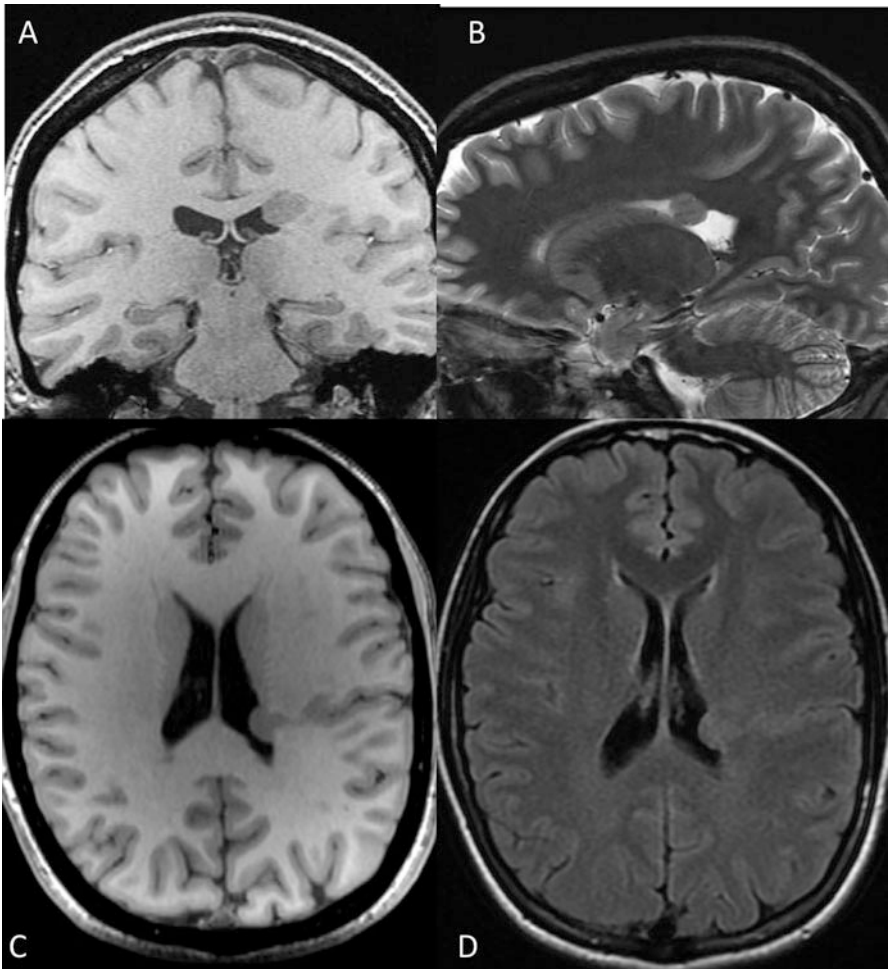

Fig. 6.18 Subependymal nodular gray matter heterotopia with a signal strictly identical to that of the cortex on T1 (**a**, **c**), T2 (**b**), and FLAIR (**d**) sequences

The gray matter heterotopia consists of normal neurons. Its signal is thus strictly identical to that of the cortex on all conventional sequences, including FLAIR (Fig. 6.18). There is no enhancement after contrast media injection. Nevertheless, a vascular structure can be observed through heterotopia in a juxtacortical position. The cortex is usually normal, but some heterotopia may be associated with other malformations of cortical development (e.g., polymicrogyria).

Functional imaging essentially allows for the differential diagnosis with brain tumors even if conventional sequences are often sufficient. In perfusion (ASL or gradient echo), the relative blood flow within heterotopia is identical to that of the cortex. In spectroscopy, unlike a tumor, the spectrum is that of the normal

parenchyma. In fMRI, focal activity consistent with activation of the normal cortex during a task is rarely observed and corresponds to the possible presence of functional neurons within heterotopia.

Tuberous Sclerosis

Tuberous sclerosis (or Bourneville tuberous sclerosis) is a genetic disease classified among phacomatosis, involving multiple organs (including the brain, skin, kidney, heart, and lung). Brain lesions are characterized by disruptions of both proliferation and migration and organization during cortical development, leading to abnormalities located from the periventricular space to the cerebral cortex. MRI features are characterized by the combination of multiple cortical tubers that have similar presentation as FCD (including transmantle sign), subependymal calcified nodules and subependymal giant cell astrocytoma. The final diagnosis relies on the presence of major criteria and/or minor criteria. Each MRI feature can be present or absent (all MRI features are considered as "major" criteria).

Mapping Cortical Brain Functions with fMRI in Patients with Epilepsy

Identifying brain functions is crucial when planning a surgical treatment. This is helpful for determining the surgical strategy, including the need of intracranial recordings and for assessment of functional risks. Due to brain plasticity, long-term epilepsy is associated with inter- or intra-hemispheric and white matter connection reorganization, especially when the epileptic focus is located in functional areas. In this context of potential reorganization, MRI may provide information about the eloquent areas within the cortex with functional MRI (fMRI) and of the underlying subcortical neuronal bundles with diffusion tensor imaging (DTI). The anatomical location of the presumed epileptogenic zone will define which paradigms are required for the presurgical workup. For example, fMRI for fronto-central epilepsy will focus on sensorimotor cortex, while mesial temporal epilepsy will require language and memory tasks, and posterior epilepsies will investigate visual tasks.

Sensorimotor Cortex

Sensory-motor function in fMRI corresponds to one of the most robust network fMRI, highlighted with easily feasible paradigms such as finger tapping, foot

flexion/extension, or lip movement tasks. It can be used to identify the primary motor cortex. Owing to its typical location in the frontal lobe and especially in the central region, FCD represents a major indication of sensory-motor task and corticospinal tract evaluation. However, other malformations of the cortical development may also affect the pre- and postcentral gyrus. In epilepsy presurgical imaging more than in other fMRI indications, each side has to be acquired separately in order to distinguish a reorganization of motor cortex near an epileptogenic lesion and to compare each response without being confound by the direct corticospinal tract contribution. Thus, the motor task for each limb has to be accomplished with the same frequency and strength.

It should be noted that a recent seizure may affect the motor cortical network with reduced responses on the side of the focus in comparison to the opposite side, in patients with extratemporal epilepsy [54]. This seizure-related alteration of the cortex function must be taken into account when interpreting motor fMRI in patients with frequent seizures.

Long-lasting epilepsy may also affect permanently the cortical organization of motor and sensory network, especially in patients with MCDs. The degree of reorganization depends on the period of the alteration during cortical development stages: early stage injuries (such as cortical dysplasias) will provide more substantial cortical reorganization than later lesions (such as gray matter heterotopia or polymicrogyria) [55, 56]. This reorganization can be present through a partial or total reduction of the response in the affected motor and sensory areas contralateral to the explored limb, in comparison to the normal hemisphere. A redistribution of the activation may also be observed with a permanent migration of the activated clusters to a different area, resulting from an adaptation process [57]. This relocation can be observed in the same hemisphere but in a different location, often in the vicinity of the expected anatomic area [58], or more rarely in the contralateral normal sensory-motor area. Consistent with this reorganization, activation within the dysplastic tissue itself is rarely observed, even if the lesion is directly located inside the central region (Fig. 6.19).

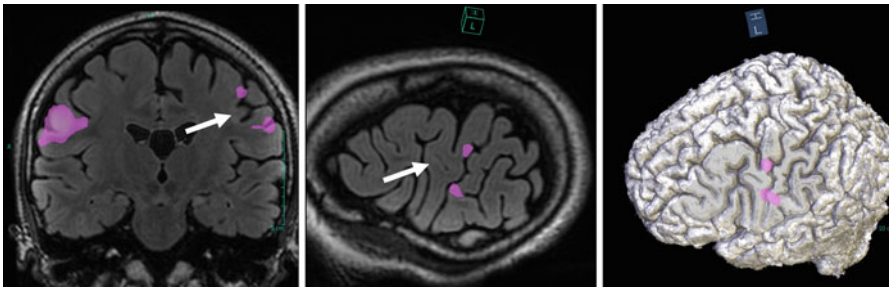

Fig. 6.19 Patient with a left precentral focal cortical dysplasia within the lateral primary motor cortex (arrow). The patient is asked to perform lip movements during a functional MRI acquisition. In comparison to the normal right side, the response near the lesion is less significant and fragmented on both side of the lesion

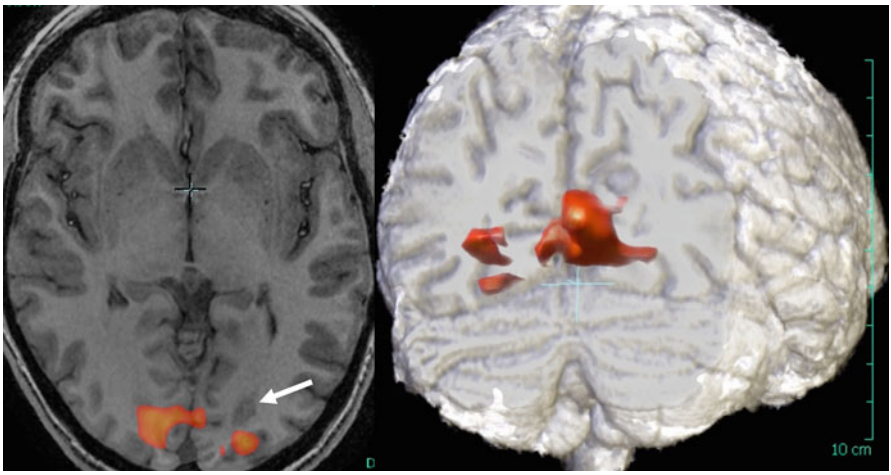

Fig. 6.20 Patient with a left occipital periventricular heterotopia. Using a blinking checkerboard as a paradigm, cortical response at the posterior part of the calcarine sulcus is more robust on the right side than on the side of the lesion

In MCDs of later stages such as heterotopia or polymicrogyria, the normal landmarks of the sensory-motor cortex may be disrupted and/or disorganized, especially in perisylvian polymicrogyria. fMRI is thus crucial before surgery or invasive procedure. Contrary to FCD however, functional activation may be preserved in polymicrogyric areas in which gyral and sulcal patterns are preserved, even if reduced in extent [59]. In patients with heterotopia, an activation within ectopic gray matter can be observed, usually coactivated with the functional areas directly overlying the heterotopia [60].

In epilepsy surgery, correlations between fMRI results and peroperative data during surgery are usually more reliable than in surgery for gliomas. However direct electrocortical stimulations are mandatory to prevent the risk of causing a lasting deficit.

Visual Cortex

In the same way as for sensory-motor cortex, primary and secondary visual cortex may reorganize in patient with occipital lesional epilepsy, leading to abnormal pattern of activation or absence of activation around calcarine region in the vicinity of the epileptogenic zone. This reorganization occurs in the presence of a MCD (Fig. 6.20) such as polymicrogyria or FCD [55, 61].

Language

There is now very good evidence that fMRI is able to determine hemispheric dominance for language in frontal (Broca's area) and temporal (Wernicke's area) regions, in line with results from the intracarotid amobarbital "Wada" test [62–65]. This agreement reaches up to 85% when using a combination of at least three language paradigms and is greater in right TLE with left language dominance, than in left TLE with left language dominance [66, 67]. This lateralization can be obtained using a visual appreciation of the numbers of activated clusters in each perisylvian region or by using a quantitative method such as the lateralization index [68]. Atypical lateralization is more frequent in patients with left hemisphere epilepsy [69]. As for sensory-motor reorganization, the atypical activations can widespread in the same hemisphere but in other areas than typical perisylvian regions or in the opposite hemisphere (Fig. 6.21), leading to the atypical dominance [70, 71]. This language "shift" is more likely observed in left-handed patients, in left TLE, and in long-lasting epilepsy with early onset [69].

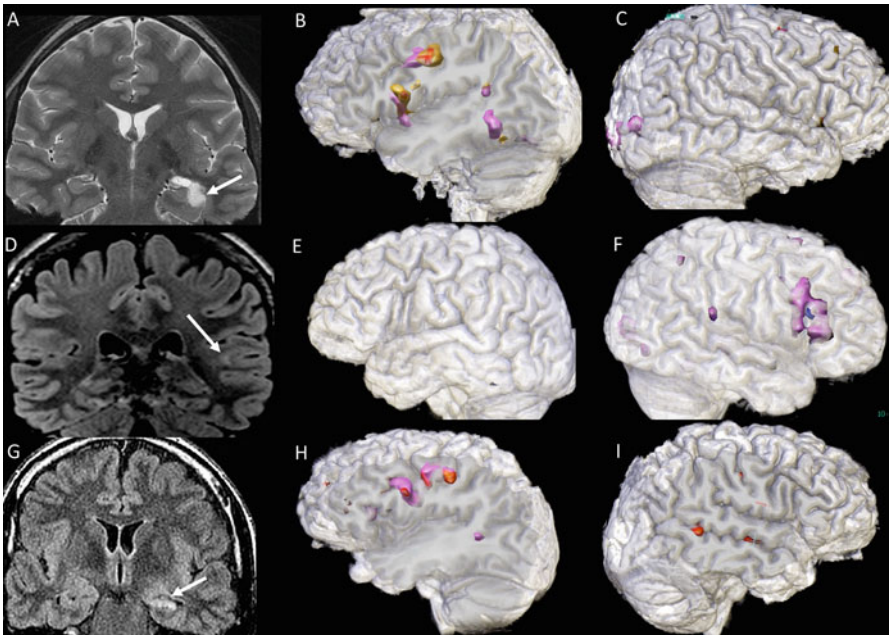

Fig. 6.21 Examples of language lateralization in three patients with temporal epilepsy: Patient 1 (**a**–**c**) with temporo-mesial DNET on T2 coronal view (**a**). Left (**b**) and right (**c**) 3D reformat of a language fMRI shows a clear left lateralization. Patient 2 (**d**–**f**) with a left temporal FCD on FLAIR coronal view (**d**). Language fMRI (**e**, **f**) shows an atypical right lateralization resulting from a reorganization of the language network. Patient 3 (**g**–**i**) with a left hippocampal sclerosis on FLAIR coronal view (**g**). Language fMRI (**h**, **i**) shows an interhemispheric dissociation of left frontal and right temporal language responses leading to a very atypical crossed language dominance

Furthermore, fMRI can be used to map language networks using various specific language tasks that activate frontal (fluency tasks) and temporal (comprehension tasks) language areas and thus determine patterns of language network, whether the lateralization is typical or not. Preoperative fMRI activations near the epileptogenic zone that is to be resected is a predictor of long-term postoperative language deficiency [72]. It is thus essential to choose the best set of paradigms in order to activate the cortical regions, frontal or temporal, that are targeted by the surgery. However, contrary to sensory-motor fMRI, language fMRI is to date not adequate to guide resection because of a lack of sensitivity when compared to direct cortical stimulation [73] even if specificity is high.

Episodic Memory

Temporal lobe surgery, especially in patients with hippocampal sclerosis, is associated with a risk of visual and/or verbal memory postsurgical complications. New paradigms are tailored for imaging the episodic memory network with encoding and retrieval tasks in order to visualize activations in mesial temporal structures [74]. Verbal event-related memory task seems to show the best reliability to distinguish between left-onset and right-onset patients [75]. As for language structures, an asymmetry index derived from activations in both hippocampi can evaluate compensatory mechanisms of the normal entorhinal cortex to counterweigh the impaired function of the sclerotic hippocampus. The aim of memory fMRI would thus be to predict the effect of resection of the sclerotic temporal structure on the postoperative memory decline [76–79]. Depending on the size of the HS, the category of memory decline risk will differ: verbal memory decline will be more frequent in patients undergoing left temporal lobe resection and visual memory decline in those with right temporal lobe surgery [80, 81]. Memory activation patterns before surgery seems to be the strongest predictor of verbal and visual memory loss as a result of anterior temporal lobe resection, and preserved function in the ipsilateral posterior hippocampus seems to help to maintain memory encoding after anterior temporal lobe resection [76].

Mapping Connectivity

As cortical eloquent area may affect one or several cognitive functions, white matter connections and functional connectivity between eloquent areas may also cause cognitive impairments when damaged. Although focal epilepsy is traditionally considered as a cortical and regional disorder based on the epileptogenic zone model from which seizures originate, recent studies suggest that widespread network alterations extend beyond this zone and may be correlated to cognitive impairments

and surgical outcome prediction. Thus, presurgical imaging workup in epilepsy may require an evaluation of functional networks.

Resting State

Focal epilepsy, whether temporal or extratemporal, is associated with modifications of the connectivity that can be observed in regions directly connected to the epileptic zone. These modifications may also widespread well beyond the seizure onset area [82]. Regional connectivity modifications may be related to the lateralization of the hemisphere of seizure onset, and thus resting state fMRI could predict laterality of the epileptogenic hemisphere [83]. In patients with TLE, most studies suggest an increased connectivity between hippocampus and other ipsilateral limbic structures (including thalamus) involved in seizure propagation, compared to controls [84, 85]. In the same way, patients with frontal lobe epilepsy shows increased connectivity in the neighborhood of the epileptic zone [86, 87]. This increase of the regional connectivity, when included in the resection area, seems to be related to a better surgical outcome. Therefore, preoperative resting state fMRI can help localize the global epileptic zone (EZ) that should be targeted by surgery [88]. Moreover, this phenomenon of higher regional connectivity near the EZ is in most of the cases associated with a diminished connectivity in widespread distant regions throughout the brain, including those involved in cognition. In resting state fMRI analysis, the evaluation of the default mode network represents a good illustration of this remote effect of connectivity disturbance. Thus, patients with TLE and extratemporal epilepsy when compared to controls show a decrease of functional connectivity among default mode regions contrasting with increased connectivity within functional networks near the seizure onset [84, 87, 88]. Other distant cognitive networks may be affected such as frontoparietal association and primary sensorimotor networks. These local and widespread connectivity disturbances evaluated by resting state fMRI may also be related to cognitive impairments as studied for verbal and nonverbal episodic memory, language, working memory, and attentional functions [89]. Thereby, resting state fMRI seems to provide important clues for the understanding of pathophysiology related to focal epilepsy. However, the clinical benefit for individual patients is not established yet.

Diffusion Tensor Imaging and Tractography

Corticospinal Tract

Motor responses authenticated with fMRI may also help to define white matter projections with DTI tractography and to provide a reliable guide for the surgeon to avoid permanent motor deficit (Fig. 6.22). As for glioma surgery in which

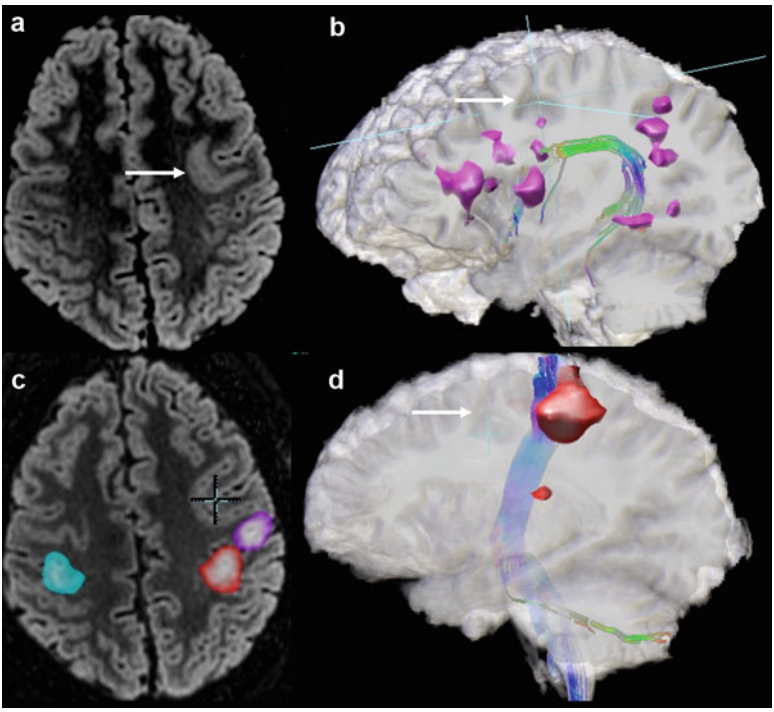

Fig. 6.22 Patient with a focal cortical dysplasia of the left precentral sulcus on axial FLAIR sequence (**a**). In this case both language and motor networks need to be analyzed. Language fMRI responses during a semantic association paradigm (clusters in pink) and arcuate fasciculus tractography (**b**) show relationship between this network and the lesion (arrow). Motor responses (**c**) during left hand (blue), right hand (red), and then mouth (violet) movements show that the lesion is near motor functions in the left hemisphere, without any functional reorganization. Pyramidal tract (**d**) is also traced from the cortical right hand motor response and the brain stem

intraoperative direct cortical stimulation supports tractography as a reliable method for showing the relationship between a glioma and the corticospinal tract [90], similar results were obtained to predict the risk of postoperative motor deficits in patients with frontal epilepsy [91].

Arcuate Fasciculus and Language Tracts

Left-right asymmetry of anisotropy along the two main language pathways, arcuate fasciculus and inferior occipitofrontal fasciculus, are observed in controls and reflect the language specialization and lateralization. In patients with left TLE, this asymmetry of anisotropy along the arcuate fasciculus lowers compared to patients with right TLE and is correlated with fMRI-based lateralization indices [92].

Visual Pathway

Temporal lobe epilepsy surgery exposes to the risk of damaging the inferior optic radiation during resection and can cause contralateral upper quadrantanopia. The preoperative tractography is predictive of the risk of a visual field alteration [93] The optic radiation can be accurately delineated by tractography and can help surgical planning and guide intraoperative procedure [94]. Correction for brain shift using intraoperative MRI also improves the accuracy of the technique [95].

Conclusion

MR diagnosis in patients with epilepsy may be difficult because of subtle cortical lesions which can be hardly distinguishable with "standard" MRI protocol. An appropriate MRI epilepsy protocol is essential in the assessment epileptogenic lesions. In this specific indication, high field MRIs and advanced sequences such as ASL, diffusion tensor, double inversion recovery, and functional MRI are especially appreciated to comfort challenging cases, to appraise the limits of the epileptic zone, and to assess its consequences on cortical network and connectivity. In all cases, MR abnormalities are valuable only when considered together with clinical, electroclinical data, and other imaging techniques.

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