

# Imaging techniques for presurgical evaluation of temporal lobe epilepsy

The surgical treatment of pharmaco-resistant focal epilepsy has increased dramatically in recent years. This evolution is undoubtedly due to an improvement of electrophysiological and neuroradiological investigations to localize the epileptic focus. Temporal lobe epilepsy is the most frequent pharmaco-resistant epileptic syndrome in adults and responds better to surgery than the so-called extratemporal epilepsy. Apart from the history and the clinical semiology, the investigations for temporal lobe epilepsy are based on core investigations, including electroencephalography (long-term video-EEG recordings) and MRI. Additional noninvasive imaging techniques to improve the localization of the epileptic focus include PET ictal and interictal SPECT, electric source imaging and magnetic source imaging, and simultaneous EEG and functional MRI. Advanced sequences and analysis of structural MRI data allow us to map subtle structural abnormalities as well as important white matter tracts while functional MRI of language/memory helps to identify eloquent cortical area and estimate the risk of postoperative deficits. Our aim is to review the current literature and summarize all available data on these validated imaging techniques for the assessment of focal temporal lobe epilepsy.

**KEYWORDS:** ESI ■ fMRI ■ imaging ■ magnetic source imaging ■ MRI ■ PET-CT ■ SPECT ■ temporal lobe epilepsy

The neurosurgical activity of epilepsy surgery has increased dramatically in recent years. In Europe, 15 operations were performed on average between 1979 and 1984; this number grew to 42 operations between 1989 and 1994 on average per center [1]. This evolution is undoubtedly owing to an improvement of electrophysiological and neuroradiological investigations. Surgery for temporal lobe epilepsy (TLE) is indicated for drug-resistant epilepsy where the epileptogenic zone (EZ) can be localized and where the surgical removal is not related to unacceptable neurological or neuropsychological outcome.

Common pathologies that could underlie TLE are hippocampal sclerosis (HS), tumors, congenital malformations, vascular abnormalities and many other pathologies, summarized in Box 1.

TLE classically presents with complex partial seizures lasting 1–4 min, often preceded by auras with epigastric sensations, fear, anxiety, experiential phenomena, olfactory or gustatory hallucinations, or autonomic symptoms. Altered consciousness and oral or manual automatisms are typical and variably associated with contralateral dystonic postures or motor symptoms. Secondary generalization is rare but can occur, as well as postictal disturbances in mood, language and memory [2].

However, even if the MRI is normal, it is worthwhile pursuing surgery for epilepsy because

if carefully selected, these patients also present good seizure control [3].

TLE is frequently drug-resistant and remains the most common cause of focal epilepsy among adults [4]. Consequently, around two-thirds of surgical procedures for intractable epilepsy are carried out on the temporal lobe. A systematic review and meta-analysis from Téllez-Zenteno *et al.* of previous studies of TLE surgery showed that seizure-free outcome was achieved in 45% of patients suffering from a nonlesional TLE and 69% of patients with lesional TLE [5]. One recent study has only included TLE patients with normal structural MRI and has reported a rate of seizure freedom in 55% of patients after resective surgery of the temporal lobe [6]. The same authors showed that the long-term rate of seizure freedom is more likely to be achieved in patients with tumoral epilepsy (76%) and is lowest in studies with patients older than 50 years at the time of surgery, suggesting that early surgery is beneficial.

Presurgical evaluation of TLE includes clinical history and semiology, electroencephalographic studies (interictal EEG and continuous EEG), structural and functional neuroimaging techniques, neuropsychological assessment (for preoperative cognitive deficits and as a baseline for postoperative follow-up), invasive monitoring (epidural or subdural and/or intracerebral

Andrea Bartoli\*<sup>1</sup>,  
Serge Vulliemoz<sup>2</sup>,  
Sven Haller<sup>3</sup>,  
Karl Schaller<sup>1</sup>  
& Margitta Seeck<sup>2</sup>

<sup>1</sup>Department of Neurosurgery Geneva University Hospital, 4, Rue Gabrielle Perret-Gentil, CH-1211 Geneva, Switzerland

<sup>2</sup>Department of Neurology, Faculty of Medicine, Geneva University Hospital, Geneva, Switzerland

<sup>3</sup>Department of Neuroradiology, Faculty of Medicine, Geneva University Hospital, Geneva, Switzerland

\*Author for correspondence:

Tel.: +41 762 013 429

Fax: +41 223 728 220

b\_and@hotmail.com

**Box 1. Pathologies underlying temporal lobe epilepsy, amenable for surgery.**

- Hippocampal sclerosis
- Dysembryoplastic neuroepithelial tumor
- Glioma or ganglioglioma
- Cavernoma or arteriovenous malformation (FIGURE 1)
- Focal cortical dysplasia
- Heterotopia and cortical abnormalities
- Granulomatous infections (cysticercosis)
- Trauma
- Infarction

electrodes), and – if necessary – intracarotid amytal test (so-called Wada test) to verify good functioning of the nonresected hippocampus.

Here, we review the literature concerning all neuroimaging techniques currently used in TLE, with special emphasis on mesial temporal sclerosis associated with TLE (MTS-TLE).

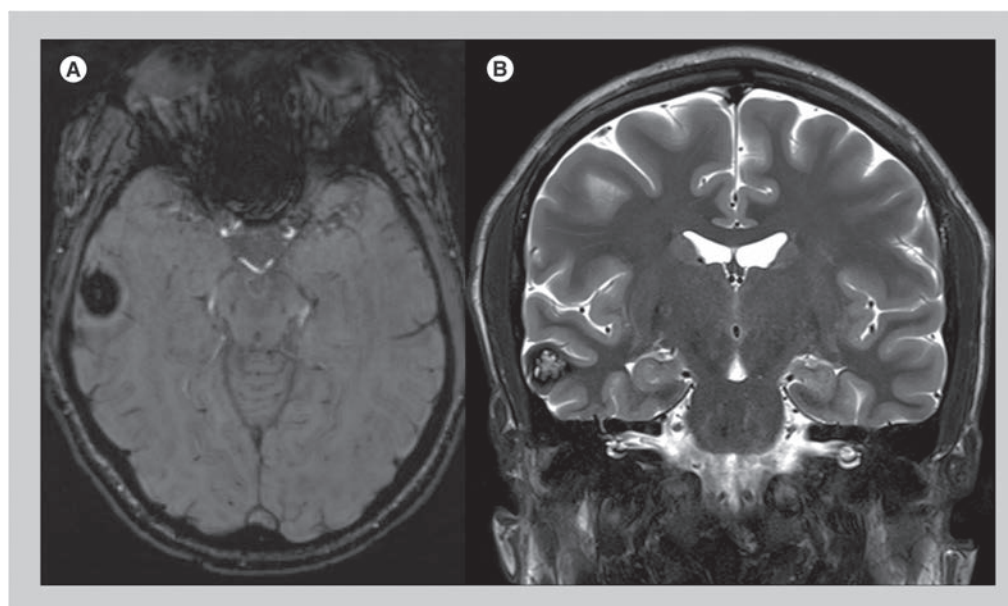
**Structural MRI****■ Standard MRI**

The principal role of MRI is to define any structural abnormality that underlies TLE, and thus to correlate the structure with brain function. A recent study on surgical decision-making in TLE included, retrospectively, 186 patients and compared <sup>18</sup>F-fluorodeoxyglucose (FDG)-PET, MRI and EEG: it was found that MRI seems to have the most influence on surgical candidacy and that FDG-PET predicts surgical outcome [7].

Since 1985 MRI has been shown to be more accurate than CT scanning regarding the etiology of epilepsy [8]. The most common MRI

abnormal findings in TLE at 1T or 1.5T with T<sub>1</sub>- and T<sub>2</sub>-weighted sequences are vascular malformation (e.g., cavernomas see FIGURE 1), HS (BOX 2 & FIGURE 2), malformation of cortical development, tumors and some acquired cortical damage (trauma, infarction or granulomas) [9–11]. On the other hand, CT can still be useful for skull fractures and intracranial calcification, which are both potentially causes of chronic TLE.

HS is the prevalent cause of TLE and is variably associated with focal cortical dysplasia (FCD) type IA in the temporo-polar region [12–14]. From a histopathological point of view, HS has been defined as loss of pyramidal neurons mainly in CA1 region with sprouting mossy fibers of dentate granule cells, often associated with CA3 and dentate neuronal loss. This lesion is frequently found with the so-called endfolium sclerosis, which is neuronal loss involving the CA4 region and dentate gyrus [15–17]. On the other hand, FCD is a dyslamination of cortical



**Figure 1. Cavernoma.** (A) MRI showing a heterogeneous lesion (cavernoma) in the right second temporal gyrus, with an hypointense peripheral border on susceptibility-weighted imaging sequence and (B) mainly hyperintense in T<sub>2</sub>-weighted sequence.

**Box 2. MRI protocol in hippocampal sclerosis (axial and coronal plane) following International League Against Epilepsy recommendations.**

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

- 3D *T*<sub>1</sub>-weighted Magnetization Prepared Rapid Gradient Echo (MPRAGE) without contrast agent with at least millimetric iso-voxel size<sup>†</sup>

***T*<sub>2</sub>-weighted**

- Coronal thin slices, oblique with respect to the temporal lobe/*T*<sub>2</sub>\*-weighted gradient-echo or susceptibility-weighted imaging

**FLAIR**

- Either 2D axial/coronal or 3D depending on MR scanner<sup>†</sup>

**DTI<sup>†</sup>**

- With typically ≥30 diffusion directions

<sup>†</sup>Details concerning each MRI sequence used in the authors' institution, no established guidelines are available.

DTI: Diffusion tensor imaging; FLAIR: Fluid-attenuated inversion recovery.

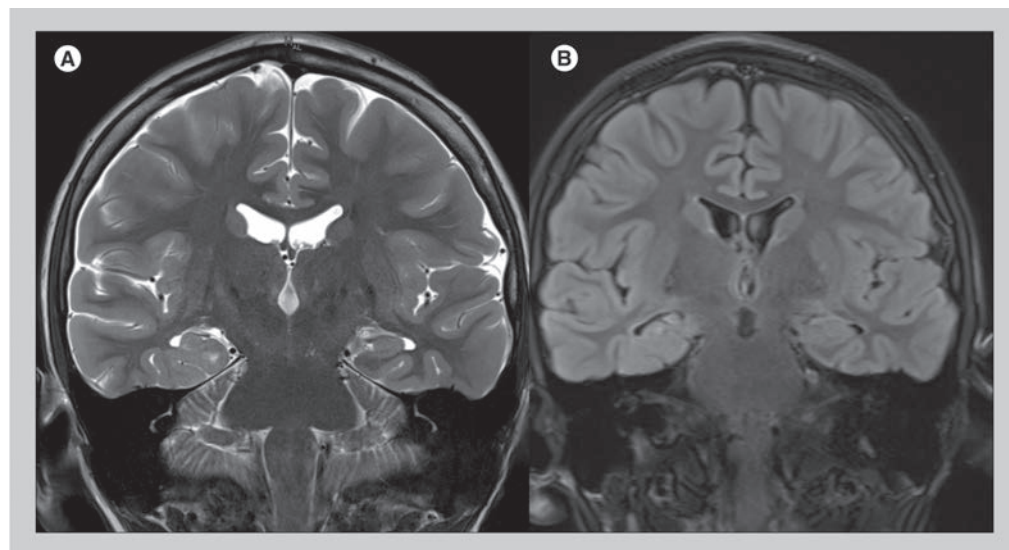
Data taken from [2].

architecture but both pathologic and radiologic diagnostic criteria remain poor [18].

The validity of structural MRI has also been consolidated by some studies that compared electroclinical, radiological and histopathological findings in patients with TLE and nodular heterotopia, another cortical abnormality. In ten cases of nodular heterotopias (seven of which were temporal), both subependymal and subcortical signal intensity were isointense (nodules vs cortex), except for three cases where nodules were hyperintense in *T*<sub>2</sub> and in fluid-attenuated inversion recovery (FLAIR) sequences. Cortex thickness was found to be normal over the nodules, gyrations altered and hemisphere size slightly reduced (mainly at temporal lobe). The histopathological study demonstrated the same microscopic organization within the nodules and that the overlying cortex was dysplastic (even if normal in thickness) [19]. Congruencies

and discrepancies between ictal and interictal EEG and lesions on structural MRI in focal epilepsies have shown different values depending on the location of the lesion: patients with temporal lesions had the highest congruence between interictal epileptiform discharges, epileptic seizure patterns and lesions, more than patients with frontal, parieto-occipital regions but surgical outcome did not differ between regions [20].

Series including both TLE and extratemporal epilepsy patients proved the usefulness of 3T MRI scanners for identifying focal cortical FCD and HS, especially with coronal and axial FLAIR sequences [21,22]. Surface coil placement did not improve the detection of previously undiagnosed focal lesions but improved the demarcation and provided more details about cortical lesions already diagnosed without coil placement [23].



**Figure 2. Hippocampal sclerosis.** MRI showing hyperintensity on *T*<sub>2</sub>-weighted sequence (A) in the right hippocampus, which is also smaller than the left one. Poor cortical–subcortical differentiation on fluid-attenuated inversion recovery sequence (B) in the hippocampus, parahippocampus and temporo-polar region, corresponding to a hippocampal sclerosis and a mesial–temporal cortical dysplasia.

With the exception of vascular malformations, tumors and other obvious lesions, subtle HS and cortical abnormalities (such as focal cortical dysplasia or cortical heterotopia) might be challenging to detect on 1 or 1.5T MRI because of the submillimetric size of these lesions, limited spatial resolution and contrast of MRI [11,23]. 3T MRI, as it is available in many centers today, provides a higher signal-to-noise ratio, leading to better identification of subtle lesions and/or better characterization of larger lesions in patients with epilepsy [21].

#### ■ Additional advanced MRI techniques High-field structural MRI

Several studies and reviews showed that structural *in vivo* MRI at 1T or 1.5T can be unremarkable in patients with TLE [11,24]. Further improvement on detecting extremely small mesiotemporal structures by increasing spatial resolution and tissue contrast can be achieved by ultrahigh field strength MRI (7T and more) [25,26]. Normal hippocampal structures have been defined at 7T in young adults [27]. A combined T<sub>2</sub>-weighted 7T scanning and histopathological study on 13 surgical specimens from TLE patients has recently shown that high-resolution MRI allows the study of intracortical organization in normal and pathologic areas [28].

Henry *et al.* explored mesial temporal structures with T<sub>1</sub>- and T<sub>2</sub>-weighted sequences at 7T in eight patients suffering from TLE and 11 healthy subjects and found selectively greater Ammon's horn atrophy in patients with TLE and HS. Furthermore, independently from hippocampal atrophy, some abnormalities of the dentate gyrus were visible, as well as paucity of digitations of the head of hippocampi and some malrotation of the hippocampus [23].

On the other hand, preliminary studies of frontal lobe malformations of cortical development using 7T MRI, multichannel coils, arterial spin labeling sequence, susceptibility-weighted imaging and diffusion tensor and spectrum imaging have been reported to show a better definition of the dysplasia than 3T MRI, and this can probably also apply in TLE [29].

#### Automated quantitative MRI-based analysis

Volumetric MRI analysis of the brain has become a common method to evaluate neurologic disorders including epilepsy and is a valuable tool, especially when structural abnormalities related to volume changes are less visible at visual inspection.

Manual hippocampal volumetry has been shown to detect unilateral or bilateral abnormality [30]. The degree of volume loss of entorhinal cortex measured by volumetry and the electrophysiological coupling of the entorhinal cortex and hippocampus measured by intracerebral recordings were strongly correlated, suggesting that volumetry can predict epileptogenesis of the entorhinal cortex [31].

On the other hand, manual volumetry is time consuming and prone to operator error. Therefore, attempts have been made to automate volume estimation of the brain, using MRI as a quantitative tool, and thus improving sensitivity and reducing subjectivity. It also has the advantage of not being restricted to only one region of interest but potentially to the whole brain.

Three automated methods are commonly used: voxel-based morphometry (VBM), deformation-based morphometry (DBM) and cortical thickness method [32–35].

VBM is a neuroimaging technique based on statistical parametric mapping of voxels derived from MRI scans and a brain template that takes into account brain anatomy differences among people. It allows the study of the probability that a given voxel is gray matter or white matter, and thus estimates the focal volumetric differences in the brain.

VBM is the most widely used automated quantitative analysis (more than 20 studies have been published concerning TLE) [33,36–41], it has been used extensively for other neurologic and neuropsychiatric disorders (e.g., schizophrenia and Alzheimer's dementia) [36]. Bonilha *et al.* used VBM in 23 patients suffering from MTS-TLE and proved its utility for a reliable discrimination between atrophic and normal hippocampi [42]. However, interpretation of VBM analysis should be made cautiously because of some false-positive results [43,44] and requires correlation with other imaging data.

Compared with VBM, DBM allows the study of brain anatomical differences on a more macroscopic scale and is based on vector fields that describe global or gross differences in brain shape between the patient and a control group [45]. Only one study has been reported on DBM in TLE, and the same study compared VBM, DBM and the cortical thickness method in 29 TLE patients (14 with MTS and 15 with normal-appearing hippocampi, respectively) and 33 healthy subjects on a 4T MRI scan. Each method detects a different aspect of brain atrophy and should be used on the basis of the suspected pathology. In particular, VBM and DBM



detect cortical and subcortical abnormalities in pathologies associated with macroscopic volume loss. Moreover, DBM seems to be an excellent method for subcortical abnormalities [33].

In contrast to VBM, cortical thickness is a more sensitive parameter, which has less group average standard deviation [46], which can be explained by the combination of a more precise spatial normalization (cortex-based alignment) and the more accurate estimation of cortical thickness.

Whole cortical thickness analysis also showed extra temporal neocortical thinning (especially bilaterally in sensorimotor cortex and to a lesser extent in the temporal, occipital and parietal lobes) in TLE patients, either with or without MTS (16 with MTS and 16 without MTS on structural MRI), compared with 44 healthy controls [47]. This finding corroborates what has been found in other reports about the co-existence of extrahippocampal lesion in MTS-TLE patients [48] and supports the hypothesis that even in TLE without MTS, abnormalities in neocortical regions may be involved in the pathophysiology of the epilepsy. However, this method is not yet routinely used nor validated for clinical practice and limitations exist with regards to its value for identifying a small volume of tissue for resection: in fact, in children with frontal lobe epilepsy, cortical thinning was extensive within the frontal lobe and also in extrafrontal areas and this concept might also apply to TLE [49].

In a recent study, automatic quantitative FLAIR analysis promises to be a useful tool in quantifying hippocampal signal alterations, detecting HS and monitoring the evolution in time of the disease (following temporal lobe seizures, status epilepticus and limbic encephalitis) [50].

### Diffusion studies

In an isotropic medium such as cerebrospinal fluid, water molecules are moving due to diffusion and they move at equal rates in all directions. Diffusion tensor imaging (DTI) is a sensitive method to measure the diffusion of water molecules in the intracellular and extracellular spaces: water molecules diffuse more rapidly along fiber bundles and more slowly perpendicular to the main axis of the fiber bundles, so that diffusion of water in the white matter is anisotropic. Decreased anisotropy of water diffusion can be due to reduced axonal density but also to the presence of crossing fibers in the region of interest. Studies comparing stereo-EEG and

DTI showed spatial concordance between epileptiform activity and diffusivity abnormalities in up to 50% of patients with refractory focal epilepsy [51,52].

Furthermore, extratemporal abnormalities in TLE have been extensively studied and a considerable literature exist about co-existing white matter alterations detected by DTI [53]; however, its validity in localization of EZ has to be proven.

Owing to increased diffusivity of water in HS, apparent diffusion coefficient (which represents the net displacement of molecules in a tissue) has been found to be abnormal in patients with normal structural MRI hippocampi and ipsilateral onset of seizure [54,55].

Reduction of fractional anisotropy (FA) and higher diffusivity in the external capsule and corpus callosum in patients with TLE compared with healthy subjects was first reported by Arfanakanis *et al.* [56]. Several studies then showed diffusion abnormalities (both FA and apparent diffusion coefficient) in temporal and extratemporal structures of patients with TLE: the thalamus and hippocampus in children with TLE had decreased FA and increased apparent diffusion coefficient [57].

Reduced symmetry of FA was found in the fornix and cingulum of TLE patients compared with control subjects [58], also after surgery [59]. The FA of the uncinate fasciculus was found to be asymmetric in normal subjects (right greater than left) while this asymmetry was no longer observed in TLE patients with right HS, suggesting widespread alterations of the limbic system in these patients [60]. Concha *et al.* provided a good correlation between *in vivo* DTI abnormalities and postsurgical histopathology in the fimbria-fornix of TLE patients [61].

Some groups tried to overcome the subjectivity of assessment of diffusion indices of the white matter in TLE patients based on the 'region of interest' method by implementing some less arbitrary (quantitative) automated methods. These studies confirmed the existence of a significant reduction of FA in epileptogenic temporal lobes, corpus callosum and inferior frontal gyrus [62,63] and showed promising results for TLE patients with no MTS [64].

Diffusion abnormalities in TLE do not yet have clear explanations or implications: diverging studies exist on the question of whether white matter alterations are due to duration of epilepsy [65–68].

Some studies showed a correlation between white matter changes and neuropsychological memory tests; in other words, FA values of

anterior temporal lobe and mesial temporal lobe were positively correlated with delayed memory and immediate memory, respectively [69,70]. Moreover, pre- and post-operative changes of white matter measured with DTI in patients undergoing anterior temporal lobe resection correlated with postoperative verbal fluency test [71].

Changes in white matter tracts, particularly an increase of FA values in the contra-lesional fornix after resective surgery, have also been demonstrated with tract-based spatial statistics on DTI sequences, a method that reduces the diffusion data to a skeleton of large white matter tract in order to allow more reliable intersubject and group comparisons [59].

Even though the clinical relevance of these findings remains unclear, white matter abnormalities seem to be extensive and bilateral in TLE patients with unilateral MTS and to a lesser extent in TLE patients without MTS [72].

Besides the still uncertain utility of DTI in the presurgical evaluation of TLE in terms of mapping subtle structural abnormalities, tractography algorithms can be used to estimate white matter tracts from the direction of preferred water diffusion measured by DTI. This technique has been shown to be useful for studying the anatomical variation in the course of the optic radiation in individual patients and to predict visual field loss after anterior temporal lobectomy (ATL): a superior homonymous quadrantanopia is a well-recognized complication following ATL and occurs because of disruption of the anterior part of the optic radiation (Meyer's loop). Wallerian degeneration of fibers directly (parahippocampal cingulum, uncinate fasciculus, inferior longitudinal fasciculus and fornix) or indirectly (inferior fronto-occipital fasciculus and corpus callosum) affected by ATL is apparent 2 months after resection and DTI can accurately define the optic radiation preoperatively and in the future could be fused with intraoperative scans to reduce the risk of postoperative visual field defects [73–75]. Although promising, this application is not yet automated, and therefore requires lengthy analysis by experts in the field.

#### Relaxometry

Relaxometry is based on the creation of a map of relaxation time in a given sequence.  $T_2$ -relaxometry is able to detect hippocampal and amygdala asymmetries in drug-resistant TLE [76,77]. Several approaches to quantitative estimation of  $T_2$  values exist and promising

results stem from algebraic  $T_2$  estimation for detection of hippocampal abnormalities [78,79] but no extensive use of this method has been published.

#### Spectroscopy

Magnetic resonance spectroscopy (MRS) can estimate different concentrations of chemicals within brain tissue. In a study by Guye *et al.*, the metabolic index on spectroscopy (measured by *N*-acetyl aspartate:choline plus creatinine ratio) was spatially concordant with the site of epileptic abnormalities determined by intracranial EEG with depth electrodes as compared with normal intracranial EEG regions and compared with healthy control subjects. The metabolic changes were not dependent on the TLE subtype, nor on the structural alteration of the temporal lobe, but were linked to ictal and inter-ictal activity and extended to extramesial structures [80].

*N*-acetyl aspartate (a marker of neuronal integrity) has been found to be diminished not only in the sclerotic hippocampus, but also in extratemporal regions [81,82], in accordance to other MR studies in patients with MTS-TLE.

Creatinine and choline, markers of energy metabolism and cell membrane integrity, respectively, are usually unchanged [83]. Concentrations of *N*-acetylaspartate/creatine and choline-containing compounds have recently been found decreased in both hippocampal and extra-hippocampal structures in both MTS-TLE and no MTS-TLE, thus reducing the value of MRS for focus lateralization [84]. In healthy control subjects, metabolite concentration differences varied in different parts of the temporal lobe depending on the volume of hippocampal tissue within the region of interest (partial volume effect), which raises further questions about the reliability of MRS in TLE [85].

#### Considerations on advanced MRI techniques

Except for the standard structural MRI, more advanced MRI-based studies that have been shown here are not routinely used in the presurgical evaluation of TLE but serve more as anatomical studies of the alterations of the brain in epilepsy.

Wagner *et al.* have compared the standard visual analysis carried out by an experienced neuroradiologist to the morphometric MRI analysis for detecting focal cortical dysplasia type II (FCD II) and found that the combined use of both approaches provides additional diagnostic sensitivity for this subtle lesion; since the

detection of FCDs can significantly improve the postsurgical outcome, his group apply the morphometric analysis in all patients with negative MRI after standard visual inspection [86].

On the other hand, studies on DTI, spectroscopy and relaxometry reported different results so they still lack true clinical validity.

Another consideration arises from the fact that many studies rely on average structure differences between TLE patients and control subjects and cannot be applied to individual patients. For example, whereas there is evidence that TLE patients have extratemporal structural abnormalities, it is unclear whether these abnormalities can guide surgical therapy.

## Functional imaging

### ■ Functional MRI

Mapping brain functions has been revolutionized by functional MRI (fMRI), particularly with blood oxygen level-dependent (BOLD) contrast, which theoretically reflects the increased oxygenated blood delivery to a particular cerebral area involved during a specific task.

The main use of fMRI in surgical activity consists in the location of eloquent functions (vision, language, motor and sensory function) for surgical planning. Generally speaking images generated by fMRI can help surgical planning for intracerebral EEG recordings and in turn electrodes can better map a certain function on the cerebral surface [11].

With regards to TLE, fMRI has demonstrated a reorganization of language localization and this finding has also been demonstrated as language network reorganization with DTI and VBM studies, with involvement of the nondominant hemisphere [87,88]. This right reorganization has been related to a potential early (congenital) insult to the left hemisphere [89]. Moreover, after ATL patients with left-TLE seem to show greater bilateral fMRI activation in the inferior/middle frontal gyri and a stronger connectivity between these areas compared with patients with right-TLE. Interestingly, preoperative fMRI activation in the left middle frontal gyrus for verbal fluency in left TLE seems to be predictive of naming decline after ATL [90].

In a study by Binder *et al.*, preoperative language fMRI has been shown to be more useful than the Wada test for identifying patients at high risk for verbal memory decline prior to left anterior temporal lobectomy [91].

The link between neocortical language and temporo-mesial memory region has been explored with fMRI in children with left-sided focal

epilepsy and it has demonstrated that an atypical language lateralization is advantageous for verbal memory performance. In other words, verbal memory function in children with left-sided focal epilepsy provides a better idea of language lateralization than handedness and side of epilepsy [92].

Language fMRI activation may predict verbal memory outcome in left mesial TLE, the activation being greater in patients with severe verbal memory decline after surgery [93].

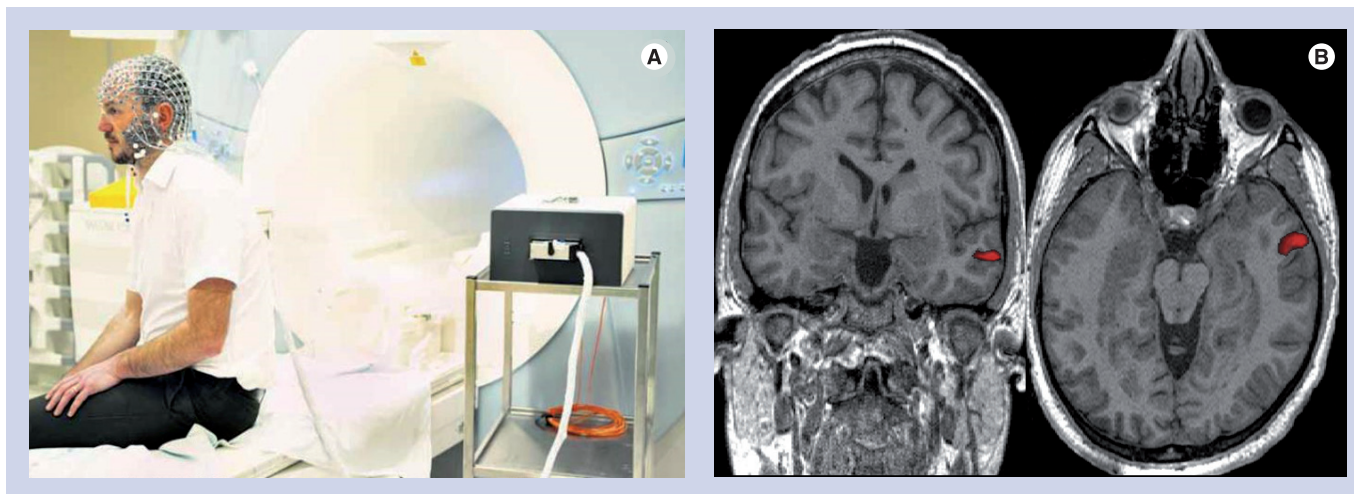
Limits exist for fMRI: variable paradigms used to explore a certain cerebral function, thresholds used to display data and spatial and temporal resolution limitation. Expertise both in neuropsychology and neuroradiology are therefore mandatory, especially in preoperative assessment of TLE and further validation with electrocorticography and postoperative follow-up is still needed.

### ■ Simultaneous EEG & fMRI

Simultaneous scalp EEG and fMRI maps hemo dynamic changes related to epileptic activity recorded on the EEG (FIGURE 3) [94]. The procedure is safe and the interaction between the EEG and fMRI equipment (artifacts) can be corrected to obtain data of high quality for analysis. The technique can provide a good spatial and temporal resolution of propagation pattern of epileptic activity [95–97] and could be useful in patients where clinical data, EEG and imaging are not concordant [98,99] and can provide further information on intracranial electrode placement [100,101]; sometimes EEG–fMRI studies of spike-correlated BOLD changes are inconclusive because of the absence of spikes during fMRI or the absence of significant spike-related BOLD changes.

Nevertheless, Grouiller *et al.* showed that it is possible to create an epilepsy-specific voltage map on a scalp EEG regardless of presence of discharges during simultaneous recording (correlating averaged interictal epileptiform discharges during long-term monitoring outside the MRI scanner with EEG recordings within the MRI scanner). This map was then correlated with BOLD hemodynamic changes in an fMRI (topography-related hemodynamic changes). The concordance between voltage changes and BOLD signals was better in patients with lateral temporal and extratemporal neocortical epilepsy compared with mesial/polar temporal epilepsy allowing good targeting for resection or implantation of intracranial electrodes [102].

In one patient suffering from a TLE, Vulliemoz *et al.* showed also a good correlation between interictal epileptiform discharges on intracranial EEG and hemodynamic changes on an fMRI



**Figure 3. EEG–functional MRI.** Simultaneous scalp EEG and functional MRI recordings can map hemodynamic changes correlated to epileptic activity recorded on the EEG. **(A)** MRI-compatible EEG system now allows us to record high-resolution EEG inside the scanner (up to 257 channels); **(B)** example of focal hemodynamic changes in patient with temporal lobe epilepsy. Courtesy of Dr F Grouiller (Department of Neurology, Geneva University Hospital, Geneva, Switzerland).

[103]. This first study on simultaneous intracranial EEG and fMRI in humans is conceptually important as it confirmed that the presence of local hemodynamic changes correlated with very focal epileptic activity.

A group has compared interictal epileptic discharge-related hemodynamic BOLD changes, intracranial recordings and postsurgical outcome in patients with focal epilepsy and focal cortical dysplasia and found fMRI–EEG to provide additional information about seizure onset zone location but that in more widespread distributed interictal epileptic discharge-related hemodynamic changes the seizure onset zone location value and postsurgical outcome were poor [104].

Recently some researchers focused their attention on the brain connectivity in TLE explored by fMRI during both cognitive tasks and resting state. Hippocampal connectivity measured by interictal resting state fMRI has been found to increase linearly after 10 years of TLE duration, maybe because of the contralateral hippocampus exerting more influence on the EZ on the contralateral side [105].

Other authors have studied the resting state functional connectivity in 22 MTS-TLE patients and showed that basal functional connectivity is increased in the nonepileptic side, which could be used as a localizer for the EZ [106]. The same authors quantified functional connectivity in the resting state by fMRI (which should reflect spontaneous neuronal activity) and made a correlation with intracranial EEG in five patients with TLE during the interictal period. Intracranial recordings found functional connectivity in regions affected by epileptiform activity (compared with

nonaffected zones), but BOLD signals showed the opposite pattern. To date, functional connectivity measurement by BOLD and iEEG does not give clinically useful information in TLE [107]. Results from functional connectivity studies during cognitive tasks are also inconclusive [11].

At the moment only a few small studies are available, understanding pathological brain networks requires replicable data and results must be assessed at the individual level to estimate any clinical benefit.

#### ■ PET

PET coupled to a CT or MRI allows assessment of cerebral metabolism or a certain chemical flux by using tracers labeled with a positron-emitting isotope. The most used tracer is FDG, which gives a good estimation of oxygen uptake and phosphorylation (usually but not always linearly related to brain oxygen utilization) FDG-PET is not readily available in many hospitals and it is mainly obtained during the interictal state; the hallmark of an interictal PET-CT for TLE (and other forms of focal epilepsy) is an area of hypometabolism that may involve more than the epileptogenic area (FIGURE 4B). It has been shown that the seizure onset better matches the margin of the hypometabolic area than the center [108]. PET-CT can be particularly useful for surgical planning of intracranial EEG in TLE patients with normal structural MRI and inconsistent video-EEG [109]. Furthermore, examining *a posteriori* the standard structural MRI in patients showing an area of hypometabolism on FDG-PET, can also reveal some structural abnormalities previously not seen [110].



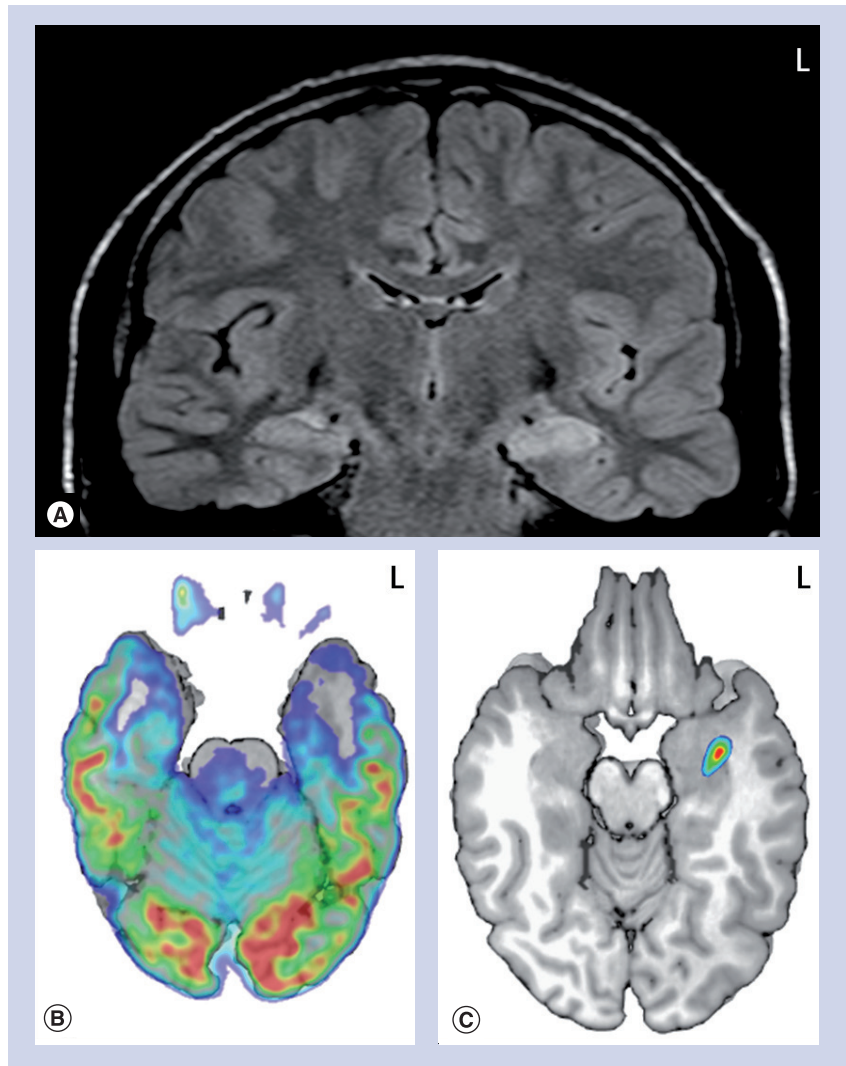
FDG-PET improves the detection of cortical abnormalities such as cortical dysplasia if coupled with MRI [111]. A hypometabolic area on FDG-PET correlates with a good-to-excellent outcome after resection surgery in TLE if it is ipsilateral to the lobe to resect [112]. Coregistration of FDG-PET and MRI is required to obtain a more precise spatial localization, and combined PET-MRI systems are promising advances in the field [113]. With regard to TLE, the extent of the resection of the hypometabolic area relates to the surgical outcome: the greater the extent of resection of hypometabolic area, the better the surgical outcome [114].

MRI-negative TLE patients also benefit from FDG-PET. Patients who were operated on on the basis of the PET without a visible lesion on a structural MRI had a similar outcome to patients with a lesion. There may be also a different pattern of hypometabolism between patients with MTS and patients without MTS on structural MRI: both MTS-positive and -negative patients had lateralized temporal hypometabolism compared with healthy control subjects, but in patients with MTS, hypometabolism was rather anteroinferomesial, while in patients without MTS the hypometabolism was seen more inferolaterally, thus probably involving the neocortical temporal cortex more [115–117].

Other tracers have been developed, such as  $^{11}\text{C}$ -flumazenil (theoretically binding the central benzodiazepine receptor) and  $^{11}\text{C}$ - $\alpha$ -methyl-L-tryptophan (AMT), in order to show cerebral abnormalities not visible on structural MRI, but their utility in clinical practice is not yet established [118,119].

A reduced level of GABA receptor binding has been demonstrated in the epileptic focus compared with the contralateral homotopic region and in the remaining neocortex [120]. Reduced binding of  $^{11}\text{C}$ -flumazenil has also been seen in frontal epilepsy patients [121]. In a study that compared  $^{11}\text{C}$ -flumazenil to FDG-PET in TLE patients, the first was found to have a more localized decreased density than the latter, being confined to the temporal lobe ipsilateral to EEG ictal onsets and not involving the extratemporal regions; true neuronal and synaptic loss and diaschisis can explain these differences in metabolic patterns between  $^{11}\text{C}$ -flumazenil and FDG [122].

Good concordance was found between HS on structural MRI and low  $^{11}\text{C}$ -flumazenil binding that was confined to the affected hippocampus [123]. Controversy still exists regarding the role of this tracer in the work-up of temporal and extratemporal epilepsy [124,125].



**Figure 4. PET-SPECT.** PET-SPECT in a 16-year-old male with left medial temporal dysplastic lesion and pharmaco-resistant epilepsy; **(A)** MRI fluid-attenuated inversion recovery showing hyperintense enlarged left medial temporal structures; **(B)** interictal FDG-PET showing left anterior medial hypometabolism; **(C)** statistical ictal SPECT coregistered to MRI showing left medial anterior focus. Courtesy of Dr L Spinelli (Department of Neurology, Geneva University Hospital, Geneva, Switzerland).

$^{11}\text{C}$ - $\alpha$ -methyl-L-tryptophan is a ligand that reflects the brain serotonin synthesis [126] and an increase of its uptake should indicate the epileptic focus, especially when more than one focus is present, such as in tuberous sclerosis [127]. High AMT uptake in epileptic foci seems to be related to the accumulation of convulsant metabolites in the kynurenine pathway of tryptophan metabolism, especially quinolinic acid [128,129].

In one recent study, increased AMT uptake predicted type IIB cortical dysplasia (with balloon cells) among children with intractable epilepsy and a good surgical outcome, but the subgroup of children with normal histopathology and increased uptake had poor surgical

outcome [130]. In another study, up to 25% of children with refractory focal epilepsy and normal structural MRI had an increased uptake in AMT-PET that correlated with epileptic focus [119].

AMT-PET sensitivity is almost 70% while its specificity is almost 100%, suggesting that a cerebral area uptaking AMT is most likely the epileptic focus that needs to be resected. AMT-PET's utility is limited as AMT is labeled with  $^{11}\text{C}$ , which has a half-life of only 20 min and has to be synthesized on site, in other words, restricted to selected centers [127].

### ■ SPECT

SPECT, with PET, is a noninvasive technique for functional imaging, which mainly assesses regional cerebral blood flow (cRBF) through tracer uptake ratios. The basic assumption in epilepsy evaluation is that the increased neuronal activity occurring during seizures is associated with increased cerebral metabolism, and thus with increased cRBF. To assess cRBF with SPECT, radiolabeled tracers such as iodine-123 and technetium-99 are available: the small molecular size and their lipophilicity allow tracers to rapidly cross the intact blood–brain barrier, to be distributed proportionally to blood flow and to be retained in the brain for enough time to permit image acquisition [131]. The most used tracers in epilepsy assessment are  $^{99\text{m}}\text{Tc}$ -hexamethylpropylamine-oxime and  $^{99\text{m}}\text{Tc}$ -ethyl-cysteinate-dimer, reaching peak uptake in the brain within 2 min after injection and fixing to brain tissue for 2–4 h without redistribution.

Several studies demonstrated the superiority of ictal SPECT to interictal SPECT, particularly in patients with TLE, to localize or lateralize the epileptic focus [132–134]. However, one of the main limits of ictal SPECT is the poor temporal resolution, which may detect not only the EZ but also the propagation pattern (which is not necessarily removed surgically) even if the tracer is injected immediately [135,136].

Even though its results may indicate the EZ to resect, SPECT is also used for surgical planning of intracerebral electrode placement and to inform on the possible secondary spread of ictal activity [137].

Interictal SPECT localizes or lateralizes the EZ in <50% and today is used only in combination with ictal SPECT (comparison of ictal and interictal SPECT) and MRI (then also known as subtraction ictal single-photon emission CT coregistered to MRI [SISCOM]; FIGURE 4C).

This approach has been proven to be superior to visual assessment only, especially in patients with normal structural MRI and discordant video-EEG [138–141].

SISCOM abnormality localized to the resection site has prognostic value given that it is associated to Engel class I outcome (free of disabling seizure) in patients with nonlesional TLE undergoing anterior temporal lobectomy [142]. Other predictors of Engel class I outcome in this study were the absence of contralateral or extratemporal interictal epileptiform discharges and subtle nonspecific MRI findings in the mesial temporal lobe. Repeated ictal SPECT with SISCOM analysis is helpful for localizing the EZ in patients with partial epilepsy who had a nonlocalized first ictal SPECT; the localizability of ictal SPECT depends on an early injection and a localizing ictal EEG pattern at the time of injection [143].

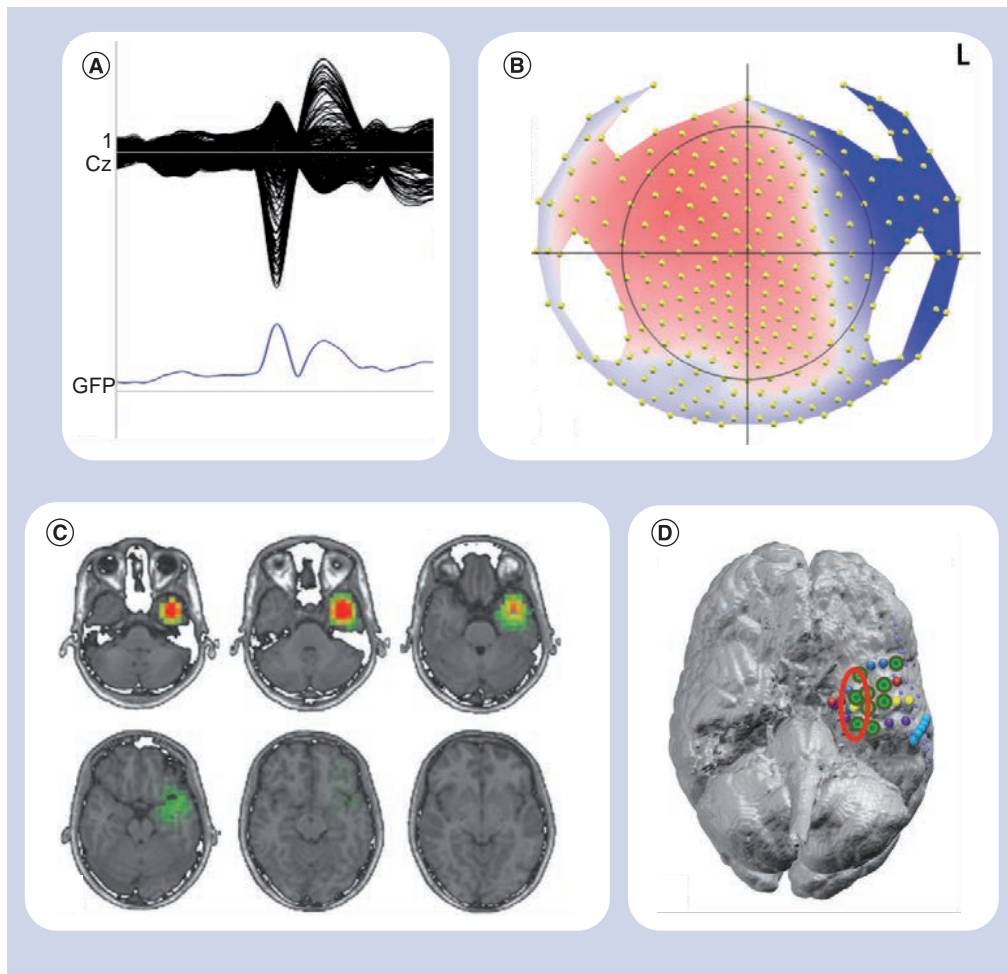
Localizing value and prognostic value (in terms of postsurgical seizure freedom) of SPECT studies has been demonstrated by a statistical analysis that also included subjects without epilepsy (statistical ictal SPECT coregistered to MRI) to determine whether the ictal-interictal subtraction difference (SISCOM) is statistically different from the expected random variation between two SPECT studies [144].

Multimodal coregistration (MRI, FDG-PET or ictal/interictal SPECT) in pediatric pharmacoresistant epilepsy (both extratemporal and temporal) significantly improves focus localization. The surgical outcome was always almost excellent if all localizing techniques showed concordant results [145].

### ■ Electric source imaging

Electric source imaging (ESI) is an emerging technique that allows determination of the locations of current sources in the brain, based on EEG recordings. In epilepsy presurgical work-up ESI provides 3D images of the source, and thus localizes precisely an EZ in particular when performed with a high number of channels and coupled with the patient's MRI (FIGURE 5).

This has recently been shown by Brodbeck *et al.* in a prospective study including 152 patients with refractory epilepsy (temporal and extratemporal) where the 'standard' presurgical work-up (MRI, PET and SPECT) was compared with ESI obtained from high-resolution EEG (128–256 channels) and coregistered with the individual MRI or a template head model. Sensitivity and specificity of ESI was reported as 84 and 88%, respectively, globally



**Figure 5. Electric source imaging.** Electric source imaging of an 18-year-old male with cryptogenic pharmacoresistant complex partial seizures. **(A)** High-resolution EEG (257 channels): average of left inferior temporal spikes; **(B)** scalp voltage map showing left temporal negativity; **(C)** inverse solution showing left basal anterior temporal source; **(D)** subdural EEG recording confirming a left anterior basal irritative zone with basal medial seizure onset zone.

superior or equal to structural MRI, PET and ictal/interictal SPECT. Its sensitivity and specificity decreased in patients that were explored with low-resolution ESI (less than 32 channels) and/or with a template head model. No major differences were observed between patients with TLE and those with extratemporal epilepsy undergoing high-resolution EEG/individual MRI ESI, suggesting that this tool can be used in all groups of patients with focal drug-resistant epilepsy [146]. Moreover, nonlesional (temporal- and extratemporal lobe) foci are correctly localized with ESI, as well as those symptomatic of large lesions with heterogenous tissue composition [147,148]. Despite being less widespread than its magnetoencephalography (MEG) source localization counterpart, and extensively validated mostly by one group, this technique has very interesting perspectives in presurgical epilepsy monitoring as it can be carried out at

the bedside, with current equipment development allowing high-density long-term recordings. In addition, EEG, contrary to MEG, can be recorded simultaneously to fMRI, and is therefore a more versatile tool for multimodal imaging.

#### ■ Magnetic source imaging

MEG is another noninvasive method based on neurophysiological signals to study focal epilepsy [149,150]. MEG maps mainly allow visualization of interictal activity from the neocortical areas close to the sensor and are supposedly less sensitive to deep sources, such as mesial temporal and frontal sources, but this is still debated. However, owing to the physics of magnetic currents, MEG does not 'see' radial dipoles as they are found in cortical gyri. MEG, like EEG, can distinguish the EZ from propagation sites, owing to its excellent temporal resolution,

and help to accurately position intracranial electrodes [151].

In selected cases, MEG can give additional information for intracranial electrodes placements. In a recent study, a few patients (18 out of 77) had additional intracranial electrodes following MEG data and seven of these 18 patients had their EZ detected by electrodes placed thanks to the MEG data [152].

Studies have recently compared the predictive value of the association of FDG-PET, ictal SPECT and magnetic source imaging to intracranial EEG and surgical outcome. Magnetic source imaging showed correlation with intracranial EEG as for localization of epileptic focus, but both PET and ictal SPECT had an additional value for localization: similar to other coregistration studies, there was larger likelihood to benefit from surgery, if all three modalities were concordant [153,154].

### Conclusion

The presurgical epilepsy work-up requires a multidisciplinary consensus for defining the EZ localization and tailoring surgical resection in well-selected patients. This consensus comes from a variety of clinical, electrophysiological and imaging data.

MRI-based techniques and nuclear imaging have revolutionized the TLE epilepsy surgery,

allowing better identification of surgical candidates. Advanced neurophysiological methods, such as ESI, EEG-fMRI and MEG, have been found useful for the precise localization of the epileptogenic focus in a number of studies. In recent years, tractography has been introduced and used to map optic pathways to predict visual field defects in TLE surgery. Coregistration allows the fusion of multimodal information (PET, ictal SPECT, MEG or ESI in the patient's brain) and if all examinations agree, there is a significant chance of postoperative seizure control.

Intracranial EEG evaluation needs to be considered nowadays only in those cases where the side or extent of the EZ is unclear or if its proximity to eloquent cortex cannot be determined by noninvasive methods. Given the availability of these tools, good-to-excellent surgical outcome at 5–10 years is also possible in patients without MRI lesions [155].

### Future perspective

The next important steps should be the improvement of existing imaging technologies, such as increasing the spatial resolution, reliable integration of all structural and functional data (both for presurgical decision-making and for image-guided surgery) based on validated algorithms and the development of uniform

#### Executive summary

- High-definition imaging using a large array of imaging techniques is an integral part of comprehensive evaluation for surgical epilepsy candidates.
- Standard structural MRI (1.5- and 3-T) plays a central role in defining morphologic abnormalities in temporal lobes and, with the clinical and electrophysiological data, in candidacy to resective surgery.
- Patients with pharmaco-resistant epilepsy should also be evaluated for surgery when the standard structural MRI is normal. Depending on the results of the more advanced MRI-based studies and of the non-MRI techniques, the chances of postoperative seizure control can be as high as in lesional cases.
- In particular, all structural MRI-based advanced studies that have been considered in this review (manual and automatic volumetric studies, diffusion studies, relaxometry and spectroscopy) are promising developments but are currently not routinely used in epilepsy surgery centers, as their added value needs further validation and harmonized methodological guidelines. They can give additional useful information when standard structural MRI does not show lesions within the temporal lobe in localizing and lateralizing the epileptogenic zone, and therefore can guide intracranial electrode placement, always taking into account all clinical and electrophysiological data.
- Functional imaging, (i.e., PET, ictal SPECT, functional MRI, EEG-functional MRI, electric source imaging or magnetic source imaging) is a valuable addition, and if consistent with EEG and MRI data, the chance of benefitting from surgery is very high.
- Interictal PET-CT and SPECT techniques help to localize the epileptogenic zone and can guide the intracranial electrode placement. It should be a part of the standard presurgical work-up, especially in temporal lobe epilepsy (TLE) patients with normal structural MRI and inconsistent video-EEG. PET or SISCO abnormalities colocalized with the resection site are associated with Engel class I outcome in patients with nonlesional TLE undergoing anterior temporal lobectomy.
- fMRI is a valuable technique to map eloquent functions and in TLE patients it plays a role mainly in mapping the language before resective surgery and in some centers it has replaced the Wada test. It can also be used in the surgical planning for intracranial EEG recordings. Paradigms used to explore eloquent functions and thresholds used to display data are its main limitations.
- Electric source imaging, magnetic source imaging and EEG-fMRI are emerging and promising techniques for localizing the epileptogenic zone. They are not widely used for routine presurgical evaluation of epilepsy but increasing invasive validating studies support their clinical usefulness.



guidelines to facilitate application, comparison across centers and the ongoing evaluation of clinical yield.

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