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Role of Neuroimaging in the Presurgical Evaluation of Epilepsy

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A significant minority of patients with focal epilepsy are candidates for resective epilepsy surgery. Structural and functional neuroimaging plays an important role in the presurgical evaluation of theses patients. The most frequent etiologies of pharmacoresistant epilepsy in the adult population are mesial temporal sclerosis, malformations of cortical development, cavernous angiomas, and low-grade neoplasms. High-resolution multiplanar magnetic resonance imaging (MRI) with sequences providing T1 and T2 contrast is the initial imaging study of choice to detect these epileptogenic lesions. The epilepsy MRI protocol can be individually tailored when considering the patient's clinical and electrophysiological data. Metabolic imaging techniques such as positron emission tomography (PET) and single photon emission tomography (SPECT) visualize metabolic alterations of the brain in the ictal and interictal states. These techniques may have localizing value in patients with a normal MRI scan. Functional MRI is helpful in non-invasively identifying areas of eloquent cortex.

Developments in imaging technology and digital postprocessing may increase the yield for imaging studies to detect the epileptogenic lesion and to characterize its connectivity within the epileptic brain.

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INTRODUCTION

About one sixth of patients with focal epilepsy are resistant to current antiepileptic medications.[1] Resective epilepsy surgery has the potential to render many of these patients seizure free.[2,3] Advances in brain imaging have considerably changed the clinical approach to the patient with epilepsy. In this review, we describe the current role of structural and functional brain imaging modalities in the presurgical evaluation of patients with pharmacoresistant epilepsy. We will focus on the main pathologies found in adult epilepsy patients. The role of neuroimaging in the surgical treatment of pediatric epilepsy has been recently reviewed.[4]

Structural neuroimaging in the presurgical evaluation of epilepsy fulfills several purposes:

Demonstrating a structural brain lesion in a patient with seizures implies a poor chance of achieving seizure freedom with antiepileptic medications alone.[5-7] On the other hand, it has been consistently shown that the chance of seizure freedom after epilepsy surgery is higher in patients with a focal lesion on MRI, both in temporal and frontal lobe epilepsy.[8,9] An epileptogenic lesion is defined as a structural radiographic abnormality that is thought to be the cause of the patient's epilepsy.

It is important to characterize a structural lesion in the brain of a patient with epilepsy, because the

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spatial relation of the lesion to the epileptogenic zone varies according to the nature of the epileptogenic lesion. The epileptogenic zone is defined as the area of brain tissue indispensable for the generation of seizures. Its removal consequently leads to seizure freedom. The epileptogenic zone is a theoretical construct; it cannot be directly visualized with current diagnostic modalities.[1]

Hippocampal sclerosis and cavernous angioma are examples of epileptogenic lesions whose location and extend overlap to a high degree with the epileptogenic zone. Consequently, removal of the MRI abnormality (lesionectomy including the immediate margins of brain tissue surrounding the lesion) leads to seizure freedom in a high percentage of patients. The epileptogenic lesion itself may or may not have intrinsic epileptogenicity. Most brain tumors, for example, may cause epileptic seizures by mass effect and consequent "irritation" of the cerebral cortex in their proximity (for a review of mechanisms, see[10]) Again, removal of the lesion also renders most of these patients seizure free.

In the presence of focal cortical dysplasia, however, removal of the visible lesion alone frequently does not lead to seizure freedom, implicating that the epileptogenic zone extends beyond what can be visualized with current structural imaging modalities.

STRUCTURAL NEUROIMAGING

Computer tomography (CT) and magnetic resonance imaging (MRI) are used to detect and characterize structural brain abnormalities.

The role of CT in the presurgical evaluation is very limited because the sensitivity and specificity of MRI for almost all pathological substrates found in patients with intractable epilepsy is far superior. Nonetheless, CT is the imaging modality of choice in the emergency room evaluation of a patient presenting with a first seizure and an abnormal neurological examination.[11] However, the diagnostic yield of CT is minimal if the patient is neurologically intact.[12] In the presurgical evaluation, CT used to be superior to MRI in demonstrating calcifications in certain pathologies, such as oligodendrogliomas or tuberous sclerosis. Furthermore, some patients that may be surgical candidates have contraindications to MRI (e. g. cardiac pacemaker). In these patients, CT may be useful to demonstrate gross brain pathology. Following placement of subdural grid or depth electrodes, high resolution CT is employed at some epilepsy centers to identify the position of electrodes by fusion of a pre-surgical MRI and the postsurgical CT scan. For the reasons stated above, MRI is the cornerstone imaging modality in patients with epilepsy. The International League against Epilepsy (ILAE) recommends MRI for every patient, unless the patient suffers from generalized, idiopathic epilepsy beyond reasonable doubt, based on history, seizure semiology, physical and neurological examination, and EEG.[13] Given the advances in MRI over the last two decades, other imaging modalities need to be scrutinized for their incremental benefit.

Brain lesions associated with pharmacoresistant epilepsy may be subtle and thus frequently require special expertise for their detection and correct characterization. Various MRI protocols have been suggested in the evaluation of candidates for epilepsy surgery. Key elements of such a protocol include sequences that provide T1 and T2 contrast (T2, T2*, FLAIR) in three dimensions, with slices as thin as possible.[14] 1-2 mm coronal MPRAGE slices (which provide T1 contrast) are typically used to evaluate the temporal lobe, whereas axial slices are obtained if extratemporal epilepsy is suspected. Gradient-echo sequences are used to demonstrate calcifications, in particular in the setting of cavernous angiomas. The use of gadolinium is indicated if a tumor or an inflammatory lesion is suspected.

The superiority of a dedicated epilepsy MRI protocol over nonspecific brain MRI studies in detecting epileptogenic lesions has been demonstrated.[15]

Information derived from the patient's history and video-EEG monitoring is often used in the interpretation of imaging studies, and this information may be used to modify the MRI protocol, for example to provide thin cuts through the suspected

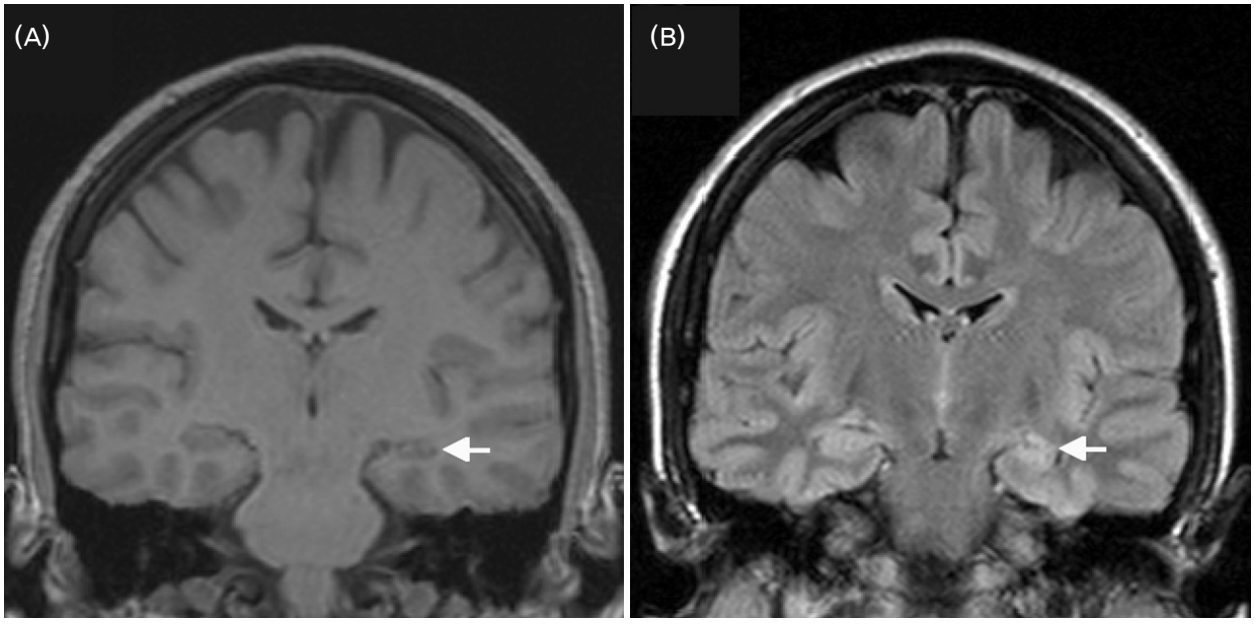

Figure 1. Left hippocampal sclerosis. The hippocampal formation is significantly smaller on the left (arrow) compared to the right on coronal T1 (A). Coronal FLAIR demonstrates subtle hyperintensity within the hippocampus on the left (arrow, B).

lobe of origin.

Increasing the static magnetic field strength to 3 Tesla and using a specific phased-array head coil further increases the yield for an MRI abnormality in the presurgical epilepsy evaluation.[16] These technical modifications revealed additional diagnostic information in 48% of patients (n=40) compared to MRI performed at 1.5 T, including the detection of a lesion in 65% of those patients (n=23) whose MRI had been considered normal at 1.5 T.

We will now discuss imaging features of the main brain lesions associated with intractable epilepsy in adult patients.

HIPPOCAMPAL SCLEROSIS

Most focal epilepsies arise from the temporal lobe, and within these, hippocampal sclerosis (HS) is the most common underlying pathological substrate. The mesial temporal structures should be carefully evaluated in every patient with focal epilepsy, since dual pathology may be present in patients whose seizure are suspected to arise from the neocortical temporal lobe or from elsewhere.[17] Classic findings of HS are atrophy of the mesial temporal structures with increased signal on T2 weighted or FLAIR images.[18] These are easiest appreciated when comparing both sides within the same subject (Fig. 1).

Several variations in hippocampal shape have been described in association with HS, such as loss of interdigitations in the hippocampal head,[19] enlargement of the CSF space in the temporal horn of the lateral ventricle, and a tilt of the hippocampal formation from the horizontal towards an oblique or even vertical plane. The impact of these abnormalities on prognosis for surgical treatment is unknown.[20]

An experienced clinician can detect hippocampal sclerosis in up to 90% of cases.[5] However, a minority of patients with mesial temporal lobe epilepsy does not demonstrate findings of HS on MRI, and some of these may have bitemporal abnormalities. This problem led to the development of quantitative analysis of hippocampal volumes and T2 relaxation times, techniques that are routinely employed only in selected epilepsy centers.

Manual or semiautomatic hippocampal volumetry is a labor intensive procedure that requires considerable experience and only marginally increases the yield of MRI for mesial temporal lobe atrophy. Hippocampal

volumes need to be corrected for hemispheric or intracranial volume and compared to a control group matched for age, sex and handedness. Nonetheless, hippocampal volumetry remains an important research tool in the radiographic study of mesial temporal lobe epilepsy, as it allows the quantification of asymmetry and the longitudinal study of hippocampal sclerosis.[21,22]

Marked elevations in hippocampal T2 relaxation time have been associated with HS, whereas intermediate values have been found in hippocampi without the characteristic imaging findings of HS, as well as in the contralateral hippocampus or in hippocampi of patients with extratemporal epilepsy.[23] Advances in MRI technology allow measuring T2 relaxation times of several hippocampal slices in a few minutes.[24] Due to the proximity of the temporal horn of the lateral ventricle, CSF may be included in the sample, introducing a source of error.

Diffusion weighted imaging (DWI) and diffusion tensor imaging (DTI) measure the molecular motion of water within brain tissue. Diffusivity and anisotropy reflect the amplitude and directionality of the molecular motion and can be calculated from the DTI sequence. In the physiologic state, the diffusion of water is restricted by cell membranes. In the white matter, the water diffusion is typically highly anisotropic; this used in the reconstruction of white matter tracts using tractography. This technique may be helpful in the exploration of functional connectivity of a given cortical area, as well as in describing the spatial relationship of a lesion and important white matter tracts. It has been reported that this information can help in the planning of resective epilepsy surgery in order to reduce morbidity.[25]

Measuring diffusivity alone takes little additional scanning time, making its addition to a routine epilepsy protocol MRI feasible. However, alterations in diffusivity are not necessarily appreciated on visual inspection and frequently require postprocessing of the scan. As with other imaging modalities, the majority of reported data refer to patients with TLE. Ictally or immediately postictal, the hippocampal formation ipsilateral to the epileptogenic zone may demonstrate decreased diffusivity, likely reflecting cytotoxic edema.[26] Interictally, mesial temporal diffusivity may be increased. These changes may reflect alterations in the histoarchitecture of the mesial structures. The data regarding interictal diffusivity in the contralateral mesial temporal lobe are equivocal, with some studies finding decreased diffusivity, whereas others reporting values not significantly different from normal controls.[27] A recent study showed that interictal DWI in patients with TLE and a normal or non-lateralizing MRI had no incremental benefit in the presurgical evaluation.[28]

MALFORMATIONS OF CORTICAL DEVELOPMENT (MCD, Fig. 2)

This term comprises a spectrum of disorders that share a common pathogenesis. They track back to the development of the central nervous system in utero. On the one extreme of this spectrum, hemimegencephaly is a rare malformation that affects an entire hemisphere. Imaging characteristics are abnormal gyration, thickened cortex, loss of gray-white matter differentiation, and signal changes on T2-weighted images.[29] Hemimegencephaly typically presents with intractable epilepsy in early childhood. Hemispherectomy is the surgical treatment of choice. The contralateral hemisphere usually appears normal on imaging; however this does not exclude the possibility of additional pathology, which may be epileptogenic as well.[30]

Polymicrogyria, schizencephaly and lissencephaly are further forms of MCD characterized by abnormal gyration patterns. In polymicrogyria, there are too many small gyri separated by shallow sulci. In schizencephaly, an abnormal cleft is lined by polymicrogyric cortex. Lissencephaly is characterized by the absence of gyri. In addition to the abnormal gyration patterns, MRI may demonstrate blurring of the grey-white junction and cortical signal abnormalities.[31]

The few available data on patients with these forms of MCD who underwent epilepsy surgery suggest that the relationship of the anatomical lesion to the epileptogenic zone is complex. The visible structural abnormality does not necessarily contain

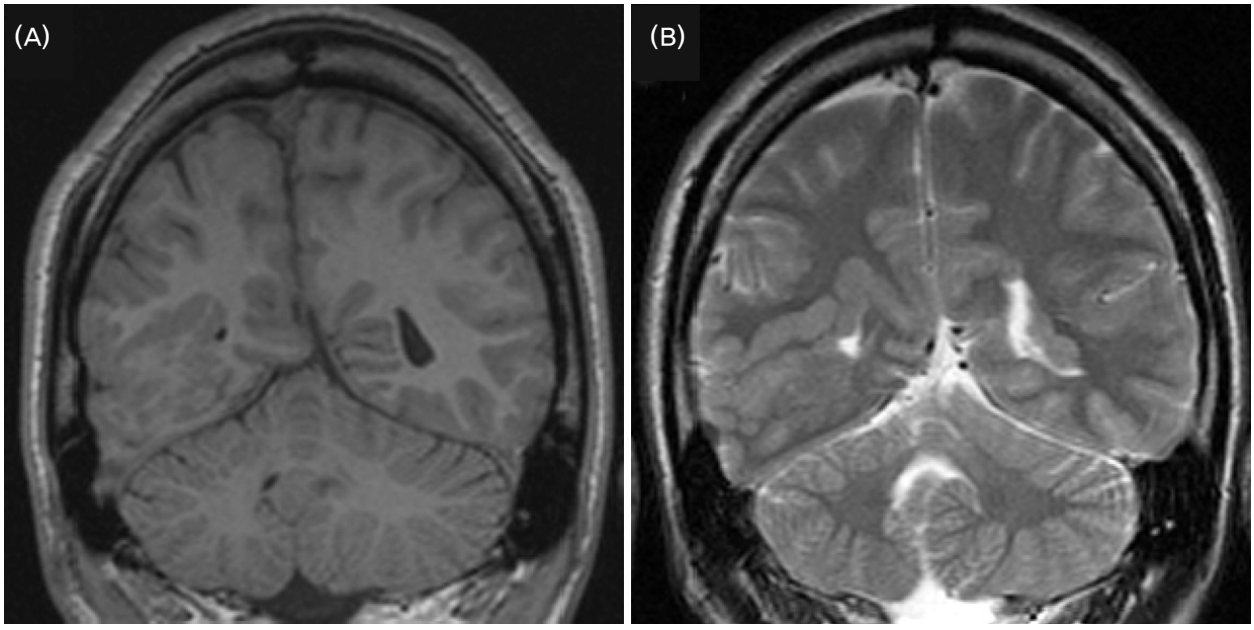

Figure 2. Malformation of cortical development in the right occipital lobe. Coronal T1 (A) shows abnormally configured cortex. Note the mass effect on the occipital horn of the lateral ventricle. On coronal T2, the heterotopic cortex is more clearly appreciated (B).

the epileptogenic zone, which may occupy cortex that appears intact on MRI.[32] Epilepsy surgery for these patients is further complicated by the fact that anatomically abnormal areas may support cognitive or motor functions.[33]

The same principle applies to subcortical heterotopias (SH) and periventricular nodular heterotopias (PNH). These are more subtle forms of MCD, characterized by the abnormal presence of gray matter in the white matter. Their intrinsic epileptogenicity has been demonstrated using intracranial electrophysiological monitoring in humans.[32] In one recent series, all seven patients with unilateral nodular heterotopia who achieved good outcome after epilepsy surgery had further ipsilateral MRI abnormalities (at least abnormal gyration patterns), and all were found to have architectural dysplasia or gliosis in the overlying cortex. Using stereo EEG, the authors found that the ictal onset never localized to the area of heterotopia alone, but always also involved overlying cortex. Thus, NH likely indicates a more widespread failure of brain development.[34]

Focal cortical dysplasia (FCD) accounts for the majority of patients with MCD in surgical series,[32] and a significant proportion of patients with intractable focal epilepsy whose MRI is normal turn out to have focal cortical dysplasia.[35,36] On T1 weighted images, FCD is characterized by a circumscribed change in the thickness of the cortical mantle, blurring of the grey-white junction, and hyperintense signal relative to the normal cortex.[37] Two out of three of these characteristics were found in all FCD lesions and all three were found in 79%, irrespective of the size of the lesion, which varied by a factor of more than one hundred.[38] On FLAIR or T2, there may be associated radial hyperintensity in the white matter underlying the FCD, which mirrors the migration of cortical neurons during the development of the brain from the subependymal zone to the cortex.[36] An expert panel recently proposed a classification of FCD into two types with two subtypes each, based on the presence of changes in the cortical architecture and the presence of dysplastic neurons, giant neurons, or balloon cells on histopathology. According to this classification, FCD type I is characterized by the absence of dysmorphic neurons or balloon cells and

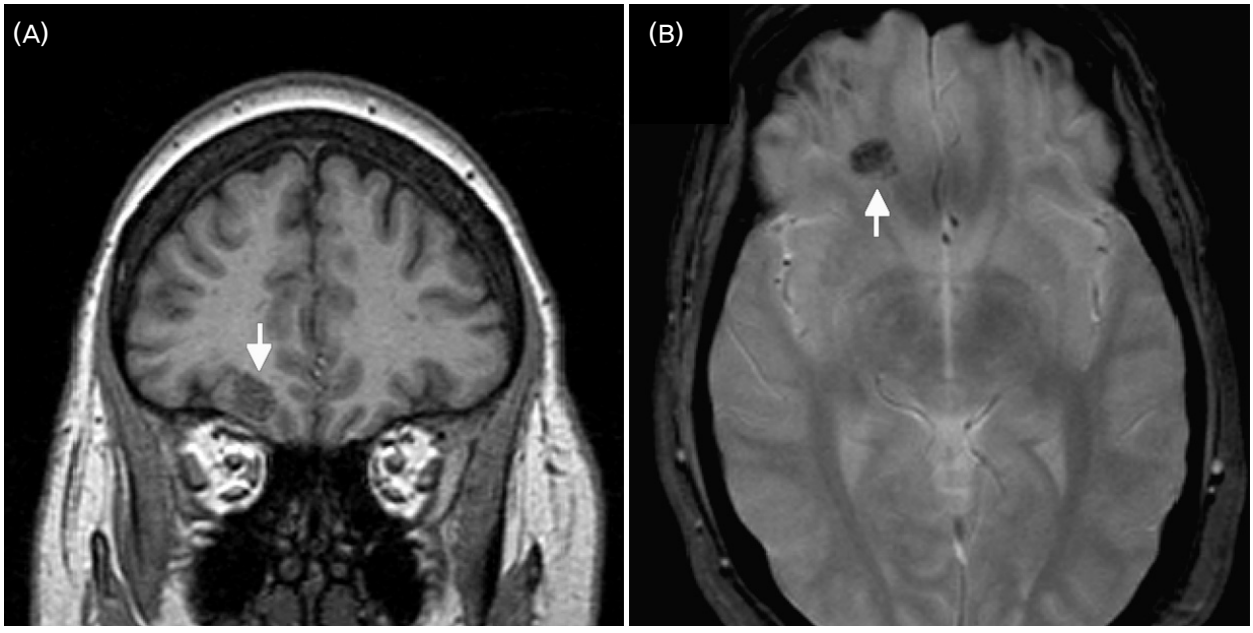

Figure 3. Cavernous angioma in the right frontal lobe. Coronal T1 shows an area of mixed signal intensity involving the orbitofrontal cortex (arrow, A). Axial gradient echo reveals a corresponding area of low signal intensity (arrow, B).

divided into type IA (isolated architectural abnormalities) and type IB (architectural abnormalities plus giant or immature, but not dysmorphic neurons). Type II refers to Taylor-type FCD, defined by architectural abnormalities and the presence of dysmorphic neurons without (type IIA) or with (type IIB) balloon cells.[39] One recent surgical series of patients with intractable epilepsy with pathologically proven focal cortical dysplasia correlated MRI findings with the above described histopathological classification.[40] MRI criteria for Taylor-type FCD were the combination of (1) focal areas of increased cortical thickening, (2) blurring of the cortical grey/white matter junction, and (3) marked hyperintensity of the subcortical white matter on T2-weighted images. MRI criteria for Non-Taylor type FCD were one of the above findings in isolation, or focal brain hypoplasia, moderate white matter signal abnormalities, or white matter core atrophy. Only 59% of patients with FCD type I had MRI abnormalities. Of these, 20% met all MRI criteria for Taylor-type FCD, whereas the findings were more subtle in nature in 80%. Two thirds of patients with histopathologically established FCD type II had MRI abnormalities, 90% of which met all MRI criteria for Taylor-type FCD. While these data suggest that MRI can differentiate between FCD type I and II, they also highlight that current MRI is only moderately sensitive to detect focal cortical dysplasia, since 41% of patients with FCD type I and 33% of patients with FCD type II had no MRI abnormality (40) In another series from the Cleveland Clinic, 31% of patients with FCD type I and 21% of patients with FCD type II had no focal MRI findings.[41]

One study addressed the relationship of epileptogenicity and language or motor function with MRI appearance and findings on histopathology in patients with FCD.[42] Using extraoperative recordings from implanted subdural electrodes, the authors found no epileptogenicity and no motor or language function in cortical areas that contained balloon cells (type IIb in the above classification), all of which had increased signal on FLAIR. Epileptogenicity was found adjacent to areas containing balloon cells. A similar relationship has been described for low grade gliomas.[42]

Several strategies have been suggested to increase the ability of MRI to detect subtle areas of MCD. 3T static magnetic field and phase-array head coils have been shown to increase the yield in particular for

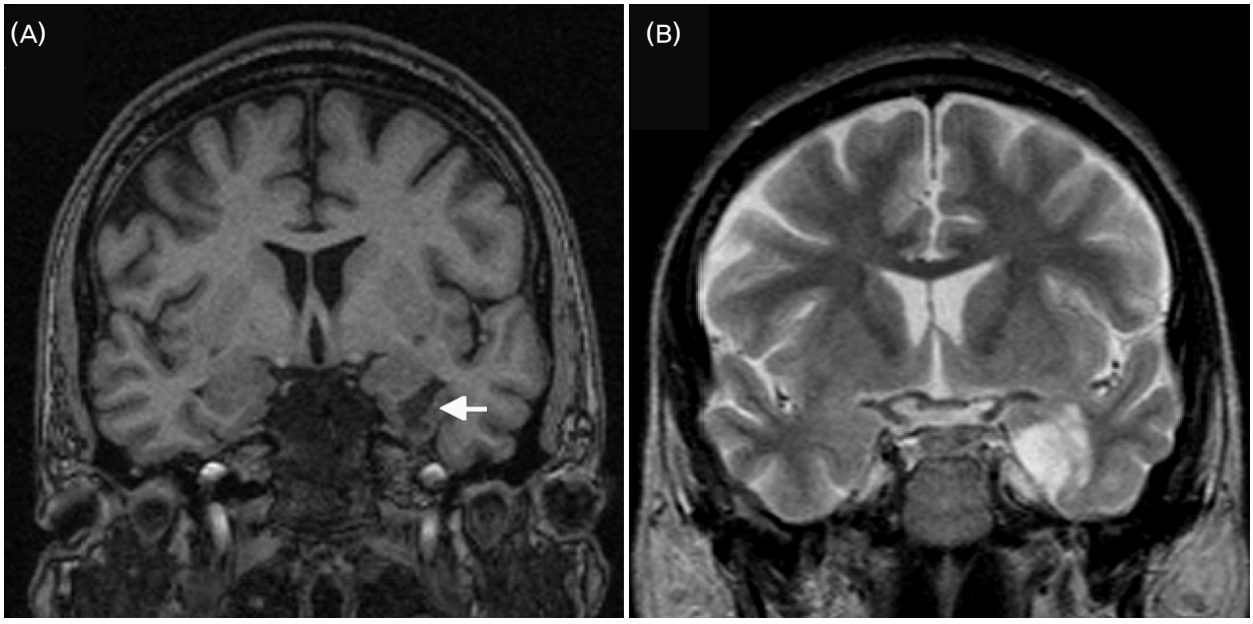

Figure 4. Dysembryoplastic neuroepithelial tumor (DNET) in the left mesial temporal lobe. Coronal T1 shows a mass with relatively homogenous hypointense signal (arrow, A). Coronal T2 reveals a more extensive area of hyperintense signal (B).

focal cortical dysplasia in patients whose MRI was considered normal at 1.5T.[16] Adjusting the epilepsy MRI protocol according to data gathered from the video-EEG evaluation, such as seizure semiology and interictal or ictal EEG activity may increase the sensitivity of MRI to detect areas of FCD in the hands of an experienced reader in patients who are considered non-lesional even on dedicated epilepsy protocol studies.[36] Besides, there is evidence that MRI postprocessing methods may increase the sensitivity to detect subtle areas of FCD by up to 30%.[43]

CAVERNOUS ANGIOMAS

Cavernous angiomas are the most frequent form of vascular malformation to cause seizures. They are benign vascular lesions with thin-walled endothelial-lined spaces that contain hemorrhage products in different stages of evolution, but no normal brain tissue. On MRI, they have a characteristic “popcorn” appearance with a core of mixed signal intensities, reflecting various stages of blood degradation, and a hypointense rim, reflecting hemosiderin deposition (Fig. 3). Gradient echo sequences increase the sensitivity of MRI by demonstrating punctuate microhemorrhages that may not be detected on other sequences.[44] The hemorrhages associated with cavernous angiomas are considered a major factor in their epileptogenicity. The rates of seizure freedom after surgery are better when the hemosiderin-stained tissue has been removed as opposed to surgeries that remove only the cavernous angioma.[45] In the setting of a single cavernous angioma and consistent electro-clinical seizures, further testing is not required; even pure lesionectomy (without removal of associated hemosiderin-stained cortical tissue) achieved seizure-freedom in two-thirds of patients follow up for a mean of four years.[46] The results of surgery regarding seizure control in patients with cavernous angiomas is greatly influenced by the duration of the seizure disorder, i.e. patients who have a long history of uncontrolled epileptic seizures frequently can not be controlled by a simple lesionectomy. These patients frequently require a more detailed work-up and a more extensive surgery to achieve seizure freedom.[47-49]

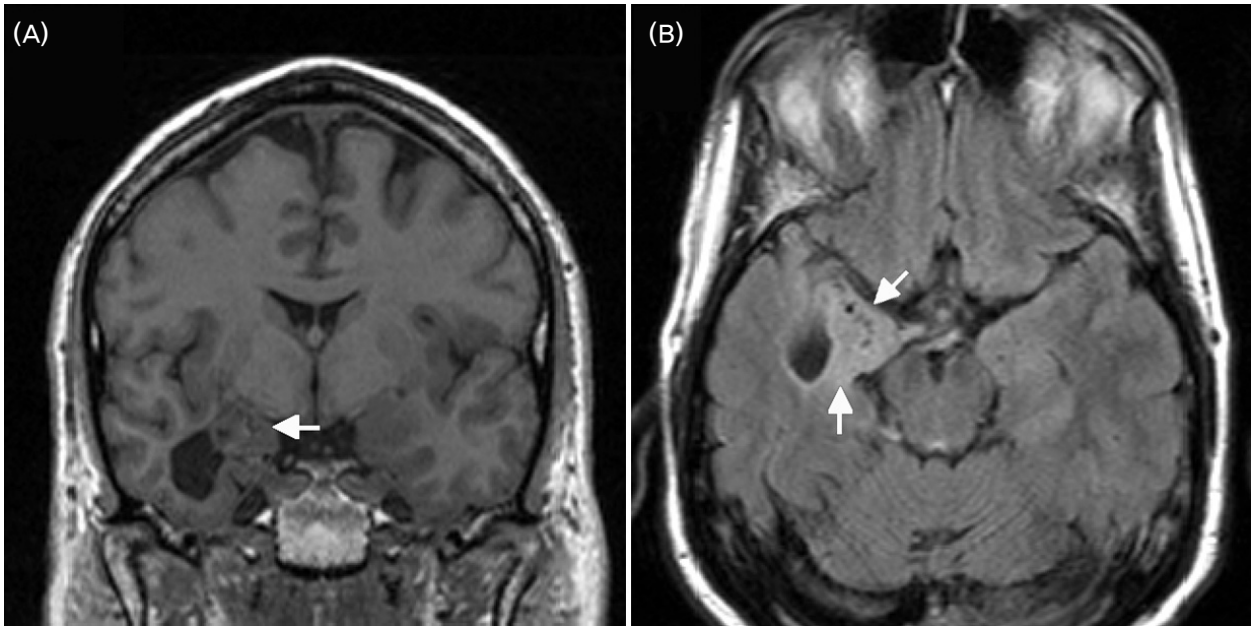

Figure 5. Ganglioglioma in the right mesial temporal lobe. Coronal T1 reveals mixed signal intensity in the right hippocampal formation (arrow, A) and a cystic-appearing structure of hypointense signal extending into the right temporal white matter. Axial FLAIR demonstrates more widespread hyperintensity in the right mesial temporal structures (arrows, B).

BENIGN BRAIN TUMORS ASSOCIATED WITH EPILEPSY

Dysembryoplastic neuroepithelial tumors (DNETs) and gangliogliomas are low grade developmental brain tumors found in about 20% of patients who underwent surgery for pharmacoresistant focal epilepsy. They are classified as benign because they exert no mass effect and, in general, have stable appearance on serial imaging. Nonetheless, removal of the lesion is necessary to achieve seizure freedom and a definite diagnosis. Both DNET and gangliogliomas are characterized by iso- or hypointense signal on T1 weighted images and hyperintensities on T2-weighted images (Fig. 4, 5). They both do not respect the grey-white matter junction, and both may have variable degree of enhancement after administration of contrast enhancement. For these reasons, they cannot be reliably differentiated from each other and from other forms of low grade gliomas using current MRI techniques.[4] However, there are reports that PET (discussed in more detail below) can differentiate them. DNETs had low uptake on 11-C-Methionine PET, a finding that differentiates them from gangliogliomas or gliomas.[50,51] 11-C-Flumazenil PET also showed hypometabolism in five patients with DNET, compared to controls.[52] DNETs and gangliogliomas may be associated with areas of epileptogenic FCD, which may be difficult to demonstrate on MRI.[5,53,54] Ictal SPECT (also discussed below) may be helpful in this situation. In one study, areas of hyperperfusion were restricted to the anatomical location of the DNET in cases without associated FCD, whereas areas of hyperperfusion were more widespread in patients with associated CD.[55]

DUAL PATHOLOGY

Dual pathology refers to patients who have two (or more) distinct lesions on MRI, classically the combination of HS with another epileptogenic lesion. Dual pathology may imply two different epileptogenic lesions, a scenario in which the term “double pathology” has also been used. Dual pathology may, however, also reflect two different manifestations of one underlying epileptogenic process. In particular,

the presence of hippocampal sclerosis might be a consequence of long-lasting epilepsy rather than its cause. The most frequent clinical scenario is the coexistence of HS with a malformation of cortical development, most commonly focal cortical dysplasia.[56] In one recent epilepsy surgery series of 67 patients with focal cortical dysplasia, 43% had additional ipsilateral mesial temporal sclerosis.[57] Interestingly, the vast majority of patients with dual pathology (93%) had FCD type I. Given the high rate of dual pathology in patients with FCD, it is imperative to look for MRI features of hippocampal sclerosis in every epilepsy patient who is considered for resective epilepsy surgery.[17] As noted above, both DNET and low grade gliomas may also be associated with areas of FCD.

IMAGING POSTPROCESSING METHODS

Another approach to increase the sensitivity of MRI is the use of post-acquisition digital processing methods such as texture analysis,[58] or statistic parametrical mapping (SPM) and voxel based morphometry (VBM). SPM and VBM compare brain scans on a voxel-by-voxel basis.[59] VBM was validated against manual volumetric analysis.[60] Patients with TLE and unilateral hippocampal atrophy were found to have structural brain abnormalities extending beyond the hippocampus, involving the cingulum, thalamus, and frontal lobe as well as ipsilateral temporopolar, entorhinal, and perirhinal white matter areas. Thus, VBM was able to confirm findings from studies that used manual segmentation of individual brain structures.[61,62] Another study confirmed widespread brain abnormalities in patient with TLE and imaging evidence of hippocampal sclerosis, but failed to demonstrate consistent imaging abnormalities in a group of patients with TLE without hippocampal sclerosis.[63] VBM has also been used to study gray matter abnormalities in patients with focal cortical dysplasia. VBM identified 79% of known areas of focal cortical dysplasia and demonstrated gray matter abnormalities extending beyond the visible lesion in 59%.[64] However, the method failed to identify 21% of visible FCDs, which were characterized by high signal abnormalities, thus failing to identify the lesion as grey matter. In another study, VBM identified 10 out of 11 visible areas of focal cortical dysplasia, and areas of abnormal gray matter concentration beyond the visible lesion were seen in 7 out of 10 patients.[65] Using SPM, one recent study detected areas of increased T2 signal in 23 out of 45 patients with normal conventional MRI.[66] It remains to be seen if the current or future versions of SPM and VBM can reveal structural abnormalities in patients without a visible lesion on current standard MRI. A recent paper by the same group examined the use of four quantitative MRI contrast parameters in combination with SPM in patients with normal conventional MRI scans. The authors found abnormalities in 31% of lobes with putative seizure origin, however the specificity of these findings was low.[67] The relationship of such abnormalities to the seizure onset zone, irritative zone and epileptogenic zone remains to be defined. At present, these labor-intensive techniques may help to develop a hypothesis to guide the placement of intracranial electrodes in order to define the ictal onset zone in some patients.[67]

SPM is also employed in functional imaging studies and was in fact developed to test hypotheses about functional imaging data.

FUNCTIONAL NEUROIMAGING

Functional imaging detects changes in cerebral metabolism or cerebral perfusion in the interictal or ictal state. Since these changes vary to a great degree ictally from interictally, it is important to have an EEG correlate of the patient's brain activity at the time of imaging.

Positron-emission tomography (PET) is widely employed in the presurgical evaluation of patients with intractable epilepsy. Most data on PET are available on patients with temporal lobe epilepsy. ^{18}F fluoro-2-deoxyglucose (FDG) is the tracer most widely used. The area of decreased glucose utilization in

temporal lobe epilepsy is typically more extensive than the epileptogenic zone and may extend into the adjacent inferior frontal or parietal lobe cortex, as well as the ipsilateral thalamus and contralateral cerebellum.[68,69] Thus, ^{18}F-FDG PET has lateralizing rather than localizing value in temporal lobe epilepsy, and its main role is to confirm hypometabolism in the area considered for surgical resection. The presence of contralateral cortical hypometabolism predicts a low chance of seizure freedom after temporal lobectomy,[70] and the extent of resection of brain areas with hypometabolism on FDG-PET correlated with better seizure outcome.[71] FDG-PET may offer localizing value in patients with TLE who do not have a structural abnormality on high-resolution MRI. One recent study[72] compared two groups of 30 patients with TLE. One group had MRI evidence of hippocampal sclerosis, whereas the patients in the other group were considered to have normal MRIs. Interestingly, this latter group had more widespread PET abnormalities than the hippocampal sclerosis group. Surgical outcome in both groups was similar with 17 out 23 patients being seizure-free in the group with HS vs. 16 out of 20 in the group without HS. The only difference on histopathology was the presence of HS in all patients in the group with HS, whereas only one patient out of 10 in the group without HS had findings consistent with HS. (The other 10 patients operated on had resections sparing the mesial structures.) This led the authors to coin the term "MRI-negative PET-positive temporal lobe epilepsy".[72]

^{11}C-Flumazenil (FMZ) is a marker for functional integrity of the GABAergic inhibitory neurotransmitter system.[73] Its main value is that it may show increased ligand binding. This finding indicates the presence of a disease trait, whereas decreased ligand binding might be explained by regional loss of tissue which is commonly seen in epilepsy.[5] In patients with cryptogenic focal neocortical epilepsy, areas of increased FMZ binding in the periventricular white matter may imply the presence of heterotopic neurons not seen on MRI.[74] Increased periventricular white matter uptake of FMZ has also been associated with a worse outcome after temporal lobectomy in patients with unilateral hippocampal sclerosis.[75]

Other ligands for different receptors (opiate-, glutamate-, acetylcholine-, peripheral benzodiazepine-, 5-HT1A- receptors) and metabolic neurotransmitter pathways (monoaminooxidase type B, serotonin synthesis) have been tested in patients with TLE and HS (reviewed in[5]). However, to our knowledge, no studies have demonstrated incremental benefit regarding surgical outcome for any of these ligands over MRI or PET using FDG or FMZ.

As it is the case with other imaging modalities, systematic data in patients with extratemporal lobe epilepsy are scarce compared to TLE. In general, FDG-PET in extratemporal epilepsy is less revealing. In cases of a clear MRI lesion, it typically shows hypometabolism coinciding with the lesion, with or without extension into the surrounding brain parenchyma. FDG-PET hypometabolism coinciding with an MRI lesion and EEG findings is a favorable prognostic factor for seizure freedom after epilepsy surgery for neocortical epilepsy.[76] Likewise, in a study of cryptogenic neocortical epilepsy (all patients had normal MRI scans), concordance of hypometabolism on FDG-PET with interictal EEG findings correlated with seizure freedom.[77] However, the localizing value of FDG-PET in this study was significantly worse in patients with extratemporal epilepsy, compared to patients with TLE.

Single Photon Emission Computed Tomography (SPECT) utilizes ^{99m}Tc-hexamethyl-propyleneamine oxime (^{99m}Tc-HMPAO) or ^{99m}Tc-ethylcysteinate dimer (^{99m}Tc-ECD) to study cerebral perfusion in the ictal and interictal state. Both these tracers have a rapid first pass uptake and a relatively long half-life. This allows storing them at the bedside for ictal injection as well as a generous time window of up to 6 hours postinjection to acquire the images. Ictal SPECT compared to the interictal study typically demonstrates areas of regional hyperperfusion, which reflects relative hypermetabolism in parts of the brain involved in seizure onset or propagation.[78]

Subtraction of the interictal from the ictal study and coregistration to the patient's MRI improves the interpretation of the study.[79] Seizure type and duration

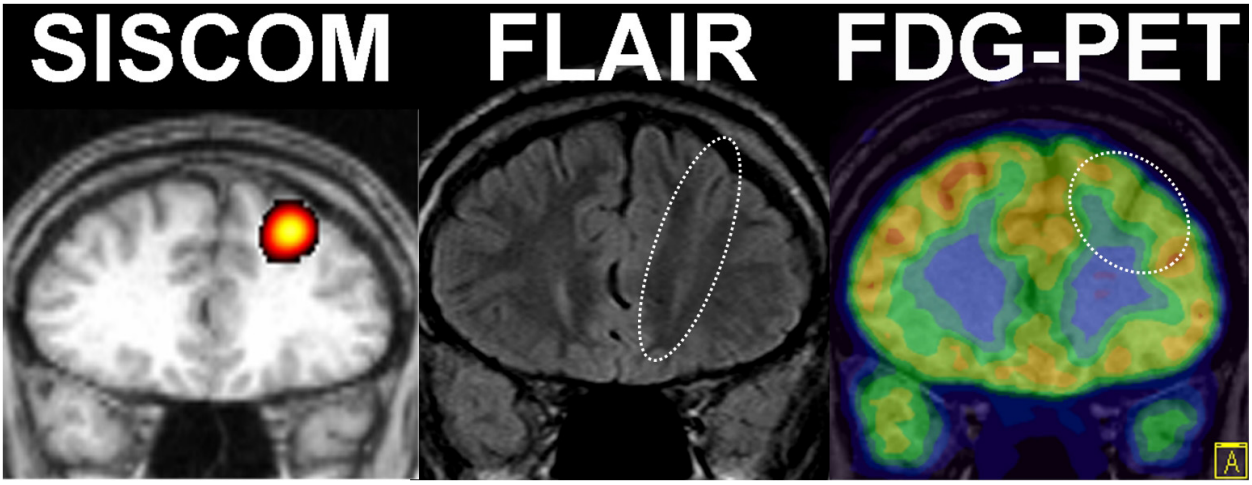

Figure 6. Convergent multimodal imaging in a patient with intractable left frontal lobe epilepsy. SISCOM demonstrated a cluster of hyperperfusion in the left superior frontal gyrus, consistent with the patient's ictal EEG. A subtle linear hyperintensity extending from the periventricular area to the left superior frontal sulcus is seen on the corresponding coronal FLAIR MRI slice. 18-FDG PET shows mildly reduced metabolism in the overlying cortex. Invasive video EEG using a combination of grid and depth electrodes revealed ictal onset from this area. Histopathology after prefrontal lobectomy showed focal cortical dysplasia.

and the timing of the injection after the seizure onset are important variables in the interpretation of the study. Early injection yields better results.[80] Local ictal hyperperfusion is followed by postictal hypoperfusion within 1-2 minutes in temporal lobe seizures; this switch may occur even earlier in extratemporal seizures. It has been estimated that the seizure should last at least 10 seconds after the injection in order to obtain localizing information.[78] It is also important to have a video-EEG correlate of the seizure during which the injection occurred. Ictal SPECT is most helpful if the patient has stereotypic seizures; if there is more than one seizure type, each type may have to be captured. Because all these parameters have to be considered in the interpretation of an ictal SPECT study, it is difficult to systematically investigate the usefulness of this imaging modality. Many studies on ictal SPECT have included patients with clear structural abnormalities. It is unclear if SPECT adds anything in this scenario.[69] Ictal SPECT is likely most useful in patients with nonlesional extratemporal focal epilepsy, where it may help to develop a hypothesis to guide the placement of intracranial electrodes in order to define the ictal onset zone (Fig. 6).[81,82] One group reported that in selected cases ictal SPECT may obviate the need for invasive electrographic evaluations in patients without obvious structural lesions.[83]

Functional MRI (fMRI) identifies changes in cerebral blood flow by measuring MRI contrast differences between oxygenated and deoxygenated hemoglobin. Increased cerebral blood flow is thought to represent functional activation of the surrounding cortex. In the presurgical epilepsy evaluation, fMRI may be used to define eloquent cortex. In a recent prospective study of 60 epilepsy surgery candidates, fMRI results changed patient management in about half of the patients.[84]

Primary sensorimotor areas can be readily identified non-invasively by fMRI, and the results correlate well, but not perfectly, with those of cortical stimulation and evoked potentials.[85-87] Areas of activation on fMRI and corresponded with eloquent cortex by intraoperative cortical mapping within 10 mm in 86% and within 20 mm in 100% of paradigms studied.[88] Another study of adult brain tumor patients quoted 90% of positive motor activations in areas activated on fMRI, and the remaining ones within 15 mm of the corresponding area.[87] This spatial "resolution" is within the magnitude of the resolution of electrocortical stimulation with typical interelectrode distances

of 10 mm. One limitation of fMRI is that its motor paradigms are restricted to distal movements (e. g. finger or toe tapping, lip contractions).

The correlation between fMRI with various neuropsychological tests and the intracarotid amybarbital procedure (IAP, Wada-test) to predict memory decline after temporal lobectomy[89] and to determine the language-dominant hemisphere has been studied.

These studies reported that fMRI was a strong predictor of memory decline following a left temporal lobectomy in right-handed patients with left mesial temporal sclerosis,[90,91] as well as following right temporal lobectomy in patients with right temporal lobe epilepsy.[92] The method has also been investigated to lateralize language, comparing it to the Wada-test. Good concordance was found between Wada test and frontal lobe activation, but not with temporal lobe activation using a semantic fluency task and a story-telling paradigm, whereas no correlation was found when covert sentence repetition was used as a task.[93]

Correlation of language fMRI with intraoperative cortical stimulation also demonstrates good but not perfect correspondence. When allowing for 10 mm separation between areas of fMRI activation and areas identified for language on cortical stimulation, sensitivity of fMRI to detect language areas was 67-100% for different language paradigms.[94] It has to be noted that the estimated error of the coregistration of intraoperative language maps to the fMRI was estimated to be up to 3 mm. To our knowledge, fMRI has not been systematically correlated with extraoperative stimulation of language areas in epilepsy patients.

In patients with extensive malformations of cortical development, fMRI showed activation of areas within the malformation, implying that areas within the malformed cortex may support cognitive or motor functions.[33]

The main limitation of fMRI is its suboptimal specificity. A significant percentage of the cortical areas that are "activated" during an fMRI paradigm are dispensable for that specific function. Further work is therefore needed to clarify the role of fMRI in localizing eloquent cortex. At present, it has to be considered a research tool rather than part of the routine diagnostic workup of patients undergoing epilepsy surgery.

CONCLUSION

Developments in structural and functional imaging had a major impact on the presurgical evaluation of patients with pharmacoresistant epilepsy. Advances in MRI technology, data postprocessing and new ligands in PET will continue to deepen our understanding of structural and functional alterations in the brains of patients with intractable epilepsy.

Ongoing research in this field is driven by several questions:

(1) How can the sensitivity and specificity of MRI to detect subtle lesions, in particular areas of focal cortical dysplasia, be increased?
(2) What brain structures aside from the epileptogenic zone are altered in patients with focal epilepsy?
(3) What is the relationship between a structural alteration on MRI and the epileptogenic zone?
(4) What is the relationship between a structural lesion on MRI and the function of the affected part of the brain?

Developments in neuroimaging of epilepsy need to be judged by its effect on the management of patients with intractable epilepsy.

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