

Magnetic Resonance Imaging of the Epilepsies

Much progress has been made over the last decade in the structural and functional imaging of the brain in epilepsy. The correlation of structure with function is essential in the understanding of the epilepsies and epileptic seizures, which may have a structural basis.

The superiority of magnetic resonance imaging (MRI) over X-ray computed tomography (CT) scanning in terms of sensitivity and specificity for identifying the cause of epilepsy in both adults and children is firmly established. The most common abnormalities identified are hippocampal sclerosis (HS), malformations of cortical development (MCD), vascular malformations, tumours, and acquired cortical damage. X-ray CT, however, may be preferred to MRI if a patient is disturbed or acutely unwell, as the patient is more accessible during the procedure. An X-ray CT scan is also valuable for the investigation of possible acute intracranial haematomas and skull fractures, and if there is a contra-indication to MRI such as a cardiac pacemaker or cochlear implants. CT is also useful as a supplement to MRI for clarification of possible intracranial calcification that is not shown easily by MRI.

Rapid advances are being made in MRI techniques so that patients who were previously regarded as being 'MRI negative' may have relevant abnormalities, which can be identified with contemporary optimal imaging.

MRI epilepsy protocol

In the non-acute situation an MRI scan should include T2-weighted, proton density and fluid attenuated inversion recovery (FLAIR) sequences to cover the whole brain in at least two orthogonal planes, with the minimum slice thickness possible. There should also be a T1-weighted volume acquisition with a partition size of 1.5mm or less, to allow reformatting in any orientation and three-dimensional reconstruction of the data set. The FLAIR sequence produces images in which parenchymal lesions have high signal and CSF gives low signal (Figure 1). This may help in the differential diagnosis of areas of high signal on T2-weighted images and increase the conspicuity of lesions. In the first two years of life, incomplete myelination results in poor grey-white matter contrast, making identification of cortical abnormalities difficult, and in these cases MRI may need to be repeated after 1-2 years.

The best practice is to obtain MRI in all patients with epilepsy, with the exception of those with a definite diag-

nosis of idiopathic generalised epilepsy or benign rolandic epilepsy of childhood with centrotemporal spikes, who go into early remission. MRI is particularly indicated in patients with one or more of the following:

- Onset of partial seizures, at any age
- Onset of generalised or unclassified seizures in the first year of life, or in adulthood
- Evidence of a fixed deficit on neurological or neuropsychological examination
- Difficulty obtaining seizure control with first-line antiepileptic drugs (AEDs)
- Loss of seizure control, or a change in the pattern of seizures.

In situations in which access to MRI is limited, essential indications for MRI are:

- Patients with partial or secondarily generalised seizures, and apparently generalised seizures, that are not controlled with AEDs
- Patients who develop progressive neurological or neuropsychological deficits.

A recent survey in the UK shows that optimal practice is not applied universally, and the quality of MRI scans obtained in community hospitals was significantly less than those obtained at an epilepsy centre.¹

Presurgical candidates

Patients who are being considered for surgical treatment merit the most sophisticated MR imaging that is available and may also benefit from functional imaging with positron emission tomography (PET) and single photon emission computed tomography (SPECT). Identification of a structural lesion, however, does not always indicate the site of seizure origin. Clinical, EEG and other data all need to be considered.

A typical presurgical MRI protocol would be:

- Volume acquisition T1-weighted data set that is acquired in an oblique coronal orientation, orthogonal to the long axis of the hippocampi, and covers the whole brain in 0.9mm partitions. This sequence produces approximately cubic voxels, allowing for reformatting in any orientation, subsequent measurement of hippocampal morphology and volumes, and for three-dimensional reconstruction and surface rendering of the brain;
- Oblique coronal spin-echo sequence, with proton density (TE = 30), heavily T2-weighted (TE = 90 or 120) and FLAIR acquisitions that are orientated perpendicular to the long axis of the hippocampus, to demonstrate any increase in T2-weighted signal intensity.

Structural cerebral abnormalities underlying epilepsy identified with MRI

Hippocampal sclerosis

Hippocampal sclerosis (HS) is the single most common pathology underlying refractory partial seizure disorders, and is amenable to surgical treatment. The hippocampus is best visualised orthogonal to its long axis. This plane is parallel to the anterior border of the brainstem.

The MRI features of HS are hippocampal atrophy, best demonstrated with coronal T1-weighted images, and increased signal intensity within the hippocampus on T2-weighted images, decreased T1-weighted signal intensity and disruption of the internal structure of the hippocampus. Atrophy of temporal lobe white matter and cortex,



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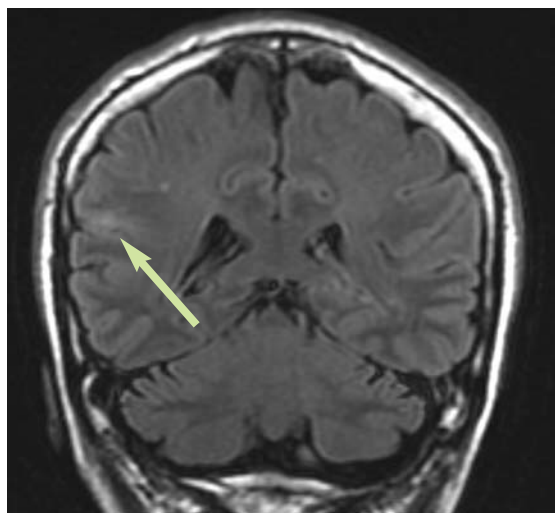


Figure 1: Coronal FLAIR sequence showing focal cortical dysplasia in right lateral inferior frontal gyrus, previous MRI had been unremarkable.

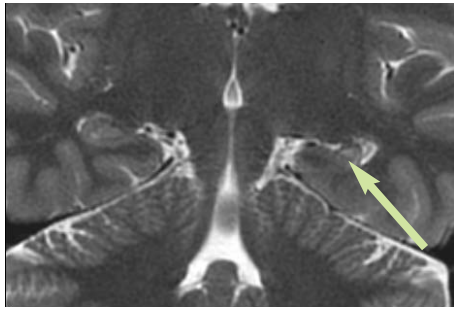


Figure 2: Coronal PROPELLER sequence showing left hippocampal sclerosis with atrophy and increased T2-signal.

dilatation of the temporal horn and a blurring of the grey-white matter margin in the temporal neocortex variably accompany HS. New sequences such as PROPELLER are showing the subregions of the hippocampus with increased definition.² (Figure 2)

Assessment of hippocampal atrophy can be improved by measuring hippocampal volumes. In clinical practice, hippocampal asymmetry of 20% or more is reliably visually apparent to skilled neuroimaging specialists, but lesser degrees of asymmetry require quantification. The T2-weighted signal intensity may be quantified by measurement of hippocampal T2 relaxation time (HT2) and this is a useful identifier of hippocampal pathology. Hippocampal T2 mapping has been shown to be robust at 3T as well as 1.5T.³

HS may be of varying severity along the length of the hippocampus and this may be identified by measurement of hippocampal cross-sectional area and T2.

Hippocampal volume corrected for intracranial volume and HT2 are useful for identifying any contralateral hippocampal abnormality which is very important when surgical resection of one hippocampus is being considered, as abnormality of the contralateral hippocampus indicates a risk of serious memory impairment.

Malformations of cortical development

Malformations of cortical development (MCD) are increasingly being recognised in patients with seizure disorders. The range of MCD identified with MRI include schizencephaly, agyria, diffuse and focal macrogyria, focal polymicrogyria, minor gyral abnormalities, subependymal grey matter heterotopias, bilateral subcortical laminar heterotopia, tuberous sclerosis, focal cortical dysplasia and dysembryoplastic neuroepithelial tumours (DNTs). Dysembryoplastic neuro-epithelial tumours are benign developmental tumours and commonly underlie refractory partial seizures. The features are of a focal, circumscribed cortical mass that may indent the overlying skull and also extend subcortically, with low signal intensity on T1-weighted images, high signal on T2-weighted images that is similar to CSF, and slightly higher signal intensity in the lesion than CSF on proton density images (Figure 3).

Hypothalamic hamartomas, sometimes associated with gelastic epilepsy, precocious puberty and cognitive impairment, are clearly demonstrable using MRI (Figure 4). More subtle abnormalities such as focal nodular hetero-

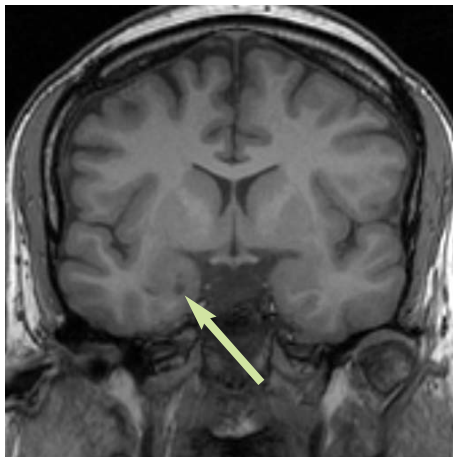


Figure 3: Coronal T1-weighted scan showing dysembryoplastic neuroepithelial tumour in right parahippocampal gyrus.

topia and band heterotopia may only be apparent if optimal MRI techniques are used.

Focal cortical dysplasia may result in refractory partial seizures, is surgically treatable and may be more easily identified on a FLAIR sequence (Figure 1)⁴ and also by reconstructing the imaging dataset in curvilinear planes and by quantitative assessment of signal and texture.

Cavernomas

Cerebral cavernomas commonly underlie epilepsy and are circumscribed and have the characteristic appearance of a range of blood products. The central part contains areas of high signal on T1- and T2-weighted images, reflecting oxidised haemoglobin, with darker areas on T1-weighted images due to deoxyhaemoglobin. The ring of surrounding haemosiderin appears dark on a T2-weighted image. There may be calcification, which usually appears dark on T1- and T2-weighted images. There is no evidence of arteriovenous shunting.

Granulomas

Worldwide, the commonest causes of refractory focal epilepsy are cysticercosis and tuberculomas. These lesions have characteristic appearances on MRI that evolve with time and which, unless calcified, may resolve and be regarded as 'disappearing lesions'.

Post-acquisition processing of MRI

Voxel-based morphometry is a research tool that is suited to comparing groups of patients and controls, but is relatively insensitive at thresholds that do not give false positive results in individual patients.^{5,6} VBM of T1-weighted datasets may be combined with T2-maps, and abnormalities largely coincide.⁷

Curvilinear reconstructions may increase the visibility of subtle neocortical lesions. Three-dimensional reconstruction of the neocortex may assist visualisation of abnormalities and surgical planning.

Longitudinal studies of the effect of epilepsy on the brain

Voxel and anatomically-based methods may be applied in longitudinal studies to identify subtle changes in the brain and to determine the

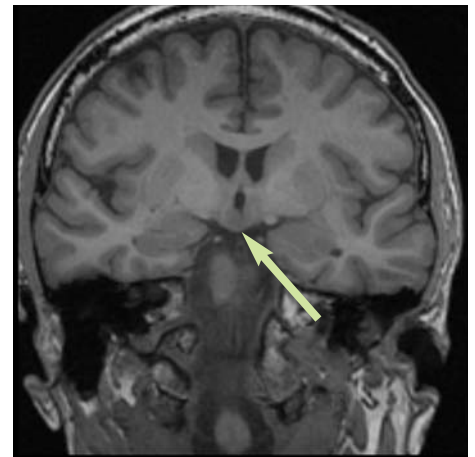


Figure 4: Coronal T1-weighted scan showing hypothalamic hamartoma.

effects of epilepsy. The majority of previous cross-sectional studies have inferred that more severe hippocampal damage is associated with a longer duration of epilepsy and a greater number of seizures. Two studies suggested atrophy of the hippocampus occurring over three years of active epilepsy in patients attending epilepsy clinics.^{8,9}

A community-based study has shown that those with a history of a prior neurological insult had smaller neocortical volumes and an accelerated rate of brain atrophy, and that in patients with newly diagnosed epilepsy without a history of prior insult the rate of atrophy was no different from age-matched controls. Patients with chronic epilepsy, however, were more likely to have had significant loss of neocortical, hippocampal or cerebellar volume over 3.5 years. 54% of those with chronic epilepsy, 39% of those with newly diagnosed seizures and 24% of controls had areas of brain volume loss,¹⁰ implying that secondary brain damage might occur in the context of chronic epilepsy.

Recent developments in MRI acquisition

Diffusion tensor imaging (DTI) reveals lesions found with conventional MRI and also abnormalities that are not visualised on routine sequences. Other new MRI sequences include magnetisation transfer ratio imaging, double inversion recovery imaging and fast FLAIR T2-mapping. The yield of these sequences, analysed with voxel-based methods, however, is limited, and there are issues of balancing sensitivity and specificity.⁶

Improved gradient performance is improving speed and spatial resolution. Phased array surface coils improve signal-to-noise ratio in superficial cortex and hippocampal regions and this may lead to improved spatial resolution, but have the limitation of restricted anatomical coverage. Imaging at high field strengths may also improve spatial resolution. 3T MRI scanners are now become increasingly regarded as standard clinical instruments.

Tractography

The visualisation of cerebral white matter tracks is a derivation of diffusion tensor imag-

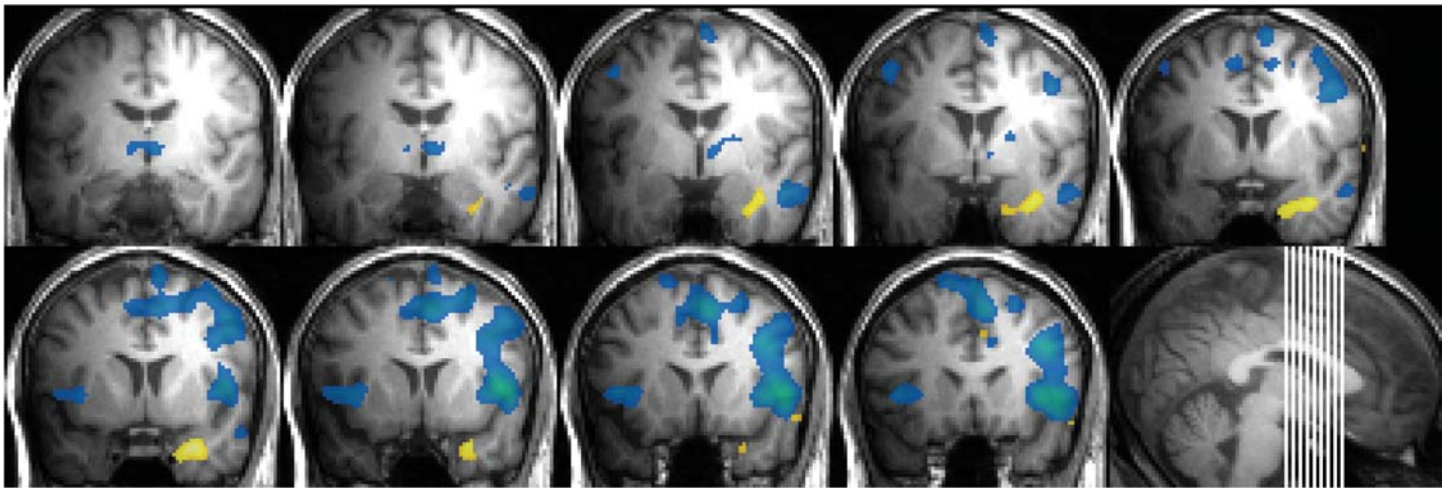


Figure 5: Coronal T1 MRI with fMRI activation associated with interictal epileptic discharges (yellow) and with language (verbal fluency) (blue).

Integrated structural and functional MRI can reveal the structural abnormalities underlying epilepsy and the relation of these to eloquent areas of the brain and areas involved in generating epileptic activity

ing. A variety of software packages is available, each with its own particular features, and the field is rapidly evolving. It needs to be appreciated that current *in vivo* tractography has a spatial resolution that is limited by voxel sizes of approximately 2mm,³ and so the images do not indicate the white matter tracks *per se*, but the movement of water related to these tracks.¹¹

Tracking from areas of functional activation gives an indication of the white matter connectivity of those functionally eloquent areas. This has been used to demonstrate the connectivity of Broca's area, the side-to-side asymmetry in healthy controls, and the relative augmentation of connections on the right side in those with left TLE.¹²

Of immediate clinical relevance is the ability to visualise the optic radiation, as compromise of this during anterior temporal lobe resection (ATLR) may result in a visual field defect that can prevent driving.^{13,14} This information can now be acquired pre-operatively and can inform the discussion with the patient regarding the risk of resection causing a visual field defect, and may lead to a modification of surgical technique.

Functional MRI

Ictal and inter-ictal epileptiform activity

Focal increases in cerebral blood delivery have been identified in patients with frequent interictal epileptic discharges (IED). Continuous recording of EEG and functional MRI (fMRI) is possible, with methods to remove the artifact on the EEG trace caused by the fMRI acquisition and the movement caused by the heart beat. Clinically, these methods will aid EEG interpretation and understanding of the pathophysiological basis of epileptic activity. Their application, utility and limitations in defining the irritative zone of the cortex (that generates IED) and its relationship with the epileptogenic zone (that gives rise to seizures) in patients in

whom surgical treatment is undergoing evaluation. At present it is evident that the area generating IED may be at some distance from the area that generates seizures.¹⁵

Distinctive patterns of increased and decreased BOLD signal changes have been described in association with generalised spike-wave discharges, that reflect changes in perfusion.¹⁶ In contrast, temporal lobe IED are associated with an increase in BOLD signal in the ipsilateral hippocampus and decreased BOLD signal in the precuneus (Figure 5).

EEG source localisation shows some concordance with areas of spike-related activations found with EEG-fMRI. Some BOLD activations are not matched by focal EEG changes. The implication is that the latter are the result of propagation of epileptic activity.¹⁷

BOLD changes may occur prior to the detection of IED on scalp EEG, implying that the pathological process precedes the appearance of scalp spikes by several seconds.¹⁸

Localisation and lateralisation of cognitive function

An important role for fMRI in patients with epilepsy is to delineate areas of brain that are responsible for specific functions, such as the primary sensory and motor cortex, and to identify their anatomical relation to areas of planned resection. In patients with cerebral lesions, the localisation of cognitive activation may differ from the pattern in normal subjects.

Lateralisation of language function may also be accomplished using fMRI¹⁹ (Figure 5). There was a strong correlation between language lateralisation measured with the carotid amygdala test, and using fMRI with a semantic decision task and other fMRI language studies have generally concurred with carotid amygdala testing. The high proportion (33%) of left-TLE patients showing bilateral or right hemispheric language-related lateralisation with fMRI implied plasticity of language representation in patients

with intractable TLE.²⁰

fMRI results do not always accord with carotid amygdala data and a combination of language tasks may be more reliable than a single task. Artefacts and technical difficulties may adversely affect both methods and false lateralisations may occur. Further, identification of the areas of brain involved in language is not the same as determining if someone can speak when half of the brain is anaesthetised.

As well as predicting the lateralisation of language function, fMRI may localise cerebral areas involved in language. For example, in a recent fMRI study of healthy right-handed subjects, tasks of reading comprehension activated the superior temporal gyri, and verbal fluency and verb generation tasks activated the left inferior and middle frontal gyri and left insula.²¹

In the future, these data may assist in planning surgical resections in the language-dominant hemisphere. There are, however, important caveats. Absence of activation on one language task does not guarantee that that part of the brain is inert. Conversely, an area that is activated may have only a peripheral and non-essential role in verbal communication.

Decline of language and memory function following anterior temporal lobe resection, particularly of verbal memory after left-sided anterior temporal lobe resection, is a major concern. The ability to localise eloquent cerebral regions and map neural networks involved in memory may lead to a more targeted / individualised surgical approach and may be able to predict post-operative memory decline.²²

Early evidence is that memory fMRI may be a better predictor of material specific memory changes after anterior temporal lobe resection than baseline neuropsychological assessment or structural MRI.^{23,24}

Functional MRI studies have also provided evidence for functional dissociation of verbal and visual memory encoding of prefrontal cor-

tices and mesial temporal lobe structures. and activation may be less on the side of the focus.

It is likely that, in the next 2-3 years, language and memory fMRI will become standard techniques in the consideration of the surgical treatment of epilepsy, and will assist in the optimal management of individual patients.

Acknowledgements

I am grateful to the Wellcome Trust, Medical Research Council, Action Medical Research, European Union, The National Society for Epilepsy and The UCL/UCLH Comprehensive Biomedical Research Centre for support.

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