Epilepsy and surgical mapping

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Drug treatment resistant epilepsy is an important public health problem. Patients with epilepsy of focal origin may have an excellent outcome following surgery that removes the source of seizures. Identification of the precise cortical region producing seizures is crucial to a good outcome; additionally, identification of eloquent cortical areas near the region to be resected is essential to prevent postoperative neurological deficit. A wide range of imaging techniques is valuable for imaging the epileptogenic zone, including high-resolution T1 MRI, T2 signal quantitation, MR spectroscopy, diffusion imaging, PET, SPECT and simultaneous EEG-fMRI. Eloquent cortex has in the past been mapped using highly invasive techniques; fMRI of motor and cognitive tasks holds great promise for future non-invasive mapping strategies.

Epilepsy is a common disorder affecting approximately 0.5–1% of the population in industrialised countries. Approximately 20% of people with epilepsy continue to have seizures despite adequate anti-epileptic drug treatment; the majority of these cases suffer from localisation-related (‘focal’) epilepsy, rather than primary generalised epilepsy. Persistent epilepsy is strongly associated with poor educational achievement, low socio-economic status, a high risk of morbidity, and a markedly increased risk of death. The failure of drug treatment in this significant minority has led to an increasing interest in neurosurgery for epilepsy, particularly surgical approaches which aim to remove the ‘epileptic focus’ and, therefore, render the patient entirely free of further seizures. The first randomised trial of surgery versus optimal drug treatment in temporal lobe epilepsy demonstrated a 7-fold increase in the likelihood of being seizure-free in the surgically treated group, with an accompanying highly significant improvement in quality-of-life. The challenge is to identify suitable candidates for surgery, locate the brain region that produces seizures, and to resect this area without causing postoperative neurological deficit.

Two important concepts in this context are eloquent cortex and the epileptogenic zone. Eloquent cortex refers to any cortical area in which injury produces symptomatic cognitive or motor deficit. Examples of such areas are primary sensorimotor cortex, essential speech areas,
occipital visual areas and mesial temporal regions crucial for episodic memory. Many other cortical areas can be resected without obvious consequences for the patient, although detailed neuropsychological testing may reveal subtle deficits. The epileptogenic zone\(^5\) refers to the region of cerebral cortex that is both necessary and sufficient to generate epileptic seizures, hence its entire removal is required for a successful outcome. This area is not necessarily the same as the region of cortex which produces interictal spikes on the scalp EEG (the irritative zone), nor is it necessarily completely overlapping with any structural lesion (epileptogenic lesion) which may be the underlying cause of the epilepsy and which may be seen on an MRI brain scan. Furthermore, any of these zones and lesions may encroach into eloquent cortex; the brain lesion itself may sustain normal functions\(^6\); and cortex around the epileptogenic zone may show impaired function prior to surgery, but recover postoperatively\(^7\). Furthermore, the normal allocation of functions to particular brain regions may be altered in patients with epilepsy – for example, language representation may be in the right hemisphere rather than the left in the presence of left hemisphere pathology present since early childhood – so cortex may be unexpectedly eloquent in a typically non-eloquent area. It will be immediately clear that planning the cortical resection in surgery for epilepsy is extremely challenging.

Quantitation of neuroimaging parameters and objective comparison of patients’ imaging with normal data has revolutionised the approach to clinical neuroimaging. Many techniques exist for quantitation of parameters in particular regions or volumes of interest; usually regions are defined by drawing and placement by eye, although automated techniques exist\(^8\). A complementary approach is to transform images to a standard brain volume using automated co-registration and non-linear warping techniques, subsequently employing a statistical test at every voxel of the image to compare images with each other; the result of such a comparison is an image of statistics which can be further analysed to detect significant regional abnormalities. A widely used technique is statistical parametric mapping (SPM)\(^9\).

**Imaging the epileptogenic zone**

In most adult epilepsy surgery centres, the majority of patients undergoing surgery have temporal lobe epilepsy (TLE), with seizures arising from mesial temporal structures and associated with a particular pathology – hippocampal sclerosis (HS), sometimes referred to as mesial temporal sclerosis. A patient with unilateral hippocampal sclerosis, no other brain lesions, and all of the seizures arising from this area has a 60–70% chance of seizure freedom life-long after surgery. Because this
Fig. 1 MRI quantitation in hippocampal sclerosis. On the left is a coronal section of a T1 weighted MRI (top) and from a T2-weighted MRI of the same subject (bottom). The volume of the hippocampus is calculated by tracing around the structure on T1; the T2 signal is quantitated from a small region placed within the hippocampus on T2. The values are displayed graphically on the right: the top graph shows the hippocampus volume (on the y-axis) for each slice (on the x-axis, slices numbered posterior-anterior). The broken lines show ± 2 SD for a normal control population; the anterior hippocampus shows marked atrophy. The lower graph shows T2 signal for each slice; the anterior hippocampus shows markedly elevated T2.
pathology is common and the outcome from surgery is good, techniques for non-invasive pre-operative identification of HS are well established. Although HS can sometimes be seen by visual inspection of MRI, quantitative techniques are usually used. The hallmarks of HS are loss of hippocampal volume and increase in hippocampal T2 signal on MRI T2 images (Fig. 1). The boundary of the hippocampus is traced manually on each slice of a high-resolution T1-weighted MRI and an automated computer routine then calculates the hippocampal volume. Using a comparison with data from normal subjects, subtle atrophy invisible to the eye may be detected\textsuperscript{10}. By using an interleaved, multislice, standard dual echo sequence of the type found on all commercial scanners, it is possible to obtain measurement of T2 values, covering the whole brain in 10 min\textsuperscript{11}, which has been called a T2 map. Again, normal values can be used to detect subtle abnormalities in the hippocampus. An important extension of hippocampal volume measurement is measurement of the adjacent entorhinal cortex volume, which has allowed detection of the seizure focus in the mesial temporal lobe in 64\% of patients with normal hippocampal volumes in a recent study\textsuperscript{12}.

As well as HS, a number of other pathologies are frequently encountered using conventional structural MRI in patients with drug treatment-resistant, localisation-related epilepsy, such as malformations of cerebral cortical development and small tumours, such as dysembryoplastic neuro-epithelial tumour. If a patient has a single circumscribed focal pathology and if this patient’s seizures can be shown to arise from this area, using prolonged scalp EEG and video telemetry to record seizures, then curative surgery is possible. However, many patients with a similar clinical history have entirely normal conventional MRI. Even if scalp EEG and video telemetry suggest a focal onset in such a patient, the lack of a visible target for the neurosurgeon necessitates further investigation. The conventional route is to undertake a craniotomy to place electrodes onto the brain surface or into the substance of the brain itself, and then undertake a period of video-EEG telemetry with these intracranial electrodes in place. This approach requires an additional craniotomy with its attendant risks and also may pose a risk for intracranial infection. Furthermore, although the epileptogenic zone may be pinpointed very accurately, the number of brain areas that can be targeted is small, hence the epileptogenic zone may sometimes be entirely missed. In this setting, a clear need exists for imaging alternatives.

Historically, the first technique to make an important contribution to mapping the epileptogenic zone in MRI-normal cases was positron emission tomography (PET) using \textsuperscript{18}F-fluorodeoxyglucose (\textsuperscript{18}F-DG). Much of the older literature compared \textsuperscript{18}F-DG PET to MRI techniques of the era, with low field strength and few quantitative methods;
patients regarded as ‘MRI-normal’ in these studies may well not have proven so with best-quality contemporary MRI. Hence the perceived advantages of $[^{18}\text{F}]$-DG PET from these studies may no longer be relevant. Temporal lobe epilepsy is characterised by an extensive area of reduced metabolism, typically encompassing a region much larger than the epileptogenic zone\textsuperscript{13}, possibly including irritative and functional deficit zones. In the current era, MRI usually reveals a lesion in such patients\textsuperscript{14,15}. $[^{18}\text{F}]$-DG PET has been much more valuable in the assessment of very young children with severe epilepsy, revealing focal hypometabolism amenable to highly successful surgical resection\textsuperscript{16}. SPM has been introduced to analyse $[^{18}\text{F}]$-DG PET\textsuperscript{17} and has been successfully applied in the evaluation of patients with epilepsy\textsuperscript{18} although its role in presurgical evaluation is not yet established. The benzodiazepine ligand $[^{11}\text{C}]$-flumazenil has also been used as a PET tracer in epilepsy patients, labelling the pathophysiologically relevant GABA\textsubscript{A} receptor; typically, a region of decreased binding has been seen in the putative epileptogenic zone (Fig. 2), much more circumscribed than the region of $[^{18}\text{F}]$-DG PET hypometabolism\textsuperscript{19}. In a large study of 100 patients\textsuperscript{20}, 81% of regions of abnormal $[^{11}\text{C}]$-flumazenil binding were concordant with an MRI abnormality. Both of these PET techniques may have a role in localising the seizure focus in MRI-normal patients. Although the serotonin system has not been the centre of attention in basic science studies of epilepsy, $\alpha-[^{11}\text{C}]$-methyl-L-tryptophan ($[^{11}\text{C}]$-AMT a marker of serotonin synthesis) has been employed in recent PET studies. In

Fig. 2 The image on the left is a section from a $[^{11}\text{C}]$-flumazenil PET scan of a patient with hippocampal sclerosis. A region of decreased binding is seen (arrow); SPM analysis of a group of similar patients showed a significant reduction of binding in the epileptogenic hippocampus (white area superimposed on MRI).
children with tuberous sclerosis, who often have multiple cortical tubers any of which could be the epileptogenic zone, uptake of \([^{11}C]\)-AMT was elevated only in those tubers subsequently shown to be epileptogenic\(^{21}\), allowing successful surgery. Focal increase of \([^{11}C]\)-AMT uptake has also been seen in patients with malformations of cerebral cortex and also in patients with both normal MRI and normal \([^{18}F]\)-DG PET; furthermore, the degree of increase of \([^{11}C]\)-AMT uptake correlated very strongly with interictal EEG spiking, suggesting this technique may become a valuable way of localising the epileptogenic zone\(^{22}\).

Single photon emission computed tomography (SPECT) using blood flow markers such as HMPAO also has a long history in the field of epilepsy surgery. The typical findings in patients with localisation-related epilepsy are a region of relative hypoperfusion interictally and an ictal focal increase in perfusion. The interictal findings alone are too insensitive and non-specific to be useful; ictal findings are much more helpful\(^{14,15,23}\). Ictal SPECT is uniquely valuable because the patient can be injected with the radiotracer at the time of seizure onset (usually in an EEG-video telemetry facility) and the patient scanned when convenient some hours later; the pattern of tracer uptake is unchanged over this delay. The period of increased blood flow may last only for the first part of a seizure; seizures may be very short and the response time of staff giving the radiotracer injection may be too slow to catch this early phase. An important advance is a technique permitting the patient to trigger radiotracer injection at the first warning of an impending seizure\(^{24}\) which promises a higher yield of useful SPECT studies. The comparison of an ictal and an interictal study from the same patient is vital for detection of a relative increase in perfusion at the time of a seizure; techniques for automated voxel-level comparison of images and co-registration of regions of significant change with the patient’s structural MRI has allowed a very clear delineation of the epileptogenic zone and the areas of seizure spread and also allowed planning of highly successful surgery\(^{25,26}\).

A number of newer MRI techniques also can locate a focal area of abnormality in patients with normal conventional structural MRI. Magnetic resonance spectroscopy (MRS) enables the simultaneous detection and quantitation of a number of brain metabolites using conventional MRI equipment. Studies in patients being evaluated for surgery usually have focused on N-acetyl aspartate (NAA), creatine + phosphocreatine (Cr) and choline-containing compounds (Cho). There is also growing interest in imaging important neurotransmitter-related compounds such as glutamate, glutamine and GABA. There is good evidence that NAA reflects numbers of neurons and Cho and Cr reflect glia\(^{27}\). In patients with HS, the typical finding in the epileptogenic hippocampus is a reduction of NAA and an elevation of Cho and Cr,
relative to normal controls (Fig. 3); the contralateral hippocampus may be normal or show a lesser degree of abnormality\textsuperscript{28,29}. These studies used a single large region to make measurements, preventing anatomical localisation; more recent studies use multiple voxels (magnetic resonance spectroscopic imaging, MRSI), permitting greatly enhanced localisation. Patients with malformations of cortical development show MRSI abnormalities, generally with reduced NAA, but increased NAA may be seen; frequently the abnormality seen with MRS is more extensive than with structural MRI\textsuperscript{30}. Despite the ability to detect in individual patients which hippocampus is more likely to be epileptogenic, it has been difficult to use MRS(I) data to guide surgery; recent work suggests that the degree of abnormality of the NAA/Cho ratio of the side opposite to proposed surgery may help predict the likelihood of success\textsuperscript{31}. Most patients in the above studies had HS; in patients with normal structural imaging, a curious recent finding has been that a greater degree of MRS(I)-detected abnormality of NAA/Cho ratio in the resected hippocampus was associated with a poorer outcome\textsuperscript{32}.

Diffusion tensor imaging (DTI) permits assessment of the diffusion properties of brain tissue. Using this technique in conjunction with SPM to compare individual patients with normal subjects, 8 of 30 patients...
with normal structural MRI were shown to have focal diffusion abnormalities\textsuperscript{33} which may become a target for successful surgery. A very exciting application of DTI, tractography, allows the calculation of the direction and three-dimensional connections of white matter nerve fibre tracts\textsuperscript{34} which may permit non-invasive visualisation \textit{in vivo} of nerve fibre tracts which connect the seizure focus to other brain areas, potentially allowing novel approaches to functionally disconnecting the seizure focus from surrounding brain (Fig. 4). Tractography may also allow nerve fibre tracts connecting eloquent cortical areas to be delineated, so that the neurosurgeon may avoid cutting them.

Functional MRI (fMRI) is widely used in scientific investigation of normal subjects to map cerebral functions non-invasively. Usually, fMRI studies involve the deliberate performance of a number of tasks which differ slightly, and \textit{post hoc} comparison of the regional haemodynamics in the different conditions allows inferences to be drawn about the brain areas which perform the task in question. Patients with epilepsy may also exhibit regional bursts of neural activity, due to interictal spikes or even due

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Fig. 4 Tractography in a patient with heterotopic grey matter. The diffusion-weighted MRI has been partially ‘cut away’ to reveal nodules of heterotopic grey matter (arrows), a congenital malformation known to be epileptogenic. Tractography demonstrates connections between the nodules and other brain regions.
to a seizure. fMRI is very prone to troublesome artefacts due to patient movement; seizures usually involve considerable movement so generally cannot be imaged; interictal spikes are asymptomatic so patient movement can be minimised. Spikes can only be detected using EEG. MRI necessitates rapidly changing strong magnetic fields which induce currents in EEG electrodes, resulting in overwhelming artefacts which completely obscure the EEG tracing and also causing electrode heating. Important advances in safety and on-line MRI artefact removal now permit continuous EEG recording in the scanner during continuous scanning. It is now possible to map the brain region which shows a haemodynamic response correlating with EEG spiking (Fig. 5).

**Imaging eloquent cortex**

Until recently, the only techniques used to map eloquent cortex in planning epilepsy surgery were the Wada test and electrical stimulation mapping. The Wada test involves injection of sodium amobarbital into the internal carotid artery of one hemisphere which temporarily...
abolishes the functions of that hemisphere; during this temporary
deficit, the language and memory functions of the remaining hemisphere
can be tested in isolation. Usually, each hemisphere is tested in turn.
Language can often be lateralised confidently; the results of memory
testing may be able to predict the likelihood of postoperative memory
dysfunction, though this is controversial. Electrical stimulation mapping
(ESM) involves directly stimulating the brain surface, which either
produces a response, such as a movement, or disrupts function, for
example causing speech arrest. ESM is thought to identify cortex
essential for a specific task directly. ESM can be performed pre-
operatively in patients with implanted electrodes or peri-operatively
with the brain exposed at surgery.

fMRI is being widely applied in an attempt to reduce the need for these
invasive and hazardous procedures. Simple motor and sensory tasks
used to map primary sensorimotor regions can produce strong
activations in individual patient studies. Although in some cases clearly
circumscribed single activations may be seen, additional activations (in
supplementary motor cortices or in the ipsilateral hemisphere) have
often been seen in patients with lesions or motor deficits; interpretation
of whether these ‘unexpected’ regions are essential for normal
postoperative function is still uncertain. In single subject clinical
studies, movement artefacts are a particular problem, sometimes
producing highly misleading artefactual activations adjacent to lesions;
also, large veins remote from the relevant cortical area, but draining
blood from activated cortex, may show very prominent haemodynamic
responses and hence apparent activations, further clouding
interpretation. An important clinical goal is to integrate pre-operative
fMRI data with peri-operative stereotactic guidance systems which
allow the neurosurgeon to view three-dimensional images of the
patient’s brain in relation to the positions of surgical instruments. This
approach is challenging because of changes in brain shape, which
inevitably occur when the skull has been opened.

Mapping cortex responsible for language function in patients has
drawn heavily on basic science approaches to language mapping in
normal subjects. An approach used in a number of patient studies has
been to compare haemodynamic responses resulting from the patient
making a semantic judgement about heard words with the haemo-
dynamic response to the patient making a judgement about the pitch of
heard tones; the contrast highlights brain regions involved in language,
controlling for auditory discrimination. This approach has shown a very
strong correlation with Wada test findings in the same subjects, though
single subject studies are insufficiently sensitive to do more than
lateralise language to one hemisphere and more detailed localisation has
been uncertain. An alternative approach, looking at language
production by contrasting internal silent generation of words with a rest state, also showed a very strong hemispheric correlation with the Wada test, but also without clear localisation\textsuperscript{43,44}. The optimal choice of language task remains unclear. It seems very unlikely that one single task can adequately delineate all essential language areas; drawing from basic science approaches, a conjunction analysis (which looks for regions activated in common across a range of tasks, eliminating areas activated in some tasks but not others) has been elegantly applied to patient

![Fig. 6 fMRI of verbal memory in epilepsy. These images obtained in the Wellcome Department of Imaging Neuroscience, UCL, show a single normal subject (top left) and three right-handed patients with hippocampal sclerosis. All subjects performed a verbal memory task which revealed activations using SPM: in the normal subject, activation is seen in the left hippocampus (cross-hairs); in patients 2 and 4 the activation is in the right hippocampus and in patient 3 bilateral activation is seen.](https://academic.oup.com/bmb/article-abstract/65/1/179/375330)
An alternative may be to identify the sum total of all regions activated across a range of language tasks. This approach has recently been applied to a large series of patients also undergoing peri-operative ESM. An important finding from this study is that language interference with ESM was only found in cortical areas where fMRI language activation was also found; the converse was not true – fMRI identified many areas where ESM did not disrupt language. This might imply that failure to find language activation in a particular cortical region with a range of fMRI language activation tasks excludes participation of that area in language.

Mapping memory functions of the mesial temporal lobe has been challenging in investigations of normal subjects and less progress has been made in patient studies. Tasks involving encoding of a complex visual scene or visual recall of familiar journeys activate both hippocampi symmetrically in normal subjects; patients with TLE show an asymmetry, with greater activation in the normal side and this asymmetry may correlate with the memory subtests of the Wada test. Verbal encoding and recall also activated the hippocampus in groups of TLE patients, but findings were relatively insensitive at the level of single subjects rather than effects across a whole group. All of these studies showed very posterior hippocampal activation, which may not be relevant to the neurosurgical context where the anterior hippocampus is removed. Progress towards activating the anterior hippocampus with a verbal task in individual patients is being made (Fig. 6).

Conclusions

Recent advances in neuroimaging have transformed the approach to surgical planning in patients with epilepsy. In the near future, it is likely that multiple modalities of imaging in the same patient will permit more accurate delineation of the epileptogenic zone, surrounding eloquent cortex and vital connections between cortical areas, allowing better surgical outcomes for seizure control and reduced postoperative deficits.

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References

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