Neuroimaging of the epilepsies

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Introduction

Much progress has been made over the last 20 years 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.

MAGNETIC RESONANCE IMAGING

The superiority of magnetic resonance imaging (MRI) over X-ray computed tomography (CT) scanning in terms of sensitivity and specificity for identifying the aetiology 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 contraindication 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.

The principal clinical applications of MRI are to identify the structural basis of epilepsy and patients who are suitable for surgical treatment. 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

Indications for neuroimaging of patients with epilepsy
The Neuroimaging Commission of the International League Against Epilepsy has produced recommendations for this. The rationale for imaging the brains of patients developing epilepsy is first to identify underlying pathologies such as vascular lesions, infections and tumours that require specific therapy; and second to assist the formulation of syndrome and aetiological diagnoses[1]. Further recommendations have been made for patients with refractory seizures[2] and for functional neuroimaging[3].

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 1.5 mm 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. This may help in the differential diagnosis of areas of high signal on T2-weighted images and

increase the conspicuity of lesions, but does not improve the identification of heterotopias[4,5,6,7]. 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.

In an acute situation when seizures occur in the context of a neurological insult, X-ray CT is an appropriate initial investigation if MRI is not readily available or not possible for technical reasons, for instance if the patient has a cardiac pacemaker or requires attention during the scan. Recent improvements in the design and manufacture of pacemakers and vagal nerve stimulators have improved MRI compatibility although safety issues at higher field strength remain an issue.

The best practice is to obtain MRI in all patients with epilepsy, with the exception of those with a definite diagnosis 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[6], and in a study in Germany, the quality of MRI scans obtained in community hospitals was significantly less than those obtained at an epilepsy centre[8].

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 0.9 mm 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 focal epilepsy, and is amenable to surgical treatment. The hippocampus is best visualised in two planes: along its long axis and orthogonal to this. These imaging planes may be readily determined on a sagittal scout image: the axial plane being in the line joining the base of the splenium of the corpus callosum to the inferior, posterior border of the frontal lobe and the coronal plane being perpendicular to this, parallel to the anterior border of the brainstem.

The features of HS identified by MRI are hippocampal atrophy, demonstrated with coronal T1-weighted images, and increased signal intensity within the hippocampus on T2-weighted spin-echo images[9], decreased T1-weighted signal intensity and disruption of the internal structure of the hippocampus[10]. Atrophy of temporal lobe white matter and cortex, dilatation of the temporal horn and a blurring of the grey-white matter margin in the temporal neocortex variably accompany HS[11–14]. Entorhinal cortex atrophy may also occur in TLE with normal hippocampi[15].

Sophisticated and computationally expensive analyses of three-dimensional hippocampal surface shape, and specifically deformation, have shown distinct regional changes, for example, in the CA1 region in hippocampal sclerosis and in the medial aspect of the head of the hippocampus in patients with temporal lobe epilepsy and normal conventional MRI. Moreover, diffuse atrophy or contralateral hippocampal abnormalities suggested a poor post-operative outcome[16].

Quantitative MRI assessment of the hippocampus
Assessment of hippocampal atrophy can be improved by measuring hippocampal volumes. The use of contiguous thin slices enhances the reliability of measurements and permits localisation of atrophy along the length of the hippocampus[17]. Hippocampal volumetry is demanding and time-consuming, requiring a skilled operator and a post-processing computer. In clinical practice, hippocampal asymmetry of 20% or more is reliably visually apparent to skilled neuroimaging specialists, but lesser degrees of asymmetry require quantification[18]. Attempts have been made to automate hippocampal volume estimations and although voxel-based approaches have given promising results, they remain inferior to expert manual assessment[19,179,180].

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. HS may be of varying severity along the length of the hippocampus, and may be confined to the anterior part of the head[20]. A T2 relaxometry technique incorporating a FLAIR sequence obviates possible contamination from high T2 in cerebrospinal fluid (CSF)[21]. Hippocampal volume corrected for intracranial volume and HT2 are useful for identifying contralateral hippocampal abnormality[22]. The same technique is useful for identifying amygdala pathology[23].

Malformations of cortical development
Malformations of cortical development (MCD) are increasingly being recognised in patients with seizure disorders previously regarded as cryptogenic. 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). DNTs 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. Cyst formation and enhancement with gadolinium may occur. Calcification is present in some cases and may be more readily demonstrated with X-ray CT. Confident differentiation from low-grade astrocytomas and ganglioglioma is not possible by MRI[24].

Hypothalamic hamartomas, sometimes associated with gelastic epilepsy, precocious puberty and cognitive impairment, are clearly demonstrable using MRI[25]. More subtle abnormalities such as focal nodular heterotopia and band heterotopia may only be apparent if optimal MRI techniques are used. Band heterotopia 'double cortex' is an example of a generalised MCD that may be present in patients with mild epilepsy and normal intellect.

Focal cortical dysplasia may result in refractory partial seizures. The possibility of surgical treatment means its identification with MRI has important consequences. Focal cortical dysplasia is not always identified with conventional MRI and may be more easily identified on a FLAIR sequence[6,26,181], by reconstructing the imaging dataset in curvilinear planes, by quantitative assessment of signal and texture[27] and by sulcal analysis[28].

Cavernomas

Cerebral cavernomas commonly underlie epilepsy and surgical removal carries up to a 70% chance of subsequent seizure remission. Cavernomas are often not identified on X-ray CT, but are readily apparent on MRI. Cavernomas 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. Arteriovenous malformations with high blood flow have a different and distinctive appearance.

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'[29].

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 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. Longitudinal studies, however, are necessary to ascribe cause and effect. Two recent studies have suggested atrophy of the hippocampus occurring over three years of active epilepsy in patients attending epilepsy clinics[30,31].

A large 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[32]. Further, on a more sensitive voxel-based analysis, 54% of those with chronic epilepsy, 39% of those with newly diagnosed seizures and 24% of controls had areas of brain volume loss[33]. These studies implied that secondary brain damage might occur in the context

of chronic epilepsy. The next step is to identify the aetiological factors and how to intervene to prevent this process.

Recent MRI developments

Diffusion-weighted imaging is very sensitive in the detection of early ischaemic changes, and shows changes in status epilepticus[34]. Diffusion tensor imaging (DTI) reveals lesions found with conventional MRI and also abnormalities that are not visualised on routine sequences[35-37]. However, these occult abnormalities may be the result of and not the cause of chronic epilepsy[38]. Tractography is a derivation of diffusion tensor imaging that allows identification of nerve fibre tracts within the brain, and demonstrates the structural basis of connectivity between brain regions[39]. Using tractography to interrogate the visual pathways it is possible to predict the occurrence and extent of a visual field defect following anterior temporal lobe resection (ATLR). A recent study found that the anterior extent of Meyer's loop ranged from 24–43 mm from the temporal pole. Significant post-operative visual field defects were only seen in those individuals in whom the anterior aspect of Meyer's loop was less than 35 mm from the temporal pole[40]. Pre- and intra-operative tractography has also been used to demonstrate the optic radiation in patients having temporal lobe resection and to predict the extent of visual field defect[41]. Similar studies have been reported in patients with tumours and may aid surgical planning of patients undergoing lesionectomy near eloquent cortex. Tractography has the potential to demonstrate the structural reorganisation of networks involved in memory and language that mirror changes in cerebral function. In a combined fMRI–tractography study, controls and right TLE patients had a left-lateralised pattern of both language-related activations and associated white matter organisation. Left TLE patients had reduced left-hemisphere and increased right-hemisphere white matter pathways, in comparison to controls and right TLE patients. Subjects with more lateralised functional activation had more lateralised white matter pathways[42]. The arcuate fasciculus was shown to be larger in the speech dominant hemisphere, and the left-right asymmetry was reduced if there was dominant hemisphere pathology[43].

Other promising new MRI sequences include magnetisation transfer ratio imaging[44], double inversion recovery imaging and fast FLAIR T2-mapping. Ultra-fast low-angle rapid acquisition and relaxation enhancement is a sequence that may be useful for patients who are restless and can only tolerate short studies[45]. A recently implemented MR sequence called 'periodically rotated overlapping parallel lines with enhanced reconstruction' ('PROPELLER') has an excellent in-plane resolution of 0.5 mm and is therefore able to demonstrate internal hippocampal structures within a clinical acceptable time-frame[46]. This may allow the detection of subtle hippocampal changes in patients with temporal lobe epilepsy.

Continuous arterial spin labelling perfusion MR imaging can detect asymmetries in mesial temporal lobe perfusion inter-ictally in patients with TLE[47] and may identify focal cortical dysplasia[182].

Improved gradient performance is anticipated to improve 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. Imaging at high field strengths may also improve spatial resolution. 3T MRI scanners are now available as mature clinical instruments and may increase the clinical yield by up to 20%[48,183]. The utility of higher field strength scanners, up to 7T, is also being evaluated and may provide further insights into subtle structural abnormalities[184].

Voxel-based morphometry may demonstrate areas of hippocampal atrophy in individual patients with clear-cut hippocampal sclerosis[49] but for the detection of occult abnormalities in individual patients it appears to be relatively insensitive at thresholds that do not give false positive results[50]. These methods are complemented by anatomical atlases, which allow quantification of brain imaging data on a lobar and sub-lobar basis[51,52]. Analysis of the texture of the neocortex on a T1-weighted volume scan may give increased sensitivity to identify focal cortical dyplasia[27]. Curvilinear reconstructions may increase the visibility of subtle neocortical lesions[53]. Three-dimensional reconstruction of the neocortex may assist visualisation of abnormalities and surgical planning[54], and this can now be automated[55].

FUNCTIONAL MRI

Ictal and inter-ictal epileptiform activity

Activation of eloquent cortex has been shown in patients with frequent partial seizures and in patients undergoing epilepsy surgery who had invasive EEG evaluation, the ictal-onset phase-related maps were concordant with the presumed seizure onset zone for all patients. The most statistically significant haemodynamic cluster within the presumed seizure onset zone was between 1.1 and 3.5 cm from the invasively defined seizure onset zone. Resection of this region was associated with a good surgical outcome[185].

Focal increases in cerebral blood delivery have been identified in patients with frequent inter-ictal spikes[56-58]. Continuous recording of EEG and functional MRI (fMRI) is possible, following introduction of methods to remove the artifact on the EEG trace caused by the fMRI acquisition, and results in much more detail and analysis of the time course of haemodynamic changes[59,60]. However, even in well-selected patients, approximately 50% do not exhibit inter-ictal epileptiform discharges during the 10–60 minute EEG/fMRI study. Of the remaining patients, approximately 50–90% lead to significant signal changes which are concordant with electroclinical data[61,62,186]. These results may be used to re-evaluate patients who have, for example, been previously rejected for epilepsy surgery[63].

The most recent and largest of these studies reported 76 patients with refractory focal epilepsy, 33 of whom had extratemporal lobe epilepsy. No discharges were seen during the 35−60 minute acquisition in 64% of the patients. The mean number of discharges during the recording in the remaining patients was 89.3. Ten patients underwent surgical treatment, seven of whom achieved seizure freedom. In six of these seven patients, the area of resection included the area of maximum BOLD (blood-oxygen-level dependent) signal increase. Interestingly, in the remaining three patients who continued to have seizures after surgery, the areas of maximal BOLD activation did not overlap with the resected area suggesting that EEG/fMRI may possess a negative predictive value for a good surgical outcome, that is, a lack of concordance with other localising investigations may predict a poor postoperative outcome[64].

The interrogation of the EEG/fMRI data for typical spike-related haemodynamic responses in patients without spikes during the recording period may also provide useful localising information and improve the yield of EEG/fMRI studies[187].

The feasibility of combining fMRI with intracranial EEGs is being studied[65]. As EEG-fMRI covers the whole brain, and as intracranial EEG has very limited spatial sampling, the BOLD changes may assist in the interpretation of intracranial EEG data. This is particularly relevant if the irritative and seizure onset zones are not being sampled directly by the EEG contacts, but these are detecting the propagation of epileptic activity, as the fMRI data can be examined for BOLD changes prior to the first detected EEG changes.

Localisation and lateralisation of cognitive function

An important use of 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[66,67]. In patients with cerebral lesions, the localisation of cognitive activation may differ from the pattern in normal subjects. These data may be helpful in the planning of neocortical resections of epileptic foci, in order to minimise the risk of causing a fixed deficit.

Lateralisation of language function may also be accomplished using fMRI[68]. There was a strong correlation between language lateralisation measured with the carotid amytal test, and using fMRI with a single-word semantic decision task[69] and other fMRI language studies have generally concurred with carotid amytal testing[70]. The high proportion (33%) of left-TLE patients showing bilateral or right hemispheric language-related lateralisation with fMRI implies plasticity of language representation in patients with intractable TLE[71].

fMRI results do not always accord with carotid amytal data[72]. A combination of language tasks may be more reliable than a single task[73,74]. Artefacts and technical difficulties may adversely affect both methods and false lateralisations may occur[75]. 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[76-78]. For example, in a 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[79]. Generally, verbal fluency usually gives stronger and wider activations than verb generation[80]. 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.

Left temporal lobe epilepsy is associated with increased likelihood of expressive language activation in the right frontal lobe, and atypical dominance is more likely with early onset of epilepsy[81]. In patients with lesions close to Broca's area expressive language function may be shown in perilesional cortex[82]. There is considerable heterogeneity of this effect between individuals, related to the underlying pathology[83], which needs to be taken into account when planning surgical treatment close to language areas. There has been concern that language lateralisation with fMRI may be less reliable in the presence of structural lesions[84], and caution is required with clinical interpretation.

Up to 40% of individuals will have significant language deficits, particularly a decline in naming ability after a left anterior temporal lobe resection. Preoperative language fMRI predicted significant language decline, with greater activation in the left hemisphere, particularly the temporal lobe, being associated with greater risk of post-operative impairment[85].

Following temporal lobe resection there is evidence of both intra- and interhemispheric reorganisation of language functions[86]. After left temporal lobe resection, reading sentences activated the right inferior frontal and right temporal lobes, in addition to the remaining left temporal lobe[87].

Decline of memory function following anterior temporal lobe resection, particularly of verbal memory after left-sided ATLR, is a major concern. Several studies have investigated the role of fMRI in predicting the effects of ATLR on memory[88-93]. Most focused on the prediction of verbal memory decline; only a few investigated visual memory decline after non-dominant ATLR. Patients with greater ipsilateral than contralateral medial temporal lobe activation on fMRI memory activation studies had greater memory decline following temporal lobe resection for both verbal memory decline following dominant temporal lobe resection, and for non-verbal memory decline following non-dominant temporal lobe resection. This investigation suggests that preoperative memory fMRI may be a useful non-invasive predictor of postoperative memory change following temporal lobe resection[93].

The choice of paradigm is important in determining activation patterns. Greater left anterior hippocampal activation on word encoding was predictive of greater post-operative decline in verbal memory after left-sided resection, and greater right anterior hippocampal activation on face encoding predicted greater decline in design learning after right-sided resection[94]. Also, greater left than right posterior hippocampal activation correlated with better postoperative verbal memory outcome and greater right than left posterior hippocampal activation correlated with better visual memory outcome. This suggests that reorganisation of function to the posterior hippocampus is associated with better preservation of memory following anterior resection[188].

MAGNETIC RESONANCE SPECTROSCOPY

The metabolites which are detectable using proton spectroscopy (^{1}H MRS) depend on the conditions used for the acquisition. In epilepsy studies *in vivo*, the principal signals of interest have been those from N-acetyl aspartate (NAA), creatine + phosphocreatine (Cr), choline-containing compounds (Cho), and lactate (Lac). There is evidence that NAA is located primarily within neurons and precursor cells and a reduction of NAA signal is usually regarded as indicating loss or dysfunction of neurons. Cr and Cho are found in both neurons and in glia.

MRS in temporal lobe epilepsy

In TLE caused by HS, MRS showed reduction of NAA and increases of choline-containing compounds, creatine + phosphocreatine, reflecting neuronal loss or dysfunction and astrocytosis[95]. Analysis of individual patients showed a reduced NAA/choline + creatine ratio on the side of the focus in 88%, with 40% having bilateral abnormalities. Quantitative short echo time MRS showed the association of HS with low NAA and raised myoinositol, and also an elevation of glutamate and glutamine in epileptic hippocampi that were structurally normal[96]. The implication from these data was that there is neuronal loss or dysfunction and astrocytosis in the temporal lobes of patients with TLE. Abnormalities of metabolite profiles may be found in temporal lobes with normal MRI[97-99] and bilateral abnormalities have been noted in up to 50% of patients with apparently unilateral structural abnormality[100], indicating that MRS may be more sensitive for detecting pathology. The role of MRS in predicting outcome is not clear: in one study of patients with TLE and normal MRI, a lower NAA/choline + creatine was found in those who did not become seizure free[101]. NAA was not reduced in the hippocampi of patients with neocortical epilepsy, either ipsilateral or contralateral to the focus[102], suggesting that hippocampal dysfunction is not a feature of neocortical epilepsy. Mesial TLE was associated with reductions of NAA in frontal grey and white matter, which is consistent with other data suggesting more widespread involvement[103].

Proton (^{1}H) MRS in extratemporal epilepsies

A multivoxel ^{1}H MRS imaging (MRSI) study reported reduced NAA in frontal lobes ipsilateral to frontal lobe epileptic seizures and the decrease in NAA was inversely related to seizure frequency, suggesting that a higher seizure frequency is associated with more neuronal dysfunction or loss[104].

Malformations of cortical development

Reduced NAA/choline and NAA/creatine have been shown in focal cortical dysplasia[105] and other malformations of cortical development[106]. Quantitative short echo time MRSI, with correction for partial volume effects, has shown that metabolic abnormalities were heterogeneous and more extensive than the structural lesions evident on MRI[107]. A post-ictal rise in lactate has been shown using MRSI in the ipsilateral temporal lobe in patients with unilateral TLE[108]. An elevation of cerebral lactate has been noted during and for a few hours after complex partial seizures, with no change in NAA[109]. MRS has shown elevated lactate, decreased NAA and elevated choline during status epilepticus. Subsequently, lactate and choline returned to normal, whereas the NAA level remained reduced, implying neuronal loss or dysfunction[110,111].

GABA

GABA is the principal inhibitory neurotransmitter in the brain, acting at up to 40% of synapses, with a resting concentration of 1−2 mmol/L and a major role in regulation of seizure activity. Proton MRS, using spectral editing, can identify cerebral GABA *in vivo* and estimate the rise in cerebral GABA concentrations that occurs after administration of vigabatrin[112], gabapentin[113] and topiramate[114]. Low GABA concentrations have been associated with continued seizure activity[115]. Low GABA levels were associated with poor seizure control in patients with complex partial seizures, but not in juvenile myoclonic epilepsy. Higher homocarnosine concentrations were associated with better seizure control in both types of epilepsy[116].

Glutamate and glutamine

Glutamate is the principal excitatory neurotransmitter in the brain and responsible for mediating excitotoxicity and initiating epileptic activity[117]. Glutamate is also an intermediary metabolite, and present at a concentration of 8−12 mmol/L. Aspartate, also an excitatory transmitter, is present at a concentration of 1−3 mmol/L. Discrimination between glutamate and glutamine *in vivo* on clinical scanners requires spectral modelling, because of the large number of coupled overlapping peaks and the limited achievable spectral resolution[118].

MRS using short echo times (30 msec), voxels tailored to individual hippocampi and quantitative assessment has shown reduced NAA and increased myoinositol (reflecting gliosis) in epileptogenic sclerotic hippocampi, and similar but less severe abnormalities contralaterally[96]. In patients with TLE and normal MRI, the MRS profile was characterised by elevation of glutamate and glutamine. An increased concentration of combined glutamate + glutamine was noted following focal status epilepticus, with resolution at three months, but persistence of low levels of NAA[119]. Malformations of cortical development, such as heteroptopia and polymicrogyria, have also shown changes in glutamate, glutamine and GABA concentrations consistent with abnormal metabolism of both inhibitory and excitatory neurotransmitters[106].

SINGLE PHOTON EMISSION COMPUTERISED TOMOGRAPHY

Single photon emission computerised tomography (SPECT) is principally used in the investigation of the epilepsies to image the distribution of cerebral blood flow (CBF). The most commonly used SPECT tracers for imaging CBF are ^{99m}Tc-hexamethyl-propylenamine oxime (^{99m}Tc-HMPAO) and ^{99m}Tc-ethyl cysteinate dimer (ECD, bicisate). ^{99m}Tc-HMPAO is given by vein and 70% brain uptake occurs in one minute. The subsequent image is stable for six hours, as after crossing the blood-brain barrier ^{99m}Tc-HMPAO reacts with intracellular glutathione, becoming hydrophilic and so is much less able to recross the blood-brain barrier. Radio-labelled ECD is stable for six hours, easing study of brief ictal events[120].

Inter-ictal SPECT studies

It was established in the 1980s that the marker of an epileptic focus studied inter-ictally in adults and children with SPECT is a region of reduced CBF, but it was soon noted that the results were not reliable. Lobar localisation (e.g. frontal versus temporal) has been more difficult with, in one large representative series, correct localisation in 38% in inter-ictal studies of patients with unilateral temporal lobe EEG focus[121]. Localisation with inter-ictal SPECT is more difficult in patients with extratemporal epilepsy[122,123]. In a blinded comparative study, inter-ictal SPECT was less effective at lateralising the focus of TLE than MRI, with correct lateralisation in 45% compared to 86%. In consequence, inter-ictal SPECT has little place in the routine investigation of patients with epilepsy.

Ictal and post-ictal SPECT studies

The increase in CBF associated with a seizure may be detected using SPECT and may provide useful localising information in patients with partial seizures. An injection of ^{99m}Tc-HMPAO at the time of a seizure results in an image of the distribution of CBF 1−2 minutes after tracer administration. The general pattern is of localised ictal hyperperfusion, with surrounding hypoperfusion, that is followed by accentuated hypoperfusion in the region of the focus, which gradually returns to the inter-ictal state. Combined data from inter-ictal and ictal SPECT scans give a lot more data than inter-ictal scans alone and may be useful in the evaluation of both temporal and extratemporal epilepsy. In complex partial seizure disorders, the epileptic focus has been identified in 69−93% of ictal SPECT studies. A meta-analysis of published data showed that in patients with TLE, the sensitivities of SPECT relative to diagnostic evaluation were 0.44 (inter-ictal), 0.75 (post-ictal) and 0.97 (ictal)[124].

In temporal lobe seizures, the occurrence of contralateral dystonic posturing was associated with an ictal increase in CBF in the basal ganglia ipsilateral to the focus[125]. A characteristic feature of temporal lobe seizures is an initial hyperperfusion of the temporal lobe, followed by medial temporal hyperperfusion and lateral temporal hypoperfusion[126].

Ictal ^{99m}Tc-HMPAO scans may be useful in the evaluation of patients with extratemporal seizures and unremarkable MRI[127]. Asymmetric tonic posturing, contralateral head and eye deviation and unilateral clonic jerking were associated with an ictal increase in CBF in the frontocentral, medial frontal or dorsolateral areas[127]. Varying patterns have been seen in patients with autosomal dominant frontal lobe epilepsy[128].

The coregistration of post-ictal SPECT images with a patient's MRI improves anatomical determination of abnormalities of CBF[129]. A greater advance, however, has been the coregistration of inter-ictal with ictal or post-ictal SPECT images, to result in an 'ictal difference image' that may be coregistered with an individual's MRI. This technique enhances objectivity and the accuracy of data interpretation[130,131]. More recently, it has been

shown that voxel-based analysis of SPECT blood flow studies, specifically of the difference between ictal and inter-ictal cerebral blood flow as a Z-score of the interscan variation of SPECT scans, was more accurate than just thresholding the subtraction images[132].

Ictal SPECT may be useful as a non-invasive presurgical method of investigation by optimising the placement of intracranial electrodes to define sites of seizure onset, but there must be caution as the technique may identify sites of seizure spread, rather than the site of onset[133]. Ictal ^{99m}Tc-HMPAO scans must always be interpreted with caution. Simultaneous video-EEG is essential to determine the relationship between the onset of a seizure and tracer delivery; without this there is the risk of confusing ictal and post-ictal data. Further, spread to other areas of the brain, such as the contralateral temporal lobe, may occur within seconds of seizure onset and so an image of cerebral blood flow distribution 1–2 minutes after the onset of a seizure may indicate other than the site of onset.

Until recently, ^{99m}Tc-HMPAO had to be constituted immediately prior to injection, resulting in a delay of up to one minute. A preparation has now been developed which is stabilised with cobalt chloride. This allows the labelled tracer to be prepared in advance and injected into a patient at any time over the subsequent six hours. The advantage of this development is that the interval between seizure onset and tracer delivery to the brain can be significantly reduced. An alternative is to use ready constituted ^{99m}Tc-ECD, or bicisate, which is stable for several hours, may be injected within 2–20 seconds of seizure onset and demonstrates a focal increase in CBF[134]. The interval between seizure onset and injection may also be shortened by the use of an automated injection device that may be activated by the patient when they detect the beginning of a seizure[135,136]. Extratemporal seizures may be very brief, increasing the need for injection of blood flow tracer as soon as possible after the start of a seizure. With the inevitable interval between injection and fixation of the tracer in the brain, however, it may not be possible to obtain true ictal studies.

In conclusion, inter-ictal SPECT imaging of CBF is only moderately sensitive and ictal SPECT improves the yield. The place of the investigation is in the presurgical work-up of patients with refractory partial seizures and normal MRI scans, in order to generate a hypothesis that may then be tested with intracranial EEG recordings.

POSITRON EMISSION TOMOGRAPHY STUDIES OF CEREBRAL BLOOD FLOW AND GLUCOSE METABOLISM

Positron emission tomography (PET) may be used to map cerebral blood flow, using ^{15}O-labelled water, and regional cerebral glucose metabolism using ^{18}F-deoxyglucose (^{18}FDG). PET produces quantitative data with superior spatial resolution to SPECT. PET data should always be interpreted in the light of high quality anatomical MRI, providing a structural-functional correlation. The development of programmes to coregister MRI and PET datasets on a pixel-by-pixel basis has been fundamental to making these correlations. Statistical parametric mapping has been shown to be useful in the evaluation of ^{18}FDG-PET scans for clinical purposes, with the advantages of allowing a rapid and objective evaluation[137]. In addition, quantitative analysis of data, with correction for partial volume effects add a further useful dimension to the analysis, and this is facilitated by the use of a template to objectively delineate multiple volumes of interest[51].

An epileptogenic focus, studied inter-ictally, is associated with an area of reduced glucose metabolism, and reduced blood flow that is usually considerably larger than the pathological abnormality. Comparison of ^{18}FDG-PET scans with ^{11}C-flumazenil (FMZ) scans[138-140] indicate that neuronal loss is confined to a more restricted area than the region of reduced metabolism.

Ictal PET scans can only be obtained fortuitously, because of the two-minute half-life of ^{15}O and the fact that cerebral uptake of ^{18}FDG occurs over 40 minutes after injection, so that cerebral glucose utilisation data will reflect an amalgam of the ictal and post-ictal conditions. The place of ^{18}FDG-PET as a tool for localising an epileptic focus has been greatly reduced following developments in MRI, as the finding of a definite focal abnormality with the latter technique, such as HS, renders an ^{18}FDG-PET scan superfluous[141]. The place of the investigation is in the presurgical work up of patients with refractory partial seizures and normal or non-definitive MRI scans, or if data are discordant, in order to generate a hypothesis that may then be tested with intracranial EEG recordings.

Temporal lobe epilepsy

Several studies of ^{18}FDG-PET have found a 60–90% incidence of hypometabolism in the temporal lobe inter-ictally in adults and children with TLE. The results of comparative studies depend critically on the relative sophistication of the techniques used. In a comparative study of patients with TLE it was concluded that ^{18}FDG-PET data did not provide clinically useful data if the MRI findings were definite, but had some additional sensitivity[142]. This was confirmed in a more recent study in which ^{18}FDG-PET data correctly lateralised the seizure focus in 87% of patients with TLE and normal conventional imaging[143]. Visual assessment of hypometabolism is less accurate than quantification with a voxel-based comparison with normative data and co-registration with MRI[144,145]. Absence of unilateral temporal hypometabolism does not preclude a good result from surgery[146]. Bilateral temporal hypometabolism was associated with a poor prognosis for seizure remission after surgery[147].

^{18}FDG-PET studies have been less reliable for precise localisation of seizure onset than for answering the question of lateralisation. In an evaluation of ^{18}FDG-PET in patients with TLE and different pathologies, those with HS had the lowest glucose metabolism in the whole temporal lobe, followed by patients whose seizures arose laterally. Patients with mesiobasal tumours generally had only a slight reduction of glucose uptake in the temporal lobe. The metabolic pattern was different between patients with mesial and lateral temporal seizure onset, but there was not a clear correlation between the location of the epileptogenic focus defined with EEG and the degree of hypometabolism[148]. Reduced glucose metabolism and FMZ binding have been reported in the insula in patients with TLE. Emotional symptoms correlated with hypometabolism in the anterior part of the ipsilateral insular cortex, whereas somaesthetic symptoms correlated with hypometabolism in the posterior part. Insula hypometabolism, however, did not affect the outcome from temporal lobe resection[149].

Although reduced glucose metabolism may occur in the face of normal structure[150], atrophy is a major determinant of cerebral metabolism measured with ^{18}FDG PET, and partial volume correction is necessary to understand the relationship between hippocampal structure and functional abnormalities[151]. There have been few studies of newly diagnosed patients; only 20% of children with new onset epilepsy had focal hypometablism[152].

Frontal lobe epilepsy

18FDG-PET shows hypometabolism in about 60% of patients with frontal lobe epilepsy. In 90% of those with a hypometabolic area, structural imaging shows a relevant underlying abnormality. The area of reduced metabolism in frontal lobe epilepsy may be much larger than the pathological abnormality. In contrast, however, the hypometabolic area may be restricted to the underlying lesion153. There have been three main patterns of hypometabolism described in patients with frontal lobe epilepsy: no abnormality; a discrete focal area of hypometabolism; diffuse widespread hypometabolism. Overall, published

clinical series indicate that 18FDG-PET does not appear to provide additional clinically useful information in the majority of patients with frontal lobe epilepsy.

Malformations of cortical development

Glucose metabolism has been detected using ^{18}FDG-PET in the layers of ectopic neurones in band heterotopia[154] and in heterotopic nodules and displaced grey matter[155,156], implying synaptic activity. Cognitive activation tasks using $H_2^{15}O$ PET, in patients with MCD have shown that heterotopia and malformed cortex may participate in higher cerebral functions, but also showed widespread atypical cortical organisation, indicating that there may be extensive disorganisation of normal structure-function correlates in these patients, that would have implications for the planning of any surgical resection[157,158].

Conclusion

Studies with ^{18}FDG-PET have defined the major cerebral metabolic associations and consequences of epilepsy but the data are non-specific with regard to aetiology and abnormalities are more widespread than the pathological lesions. The place of the investigation is in the presurgical work up of patients with refractory partial seizures and normal or non-definitive MRI scans, or if data are discordant, in order to generate a hypothesis that may then be tested with intracranial EEG recordings. Activation studies with $H_2^{15}O$ may determine the functional anatomy of cerebral processes in both healthy and pathological brains; but these studies are now increasingly performed with functional MRI.

POSITRON EMISSION TOMOGRAPHY STUDIES OF SPECIFIC LIGANDS

Positron emission tomography may be used to demonstrate the binding of specific ligands, for example, ^{11}C-flumazenil (FMZ) to the central benzodiazepine-GABA$_A$ receptor complex (cBZR), ^{11}C-diprenorphine and ^{11}C-carfentanil to opiate receptors and ^{11}C-deprenyl to MAO-B. The technique is costly and scarce, but gives quantitative data with superior spatial resolution to SPECT.

Central benzodiazepine receptors

The most important inhibitory transmitter in the central nervous system, gamma amino-butyric acid (GABA) acts at the GABA$_A$-central benzodiazepine receptor complex. Flumazenil is a specific, reversibly bound antagonist at the alpha subunit types 1,2,3 and 5 of the cBZR and ^{11}C-FMZ is a PET ligand that acts as a useful marker of the GABA$_A$-cBZR complex *in vivo*.

Comparative studies with ^{18}FDG-PET scans have shown the area of reduced ^{11}C-FMZ binding to be more restricted than is the area of reduced glucose metabolism in TLE[138,139,159-161]. Patients who were seizure free after neocortical resection had smaller non-resected cortex with preoperative FMZ PET abnormalities. In contrast there were no significant correlations between non-resected FDG PET abnormalities and outcome. This implied that abnormalities of FMZ PET indicated epileptic tissue, whereas FDG PET abnormalities were not so predictive[140].

In patients with unilateral HS, reduction of cBZR binding was initially thought to be confined to the sclerotic hippocampus[162]. A combination of voxel-based and partial volume corrected regional analyses, however, detected extrahippocampal abnormalities of cBZR binding in 50% patients with HS, and identified bilateral hippocampal abnormalities of cBZR in one-

third of patients implying the presence of more widespread abnormalities than previously thought[163-165].

Quantitative autoradiographic and neuropathological studies of resected HS showed that cBZR density (Bmax) was reduced in the CA1 subregion of the hippocampus, over and above the loss of receptors that was attributable to neurone loss. In other hippocampal subregions, loss of receptors paralleled loss of neurones and increases in affinity were noted in the subiculum, hilus and dentate gyrus[166]. A direct comparison of quantitative *in vivo* hippocampal ^{11}C-FMZ binding and *ex vivo* quantitative ^{3}H-FMZ autoradiographic studies showed a mean 42% reduction of the two measures in patients with HS and a good correlation in individual patients[167].

Utility of ^{11}C-flumazenil PET in the investigation of epilepsy
It seems most likely that cBZR changes reflect localised neuronal and synaptic loss in the epileptogenic zone and that the more extensive hypometabolism is a result of diaschisis. In clinical terms, ^{11}C-FMZ PET may be superior to ^{18}FDG for the localisation of the source of the seizure. These data do not confer additional clinically useful information in patients with clear-cut MRI findings of unilateral HS. In a clinical series of 100 patients with partial seizures having pre-surgical evaluation, 94% of those with TLE had an abnormality of ^{11}C-FMZ PET detected, as did 50% of those with other forms of partial epilepsy; 81% of abnormalities found using ^{11}C-FMZ PET were concordant with abnormalities on MRI. ^{11}C-FMZ PET was useful in the identification of bilateral temporal lobe pathology[168].

^{11}C-FMZ PET is likely to be most useful in conditions in which the epileptogenic area is difficult to define by other means, i.e. patients with focal epilepsy and normal high quality MRI ('MRI-negative') and patients with epilepsy due to malformations of cortical development.

Opioid receptors

Endogenous opioids are released following partial and generalised tonic-clonic seizures and contribute to the post-ictal rise in seizure threshold. Investigations of opioid receptors in patients with TLE have shown an increase of the binding of the specific mu-agonist ^{11}C-carfentanil to mu-receptors in lateral temporal neocortex, reflecting an increase in number of available receptors or increased affinity. It has been speculated that an increase in mu-opioid receptors in the temporal neocortex may be a manifestation of a tonic antiepileptic system that serves to limit the spread of electrical activity from other temporal lobe structures[169].

Dynamic ictal studies of opioid receptors have been carried out in reading epilepsy, using ^{11}C-diprenorphine. In order to localise dynamic changes of opioid neurotransmission associated with partial seizures and higher cognitive function, release of endogenous opioids in patients with reading epilepsy was compared with that in healthy volunteers[170]. Reading-induced seizures were associated with reduced ^{11}C-diprenorphine binding to opioid receptors in the left parieto-temporo-occipital cortex and to a lesser extent the left middle temporal gyrus and the posterior parieto-occipital junction. These data gave evidence for localised endogenous opioid peptide release during seizures induced by reading and demonstrate the potential of PET to image release of specific neurotransmitters in response to brain activity in specific cerebral areas *in vivo*.

NMDA receptor

11C-(S)-[N-methyl]ketamine binds to the NMDA receptor, and is thus of interest in studies of epilepsy. In eight patients with medial TLE there was a reduction in tracer binding that

paralleled hypometabolism. It is not clear, however, whether the reduction was due to reduced perfusion, loss of tissue or reduction of receptor binding[171] and further work is needed to clarify this.

Serotoninergic neurones

Alpha-[11C]methyl-L-tryptophan ([11C]AMT) is a marker for serotonin synthesis. In children with tuberous sclerosis, uptake was increased in some tubers that appeared to be the sites of seizure onset. Other tubers showed decreased uptake. In contrast, FDG-PET showed hypometabolism in all tubers. This study suggests that [11C]AMT PET may be useful to detect epileptogenic foci, in patients with tuberous sclerosis, and possibly other forms of cerebral malformation[172,173]. In 39% of patients with MCD or cryptogenic focal epilepsies there was focal increased uptake of alpha-MT in the epileptogenic area. This may be a further useful tool for localising epileptic foci[174]. Increased AMT uptake has been reported to be more specific, but less sensitive for identifying the epileptic focus in children with refractory epilepsy[175], and to be increased in the hippocampus ipsilateral to the focus in TLE[176].

In summary, studies with PET are useful for investigating the neurochemical abnormalities associated with the epilepsies, both static inter-ictal derangements and dynamic changes in ligand-receptor interaction that may occur at the time of seizures. The development of further ligands in the coming years, particularly tracers for excitatory amino acid receptors, subtypes of the opioid receptors and the $GABA_B$ receptor, are necessary to further understand the processes that give rise to and respond to the various forms of the epilepsies. All functional data needs to be interpreted in the light of the structure of the brain. Coregistration with high quality MRI is essential. It will also be important to carry out parallel studies with *in vitro* autoradiography and quantitative neuropathological studies on surgical specimens and post-mortem material.

Conclusion

There have been significant advances in brain imaging that have revolutionised epilepsy management and particularly surgery. Structural MRI continues to improve and contemporary optimal scans may reveal lesions that were previously not evident. In consequence, rescanning individuals with previously unremarkable MRI is appropriate.

If structural MRI does not indicate a plausible structural cause of the epilepsy, or if a demonstrated lesion is discordant with clinical and EEG data, functional imaging with ^{18}F-fluorodeoxyglucose PET, and SPECT of ictal–inter-ictal cerebral blood flow can infer the area that contains the epileptic focus and guide intracranial electrode placements. PET with specific ligands is scientifically attractive, but has not had a major impact on epilepsy surgery practice due to limited availability. A recent study assessed the relative predictive value of FDG PET, ictal SPECT and magnetoencephalography against the gold standards of intracranial EEG and outcome of epilepsy surgery. Magnetoencephalography had a high correlation with intracranial EEG, and both PET and ictal SPECT were of additional localising value[177]. All three modalities were of benefit in predicting seizure-freedom following surgery[178].

Simultaneous EEG and fMRI can visualise the location of inter-ictal epileptic discharges. These data can assist in deciding on the placement of intracranial electrodes to define the site of seizure onset.

Functional MRI to lateralise language and localise primary motor and somatosensory cortex has entered clinical practice and contributed to the decline of the carotid amytal test. If

resections are to be made close to eloquent cortex it is recommended to undertake precise mapping of eloquent function, the site of seizure onset and the irritative zone, to minimise the risk of causing new deficit, and optimise the chance of success. Memory fMRI is less developed, and at present shows promise for predicting the effects of temporal lobe resection in individual patients.

Tractography is used to visualise the major cerebral white matter tracts, and to predict and reduce the risks of surgery. Display of the optic radiation and pyramidal tract are the most relevant for epilepsy surgery at present. The next important step will be reliable integration of all structural and functional data into surgical image-guidance systems so that the data are available real time as surgery progresses.

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