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INVITED REVIEW

Imaging and epilepsy

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Summary

MRI has been applied to the investigation of epilepsy for 12 years. The principle role of MRI is in the definition of structural abnormalities that underly seizure disorders. Hippocampal sclerosis may be reliably identified, quantitative studies are useful for research and, in equivocal cases, for clinical purposes. A range of malformations of cortical development (MCD) may be determined. In patients with refractory partial seizures who are candidates for surgical treatment, a relevant abnormality is identifiable using MRI in 85%, it is likely that subtle MCD or gliosis accounts for the majority of the remainder. The proportion of cryptogenic cases will decrease with improvements in MRI hardware, signal acquisition techniques and post-processing methodologies. Functional MRI is used to identify the cerebral areas that are responsible for specific cognitive processes, and is of importance in planning resections close to eloquent cortical areas. Magnetic resonance spectroscopy (MRS) provides a means of investigating cerebral metabolites and some neurotransmitters, non-invasively. The concentrations of N*-acetyl-aspartate (NAA), creatine and choline-containing compounds may be estimated using proton MRS. Reduction of the ratio of NAA/(creatine+choline) is a feature of cerebral regions that include epileptic foci. Cerebral concentrations of GABA and glutamate, and the effects of antiepileptic drugs on these, may be estimated. Concentrations of high energy phosphate compounds, inorganic phosphate and pH may be assessed using ^{31}P-MRS. In general, epileptic foci are associated with an increase in pH, increased inorganic phosphate and decreased phosphate monoesters. Carbon-13 spectroscopy promises to be a useful method for investigating cerebral metabolism* in vivo. *PET may provide data on regional cerebral blood flow (rCBF), glucose metabolism and the binding of specific ligands to receptors. Correlation of functional and structural imaging data is necessary for adequate interpretation. The hallmark of an epileptic focus is an area of reduced glucose metabolism, identified using [^{18}F]fluorodeoxyglucose (^{18}FDG), that is commonly more extensive than the underlying anatomical abnormality. The clinical role of ^{18}FDG-PET requires re-evaluation in the light of the advances in structural imaging with MRI. Specific ligands are used to investigate specific receptors. Benzodiazepine and opioid receptors have been studied most. Reduced benzodiazepine receptor binding is commonly seen at an epileptic focus, in a more restricted distribution than an area of hypometabolism. Focal increases and decreases in benzodiazepine receptor binding have been demonstrated in MCD in areas that appear normal on MRI, indicating the widespread nature of the abnormalities. It has been found that μ-opioid receptors are increased in temporal neocortex overlying mesial temporal epileptic foci. Dynamic studies of ligand-receptor binding are possible using PET, for example the release of cerebral endogenous opioids has been implied at the time of serial absences. The main use of single photon emission computed tomography (SPECT) is to produce images reflecting rCBF. Interictal studies alone are not reliable. A strength of SPECT is the ability to obtain images related to rCBF at the time of seizures. Concomitant video-EEG recording is necessary. Ictal scans need to be considered in comparison with an interictal scan and an MRI. Interpretation must be cautious, but may yield data that is useful in the investigation of patients for possible surgical treatment.*

Keywords: epilepsy; magnetic resonance imaging (MRI); magnetic resonance spectroscopy (MRS); positron emission tomography (PET); single photon emission computed tomography (SPECT)

Abbreviations: cBZR = central benzodiazepine receptors; CR = creatine+phosphocreatine; CSI = chemical shift imaging; ECD = ethyl cysteinate dimer; ^{18}FDG = [^{18}F]fluorodeoxyglucose; fMRI = functional MRI; FLAIR = fluid attenuated inversion recovery; HCT_2 = hippocampal T_2 relaxation time; HMPAO = hexamethylpropylenamine oxime; HS = hippocampal sclerosis; MCD = malformation of cortical development; MAO = monoamine oxidase; MRS = magnetic resonance spectroscopy; NAA = *N*-acetyl aspartate; PCr = phosphocreatine; PDE = phosphodiesters; P_i = inorganic phosphate; PME = phosphomonoesters; rCBF = regional cerebral blood flow; SPECT = single photon emission computed tomography; SPM = statistical parametric mapping; TE = echo time

Introduction

There have been great strides made in the structural and functional imaging of the brain in epilepsy in the last decade, resulting in a wealth of scientific data and clinical applications. The correlation of structure with function is essential in the understanding of transient disorders of brain function, which often has a structural basis. Accordingly, in this review, MRI is considered first. This is followed by the functional imaging applications of MR: studies of cerebral blood flow (CBF) and spectroscopic studies of cerebral metabolites and neurotransmitters. Isotope studies are then considered: PET and single photon emission computed tomography (SPECT), with a consideration of areas of recent and current research and clinical application.

MRI

The investigation and treatment of patients with epilepsy has been revolutionized in the last decade with the advent of MRI. Since its initial application in 1984 (Oldendorf, 1984; Sostman *et al*., 1984), the superiority of MRI over X-ray CT scanning in terms of sensitivity and specificity for identifying the aetiology of epilepsy in both adults and children has become firmly established (McLachlan *et al*., 1985; Jabbari *et al*., 1986; Latack *et al*., 1986; Lesser *et al*., 1986; Ormson *et al*., 1986; Sperling *et al*., 1986; Theodore *et al*., 1986*a*; Kuzniecky *et al*., 1987; Schorner *et al*., 1987; Triulzi *et al*., 1988; Bergen *et al*., 1989; Franceschi *et al*., 1989; Froment *et al*., 1989; Furune *et al*., 1989; Heinz *et al*., 1989, 1990; Peretti *et al*., 1989; Brooks *et al*., 1990; Convers *et al*., 1990; Dowd *et al*., 1991; Cross *et al*., 1993; Kuzniecky *et al*., 1993*a*). 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 an X-ray CT scan. It is also valuable for the investigation of possible acute intracranial haematomas and skull fractures, and as a supplement to MRI for clarification of possible intracranial calcification that is not shown easily by MRI.

The principal clinical applications of MRI to patient care have been the identification of patients who are suitable for surgical treatment and the elucidation of the structural basis of epilepsy that was previously regarded as being cryptogenic.

Rapid advances are being made in MRI techniques; this has several consequences. First, a review such as this is soon out of date. Secondly, patients who were previously regarded as being 'MRI negative' may have relevant abnormalities identified with contemporary optimal imaging. Thirdly, studies comparing different imaging modalities, such as MRI and PET, need to be explicit about the details of the imaging methods used and their technical limitations, particularly when conclusions are being drawn regarding the relative sensitivity of the methods.

MRI epilepsy protocol

There have been many advances made in recent years and these continue. There is not a uniformity of opinion regarding the optimum imaging protocols for the generality of patients with epilepsy and for patients with refractory partial seizures in whom surgical treatment is being considered.

Indications for neuroimaging of patients with epilepsy

The Neuroimaging Commission of the International League against Epilepsy has recently produced a consensus statement of recommendations on this topic (Neuroimaging Commission, 1997). The rationale of imaging the brains of patients developing epilepsy is (i) to identify underlying pathologies such as tumours, vascular lesions and tumours that require specific therapy and (ii) to assist the formulation of syndrome-based and aetiological diagnoses.

In the non-acute situation, MRI is preferable to X-ray CT as the first imaging investigation. Imaging should include T_1- and T_2-weighted sequences to cover the whole brain in at least two orthogonal planes, with the minimum slice thickness possible on the scanner used. The routine use of gadolinium contrast enhancement is not indicated, but may be useful occasionally to clarify findings (Cascino *et al*., 1989; Elster and Mirza, 1991). Ideally, sequences should include a volume acquisition with a partition size of $\leqslant$1.5 mm to allow for the possibility of reformatting in any orientation and three-dimensional reconstruction of the dataset. In the first 2 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.

When used, X-ray CT scans would usually be obtained without the use of contrast material. If such a scan is unclear,

further information may be obtained using contrast material, but an MRI scan is likely to give more information. In an acute situation of seizures occurring in the context of a neurological insult, X-ray CT is an appropriate initial investigation if MRI is not readily available or is not possible for technical reasons, such as the patient having a cardiac pacemaker or needing attention during the scan.

The best practice is to obtain MRI in all patients with epilepsy, with the exception of those with a definite diagnosis of idiopathic generalized epilepsy or benign rolandic epilepsy of childhood with centro-temporal spikes. MRI is particularly indicated in patients with one or more of the following: (i) the onset of partial seizures, at any age; (ii) the onset of generalized or unclassified seizures in the first year of life, or adulthood; (iii) evidence of a fixed deficit on neurological or neuropsychological examination; (iv) difficulty obtaining seizure control with first line antiepileptic drugs; (v) loss of seizure control, or a change in the pattern of seizures.

Patients who are candidates for surgical treatment of epilepsy require detailed brain imaging (*see* below).

In situations in which access to MRI is limited, essential indications for MRI are: (i) patients with partial or secondary generalized seizures, and apparently generalized seizures, that are not controlled with anti-epileptic drugs; (ii) patients who develop progressive neurological or neuro-psychological deficits.

Presurgical candidates

These patients merit the most sophisticated MR imaging that is available and may also benefit from functional imaging with PET and SPECT.

A typical presurgical MRI protocol would be as follows. (i) A volume acquisition T_1-weighted data set that is acquired in an oblique coronal orientation, orthogonal to the long axis of the hippocampi, covering 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. (ii) An oblique coronal spin echo sequence, with proton density (echo time, TE = 30) and heavily T_2-weighted (TE = 90 or 120) acquisitions that are orientated perpendicular to the long axis of the hippocampus, to demonstrate any increase in T_2-weighted signal intensity. Hippocampal T_2 relaxation times (HCT_2) may also be obtained using the data from a dual echo sequence or from a separate multiecho sequence.

A key feature of a volumetrically acquired sequence is the ability to coregister the structural information with functional imaging data. Further sequences such as fluid attenuated inversion recovery (FLAIR), and the application of surface phased-array coils may also be useful to obtain further information (*see* below).

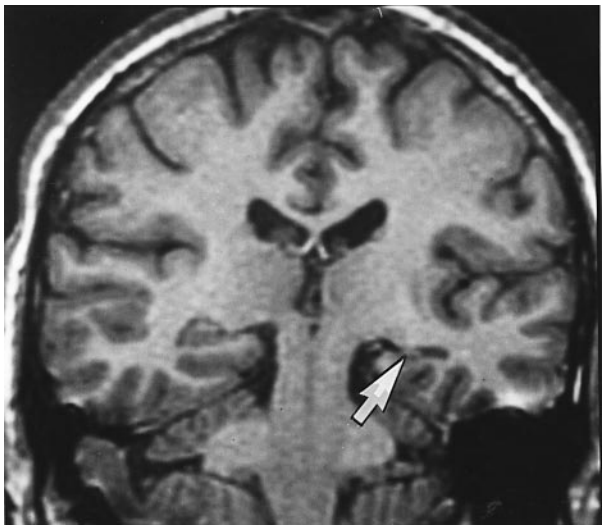

Fig. 1 Coronal T_1-weighted MRI [Inversion recovery prepared Radiofrequency Spoiled Gradient Recalled acquisition in the steady state (Ir SPGR)] showing an atrophic left hippocampus (on right of image), characteristic of hippocampal sclerosis (arrow).

The range of structural cerebral abnormalities underlying epilepsy and identified with MRI

Hippocampal sclerosis (HS)

Until 1990, it was held that MRI could not reliably identify HS (Heinz *et al*., 1990; Jackson *et al*., 1990; Berkovic *et al*., 1991), which is the single most common pathology underlying partial seizure disorders that do not respond to antiepileptic drug therapy, but which are amenable to surgical treatment. Two-thirds of patients with HS become seizure-free after an anterior temporal lobe resection (Babb and Brown, 1987; Bruton, 1988) and a similar success rate has been found in patients with HS identified using MRI (Berkovic *et al*., 1995).

Several factors underly the ability of MRI to identify HS: appreciation of hippocampal anatomy and use of optimally orientated scanning planes, awareness of relevant imaging abnormalities, and advances in MRI instrumentation, acquisition sequences and post-acquisition processing of data (Duvernoy, 1988; Jackson *et al*., 1990; Berkovic *et al*., 1991). The hippocampus is a curved structure with its concave surface facing the brainstem and with its longitudinal axis at ~35° to the orbito-meatal line, that was traditionally used as the axial imaging plane for both X-ray CT and MRI. To minimize partial volume effects, the hippocampus is best visualized 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 initially identified MRI features of HS were hippocampal atrophy, demonstrated with coronal T_1-weighted images (Fig. 1) and increased signal intensity within the hippocampus on T_2-weighted spin echo images (Fig. 2)

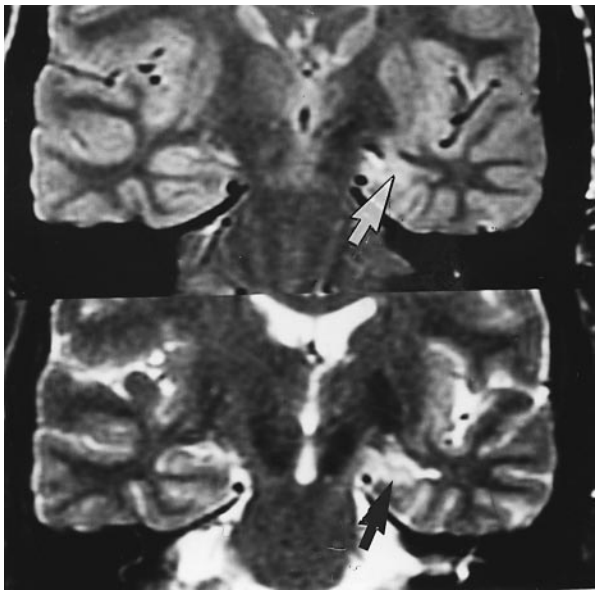

Fig. 2 The images are of the same patient as in Fig. 1. *Upper panel*: coronal proton density image (spin echo, TE 30) showing atrophic left hippocampus, on right of image, with increased signal (arrow head). *Lower panel*: coronal T_2-weighted image (spin echo, TE 120) showing atrophic left hippocampus, on right of image, with increased signal (arrow head). These features are characteristic of hippocampal sclerosis.

(Jackson *et al*., 1990). Increased T_2-weighted signal is, in itself, a non-specific finding and may result from foreign tissue lesions or from pixels containing partial volumes of CSF. In order to avoid such errors it is necessary that the finding of increased signal on T_2-weighted imaging is interpreted in the light of high quality T_1-weighted anatomical imaging. Further MRI features of HS, in addition to atrophy, increased T_2-weighted signal and being well demonstrated on heavily T_1-weighted coronal inversion recovery images, include decreased T_1-weighted signal intensity and disruption of the internal structure of the hippocampus (Jackson *et al*., 1993*a*). There may be associated atrophy of the ipsilateral fornix (Baldwin *et al*., 1994), although this measure is not likely to add clinically useful information. 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 (Meiners *et al*., 1994) are variably accompanying features to the changes of HS but are not reliable in their own right.

Although fast spin-echo sequences have been advocated by some (Tien *et al*., 1993), a careful comparison of conventional spin-echo and fast spin-echo T_2-weighted sequences for visual assessment of the hippocampus showed that, although the latter takes less time, the data are less accurate, so the sequence is not recommended in the evaluation of patients with epilepsy (Jack *et al*., 1994*a*).

Qualitatively it has been noted that atrophy and increased signal on T_2-weighted images are often not uniform along the length of the hippocampus, but affect the body of the hippocampus most commonly, followed by the tail and the head (Bronen *et al*., 1995). In a series of 30 patients Kim *et al*. (1995) concluded from cross-sectional area measurements and qualitative assessment of signal on T_2-weighted images that HS was diffuse in 29 cases. This is a higher incidence of diffuse HS than has been commonly found and clearly patient selection criteria have a great effect on such a study. Quantitative assessments of both hippocampal cross-sectional area and T_2 relaxation time along the length of the hippocampus are necessary to evaluate this further.

Misalignment of the patient in the MRI scanner may cause difficulties with the visual assessment of hippocampal atrophy if thick, e.g. 5 mm, and non-contiguous slices are used. An advantage of volume acquisitions of T_1-weighted scans using a gradient echo technique is the facility to reformat the images in any orientation, with minimal loss of spatial resolution.

Several studies have found that ipsilateral hippocampal atrophy is a good prognostic feature for seizure control following anterior temporal lobe resection (Berkovic *et al*., 1991; Grattan-Smith *et al*., 1993; Murro *et al*., 1993; Garcia *et al*., 1994*a*). This finding has greatly reduced the need for invasive EEG studies in patients with temporal lobe epilepsy, in whom surface EEG data and other features are concordant.

Quantitative MRI assessment of the hippocampus.

The assessment of hippocampal atrophy can be improved by measurement of the volumes of hippocampi (Jack *et al*., 1990). In this initial study, measurements of hippocampal volume ratios gave correct lateralization in 76% of cases, with no false lateralizations and they were superior to qualitative inspection of hippocampal asymmetry, measurements and visual assessment of anterior temporal lobe, and of mesial parenchymal T_2-weighted signal intensity. The same group subsequently showed hippocampal atrophy on MRI in 14 out of 15 patients with mesial temporal sclerosis and in three out of nine patients with lesser degrees of neuronal loss or no abnormality (Cascino *et al*., 1991). Hippocampal atrophy has been correlated with reduction of neuronal density in all hippocampal regions except CA2 (Bronen *et al*., 1991; Lencz *et al*., 1992). In a complex group of patients, hippocampal atrophy on MRI compared favourably with all other non-invasive means of localization, using ictal depth EEG as a gold standard (Spencer *et al*., 1993).

Asymmetrical hippocampal atrophy was associated with the site of seizure onset (Ashtari *et al*., 1991; Cendes *et al*., 1993*a*; Baulac *et al*., 1994). Further, asymmetrical atrophy of the resected hippocampus on MRI was associated with a good prognosis for seizure control (Bronen *et al*., 1991). Atrophy of the contralateral nonresected hippocampus was associated with a worse outcome and two patients with bilateral atrophy and no side-to-side difference did poorly (Jack *et al*., 1992). Subsequently, however, the same author reported that ‘A satisfactory operative outcome is possible in patients with bilaterally symmetrical mesial temporal sclerosis by MRI criteria’ (Jack *et al*., 1995), underlining the

fact that factors other than the MRI appearance need to be taken into account in the presurgical decision making process.

The severity of hippocampal atrophy on the side of the language-dominant hemisphere is an important determinant of impairment of verbal memory following hippocampal resection. The more severe the atrophy preoperatively, the less likely it is that there will be a significant decline of verbal memory after surgery (Trenerry *et al*., 1993*a*).

Cook *et al*. (1992) used contiguous 1.5 mm slices through hippocampus and amygdala with a spoiled gradient echo technique, thresholding and a manually driven cursor to outline the hippocampus and amygdala in individual slices, and then generated cross-sectional contour maps. Asymmetry of hippocampi was not found in 10 normal right-handed subjects, but focal or diffuse hippocampal atrophy was noted in patients with well-defined temporal lobe epilepsy. With technological and software developments, quantitative volumetric techniques have advanced considerably in recent years. The use of contiguous thin slices enhances the accuracy and reliability of measurements and permits localization of atrophy along the length of the hippocampus. Images obtained with increased T_1 contrast, by including an inversion recovery pulse prior to the gradient echo acquisition, and acquisition of images perpendicular to the hippocampus may increase precision further. Attempts are being made to automate the assessment of hippocampal volume and morphology, however, at present the methodology of hippocampal volumetry is demanding and time-consuming, requiring a post-processing computer and a skilled operator.

In clinical practice, hippocampal asymmetry of $\geqslant$20% is reliably visually apparent to skilled neuro-imaging specialists, but lesser degrees of asymmetry require quantification (Van Paesschen *et al*., 1995). Because of the time-consuming nature of hippocampal volume measurements, measuring just the hippocampal body on T_2-weighted images has been advocated (Kim *et al*., 1994). Whilst this may give an indicator of hippocampal asymmetry in the gross case, it is not likely to add anything to a visual assessment of coronal T_1- and T_2-weighted sequences and, in a patient with borderline or focal atrophy, it may be misleading and is not to be recommended.

In confirmation of previous pathological data, severe and diffuse hippocampal volume loss has been associated with complicated early childhood convulsions (Cendes *et al*., 1993*a*; Kuks *et al*., 1993).

A visually evident increase in hippocampal T_2-weighted signal intensity generally has been reported in 0–60% of cases of HS (McLachlan *et al*., 1985; Sperling *et al*., 1986; Kuzniecky *et al*., 1987; Triulzi *et al*., 1988; Brooks *et al*., 1990; Jack *et al*., 1990; Jackson *et al*., 1990; Ashtari *et al*., 1991; Bronen *et al*., 1991). In an analogous way to the quantification of hippocampal atrophy by volumetric analysis, T_2-weighted signal intensity may be quantified reproducibly by measurement of HCT_2.

HCT_2s have been reproducibly estimated from 16 images, with TEs from 22 to 262 ms (Jackson *et al*., 1993*b*; Grunewald *et al*., 1994). Using these techniques, it was concluded that T_2 relaxation-time measurements are a useful identifier of hippocampal pathology, with marked elevations being associated with HS and intermediate values being seen in patients without qualitative MRI evidence of HS, contralateral to HS and in some patients with extratemporal seizure onset. The T_2 times in the contralateral hippocampus were outside the normal range in 32% of patients, possibly reflecting bilateral HS. Subsequent studies on the same system, however, and correlative quantitative neuropathological investigations have shown that whilst HS is usually associated with an abnormal HCT_2, some patients with definite HS may have a normal HCT_2 (Van Paesschen *et al*., 1995), and that there is an inverse correlation between HCT_2 and the ratio of glial to neuronal density in the hippocampus (Van Paesschen *et al*., 1994). Similarly, there is a close correlation between HCT_2 and severity of hippocampal volume loss, allowing delineation *in vivo* of a spectrum of the severity of HS (Van Paesschen *et al*., 1995, 1997). Quantitative MRI may be very useful in the evaluation of patients for possible surgical treatment and may also be applied in a longitudinal fashion to determine whether there is any evidence of progression of the hippocampal damage.

A limitation of this technique has been that only a single measure of T_2, from the body of the hippocampus, has been hitherto possible. HS may be of varying severity along the length of the hippocampus, and may be confined to the anterior part of the head. This is the probable explanation for patients who have HS but a normal HCT_2. Developments in the technique to allow the acquisition of a series of HCT_2 measurements along the length of the hippocampus represent a significant step forwards in the MRI assessment of this structure (Duncan *et al*., 1996*a*).

Data from healthy subjects indicate that there is a narrow range of normal HCT_2, resulting in the parameter being a potentially useful absolute measure. Until recently, the wide normal range of hippocampal volume measurements, for which absolute values limited assessment of asymmetry by calculation of hippocampal volume ratios, precluding identification of bilateral HS and lesser degrees of contralateral hippocampal damage. The development of methods of correcting the hippocampal volume for the total intracranial volume has largely obviated this limitation (Free *et al*., 1995; Van Paesschen *et al*., 1997).

It is likely that research in next decade will define the role of measurement of tissue volumes and relaxation times in the assessment of the hippocampus and that improvements in spatial resolution will reveal details of hippocampal substructure, *in vivo*.

MRI measures of amygdala volume have been made (Cendes *et al*., 1993*a*, *b*), but are not sufficiently reliable to be of great clinical utility. T_2 relaxometry has been shown, however, to be a sensitive means of detecting amygdala pathology (Van Paesschen *et al*., 1996).

The technique of T_2 relaxometry has also been used to evaluate the possible neurotoxic effects of drugs and has

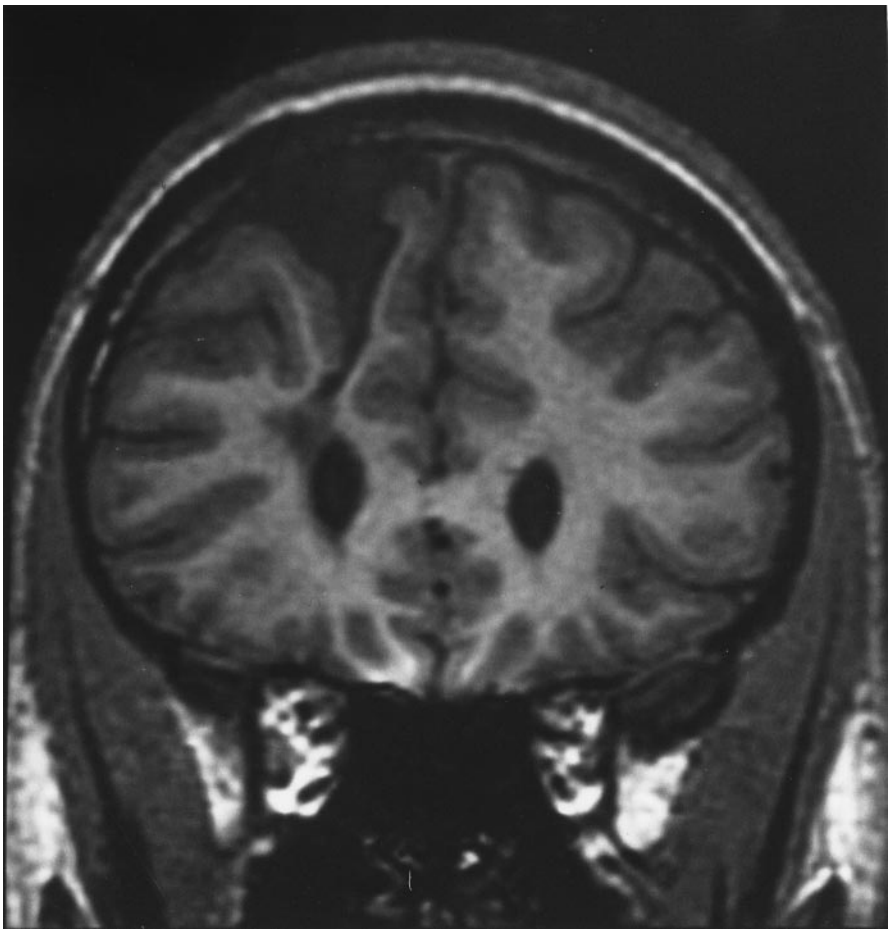

Fig. 3 Coronal T_1-weighted MRI (Ir SPGR) showing schizencephaly that extends to the right lateral ventricle.

been shown to be sensitive to the development of intramyelinic oedema in rats treated with the antiepileptic drug vigabatrin (Jackson *et al*., 1994*a*). Similar studies in patients did not show any changes suggestive of this pathology (Jackson *et al*., 1994*b*).

Although MRI has made a considerable difference to the evaluation of patients with refractory seizures who are candidates for surgical treatment, the technique does not make other investigations redundant. Clinical and functional data (neurophysiological and psychological and in some cases functional imaging) all need consideration in reaching a consensus for individual patients (Spencer, 1995). Contrary to initial reports (Cook *et al*., 1992), further experience with larger numbers of patients has shown that some patients with seizure onset outside the temporal lobe may have MRI features of HS (Cascino *et al*., 1993*a*; Adam *et al*., 1994; Baulac *et al*., 1994; Fish and Spencer, 1995; Spencer 1995). A detailed assessment using all investigatory modalities is particularly important in the 15% of patients with HS being considered for surgery, in whom cortical dysgenesis and other structural pathology is also evident on MRI (Raymond *et al*., 1994*a*).

Progression of hippocampal damage. A retrospective study did not find a relationship between hippocampal atrophy and duration of habitual epilepsy (Trenerry et al., 1993*b*). In a mixed group of patients with partial seizures, hippocampal atrophy was significantly correlated with longer duration of epilepsy (Spencer *et al*., 1993). In a further series of 50 patients with intractable temporal lobe epilepsy, neither hippocampal nor amygdala volume were correlated with duration of epilepsy, estimated seizure frequency, age or occurrence of generalized seizures. As expected, patients with prolonged febrile convulsions in early childhood had significantly smaller hippocampal and amygdala volumes than those without such a history. These findings did not suggest continuing hippocampal or amygdala atrophy during chronic temporal lobe epilepsy, that could be detected by volumetric MRI, but did not exclude the possibility of progression of hippcampal damage in the early years of the habitual epilepsy (Cendes *et al*., 1993*b*).

A cross-sectional study comparing control subjects, patients with newly diagnosed apparently cryptogenic temporal lobe epilepsy and those with chronic refractory temporal lobe seizure disorders found that both patient groups tended to have smaller hippocampi than the control group, and that the hippocampi were smaller in the chronic group than in those with newly diagnosed epilepsy (Saukkonen

et al., 1994). The differences were not marked; a prospective longitudinal quantitative MRI study is necessary to determine whether progressive hippocampal damage does occur during the course of a patient's epilepsy.

Malformations of cortical development

Malformations of cortical development (MCDs) are commonly identified as causes of epilepsy and neurodevelopmental deficits. The clarity with which these malformations may be demonstrated by MRI, compared with X-ray CT is striking. These abnormalities are increasingly being recognized in patients with seizure disorders that were previously regarded as being cryptogenic. Such data may lead to a reclassification of a patient's epilepsy syndrome from being cryptogenic and generalized to being symptomatic and localization-related and may have important implications for treatment (Kuzniecky, 1994; Palmini *et al*., 1994). Gross abnormalities such as lissencephaly or schizencephaly may be identified on X-ray CT, but are seen much more clearly using MRI, which demonstrates significantly more detail (Chamberlain *et al*., 1990) (Fig. 3).

The range of MCDs 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. Sixty-eight out of 100 patients in a recent series had normal X-ray CT and 19 out of 36 patients had normal previous (conventional) MRI. In general there was not a good correlation between the epileptic syndromes and EEG abnormalities and the location or extent of the dysgenesis as shown by MRI (Raymond *et al*., 1995). The classification of these malformations is in a state of evolution and is currently based largely on MRI features. Some require histopathology to allow a definitive diagnosis to be made. The elucidation of the genetic basis of MCDs will result in a further reclassification. One scheme, currently under consideration by the Neuroimaging Commission of the International League against Epilepsy, is to subdivide malformations of cortical development as follows: (i) diffuse cortical malformations: agyria pachygyria, polymicrogyria, microcephaly, megalencephaly, microdysgenesis; (ii) focal or multifocal cortical malformations: focal cortical dysplasia, hemimegalencephaly, focal polymicrogyria, tuberous sclerosis; (iii) heterotopias.

Other, more detailed classifications also under consideration separate MCDs into four basic categories, with subdivision of each category into generalized and focal: (i) abnormal neuronal and glial proliferation; (ii) abnormal neuronal migration; (iii) abnormal cortical organization; (iv) malformations, not otherwise classified.

There are many technical issues concerned with MRI of MCDs. The best results are obtained using T_2-weighted and high resolution T_1-weighted volumetric techniques with thin partitions, covering the whole brain and allowing viewing of the structures in two orthogonal planes. Interpretation needs analysis of the cortical grey matter, the grey–white boundary, white matter and ventricles. It is often difficult to be certain whether subtle abnormalities of sulcal morphology are outside the normal range. Analysis of MRIs of young children (<2 years old) needs to take into account the normal development of myelination and the indistinct grey–white matter boundary on T_2-weighted images.

Malformations of cortical development were found in 4.3% of 303 patients with epileptic seizures referred for MRI, in 6.7% of patients with established epilepsy and in 13.7% of patients with concomitant mental retardation (Brodtkorb *et al*., 1992). Seven percent of 222 patients with temporal lobe epilepsy had MCDs revealed with MRI, comprising focal cortical dysplasia, nodular heterotopia, abnormal gyration, limited schizencephaly and hippocampal malformations. Clinical and EEG features did not differentiate these patients from the others with temporal lobe epilepsy, indicating the key role of MRI in their investigation (Lehericy *et al*., 1995). Interpretation of these studies and extrapolation to other populations is dependent on the selection bias regarding criteria for referring patients for MRI scans and on the sophistication of the MRI instrument and techniques used in the study.

Identification of the structural cerebral abnormality in hemimegalencephaly using MRI is essential in the consideration of surgical treatment, which can be dramatically beneficial (Kalifa *et al*., 1987; Palmini *et al*., 1994).

Dysembryoplastic neuroepithelial tumours are regarded as benign developmental tumours and not infrequently 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 T_1-weighted images, high signal on T_2-weighted images similar to those of CSF, and slightly higher signal intensity in the lesion than CSF on proton density images. Cyst formation may occur and may be revealed with gadolinium-DTPA (diethylenteriamine penta-acetic acid) enhancement. Calcification is present in some cases and may be more readily demonstrated with X-ray CT. Despite some claims to the contrary (Kuroiwa *et al*., 1994), confident differentiation from low-grade astrocytomas and ganglioglioma is not possible with MRI (Koeller and Dillon, 1992; Raymond *et al*., 1994*b*).

Tuberous sclerosis has a characteristic appearance on MRI and was the diagnosis in five patients in a recent series of 100 patients with MCDs and epilepsy (Raymond *et al*., 1995). Identified large tubers commonly show concordance with surface EEG signs in terms of localization and lateralization, but this is not invariable (Curatolo and Cusmai, 1988; Cusmai *et al*., 1990; Tamaki *et al*., 1990). MRI has not been able to differentiate reliably between the forme fruste of tuberous sclerosis and other cortical dysgeneses (Palmini *et al*., 1991*a*).

Characteristic clinical-MRI syndromes have been described such as that of bilateral central rolandic and sylvian

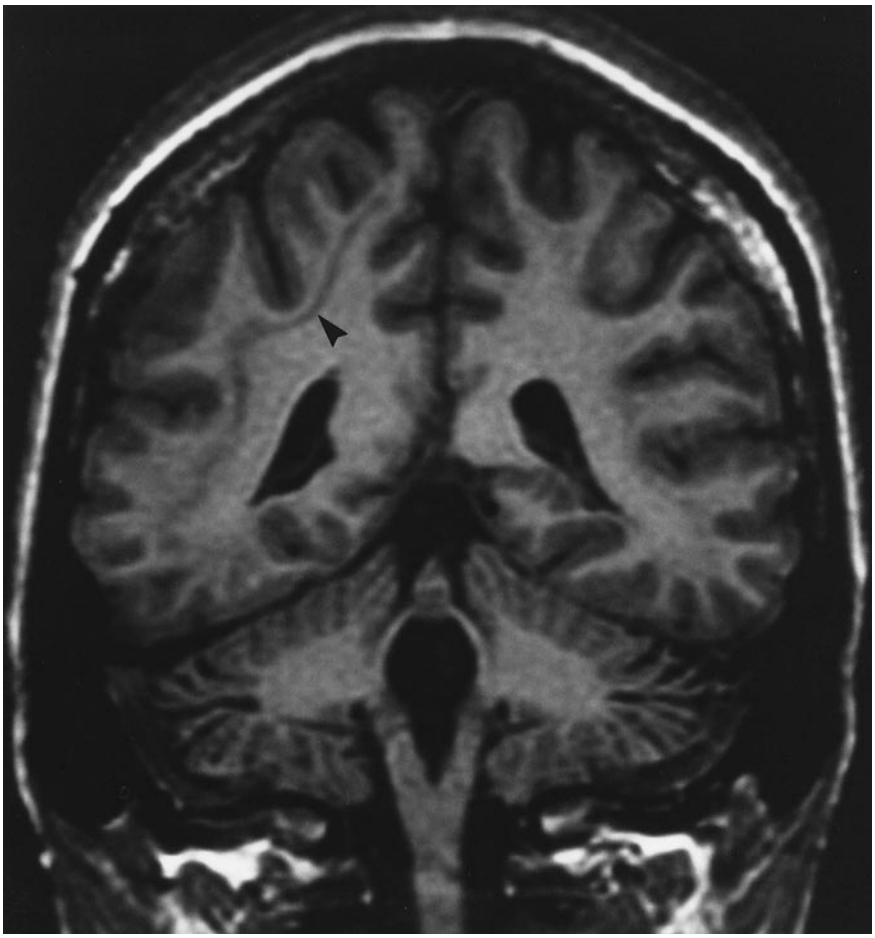

Fig. 4 Coronal T_1-weighted MRI (Ir SPGR) showing extensive band heteropia in the right cerebral hemisphere (arrow head).

macrogyria and polymicrogyria, with a pseudobulbar palsy and cognitive impairment (Kuzniecky *et al*., 1989; Kuzniecky *et al*., 1994). Hypothalamic hamartomas, sometimes associated with gelastic epilepsy, precocious puberty and cognitive impairment, are clearly demonstrable using MRI (Berkovic *et al*., 1988; Nishio *et al*., 1989; Marliani *et al*., 1991).

More subtle abnormalities such as focal nodular heterotopia and band heterotopia may only be apparent if optimal MRI techniques are used. Heterotopias produce a signal that is isointense to grey matter and are recognized and characterized by their location and distribution in adults and children (Schuierer *et al*., 1995). Heterotopias may be associated with other cerebral abnormalities.

Band heterotopia 'double cortex' is an example of a generalized MCD that may be present in patients with mild epilepsy and normal intellect or a minor degree of cognitive impairment (Fig. 4). On X-ray CT the white matter may appear hypodense (Livingston and Aicardi, 1990). The overlying cortex may be normal or macrogyric. Band heterotopia may be associated with the Lennox–Gastaut syndrome (Palmini *et al*., 1991*b*; Ricci *et al*., 1992). Thicker bands and more severe associated pachygyria have been associated with generalized seizures, cognitive impairment and neurological deficit (Palmini *et al*., 1991*b*; Barkovich *et al*., 1994).

Females are predominantly affected by subependymal heterotopia. The heterotopia is more commonly nodular than diffuse, bilateral more often than unilateral, and most frequent in the occipital horn of the lateral ventricle (Fig. 5). The associated seizures are usually partial, but some patients had been previously thought to have a generalized epilepsy (Huttenlocher *et al*., 1994; Raymond *et al*., 1994*c*).

Focal cortical dysplasia may result in refractory partial seizures and its identification with MRI has important consequences, with the possibility of surgical treatment (Kuzniecky *et al*., 1988; Palmini *et al*., 1991*a*; Kuzniecky *et al*., 1995). Macrogyria, microgyria and other derangements of gyrus formation may be apparent (Guerrini *et al*., 1992). However, focal cortical dysplasia underlying temporal lobe epilepsy (Kuzniecky *et al*., 1991) and refractory status epilepticus is not always identified with MRI (Desbiens *et al*., 1993) and a major thrust of ongoing imaging research is to be able to identify cortical dysplasia that is currently occult.

Minor anomalies of the morphology and arrangement of cortical gyri may only be visualized if the data is processed

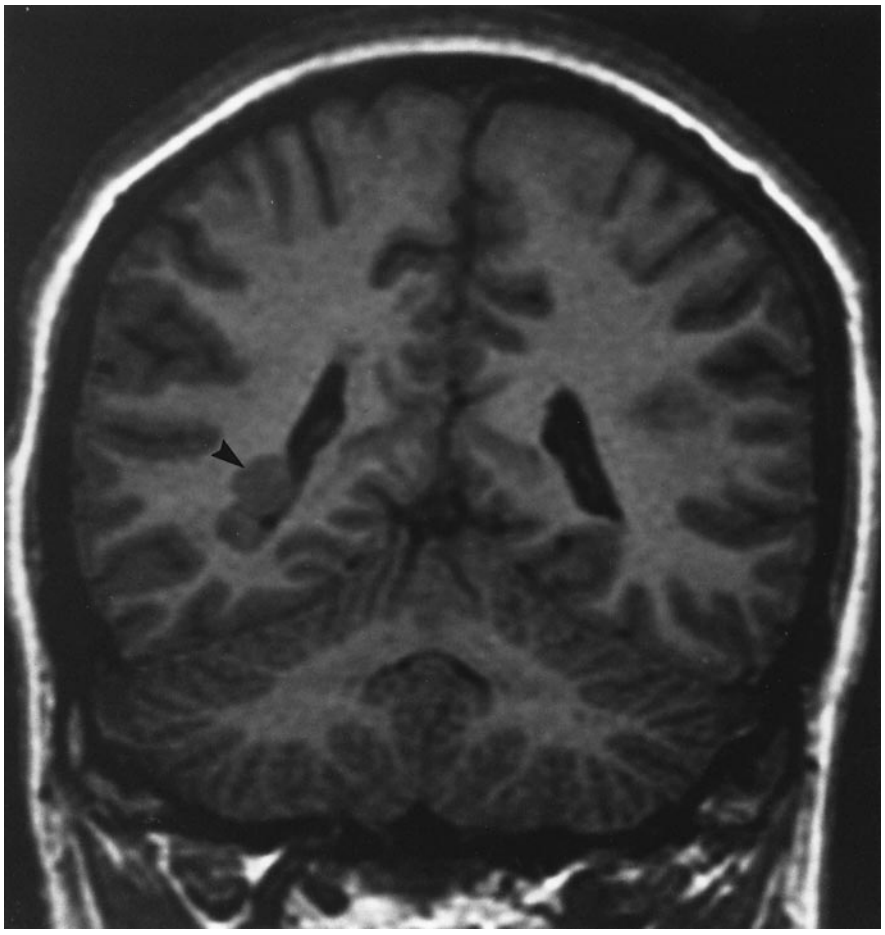

Fig. 5 Coronal T_1-weighted MRI (Ir SPGR) showing nodular subependymal heterotopia in the inferior-lateral wall of the right lateral ventricle (arrow head).

after acquisition and reformatted to display the abnormalities. A focal area of polymicrogyria, for example, may not be evident on sagittal, coronal or axial scans and only be evident on a reformatted tangential slice that cuts across the affected area or on a three-dimensional reconstruction of the surface of the brain (Barkovich *et al*., 1995). Quantitative analysis of the relative volumes of grey and white matter in a cerebral hemisphere that appears macroscopically normal, in patients with apparently localized neuronal migration defect, may reveal widespread abnormalities (Sisodiya *et al*., l995) implying that the migration disorder is more extensive. To date, there has not been pathological confirmation of these findings. Hitherto unsuspected widespread abnormalities have also been implied by recent PET studies of central benzodiazepine receptors (cBZR) (*see* below) and these findings are compatible with the poor likelyhood of a focal cortical resection rendering a patient with a MCD seizure-free and with the contention that even high resolution contemporary MRI only reveals the 'tip of the iceberg' of abnormal cortical development.

Gangliogliomas

Gangliogliomas and gangliocytomas are uncommon benign neuronal tumours. X-ray CT often shows a calcified contrast-enhanced cystic lesion. On MRI, the lesions have low signal-intensity on T_1-weighted sequences and a high signal-intensity on T_2-weighted sequences and may show enhancement after injection of gadolinium DPTA. There may be signal inhomogeneity on proton density-weighted images. The imaging findings are not specific, however, and have much in common with those of a dysembryoplastic neuroepithelal tumour. Identification of gangliogliomas is important as surgical resection carries a good chance of seizure control (Chamberlain and Press, 1990; Otsubo *et al*., 1990; Peretti *et al*., 1991; Tampieri *et al*., 1991; Smith *et al*., 1992).

Granulomas

Tuberculomas and cysticercosis are the most common identified causes of epilepsy in developing countries. Epilepsy is the most common manifestation of neurocysticercosis (Aubry *et al*., 1995). In a recent Indian series of 170 children with chronic epilepsy, MRI revealed 64 tuberculomas, 27 cases of cysticercosis and three gliomas (Gulati *et al*., 1991). Whilst X-ray CT will often demonstrate neurocysticercosis, MRI is more sensitive in demonstrating various stages in the development of noncalcified cerebral cysticercosis lesions (Sanchetee *et al*., 1991).

Cavernomas

Cerebral cavernomas commonly underly epilepsy and are an important diagnostic group as surgical removal carries up to a 70% chance of subsequent seizure remission. Cavernomas are often not identified on X-ray CT, but have a characteristic appearance on MRI (Requena *et al*., 1991). Cavernomas are circumscribed and have the characteristic appearance of a range of blood products. The central part contains areas of high signal on T_1- and T_2-weighted images, reflecting oxidized haemoglobin, with darker areas on T_1-weighted images due to deoxyhaemoglobin. The ring of surrounding haemosiderin appears dark on a T_2-weighted image. There may be calcification, which usually appears dark on T_1- and T_2-weighted images. There is no evidence of arteriovenous shunting. Arteriovenous malformations with high blood flow have a different and distinctive appearance.

Other pathologies

Focal and generalized atrophy, tumours, scars, cysts, ischaemic and traumatic lesions underlying and associated with epilepsy are all well demonstrated with MRI. Ischaemic lesions associated with epilepsy are particularly common in the older age group and are well demonstrated with MRI (Kilpatrick *et al*., 1991).

Indolent gliomas are clearly identified using MRI. These lesions are most commonly ill-defined, non-cystic, do not enhance with contrast media, and appear to arise from deep white matter. Intracranial epidermoid cysts may give rise to refractory partial seizures and a fixed neurological deficit that is stable over many years.

There are, of course, limitations to the resolution of even the highest quality contemporary MRI and, as with MCDs, the extent of microscopic abnormality evident on pathological analysis frequently exceeds that apparent *in vivo* on the MRI.

Transient MRI changes in relation to seizures

Generally, single brief complex partial seizures do not appear to affect the signal on T_2-weighted images (Grunewald *et al*., 1994). Complex partial status and generalized status may result in transient increased signal on T_2-weighted images (Fujikawa *et al*., 1991; Horowitz *et al*., 1992; Lee *et al*., 1992; Monte-Secades *et al*., 1994) and this finding needs to be differentiated from an underlying structural lesion such as a glioma or inflammatory process (Henry *et al*., 1994*a*).

MRI in evaluation for surgical treatment of epilepsy

The improvement in MRI over recent years has had a marked impact on the nature of presurgical evaluation (Cascino, 1994; Spencer, 1995; Zentner *et al*., 1995). As noted previously, whilst MRI may identify lesions that may be giving rise to refractory epilepsy, such as HS, malformations of cortical development and cavernomas, clinical and functional data (neurophysiological and psychological and in some cases functional imaging) all need consideration in reaching a consensus for individual patients (Cascino, 1994; Spencer, 1995). A small but definite group of patients have unilateral HS evident on MRI, but partial seizures that arise from elsewhere in the brain. Also, in ~10% of patients with refractory partial epilepsy who are presurgical candidates, and who have hippocampal atrophy, the atrophy is bilateral. In these patients EEG studies are essential for determining the site of seizure onset (Fish and Spencer, 1995).

The nature of the pathology, revealed by MRI, is an important factor in postoperative outcome. In a recent series of 135 patients followed up for 5 years after temporal lobectomy, 69% of patients with foreign tissue lesions, 50% with HS, and 21% with normal MRIs had no postoperative seizures (Berkovic *et al*., 1995).

The complete removal of discrete neocortical lesions, identified with MRI, that cause epilepsy has a high success rate (Williamson *et al*., 1992; Cascino *et al*., 1993*b*; Kuzniecky *et al*., 1993*b*; Montes *et al*., 1995). If no lesion is identifiable on a high quality MRI, or if there is incomplete removal of a lesion, such as multilobar gliosis, there is not a good chance of relief of seizures (Cascino *et al*., 1992; Lorenzo *et al*., 1995). Functional imaging and invasive EEG recordings may still be needed if no lesion is evident on a high quality MRI, if there is dual pathology or if the clinical and EEG features are discordant with the MRI. If MRI reveals the dual pathology of a neocortical temporal lobe lesion and HS, removal of just the former has a poor prognosis, whereas also resecting the sclerosed hippocampus appears to improve the prognosis (Cascino *et al*., 1993*c*). The coincidence of hippocampal atrophy and other pathology is ~15% overall, but varies with the nature of the other lesion: being 25% in patients with MCD, 31% in the presence of porencephalic cysts, 9% with vascular lesions and 2% with low grade gliomas. MCD associated with hippocampal atrophy was located anywhere, whereas vascular lesions were most commonly close to the atrophic hippocampus (Cendes *et al*., 1995).

MRI has an important role in the assessment of patients after surgery for epilepsy, particularly if seizures have not remitted and the possibility of a second operation is being contemplated. In patients with HS, the extent of hippocampal resection may be determined from the MRI and a larger resection has generally been correlated with better outcome (Jack *et al*., 1988; Awad *et al*., 1989; Siegel *et al*., 1990; Nayel *et al*., 1991). More extensive left temporal resections have been associated with a tendency towards greater impairment of verbal memory (Katz *et al*., 1989). The extent of hippocampal damage preoperatively is an important factor as is the extent of resection. If there is severe HS evident on MRI preoperatively, memory, particularly verbal memory in patients having a resection of a speech dominant temporal lobe, is less likely to be worse after surgery, even if there is an extensive resection. It is removal of a hippocampus that

appears normal on MRI that carries a high risk of noticeable memory impairment (Hermann *et al*., 1992; Lencz *et al*., 1992; Miller *et al*., 1993; Trenerry *et al*., 1993*a*; Sass *et al*., 1994).

A further common use of MRI in the surgical treatment of epilepsy is MRI-based stereotactic placement of intracerebral recording electrodes (Pillay *et al*., 1992). MRI-based stereotactic procedures have also been used in selective removal of the hippocampus and amygdala (Kelly *et al*., 1987). MRI-based surgical guidance systems have been developed, that enable structural and superimposed functional imaging data to be presented to the surgeon, with real-time feedback of the position of a manually controlled pointer in relation to the patient's MRI scan (Meyer *et al*., 1996).

MRI may also verify whether a structural lesion has been removed, which is an important prognostic factor with regards to outcome (Nayel *et al*., 1991). Volumetric analysis of pre- and postoperative MRI scans allow an estimation of the volume of excized cerebral tissue and can provide an audit of surgical technique (Kitchen *et al*., 1993, 1994, 1995). In patients having a corpus callosotomy, preoperative MRI is necessary to determine the anatomy of the corpus callosum and, postoperatively, the extent of the section (Bogen *et al*., 1988; Chadan *et al*., 1992).

Recent developments in MRI

The fluid attenuated inversion recovery (FLAIR)–MRI sequence produces images in which parenchymal lesions have a high signal and CSF gives a low signal. This may help in the differential diagnosis of areas of high signal on T_2-weighted images and increase the conspicuity of lesions, but it does not improve the identification of heterotopias (Fig. 6) (Segawa *et al*., 1994; Bergin *et al*., 1995; Wieshmann *et al*., 1996). The increased yield from FLAIR depends on the quality of the 'standard imaging'. If the latter is good there is little extra information obtained. Suppression of CSF signal may be poor in the mesial temporal areas, sometimes resulting in the appearance of high signal in the hippocampi and amygdalae in normal subjects; this markedly impairs the utility of the sequence in the evaluation of possible HS.

Diffusion-weighted imaging has been shown to be very sensitive in the detection of early ischaemic changes, and to show changes in animal models of status epilepticus (Prichard, 1994; Helpern and Huang, 1995). It is not yet clear whether this technique will be a useful clinical or research tool in the investigation of human epilepsies.

Improved gradient performance underpins echoplanar imaging and further improvements in speed and spatial resolution are anticipated (Riederer *et al*., 1995). Phased array surface coils may improve signal-to-noise ratio in superficial cortex and hippocampal regions by 1.7 and this may lead to improved spatial resolution (Hayes *et al*., 1993). Imaging at high field strengths, such as 4.1 T may improve spatial resolution of gyral anatomy (Kuzniecky, 1995).

Developments in the processing of data after acquisition may increase the yield of useful information. A volumetrically acquired dataset may be resliced in nonconventional orientations to display an abnormality better (Barkovitch *et al*., 1995). Abnormalities of gyral pattern may be best displayed using curvilinear reconstructions (Bastos *et al*., 1995). Three-dimensional reconstructions may be used to give a simulation of the surface of the brain and an indication of gyral morphology. In one study employing this technique, gyral abnormalities were reported in six out of 16 patients with extratemporal seizure disorders and unremarkable two-dimensional MRI scans (Sisodiya *et al*., 1996). A limitation of the current methodologies is that assessment is entirely visual and subjective, and has to take the normal variations in gyral morphology into account.

The surface area of grey and white matter and measures of the curvature of gyri may be made. These measurements can show subtle abnormalities in neocortical structure in temporal lobe epilepsy, but their relationship to epileptic foci and the occurrence of seizures is not clear (Lee *et al*., 1995).

Functional MRI

The first functional MRI (fMRI) study applied to epilepsy was in 1988: abnormal perfusion was demonstrated using MRI with a phase mapping technique in a patient with epilepsia partialis continua (Fish *et al*., 1988). Considerable technical advances have been made since that time. Increased perfusion in temporoparietal cortex in a patient with partial status epilepticus was demonstrated using a susceptibility-weighted sequence and dynamic contrast enhancement with gadolinium (Warach *et al*., 1994).

fMRI that is sensitive to the oxygenation status of haemoglobin provides images that are sensitive to changes in regional cerebral blood volume and flow, producing data that is analogous to that obtained with blood flow tracers and PET, but with an improved temporal resolution, to the order of 5 s. This technique can detect ictal changes in CBF (Jackson *et al*., 1994*c*; Detre *et al*., 1995; Warach *et al*., 1996). Limitations of the method include the effects of movement artefact through a series of scans, although this may be compensated for by image coregistration, and the fact that it is impracticable for a patient, even with very frequent seizures, to lie for hours in an MRI scanner awaiting the onset of a seizure. It is possible that fMRI studies will be able to identify areas of brain involved in the generation of interictal epileptiform activity. This will be dependent on technical advances to allow safe, reliable collection of EEG during echoplanar scanning, and on EEG triggering of scan acquisitions.

A further important use of this technique 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 neurosurgical resection (Hammeke *et al*., 1994; Jack *et al*., 1994*b*; Morris *et al*., 1994; Puce *et al*., 1995). Lateralization of language function may also be accomplished using fMRI (Binder *et al*.,

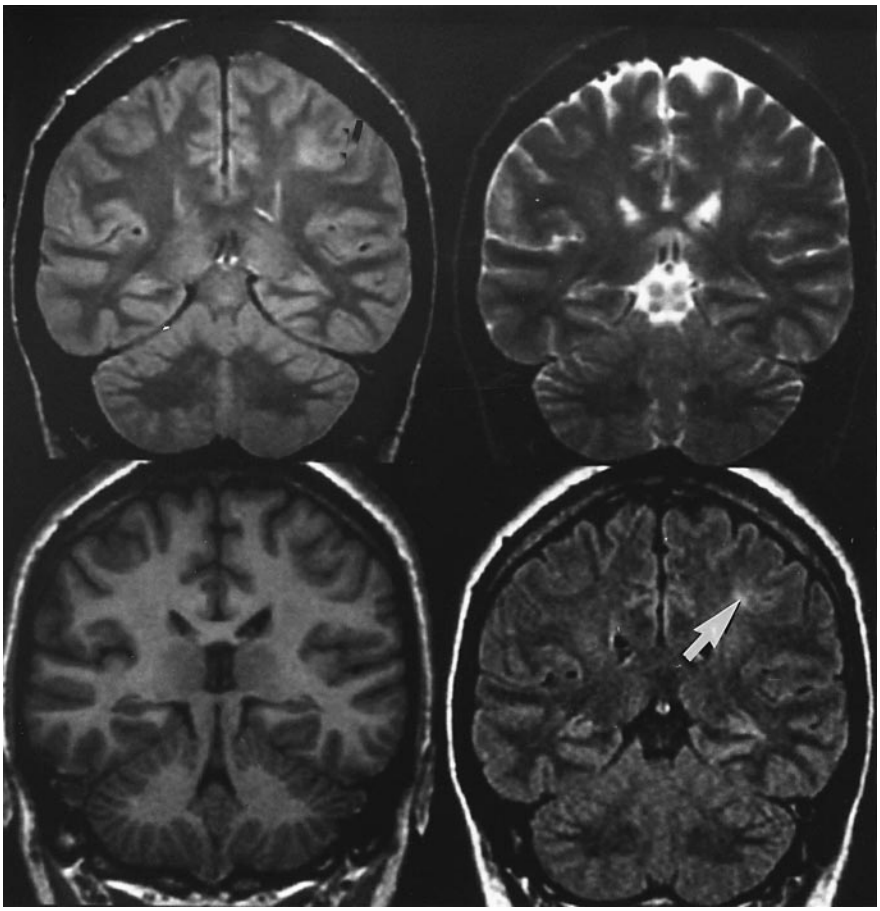

Fig. 6 Coronal MRI of focal area of dysgenesis in region of left central sulcus. Four images from the same plane: *upper left*, proton density (TE 30); *upper right*, T_2-weighted (TE 120); *lower left*, T_1-weighted (Ir SPGR); *lower right*, FLAIR. The abnormality is apparent on the proton density and T_2-weighted images, but is more conspicuous on the FLAIR image (arrow).

1995; Desmond *et al*., 1995). It is not yet known whether any suitable paradigms could be developed to lateralize and localize memory functions satisfactorily, in a way that could obviate the need for a carotid Amytal test in some patients who are candidates for a temporal lobe resection (Perrine, 1994).

Conclusion

Over the last decade, the development of MRI has revolutionized the investigation and treatment of epilepsy. The aetiological basis of partial seizures may commonly be demonstrated, with significant consequences for possible surgical treatment. Minor abnormalities, for example subtle MCDs and areas of gliosis, may not be detected at present. The spatial resolution of MRI will improve over the coming years, with improved diagnostic yield. Quantitative studies provide further sophistication, and serial quantitative scans will increase the understanding of the consequences of epilepsy and its treatment.

Magnetic resonance spectroscopy

The basic principles underlying magnetic resonance spectroscopy (MRS) are the same as those for MRI. In MRS the resonance frequency of a nucleus provides chemical information which may be displayed as a spectrum of signal intensity against frequency and in which the area under the trace indicates amplitude of the signal at that frequency.

Not all nuclei show magnetic resonance and the most common naturally occurring isotopes of carbon and oxygen (^{12}C and ^{16}O) do not resonate. Nuclei which resonate include ^{1}H, ^{31}P, ^{13}C, ^{19}F and ^{23}Na. The physical principles of MRS have been covered in more detail in a recent review (Connelly and Duncan, 1995).

Both ^{1}H and ^{31}P are naturally abundant (99.98% and 100%, respectively) and are present in compounds that are of interest in sufficient concentration to be detectable in the brain *in vivo*. The MR sensitivity to ^{31}P is only 7% that of ^{1}H so it is necessary to use larger volumes of tissue for ^{31}P than for ^{1}H-MRS, with a consequent loss of the spatial resolution of information. To a limited extent the signal-to-noise ratio can be improved upon by increasing the number of acquisitions, but this is not efficient and the feasible duration of MRS examinations of patients is limited to 60 min.

The volume of brain from which MR spectra are obtained may be defined in two main ways. (i) Single voxel techniques in which data are acquired from a single volume of interest

(usually a cube of ~8 ml for ^{1}H, or 60–100 ml for ^{31}P). A limitation of single voxel methods is the need to have *a priori* data on the location of the epileptogenic focus, or area that is of interest for some other reason. (ii) Chemical shift imaging (CSI, also known as MRS imaging) in which a large region is excited before the metabolite signals are spatially encoded using phase encoding gradients, as is done in MRI. Using this technique, data from many voxels can be acquired simultaneously, and the increase in efficiency can be used to obtain smaller voxels (1–2 ml for ^{1}H or 25 ml for ^{31}P) than is feasible with single voxel methods.

Accurate definition of brain anatomy and the identification of structural abnormalities using MRI is necessary for the interpretation of all functional imaging studies, including PET, SPECT, fMRI and MRS. The latter techniques may be carried out with MRI in a single session. *In vivo* MRS investigations in epilepsy have examined the nuclei ^{31}P and ^{1}H and have principally been carried out in patients with temporal lobe epilepsy who are candidates for surgical treatment.

Proton (^{1}H) spectroscopy

The metabolites which are detectable using ^{1}H-MRS depend on the conditions used for the acquisition. Some molecules, for example GABA, glutamate, glutamine and lactate give rise to MR signals that exhibit spin–spin coupling, which results in the signals changing with time. As a result, the detection of their resonance is dependent on the TE used. The detection of GABA *in vivo* has been shown to be facilitated by the use of spectral editing techniques (Rothman *et al*., 1993). In epilepsy studies *in vivo*, the principal signals of interest have been those from *N*-acetyl aspartate (NAA, 2.01 p.p.m.), creatine+phosphocreatine (CR, 3.0 p.p.m.), choline-containing compounds (choline, 3.2 p.p.m.) and lactate (doublet signal centred at 1.35 p.p.m.). There is evidence, principally from cell culture studies (Urenjak *et al*., 1992, 1993), that NAA is located primarily within neurons and precursor cells and a reduction of the NAA signal is usually regarded as indicating loss or dysfunction of neurons. In support of this, a reduction in NAA has been found in situations in which neuronal loss would be anticipated, such as in infarcts, tumours, or in epileptic foci. CR and choline are found both in neurons and in glial cells, and cell studies suggest that they are present at much higher concentrations in glia than in neurons (Urenjak *et al*., 1992, 1993).

Proton spectroscopy has a greater signal-to-noise ratio and better spatial resolution than ^{31}P-MRS and is more easily carried out in a single examination, with MRI. In one of the earliest studies, an increase of lactate was shown by ^{1}H-MRS in the brains of rabbits after bicuculline-induced status epilepticus (Petroff *et al*., 1986).

Matthews *et al*. (1990) reported reduced NAA in the temporal lobes of two patients with Rasmussen's encephalitis, and focally increased lactate in a patient who had epilepsia partialis continua. Using MRS, a reduction of NAA and increase of glutamate and/or glutamine has been reported following partial status epilepticus, although it was not possible to distinguish between these latter two compounds (Fazekas *et al*., 1995)

^{1}H-MRS investigation in the temporal lobe

Localized water suppressed MR spectra were obtained from 82 patients with a variety of epilepsies, on a 1.5 Tesla system, from single 8 ml voxels that were placed in the left and right medial temporal lobes, including part of the hippocampus, temporal white matter and neocortical grey matter (Gadian *et al*., 1994). The volume of interest was localized using a spin echo sequence, with a TE of 135 ms. Signal intensities from 2.0 p.p.m. (NAA), 3.0 p.p.m. (CR) and 3.2 p.p.m. (choline) were identified on spectra and the areas under the peaks were measured. In comparison with a group of normal subjects, the patients with epilepsy showed a reduction in the signal intensity of NAA and increases in signal intensities of (choline) and CR, resulting in a decrease of the NAA/(choline+CR) ratio. These results implied a loss or dysfunction of neurons in the medial temporal lobe in patients with epilepsy. Further, as the concentrations of creatine, phosphocreatine and choline-containing compounds appear to be much higher in oligodendrocytes and astrocytes than in neurons (Urenjak *et al*., 1993) the increased signal from these compounds may reflect gliosis.

In a subsequent study of 25 adults with well-defined intractable temporal lobe epilepsy and 13 age-matched control subjects (Connelly *et al*., 1994), 19 of the patients had HS, three had foreign tissue lesions, one had widespread signal change suggestive of gliosis and two had no abnormality evident on MRI. In comparison with the normal subjects, the patients with temporal lobe epilepsy showed a mean 22% reduction of NAA, 15% increase of CR and 25% increase in choline in the epileptogenic temporal lobe. The mean NAA/(choline+CR) ratios were significantly less in the patients with epilepsy than in the control subjects, both ipsilateral and contralateral to the focus, with the ipsilateral side being more affected.

An analysis of individual patients showed a reduced NAA/(choline+CR) ratio in 22 of 25 patients (88%) on the side of the focus, with 10 (40%) having bilateral abnormalities. In six out of the 10 patients with bilateral abnormalities, one temporal lobe was judged to be significantly more abnormal than the other. When lateralization was possible with MRS this concurred with MRI findings in all but one case. However, two patients with no abnormality shown on MRI had abnormal MRS and three patients with normal MRS on both sides had HS. The number of patients was not sufficient to ascribe any prognostic significance to the data. All 15 of these patients, who had been followed for $>$1 year after temporal lobectomy, had a good seizure outcome. Seven out of eight with unilateral abnormalities were seizure-free or had auras only, and one had $>$90% seizure reduction. Four out of the six with bilateral abnormalities were seizure-free or had auras only, and two

had had single seizures following surgery. Similar results have been reported, using the same technique, in 20 children with temporal lobe epilepsy (Cross *et al*., 1996). Abnormalities of the NAA/(choline+CR) ratio were found in 75%, with bilateral abnormalities in 45% and correct lateralization of the seizure focus in 55%. Bilateral increases in choline and CR were noted, suggesting gliosis.

The implication from these data was that there is neuronal loss or dysfunction and astrocytosis in the temporal lobes of patients with temporal lobe epilepsy. The magnitude of the reduction of NAA was such that the abnormality could not be confined to the hippocampus, as that structure occupies only a small proportion of the 8 ml voxel used. This finding is consistent with PET data on cerebral glucose metabolism in which there is commonly an area of hypometabolism that is larger than the anatomically defined focus (Engel *et al*., 1982*a*; Sackellares *et al*., 1990). The basis of the regional area of hypometabolism and, by inference NAA reduction, is not certain. Comparative PET studies with [^{11}C]flumazenil and [^{18}F]fluorodeoxyglucose (^{18}FDG) in patients with temporal lobe epilepsy have suggested that diaschisis is a more likely explanation than is neuronal loss (Henry *et al*., 1993*a*; Savic *et al*., 1993). The cellular mechanisms that underly the reduction of NAA, and the elevation of choline and CR need to be clarified with correlative neuropathological studies. The dynamic changes in the concentrations of NAA and other metabolites in relation to the occurrence of seizures also need further evaluation.

CSI has the advantages of giving information on the regional distribution of metabolites and identifying areas of maximal abnormality, but is more susceptible to artefacts. In a CSI study of 10 patients with temporal lobe epilepsy and five controls, the left–right asymmetry of NAA/CR ratios was found to be significantly different from controls in all cases (Cendes *et al*., 1994). This ratio was low in the mid-temporal lobe in five cases and in the posterior temporal lobes in eight patients. The asymmetry was maximal in the mid-temporal region in three patients and in the posterior temporal region in six. The use of an asymmetry index alone precludes the detection of bilateral abnormalities. Comparison of NAA/CR ratios in patients and controls, however, indicated that two patients had a bilateral reduction in the NAA/CR ratio in the posterior temporal region, and that the greatest reduction was ipsilateral to the maximum EEG disturbance. One of the 10 patients had no MRI evidence of hippocampal atrophy, but had a decrease of the NAA/CR ratio in the mid-posterior temporal lobe, and the resected specimen revealed mild mesial temporal sclerosis.

A further CSI study on eight patients with unilateral complex partial seizures and eight controls (Hugg *et al*., 1994) found a significant asymmetry in the intensity of the NAA signal in all of the patients. In each case the lower NAA was found on the side of EEG focus. No significant changes in choline or CR were observed.

Using high resolution single slice CSI obtained on a 4.1 Tesla instrument, and mapping MRS data onto the equivalent MRI slice, a reduced NAA/CR ratio was found in the epileptogenic hippocampus in all of 10 patients with temporal lobe epilepsy. Four out of the 10 patients also had abnormalities in the NAA/CR ratio in the contralateral hippocampus and in two of these four, invasive EEG recordings demonstrated seizure onset from both hippocampi. Significant reductions in the NAA/choline ratio were found in eight out of the 10 patients. In this population, MRI showed hippocampal atrophy in seven patients, and was normal in three. In the three patients with normal MRI, the pathological specimen showed gliosis and minimal neuronal loss, suggesting that this technique may be useful for the *in vivo* identification of subtle pathology (Fig. 7) (Hetherington *et al*., 1995). The findings differ from those of Connelly *et al*. (1994) in that the latter found normal proton ^{1}H-MRS data in some patients with abnormalities on MRI. The likely explanation of this is the superior spatial resolution and reduced partial volume effects in Hetherington's (1995) investigation.

In a postoperative study of 48 children who had had temporal lobe resections, normal or abnormal proton MRS on the unoperated side was not a prognostic factor for seizure outcome. Patients who had right temporal resections and who had abnormalities of MRS in the left temporal lobe had some verbal memory deficits, suggesting that the MRS data may be a useful indicator of the functional integrity of this part of the brain (Incisa-della-Rocchetta *et al*., 1995).

Using *in vivo* ^{1}H/^{13}C-MRS, cortical electroshock was shown to cause a prolonged rise of brain lactate levels without significant change in intracellular pH or high-energy phosphorylated compounds. The brain lactate approached equilibrium with blood glucose within 1 h, with nearly complete turnover of the raised brain lactate pool. These techniques may be usefully implemented in the investigation of human brain to derive further information of the metabolic state of cerebral lactate pools in epilepsy (Petroff *et al*., 1992).

A postictal rise in lactate has been shown using ^{1}H-CSI in the ipsilateral temporal lobe in patients with unilateral temporal lobe epilepsy, and was also confined to one side in patients who appeared to have bilateral temporal lobe epilepsy. The elevation in lactate persisted for up to 6.5 h, hence this may be a useful technique for lateralizing seizure foci (Comair *et al*., 1994).

CSI is superior to single voxel techniques in terms of coverage of the brain, and is becoming the method of choice in a number of centres for the study of epilepsy. However, it is technically more demanding than single voxel MRS, with respect to problems with magnetic field homogeneity (shimming), water suppression and leakage of signal from subcutaneous fat into voxels other than just those adjacent to the scalp. This is a particular problem with studies of the temporal lobes, because of the proximity of the petrous temporal bones. Cendes *et al*. (1994) noted that anterior temporal lobe structures were more accessible to single voxel methods, and reported only posterior and mid-temporal results

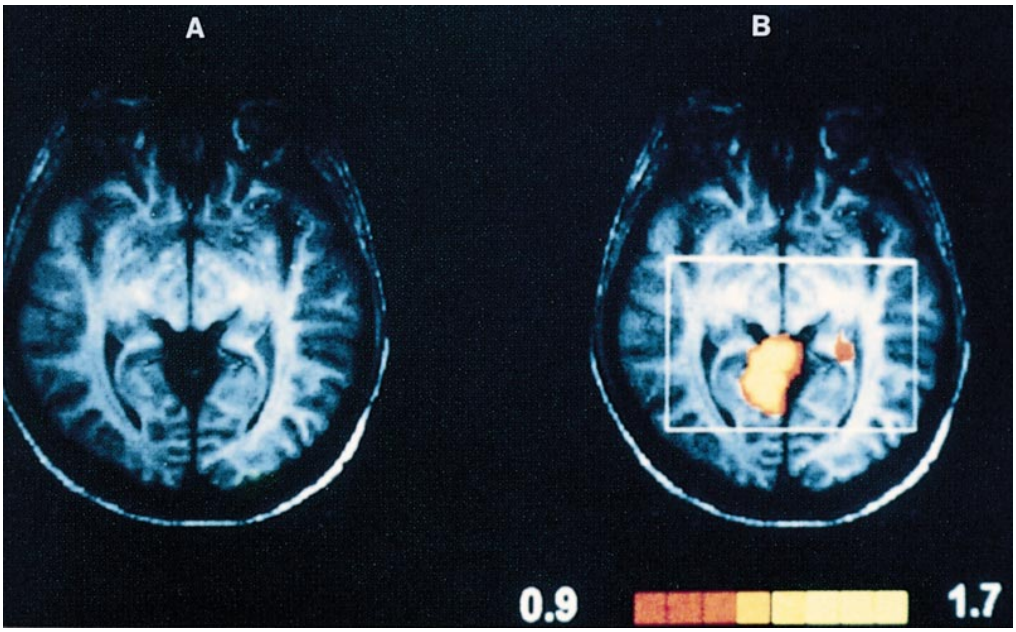

Fig. 7 (**A**) An oblique axial MRI scan through the posterior body of each hippocampus in a patient with left temporal lobe epilepsy. (**B**) Regions in which the CR/NAA ratio is >0.9 are overlaid onto the MRI image, showing elevation of this ratio in the posterior left hippocampus and the cerebellar vermis. The former suggests neuronal loss or dysfunction, but the latter is a normal finding in groups of healthy control subjects. (Reprinted by permission of the publisher from 'Application of high field spectroscopic imaging in the evaluation of temporal lobe epilepsy' by Hetherington *et al*., Magn Reson Imaging 1995; 13: 1179. © Elsevier Science Inc.)

from their CSI study. Xue *et al*. (1993) also reported problems with sub-optimal shimming when performing CSI in a large region including both temporal lobes and, in consequence, adopted the strategy of acquiring CSI volumes from each temporal lobe separately. The same group have subsequently reported localized reductions of NAA/choline in 53 patients with temporal lobe epilepsy, unilateral in 34 and bilateral in 19 (Xue *et al*., 1994). Sauter *et al*. (1991) have shown in a comparative study (CSI versus single voxel localization) that the CSI data must be interpreted with caution. Nevertheless, in the long run, it is likely that CSI will provide data that cannot be obtained using other techniques.

The place of ^{1}H-MRS in the clinical evaluation of patients with temporal lobe epilepsy is not yet clear. Issues that need to be addressed include the following. (i) Definition of the clinical significance and reliability of ^{1}H-MRS data when it is discordant with other information and when data from other investigations are equivocal. (ii) Is a bilateral abnormality of ^{1}H-MRS an adverse prognostic factor for a good outcome from temporal lobectomy? (iii) Interpretation of the range of ^{1}H-MRS findings in the temporal lobes of patients with epileptic seizures of extratemporal onset.

At present, ^{1}H-MRS appears to be a sensitive method for detecting regional neuronal integrity and may identify areas of gliosis. In future, the technique may contribute in clinical practice to the lateralization and localization of the epileptic focus and the identification of bilateral abnormalities and it may further reduce dependence on invasive EEG studies. It will be difficult to establish this role firmly, as presurgical evaluation depends on establishing a consensus between different strands of data. Examination of a larger number of patients is needed to determine the strength of the associations between ^{1}H-MRS and other investigatory data and the clinical significance of discrepancies.

^{1}H-MRS investigations in extratemporal seizure disorders

Single voxel ^{1}H-MRS applied to the supplementary motor area in patients whose seizures were believed to originate from this region, without structural abnormalities on MRI to guide voxel placement, was not helpful in one study (Cook *et al*., 1991). A ^{1}H-CSI study reported reduced NAA in frontal lobes ipsilateral to frontal lobe epileptic foci in eight patients (Garcia *et al*., 1993). This finding needs to be replicated and it is necessary to determine the extent of the area of NAA reduction in patients with seizures of frontal, temporal and posterior hemisphere onset. It is likely that technical advances in MR hardware and software technology, CSI and automated MRS examinations will allow further clinical applications, such as the ability to localize focal abnormalities that underly seizure disorders, in the temporal and extratemporal neocortex, when MRI does not reveal a structural abnormality.

As yet there have not been systematic MRS studies of

MCD. In a recent report of two children with hemimegalencephaly, the white matter of the affected hemisphere had markedly reduced concentrations of NAA and glutamate, with mild abnormalities in the contralateral hemisphere, and with less marked changes in the grey matter. One child had increased myoinositol- and choline-containing compounds in grey matter, suggesting gliosis (Hanefield *et al*., 1995).

^{1}H-MRS investigations of neurotransmitters

^{1}H-MRS can identify cerebral GABA *in vivo* and estimate the rise in GABA concentrations that occurs after administration of vigabatrin to humans (Rothman *et al*., 1993) and to rats (Preece *et al*., 1994). This technique has also been used to elucidate the dose–response curve of this effect, and to measure glutamate and glutamine levels. These experiments have implicated feedback inhibition of the conversion of glutamine to glutamic acid by elevated cerebral GABA concentrations, offering an explanation as to why the latter do not continue to rise, in human brain, with doses of vigabatrin in excess of 3 g/day (Petroff *et al*., 1995). Increased cerebral GABA concentrations have also been noted following gabapentin administration, using MRS (Petroff *et al*., 1996). Decreased glutamate and increased myoinositol have also been noted in 2 ml voxels in epileptogenic hippocampi (Wieser *et al*., 1995).

A limitation at present is the inability to distinguish, non-invasively, between the metabolic and neurotransmitter pools of these compounds. Development of this area of research, however, opens the possibility of a non-invasive characterization of regional cerebral neuro-metabolic profiles of patients developing seizure disorders. It is possible that these data could be used to help in the initial selection of drug therapy in each individual patient, to monitor the effects of therapy and to identify focal abnormalities that may be of relevance in the presurgical evaluation of medically refractory patients.

^{31}P spectroscopy

Cerebral metabolites detectable with ^{31}P-MRS in epilepsy include compounds related to high energy phosphate and phospholipid metabolism such as ATP, phosphomonoesters (PME), phosphodiesters (PDE), phosphocreatine (PCr), and inorganic phosphate (P_i). At neutral pH, P_i exists principally as HPO_4 and H_2PO_4. The chemical shift of ^{31}P in these two molecules differs by ~2.4 p.p.m., but rapid exchange between the two forms results in only a single MR spectral peak being detected. The resonance frequency of the peak is determined by the proportion of the two species present and as the equilibrium is dependent on the pH of the tissue, this is reflected in the effective chemical shift of P_i and is measurable *in vivo*.

In animal models, epileptic seizures can produce marked changes in energy metabolism and tissue pH (Siesjo, 1978). ^{31}P-MRS has been used in several recent clinical studies to investigate the metabolic changes associated with partial seizure foci.

Laxer *et al*. (1992) studied the anterior temporal lobes of eight patients with complex partial seizures and HS and found no significant asymmetries between ipsilateral and contralateral temporal lobes of ATP, PCr or PDE concentrations. In seven out of the eight patients, the temporal lobe ipsilateral to the focus had an increased pH (mean in all eight patients of 7.25 versus 7.08) and, in all eight, increased P_i (mean 1.9 versus 1.1 mM). Concentrations of PME were less on the side of the focus, although this was not statistically significant. No significant side to side asymmetries were noted in eight normal subjects. There was no apparent relationship between the pH and P_i levels and severity of abnormality shown by MRI. The spatial resolution of this study was very limited and tissue heterogeneity may have confounded interpretation of the data. The same group subsequently investigated eight patients with partial seizures (seven temporal, one frontal) using ^{31}P-CSI, with an effective voxel size of 25 cm^3, enabling more precise delineation of regions of interest (Hugg *et al*., 1992). The same lateralizing abnormalities were found; that is increased P_i, decreased PME and increased pH (7.17 ipsilateral versus 7.06 contralateral, $P < 0.01$). The side to side asymmetry of all metabolite intensities in a control group was $<$10%. Using ^{31}P-CSI, Laxer *et al*. (1993) found increased pH (7.13 ipsilateral versus 6.97 contralateral), higher Pi and reduced PME in the anterior hippocampus of 11 patients with seizures arising from the anterior hippocampus. In the temporal lobe, apart from the hippocampus, PME and Pi showed similar asymmetries, but pH did not. In a later study of eight patients with frontal lobe epilepsy, increased pH in all eight and decreased PME in seven patients were found in the epileptogenic frontal lobes, but no alteration in P_i levels, were detected (Garcia *et al*., 1994*b*).

Kuzniecky *et al*. (1992) obtained ^{31}P-spectra from single voxels in seven patients with temporal lobe epilepsy and five control subjects. There was no statistically significant difference in the pH in either of the temporal lobes. These were 7.11 (ipsilateral) and 7.05 (contralateral) with the ipsilateral value being closer to that measured in controls (mean control pH was 7.12). Although not statisitically significant, these findings (with the ipsilateral pH larger) were similar to those described by Laxer *et al*. (1992, 1993). Of the frontal lobe studies, only that of Garcia *et al*. (1994*b*) quoted a control value for pH, and this was similar to the contralateral values in patients.

No changes in PME levels were reported by Kuzniecky *et al*. (1992). The PCr/P_i ratios were lower in the ipsilateral than in the contralateral temporal lobe of the patients, and the ratios on both sides were lower than those in the control data. This appears consistent with the studies of Laxer *et al*. (1992) and Hugg *et al*. (1992) in that each of these two studies reported an increase in P_i with no change in PCr (giving a decrease in PCr/P_i). It should be noted, however,

that Kuzniecky *et al*. (1992) interpreted this change in terms of a decrease in PCr, and not an increase in P_i, but did not report intensity levels for the individual metabolites.

The pathophysiological significance of these data are not certain at present. It has been suggested that a decrease in PME may reflect altered metabolism associated with neuronal cell loss and glial proliferation (Hugg *et al*., 1992), both of which are associated with HS and cortical lesions, although the data do not provide direct evidence of this. All studies found a higher pH on the ipsilateral side compared with the contralateral side. In one series, this difference was not found to be significant (Kuzniecky *et al*., 1992), while the other three studies reported a higher ipsilateral pH that was statistically significant. Kuzniecky *et al*. (1992) found that the higher ipsilateral pH values were similar to control measurements, while Garcia *et al*. (1994*b*) reported that the contralateral pH in the frontal lobe was similar to control values. In conclusion, the evidence for an increase in pH in the region of a seizure focus is not yet definitive, and further work is needed on larger groups of both patients and control subjects.

If confirmed, the neurobiological significance of an increase in pH associated with a seizure focus is not clear. Seizures have been shown to produce acidosis. Hugg *et al*. (1992) postulated that an increase in pH might be the consequence of an adaptation in brain buffering in response to repeated acidotic episodes associated with seizures, but there is no direct evidence for this.

In several of the above studies, ^{31}P-MRS appeared to be superior to MRI in determining the lateralization of the seizure focus. The MRI methods and analysis used were not described, however, and MRI methods that detect HS and other subtle cortical abnormalities reliably have only been reported recently (*see* previous section). It is not clear whether ^{31}P-MRS provides useful lateralizing and localizing data over and above that available from optimal MRI, and comparative studies using suboptimal MRI should be treated with caution. Even with this caveat, ^{31}P-MRS yields potentially very useful data which will be enhanced by technological developments such as the use of improved radiofrequency coils, particularly double-tuned coils which would allow ^{1}H-imaging and ^{31}P-spectroscopy to be carried out in the same examination without changing coils. This would simplify investigations and the anatomical localization of the spectra. Future studies will need to compare ^{31}P-MRS data with optimal MRI and to address the question of whether CSI can make a useful contribution to the precise localization of epileptic foci, in addition to lateralization.

Carbon (^{13}C) spectroscopy

Carbon 13 is only present in 1% of naturally occurring compounds. Compounds labelled with ^{13}C need to be administered to subjects for studies to be carried out. Dynamic investigations allow measurement of glucose transport, oxidation, glutamate turnover and glutamine synthesis in brain, *in vivo* (Gruetter *et al*., 1992; Rothman *et al*., 1992; Mason *et al*., 1995; Van Zijl and Rothman, 1995). Studies in patients with epilepsy are only just beginning, but they promise important data on the metabolic abnormalities associated with epileptogenesis.

Conclusion

Over the last 5 years, MRS has advanced as a non-invasive tool for obtaining data on cerebral metabolism. Implementation of the rapid developments now being made in MR hardware and software may enable parametric imaging of the cerebral concentrations of these compounds, and this may have significant consequences for the medical and surgical treatment of patients with epilepsy.

Positron emission tomography (PET)

PET may be used to map CBF, using ^{15}O-labelled water, and regional cerebral glucose metabolism using ^{18}FDG. PET may also be used to demonstrate the binding of specific ligands, e.g. [^{11}C]flumazenil to the central benzodiazepine–$GABA_A$ receptor complex, [^{11}C]diprenorphine and [^{11}C]carfentanil to opiate receptors and [^{11}C]deuterium deprenyl to monoamineoxidase (MAO) B receptors. The technique is costly and scarce, but produces quantitative data with superior spatial resolution to single photon emission computerized tomography (SPECT) (*see* below). The radiation exposure from an ^{18}FDG-PET scan is ~5 mSv, which is similar to that received from a series of $H_2{}^{15}O$ scans to determine areas of brain involved in a cerebral task. SPECT blood flow scans result in an exposure of ~4 mSv and ^{11}C-ligand studies in 1–2 mSv. These exposures limit the comparative studies that may be carried out on patients and normal volunteers.

PET has been available for longer than MRI. Enormous strides have been made using MRI in the last 10 years and this has has had two major consequences for the application of PET techniques to epilepsy. First, the role of PET in the clinical investigation of patients needs to be re-evaluated, as contemporary MRI may make PET data superfluous. Secondly, clinical and research PET data should always be interpreted in the light of high quality anatomical MRI, to provide a structural–functional correlation. Fundamental to making these correlations has been the development of computer programs that may be used to coregister MRI and PET datasets on a pixel-by-pixel basis, as demonstrated initially by Woods *et al*. (1993).

PET studies of generalized epilepsy

Blood flow and glucose metabolism

There have been three studies of cerebral glucose metabolism using ^{18}FDG and PET in patients with idiopathic generalized epilepsy. Interictal studies have been unremarkable; studies

carried out when frequent absences were occurring have shown a diffuse increase in cerebral glucose metabolism of 30–300%, with greater increases being seen in children. Absence status, however, was associated with a reduction in cerebral glucose metabolism. There were no focal abnormalities and the rate of metabolism did not correlate with the amount of spike-wave activity (Engel *et al*., 1985; Theodore *et al*., 1985; Ochs *et al*., 1987). ^{18}FDG-PET studies have poor temporal resolution, 70–80% of cerebral uptake occurring over 15 min following intravenous injection, with the consequence that in a patient with frequent absences, there is an amalgam of pre-ictal, ictal and postictal periods contributing to one scan.

In an autoradiographic study of cerebral glucose utilization in a rat model of spontaneous generalized absences, there was a widespread increase in cerebral glucose metabolism, compared with controls. The relationship between spike wave activity and cerebral glucose utilization is not straightforward, however, as a dose of ethosuximide that suppressed all spike-wave activity was not associated with a reduction of glucose metabolism (Nehlig *et al*., 1991, 1992).

Regional CBF (rCBF) has been assessed using PET and bolus injections of $H_2{}^{15}O$, achieving a temporal resolution of $<$30 s and a spatial resolution of $8\times8\times4.3$ mm^3. Typical absences were precipitated with hyperventilation and the distribution of rCBF which resulted was compared with that when there were no absences. During absences there was a global 15% increase in CBF and, in addition, a focal 4–8% increase in blood flow in the thalamus. There were no focal increases in CBF in the cortex and no focal decreases (Prevett *et al*., 1995*a*). Spike-wave activity in typical absences oscillates in thalamo-cortical circuits and the site of primary abnormality remains uncertain. The preferential increase in thalamic blood flow is evidence to the key role of this structure in the pathophysiology of absences in man, but does not clarify whether this is the result of converging activated thalamo-cortical pathways or reflects a primary thalamic process. No significant increases in thalamic blood flow were detected in the 30 s prior to generalized spike-wave activity on the EEG. It would be most unlikely for a focal increase in blood flow, developing 5 s before generalized spike-wave activity appeared, to be detected with this technique. fMRI has superior temporal resolution (*see* above), but as the blood-flow response to increased neuronal activity lasts ~2 s, it may not be fine enough to show whether abnormal activity commences in the cortex or the thalamus.

Benzodiazepine and opioid receptors

Savic *et al*. (1990) reported a slight reduction in cortical binding of [^{11}C]flumazenil to cBZR in a heterogenous group of patients with generalized seizures, compared with the 'nonfocus' areas of patients with partial seizures. It was subsequently reported that, compared with normal subjects, patients with primary generalized tonic-clonic seizures had an increased BZR density in the cerebellar nuclei and a decreased density in the thalamus (Savic *et al*., 1994). Reliable identification of cerebellar nuclei is not easy on [^{11}C]flumazenil PET images and these results have not been replicated. Prevett *et al*. (1995*b*) found no significant difference in [^{11}C]flumazenil binding in the cerebral cortex, thalamus or cerebellum between patients with childhood and juvenile absence epilepsy, not taking valproate, and control subjects. The volume of distribution of [^{11}C]flumazenil, however, was 9% less in patients receiving valproate suggesting that this drug may result in reduced number of available BZR. In a further study comparing 10 patients with idiopathic generalized epilepsy, before and after introduction of valproate, with 20 control subjects, patients with idiopathic generalized epilepsy had an 11% higher binding to cBZR in neocortex, a 14% increase in the thalamus and 13% increase in cerebellar cortex; the introduction of valproate was not associated with a significant change in cBZR (Duncan *et al*., 1996*b*). The diversity of findings reflect criteria used to select patients for study and methodological differences, including improvements in scanner sensitivity in later studies. These data provide evidence for the structural and functional basis of idiopathic generalized epilepsy. It is not certain whether this is the result of an increased number of neurons or a functional change in available receptors. Correlative neuropathological studies will be needed to answer this question. Results suggest, however, that valproate does not affect the numbers of available $GABA_A$-BZR, but do not exclude a modulatory effect on receptor function.

Acutely, the cerebral binding of [^{11}C]flumazenil, was not affected by flurries of absences in any area of neocortex or the thalamus implying that binding to this part of the $GABA_A$-BZR is not involved in the pathophysiology of absences (Prevett *et al*., 1995*c*).

Systemic administration of opioids tends to cause an increase in generalized spike-wave activity, in contrast to the anticonvulsant effect of opiates and endogenous opioids on generalized tonic-clonic seizures, suggesting that opioid transmission may have a role in the pathogenesis of absences (Frey and Voits, 1991). Diprenorphine is a weak opiate receptor partial agonist with similar *in vivo* affinities for the μ-, κ- and δ-receptor subtypes. There was no significant difference in [^{11}C]diprenorphine binding between control subjects and patients with childhood and juvenile absence epilepsy, suggesting there is no overall abnormality of opioid receptors in this condition (Prevett *et al*., 1994).

In a dynamic study, however, it was found that serial absences were associated with an acute 15–41% reduction in [^{11}C]diprenorphine binding to association areas of neocortex, with no effect on binding to thalamaus, basal ganglia or cerebellum. The results implied release of endogenous opioids in the neocortex that may have a role in the pathophysiology of typical absences (Bartenstein *et al*., 1993). Further studies with subtype-specific ligands may provide information about the role of different opioid receptor subtypes in typical absences. Ligands to investigate $GABA_B$ and excitatory amino acid receptors will give useful information on the

involvement of these systems in the pathogenesis of typical absences and idiopathic generalized epilepsy.

PET studies of localization-related epilepsies

Blood flow and glucose metabolism

The hallmark of an epileptogenic focus, studied interictally, is an area of reduced glucose metabolism and reduced blood flow that is usually considerably larger than the pathological abnormality (Engel *et al*., 1982*a*, Franck *et al*., 1986). ^{18}FDG-PET scans provide superior resolution and greater reliability for identifying a focal deficit than do PET scans using $H_2{}^{15}O$ or SPECT scans of CBF (Leiderman *et al*., 1992; Ryvlin *et al*., 1992*a*; Theodore *et al*., 1994).

The most likely reason for the large region of reduced blood flow and metabolism is inhibition or deafferentation of neurons around an epileptogenic focus. Comparison of ^{18}FDG-PET scans with [^{11}C]flumazenil scans (*see* below) (Henry *et al*., 1993*a*; Savic *et al*., 1993) indicate that the neuronal loss is confined to a more restricted area than the region of reduced metabolism.

Partial seizures are associated with an increase in regional cerebral glucose metabolism and blood flow in the region of the epileptogenic focus, and often a suppression elsewhere (Engel *et al*., 1983; Chugani *et al*., 1994). In general, ictal PET scans can only be obtained fortuitously, because of the 2 min half-life of ^{15}O and the fact that cerebral uptake of ^{18}FDG occurs over a 40 min period after injection, so that cerebral glucose utilization data will reflect an amalgam of the ictal and postictal conditions. Hypometabolism is accentuated after a seizure and may not return to the interictal state for $>$24 h (Leiderman *et al*., 1994).

Over the last decade, some epilepsy surgery programmes have relied extensively on ^{18}FDG-PET as a tool for localizing the epileptic focus. The current place of this technique needs to be re-evaluated in the light of developments in MRI as the finding of a definite focal abnormality with the latter technique, such as HS, may render an ^{18}FDG-PET scan superfluous (Heinz *et al*., 1994; Gaillard *et al*., 1995*a*). Comparative studies of two imaging techniques, such as MRI and PET are difficult to interpret, however, because of the likelyhood that the methodologies and equipment will not both be developed to the same degree in any one centre.

Temporal lobe epilepsy. Several studies of ^{18}FDG-PET have found a 60–90% incidence of hypometabolism in the temporal lobe interictally in adults and children with temporal lobe epilepsy (Kuhl *et al*., 1980; Engel *et al*., 1982*a–c*; Theodore *et al*., 1983; Franck *et al*., 1986; Abou-Khalil *et al*., 1987; Stefan *et al*., 1987*a*; Ryvlin *et al*., 1991; Sadzot *et al*., 1992; Gaillard *et al*., 1995*b*). In studies carried out before the recent developments in assessment of the hippocampus using MRI, ^{18}FDG-PET was thought to be a highly useful clinical tool, particularly in patients in whom scalp EEG recordings were non localizing (Engel *et al*., 1990; Theodore *et al*., 1992*a*). The results of comparative studies depends critically on the relative sophistication of the techniques used. In a recent comparative study, 16 out of 18 patients with temporal lobe epilepsy had temporal lobe hypometabolism on ^{18}FDG-PET and 11 of these had clear concordant MRI abnormalities (lesions in two and features of HS in nine). It could be concluded that ^{18}FDG-PET data did not provide clinically useful data if the MRI findings were definite, but that it had some additional sensitivity (Gaillard *et al*., 1995*a*).

It was noted that the visual assessment of hypometabolism was less accurate than quantification. The asymmetry of lateral but not mesial temporal glucose metabolism was greater in patients who became seizure-free following surgery. Patients with $\geqslant$15% hypometabolism were more likely to become seizure-free (Theodore *et al*., 1992*a*). The degree and extent of temporal lobe hypometabolism has been strongly correlated with the seizure outcome following temporal lobectomy (Radtke *et al*., 1993). In a similar study, the degree of hypometabolism in the medial temporal lobe, but not in the lateral temporal lobe, correlated with the chances of being rendered seizure-free by anterior temporal lobe resection (Manno *et al*., 1994). Absence of unilateral temporal hypometabolism, however, does not preclude a good result from surgery (Chee *et al*., 1993).

The area of hypometabolism often extends beyond the temporal lobe. In a series of 27 patients, with no specific abnormality evident on the MRI available at the time, this involved the thalamus in 63%, the basal ganglia in 41% and the frontal lobe in 30% (Henry *et al*., 1993*b*). Similar results were found in other series (Sperling *et al*., 1990). In patients with medial temporal lobe foci the hypometabolism has frequently been found to be more pronounced in lateral neocortex (Sackellares *et al*., 1990; Sadzot *et al*., 1992). This finding may reflect the limited spatial resolution of the cameras used; but in consequence ^{18}FDG-PET studies have been felt to be less reliable for answering the question of precise localization of seizure onset, e.g. inferior frontal versus medial or lateral temporal lobe, than for answering the question of lateralization, e.g. left or right temporal lobe. In an evaluation of ^{18}FDG-PET in patients with temporal lobe epilepsy 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 (Hajek *et al*., 1993). Studies such as this are of interest in understanding the metabolic consequences of epilepsy of different aetiologies, but from a clinical perspective have been rendered less useful by modern MRI.

In one study, hippocampal neuron loss was not correlated with the degree of temporal lobe hypometabolism (Henry *et al*., 1994*b*). In contrast, a recent comparison of hippocampal

atrophy and glucose metabolism in patients with temporal lobe epilepsy found that there was most marked hypometabolism in the hippocampus and temporal pole and that the degree of hippocampal atrophy correlated with the degree of hypometabolism in these structures, but not elsewhere in the temporal lobe (Semah *et al*., 1995). In a separate series, there was a significant correlation between hippocampal volume and inferior mesial and lateral temporal lobe cerebral metabolic rate of glucose, suggesting that hypometabolism may reflect hippocampal atrophy (Gaillard *et al*., 1995*a*).

In the presurgical evaluation of temporal lobe epilepsy ^{18}FDG-PET scans provide superior resolution and greater reliability for identifying a focal deficit than do PET scans using $H_2{}^{15}O$ (Leiderman *et al*., 1992; Theodore *et al*., 1994).

False lateralizations may occur with ^{18}FDG-PET in patients with temporal lobe epilepsy. The risk of false lateralization may be reduced by undertaking quantitative rather than just qualitative assessment of scans. An area of reduced glucose metabolism indicates a focal deficit in function and this does not necessarily imply epileptogenicity, which must still be verified neurophysiologically. Another important potential source of error may be seizure activity during the scan that is unrecognized clinically or by scalp EEG recordings (Sperling *et al*., 1995).

In patients with mesial temporal lobe epilepsy, the degree of left hemisphere hypometabolism has been correlated with impairment of verbal IQ, and lateral left temporal lobe hypometabolism with impairment of verbal memory (Rausch *et al*., 1994).

After selective amygdalo-hippocampectomy in patients with temporal lobe epilepsy, there was an increase of regional cerebral glucose metabolism in the ipsilateral and also the contralateral hemisphere in patients with mesiobasal temporal lobe epilepsy and HS. There was also a trend toward a normalization of cerebral glucose metabolism in the ipsilateral temporal neocortex 12 months after surgery in these patients, implying a consequence of the removal of the epileptic focus (Hajek *et al*., 1994).

Cavernomas may be associated with an area of hypometabolism around the lesion, particularly in overlying temporal neocortex if connections from limbic structures are disrupted. This finding did not correlate with the size of the abnormality, or it being associated with epilepsy, implying that the hypometabolism was a consequence of deafferentation (Ryvlin *et al*., 1995).

In patients with cryptogenic temporal lobe epilepsy, who had never received antiepileptic drugs, significantly increased glucose metabolism was found in the temporal lobes, thalami, basal ganglia and cingulate cortex, and also in frontal, mesial temporal and cerebellar cortex (Franceschi *et al*., 1995). Hypermetabolic areas have also been found in children with partial seizures, who were not having overt seizures. In some, this was associated with focal spike-wave activity, indicating the likelyhood of increased neuronal activity underlying the increased glucose metabolism and the need to have EEG recordings during ^{18}FDG-PET studies (Chugani *et al*., 1993). An alternative explanation is that the increased glucose metabolism reflects increased neuronal numbers, as may occur in a focal MCD, resulting in thickening of the neocortical ribbon (Richardson *et al*., 1996*a*).

^{18}FDG-PET scans have also been used to investigate the metabolic consequences of partial epilepsy and its treatment. The administration of the $GABA_A$-receptor agonist THIP (4,5,6,7-tetrahydroisoxazolo(*5,4-c*)-pyridin-3-ol) to patients with temporal lobe epilepsy was followed by an increase in glucose metabolism, measured with ^{18}FDG-PET, in areas with reduced interictal glucose metabolism, that was greater than the increase seen in the brain as a whole (Peyron *et al*., 1994*a*, *b*). These data suggested that activation of GABAergic neurons results in increased metabolic demands and that $GABA_A$ receptors are not lost in the neocortex in temporal lobe epilepsy. Regions of interest were placed in medial and lateral temporal lobe and the spatial resolution of the study was not sufficient to identify the hippocampus separately, but the results were consistent with the results of studies of [^{11}C]flumazenil binding in HS (Koepp *et al*., 1996). In patients with complex partial seizures, interictal cerebellar metabolism was reduced bilaterally, and this did not appear to be entirely attributable to the usage of phenytoin (Theodore *et al*., 1987*a*).

Frontal lobe epilepsy. ^{18}FDG-PET shows hypometabolism in ~60% of patients with frontal lobe epilepsy. In 90% of those with a hypometabolic area, structural imaging shows a relevant underlying abnormality. In common with temporal lobe epilepsy, 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 lesion (Henry *et al*., 1991; Engel *et al*., 1995).

There have been three main patterns of hypometabolism described in patients with frontal lobe epilepsy: (i) no abnormality; (ii) a discrete focal area of hypometabolism; (iii) diffuse widespread hypometabolism (this may be multilobar and involve subcortical structures; there is often an area of particularly reduced metabolism in one part of the frontal lobe).

An uncommon finding has been the patient with a multilobar or an extensive structural lesion and a small area of hypometabolism (Swartz *et al*., 1989). It has been the general experience that the epileptic focus is contained within the hypometabolic area, if one exists (Theodore *et al*., 1986*b*; Swartz *et al*., 1989; Henry *et al*., 1991; Sadzot *et al*., 1992). Quantitative analysis of ^{18}FDG-PET scans was found to enhance sensitivity and accuracy of determination over visual assessment (Swartz *et al*., 1995).

Overall, published clinical series indicate that ^{18}FDG-PET does not appear to provide additional clinically useful information in the majority of patients with frontal lobe epilepsy. Future research will determine whether studies with specific ligands may be more effective in identifying focal

abnormalities in patients in whom structural imaging has not revealed an aetiology for the seizure disorder.

Status epilepticus arising from the motor cortex has been associated with both hypermetabolism and hypometabolism (Engel *et al*., 1983; Franck *et al*., 1986; Hajek *et al*., 1991). Scans performed with $H_2{}^{15}O$ have shown increased blood flow and oxygen consumption and reduced oxygen extraction fraction in the frontal lobe in patients with epilepsia partialis continua (Franck *et al*., 1986). A rare finding, in patients with frontal epilepsy of early childhood onset, has been an interictal focal increase in metabolism (Chugani *et al*., 1993) (*see* above).

Malformations of cortical development. Focal cortical hypometabolism is commonly seen in patients with tuberous sclerosis (Szelies *et al*., 1983; Pawlik *et al*., 1990). Glucose metabolism has been detected using ^{18}FDG-PET in the layers of ectopic neurons in band heterotopia (Miura *et al*., 1993; De Volder *et al*., 1994) and in heterotopic nodules and displaced grey matter (Bairamian *et al*., 1985; Falconer *et al*., 1990), implying synaptic activity.

In 15 out of 17 patients with MCD, both MRI and ^{18}FDG-PET identified ectopic grey matter, and hypometabolism concurred with MRI findings of abnormal cortex. Analysis was by visual inspection and ^{18}FDG-PET did not identify abnormalities that were not evident on MRI, although in some cases the area of hypometabolism was more extensive than the MRI lesion (Lee *et al*., 1994). This finding contrasts with the quantitative analysis of [^{11}C]flumazenil PET data in patients with MCD (Richardson *et al*.,1996*a*) (*see* below).

Abnormalities of glucose metabolism, identified with ^{18}FDG-PET, in the contralateral hemisphere in patients with hemimegalencephaly have been associated with a less good prognosis following surgery (Rintahaka *et al*., 1993).

Other syndromes. Some patients with severe secondarily generalized epilepsies and syndromes such as West's syndrome, Lennox–Gastaut syndrome, Landau–Kleffner syndrome and other paediatric epilepsy syndromes, appear to be of cryptogenic aetiology on MRI. There may, however, be single or multiple cortical areas of hypometabolism on ^{18}FDG-PET scans which indicate areas that may be epileptogenic, the pathological correlate of which is MCD (Chugani, 1994). Patients with the Lennox–Gastaut syndrome have shown a variety of cerebral metabolic patterns: normal, focal and diffuse (unilateral and bilateral) hypometabolism (Chugani *et al*., 1987; Theodore *et al*., 1987*b*). This heterogeneity is not surprising, and reflects the diverse aetiologies of the syndrome. Operative electrocorticography studies have found epileptic activity in areas shown to be hypometabolic on ^{18}FDG-PET scans (Olson *et al*., 1990).

Continuous spike-wave discharges may be associated with a focal increase in glucose metabolism (Park *et al*., 1994). In one study of patients with the Landau–Kleffner syndrome, the metabolic pattern was variable, but abnormalities were most evident over the temporal lobes (Maquet *et al*., 1990). In another, widespread bilateral hypometabolism or a mild increase in glucose metabolism were noted in the left inferior temporal cortex in the awake state. In scans performed during slow-wave sleep there was a marked bilateral increase in glucose metabolism in temporal cortex, supporting the hypothesis that the increase in glucose metabolism reflected areas of epileptic activity (Rintahaka *et al*., 1995).

Studies of the effect of antiepileptic drugs. The effects of antiepileptic drugs on cerebral glucose metabolism has also been studied with ^{18}FDG-PET; carbamazepine was associated with a diffuse 12% reduction, valproate a 22% reduction, phenytoin a non-uniform reduction (mean 13%) and phenobarbitone a 37% reduction (Theodore 1988; Theodore *et al*., 1989; Leiderman *et al*., 1991)

Activation studies. Activation studies using ^{18}FDG-PET in attempts to highlight the hypometabolic area have been reported; they may improve the delineation of dysfunctional areas of brain (Pawlik *et al*., 1990; Bromfield *et al*., 1991; Pawlik *et al*., 1994). However, these studies have the severe limitation of cerebral uptake of ^{18}FDG continuing for $\geqslant$15 min. Activation studies performed with $H_2{}^{15}O$ have been used for some years to delineate the functional anatomy of a variety of cognitive and other cerebral tasks. These may be used in surgical planning in patients with epileptogenic areas close to eloquent areas (Hojo *et al*., 1995). Ongoing studies are applying these tests to patients with partial seizures on the basis of MCD in order to determine the perturbation and rearrangement of cerebral functions associated with this condition (Richardson *et al*., 1996*b*). In the future, however, it is likely that fMRI studies will fulfil this important role.

Ligands

Central benzodiazepine receptors. The binding of [^{11}C]flumazenil to cBZR in epileptogenic foci was initially found to be reduced by an average of 30%, with no change in the affinity of the ligand for the receptor (Savic *et al*., 1988). Other groups have also found this and comparative studies with ^{18}FDG-PET scans have shown the area of reduced [^{11}C]flumazenil binding to be more restricted than is the area of reduced glucose metabolism in temporal lobe epilepsy (Henry *et al*., 1993*a*; Savic *et al*., 1993). Using the novel, objective analytical approach of statistical parametric mapping (SPM) (Friston *et al*., 1995) applied to parametric images of cerebral [^{11}C]flumazenil binding, coregistered with MRI, it was found, in patients with unilateral HS, that reduction of cBZR was confined to the sclerotic hippocampus with no significant abnormalities elsewhere (Koepp *et al*., 1996).

The underlying pathological basis of reduced [^{11}C]flumazenil binding in HS is still under study. Autoradiographic and histopathological studies of surgically removed sclerotic hippocampi have shown reduced neuron

counts and cBZR densities, with a further reduction of density of cBZR per remaining neuron (Johnson *et al*., 1992). Burdette *et al*. (1995) found a highly statistically significant correlation between neuron loss and reduced cBZR binding on autoradiographic analysis of hippocampi from patients treated surgically for HS, and concluded that neuron loss was the basis of reduced [^{11}C]flumazenil binding *in vivo*. This analysis did not exclude an additional reduction of cBZR per neuron. Further correlational studies with quantitative *in vivo* hippocampal [^{11}C]flumazenil binding have indicated that, in HS, there is additional loss of cBZR in the CA1 subregion of the hippocampus, over and above the loss of neurons (Hand *et al*., 1996).

It seems most likely that, in addition to any functional change, cBZR changes reflect localized neuronal and synaptic loss in the epileptogenic zone and that the more extensive hypometabolism is a result of diaschisis. In clinical terms it appears that [^{11}C]flumazenil PET may be superior to ^{18}FDG for the localization of the source of the seizure. It is not certain, however, whether this data confers additional clinically useful information in patients with clearcut MRI findings of HS.

The use of [^{11}C]flumazenil PET in the clinical investigation of patients with refractory partial seizures, but who have unremarkable high quality MRI, is currently under investigation. In six patients with frontal lobe epilepsy, reduction in cBZR binding was demonstrated with [^{11}C]flumazenil PET, that was consistent with clinical and EEG data (Savic *et al*., 1995). In two out of four patients who also had ^{18}FDG scans, the focus was characterized by a region of reduced metabolism that was more extensive than the reduction in cBZR. The MRI was unremarkable in five, implying superior sensitivity of the PET technique over the MRI. Comparisons of this nature, however, clearly depend on the relative sophistication of the instruments and methodologies used. Greater reductions of [^{11}C]flumazenil binding have been reported in patients with frequent seizures, in comparison with those with less frequent seizures (Savic *et al*., 1996). It is not yet clear whether this finding represents the cause or consequence of epileptic activity.

Malformations of cortical development are of heterogenous appearance and may not be detectable with MRI (*see* above). Epilepsy surgery in patients with MCD is less successful than in those with discrete lesions, most likely because the anatomical and functional abnormality is more widespread than a feasible resection. An SPM analysis of cBZR visualized with [^{11}C]flumazenil PET and coregistered with high quality MRI in 12 patients with partial seizures and MCD revealed areas of abnormal cerebral cBZR binding in 10. These abnormal regions were frequently more extensive than the abnormalities seen with MRI, and they were also noted at distant sites where the cortex had appeared unremarkable on MRI (Fig. 8) (Richardson *et al*., 1996*a*). Similar observations have been made in patients with refractory partial seizures but unremarkable MRI scans, suggesting the possibility of occult MCD (Richardson *et al*., 1996*c*). In contrast to studies with ^{18}FDG, in which reduced metabolism may be the result of diaschisis, reduced [^{11}C]flumazenil binding implies neuronal deficits. A further, novel finding of this investigation was of areas of increased binding to cBZR in many patients with MCD, which has not been found in patients with epilepsy caused by other pathologies. Possible explanations include increased neuron density, the presence of ectopic neurons bearing cBZR and of an increased number of available receptors, that may reflect abnormal neurons or a response to the abnormal circuitry implicit in MCD. Elucidation of the neurobiological basis of these findings awaits correlative pathological and *in vitro* receptor studies. These findings may also be of clinical importance in the evaluation of patients with MCD for possible surgical treatment. Further studies need to be done to determine whether the finding of widespread abnormalities of cBZR is

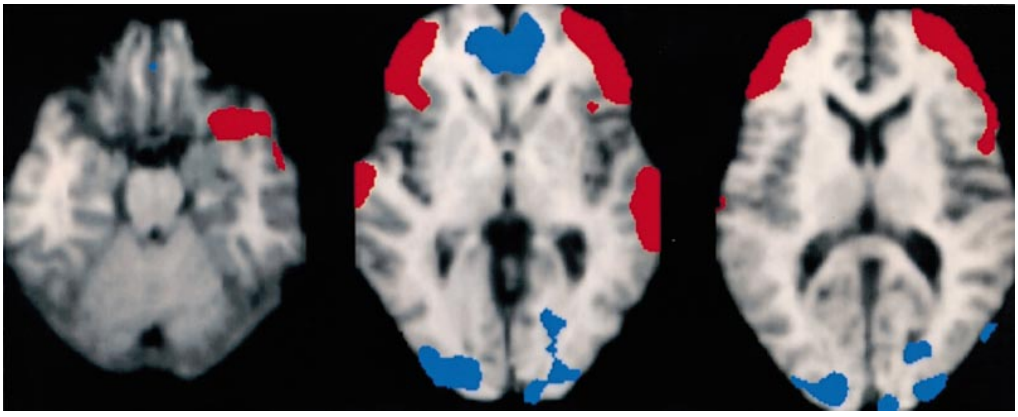

Fig. 8 Statistical parametric map (SPM) of [^{11}C]flumazenil PET scan of a patient with bilateral subependymal heterotopia whose cortex appeared normal on high resolution MRI. The individual patient's PET scan has been compared with a bank of 24 normal subjects on a pixel-by-pixel basis, and the results mapped onto the patient's MRI scan. Areas of significantly increased binding to benzodiazepine receptors are shown in red and areas of significantly reduced binding in blue (figure supplied by Dr Mark Richardson).

an adverse prognostic factor for surgical outcome in patients in whom MRI and other investigatory data implicate a single restricted focus; such studies will not, however, be easy to undertake.

Studies of drug action *in vivo* in patients with epilepsy may also be carried out using [^{11}C]flumazenil PET. It was shown that 1.5 mg intravenous flumazenil occupied 55% of BZR, whereas 15 mg occupied nearly all receptors (Savic *et al*., 1991).

In conclusion, [^{11}C]flumazenil PET scan data are good markers for neuronal integrity in hippocampus and neocortex and may also identify ectopic neurons in MCD. There are suggestions that there may also be abnormalities of cBZR availability on neurons, but definitive correlative *in vitro* studies have not yet been completed. The future clinical role of [^{11}C]flumazenil PET is likely to be in the presurgical evaluation of those patients in whom MRI is not definitive and in those in whom there is evidence of MCD.

Opioid receptors. Endogenous opioids are released following partial and generalized tonic–clonic seizures and contribute to the postictal rise in seizure threshold (Bajorek *et al*., 1986). Investigations of opioid receptors in patients with temporal lobe epilepsy have shown an increase in the binding of the specific μ-agonist [^{11}C]carfentanil to μ-receptors in lateral temporal neocortex, reflecting an increase in the number of available receptors, or increased affinity, in areas which also showed reduced glucose metabolism (Frost *et al*., 1988). It has been speculated that an increase in μ-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. In a second study the increase in [^{11}C]carfentanil binding to lateral temporal neocortex was confirmed and reduced binding to the amygdala was noted (Mayberg *et al*., 1991). The finding of reduced signal from a structure may be due, at least in part, to partial volume effects. Methods to correct for this are now being developed and implemented (Muller-Gartner *et al*., 1992; Frost *et al*., 1995). The same patients were also studied with [^{11}C]diprenorphine, which binds with similar affinities *in vivo* to the μ-, κ- and δ-subtypes of opioid receptors. There were no overall asymmetries of binding of [^{11}C]diprenorphine in the temporal lobe or elsewhere (Mayberg *et al*., 1991); this observation has been confirmed by others (Bartenstein *et al*., 1994). In concordance with this, there was no overall asymmetry of binding of the PET tracer ^{18}F-cyclofoxy, which binds to μ- and κ-opioid receptors, in patients with temporal lobe epilepsy, although some patients had higher binding of the ligand in the temporal lobe ipsilateral to the EEG focus (Theodore *et al*., 1992*b*).

These data suggest a differential alteration of μ- and non-μ-opioid receptors in patients with temporal lobe epilepsy. The different patterns of [^{11}C]carfentanil, [^{18}F]cyclofoxy and [^{11}C]diprenorphine binding indicate that μ- and κ-opioid receptors are not affected similarly in unilateral temporal lobe epilepsy. The precise explanation of these findings is not clear. Hypotheses include an upregulation of μ-receptors and a reduction in the number or affinity of κ-receptors, or upregulation of μ-receptors and occupation of κ-receptors by an endogenous opioid ligand. Further investigations with a κ-specific opioid PET tracer may clarify this issue.

These studies have all been carried out in patients with temporal lobe epilepsy. No PET investigations of opioid receptors *in vivo* have been reported in patients with extratemporal seizure disorders or MCD.

MAO-B receptors. Deprenyl binds with high specificity and affinity to MAO-B receptors, which are mainly located on astrocytes. In nine patients with temporal lobe epilepsy, uptake of [^{11}C]deuterium deprenyl was increased in the epileptogenic temporal lobe, possibly reflecting gliosis (Kumlien *et al*., 1995). This technique does not appear likely to contribute to precise localization of an epileptic focus within the temporal lobe, but the anatomical discrimination of medial temporal lobe structures was rather limited in that study. It is possible that higher resolution images may produce more refined findings. The technique has not yet been evaluated in extra-temporal seizure disorders.

Histamine receptors. An increase of histamine H1 receptors, visualized with PET and [^{11}C]doxepin in epileptic foci that also show reduced interictal glucose metabolism, has been reported (Iinuma *et al*., 1993; Itoh *et al*., 1995). It has been suggested that this finding is compatible with an increase of μ-opioid receptors. It is not certain, however, how specific this tracer is for H1 receptors and the results have not been replicated by other groups.

Conclusion

Studies with ^{18}FDG-PET have defined the major cerebral metabolic associations and consequences of epilepsy but the data are nonspecific with regard to aetiology, and abnormalities are more widespread than the pathological lesions. The role of ^{18}FDG-PET in the clinical evaluation of patients has been reduced by the advances made in MRI over the last 5 years. Activation studies with $H_2{}^{15}O$ are useful for determining the functional anatomy of cerebral processes in both healthy and pathological brains; however, over the next 5 years such studies are likely to become dominated by fMRI techniques.

Investigations with specific ligands can identify the neurochemical abnormalities associated with the epilepsies, both static interictal 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 that are specific for excitatory amino acid receptors, subtypes of the opioid receptors and the $GABA_B$ receptor, are necessary to understand the processes that give rise to, and respond to, the various forms

of the epilepsies further. All functional data needs to be interpreted in the light of the corresponding brain structure. Coregistration with high quality MRI is now readily achievable and 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.

Single photon emission computerized tomography

Single photon emission computerized tomography (SPECT) may be used to image the distribution of CBF and of specific receptors in the brain.

Cerebral blood flow tracers

The currently most commonly used SPECT tracer for imaging CBF is ^{99m}Tc-hexamethylpropylenamine oxime (^{99m}Tc-HMPAO; Ceretec, Amersham, UK). The superiority of this tracer over radioxenon and iodoamphetamine was noted over 10 years ago (Longostrevi, 1986). Other CBF tracers in current use include ^{123}I-*N*-isopropyl-*p*-iodoamphetamine and ^{99m}Tc-ethyl cysteinate dimer (ECD; Neurolite, Du Pont, France).

^{99m}Tc-HMPAO is convenient to use, being given intravenously and having 70% brain uptake in 1 min. The subsequent image is stable for 6 h, as after crossing the blood–brain barrier ^{99m}Tc-HMPAO reacts with intracellular glutathione, becoming hydrophilic, and it is then much less able to move back across the blood–brain barrier. A limitation of the tracer is that it is chemically unstable 30 min after preparation. This is less of a problem for interictal than ictal studies. Derivatives, stabilized with cobalt chloride, with a longer shelf-life have recently been developed. Radiolabelled ECD is stable for 6 h, and so is convenient for the study of brief ictal events (Grunwald *et al*., 1994).

Hardware

The spatial resolution depends on the imaging equipment used, being 14–17 mm (full-width half-maximum) for single-head rotating γ-cameras, 8–10 mm for three-headed instruments and 7–8 mm for ring-type cameras. Unlike PET, the data remains, at best, semiquantitative, with the use of a reference region as an internal standard. The correct orientation of imaging planes is important, in order to visualize the structures optimally. The commonly used orbito-meatal line is ~40° off the long axis of the temporal lobe. It follows that there are inevitable partial volume effects causing difficulty discriminating between inferior frontal and superior temporal lobe, with loss of potentially useful localizing information. If thin slices are acquired, this deficit can, to some extent, be corrected for by reformatting. This is of limited utility, however, if slices are 8 mm thick and it is much more satisfactory to acquire data in the optimum plane.

As with PET data, coregistration with MRI allows for a structure–function correlation which enhances the interpretation of both individual data sets and the consensus diagnosis (Woods *et al*., 1993; Zubal *et al*., 1995).

Interictal SPECT studies

It has been established for a decade that the marker of an epileptic focus studied interictally in adults and children with SPECT, is a region of reduced CBF. However, it was soon noted that the results were not always reliable (Podreka *et al*., 1987; Stefan *et al*., 1987*b*; Denays *et al*., 1988; Chiron *et al*., 1989; Andersen *et al*., 1990; Cordes *et al*., 1990; Duncan *et al*., 1990; Iivanainen *et al*., 1990; Vles *et al*., 1990; Dietrich *et al*., 1991; Ryvlin *et al*., 1992*b*; Andersen *et al*., 1994). Focal abnormalities of rCBF have been visualized with SPECT in patients with infantile spasms (Chiron *et al*., 1993), Landau–Kleffner syndrome (O'Tuama *et al*., 1992), continuous spike waves during slow-wave sleep (Gaggero *et al*., 1995), tuberous sclerosis (Tamaki *et al*., 1991) and Lennox–Gastaut syndrome (Heiskala *et al*., 1993). It was noted in several of the above studies that the sensitivity of SPECT imaging appeared to be superior to the MRI available at the time. Interictal ^{99m}Tc-HMPAO SPECT imaging has recently revealed identical or increased cerebral perfusion of laminar heterotopia in comparison with the overlying neocortical grey matter (Matsuda *et al*., 1995).

In ^{99m}Tc-HMPAO SPECT studies of patients with temporal lobe epilepsy a significant asymmetry of CBF has been noted in ~50% of cases, the range across different studies is 11–80%. Concordance with interictal EEG lateralization has been noted in 65%. In one large representative series, localization (e.g. frontal versus temporal) has been shown to be more difficult, with correct localization in 38% of cases in interictal studies of patients with a unilateral temporal lobe EEG focus (Rowe *et al*., 1991*a*, *b*). Localization with interictal SPECT is more difficult in patients with extratemporal epilepsy, widespread hypoperfusion being seen in two out of 12 cases in a recent investigation (Marks *et al*., 1992). Similar results have come from other series (Dasheiff, 1992). In consequence to this poor sensitivity and specificity, interictal SPECT studies have little place in the routine investigation of patients with epilepsy. In a blinded comparative study, interictal SPECT was less effective in lateralizing the focus of temporal lobe epilepsy than MRI, with correct lateralization in 45% of cases compared with 86% with MRI. Furthermore, agreement of MRI and EEG data was a good predictor of a satisfactory result from surgical treatment, whereas SPECT was not and tended to give an incorrect result in patients whose MRI was not lateralizing (Jack *et al*., 1994*c*).

Interictal HMPAO SPECT has been shown to have inferior resolution and reliability for identifying a focal deficit compared with ^{18}FDG-PET in the evaluation of patients with

partial seizures (Leiderman *et al*., 1992; Ryvlin *et al*., 1992*a*; Coubes *et al*., 1993; Theodore *et al*., 1994; Nagata *et al*., 1995).

Ictal SPECT studies

It was established over a decade ago that the increase in CBF associated with a seizure may be detected using SPECT (Bonte *et al*., 1983; Lee *et al*., 1986). This may provide useful localizing 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 min after tracer administration, which is then stable for several hours so that the patient may be imaged when the seizure is over. The general pattern is of localized ictal hyperperfusion, with surrounding hypoperfusion, that is followed by accentuated hypoperfusion in the region of the focus, which gradually returns to the interictal state. Combined data from interictal and ictal SPECT scans give a lot more data than interictal 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 (Lee *et al*., 1988; Shen *et al*., 1990; Stefan *et al*., 1990; Rowe *et al*., 1991*a*; Marks *et al*., 1992; Duncan *et al*., 1993*a*; Harvey *et al*., 1993*a*; Markand *et al*., 1994; Cross *et al*., 1995). In a recent overview of the extensive experience from the Austin Hospital, ictal SPECT achieved 97% correct localization in unilateral temporal lobe epilepsy, compared with 71% for postictal SPECT and 48% for interictal scans. In extratemporal seizures ictal SPECT studies localized the focus in 92%, compared with 46% for postictal studies and interictal SPECT was of little value (Newton *et al*., 1995).

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 (Newton *et al*., 1992*a*). A characteristic feature of temporal lobe seizures is an initial hyperperfusion of the temporal lobe, followed by medial temporal hyperperfusion and lateral temporal hypoperfusion (Fig. 9) (Newton *et al*., 1992*b*).

Ictal ^{99m}Tc-HMPAO scans may be useful in the evaluation of patients with extra-temporal seizures who do not have an identifiable abnormality on MRI. This technique localized the seizure focus in 10 out of 12 such patients in one recent series (Marks *et al*., 1992), and in 20 out of 22 in another (Harvey *et al*., 1993*b*). In the latter study, asymmetrical 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.

Focal ictal increases in CBF have also been found in patients with parietal lobe epilepsy, both with and without demonstrable parietal lesions, and they correspond with the lesions when present (Ho *et al*., 1994). 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.

Postictal SPECT has shown a focal increase in CBF in areas of focal cortical dysplasia (Otsubo *et al*., 1993). A focal ictal CBF rise has been demonstrated in patients with MCD and non-localizing ictal scalp EEG, and can be used to identify surgically resectable epileptic tissue (Kuzniecky *et al*., 1993*c*).

A focal increase in CBF may be seen in epilepsia partialis continua, even when the EEG does not show focal epileptic activity (Katz *et al*., 1990).

The coregistration of interictal and ictal SPECT images, to result in an 'ictal difference image' that may be coregistered with an inidividual's MRI enhances the accuracy of data interpretation (Zubal *et al*., 1995). Ictal ^{99m}Tc-HMPAO scans, however, must be interpreted with caution. Simultaneous video-EEG is essential to determine the relationship between the onset of a seizure and tracer delivery; without this precaution there is risk of confusing ictal and postictal data. A further problem is that 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 CBF distribution 1–2 min after the onset of a seizure may indicate sites other than that of onset.

Until recently, ^{99m}Tc-HMPAO had to be constituted immediately prior to injection, resulting in a delay of up to 1 min. A preparation has now been developed which is stabilized with cobalt chloride for at least 6 h. This allows the labelled tracer to be prepared in advance, and may be injected into a patient at any time over the subsequent 6 h, without the need for further preparatory work. 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, which may be injected within 2–20 s of seizure onset and demonstrates a focal increase in CBF (Grunwald *et al*., 1994)

Although the technique has been reported as being of use (Biersack *et al*., 1988), ictal ^{99m}Tc-HMPAO studies do not reliably differentiate between epileptic and non-epileptic attacks. Cases of non-epileptic attacks which were not associated with a focal increase in CBF have been reported, but a focal increase in CBF may occur, particularly if there is prominent motor activity.

In patients with temporal lobe epilepsy ictal SPECT data was of superior lateralizing ability than was interictal ^{18}FDG-PET, particularly when MRI did not show a structural lesion; however, the investigations had complementary roles when localization was difficult (Ho *et al*., 1995). When compared against EEG data, ictal SPECT and interictal PET had lower sensitivity and higher specificity for extratemporal than temporal seizures (Spencer, 1994).

In conclusion, although interictal SPECT imaging of CBF is only moderately sensitive, ictal SPECT markedly improves the yield. PET imaging of interictal cerebral glucose metabolism is more sensitive than measurement of interictal CBF in temporal lobe epilepsy. Furthermore, PET has greater spatial resolution and versatility in that multiple tracers can image various aspects of cerebral function.

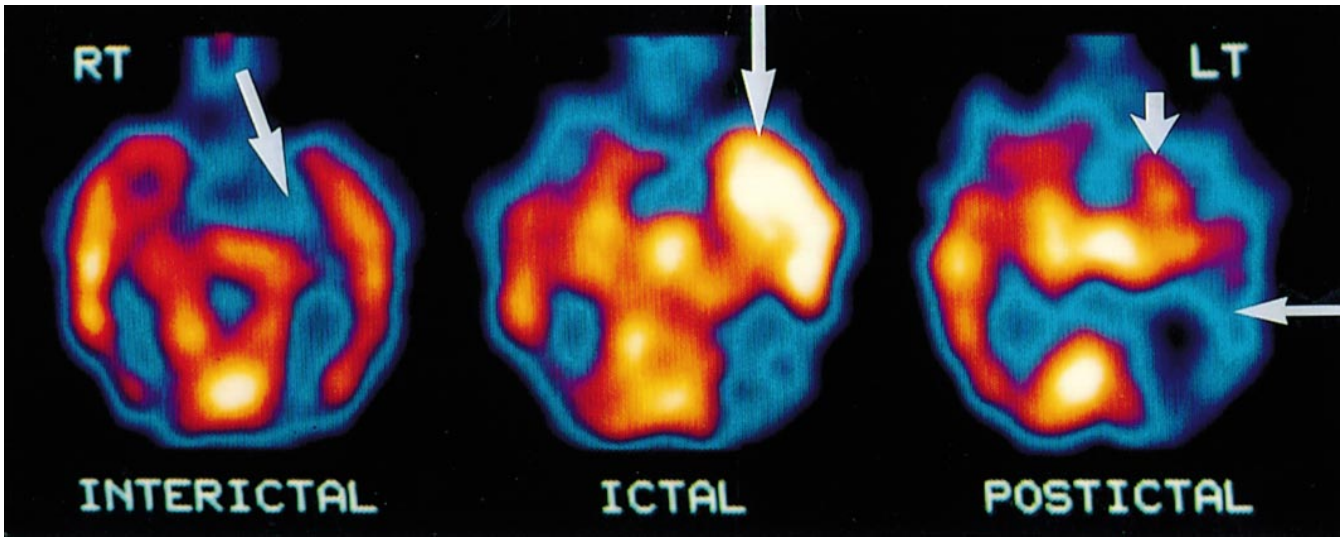

Fig. 9 Transverse interictal, ictal and postictal HMPAO SPECT scans of a patient with left temporal lobe seizures. The colour scale from white to red to blue indicates a spectrum of high to low counts. Interictally, there is a small region of hypoperfusion in the left mesial temporal lobe (arrow). The ictal study shows marked left temporal hyperperfusion (large arrow). The 1.5 min postictal scan shows lateral temporal hypoperfusion (horizontal arrow) with residual mesial hyperperfusion (vertical arrow) on the left. (Reprinted with permission of the publisher from Newton *et* al., J Neurol Neurosurg Psychiat 1992; 55: 893. © BMJ Publishing Group).

Carotid amytal testing and SPECT

Intravenous HMPAO and SPECT have been used to demonstrate a unilateral hemispheric reduction of CBF of 50–90% following intracarotid injection of sodium amytal to assess language lateralization and memory function (Biersack *et al*., 1987). The distribution of hypoperfusion was variable between patients and did not always involve the medial temporal lobe, and the degree of hypoperfusion correlated with the duration of hemiplegia and of drug-induced δ-activity in the EEG (Coubes *et al*., 1995). A different approach has been to inject the tracer and the sodium amytal together into the carotid artery. This has also shown that distribution of the tracer varied from patient to patient and did not always include the medial temporal lobe (Jeffery *et al*., 1991; Hart *et al*., 1993). Although of interest and potential importance, it is not yet clear whether such investigations are of clinical benefit.

Iomazenil

[^{123}I]Iomazenil is a derivative of the central benzodiazepine receptor antagonist flumazenil. Early studies with [^{123}I]iomazenil showed a reduction in binding in the region of the epileptic focus (Van Huffelen *et al*., 1990; Bartenstein *et al*., 1991). In the former, in 16 out of 17 patients, [^{123}I]iomazenil SPECT gave concordant results with ictal EEG recordings. ^{18}FDG-PET concurred with ictal EEG in all cases. Analysis of the former was by visual assessment, whereas the ^{18}FDG data were quantified, resulting in greater precision (van-Huffelen *et al*., 1990). In the latter investigation, 10 out of the 12 patients had reduced CBF demonstrable with ^{99m}Tc-HMPAO and it was suggested that [^{123}I]iomazenil did not confer additional benefits (Bartenstein *et al*., 1991). Similar results have been reported elsewhere (Cordes *et al*., 1992; Haldemann *et al*., 1992; Duncan *et al*., 1993*b*). Studies with higher resolution cameras and optimal scan orientation, however, have suggested that the area of reduced specific binding of [^{123}I]iomazenil is more restricted than the defect of CBF, and is of greater sensitivity for the localization of an epileptogenic focus (Johnson *et al*., 1992; Venz *et al*., 1994; Sjoholm *et al*., 1995). Reduced binding of [^{123}I]iomezanil has been found in a focal area of MCD, in which reduced CBF was not detectable, implying that the former may have greater sensitivity for detecting areas of cortical abnormality (Bartenstein *et al*., 1992). In this case an abnormality was very evident on MRI, and it appeared to be as extensive as the abnormal BZR binding.

Iododexetimide

Another tracer that may prove to be of clinical utility is [^{123}I]iododexetimide that labels muscarinic acetylcholine receptors. Reduced binding of this tracer has been found at epileptic foci; at present it is not certain whether this represents more than loss of neurons (Muller-Gartner *et al*., 1993).

Conclusion

A principle advantage of SPECT over PET is that the former is much less expensive and the equipment is more widespread. A further advantage is the ability to obtain images representative of CBF at the time of seizures. These data need careful and cautious interpretation and are non-quantitative. If further SPECT tracers that probe the integrity

of specific receptors and neurotransmitters are developed, the technique may have further applications in the future in the investigation and management of epilepsy.

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