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Functional imaging in epilepsy

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Functional imaging plays a growing role in the clinical assessment and research investigation of patients with epilepsy. This article reviews the literature on functional MRI (fMRI) investigation of EEG activity, fMRI evaluation of cognitive and motor functions, magnetic resonance spectroscopy (MRS), single photon emission computed tomography (SPECT) and positron emission tomography (PET) in epilepsy. The place of these techniques in clinical evaluation and their contribution to a better neurobiological understanding of epilepsy are discussed.

Key words: epilepsy; fMRI; MRS; SPECT; PET; review.

INTRODUCTION

The investigation, management and scientific study of patients with epilepsy has been transformed over the last 15 years with the advent of increasingly sophisticated brain imaging techniques. Prominent amongst these, and widely used in many epilepsy centres, are high resolution structural imaging with magnetic resonance imaging (MRI), imaging of cerebral metabolic rate with 18-fluorodeoxyglucose (^{18}FDG) positron emission tomography (PET) and imaging of cerebral blood flow with single photon emission computed tomography (SPECT). Many other techniques are in occasional clinical use, are undergoing clinical development, or have been used in research studies, such as magnetic resonance spectroscopy (MRS), functional magnetic resonance imaging (fMRI) and neuroreceptor imaging studies with both PET and SPECT. Epilepsy is particularly challenging from an imaging point of view because fixed abnormalities may be present (structural lesions such as hippocampal sclerosis (HS) or malformations of cortical development (MCD)) in addition to transient abnormalities related to interictal EEG spikes or seizures, which may be detected with a variety of functional imaging techniques. Furthermore, the presence of a focal abnormality in the brain of a patient with epilepsy may give rise to a reorganization of the topographical representation of cortical functions, which may be of research interest or may be of clinical importance when mapping essential functions prior to resective surgery in eloquent areas. Because of these many interesting challenges, imaging in epilepsy encompasses the full range of currently available imaging acquisition and analysis techniques; this brief review attempts to provide an overview and interpretation of the current state of the art in functional imaging, both from a research and clinical standpoint.

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FUNCTIONAL IMAGING TECHNIQUES

SPECT has been the most widely used functional imaging technique in epilepsy. Usually, a commercially available compound labelled with a long-lived radioisotope is injected intravenously and a single image of radiotracer distribution in the brain is obtained hours later using relatively cheap, simple and widely available gamma-camera technology. Cost, availability and ability to image ictal events are the advantages of this technique; relatively low resolution, lack of quantitation of measured parameters and relatively limited choice of measurable variables are the disadvantages: currently, only techniques to image blood flow and a small number of neuroreceptors are in general use.

PET has also been widely employed. Some of the principles are similar to those of SPECT, but PET relies on short-lived positron-emitting isotopes and on simultaneous detection of pairs of photons. Hence, an on-site cyclotron is usually required and the detector hardware and imaging software are vastly more expensive than for SPECT. Quantitation and high resolution have been strengths of PET in comparison with SPECT, although in theory there is no reason for SPECT to be non-quantifiable or lower resolution than PET; the difference reflects the fact that PET has largely been a research technique in academic centres whereas SPECT has been marketed as a clinical technique potentially usable in a wide range of clinical facilities. PET is scarce and costly, but blood flow, metabolic rate and a very wide range of receptor, enzyme and transporter parameters can be measured accurately and with relatively high spatial resolution. Despite this wide potential, however, most centres only image glucose metabolism and cerebral blood flow.

MRS requires exactly the same equipment as conventional MRI, hence, potentially, is very widely available. However, obtaining reliable magnetic resonance spectra is highly technically demanding and MRS has remained a little-used technique in epilepsy, confined largely to academic centres. The basic principle is that the resonance frequency of an atomic nucleus within an applied magnetic field is shifted in different chemical environments, allowing concentrations of a variety of substances to be measured from a magnetic resonance spectrum. Spectra may be obtained from various nuclei, of which the most widely used have been ^{1}H and ^{31}P. These spectra may be obtained under a range of acquisition techniques, permitting concentrations of a variety of substances to be measured. The technical demands and very low spatial resolution are current limiting factors; the ability to measure many substances non-invasively promises an exciting future.

fMRI depends on a specific MRI acquisition technique allowing detection of signals which are probably dependent on blood oxygenation level. Hence, the magnitude of this signal in a particular brain region will depend on the local neuronal metabolic rate. Rapid image acquisition techniques coupled with multiple image acquisitions under different conditions allow the detection of regions with significant change in blood oxygenation level between these conditions (blood oxygenation-level-dependent contrast—BOLD).

EEG-based dipole source imaging and MEG-based magnetic source imaging are techniques allowing interictal electrical and magnetic activity, respectively, to be mapped into three-dimensional space, often into an MRI volume. EEG technology is ubiquitous, although large numbers of digitally recorded channels are needed for transformation to useful dipole source imaging; MEG requires extremely expensive magnetically shielded rooms and ultra-low temperature detectors. The temporal resolution of these techniques is extremely high, but spatial resolution is uncertain, relying on assumptions about the geometry of the head. They will not be discussed further here.

All functional imaging techniques should be interpreted with reference to high-quality high-resolution MRI structural imaging; techniques to allow coregistration of functional to structural imaging are available[1], as are techniques to correct for the partial volume averaging effects of relatively low-resolution PET and SPECT, allowing more accurate regional parameter measurements[2–8]. Finally, a growing trend is the objective, automated analysis of functional imaging data, allowing individual patient scans to be compared with a normal control group and significant abnormalities in the patient to be defined in a statistically rigorous manner[9–11]. A novel technique permits the simultaneous comparison of both structural and functional imaging from the same patient with normal controls, in order to detect areas with discordance between structural and functional abnormalities[12].

COMPARISON OF IMAGING TECHNIQUES

It is important to emphasize at the outset that structural imaging with MRI is of paramount importance in the routine clinical investigation of patients with epilepsy, including pre-operative assessment. Indeed, it is essential that any functional imaging study, undertaken for any purpose, should be interpreted with reference to current structural imaging. Furthermore, the imaging literature is clouded by studies in which imaging techniques have been compared with one another (e.g. the sensitivity of structural MRI to detect a putative seizure focus has often been compared with

the sensitivity of ^{18}FDG PET) without taking into account the relative methodological development of each technique at the time of the study—for example, early studies comparing relatively primitive MRI with well-developed ^{18}FDG PET found PET to be generally superior, whereas today this is not the case. Hence, the role and relative utility of each imaging technique needs to be constantly re-evaluated in the light of current developments in imaging techniques. Even amongst internationally renowned epilepsy surgery centres, the extent to which functional imaging techniques are employed is extremely variable and may often reflect local experience in the scientific development of particular imaging techniques rather than a clear adherence to the evidence for their role. The techniques of structural imaging, the impact of this approach and its role in clinical investigation has been extensively reviewed elsewhere[13].

FUNCTIONAL MRI

fMRI has been applied in the epilepsies for a relatively short time and the literature is not extensive. Recent reviews of this area have been published[14, 15].

Ictal and interictal epileptiform activity

For most patients with epilepsy, EEG is the most useful technique employed to localize the seizure focus. Interictal epileptiform activity may be detected and ictal recordings may localize the onset of the seizure. Although EEG generally only records electrical potential at the scalp surface, a number of techniques have been devised to allow a three-dimensional reconstruction of the origin of EEG electrical activity (source localization). These techniques have a number of inherent assumptions and disadvantages (reviewed in Ref. 16). Therefore, in the context of pre-surgical evaluation, invasive electrode studies are often used to add further anatomical information. Such studies have a small but significant morbidity, hence alternatives to this technique have been sought in functional imaging. The transient bursts of neural activity associated with interictal spikes or seizures are usually accompanied by a transient and relatively localized increase in cerebral blood flow (CBF); fMRI permits changes in CBF to be detected via the paradoxical decrease in local blood deoxyhaemoglobin concentration which occurs with an increase in CBF; the change in deoxyhaemoglobin concentration alters the magnetic properties of blood and this change is detected using MRI. Technically demanding to perform, the technique is conceptually very simple: EEG data is collected while a subject is scanned very frequently; images following spikes or during seizures are compared with images at 'rest' using voxel-based statistics, resulting in an image of significant change in CBF. Limitations of the method include movement artefact, although this may be compensated for by image coregistration, and the fact that it is impracticable for a patient to lie for hours in an MRI scanner awaiting the onset of a seizure. Most studies to date have used spike-triggered imaging; that is, an EEG spike is used as the cue to scan; current developments allow continuous EEG recording and continuous scanning, allowing more subtle EEG changes to also be included within the data analysis, potentially improving the sensitivity.

The first study successfully localizing seizure onset with fMRI was undertaken in an unusual patient who had frequent partial seizures which were clinically obvious and which did not result in excessive movement artefact[17], hence simultaneous EEG recording was not required. Such patients are exceptionally unusual and although such studies are of very great interest, this approach is not likely to be clinically useful for most patients. In general, most subjects do not have seizures which are compatible with continuing an MRI study. Therefore the approach usually taken has been to map with fMRI the correlates of interictal epileptiform activity on the EEG. One approach has been to look for brain regions which show marked changes in CBF during an interictal fMRI study and attempt to correlate these regions with EEG recorded on a separate occasion[18]. Although this technique is inherently relatively simple, the lack of simultaneous EEG renders the findings open to misinterpretation. Nonetheless, this technique has been used to demonstrate activation of the thalamus correlated in time with activation of a frontal seizure focus in a patient with frequent partial seizures, indicating activation of a neural network[19].

Simultaneous EEG during fMRI image acquisition is technically extremely demanding[20] and is still in development, though is highly promising. fMRI-compatible EEG equipment is now available commercially and this approach is likely to become widely used in the near future. Issues with regard to safety and artefacts from the patient's pulse and due to the scanner itself[21–24] have been largely overcome. In 24 studies of 10 patients selected for spike-triggered fMRI study on the basis of frequent interictal spikes, six of the 10 patients showed reproducible focal changes, which occurred in close spatial relationship to the maximum of the epileptiform discharges in the concurrent EEG; no reproducible signal changes were observed in the remaining four patients[25]. In a separate study, 11 patients in pre-surgical evaluation underwent spike-triggered fMRI. Seven showed focal signal changes; six of these patients

had intracranial electrode recording and this site of seizure onset was confirmed in five[26]. A further spike-triggered study showed focal signal change in nine of 10 patients[27]. Further studies are required to optimize the method and to determine the sensitivity specificity of the technique for location of the seizure focus in larger, unselected groups of patients. In particular, defining the irritative zone of the cortex (that generates interictal spikes) and its relationship with the epileptogenic zone (that gives rise to seizures) in patients in whom surgical treatment is being considered will need critical evaluation. An important application of the technique may be in constraining the solution to the 'inverse problem' inherent in EEG source analysis.

Localization and lateralization of cognitive function

In the context of pre-surgical planning, the identification of cortex necessary for important cognitive and motor functions is essential to limit operative morbidity. Intraoperative electrocorticography, recording from and stimulation of invasive implanted electrodes and the intracarotid sodium amytal test (Wada test) are all frequently used for this purpose. All have the limitations of risk and restricted sampling. Functional imaging, especially with fMRI, holds the promise to permit detailed mapping studies to be performed on an individual basis pre-operatively. A preliminary study showed that the BOLD signal contrast obtained in simple tests of language and motor function was very similar between subjects with epilepsy and normal controls, demonstrating the feasibility of the technique in studies of patients with epilepsy[28].

Pre-operative assessment of language lateralization is important in many operative candidates. An early study[29] examined post-operative patients only and compared the BOLD signal correlates of a semantic decision task with a pre-operative Wada test in seven subjects with temporal lobe epilepsy (TLE); in all cases, using a region-of-interest based analysis looking only at inferior frontal regions, the lateralization by fMRI was the same as by the Wada test. Another early study[30] showed that in two subjects with temporal lobe lesions the pattern of activation during an auditory comprehension task was greatly altered anatomically by the presence of the lesion. A much larger study attempted to correlate the Wada test and fMRI assessment of language laterality, using a laterality index for the Wada test (a continuous variable) and a laterality index from fMRI calculated as an asymmetry in the voxels activated in each hemisphere by a semantic decision task[31]. The correlation was extremely strong ($r = 0.96$, $P < 0.0001$) and all subjects were classified to the same laterality by the two tests. A similar approach has also been used in children[32]. Using a different activation paradigm (word generation), a study of 15 subjects failed to show a convincing correlation with the Wada test[33]. An interesting approach matched a group of left TLE subjects to a group of right TLE patients, in terms of handedness, verbal memory scores and approximate number of voxels activated by a semantic decision task[34]; comparison of the two groups showed that the right TLE group activated the left mesial temporal lobe, whereas the left TLE group did not. A further study mostly in patients with lateralized lesions but not epilepsy[35] examined a range of activation tasks to find those most strongly correlated with the Wada test; despite the conflicting data above, this was found to be a verb generation task.

Patients undergoing pre-surgical assessment may be evaluated using the Wada test; this is undertaken primarily to reveal the ability of each hemisphere to sustain verbal memory, rather than to determine language dominance. Tasks which reliably activate the mesial temporal structures in normal subjects using fMRI have been developed only relatively recently and widespread application in epilepsy is awaited. An early study employed a complex visual encoding task known to activate both mesial temporal regions in normal patients. In patients with TLE, the activation was asymmetric and strongly correlated with the results of Wada testing of memory[36]. Another study used a verbal memory encoding and retrieval paradigm to compare patients with left TLE against normals[37]; normals activated parahippocampal regions, right more than left, during retrieval; this pattern was less marked in the patients, but in the patient group a left frontal region participated. The authors interpret this as a difference in pattern of activation but overlook the vast difference in performance between the patient and normal control groups—the patients recalled with far less accuracy ($P < 0.0007$).

There are many caveats in using fMRI to map cortical function in patients with epilepsy. Firstly, there are many important differences in the methodological approaches taken. There is no single 'test' which identifies, for example, 'language cortex'. Most studies employ a paradigm in which one functional state is compared with another, e.g. the BOLD signal during a task requiring attention to the phonological attributes of a word (its sound) is compared with the BOLD signal during a very similar task requiring attention to the semantic attributes of a word (its meaning), hopefully isolating the brain regions associated with meaning. A different language-related task might activate a different set of brain regions, however. Secondly, it cannot be assumed that these regions include all of those necessary and responsible

for language; neither can it be determined which of these regions are sufficient for language production. Thirdly, the many differences in scanner field strength, acquisition parameters, paradigm design and image analysis are so variable between studies that comparability is almost impossible. Hence, although fMRI as an approach to brain mapping in normal subjects is very well established, the need for an interpretation of the imaging result which can then adequately inform resective surgery has limited the application of this technique in epilepsy to date.

MAGNETIC RESONANCE SPECTROSCOPY

Proton (^{1}H) spectroscopy

In epilepsy studies *in vivo*, the principal signals of interest have been those from N-acetyl aspartate (NAA), creatine + phosphocreatine (Cr), choline-containing compounds (Cho), and lactate (Lac). There is evidence that NAA is located primarily within neurones and precursor cells and a reduction of NAA signal is usually regarded as indicating loss or dysfunction of neurones. Cr and Cho are found both in neurones and in glial cells, and cell studies suggest that they are present at much higher concentrations in glia than neurones[38].

Proton (^{1}H) MRS in TLE

In TLE caused by hippocampal sclerosis, the essential finding has been a reduction of NAA and an increase of choline-containing compounds (Cho), creatine + phosphocreatine (Cr), reflecting neuronal loss or dysfunction and astrocytosis[39,40]. The mean NAA/Cho + Cr ratios were significantly less in patients with epilepsy than in control subjects, and were more marked on the ipsilateral than contralateral side. At an individual level, a reduced NAA/Cho + Cr ratio on the side of the focus was found in 88%, though 40% had bilateral abnormalities. Similar findings have been made in children with TLE[41]: an abnormal NAA/(Cho + Cr) ratio was found in 75%, bilateral in 45%, allowing correct lateralization of the seizure focus in 55%.

The hippocampus occupies only a small volume of the voxel used for these analyses, hence the reduction of NAA was such that the abnormality could not be confined to the hippocampus. This finding is analogous with the findings of ^{18}FDG PET and blood flow SPECT studies described below, which have found a much wider area of functional abnormality beyond the bounds of the structurally abnormal sclerotic hippocampus. Comparisons of quantitative MRS and ^{18}FDG PET showed a correlation between the NAA/Cho + Cr ratio detected on MRS and the degree of hypometabolism in TLE[42]; a similar correlation was found between SPECT hypoperfusion and abnormalities demonstrated by ^{1}H MRS[43]. After successful temporal lobe resection, there is a tendency for the NAA in the contralateral medial temporal lobe to normalize[44].

The studies above examined single large voxels; these preclude the accurate delineation of the origin of the abnormal signals. Magnetic resonance spectroscopic imaging (MRSI) has the advantage of greater anatomical information, but at the expense of greater susceptibility to artefacts. Localized reductions of NAA/Cho in 53 patients with temporal lobe epilepsy, unilateral in 34 and bilateral in 19, have been reported with this technique[45]. In 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[46]. In a large series of 100 patients with temporal lobe epilepsy, strong concordance was found between EEG, MRSI, and hippocampal volumetry[47].

A further methodological advance has been imaging at very high field strength, using high-resolution single slice MRSI obtained at 4.1 Tesla, and mapping MRS data onto the equivalent MRI slice[48]. This approach allowed a clear anatomical delineation of the origin of the abnormal signals: a reduced NAA/Cr ratio was found in the epileptogenic hippocampus in all of 10 patients with TLE. Four also had abnormalities in the contralateral hippocampus and in two of these invasive EEG recordings demonstrated bilateral independent seizure onset. Furthermore, 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. Interestingly, in another study NAA was not reduced in the hippocampi of patients with neocortical epilepsy[49], implying that hippocampal dysfunction is not found in neocortical epilepsy.

Temporal lobe MRS data may correlate with cognitive problems: patients who had right temporal resections and who had abnormalities of MRS in the left temporal lobe had some verbal memory deficits[50]. Furthermore, abnormalities of proton MRS in the left temporal lobe were associated with a loss of verbal cognitive functions, and abnormalities on the right were associated with impaired non-verbal functions[51].

A post-ictal rise in lactate has been shown using ^{1}H MRSI in the ipsilateral temporal lobe in patients with unilateral temporal lobe epilepsy, and also confined to one side in patients who appeared to have bilateral TLE[52]. An elevation of cerebral lactate has been noted during and for a few hours after complex partial seizures, with no change in NAA. In contrast, there

were no changes following absences[53].

Neurotransmitters

GABA is the principal inhibitory neurotransmitter and glutamate the principal excitatory neurotransmitter in human brain. Many hypotheses explaining the origin of epilepsy implicate an imbalance between GABA-mediated inhibition and glutamate-mediated excitation. Proton (^{1}H) MRS, using spectral editing, can identify cerebral GABA *in vivo* and estimate the rise in cerebral GABA concentrations that occurs after administration of vigabatrin[54,55], gabapentin[56] and topiramate.

Measurement of glutamate is technically very demanding because of the overlap of several spectral peaks; important recent methodological advances now set the stage for the measurement of GABA and glutamate regionally in a variety of syndromes, permitting a new approach to the phenomenological description of epileptic syndromes.

^{31}P spectroscopy

Cerebral metabolites detectable with ^{31}P MRS include adenosine triphosphate (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 approximately 2.4 ppm, but rapid exchange between the two forms results in only a single MR spectral peak being detected. The resonance frequency of the peak 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 eight patients with TLE, no significant asymmetries between ipsilateral and contralateral temporal lobes of ATP, PCr or PDE concentrations were found, but in seven of the eight patients, the temporal lobe ipsilateral to the focus had increased pH and, in all eight, increased P_i[57]; this finding was replicated[58]. If confirmed, the neurobiological significance of an increase in pH associated with a seizure focus is not clear.

Conclusion

Over the last decade MRS has advanced as a non-invasive tool for investigating cerebral metabolism. 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 important consequences for the non-invasive investigation and the medical and surgical treatment of patients with epilepsy.

SINGLE PHOTON EMISSION COMPUTERIZED TOMOGRAPHY (SPECT)

Single photon emission computerized tomography is principally used, in the investigation of the epilepsies, to image the distribution of CBF. In addition, there have been a few studies of specific receptors in the brain.

Cerebral blood flow tracers

SPECT may be used to indicate relative regional cerebral blood flow (rCBF) using a variety of radiotracers, currently usually ^{99m}Tc-hexamethylpropyleneamine-oxime (HMPAO) or ^{99m}Tc-ethyl cysteinate dimer (ECD). Investigations using these methods began before the era of high-resolution MRI, when a considerably higher proportion of patients would have been found normal with other imaging modalities; comparisons between imaging modalities in this substantial older literature now need cautious re-interpretation. Insufficient data exist to determine whether ECD is superior to HMPAO; ECD does not require to be reconstituted at the bedside, hence it is likely ECD can be injected sooner after the seizure onset in ictal studies. HMPAO is taken up rapidly into the brain (70% within 1 minute); the image is then stable for about 6 hours since HMPAO reacts with glutathione and becomes trapped. ECD and HMPAO have slightly different uptake patterns.

One of the earliest studies revealed the essential phenomena of increased local blood flow in the ictal state and reduced flow interictally[59]. The particular value of regional hyperperfusion during ictal studies was soon amply confirmed[60], both in secondary generalized, as well as partial, seizures[61,62]. In the early MRI era, and with EEG used as a gold standard, interictal SPECT correlated with EEG in 75% and with MRI in only 61%, leading to the conclusion that, with these technologies, SPECT was superior to MRI for focus localization[63]. With rapid progress in MRI technology, interictal SPECT was recognized to be inferior to MRI for focus localization[64]. Further studies revealed the paradoxical and clinically limiting observations of interictal diffuse, multifocal and bilateral hypoperfusion, or focal hyperperfusion, as well as focal hypoperfusion[65,66] in addition to limited concordance with EEG[67–71]. Five hundred and thirty-nine patients reported in the literature with interictal SPECT have been reviewed[72]. Two hundred and ninety-one patients were localized by SPECT to the temporal lobe, 65 to extra-temporal locations and 183 were unlocalized. Seventy-nine percent showed concordance of the interictal SPECT and EEG

localization. Interictal SPECT localization did not contribute to prediction of good seizure outcome[73].

Further investigations have confirmed the greater sensitivity of ictal SPECT: interictal studies were localizing in 46–76% compared to 75–97% of ictal studies[74–82]. In extratemporal seizures ictal SPECT studies localized the focus in 92%, compared to 46% for post-ictal studies and interictal SPECT was of little value[82]. Ictal scans may be especially useful in the evaluation of patients with extra-temporal seizures with normal MRI, localizing the seizure focus in 10 of 12 patients in one series and in 20 of 22 in another[83,84]. The technical difficulties of ictal studies were somewhat assuaged by the finding that early post-ictal SPECT was more sensitive than interictal SPECT[82,85,86].

Recently, a highly promising semi-automated computerized technique allowing interictal studies to be 'subtracted' from coregistered ictal studies has been developed (Fig. 1)[87–89]. The automated technique permitted more than twice as many seizure foci to be located as a traditional 'side-by-side' qualitative visual comparison. Furthermore, those patients in which the ictal onset zone as defined by the automated technique was resected were more likely to have an excellent outcome than those patients in which the resection did not include the ictal zone identified in this manner. The resection of seizure foci located with the traditional 'side-by-side' qualitative comparison did not predict outcome.

In conclusion, interictal SPECT alone is of little value in the current era; ictal SPECT may be helpful in patients with normal imaging, especially in temporal lobe epilepsy; the experience with ictal SPECT in extra-temporal seizure disorders is still limited, though promising. The coregistration of interictal and ictal SPECT images, to result in an 'ictal difference image' that may be coregistered with an individual's MRI enhances the accuracy of data interpretation and is likely to become the most useful SPECT technique in pre-surgical evaluation.

Some regional abnormalities in blood flow SPECT were possibly related to neuropsychological defects[90,91]. Serial SPECT studies in the interictal, ictal and immediate post-ictal states were performed in 12 patients with refractory TLE to define the patterns and duration of peri-ictal CBF changes. Visual and quantitative analysis showed a constant pattern of unilateral global increases in temporal lobe perfusion during seizures which suddenly switched to a pattern of relative mesial temporal (hippocampal) hyperperfusion and lateral temporal hypoperfusion in the immediate post-ictal period[78,92]. 'Reversed' crossed cerebellar diaschisis was observed in ictal studies, with cerebellar hyperperfusion contralateral to the cerebral focus[93]. Focal hyperperfusion was demonstrated in epilepsia partialis continua with normal EEG[94]. In temporal lobe epilepsy, ictal dystonia was associated with a relative increase in perfusion of the basal ganglia opposite the dystonic limb. Additionally, slight increases in cortical blood flow on the side opposite the direction of version were associated with head-turning, irrespective of the side of seizure focus[84,95]. The latter study revealed asymmetric tonic posturing, contralateral head and eye deviation and unilateral clonic jerking were associated with an ictal increase in CBF in the frontocentral, medial frontal or dorsolateral areas. Different perfusion patterns were seen in different aetiologies of TLE with ictal SPECT[96].

Benzodiazepine receptors

^{123}I-Ro16-0154 (^{123}I-iomazenil) was shown to have intracerebral retention parallel to the known distribution of benzodiazepine receptors (BZR) in man[97]. In comparative studies of HMPAO and ^{123}I-iomazenil SPECT, most subjects show concordant regions of reduced uptake with both tracers; some studies show a small difference in sensitivity, a more marked reduction or a more restricted area of reduced tracer uptake with ^{123}I-iomazenil[98–103]. These studies suggest little advantage in imaging BZR over blood flow. However, in a patient with focal epilepsy due to MCD a marked focal decrease in ^{123}I-iomazenil uptake was seen in this area but normal HMPAO uptake[104]. Some animal evidence suggests BZR imaging should be clinically useful. In hippocampal kindled rabbits, *in vivo* double tracer autoradiography using ^{125}I-Iomazenil and ^{99m}Tc-HMPAO, ^{125}I-Iomazenil accumulation was more markedly and extensively decreased than ^{99m}Tc-HMPAO accumulation[105].

The reason for the disappointing results of clinical application of SPECT BZR imaging may be methodological. A single image of iomazenil binding, without any kinetic modelling, may be seriously confounded by changes in regional blood flow[106–109]. Hence, without performing multiple scans in the same session coupled with measurements of radiotracer in blood, ^{123}I-iomazenil SPECT may actually be mainly indicating regional blood flow rather than BZR density.

POSITRON EMISSION TOMOGRAPHY (PET) STUDIES OF CEREBRAL GLUCOSE METABOLISM

^{18}FDG has been used with PET to measure regional cerebral metabolic rate for glucose (rCMRgluc). Most human studies have been of the interictal state; the

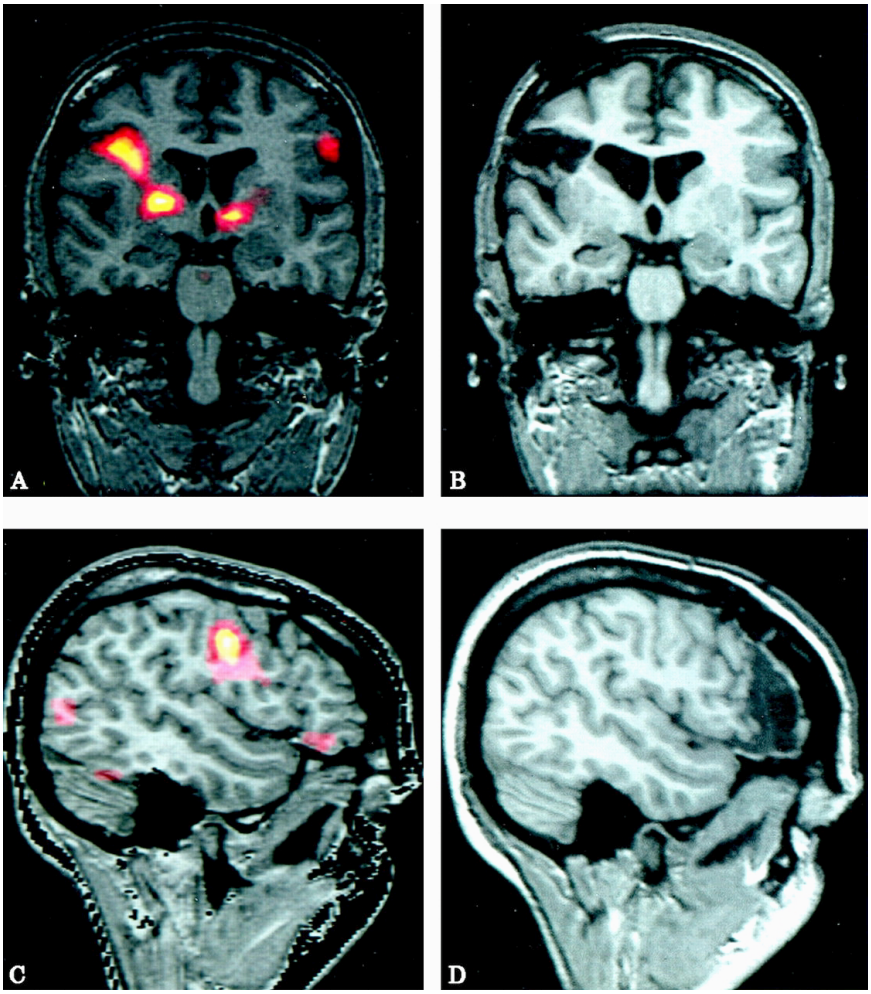

Fig. 1: Pre-operative subtraction ictal SPECT coregistered with MRI (SISCOM) images (A and C) and post-operative coregistered MRI (B and D). A and B, complete excision of neocortical region underlying SISCOM focus. C and D, non-excision of neocortical region underlying SISCOM focus. In the accompanying paper (O'Brien *et al.* Subtraction peri-ictal SPECT is predictive of extratemporal epilepsy surgery outcome. *Neurology* 2000; **55**: 1668–1677) it was shown that resection of the SISCOM focus was significantly more likely to result in a good post-operative outcome. Copyright 2000 AAN Enterprises, Inc. Used with permission.

hallmark in localization-related epilepsy has been a regional decrease in rCMRgluc interictally, although a study of drug-naive patients found interictal increased rCMRgluc[110]. Several studies of ^{18}FDG PET have found a 60–90% incidence of hypometabolism in the temporal lobe interictally in adults and children with TLE [64, 111–119]. Surgical ECoG findings have confirmed the epileptogenic nature of regions of interictal hypometabolism[120]. The hypometabolic zone is frequently extensive and, particularly in TLE, may involve regions outside the ictal onset area; in patients with a unilateral temporal lobe focus the asymmetry of metabolism may be more pronounced in the lateral temporal cortex than in the mesial part of the temporal lobe; indeed, in most cortical and subcortical regions on the side of the epileptic focus, glucose consumption rate is lower than in the contralateral region or than in controls[119, 121]. A well-localized region of decreased glucose metabolism is found less frequently in extratemporal seizure disorders than in TLE, usually in association with a concordant MRI abnormality[122, 123].

Although regional hypometabolism may be detected in patients with lesions or normal MRI, the clinical utility of such a finding is controversial. In patients judged to have TLE, the presence of temporal lobe hypometabolism was associated with a better outcome after ipsilateral temporal lobectomy than in patients without hypometabolism[124]; another study found the degree of lateral temporal (rather than mesial temporal) hypometabolism to be a predictor of good outcome[125]; a further study found the opposite (mesial temporal metabolism was the better predictor)[126]; and yet another study found that even with no hypometabolic region, good outcome could be obtained[127]. A false localizing PET result for lobe of

onset has been reported in as many as 36%, limiting the usefulness of such data[128]. However, in patients with concordant findings with non-invasive EEG and ^{18}FDG PET, depth studies were never discordant, suggesting ^{18}FDG PET might obviate the need for depth recording[129].

In more recent comparative studies of MRI and PET, although the yield of abnormalities with ^{18}FDG PET may be high, usually these abnormalities are concordant with an MRI abnormality, suggesting ^{18}FDG PET does not provide clinically useful data if the MRI findings are definite, but may have some additional sensitivity[118, 123, 130, 131].

The superiority of quantitative over visual interpretation of ^{18}FDG PET in TLE has been demonstrated[132]. It may be possible to improve the delineation of the hypometabolic zone in TLE by performing activation tasks during the scan, such as 'emotional speech', which increase the contrast between normal and abnormal regions in the temporal lobe[133].

In paediatric practice ^{18}FDG PET may have a more valuable role. ^{18}FDG PET has enabled a characterization of the functional abnormalities in children with severe epilepsies, in some cases enabling remarkably effective surgical intervention in children with normal MRI[134]. In eight children with intractable neonatal onset seizures, interictal PET revealed unilateral diffuse hypometabolism in three, leading to highly effective hemispherectomy. In one child, ictal PET showed hypermetabolism in the left frontal cortex, left striatum, and right cerebellum; again, a large resection was immensely successful[135]. In 13 children with infantile spasms of undetermined cause, unilateral hypometabolism involving the parieto-occipito-temporal region was found in five; MRI was normal in four of these. Four of these five infants underwent surgical removal of the cortical focus with seizure-free outcome; pathological examination of resected tissue in each showed microscopic cortical dysplasia[136].

In summary, although ^{18}FDG PET has been useful in the past for detecting a seizure focus possibly amenable to surgery, the improvements in MRI technology have rendered such routine clinical investigation superfluous in the majority of patients. However, in selected MRI normal patients, particularly children, a place remains for evaluation with ^{18}FDG PET, with the caveat that the hypometabolic region may be found to be more extensive than the ictal onset zone. However, ^{18}FDG PET has provided valuable information about metabolic abnormalities in an extensive cortical-subcortical network and an insight into patterns of ictal metabolism.

Despite reservations about the current place of ^{18}FDG PET in clinical investigation, this technique has yielded interesting information relating to the neurobiology of seizure disorders. Some differences exist in the metabolic patterns associated with different aetiologies of TLE: patients with HS have the lowest ^{18}FDG uptake in the entire temporal lobe, followed by patients with lateral temporal seizure origin. Patients with tumours in the mesiobasal temporal lobe show only a slight decrease of glucose metabolism[137]. The comparison of metabolic patterns on ^{18}FDG PET with video EEG telemetry in 48 patients revealed patients with frontal hypometabolism alone had shorter ictal and post-ictal durations; auras were more likely to be present in patients with temporal hypometabolism alone; other metabolic patterns did not predict specific ictal clinical features[138]. Hypometabolism of basal ganglia and thalamus has been observed in patients with TLE of both limbic and neocortical origin[139, 140]. Relative hypometabolism of the left hemisphere correlated with lower cognitive performance in 13 unilateral TLE patients. Hypometabolism of the left lateral temporal lobe and thalamus independently correlated with verbal memory difficulties[141]. Patients with localization-related epilepsy had bilateral cerebellar hypometabolism that was not fully explained by treatment with phenytoin[132]. The metabolic consequences of successful surgery have been investigated. After selective amygdalo-hippocampectomy in patients with HS there was an increase of rCMRgluc in the ipsilateral and also the contralateral hemisphere[142].

^{18}FDG PET has been employed to examine patients with MCD. Glucose metabolism similar to normal cortex has been detected using ^{18}FDG PET in the ectopic neurones in band heterotopia[143, 144] and in heterotopic nodules and displaced grey matter[145, 146]. Of 17 patients with MCD, 15 had abnormal PET findings, consisting of focal hypometabolism in nine patients and displaced metabolic activity of normal grey matter, reflecting underlying grey matter heterotopia, in six. All 15 patients had MRI abnormalities[147]. Four of eight children with hemimegalencephaly had regions of reduced metabolism in the unaffected hemisphere[148]. Multiple regions of focal hypometabolism have been demonstrated in patients with tuberous sclerosis[149]. A study including both patients with acquired lesions and congenital abnormalities such as tuberous sclerosis and agenesis of the corpus callosum showed regions of decreased metabolism which were more extensive than the MRI lesions in some cases[150]. Attempts have been made to determine the functional capacity of dysgenetic regions. A medical student with extensive unilateral heterotopic grey matter underwent a resting ^{18}FDG PET in which metabolic activity similar to normal cortex was seen in the heterotopia; during a second scan the patient undertook a verbal fluency task which resulted in a slight increase in the metabolic rate in the heterotopic region[151].

A small number of studies have examined ictal metabolic patterns. By chance, 18 children undergoing ^{18}FDG PET had seizures during the ^{18}FDG uptake period. Three major metabolic patterns were determined based on degree and type of subcortical involvement. Nine children had asymmetric glucose metabolism of striatum and thalamus, usually involving unilateral cortical hypermetabolism and crossed cerebellar hypermetabolism. Five children had symmetric metabolic abnormalities of striatum and thalamus; this pattern was accompanied by hippocampal or insular cortex hypermetabolism, diffuse neocortical hypometabolism, and absence of any cerebellar abnormality. Four children had hypermetabolism restricted to cerebral cortex[152]. Focal hypermetabolism has been noted in EPC[153]. Hypometabolism is accentuated after a seizure and may not return to the interictal state for more than 24 hours[154].

POSITRON EMISSION TOMOGRAPHY STUDIES OF SPECIFIC LIGANDS

Benzodiazepine receptors

The benzodiazepine receptor ligand ^{11}C-flumazenil binds to the central benzodiazepine receptor (cBZR) which is present on the majority of $GABA_A$ receptors. Hence, ^{11}C-flumazenil PET can provide images indexing $GABA_A$ receptor density. The first such study showed focal decreased BZR density in cortical seizure foci[155] which were more closely localized than reduction in glucose metabolism as indicated by ^{18}FDG PET (Fig. 2)[156]. The reduction in BZR density in the epileptogenic hippocampus has been further confirmed in other studies[9, 157, 158]. Recent studies have shown marked increase in sensitivity through techniques for correction of partial volume effects in patients with hippocampal sclerosis[8] and precise correlation of BZR binding measured by ^{11}C-flumazenil PET and by *ex vivo* autoradiography of resected specimens in the same patients[159]. Epileptic foci outside the hippocampus have not been systematically studied, although small numbers of cases have been described with focal decrease in receptor density (Fig. 3)[155]. In the great majority of these studies, PET abnormalities were concordant with known MRI abnormalities. In patients with malformations of cortical development, multiple areas of abnormal BZR binding were frequently detected, often remote from the MRI-defined abnormality[10]; these abnormalities were not explained by unsuspected structural abnormalities[12]. It remains to be established if such findings correlate with poor surgical outcome.

Quantification of PET data requires a volume-of-interest based approach, and in view of the size of the hippocampus and the limited spatial resolution of PET, correction for partial volume effects[3, 160]. Correction of partial volume effects resulted in increased sensitivity of ^{11}C-flumazenil PET in detection of unilateral hippocampal sclerosis[8] and also identified bilateral hippocampal abnormalities of BZR in one third of patients who appeared to have unilateral HS on MRI[161]. Further, after correction of partial volume effects, ^{11}C-flumazenil binding *in vivo* in patients with HS undergoing surgical resection was reduced by a mean of 38%, indicating that the loss of binding was not simply due to hippocampal atrophy[8].

The place of ^{11}C-flumazenil PET in the clinical investigation of patients with refractory localization-related and unremarkable high quality MRI has been little investigated. In six patients with frontal lobe epilepsy, five with normal MRI, reduction in cBZR binding was demonstrated with ^{11}C-flumazenil PET, which was consistent with clinical and EEG data[162]. Using an automated, objective technique for comparing individual patient scans with a normal control group, 13 of 18 patients with neocortical localization-related epilepsy and normal MRI had regional abnormalities of BZR binding; in 10 these regions had increased BZR binding. In a subgroup with frontal lobe seizures, 60% had focal BZR abnormalities concordant with clinical and EEG data[163]. Greater reduction of ^{11}C-flumazenil binding has been reported in patients with frequent seizures compared to those with less frequent seizures[164]. This finding has not been confirmed by other studies.

In a clinical series of 100 patients with partial seizures having pre-surgical evaluation, 94% of those with TLE had an abnormality of ^{11}C-flumazenil PET detected, as did 50% of those with other forms of partial epilepsy; 81% of abnormalities found using ^{11}C-flumazenil PET were concordant with abnormalities on MRI. ^{11}C-flumazenil PET was useful in the identification of bilateral temporal lobe pathology[165]. Currently, there is insufficient data to support the routine clinical use of BZR PET imaging, though it is a technique showing great promise in the evaluation of MRI-normal subjects.

Primary generalized epilepsy has been much less studied than focal epilepsy. Diagnostic classification is often difficult; this may explain the contradictory results noted in different studies. There is increasing evidence that the fundamental abnormality underlying primary generalized epilepsy appears to lie outside the $GABA_A$ system[166], so abnormalities of ^{11}C-flumazenil binding might not be expected. Childhood and juvenile absence epilepsy patients were shown to have normal interictal ^{11}C-flumazenil binding[167]; other primary generalized epilepsy patients have been shown to be not significantly different from normals[168] or to have increased receptor density in the cerebellar nuclei and decreased receptor density

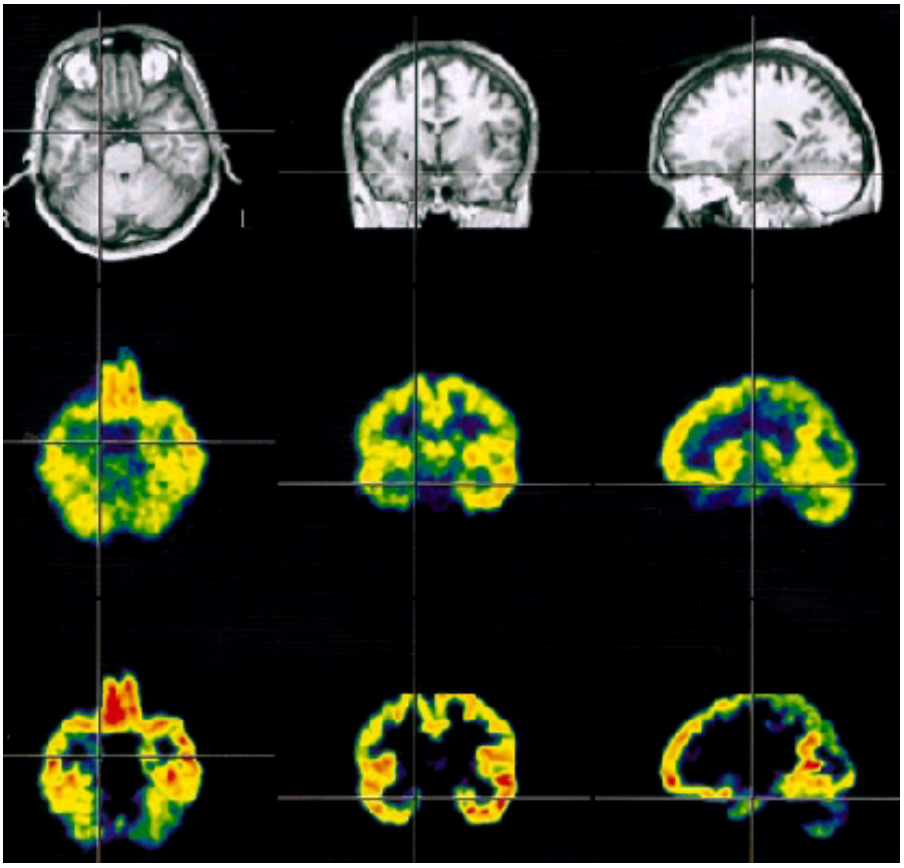

Fig. 2: The top row shows three sections through a T1-weighted MRI of a subject with onset of seizures in the right temporal lobe (left side of the figure). 1T MRI was normal. The second row shows a coregistered ^{18}FDG PET; extensive right temporal hypometabolism is demonstrated. However, the bottom row depicts ^{11}C-flumazenil PET from the same subject; the region of reduced flumazenil binding is much more restricted, confined only to the right mesial temporal structures. From: Szelies *et al. MRI-Guided Flumazenil- and FDG-PET in Temporal Lobe Epilepsy Neuroimage* 1996: **3**; 109–118 (Fig. 3(a)). Copyright Academic Press 1996, used with permission.

in the thalamus[169]. This latter finding is intriguing, pointing to abnormalities outside the thalamocortical loop usually regarded as the substrate of generalized seizure discharges[170]; the finding has not yet been replicated in man or confirmed in animal studies. Further work is needed to clarify the findings in well-defined diagnostic groups.

The effects of drugs on BZR binding in man have not been widely examined using ^{11}C-flumazenil PET. Treatment with sodium valproate was associated with a significant reduction in receptor density in a cross-sectional study of patients with childhood and juvenile absence epilepsy[167], suggesting a possible mechanism of therapeutic action.

Absence seizures were induced by hyperventilation in susceptible volunteers during the course of a study. Comparing the ^{11}C-flumazenil binding with that in a scan without seizure provocation in the patients, with scans of normals and with computer simulations of the effects of changes in blood flow or receptor binding due to seizures, alterations of benzodiazepine receptor characteristics during absences were not detected[171].

Opioid receptors

The rationale for employing opiate receptor ligands is the demonstration that endogenous opioids are released following partial and generalized tonic–clonic seizures and contribute to the post-ictal rise in seizure threshold[172]. An increase in μ-agonist ^{11}C-carfentanil binding to μ-receptors in lateral temporal neocortex in areas which also showed reduced glucose metabolism has been shown[173]. This may be a tonic antiepileptic system that serves to limit the spread of electrical activity. The increase in ^{11}C-carfentanil binding to lateral temporal neocortex was confirmed and reduced binding to the amygdala was noted[174], though this may be an artefact of partial volume effects. Using ^{11}C-diprenorphine, which binds

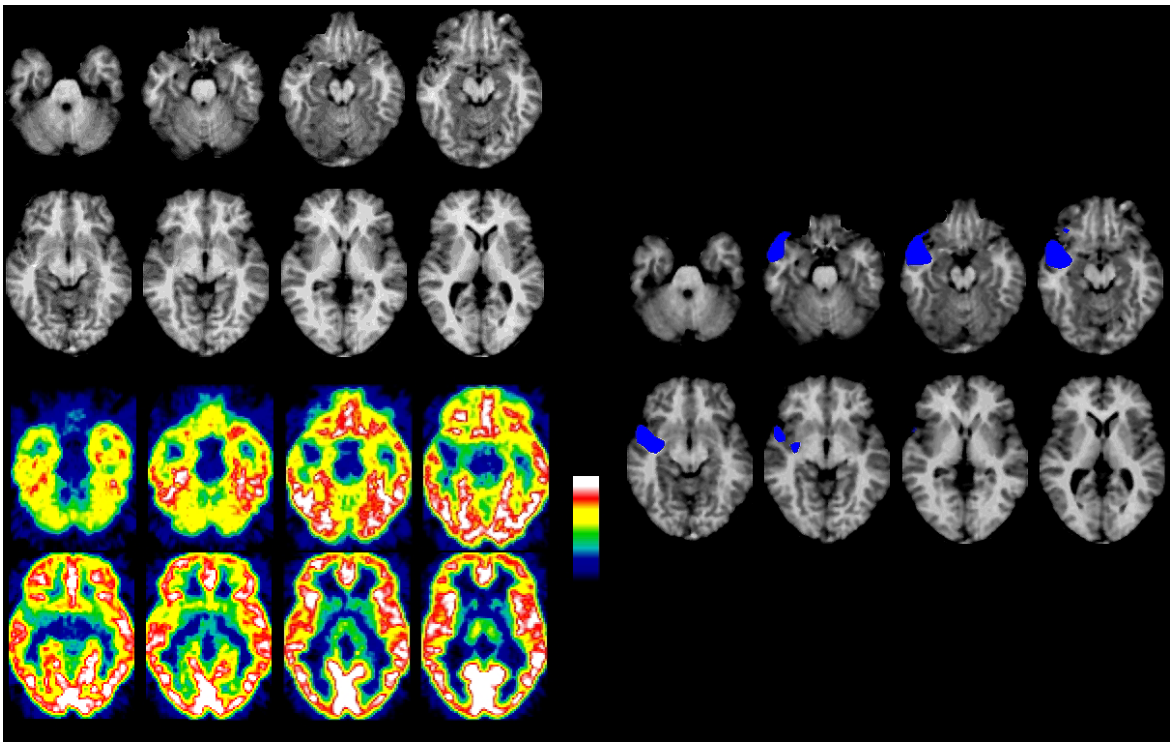

Fig. 3: On the left of the figure is shown sections from a T1-weighted MRI of a patient with a right anterior temporal DNET (above) and coregistered ^{11}C-flumazenil PET from the same subject. Using statistical parametric mapping (SPM), an objective and automated means for comparing images, the right side of the figure shows (in blue rendered onto the MRI) the region having a significantly reduced flumazenil binding compared with 24 normal controls.

with similar affinities to μ, κ and δ subtypes of opioid receptors, there were no abnormalities of binding of ^{11}C-diprenorphine in the temporal lobe or elsewhere[174, 175]. In addition, there was no overall asymmetry of binding of ^{18}F-cycloFOXY, which binds to μ and κ receptors in patients with TLE[176]. The explanation of these findings is not clear, although either an upregulation of μ receptors and reduction of number or affinity of κ receptors, or upregulation of μ receptors and occupation of κ receptors by an endogenous opioid ligand would fit the evidence.

Dynamic ictal studies of opioid receptors have been carried out in patients with reading epilepsy, using ^{11}C-diprenorphine. In order to localize dynamic changes of opioid neurotransmission associated with partial seizures and higher cognitive function, release of endogenous opioids in patients with reading epilepsy was compared with that in healthy volunteers[177]. Reading-induced seizures were associated with reduced ^{11}C-diprenorphine binding to opioid receptors in the left parieto-temporo-occipital cortex and to a lesser extent the left middle temporal gyrus and the posterior parieto-occipital junction. These data gave evidence for localized endogenous opioid peptide release during seizures induced by reading and demonstrate the potential of PET to image release of specific neurotransmitters in response to brain activity in specific cerebral areas *in vivo*.

Other ligands

MAO-B receptors

Deprenyl binds to monoamineoxidase (MAO)-B receptors, which are mainly located on astrocytes. In nine patients with TLE ^{11}C-deuterium deprenyl binding was increased in the epileptogenic temporal lobe, possibly reflecting gliosis[178].

NMDA receptors

^{11}C-(S)-[N-methyl]ketamine binds to the NMDA receptor, and is thus of interest in studies of epilepsy. In eight patients with medial TLE there was a reduction in tracer binding potential that paralleled hypometabolism. It is not clear, however, whether the reduction was due to reduced perfusion, loss of tissue or reduction of receptor binding[179] and further work is needed to clarify this.

Serotoninergic neurones

Increased concentrations of serotonin and serotonin-immunoreactivity have been reported in resected human epileptic cortex. Alpha-[^{11}C]methyl-L-tryptophan ([^{11}C]AMT) is a marker for serotonin synthesis. In children with tuberous sclerosis, uptake was increased in some tubers that appeared to be the sites of seizure onset. Other tubers showed decreased uptake. In contrast, ^{18}FDG PET showed hypometabolism in all tubers. This study suggests that [^{11}C]AMT PET may be useful to detect epileptogenic foci, in patients with tuberous sclerosis, and possibly other forms of cerebral malformation[180].

Histamine receptors

An increase of H_1 receptors, visualized with PET and ^{11}C-doxepin in epileptic foci, that also show reduced interictal glucose metabolism, has been reported[181]. 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 H_1 receptors.

Peripheral benzodiazepine receptors

The peripheral benzodiazepine receptor ligand, ^{11}C-PK11195, labels macrophages and activated microglia, and as such is a marker of inflammatory responses in the brain. Increased binding has been demonstrated in Rasmussen's encephalitis, reflecting the inflammatory nature of the condition, and is in contrast to hippocampal sclerosis in which there is no increased binding[182].

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