ABSTRACT – Functional neuroimaging over the past 10 years has led to greater insights into the pathophysiology underlying symptomatic epilepsy. Such imaging has been used to localize cerebral dysfunction, predominantly through disturbances in metabolism or blood flow. Techniques available include single photon emission computed tomography (SPECT), positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). Although the use of these diagnostic techniques is widely reported for presurgical evaluation, there has been little work with specific reference to malformations of cortical development.

KEY WORDS: functional imaging, cortical dysplasia, epilepsy surgery

Functional abnormalities in relation to the epileptogenic region

Single photon emission computed tomography (SPECT) can be used to image regional cerebral blood flow (rCBF) and has been shown to help localize the site of seizure onset in partial epilepsies. A scan following injection of a radiolabelled ligand, for example $^{99m}$Tc Hexamethyl-amine oxime (HMPAO) or ethyl cysteinate dimer (ECD), enables detection of the pattern of cerebral blood flow within a short time of the injection. Interictally, a rCBF scan may show an area of low cerebral blood flow when compared to a contralateral, similar anatomical area, suggestive of an epileptogenic region, whereas relative hyperperfusion may be seen where the injection is made during or immediately following the seizure. A scan following an ictal injection of the ligand has been shown to demonstrate hyperperfusion correlating with the epileptogenic region in more than 90% of temporal lobe epilepsies and 71-95% of neocortical epilepsies [1-4]. Interictal rCBF may be less reliable, particularly in neocortical epilepsy [3], and is more likely to reflect any underlying structural abnormality seen on MRI scan [5].

Few studies have examined the possible relationship between SPECT and underlying pathology. A recent work correlated findings on preoperative rCBF studies with postoperative histopathological results, as well as outcome [5]. Preoperative ictal and interictal SPECT studies were available from thirty five children who had been reviewed for at least three years following resective surgery. Eight of the thirty five children were determined to have cortical dysplasia in the surgical specimen; one of whom had a normal preoperative structural MRI scan. All eight children had localising or lateralisng ictal rCBF concordant with the area resected, whereas only six (75%) demonstrated localized hypoperfusion on interictal rCBF. There was therefore a consistent ictal hyperperfusion concordant with the epileptogenic region, in all those with pathologically confirmed developmental abnormalities. This is striking in view...
of the evidence that rCBF does not always increase with seizures in focal epilepsy, with some data to suggest that there may be a reduction in rCBF in some cases [6,7]. Of six children within this latter study who had developmental tumours, thought to be within the spectrum of malformations of cortical development, only two showed an ictal increase in perfusion. Overall however, ictal SPECT may be particularly useful in the context of focal epilepsy and apparently normal structural imaging (figure 1), or where data may be discordant (figure 2).

The increase in ictal rCBF seen in epileptogenic regions has been assumed to be due to increased metabolic demands, although the exact mechanisms underlying enhanced CBF remains unclear. Animal studies have demonstrated a close correlation (or ‘coupling’) between CBF and glucose metabolism in normal tissue [8]. There appear to be two components to this; static coupling related to the local capillary density, which is, in turn, closely related to the metabolic rate of a region [9] and dynamic coupling dependent on the regulatory action of the cerebral resistance vessels. The overall mechanism is likely to be multifactorial, with focal seizure discharges causing an increase in local blood flow through release of metabolites, and a higher capillary density at an active site of seizure generation. Animal studies have suggested the latter is related to the number of synaptic structures rather than neuronal mass [10]. With developmental abnormalities, it is likely that abnormalities in cerebrovascular architecture coexist with abnormalities of cortical development [11]. Although developmental tumours are believed to lie within the cortical dysplasia spectrum, the poor localisation with rCBF seen [5] could be related to a relatively poor intralesional blood supply in comparison to the pure developmental malformations. On review of the postsurgical outcome in relation to pathology, this study did not show any relationship in the malformation group between preoperative rCBF studies and seizure outcome. This is not necessarily surprising, in view of the many factors that influence outcome in this disorder, including whether all structurally [12] or electrographically [13] determined epileptogenic tissue has been removed given that dysplasia may be diffuse and nonapparent on MRI.

Other groups have examined the relationship between rCBF studies and developmental outcome in children. Chiron et al. reviewed ten patients (mean age 10 months) with hemimegalencephaly, and related preoperative inter-

![Figure 1. MRI (A) of a 9 year-old girl with epilepsy and a clinical and electrographic left frontal lobe focus; the MRI was normal (A). Ictal SPECT (B) showed an area of hyperperfusion concordant with the EEG. Following resection, histopathology at low power (C) showed apparently normal cortex. However, high power (D) showed disorganisation of cells with no evidence of lamination.](image-url)
ictal 133Xenon SPECT scans to postoperative outcome [14]. Cerebral blood flow seen in the abnormal hemisphere showed no correlation with outcome, but with the apparently normal hemisphere, a preoperative increase appeared to correlate with an unfavourable outcome, whereas normal CBF correlated with a good outcome.

Positron emission tomography enables visualization of cerebral function by use of a ligand to examine glucose metabolism (18Fluorodeoxyglucose-FDG), cerebral blood flow (15H2O) or neurotransmitter function (e.g., flumazenil, [11C]methyl-L-tryptophan). Studies have been performed to determine the area of abnormality thought to be responsible for seizures, or the localisation of normal brain function. Early reports of the use of 18FDG PET involved children with infantile spasms; an epilepsy syndrome presenting in infancy with characteristic flexor spasms and a disorganised EEG, not necessarily classic hypsarrhythmia. Chugani et al. initially reported 18FDG PET in 13 children, where PET demonstrated unilateral hypometabolism involving the parieto-occipital cortex in five [15]. In four of these, the MRI had been normal. Four underwent resective surgery of this area, with subsequent seizure freedom.

Figure 2. Ictal EEG recording (A) and ictal SPECT (B) of a 14 month-old boy with linear sebaceous naevus syndrome, and left temporo-occipital dysplasia. He underwent an initial temporal lobe resection. He returned for evaluation as seizures continued. EEG was difficult to lateralise, with the ictal EEG (A) showing generalised attenuation. Ictal SPECT (B) showed hyperperfusion of the left posterior region; he underwent a left parieto-occipital resection and remains seizure-free at 2 years following surgery.
Neuropathological evaluation revealed microscopic cortical dysplasia in all. They then reported a subsequent series of 23 children with infantile spasms who all underwent surgery; in 14 of these, areas of hypometabolism on PET were concordant with EEG [16] and were the only neuroimaging abnormalities on preoperative assessment. In 12, the underlying pathology was cortical dysplasia or another malformative lesion. There was also a suggestion that multifocal abnormalities on PET predicted a poor outcome in three cases, perhaps suggesting more widespread malformations than the preoperatively determined epileptogenic zone. Later, the group went on to suggest, on review of data from 140 children with infantile spasms, that PET increased the proportion of symptomatic cases, from 30% to 95.7%, by detecting cortical malformations not apparent using other means of investigation [17].

Certainly, if PET may be useful in highlighting areas of malformation in children where there is a high suspicion of lateralised abnormality, particularly in infants where immaturity of myelination make detection of grey matter abnormalities difficult. However, this is detection of a structural abnormality, and determination of epileptogenicity requires correlation with clinical and electrophysiological data. MRI may now also be used to visualise the epileptogenic region or localised epileptic activity. Interictal EEG activity can be imaged using time locked EEG triggered blood oxygen level-dependent (BOLD) functional magnetic resonance imaging. Such imaging is based on the signal intensity differences between two different physiological states. The presence of paramagnetic deoxyhaemoglobin generates local magnetic field gradients, which cause a focal signal decrease on $T_2$-weighted images. Neuronal activation causes a local decrease in deoxyhaemoglobin in microvasculature. Activation therefore results in a local increase in the MR signal intensity by subtraction of images taken during ‘active’ and ‘inactive’ states. Functional MRI has mostly been used to determine eloquent cortex (see below); however, ictal changes have been seen in the apparent epileptogenic region [18]. The detection of time locked BOLD changes within fMRI data related to interictal EEG has been reported by a number of centres. Some of the reports have included patients with malformations of cortical development, and activation of the identified structural changes have been seen [19-21]. Electrophysiological studies of MCD show widespread, often multifocal interictal spiking. The relationship of these EEG discharges to the epileptogenic zone or the underlying structural malformation is often unclear [22, 23], although focal continuous epileptiform discharges on cortigraphy have been linked to outcome [23].

**Neurotransmitter function**

Interesting work has been published on the use of $[11\text{C}]$ methyly-L-tryptophan (11C/AMT) PET in the detection of epileptogenic tubers in tuberous sclerosis complex (TSC) [24]. This was based on the hypothesis that serotonin is increased interictally in epileptogenic tubers in patients with TSC. Nine children with tuberous sclerosis and epilepsy were studied, and 11C/AMT uptake was increased in at least one tuber in eight of these children (1 in 3, 2 in 3, 3 in 1 and 4 in 1). Increased uptake was correlated with the site of EEG seizure onset in four cases; in two the EEG was nonlocalising. All other tubers showed decreased uptake. FDG PET showed multifocal cortical hypometabolism corresponding to the location of the tubers in all nine. The one child in whom no increase in uptake of 11C/AMT was seen had a left frontal focus on EEG but at the time of the PET scan his seizures were under control. Two children went on to surgical resection after verification of seizure onset with invasive EEG recording, and seizure control improved post-operatively. Obviously such work needs to be verified; however, as it becomes apparent that children with tuberous sclerosis and focal seizures may be candidates for focal resection [25], such work may obviate the need for invasive EEG recording in a very challenging group of patients. Two further reports have suggested that use of this ligand may not be limited to those with TSC. Fedi et al. [REF??] assessed the uptake of 11C/methyl-L-tryptophan in 18 patients with intractable partial epilepsy (seven with cortical dysplasia). In seven, uptake was focally increased in the epileptogenic area. In four of these the pathology was cortical dysplasia. Madakasira and colleagues report one case of an adult with intractable epilepsy and an area of dysplasia in the right occipital lobe [26]. 11C methionine PET showed this region to have enhanced uptake, concordant with the EEG focus.

Richardson et al. studied 12 patients with cortical dysplasia as identified by high resolution magnetic resonance imaging and compared results to those from 24 normal subjects [27]. Spectral analysis was used to produce a parametric image of 11C-flumazenil volume of distribution for each subject. Maps of regions of abnormal 11C-flumazenil binding were produced by comparing the entire brain volume of each patient with the brains of the normal group using volumetric normalisation and statistical parametric mapping. These were then rendered into the volumetric magnetic resonance images, allowing a correlation of structure and function. Ten of the 12 patients showed at least one abnormal region of 11C-flumazenil binding, and in seven, abnormalities were seen over a larger area than that seen on structural magnetic resonance imaging. Non-contiguous regions of abnormal binding were seen remote from the abnormality seen on the MRI. The two who showed no abnormalities included one with bilateral band heterotopia and one with a small heterotopic nodule in the white matter. Although the authors acknowledged methodological problems with this study, the results revealed regions of increased and decreased uptake, suggesting, in some cases, that the epileptogenic area may be characterised by a region of increased benzodiazepine receptor (BZR) and GABA$_\alpha$ receptor density surrounded by a region of reduced BZR and GABA$_\alpha$. 

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receptor density (perhaps resulting from increased GABA release in a region of increased inhibition as a response to seizure activity). Subsequent work, performed with appropriate methodological adjustment to account for possible partial volume effect, has shown similar results, with decreased $^{11}$C FMZ binding in areas of increased grey matter volume, e.g., heterotopic nodules or polymicrogyria, and increased binding in adjacent or overlying areas of normal cortex across the various subtypes of malformation. Localisation of abnormal binding correlated with EEG and clinical data in the cortical forms of MCD [28]. Arnold et al. [29] report on $^{11}$C-flumazenil and $^{18}$FDG PET in two patients with focal cortical dysplasia who subsequently underwent resective surgery. They found that in both patients, the FDG PET showed a wide area of hypometabolism extending beyond the visibly apparent dysplastic cortex, whereas the $^{11}$C Flumazenil PET abnormality was confined to the seizure onset zone as determined by invasive ictal EEG recording, and to the region of cortical dysplasia. Both patients however, underwent wide resections to include visible dysplasia, and both remain seizure-free.

**Functional cortical mapping**

PET has also been used to map normal cortical function. However, few studies address this with regard to malformations of cortical development. Richardson et al [30] studied five patients with malformations of the occipital region and seven normal subjects using $^{15}$O PET whilst they were performing a visual attention task. They also studied five right-handed patients known to have a malformation of cortical development of the left frontal lobe and seven right-handed normal subjects whilst they were performing a motor learning task with the right hand. Eight of the ten patients with MCD showed a significant change in relative regional cerebral blood flow during the task compared to when resting in the affected brain region. With regard to visual stimulation, all undertook the Rapid Visual Information Processing (RVIP) task. Two experimental conditions were used, rest and RVIP. Each condition was repeated six times. The RVIP task has been shown to give rise to significant increases in rCBF in bilateral calcarine sulci, fusiform gyri, superior parietal cortex, inferior frontal gyri, supplementary motor areas and right superior frontal gyrus. All five patients showed regions of significantly increased blood flow with the task relative to rest; four of the five showed significant change in rCBF in the region of MCD. With regard to motor stimulation, the five patients and seven normal subjects undertook the motor sequence learning task; this task gives rise to significant increases in rCBF in the left sensorimotor cortex, bilateral premotor cortices, supplementary motor cortex, dorsal prefrontal cortex, bilateral cerebellar cortex and nuclei and bilateral putamina. All five patients showed regions of significantly increased blood flow with the task relative to rest, four of whom showed significant activation in the region affected by MCD. The MCD affected in both were focal cortical dysgeneses, cortex lining schizencephalic clefts, subependymal grey matter heterotopia and in cortex overlying band and subependymal heterotopia. Two subjects showed no change in an area affected by MCD, both of whom had focal cortical dysgenesis. Generally, the brain regions recruited during the performance of the visual and motor tasks by the patients were similar to those recruited by the normal group. Additionally, the alterations in the activation patterns seen were related anatomically to the site of dysgenesis in most of the patients. The authors conclude that MCD may participate in normal cognitive activity and that the presence of even localised MCD can be associated with an abnormal localisation of cortical function. This has also been suggested from invasive EEG studies with regard to language function [31].

Magnetic resonance imaging has also been used to locate cortex responsible for movement and language function. Using BOLD-IMRI, images are acquired repeatedly during periods of a task and periods of rest. There are now many reports of its use with motor and language cortex localisation; reports however, are limited with regard to activation...
Figure 4A. Functional MRI to a verb generation task in a 16 year-old boy with focal cortical dysplasia in the left superior temporal gyrus (arrowed). Activation is seen predominantly within the left hemisphere ($L = 0.6$; see figure 4). The Wada test confirmed left hemisphere dominance.

Figure 4B. Functional MRI to a verb generation task in a 15 year-old boy with a dysembryoplastic epithelial tumour in the left temporal lobe (arrowed). Activation is seen only in the right frontal region. Laterality index ($L = +1$; $L = +1$ = right lateralised, $L = -1$ = left lateralised). The Wada test confirmed right hemisphere dominance of language.
in relation to MCD, but similar findings to those with PET have been reported. Pinard et al. [32] have been able to demonstrate coactivation within MCD in a child with subcortical laminar heterotopia during a finger tapping task. Spreer et al. have also reported on three similar patients showing coactivation of the outer cortex of the inner neuronal band during performance of a motor task, and in one of these patients, coactivation was also evident inward along the route of embryonic neuronal migration from the occipital cortex toward the ventricular wall, during a visual task [33]. Figure 3 shows fMRI performed on a boy with a mild left hemiplegia and right polymicrogyria. The scan shows that cortical activation from hand movement of the hemiparetic side, is bilateral, as seen in controls, and in particular involves the area of visible malformation.

There are now many reports of language activation using a variety of tasks precluding the need for presurgical WADA lateralisation of language function [34-36] and in others showing agreement with cortical stimulation [37, 38]. Figure 4 illustrates the results of fMRI using a verb generation paradigm in two children compared to Wada testing; one with a dysembryoplastic neuroepithelial tumour of the left amygdala (Figure 4A) and one cortical dysplasia of the left superior temporal gyrus (Figure 4B). The child with the left amygdala lesion shows clear lateralisation to the right whereas the second demonstrates clear dominance to the left. Another child underwent surgery following intracortical stimulation, although resection had to be limited due to the location of language cortex anterior to the apparent lesional margin. Subsequent fMRI was concordant with the findings of cortical stimulation (Figure 5), demonstrating active cortex on the superior temporal gyrus. Duchowny et al. [31] used cortical stimulation to demonstrate that language cortex remained in proximity to, or overlapped with, the epileptogenic region and structural lesion in children with developmental pathology. This was in contrast to children with early postnatal insults, that is less than 5 years of age, where relocation of language to the contralateral hemisphere was seen. The demonstration of functional cortex within developmental lesions shows care must be taken in presurgical evaluation.

Conclusions

Functional imaging in malformations of cortical development has been widely studied although in limited numbers of patients. The use of techniques currently available remain directed at presurgical evaluation but provide interesting insights into pathophysiology. Scans demonstrating changes in rCBF may predict location of an epileptogenic region associated with an underlying malformation, which may be particularly helpful in the absence of any overt structural abnormality as seen on MRI. Functional MRI and PET scans have shown functional cortex located within malformations, confirming findings from invasive EEG studies and illustrating that extreme care is required when surgical resection is contemplated. Work with neurotransmitters has primarily been interpreted as helping determine the epileptogenic region in association with malformations, but may ultimately lead to understanding of mechanisms involved. Further studies are required to optimise the use of functional imaging techniques now available in the study of these patients. □
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References