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Neuroimaging techniques in epilepsy

Objective
To review state-of-the-art neuroimaging modalities in epilepsy and their clinical applications.

Data sources and study selection
PubMed literature searches to March 2010, using the following key words: ‘epilepsy’, ‘positron emission tomography (PET)’, ‘single photon emission computed tomography (SPECT)’, ‘MR volumetry’, ‘diffusion tensor imaging’, and ‘functional MR imaging’.

Data extraction
All articles including neuroimaging techniques in epilepsy were included in the review.

Data synthesis
High-field magnetic resonance imaging is fundamental for high-resolution structural imaging. Functional radionuclide imaging (positron emission tomography/single-photon emission computed tomography) can provide additional information to improve overall accuracy, and show good results with high concordance rates in temporal lobe epilepsy. Magnetic resonance spectroscopy is a useful adjunct consistently demonstrating changing metabolites in the epileptogenic region. Magnetic resonance volumetric imaging shows excellent sensitivity and specificity for temporal lobe epilepsy but thus far it has been inconsistent for extratemporal epilepsy. Diffusion tensor imaging with tractography allows visualisation of specific tracts such as connections with the language and visual cortex to enhance preoperative evaluation. Functional magnetic resonance imaging using blood oxygen level–dependent activation techniques is mainly used in presurgical planning for the high-sensitivity mapping of the eloquent cortex. Both contrast-bolus and arterial spin labelling magnetic resonance perfusion imaging show good correlation with clinical lateralisation of seizure disorder.

Conclusion
Structural imaging is essential in localisation and lateralisation of the seizure focus. Functional radionuclide imaging or advanced magnetic resonance imaging techniques can provide complementary information when an epileptogenic substrate is not identified or in the presence of non-concordant clinical and structural findings.

Introduction
Epilepsy is a common disorder worldwide, with a prevalence of 4.5/1000 (0.45%) for children and adolescents,1 and 1.54/1000 (0.15%) for the adult Chinese population in Hong Kong.2 It has been estimated that about 7 to 8% of the population experience at least one seizure during their lifetime. Epilepsy is characterised by recurrent seizures unprovoked by an acute systemic or neurologic insult.

Prior to possible surgical cure, neuroimaging becomes important and mandatory in the work-up of epilepsy localisation and the lateralisation of seizure foci. Magnetic resonance (MR) imaging has become the technique of choice and is fundamental for high-resolution structural imaging in epilepsy. This is due to its ability to achieve superior soft tissue contrast, multiplanar imaging capability, and lack of beam-hardening artifacts, which allows visualisation of epileptogenic substrates with greater sensitivity and accuracy. Optimised and dedicated protocols are necessary for evaluation of the hippocampus and temporal lobe for atrophy and subtle signal intensity alterations, as well as for detecting certain structural abnormalities such as cortical dysplasias (Fig 1) or other developmental abnormalities. With the development of MR imaging, it has become more sensitive with
high-field technology, newer hardware, as well as special acquisition and post-processing methods. Yet, up to 15% of patients with epilepsy can still escape detection of any structural lesion. In addition, the structural lesions detected on structural MR images may not reflect the true extent and functional status of the abnormalities, especially with respect to malformations of cortical development. Therefore, other neuroimaging techniques become useful and can provide additional information on the location of the seizure focus so as to improve overall accuracy. This is important to achieving a successful and ideally seizure-free surgical outcome. In this article, we review and discuss the feasibility of various other neuroimaging techniques.

Methods
A PubMed search of literatures up to March 2010 was conducted using the following key words: ‘epilepsy’, ‘positron emission tomography (PET)’, ‘single photon emission computed tomography (SPECT)’, ‘MR volumetry’, ‘diffusion tensor imaging’, and ‘functional MR imaging’. A total of 86 articles were retrieved. Only those concerning neuroimaging techniques related to epilepsy published in or after 1995 were included. During article selection, prospective studies had a higher ranking than retrospective studies, while case reports were not included. For articles on the same or related topics, those published at later or more recent dates were selected. In all, 52 articles were included and formed the basis of our review.

Functional radionuclide imaging
Positron emission tomography and PET–computed
Ictal single-photon emission computed tomography (SPECT) is complementary in defining an epileptogenic zone. It entails use of 99mTc-HMPAO (technetium-99m hexamethylpropylene amine oxime) or 99mTc-ECD (technetium-99m-ethyl cysteinate diethylester) as a substrate to assess regional cerebral blood flow changes during both the ictal and interictal periods. The epileptogenic focus will typically manifest as an area of hyperperfusion in the ictal stage, and hyperperfusion in the interictal stage (Fig 4). Ictal SPECT has a higher rate of correct localisation but often proves difficult, as the agent has to be injected within 90 seconds of seizure onset to demonstrate the expected localised increase in cerebral perfusion.

Past studies in temporal lobe epilepsy have shown that the correct localisation rates of MR imaging, interictal PET and ictal SPECT were 64%, 87%, and 81%, respectively. Corresponding rates in non-temporal lobe epilepsy were 57%, 71%, and 64%, respectively. A more recently reported study by Kim et al revealed the correct localisation rates of MR imaging, interictal PET, and ictal SPECT were 83%, 73%, and 67%, respectively for temporal lobe epilepsy. Whilst for non-temporal lobe epilepsy, the respective rates were 84%, 68%, and 85%. The discrepancy in results illustrates the difficulty in detecting epileptogenic foci, especially in non-temporal lobe/neocortical group. Nevertheless, for interictal PET and ictal SPECT for temporal lesions, concordance rates are remarkably high (96% and 100%, respectively) and for extratemporal lesions respective rates were 68% and 92%. This finding supports their complementary usefulness in instances of non-concordance between ictal electroencephalography (EEG) and MR imaging. The superior results of PET in temporal lobe epilepsy have led to improved positive and negative predictive values, and allowed more precise presurgical evaluation. On the contrary, the inferior results for non-temporal lobe lesion detection reflect the relative insensitivity of structural and functional imaging for neuronal migration disorders, which constitute majority of the cases, especially those with mild dysplasia only. The relatively poor results with PET scans may be attributed to the mixed responses from various types of malformations. Such responses include: decreased uptake in most cases of focal cortical malformations, normal-to-increased uptake in band heterotopias, as well as increased uptake in focal subcortical heterotopia and lobar dysplasia.

Coregistration of MR imaging with PET/SPECT has been used for precise lesion localisation in the preoperative evaluation for such patients, even though the results to date have been inconsistent. Non-lesional epilepsy (including patients with negative MR imaging findings) poses a major problem. In general, 18F-FDG PET has shown relatively constant congruent hypometabolism with EEG lateralisation, and can sometimes lateralise hypometabolism in patients in bitemporal seizure onset as depicted by Liew et al. They even reported the use of 18F-FCWAY (18F-trans-4-fluoro-N-2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl-N-(2-pyridyl)cyclohexane carboxamide) PET as a superior and more accurate modality to detect epileptic foci and lateralisation of MR imaging–negative mesial temporal lobe epilepsy. This entailed more specific 5-HT(1A)-receptor binding reduction in seizure initiation than propagation regions. Yet this would require a larger study to validate its use and accuracy. Recently, Akman et al reported the use of statistical parametric mapping to quantify the duration of epilepsy in PET scans of patients with temporal lobe epilepsy. They found that temporal lobe (parahippocampal gyrus, uncus, middle, and superior temporal gyr) hypometabolism was consistently present in patients with longer-duration epilepsy (10 years, P<0.05 corrected), the two being inversely correlated. Buch et al also reported the use of statistical parametric mapping to create a functional image by spatially registering the PET and SPECT images, allowing the calculation of perfusion-
to-metabolism ratio. In their study of 21 patients with lesional temporal lobe epilepsy, the ratio-images demonstrated a correct hemispheric localisation rate, sensitivity, and specificity of 83%, 68% and 96% respectively, as compared with 70%, 63% and 96% with PET images only, revealing a significantly improved hemispheric localisation. This would also be beneficial in cases of non-lesional temporal lobe epilepsy.

### Advanced magnetic resonance imaging techniques

These include proton spectroscopy (MR spectroscopy), MR volumetry, diffusion tensor imaging (DTI), MR perfusion, and functional MR imaging (fMRI) with blood oxygen level–dependent (BOLD) activation. The widespread application of most of these techniques in clinical practice depends on the availability of high-performance MR imagers capable of performing fast echo-planar pulse sequences (echo-planar imaging), as well as substantial data processing capabilities.

Single-voxel proton MR spectroscopy is a non-invasive technique that depicts the anatomic distribution of metabolite signals, including those of compounds containing N-acetylaspartate (NAA), creatine and phosphocreatine (Cr), and choline (Cho). It has consistently demonstrated metabolite changes in the epileptogenic region of the brain. Patients with mesial temporal lobe epilepsy typically demonstrate extensive reduction in NAA in the temporal lobe and insular cortex, whereas symmetrical generalised reduction of NAA (Fig 5) can occur in both cerebral hemispheres as demonstrated on multi-voxel MR spectroscopy, and probably reflects metabolic impairment due to repeated seizures. Therefore NAA asymmetry in the temporal lobe and insular cortex robustly lateralises the seizure focus. Achten et al even postulated an asymmetry index (NAA/Cho+Cr) of more than 0.05 to 0.10 that would point to the diseased side. Chernov et al also found frequent presence of lactate on the side of epileptogenic zone in addition to decrease in NAA. They continued to postulate a decrease of NAA content below 0.75 and/or unilateral presence of lactate would provide 86% (95% confidence interval, 68-100%) lateralisation accuracy. Hence, MR spectroscopy is a useful adjunctive presurgical test for localising seizure foci, particularly in temporal lobe epilepsy, and has the potential to reduce the need for intracranial-depth electrode EEG recordings. Multi-voxel MR spectroscopy can achieve higher sensitivity and better spectral quality, improving lateralisation of the seizure focus.

Magnetic resonance volumetric imaging can detect decreases in volumes of structures functionally connected to the hippocampus, such as the amygdala, entorhinal cortex, fornix, mamillary body and thalamus, and to a far lesser degree, in more remotely connected structures such as striatum and cerebellar hemispheres. It is still unclear to what extent the volume loss is related to a pre-existent injury or the result of recurrent seizure, but several cross-sectional volumetric studies have shown a definite relation to the duration of epilepsy. This was probably due to a combination of neurodevelopmental and progressive effects, characterised by a prominent disruption in the ipsilateral hippocampus and neural connectivity (white matter volume loss) that extended beyond the temporal lobe, and affected both ipsilateral and contralateral hemispheres. It has shown excellent sensitivity, ranging from 75 to 92%, and with specificities of 64 to 100% for temporal lobe seizure foci. Thalamic volume loss is typically bilateral, but in the presence of asymmetry, the smaller side correlates strongly with the onset and duration of epilepsy. This reflects either a remote acute injury in the setting of status epilepticus or chronic injury due to seizure propagation. The results of MR volumetry in the evaluation of extratemporal epilepsy have been inconsistent so far. Bearing in mind the variation of total cerebral brain volume across different ages, genders, and congenital insults, potential errors can occur. Several authors have even advocated scaled measurements in relation to total brain volume or direct measurements in a stereotaxic space. Nevertheless, volume measurement generally indicates a later stage of the disease process.

A new imaging technique, DTI, makes use...
of the anisotropic diffusion of water to delineate microstructural tissue organisation, allowing axonal fibre delineation based on the observation that the diffusion of water in white matter is greater in directions parallel to fibre tracts but more limited in other directions. Thereby it differentiates pathologic from normal tissue. Data can be displayed in a three-dimensional format referred to as fibre tractography (Fig 6a), which allows illustration and visualisation of specific tracts such as connections with the language cortex. It has been shown useful in studying cerebral ischaemia, acute stroke, multiple sclerosis, schizophrenia, and more recently in epilepsy. In general, increased mean diffusivity and decreased fractional anisotropy are observed at the seizure focus. The former is more sensitive, whilst a right-left diffusivity index/difference can be established to lateralise the epileptogenic focus. It is of proven value in the evaluation of language connectivity areas in patients undergoing dominant hemisphere anterior temporal lobe resection. Greater lateralisation of tracts to the dominant hemisphere was associated with greater decline in naming function, hence the potential to predict language deficits in such patients. Visualisation of the optic radiation is another useful preoperative imaging technique in patients undergoing temporal lobe resection, by helping to predict visual field defects (superior homonymous quadrantanopia) due to disruption of the Meyer loop. Temporal lobe epilepsy has attracted much attention. Past studies reported substantial white matter abnormalities but with limited data on the extent of such abnormalities and their association with clinical factors. Riley et al identified important cognitive and clinical consequences associated with widespread disturbances in white matter tracts, including positive correlation of mean fractional anisotropy with delayed memory related to the anterior temporal lobe, and immediate memory impairment linked to the mesial temporal lobe. Lower fractional anisotropy values in the posterior region of corpus callosum were also related to earlier age of seizure onset.

Functional MR imaging using the BOLD technique has been assessed as a mean of non-invasive mapping of the eloquent cortex (Fig 6b) and for assessing memory function in temporal lobe structures. This was in contrast to the invasive intra-operative electrocortical stimulation and intracarotid amobarbital procedure (Wada test), mainly used in presurgical planning and shown to influence diagnostic and therapeutic decisions. Being based on the magnetic property of blood (oxygenation state of haemoglobin) to measure haemodynamic changes as major determination of BOLD signals, any consequent increase in local blood oxygenation leads to an increase of the resulting MR signal. Mapping of motor cortex has shown consistently good results, as motor paradigms to activate the cortex are simple and robust. Functional MR imaging in mapping language centres, however, yields variable results as language tasks show greater variability and difficulty. Nevertheless, it can help determine the dominant hemisphere in both epilepsy and non-epilepsy populations and can also act as a predictor of deficits resulting from temporal lobe resection. This is of particular importance in patients with temporal lobe epilepsy as reorganisation of language functions with structural fibre tract distortion and greater involvement of the non-dominant hemisphere had been demonstrated. Even so, its clinical application is still debatable as it is generally considered inferior to intra-operative electrocortical stimulation, largely because of technical and conceptual problems.
Moreover, it shows poor concordance with Wada tests, especially in patients with left-sided temporal lobe epilepsy.\textsuperscript{39} Gurtet et al\textsuperscript{40} developed a clinical fMRI overt language design at the sentential level, so as to optimise sensitivity for language-related areas of the brain. This included the application of semantic and syntactic error–detection tasks (constructed to represent the most relevant aspects of everyday language demands). These are believed to integrate relevant aspects of everyday language demands and enable robust localisation of core language areas. Task-free paradigm fMRI has been explored by Liu et al.\textsuperscript{41} It uses low-frequency components of spontaneous MR signals to provide information about the intrinsic functional and anatomical organisation of the brain. Liu et al\textsuperscript{42} were able to demonstrate comparable results in motor function mapping to those obtained by actual movement tasks and cortical stimulation. This provided a powerful approach to mapping the functional anatomy in patients lacking task compliance. Mapping memory, however, is more challenging, as different sites of activation have been demonstrated for different memory processing tasks and it is difficult to separate brain activity related to memory from other cognitive processes.\textsuperscript{43} In patients with temporal lobe epilepsy, it appeared useful in studying lateralisation of memory encoding processes (patterns, faces, scenes, and words) within the mesial temporal lobe.\textsuperscript{44,45} It was also shown to predict postoperative memory deficits following anterior temporal lobe resection; increased activation ipsilateral to the seizure focus being associated with greater memory decline.\textsuperscript{45,46} Apart from the mapping of motor, language and memory cortices, a study involving correlations with EEGs by Patel et al\textsuperscript{47} showed that it could yield a sensitivity of 90% in identifying sites of cerebral activation corresponding to sites of potential epileptogenesis. Several confounding factors remain unresolved however, and possibly explain the variable responses to BOLD activation.

Arterial spin labelling (ASL) is another non-invasive technique for quantitative perfusion MR imaging.\textsuperscript{48} Relative mesial temporal hypoperfusion demonstrated by continuous ASL perfusion MR imaging correlated well with clinical lateralisation of the seizure side, as well as with \textsuperscript{18}FDG-PET hypometabolism\textsuperscript{49} and hippocampal volume loss.\textsuperscript{50} Similar findings were reported using a contrast-bolus MR perfusion technique, measuring interictal relative cerebral blood volume in patients with temporal lobe epilepsy.\textsuperscript{51} The continuous ASL technique has the advantage of providing a diffusible tracer and therefore measures classical tissue perfusion.\textsuperscript{52} A previous study combining contrast-enhanced MR perfusion and diffusion-weighted imaging also provided lateralising information in non-lesional temporal lobe epilepsy; lower cerebral blood flow and a larger apparent diffusion coefficient in the lesional side.\textsuperscript{53} Since there is coupling of cerebral blood flow and metabolism, MR perfusion can act as a surrogate marker of metabolism as measured by PET. Magnetic resonance perfusion holds promise as a better alternative since it is less expensive, does not involve ionising radiation, and is more readily available. Yet more and larger clinical trials are needed to validate its use, and determine whether these techniques provide independent data to established MR quantitative measures. Nevertheless, such techniques are expected to continue evolving and provide a means of determining the exact site of origin and propagation pathways for seizures.

**Conclusion**

Both structural and functional neuroimaging play essential roles in non-invasive localisation of epileptogenic foci. Both functional radionuclide and advanced MR techniques can provide complementary information to structural MR imaging whenever an epileptogenic substrate is not identified or is non-concordant clinically (ictal EEG and semiology) or structurally.

**References**


