Brain imaging in the assessment for epilepsy surgery

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Abstract

Brain imaging has a crucial role in the presurgical assessment of patients with epilepsy. Structural imaging reveals most cerebral lesions underlying focal epilepsy. Advances in MRI acquisitions, including diffusion, post-acquisition image processing techniques, and quantification are increasing the yield. Functional MRI identifies eloquent cortex sustaining language, motor function and memory and, with tractography, can highlight critical tracts, reducing the risk of epilepsy surgery causing new morbidity. Positron emission tomography, single photon emission computed tomography, EEG-fMRI, electrical and magnetic source imaging infer the localization of epileptic foci and assist the design of intracranial EEG recording strategies. Progress in semi-automated methods to register imaging data into a common space is now enabling the creation of multimodal 3D patient-specific datasets. These techniques show promise for visualizing the complex relationships between normal and abnormal structural and functional data and could be used to direct precise intracranial navigation and surgery for individual patients.

Key words: epilepsy * MRI * functional MRI * diffusion * PET * SPECT

Search strategy: Search strategy and selection criteria: PubMed from January 2005 2005 to October 2015 for English language articles, and key earlier references from the authors' files. Key words: epilep* and 1 or more of: MRI, fMRI, functional MRI, PET, SPECT, MEG, electric* source imaging, EEG, DTI, diffusion MRI, surgery. Space constraints necessitated selection of results that we judged to be most relevant to clinical practice.

Introduction

Epilepsy develops in 50/100,000 population per year and, in one third antiepileptic drugs do not control seizures[1]. Approximately half of these individuals have focal epilepsy and are potentially amenable to neurosurgical treatment, if there is evidence to suggest a single focal network underlying the epilepsy and if the individual would be able to withstand neurosurgery[2], and does not have severe co-morbidities, such as active cancer, advanced vascular disease or dementia, which would preclude this.

Brain imaging is of fundamental importance to diagnosing and treating epilepsy, particularly when neurosurgical treatment is being considered. There have been dramatic advances in brain imaging applied to epilepsy in the last 20 years, principally due to advances in MRI, image processing, and nuclear medicine.[3] We focus here principally on advances made since 2005 that are of current and potential clinical importance to the practicing neurologist.

We firstly review developments in structural brain imaging with MRI and post-acquisition processing to identify cerebral abnormalities that may cause epilepsy, identification of which may lead to consideration of surgery. We then consider the mapping of eloquent functions and the major critical white matter pathways in the brain. Next, we consider positron emission tomography (PET) and other imaging methods to infer the localization of cerebral networks that generate epileptic seizures in the context of MRI findings that are inconclusive or discordant from clinical and EEG data. Finally, we demonstrate the integration of multimodal 3D imaging and how these methods have an evolving role in the design of treatment strategies for individual patients, and consider forthcoming advances. Panel 1 comprises a glossary of MRI terms used in this article.

In the interpretation of imaging studies, it is of key importance to recognize the difference between group studies, as employed in neuroscience investigations, to infer the functional anatomy of the brain and its derangement in a condition, from clinical studies in which the results affect the diagnostic and treatment pathways of individual patients. The latter are focused on individuals with medically refractory focal epilepsies, and to its surgical treatment, when the finding of focal abnormalities may lead to a surgical solution, and demonstration of critical structures may constrain the surgical approach.

The sequence of presurgical imaging investigations

The prerequisite for imaging investigations in the presurgical assessment of patients with epilepsy is high quality structural MRI, interpreted in the light of clinical and EEG data, with hippocampal quantification to identify an epileptogenic lesion. If there is a relevant structural lesion that is concordant with the results of scalp video-EEG telemetry and not close to eloquent cortex, the patient may be recommended for surgery, with language fMRI at this time to assess language lateralization. If a resection is planned that is close to optic radiation or corticospinal tract, diffusion imaging and tractography to help to optimize the surgical approach and minimize the risks of surgery is recommended. Figure 1 illustrates the place of imaging studies in the presurgical pathway.[4]

If an individual has no relevant lesion on an MRI, further acquisitions using the latest MRI hardware and techniques, and post-acquisition processing methods may reveal a subtle abnormality, with interpretation being cautioned by the possibility of false-positive findings. FDG PET is a useful next step, looking for a single area of hypometabolism that may lead directly to resection, eg if there is anterior temporal lobe reduced uptake in the non language dominant hemisphere or, more commonly, to inform an intracranial EEG recording. If FDG PET is not contributory the subsequent investigations are geared towards generating a hypothesis regarding localization for the epileptogenic zone that may be tested with intracranial EEG. These include ictal single photon emission

computed tomography (SPECT) and the visualisation of interictal, and rarely ictal, epileptic activity with electrical source imaging (ESI), magnetic source imaging (MEG) and simultaneous electroencephalography and functional magnetic resonance imaging (EEG-fMRI). In practical terms, the hierarchy of these investigations will depend on their availability in individual Centres. 3D multimodal imaging has an evolving role in the integration of structural and functional data for the planning of invasive EEG studies and resections.

Identifying structural cerebral abnormalities

Structural MRI is the main neuroimaging technique for identifying an epileptogenic lesion. Localizing and delineating the extent of the underlying lesion and its relationship to eloquent cortex forms a critical part of the assessment for surgery. Identification of a lesion yields a greater chance of seizure freedom following surgery.[5,6] However, 15-30% of patients with refractory focal epilepsy remain "MRI-negative".[7,8] The underlying pathology, the acquisition protocol and the interpretation, by human or computational analysis, are key determinants of the diagnostic yield.

Acquisition Protocol

Acquiring images using an optimized epilepsy protocol maximises yield. The basic protocol established by the ILAE includes whole-brain T1 and T2 imaging acquired with the minimum slice thickness possible in two orthogonal planes with a volumetric T1 acquisition[9](Fig 2). This guideline is now 18 years old and updated guidance would now be appropriate, to reflect the recent advances made in brain imaging.

Additional sequences, in particular FLAIR, have become available and scanner hardware has improved (Fig 2).[10] Analysis of MRI data showing epileptogenic lesions in 2740 surgical patients in Bonn led to a proposal for a specific MRI protocol (Panel 2) that is advantageous from both a sensitivity and economic point-of-view and is now widely accepted.[11]

Imaging Hardware

Imaging hardware has improved, with increased field strength and better coils and gradients. Increased field strength improves signal-to-noise ratio and enables greater spatial resolution. Rescanning surgical candidates who were MRI-negative on a 1.5T scanner using a 3T scanner with phased-array coil identified a lesion in 65%.[13] A retrospective review of 804 unselected patients who had MRI at 1.5T and subsequently at 3T showed relevant new diagnoses in 5%, in particular hippocampal sclerosis, focal cortical dysplasia and dysembryoplastic neuroepithelial tumour.[14] It is anticipated that 7T imaging will reveal further anatomical detail including delineation of hippocampal subfields[15,16] and an increased pick-up of currently covert abnormalities. Higher field strength, however, brings with it challenges including image distortion and artefacts and patient tolerance that may make clinical interpretation and decisions on the relevance of findings difficult.

Scan Interpretation

Even with optimal acquisition, scan interpretation is subject to the expertise of the radiologist. In patients undergoing surgery, diagnostic yield was 39% from non-optimised imaging reported by non-experts, 50% when reported by experts and 91% when an optimised acquisition was used.[17] Curvilinear reformatting of volumetric T1 images improves the display of gyral structure and helps to identify subtle abnormalities not seen on planar slices.[18] The clear message is that both acquisition using an epilepsy

protocol and reporting by a skilled neuroradiologist, who is in possession of all the relevant clinical data greatly increase the identification of relevant lesions that may underlie epilepsy.

Assessment of Structural Data

A significant development in the last decade has been the automated quantitative assessment of structural data, which can be applied to the individual.[19] The most commonly missed diagnoses in MRI-negative patients are hippocampal sclerosis and focal cortical dysplasia.

Hippocampal assessment

Hippocampal sclerosis is the most common cause of surgically remediable temporal lobe epilepsy and can be assessed by volumetry and T2 relaxometry. Hippocampal quantification is particularly important, and strongly recommended, when considering epilepsy surgery, to detect subtle atrophy and signal change that may not be appreciated visually and to determine if the contralateral hippocampus is structurally normal. Bilateral hippocampal abnormalities raise concerns of reduced chance of seizure freedom after anterior temporal lobe resection and increased risk of causing memory impairment.[20] Time-consuming manual volumetry can now be replaced by automated segmentation that is now freely available on the Web[21] and localized shape changes can be detected even in patients who appear MRI negative.[22] Voxel-based approaches to T2 relaxometry may be more sensitive than traditional region-of-interest based approaches.[23]

Computerized analysis of hippocampal FLAIR signal was found able to identify hippocampal sclerosis with 97% sensitivity and 95% specificity[24] and a combination of hippocampal volumetry and FLAIR signal measurements identified moderate and severe hippocampal sclerosis.[25] A direct comparison between automated FLAIR signal analysis and hippocampal T2 mapping, however, indicated that T2 relaxometry was more sensitive.[26]

Apart from manual hippocampal volumetry, the use of these techniques have largely remained confined to the Centres that developed them and a few collaborating Centres. For wide dissemination, validated methods need to be readily available on the Web, be quick and intuitive to use, and to be supported.

Focal cortical dysplasia

Cortical malformations, in particular focal cortical dysplasia (FCD), underlie many paediatric and around a quarter of adult MRI-negative refractory epilepsies.[27] Imaging findings include focal cortical thickening, blurring of the grey/white matter junction, and high signal on T2-weighted/FLAIR images in underlying white matter.[28] MR Imaging, however, is often normal particularly in type I FCD and up to 80% of FCD can escape visual detection when located in the depth of a sulcus.[29] Advances in imaging acquisition protocols may enable the detection of previously covert abnormalities such as FCD. For example, double inversion recovery nulls signal from both CSF and white matter, improving contrast in the cortex.[30] Arterial spin labelling visualizes tissue perfusion and reduced blood flow may co-localize with FCD.[31] Developments of diffusion imaging such as NODDI or diffusional kurtosis imaging, which provide more detail on tissue microstructure may be more sensitive to the detection of FCD (Fig 3).[32]

Voxel-based morphometry (VBM) was originally applied to T1-weighted images to perform a quantitative analysis of grey and white matter distribution,[33] initially for group comparisons but subsequently to compare an individual to a control population.[19] Initial studies showed that 78% of FCD were identified.[32] Voxel-based analysis has been applied to T2 maps[35] and FLAIR images to increase sensitivity for FCD[36] and MRI-

negative patients.[37] An extension of VBM of T1-weighted images, Morphometric Analysis Program, improves the detection of FCD using a junction map to highlight blurring of the grey/white matter boundary and an extension map to delineate abnormally deep sulci (Fig 2G).[10] Morphometric analysis has been shown to complement visual reading of MRI scans by an expert neuroradiologist.[38] As with many other image analysis tools, there has not been wide uptake of these methods, which are often perceived by clinicians outside specialist units as being complicated and non-intuitive.

Focal cortical dysplasia can be associated with abnormal gyral/sulcal patterns not detected by VBM. Surface-based morphometry (SBM) techniques generate geometrical models of the cortical surface that allow features such as cortical thickness to be determined. This can be extended to analyse multiple morphological (cortical thickness, curvature and depth) and textural features (blurring of grey/white matter interface, T1 hyperintensity) to enable the detection of FCD.[39] Combining multiple parameters with machine learning techniques to classify lesional and non-lesional vertices detected FCD in 58% of MRI-negative patients.[40] An automated classifier based on surface morphology and intensity gave 67% specificity to detect FDC type II (3 of 8 with type IIA and 7 of 8 with type IIB), that was not evident on visual reading, with no false positive detections but with some extralesional clusters.[41] Automated detection methods have a promising role in augmenting visual assessment, particularly with FDC type IIB.

Advanced imaging methods: data interpretation

An important caveat is that whilst advances in field strength, gradients, acquisitions and post-acquisition processing and quantification will result in increased pick-up of subtle abnormalities that may underlie epilepsy, it is not likely to be realistic to expect a yield above 20-30% in individuals with unremarkable conventional MRI scans.[42] Undoubtedly there are some patients with focal epilepsy, for example those with a neurochemical derangement, who do not have a focal cerebral structural abnormality. In these, functional imaging, including perfusion and nuclear medicine methods may be used to infer the location of an epileptogenic network (see below). A further important caveat is that more sensitive methods will inevitably produce some spurious findings which may include false-positive artefacts and true findings, such as increased T2 signal around the lateral ventricle that are not relevant to the epilepsy. It is crucial, therefore, to apply sceptical expert "fuzzy logic" to interpretation of all imaging data and, as with all imaging data, to interpret the findings in the light of clinical and EEG information.

Mapping eloquent brain functions

Identifying the cerebral lateralization of speech and the localization of eloquent functions is crucial when planning surgical resection close to these areas of the brain, so that the risk of creating new deficits can be taken into account when making a decision about surgery, and the surgical approach planned to minimise the risk.

Language

Functional MRI can map language networks in patients with epilepsy for clinical and research purposes. Various language paradigms that activate anterior (Broca's area) and posterior (Wernicke's area) language areas have been used to lateralize typical and atypical language representation.[43] Verbal fluency, verb generation and semantic decision tasks are commonly used for language evaluation in a clinical context, providing complementary information.[44] In addition to visual reading of the numbers of voxels showing activation, the lateralization index of activation in preselected regions of frontal and temporal lobes gives a quantitative measure of left-bilateral-right dominance that brings objectivity to decisions relating to epilepsy surgery and is useful for research

studies. Conventional and adaptive thresholds and bootstrap techniques have been used. The latter has the advantage of being more specific and identifies outliers.[45]

Individuals with left hemisphere epilepsy are more likely to have atypical language lateralization than those with right hemisphere epilepsy.[46] Individuals with left TLE and left language dominance recruit homologous right hemisphere areas for language processing, suggesting widespread language representation.[47] Individuals with TLE have more atypical language in Wernicke's area, whereas frontal lobe foci affect more anterior language areas.[48] Many factors combine to effect language laterality. Greater left-handedness is associated with greater language shift to the right in TLE, as is a left-sided focus, intermediate age at onset of epilepsy, and absence of a genetic predisposition for left-handedness.[46,49] Increased grey matter in language networks in the hemisphere contralateral to the epileptic focus suggests hard-wired compensatory reorganization mechanisms.[50]

Language lateralization inferred from fMRI concurs with the intracarotid Amytal (ICA) test in 80-90% of patients when using conjunction analysis of three language paradigms.[51] Concordance between fMRI and ICA is greatest for right TLE patients with left language dominance; and lowest for left TLE patients with left language dominance.[52] The consensus in most epilepsy surgery centres is that fMRI language lateralization can replace ICA in most patients, to determine hemispheric dominance. The latter, however, may be required when a patient cannot perform the fMRI task, if fMRI is contraindicated and, in some cases for the validation of atypical, inconclusive or not clearly lateralised language activation with fMRI.[53]

Preoperative verbal fluency fMRI activation in the middle and inferior frontal gyri predicts significant naming decline following left temporal lobe resection, with good sensitivity but poor specificity.[54] It is intuitive that a language activation paradigm that primarily activates the part of temporal lobe this is to be removed in surgery will be a better predictor of word-finding difficulties after temporal lobe resection than is a paradigm that primarily activates the adjacent frontal lobe. Auditory and visual naming paradigms have promise in this regard and may give more specific prediction of naming difficulties after anterior temporal lobe resection.[55]

Cortical language function can also be localized with navigated transcranial magnetic stimulation (rTMS), and the results mapped onto the individual subject's MRI. Concordance with the standard of direct cortical stimulation was impaired in those with lesions.[56]

When a cortical resection is needed close to eloquent language cortex, the localization inferred from language fMRI is not adequate to guide resection as areas that do not appear to be activated at the threshold used to display data may be necessary for language function, and areas that do activate may not be critical. In consequence, it is necessary to carry out electrocortical stimulation and/or awake resections.[57] An active area of current research is to determine whether non-invasive language mapping may render this unnecessary.

Episodic memory

Memory impairment commonly accompanies TLE and a clinical concern is the risk of temporal lobe surgery causing worsened memory. Verbal memory encoding activates a bilateral network including temporal, parietal and frontal lobes. Greater left hippocampal activation for word encoding is correlated with better verbal memory in patients with left TLE.[58] Visual memory encoding recruits a more widespread bilateral cortical network and greater right hippocampal activation for face encoding is correlated with better visual memory in right TLE patients. Functional reorganization of networks involving extra-

temporal and temporal structures for verbal and visual specific memory encoding suggests compensatory mechanisms are in operation, to mitigate the failure of the sclerosed hippocampus.[59,60]

Verbal and visual memory declines in one third of patients undergoing left or right temporal lobe resection, respectively. It is important to be able to predict this, in order to advise individual patients of their risks. Preoperative memory performance, age at onset of epilepsy, language lateralization and asymmetry of activation on fMRI for verbal and visual memory can predict verbal memory decline in left ATLR but are less able to predict visual memory decline in right ATLR.[58,61] Verbal memory encoding fMRI was the most consistent and discriminating factor between left and right TLE.[62]

In individuals with left temporal lobe epilepsy, having predominantly left sided anterior hippocampal activation on word encoding correlated with greater decline of verbal memory after left anterior temporal lobe resection. Conversely, predominantly left sided posterior hippocampal activation correlated with better verbal memory after resection.[58] In those with right temporal lobe epilepsy, predominantly right sided anterior hippocampal activation with face encoding was associated with more decline of visual memory following right anterior temporal lobe resection, and predominantly right posterior hippocampal activation was associated with superior visual memory after surgery. Memory activation patterns before surgery were the strongest predictor of verbal and visual memory loss as a result of anterior temporal lobe resection and preserved function in the ipsilateral posterior hippocampus may help to maintain memory encoding after anterior temporal lobe resection.[58] A clinically applicable verbal memory fMRI paradigm, that assessed lateralization index of memory, and associated language functions, in the medial temporal and frontal lobes was the best predictor of verbal memory decline after temporal lobe resection (Fig 4).[63] Replication studies are now needed to determine whether this would be suitable for widespread use.

Motor function

Motor fMRI with finger and foot tapping identifies the primary motor cortex, which is beneficial when planning intracranial EEG implantations and resections. fMRI generally gives concordant results to cortical stimulation and high gamma electrocorticography.[64] In those with FLE, there is reduced activation on the side of the focus after seizures. This implies seizures affect motor circuitry, but it is not suggested that the location of the primary activation is affected.[65] Navigated rTMS mapped activations with a Euclidean separation from direct cortical stimulation of 11 ± 4 mm for the hand and 16 ± 7 mm for arm muscle representation areas, with locations being in the same gyrus, thus giving an accuracy suitable for epilepsy surgical evaluations.[66] Resections close to motor cortex still require direct electrocortical stimulation mapping and/or awake resections to minimize the risk of causing a fixed deficit.

Resting state and connectivity

It is a sound aphorism that impaired brain function occurs as much if the connections of eloquent areas are affected as if the eloquent area itself is damaged. Children with frontal lobe epilepsy (FLE) show cognitive impairment in association with decreased frontal lobe connectivity, despite intact working memory fMRI activations suggesting that impaired connectivity contributes to cognitive difficulties.[67] In adults with TLE, resting-state thalamo-temporal functional connectivity reflected long-term memory performance, and thalamo-prefrontal functional connectivity reflected short-term memory performance.[68] A machine learning-based analysis of resting-state functional connectivity has been proposed as a method to lateralize temporal lobe epilepsy.[69] Impaired connectivity in a network involving the anterior nucleus and pulvinar of the thalamus has been reported in TLE.[70] Whilst these methods probe the pathophysiology

of epileptic networks, the potential benefits for clinical studies of individual patients is not established at this time, but have promise for assisting the prediction of the outcome of epilepsy surgery.

Mapping cerebral white matter connections

Functional MRI identifies eloquent cortex, but surgical damage to white matter connections must also be avoided to prevent postoperative neurological deficits. Tractography derived from diffusion-weighted imaging enables the non-invasive *in vivo* delineation of white matter tracts.

Most work in epilepsy focuses on the optic radiation as damage to Meyer's loop during anterior temporal lobe resection can cause a visual field deficit (VFD) that may preclude driving.[71] The extent of resection and distance from Meyer's loop to the temporal pole on preoperative tractography predict the risk of VFD.[72] Tractography assists surgical planning and risk stratification.[73] Display of tractography data during surgery with correction for brain shift using intraoperative MRI reduced the risk of VFD (Fig 5).[74,75]

Delineation of the corticospinal tract in patients undergoing frontal lobe surgery is beneficial, particularly in children in whom fMRI may be challenging. Localization inferred by tractography gives similar results to invasive electrical stimulation mapping and can predict the risk of postoperative motor deficits.[76] Much work on the corticospinal tract has been performed in patients with gliomas which can readily be translated to patients with epilepsy.

More limited data is available on the arcuate fasciculus, which may reflect poorer correlation between damage and postoperative outcomes arising from the multiplicity of language pathways. Nevertheless, it may have a role in paediatric epilepsy surgery.[77] Tractography of all three tracts with intra-operative MRI was beneficial in reducing the risk of deficits following ganglioglioma surgery.[78]

Tractography has limitations. The tracts obtained are assumed to be a faithful representation of the underlying anatomy, but spatial resolution and modelling limitations result in inaccuracy. Different algorithms give varying results.[79] Data derived from diffusion-weighted data are distorted compared to anatomical scans and use during surgery ideally involves correction for brain shift. Whilst intra-operative MRI is helpful, the expense and access are limiting. Future developments include better diffusion models, automation of tractography, its use with standard neuronavigation systems, and correction for brain shift using alternative techniques such as ultrasound.

Localization of epileptic activity

If MRI does not show a structural lesion that is concordant with clinical and EEG data, it is necessary to carry out further investigations to infer the localization of the epileptic network (Fig 1).[4]

PET imaging

PET is an important investigation for noninvasively localizing epileptogenic brain regions in MRI-negative focal epilepsies, in patients with more than one abnormality, or if MRI and ictal EEG are not concordant.

^{18}F-Fluorodeoxyglucose PET has been used for epilepsy surgery evaluations since before the advent of MRI. The wide availability of the method in oncology centres, and its use

as an interictal investigation, results in this generally being used in preference to ictal SPECT (see below) in the epilepsy surgery pathway.

Regional cerebral hypometabolism demonstrated with ^{18}F-FDG PET often has a wider distribution than that of the seizure focus, which may represent both the focus and projection areas of seizure activity (Fig 6). This lack of specificity makes surgical decisions on the extent of resective surgery difficult. Of note, however, post-operatively seizure free patients had more of the hypometabolic area resected than individuals who continued to suffer from seizures.[80]

The main advantage for the future use of clinical PET is that it is very versatile, allowing not only mapping of in-vivo processes, such as perfusion and metabolism, but also the quantification of the distribution of radiolabelled markers with concentrations in the nanomolar range. This versatility depends on the availability of a cyclotron and radiochemistry laboratory. For tracers labelled with ^{11}C, which has a half-life of 20 minutes, this has to be in the same location as the scanner, which greatly reduces the applicability outside of a very few centres. ^{18}F has a half-life of 2 hours, so production can be at a distant facility and shipped to the scanner.

Several PET receptor ligands have been used to assess neurotransmitter systems involved in the pathophysiology of epilepsy.

[^{11}C]flumazenil (FMZ) images availability of γ-aminobutyric acid receptor A, and has shown limited extra-yield in localizing epileptic foci in patients with normal MRI.[81] [^{18}F]FMZ may be more widely available and thus better define the clinical benefit of benzodiazepine receptor imaging.[82] In a group of difficult to treat focal epilepsies, reduced FMZ binding was found in the temporal piriform cortex, which was associated with increased seizure frequency. This finding raised the concept of a common network and that removal of the temporal piriform cortex might be relevant for achieving post-operative seizure-freedom.[83]

Alpha[^{11}C]methyl-L-tryptophan (AMT) was originally considered to be a marker of serotonin synthesis, but is now considered to image both excitatory amino acids as well as inflammatory pathways. An increased uptake reliably indicates the epileptogenic tuber in patients with tuberous sclerosis when more than one tuber is present.[84] If replicated this could be very useful in this context and to identify abnormalities in individuals with normal MRI.

SPECT imaging

Single photon emission computed tomography (SPECT) imaging can provide information about dynamic changes in cerebral perfusion before, during and after a seizure. Timing of injection and duration of the seizure is important for correct interpretation of the SPECT images, as delayed injection may result in a variable pattern of blood flow changes as the seizure evolves and propagates. True ictal SPECT shows an area of hyperperfusion in the epileptogenic region, surrounded by an area of hypoperfusion that may be caused by shifting of blood flow to the seizure focus or may reflect an inhibitory zone trying to limit the seizure spread.[85] Limitations of ictal SPECT are the complex logistics required, the fact that only a single dataset representing cerebral blood flow is obtained and the temporal aspects. After intravenous injection it takes at least 40 seconds for the tracer to reach the brain, cross the blood brain barrier and become fixed. It follows that, with a short seizure of less than 30 seconds, it is inevitable that the image of cerebral blood flow will be post-ictal rather than ictal, and even with a longer seizure, areas of propagation rather than onset will be visualised. The place of ictal SPECT is in the presurgical evaluation of patients with refractory focal epilepsy who have

MRI that is normal or discordant with clinical and EEG data, and to assist with formulating a hypothesis of seizure onset localization that may be tested with intracranial EEG. It would be unusual for ictal SPECT to lead directly to a resection.

EEG-fMRI, electrical source imaging, and magnetic source imaging

Simultaneous scalp EEG-fMRI recordings can map haemodynamic changes associated with interictal epileptic discharges, with 30-40% sensitivity[86] and may be useful for planning intracranial implantations,[87] with widespread abnormalities warning of poor outcome from resection.[88] If an individual has frequent seizures, an ictal EEG-fMRI recording may be obtained. Focal or widespread haemodynamic changes are often seen prior to the onset of seizure on scalp EEG, suggesting that haemodynamic changes start prior to the seizure onset on scalp EEG[89] and highlighting the low sensitivity of scalp EEG.[90] In generalized epilepsies, EEG-fMRI has demonstrated the involvement of cortico-subcortical networks in generalized spike wave discharges.[91] The current clinical role of scalp EEG-fMRI is that localization of ictal and interictal networks revealed can be useful during presurgical assessment, helping to design intracranial EEG sampling strategies and indicating if there is likely to be a poor outcome, which may dissuade from proceeding.

Simultaneous recording of intracranial EEG and fMRI is possible[92] and can show haemodynamic alterations occurring before the first detected EEG changes, indicating the presence of a distributed network and that the implanted electrodes are at a distance from the site of epileptic activity.[93]

Electrical source imaging (ESI) derived from high-density scalp EEG has the advantage that more prolonged recordings are feasible than with EEG-fMRI or MEG and can identify the irritative zone generating interictal epileptic activity. A large number of channels, eg 128, are needed for high quality ESI. The results need to be computed with the individual's MRI. Inaccurate modelling of the electromagnetic field propagation may result in errors. Comparison with subsequent intracranial EEG has shown a median separation of 13-16 mm between the ESI and the intracranial contact showing maximum discharges.[94] Resection of the interictal ESI maximum has been associated with a good surgical outcome[95] and the concordance of an ESI focus with an MRI lesion has been associated with a 92% chance of good seizure outcome following resection.[96] If replicated, this suggests a role for ESI early in the epilepsy surgery pathway, with the possibility of other investigations becoming redundant.

Magnetic source imaging (MSI), derived from MEG, of interictal epileptic activity appears promising in retrospective studies, with higher seizure freedom rates if there was a concordant MEG dipole, than if MEG data were discordant or nonspecific.[97,98] The combination of electrical and magnetic source localization are complementary and improve the accuracy of source localization and identification of propagated activity.[99]

In practical terms, EEG-fMRI, ESI and MSI are used to map interictal epileptic activity, with a small chance of including ictal activity, the possibility being greater with ESI as more prolonged recordings are feasible. The relative places of these techniques in the presurgical algorithm are not yet determined. For individuals with concordant MRI and ictal and interictal video EEG, further data are redundant. The group who stand to benefit are those in whom there is not a clear surgical solution and who would require intracranial EEG to define the epileptogenic zone. Useful data helps to generate a hypothesis that may be tested with intracranial EEG and to identify those in whom there are widespread abnormalities, and in whom invasive studies should not be carried out. Prospective studies to evaluate these issues will be very challenging as the three

techniques are not likely to be developed to a similar level in any one Centre, and a multicentre study with at least 12 months postoperative follow-up would be required. It seems likely that each method would show some utility, with all three contributing in a majority, and any one technique being uniquely helpful in a subset.

Integration of multimodal 3D imaging in the epilepsy surgery pathway

In 20-30% of candidates for epilepsy surgery, intracranial EEG is needed to define the epileptogenic zone.[100] Increasingly, this is accomplished with multiple (12-20) stereotactically placed depth EEG (SEEG) electrodes. SEEG electrodes record from a 1 cm core around the cerebral entry to the distal end (target), which may be placed in the hippocampus, amygdala, or midline or inferior neocortex. Electrode implantation carries a risk of haemorrhage, neurologic deficit, and infection.[101] Preoperative planning of electrode trajectories using multi-modal imaging, defining deep and superficial targets and skull entry points, can minimise implantation risk by ensuring that the electrodes avoid critical structures (particularly arteries and veins) and contact with other electrodes. Precise planning can also improve the efficiency of the recording by ensuring that electrode contacts sample grey rather than white matter. Current clinical practice for planning electrode trajectories involves manual evaluation of individual trajectories in series, which is a time-consuming and complex task requiring the integration of information across many imaging modalities to locate critical structures, the targets and grey matter (Fig 7). It is necessary to optimize several parameters for each trajectory to reach the target, avoid critical structures, obtain a suitable entry angle through the skull, and finally adjusting the different trajectories to maximise grey matter sampling and avoid conflicts between electrodes. Placing a new electrode may require adjusting previously planned trajectories, making the planning process even more time consuming.

Recently, great progress has been made to develop semi-automated computer-assisted planning software that markedly reduces the planning time by calculating quantitative measures of trajectory suitability. These measures can be used to select the best trajectory or inform manual trajectory selection.[102-105] This planning requires the integration of multi-modal imaging, with each single modality being combined together into a patient-specific 3D map of the brain. The most critical data are the skull surface (CT), the grey matter map (T1-w MRI), and the arteries and veins (MR or CT angiography), and T1-weighted MRI with gadolinium enhancement. Different areas of interest coming from fMRI, PET or SPECT can also be added to this 3D map and included for the planning of different trajectories. Automatic solutions were recently evaluated, demonstrating the potential of these approaches in clinical settings.[106]

After intracranial electrodes have been placed, seizures are recorded with simultaneous videoing of the patient and EEG recording from the intracranial electrodes. The electrode contacts that record the earliest seizure activity are analyzed, as is the subsequent spread of the activity. The area to be resected is determined from the epileptogenic zone, with regard to any structural lesion, and the location of eloquent cortex, as inferred by fMRI, and precisely located by electrical stimulation studies and critical white matter tracts that have been visualised with tractography, and the major arteries and veins, and the location of any prior craniotomy and burr-holes. Planning the surgical approach and the extent of the resection is particularly challenging if not located on the convexity of the cerebral hemisphere, and if there is no evident lesion. The use of multimodal 3D imaging to assist this planning has considerable promise, but it is essential to keep in mind that all imaging and registration has the potential for some error and does not obviate the need for expert surgical technique.

Future view

Over the next decade we anticipate increased sensitivity from MRI with 7T clinical scanners, improved imaging technology and new MR contrasts and analyses that will improve detection of subtle lesions that underlie refractory focal epilepsies and which may be amenable to surgical treatment. With the adoption of uniform protocols for acquisition and processing we expect that computerized-analysis of the much larger datasets than are acquired at present will become standard, to effect data reduction and detection of suspicious areas of focal abnormality for human review. Greater sensitivity is likely to be accompanied by reduced specificity so it will be essential to critically evaluate the relevance of possible abnormalities. High field MRI of ex vivo cerebral resection specimens will allow MRI-histological correlation at a fine scale and has the potential to inform optimization of MRI sequences for in vivo use and the identification and prediction of the nature of abnormalities. Integration of multiple structural and functional imaging datasets will become routine and inform clinical decision making in the presurgical pathway, so that the risk-benefit ratio can be quantified for individual patients, and optimized.

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Figure legends

Fig 1. The pathways of evaluation for epilepsy surgery, showing the place of brain imaging[4]

Fig 2. Structural MRI scans. Focal cortical dysplasia with cortical thickening and blurred grey/white matter junction on T1-weighted images (A) and high intensity on T2 FLAIR (B). Right hippocampal sclerosis with volume loss on T1-weighted image (C), high signal intensity on T2 FLAIR (D) and loss of internal architecture on T2-weighted coronal oblique PROPELLER (E). A cavernoma in the left inferior temporal gyrus appears clearly as an area of signal dropout on T2*-weighted images (F). The left side of the images is the right side of the patient.

Morphometric Analysis Program highlights FCD on the junction image (blurred grey/white matter junction) and extension image (grey matter extending abnormally into white matter) (G), adapted from Huppertz et al (2005) with permission.[10]

Panels A-F were acquired on a 3T GE Signa Excite HDx scanner with a 3D FSPGR T1-weighted sequence (0.9375x0.9375mm inplane resolution, 1.1mm slice thickness), a coronal oblique T2 FLAIR-weighted sequence (0.9375x0.9375mm inplane resolution, 5mm slice thickness), a coronal oblique T2-weighted PROPELLER sequence (0.43x0.43mm inplane resolution, 2mm slice thickness) smf a FGRE T2* weighted sequence (0.9375x0.9375mm inplane resolution, 5mm slice thickness).

Fig 3. NODDI for detecting the abnormality in a patient with left inferior temporal gyrus focal cortical dysplasia (FCD). The area is poorly defined on structural images including volumetric T1-weighted (A) and T2-weighted coronal oblique (B) and standard diffusion images including fractional anisotropy (C) and mean diffusivity (D). It is easily visible as reduced intracellular volume fraction derived from NODDI (E). Reproduced from Winston et al (2014).[32]

Fig 4. **Verbal episodic memory fMRI** (A) Correlation of words remembered activations with postoperative verbal memory decline in left temporal lobe epilepsy (TLE) (LTLE; upper panel) and right TLE (RTLE; lower panel) patients. In both LTLE and RTLE patients, the rendered images show left frontal activations correlated with greater postoperative verbal memory decline. The sliced images show that predominantly left medial temporal lobe activations correlated with greater postoperative verbal memory decline in LTLE patients.

(B) Correlation of individual lateralization indices for words remembered in an anatomical fronto-temporal mask with change in list learning 4 months following left anterior temporal lobe resection (R^2=0.43). The dotted vertical red line indicates the level of significant decline calculated by reliable change index using control data. The horizontal black dotted line indicates a LI of 0.5 (L>R). Seven of 8 patients who experienced a significant verbal memory decline had LI $\geq$0.5. Reproduced from Sidhu et al (2015).[63]

Fig 5. Optic radiation tractography for surgical guidance. Optic radiation tractography can be superimposed on the coronal FLAIR to demonstrate the relationship to a cavernoma to aid surgical planning (A) and also displayed in 3D renderings (B) [reproduced from Winston et al (2011)].[74] Tractography can then be displayed on the operating microscope display in real time for surgical guidance (C) [adapted from Winston et al (2014)][75].

Fig 6. 18F-FDG PET showing left temporal hypometaboism in an individual with left TLE and normal MRI.

Fig 7. **Integration of multimodal 3D imaging in the epilepsy surgery pathway**. Stereo EEG implantation plan. Each electrode is colour coded.
7A: Veins (cyan) extracted from Gd-Enhanced T1-weighted MRI, arteries (red) extracted from CT angiogram.

7B: Lesion identified from T2-weighted FLAIR (purple) and motor (green) and language (orange) region identified from fMRI.

7C: Lesion identified from T2-weighted FLAIR (purple) and motor (green) and language (orange) region identified from fMRI and volume rendering of T1-weighted MRI.

Panel 1:

GLOSSARY OF MRI TERMS

Arterial spin labelling: an MRI technique used to produce quantitative maps of tissue perfusion without the need for intravenous contrast by magnetically labelling inflowing blood

Curvilinear reformatting: an alternative approach to traditional cross-sectional display (sagittal, axial, coronal) in which the brain is displayed at different depths from the surface (like peeling the layers from an onion); this enhances the localisation and detection of dysplastic lesions

Diffusional kurtosis imaging (DKI): a more advanced model of diffusion than DTI that measures both Gaussian and non-Gaussian diffusion to provide greater detail on complex tissue microstructure

Diffusion-tensor imaging (DTI): a development of DWI in which the diffusion is measured in multiple different directions in each voxel so the predominant direction of diffusion can be determined and used for tractography; further calculations can derive quantitative tissue properties

Diffusion-weighted imaging (DWI): an MRI technique in which the signal is modulated by the random diffusion of water molecules; the signal loss in areas of increased diffusion was first used clinically to detect early ischaemic stroke

Double inversion recovery: an MRI sequence with two additional pulses to suppress the signal from both white matter and CSF to increase grey/white matter contrast; this facilitates the identification of grey matter lesions

Fluid-attenuated inversion recovery imaging (FLAIR): a T2-weighted sequence with an additional pulse to suppress the signal from CSF; this improve the identification of periventricular lesions

Intracarotid sodium amytal (Wada) test: a procedure in which one hemisphere is temporarily anaesthetised by intracarotid injection of sodium amytal in order to determine the laterality of language and memory functions

Neurite orientation dispersion and density imaging (NODDI): an advanced model of diffusion applied to DWI data to determine tissue properties such as intracellular volume fraction and the degree of dispersion of neurites (axons, dendrites)

Phased-array coil: a type of MRI coil receiving the signal to produce the image from multiple coils rather than a single coil to improve signal-to-noise ratio and facilitate faster imaging

Region-of-interest-based approach: a type of MRI image analysis in which a specific region (e.g. hippocampus) is delineated manually or automatically to measure a property in this area

***Surface-based morphometry*:** an approach to studying brain shape and size (morphometry) that looks at features from the brain surface such as cortical thickness and curvature

Susceptibility weighted imaging: a newer MRI technique than T2*-gradient echo imaging sensitive to effects of paramagnetic and diamagnetic compounds such as blood products and calcium; it may help to better identify lesions such as cavernomas

T1-weighted imaging: one of the basic MRI sequences that produces an image with contrast depending upon T1 relaxation, typically used to identify anatomy

T2 relaxometry: a quantitative MRI technique to measure T2 relaxation, in contrast to producing an image qualitatively affected by T2 relaxation (T2-weighted imaging); helpful to identify hippocampal sclerosis

T2-weighted imaging: one of the basic MRI sequences that produces an image with contrast dependent upon T2 relaxation, which is sensitive to pathology

T2*-gradient echo imaging: a commonly used clinical MRI sequence that produces images sensitive to iron-containing compounds such as blood products; helpful for identifying vascular malformations and microbleeds

Tractography: a non-invasive method to delineate white matter connections from DWI; one approach is to trace the predominant direction of diffusion from DTI data

Volumetry: the technique of measuring the volume of a structure, either manually or automatically; useful for measuring hippocampal volumes to detect hippocampal atrophy

Voxel-based morphometry: a statistical approach to studying brain shape and size (morphometry) that matches an individual brain to a template to determine where focal changes in properties such as grey matter volume occur

Panel 2

MRI acquisition protocol for epilepsy

1. **3D volumetric T1-weighted image (1mm isotropic)**. This provides excellent grey/white matter contrast, allows the assessment of cortical thickness and detection of malformations of cortical development. It can be reformatted into any plane or post-processed as discussed below.
2. **T2-weighted image (axial, coronal)**. These allow assessment of hippocampal architecture and cystic tissue components of other lesions. The two orthogonal planes allow small lesions to be distinguished from partial volume effects, which are minimised by acquiring orthogonal to the long axis of the hippocampus.
3. **FLAIR image (axial, coronal)**. These are sensitive to hippocampal sclerosis, focal cortical dysplasia, tumours, inflammation and scars.
4. **T2* gradient echo/susceptibility weighted imaging (axial)**. This is sensitive to calcified and vascular lesions, such as cavernomas and arterio-venous malformations.[12]

Contributors statements.

Prof JS Duncan, Dr GP Winston, Prof MJ Koepp and Prof S Ourselin were all involved in literature searches, interpretation, writing and editing of this review. The corresponding author, Prof JS Duncan, takes final responsibility for the decision to submit this review article for publication.

Conflict of interest statement

Prof. Duncan reports personal fees from Eisai, non-financial support from Medtronic. In addition, Dr. Duncan has a patent Computer assisted planning for neurosurgery pending.

Dr Winston reports no conflicts to declare.

Prof Koepp reports personal fees from GE concerning PET tracer development, and from UCB, BIAL and Eisai concerning antiepileptic drug development

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