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## 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-weighted imaging, post-acquisition image processing techniques, and quantification of imaging data are increasing the accuracy of lesion detection. Functional MRI can be used to identify areas of the cortex that are essential for language, motor function, and memory, and tractography can reveal white matter tracts that are vital for these functions, thus reducing the risk of epilepsy surgery causing new morbidities. PET, SPECT, simultaneous EEG and functional MRI, and electrical and magnetic source imaging can be used to infer the localisation of epileptic foci and assist in the design of intracranial EEG recording strategies. Progress in semi-automated methods to register imaging data into a common space is enabling the creation of multimodal three-dimensional patient-specific datasets. These techniques show promise for the demonstration

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#### Contributors

JSD, GPW, MJK, and SO did the literature searches, interpretation, writing, and editing of this Review.

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JSD has received personal fees from Eisai and non-financial support from Medtronic and has a patent pending for computer-assisted planning for neurosurgery. MJK has received personal fees from General Electric for PET tracer development, and from UCB, BIAL, and Eisai for antiepileptic drug development. SO has received grants from General Electric, Siemens, IXICO, MIRADA Medical, and IcoMetrix, and has a patent pending for computer-assisted planning for neurosurgery. GPW declares no competing interests.

of the complex relations between normal and abnormal structural and functional data and could be used to direct precise intracranial navigation and surgery for individual patients.

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## Introduction

Epilepsy develops in 50 in every 100 000 people per year; in a third of these people, antiepileptic drugs do not control seizures.<sup>1</sup> About half of these latter individuals have focal epilepsy that is potentially amenable to neurosurgical treatment if there is evidence to suggest a single focal network underlying the epilepsy, if the individual would be able to withstand neurosurgery,<sup>2</sup> and if they do not have severe comorbidities, such as active cancer, advanced vascular disease, or dementia.

Brain imaging is of fundamental importance to diagnosis and treatment of epilepsy, particularly when neurosurgical treatment is being considered. Dramatic advances have been made in brain imaging applied to epilepsy in the past 20 years, principally because of advances in MRI scanner technology, acquisition protocols, and image processing methods, and in nuclear medicine.<sup>3</sup> In this Review, we focus principally on advances made since 2005 that are of potential clinical importance to the practising neurologist. We first review developments in structural brain imaging with MRI and post-acquisition processing methods to identify cerebral abnormalities that might cause epilepsy, the identification of which might lead to consideration of surgery. We then describe the mapping of areas of cortex that are essential for language, motor, and memory functions (eloquent cortex) and the crucial white matter pathways in the brain. Next, we review PET and other imaging methods to infer the localisation of cerebral networks that could generate epileptic seizures in the context of MRI findings that are inconclusive or discordant with clinical and EEG data. Finally, we review the integration of multimodal three-dimensional imaging data 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 Review.

In the interpretation of imaging studies, an important factor is recognition of the difference between group studies, as used in neuroscience investigations to infer the functional anatomy of the brain and its abnormalities in a disorder, and 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 their surgical treatment, in whom the finding of focal abnormalities might lead to a surgical solution and identification of critical structures might 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 context of clinical and EEG data, with quantification of hippocampal volumes and T2 signal, 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 can be recommended for surgery, with functional MRI (fMRI) at this time to assess language lateralisation. If a

resection is planned that is close to the optic radiation or corticospinal tract, diffusion imaging and tractography to help to optimise the surgical approach and minimise the risks of surgery is recommended. Figure 1 shows the place of imaging studies in the presurgical pathway.<sup>4</sup>

If an individual has no relevant lesion on MRI, further acquisitions using the latest MRI hardware and techniques and post-acquisition processing methods might reveal a subtle abnormality, but findings should be interpreted with caution owing to the possibility of false-positive results. <sup>18</sup>F-fluorodeoxyglucose (<sup>18</sup>F-FDG) PET is a useful next step because it can be used to identify a single area of hypometabolism that might lead directly to resection—eg, if there is reduced uptake in the anterior temporal lobe in the non-language dominant hemisphere—or, more commonly, to inform an intracranial EEG recording. If abnormalities are not identified on <sup>18</sup>F-FDG PET imaging, subsequent investigations are geared towards generation of a hypothesis regarding the location of the epileptogenic zone that can be tested with intracranial EEG. These investigations include ictal SPECT and visualisation of interictal, and rarely ictal, epileptic activity with electrical source imaging (ESI), magnetic source imaging (MSI), and simultaneous EEG and fMRI (EEG-fMRI). In practical terms, the hierarchy of these investigations will depend on their availability in individual centres. Three-dimensional multimodal imaging has an evolving role in the integration of structural and functional data for the planning of invasive EEG studies and resections.

## Identification of structural cerebral abnormalities

Structural MRI is the main neuroimaging technique for identification of an epileptogenic lesion. Localising and delineating the extent of the underlying lesion and its relation to eloquent cortex forms a crucial part of the assessment for surgery. Identification of a lesion leads to a greater chance of seizure freedom after surgery.<sup>5,6</sup> However, 15–30% of patients with refractory focal epilepsy do not have distinct lesions on MRI (ie, they are MRI negative).<sup>7,8</sup> The underlying pathological abnormalities, the acquisition protocol, and the interpretation, by human or computational analysis, are key determinants in the identification of structural abnormalities.

## Acquisition protocol

Acquiring images using an optimised epilepsy protocol maximises the potential to identify structural abnormalities. The basic protocol established by the International League Against Epilepsy<sup>9</sup> includes whole-brain T1-weighted and T2-weighted imaging acquired with the minimum slice thickness possible in two orthogonal planes and a volumetric T1-weighted acquisition for three-dimensional reconstruction (figure 2). This guideline is 18 years old and updated guidance that takes into consideration recent advances made in brain imaging would now be appropriate.

Additional sequences, in particular fluid-attenuated inversion recovery (FLAIR) MRI, have become available, and scanner hardware has improved (figure 2).<sup>10</sup> Analysis of MRI data showing epileptogenic lesions in 2740 surgical patients in Bonn, Germany, led to a proposal for a specific MRI protocol (panel 2)<sup>11</sup> that is advantageous from both a sensitivity and economic point of view and is now widely accepted.<sup>12</sup>

## Imaging hardware

Imaging hardware has improved, with increased field strength and better coils and gradients. An increased field strength improves signal-to-noise ratio and enables greater spatial resolution. Rescanning surgical candidates who were MRI negative on a 1.5 T scanner using a 3 T scanner with phased-array coil MRI enabled identification of a lesion in 15 of 23 patients.<sup>13</sup> A retrospective review of 804 unselected patients who had MRI at 1.5 T and subsequently at 3 T showed relevant new diagnoses in 37 (5%), in particular hippocampal sclerosis, focal cortical dysplasia, and dysembryoplastic neuroepithelial tumour.<sup>14</sup> 7 T imaging is anticipated to reveal further anatomical detail, including delineation of hippocampal subfields<sup>15,16</sup> and increased identification of abnormalities that are not evident on conventional clinical MRI. However, higher field strength brings with it challenges, including image distortion and artifacts, and issues with patient tolerance that can make clinical interpretation and decisions on the relevance of findings difficult.

## Scan interpretation

Even with optimum acquisition, scan interpretation is subject to the expertise of the radiologist. In patients undergoing surgery, sensitivity in detection of focal epileptogenic lesions was 39% from non-optimised imaging reported by non-experts, 50% when reported by experts, and 91% when an optimised acquisition was used and reported by experts.<sup>17</sup> Curvilinear reformatting of volumetric T1-weighted images improves the display of gyral structure and helps to identify subtle abnormalities not seen on planar slices.<sup>18</sup> The clear message is that both acquisition using an epilepsy protocol and reporting by a skilled neuroradiologist who has all the relevant clinical data increase greatly the identification of relevant lesions that might underlie epilepsy.

## Assessment of structural data

A substantial development in the past decade has been the automated quantitative assessment of structural data, which can be applied to datasets from individuals.<sup>19</sup> The most commonly missed diagnoses in MRI-negative patients are hippocampal sclerosis and focal cortical dysplasia.

**Hippocampal sclerosis**—Hippocampal sclerosis is the most common cause of surgically remediable temporal lobe epilepsy and can be assessed with volumetry and T2 relaxometry. Quantification of hippocampal changes is particularly important, and strongly recommended, when considering epilepsy surgery, to detect subtle atrophy and signal changes that might not be identified visually and to establish whether the contralateral hippocampus is structurally normal. Bilateral hippocampal abnormalities raise concerns of a reduced chance of seizure freedom after anterior temporal lobe resection and an increased risk of memory impairment.<sup>20</sup> Time-consuming manual volumetry can be replaced by automated segmentation, which is available freely on the internet,<sup>21</sup> and localised shape changes can be detected even in patients who seem to be MRI negative.<sup>22</sup> Voxel-based approaches to T2 relaxometry might be more sensitive than traditional approaches based on region of interest analyses.<sup>23</sup>

Computerised analysis of hippocampal FLAIR signal has been used to identify hippocampal sclerosis with 97% sensitivity and 95% specificity,<sup>24</sup> and a combination of hippocampal volumetry and FLAIR signal measurements has been used to identify moderate and severe hippocampal sclerosis.<sup>25</sup> However, findings from a direct comparison between automated FLAIR signal analysis and hippocampal T2 relaxometry suggested that T2 relaxometry was more sensitive.<sup>26</sup>

Apart from manual hippocampal volumetry, the use of these techniques has largely remained confined to the centres that developed them and a few collaborating centres. For wide dissemination, validated methods need to be readily available, be quick and intuitive to use, and have adequate technical support in place.

**Focal cortical dysplasia**—Cortical malformations, in particular focal cortical dysplasia, underlie many paediatric and around a quarter of adult MRI-negative refractory epilepsies.<sup>27</sup> Imaging findings include focal cortical thickening, blurring of the grey–white matter junction, and high signal on T2-weighted or FLAIR images in underlying white matter.<sup>28</sup> However, MRI is often normal, particularly in type I focal cortical dysplasia, and up to 80% of focal cortical dysplasia lesions cannot be visually detected when located in the depths of a sulcus.<sup>29</sup> Advances in imaging acquisition protocols are likely to enable the detection of previously unidentified abnormalities such as focal cortical dysplasia. For example, double-inversion recovery suppresses signal from both CSF and white matter, improving contrast in the cortex.<sup>30</sup> Arterial spin labelling can be used to visualise tissue perfusion, and reduced blood flow might co-localise with focal cortical dysplasia.<sup>31</sup> Development in diffusion imaging methods such as neurite orientation dispersion and density imaging or diffusional kurtosis imaging, which provide more detail on tissue microstructure, increase sensitivity for the detection of focal cortical dysplasia (figure 3).<sup>32</sup>

Voxel-based morphometry (VBM) was originally applied to T1-weighted images for the quantitative analysis of grey and white matter distribution,<sup>33</sup> initially for group comparisons, but subsequently to compare an individual with a control population.<sup>19</sup> Findings from an initial study showed that 21 of 27 patients with focal cortical dysplasia were correctly identified.<sup>34</sup> Voxel-based analysis has been applied to T2 relaxometry maps<sup>35</sup> and FLAIR images to increase sensitivity for detection of focal cortical dysplasia<sup>36</sup> and for detection of abnormalities in those who are MRI negative.<sup>37</sup> Improved detection of focal cortical dysplasia has been achieved with a morphometric analysis procedure based on VBM methods that produces a junction map to highlight blurring of the grey–white matter boundary and an extension map to delineate abnormally deep sulci (figure 2G).<sup>10</sup> In one study, morphometric analysis complemented visual reading of MRI scans by an expert neuroradiologist.<sup>38</sup> As with many other image analysis instruments, there has not been widespread 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 and sulcal patterns not detected with VBM. Surface-based morphometry techniques generate geometric models of the cortical surface that allow features such as cortical thickness to be measured. This technique can be extended to analyse many morphological (cortical thickness, curvature, and

depth) and textural (blurring of grey–white matter interface and T1 hyperintensity) features to enable the detection of focal cortical dysplasia.<sup>39</sup> By combining many parameters with machine learning techniques to classify lesional and non-lesional vertices, focal cortical dysplasia was detected in 14 of 24 MRI-negative patients.<sup>40</sup> An automated classifier based on surface morphology and intensity gave 60% sensitivity to detect type II focal cortical dysplasia (three of seven with type IIA and six of eight with type IIB) that was not evident on visual reading, with no false-positive findings but with some extralesional clusters.<sup>41</sup> Automated detection methods have a promising role in augmenting visual assessment, particularly with focal cortical dysplasia type IIB.

### Data interpretation for advanced imaging methods

An important caveat is that although advances in field strength, gradients, acquisitions, and post-acquisition processing and quantification will result in increased identification of subtle abnormalities that might underlie epilepsy, a detection rate of above 20–30% cannot be expected in individuals with no clear abnormalities on conventional MRI scans.<sup>42</sup> Undoubtedly, some patients with focal epilepsy (eg, those with a neurochemical derangement) will not have a focal cerebral structural abnormality. In these patients, functional imaging, including perfusion and nuclear medicine techniques, could be used to infer the location of an epileptogenic network (see later). A further important caveat is that more sensitive methods will inevitably produce some spurious findings, which might include false-positive artifacts and true findings, such as increased T2 signal around the lateral ventricle, that are not relevant to the epilepsy. It is important, therefore, to apply so-called fuzzy logic by a sceptical expert to assessment of all imaging data and to interpret the findings in the context of clinical and EEG information.

### Mapping eloquent brain functions

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

#### Language

fMRI can be used to map language networks in patients with epilepsy for clinical and research purposes. Various language tasks that activate anterior (ie, Broca's area) and posterior (ie, Wernicke's area) language areas have been used to establish patterns of typical and atypical language lateralisation.<sup>43</sup> Verbal fluency, verb generation, and semantic decision tasks are used commonly for assessment of language in a clinical context, providing complementary information.<sup>44</sup> In addition to visual reading of the numbers of activated voxels, the lateralisation 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 able to identify outliers.<sup>45</sup>

Individuals with left hemisphere epilepsy are more likely to have atypical language lateralisation than those with right hemisphere epilepsy.<sup>46</sup> Individuals with left temporal lobe epilepsy and left language dominance recruit homologous right hemisphere areas for language processing, suggesting widespread language representation.<sup>47</sup> Individuals with temporal lobe epilepsy are more likely to have atypical language lateralisation in Wernicke's area, whereas anterior language areas are more affected in those with frontal lobe foci.<sup>48</sup> Many factors combine to affect language laterality. Left handedness is associated with an increased likelihood of a language shift to the right hemisphere in temporal lobe epilepsy, as is a left-sided focus, onset of epilepsy at 12–20 years, and absence of a genetic predisposition for left handedness.<sup>46,49</sup> Increased grey matter volume in language networks in the hemisphere contralateral to the epileptic focus suggests hard-wired compensatory mechanisms of reorganisation.<sup>50</sup>

Language lateralisation inferred from fMRI findings concurs with findings from the intracarotid amobarbital test (also known as the Wada test) in 80–90% of patients when using conjunction analysis of three language tasks.<sup>51</sup> Concordance between fMRI and intracarotid amobarbital test findings is greatest for patients with right temporal lobe epilepsy with left language dominance, and lowest for patients with left temporal lobe epilepsy with left language dominance.<sup>52</sup> The consensus in most epilepsy surgery centres is that fMRI language lateralisation can replace the intracarotid amobarbital test in most patients to establish hemispheric dominance. However, the latter might be needed 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 on fMRI.<sup>53</sup>

Preoperative fMRI activation in response to a verbal fluency task in the middle and inferior frontal gyri predicts substantial decline in verbal naming after left temporal lobe resection, with good sensitivity but poor specificity.<sup>54</sup> It is intuitive that a language activation task that primarily activates the part of the temporal lobe that is to be removed in surgery will be a better predictor of word-finding difficulties after temporal lobe resection than a task that primarily activates the adjacent frontal lobe. Auditory and visual naming tasks have promise in this regard and might enable more specific prediction of naming difficulties after anterior temporal lobe resection.<sup>55</sup>

When a cortical resection is needed close to eloquent language cortex, the localisation inferred from language fMRI is not adequate to guide resection because areas that do not seem to be activated at the threshold used to display data might be necessary for language function, and areas that are activated might not be crucial. As a consequence, electrocortical stimulation or awake resections, or both, are necessary in such cases.<sup>56</sup> Cortical language function can also be localised with navigated transcranial magnetic stimulation and the results mapped onto the individual's MRI scan. However, concordance with the standard of direct cortical stimulation was impaired in those with lesions.<sup>57</sup> An active area of research is assessment of whether non-invasive language mapping with fMRI or transcranial magnetic stimulation might render direct cortical stimulation unnecessary.

## Episodic memory

Memory impairment commonly accompanies temporal lobe epilepsy 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 temporal lobe epilepsy.<sup>58</sup> 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 patients with right temporal lobe epilepsy.<sup>58</sup> Functional reorganisation of networks involving extra-temporal and temporal structures for verbal-specific and visual-specific memory encoding suggests that compensatory mechanisms are in operation to mitigate the impaired function of the sclerotic hippocampus.<sup>59,60</sup>

Verbal memory declines in a third of patients undergoing left temporal lobe resection and visual memory declines in a third of those who have right temporal lobe resection.<sup>58,60,61</sup> The ability to predict this decline is important to be able to advise individual patients of their risks. Preoperative memory ability, age at onset of epilepsy, language lateralisation, and asymmetry of activation on fMRI for verbal and visual memory can be predictive of verbal memory decline after left anterior temporal lobe resection, but are less accurate predictors of visual memory decline after right anterior temporal lobe resection.<sup>58,61</sup> In a comparison of seven fMRI protocols, a verbal memory task showed the most consistent activation and was best able to discriminate between patients with left and right temporal lobe epilepsy,<sup>62</sup> suggesting that fMRI assessment of verbal memory is useful for identifying abnormal temporal lobe function.

In individuals with left temporal lobe epilepsy, predominantly left-sided anterior hippocampal activation in response to a word encoding task was correlated with greater decline of verbal memory after left anterior temporal lobe resection.<sup>58</sup> Conversely, predominantly left-sided posterior hippocampal activation was correlated with better verbal memory after resection.<sup>58</sup> In those with right temporal lobe epilepsy, predominantly right-sided anterior hippocampal activation in response to face encoding was associated with greater decline of visual memory after right anterior temporal lobe resection, and predominantly right-sided 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 seems to help to maintain memory encoding after anterior temporal lobe resection.<sup>58</sup> In another study, a clinically applicable fMRI verbal memory task that was used to assess the lateralisation 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 (figure 4), compared with language fMRI and clinical parameters.<sup>63</sup> Replication of these findings is needed to establish whether this method would be suitable for widespread use.



## Motor function

fMRI with finger and foot tapping tasks can be used to identify the primary motor cortex, which is beneficial when planning intracranial EEG implantations and resections. fMRI generally gives results that are concordant with findings from cortical stimulation and high gamma electrocorticography.<sup>64</sup> In patients with frontal lobe epilepsy, activation is reduced on the side of the focus after seizures. This finding implies that seizures affect motor circuitry, but does not suggest that the location of the primary area of activation is affected.<sup>65</sup> Navigated transcranial magnetic stimulation has been used to map activations with a mean Euclidean separation from the direct site of invasive cortical stimulation of 11 mm (SD 4) for the hand and 16 mm (SD 7) for arm muscle representation areas, with locations within the same gyrus, thus giving an accuracy suitable for epilepsy surgical assessments.<sup>66</sup> Resections close to motor cortex still need direct electrocortical stimulation mapping or for resections to be done while the patient is awake, or both, to minimise the risk of causing a lasting deficit.

## Resting state and connectivity

Impaired brain function occurs not only if an eloquent area is damaged, but also if functional connectivity within and between eloquent areas is affected. Cognitive impairment has been reported in children with frontal lobe epilepsy in association with decreased functional frontal lobe connectivity, despite having intact fMRI activation in response to a working memory task, emphasising the effect of impaired functional networks on cognition.<sup>67</sup> In adults with temporal lobe epilepsy, resting-state thalamo-temporal functional connectivity was associated with long-term memory performance, and thalamo-prefrontal functional connectivity was associated with short-term memory performance.<sup>68</sup> A machine-learning-based analysis of resting-state functional connectivity has been proposed as a method to establish lateralisation of the seizure focus in temporal lobe epilepsy.<sup>69</sup> Impaired connectivity in a network involving the anterior nucleus and pulvinar of the thalamus has been reported in temporal lobe epilepsy.<sup>70</sup> Although fMRI studies of functional connectivity can be used to investigate the pathophysiology of epileptic networks, and hold promise for assisting with the prediction of epilepsy surgery outcome, the potential benefit for clinical studies of individual patients is not established.

## Mapping cerebral white matter connections

fMRI can be used to identify eloquent cortex, but surgical damage to white matter connections must also be avoided to prevent postoperative neurological deficits. Tractography data derived from diffusion-weighted MRI, usually diffusion tensor imaging, enables the non-invasive in-vivo delineation of white matter tracts.

Most clinical research into white matter tracts in patients with epilepsy has focused on the optic radiation because damage to Meyer's loop during anterior temporal lobe resection can cause a visual field deficit that can preclude driving.<sup>71</sup> The extent of resection and distance from Meyer's loop to the temporal pole on preoperative tractography are predictive of the risk of a visual field deficit,<sup>72</sup> and tractography therefore can be used to assist with surgical planning and risk stratification.<sup>73</sup> Display of tractography data during surgery with

correction for brain shift using intraoperative MRI reduces the risk of a visual field deficit (figure 5).<sup>74,75</sup>

Delineation of the corticospinal tract in patients undergoing frontal lobe surgery is beneficial, particularly in children for whom fMRI is challenging. Localisation inferred by tractography gives similar results to invasive electrical stimulation mapping and can be used to predict the risk of postoperative motor deficits.<sup>76</sup> Much work on the corticospinal tract has been done in patients with gliomas, which can readily be translated to patients with epilepsy.

More limited data are available on the arcuate fasciculus, which might be a result of a weaker association between damage and postoperative outcomes arising from the multiplicity of language pathways. Nevertheless, tractography might have a role in the assessment of paediatric patients for epilepsy surgery.<sup>77</sup> Moreover, tractography of all three tracts with intra-operative MRI was beneficial in reducing the risk of deficits after ganglioglioma surgery in adults.<sup>78</sup>

However, 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.<sup>79</sup> Data derived from diffusion-weighted images are distorted compared with anatomical scans, and their use during surgery ideally involves correction for brain shift with intraoperative MRI. Although intraoperative MRI is helpful, cost and availability are restrictive. Future developments should include better diffusion models, automation of tractography, its use with standard neuronavigation systems, and correction for brain shift using alternative techniques such as ultrasound.

## Localisation of epileptic activity

If MRI does not show a structural lesion that is concordant with clinical and EEG data, further investigations are necessary to infer the localisation of the epileptic network (figure 1).<sup>4</sup>

## PET imaging

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

<sup>18</sup>F-FDG PET has been used for epilepsy surgery assessments since before the advent of MRI. The wide availability of the method in oncology centres, and its use as an interictal investigation, results in <sup>18</sup>F-FDG PET generally being used in preference to ictal SPECT (see later) in the epilepsy surgery pathway.

Regional cerebral hypometabolism identified with <sup>18</sup>F-FDG PET often has a wider distribution than that of the seizure focus, which can represent both the focus and projection areas of seizure activity (figure 6).<sup>80</sup> This absence of specificity makes surgical decisions on the extent of resective surgery difficult. However, in a study of post-operative outcomes,

patients who were seizure free after surgery had more of the hypometabolic area resected than did individuals who continued to experience seizures.<sup>81</sup>

The main advantage of clinical PET imaging for its future use is that it is 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 <sup>11</sup>C, which has a half-life of 20 min, the cyclotron and radiopharmacy laboratory has to be in the same location as the scanner, which greatly reduces the applicability outside a few centres. <sup>18</sup>F has a half-life of 2 h, so production can be at a distant facility and the tracer shipped to the scanner.

Several PET receptor ligands have been used to assess neurotransmitter systems involved in the pathophysiology of epilepsy. <sup>11</sup>C-flumazenil PET imaging can be used to detect reductions in GABA<sub>A</sub> receptor binding, but with limited success in localisation of epileptic foci in patients with normal MRI.<sup>82</sup> In a group of patients with difficult-to-treat focal epilepsies, reduced <sup>11</sup>C-flumazenil binding was found in the temporal piriform cortex, which was associated with increased seizure frequency.<sup>83</sup> This finding raised the possibility of the existence of a common network and that removal of the temporal piriform cortex might be relevant for achieving postoperative seizure freedom.<sup>83</sup> <sup>18</sup>F-flumazenil is, in some centres, more widely available than <sup>11</sup>C-flumazenil and thus might be more useful in understanding the clinical benefit of benzo-diazepine receptor imaging.<sup>84</sup>

$\alpha$ -<sup>11</sup>C-methyl-L-tryptophan was considered originally to be a marker of serotonin synthesis, but uptake of this tracer in PET imaging is now thought to be an indicator of altered excitatory aminoacid concentrations and inflammatory pathways. An increased uptake can be used to reliably identify an epileptogenic tuber in patients with tuberous sclerosis when more than one tuber is present.<sup>85</sup> If replicated, this imaging method could be very useful in this context and in the identification of abnormalities in individuals with normal MRI.

## SPECT imaging

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 are important for correct interpretation of the SPECT images, because delayed injection can 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 hypo-perfusion that might be caused by shifting of blood flow to the seizure focus or might represent an inhibitory zone that limits the seizure spread.<sup>86</sup> Limitations of ictal SPECT include the complex logistics needed, the fact that only one dataset representing cerebral blood flow is obtained, and timing issues. After intravenous injection, the tracer takes at least 40 s to reach the brain, cross the blood–brain barrier, and become fixed. Thus, with a short seizure of less than 30 s, the image of cerebral blood flow will inevitably be post-ictal rather than ictal, and even with a longer seizure, areas of propagation rather than onset will be visualised. Ictal SPECT in the presurgical assessment pathway is most useful in patients with refractory focal epilepsy who have MRI that is normal or discordant with clinical and EEG data, and to assist with formulation of a hypothesis of seizure onset

localisation that can be tested with intracranial EEG. Ictal SPECT imaging would not usually be used to directly support a resection.

### EEG-fMRI, ESI, and MSI

Simultaneous scalp EEG-fMRI recordings can be used to map haemodynamic changes associated with interictal epileptic discharges with 30–40% sensitivity<sup>87</sup> and might be useful for planning intracranial implantations,<sup>88</sup> with widespread abnormalities taken as a warning sign of poor outcome from resection.<sup>89</sup> If an individual has frequent seizures, an ictal EEG-fMRI recording can be obtained. Focal or widespread haemodynamic changes are often seen before the onset of seizures on scalp EEG recordings, suggesting that additional brain networks might be involved before seizure onset on scalp EEG,<sup>90</sup> and highlighting the low sensitivity of scalp EEG.<sup>91</sup> In generalised epilepsies, EEG-fMRI has shown involvement of cortico-subcortical networks during generalised spike wave discharges.<sup>92</sup> The clinical role of scalp EEG-fMRI is that localisation of identified ictal and interictal networks can be useful during presurgical assessment, helping with the design of intracranial EEG sampling strategies and showing whether there is likely to be a poor outcome, which may dissuade the clinician from proceeding.

Simultaneous recording of intracranial EEG and fMRI is possible<sup>93</sup> and can show haemodynamic alterations occurring before the first detected EEG changes, suggesting the presence of a distributed network and that the implanted electrodes are at a distance from the site of epileptic activity.<sup>94</sup>

ESI, based on reconstruction of electrical activity derived from high-density scalp EEGs, can produce more prolonged recordings than is possible with EEG-fMRI or MEG and can be used to 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 data. Inaccurate modelling of electromagnetic field propagation can result in errors. Comparison with subsequent intracranial EEGs has shown a median separation of 13–16 mm between the ESI and the intracranial contact showing maximum discharges.<sup>95</sup> Resection of the interictal ESI maximum has been associated with a good surgical outcome,<sup>96</sup> and the concordance of an ESI focus with an MRI lesion has been associated with a 92% chance of good seizure outcome after resection.<sup>97</sup> If replicated, these findings suggest a role for ESI early in the epilepsy surgery pathway, with the possibility of other investigations becoming redundant.

MSI, based on a combination of magnetoencephalography (MEG) and MRI data, when used to map interictal epileptic activity, seems promising in retrospective studies, with higher seizure freedom rates if a computed dipole was concordant with other data than if dipoles were discordant or non-specific.<sup>98,99</sup> Electrical and magnetic source localisation are complementary and their combination improves the accuracy of source localisation and identification of propagated activity.<sup>100</sup>

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 because more prolonged recordings are feasible. The roles of these techniques in the presurgical

algorithm have not yet been established. For individuals with concordant MRI and ictal and interictal video EEG findings, further data are redundant. The patients who stand to benefit are those for whom there is not a clear surgical solution and who would need intracranial EEG to define the epileptogenic zone. Data from additional techniques can help to generate a hypothesis that can be tested with intracranial EEG and to identify patients in whom abnormalities are widespread and in whom invasive studies should not be done. Prospective studies to assess the role of these techniques in the presurgical algorithm will be challenging because 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 of postoperative follow-up would be needed. Each method would probably show some usefulness, with all three contributing to localisation of seizure source in some cases, and any one technique being uniquely helpful in a subset of patients.

## **Integration of multimodal three-dimensional imaging in the epilepsy surgery pathway**

In 20–30% of candidates for epilepsy surgery, intracranial EEG is needed to define the epileptogenic zone.<sup>101</sup> Increasingly, this is accomplished with stereotactic placement of several (ie, 12–20) depth electrodes (stereo-electroencephalography; SEEG). SEEG electrodes can be used to record from a 1 cm core around the cerebral entry point to the distal end (ie, target), which can be placed in the hippocampus, amygdala, or midline or inferior neocortex. Electrode implantation carries a risk of haemorrhage, neurological deficit, and infection.<sup>102</sup> Preoperative planning of electrode trajectories using multimodal 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. At present, standard clinical practice for planning electrode trajectories involves manual assessment of individual trajectories in series, which is a time-consuming and complex task that requires the integration of information across many imaging methods (figure 7). Optimisation of several parameters for each trajectory is necessary to reach the target, avoid critical structures, and obtain a suitable entry angle through the skull, and the different trajectories need to be adjusted to maximise grey matter sampling and avoid conflicts between electrodes. When placing a new electrode, adjustment of previously planned trajectories might be needed, making the planning process even more time-consuming.

Recently, substantial progress has been made in the development of 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 to inform manual trajectory selection.<sup>103–106</sup> This planning requires the integration of multimodal imaging data, with each single method being combined together into a patient-specific three-dimensional map of the brain. The most crucial data are from CT to show the skull surface, T1-weighted MRI for the grey matter map, and magnetic resonance angiography, CT angiography, or T1-weighted MRI with gadolinium

enhancement to show the arteries and veins. Different areas of interest indicated by fMRI, PET, or SPECT imaging can also be added to this three-dimensional map and included in the planning of different trajectories. Automatic solutions were recently assessed, showing the potential of these approaches in clinical settings.<sup>107</sup>

After intracranial electrodes have been placed, seizures can be documented with simultaneous videoing of the patient and EEG recording from the intracranial electrodes. Signals from the electrode contacts that record the earliest seizure activity are analysed, as is the subsequent spread of the activity. The area to be resected is decided after identification of the epileptogenic zone, taking into account the following: any structural lesion; the location of eloquent cortex, as inferred from fMRI and precisely located with electrical stimulation studies; crucial white matter tracts visualised with tractography; the major arteries and veins; and the location of any previous craniotomy and burr holes. Planning the surgical approach and the extent of the resection is particularly challenging if the epileptogenic zone is not located on the convexity of the cerebral hemisphere or if there is no evident lesion. The use of multimodal three-dimensional imaging to assist this planning has substantial promise, but one must 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 perspectives

Over the next decade, we anticipate increased availability of 7 T clinical MRI scanners with enhanced sensitivity and improved imaging technology, and development of new magnetic resonance contrasts and analyses that will improve detection of subtle lesions that underlie refractory focal epilepsies and that might be amenable to surgical treatment. With the implementation of uniform protocols for acquisition and processing, we expect that computerised analysis of the much larger datasets than are acquired at present will become standard, to achieve data reduction and detection of suspicious areas of focal abnormality for review by clinicians. Greater sensitivity is likely to be accompanied by reduced specificity; thus, thorough assessment of the relevance of possible abnormalities will be essential. High-field MRI of ex-vivo cerebral resection specimens will allow detailed MRI–histological correlation and has the potential to inform optimisation of MRI sequences for in-vivo use and identification and prediction of the nature of abnormalities. Integration of several structural and functional imaging datasets will become routine and will inform clinical decision making in the presurgical pathway, so that the risk–benefit ratio can be quantified and optimised for individual patients.

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**Panel 1: Glossary of MRI terms****Arterial spin labelling**

An MRI technique that is 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 (ie, sagittal, axial, and coronal) in which the brain is displayed at different depths from the surface, like the layers of an onion; this method enhances the localisation and detection of dysplastic lesions.

**Diffusion imaging**

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.

**Diffusion tensor imaging**

A development of diffusion-weighted imaging in which diffusion is measured in several directions in each voxel so that the predominant direction of diffusion can be established and used for tractography; further calculations can be used to derive quantitative tissue properties.

**Diffusional kurtosis imaging**

An extension of diffusion-tensor imaging methods that is used to measure both Gaussian and non-Gaussian distribution of diffusion to provide greater detail about complex tissue microstructure.

**Double-inversion recovery**

An MRI sequence with two additional pulses to suppress the signal from both white matter and CSF, which increases grey–white matter contrast and therefore facilitates the identification of grey matter lesions.

**Fluid-attenuated inversion recovery (FLAIR) imaging**

A T2-weighted sequence with an additional pulse to suppress the signal from CSF, which improves the identification of periventricular lesions.

**Intracarotid amobarbital test (Wada test)**

A procedure in which one hemisphere is temporarily anaesthetised by intracarotid injection of sodium amobarbital to measure the laterality of language and memory functions.

**Neurite orientation dispersion and density imaging (NODDI)**

An advanced model-based diffusion-weighted imaging method that is used to measure tissue properties such as intracellular volume fraction and the amount of dispersion of neurites (ie, axons and dendrites).

**Partial volume effects**

An artifact that leads to an error in characterisation of tissue type owing to the effects of averaging signal within a voxel as a result of limited resolution of the imaging system.

**Phased-array coil**

A type of MRI coil that receives signal to produce an image from several coils rather than a single coil to improve signal-to-noise ratio and facilitate faster imaging.

**Region-of-interest-based approach**

A type of analysis applied to MRI data in which a specific region (eg, the hippocampus) is delineated manually or automatically to measure a property of that region.

**Surface-based morphometry**

An approach to the study of brain shape and size (morphometry) that is used to investigate features of the brain surface such as cortical thickness and curvature.

**Susceptibility-weighted imaging**

A newer MRI technique than T2\*-gradient echo imaging that is sensitive to the effects of paramagnetic and diamagnetic compounds such as blood products and calcium; this method improves the identification of lesions such as cavernomas.

**T1-weighted imaging**

One of the basic MRI sequences that produces images in which contrast predominantly depends on the T1 relaxation times of the tissues; this weighting is typically used to emphasise anatomical structure.

**T2 relaxometry**

A quantitative MRI technique used to measure T2 relaxation, in contrast to methods that produce images qualitatively affected by T2 relaxation (T2-weighted imaging); the resulting maps are helpful for the identification of hippocampal sclerosis.

**T2-weighted imaging**

One of the basic MRI sequences that produces images in which contrast predominantly depends on the T2 relaxation times of the tissues; this weighting is typically used to emphasise pathological abnormalities.

**T2\*-gradient echo imaging**

A commonly used clinical MRI sequence that produces images sensitive to iron-containing compounds such as blood products; this method is helpful for the identification of vascular malformations and microbleeds.

**Tractography**

A non-invasive method to delineate white matter connections from diffusion-weighted imaging data; one approach is to trace the predominant direction of diffusion from diffusion-tensor imaging data.

**Volumetry**

The technique of measuring the volume of a structure, either manually or automatically; this method is useful for measuring hippocampal volumes to detect hippocampal atrophy.

**Voxel-based morphometry**

A statistical approach to the study of brain shape and size (morphometry) that enables comparisons of brain imaging data from groups of people or from an individual with reference to template images, to identify where focal changes occur in properties such as grey matter volume.

**Panel 2: MRI acquisition protocol for the identification of structural abnormalities in patients with epilepsy**

**Three-dimensional volumetric T1-weighted imaging (1 mm isotropic voxels)**

This method provides excellent grey–white matter contrast and allows the assessment of cortical thickness and detection of malformations of cortical development. Images can be reformatted into any plane and post-processing techniques can be used to improve detection of abnormalities.

**T2-weighted imaging (axial and coronal)**

This imaging method allows 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 images orthogonal to the long axis of the hippocampus.

**Fluid-attenuated inversion recovery imaging (axial and coronal)**

This imaging method is sensitive to hippocampal sclerosis, focal cortical dysplasia, tumours, inflammation, and scars.

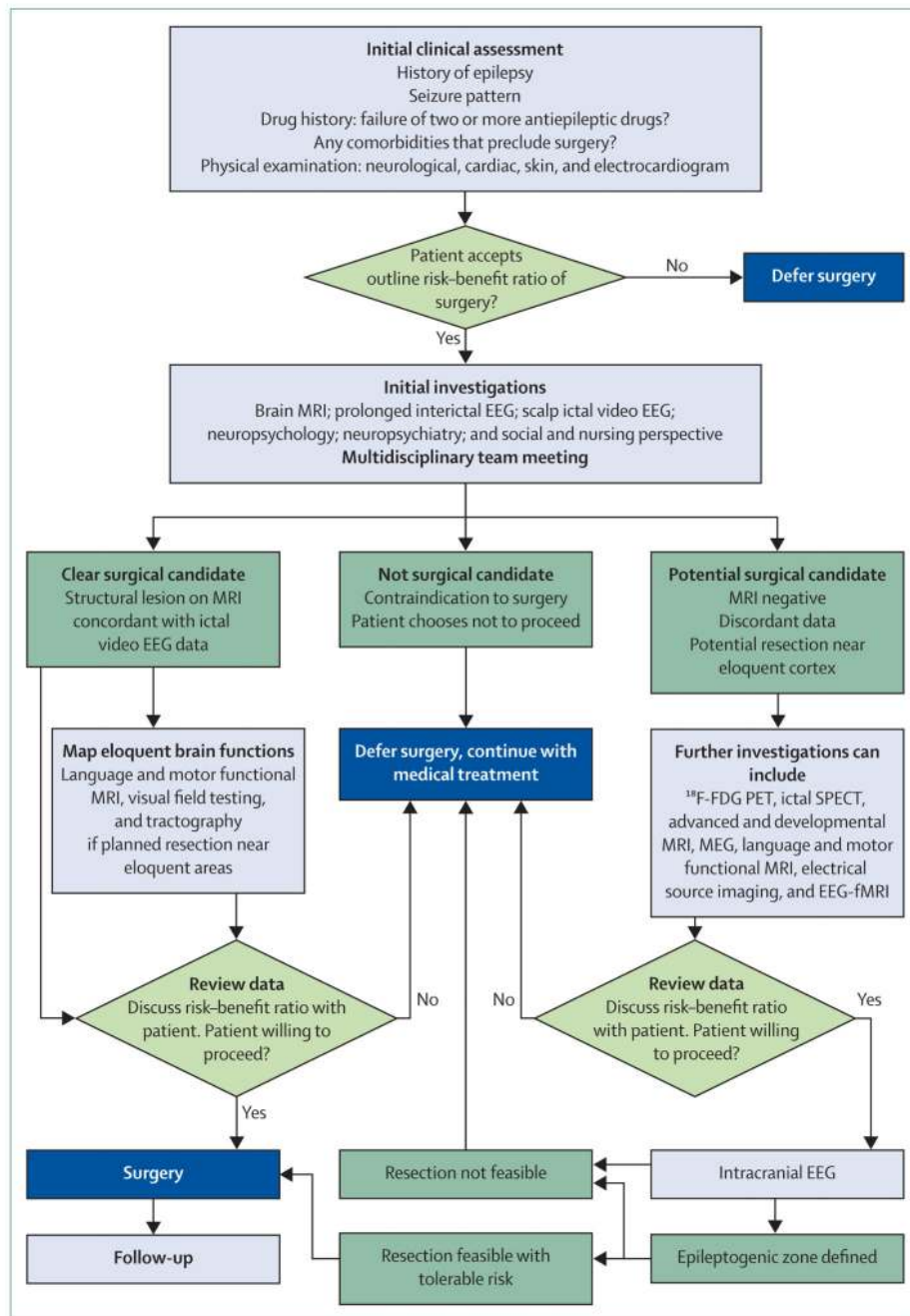
**T2\* gradient echo or susceptibility-weighted imaging (axial)**

This method is sensitive to calcified and vascular lesions, such as cavernomas and arteriovenous malformations.<sup>11</sup>

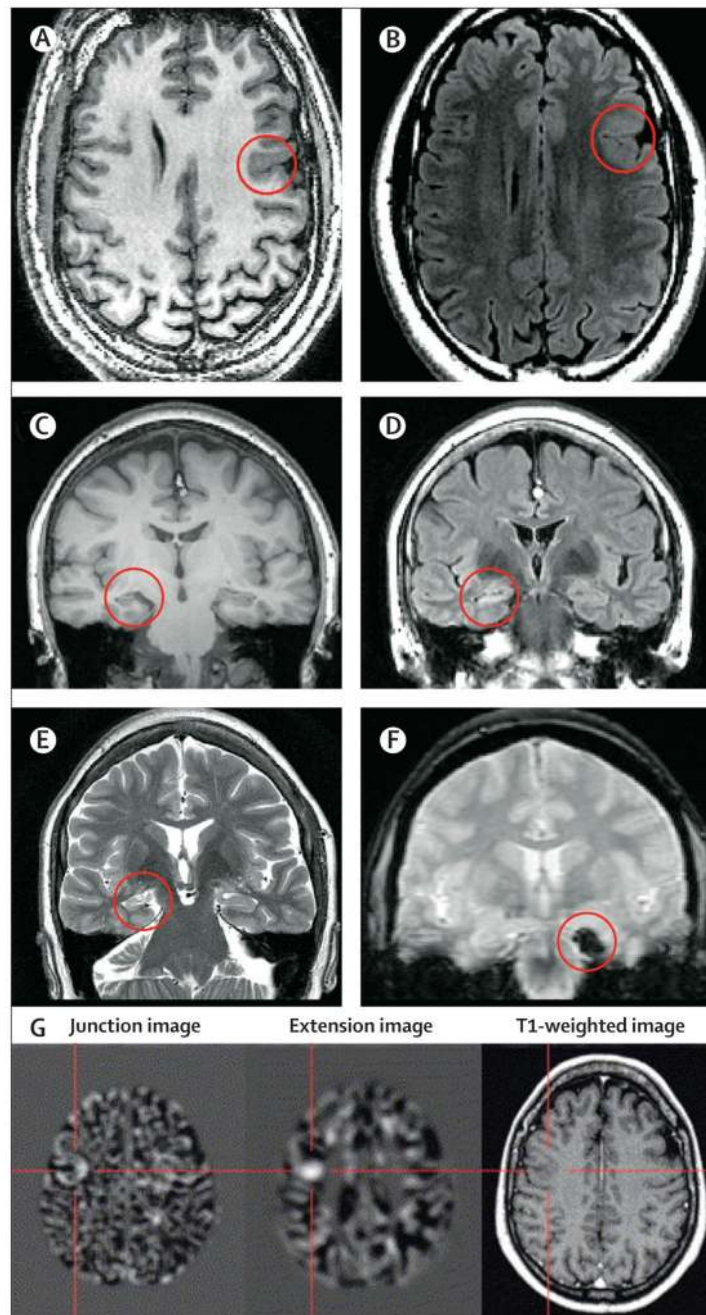


### Search strategy and selection criteria

We searched PubMed for English language articles published between Jan 1, 2005, and Nov 1, 2015, with the search terms “epilep\*” and one or more of “MRI”, “fMRI”, “functional MRI”, “PET”, “SPECT”, “MEG”, “electric\* source imaging”, “EEG”, “DTI”, “diffusion MRI”, and “surgery”. We also included key earlier references from the authors’ files. We selected reports for inclusion in this paper that we judged to be most relevant to clinical practice.



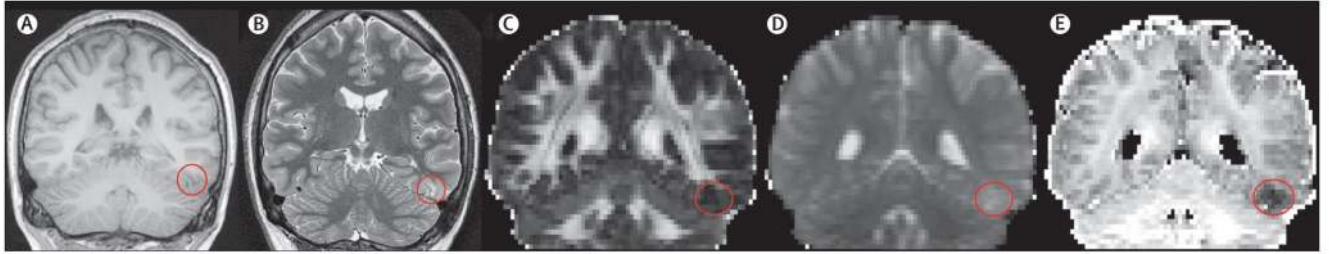
**Figure 1. The pathways of assessment for epilepsy surgery, showing the place of brain imaging**  
<sup>18</sup>F-FDG=<sup>18</sup>F-fluorodeoxyglucose. EEG=electroencephalography.  
 MEG=magnetoencephalography. Adapted from Duncan,<sup>4</sup> by permission of Elsevier.



**Figure 2. MRI acquisition protocols for the identification of structural cerebral abnormalities in epilepsy**

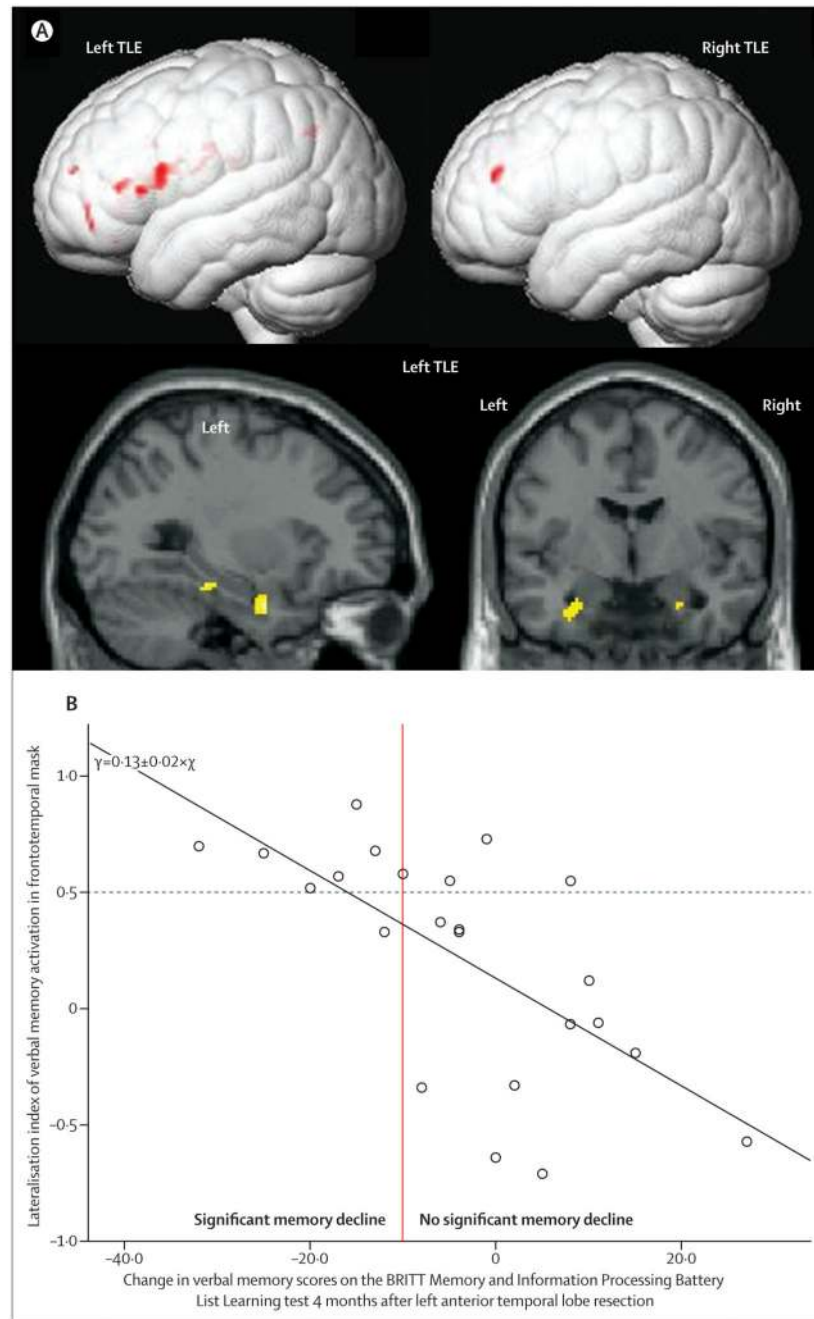
Focal cortical dysplasia with cortical thickening and a blurred grey–white matter junction (circled) on (A) T1-weighted imaging and (B) with high signal intensity on T2-weighted FLAIR imaging. Right hippocampal sclerosis with volume loss (circled) on (C) T1-weighted imaging, (D) with high signal intensity on T2-weighted FLAIR imaging, and (E) with loss of internal architecture on T2-weighted PROPELLER imaging. (F) A cavernoma in the left inferior temporal gyrus (circled) can be seen clearly as an area of signal dropout on T2\*-weighted images. (G) Application of a voxel-based image post-processing method to T1-

weighted three-dimensional MRI data from a 38-year-old woman enabled enhanced visualisation of focal cortical dysplasia on the resulting junction image (blurred grey–white matter junction) and extension image (grey matter extending abnormally into white matter). The corresponding slice is shown on the original T1-weighted image. (A–F) were acquired on a 3 T scanner with (A, C) a three-dimensional fast spoiled gradient echo T1-weighted sequence (0.9375 × 0.9375 mm in-plane resolution, 1.1 mm slice thickness), (B) an axial and (D) an oblique coronal T2-weighted FLAIR sequence (0.9375 × 0.9375 mm in-plane resolution, 5 mm slice thickness), (E) a coronal oblique T2-weighted PROPELLER sequence (0.43 × 0.43 mm in-plane resolution, 2 mm slice thickness), and (F) a coronal fast gradient recalled echo T2\*-weighted sequence (0.9375 × 0.9375 mm in-plane resolution, 5 mm slice thickness). For all images, left side of image=right side of brain. FLAIR=fluid-attenuated inversion recovery. PROPELLER=periodically rotated overlapping parallel lines with enhanced reconstruction. Panel G adapted from Huppertz and colleagues,<sup>10</sup> by permission of Elsevier.



**Figure 3. Neurite orientation dispersion and density imaging for the detection of focal cortical dysplasia**

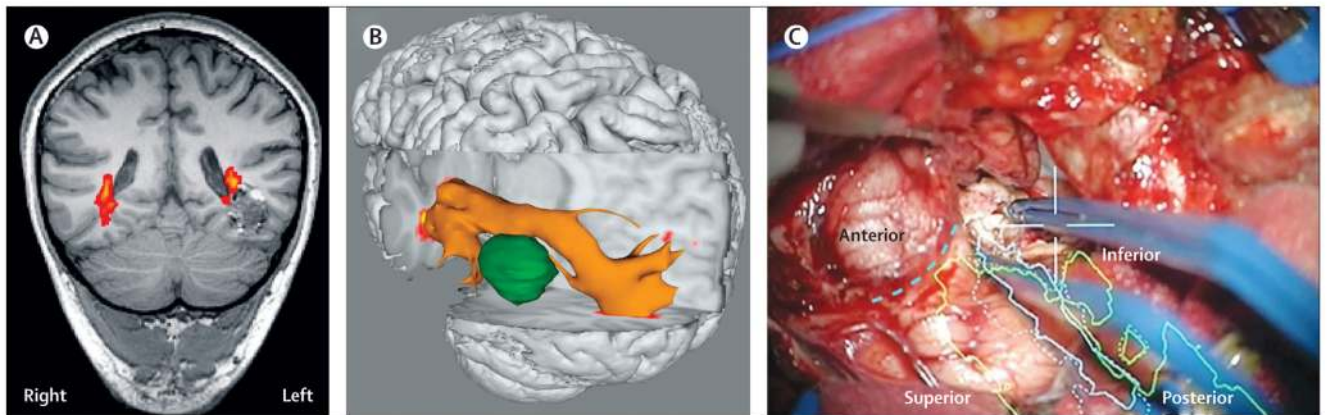
A 27-year-old male with focal cortical dysplasia in the left inferior temporal gyrus. The area (circled) is defined poorly on structural images including volumetric T1-weighted (A) and T2-weighted coronal oblique (B) images and on standard diffusion images including fractional anisotropy (C) and mean diffusivity (D) maps. Focal cortical dysplasia is easily visible as a reduced intracellular volume fraction on neurite orientation dispersion and density imaging, an advanced diffusion MRI sequence (E). Reproduced from Winston and colleagues.<sup>32</sup>



**Figure 4. Functional MRI for prediction of changes in verbal memory after temporal lobe surgery**

(A) Correlations between functional MRI activation in response to words remembered and postoperative verbal memory decline in patients with left TLE (n=23) and right TLE (n=27). In patients with both left TLE and right TLE, the surface-rendered whole-brain images (upper panel) show that left frontal activations were significantly correlated with greater postoperative verbal memory decline. No correlation was found in the right hemisphere in patients with left or right TLE. The sliced images (lower panel) show that predominantly left medial temporal lobe activations were significantly correlated with greater postoperative

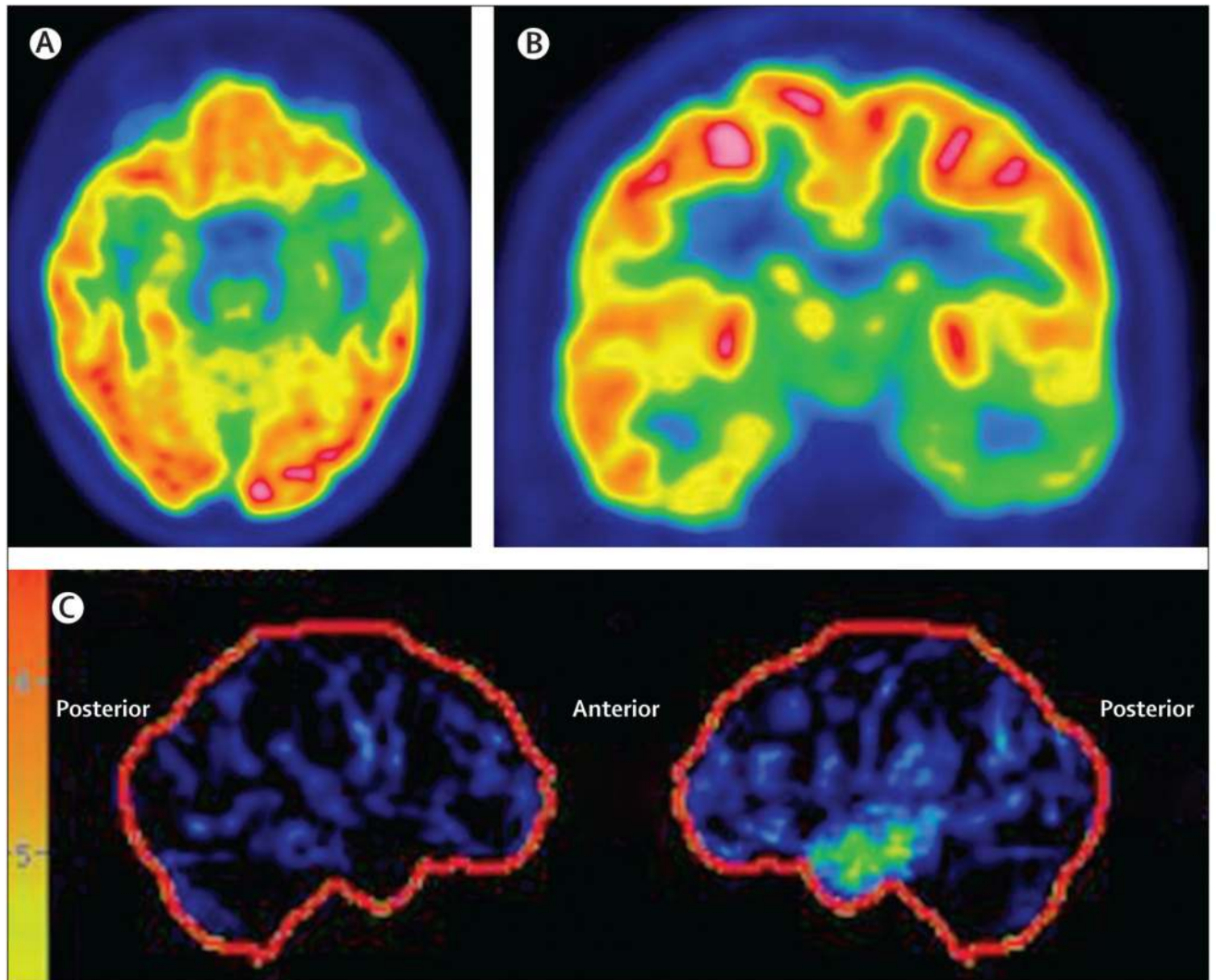
verbal memory decline in patients with left TLE. A similar correlation was not found for patients with right TLE. (B) Correlation of individual lateralisation indices for words remembered in the frontotemporal region (using an anatomical mask) in patients with left TLE (n=23) with change in list learning 4 months after left anterior temporal lobe resection ( $R^2=0.43$ ). Each circle represents one patient. The vertical red line shows the level of significant decline calculated by the reliable change index using control data. The horizontal dashed line shows a lateralisation index of 0.5 (left>right), with scores of  $\geq 0.5$  indicative of strong left lateralisation. Seven of eight patients who experienced a significant verbal memory decline had a lateralisation index of at least 0.5, which was the strongest predictor of postoperative verbal memory decline. TLE=temporal lobe epilepsy. Reproduced from Sidhu and colleagues,<sup>63</sup> by permission of Wolters Kluwer Health.



**Figure 5. Optic radiation tractography for surgical guidance**

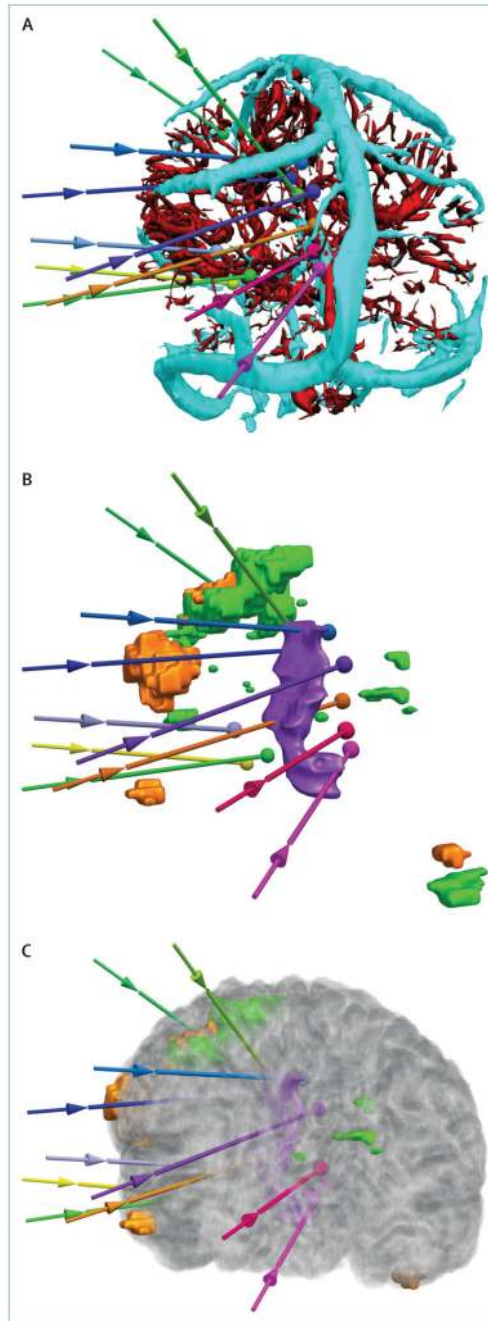
(A) Optic radiation tractography data can be superimposed on the coronal fluid-attenuated inversion recovery MRI scan to show the relation with a cavernoma to aid surgical planning and (B) can also be displayed in three-dimensional renderings. Panels A and B reproduced from Winston and colleagues,<sup>74</sup> by permission of John Wiley & Sons. (C) Tractography data can then be displayed on the operating microscope display in real time for surgical guidance. Panel C adapted from Winston and colleagues,<sup>75</sup> by permission of Wolters Kluwer Health.





**Figure 6.  $^{18}\text{F}$ -fluorodeoxyglucose PET imaging for the localisation of epileptogenic brain regions in MRI-negative focal epilepsy**

$^{18}\text{F}$ -fluorodeoxyglucose PET scan showing left temporal hypometabolism in a 32-year-old man with normal MRI and left temporal lobe epilepsy (A, axial slice; B, coronal slice). (C) Results of a statistical voxel-based comparison of surface-rendered glucose uptake in the patient, compared with a set of control data (using Neurostat-3D SSP software). An area of hypometabolism (green) is evident in the left temporal lobe (right panel). The patient became seizure free after left temporal lobe resection. Reproduced from Rathore and colleagues,<sup>80</sup> by permission of Elsevier.



**Figure 7. Integration of multimodal three-dimensional imaging in the epilepsy surgery pathway** Stereo-EEG implantation plan. Each electrode is depicted in a separate colour. All images are taken from the left posterolateral direction. (A) Veins (blue) extracted from gadolinium-enhanced T1-weighted MRI and arteries (red) extracted from CT angiogram. (B) A lesion identified from T2-weighted FLAIR MRI (purple) and motor (green) and language (orange) regions identified from functional MRI. (C) The lesion and motor and language regions in

(B) are shown on a volume-rendered T1-weighted MRI. FLAIR=fluid-attenuated inversion recovery.