Review

Epilepsy surgery in children and adults

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Epilepsy surgery is the most effective way to control seizures in patients with drug-resistant focal epilepsy, often leading to improvements in cognition, behaviour, and quality of life. Risks of serious adverse events and deterioration of clinical status can be minimised in carefully selected patients. Accordingly, guidelines recommend earlier and more systematic assessment of patients' eligibility for surgery than is seen at present. The effectiveness of surgical treatment depends on epilepsy type, underlying pathology, and accurate localisation of the epileptogenic brain region by various clinical, neuroimaging, and neurophysiological investigations. Substantial progress has been made in the methods of presurgical assessment, particularly in patients with normal features on MRI, but evidence is scarce for the indication and effect of most presurgical investigations, with no biomarker precisely delineating the epileptogenic zone. A priority for the development of epilepsy surgery is the generation of high-level evidence to promote the harmonisation and dissemination of best practices.

Introduction

Epilepsy surgery is now accepted for the management of drug-resistant focal epilepsy. Seizure freedom is achieved in a variable proportion of patients according to epilepsy type, underlying pathology, duration of follow-up, and series reported. In specific situations in which a surgical cure is not possible, palliative epilepsy surgery might be offered with the main aim of minimising the frequency and severity of seizures. Cognition, behaviour, and quality of life can improve substantially after epilepsy surgery, particularly in children. The risks of serious adverse events and deterioration of clinical status should not be neglected, but can be minimised in carefully selected patients in whom surgical treatment offers a favourable risk–benefit balance. Epilepsy surgery has consistently proved to be a cost-effective strategy in both adults and children.[1–3]

The location and volume of brain tissue to be surgically targeted is identified during presurgical assessment, and ranges from a few millimetres (eg, hypothalamic hamartoma) to an entire hemisphere (eg, hemimegalencephaly; figure 1). Delineation of the so-called epileptogenic zone (ie, the brain region for which resection or destruction or disconnection is both necessary and sufficient to ensure a surgical cure) is complicated by the absence of a gold-standard biomarker and paucity of evidence for the indications, methods of acquisition, and data analysis for most presurgical investigations.

In this Review, we focus on present indications for epilepsy surgery, state-of-the-art presurgical investigations, outcomes of epilepsy surgery, and postoperative management of antiepileptic drugs.

Indications and referral for epilepsy surgery

Current guidelines and recommendations

The first practice parameters for epilepsy surgery in adults were published by the American Academy of Neurology (AAN) in 2003 and have not since been revised.[4] These parameters were developed on the basis of a single class I randomised controlled trial for temporal lobe surgery and a further 24 class IV studies. For localised neocortical resections, eight class IV studies were considered. The panel concluded that "Patients with disabling complex partial seizures, with or without secondarily generalized seizures, who have failed appropriate trials of first-line antiepileptic drugs should be considered for referral to an epilepsy surgery centre (level A)". Although they outlined evidence available to recommend temporal lobe resection in individuals who met established criteria, it was accepted that there was "insufficient evidence at [that] time to make a definitive recommendation as to whether patients with a localized neocortical epileptogenic region will benefit or not benefit from surgical resection (level U)". The panel acknowledged limited applicability to children since paediatric series were excluded from the analysis of evidence. This restricted applicability was addressed by the International League Against Epilepsy (ILAE) Subcommission for Paediatric Epilepsy Surgery, who declined to recommend practice guidelines because of the absence of class I evidence in this age group, but did produce consensus recommendations.[5] Specifically, the ILAE recognised that the diversity of childhood epilepsy syndromes and the effect of uncontrolled seizures on cognitive and behavioural development should prompt timely assessment of children with drug-resistant epilepsy by paediatric specialty centers.[5]

Current trends in indications and referral patterns

Since the 2003 guidelines were published,[4] efforts have been made to promote and monitor increased and earlier access to epilepsy surgery. One important move forward has been the proposal of a working definition of drug resistance by the ILAE as "failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom".[6]

The Early Randomized Surgical Epilepsy Trial[7] compared early surgical with continued medical treatment in patients with mesial temporal lobe epilepsy, hippocampal sclerosis, and disabling drug-resistant seizures for less than 2 consecutive years. Despite a much lower enrolment rate than initially planned, the benefits of early surgery were shown: none of the 23 patients in the medical group and

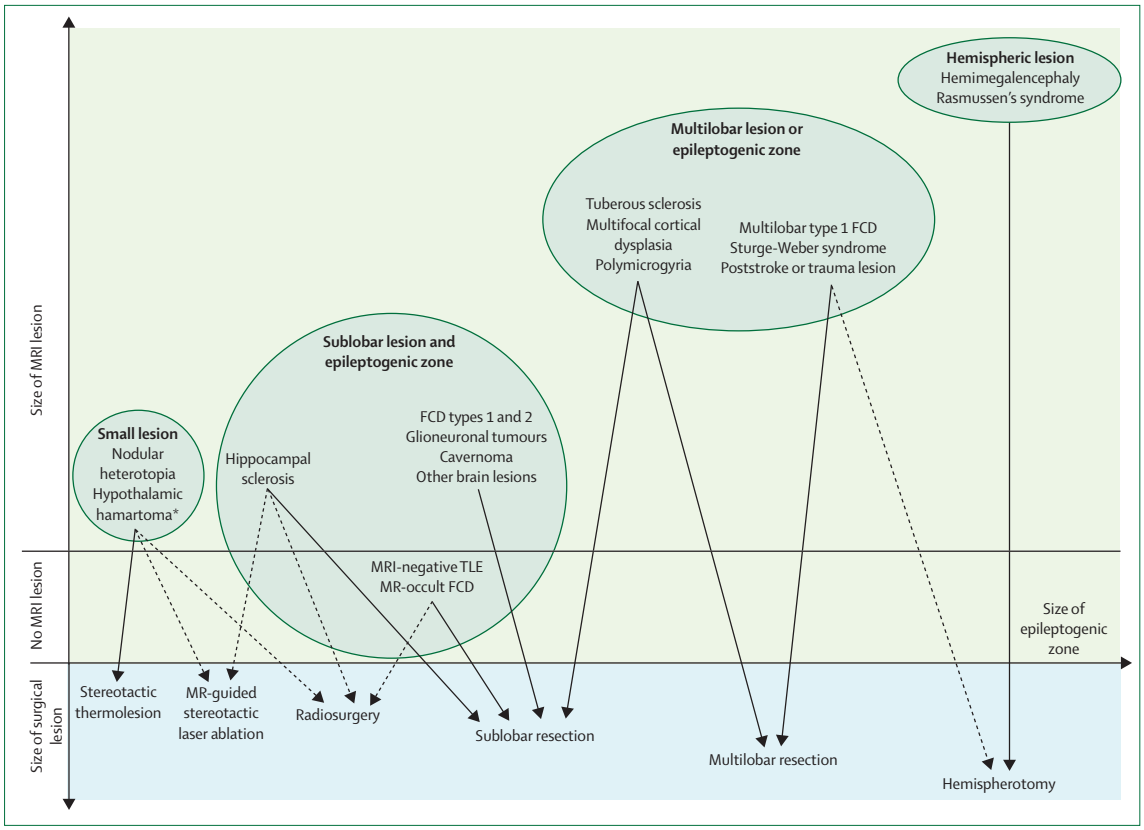

Figure 1: **Indications for the various forms of epilepsy surgery**
Indications are shown according to the cause of epilepsy, size of the MRI lesion, and size of the epileptogenic zone. Dotted arrows represent surgical indications that remain exceptions compared with those delineated by solid arrows. FCD=focal cortical dysplasia. MR=magnetic resonance. TLE=temporal lobe epilepsy, FCD=focal cortical dysplasia. *Can additionally be treated with surgical disconnection or resection, with or without an intraventricular endoscopic approach.

11 of the 15 in the surgical group were seizure free during the 2 years of follow-up (odds ratio ∞, 95% CI 11·8 to ∞, p<0·001). Greater improvement in quality of life was also seen in operated patients. In terms of serious adverse events, surgery caused a verbal memory decrease in 36% of operated patients and transient neurological deficit due to postoperative stroke for one patient, whereas three patients from the medical group had status epilepticus.

The difficulty in recruitment of individuals to this study echoes the fact that the duration from diagnosis of epilepsy to referral for surgery remains steadily high. At Columbia University (New York, NY, USA), this duration was a mean of 22·6 (SD 12·7) years from 1996 to 1999 and 21·1 (14·2) years from 2004 to 2007,[8] which are the respective periods before and after the publication of the 2003 AAN practice parameters on epilepsy surgery.[4] Similarly, at the University of California, Los Angeles (CA, USA), the mean duration was 17·1 (SD 10·0) years from 1995 to 1998 and 18·6 (12·6) from 2005 to 2008.[9] However, this apparent stability might mask dual changes that associate earlier referral of straightforward temporal lobe epilepsy together with more delayed assessment of complex cases previously deemed to be non-operable.[9] In the paediatric population, an international survey of epilepsy surgery centres[10] showed that only a third of children had proceeded to surgery within 2 years of epilepsy onset, despite this onset having occurred at less than 2 years of age in 60% of the children.

These findings do not seem to be because of restricted access to epilepsy centres. On the contrary, findings from a survey of the Nationwide Inpatient Sample of non-federal US hospitals[11] showed that admissions for medically refractory focal epilepsy doubled between 1990 and 2008, although admissions at the highest-volume epilepsy centres have decreased by 50% during the same period. Furthermore, the overall number of surgical procedures remained stable, possibly because of the fact that low-volume and less experienced centres are less inclined to proceed to surgery after presurgical assessment.[11]

Other data even suggest that what might be regarded as classic epilepsy surgery disorders are less common, particularly mesial temporal lobe epilepsy. The Rochester Epidemiology Project[12] based in Olmsted County (MN, USA) reported that referral for anterior temporal lobectomy decreased from 1·9 to 0·7 per 100 000 person-years between 1993–2000 and 2001–09. Similarly, nationwide

Panel 1: **Specific epilepsy surgery issues in children**

General considerations

- Children should be assessed in a paediatric specialist epilepsy unit[5,18]
- Presurgical assessment should be done as early as possible in appropriate surgical candidates[5,18]
- Shortening the duration of epilepsy might result in improved long-term seizure outcome[5,19]
- Early surgery might improve cognitive development and quality of life in children[5,19–21]
- Developmental delay or psychiatric morbidity do not contraindicate paediatric epilepsy surgery[19,22–26]
- Optimised MRI and review is essential in young children to detect epileptogenic lesions[5,18]
- Diffuse electroencephalogram abnormalities, including early-onset catastrophic epilepsy, can be seen in children with resectable focal brain lesions[5,26–28]

Specific indications

Focal epileptogenic lesions can be associated with developmental regression[5,19]

- Hypothalamic hamartoma
- Glioneuronal tumours

Tailored resection of the epileptogenic lesion can be effective in multifocal or multilobar lesions[5,26,29–31]

- Tuberous sclerosis
- Sturge-Weber syndrome
- Multifocal cortical dysplasia

Hemidisconnection can control seizures and prevent severe comorbidity, especially cognitive deficits[5,24–26,30]

- Unilateral congenital ischaemic lesions
- Hemimegalencephaly
- Hemipolymicrogyria
- Sturge-Weber syndrome
- Rassmussen's syndrome

Surgical treatment of an epileptogenic lesion can be offered with the main aim of cognitive progress restoration in specific situations such as electrical status epilepticus of slow-wave sleep and related regression of cognitive development[32,33]

prospective surveys of British epilepsy neurosurgeons showed a decrease in annual adult temporal lobe epilepsy surgery from 0·71 per 100 000 person-years in 2000 to 0·37 per 100 000 in 2011.[13] A similar decrease, from 0·22 to 0·12 per 100 000 person-years, was seen for extratemporal resections.[13] Since most of these surgical procedures are done in patients with childhood-onset epilepsy, the downward trend might partly be due to the development of paediatric epilepsy surgery, leaving fewer adults with refractory epilepsy later in life.

In children, the incidence of childhood-onset drug-resistant focal epilepsy estimated from a US community-based cohort was 11·3 per 100 000 per year, whereas that of epilepsy-related surgical procedures in the same population, excluding vagus nerve stimulation, was 1·3 per 100 000 per year.[14] Accordingly, a 2011 British survey reported 1·0 per 100 000 epilepsy surgery procedures in children in the assessment period, again excluding vagus nerve stimulation.[13] The ninefold difference between the incidence of refractory focal epilepsy and annual number of epilepsy surgeries might be due partly to suboptimum access to comprehensive assessment, which is offered to only 45% of children with drug-resistant epilepsy.[14]

By contrast with the trends seen in the UK and the USA, epilepsy surgery has undergone rapid development in countries with restricted resources, but with substantial variability between countries and specific challenges in terms of access to expensive presurgical investigations.[15,16]

In adults, most procedures are temporal lobe resections, with lower numbers of extratemporal resections and very few multilobar procedures or hemispherectomies.[13,17] By contrast, a survey of epilepsy surgery done in children in the USA, Europe, or Australia showed most procedures to be multilobar or hemispherotomies, with temporal lobe resections accounting for only 23%. The three leading pathologies were cortical dysplasia (42%), tumours (19%), and stroke or atrophic lesions (10%).[10] Panel 1 summarises specific issues relating to epilepsy surgery in children.

Novel concepts in epilepsy surgery

Novel epilepsy surgery indications or approaches have emerged during the past 5 years, prompted by progress in our understanding of some epileptic disorders or in surgical methods. One growing concept is that successful epilepsy surgery outcome can be achieved in some patients with electroencephalography (EEG) or MRI abnormalities that are more widespread than the region that can be safely resected. This concept is shown by early-onset catastrophic epilepsies in which generalised semiology and EEG abnormalities can manifest in the presence of a definitive localised or lateralised brain lesion;[26] by tuberous sclerosis with many lesions or multifocal cortical dysplasia, in which resection of the most epileptogenic lesion can lead to seizure control;[27] and by unilateral or bilateral polymicrogyria, in which partial lesionectomy, guided by intracerebral EEG, often leads to seizure freedom.[28] However, the specific nature of the above disorders and the general rule that completeness of lesionectomy is associated with better seizure outcome in most circumstances should be acknowledged.

The substantial proportion of failed temporal lobe epilepsy surgeries remains a challenge, showing indirectly the many epileptogenic networks and disorders underlying or mimicking mesial temporal lobe epilepsy.[34,35] One such proposed disorder has been termed temporal plus epilepsy to account for the epileptogenic zone mainly including temporal lobe structures, but extending outside the boundaries of the anterior temporal lobe, up to the temporo–parieto–occipital junction, the insula and suprasylvian operculum, and orbitofrontal cortex.[36]

The development of stereotactic thermoablation, done at the end of a stereoelectroencephalography (SEEG) procedure, has allowed safe and effective treatment of patients with a single periventricular heterotopic nodule.[37] Although promising in this indication, thermo-ablation remains limited by the shape and size of the

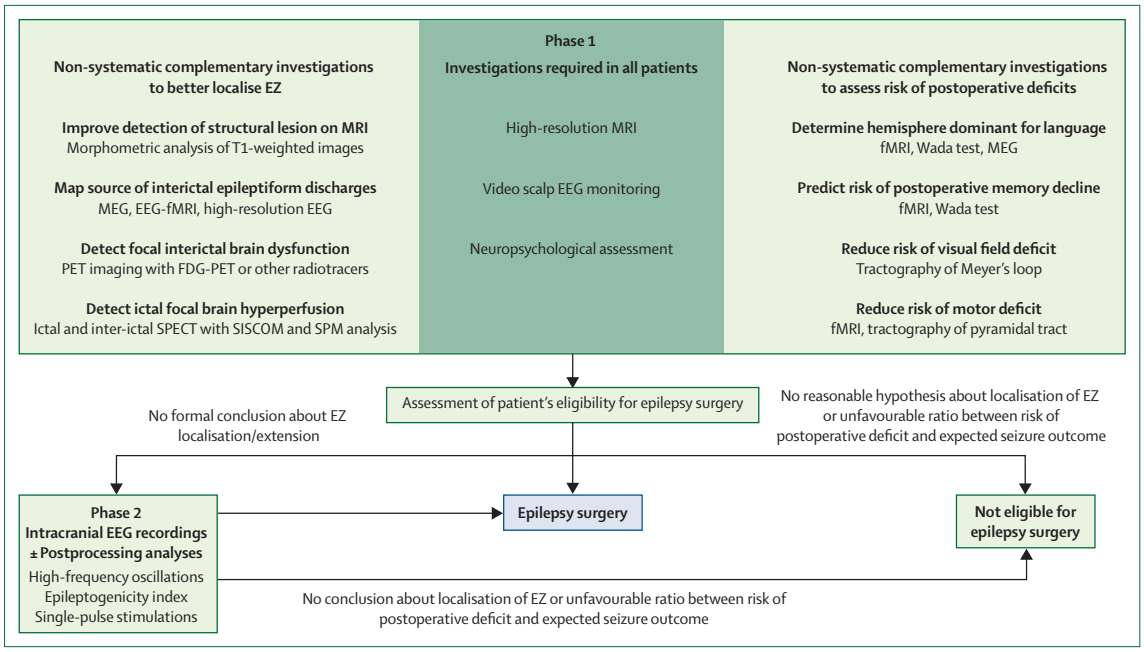

Figure 2: **Role of and indications for available presurgical investigations**
Phase 1 investigations are undertaken to localise the EZ and to assess the suitability of the patient for surgery. Phase 2 investigations are recommended to more clearly delineate the EZ if the risk:benefit ratio is acceptable. EEG=electroencephalography. EZ=epileptogenic zone. ^{18}F-FDG=^{18}F-fluorodeoxyglucose. fMRI=functional MRI. MEG=magnetoencephalography. SISCOM=subtraction ictal SPECT coregistered with MRI. SPECT=single-photon emission CT. SPM=statistical parametric mapping.

resulting spherical lesion, 5–7 mm in diameter, between the heated bipolar contacts.[38] Conversely, the development of magnetic resonance-guided stereotactic laser ablation offers the potential to target larger epileptogenic foci of various shapes.[39]

This approach was tested in five children with refractory epilepsy that resulted from hypothalamic hamartoma, focal cortical dysplasia, tuberous sclerosis, or hippocampal sclerosis, leading to seizure freedom in all cases;[40] in two adults with periventricular nodular heterotopias who also achieved seizure freedom;[41] and in 13 adults with mesial temporal lobe epilepsy, including nine with hippocampal sclerosis.[42] In the last series, a mean 60% of the volume of the amygdalohippocampal complex was ablated, resulting in seizure freedom in 54% of cases.[42]

Presurgical investigations

General issues

The general concept of presurgical investigation has remained unchanged for decades, and is summarised in figure 2. The main objective is to identify the brain regions that need to be resected, destroyed, or disconnected to offer the optimum chance of seizure freedom, and to minimise the risk of postoperative neurological or cognitive deficit.

As previously mentioned, no one biomarker allows this issue to be comprehensively addressed. Rather, complementary investigations need to be done to assess the different dimensions of the epileptogenic zone. These include the presence of an underlying lesion, usually delineated by MRI and viewed as the cause of the seizure disorder, and the areas of ictal onset, typically defined by seizure phenomenology, scalp EEG or, to some degree, ictal single-photon emission CT (SPECT), and, ultimately, intracranial EEG. Areas of interictal brain dysfunction should be established by neuropsychology, scalp EEG, magnetoencephalography (MEG), functional MRI (fMRI) coupled with EEG, PET using ^{18}F-fluorodeoxyglucose (^{18}F-FDG) or other tracers, or, ultimately, intracranial EEG. Finally, the functional role of all above regions can be assessed by neuropsychology, fMRI, diffusion tensor imaging, MEG, Wada test, and electrical brain stimulation.

The epileptogenic zone cannot be defined solely by the areas of ictal onset seen in such investigations because of the restricted temporal or spatial resolution of available methods, and the possibility that part of an epileptogenic brain lesion, not implicated at the onset of preoperatively recorded seizures, might generate seizures postoperatively, if spared by surgery. Structural and functional interictal abnormalities therefore serve as surrogate markers of the epileptogenic zone.

However, the level of evidence for the use of each of the above techniques remains low.[4] A comprehensive and well designed systematic review of non-invasive presurgical investigations other than standard EEG and MRI[43] identified no randomised controlled trial assessing the clinical effectiveness or diagnostic

accuracy of these methods, no cohort study comparing outcomes between patients who received different combinations of imaging techniques, and only one study reporting the effect of ^{18}F-FDG-PET on the decision-making process.

With these limitations in mind, the 2006 recommendations of the ILAE Subcommission for Pediatric Epilepsy Surgery[5] concluded that: interictal scalp EEG (including sleep-EEG), a dedicated MRI protocol for epilepsy, and neuropsychological assessment, are mandatory; video scalp EEG recording of seizures is strongly recommended; and access to functional imaging should be possible when judged necessary. They have also assessed the relative role of additional investigations for specific disorders in children.[18]

These pragmatic recommendations reflect the practice of most epilepsy surgery centres at present, which do a phase 1 assessment, including MRI, long-term video scalp EEG monitoring to capture interictal abnormalities and seizures, and neuropsychological assessment in every surgical candidate, whereas other investigations are either patient or centre selective (figure 2). In particular, intracranial EEG recording, referred to as phase 2, should only be done in patients if the conclusion of non-invasive data does not allow them to proceed directly to surgery, but provides reasonable hypotheses for the localisation of the epileptogenic region to be tested with depth or subdural electrodes.

Recent progress in presurgical investigations

We will only briefly review the most relevant data published during the past 5 years in this section, with the understanding that no recommendation is available for the use of these techniques.

The detection of focal cortical dysplasia not seen on standard visual analysis of MRI (MR-occult focal cortical dysplasia) can be substantially improved by optimum fluid-attenuated inversion recovery (FLAIR) imaging using 3T MRI and various postprocessing methods, including curvilinear reformatting and morphometric analysis of FLAIR or T1-weighted images.[44–47] Additionally, tractography of the Meyer's loop can be used to reduce the risk of superior quadrantic visual field deficit,[48] a frequent complication of anterior temporal lobectomy that can be severe enough to preclude driving.[49] Indeed, the two main predictors of postoperative visual field defect are preoperative distance from the tip of Meyer's loop to the temporal pole, which is reported to range from 24 to 43 mm, and size of resection.[50]

Several techniques have been developed to map the source of interictal epileptiform discharges (IEDs), including high-resolution EEG coupled with electrical source imaging, MEG with magnetic source imaging, and EEG-fMRI. All these methods underwent validation studies showing that IED-related abnormalities had high spatial concordance with the epileptogenic zone, as defined by other methods, or with IEDs recorded with intracranial EEG;[51–54] and that the greater the overlap between the area of IED-related abnormalities and the resected brain region, the better the seizure outcome.[52,53,55]

For electrical source imaging, the number of recorded EEG channels is reported to be instrumental, with much higher sensitivity for recordings with 128 or more channels than for those with 32 or fewer channels (ie, 84% *vs* 58%).[52] MEG was more sensitive for the detection of interhemispheric and frontal orbital IEDs (≥90% sensitivity) than for the capture of mesial temporal spikes (25% sensitivity).[51] Progress in the discipline of EEG-fMRI includes the development of methods to overcome the absence of visually detectable IEDs during the fMRI session using voltage maps previously built from the average of many IEDs as the regressor of haemodynamic changes.[56]

^{18}F-FDG-PET assesses aspects of interictal brain dysfunction distinct from those assessed by IEDs, and has proved to be particularly useful in MRI-negative patients by often showing hypometabolism predominating in the epileptogenic lobe. In those with presumed temporal lobe epilepsy, the presence of temporal hypometabolism ipsilateral to the suspected seizure onset zone is associated with better outcome[57] and rates of seizure freedom are similar to those of patients with hippocampal sclerosis on MRI.[58] In patients with MRI-negative neocortical epilepsies, ^{18}F-FDG-PET coregistered on MRI helps to detect occult focal cortical dysplasia,[59] reducing the proportion of patients needing intracranial EEG investigation (figure 3). Accordingly, ^{18}F-FDG-PET has been reported to substantially affect surgical decision-making.[43,60]

Ictal SPECT can show focal hyperperfusion at the seizure focus. The main advance in the discipline is the development of more effective postprocessing analysis than the standard subtraction of ictal and interictal SPECT from the same patient coregistered with MRI (SISCOM). For example, in one study, individual SISCOM patients' data were compared with the random variation from one SPECT study to another in healthy volunteers, improving interobserver agreement, sensitivity, and rate of correct identification of temporal lobe epilepsy subtypes.[61] In patients with MRI-negative temporal lobe epilepsy, resection of the hyperperfused brain region delineated by this method was associated with an excellent postoperative seizure outcome ($p=0\cdot005$), whereas this association was not true for standard SISCOM findings.[62]

The question of which hemisphere is dominant for language is often raised during presurgical assessment, and is now routinely assessed with fMRI rather than the invasive Wada test. The reliability of language fMRI has been assessed in many studies, including a meta-analysis of 22 series that included 504 patients with epilepsy who also underwent a Wada test.[63] This study confirmed that fMRI is highly reliable when showing clearcut dominance for language within the left

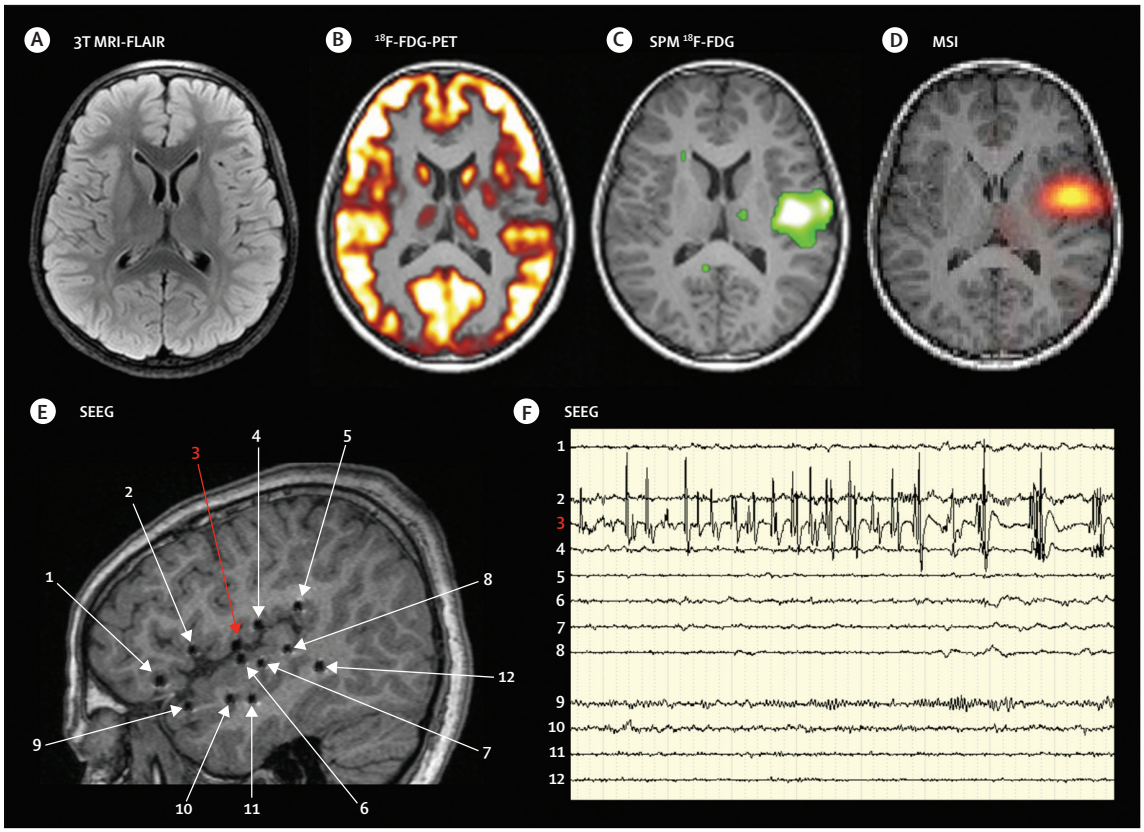

Figure 3: **Presurgical investigations in a patient with refractory epilepsy symptomatic of an MRI-occult type 2 focal cortical dysplasia in the frontal operculum on the side dominant for language.**
(A) 3T MRI with axial FLAIR sequence with no detectable abnormality over the left perisylvian region; (B) ^{18}F-FDG-PET coregistered on MRI, showing marked glucose hypometabolism over the left perisylvian region, with well delineated borders; (C) SPM-^{18}F-FDG-PET findings compared with healthy controls, indicating that maximum hypometabolism affects the superior and posterior aspect of the perisylvian region, including the insula; and (D) MSI deriving from magnetoencephalography recording with synthetic aperture magnetometry coregistered on MRI, showing a focus of interictal discharges over the same region. (E) and (F) SEEG procedure and findings. (E) The 12 intracerebral electrodes implanted in the left hemisphere appear as black dots (susceptibility artefacts) on a sagittal T1-weighted MRI. Anatomical targets were the following: (1) posterior frontobasal cortex; (2) pars opercularis of inferior frontal gyrus; (3) anterior portion of frontal operculum (red); (4) posterior portion of frontal operculum; (5) parietal operculum; (6) and (7) midportion of temporal operculum; (8) posterior portion of temporal operculum; (9) temporal pole; (10) and (11) anterior portion of midtemporal gyrus; (12) posterior portion of midtemporal gyrus. Note that the deepest contacts of electrodes 2–8 sample the insula, whereas those of electrodes 10–12 sample the amygdala and hippocampus. (F) Interictal recording from the 12 implanted electrodes, displaying a permanent focus of high-voltage spikes selectively over the anterior portion of the frontal operculum (electrode 3). This region was resected, leading to the diagnosis of MRI-occult type 2 focal cortical dysplasia and long-term seizure freedom without language deficit. ^{18}F-FDG=^{18}F-fluorodeoxyglucose. FLAIR=fluid-attenuated inversion recovery. MSI=magnetic source imaging. SEEG=stereoelectroencephalography. SPM=statistical parametric mapping.

hemisphere. However, in patients with atypical dominance for language or severe developmental delay, a Wada test can be useful to ascertain lateralisation of language functions.[63,64] Functional transcranial doppler sonography and MEG are being developed to lateralise dominance for language using various stimuli, including passive verbal auditory tasks not requiring participation from the subject.[65,66]

In patients with mesial temporal lobe epilepsy, fMRI is being developed to predict risk of postoperative memory decline. Currently available data suggest that postoperative memory decline is associated with the extent of preoperative asymmetry in hippocampal activation after an encoding task.[67] At the individual level, asymmetry of hippocampal activation coupled with neuropsychological data has been shown to predict clinically significant verbal memory decline in all patients undergoing resection of their left dominant temporal lobe. By contrast, such prediction could not be achieved for visual memory decline after right temporal lobe epilepsy surgery.[67] Similar findings were reported with an equation integrating the side of EEG focus, left mesial temporal fMRI activation during a delayed recognition task, and preoperative global verbal memory score.[68]

Several methods have been developed to enrich the information derived from intracranial EEG recordings. These include the following: detection of interictal bursts of abnormal high-frequency oscillations, defined as ripples (80–250 Hz) and fast ripples (250–500 Hz), which have proved to be more reliable as markers of the

epileptogenic zone than IEDs;[69–71] quantification of a so-called epileptogenicity index, indicating the propensity of sampled brain regions to generate fast EEG discharge and their time of involvement during seizures;[72] and single-pulse electrical stimulations that might allow generation of abnormal evoked potentials or high-frequency oscillations when the epileptogenic zone is stimulated or recorded.[73,74]

Overall, substantial methodological developments have occurred during the past 5 years. However, most of these advances need noncommercial postprocessing methods and substantial time and effort of dedicated staff with high-level expertise. These developments foster technical progress in the epilepsy discipline, but they also aggravate the heterogeneity of practices across centres and further complicate attempts to harmonise these practices.[75]

Epilepsy surgery outcome and its predictors

A 2005 meta-analysis of epilepsy surgery[76] reported that the median proportion of long-term seizure-free patients was 66% with temporal lobe resections, 46% with occipital and parietal resections, and 27% with frontal lobe resections. Spencer and Huh[30] concluded in their 2008 Review of epilepsy surgery outcome that the rate of postoperative seizure freedom after at least 1 year of follow-up was 53–84% in patients with mesial temporal lobe epilepsy, 36–76% in patients with localised neocortical epilepsy, and 43–79% in patients undergoing hemispherotomy. We will emphasise knowledge accumulated since 2008 in this section. If not otherwise specified, seizure freedom will refer to the absence of disabling seizures with or without non-disabling simple focal seizures since surgery.

Seizure outcome in temporal lobe epilepsy surgery

Studies of outcome after temporal lobe epilepsy surgery have recently concentrated on long-term follow-up and on MRI-negative patients; these studies have confirmed the large range of outcomes noted in 2008, which is still unexplained.[30] In a series of 497 anterior temporal resections, the estimated seizure-free rate 10 years after surgery was 49% (95% CI 44–54),[17] whereas a smaller study reported an 83% rate of seizure freedom at a mean follow-up of 9·6 years.[77] Outcomes were similar in patients younger or older than 50 years.[77]

In patients with MRI-negative temporal lobe epilepsy, long-term postoperative seizure-free rates vary from 40% to 60%.[57,58,78,79] In one study,[58] seizure-free rates at 5 years of follow-up were similar in patients with mesial temporal lobe epilepsy with or without MRI signs of hippocampal sclerosis. Predictors of successful outcome in MRI-negative patients include positive histology,[80] absence of contralateral or extratemporal IEDs and concordant SISCOM,[78] congruent temporal hypometabolism on ^{18}F-FDG-PET,[57,58] low baseline seizure frequency, and absence of preoperative generalised tonic-clonic seizures (panel 2).[79]

The absence of psychiatric history has been reported as an independent predictor of favourable outcome after temporal lobe epilepsy surgery,[82] but this remains disputed.[91] Younger age at surgery might also be associated with a more favourable outcome. The authors of a study of children who underwent temporal lobe resection and were followed to adulthood[81] suggested seizure-free rates of 85%. Type of temporal lobe epilepsy surgery also seems to affect outcome. Two meta-analyses showed that anterior temporal lobectomy might be more effective than selective amygdalohippocampectomy, with a risk ratio of 1·32 (95% CI 1·12–1·57, p<0·01)[83] and an odds ratio of 0·65 (95% CI 0·51–0·82, p=0·0005),[92] respectively.

Seizure outcome in extratemporal lobe surgery and malformations of cortical development

Extratemporal resections remain less effective than temporal lobe epilepsy surgery, and are characterised by large differences in outcome between series. In a study of 81 patients,[93] the seizure-free rate 5 years after surgery was 14·7% (95% CI 8–23). By contrast, the estimated chance of seizure freedom without aura at 5 years of follow-up and beyond was 44% (95% CI 39–49) in a series of 158 patients who underwent frontal lobe surgery.[86] Two other series of frontal lobe surgery reported seizure-free rates of 41%[90] and 38%[87] at 9 years of follow-up, one of which included only MRI-negative patients.[87] For epilepsy surgery in the posterior cortex, postoperative seizure-free outcome at 5 years of follow-up has been reported at 65·8%, but with important differences between parietal resections (52%) and occipital (89%) or parietooccipital (93%) surgery.[94]

Predictors of poor outcome were the presence of focal cortical dysplasia type 1 and incomplete resection of the epileptogenic zone,[93] absence of focal IEDs on scalp EEG,[87] and longer epilepsy duration (panel 2).[86] Conversely, the presence of a focal MRI abnormality has not been significantly associated with outcome.[90]

Multilobar resection and hemidisconnection procedures are more common in children, and seem to have substantial benefit in selected individuals, even in the presence of progressive pathological changes (eg, Rasmussen's syndrome), both in the short[25] and long[24] term.

Although most malformations of cortical development lie in extratemporal brain regions, the chance of a favourable outcome after their resection seems higher than that of extratemporal lobe surgery in general. In a series of 143 resected malformations of cortical development,[95] seizure-free rate at 10 years of follow-up was 67% according to the ILAE classification. Even better results were reported in a study of focal cortical dysplasia type 2B,[88] with up to 92% of patients achieving seizure freedom after a mean follow-up of 4 years, and no difference between MRI-positive and MRI-negative patients. The main predictor of surgical success has been shown to be complete resection of both the focal cortical dysplasia and associated epileptogenic zone.[89,95,96]

Seizure outcome in glioneuronal tumours and tuberous sclerosis

Seizure-free rates were 83% in a series of 78 patients with dysembryoplastic neuroepithelial tumours[97] and 80% in a meta-analysis of 39 studies of 910 patients with either dysembryoplastic neuroepithelial tumours or ganglioglioma.[98] These two types of glioneuronal tumour shared similar prognosis.[98] Both studies showed completeness of tumour resection and short duration of epilepsy to predict favourable seizure outcome.[97,98]

A meta-analysis of epilepsy surgery for tuberous sclerosis[29] analysed 20 articles reporting on 181 participants. Seizure freedom was achieved in 56% of patients and predicted by the absence of generalised seizures, the absence or mild presence of developmental delay, and the presence of unifocal ictal scalp EEG onset concordant with MRI findings. Similar findings (67% seizure free) were reported in a series of 28 children with tuberous sclerosis operated on the basis of non-invasive investigations only, including magnetic source imaging and ^{18}F-FDG-PET.[31]

Seizure outcome after radiosurgery

The role and effectiveness of epilepsy radiosurgery are disputed, despite experimental and clinical evidence of its antiepileptic properties.[99] A multicentre prospective randomised study assessed 20 Gy and 24 Gy 50% isodose radiosurgery centred on the amygdala, 2 cm of the anterior hippocampus, and the parahippocampal gyrus, in 30 patients with mesial temporal lobe epilepsy.[100] At 3 years of follow-up, 77% of patients allocated the highest dose had been seizure free for the past 12 months versus 59% of those who received the low dose. The intensity and time of appearance of vasogenic oedema varied as a function of dose, but also within groups, and was associated with onset of seizure remission.[101] These MRI and clinical changes typically occurred between 9 and 12 months after radiosurgery, and could be deferred to 2–3 years.[100,101] Whereas radiosurgery offers a safer alternative to surgical resection, it is still associated with side-effects, including superior quadrantanopsia in 50% of cases, verbal memory impairment in 25% of dominant hemisphere radiosurgery cases, new types of headache in 70% of cases, and severe oedema of the targeted temporal lobe that might need temporal lobectomy in 3% of cases.[100]

Morbidity and mortality of presurgical assessment and epilepsy surgery

Presurgical assessment carries the risk of serious adverse events associated with video EEG monitoring, Wada testing, and invasive EEG investigations. The risk of seizure-related cardiorespiratory arrest and sudden unexpected death in epilepsy (SUDEP) during video EEG was recently emphasised by the Mortality in Epilepsy Monitoring Unit Study, which showed that the incidence of SUDEP in epilepsy monitoring units was similar to that seen outside hospital settings in adult patients with refractory epilepsy.[102] Although SUDEP in monitoring units remains a very rare event, efforts should be made to increase the safety of these units because seizure-related serious adverse events, such as status epilepticus, bone fracture, or postictal psychosis, seem to occur in up to 10% of patients undergoing video EEG.[103]

Neurological complications of epilepsy surgery decreased substantially between the periods 1980–1995 and 1996–2012.[104] Persistent neurological deficits after temporal lobe resection decreased from 9·7% to 0·8%, whereas those seen after extratemporal or multifocal resections decreased from 9·0% to 3·2%. Wound infections or meningitis decreased from 2·5% to 1·1%

***Panel 2:* Predictors of postoperative outcomes**

Predictors of favourable postoperative seizure outcome in TLE

Clinical characteristics

- History of febrile convulsions in childhood[30]
- Younger age at surgery or onset of epilepsy[30,81]
- Low baseline seizure frequency[79]
- Absence of preoperative generalized tonic-clonic seizures[30,79]
- Absence of psychiatric history[82]

Results of presurgical investigations

- MRI lesion,* including unilateral hippocampal sclerosis[30]
- Absence of contralateral or extratemporal IEDs[30,78]
- Concordant SISCOM[78]
- Congruent temporal hypometabolism on ^{18}F-FDG-PET[56,57]

Surgical approach

- Anterior temporal lobectomy (*vs* selective amygdalohippocampectomy)[83]

Pathological findings

- Abnormality at pathological examination of resected tissue in MRI-negative patients[80]

Predictors of verbal memory preservation after TLE surgery over the side dominant for language

- Low preoperative verbal memory performance[30,84]
- Hippocampal atrophy on side dominant for language[30,85]
- Lower ipsilateral than contralateral fMRI activation in anterior hippocampus during encoding[67]
- Altered memory performance on Wada test contralateral to seizure focus[30]
- Abnormality at pathological examination of resected hippocampus[30,85]

Predictors of favourable postoperative seizure outcome in extraTLE

Clinical characteristics

- Short epilepsy duration[86]

Results of presurgical investigations

- MRI lesion*[30]
- Focal IEDs[30,87]
- Concordant hypometabolism on ^{18}F-FDG-PET[30]

Surgical approach

- Complete resection of epileptogenic zone[24,30,83,88,89]

Pathological findings

- Focal cortical dysplasia type 2[88]

^{18}F-FDG=^{18}F-fluorodeoxyglucose. fMRI=functional MRI. IED=interictal epileptiform discharge. SISCOM=subtraction ictal SPECT coregistered with MRI. TLE=temporal lobe epilepsy. *This classic predictor is now disputed by several series.[80,88,90]

after temporal lobe resection and from 5·3% to 1·9% after extratemporal or multifocal resections. By contrast, after placement of intracranial electrodes, wound infections or meningitis increased from 2·3% to 4·3% and haemorrhage or haematoma increased from 1·9% to 4·2%. These surprising findings might indicate the greater proportion of subdural versus depth electrodes used during the 1996–2012 period compared with the 1980–1995 period,[104] a trend that more recently reversed with the dissemination of SEEG.[105] Permanent neurological deficit after invasive EEG was shown to be equally rare before and after 1995, with an overall risk of 0·5%.[104] This risk was confirmed by another systematic review of complications associated with invasive monitoring,[106] which reported a 7% rate of minor complications (defined as those resolving completely within 3 months) and a 0·6% rate of major complications (not resolving within 3 months). In a series of 242 patients undergoing invasive monitoring,[107] the rate of adverse events was 23%, but without permanent morbidity or mortality. Implantation of grids was associated with a significantly higher risk of major complications than that of depth electrodes. In a large series of 500 consecutive SEEG procedures,[108] the rate of major complications was 2·4%, including 1·0% of intracranial haemorrhages and one death. Another series of 100 SEEG procedures[105] reported a 3% rate of haemorrhagic complications without permanent deficit.

After resective surgery, major neurological complications, not wholly resolving within 3 months, have been reported in 4·7% of patients, with the most common being major visual field defects, whereas perioperative mortality has been shown to occur in 0·4% of temporal lobe epilepsy surgeries and 1·2% of extratemporal surgeries[106] Cerebral vasospasm is the most likely mechanism underlying perioperative stroke, which is a rare complication of temporal lobe epilepsy surgery. To further explore this issue, a systematic transcranial doppler sonography assessment was done in 107 patients undergoing either anterior temporal lobectomy or selective amygdalohippocampectomy.[109] 35 of these patients (33%) showed postoperative cerebral vasospasm, with similar results for the two surgical procedures. Similar findings were reported in another series of 48 transsylvian selective amygdalohippocampectomies,[110] in which systematic postoperative MRI detected infarction in 58% of patients, none of which was associated with a clinically overt neurological deficit. However, the presence of postoperative infarction in the dominant temporal lobe was associated with worse verbal memory outcome (p=0·011), whereas temporal lobe infarction in general was associated with better seizure outcome (p=0·046).

In a series of 161 children who collectively underwent 200 admissions for invasive monitoring followed by resection (n=159) or invasive monitoring only (n=41),[111] complication rates per admission were 2·0% for permanent hemiparesis, 1·5% for active infections of the CNS and 1·5% for other infections, 3·0% for hydrocephalus, 3·0% for wound complications, and 5% for bone absorption. Overall, 15·0% of admissions were associated with a complication necessitating additional surgery.

Cognitive, behavioural, and psychosocial outcomes of epilepsy surgery

Cognitive, behavioural, and psychosocial outcomes of epilepsy surgery are complex and important issues, as discussed in the 2008 Review,[30] and the knowledge accumulated since then has largely supported its main findings, as summarised below.

As a rule and at a group level, epilepsy surgery, when achieving seizure freedom, is associated with improved cognitive abilities (especially in children),[19,23,81] psychiatric status,[112,113] social function,[114] and quality of life.[115,116] However, any of these outcomes can deteriorate at the individual level.

Pronounced neurodevelopmental gains are more likely to be seen with a short duration of epilepsy,[20,21] a history of infantile spasms,[117,118] long postoperative follow-up,[20,81] and when antiepileptic drugs have been weaned.[81]

One exception to the positive cognitive outcome associated with epilepsy surgery is verbal memory, which tends to decrease after temporal lobe epilepsy surgery over the side dominant for language.[84,85,119–123] In addition to the predictive value of fMRI assessments of memory, previously discussed,[67] the risk of a clinically significant decrease in verbal memory is increased when preoperative performance is high,[84] hippocampal volume is normal and its pathology unremarkable,[85] and seizures are not controlled postoperatively.[122] Children seem to show a greater likelihood of recovery 1 year from surgery than do adults.[124] Although this has long been debated, two series[125,126] provided evidence that when the side dominant for language was operated on, resection of the temporal pole, together with the mesial temporal structures, was associated with less verbal memory decrease than was selective amygdalohippocampectomy. The opposite finding was seen for non-verbal memory performance when the non-dominant side was operated on (ie, smaller decrease with selective amygdalohippocampectomy). Several types of selective amygdalohippocampectomy, using transsylvian, transcortical, and subtemporal approaches, have been compared, but no significant difference has been shown in terms of cognitive outcome.[127,128]

Neuropsychological investigations of patients with temporal lobe epilepsy have delineated specific changes in semantic memory after dominant temporal lobe surgery[129] and long-term accelerated forgetting for both verbal and non-verbal material.[130] This forgetfulness seems to be driven mainly by seizures, and seems to be reduced by successful epilepsy surgery.[131]

The risk of postoperative psychiatric disorders is largely predicted by the presence of preoperative psychiatric morbidity.[30] However, the occurrence of postoperative

de-novo psychiatric disorders is reported in 1·1–18·2% of series.[113] In children with surgically remediable epilepsy, rates of psychiatric disorder are particularly high, both preoperatively and postoperatively.[22,132,133] Many psychiatric disorders can be diagnosed in one patient, and diagnoses can be lost or can evolve after surgery. Although a relation between improvement in psychiatric manifestations and seizure freedom has been suggested,[132] it generally cannot be predicted or guaranteed after surgery.[22,133] The presence of postoperative mood and anxiety disorders, and postoperative seizures, strongly and independently predict poor quality of life.[134]

Postoperative withdrawal of antiepileptic drugs

Antiepileptic drugs can be gradually withdrawn in patients who are postoperatively seizure free. In a long-term prospective study of epilepsy surgery,[135] 86% of children and 43% of adults who achieved sustained postoperative seizure freedom were free of antiepileptic drugs 10 years after surgery versus none of 93 non-operated patients with refractory focal epilepsy included in the same cohort. The risk of seizure recurrence after treatment discontinuation varies: 12% in a large paediatric series,[136] 25% after mesial temporal lobe epilepsy surgery,[137] and 46% in neocortical epilepsy.[138,139] Chances to regain seizure freedom after seizure recurrence and adjusted antiepileptic drug regimen varied: 88% in mesial temporal lobe epilepsy,[137] 70% in children,[136] and 68%[138] and 46%[139] in neocortical epilepsy according to two different studies. Although early drug tapering was associated with an increased risk of short-term seizure relapse, it did not affect long-term seizure outcome or cure in children.[136]

Conclusion

Epilepsy surgery remains the most effective way to achieve long-term seizure freedom in patients with drug-resistant focal seizures. Advances in neuroimaging, neurophysiological investigations, and development of methods for data postprocessing have increased the possibility of accurately localizing the epileptogenic zone to be resected, particularly in patients with normal MRI. However, despite this progress, the development of guidelines, and an increased number of epilepsy surgery centres, epilepsy surgery has failed to expand during the past decade, especially in adults and in western countries where referral of patients with mesial temporal lobe epilepsy and hippocampal sclerosis has tended to decrease. Although this trend could be due partly to previous overestimation of the incidence and prevalence of surgically remediable epilepsies, a gap in knowledge among physicians is also likely to preclude many patients from surgery.[140] This knowledge gap has led to the development of web-based tools to assess patients' suitability for presurgical assessment[141] and an EU-funded network of cooperation for dissemination of knowledge about the surgical treatment of epilepsy,[142] with the main objective to promote the systematic assessment of patients with refractory epilepsy at comprehensive epilepsy centres. Although web-based tools might prove useful to inform patients and caregivers about eligibility criteria for epilepsy surgery, these criteria still need to be assessed at a specialised epilepsy surgery centre in all patients with drug-resistant seizures. These initiatives, together with the development of minimally invasive surgical techniques, should allow harmonisation of best practices and translate into safer and more effective epilepsy surgery.

Search strategy and selection criteria

We identified references for this Review by searches of PubMed according to the following queries: original research articles and reviews between Jan 1, 2009 and May 11, 2014, with the search term "epilepsy surgery" and filter "Abstract available"; and randomised controlled trials, guidelines, and practice parameters between Jan 1, 1969 and May 11, 2014, with the search terms "epilepsy surgery" AND ("practice parameter" in title OR "guideline" in title OR "randomised" in title OR "randomized" in title). We imposed no language restrictions. This search resulted in 4155 references, 893 of which we further assessed by reading the abstract or full text. We further assessed the references of all selected publications. We generated the final reference list on the basis of relevance to the topics covered in this Review.

Contributors

All authors contributed equally to the literature search, selection of relevant references, and writing of the Review.

Declaration of interests

We declare no competing interests.

References

1 Langfitt JT, Holloway RG, McDermott MP, et al. Health care costs decline after successful epilepsy surgery. *Neurology* 2007; **68:** 1290–98.
2 Silfvenius H. Cost and cost-effectiveness of epilepsy surgery. *Epilepsia* 1999; **40** (suppl 8)**:** 32–39.
3 Widjaja E, Li B, Schinkel CD, et al. Cost-effectiveness of pediatric epilepsy surgery compared to medical treatment in children with intractable epilepsy. *Epilepsy Res* 2011; **94:** 61–68.
4 Engel JJ, Wiebe S, French J, et al. Practice parameter: temporal lobe and localized neocortical resections for epilepsy: report of the Quality Standards Subcommittee of the American Academy of Neurology, in association with the American Epilepsy Society and the American Association of Neurological Surgeons. *Neurology* 2003; **60:** 538–47.
5 Cross JH, Jayakar P, Nordli D, et al. Proposed criteria for referral and evaluation of children for epilepsy surgery: recommendations of the Subcommission for Pediatric Epilepsy Surgery. *Epilepsia* 2006; **47:** 952–59.
6 Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia* 2010; **51:** 1069–77.
7 Engel JJ, McDermott MP, Wiebe S, et al. Early surgical therapy for drug-resistant temporal lobe epilepsy: a randomized trial. *JAMA* 2012; **307:** 922–30.
8 Choi H, Carlino R, Heiman G, Hauser WA, Gilliam FG. Evaluation of duration of epilepsy prior to temporal lobe epilepsy surgery during the past two decades. *Epilepsy Res* 2009; **86:** 224–27.
9 Haneef Z, Stern J, Dewar S, Engel JJ. Referral pattern for epilepsy surgery after evidence-based recommendations: a retrospective study. *Neurology* 2010; **75:** 699–704.

10 Harvey AS, Cross JH, Shinnar S, Mathern GW. Defining the spectrum of international practice in pediatric epilepsy surgery patients. *Epilepsia* 2008; **49:** 146–55.

11 Englot DJ, Ouyang D, Garcia PA, Barbaro NM, Chang EF. Epilepsy surgery trends in the United States, 1990–2008. *Neurology* 2012; **78:** 1200–06.

12 Van Gompel JJ, Ottman R, Worrell GA, et al. Use of anterior temporal lobectomy for epilepsy in a community-based population. *Arch Neurol* 2012; **69:** 1476–81.

13 Neligan A, Haliasos N, Pettorini B, Harkness WF, Solomon JK. A survey of adult and pediatric epilepsy surgery in the United Kingdom. *Epilepsia* 2013; **54:** e62–65.

14 Berg AT, Mathern GW, Bronen RA, et al. Frequency, prognosis and surgical treatment of structural abnormalities seen with magnetic resonance imaging in childhood epilepsy. *Brain* 2009; **132:** 2785–97.

15 Campos MG. Epilepsy surgery in developing countries. *Handb Clin Neurol* 2012; **108:** 943–53.

16 Qiu J. Epilepsy surgery: challenges for developing countries. *Lancet Neurol* 2009; **8:** 420–21.

17 de Tisi J, Bell GS, Peacock JL, et al. The long-term outcome of adult epilepsy surgery, patterns of seizure remission, and relapse: a cohort study. *Lancet* 2011; **378:** 1388–95.

18 Jayakar P, Gaillard WD, Tripathi M, Libenson MH, Mathern GW, Cross JH. Diagnostic test utilization in evaluation for resective epilepsy surgery in children. *Epilepsia* 2014; **55:** 507–18.

19 Wethe JV, Prigatano GP, Gray J, Chapple K, Rekate HL, Kerrigan JF. Cognitive functioning before and after surgical resection for hypothalamic hamartoma and epilepsy. *Neurology* 2013; **81:** 1044–50.

20 Freitag H, Tuxhorn I. Cognitive function in preschool children after epilepsy surgery: rationale for early intervention. *Epilepsia* 2005; **46:** 561–67.

21 Jonas R, Nguyen S, Hu B, et al. Cerebral hemispherectomy: hospital course, seizure, developmental, language, and motor outcomes. *Neurology* 2004; **62:** 1712–21.

22 Colonnelli MC, Cross JH, Davies S, et al. Psychopathology in children before and after surgery for extratemporal lobe epilepsy. *Dev Med Child Neurol* 2012; **54:** 521–26.

23 de Koning T, Versnel H, Jennekens-Schinkel A, et al. Language development before and after temporal surgery in children with intractable epilepsy. *Epilepsia* 2009; **50:** 2408–19.

24 Moosa AN, Jehi L, Marashly A, et al. Long-term functional outcomes and their predictors after hemispherectomy in 115 children. *Epilepsia* 2013; **54:** 1771–79.

25 Ramantani G, Kadish NE, Brandt A, et al. Seizure control and developmental trajectories after hemispherotomy for refractory epilepsy in childhood and adolescence. *Epilepsia* 2013; **54:** 1046–55.

26 Wyllie E, Lachhwani DK, Gupta A, et al. Successful surgery for epilepsy due to early brain lesions despite generalized EEG findings. *Neurology* 2007; **69:** 389–97.

27 Fauser S, Sisodiya SM, Martinian L, et al. Multi-focal occurrence of cortical dysplasia in epilepsy patients. *Brain* 2009; **132:** 2079–90.

28 Ramantani G, Koessler L, Colnat-Coulbois S, et al. Intracranial evaluation of the epileptogenic zone in regional infrasylvian polymicrogyria. *Epilepsia* 2013; **54:** 296–304.

29 Fallah A, Guyatt GH, Snead OC 3rd, et al. Predictors of seizure outcomes in children with tuberous sclerosis complex and intractable epilepsy undergoing resective epilepsy surgery: an individual participant data meta-analysis. *PLoS One* 2013; **8:** e53565.

30 Spencer S, Huh L. Outcomes of epilepsy surgery in adults and children. *Lancet Neurol* 2008; **7:** 525–37.

31 Wu JY, Salamon N, Kirsch HE, et al. Noninvasive testing, early surgery, and seizure freedom in tuberous sclerosis complex. *Neurology* 2010; **74:** 392–98.

32 Loddenkemper T, Cosmo G, Kotagal P, et al. Epilepsy surgery in children with electrical status epilepticus in sleep. *Neurosurgery* 2009; **64:** 328–37; discussion 337.

33 Peltola ME, Liukkonen E, Granstrom ML, et al. The effect of surgery in encephalopathy with electrical status epilepticus during sleep. *Epilepsia* 2011; **52:** 602–09.

34 Thom M, Mathern GW, Cross JH, Bertram EH. Mesial temporal lobe epilepsy: how do we improve surgical outcome? *Ann Neurol* 2010; **68:** 424–34.

35 Wieser HG. ILAE Commission Report. Mesial temporal lobe epilepsy with hippocampal sclerosis. *Epilepsia* 2004; **45:** 695–714.

36 Ryvlin P, Kahane P. The hidden causes of surgery-resistant temporal lobe epilepsy: extratemporal or temporal plus? *Curr Opin Neurol* 2005; **18:** 125–27.

37 Cossu M, Fuschillo D, Cardinale F, et al. Stereo-EEG-guided radio-frequency thermocoagulations of epileptogenic grey-matter nodular heterotopy. *J Neurol Neurosurg Psychiatry* 2013; **85:** 611–17.

38 Catenoix H, Mauguiere F, Guenot M, et al. SEEG-guided thermocoagulations: a palliative treatment of nonoperable partial epilepsies. *Neurology* 2008; **71:** 1719–26.

39 Tovar-Spinoza Z, Carter D, Ferrone D, Eksioglu Y, Huckins S. The use of MRI-guided laser-induced thermal ablation for epilepsy. *Childs Nerv Syst* 2013; **29:** 2089–94.

40 Curry DJ, Gowda A, McNichols RJ, Wilfong AA. MR-guided stereotactic laser ablation of epileptogenic foci in children. *Epilepsy Behav* 2012; **24:** 408–14.

41 Esquenazi Y, Kalamangalam GP, Slater JD, et al. Stereotactic laser ablation of epileptogenic periventricular nodular heterotopia. *Epilepsy Res* 2014; **108:** 547–54.

42 Willie JT, Laxpati NG, Drane DL, et al. Real-time magnetic resonance-guided stereotactic laser amygdalohippocampotomy for mesial temporal lobe epilepsy. *Neurosurgery* 2014; **74:** 569–85.

43 Burch J, Hinde S, Palmer S, et al. The clinical effectiveness and cost-effectiveness of technologies used to visualise the seizure focus in people with refractory epilepsy being considered for surgery: a systematic review and decision-analytical model. *Health Technol Assess* 2012; **16:** 1–157, iii-iv.

44 Focke NK, Bonelli SB, Yogarajah M, Scott C, Symms MR, Duncan JS. Automated normalized FLAIR imaging in MRI-negative patients with refractory focal epilepsy. *Epilepsia* 2009; **50:** 1484–90.

45 Huppertz HJ, Wellmer J, Staack AM, Altenmuller DM, Urbach H, Kroll J. Voxel-based 3D MRI analysis helps to detect subtle forms of subcortical band heterotopia. *Epilepsia* 2008; **49:** 772–85.

46 Mellerio C, Labeyrie MA, Chassoux F, et al. 3T MRI improves the detection of transmantle sign in type 2 focal cortical dysplasia. *Epilepsia* 2014; **55:** 117–22.

47 Wagner J, Weber B, Urbach H, Elger CE, Huppertz HJ. Morphometric MRI analysis improves detection of focal cortical dysplasia type II. *Brain* 2011; **134:** 2844–54.

48 Winston GP, Daga P, Stretton J, et al. Optic radiation tractography and vision in anterior temporal lobe resection. *Ann Neurol* 2012; **71:** 334–41.

49 Jeelani NU, Jindahra P, Tamber MS, et al. 'Hemispherical asymmetry in the Meyer's Loop': a prospective study of visual-field deficits in 105 cases undergoing anterior temporal lobe resection for epilepsy. *J Neurol Neurosurg Psychiatry* 2010; **81:** 985–91.

50 Yogarajah M, Focke NK, Bonelli S, et al. Defining Meyer's loop-temporal lobe resections, visual field deficits and diffusion tensor tractography. *Brain* 2009; **132:** 1656–68.

51 Agirre-Arrizubieta Z, Huiskamp GJ, Ferrier CH, van Huffelen AC, Leijten FS. Interictal magnetoencephalography and the irritative zone in the electrocorticogram. *Brain* 2009; **132:** 3060–71.

52 Brodbeck V, Spinelli L, Lascano AM, et al. Electroencephalographic source imaging: a prospective study of 152 operated epileptic patients. *Brain* 2011; **134:** 2887–97.

53 Jung J, Bouet R, Delpuech C, et al. The value of magnetoencephalography for seizure-onset zone localization in magnetic resonance imaging-negative partial epilepsy. *Brain* 2013; **136:** 3176–86.

54 Knowlton RC, Razdan SN, Limdi N, et al. Effect of epilepsy magnetic source imaging on intracranial electrode placement. *Ann Neurol* 2009; **65:** 716–23.

55 Thornton R, Vulliemoz S, Rodionov R, et al. Epileptic networks in focal cortical dysplasia revealed using electroencephalography-functional magnetic resonance imaging. *Ann Neurol* 2011; **70:** 822–37.

56 Grouiller F, Thornton RC, Groening K, et al. With or without spikes: localization of focal epileptic activity by simultaneous electroencephalography and functional magnetic resonance imaging. *Brain* 2011; **134:** 2867–86.

57 Immonen A, Jutila L, Muraja-Murro A, et al. Long-term epilepsy surgery outcomes in patients with MRI-negative temporal lobe epilepsy. *Epilepsia* 2010; **51:** 2260–69.

58 LoPinto-Khoury C, Sperling MR, Skidmore C, et al. Surgical outcome in PET-positive, MRI-negative patients with temporal lobe epilepsy. *Epilepsia* 2012; **53:** 342–48.

59 Chassoux F, Rodrigo S, Semah F, et al. FDG-PET improves surgical outcome in negative MRI Taylor-type focal cortical dysplasias. *Neurology* 2010; **75:** 2168–75.

60 Uijl SG, Leijten FS, Arends JB, Parra J, van Huffelen AC, Moons KG. The added value of [18F]-fluoro-D-deoxyglucose positron emission tomography in screening for temporal lobe epilepsy surgery. *Epilepsia* 2007; **48:** 2121–29.

61 Kazemi NJ, Worrell GA, Stead SM, et al. Ictal SPECT statistical parametric mapping in temporal lobe epilepsy surgery. *Neurology* 2010; **74:** 70–76.

62 Sulc V, Stykel S, Hanson DP, et al. Statistical SPECT processing in MRI-negative epilepsy surgery. *Neurology* 2014; **82:** 932–39.

63 Bauer PR, Reitsma JB, Houweling BM, Ferrier CH, Ramsey NF. Can fMRI safely replace the Wada test for preoperative assessment of language lateralisation? A meta-analysis and systematic review. *J Neurol Neurosurg Psychiatry* 2013; **85:** 581–88.

64 Jansen FE, Jennekens-Schinkel A, Van Huffelen AC, et al. Diagnostic significance of Wada procedure in very young children and children with developmental delay. *Eur J Paediatr Neurol* 2002; **6:** 315–20.

65 Findlay AM, Ambrose JB, Cahn-Weiner DA, et al. Dynamics of hemispheric dominance for language assessed by magnetoencephalographic imaging. *Ann Neurol* 2012; **71:** 668–86.

66 House PM, Bruckner KE, Lohmann HH. Presurgical functional transcranial Doppler sonography (fTCD) with intravenous echo enhancing agent SonoVue enables determination of language lateralization in epilepsy patients with poor temporal bone windows. *Epilepsia* 2011; **52:** 636–39.

67 Bonelli SB, Powell RH, Yogarajah M, et al. Imaging memory in temporal lobe epilepsy: predicting the effects of temporal lobe resection. *Brain* 2010; **133:** 1186–99.

68 Dupont S, Duron E, Samson S, et al. Functional MR imaging or Wada test: which is the better predictor of individual postoperative memory outcome? *Radiology* 2010; **255:** 128–34.

69 Jacobs J, Levan P, Chatillon CE, Olivier A, Dubeau F, Gotman J. High frequency oscillations in intracranial EEGs mark epileptogenicity rather than lesion type. *Brain* 2009; **132:** 1022–37.

70 Jacobs J, Zijlmans M, Zelmann R, et al. High-frequency electroencephalographic oscillations correlate with outcome of epilepsy surgery. *Ann Neurol* 2010; **67:** 209–20.

71 Wu JY, Sankar R, Lerner JT, Matsumoto JH, Vinters HV, Mathern GW. Removing interictal fast ripples on electrocorticography linked with seizure freedom in children. *Neurology* 2010; **75:** 1686–94.

72 Aubert S, Wendling F, Regis J, et al. Local and remote epileptogenicity in focal cortical dysplasias and neurodevelopmental tumours. *Brain* 2009; **132:** 3072–86.

73 Valentin A, Alarcon G, Honavar M, et al. Single pulse electrical stimulation for identification of structural abnormalities and prediction of seizure outcome after epilepsy surgery: a prospective study. *Lancet Neurol* 2005; **4:** 718–26.

74 van 't Klooster MA, Zijlmans M, Leijten FS, Ferrier CH, van Putten MJ, Huiskamp GJ. Time-frequency analysis of single pulse electrical stimulation to assist delineation of epileptogenic cortex. *Brain* 2011; **134:** 2855–66.

75 Burch J, Marson A, Beyer F, et al. Dilemmas in the interpretation of diagnostic accuracy studies on presurgical workup for epilepsy surgery. *Epilepsia* 2012; **53:** 1294–302.

76 Tellez-Zenteno JF, Dhar R, Wiebe S. Long-term seizure outcomes following epilepsy surgery: a systematic review and meta-analysis. *Brain* 2005; **128:** 1188–98.

77 Murphy M, Smith PD, Wood M, et al. Surgery for temporal lobe epilepsy associated with mesial temporal sclerosis in the older patient: a long-term follow-up. *Epilepsia* 2010; **51:** 1024–29.

78 Bell ML, Rao S, So EL, et al. Epilepsy surgery outcomes in temporal lobe epilepsy with a normal MRI. *Epilepsia* 2009; **50:** 2053–60.

79 Fong JS, Jehi L, Najm I, Prayson RA, Busch R, Bingaman W. Seizure outcome and its predictors after temporal lobe epilepsy surgery in patients with normal MRI. *Epilepsia* 2011; **52:** 1393–1401.

80 Bien CG, Szinay M, Wagner J, Clusmann H, Becker AJ, Urbach H. Characteristics and surgical outcomes of patients with refractory magnetic resonance imaging-negative epilepsies. *Arch Neurol* 2009; **66:** 1491–99.

81 Skirrow C, Cross JH, Cormack F, Harkness W, Vargha-Khadem F, Baldeweg T. Long-term intellectual outcome after temporal lobe surgery in childhood. *Neurology* 2011; **76:** 1330–37.

82 Kanner AM, Byrne R, Chicharro A, Wuu J, Frey M. A lifetime psychiatric history predicts a worse seizure outcome following temporal lobectomy. *Neurology* 2009; **72:** 793–99.

83 Josephson CB, Dykeman J, Fiest KM, et al. Systematic review and meta-analysis of standard vs selective temporal lobe epilepsy surgery. *Neurology* 2013; **80:** 1669–76.

84 Sherman EM, Wiebe S, Fay-McClymont TB, et al. Neuropsychological outcomes after epilepsy surgery: systematic review and pooled estimates. *Epilepsia* 2011; **52:** 857–69.

85 Helmstaedter C, Petzold I, Bien CG. The cognitive consequence of resecting nonlesional tissues in epilepsy surgery—results from MRI- and histopathology-negative patients with temporal lobe epilepsy. *Epilepsia* 2011; **52:** 1402–08.

86 Simasathien T, Vadera S, Najm I, Gupta A, Bingaman W, Jehi L. Improved outcomes with earlier surgery for intractable frontal lobe epilepsy. *Ann Neurol* 2013; **73:** 646–54.

87 Noe K, Sulc V, Wong-Kisiel L, et al. Long-term outcomes after nonlesional extratemporal lobe epilepsy surgery. *JAMA Neurol* 2013; **70:** 1003–08.

88 Chassoux F, Landre E, Mellerio C, et al. Type II focal cortical dysplasia: electroclinical phenotype and surgical outcome related to imaging. *Epilepsia* 2012; **53:** 349–58.

89 Kim DW, Lee SK, Chu K, et al. Predictors of surgical outcome and pathologic considerations in focal cortical dysplasia. *Neurology* 2009; **72:** 211–16.

90 Lazow SP, Thadani VM, Gilbert KL, et al. Outcome of frontal lobe epilepsy surgery. *Epilepsia* 2012; **53:** 1746–55.

91 Lackmayer K, Lehner-Baumgartner E, Pirker S, Czech T, Baumgartner C. Preoperative depressive symptoms are not predictors of postoperative seizure control in patients with mesial temporal lobe epilepsy and hippocampal sclerosis. *Epilepsy Behav* 2013; **26:** 81–86.

92 Hu WH, Zhang C, Zhang K, Meng FG, Chen N, Zhang JG. Selective amygdalohippocampectomy versus anterior temporal lobectomy in the management of mesial temporal lobe epilepsy: a meta-analysis of comparative studies. *J Neurosurg* 2013; **119:** 1089–97.

93 McIntosh AM, Averill CA, Kalnins RM, et al. Long-term seizure outcome and risk factors for recurrence after extratemporal epilepsy surgery. *Epilepsia* 2012; **53:** 970–78.

94 Jehi LE, O'Dwyer R, Najm I, Alexopoulos A, Bingaman W. A longitudinal study of surgical outcome and its determinants following posterior cortex epilepsy surgery. *Epilepsia* 2009; **50:** 2040–52.

95 Chang EF, Wang DD, Barkovich AJ, et al. Predictors of seizure freedom after surgery for malformations of cortical development. *Ann Neurol* 2011; **70:** 151–62.

96 Krsek P, Maton B, Jayakar P, et al. Incomplete resection of focal cortical dysplasia is the main predictor of poor postsurgical outcome. *Neurology* 2009; **72:** 217–23.

97 Chassoux F, Rodrigo S, Mellerio C, et al. Dysembryoplastic neuroepithelial tumors: an MRI-based scheme for epilepsy surgery. *Neurology* 2012; **79:** 1699–1707.

98 Englot DJ, Berger MS, Barbaro NM, Chang EF. Factors associated with seizure freedom in the surgical resection of glioneuronal tumors. *Epilepsia* 2012; **53:** 51–57.

99 Romanelli P, Anschel DJ. Radiosurgery for epilepsy. *Lancet Neurol* 2006; **5:** 613–20.

100 Barbaro NM, Quigg M, Broshek DK, et al. A multicenter, prospective pilot study of gamma knife radiosurgery for mesial temporal lobe epilepsy: seizure response, adverse events, and verbal memory. *Ann Neurol* 2009; **65:** 167–75.

101 Chang EF, Quigg M, Oh MC, et al. Predictors of efficacy after stereotactic radiosurgery for medial temporal lobe epilepsy. *Neurology* 2010; **74:** 165–72.

102 Ryvlin P, Nashef L, Lhatoo SD, et al. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study. *Lancet Neurol* 2013; **12:** 966–77.

103 Rheims S, Ryvlin P. Patients' safety in the epilepsy monitoring unit: time for revising practices. *Curr Opin Neurol* 2014; **27:** 213–18.

104 Tebo CC, Evins AI, Christos PJ, Kwon J, Schwartz TH. Evolution of cranial epilepsy surgery complication rates: a 32-year systematic review and meta-analysis. *J Neurosurg* 2014; **120:** 1415–27.

105 Gonzalez-Martinez J, Mullin J, Vadera S, et al. Stereotactic placement of depth electrodes in medically intractable epilepsy. *J Neurosurg* 2014; **120:** 639–44.

106 Hader WJ, Tellez-Zenteno J, Metcalfe A, et al. Complications of epilepsy surgery: a systematic review of focal surgical resections and invasive EEG monitoring. *Epilepsia* 2013; **54:** 840–47.

107 Wellmer J, von der Groeben F, Klarmann U, et al. Risks and benefits of invasive epilepsy surgery workup with implanted subdural and depth electrodes. *Epilepsia* 2012; **53:** 1322–32.

108 Cardinale F, Cossu M, Castana L, et al. Stereoelectroencephalography: surgical methodology, safety, and stereotactic application accuracy in 500 procedures. *Neurosurgery* 2013; **72:** 353–66; discussion 366.

109 Lackner P, Koppelstaetter F, Ploner P, et al. Cerebral vasospasm following temporal lobe epilepsy surgery. *Neurology* 2012; **78:** 1215–20.

110 Martens T, Merkel M, Holst B, et al. Vascular events after transsylvian selective amygdalohippocampectomy and impact on epilepsy outcome. *Epilepsia* 2014; **55:** 763–69.

111 Roth J, Carlson C, Devinsky O, Harter DH, Macallister WS, Weiner HL. Safety of staged epilepsy surgery in children. *Neurosurgery* 2014; **74:** 154–62.

112 Hamid H, Liu H, Cong X, et al. Long-term association between seizure outcome and depression after resective epilepsy surgery. *Neurology* 2011; **77:** 1972–76.

113 Macrodimitris S, Sherman EM, Forde S, et al. Psychiatric outcomes of epilepsy surgery: a systematic review. *Epilepsia* 2011; **52:** 880–90.

114 Hamiwka L, Macrodimitris S, Tellez-Zenteno JF, et al. Social outcomes after temporal or extratemporal epilepsy surgery: a systematic review. *Epilepsia* 2011; **52:** 870–79.

115 Fiest KM, Sajobi TT, Wiebe S. Epilepsy surgery and meaningful improvements in quality of life: results from a randomized controlled trial. *Epilepsia* 2014; **55:** 886–92.

116 Taft C, Sager Magnusson E, Ekstedt G, Malmgren K. Health-related quality of life, mood, and patient satisfaction after epilepsy surgery in Sweden-a prospective controlled observational study. *Epilepsia* 2014; **55:** 878–85.

117 Loddenkemper T, Holland KD, Stanford LD, Kotagal P, Bingaman W, Wyllie E. Developmental outcome after epilepsy surgery in infancy. *Pediatrics* 2007; **119:** 930–35.

118 Vendrame M, Alexopoulos AV, Boyer K, et al. Longer duration of epilepsy and earlier age at epilepsy onset correlate with impaired cognitive development in infancy. *Epilepsy Behav* 2009; **16:** 431–35.

119 Andersson-Roswall L, Engman E, Samuelsson H, Malmgren K. Cognitive outcome 10 years after temporal lobe epilepsy surgery: a prospective controlled study. *Neurology* 2010; **74:** 1977–85.

120 Baxendale S, Thompson PJ, Sander JW. Neuropsychological outcomes in epilepsy surgery patients with unilateral hippocampal sclerosis and good preoperative memory function. *Epilepsia* 2013; **54:** e131–34.

121 Helmstaedter C, Reuber M, Elger CC. Interaction of cognitive aging and memory deficits related to epilepsy surgery. *Ann Neurol* 2002; **52:** 89–94.

122 Helmstaedter C, Kurthen M, Lux S, Reuber M, Elger CE. Chronic epilepsy and cognition: a longitudinal study in temporal lobe epilepsy. *Ann Neurol* 2003; **54:** 425–32.

123 Rausch R, Kraemer S, Pietras CJ, Le M, Vickrey BG, Passaro EA. Early and late cognitive changes following temporal lobe surgery for epilepsy. *Neurology* 2003; **60:** 951–59.

124 Gleissner U, Sassen R, Schramm J, Elger CE, Helmstaedter C. Greater functional recovery after temporal lobe epilepsy surgery in children. *Brain* 2005; **128:** 2822–29.

125 Helmstaedter C, Richter S, Roske S, Oltmanns F, Schramm J, Lehmann TN. Differential effects of temporal pole resection with amygdalohippocampectomy versus selective amygdalohippocampectomy on material-specific memory in patients with mesial temporal lobe epilepsy. *Epilepsia* 2008; **49:** 88–97.

126 Tanriverdi T, Dudley RW, Hasan A, et al. Memory outcome after temporal lobe epilepsy surgery: corticoamygdalohippocampectomy versus selective amygdalohippocampectomy. *J Neurosurg* 2010; **113:** 1164–75.

127 Lutz MT, Clusmann H, Elger CE, Schramm J, Helmstaedter C. Neuropsychological outcome after selective amygdalohippocampectomy with transsylvian versus transcortical approach: a randomized prospective clinical trial of surgery for temporal lobe epilepsy. *Epilepsia* 2004; **45:** 809–16.

128 von Rhein B, Nelles M, Urbach H, Von Lehe M, Schramm J, Helmstaedter C. Neuropsychological outcome after selective amygdalohippocampectomy: subtemporal versus transsylvian approach. *J Neurol Neurosurg Psychiatry* 2012; **83:** 887–93.

129 Lambon Ralph MA, Ehsan S, Baker GA, Rogers TT. Semantic memory is impaired in patients with unilateral anterior temporal lobe resection for temporal lobe epilepsy. *Brain* 2012; **135:** 242–58.

130 Wilkinson H, Holdstock JS, Baker G, Herbert A, Clague F, Downes JJ. Long-term accelerated forgetting of verbal and non-verbal information in temporal lobe epilepsy. *Cortex* 2012; **48:** 317–32.

131 Evans SJ, Elliott G, Reynders H, Isaac CL. Can temporal lobe epilepsy surgery ameliorate accelerated long-term forgetting? *Neuropsychologia* 2014; **53:** 64–74.

132 Lendt M, Helmstaedter C, Kuczaty S, Schramm J, Elger CE. Behavioural disorders in children with epilepsy: early improvement after surgery. *J Neurol Neurosurg Psychiatry* 2000; **69:** 739–44.

133 McLellan A, Davies S, Heyman I, et al. Psychopathology in children with epilepsy before and after temporal lobe resection. *Dev Med Child Neurol* 2005; **47:** 666–72.

134 Hamid H, Blackmon K, Cong X, et al. Mood, anxiety, and incomplete seizure control affect quality of life after epilepsy surgery. *Neurology* 2014; **82:** 887–94.

135 Edelvik A, Rydenhag B, Olsson I, et al. Long-term outcomes of epilepsy surgery in Sweden: a national prospective and longitudinal study. *Neurology* 2013; **81:** 1244–51.

136 Boshuisen K, Arzimanoglou A, Cross JH, et al. Timing of antiepileptic drug withdrawal and long-term seizure outcome after paediatric epilepsy surgery (TimeToStop): a retrospective observational study. *Lancet Neurol* 2012; **11:** 784–91.

137 Rathore C, Sarma SP, Radhakrishnan K. Prognostic importance of serial postoperative EEGs after anterior temporal lobectomy. *Neurology* 2011; **76:** 1925–31.

138 Menon R, Rathore C, Sarma SP, Radhakrishnan K. Feasibility of antiepileptic drug withdrawal following extratemporal resective epilepsy surgery. *Neurology* 2012; **79:** 770–76.

139 Park KI, Lee SK, Chu K, et al. Withdrawal of antiepileptic drugs after neocortical epilepsy surgery. *Ann Neurol* 2010; **67:** 230–38.

140 Erba G, Moja L, Beghi E, Messina P, Pupillo E. Barriers toward epilepsy surgery. A survey among practicing neurologists. *Epilepsia* 2012; **53:** 35–43.

141 Jette N, Quan H, Tellez-Zenteno JF, et al, for the CASES Expert Panelists. Development of an online tool to determine appropriateness for an epilepsy surgery evaluation. *Neurology* 2012; **79:** 1084–93.

142 European Commission. Project database. http://ec.europa.eu/chafea/projects/database.html?prjno=20131203 (accessed May 29, 2014).