Original article

Epileptic Disord 2015; 17 (3): 263-74

Minimally resective epilepsy surgery in MRI-negative children

Ann Hyslop [1], Ian Miller [1], Sanjiv Bhatia [2,3], Trevor Resnick [1,4], Michael Duchowny [1,4], Prasanna Jayakar [1]

[1] Department of Neurology, Miami Children's Hospital
[2] Department of Neurosurgery, Miami Children's Hospital
[3] Department of Neurosurgery, Miller School of Medicine, University of Miami
[4] Department of Neurology, Miller School of Medicine, University of Miami, Miami, FL, USA

Received January 14, 2015; Accepted June 27, 2015

ABSTRACT – *Aim*. Performing epilepsy surgery on children with non-lesional brain MRI often results in large lobar or multilobar resections. The aim of this study was to determine if smaller resections result in a comparable rate of seizure freedom.

Methods. We reviewed 25 children who had undergone focal corticectomies restricted to one aspect of a single lobe or the insula at our institution within a 5.5-year period. Data collected in the comprehensive non-invasive pre-surgical evaluation (including scalp video-EEG, volumetric MRI, functional MRI, EEG source localization, and SPECT and PET), as well as from invasive recordings performed in each patient, was reviewed. Data from each functional modality was identified as convergent or divergent with the epileptogenic zone using image coregistration. Specific biomarkers (from extra-operative and invasive testing) previously indicated to be indicative of focal epileptogenicity were used to further tailor each resection to an epileptogenic epicentre. Tissue pathology and postoperative outcomes were obtained from all 25 patients.

Results. Two years postoperatively, 15/25 (60%) children were seizure-free, three (12%) experienced >90% reduction in seizure frequency, two (8%) had a 50-90% reduction in seizure frequency, and the remaining five (20%) had no change in seizure burden. There was no significant difference in outcome based on numerous pre- and postoperative factors including location of resection, the number of preoperative functional tests providing convergent data, and tissue pathology.

Conclusion. In MRI-negative children with focal epilepsy, an epileptogenic epicentre within a larger epileptogenic zone can be identified when specific biomarkers are recognized on non-invasive and invasive testing. When such children undergo resection of a small, well-defined epileptogenic epicentre, favourable outcomes can be achieved.

Key words: epilepsy surgery, MRI-negative, seizure freedom, focal epilepsy, EEG, SPECT, PET, ECoG

Correspondence:
Ann Hyslop
Department of Neurology,
Miami Children's Hospital,
3100 62nd Court, #302,
Miami, FL 33155, USA
<ann.hyslop@mchdocs.com>

doi:10.1684/epd.2015.0766

Resective surgery is an established therapeutic option for medically resistant childhood epilepsy. While extended resections guided by EEG or functional imaging may enhance rates of seizure freedom, incomplete removal of lesions or functional concerns often compromise outcomes. One quarter to one third of children undergoing excisional procedures have no detectable lesion despite increasing MRI magnetic field-strengths and multichannel head coils (Semah *et al*., 1998). This MRI-negative cohort is arguably the most challenging subset of surgical candidates. Defining their epileptogenic zone (EZ) may require scalp EEG, 3D source localization, MEG, SPECT, and/or PET in conjunction with invasive EEG recordings. Nonetheless, the EZ is often quite extensive in the MRI-negative cohort and most children undergo large lobar or multilobar resections.

We have previously reported that incomplete resections due to subtotal resection of either the epileptogenic zone or the anatomical lesion can still lead to seizure freedom in a significant number of children (Perry *et al*., 2010). While large resections lead to seizure control in a majority of MRI-negative patients, it is unclear whether, in a subset of carefully chosen patients, conservative resection sizes could lead to favourable results. To explore this possibility, we reviewed the presurgical characteristics and outcomes of the MRI-negative patients who underwent corticectomies at our institution. In each child, an EZ was identified by non-invasive testing modalities, aggressively physiologically sampled with invasive recordings, and then resected. Based on careful analysis of the pre-surgical demographic and physiological data of these patients, we describe how a method, by which favourable outcomes can be achieved when an "epicentre of the EZ" is identified, utilising multimodal functional data.

Methods

Patient population

We identified 76 MRI-negative children under age 19 years who underwent excisional surgery between January 2006 and April 2011 at our institution. Of those, 25 children had focal corticectomies and 51 underwent standard precoronal frontal lobectomy, temporal, parietal, or occipital lobectomies, or multi-lobar resections. In those who underwent corticectomy, tissue removal was restricted to one aspect of a single lobe or the insula and adjacent opercular or orbitofrontal region. Children who had a second surgery were included as long as the resection did not complete a lobar removal and involved only removal of minimal residual cortical region contiguous with the first resection.

Presurgical evaluation

Each patient underwent a detailed history and physical examination, including review of seizure risk factors, age at epilepsy onset, seizure semiology, consistency of seizure semiology over time, and seizure frequency. Every patient had a comprehensive non-invasive presurgical evaluation including scalp video-EEG, 3D volumetric MRI, and one or more of the following: EEG source localization, SPECT scan(s), PET scan, and functional MRI (fMRI).

EEG

All patients had at least two prolonged scalp video-EEG monitoring sessions, scheduled at least several months apart to document semiological and localization consistency. Electrodes were placed using the standard 10-20 system and recordings obtained with a 32-channel digital acquisition system. When appropriate, additional closely spaced electrodes were applied in the region of interest in order to increase EEG sensitivity and facilitate 3D source localization.

MRI

At least one brain MRI scan was obtained for every patient, either with a 1.5 or 3 Tesla magnet (Philips Intera 1.5 T, Philips Achieva 3.0 T, GE HDX 1.5 T). Sequences acquired from all patients included T1 and T2 weighted imaging, fluid attenuation inversion recovery (FLAIR), and volumetric sequences. Exhaustive review of images was performed at least twice; once by a paediatric neuroradiologist blinded to details of patient seizure history and, again, during a multidisciplinary case conference in which the results of all presurgical epilepsy evaluation testing were presented.

3D EEG source localization

NeuroScan software CURRY v7 (Biomedics) was used to generate moving dipole and dipole orientation solutions of representative spikes in each patient. Solutions were derived for individual as well as multiple spike averages. Volumetric MRIs were used to construct subject-dependent head models and display derived spike sources.

PET

Interictal PET (GE Discovery PET/CT) studies were performed with simultaneous scalp EEG. Performance of a PET scan at less than 24 hours following seizure activity was documented, but rare.

SPECT

Ictal SPECT scans were performed using technetium-99m hexamethylpropylamine oxime (Tc99m HMPAO,

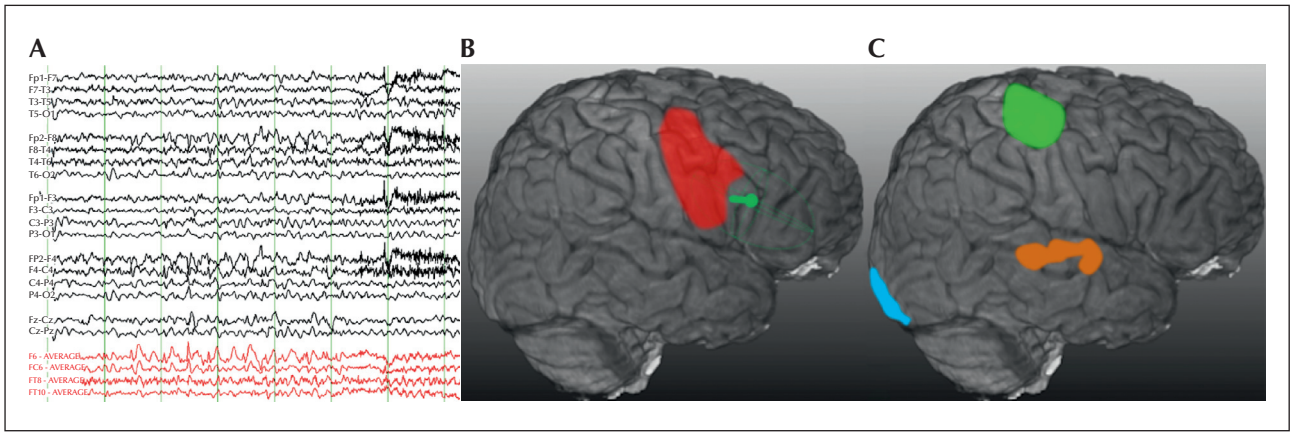

Figure 1. Presurgical testing for Patient 25. (A) Ictal onset on scalp EEG. (B) SPECT hyperperfusion (red) and 3D EEG source localization (green) coregistered to the volumetric MRI. (C) fMRI BOLD signals for left-hand motor (green), receptive language (orange), and vision (blue) paradigms. PET was performed, but was non-localizing and, therefore, not shown. 20×5mm (300×300 DPI).

300 uCi/kg) and the Siemens MultiSPECT scanner. Early ictal injections were attempted with seizure onset recognition by parents or staff; the injection timing and simultaneous EEG recordings were later reviewed by a neurophysiologist.

Image coregistration

For each patient, volumetric magnetic resonance imaging was coregistered with the SPECT and/or PET data, using Amide Medical Image Data Examiner (AMIDE) software (Stanford Molecular Imaging Program), yielding a 3D representation ultimately viewed in neuronavigation software. These data were used to plan each craniotomy and placement of subdural electrodes.

Invasive evaluation

Platinum subdural electrodes (Ad-Tech; Racine, WI) were used in intra- and extra-operative electrocorticography (ECoG). A combination of subdural and depth electrodes were utilised in most patients; depth electrodes were targeted towards deep sites identified by 3D source localization, focal SPECT or PET abnormalities or focal discharges on the subdural electrode recordings. Intraoperative ECoG recording typically lasted less than 30 minutes and involved electrode relocation and adjustment to ensure appropriate placement. Intraoperative ultrasound was used to confirm electrode location when necessary.

Each implanted patient underwent postoperative head CT to confirm accuracy of subdural electrode location in comparison with intraoperative photos. CT images were co-registered with the pre-surgical imaging including the anatomical MRI, fMRI, source localization, PET, and/or SPECT scans (*figure 1*). Subdural recording typically lasted seven days (range: 5-20 days). Intraoperative photos were also taken and used to confirm electrode orientation.

Biomarkers used to define the epicentre

Data from each modality was classified as convergent or divergent with the EZ or non-localizing. The epicentre was defined as a subset of the EZ by differentially weighting specific functional abnormalities identified by each testing modality, the degree of overlap, and primarily by invasive electrocorticography.

At our institution, biomarkers defining an epicentre have been identified as the following, based on our experience and research published by many others in the field. Those utilised in the final resection planning in this cohort were:

- Invasive EEG:
  - continuous ictal/interictal discharges on ECoG or extra-operative recordings characteristically seen in dysplastic substrate (Palmini *et al*., 1994);
  - discrete ictal onsets similar to those captured on extra-operative recordings limited to <4 contiguous electrodes (Lee *et al*., 2000);
  - a single interictal focus with dipole orientation correlating with sulcal or gyral anatomy on coregistration of subdural electrodes and brain MRI;
  - continuous focal burst suppression or marked background attenuation on extra-operative recording.
- Focal hypermetabolism on PET.
- Convergent regions of 3D EEG source localization, PET hypometabolism, SPECT hyperperfusion or ictal/interictal SPECT subtraction (Knowlton *et al*., 2008).

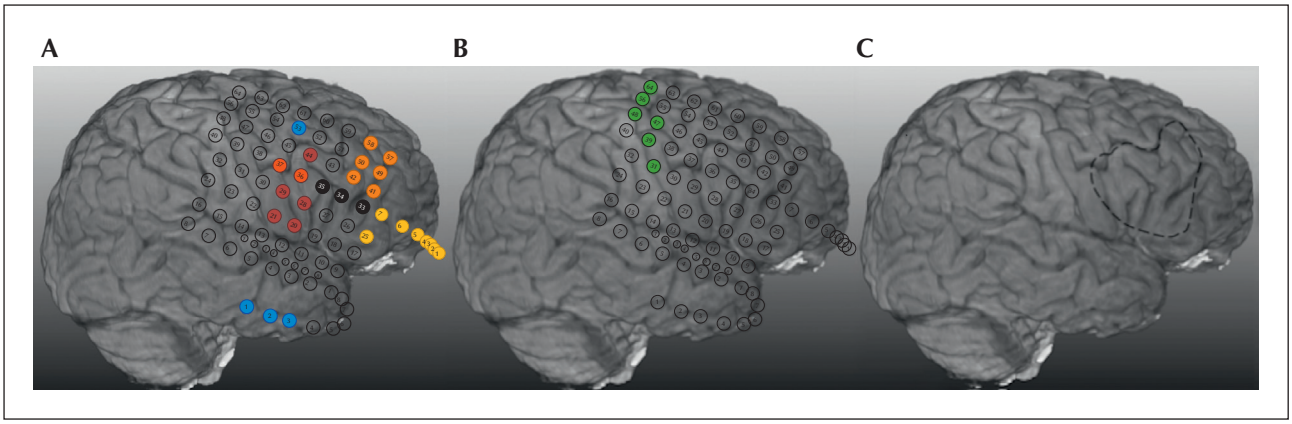

Figure 2. Data acquired from invasive EEG for Patient 25. (A) Electrodes showing interictal slowing (yellow), slowing and attenuation (orange), interictal spikes (blue), and ictal onset (red) with early spread (light red). (B) Functional mapping results for left hand motor function (green). (C) The final corticectomy. The patient is presently off medication and has been seizure-free for 2.5 years.

Other features considered to represent the EZ in MRI-negative patients, such as scattered interictal discharges, background slowing or early ictal propagation on invasive EEG, and non-overlapping regions of functional imaging abnormalities, were not regarded as part of the epicentre and not included in the resection (*figure 2*).

Resection of the epicentre

Surgical resections were restricted to the epicentre of the EZ as defined above. When invasive EEG recording did not offer discrete ictal onset, or electrode coverage was believed to be inadequate, additional recordings were utilised at the time of surgery to finalize resection plans facilitated by the use of multimodal data navigational platforms. When warranted, periodic ECoG recordings were obtained during the course of surgery and the resection was extended until no further significant ictal or continuous interictal EEG abnormalities were evident (*figure 3*).

Results

Clinical variables

Twenty-five patients (12 male and 13 female) met inclusion criteria with a mean age at seizure onset of 5.4 years (range: one day of life to 14 years) and average age at surgery of 11 years (range: six months to 19.9 years). All but five had normal neurological examinations; abnormalities found were microcephaly, hemihypertrophy, hypertonia, subtle weakness of a unilateral bicep, and subtle unilateral arm and leg incoordination. On neuropsychological evaluation, 19 had normal language function, five had abnormal language function or absent language, and one patient was preverbal. The majority (16/25) had normal cognitive functioning, eight were known to have some type of learning disability, and one was intellectually disabled.

The majority of children had daily seizures (17/25) and complex partial seizures accounted for the most common seizure type, seen in 21 of the 25 children. Eight children had MRI findings located outside of, and not adjacent to, their primary epileptic region, including: a FLAIR signal abnormality in the corpus callosum (one patient), arachnoid cyst (one patient), prominent CSF spaces (one patient), developmental venous anomaly (two patients), mild diffuse atrophy (one patient), hippocampal sclerosis (one patient), and a pineal cyst (one patient).

Pre-resection investigation

Overlap between the ultimately resected tissue and abnormality based on each functional test, including scalp EEG, PET, SPECT, source localization, intraoperative ECoG, and subdural EEG, is presented in *table 1*. PET overlap was identified when the resection included a region of hypometabolism *or* a focal region of hypermetabolic activity surrounded by an area of hypometabolism. Timing and existence of overlap of each ictal SPECT injection was documented, the majority of which occurred during non-localizing electrographic activity. When the ellipsoid of confidence of the 3D source localization contained the ultimately resected tissue, it was considered to overlap. All but one patient had subdural electrode implantation and, when appropriate, functional mapping by cortical stimulation to delineate eloquent regions. Repeat surgeries were one stage, performed with intraoperative ECoG and no electrode implantation. Analysis of pre-implantation and post-implantation recordings

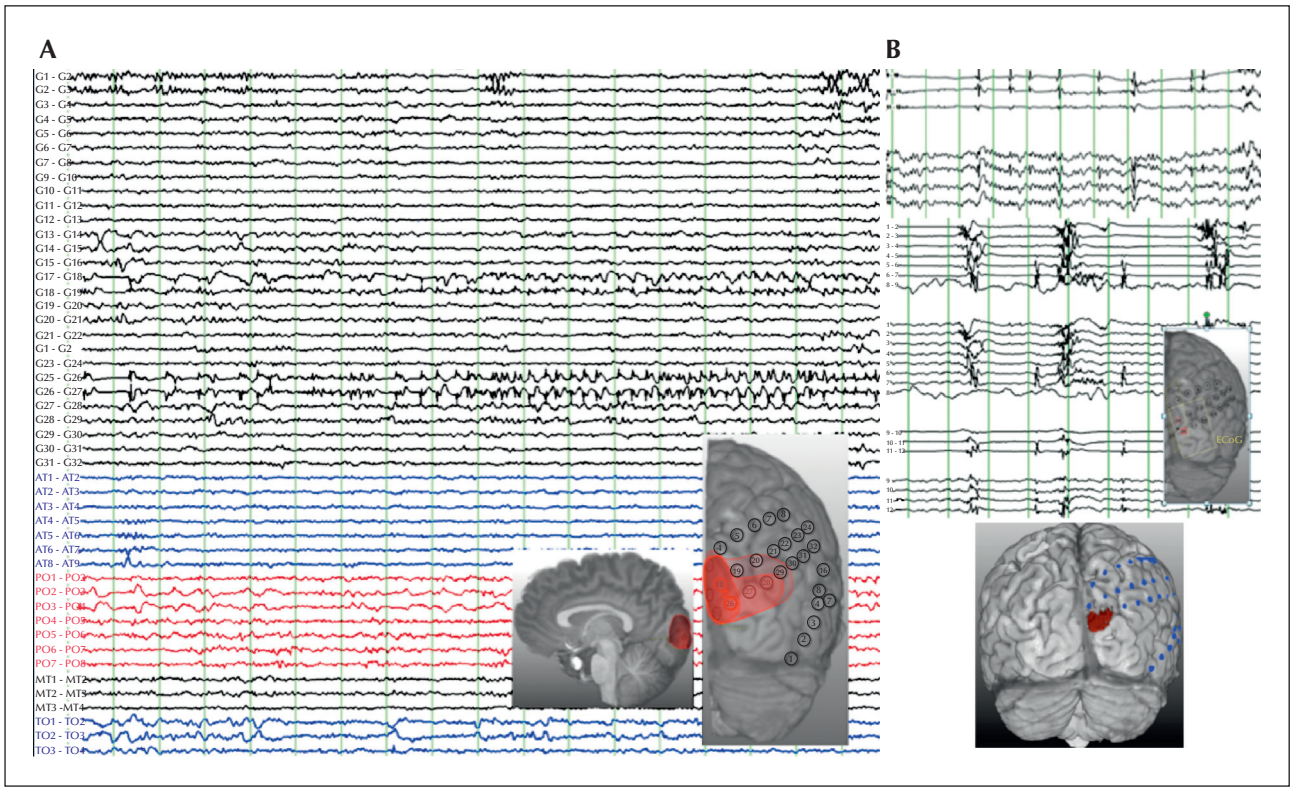

Figure 3. Subdural electrode placement and ictal onset for Patient 21, the only patient in the series to have hippocampal sclerosis. (A) The EZ defined by scalp EEG and 3D source localization in this patient with olfactory auras, prompting electrode implantation within the right posterior quadrant. Coverage of the mesial and anterior temporal structures was included, but seizure onset was localized to the high occipital region. (B) Post-implantation ECoG was performed to delineate the borders of resection.
(C) The final corticectomy (red). The patient is presently off medication and has been seizure-free for three years.

was performed in order to determine whether or not the previously defined electrographic findings overlapped the ultimately resected tissue.

Surgical variables

Overall, there were 28 surgeries performed on the 25 patients included in the study; three patients underwent a second surgical resection within one year of the first surgery (Patients 8, 18, and 22). The three children who underwent repeat surgery had minimal extension of their prior corticectomy into an adjacent cortical region. *Table 2* summarizes the location of the resections. No corticectomy was performed in a temporal lobe. Only one resection was limited due to proximity to an eloquent region. Five children suffered complications including: epidural haematoma (two patients; one of which was associated with an unexpected quadrantanopia), bacteraemia during implantation (two patients), and an ipsilateral middle cerebral artery stroke (one patient) following insular resection.

Pathology

Table 2 summarizes the Palmini subtypes of focal cortical dysplasia (FCD) found. Palmini type II FCD was the most common pathology found, seen in the resected tissue of 12 children. Six surgical specimens were comprised of cortex with characteristics of mild cortical dysplasia, but did not meet criteria for a definite FCD. None showed abnormalities consistent with another type of identifiable pathology, such as tumour, Rasmussen's syndrome, or infection.

Outcomes

Table 3 shows two-year follow-up data for all patients. For those (Patients 8, 18, and 22) who had a second surgical resection (all of which occurred within one year of the first), follow-up data included in this analysis was that documented two years after their second surgery. Postoperatively, 15 (60%) were seizure-free, three (12%) experienced >90% reduction in seizure frequency, two (8%) had a 50-90% reduction in seizure frequency, and the remaining five (20%) had no change in seizure burden. The rate of seizure freedom

Table 1. Overlap between abnormality found on functional testing and ultimately resected cortical tissue in 25 MRI-negative patients.

Functional Test	Total	Overlap	No overlap	Non-localizing
Scalp EEG				
focal interictal slowing	9	9		
focal interictal epileptiform	24	22	1	1
focal ictal onset	25	25		
PET (interictal)	19	13	3	3
SPECT				
ictal <16s	3	3		
ictal 16-30s	8	7		1
ictal 30s+	4	2		2
interictal	2	1		1
Source Localization				
interictal	12	11		1
ictal	4	4		
Intraoperative ECoG	24	24		
Subdural EEG (implantation)	24	22		2

in children with Palmini type I FCD, Palmini type II FCD, and MMCD was 3/7 (43%), 8/12 (67%) and 3/6 (50%), respectively. Further, either seizure freedom or a seizure reduction was seen in 6/7 (86%) of children with type I FCD and in 9/12 (75%) of children with type II FCD, but only in 3/6 (50%) of the children with mMCD. However, all three histopathologies were represented in the subset of children that had no reduction in seizure frequency.

Statistical analysis

The Statistical Package for Social Sciences (SPSS 19®) was used in order to organize, validate and analyse the collected data. Indicators of central tendency and dispersion (medians, means, standard deviations, standard errors of the mean, and 95% confident intervals) were estimated for quantitative variables while frequencies and percentages were used for qualitative variables. Analyses were performed with patients' Engel classes treated as a continuous variable and, separately, performed with the outcomes treated as a binary variable, such that Engel class outcomes II-IV (*i.e.* surgical failures) were combined into one group and compared to the Engel class I (surgical successes) outcome group. Correlation analysis was performed to identify significant relationships between continuous variables and a logistic regression was used when the response variable was treated as a binary variable. A level of significance of 0.05 was selected for all tests of significance.

Predictors of outcome

There was no significant difference in outcome based on age at seizure onset, age at surgery, preoperative seizure type or frequency, abnormalities seen on neurological examination, cognitive deficits, location of resection, or the number of preoperative functional tests providing convergent data. There was no significant difference in outcome based on pathology. However, upon removing the three insular cases and grouping the patients into surgical successes (Engel class I) vs. surgical failures (Engel classes II-IV) there was a significant inverse correlation between the Engel class outcome and the number of modalities that indicated abnormal cortical function overlapping the region of ultimately resected tissue; r=-0.57, p<0.05. This finding implies that in the extra-insular cases, for the more functional studies that showed overlap with the region, the more likely the patient was to have an Engel class I outcome. In grouping the surgical successes (Engel class I) vs. surgical failures (Engel classes II-IV), no significant correlations were found otherwise.

Discussion

It is well established that the achievement of seizure freedom or significant seizure reduction in children with MRI-negative epilepsy is more challenging than those with structural lesions (Blume *et al.*, 2004; Krsek *et al.*, 2009a). In non-lesional patients, definition of the EZ relies on our ability to identify epileptogenic lesions

Table 2. Location and pathology by Engel class outcome.

		Total	Class 1	Class 2	Class 3	Class 4
Location	Frontal	13	7	2	1	3
	Parietal	7	5	1	1	0
	occipital	2	2	0	0	0
	orbitofrontal/insular	3	1	0	0	2
FCD Palmini Subtype						
	Type 1a	3	2	1	0	0
	Type 1b	4	2	1	0	1
	Type 2a	10	7	1	0	2
	Type 2b	2	1	0	0	1
	MMCD	6	3	0	2	1

that are abnormal based on measurable electrophysiological or functional properties (Obeid *et al*., 2009). In this MRI-negative patient population, our review of the pre-surgical data shows that patients in our cohort had a significant amount of convergent data from 3D EEG source localization, SPECT, PET, ECoG, and subdural EEG. The results suggest that in carefully chosen MRI-negative children, a minimally resective approach offers a high likelihood of seizure freedom or reduction in seizure frequency in the first two post-operative years. In this study, 72% of children had an Engel class I or II outcome following small resections.

Several preoperative factors likely contributed to the good outcomes seen in this cohort. First, the cohort consisted of relatively few intellectually disabled patients in this cohort compared to other studies. This suggests that the pathological substrate in most of the children was less likely to be diffuse and, thus, more likely to be contained in a small resection compared to children in studies with high rates of cognitive disability. Second, and most importantly, the study is retrospective and the major inclusion criterion was that the child had to have undergone a corticectomy, a surgical approach that implies that a patient had convergent preoperative data and, therefore, guarantees a significant pre-selection bias in this cohort. To mitigate this pre-selection bias, every MRI-negative child who had a corticectomy for epilepsy at our institution within the time period specified was included, regardless of: age, seizure type and frequency, pre-surgical testing performed or not, location of resection, the number of surgeries, and tissue pathology.

Although it is difficult to compare results from this series of patients to cohorts that did not have this inherently strong pre-selection bias, our outcomes are similar to those seen in non-lesional paediatric cohorts in which larger resections were standard. A 2008 retrospective review of 101 non-lesional paediatric patients who underwent large (unilobar or multilobar) resections at our institution showed that 58% had Engel class I or II ("good") outcomes, two or more years after surgery (Jayakar *et al*., 2008). Over a decade ago, a review of lesional and MRI-negative children who had undergone epilepsy surgery was performed at our institution. One year postsurgically, 74% of the non-lesional cases achieved good outcome and 51% were seizure-free, but, again, resections were primarily lobar or multi-lobar (Paolicchi *et al*., 2000). Studies inclusive of adult and paediatric patients describe utilisation of lobectomies and multilobar resections with good postoperative outcomes in 61-80% and seizure freedom rates ranging between 37 and 47% were reported (Blume *et al*., 2004; Chapman *et al*., 2005; Lee *et al*., 2005).

Utility of convergent data from multiple testing modalities

Numerous studies have evaluated the utility of PET, SPECT, 3D source localization, and advanced MRI techniques in the pre-surgical evaluation of individuals with MRI-negative epilepsy. Magnetoecephalography (MEG), while not available at our institution, is a testing modality that offers epileptogenic source localization that may also contribute to definition of an EZ.

Nineteen of our patients had PET scans, a commonly used functional test in MRI-negative cases. The majority of PET scans in this cohort revealed areas of abnormal glucose metabolism in regions of cortex ultimately resected. Since these areas of hypometabolism often overestimate the EZ and can increase in size with increasing seizure frequency (Juhasz *et al*., 2000; Benedek *et al*., 2006), it is not surprising that regions of abnormality were not typically resected in their entirety in our cohort.

SPECT has also been shown to be helpful in the localization of FCD in children with non-lesional MRI (Gupta *et al*., 2004). In our cohort, of the 15 children

Table 3. Patient summary of convergence of functional testing data with ultimately resected cortical tissue, region of corticectomy, pathology, and Engel class outcome.

Patient	EEG (interictal)	SL (ictal, interictal)	SPECT (ictal)	PET (interictal)	ECoG (interictal)	Subdural (ictal)	Region	Palmini Pathology	Engel Class Outcome
1	CONV		NL		CONV	CONV	P	1a	2
2	CONV		NL		CONV	CONV	F	MMCD	3
3	NL		NL	CONV	CONV	CONV	P	2a	1
4	CONV		CONV		CONV	CONV	F	2b	4
5	DIV					CONV	F	1b	4
6	CONV		CONV	NL	CONV	CONV	F	2b	1
7	CONV		CONV	CONV	CONV	CONV	F	1b	1
8	CONV		CONV	CONV, MF	CONV	CONV	I	1b	1
9	NL		CONV	DIV	CONV	CONV	F	1a	2
10	CONV	CONV		CONV, MF	CONV*	(no sz)	P	2a	1
11	CONV	CONV	CONV		CONV	(no sz)	F	2a	1
12	CONV	CONV	CONV	CONV	CONV	CONV	P	2a	1
13	CONV			CONV	CONV	CONV	P	2a	1
14	CONV			CONV, MF	DIV	CONV	F	MMCD	1
15	CONV	NL		CONV, MF	CONV	CONV	P	MMCD	1
16	CONV	CONV			CONV	CONV	F	MMCD	4
17	CONV			CONV	CONV	CONV	O	1b	1
18	CONV	CONV	CONV	CONV	DIV	CONV	I	2a	4
19	CONV	CONV	CONV	CONV	CONV	CONV	F	2a	1
20	CONV	CONV		DIV	CONV	CONV	P	MMCD	3
21	CONV	CONV		DIV	CONV	CONV	O	MMCD	1
22	CONV	CONV	CONV	CONV	CONV	CONV	I	2a	4
23	CONV	CONV	NL	NL	CONV	CONV	F	2a	2
24	CONV	CONV	CONV	CONV	CONV		F	2a	1
25	CONV	CONV	CONV	NL	CONV	CONV	F	1a	1

CONV: convergent with ultimate resection; NL: non-localizing; CONV, MF: convergent but multifocal; DIV: divergent; CONV*: convergent *ictal* capture; (no sz): no seizure captured; F: frontal; P: parietal; I: insular/orbitofrontal; O: occipital.

who underwent SPECT, the majority had regions of hyperperfused cortex that were included in their resection. However, the region of hyperperfusion was not resected in its entirety in the children whose cortical resection margins were made smaller by invasive EEG. Not surprisingly, later ictal injections were less likely to yield localizing information (see *table 2*). However, even with early injection of a tracer after seizure onset, the poor resolution of the tracer within the regional cerebral blood flow images can implicate propagation pathways outside of the primary epileptogenic zone (Kaminska *et al*., 2003). This likely contributes to the finding that most patients who underwent SPECT achieved seizure freedom even if

they did not have the entirety of the hyperperfused cortex resected.

It is now feasible to perform image coregistration on every surgical case. In order to prevent sampling errors from limited coverage and inaccurate electrode placement, all of our cases have coregistration of functional and MRI data prior to planning of the craniectomy. After ECoG and placement of subdural electrodes, the CT electrode images are added to the coregistration. We have found that the routine use of image coregistration at our institution results in more accurate subdural electrode placement and improves our interpretation of electrocorticography data, both of which give rise to a more precise cortical resection.

In evaluating the number of modalities used to determine focality and minimize resection, it is apparent that children with insular epilepsy had more preoperative studies despite the fact that two of three had Engel class IV outcomes. Insular cases are particularly challenging, not only due to difficulty in preoperative localization, but because of the technical nature of resection. Therefore, these patients routinely undergo more preoperative testing and are more likely to have residual epileptogenic tissue after resection.

Navigating the data generated in evaluation of non-lesional paediatric epilepsy patients is complex and requires clinical acumen that cannot be measured. However, our data supports the previously established finding that a greater number of functional studies may yield a more accurate identification of the EZ, resulting in a more complete resection and favourable outcome. It also supports the use of specific biomarkers previously reported to accurately define the EZ. Unfortunately, the small size of this study does not generate the power needed to determine a preoperative test's independent predictive value for a seizure-free outcome, nor does it suggest the minimum number of studies needed to show convergence. It does highlight the fact that more effective methods of localizing epileptogenic cortical dysplasia in this MRI-negative population are needed.

The role of pathology in the MRI-negative population

Much work has gone into the identification, description, and classification of FCDs (Palmini *et al*., 2004; Blumcke and Spreafico, 2011; Blumcke *et al*., 2011). Because of the prognostic implications offered by classifying the pathology presurgically, researchers have sought to describe the MRI characteristics of subsets of cortical dysplasia (Lerner *et al*., 2009; Krsek *et al*., 2009b). In the MRI-negative population, since FCD type is not revealed until after resection, no surgical decisions can be made based on the suspected pathology, but its presence can be reassuring, implying that epileptogenic cortex was removed. In our cohort, all patients had abnormal cortical findings on histological analysis and 19/25 (76%) had definite FCD, a relatively high percentage compared to findings in prior studies (Siegel *et al*., 2001; Blume *et al*., 2004; Lee *et al*., 2005; Chapman *et al*., 2005; RamachandranNair *et al*., 2007; Jayakar *et al*., 2008).

Normal or non-specific MRI findings are more often associated with Palmini type I cortical dysplasia (Tassi *et al*., 2010). However, in identifying candidates for minimal resection, we selected those who had the most focal or well-defined electrophysiological abnormalities and, since these are properties inherent to most Palmini type II FCDs, it is not surprising that almost half of our cohort harboured this type of FCD. In turn, our relatively high rate of seizure freedom can be attributed, at least in part, to the fact that patients with type II dysplasia are more likely to have a seizure-free outcome compared to those with type I (Krsek *et al*., 2009b; Sisodiya *et al*., 2009). Additionally, at our institution, MRI-negative patients who have a suspected seizure focus in the temporal lobe will typically undergo a temporal lobectomy rather than a corticectomy. Since type I FCDs are more commonly found in the temporal lobes and type II FCDs in extra-temporal sites (Widdess-Walsh *et al*., 2005), we were more likely to reveal type II FCDs.

Surgical failures in the MRI-negative population

Based on close examination of the 10 children who were not seizure-free postoperatively, no clear trend in preoperative data was identified. All had at least one of the previously listed biomarkers defining an epicentre either on invasive EEG recording, a hypermetabolic PET or convergence between 3D EEG source localization, PET hypometabolism, and SPECT hyperperfusion. One child (Patient 4) had a resection that was limited and considered incomplete due to overlap between the epileptogenic region and Broca's area. Two children (Patients 18 and 22) had partial insular resections and were believed to have residual, adjacent epileptogenic tissue.

The definition of completeness in the MRI-negative patient

In lesional cases, it is well known that incomplete resection of anatomical lesions is associated with a less favourable outcome (Paolicchi *et al*., 2000; Krsek *et al*., 2009a; Sarkis *et al*., 2012). Previously, we have defined "completeness," as it pertains to surgical resection of an epileptogenic region, as complete excision of the electrophysiologically abnormal cortex (Duchowny,

2009). By this definition, almost all of our cases would be considered incomplete, including many of those with Engel class I outcomes, since electrophysiologically abnormal cortex was electively left in for most cases. Aside from the rare patient with a focal region of electrophysiological abnormality removed entirely by a corticectomy, this term as it is currently defined does not provide meaningful prognostic information for an MRI-negative patient undergoing a minimal resection. More work is needed to identify the most sensitive and specific biomarkers of the epileptogenic epicentre, such that "completeness" can be redefined as complete excision of this epicentre.

Complication rates

In our cohort, two (8%) children suffered unexpected permanent neurological sequelae; one experienced a quadrantanopia due to a small ischaemic insult and the other experienced an MCA stroke, likely from disruption of vasculature coursing through the insula, at the location of corticectomy. Alarcon and colleagues (2006) reported a ~5% complication rate in 105 patients who underwent subdural electrode implantation and, most often, a large cortical resection (Alarcon *et al*., 2006). A recent study of 865 epilepsy surgery cases, inclusive of all types of epilepsy surgery in adults and children, reported a major complication rate of 3%, a rate that was similar between those with and without invasive recording (Bjellvi *et al*., 2015). Complication rates are likely higher in our population compared to others due to the small sample size and, possibly, the surgical skills involved in tailored corticectomy (versus lobectomy).

Follow-up

We often maintain our postoperative patients on at least one antiepileptic medication following surgery for two years. However, 8/15 (53%) of our patients with Engel class I outcome were completely off medications at the two-year postoperative time point. A five-year follow-up duration, inclusive of medication continuation data, is needed to evaluate the seizure recurrence rate among these individuals.

Conclusion

Performing small resections of epileptogenic epicentres in a carefully chosen cohort of MRI-negative children with medically intractable epilepsy can result in seizure freedom in the majority. A longer follow-up period is required to show that risk of seizure recurrence is not higher in this population compared to those who have undergone larger resections. Future studies are needed to show that children who have undergone minimal resections actually perform better on postoperative neuropsychological testing than those with more extensive resections. □

Disclosures.
None of the authors have any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

References

Alarcon G, Valentin A, Watt C, *et al*. Is it worth pursuing surgery for epilepsy in patients with normal neuroimaging? *J Neurol Neurosurg Psychiatry* 2006; 77: 474-80.

Benedek K, Juhasz C, Chugani DC, Muzik O, Chugani HT. Longitudinal changes in cortical glucose hypometabolism in children with intractable epilepsy. *J Child Neurol* 2006; 21: 26-31.

Bjellvi J, Flink R, Rydenhag B, Malmgren K. Complications of epilepsy surgery in Sweden 1996-2010: a prospective, population-based study. *J Neurosurg* 2015; 122: 519-25.

Blumcke I, Spreafico R. An international consensus classification for focal cortical dysplasias. *Lancet Neurol* 2011; 10: 26-7.

Blumcke I, Thom M, Aronica E, *et al*. The clinicopathologic spectrum of focal cortical dysplasias: a consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission. *Epilepsia* 2011; 52: 158-74.

Blume WT, Ganapathy GR, Munoz D, Lee DH. Indices of resective surgery effectiveness for intractable nonlesional focal epilepsy. *Epilepsia* 2004; 45: 46-53.

Chapman K, Wyllie E, Najm I, *et al*. Seizure outcome after epilepsy surgery in patients with normal preoperative MRI. *J Neurol Neurosurg Psychiatry* 2005; 76: 710-3.

Duchowny M. Clinical, functional, and neurophysiologic assessment of dysplastic cortical networks: implications for cortical functioning and surgical management. *Epilepsia* 2009; 50(9): 19-27.

Gupta A, Raja S, Kotagal P, Lachhwani D, Wyllie E, Bingaman WB. Ictal SPECT in children with partial epilepsy due to focal cortical dysplasia. *Pediatr Neurol* 2004; 31: 89-95.

Jayakar P, Dunoyer C, Dean P, *et al*. Epilepsy surgery in patients with normal or nonfocal MRI scans: integrative strategies offer long-term seizure relief. *Epilepsia* 2008; 49: 758-64.

Juhasz C, Chugani DC, Muzik O, *et al*. Electroclinical correlates of flumazenil and fluorodeoxyglucose PET abnormalities in lesional epilepsy. *Neurology* 2000; 55: 825-35.

Kaminska A, Chiron C, Ville D, *et al*. Ictal SPECT in children with epilepsy: comparison with intracranial EEG and relation to postsurgical outcome. *Brain* 2003; 126: 248-60.

Knowlton RC, Elgavish RA, Limdi N, *et al*. Functional imaging: I. Relative predictive value of intracranial electroencephalography. *Ann Neurol* 2008; 64: 25-34.

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

Krsek P, Pieper T, Karlmeier A, *et al*. Different presurgical characteristics and seizure outcomes in children with focal cortical dysplasia type I or II. *Epilepsia* 2009b; 50: 125-37.

Lee SA, Spencer DD, Spencer SS. Intracranial EEG seizure-onset patterns in neocortical epilepsy. *Epilepsia* 2000; 41: 297-307.

Lee SK, Lee SY, Kim KK, Hong KS, Lee DS, Chung CK. Surgical outcome and prognostic factors of cryptogenic neocortical epilepsy. *Ann Neurol* 2005; 58: 525-32.

Lerner JT, Salamon N, Hauptman JS, *et al*. Assessment and surgical outcomes for mild type I and severe type II cortical dysplasia: a critical review and the UCLA experience. *Epilepsia* 2009; 50: 1310-35.

Obeid M, Wyllie E, Rahi AC, Mikati MA. Approach to pediatric epilepsy surgery: state of the art. *Part I: General principles and presurgical workup. Eur J Paediatr Neurol* 2009; 13: 102-14.

Palmini A, Gambardella A, Andermann F, *et al*. Operative strategies for patients with cortical dysplastic lesions and intractable epilepsy. *Epilepsia* 1994; 35(6): S57-71.

Palmini A, Najm I, Avanzini G, *et al*. Terminology and classification of the cortical dysplasias. *Neurology* 2004; 62: S2-8.

Paolicchi JM, Jayakar P, Dean P, *et al*. Predictors of outcome in pediatric epilepsy surgery. *Neurology* 2000; 54: 642-7.

Perry MS, Dunoyer C, Dean P, *et al*. Predictors of seizure freedom after incomplete resection in children. *Neurology* 2010; 75: 1448-53.

RamachandranNair R, Otsubo H, Shroff M, *et al*. MEG predicts outcome following surgery for intractable epilepsy in children with normal or nonfocal MRI findings. *Epilepsia* 2007; 48: 149-57.

Sarkis RA, Jehi L, Bingaman W, Najm IM. Seizure worsening and its predictors after epilepsy surgery. *Epilepsia* 2012; 53: 1731-8.

Semah F, Picot MC, Adam C, *et al*. Is the underlying cause of epilepsy a major prognostic factor for recurrence? *Neurology* 1998; 51: 1256-62.

Siegel AM, Jobst BC, Thadani VM, *et al*. Medically intractable, localization-related epilepsy with normal MRI: presurgical evaluation and surgical outcome in 43 patients. *Epilepsia* 2001; 42: 883-8.

Sisodiya SM, Fauser S, Cross JH, Thom M. Focal cortical dysplasia type II: biological features and clinical perspectives. *Lancet Neurol* 2009; 8: 830-43.

Tassi L, Garbelli R, Colombo N, *et al*. Type I focal cortical dysplasia: surgical outcome is related to histopathology. *Epileptic Disord* 2010; 12: 181-91.

Widdess-Walsh P, Kellinghaus C, Jeha L, *et al*. Electro-clinical and imaging characteristics of focal cortical dysplasia: correlation with pathological subtypes. *Epilepsy Res* 2005; 67: 25-33.

TEST YOURSELF

(1) Based on clinical presentation and scalp EEG, what factors would prompt a pre-surgical evaluation and raise suspicion that a corticectomy would be appropriate in a MRI-negative child?

(2) The authors describe an approach by which they performed corticectomies in MRI-negative children with epilepsy after defining an epicentre of the epileptogenic zone (EZ) in each child. What were the basic steps to this approach?

(3) What patterns seen on invasive EEG recording were used by the authors to define the epicentre of the EZ in the final resection planning for each patient?

(4) What patient characteristics likely contributed to the high incidence of cortical pathology and seizure freedom rate reported in this series?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".