Functional Network Analysis in Epileptic Children Using Multimodal Imaging, SEEG, and Surgical Pathology

Roy Dudley MD, PhD
Department of Pediatric Surgery
Division of Neurosurgery
Montreal Children’s Hospital
Montreal Neurological Institute
McConnell Brain Imaging

Canadian League Against Epilepsy
2017 Scientific Meeting
Vancouver
October 13 – 15, 2017
Disclosures

No Disclosures
No relationships with commercial interests
Outline

Evolution of our surgical thinking about focal epilepsy
• *Failures of intraoperative MRI for epilepsy surgery*

How we changed our imaging strategies with networks in mind
• *Much more functional imaging*

Advanced surgical planning
• *Based less on what we see on MRI*

Using surgical pathology to define the borders
• *Where do we go next time if seizures recur?*

Other clues from surgical pathology
• *New Horizons: Oligodendrocytes? Somatic Mutations?*
Epileptogenic Focus

Epileptogenic Zone
(Local Network)

Epileptogenic Network
(Extended Network)

MRI
Sometimes non-invasive functional mapping (fMRI, fMEG)

MRI
Sometimes Non-invasive functional mapping
PET
SPECT
MEG
Sometimes intracranial recording (Grids vs SEEG)

Figure 4. A diagram showing the actual seizure-onset zone, the potential seizure-onset zone, and a surgical resection that includes both seizure-onset zones. Complete resection of both seizure-onset zones should result in seizure-freedom.


MRI
Sometimes Non-invasive functional mapping
PET
SPECT
MEG
EEG-fMRI
Intracranial recording (SEEG)
Connectivity Analysis

EVOLUTION IN SURGICAL THINKING ABOUT FOCAL EPILEPSY DERIVED OUT OF NECESSITY NEED TOOLS AVAILABLE – (i.e., collaborations)
3-T intraoperative MRI (iMRI) for pediatric epilepsy surgery

Nebnas M. Wani, Oliver Lavry, Adel Farah, Christine Saint-Martin, Jose L. Montes, Jeffrey Atkinson, Jean-Pierre Farmer, Roy W.R. Dudley

Abstract

Purpose Three-totlas iMRI is a promising tool that could help confirm complete resections and disconnections in pediatric epilepsy surgery, leading to improved outcomes. However, a large proportion of epileptogenic pathologies in children are poorly defined on imaging, which brings into question the utility of iMRI for these cases. Our aim was to compare postoperative seizure outcomes between iMRI and non-iMRI-based epilepsy surgeries.

Methods We performed a comparative retrospective analysis of non-iMRI versus iMRI-based epilepsy surgeries with 2-year follow-up. Patients were stratified into well-defined cases (WDCs), poorly defined cases (PDCs), and diffuse hemispheric cases (DHCs). Primary outcomes were rates of complete seizure freedom and surgical complications. Secondary outcomes included good (Engel class I/II) seizure outcome, ex- tent of resection/disconnection, and operative duration. Regression models were used to adjust for confounding.

Results Thirty-nine iMRI-based and 39 non-iMRI-based surgeries were included. The distributions of age, sex, and lesion class in each era were similar, but the distributions of individual pathologies varied. Seizure freedom and complication rates at 2-year follow-up were not different between the groups, but Engel class I/II outcome was more common in the iMRI group. Extent of resection/disconnection and length of surgery were similar in both groups. PDCs had the worst outcomes, which were unchanged by the use of iMRI.

Conclusion Three-totlas iMRI-based epilepsy surgery may have the potential to improve patient outcomes. However, we conclude that iMRI, in its current state of use at our institute, does not improve outcomes for children undergoing epilepsy surgery. Given that its use appears safe, further research on this technology is warranted, particularly for the most challenging PDCs.

Keywords Epilepsy - Intraoperative MRI - Outcomes - Complications - Imaging

Introduction

Epilepsy surgery is used to cure intractable focal epilepsy by performing tailored resections or disconnections of epileptogenic foci while preserving normal surrounding brain. Detailed, multi-
Other reported outcomes for Focal Cortical Dysplasia in children
Most studies report 50–55% success rate

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Patients (total number and other features)</th>
<th>Hemispherectomy dual pathology</th>
<th>MRI-visible lesion (%)</th>
<th>Invasive monitoring</th>
<th>Mean follow-up period</th>
<th>Overall outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krsek et al., 2009</td>
<td>r = 149 144 were &lt;20 years; FCD Type I, 68; Type II a and b, 52</td>
<td>Hemispherectomy, 21; hippocampal sclerosis, 22</td>
<td>71/108 (66 %); non-FCD abnormalities in additional 18 patients</td>
<td>100 (67 %)</td>
<td>Mean 6.5 years; 113 with 5-year and 55 with 10-year follow-up</td>
<td>Engel I, 55 %; Engel II, 12 %</td>
</tr>
<tr>
<td>Cosset et al., 2008</td>
<td>r = 113 64 with various forms of MCD</td>
<td>Also includes tumors; MTS, 11</td>
<td>108 (96 %); 10 multifocal and 9 hemispheric</td>
<td>41 (36 %)</td>
<td>2 years or more</td>
<td>Engel I, 60 % Engel II, 9 %</td>
</tr>
<tr>
<td>Kloss et al., 2002</td>
<td>r = 68 FCD type I, 60 %, FCD type II, 40 %</td>
<td>Excluded tumors and dual pathology</td>
<td>95 %</td>
<td>34 (50 %)</td>
<td>2 years or more</td>
<td>Engel I, 50 %</td>
</tr>
<tr>
<td>Otsubo et al., 2013</td>
<td>r = 36 FCD, 29; hemi-megalencephaly, 16; polymicrogyria, 5</td>
<td>Hemispherectomy 18; multilobar 7</td>
<td>91 %</td>
<td>7 (12.5 %)</td>
<td>4.3 years</td>
<td>Engel I, 66 %</td>
</tr>
<tr>
<td>Kim et al., 2011</td>
<td>r = 48 FCD type I, 6; FCD type II, 24; mild MCD, 18; 23 patients with epileptic encephalopathy</td>
<td>None</td>
<td>62 %</td>
<td>unavailable</td>
<td>2.13 years (0.7–5.5 years)</td>
<td>Engel I, 56 %</td>
</tr>
<tr>
<td>Fujiwara et al., 2012</td>
<td>r = 44 FCD, 34; tuberous sclerosis complex, 8; others, 2</td>
<td>Hemispherectomy excluded</td>
<td>59 %</td>
<td>100 %</td>
<td>14 months (12–26 months)</td>
<td>Engel I, 52 %</td>
</tr>
<tr>
<td>Phi et al., 2010</td>
<td>r = 41 FCD type I, 54 %, type IIa, 20 %, II b, 27 %</td>
<td>Excluded</td>
<td>54 %</td>
<td>36 (88 %)</td>
<td>73 month (24–153 months)</td>
<td>Engel I 49 % at 1 year; 44 % at 2 years; 33 % at 3 years</td>
</tr>
<tr>
<td>Hader et al., 2004</td>
<td>r = 39 mean age 9.6 years</td>
<td>No hemispherectomy; 7 with dual pathology</td>
<td>82 %</td>
<td>15 (58 %)</td>
<td>3.6 years</td>
<td>Engel I, 54 %</td>
</tr>
<tr>
<td>Wyllie et al., 1998</td>
<td>r = 36 FCD, 22; hemispheric, 2; extratemporal, 9; extratemporal/multilobar, 22</td>
<td>Hemispherectomy, 2</td>
<td>At least 5 (of 36) patients with dysplasia had normal MRI</td>
<td>Unknown; 22 % in the overall group of 136</td>
<td>3.6 years (for the whole group)</td>
<td>Engel I, 52 %</td>
</tr>
<tr>
<td>Kang et al., 2013</td>
<td>r = 30 FCD type I a, 12; I b, 9; II a, 6; II b, 1. 2 with MRI diagnosis of FCD</td>
<td>Hemispherectomy, 2</td>
<td>80 %</td>
<td>None</td>
<td>54 months (13–103 months)</td>
<td>Engel I, 73 %</td>
</tr>
<tr>
<td>Noll et al., 2013</td>
<td>r = 31 (all FCD type I)</td>
<td>Hemispherectomy, 2</td>
<td>100 %</td>
<td>11 (54 %)</td>
<td>4.7 years (1–9 years)</td>
<td>Engel I, 67 %</td>
</tr>
</tbody>
</table>

FCD focal cortical dysplasia, MTS mesial temporal sclerosis


Recent study of the use of SEEG in young children showed 84% seizure freedom mean F/U 29 mo


How can we do better?
Decided to change the Pre-Surgical & “Post-Surgical” Evaluation

What have we done in the past?

- Scalp EEG & Video-EEG
- MRI (3T MRI)
- Semiology Discussion
- Neuropsychology

Many studies have shown that PET, SPECT, MEG can assist in the pre-surgical localization of epileptogenic zone.

Not a lot of PET/SPECT: 15/46 PDLs, 32.6%

No MEG

MEG & PET have been shown to be complimentary


Intracranial Recording (only Grids) 10/46 PDLs, 21.7%

Did not use SEEG

SEEG is the only way to truly map extended 3D epileptogenic networks

No dedicated pathological or genetic analysis of sub-specimens

How do we know what’s happening at the borders? Could somatic mutations play a role?

http://my.clevelandclinic.org/services/neurological_institute/epilepsy/diagnostics-testing/pre-surgical-process
New Advanced Pre-Surgical & Post-Surgical Evaluation Strategy

Scalp EEG & Video-EEG
MRI (3T MRI)
Semiology Discussion
Neuropsychology

PET & SPECT & Arterial Spin Labeling (ASL) Perfusion MRI

MEG
Jeremy Moreau, Elizabeth Simard-Tremblay, Bernard Rosenblatt, Sylvain Baillet, BIC, McGill
Steffen Albrecht
Andrea Accogli, Myriam Srour, McGill

Dedicated pathological or genetic analysis of sub-specimens
Patricia Tomaszewski, McGill

If Needed

Advanced MEG Analyses
- Frequency Band Analysis
- Connectivity Analysis
- Overnight Ictal MEG
Jeremy Moreau, Sylvain Baillet, BIC, McGill

EEG-fMRI
Hui Ming Khoo, Jean Gotman, MNI, McGill

SEEG (as opposed to subdural grids)
Jeff Hall, Andre Olivier, Birgit Frauscher, Francois Dubeau
MNI, McGill
3 yr old boy with 60-100 fencing-posture seizures per day, on 4 meds

PET/SPECT/ASL extended beyond borders of structural MRI lesion

*Pathology of Lateral Borders*: “Positive for dysmorphic neurons. Although full-fledged changes of FCD IIb are not seen, a few dysmorphic neurons are present in the cortex, consistent with the edge of FCD.”

Surgical resection plan based on PET

Seizure free 23 months. Off all meds
5 yr old girl with episodes of loss of contact, fumbling with hands, secondarily generalized seizures

Ictal MEG: Beta Power (i.e., low voltage fast activity)
5 yr old girl with episodes of loss of contact, fumbling with hands, secondarily generalized seizures

Hypothesized epileptogenic network based on concordant EEG, MRI, PET, SPECT, ASL, MEG
Surgical resection based on PET-MRI Lesion Co-registration
Overlap with Eloquent Cortex

Angular Gyrus BA39
Sometimes part of Wernicke’s area
Language, Math, Cognition

Supramarginal Gyrus BA40
Sometimes part of Wernicke’s area
Language perception and processing

Superior Temporal Gyrus BA22
Part of Wernicke’s area

MEG Language task
(passive story listening)
suggested LEFT language dominance
Only mild transient word finding difficulties
Seizure Free >11 months
18 yr girl had left frontal tumor resected at 5 months; has had Sz ever since; getting worse

**MEG Interictal Power Analysis** suggested Left Frontal Opercular abnormalities, but this is experimental

**MEG language Task:** 
Apparent Right Frontal Language Localization. Confirmed with ESAM

**EEG-fMRI**
Apparent Left Frontal Opercular Seizure Onset Zone

Resection based on MEG & EEG-fMRI

Seizure Free 9 months
13 yr old boy: Sz since 5yrs old; already had 2 resections based on Subdural Grid Placement. **No** improvement.

Grids: “Multiple electroclinical Sz captured with onset arising R. Frontal & Fronto-polar regions.”

Difficult to interpret due to resection
SEEG Implantation

R. Posterior Cingulate  R. Posterior SMA  R. Parietal above lesion
R. Middle SMA  
R. Middle Cingulate  
R. Anterior SMA  
R. Anterior Cingulate  
R. Frontopolar  
R. Orbitofrontal  
R. Parietal behind lesion

Implantation performed together with F. Dubeau & J. Hall, MNI

Interictal activity: very active anterior and posterior
SEEG Implantation

R. Orbitofrontal
R. Frontopolar
R. Anterior Cingulate
R. Anterior SMA
R. Middle Cingulate
R. Middle SMA
R. Posterior Cingulate
R. Posterior SMA
R. Parietal above lesion
R. Parietal behind lesion
R. Parietal above lesion

Ictal activity: Orbito-Frontal, stereotypical seizures and auras
Initial spread to frontopolar, anterior cingulate, anterior SMA, then the rest

Implantation performed together with F. Dubeau & J. Hall, MNI
SEEG-based Resection: Orbito-Frontal, Fronto-Polar, Ant SMA, Ant Cingulate
Dedicated Pathological Analysis of Sub-Specimens

SFG, MFG, IFG had rare dysmorphic neurons only

Ant Cingulate gyrus had several dysmorphic neurons

Gurus rectus had FCD IIb

Orbitofrontal gyrus had FCD IIb

Seizure free for 13 months
Screening of 22 genes of PI3K-AKT-mTOR or RAS-MAPK pathways at different sites throughout the epileptigenic network

<table>
<thead>
<tr>
<th>PATIENT ID</th>
<th>1220854</th>
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</thead>
<tbody>
<tr>
<td>Gene</td>
<td>MTOR</td>
</tr>
<tr>
<td>Variant</td>
<td>c.4447T&gt;C</td>
</tr>
<tr>
<td></td>
<td>p.Cys1483Arg</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>R frontal lobe epilepsy</td>
</tr>
<tr>
<td>Histology</td>
<td>FCDIIa, FCDIIb</td>
</tr>
<tr>
<td>Tissue 1(_H)</td>
<td>1476,38 (2.57%)</td>
</tr>
<tr>
<td>Tissue 1(_N) (validation)</td>
<td>99848,1126 (1.1%)</td>
</tr>
<tr>
<td>Tissue 2(_N) (validation)</td>
<td>92371,227 (0.25%)</td>
</tr>
<tr>
<td>Blood</td>
<td>-</td>
</tr>
<tr>
<td>Saliva</td>
<td>n.d.</td>
</tr>
<tr>
<td>Mother</td>
<td>n.d.</td>
</tr>
<tr>
<td>Father</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

1st resection 0.17-1.19% mutant allele, 4 samples
2nd resection 5.92-8.79% mutant allele, 2 samples
3rd resection 0.83-3.55% mutant allele, 3 samples

H: Haloplex; N: Nextera; n.d. not detectable
Screening of 22 genes of PI3K-AKT-mTOR or RAS-MAPK pathways at different sites throughout the epileptigenic network

Andrea Accogli
Myriam Srour
McGill

MTOR c.4447T>C p.Cys1483Arg (0.17-8.79%)

<table>
<thead>
<tr>
<th>specimen</th>
<th>location</th>
<th>% mutant allele</th>
<th>Histopathological notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFPE 1</td>
<td>R parietal lesion (aspiration)</td>
<td>280124,3100 (1.09%)</td>
<td>Gliosis, subcortical ectopic neurons, focal perivascular spindled histocytes</td>
</tr>
<tr>
<td>FFPE 2</td>
<td>R parietal lesion biopsy</td>
<td>82765,161 (0.19%)</td>
<td>Unremarkable cortex</td>
</tr>
<tr>
<td>FFPE 3</td>
<td>R parietal lesion biopsy</td>
<td>88596,148 (0.17%)</td>
<td>No pathological</td>
</tr>
<tr>
<td>FFPE 4</td>
<td>R parietal lesion biopsy</td>
<td>64596,778 (1.19%)</td>
<td>No pathological</td>
</tr>
<tr>
<td>FFPE 5</td>
<td>R anterior frontal lobe (excision)</td>
<td>104913,6600 (5.92%)</td>
<td>FCDIIb</td>
</tr>
<tr>
<td>FFPE 6</td>
<td>R anterior frontal lobe (aspiration)</td>
<td>81226,7836 (8.79%)</td>
<td>FCDIIa</td>
</tr>
<tr>
<td>FFPE 7</td>
<td>R superior frontal gyrus (excision)</td>
<td>11424,126 (1.09%)</td>
<td>Dyssmorphic neurons without FCD</td>
</tr>
<tr>
<td>FFPE 8</td>
<td>R inferior frontal gyrus (excision)</td>
<td>125144,1045 (0.83%)</td>
<td>Dyssmorphic neurons without FCD</td>
</tr>
<tr>
<td>FFPE 9</td>
<td>R frontal lobe (aspiration)</td>
<td>94670,3480 (3.55%)</td>
<td>FCDIIb</td>
</tr>
</tbody>
</table>

2nd resection 5.92-8.79% mutant allele, 2 samples

1st resection 0.17-1.19% mutant allele, 4 samples

3rd resection 0.83-3.55% mutant allele, 3 samples
13 yr old boy with recurrent epilepsy after previous Left Anterior Temporal Resection (prev. FCD IIa)

T1 MRI  PET  SPECT  MEG  ASL

Language fMRI (Synonym Gen.)
Denise Klein, MNI, McGill

EEG-fMRI suggested L. Temporal & Frontal Network
Hui Ming Khoo & Jean Gotman, MNI, McGill

Pathology: No FCD this time, but oligodendrocyte hyperplasia found throughout specimen, including all borders
Pathology: No FCD this time, but oligodendrocyte hyperplasia found throughout specimen, including all borders; rare disabling seizures but not seizure free

Oligodendrocyte hyperplasia has been associated with:
• difficult to treat epilepsy
• wide epileptogenic networks
• often requiring multiple lobe resections

Subcortical oligodendrocyte hyperplasia may connect diffuse epileptogenic zones?

Sakuma S, et al., Increased subcortical oligodendroglia-like cells in pharmacoresistant focal epilepsy in children correlate with extensive epileptogenic zones. Epilepsia. 2016 Dec;57(12):2031-2038


5 yr old girl previous LEFT functional hemispherectomy
Started having seizures again: Staring and RIGHT-sided arm posturing

Ictal MEG
- 2s time window
- MIP (glass brain) view

Parameters
- 33.8 to 34.8s baseline
- 1-70 Hz bandpass, 60Hz notch
- OS vol head model
- MN source model
- Unthresholded

Suggests the disconnection is incomplete
Ictal MEG

- First 4 peaks of MEG burst (36.31s, 36.67s, 36.93s, 37.20s)
- Same data as video on previous slide (but without MIP)

Suggests the disconnection is incomplete

5 yr old girl previous LEFT functional hemispherectomy
Started having seizures again: Staring and RIGHT-sided arm posturing
**Connectivity Results**

Phase locking value (PLV) was computed between seed regions of interest (ROIs) in a 10 min run of spontaneous MEG

**Delta (2-4 Hz)**

R posterior middle temporal gyrus ROI shows a surprisingly high degree of connectivity with L hemisphere structures

PLV value between R & L frontal operculum is also high

Might suggest persistent connections between R & L hemispheres

Other possibilities:
- One or more intermediary structure (e.g. the thalamus)
- External stimulus presented bilaterally could drive neural populations in both hemispheres to fire in sync.

**Theta (5-7 Hz)**

Intensity Threshold: 0.15
Surgical outcomes of 9 consecutive patients using **New Presurgical Evaluation Strategy**

- 28 Months
- 23 Months
- **Not Seizure Free**: Overlapped Language Areas
- 14 Months
- 13 Months
- EEG-fMRI suggested extensive network
- 11 Months
- Oligodendrocyte hyperplasia throughout
- 23 Months
- 8 Months
- 4 Months

**New Advanced Presurgical Evaluation Strategy**

- Scalp EEG & Video-EEG
- MRI (3T MRI)
- Semiology Discussion
- Neuropsychology
- PET & SPECT & Arterial Spin Labeling (ASL) Perfusion MRI
- MEG
  - Jeremy Moreau, Elizabeth Smart-Trainblay, Bernard Rosenblatt, Sylvain Balllat, BIC, McGill
  - Dedicated pathological or genetic analysis of sub-specimens
  - Steffen Albrecht, Andrea Assogli, Myriam Sour, McGill
- Advanced MEG Analyses
  - Overnight local MEG
  - Frequency Band Analysis
  - Connectivity
- If Needed
- EEG-fMRI
  - Hui Ving Khoi & Jean Getman, MRI, McGill
- SEEG (as opposed to subdural grids)
  - Jeff Hall, Andre Oliver, Siegfried Frauendorf, Francois Dubeau, MH, McGill
Thank You
Jeremy Moreau
Patricia Tomaszewski
Nebras Warsi
Oliver Lasry
Nassima Addour
Elizabeth Bock
Sylvain Baillet
Hui Ming Khoo
Jean Gotman
Boris Bernhardt
Bernard Rosenblatt
Francois Dubeau
Birgit Frauscher
Christine Saint-Martin
Nagwa Wilson
Gilbert Guillaume
Pia Wintermark
Steffen Albrecht
Myriam Srour
Jeff Hall
Andre Olivier
Lili Orsini
Jeff Atkinson
Jean-Pierre Farmer
Bruce Mazer