

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

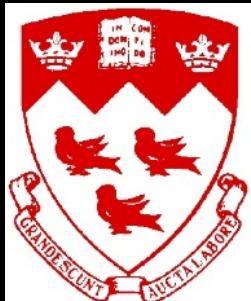
McConnell Brain Imaging

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

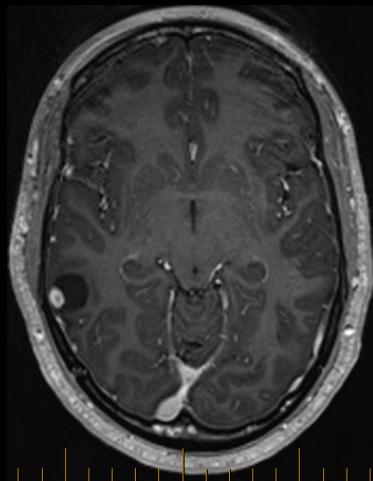
- *Where we have to go next time if seizures recur*

Clues from surgical pathology

- *New Horizons: Oligodendrocytes? Local Genetics?*

EVOLUTION IN SURGICAL THINKING ABOUT FOCAL EPILEPSY DERIVED OUT OF NECESSITY NEED TOOLS AVAILABLE – (i.e., collaborations)

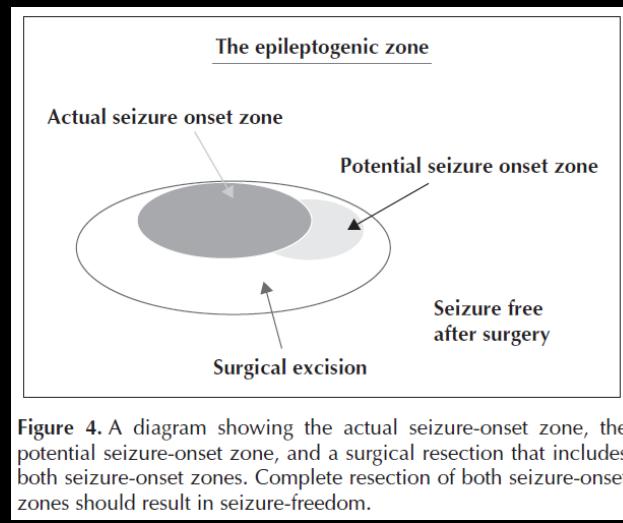
Epileptogenic Focus



MRI

Sometimes non-invasive functional mapping
(fMRI, fMEG)

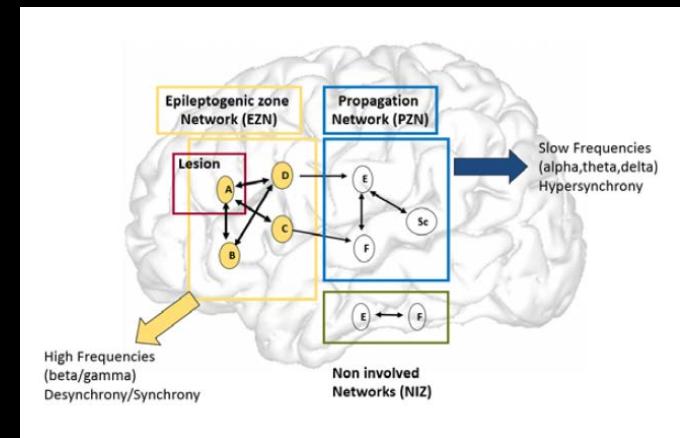
Epileptogenic Zone (Local Network)



Lüders HO, et al., 2006 Aug;8 Suppl 2:S1-9.

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

Epileptogenic Network (Extended Network)



Bartolomei F, et al., Epilepsia. 2017 Jul;58(7):1131-1147.

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

NETWORK THINKING DERIVED OUT OF NECESSITY

Failures of intra-operative MRI

Childs Nerv Syst (2016) 32:2415–2422
DOI 10.1007/s00381-016-3263-3

ORIGINAL PAPER

3-T intraoperative MRI (iMRI) for pediatric epilepsy surgery

Nebras M. Warsi¹ · Oliver Lasry^{1,2}  · Adel Farah¹ · Christine Saint-Martin³ ·
Jose L. Montes¹ · Jeffrey Atkinson¹ · Jean-Pierre Farmer¹ · Roy W. R. Dudley¹

Received: 17 February 2016 / Accepted: 3 October 2016 / Published online: 18 October 2016
© Springer-Verlag Berlin Heidelberg 2016

Abstract

Purpose Three-tesla intraoperative MRI (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, extent 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.

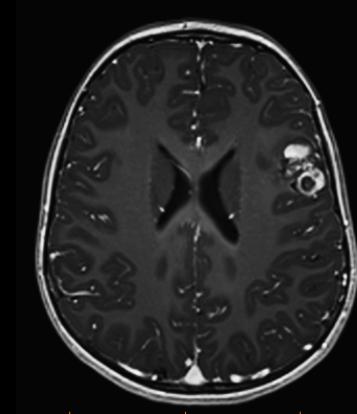
Conclusion Three-tesla iMRI-based epilepsy surgery may have the potential to improve patient outcomes. However, we conclude that iMRI, in its current state of use at our institute, does not improve outcomes for children undergoing epilepsy surgery. Given that its use appears safe, further research on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

Keywords Epilepsy · Intraoperative MRI · Outcomes · Complications · Imaging

Introduction

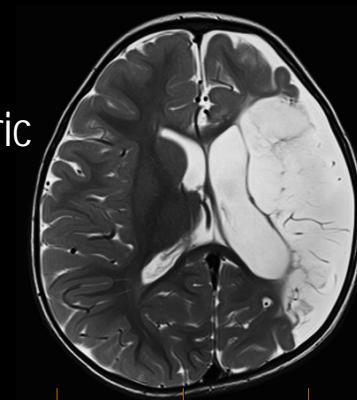
Epilepsy surgery is used to cure intractable focal epilepsy by performing tailored resections or disconnections of epileptogenic foci while preserving normal surrounding brain. Detailed, multi-

Well Defined
Lesions/Cases



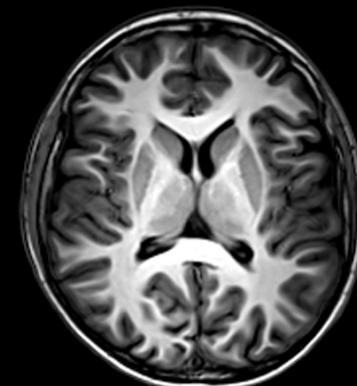
WDCs

Diffuse Hemispheric
Cases



DHCs

Poorly Defined
Lesions/Cases

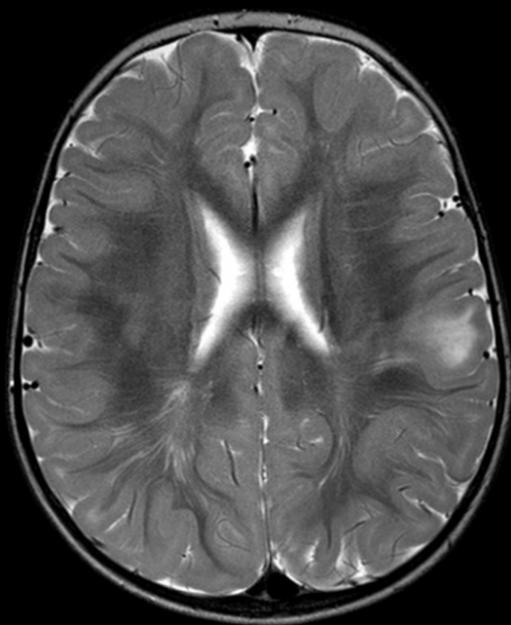
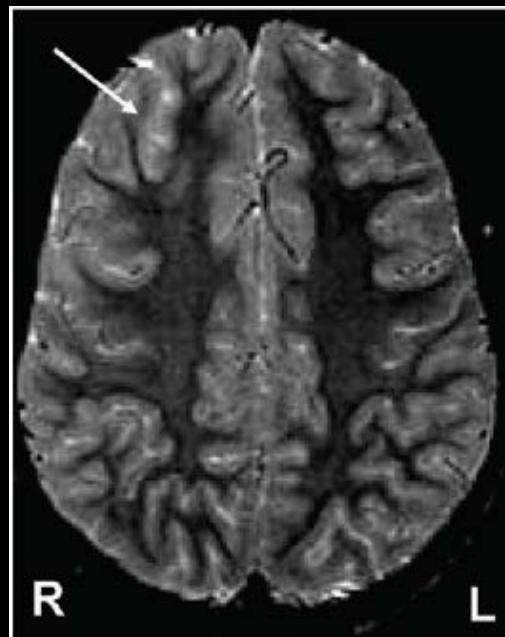
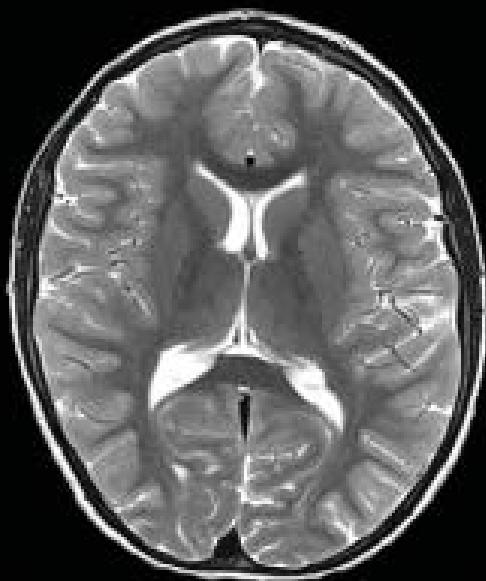


PDCs

Poorly Defined Cases

These most challenging cases include:

1. Nothing on MRI (i.e., Non-lesional, MRI Negative)
2. Subtle lesions: Is it an anatomical lesion or not? Could be misleading.
3. Lesions that would be expected to extend beyond what is seen on MRI (FCD, TS)



iMRI did not help at all for Poorly Defined Cases

Childs Nerv Syst (2016) 32:2415–2422
DOI 10.1007/s00381-016-3263-3



ORIGINAL PAPER

3-T intraoperative MRI (iMRI) for pediatric epilepsy surgery

Nebras M. Warsi¹ · Oliver Lasry^{1,2} · Adel Farah¹ · Christine Saint-Martin³ · Jose L. Montes¹ · Jeffrey Atkinson¹ · Jean-Pierre Farmer¹ · Roy W. R. Dudley¹

Received: 17 February 2016 / Accepted: 3 October 2016 / Published online: 18 October 2016
© Springer-Verlag Berlin Heidelberg 2016

Abstract

Purpose Three-tesla intraoperative MRI (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, extent 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

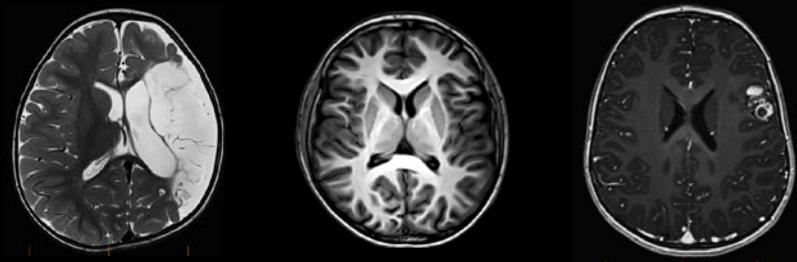
rates at 2-year follow-up were not different between the groups, but Engel class I/II outcome was more common in the iMRI group. Extent of resection/disconnection and length of surgery were similar in both groups. PDCs had the worst outcomes, which were unchanged by the use of iMRI.

Conclusion Three-tesla 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.

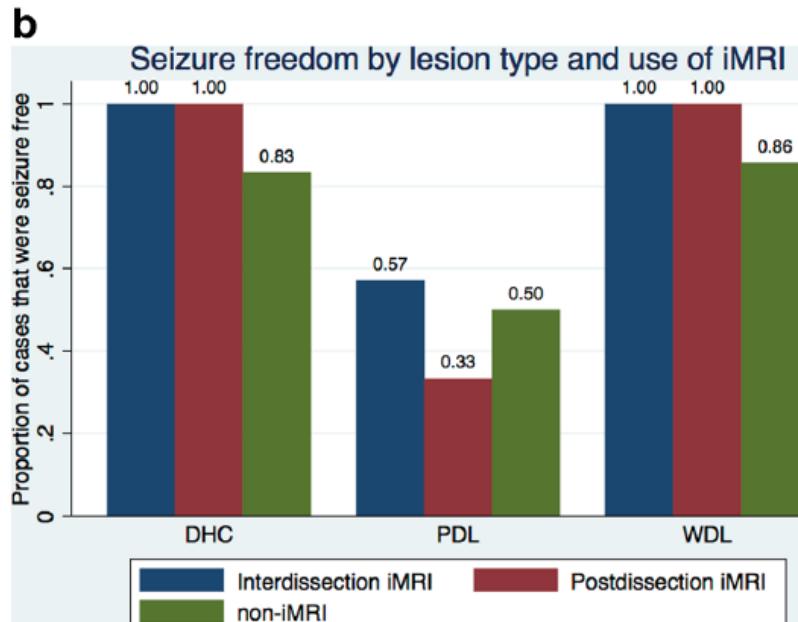
Keywords Epilepsy · Intraoperative MRI · Outcomes · Complications · Imaging

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-



Childs Nerv Syst (2016) 32:2415–2422



iMRI did not help with poorly defined cases

Conclusion: iMRI does not improve outcomes for children undergoing epilepsy surgery.

Other reported outcomes for Focal Cortical Dysplasia in children

The overall seizure freedom rates range from 40-73%, ~2 years after surgery;
most studies report 50–55% success rate

Table 1 Outcome after epilepsy surgery in children with focal cortical dysplasia/malformation of cortical development

Study, year	Patients (total number and other features)	Hemispherectomy dual pathology	MRI-visible lesion (%)	Invasive monitoring	Mean follow-up period	Overall outcome
Krsek et al., 2009 [7]	n=149 144 were <20 years; FCD Type I, 68; Type II a and b, 52	Hemispherectomy, 21; hippocampal sclerosis, 22	71/108 (66 %); non-FCD abnormalities in additional 18 patients	100 (67 %)	Mean 6.5 years; 113 with 5-year and 55 with 10-year follow-up	Engel I, 55 %; Engel II, 12 %
Cossu et al., 2008 [16]	n=113 94 with various forms of MCD	Also includes tumors; MTS, 11	108 (96 %); 10 multifocal and 9 hemispheric	41 (36 %)	2 years or more	Engel I, 60 %; Engel II, 9 %
Kloss et al., 2002 [17]	n=68 FCD type I, 60 %; FCD type II, 40 %	Excluded tumors and dual pathology	95 %	34 (50 %)	2 years or more	Engel I, 50 %; Engel II, 10 %
Otsuki et al., 2013 [18]	n=56 FCD, 29; hemi-megalencephaly, 16; polymicrogyria, 5	Hemispherectomy 18; multilobar 7	91 %	7 (12.5 %)	4.3 years	Engel I, 66 %
Kim et al., 2011 [4]	n=48 FCD type I, 6; FCD type II, 24; mild MCD, 18; 23 patients with epileptic encephalopathy	None	62 %	unavailable	2.13 years (0.7–5.5 years)	Engel I, 56 %; Engel II, 25 %
Fujiwara et al., 2012 [8]	n=44 FCD, 34; tuberous sclerosis complex, 8; others, 2	Hemispherectomy excluded	59 %	100 %	14 months (12–26 months)	Engel I, 52 %
Phi et al., 2010 [20]	n=41 FCD type I, 54 %; type II a, 20 %, II b, 27 %	Excluded	54 %	36 (88 %)	73 month (24–153 months)	Engel I 49 % at 1 year; 44 % at 2 years; 33 % at 3 years
Hader et al., 2004 [14]	n=39 mean age 9.6 years	No hemispherectomy; 7 with dual pathology	82 %	15 (38 %)	3.6 years	Engel I, 54 %; Engel II, 18 %
Wyllie et al., 1998 [21]	n=36 dysplasia (total 136 patients in the study with various etiologies)	Hemispherectomy, 2; temporal, 9; extra-temporal/multilobar, 22	At least 5 (of 36) patients with dysplasia had normal MRI	Unknown; 22 % in the overall group of 136	3.6 years (for the whole group)	Engel I, 52 %; Engel II, 19 %
Kang et al., 2013 [22]	n=30 FCD type I a, 12; I b, 9; II a, 6; II b, 1. 2 with MRI diagnosis of FCD	Hemispherectomy, 2	80 %	None	54 months (13–103 months)	Engel I, 73 %
Noli et al., 2013 [23]	n=31 (all FCD type II)	Hemispherectomy, 2	100 %	11 (54 %)	4.7 years (1–9 years)	Engel I, 67 %; Engel II, 10 %

FCD focal cortical dysplasia, MTS mesial temporal sclerosis

Moosa AN, Gupta A. Outcome after epilepsy surgery for cortical dysplasia in children. *Childs Nerv Syst.* 2014 Nov;30(11):1905-11.

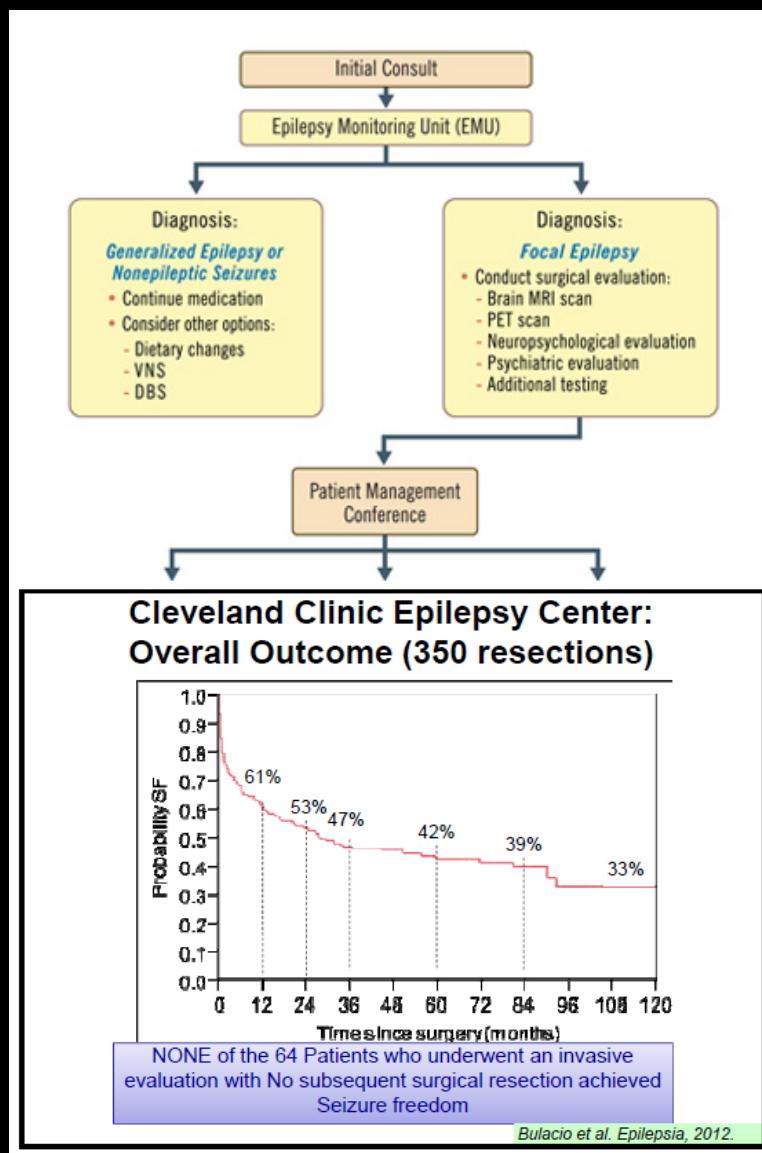
Recent study of the use of SEEG in young children showed 84% seizure freedom mean F/U 29 mo

Dorfmüller et al., . Outcome of surgery in children with focal cortical dysplasia younger than 5 years explored by stereo-electroencephalography. *Childs Nerv Syst.* 2014 Nov;30(11):1875-83

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 complimentary
Widjaja E, et al., Epilepsia 2013;54:691–699

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

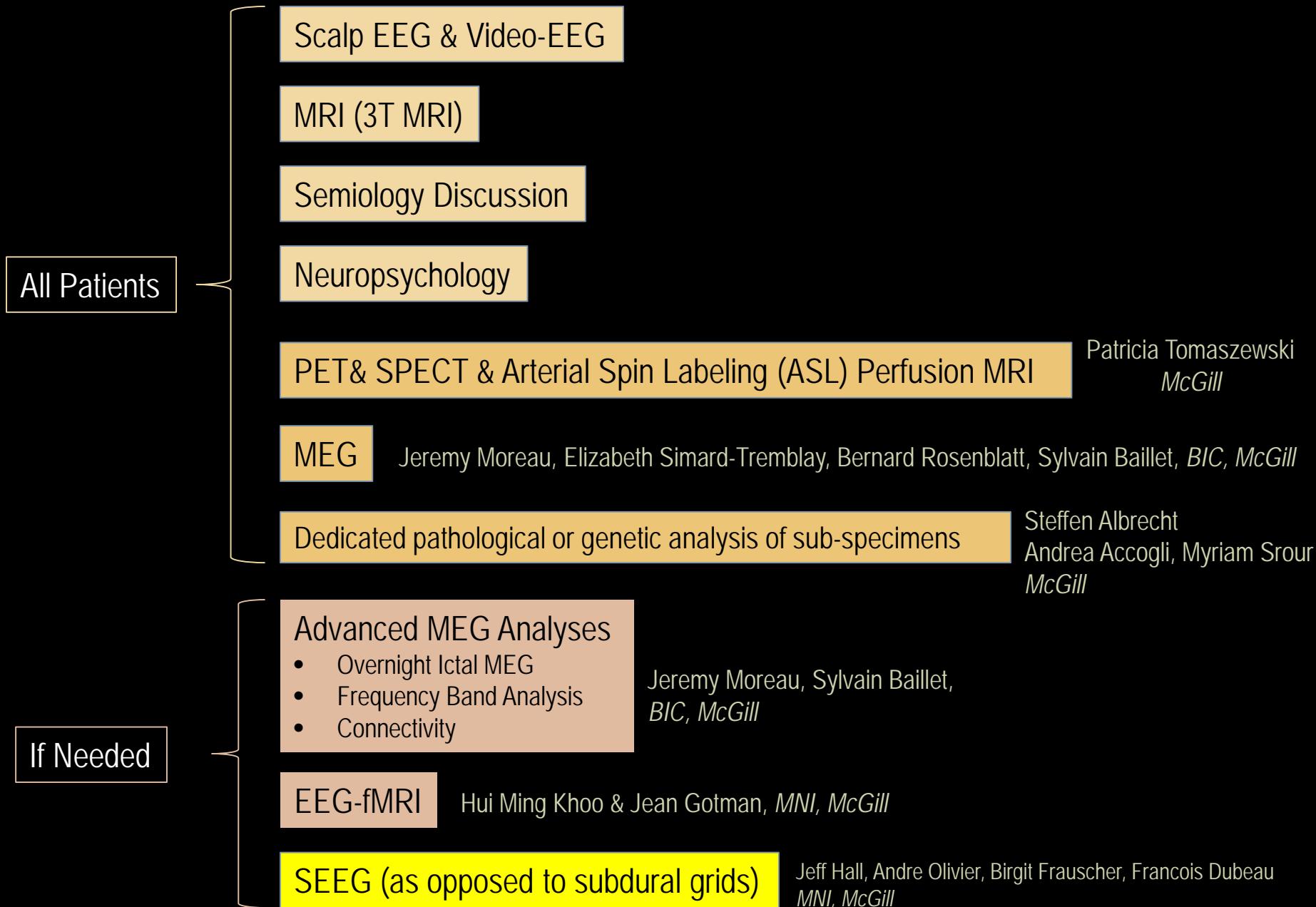
Didn't use SEEG

SEEG is the only true way to map extended epileptogenic networks

No dedicated pathological or genetic analysis of sub-specimens

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

New Advanced Presurgical Evaluation Strategy

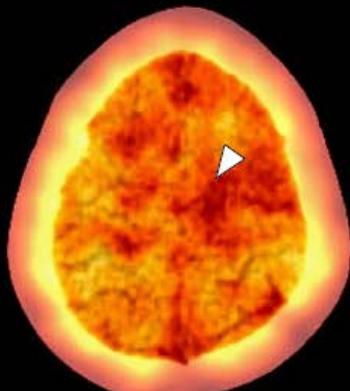


3 yr old boy with 60-100 fencing-posture seizures per day, on 4 meds

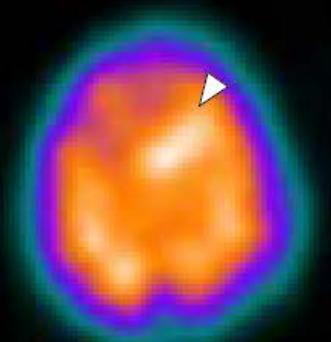
PET/SPECT/ASL extended beyond borders of structural MRI lesion



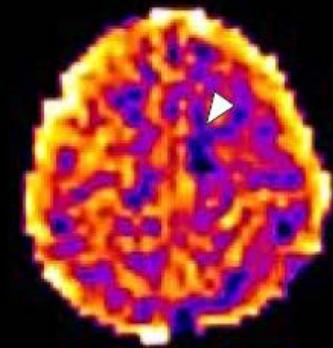
T1 MRI



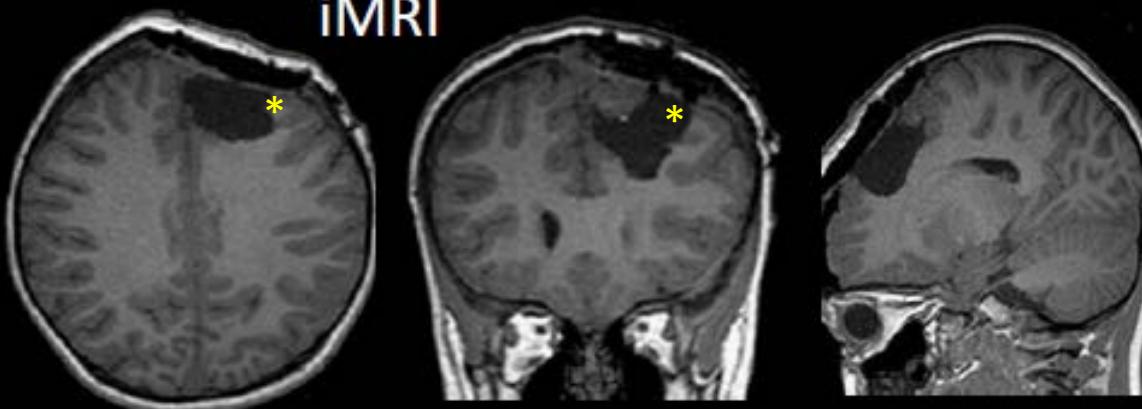
PET



Ictal SPECT



ASL

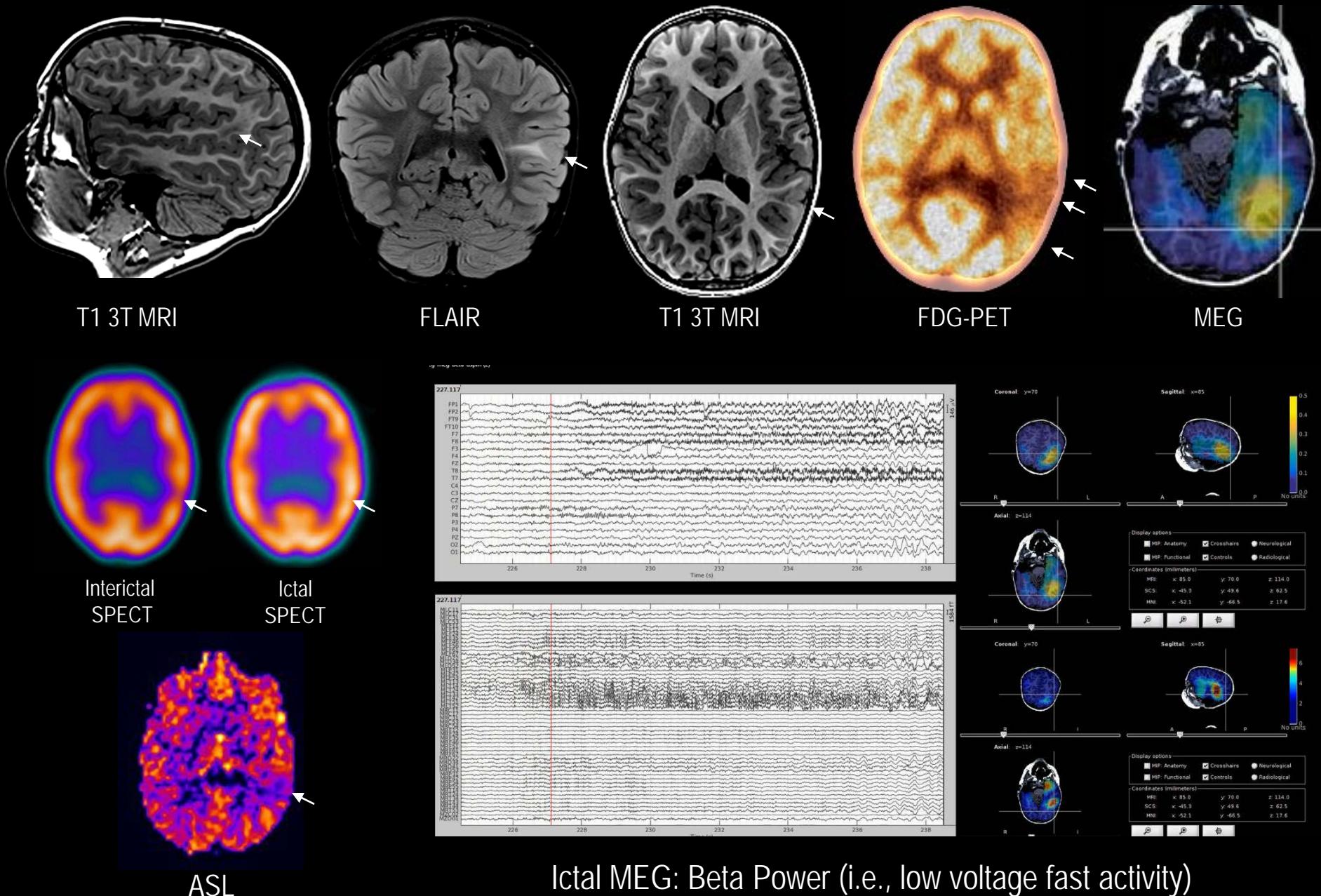


Surgical resection
plan based on PET

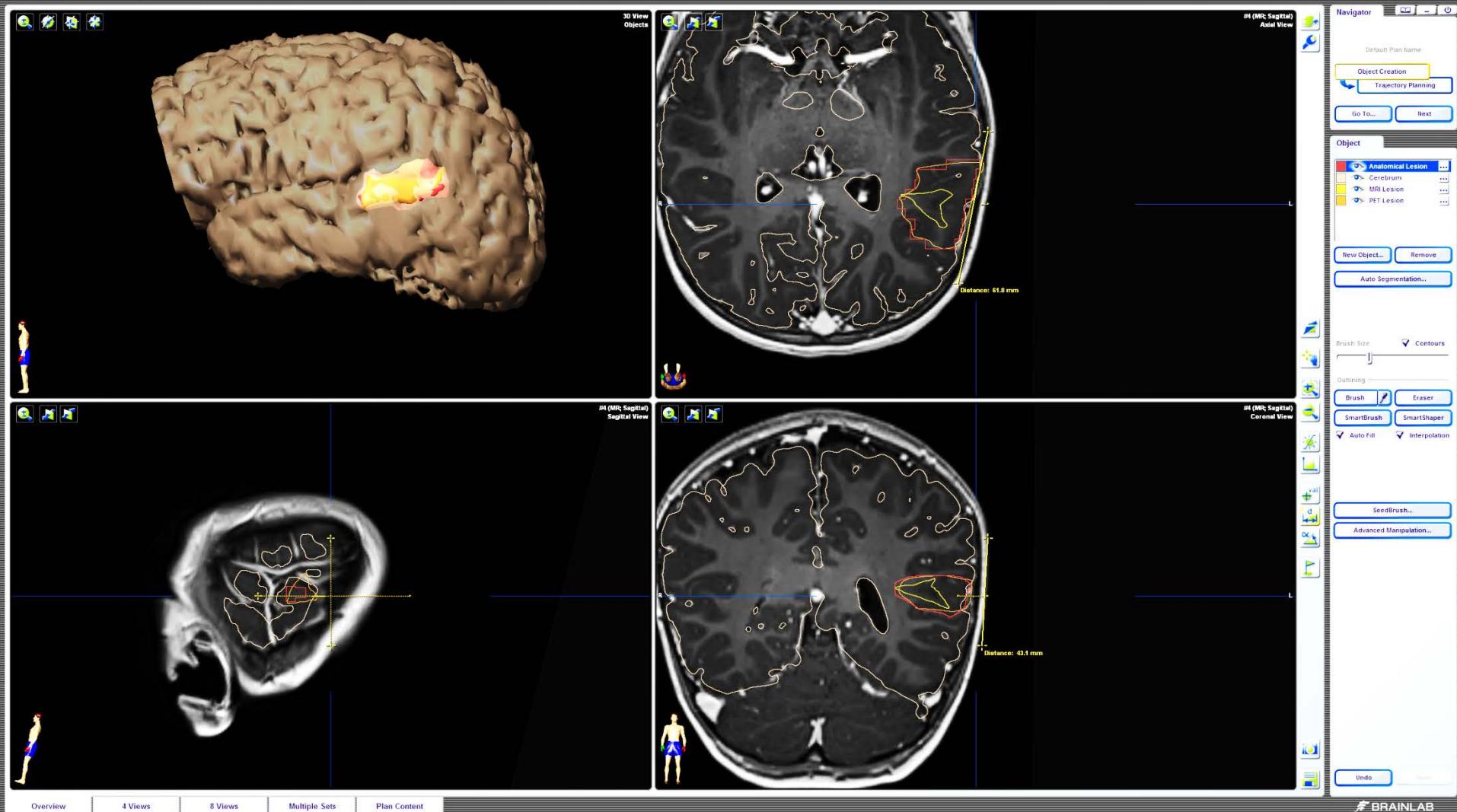
Seizure free
23 months

***Pathology of Lateral Border:** “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.”

5 yr old girl with episodes of loss of contact, fumbling with hands, secondarily generalized seizures

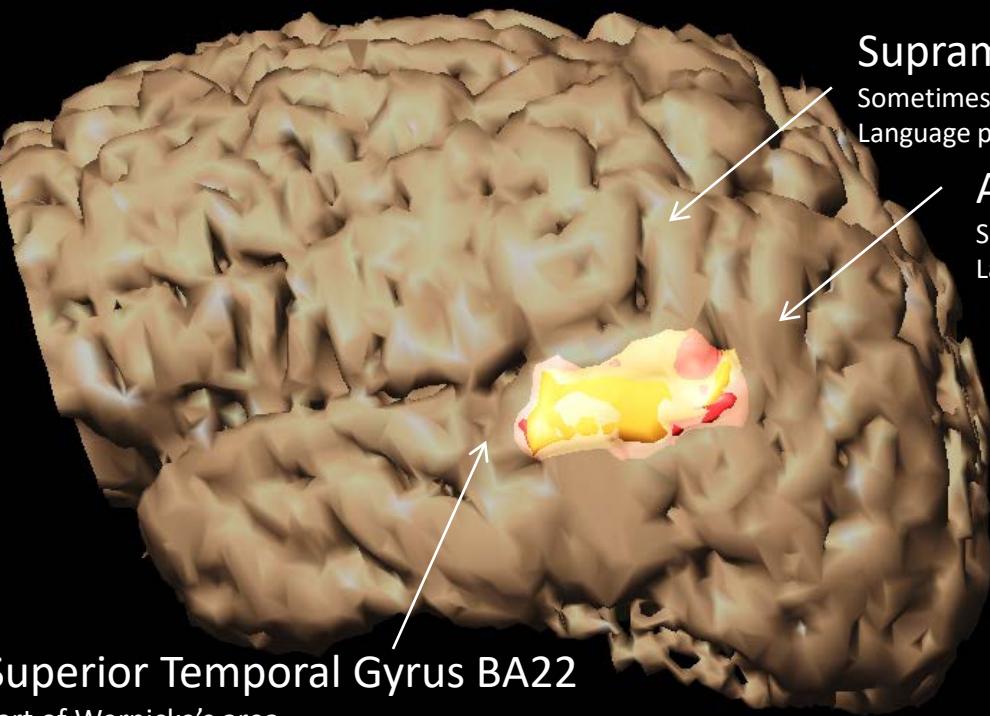
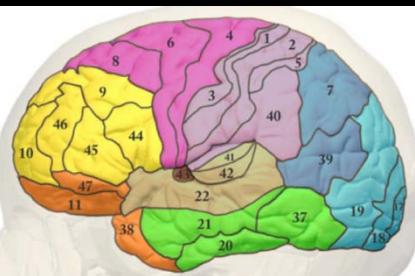


5 yr old girl with episodes of loss of contact, fumbling with hands, secondarily generalized seizures



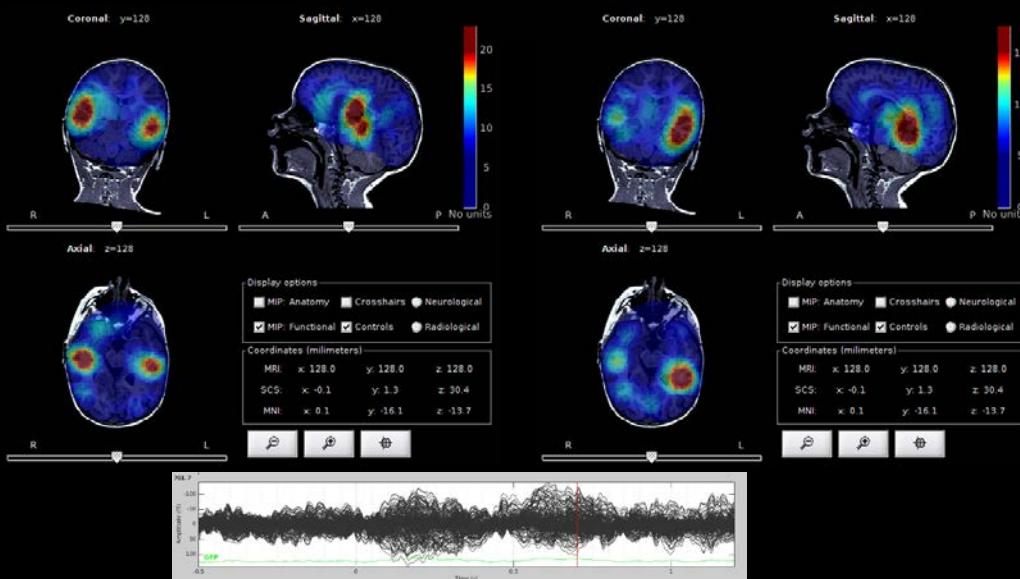
Hypothesized epileptogenic network based on EEG, MRI, PET, SPECT, ASL, MEG
Surgical resection based on PET

Overlap with Eloquent Cortex



Superior Temporal Gyrus BA22

Part of Wernicke's area



Supramarginal Gyrus BA40

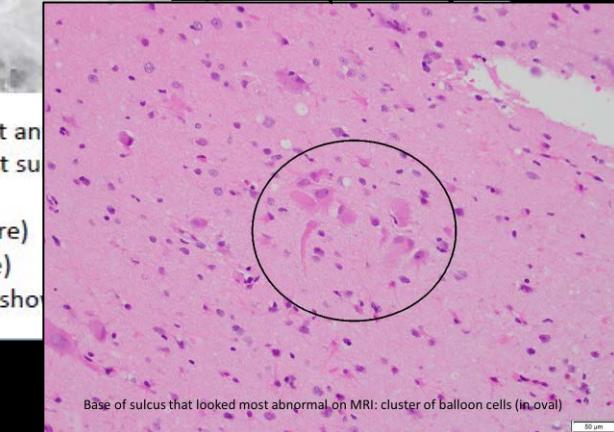
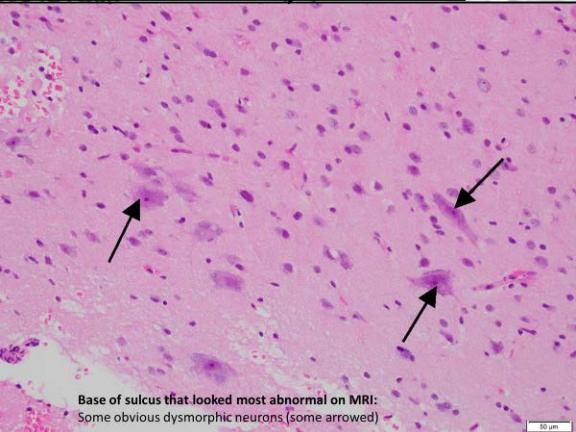
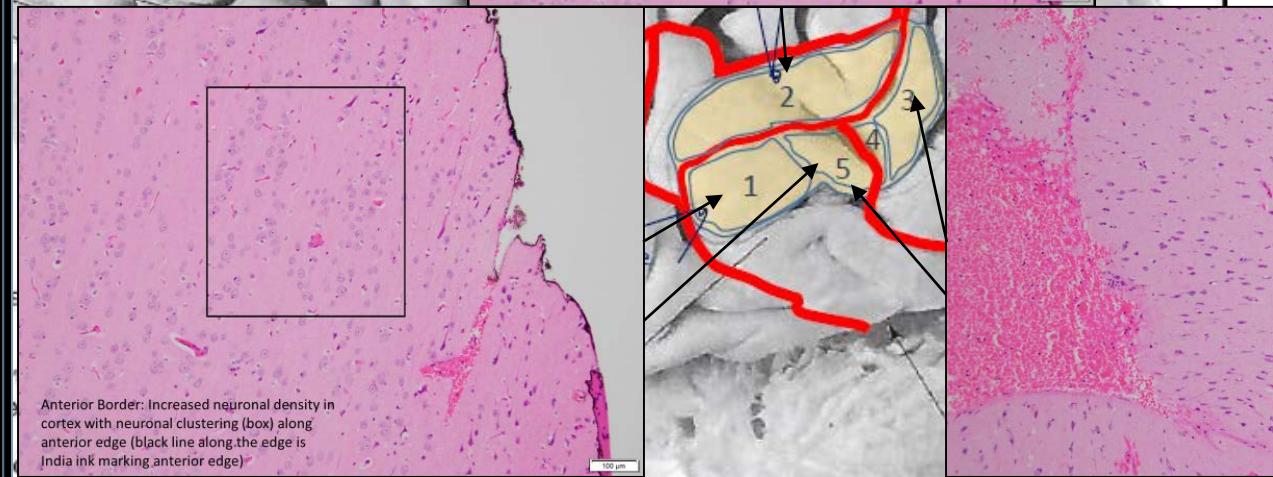
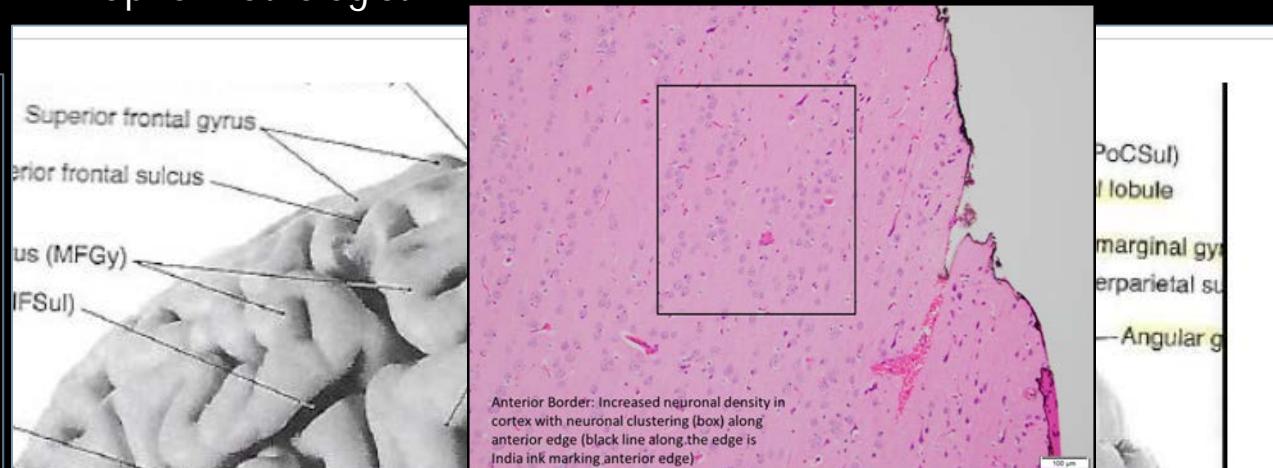
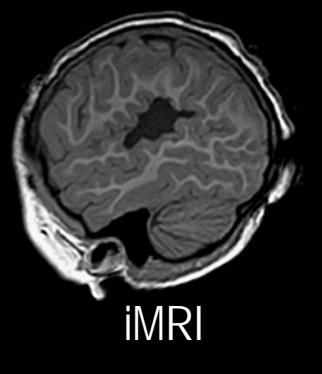
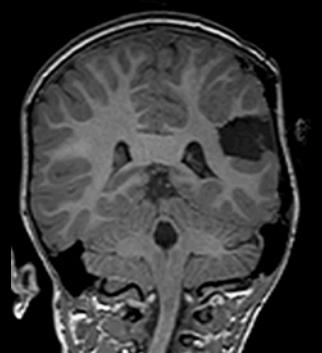
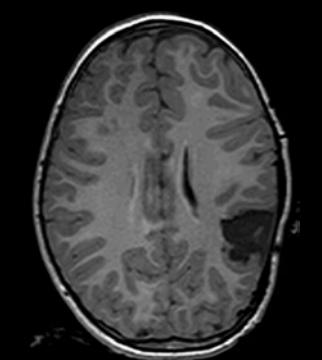
Sometimes part of Wernicke's area
Language perception and processing

Angular Gyrus BA39

Sometimes part of Wernicke's area
Language, Math, Cognition

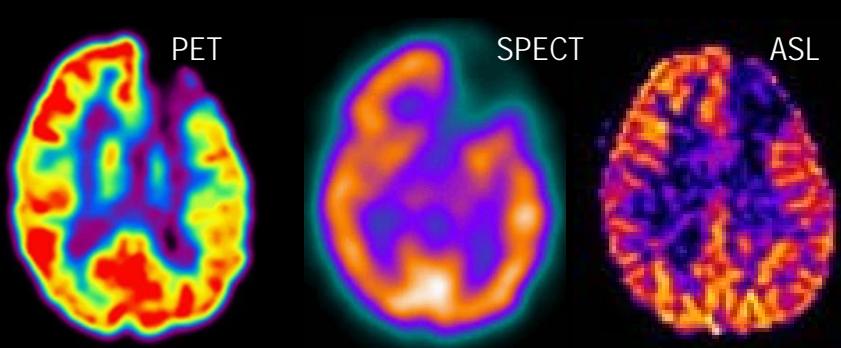
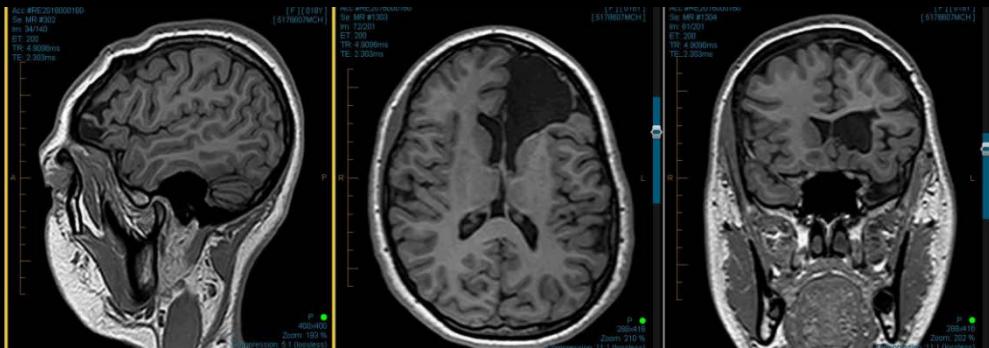
MEG Language task
(passive story listening)
suggested LEFT language
dominance

Map for Pathologist

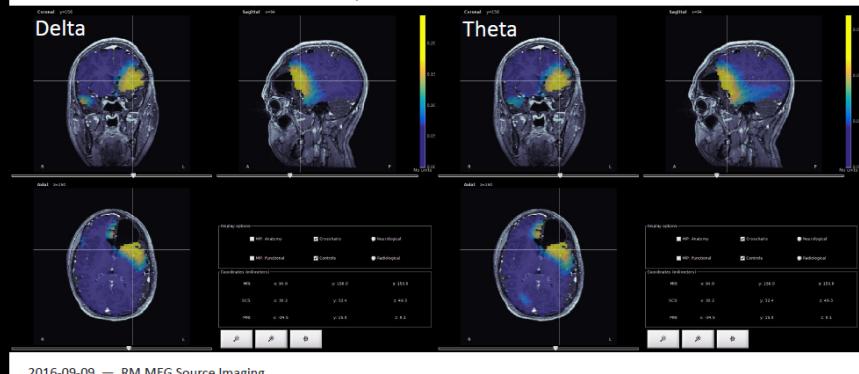


Seizure Free >11 months

18 yr girl had left frontal tumor resected at 5 months; has had Sz ever since; getting worse

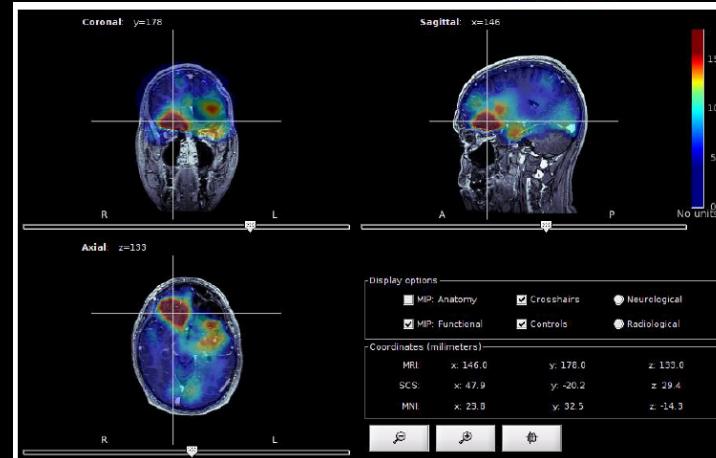


MEG Interictal Power Analysis suggested Left Frontal Opercular abnormalities, but this is experimental

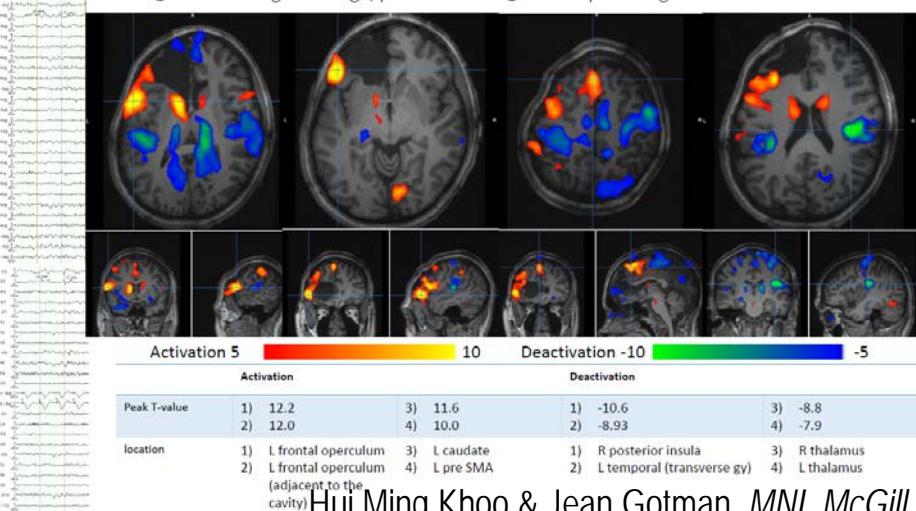


2016-09-09 — RM MEG Source Imaging

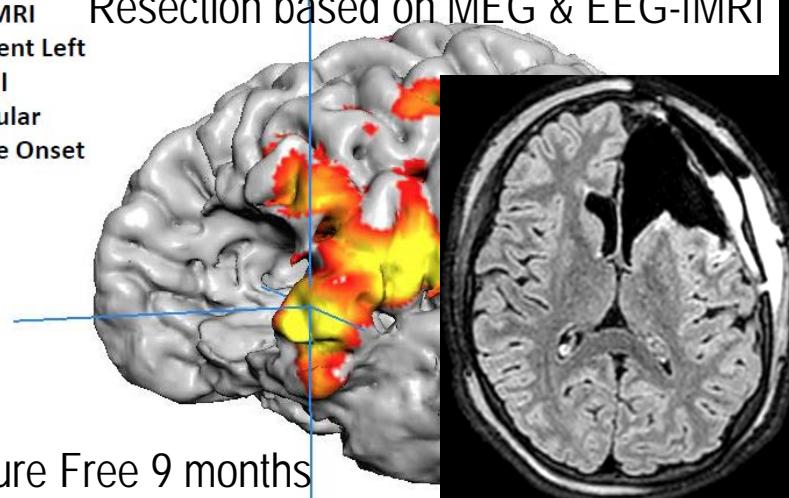
MEG language Task:
Apparent Right
Frontal Language
Localization.
Was recently
confirmed with
ESAM



Burst of IFDs max @ F3 on average montage, phase reversal @F3 on bipolar mtg.



Resection based on MEG & EEG-fMRI

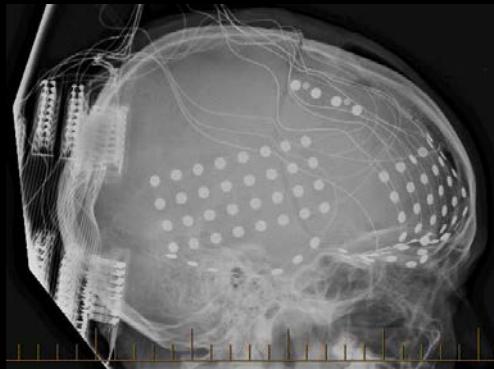


13 yr old boy Sz since 5yrs old; already had 2 resections.

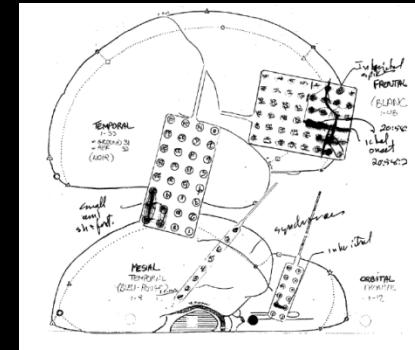
Subdural Grid Placement. No improvement.



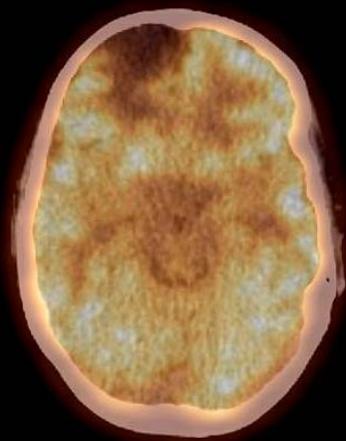
3T-MRI



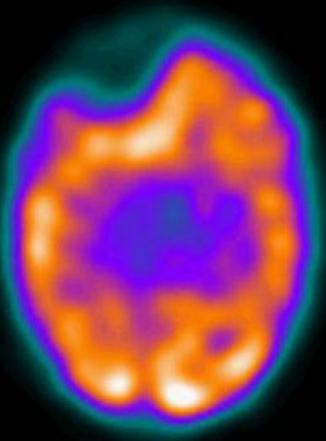
Subdural Grid Intracranial Recording



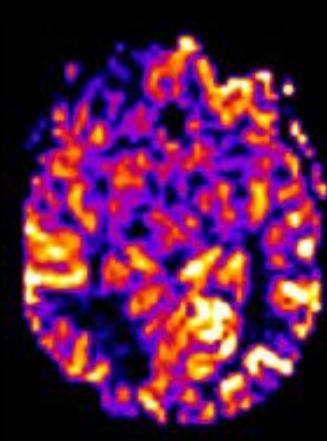
Grids: "Multiple electroclinical Sz captured with onset arising R. Frontal & Fronto-polar regions."



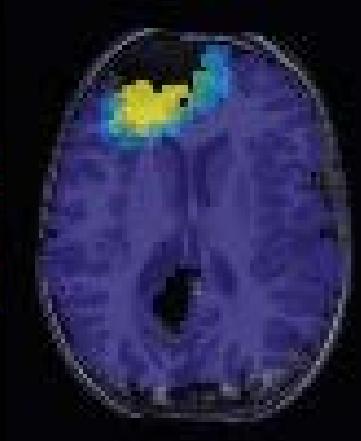
PET



Ictal SPECT

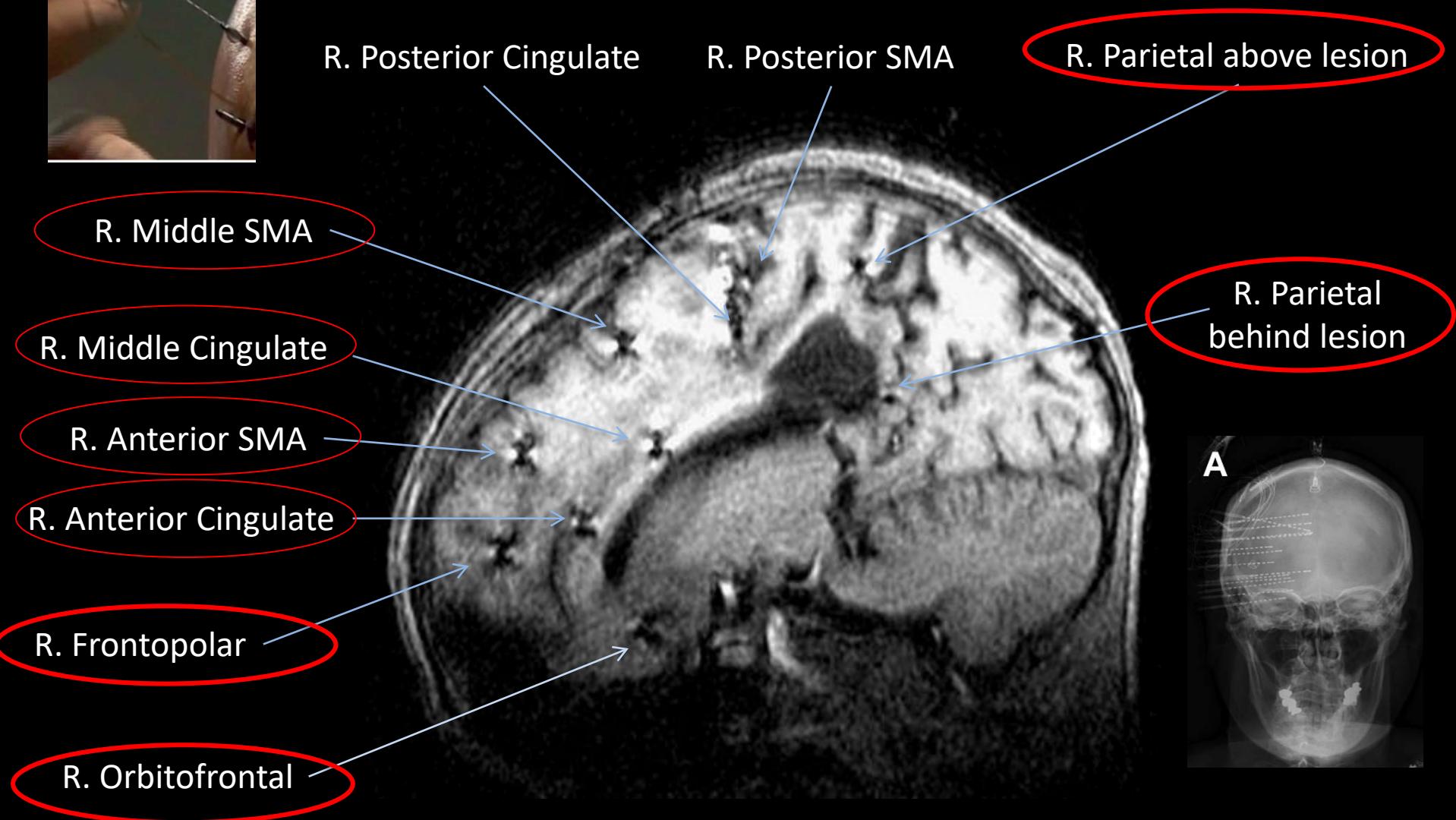
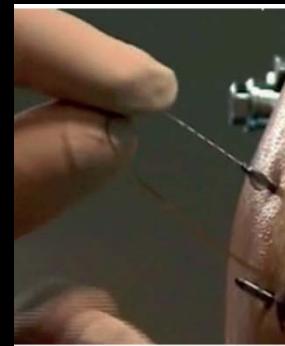


ASL



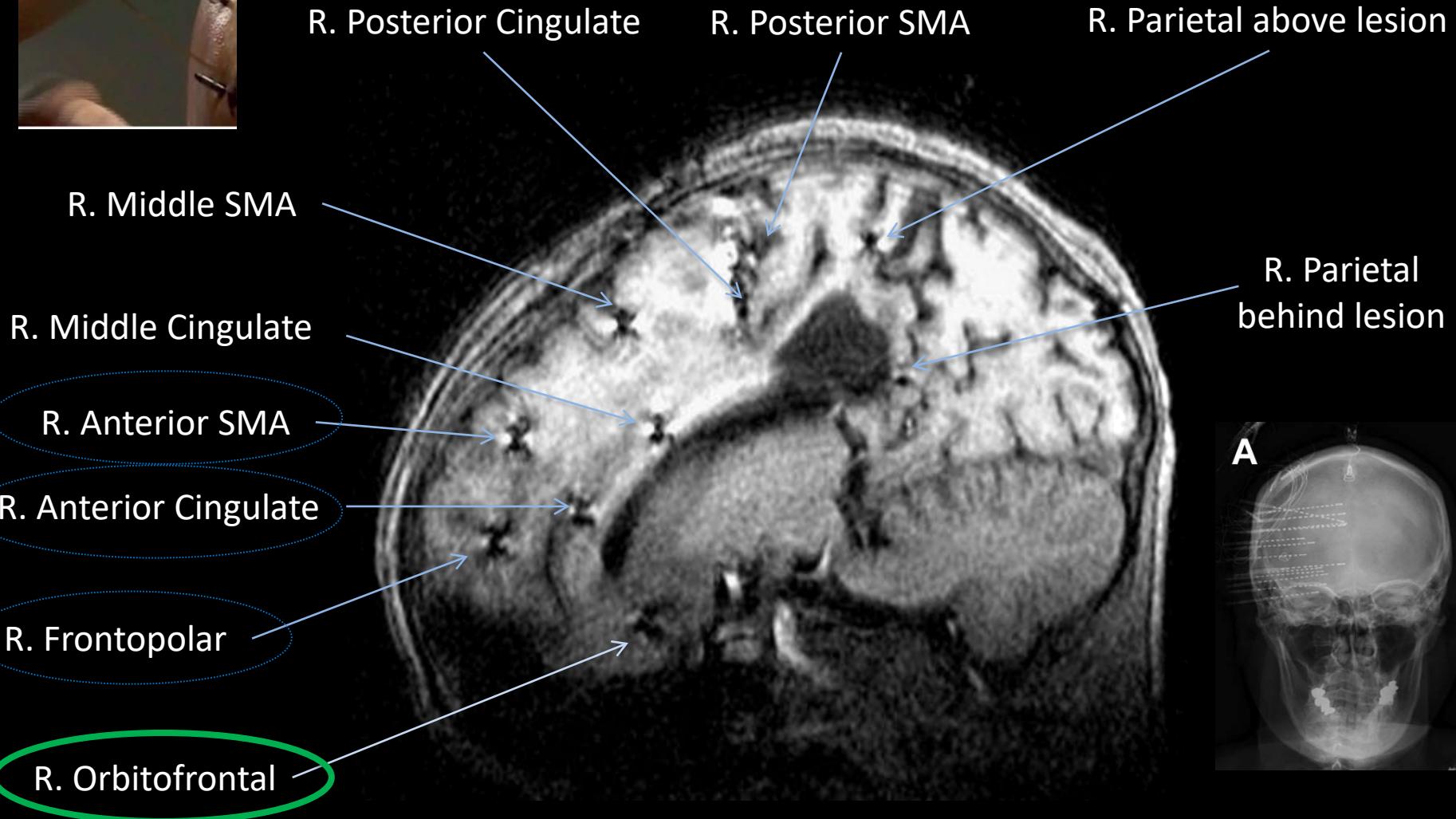
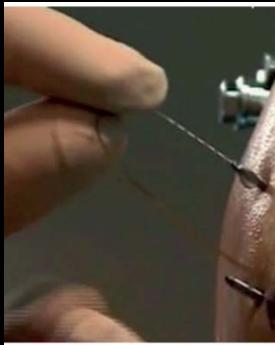
MEG

SEEG Implantation



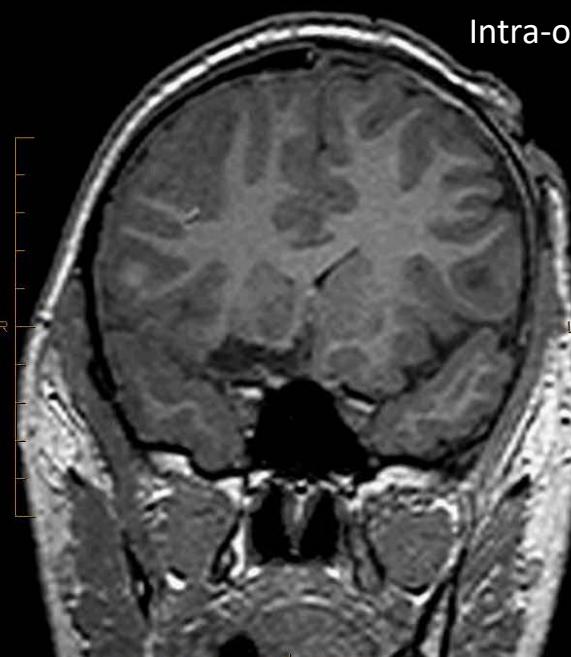
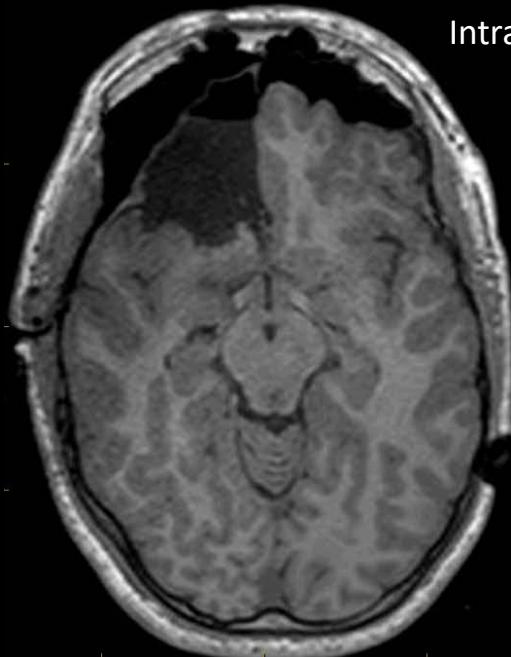
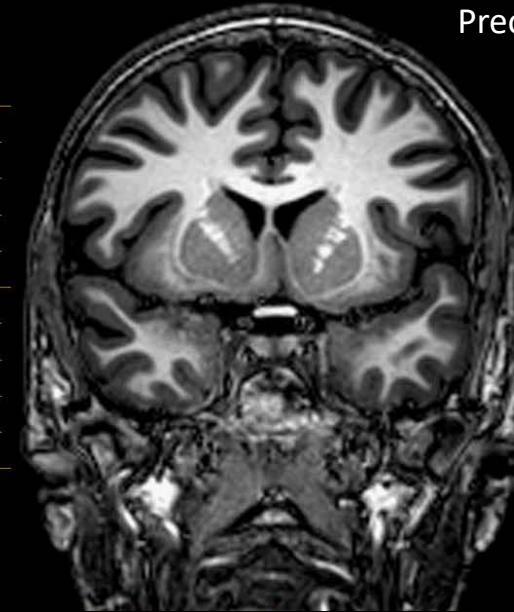
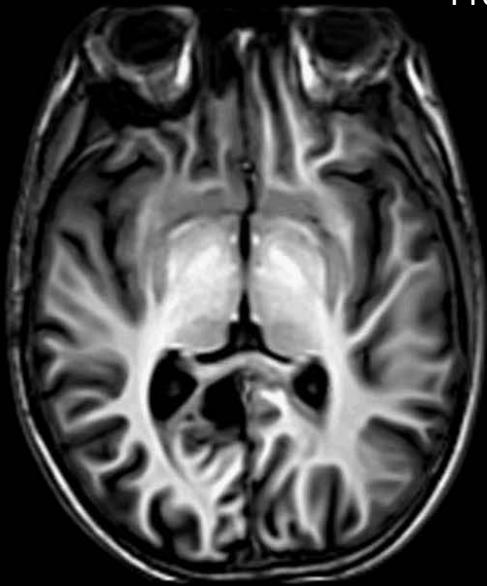
Interictal activity: very active anterior and posterior

SEEG Implantation



Ictal activity: 2 stereotypical seizures, several auras

Initial Spread to frontopolar, anterior cingulate, anterior SMA, then the rest

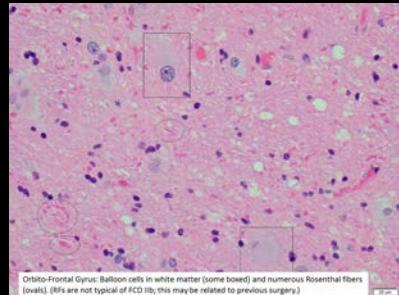
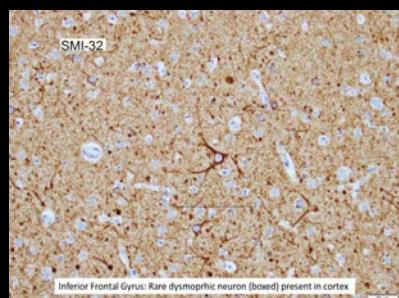
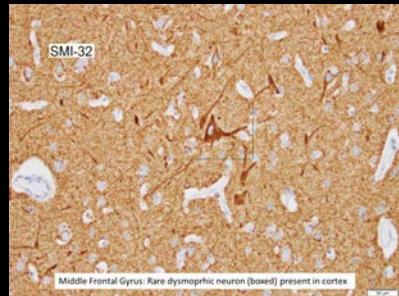


13 Months seizure free, but still has active EEG

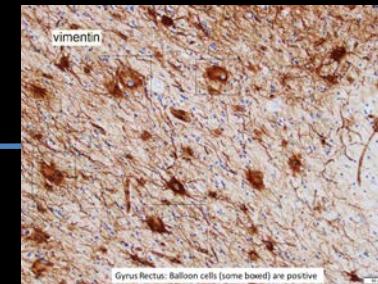
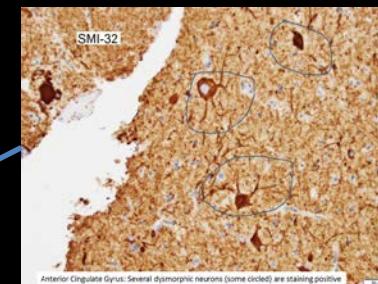
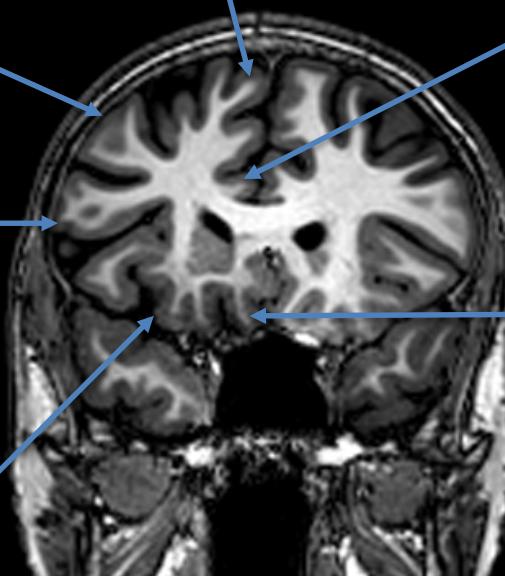
SFG, MFG, IFG Dedicated Pathological Analysis of Sub-Specimens

had rare
dysmorphic
neurons only

Steffen Albrecht, McGill



Orbitofrontal
gyrus had FCD IIb



Gurus rectus had
FCD IIb

Different pathology results throughout the network

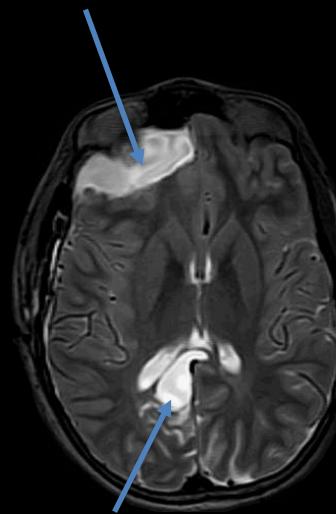
Screening of 22 genes of PI3K-AKT-mTOR or RAS-MAPK pathways at different sites throughout the epileptogenic network

Andrea Accogli
Myriam Srour
McGill

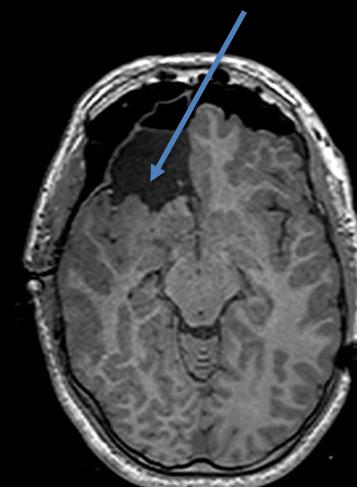
PATIENT ID	1220854
Gene	MTOR
Variant	c.4447T>C p.Cys1483Arg
Diagnosis	R frontal lobe epilepsy
Histology	FCDIIa, FCDIIb
Tissue 1 _(H)	1476,38 (2.57%)
Tissue 1 (validation) _(N)	99848,1126 (1.1%)
Tissue 2 (validation) _(N)	92371,227 (0.25%)
Blood	-
Saliva	n.d.
Mother	n.d.
Father	n.d.

H: Haloplex; N: Nextera; n.d. not detectable

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



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

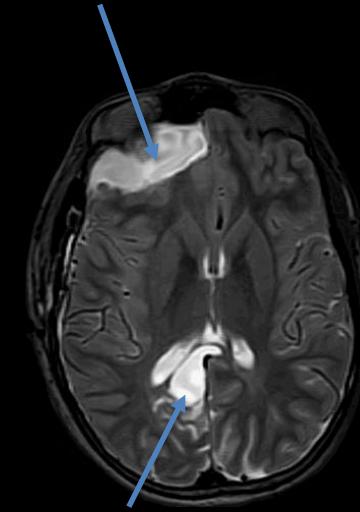


3rd resection 0.83-3.55% mutant allele, 3 samples

Screening of 22 genes of PI3K-AKT-mTOR or RAS-MAPK pathways at different sites throughout the epileptogenic network

Andrea Accogli
Myriam Srour
McGill

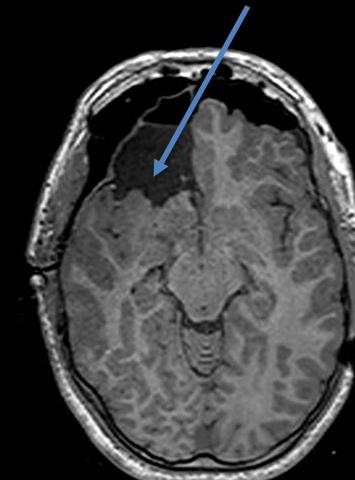
2nd resection 5.92-8.79% mutant allele, 2 samples



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

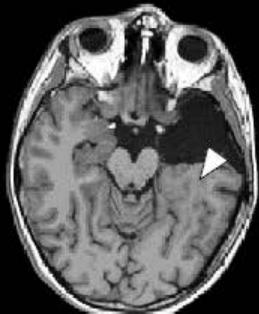
specimen	location	% mutant allele	Histopathological notes
FFPE 1	R parietal lesion (aspiration)	280124,3100 (1.09%)	Gliosis, subcortical ectopic neurons, focal perivascular spindled histocytes
FFPE 2	R parietal lesion biopsy	82765,161 (0.19%)	Unremarkable cortex
FFPE 3	R parietal lesion biopsy	88596,148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

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



3rd resection 0.83-3.55% mutant allele, 3 samples

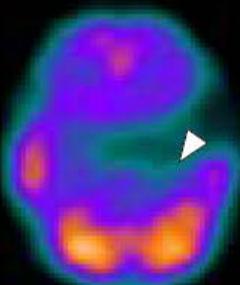
13 yr old boy with recurrent epilepsy after previous Left Anterior Temporal Resection (prev. FCD IIa)



T1 MRI



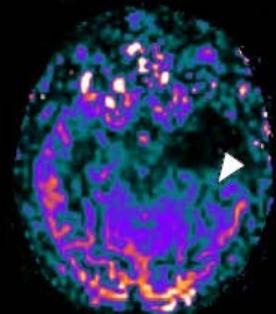
PET



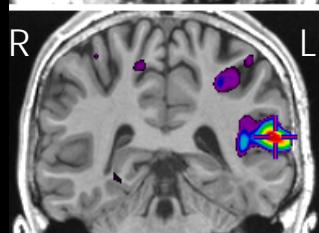
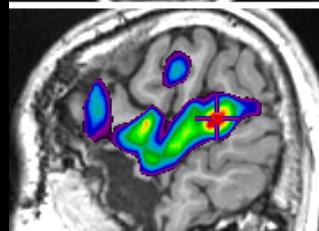
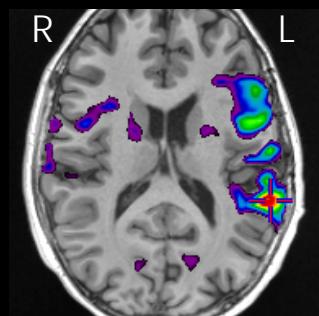
SPECT



MEG

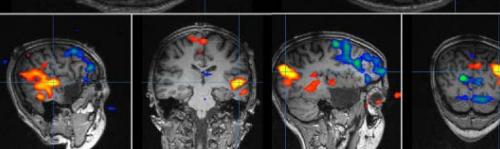
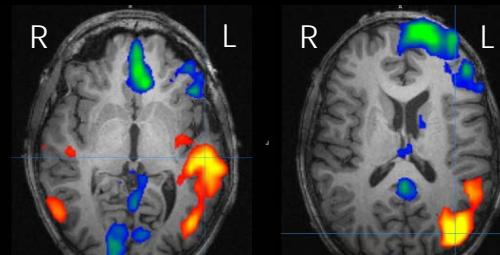
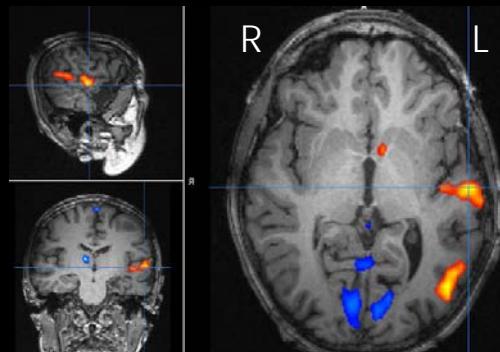


ASL



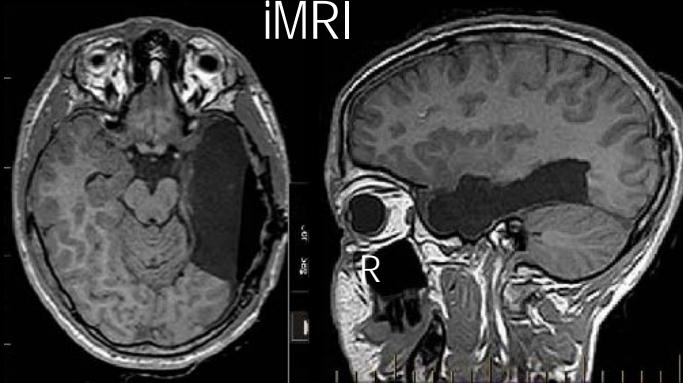
Language fMRI (Synonym Gen.)

Denise Klein, MNI, McGill



EEG-fMRI suggested L. Temporal & Frontal Generators

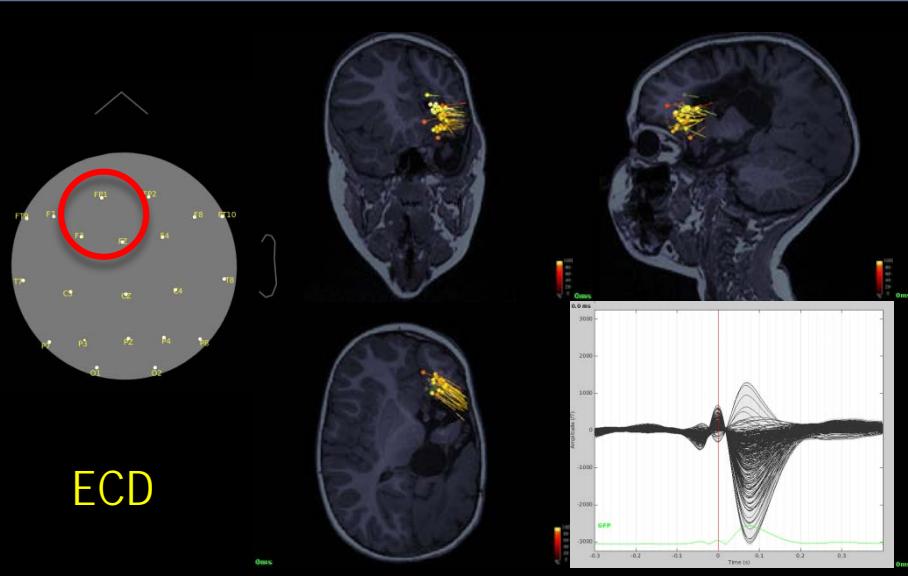
Hui Ming Khoo & Jean Gotman, MNI, McGill



Should we have removed more dipoles?

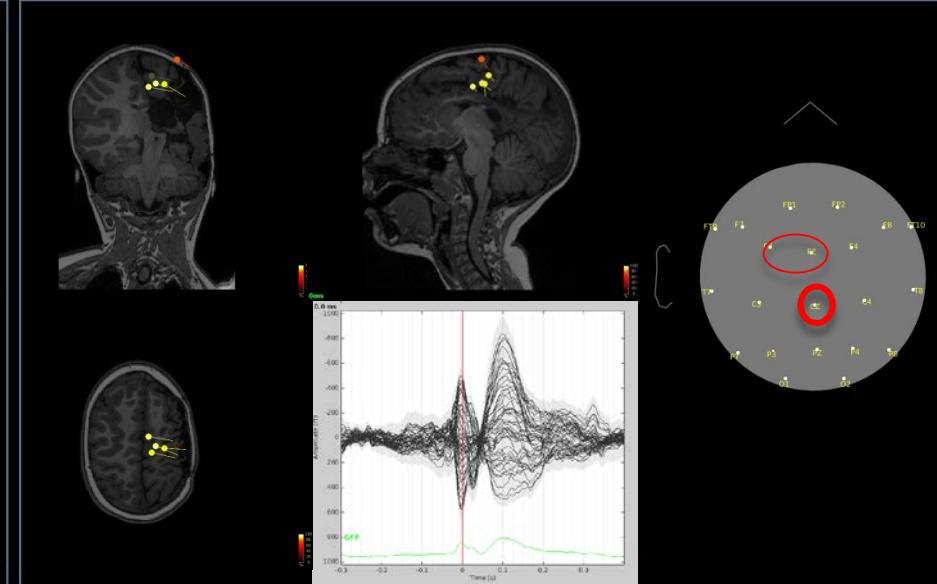
Pathology: No FCD this time, but oligodendrocyte hyperplasia found throughout specimen, including all borders

5 yr old girl previous functional hemispherectomy started having seizures again

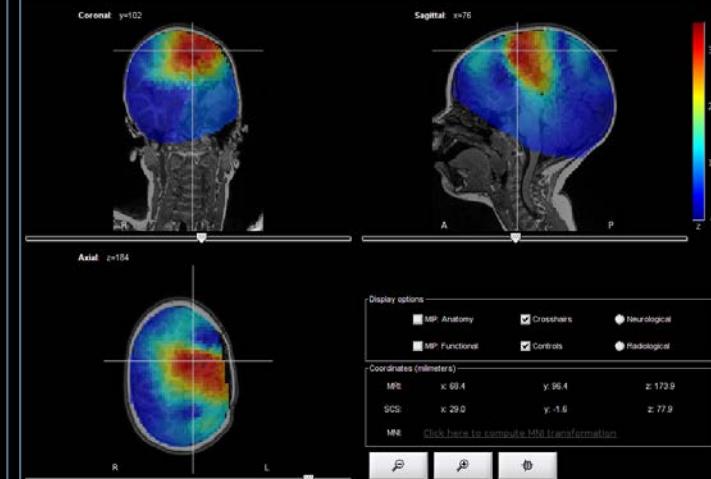
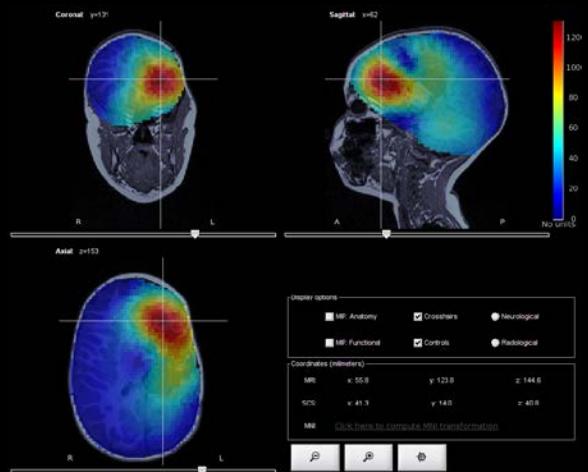


ECD

Nearly continuous SWCs centred at Fp1/F3/Fz (0.5-2 spikes/s) throughout recording.



DSM



5 yr old girl previous functional hemispherectomy started having seizures again

Ictal

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

Parameters

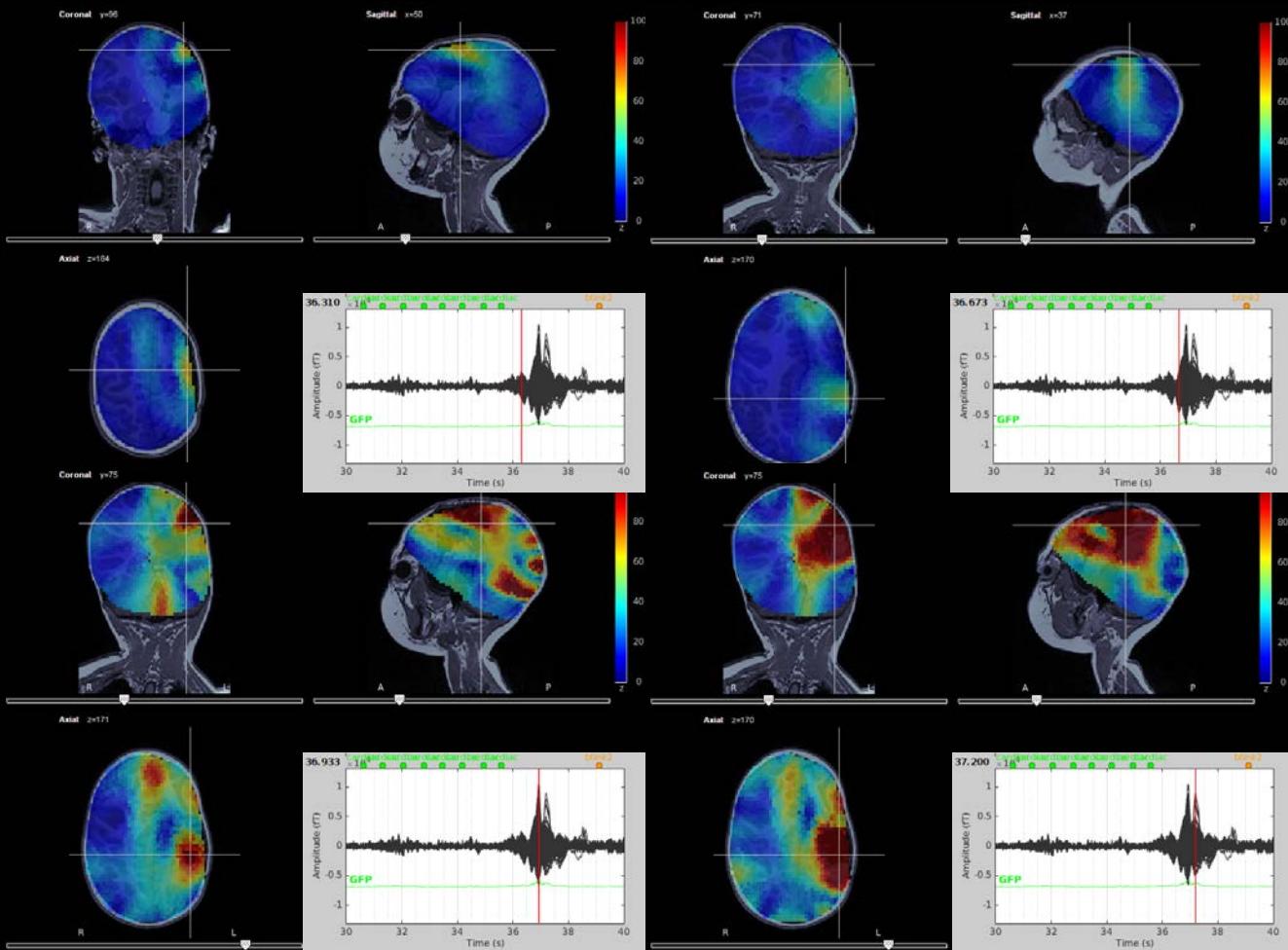
- 33.8 to 34.8s baseline
- 1-70 Hz bandpass, 60Hz notch
- OS vol head model
- MN source model
- Unthresholded



5 yr old girl previous functional hemispherectomy started having seizures again

Ictal

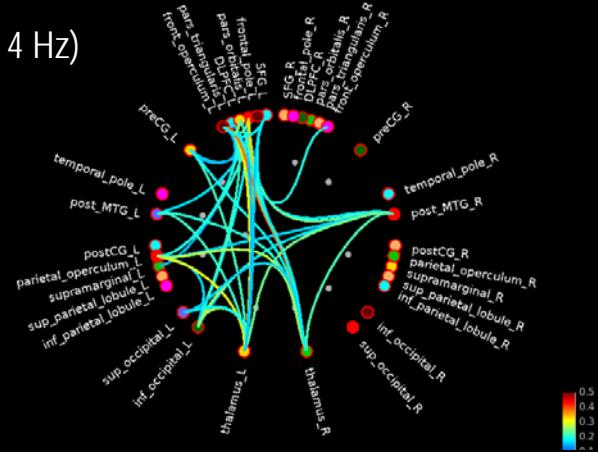
- First 4 peaks of MEG burst (36.31s, 36.67s, 36.93s, 37.20s)
- Same data as video on previous slide (but without MIP)



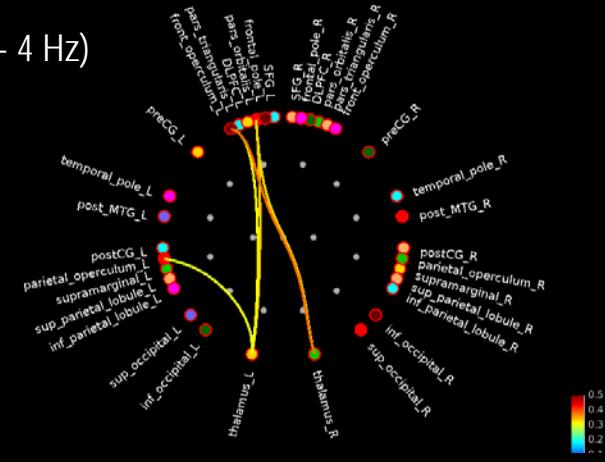
Experimental Connectivity Results

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

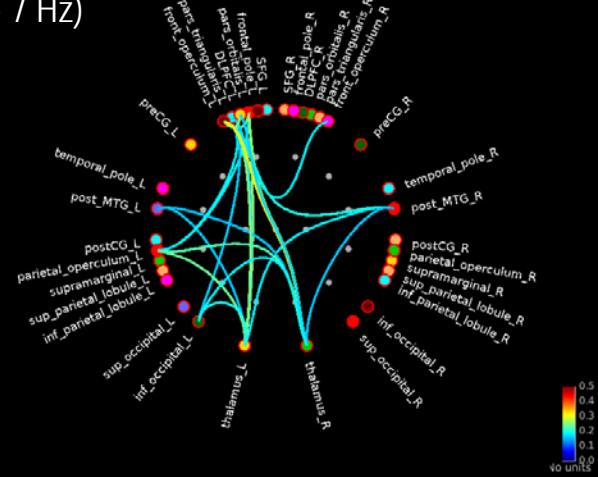
Delta (2- 4 Hz)



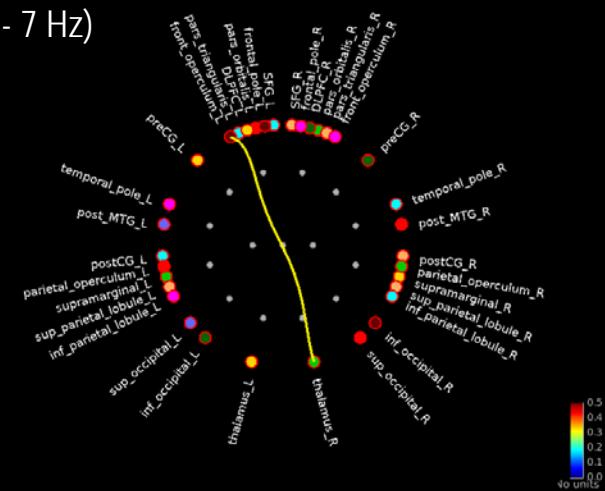
Delta (2- 4 Hz)



Theta (5- 7 Hz)



Theta (5- 7 Hz)



Intensity Threshold: 0.15

Higher PLV in the LEFT hemisphere

Intensity Threshold: 0.30

High degree of connectivity to subcortical structures

Experimental Connectivity Results

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

Shows only connections between R & L hemispheres

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

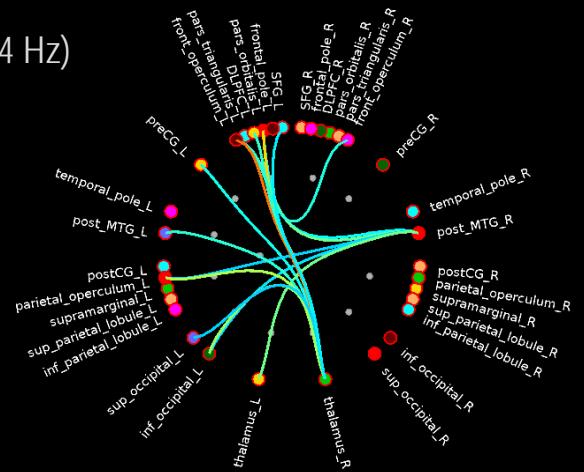
PLV value between R & L frontal operculum is also relatively high

Might suggest persistent connections between R & L hemispheres

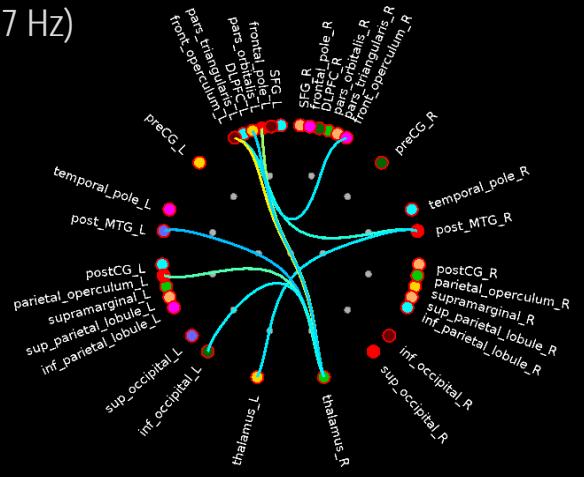
Other possibilities:

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

Delta (2- 4 Hz)

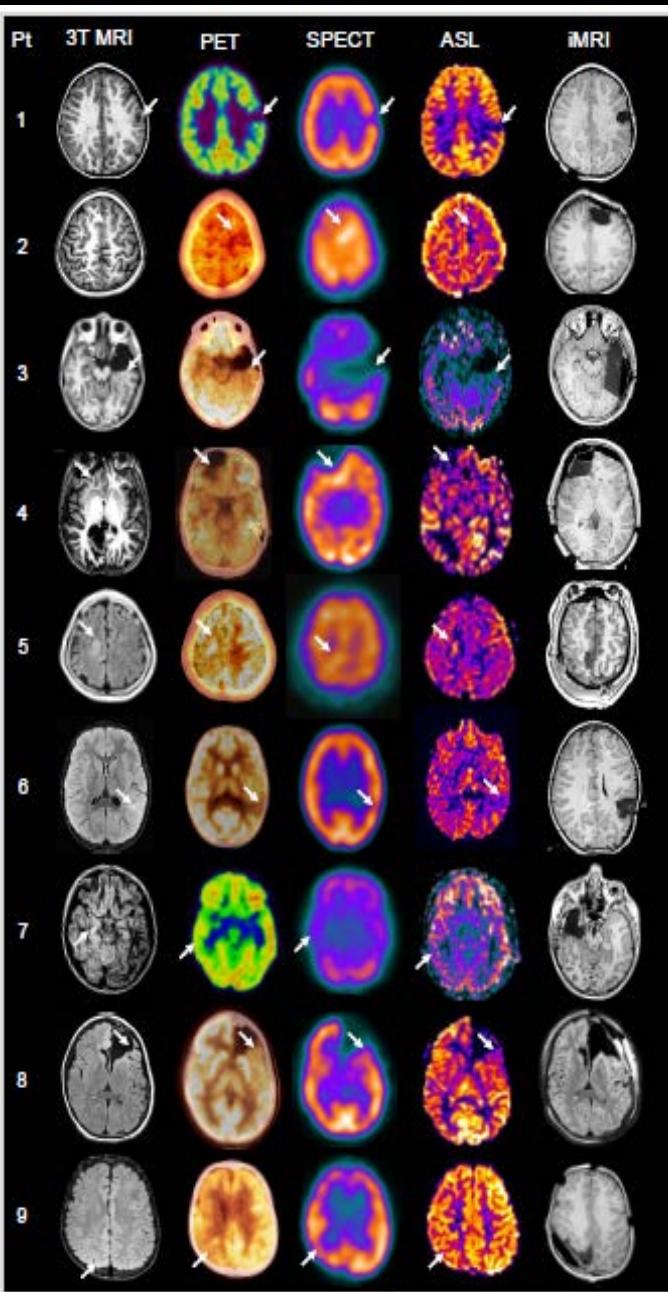


Theta (5- 7 Hz)



Intensity Threshold: 0.15

Sz outcomes of 9 consecutive patients using new presurgical evaluation strategy



28 Months

23 Months

Not Seizure Free

14 Months

13 Months

11 Months

23 Months

8 Months

4 Months

- Overlapped Language Areas
- EEG-fMRI suggested extensive network
- Oligodendrocyte hyperplasia through

New Advanced Presurgical Evaluation Strategy

Scalp EEG & Video-EEG

MRI (3T MRI)

Semiology Discussion

Neuropsychology

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

Patricia Tomaszewski
McGill

MEG Jeremy Moreau, Elizabeth Simard-Tremblay, Bernard Rosenblatt, Sylvain Baillet, B/C, McGill

Dedicated pathological or genetic analysis of sub-specimens

Steffen Albrecht
Andrea Accogli, Myriam Srour
McGill

Advanced MEG Analyses

- Overnight Ictal MEG
- Frequency Band Analysis
- Connectivity

Jeremy Moreau, Sylvain Baillet,
B/C, McGill

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

Jeff Hall, Andre Olivier, Birgit Frauscher, Francois Dubeau
MNI, McGill

SEEG (as opposed to subdural grids)

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