Recent Advances in Surgery for Drug Resistant Epilepsy

2019 Annual Meeting of the Epilepsy Society of Thailand

Dr. A. Simon Harvey
Royal Children's Hospital, Melbourne, Australia

Epilepsy surgery

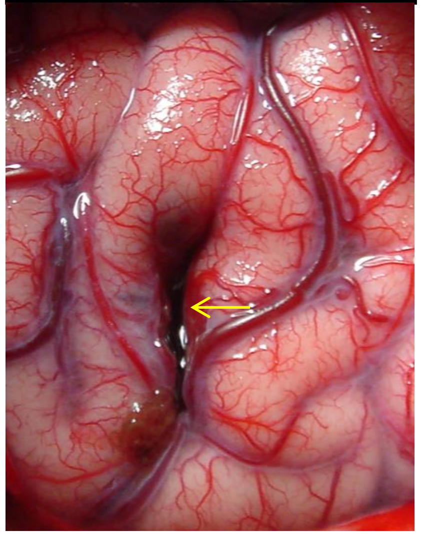
- 20% patients with epilepsy have uncontrolled seizures and a proportion of these will benefit from epilepsy surgery
- the superiority of epilepsy surgery over other treatments for uncontrolled epilepsy (AEDs, ketogenic diet, VNS, DBS) relates to the potential for complete seizure control with associated QOL and economic benefits
- epilepsy surgery is being increasingly performed in (younger) children, in complex settings (multi-lesional, MRI-negative) and in countries with limited healthcare resources
- however, epilepsy surgery remains underutilized, delays to epilepsy surgery with consequences are common, long-term seizure-free rates remain about 50-60%, comorbidities are inadequately managed, and epilepsy surgery is under-resourced in most countries

Recent advances in epilepsy surgery

- targeted, image-guided, microsurgical resection of epileptogenic lesions
  e.g. BOSDs, tuber centres, tiny operative corridors
- minimally-invasive surgical approaches
  e.g. LITT, radiosurgery, focused ultrasound
- computer-based automation and machine learning
  e.g. analysis of presurgical data, patient selection, outcome prediction
- biomarkers of the epileptogenic zone *eg. HFOs*
- incorporation of genomics in epilepsy surgery
  e.g. genetic focal epilepsies, somatic mutations
- not stereo-EEG

Targeted, microsurgery: Bottom-of-sulcus dysplasia

- many intellectually-normal patients with DRE and focal seizures have small FCD-2a/b at the bottom-of-sulci
- typically single, commonly dorsolateral or medial frontal
- MRI obvious/subtle/occult, localized focal hypometabolism on PET, localized focal hyperperfusion on SPECT
- high-frequency stereotyped focal seizures
- drug responsive/resistant, relapsing/remitting
- easily operated 1-stage with ECoG and MRI
  - intracranial EEG is unnecessary if BOSD identified
- >90% seizure-free following resection
  - some need reoperation if residual dysplasia

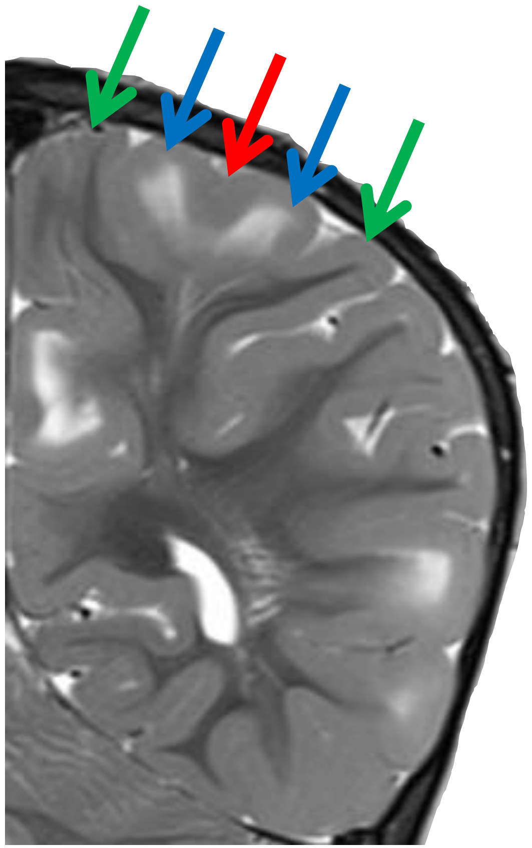


Harvey et al. The surgically-remediable syndrome of epilepsy associated with BOSD. *Neurology* 2015.

Targeted, microsurgery: centres of cortical tubers

Our research suggests epileptogenicity in TSC is based on:

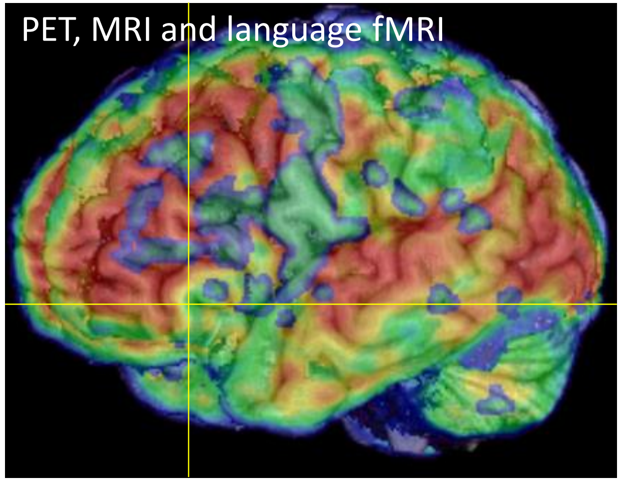
- a “dysplastic” **tuber centre**
  - rhythmic IEDs and seizures recorded on ECoG/iEEG
  - pit with cortical thickening and abnormal signal on MRI
  - concentration of dysmorphic neurons on pathology
- surrounded by an “inactive” **tuber rim**
- surrounded by “inactive” or “reactive” **peritubaral cortex**



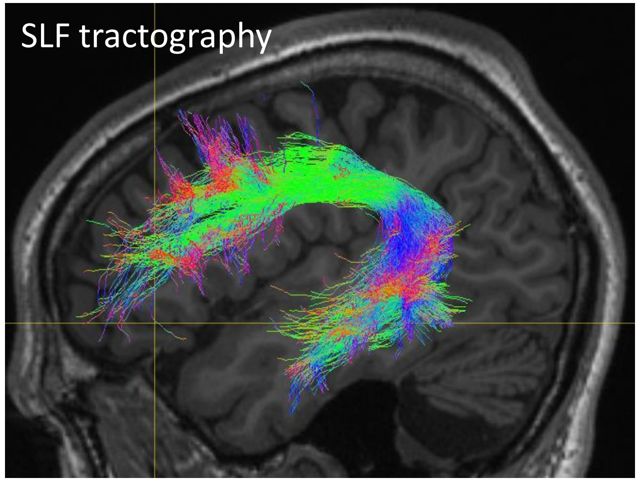
Mohamed AR et al. Intrinsic epileptogenicity of cortical tubers revealed by intracranial EEG monitoring. *Neurology* 2012
Kannan L, et al. Centre of epileptogenic tubers generate and propagate seizures in tuberous sclerosis. *Brain* 2016

Targeted, microsurgery: tiny operative corridors

- combining multiple imaging modalities to build a virtual 3D model of lesional, epileptic and functional regions
  - MRI (*lesions*)
  - FDG-PET (*metabolic activity*)
  - SPECT (*seizures*)
  - tractography (*white matter pathways*)
  - functional MRI (*motor, sensory, language,seizures, resting)*
- plan surgical approaches and load onto neuronavigation systems, update and monitor with intraoperative MRI
- potentially operate safely without need for
  - intracranial EEG monitoring
  - cortical stimulation
  - awake craniotomy

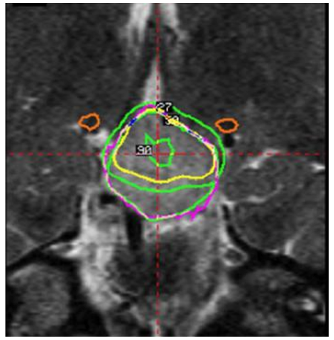


pars orbitalis approach to a left anterior insular FCD beneath language cortex and pathways

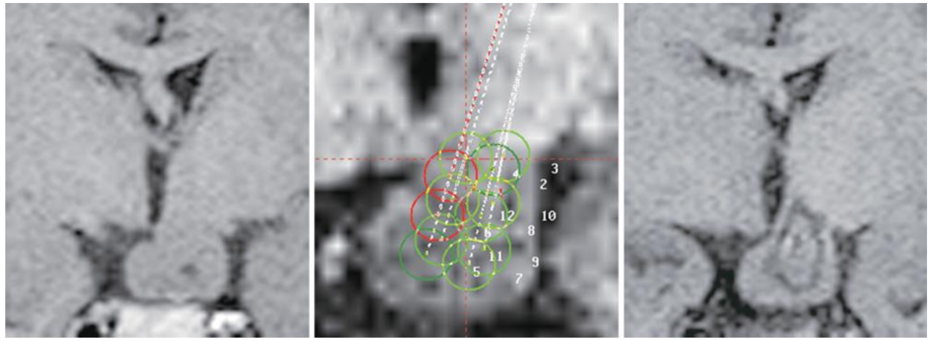


Minimally-invasive surgery: stereotactic radiation or thermal

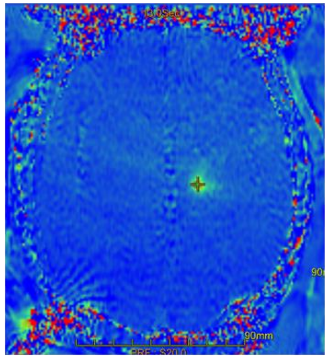
- ideal for small, deep lesions
- advantages
  - no craniotomy required (extracranial or burr holes only)
  - reduced hospital stay and costs
  - reduced discomfort, blood loss
  - reduced morbidity (traversing cortex and pathways)
- disadvantages
  - delayed efficacy
  - no EEG or histopathology
  - less controlled lesion than with open microsurgery



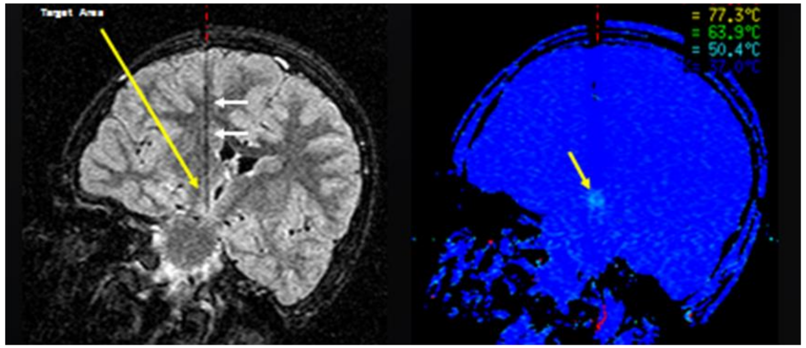
Gamma Knife radiosurgery
(Regis, 2017 – Marseille, France)



stereotactic radiofrequency thermocoagulation
(Kameyama, 2009 – Niigata, Japan)



focussed ultrasound
(Fountain, 2016 – Virginia, USA)



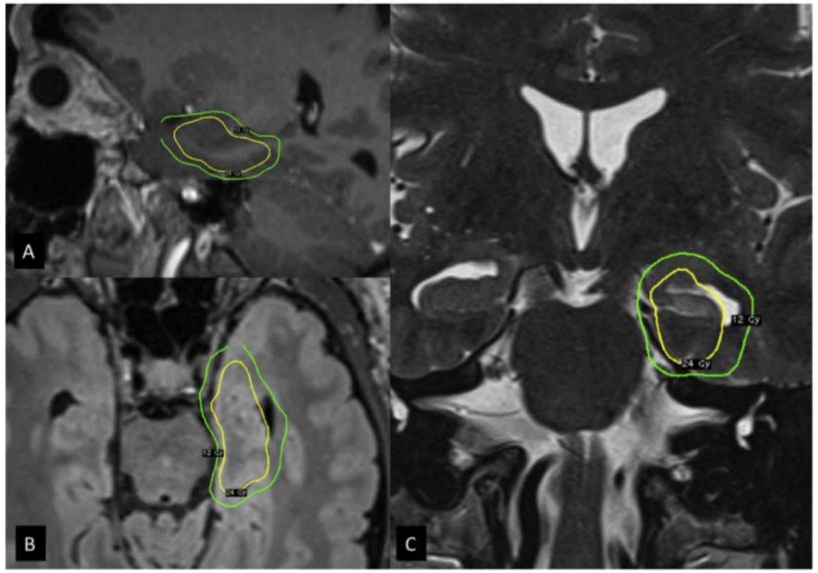
laser interstitial thermal therapy
Dan Curry – Texas Children's Hospital, USA

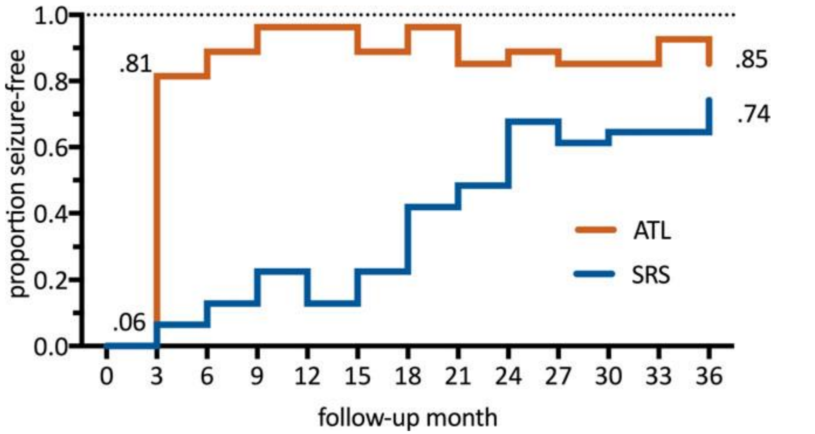
Minimally-invasive surgery: Gamma Knife radiosurgery

- Gamma Knife® (Elekta) is one of several forms of stereotactic radiosurgery, others being Linac and proton beam therapy
- averaging of multiple beams of γ radiation from 200 precisely collimated ^{60}Co sources distributed on the surface of a sphere, further tailored by secondary collimators in an adjustable helmet and dose planning software
- low doses (<20 Gy) to small volumes bring about functional change in tissue
- epilepsy associated with HH, tumours, AVMs, cavernomas, HS, callosotomy
- disadvantages
  - delayed seizure improvement
  - delayed radionecrosis syndrome
  - ? risk of secondary tumors
  - ? risk of cognitive / endocrine impairment

Minimally-invasive surgery: GKS in temporal lobe epilepsy

- RCT of adults with mTLE randomised to SRS targeting medial temporal structures (31) or standard ATL (27)
- outcomes were absence of disabling seizures verbal memory and QOL at 36 months
- 52% SRS and 78% ATL patients achieved seizure remission
- mean VM changes from baseline for 21 English-speaking, dominant-hemisphere patients did not differ between groups
- symptomatic cerebral oedema in some SRS patients cerebritis or subdural hematoma in some ATL patients
- SRS is an alternative to ATL for patients with contraindications or reluctance to undergo open ATL

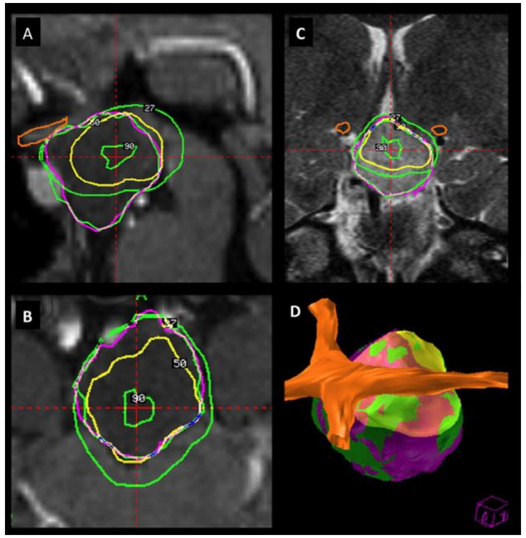


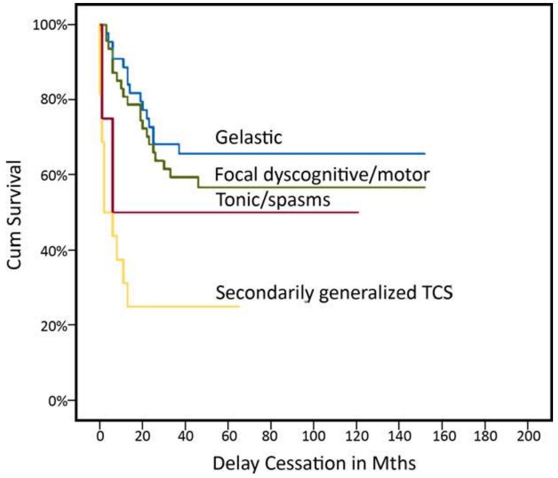


Barbaro et al. Radiosurgery versus open surgery for mTLE (ROSE trial). *Epilepsia* 2018

Minimally-invasive surgery: GKS in hypothalamic hamartoma

- 57 patients with HH treated by GKS in Marseilles 2000-7
- follow-up >3 yrs in 48 patients (median 71 months)
- HH type I in 11, type II in 15, type III in 17, type IV-VI in 4
- median marginal dose was 17 (14-25) Gy
- 58.3% required a second treatment
- Engel I = 40%, Engel II = 29%, Engel III = 20%
- psychiatric comorbidities cured 28%, improved 56%, stable 8%, continued worsening 8%
- no permanent neurological or memory deficits
  transient poikilothermia = 6

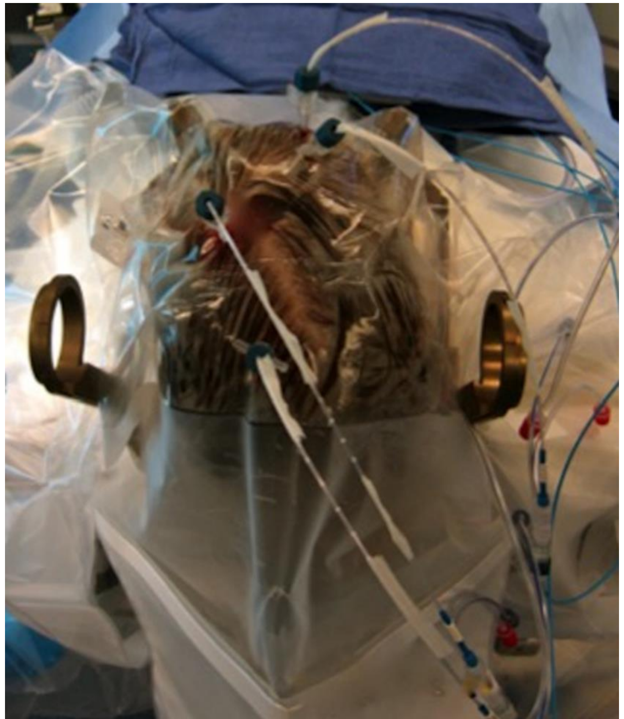




Regis J et al. Safety and efficacy of GK radiosurgery in HH. *Epilepsia* 2017

Minimally-invasive surgery: Laser interstitial thermal therapy

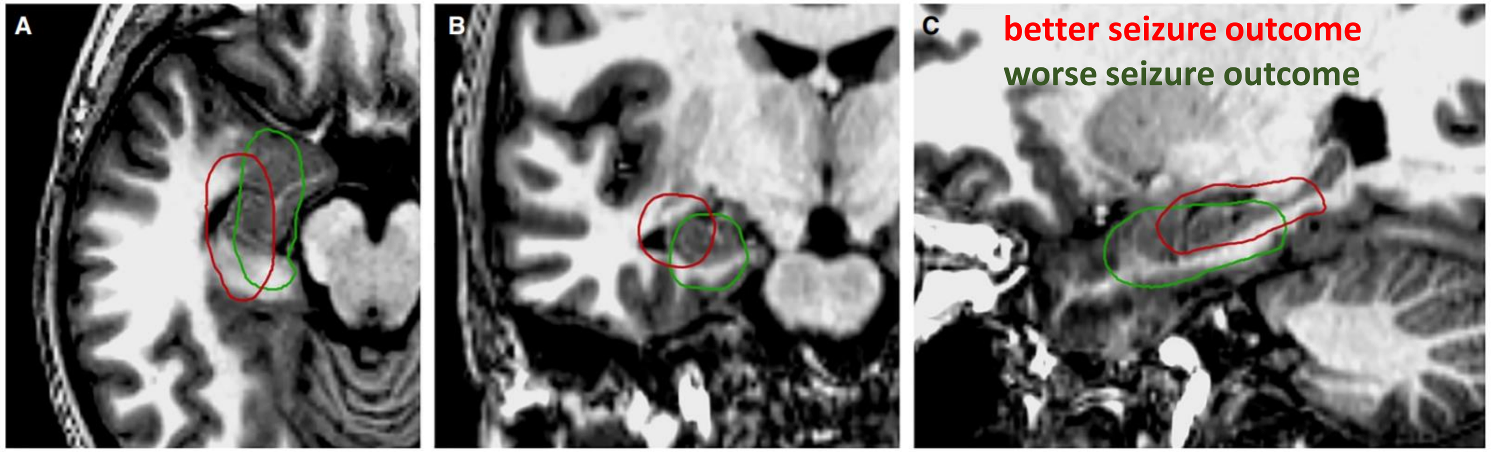
- laser interstitial thermal therapy (LITT) = laser thermal ablation with MRI-guided stereotactic probe and real-time MRI thermography (Visualase® by Medtronic, NeuroBlate® by Monteris)
- advantages
  - small incision, short hospital stay, reduced morbidity
  - plan and monitor ablation in real time under MRI
  - reach small deep targets
- disadvantages
  - limited control of size and shape of thermal lesion (heat sinks)
  - need for cranial fixation (>2-3 years old)
- similar efficacy to open craniotomy surgery in mTLE insula epilepsy, hypothalamic hamartoma, heterotopia, cavernoma, corpus callosotomy



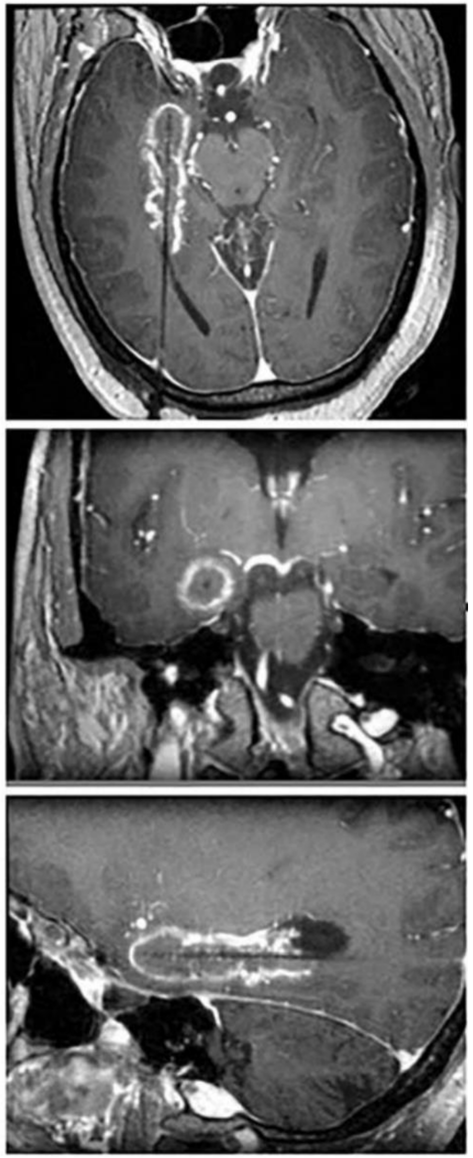
Tovar-Spiinoza, *Neurosurg Focus*, 2018

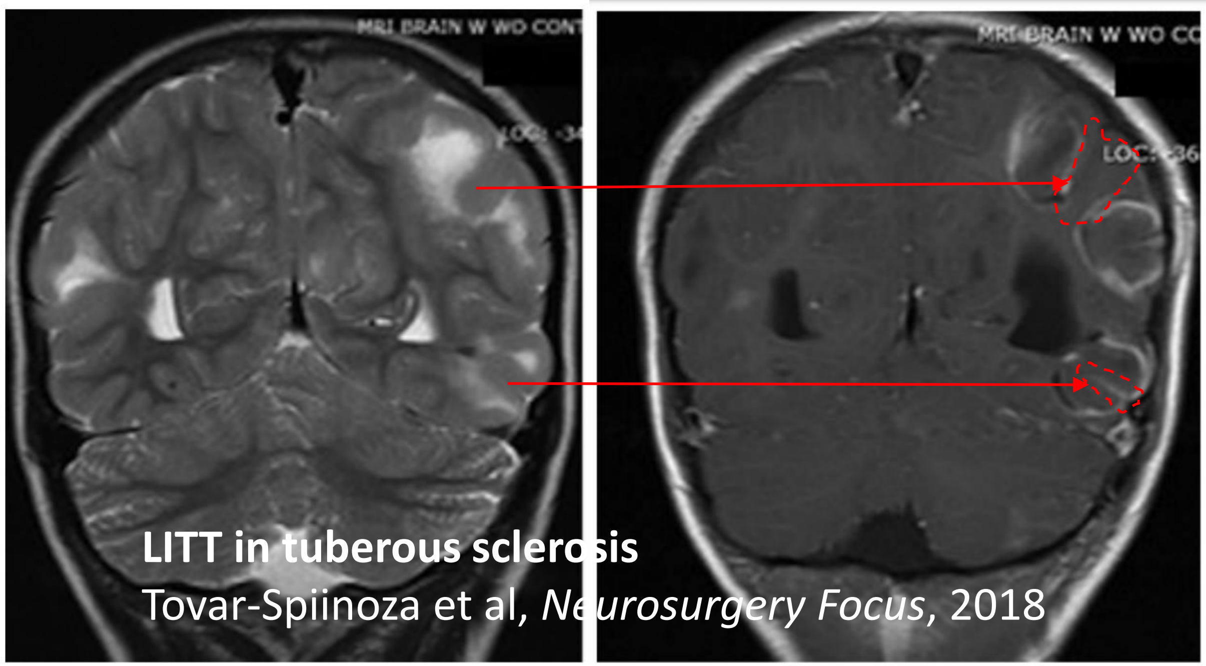
Minimally-invasive surgery: LITT in temporal lobe epilepsy

- seizure freedom in medial TLE between 36-78% at >1 year
  - 60-90% if hippocampal sclerosis
- briefer hospitalisation, better cognition and language
- risk of visual field defect from LGN heating
- better when the ablative volume involves amygdala, head of hippocampus, parahippocampal gyrus, rhinal cortices

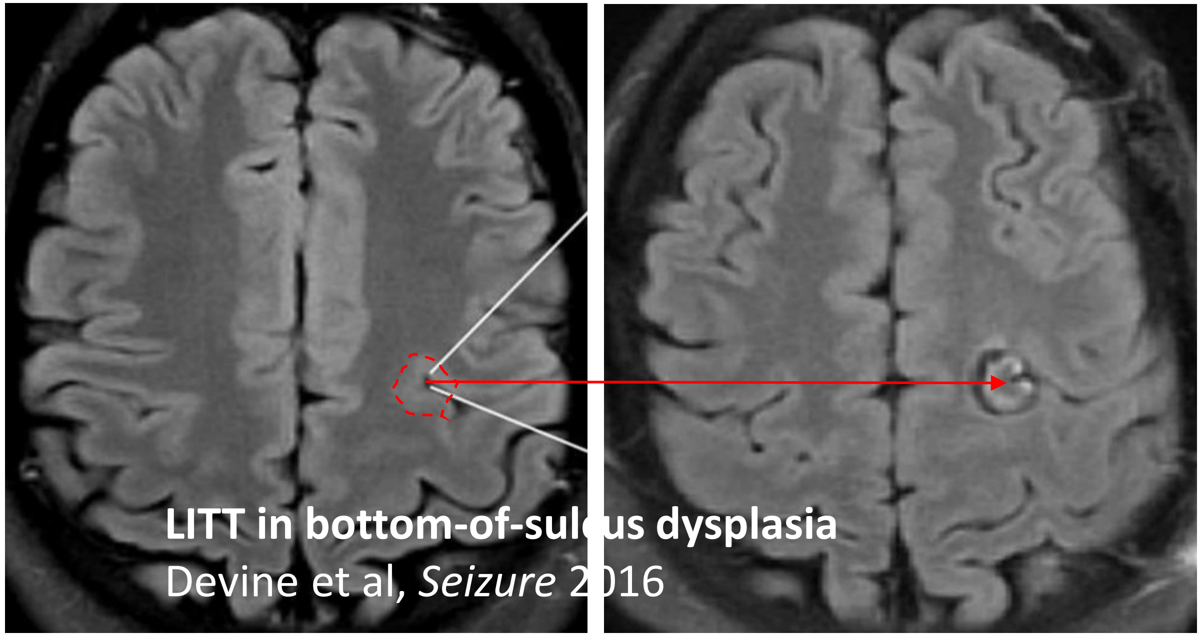


(Wu et al, *Epilepsia* 2019)

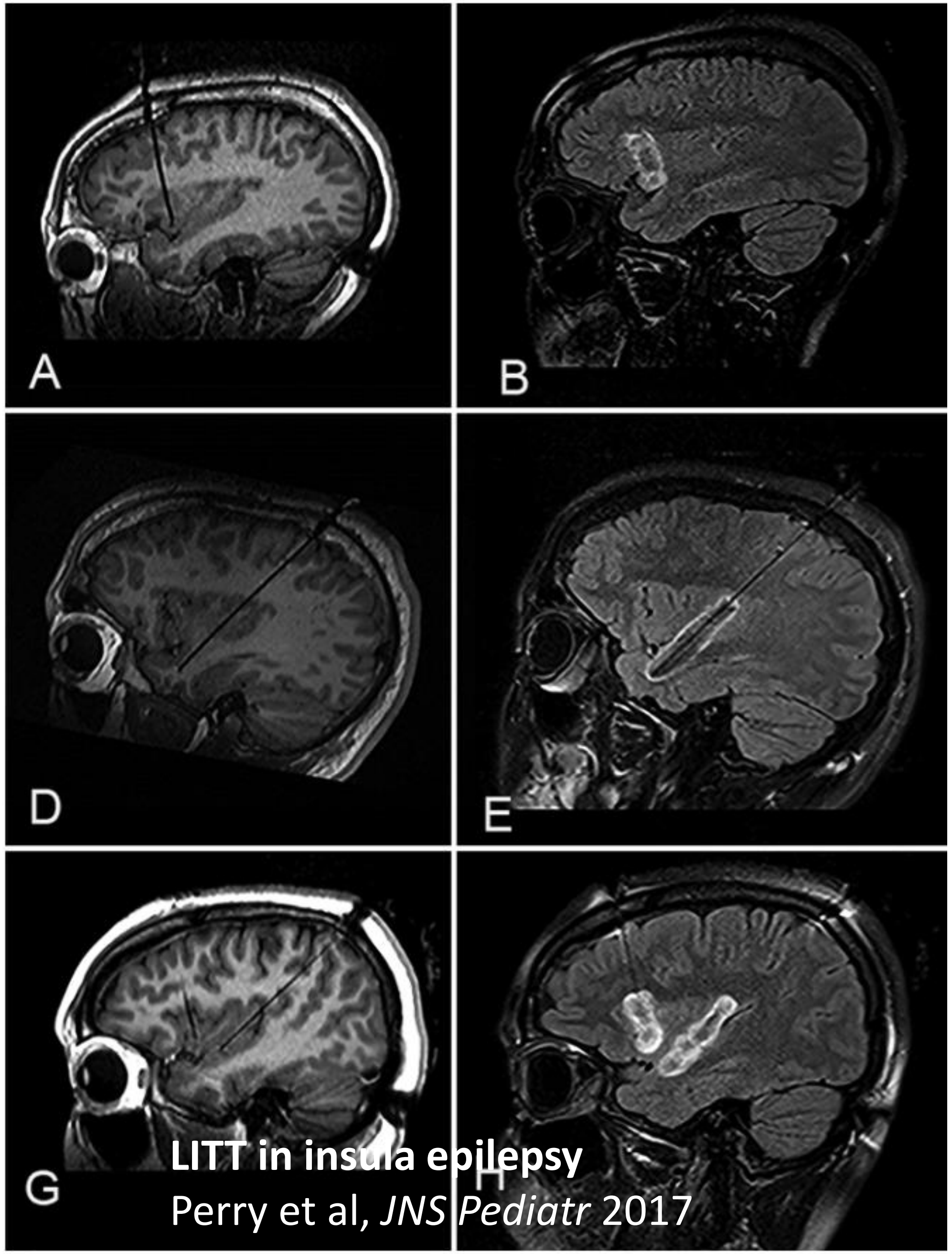




LITT in tuberous sclerosis
Tovar-Spiinoza et al, *Neurosurgery Focus*, 2018



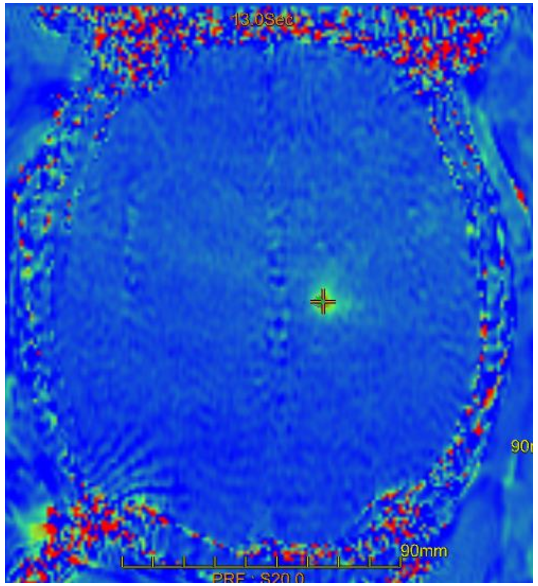
LITT in bottom-of-sulcus dysplasia
Devine et al, *Seizure* 2016

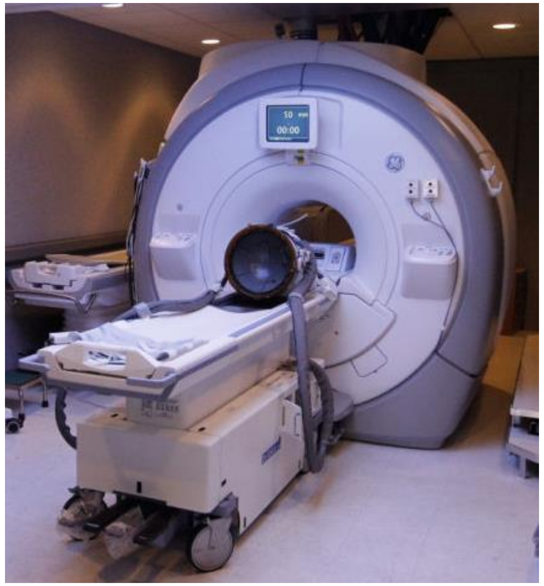


LITT in insula epilepsy
Perry et al, *JNS Pediatr* 2017

Minimally-invasive surgery: Focused ultrasound

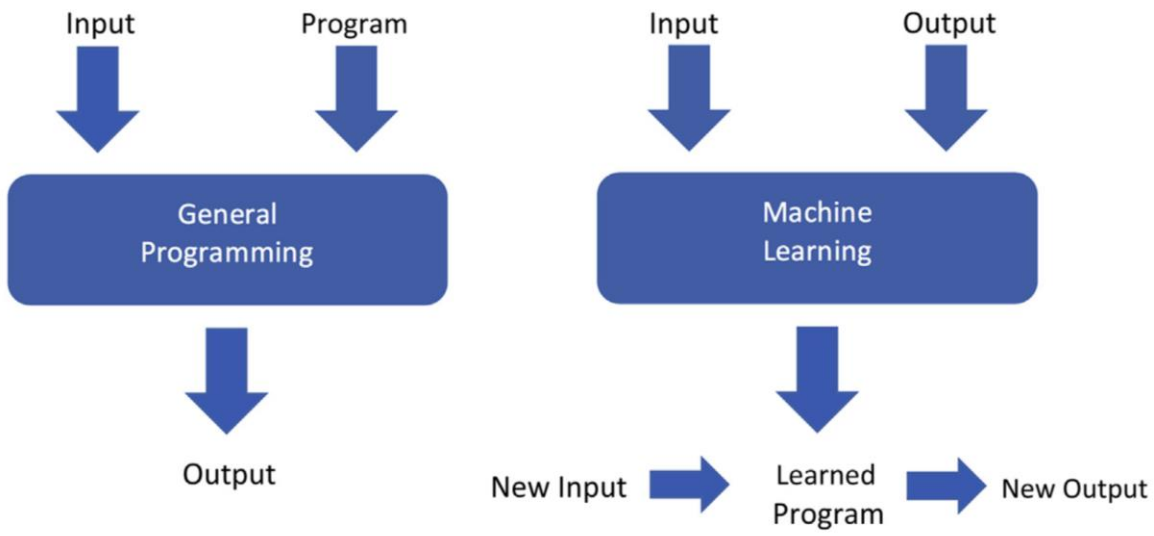
- focused ultrasound (FUS) = thermal ablation of tissue by focally concentrated sound wave energy delivered by a helmet array of FUS transducers inside MRI with real-time MR thermography monitoring
- essential tremor, Parkinson's disease, obsessive-compulsive disorder, depression, neuropathic pain (trials in epilepsy underway e.g. HH, insula)
- advantages
  - no craniotomy, no traversing brain injury
  - no anaesthesia
  - ideal for deep lesions in centre of head
- disadvantages
  - 2-4 hours therapy (may need sedation)
  - no good for eccentric cortical lesions





Computerised automation and machine learning

- ultrafast processing speeds, tandem parallel computing, massive data storage (local and cloud), rapid data transfer
- secure database linkage (research, clinical, govt, industry), crowd sourcing
- machine learning or deep learning
  - a type of AI in which computer-based algorithms are used to recognise patterns in large, complex data sets, with supervised training but no explicit programming



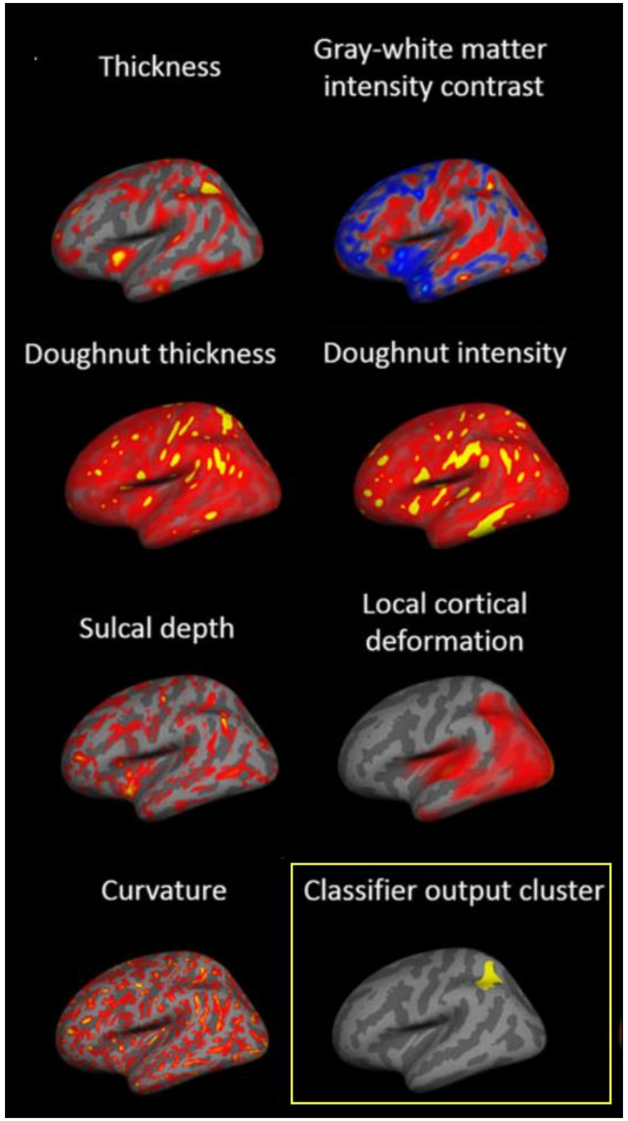
Senders et al. Machine Learning and Neurosurgical Outcome Prediction. *World Neurosurgery* 2018

Computerised automation in epilepsy surgery

- neuroimage analysis
  - automated hippocampal volumetry, pipelines for multimodal image processing
  - 3D virtual surgery and planning
  - detection of occult lesions with VBM or surface/textural analysis
- seizure analysis
  - spike, seizure and HFO detection in intracranial EEG monitoring and ECoG
  - seizure forecasting from EEG and other biophysical data in medical devices for patient alerting and RNS
  - analysis of seizure semiology
- patient classification/selection and outcome prediction
  - predicting drug resistant epilepsy from clinical data, insurance data
  - predicting seizure freedom following surgery
- individualised "virtual epileptic brain" (Jirsa et al, *Brain* 2014 & *Neuroimage* 2016)

Computerised automation in epilepsy surgery: FCD detection

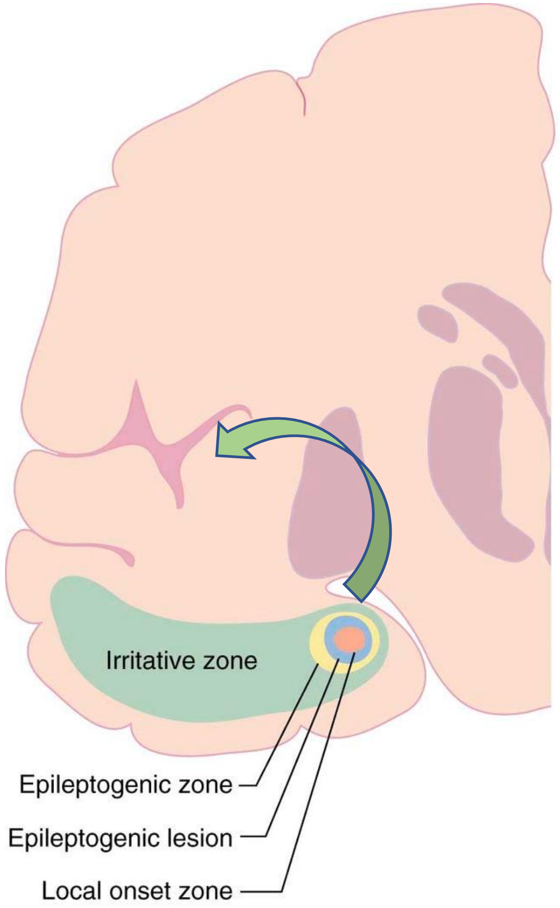
- 61 patients with drug-resistant focal epilepsy
  - scanned and operated at 3 centres
  - MRI evidence of FCD (subtle or obvious)
  - histologically proven FCD type 2
- normal database (120 healthy controls) for learning
- 35 healthy controls and 15 mTLE-HS patients for testing
- T1 images post-processed, cortical surface features calculated, FCD marked on MRI, trained in a non-linear neural network to discriminate FCD from normal cortex
- FCD detection: sensitivity = 74%, specificity = 90% and AUC for the ROC analysis = 0.75 (discriminative)
  - better in MRI obvious cases



Jin B, Krishnan B, Adler S et al. Automated detection of FCD type II with surface-based MRI postprocessing and machine learning. *Epilepsia* 2018

Biomarkers of the epileptogenic zone

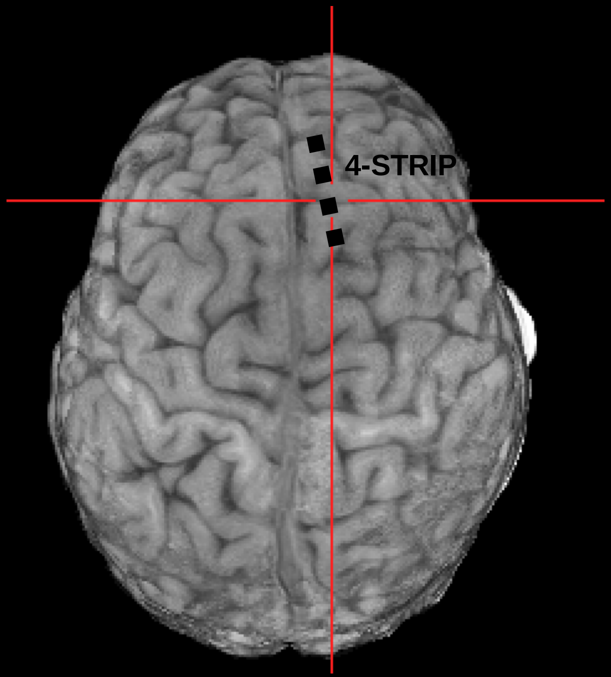
- epileptogenic zone = the minimal region of cortex necessary to resect for the patient to become seizure free, informed by
  - seizure (local) onset zone
  - epileptogenic lesion
  - interictal abnormalities (irritative)
  - secondarily involved (connected) regions
- depends on underlying pathology e.g. in FCD2
  - visible cortical lesion on MRI
  - runs of CEDs on interictal ECoG
  - seizure onset with preictal rhythmic spiking and LVFA
  - pathological lesion, especially dysmorphic neurons
  - ? mutated neurons in dysplastic cortex

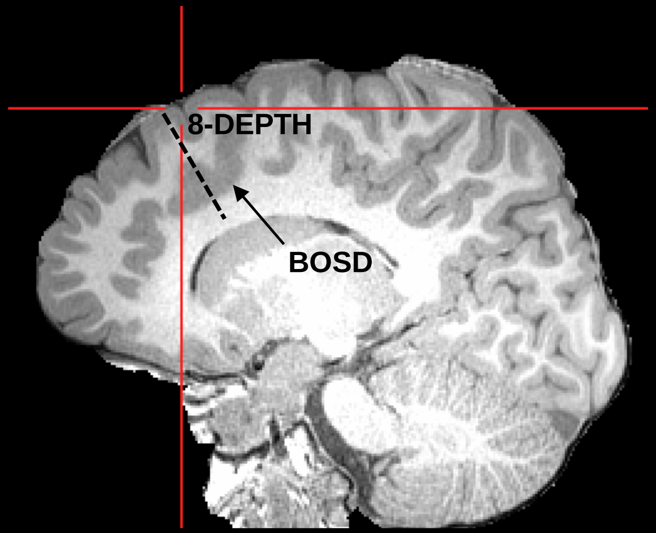


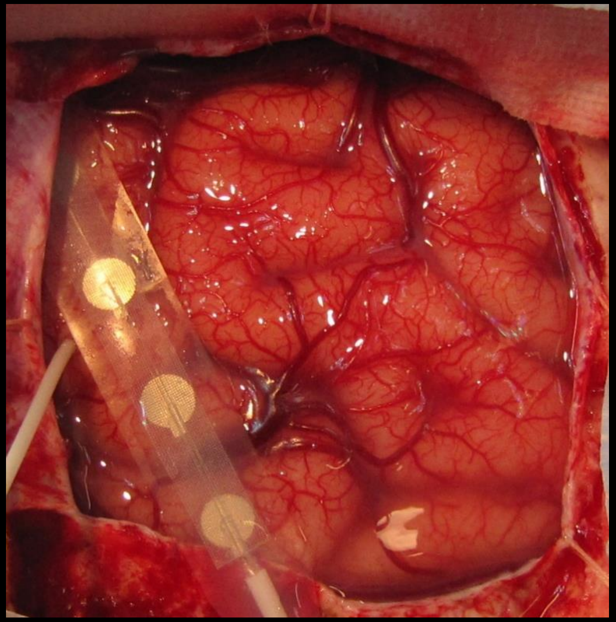
http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/neurology/epileptic-syndrome/

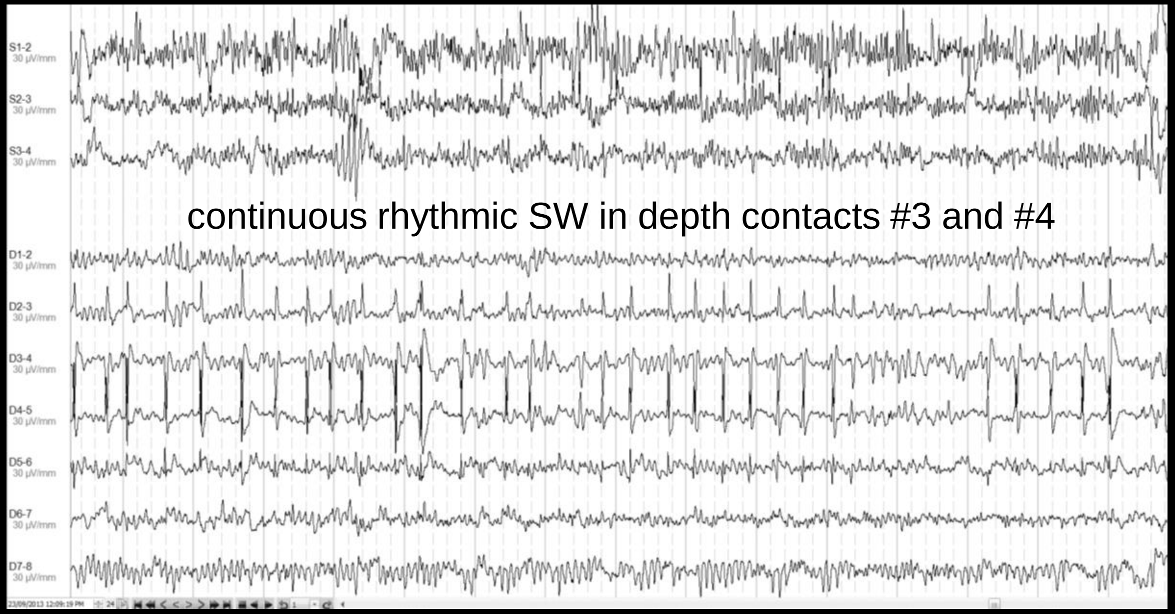
Biomarkers of the epileptogenic zone: HFOs

- high frequency oscillations are bursts EEG activity > 80Hz
  - 80-240 Hz = ripples, 250-500 Hz = fast ripples
- first described in epilepsy in 1999 with microelectrodes in hippocampi of rats
  (Bragin A et al, *Hippocampus* 1999; *Epilepsia* 1999; *Ann Neurol* 2002, 2004)
- now widely reported in patients with epilepsy, with 100s of publications on their presence and associations
  - interictal or ictal, with or without spikes
  - with microelectrodes, macroelectrodes or scalp electrodes
  - physiological (? ripples) or pathological (? fast ripples)
  - visual or automated detection from intracranial EEG (chronic iEEG or intraop ECoG)
- proposed as a "biomarker" of epileptogenesis and the epileptogenic zone
  - greater association with seizures than IEDs and lesions
  - association with surgical outcome


4-STRIP


8-DEPTH
BOSD




S1-2
S2-3
S3-4
continuous rhythmic SW in depth contacts #3 and #4
D1-2
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D3-4
D4-5
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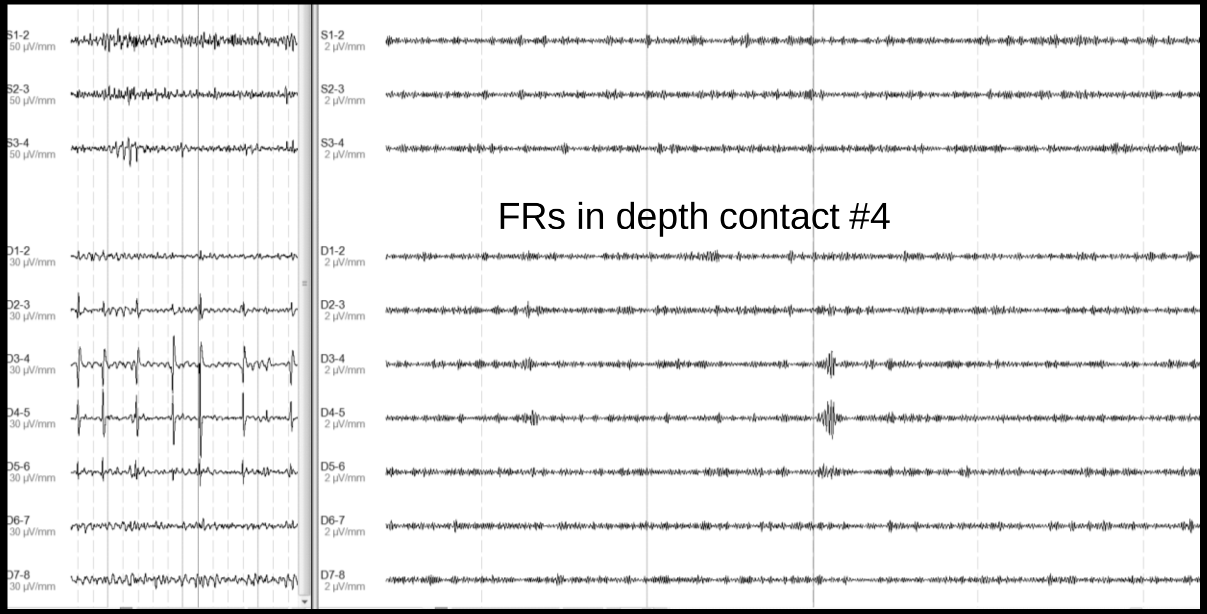
D6-7
D7-8


S1-2
S2-3
S3-4
FRs in depth contact #4
D1-2
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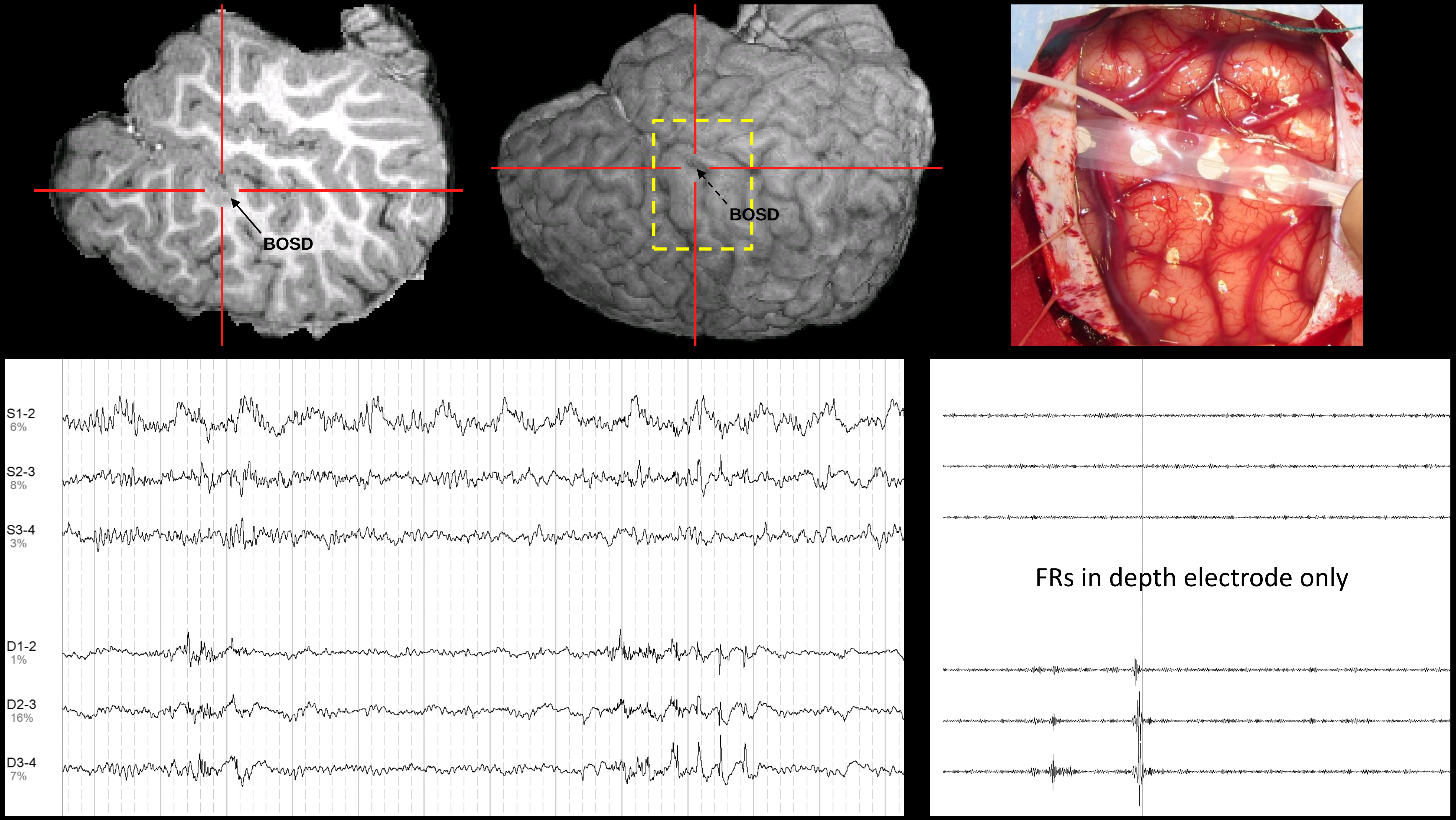
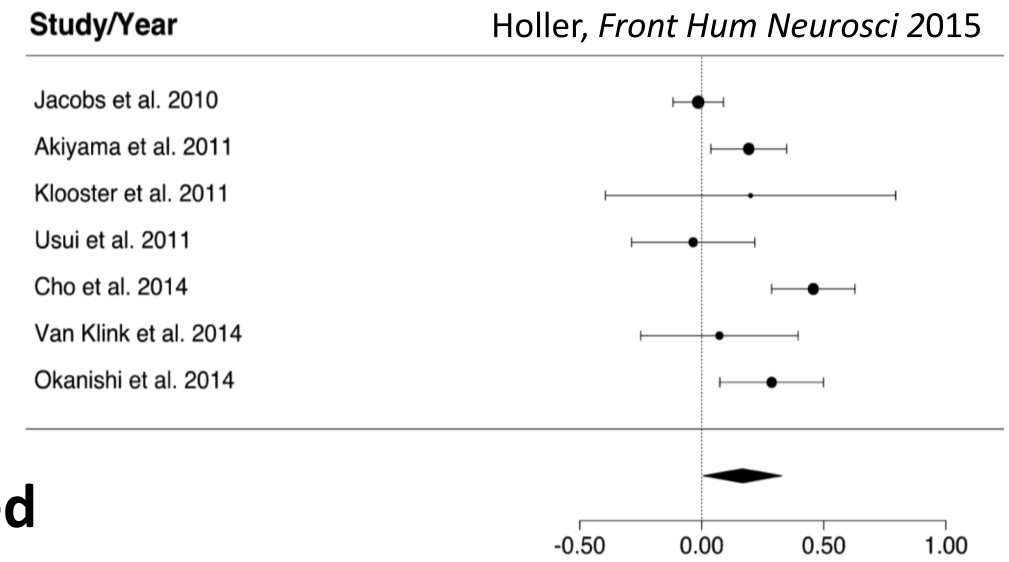
D7-8


BOSD
BOSD
S1-2
6%
S2-3
8%
S3-4
3%
D1-2
1%
D2-3
16%
D3-4
7%
FRs in depth electrode only

Biomarkers of the epileptogenic zone: HFOs

- HFOs increase before but not after seizures (unlike IEDs)
- HFOs increase when AEDs reduced, like seizures (unlike IEDs)
- HFOs decrease with propofol, like seizures (unlike IEDs)
- HFOs evoked with single-pulse stimulation
- HFOs occur in regions with low AD threshold
- HFOs found more frequently in the seizure-onset zone, irrespective of lesion
- HFOs present at seizure onset and spread with interruption of local inhibition
- **surgery outcome better when HFO region resected**
- **surgery outcome even better when no HFOs on postop ECoG**

Holler, *Front Hum Neurosci* 2015



Difference in means of fast ripple resection ratios for SF and NSF patients

Jacobs , *Epilepsia* 2008; Urrestarazu, *Brain* 2007; Jacobs, *Brain* 2009; Bagshaw, *Epilepsia* 2009; Zijlmans, *Neurology* 2009; Jacobs, *Ann Neurol* 2010; Wu, *Neurology* 2010; Akiyama, *Epilepsia* 2011; Nairai, *Epilepsia* 2011, Holler, *Front Hum Neurosci* 2015; Frauscher et al, *Epilepsia* 2017

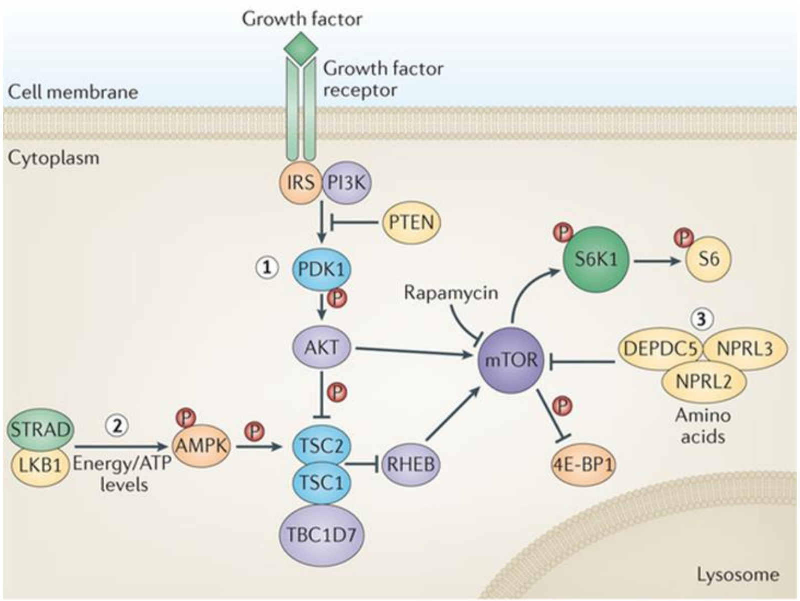
Biomarkers of the epileptogenic zone: HFOs

- 52 patients at 3 centres (Freiburg, UCLA, MNI) recruited patients over 1 year
  - HFOs recorded with chronic iEEG or intraoperative ECoG
- *post hoc*, standardised, blinded, automated and visual analysis of HFOs
- correlation between resection of HFO-generating regions and seizure-free outcome at the group level
- no correlation at the centre level or patient level
  - individual prognostication of seizure outcome in only 67% patients
  - some seizure-free patients without removal of all HFO-generating tissue
- “HFOs may be less specific for epileptic tissue than earlier studies indicated”
- ? HFOs an artefact of filtered spikes
  ? HFOs just an EEG epiphenomena
  ? better outcome related to bigger resection

Jacobs et al. Removing HFOs: A prospective multicenter study on seizure outcome. *Neurology* 2018

Incorporation of genomics in epilepsy surgery

- recognition of drug-resistant, MRI-pos/neg, focal epilepsies evaluated for surgery that have a genetic (germline) basis
  - surgically-remediable e.g. *TSC1/2, DEPDC5, NPRL2/3, NF1*
  - non-surgically-remediable e.g. *SCN1A, POLG, PCDH19, DCX*
- recognition of somatic mutations underlying surgical MCDs and FCDs
  - HMG: *PIK3CA, AKT3, MTOR*
  - SWS : *GNAQ*
  - FCD2: *TSC1/2, DEPDC5, NPRL2/3, MTOR, RHEB*
  - FCD1: *SLC35A2*
- impression of epileptogenicity correlated with
  - mutation gradient (allele frequency)
  - dysmorphic neuron gradient



Nature Reviews | Neurology

Incorporation of genomics in epilepsy surgery

- family history taking and potentially genetic testing to inform
  - patient selection for surgery
  - prognosis following surgery
  - genetic counseling following surgery
  - research
- specimen collection in operating theatre
  - blood, skin and CSF for genetic testing
  - fresh brain tissue (frozen <80^{o}) for genetic testing (deep sequencing, ddPCR)
  - FF-PE brain tissue for histopathology (H&E, NeuN, phospho-S6, neurofilament)
  - meticulous labeling, photographing, correlation with MRI & ECoG
  - collaboration with research centres

ANNALS of Clinical and Translational Neurology
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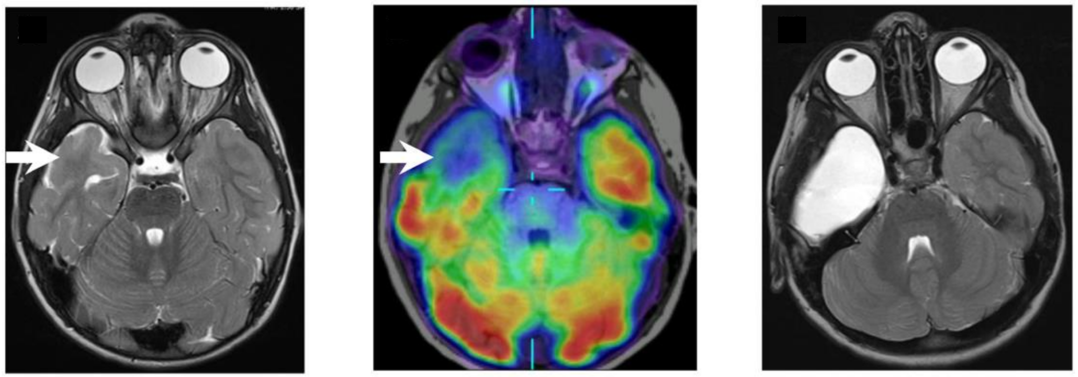
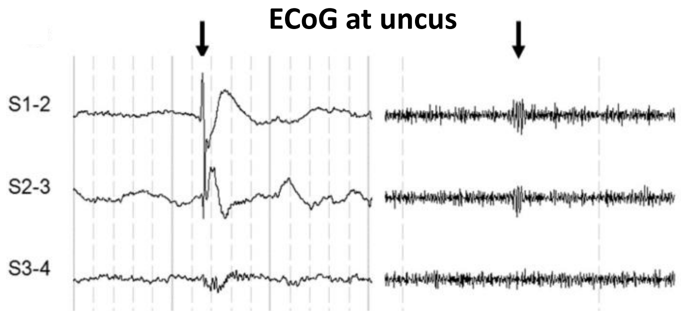
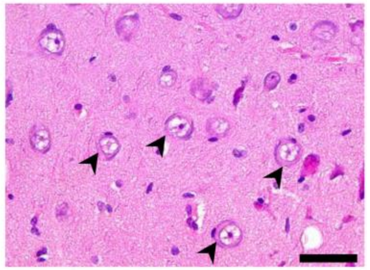
BRIEF COMMUNICATION

Second-hit *DEPDC5* mutation is limited to dysmorphic neurons in cortical dysplasia type IIA

Wei Shern Lee[1,2], Sarah E. M. Stephenson[1,2], Katherine B. Howell[1,2,3,4], Kate Pope[1], Greta Gillies[1], Alison Wray[1,5], Wirginia Maixner[1,5], Simone A. Mandelstam[1,2,4,6], Samuel F. Berkovic[2,4], Ingrid E. Scheffer[1,2,3,4], Duncan MacGregor[1,7], Anthony Simon Harvey[1,2,3], Paul J. Lockhart[1,2,*] & Richard J. Leventer[1,2,3,*]



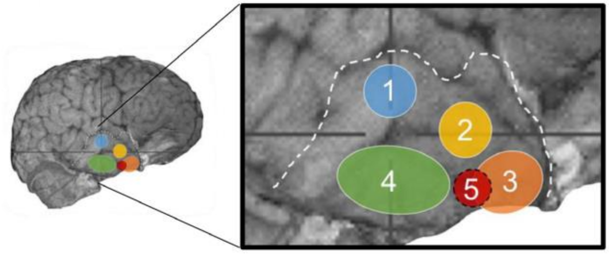


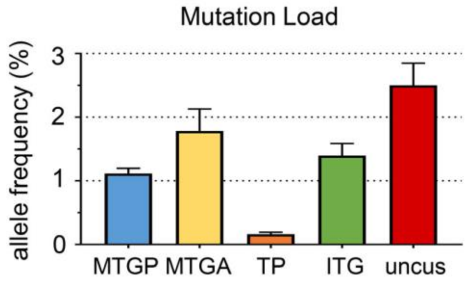


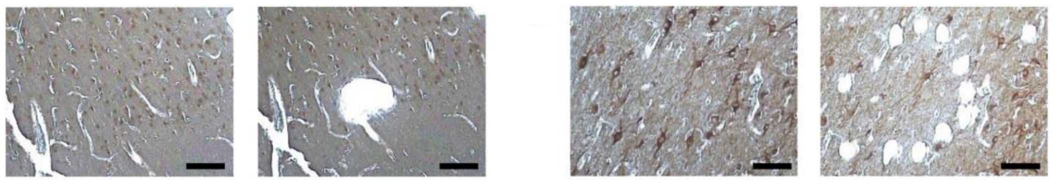
A boy with DRE, FCD, and a germline DEPDC5 pathogenic variant:

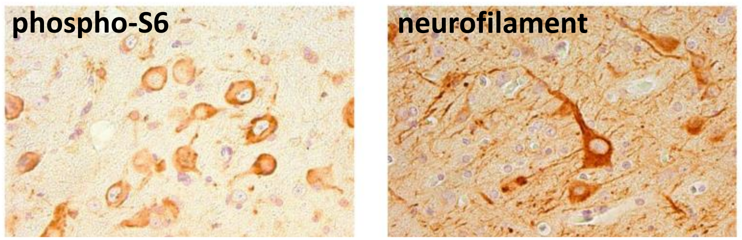
- a second-hit DEPDC5 variant was found limited to DNs

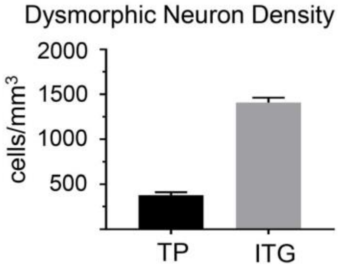
- the somatic mutation load correlated with DN density and the EZ

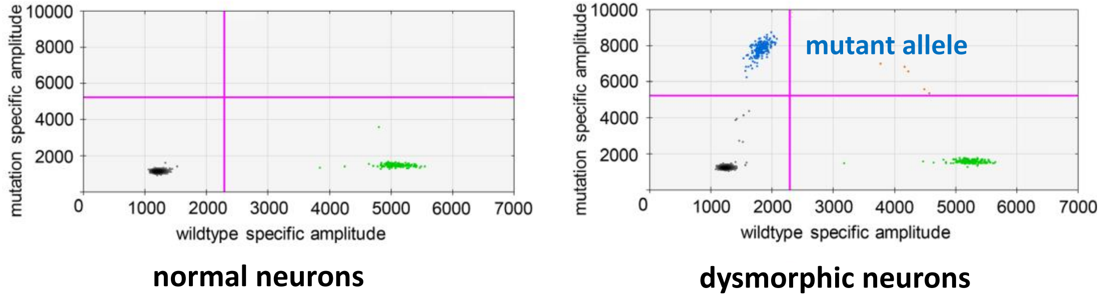












Future advances in epilepsy surgery: Precision surgery

- gathering more detailed patient data (clinical, imaging, EEG, genetic, SES)
- pooling of patient data at a population level into large databases
- machine learning approaches to patient classification, surgical selection, and identification of epileptogenic lesions and foci
- development of patient-specific, virtual models of normal and epileptic structures and networks to identify surgical targets and approaches
- image-guided, robotic-assisted, non/minimally-invasive technologies for cortical lesioning or functional disruption to control seizures
- feedback of patient outcomes (seizures, comorbidities, QOL, economic) into machine learning algorithms for more informed future decisions