

Secondary Epileptogenesis

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Secondary Epileptogenesis

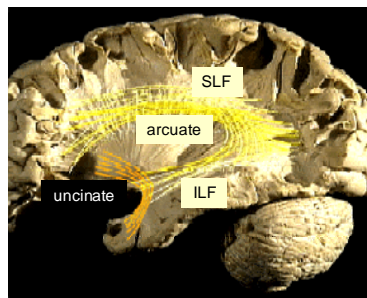
A process by which an eventually irreversible, **secondary epileptic focus** is established in an area remote from the primary epileptic focus, in a homotopic or ipsilaterally connected location, due to repeated invasion by seizures and IEDs.

The concept of secondary epileptogenesis does not encompass:

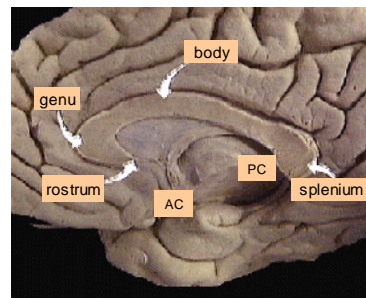
- development of epilepsy following early life insults *eg. mTLE following PFC*
- worsening of epilepsy due to locally recurrent seizures
- detrimental, non-seizure effects of epilepsy *eg. cognition, behaviour, MRI*

Secondary Epileptogenesis

A process by which an eventually irreversible, **secondary epileptic focus** is established in an area remote from the primary epileptic focus, in a **homotopic or ipsilaterally connected** location, due to repeated invasion by seizures and IEDs.



intrahemispheric fasciculi



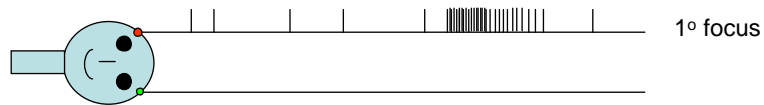
interhemispheric commissures

Scope

- experimental models of 2^o epileptogenesis in animals
 - limbic kindling
 - “mirror focus”
- examples of 2^o epileptogenesis in human focal epilepsy
 - “mirror foci” in neocortical tumoural epilepsy
 - “mirror foci” in mTLE
 - remote ipsilateral foci eg. occipitotemporal, frontotemporal
 - symptomatic generalised epilepsy in HH and FCD
- pathophysiological basis of 2^o epileptogenesis
- practical implications of 2^o epileptogenesis

Animal Models – Mirror Focus

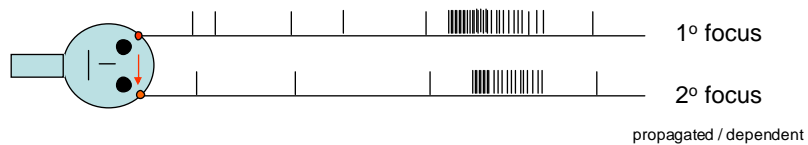
- create a 1° cortical focus with a single freezing or chemical lesion
→ 1° focus exhibits IEDs and seizures



Morrell F. J Clin Neurophysiol 1989

Animal Models – Mirror Focus

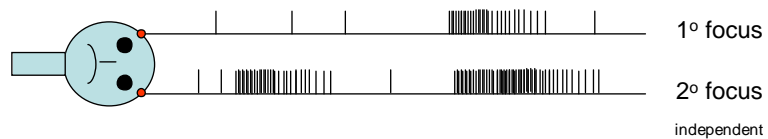
- create a 1° cortical focus with a single freezing or chemical lesion
→ 1° focus exhibits IEDs and seizures
→ IEDs and seizures propagate to contralateral homotopic cortex



Morrell F. J Clin Neurophysiol 1989

Animal Models – Mirror Focus

- create a 1° cortical focus with a single freezing or chemical lesion
 - 1° focus exhibits IEDs and seizures
 - IEDs and seizures propagate to contralateral homotopic cortex
 - IEDs and seizures arise independently in the “mirror” 2° focus



Morrell F. J Clin Neurophysiol 1989

Animal Models – Mirror Focus

- create a 1° cortical focus with a single freezing or chemical lesion
 - 1° focus exhibits IEDs and seizures
 - IEDs and seizures propagate to contralateral homotopic cortex
 - IEDs and seizures arise independently in the “mirror” 2° focus
- intravenous methohexital (Brevital®) suppression of IEDs:
 - early on, MHT suppresses the 2° focus well before the 1° focus
 - later on, the 2° focus is resistant to MHT suppression

Morrell F. J Clin Neurophysiol 1989

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- resection or disconnection of the 1° focus:
 - early on, leads to immediate or gradual remission of the 2° focus



Morrell F. J Clin Neurophysiol 1989

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 - later on, the 2° focus is resistant to MHT suppression
- resection or disconnection of the 1° focus:
 - early on, leads to immediate or gradual remission of the 2° focus
 - later on, leads to persistent IEDs and seizures from the 2° focus



Morrell F. J Clin Neurophysiol 1989

Animal Models – Mirror Focus

- create a 1° cortical focus with a single freezing or chemical lesion
 - 1° focus exhibits IEDs and seizures
 - IEDs and seizures propagate to contralateral homotopic cortex
 - IEDs and seizures arise independently in the “mirror” 2° focus
- intravenous methohexital (Brevital®) suppression of IEDs:
 - early on, MHT suppresses the 2° focus well before the 1° focus
 - later on, the 2° focus is resistant to MHT suppression
- resection or disconnection of the 1° focus:
 - early on, leads to immediate or gradual remission of the 2° focus
 - later on, leads to persistent IEDs and seizures from the 2° focus
- the effectiveness and latency of mirror focus development depends on:
 - species studied
 - synaptic connectivity of the 1° focus (eg. not in precentral gyrus)

Morrell F. J Clin Neurophysiol 1989

Stages of 2° Epileptogenesis (Morrell)

1st stage = **dependent** stage of 2° epileptogenesis

- IEDs occur synchronously with the 1° focus only
- removal of 1° focus leads to immediate cessation of IEDs

2nd stage = **intermediate** stage of 2° epileptogenesis

- ↑ IEDs and occasional seizures occur independent of the 1° focus
- removal of 1° focus leads to delayed cessation of seizures and IEDs

3rd stage = **independent** stage of 2° epileptogenesis

- IEDs and ↑ seizures occur independently from the 1° focus
- removal of 1° focus followed by persistence of seizures and IEDs

Morrell F. J Clin Neurophysiol 1989

Tumour-related, Neocortical Epilepsy

Morrell F. *J Clin Neurophysiol* 1989;6

- 116 operated patients with tumoural, neocortical epilepsy (MNI & Chicago)
- bilateral IEDs 21-38%
- independent contralateral seizures in 15%
- 2/3 gradual postop seizure remission, 1/3 seizure persistence
- persistent seizures in patients with MHT-resistant focus

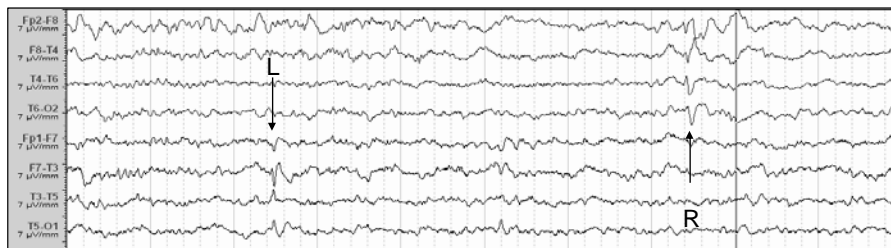
Lim SH et al. *Arch Neurol* 1991;48

- 60 TLE patients undergoing ATL (Cleveland Clinic)
- 30 with unilateral IEDs and 30 with bilateral IEDs
- tumours (? localised pathology) associated with bilateral IEDs
- prolonged FC/encephalitis (? diffuse pathology) associated with unilateral IEDs

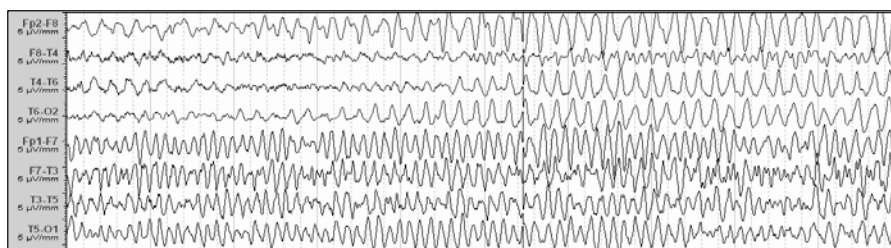
Gilmore R et al. *Epilepsia* 1994;35

- 22 patients with tumoural TLE undergoing surgery (Cleveland Clinic)
- 7 with mirror foci and 15 without mirror foci
- no difference in seizure onset, epilepsy duration, seizure frequency or outcome

Bilateral EEG in mTLE



bilateral interictal epileptiform discharges (IEDs)



contralateral seizure propagation and independent bilateral seizures

Bilateral EEG and ATL Outcome in mTLE -1

Hufnagel A, Elger CE et al. *Epilepsia* 1994; 35

- 59 TLE patients, bilateral subdural EEG monitoring
- seizure-freedom in 87% with unilateral seizures & IEDs, 40-56% with unilateral seizures but bilateral IEDs, and 13% with bilateral seizures

Lee et al. *Epilepsia* 2000;41

- depth EEG recordings of seizures in TLE patients
- seizure freedom in 84% with unilateral seizures and 47% with contralateral seizure propagation

Schulz R et al. *Epilepsia* 2000;41

- 58 TLE patients with MTS or no lesion
- seizure freedom in 89% with unilateral seizures & IEDs, 74% with contralateral IEDs or seizure propagation, and 33% with contralateral IEDs and seizure propagation

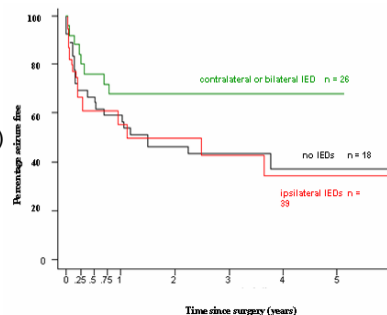
Bilateral EEG and ATL Outcome in mTLE -2

Malow et al. *Epilepsia* 1999;40

- bitemporal IEDs associated with poor postop outcome if normal MRI
- good outcome with bitemporal IEDs if unilateral hippocampal abnormality

Lee et al. *ESA* 2006 (poster 556)

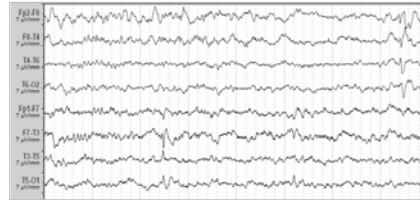
- 83 pts with refractory, lesional TLE
- unilateral lesions (HS 55, FTL 14, other 14)
- lesionectomy or lobectomy (2-6 yrs follow-up)
- 48% patients seizure free
- no negative effect on seizure outcome of:
 - contralateral IEDs
 - contralateral seizure propagation



Epilepsy Duration in mTLE

Janszky J et al. *Seizure* 2003;12

- 243 patients with mTLE and unilateral HS
- 2/3 unilateral IEDs, 1/3 bilateral IEDs
- no difference in epilepsy duration
- late-onset TLE assoc with bilateral IEDs



McIntosh AM et al. *Brain* 2004;127

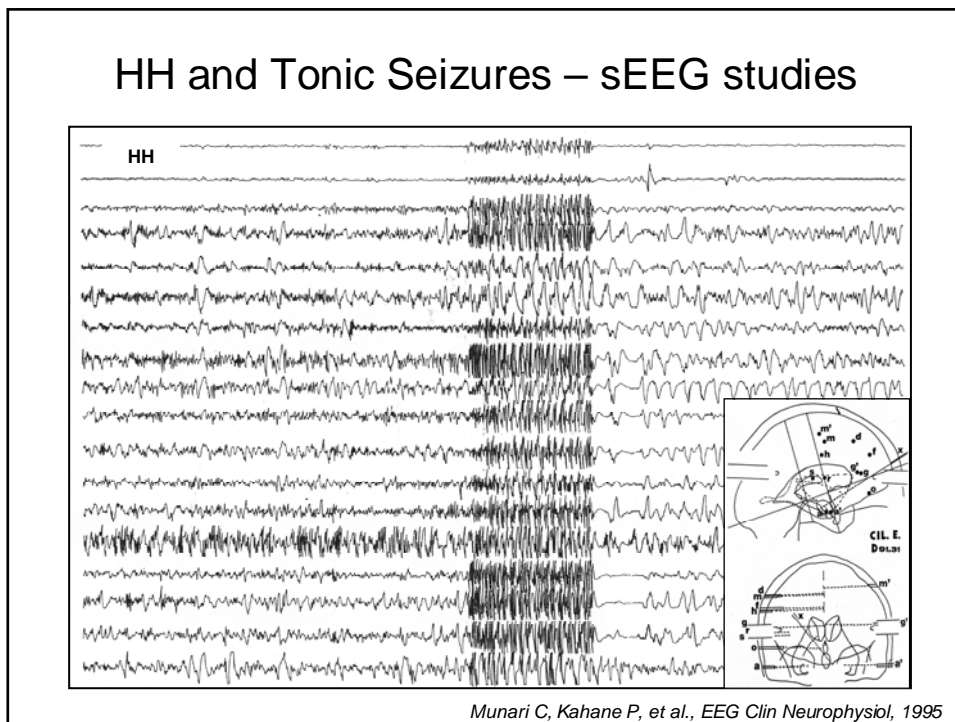
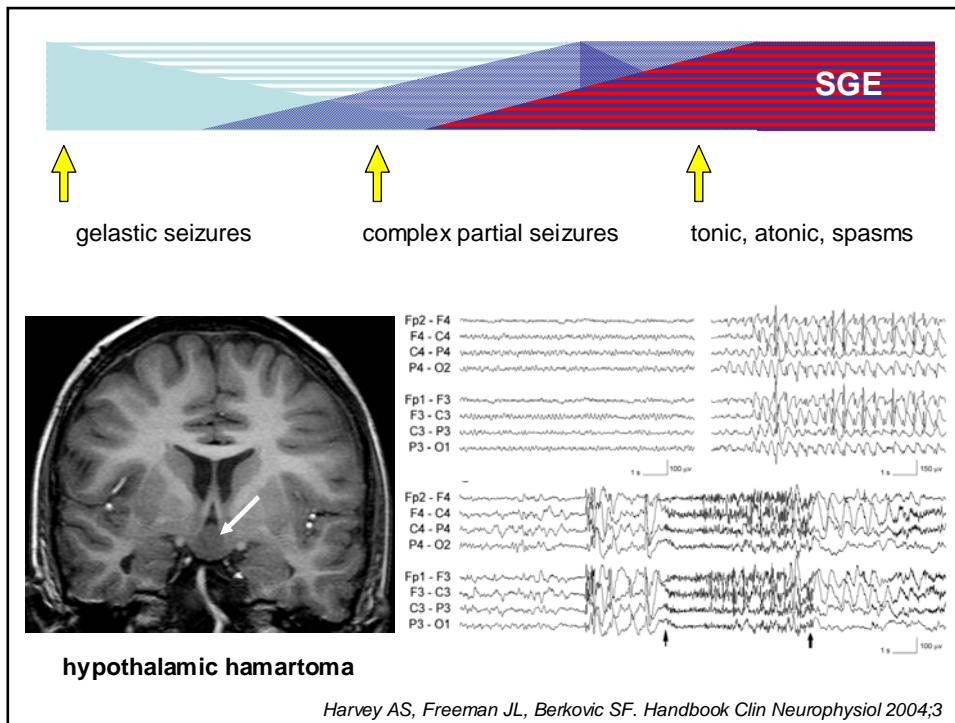
- 325 patients with mTLE underwent ATL with mean follow-up 9.6 yrs
- 48% seizure free at 5 years
- after adjustment for preoperative pathology, no effect of
 - age at seizure onset
 - age at surgery
 - duration of epilepsy

? Human Examples of Mirror Foci

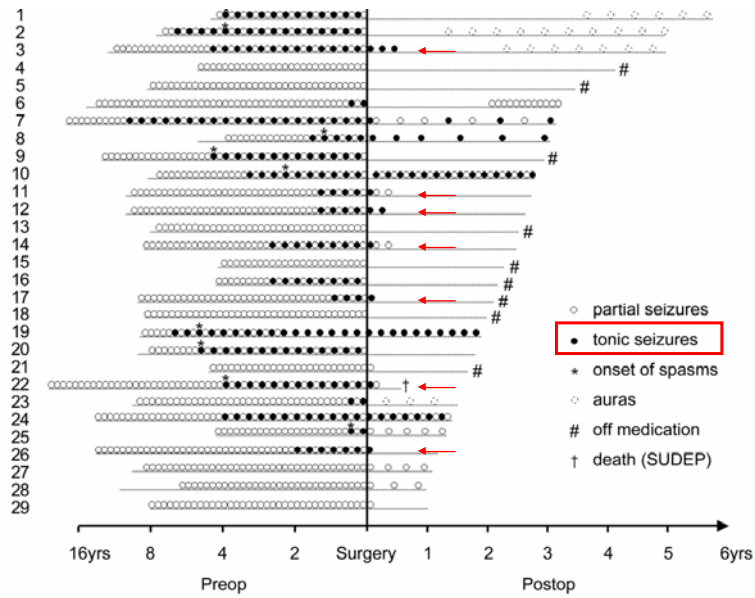
- conflicting evidence in humans and few proven cases
- clinical research confounded by:
 - heterogeneity of epilepsy samples studied and small numbers
 - aetiologies with potential for bilateral pathology
 - insensitivity and unreliability of scalp EEG
 - short follow-up in seizure outcome studies
- lack of correlation between markers of 2^o epileptogenesis (bilateral IEDs/seizures, postop sz) and expected biological factors (duration of epilepsy, lifetime seizures)

Frank Morrell

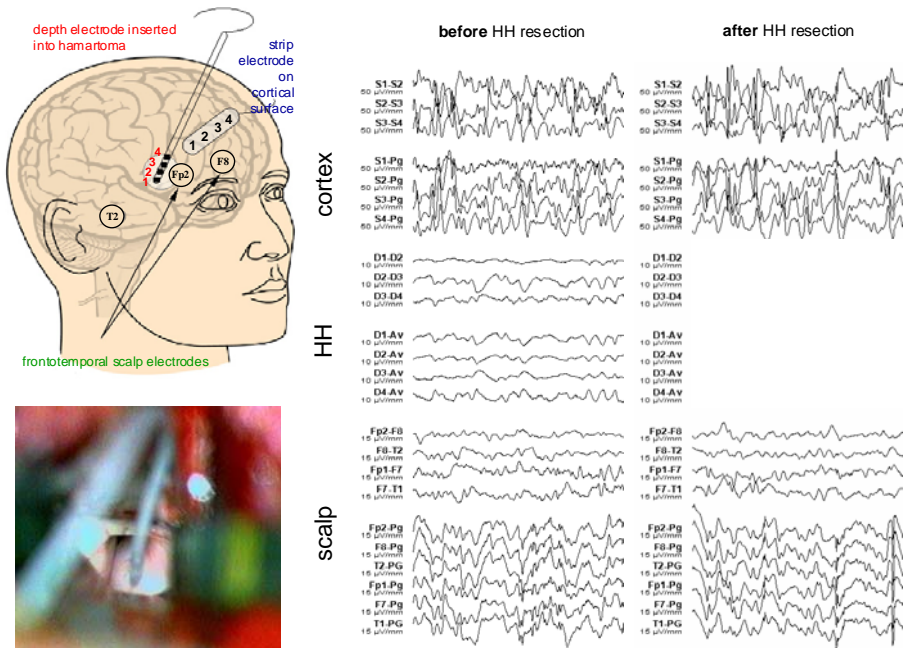
- 2^o epileptogenesis altered by AEDs in humans
- good outcomes in mirror foci cases = stage 2 (intermediate)



Evolution and Postoperative Resolution of Seizures in HH

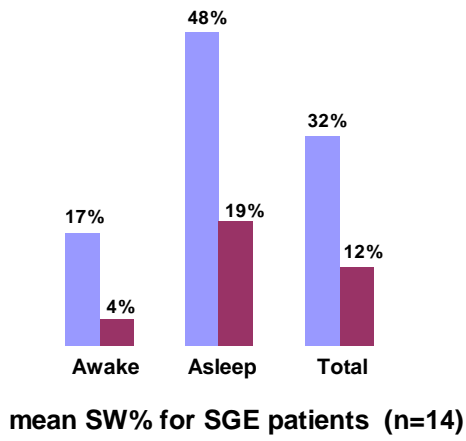


Harvey et al, *Epileptic Disorders* 2003

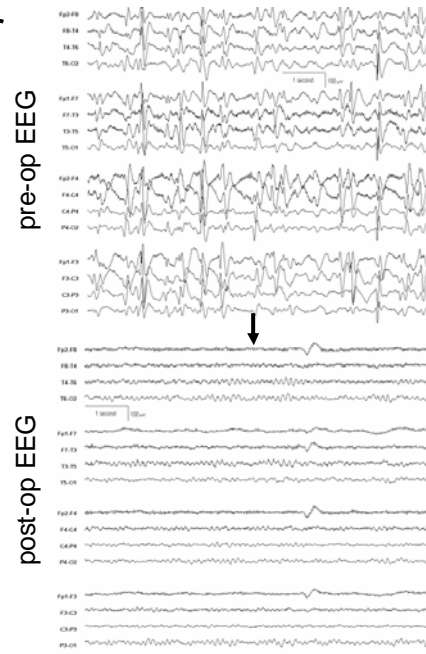


Freeman et al, *Neurology* 2003

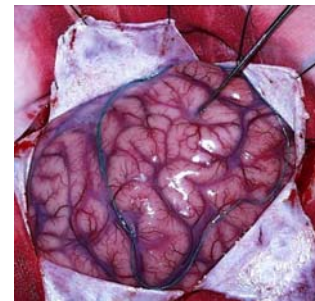
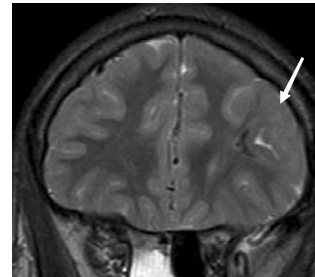
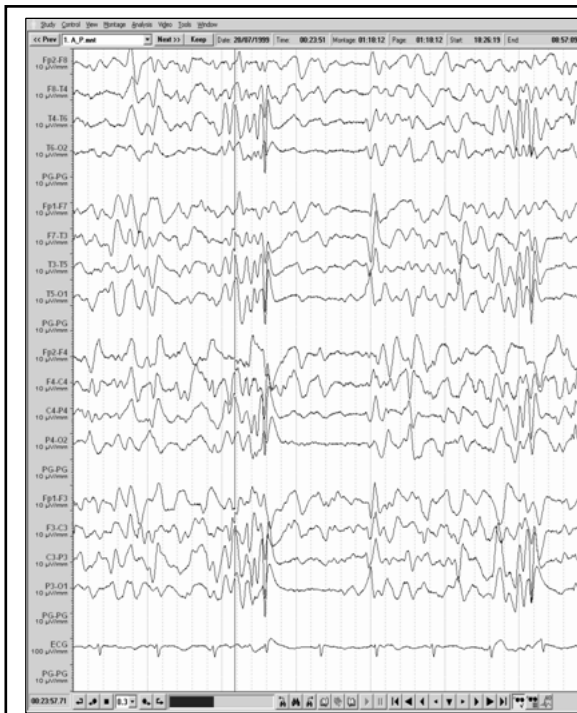
EEG improvement after HH surgery



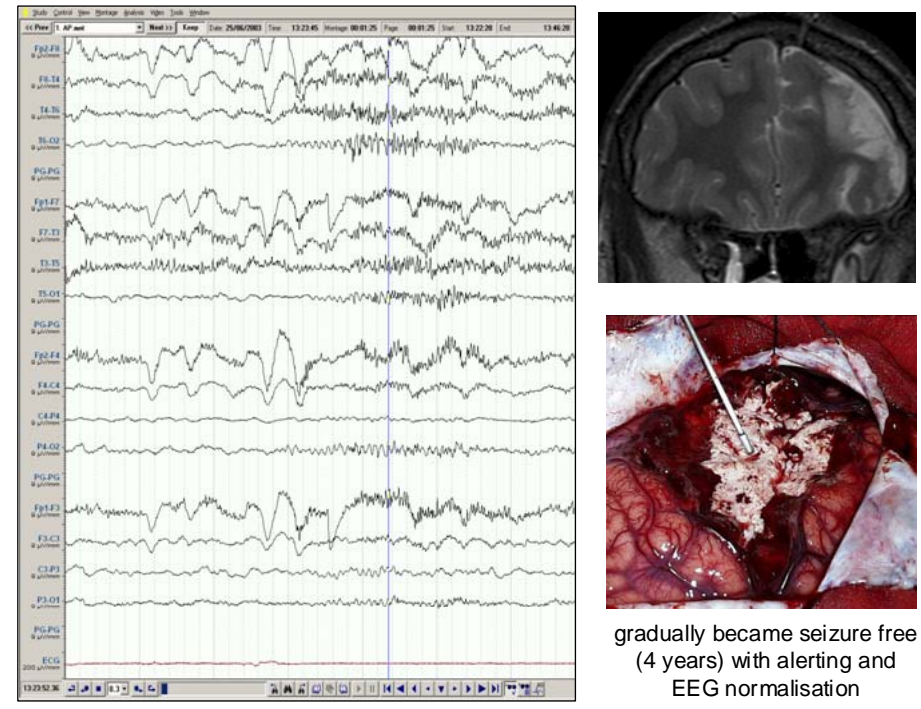
- pre-op (median 1 week)
- post-op (median 2 weeks)



Freeman et al, Neurology 2003

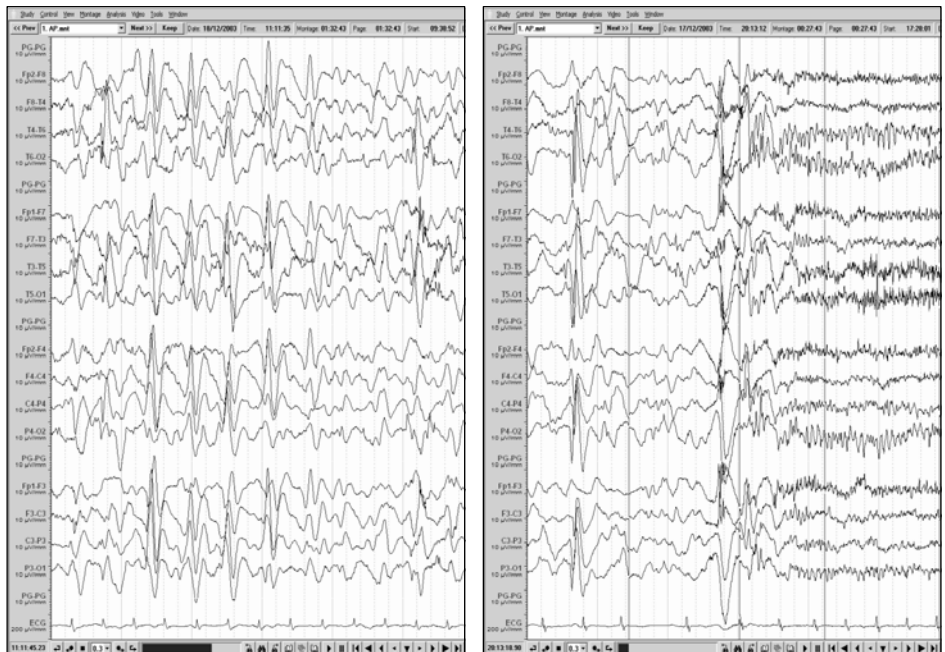


15 yrs old boy: LGS with tonic seizures, intellectual disability and left frontal dysplasia



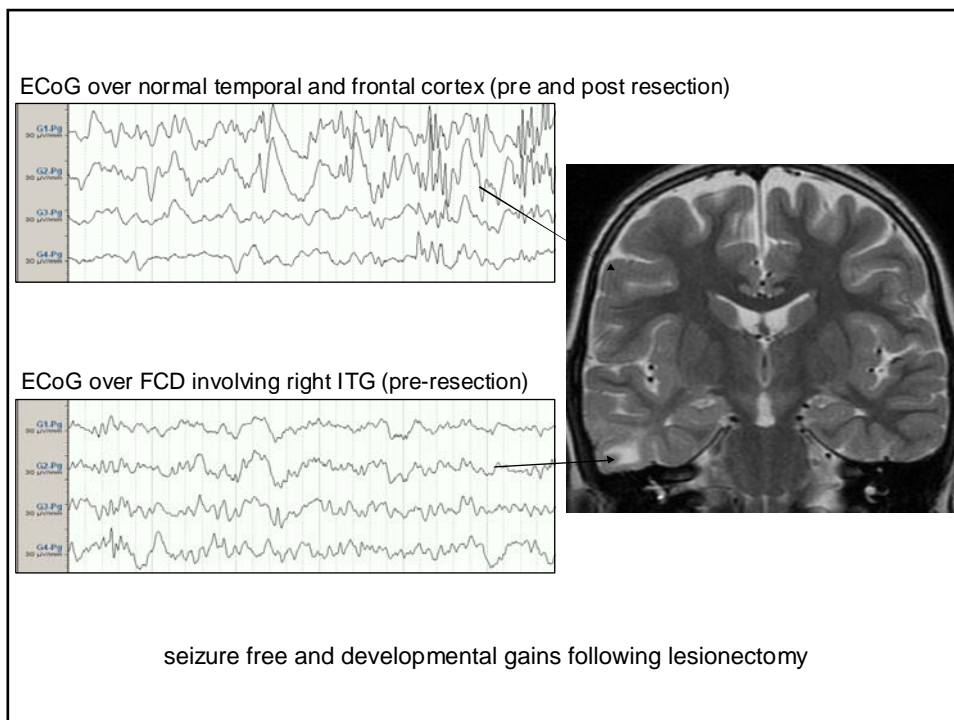
The top left image shows a series of EEG traces from various scalp electrodes (Fp2-F8, T4-T8, T6-O2, PG-PG, Fp1-F7, F7-T3, T3-T5, T5-O1, PG-PG, Fp2-F4, F4-C4, C4-P4, P4-O2, PG-PG, Fp1-F3, F3-C3, C3-P3, P3-O1, PG-PG, ECG) with a vertical blue line indicating a seizure onset. The top right image is a coronal MRI scan of the brain showing a focal lesion in the right hemisphere. The bottom right image is an intraoperative photograph showing the surgical resection of the lesion.

gradually became seizure free
(4 years) with alerting and
EEG normalisation



The image displays two side-by-side EEG traces. The left trace shows a tonic seizure with sustained, high-amplitude, rhythmic activity across multiple channels. The right trace shows a tonic seizure with similar sustained activity. Both traces include the same set of electrodes as the top image (Fp2-F8, T4-T8, T6-O2, PG-PG, Fp1-F7, F7-T3, T3-T5, T5-O1, PG-PG, Fp2-F4, F4-C4, C4-P4, P4-O2, PG-PG, Fp1-F3, F3-C3, C3-P3, P3-O1, PG-PG, ECG).

7 yrs girl: LGS with tonic seizures and spasms, developmental regression and slow SW

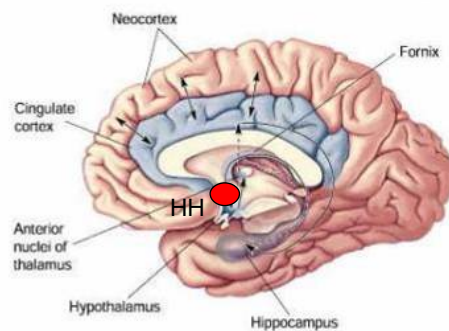
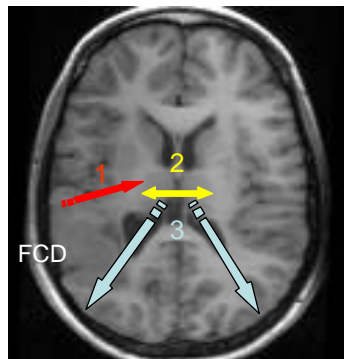


SGE and Focal Cerebral Lesions

- not (necessarily) diffuse (occult) cortical dysplasia
- not irreversible secondary damage from seizures
- tonic seizures are not secondarily generalised partial sz
- GSW on EEG is not secondary bilateral synchrony
- evolves over time in an age-dependent manner
- may remit with surgery, AEDs or spontaneously
- immediately after surgery, seizures and EEG disturbances may persist (in sleep) and then run down
- a potentially-reversible, generalised functional disturbance overlaid on a focal seizure disorder

SGE and Focal Cerebral Lesions

- ? generalised form of secondary epileptogenesis via a complex cortical-subcortical interaction
- ie. maladaptive changes in response (reactive) to seizure focus



Implications of 2° Epileptogenesis

- ? AEDs should ideally have anti(2°)epileptic effects
- ? counsel about diminished surgery outcome if contralateral IEDs or seizures
- ? need to act urgently in someone who develops a mirror or remote EEG focus
- or
- ? it probably exists, but has no practical implications, as you can't tell the difference between stages 2 and 3 !



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A process by which an eventually irreversible, **secondary epileptic focus** is established in an area remote from the primary epileptic focus, in a homotopic or ipsilaterally connected location, due to repeated invasion by seizures and IEDs.

A form of maladaptive plasticity.

Morrell F. Varieties of Human Secondary Epileptogenesis.
J Clinical Neurophysiology 1989;6(3):227-275.

Frank Morrell
1926-1996

