Diagnosing Complicated Epilepsy: Mapping of the Epileptic Circuitry

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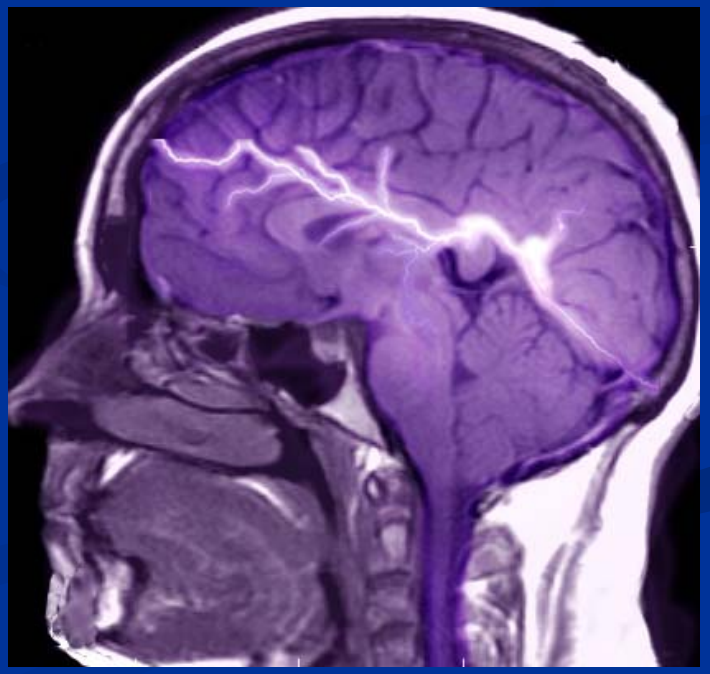


Overview

- Definition of epileptic circuitry
- Methods of mapping epileptic circuits
  - EEG: focus of this talk
    - Only tool to provide high degree of temporal resolution – millisecond level
  - Other: behavioral, SPECT, fMRI, DTI, fcMRI, MEG
- Results of mapping studies
  - Seizure initiation sites
  - Propagation routes
- Mapping cortical function
- Conclusion

Epileptic Circuitry

- Interictal: spikes and dysfunctional areas (examination, neuropsychological deficits, EEG, PET, CBF)
  - Areas that participate in seizure initiation or spread
- Ictal onset zone – where seizures begin
  - Aura and early ictal behaviors provide important clues regarding location of onset zone
  - EEG shows electrical evidence of seizure initiation
- Areas of seizure propagation or spread
  - Progressive involvement of non-primary areas in ictal discharge
    - Orderly or “explosive” spread or involvement
  - Determine behaviors seen during and after a seizure
  - Bilateral spread vs. unilateral spread; subcortical spread
- Termination patterns
  - Synchronous vs asynchronous – influence late behavior

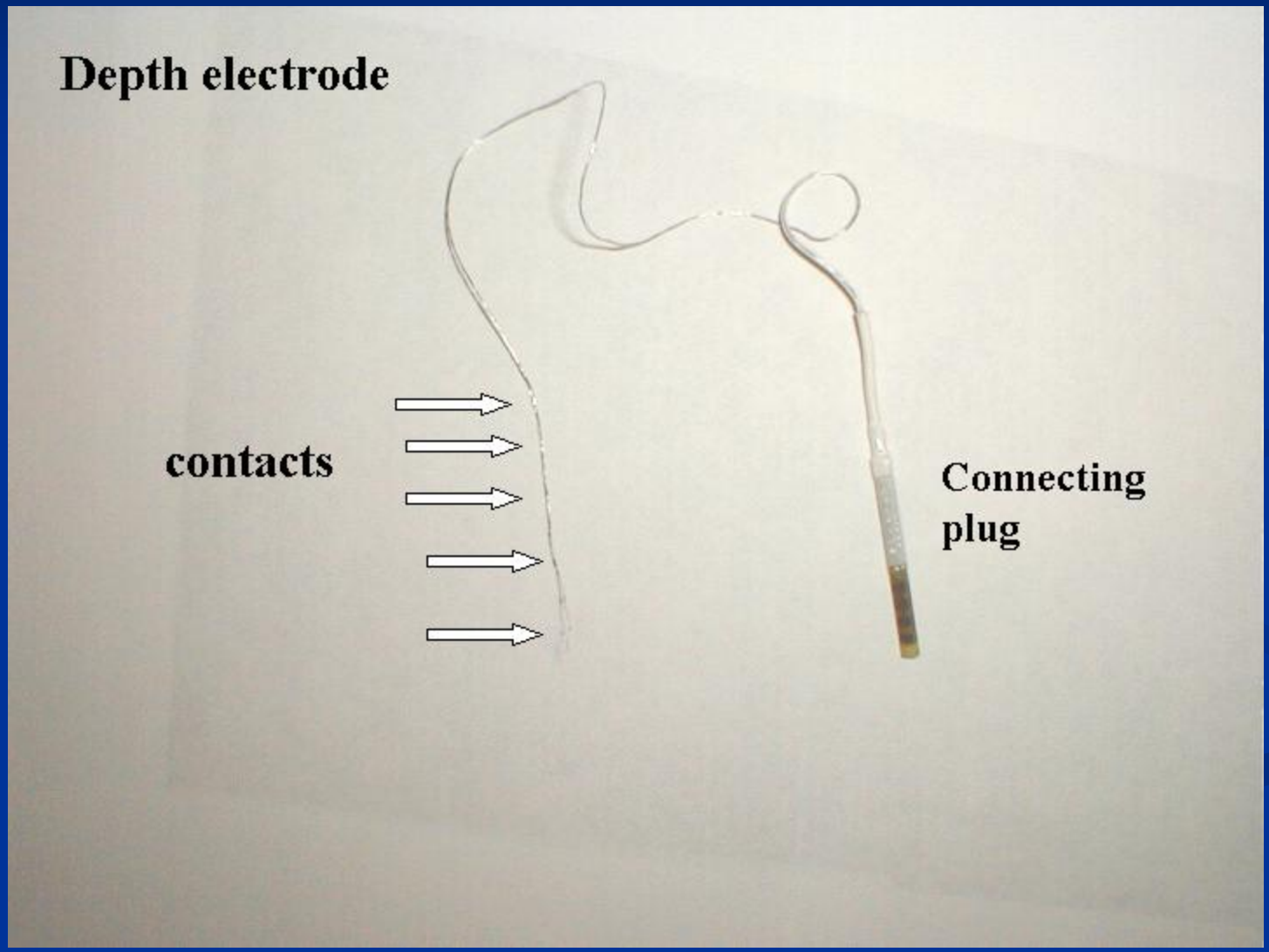
Ictal Onset Zone

- Area where seizures begin
- Non-invasively defined by concordance of test data
  - History, MRI, EEG, PET, MEG suggest abnormality in same area/lobe
- Invasively defined by EEG
  - Intracranial electrodes placed directly over or within suspect cortex
  - Establish area where seizures start
- End result: excision of cortex implicated in initiating seizures
  - Must determine that excision is reasonably safe and will not produce major deficit

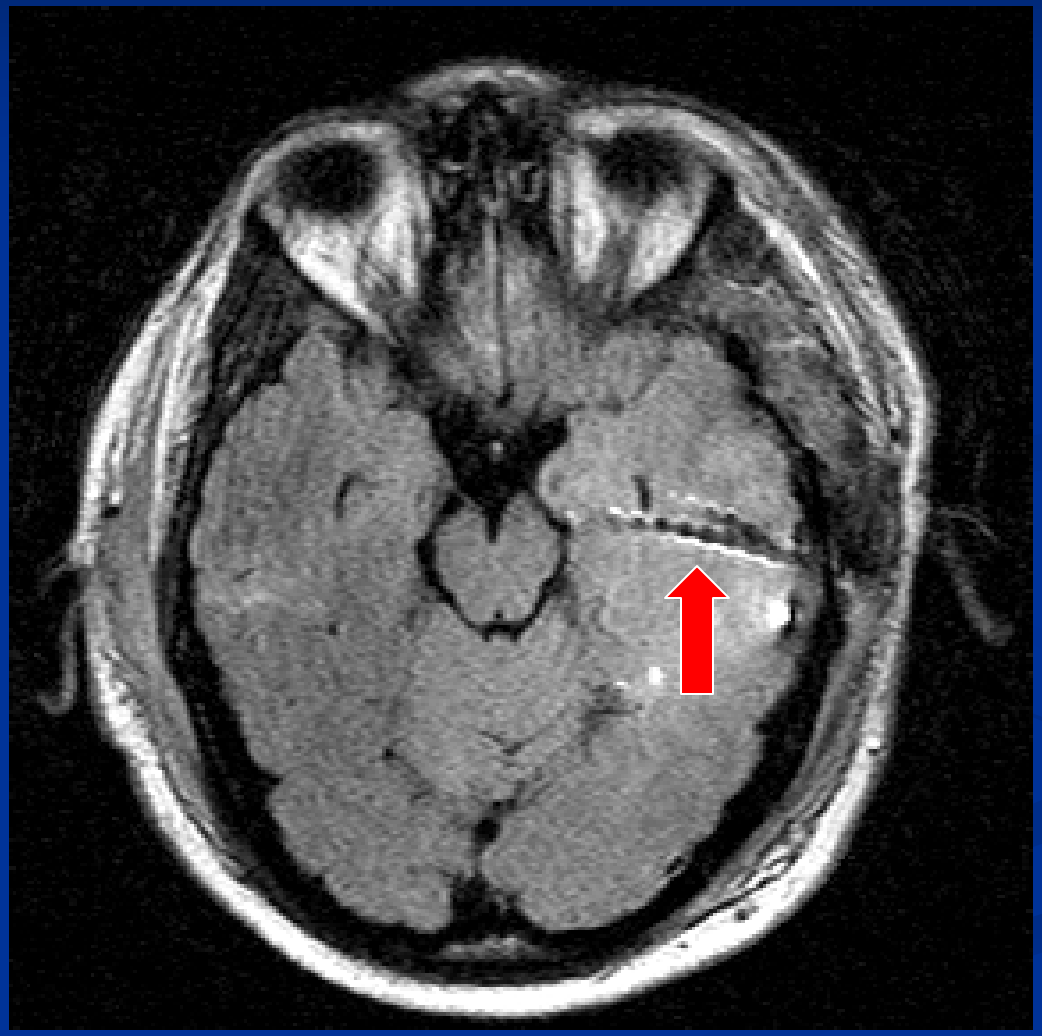
Intracranial EEG

- Different electrode types are used
  - Depth electrodes
  - Subdural or epidural electrodes
- Neurosurgical procedure required for insertion
- Prior to electrode placement, a hypothesis is needed regarding location of seizure onset
  - Good luck – essential
- Associated risk is small
  - Permanent neurological deficit: 1%
- Need depends upon epilepsy syndrome/seizure type
  - Lacking a structural lesion, often needed

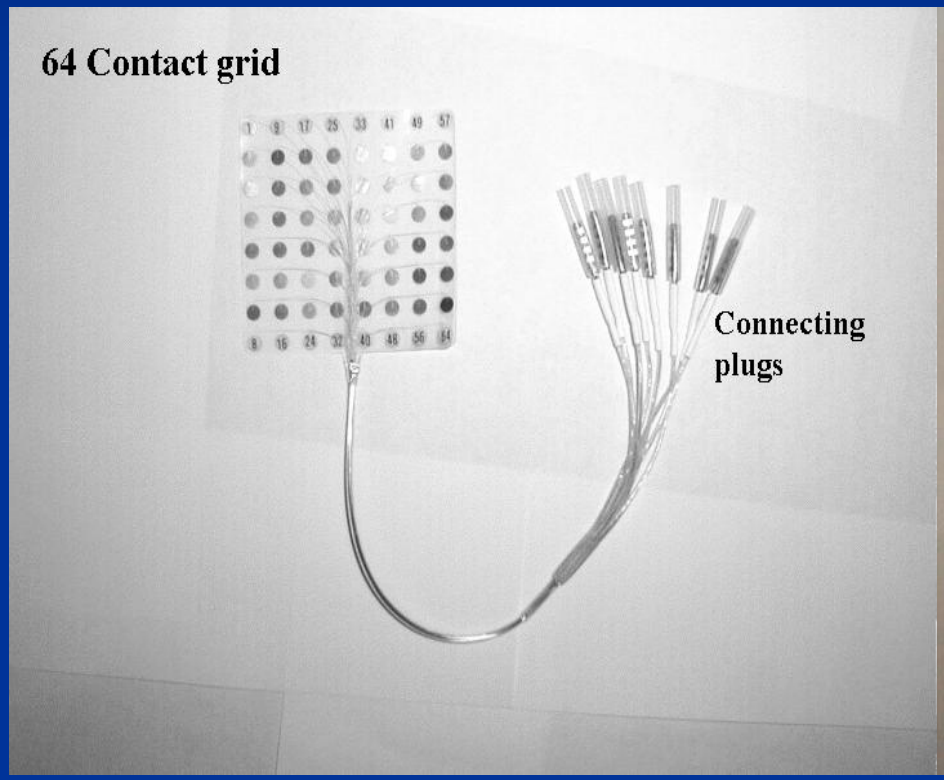
Depth Electrode

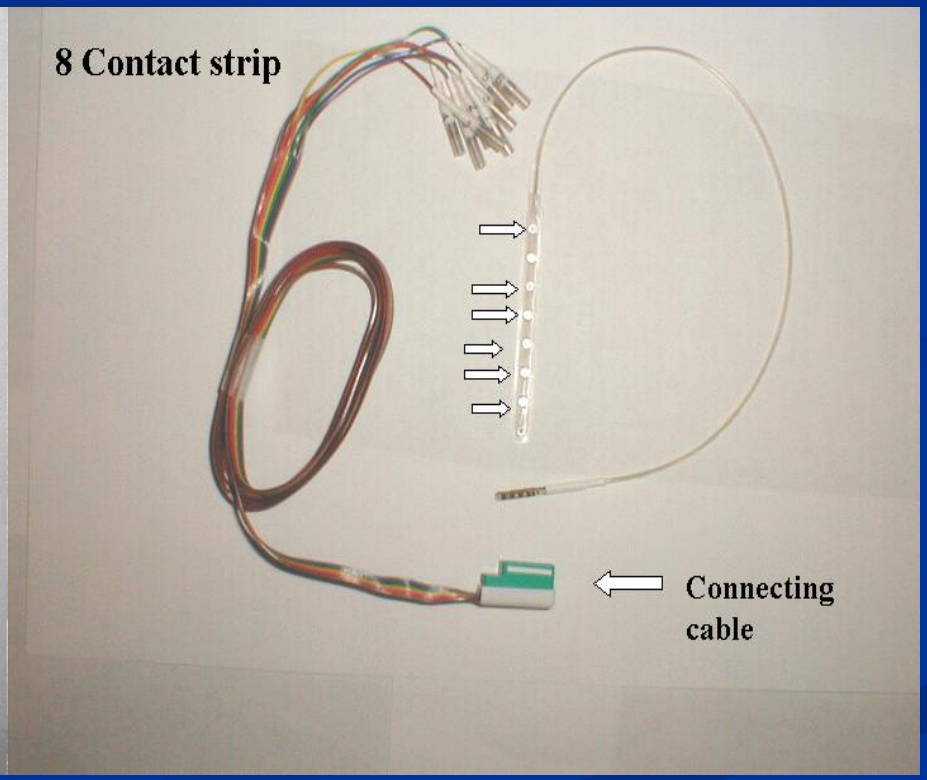


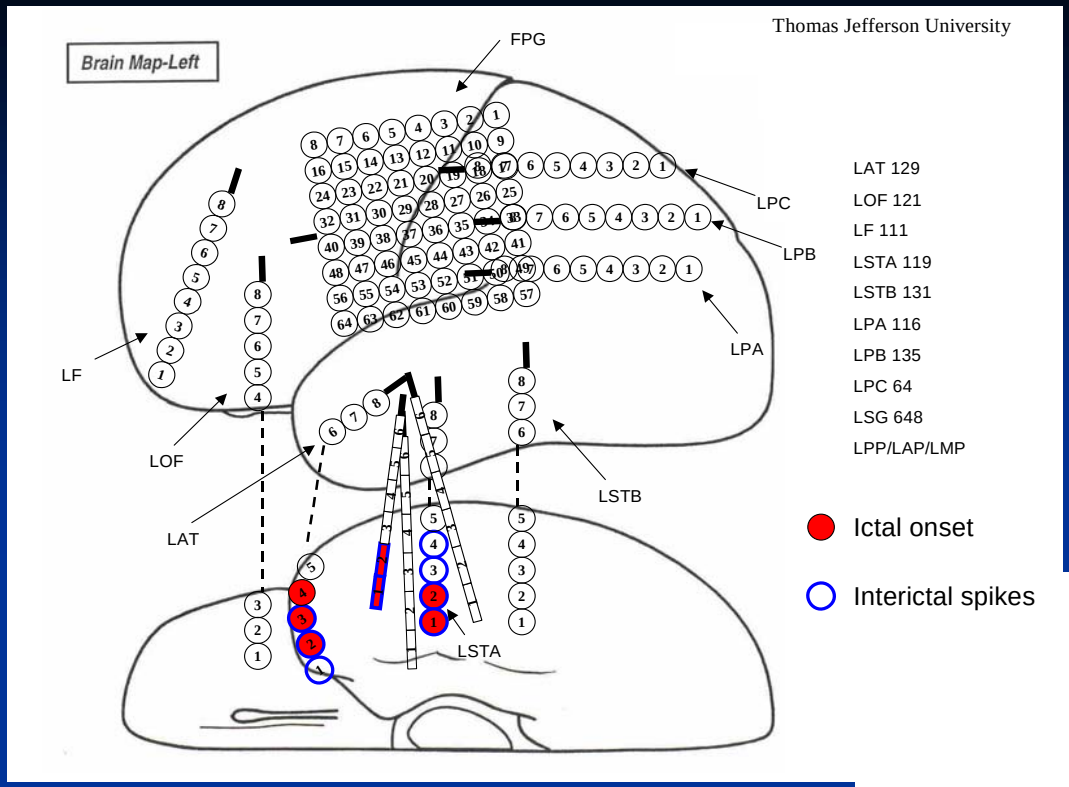
Depth Electrodes



Subdural Electrodes



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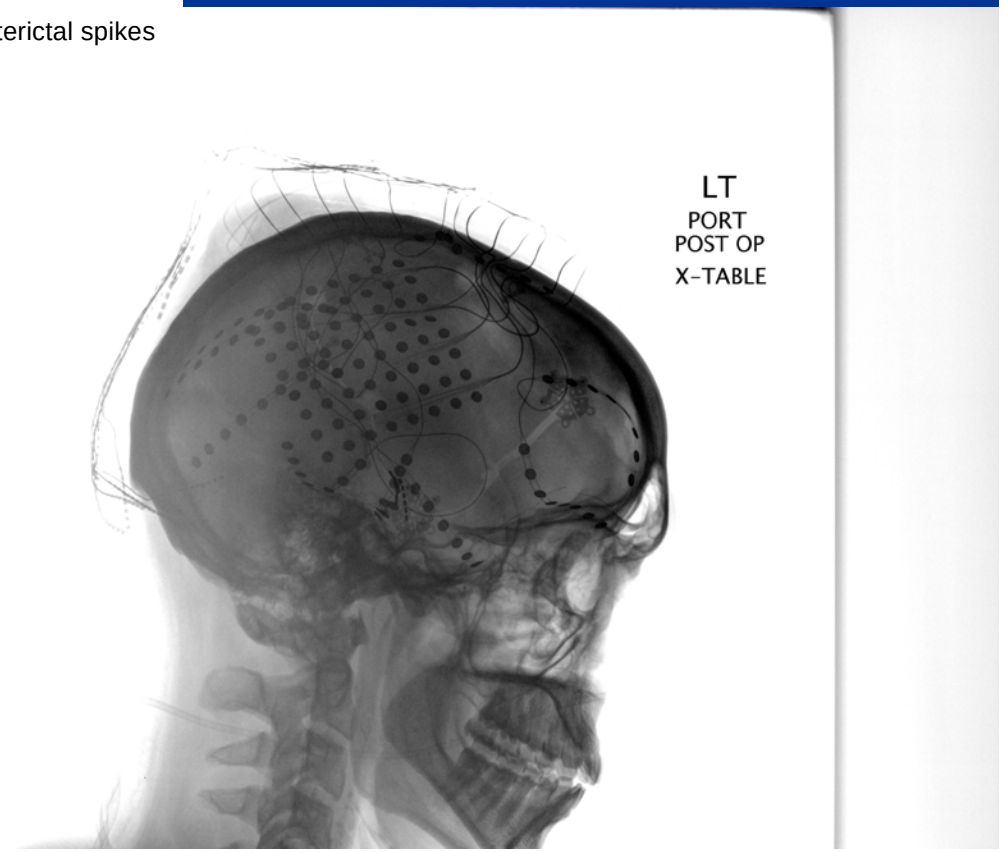
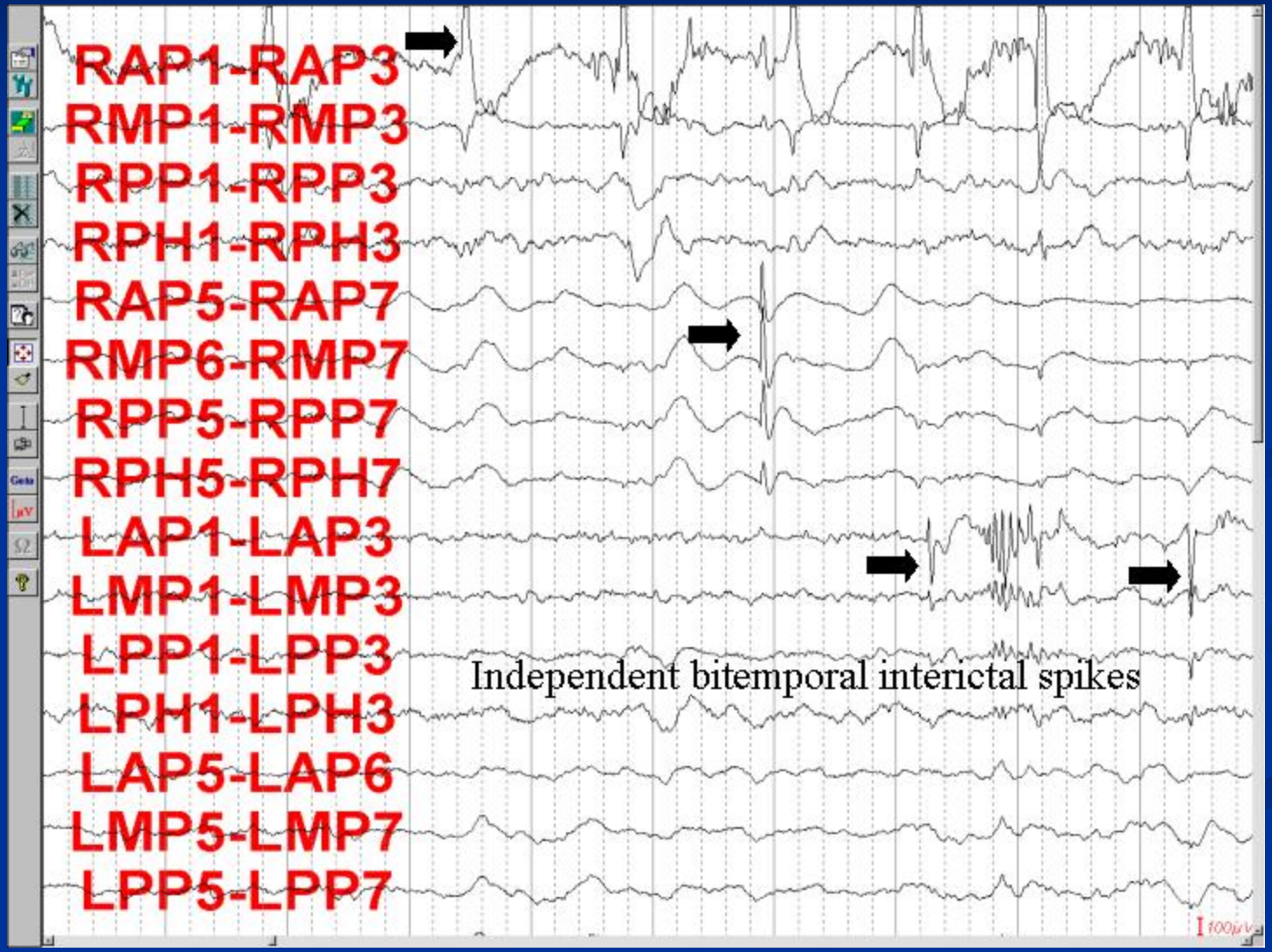
Brain Map-Left
FPG
LPC
LPB
LPA
LF
LOF
LAT
LSTB
LSTA
LAT 129
LOF 121
LF 111
LSTA 119
LSTB 131
LPA 116
LPB 135
LPC 64
LSG 648
LPP/LAP/LMP
Ictal onset
Interictal spikes


LT
PORT
POST OP
X-TABLE

Interictal EEG

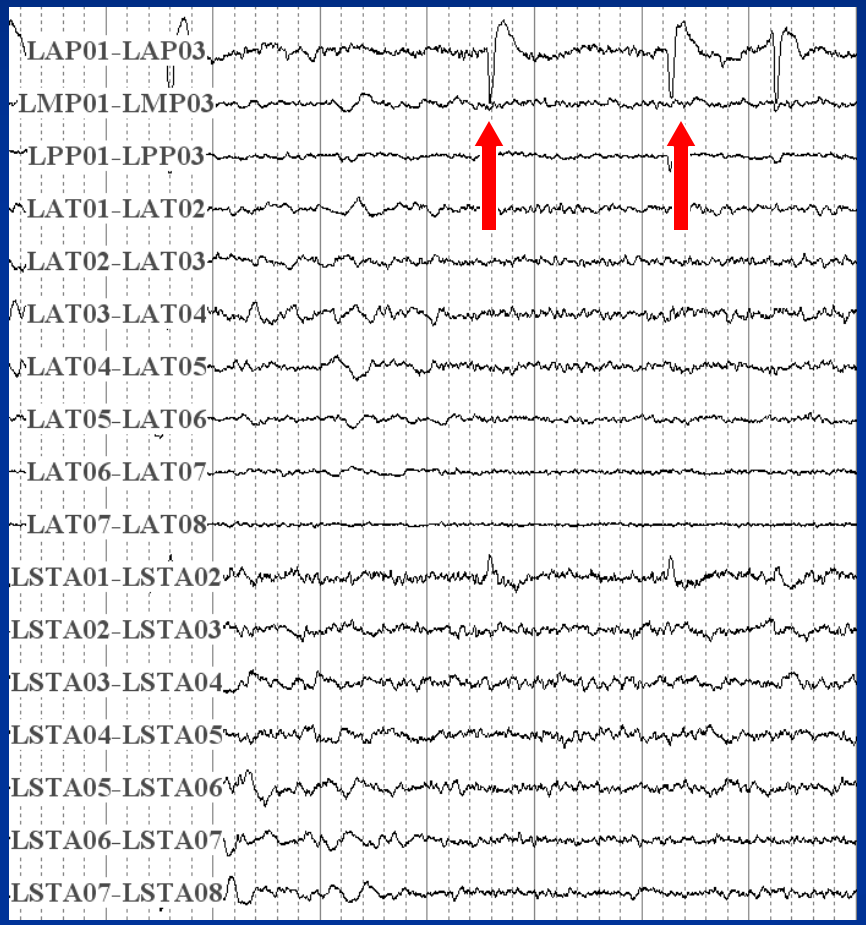


Ictal EEG Patterns

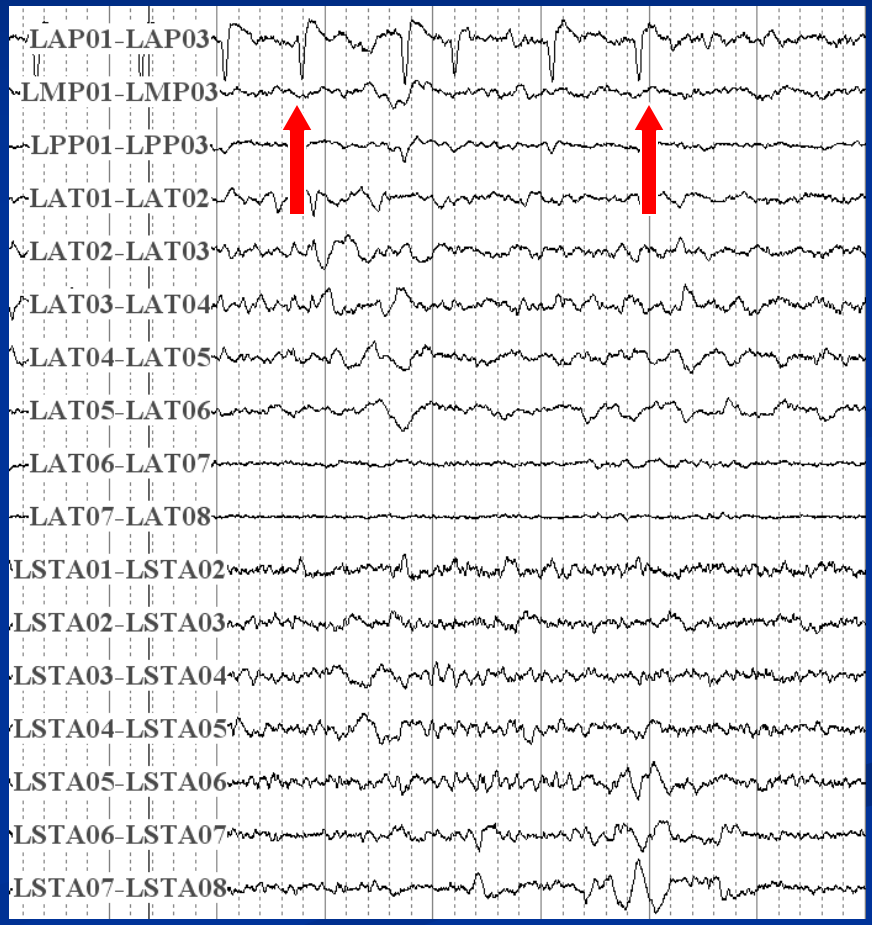
- Onset Patterns
  - Focal
  - Regional
  - Lobar
  - Multilobar
- Spread patterns
  - Variable, depend upon site of origin
  - With hippocampal and orbitofrontal seizures, often slow, orderly propagation to other areas
  - With neocortical seizures, often rapid spread throughout brain

Focal Anterior Hippocampal Onset

Rhythmic spikes start

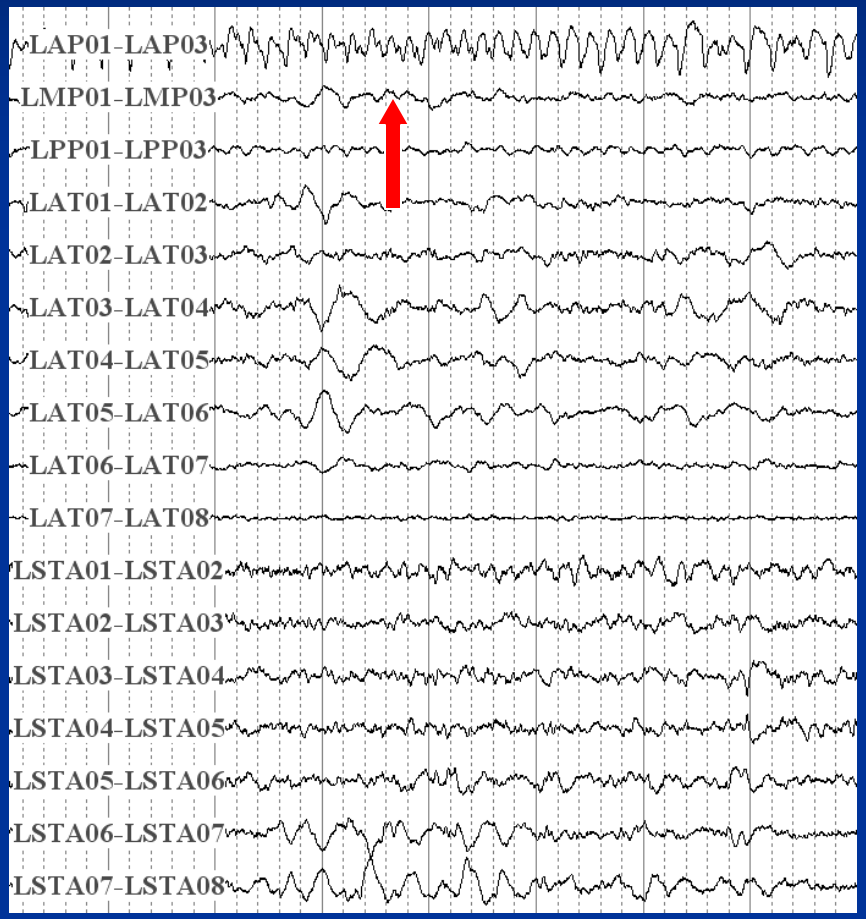


Rhythmic spikes continue

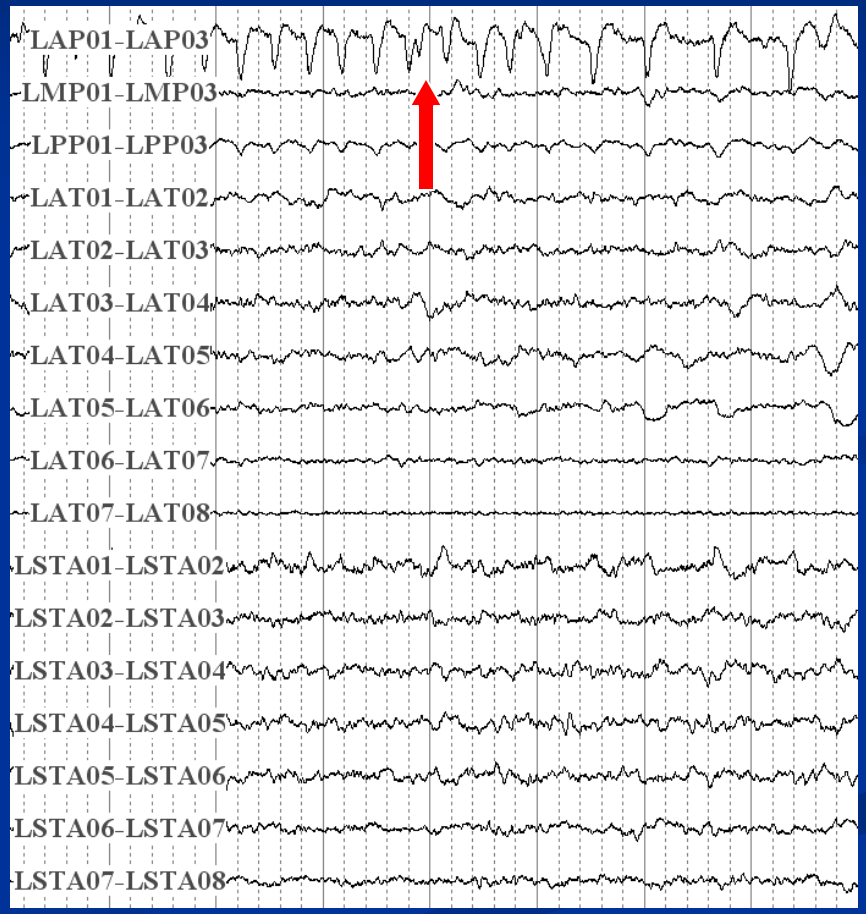


Focal Anterior Hippocampal Onset

Transition to faster activity

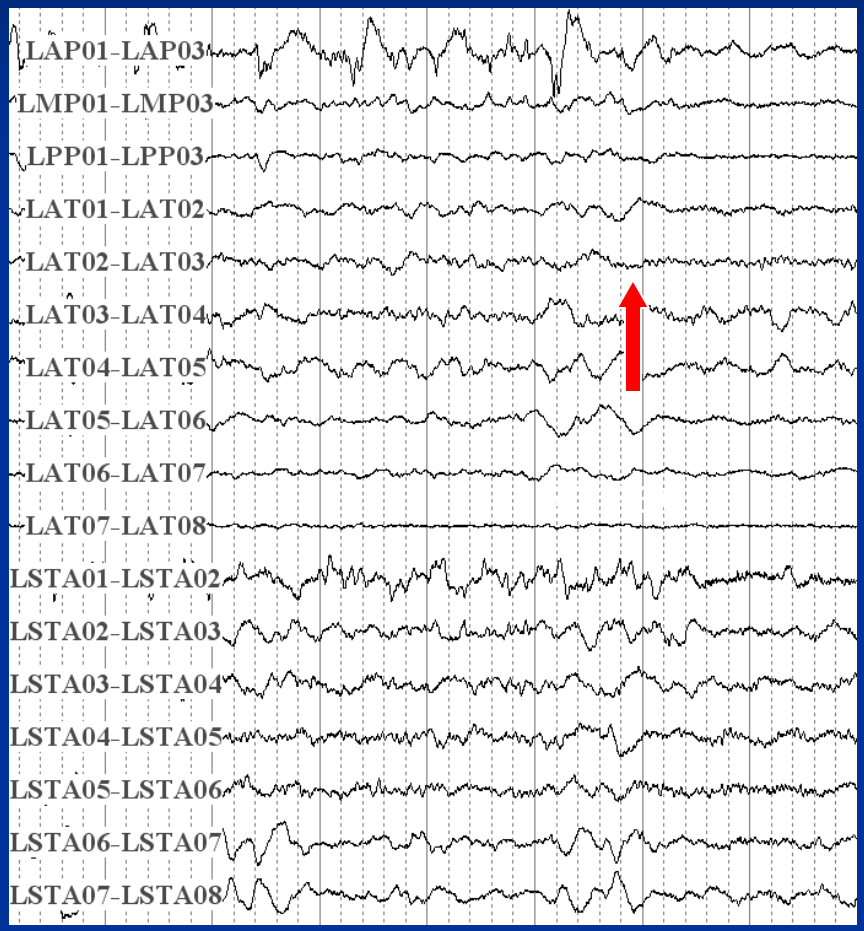


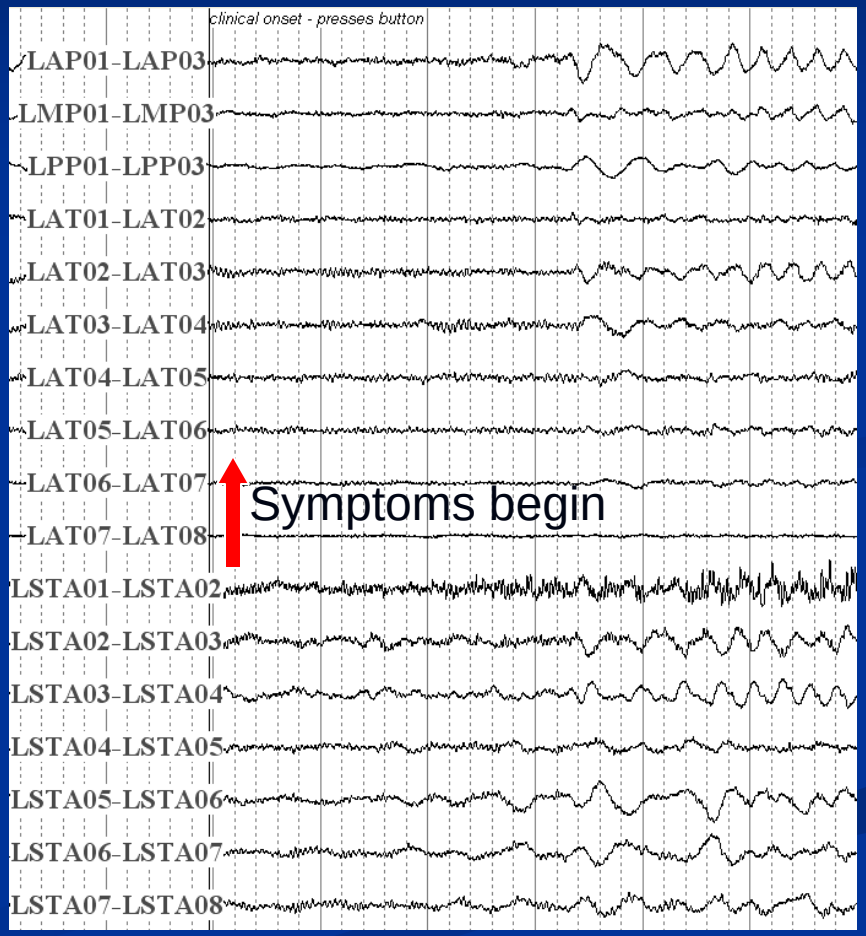
Fast activity evolves



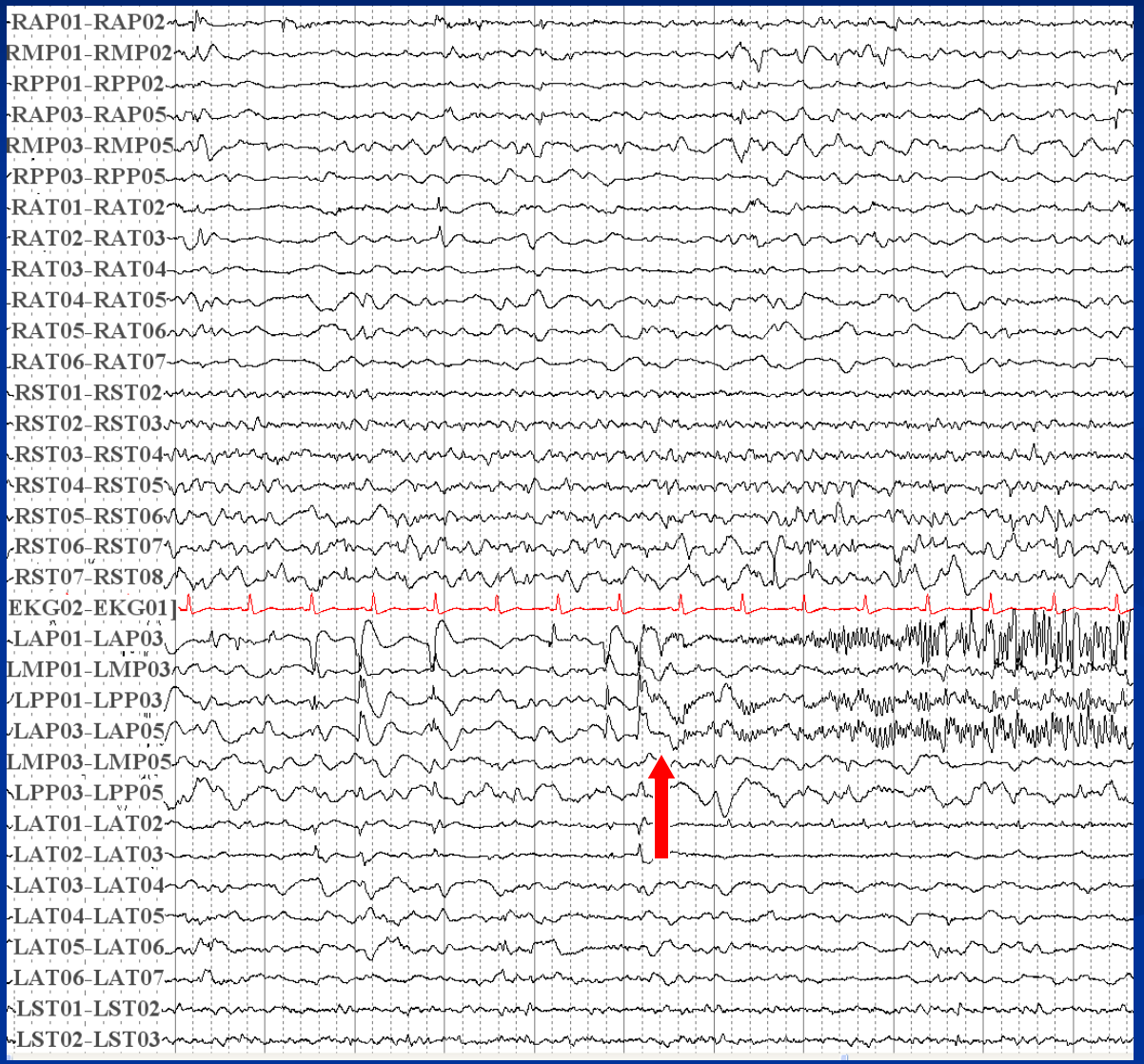
Focal Anterior Hippocampal Onset

Spread to subdural contacts with flattening of amplitude

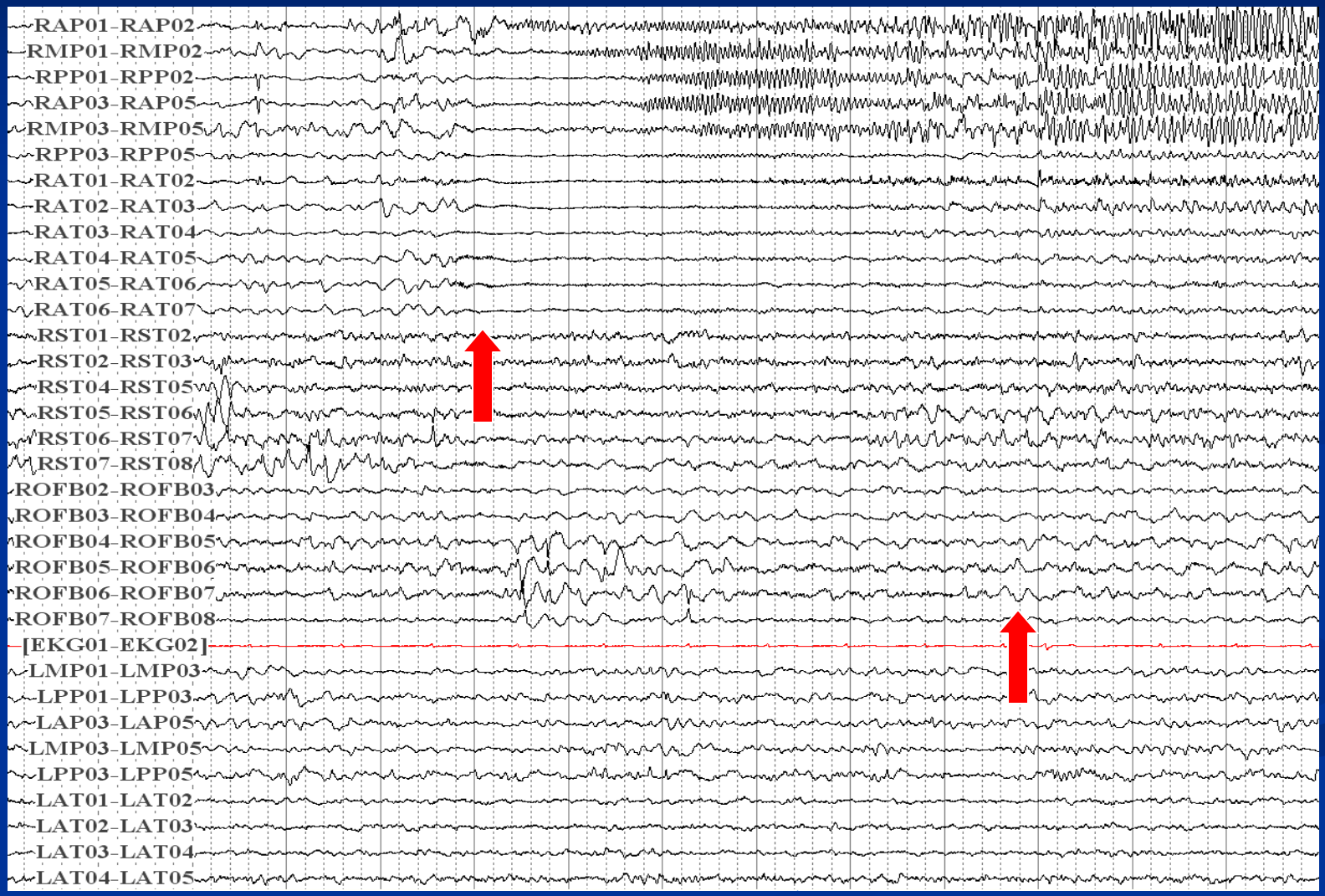




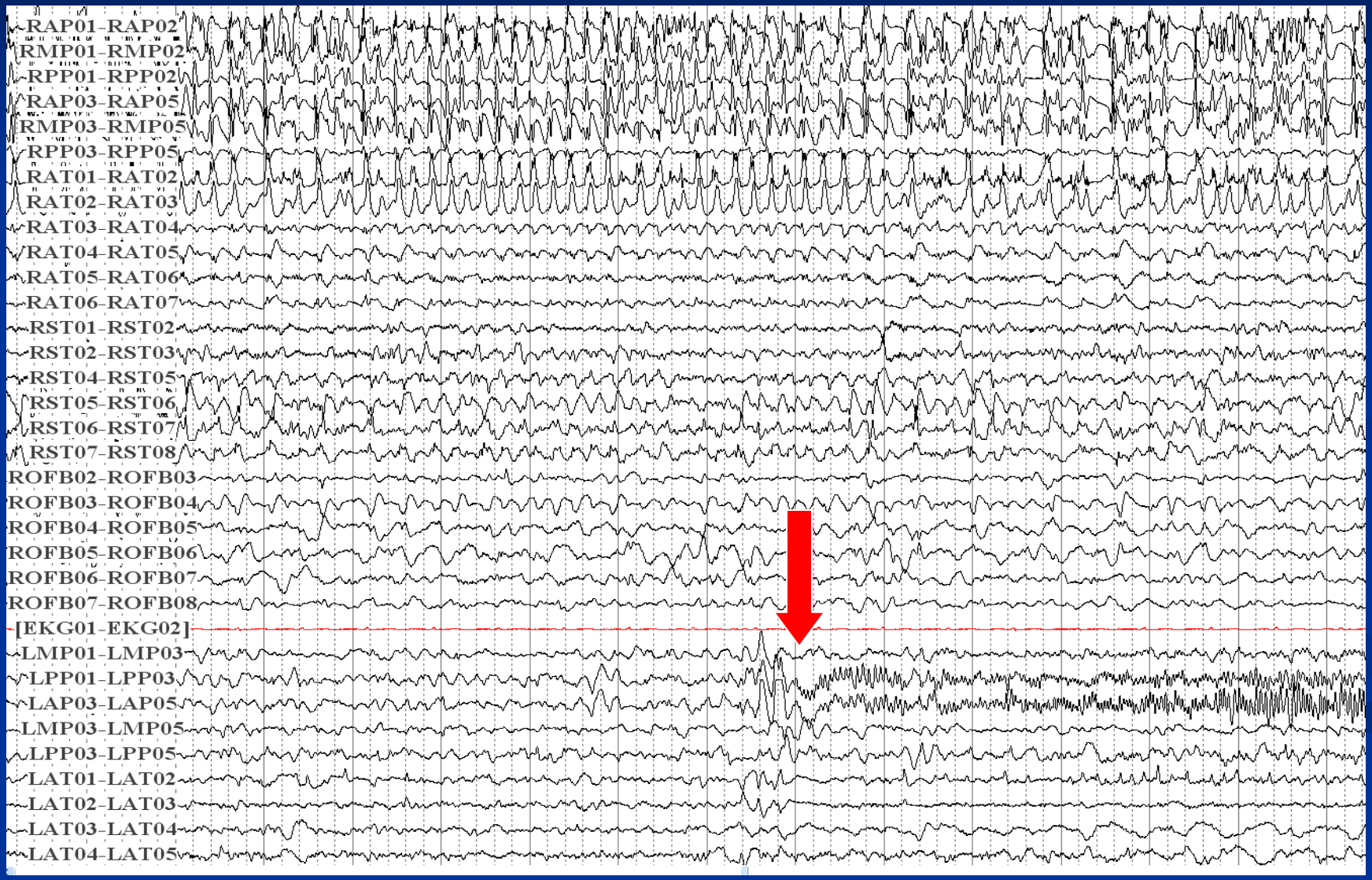
Regional Seizure Onset in Left Hippocampus (not focal)



Lobar Seizure Onset in Right Temporal Neocortex and Hippocampus



Spread to Left Hippocampus

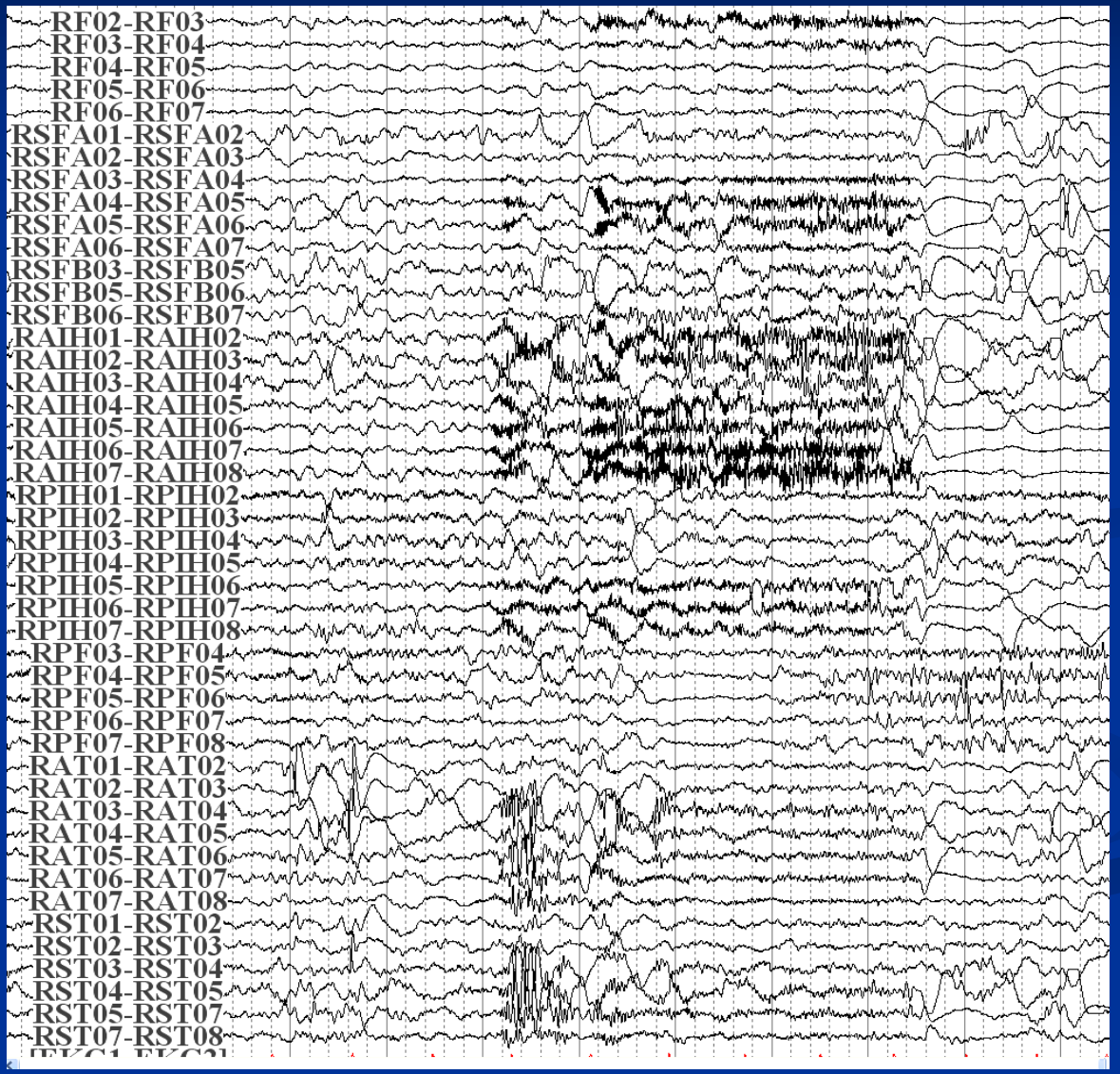


Multilobar Seizure Onset

Frontal, Dorsolateral

Frontal, Interhemispheric

Temporal



Seizure Propagation

- Multiple methods to study propagation
  - EEG offers best and most precise temporal resolution though sometime difficult to define (MEG has practical limitations)
  - PET, SPECT, optical imaging, behavior all have poor temporal resolution
- Location of seizure onset associated with predictable spread patterns
  - Medial frontal to contralateral homotopic first
  - Orbitofrontal to contralateral OF or ipsilateral mesial temporal first
  - Dorsolateral frontal to ipsilateral temporal first
  - Mesial temporal to ipsilateral temporal > contra temporal > ipsi frontal first
  - Temporal neocortical has variable spread
  - Parietal to ipsilateral frontal > ipsilateral temporal first
  - Occipital to ipsilateral temporal first

Onset Location Determines Propagation Times

Zone	Mean IPT (sec)	Mean CPT (sec)
Med Front	3.5	0.6
Lat Front	9.0	14.2
Orb Front	47.3	41.5
Med Temp	12.4	35.5
Lat Temp	15.5	17.6
Parietal	6.7	23.3
Occipital	18.1	35.5

IPT = Ipsilateral propagation time

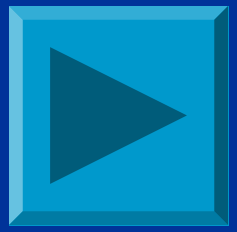
CPT = Contralateral propagation time

Jenssen and Sperling, submitted

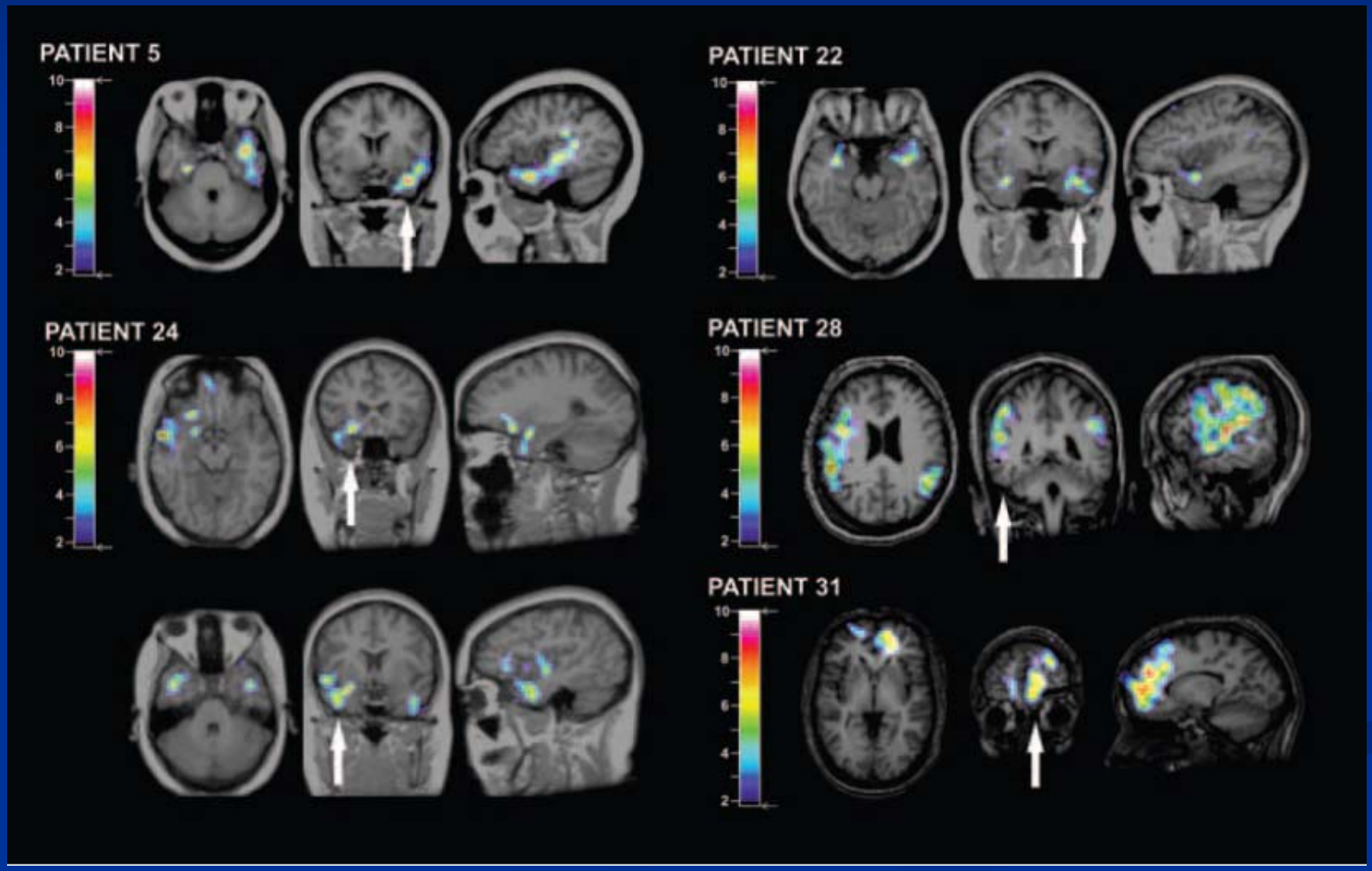
Propagation and Prognosis

- For hippocampal seizures, time to contralateral spread correlates with surgical outcome
  - < 5 second to contralateral spread = poor outcome
  - > 50 seconds to contralateral spread = best outcome
- Shorter contralateral propagation time correlates with lower neuronal hippocampal cell count in CA 4 (has contralateral commissural connections)
- Rapid propagation associated with worse surgical outcome in neocortical seizures as well
- Conclusion: knowledge of typical routes of spread and timing help verify presumed source of seizures and offer prognostic information

Video



Ictal SPECT Reveals Early Propagation of Seizures



Huberfield et al 2006

Isotope uptake over 1 minute

Limitations: Intracranial EEG

- Need electrodes in the right place – electrode might be in area of spread rather than onset zone
- Seizure onset can be difficult to discern
- Could have multiple onset zones
- Could have variable propagation routes from one seizure to the next, making interpretation difficult
- Despite multiple onset zones, successful surgery could still be performed if a structural lesion is present
- Despite well-localized single onset zone, surgery might still be unsuccessful – only 20-60% seizure-free
- Might not record any seizures – bad luck
- Might cause brain injury with electrode placement, causing deficits or false seizure onset

Cortical Mapping: Rationale

- Practical: reduce risk of causing neurosurgical deficits
  - Epilepsy surgery
  - Tumor surgery
- Academic: enhance understanding of brain function, organization
- This talk will address electrical stimulation and evoked potential mapping
- MEG, fMRI and other techniques can be used

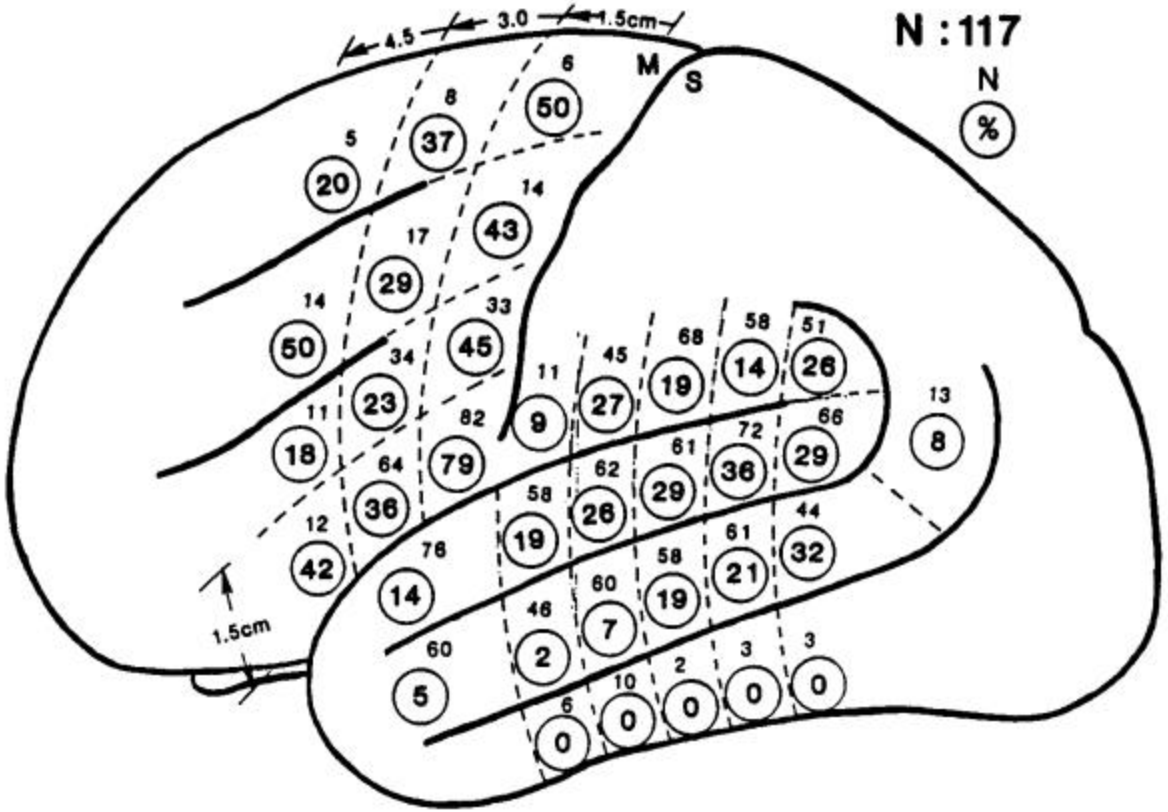
Electrical Stimulation

- Current is applied directly to pial surface
- Two types of response
  - Positive: e.g., jerking of limb, auditory or visual hallucination
  - Negative: speech arrest
- Constant current stimulation
  - fixed charge density
  - Biphasic square wave pulse to avoid ion deposition
  - 0.1-0.3 millisecond pulse duration
- 5-60 Hz, 1-15 milliamperes, train duration of 2-15 seconds
- Maintain charge density below 55 uC/sq cm

Electrical Stimulation: Clinical Effects

- Motor cortex: jerking or tonic contraction
- Premotor cortex: tonic contraction or negative motor, may be bilateral in SMA
- Somatosensory cortex: tingling
- Visual cortex: unformed or formed illusions
- Temporal lobe: variable findings, including memories, complex visual or auditory illusions, psychic feelings, naming defect
- Broca's area: speech arrest
- Other speech areas: isolated deficits

Localization of Language



Ojemann et al 1989

Stimulation Frequency in Cortical Brain Mapping

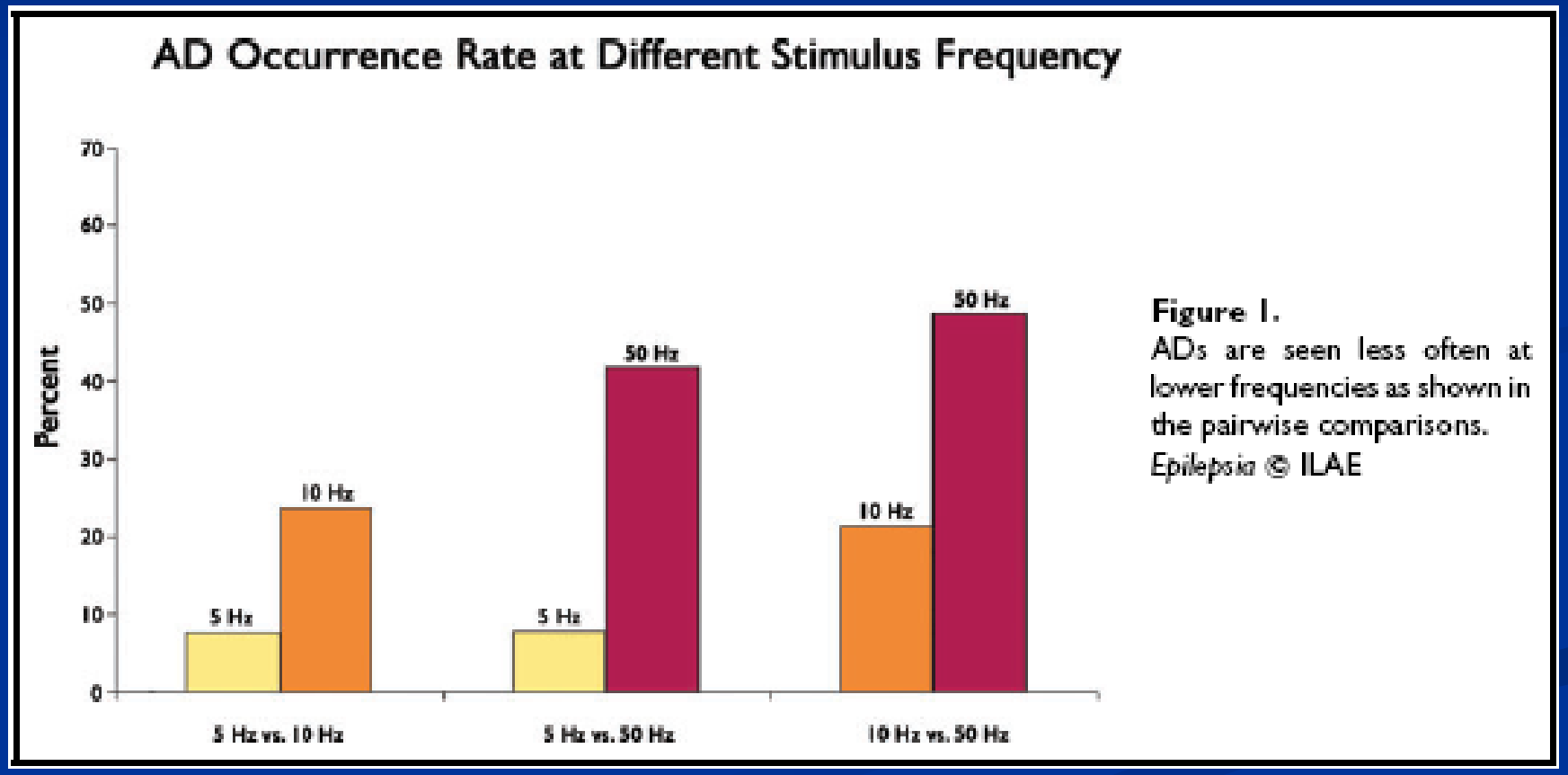


Figure 1.
ADs are seen less often at lower frequencies as shown in the pairwise comparisons.
Epilepsia © ILAE

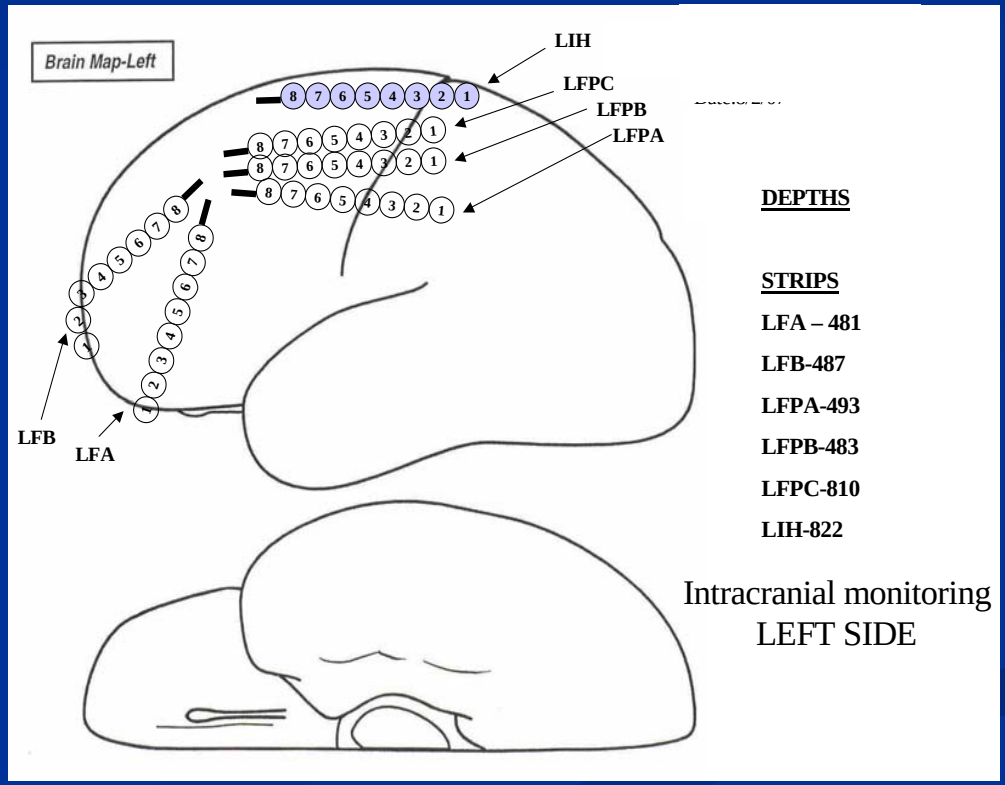
Zangaladze et al. Epilepsia, 2008

Localization of Neurologic Function: Caution

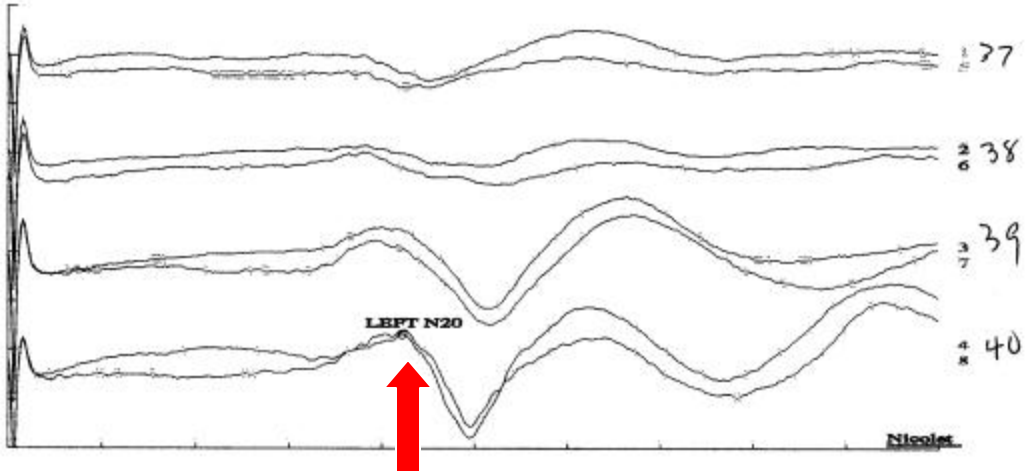
- Patients may not have “read the book” - specific neurological functions may be atypically localized or widely distributed
- One cannot be certain that a function is not located in a particular area unless its location is demonstrated elsewhere
- Postop deficits may occur despite lack of stimulation effect (how well do we test?)
- No postop deficit may occur though stimulation shows an area is not safe (redundant function)

Evoked Potential Mapping

- Somatosensory evoked potentials locate the post-central gyrus
- Usual peripheral nerve stimulation technique is used, recording from cortex instead of scalp
- Can use fast nerve stimulation rate to speed data acquisition, few stimuli per trial



Median SSEP: N20 at 21.1 msec



Sensitivity and Sweep Time Per Division

1	6.22 uV	5.0 msec	2	6.22 uV	5.0 msec	3	6.22 uV	5.0 msec	4	6.22 uV	5.0 msec
5	6.22 uV	5.0 msec	6	6.22 uV	5.0 msec	7	6.22 uV	5.0 msec	8	6.22 uV	5.0 msec

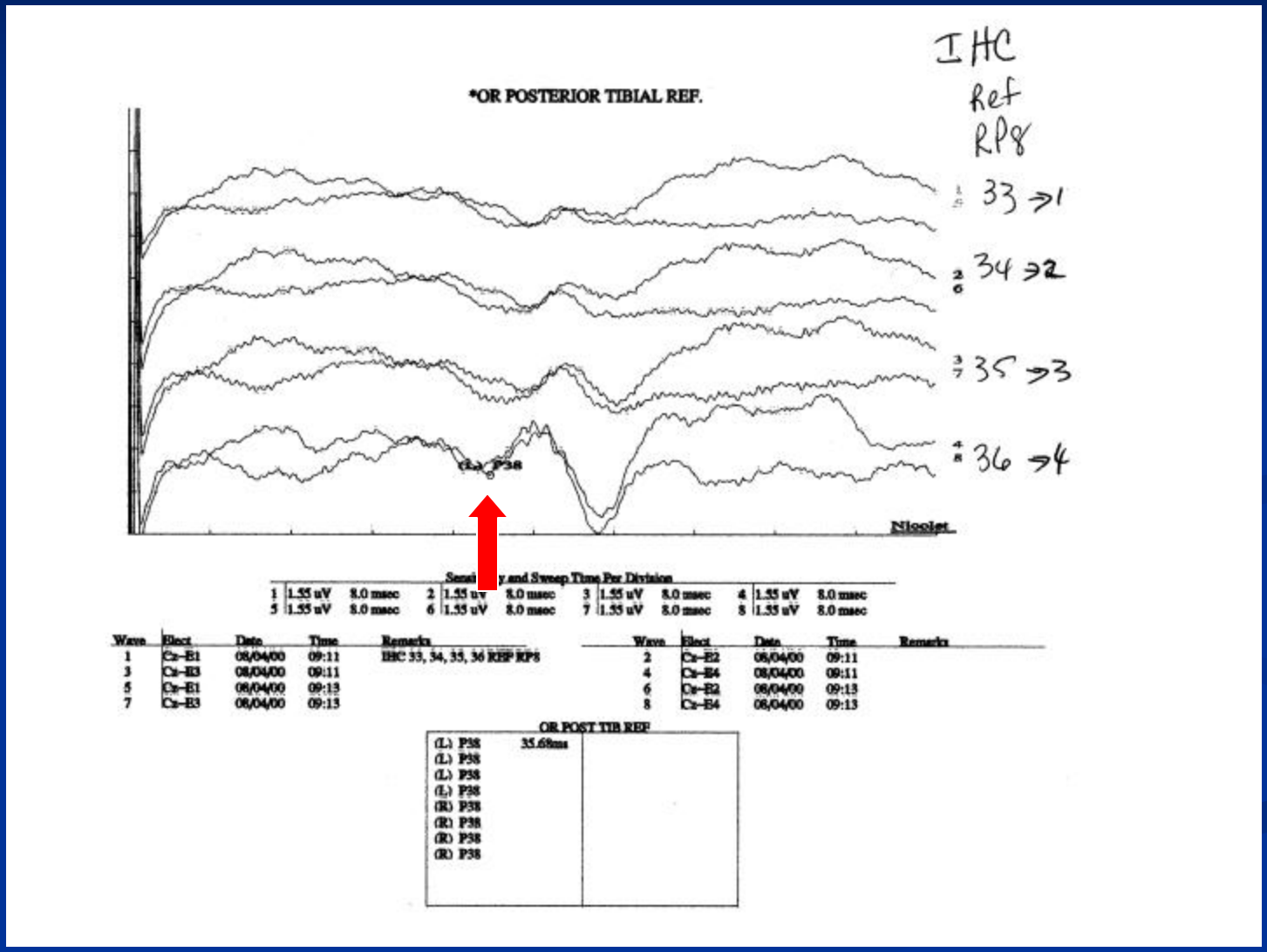
Wave	Elect	Date	Time	Remarks
1	Cz–E1	08/03/00	09:39	37 to 40 ref rp8=24
3	Cz–E3	08/03/00	09:39	
5	Cz–E1	08/03/00	09:40	
7	Cz–E3	08/03/00	09:40	

Wave	Elect	Date	Time	Remarks
2	Cz–E2	08/03/00	09:39	
4	Cz–E4	08/03/00	09:39	
6	Cz–E2	08/03/00	09:40	
8	Cz–E4	08/03/00	09:40	

OR MED. REF. LEFT–RIGHT

LEFT N20	21.10ms
LEFT N20	
LEFT N20	
LEFT N20	
RIGHT N20	
RIGHT N20	
RIGHT N20	
RIGHT N20	

Posterior Tibial SSEP: P38 at 35.7 msec



Conclusion

- Use of intracranial EEG enables some patients to have epilepsy surgery who would otherwise not be candidates
  - Offers unparalleled temporal resolution
  - Offers spatial precision
  - Suffers from significant limitations – not a “gold standard”
- Intracranial EEG electrodes can be used to map cortical function
  - Reduces risk of neurological deficit
- Epilepsy surgery involves balancing risks and benefits
  - Risks of surgery generally outweigh the risks of uncontrolled seizures
- Key skill is knowing which patients are good candidates and which are poor candidates

First Site of Seizure Propagation

- Medial frontal
  - 70% to contralateral mesial frontal zone, 30% to ipsilateral frontal lobe
- Lateral frontal
  - 70% to ipsilateral temporal lobe, 30% to frontal lobe
- Orbitofrontal
  - All to contralateral oritofrontal area and ipsilateral temporal lobe
- Mesial temporal
  - 50% to ipsilateral lateral temporal zone
  - 35% to contralateral mesial temporal
  - 15% to ipsilateral frontal lobe
- Lateral temporal
  - 62% to ipsilateral mesialtemporal zone
  - 28% to contralateral lateral temporal
  - 10% to frontal lobes
- Parietal
  - 60% to ipsilateral frontal lobe
  - 33% to ipsilateral temporal lobe
  - 7% to occipital lobe
- Occipital
  - all to ipsilateral temporal lobe

Jenssen and Sperling, submitted

Subclinical Seizures: Seizures with Insufficient Spread to Produce Symptoms

- Occurred in 64% of patients (n = 111)
- Infrequently spread to other areas within the same lobe, and rarely spread outside their lobe of origin
- 83% of SCS did not spread beyond the area of origin
- 12% of SCS spread within the lobe and only 5% spread beyond the lobe, predominantly in the ipsilateral hemisphere

Table 2. Localization of SCS

SCS localization	Number of SCS (%)
Temporal	2642 (94)
Mesial	2588 (92)
Neocortical	54 (2)
Extratemporal	179 (6)
Frontal	129 (4)
Parietal	40 (1)
Occipital	10 (<1)

There were a total of 2,821 SCS recorded in 71 patients.

Zangaladze et al. Epilepsia 2008

Subclinical Seizures and Outcome

- Percent seizure-free
  - With SCS: 68%
  - Without SCS: 66%
- Percent seizure-free*
  - Complete co-localization 77.5%
  - Incomplete co-localization 37.5%
- Conclusion
  - SCS should count as seizures for prognostic purposes
  - Varying sites of onset is less desirable

* p = .003

Zangaladze et al. Epilepsia 2008