The Neurological Institute of New York

Columbia University College of Physicians and Surgeons

The ictal interictal continuum

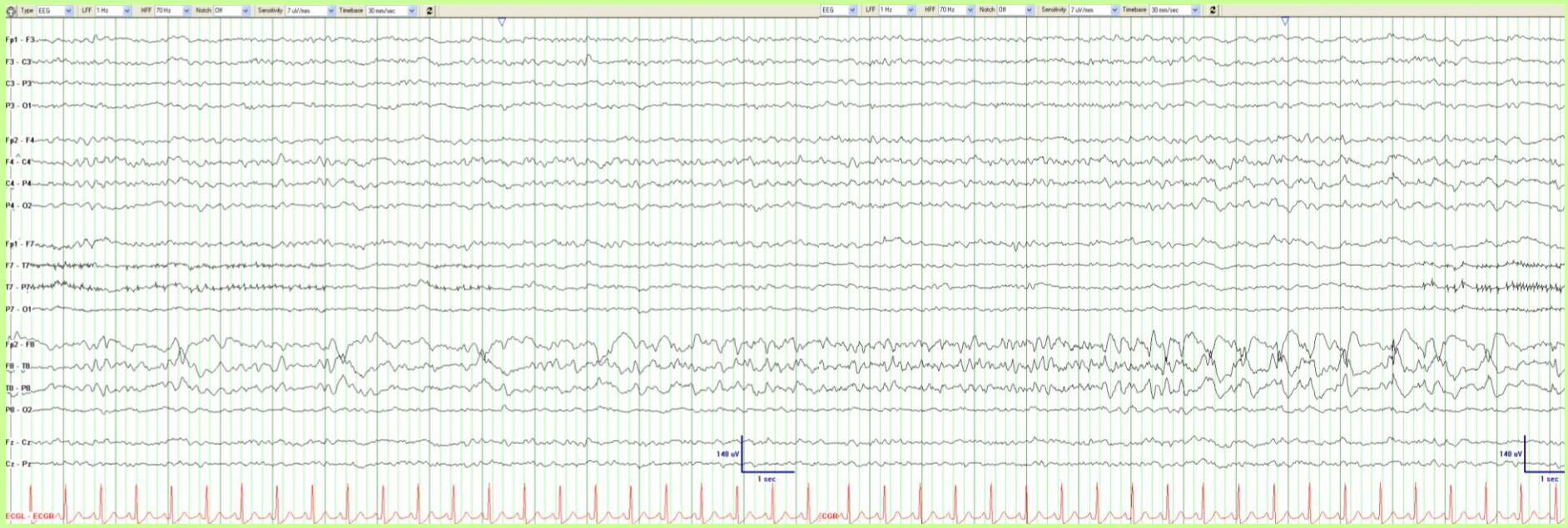
Jan Claassen, MD, PhD
Division of Critical Care Neurology
Columbia University College of Physicians & Surgeons
New York, NY 10032

Disclosures:
Research Support: Columbia University Clinical Translational Science Award (CTSA), Irving Institute for Clinical and Translational Research

Case history

- CC: 69 yo Woman p/w unresponsiveness
- PMHx: SAH s/p right MCA clipping 17 yrs prior to admission, LRE, HTN
- OSH ER: BP 210/11, HR 80, NIHSS 21, no commands, R eye did not doll, L did not cross midline, left hemiparesis
- Transferred for possible ia-tPA
- NICU: on arrival 2nd GTC seizure, CTA normal, LP unremarkable
- Convulsions stopped with LRZ 6 mg fDPH 1.5 gm but remained comatose

Emergent cEEG



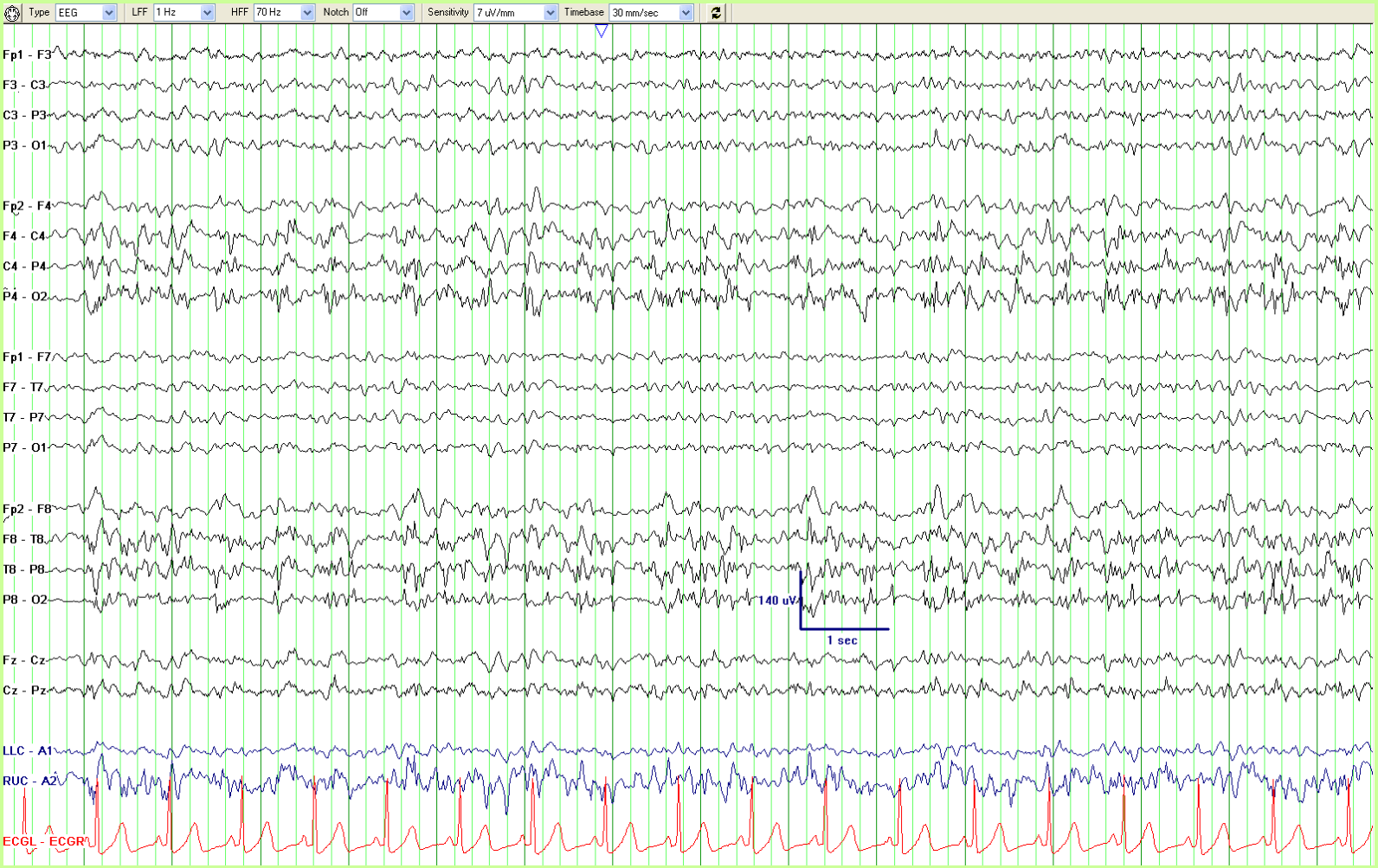
→ Loaded with Valproic Acid 30 mg/kg

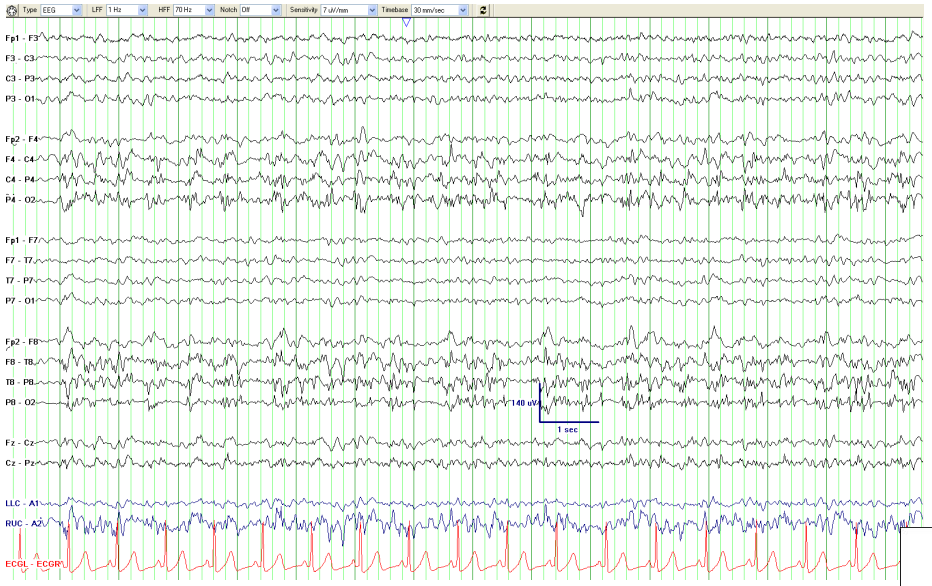
EEG post clinically successfully treated GCSE

- 20 - 48% electrographic seizures
- 14% NCSE
- Most without any clinical signs

DeLorenzo Epil 1998, Treiman NEJM 1998

- Seizures stopped but cEEG showed PLEDs plus: periodic discharges with superimposed rhythmic slowing
- No change in mental status

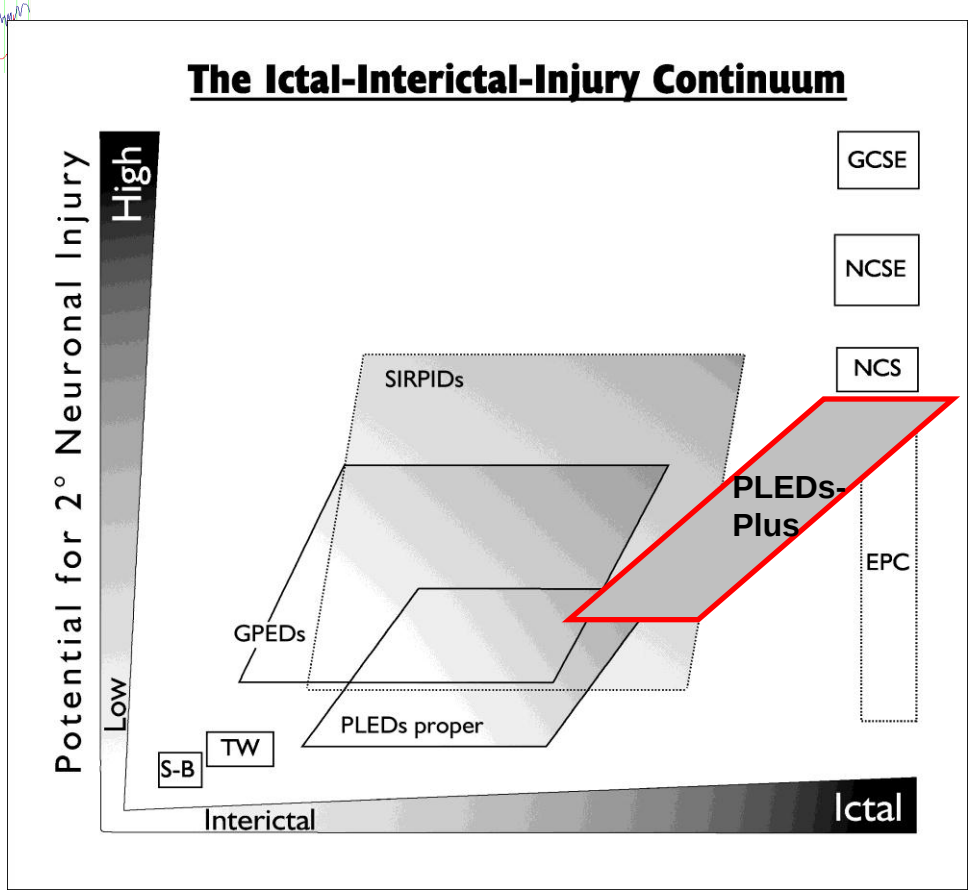




PLEDs plus: periodic discharges with superimposed rhythmic slowing

Neuronal damage from ictal-interictal patterns?

Chong & Hirsch, 2005



Are PEDs ictal?

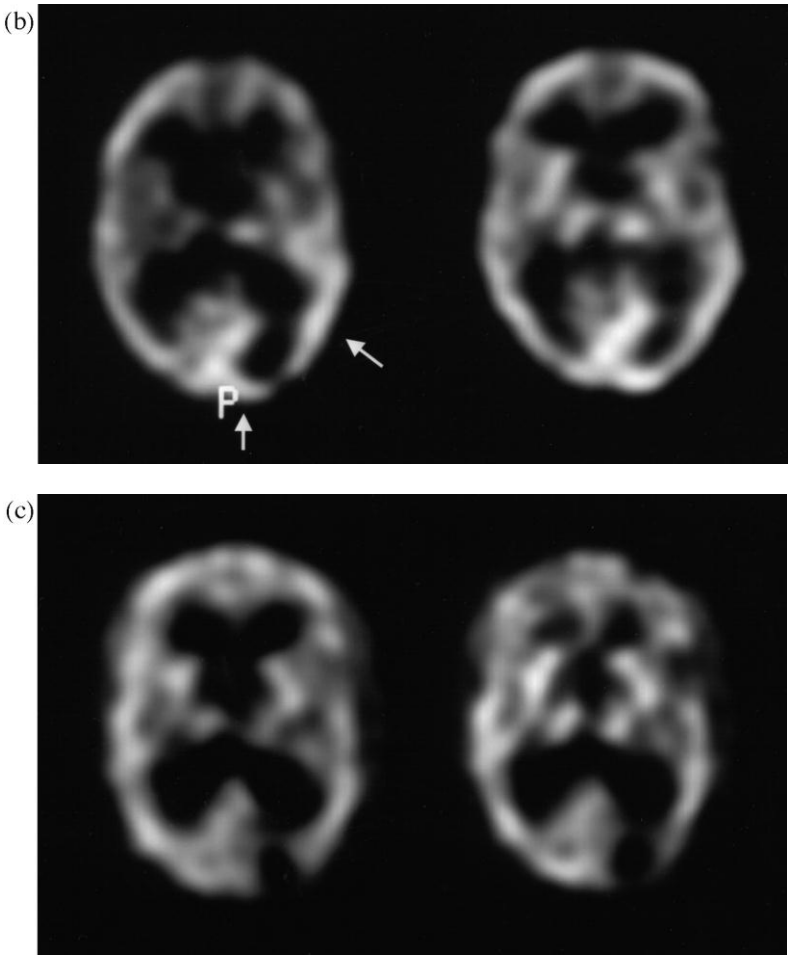
Pro

- **Reversible confusional** state akin to NCSE during PLEDs in the elderly Terzano 1986
- **Glc metabolism:** local increase during PLEDs similar to seizure pattern on FDG-PET

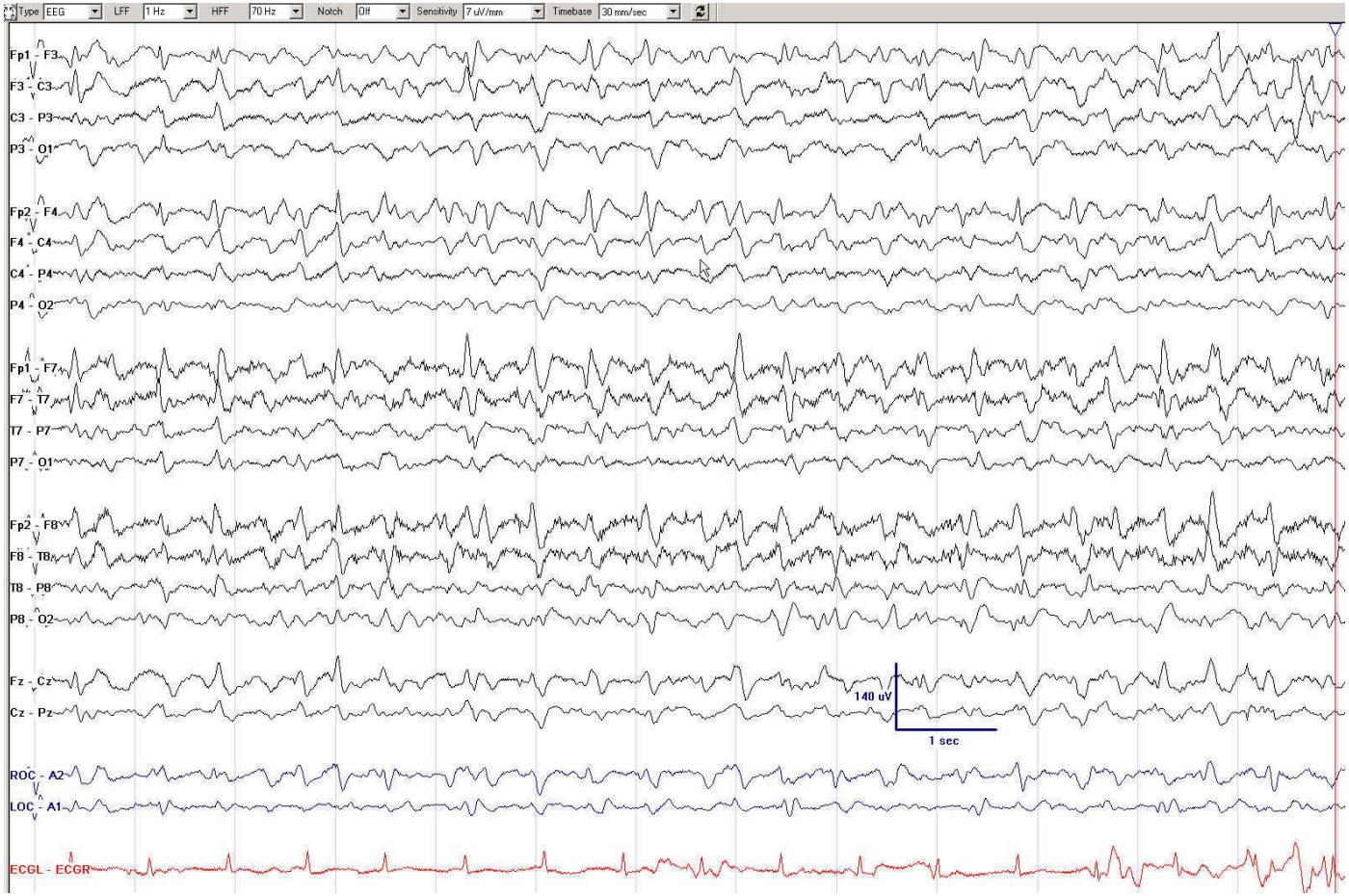
  Handforth 1994
- **CBF**: increase during PLEDs on SPECT, reversed with successful treatment Assal 2001; Bozkurt 2002
- **EPC** (focal motor status epilepticus) may occur with PLEDs Snodgrass 1989, Baykan 2000, Kuroiwa 1980

Contra

- May have benign clinical courses with longstanding PEDs
- Chronic PLEDs Westmoreland 1986 or BIPLEDs Fushimi 2003



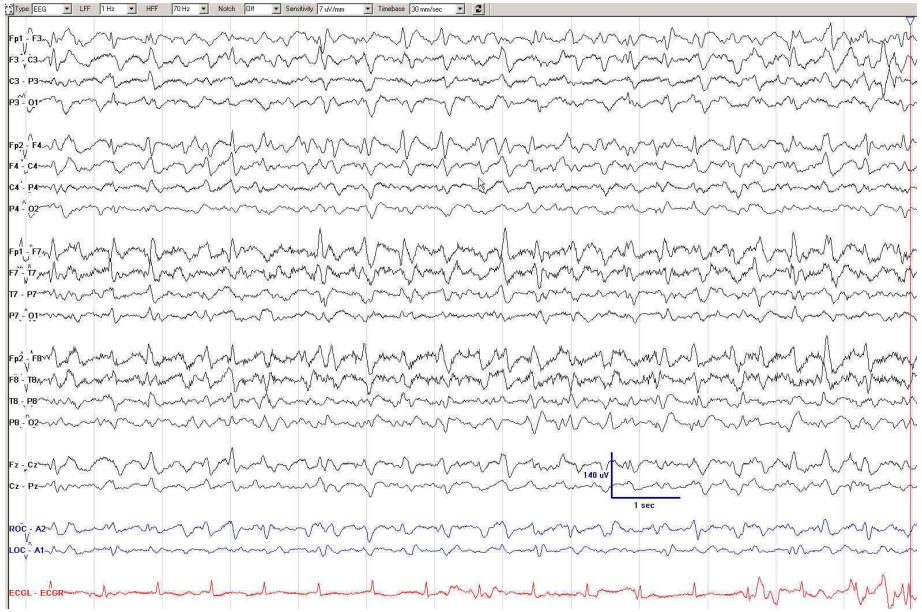
Ictal-interictal continuum and focal nonconvulsive seizures: Patient with encephalitis and RSE



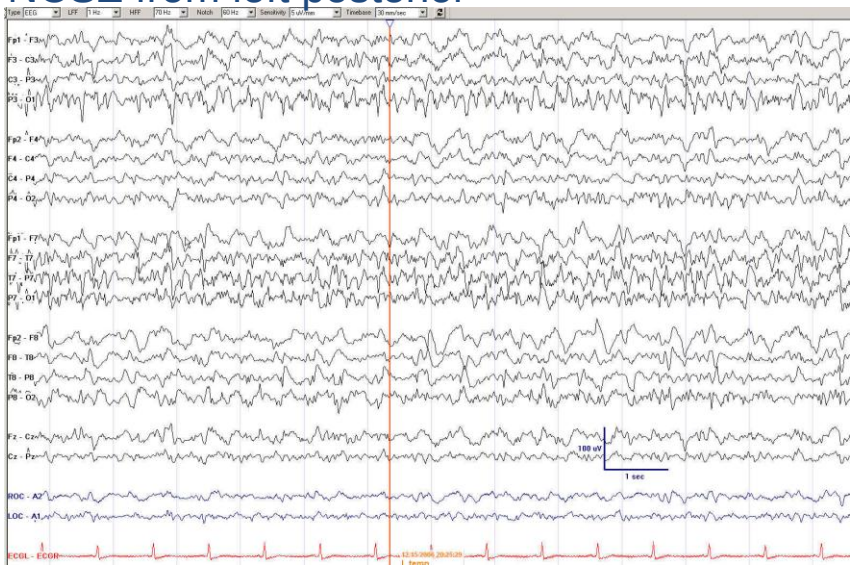
Irregular 2 Hz generalized periodic discharges superimposed on diffuse rhythmic 2 Hz delta activity.

“GPDs-plus” = ictal-interictal continuum

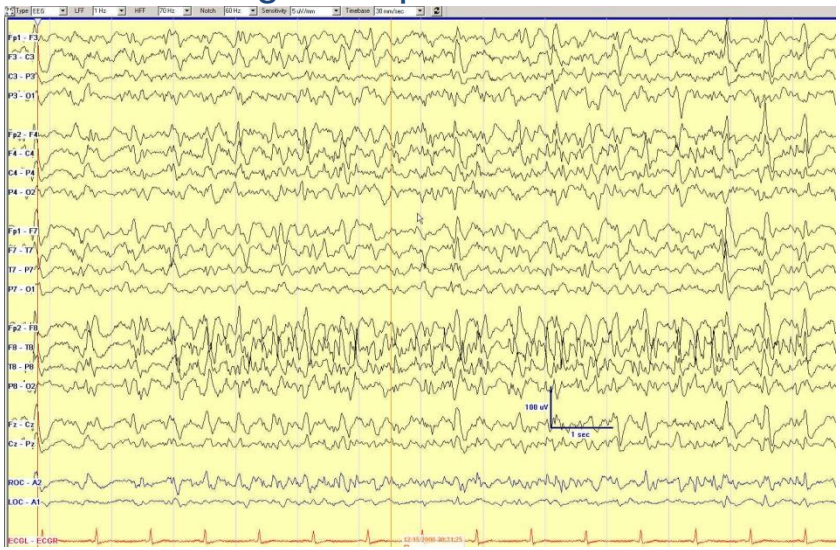
Ictal-interictal continuum and focal nonconvulsive seizures: Patient with encephalitis and RSE



NCSZ from left posterior



NCSZ from right temporal



Irregular 2 Hz generalized periodic discharges superimposed on diffuse rhythmic 2 Hz delta activity.
“GPDs-plus” = ictal-interictal continuum

What do PEDs mean? Controversial if PEDs ictal but definitely predictors of electrographic seizures

Predictors of electrographic seizures:

- Coma on exam: 56% of comatose pts vs. 12%
- Young age: 36% of pts <18 yo vs. 17% of pts > 18.
- Epilepsy in the past medical history: 41% vs. 16%, or remote risk factors for szs
- Convulsive seizures prior to monitoring: 43% of pts with vs. 12%
- **Periodic discharges (PLEDs or GPEDs)** or Suppression-burst
- Oculomotor abnl's: nystag, hippus or eye deviation
- Cardiac or respiratory arrest
- Sepsis

Varelas Neurology 2003; Husain JNNP 2003, Claassen 2004; Oddo CCM 2009

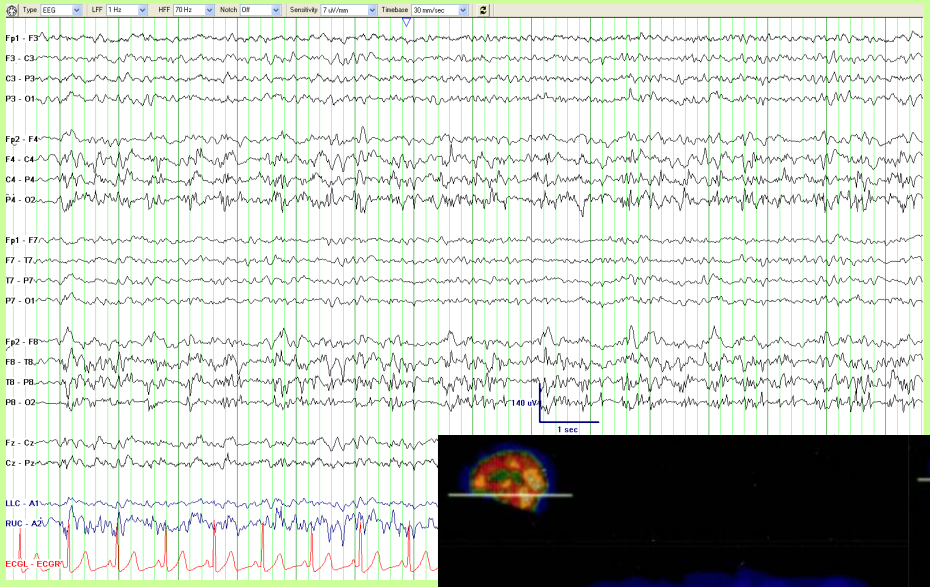
Incidence of seizures in the acute setting of PLEDs 58% to 100% Pohlmann-Eden et al., 1996

PEDs and seizures

Table 4 *Other cEEG findings in patients with seizures on cEEG, n = 110*

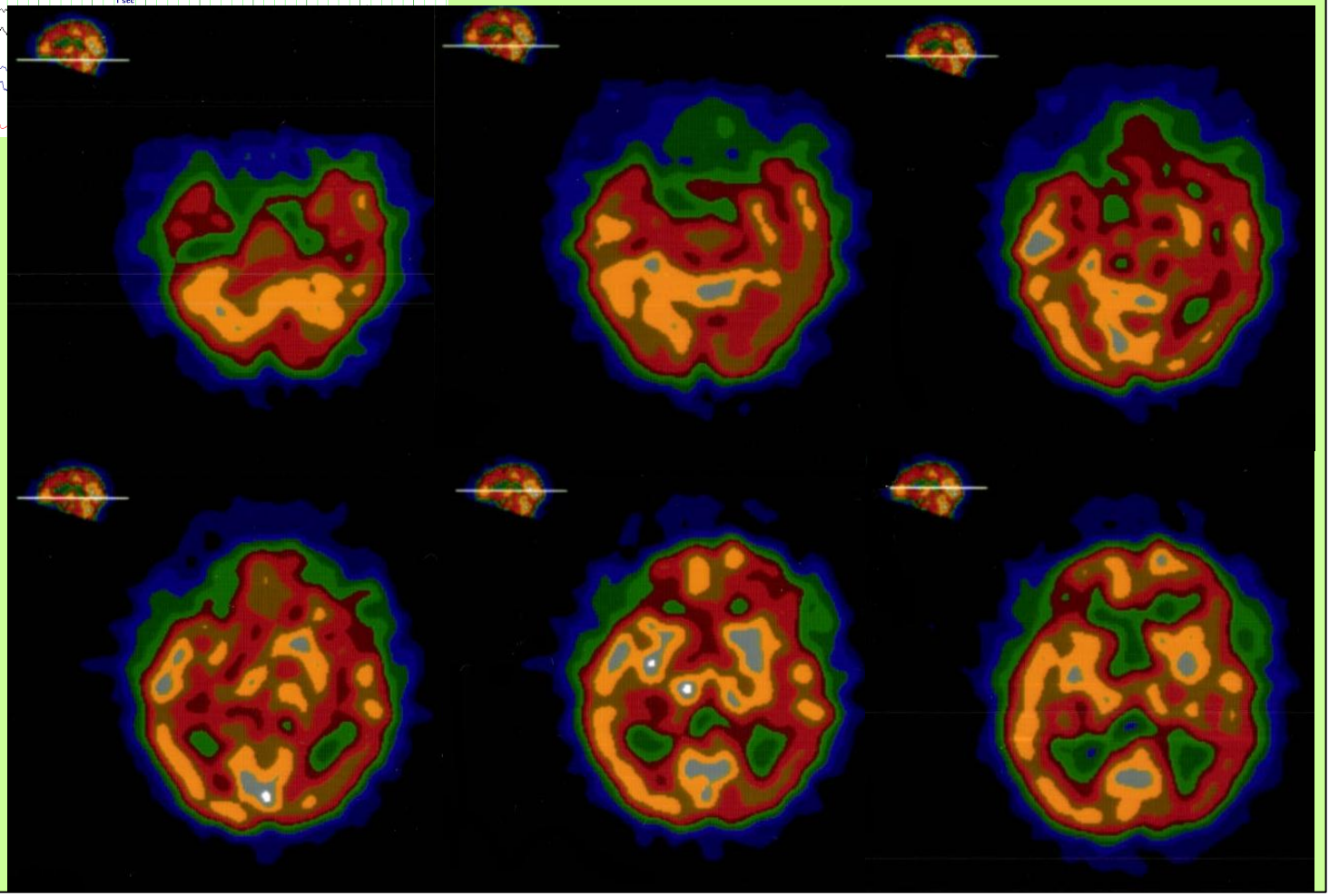
	Seizures on cEEG monitoring		
Findings	Yes, n = 110	No, n = 460	*p*
Periodic epileptiform findings			
Any	49 (45)	82 (20)	<0.001
PLED	44 (40)	46 (11)	<0.001
GPED	19 (17)	24 (6)	<0.001
BiPLED	7 (6)	13 (3)	NS
Triphasic waves	4 (4)	25 (6)	NS
Frontal intermittent rhythmic delta activity	11 (10)	35 (9)	NS
Suppression burst	35 (32)	13 (3)	<0.001

Claassen, Neurology 2004

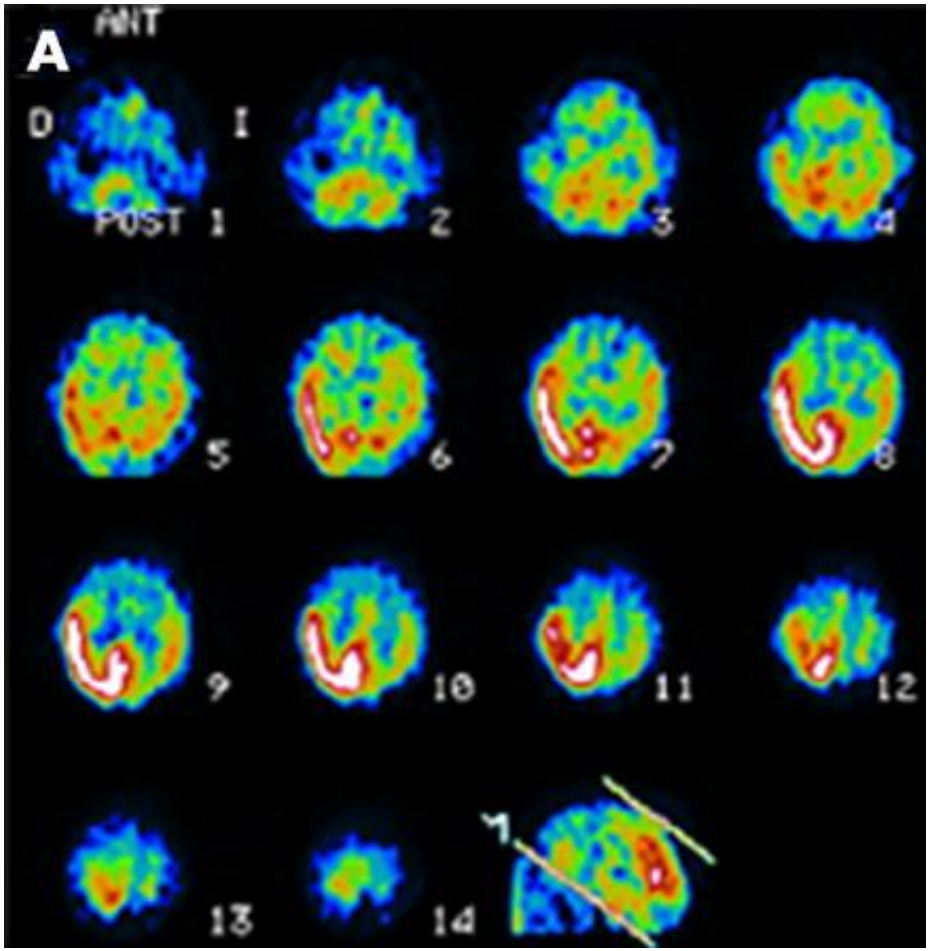


PLEDs plus: periodic discharges with superimposed rhythmic slowing

Technetium-99m-HMAPO SPECT: R TL increased blood flow

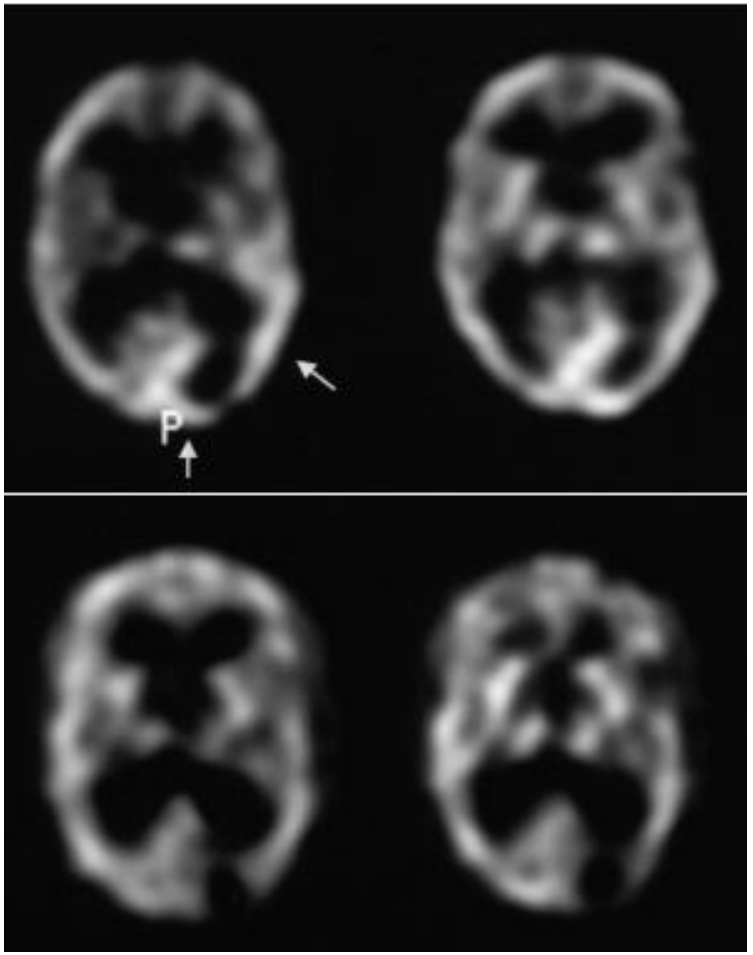


Ictal 99mHMPAO SPECT: Prolonged focal SE that progressed to PLEDs



Donaire JNNP 2006

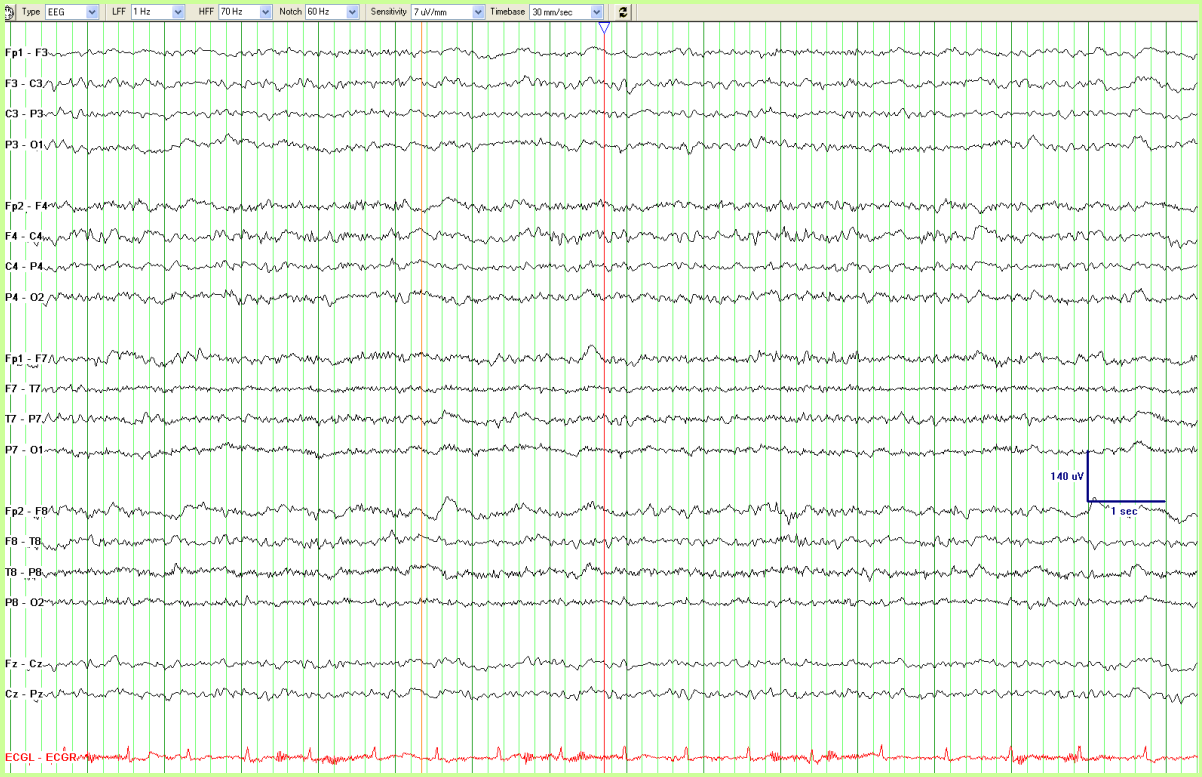
SPECT during and after PLEDs in alcoholic patient post GTC seizure



Assal 2001

- Levetiracetam 1000 mg BID
- AED serum levels: VPA 114 ug/ml, DPH 14 ug/ml, free DPH 3.1 ug/ml

EEG: isolated epileptiform discharges



Mental status improved slowly, discharged to subacute rehab 2 wks after presentation on DPH, VPA, and LEV

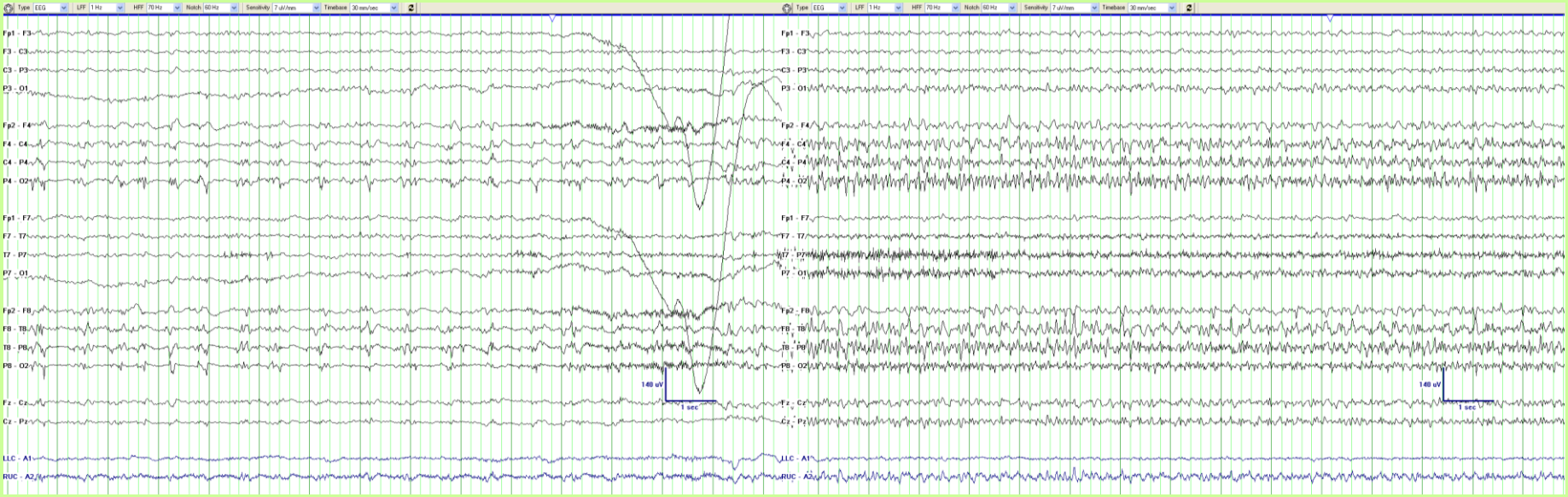
Done!

Successful rehabilitation: she was tapered off all AEDs for a secondary cognitive deterioration and returned to her neurological baseline

Happy ending, but …

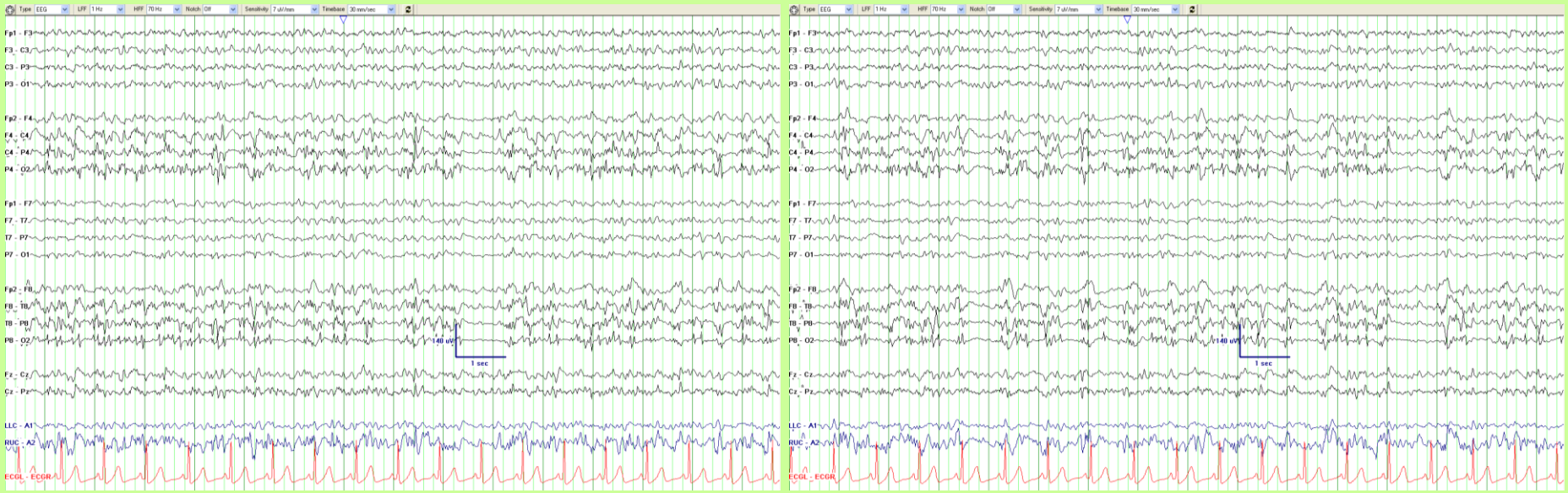
- One month later presented to OSH with recurrent CPSE
- Restarted DPH, LEV, VPA but unresponsive

NCSE



Midazolam load of 14 mg and drip up to 0.4 mg/kg/hr

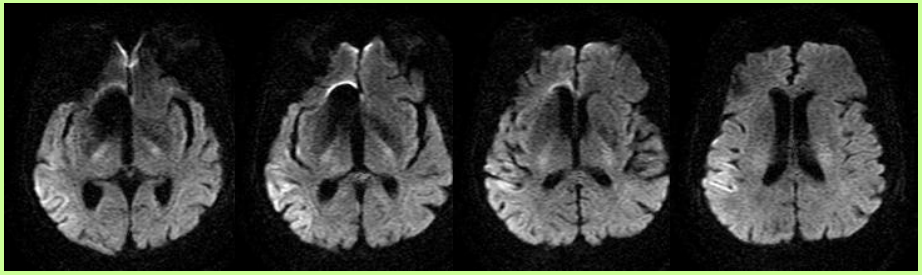
EEG on midazolam gtt



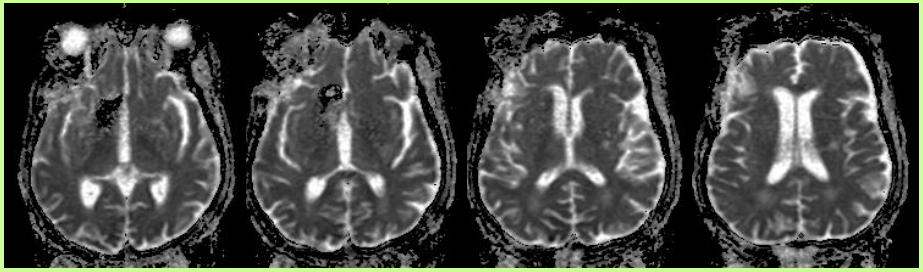
PLEDs plus: with superimposed rhythmic slowing and fast activity

MRI during the ictal interictal continuum: restricted diffusion, increased CBF & CBV, decreased mean transit time (MTT)

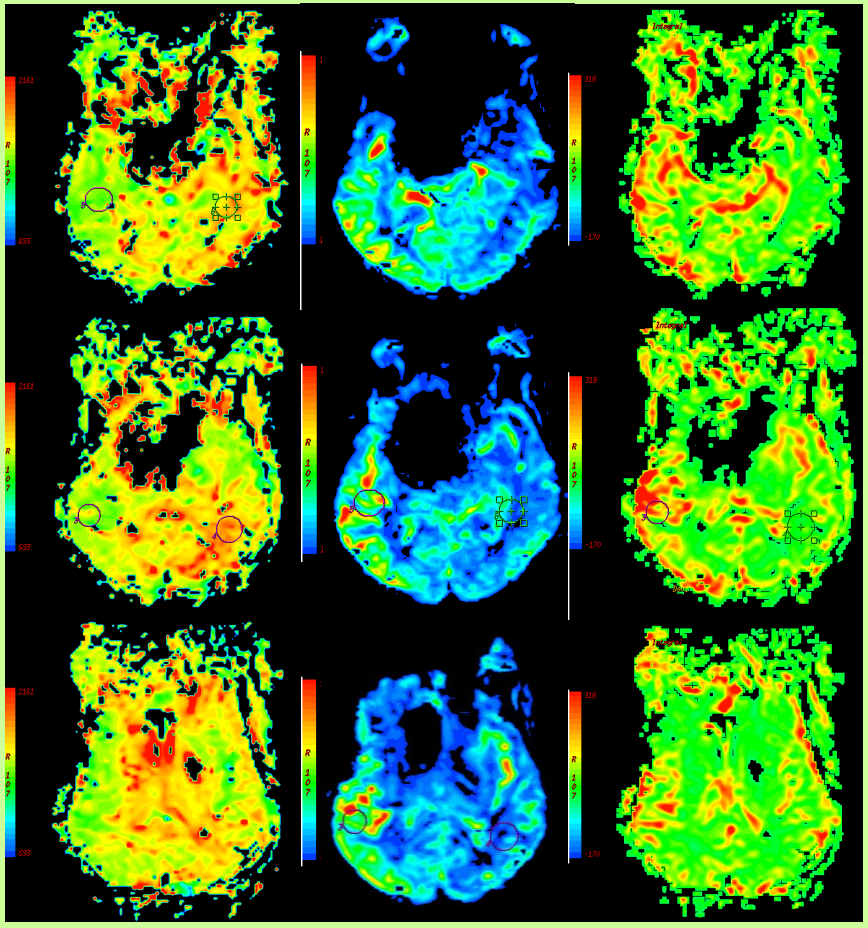
DWI: restricted diffusion R TL



ADC: minimal changes

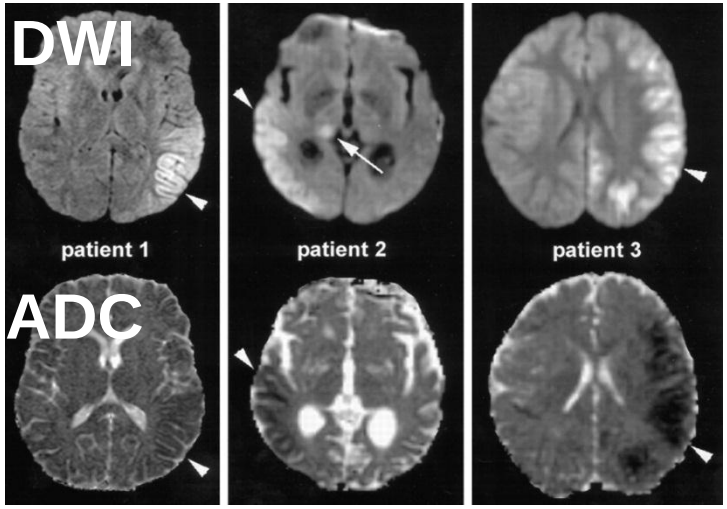


MTT | **CBF** | **CBV**



- MDZ gtt ↑ 1 mg/kg/hr
- VPA ↑
  (goal level 80-100 ug/ml)

Imaging ictal patterns



Decrease ADC/increased DWI after CPSE & seizures
- Hippocampal formation
- Cortical areas adjacent to the primary pathology
- Posterior part/pulvinar of the thalamus

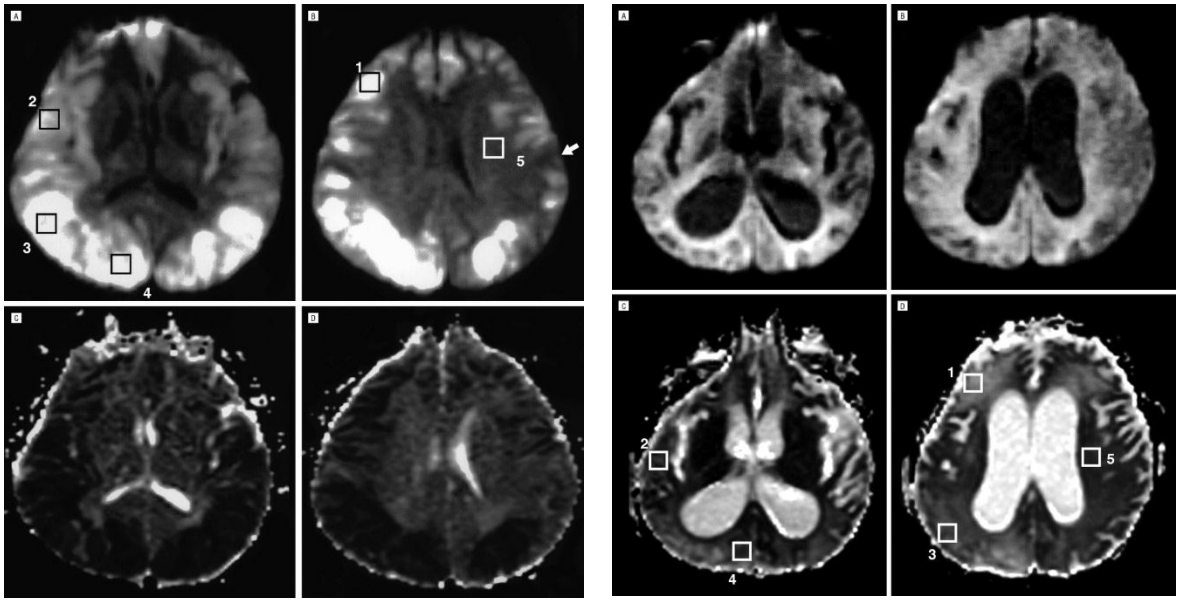
Szabo 2005, Kim 2001, Farina 2004

MR perfusion: increased perfusion in region of decreased diffusion Szabo 2005

Lansberg '99

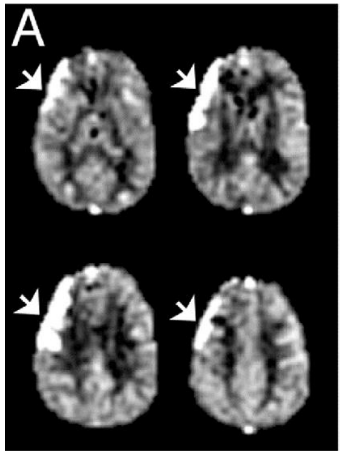
Initial DWI shows diffuse, gyriform cortical hyperintensities

5 months later diffuse low signal intensities



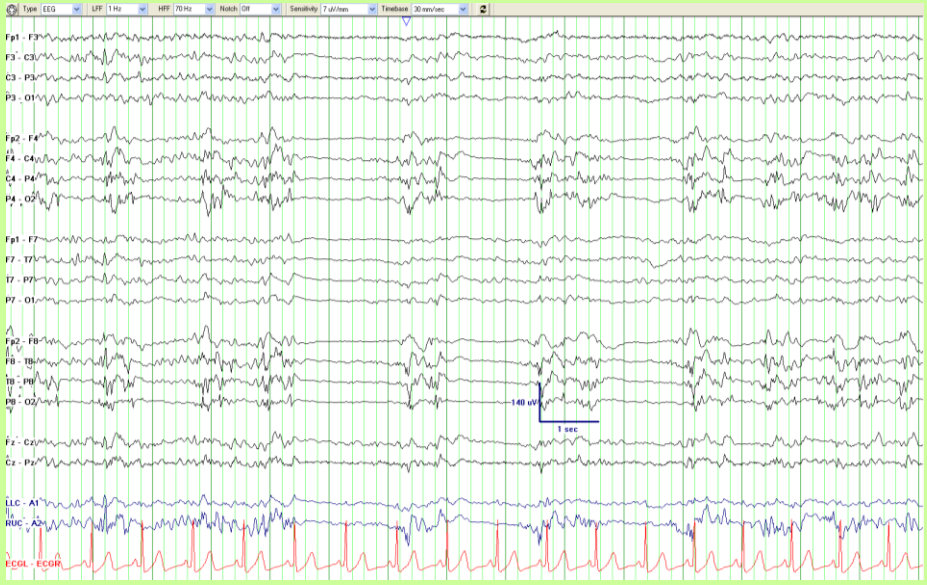
Chu 01

ASL

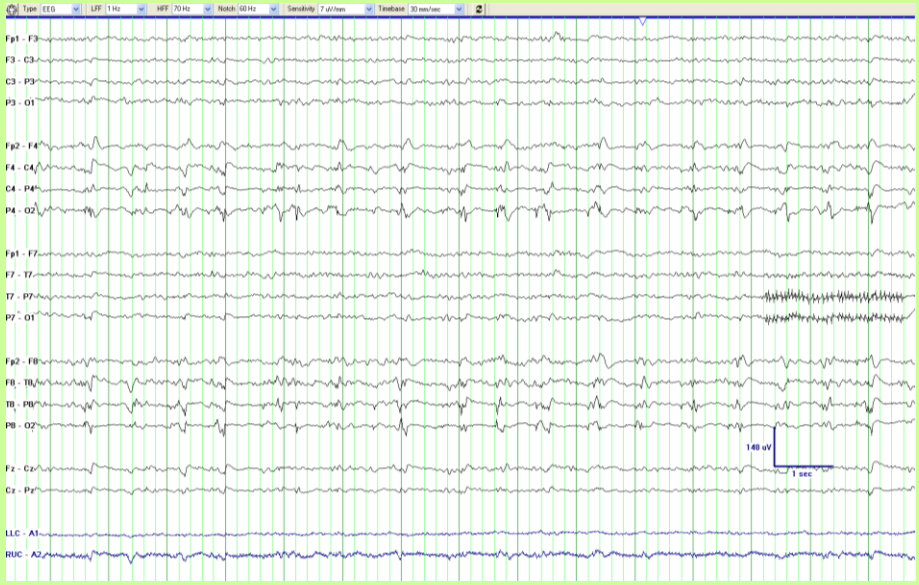


Detre 1996

Suppression burst

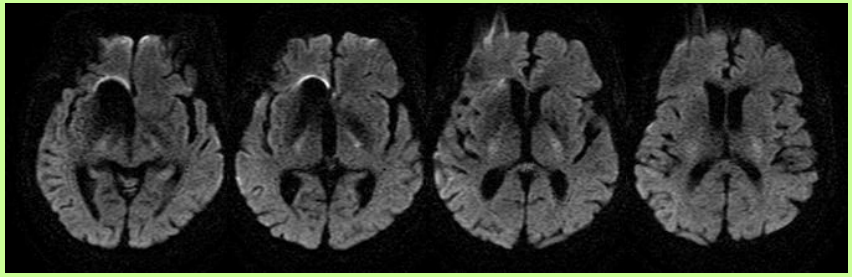


Wean off MDZ without recurrent seizures. PLEDs persisted for almost 2 wks.

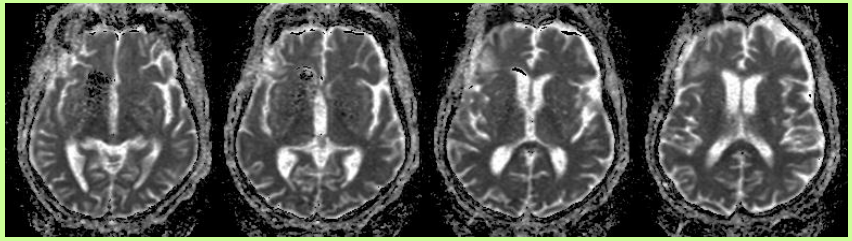


MRI during the ictal interictal continuum: almost complete resolution of the previously noted changes

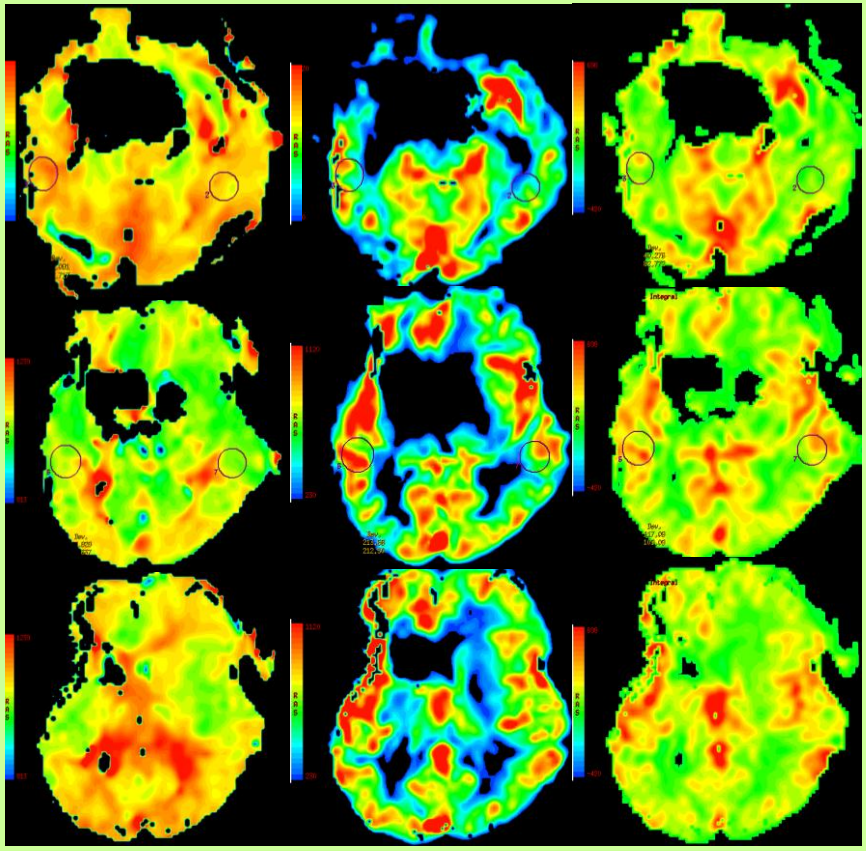
DWI



ADC



MTT | **CBF** | **CBV**



Benzodiazepine Trial for the Diagnosis of Non-Convulsive Status Epilepticus.

Monitoring: EEG, pulse ox, BP, ECG, respiratory rate, with dedicated nurse.

Antiepileptic Drug Trial:

- Sequential small doses of rapidly-acting short-duration benzodiazepine such as midazolam at 1mg/dose.
- Between doses, repeated clinical and EEG assessment.
- Trial is stopped after any of the following:
  - Persistent resolution of the EEG pattern (and exam repeated)
  - Definite clinical improvement
  - Respiratory depression, hypotension, or other adverse effect
  - A maximum dose is reached (such as 0.2 mg/kg midazolam, though higher may be needed if on chronic benzodiazepines)

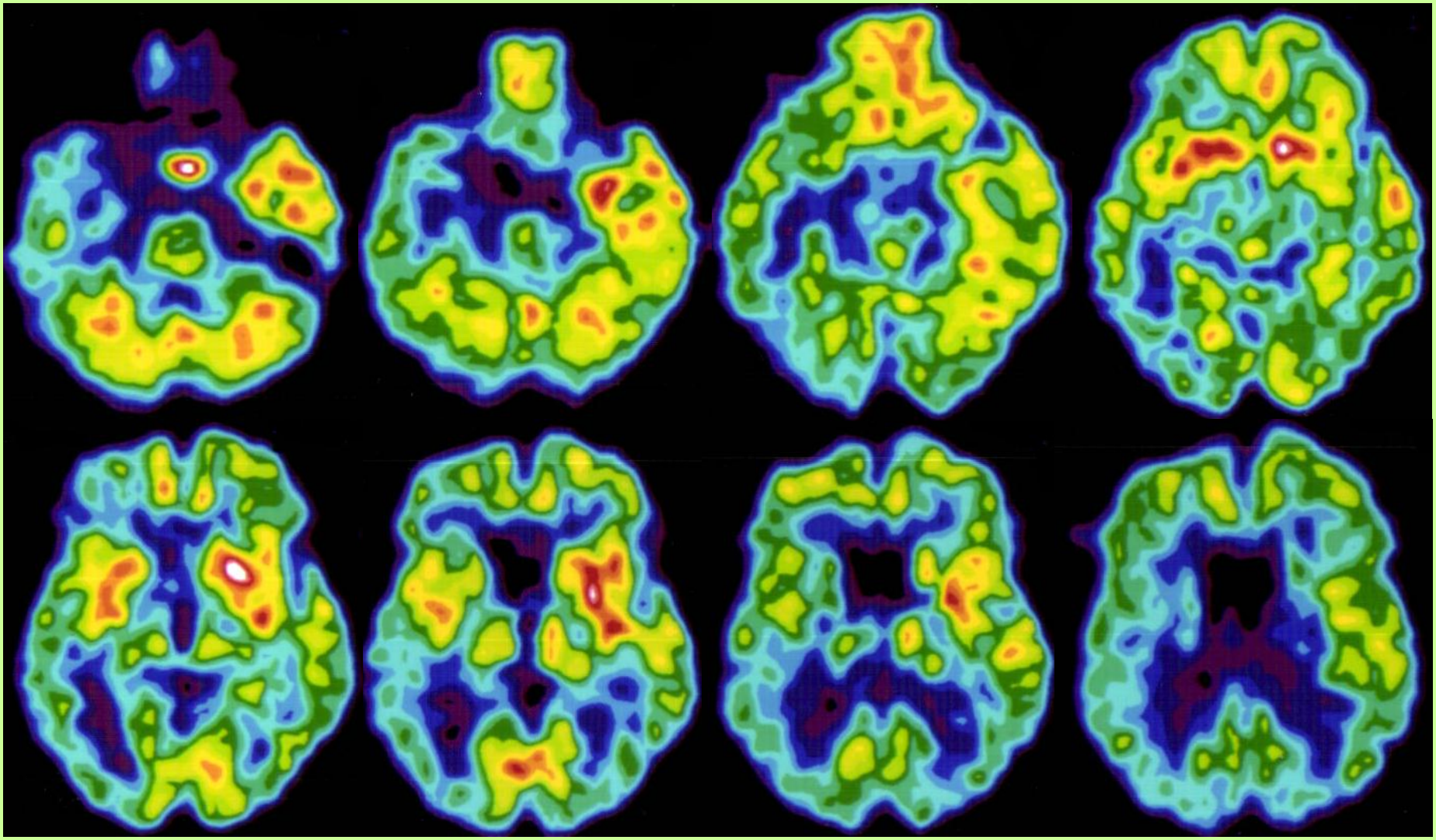
- Test is considered positive if there is resolution of the potentially ictal EEG pattern AND either an improvement in the clinical state or the appearance of previously-absent normal EEG patterns (eg. posterior dominant “alpha” rhythm). If EEG improves but patient does not, the result is equivocal.

- Due to thrombocytopenia VPA stopped
- Recurrence of NCSE -> Phenobarbital started
- Neuro: encephalopathic
- While weaning phenobarbital started on LTG

- Left > right facial twitching developed with PLEDs proper
- Benzodiazepine trial: 1 mg midazolam repeated doses of (total of 4 mg) -> facial twitching resolved and PLEDs gone but otherwise no neuro improvement = Equivocal

- Serial NSE levels throughout hospital course did not correlate with EEG activity

FDG-PET: decreased metabolism in the right temporal lobe



Phenobarbital discontinued.
Discharged to NH 1 month after admission on TPM, DPH, and LEV

Outcome: 2 months after discharge

- continuing to improve in an active rehabilitation program
- Interactive
- able to recognize family members
- moves all four extremities
- mobilized to a chair
- undergoing ventilator weaning

Criteria for Nonconvulsive Seizure

Any pattern lasting ≥ 10 secs satisfying any one of these 3 primary criteria:

Primary Criteria:

1. Repetitive generalized or focal spikes, sharp-waves, spike-and-wave or sharp-and-slow wave complexes at **≥3/sec**
2. Repetitive generalized or focal spikes, sharp waves, spike-and-wave or sharp-and-slow wave complexes at **<3/sec *and* secondary criterion**
3. Sequential rhythmic, periodic, or quasi-periodic waves at ≥ 1/sec *and* unequivocal **evolution in *frequency*** (gradually increasing or decreasing by at least 1/sec, e.g. from 2 to 3/sec), ***morphology*, *or location*** (gradual spread into or out of a region involving at least 2 electrodes).
   - Evolution in amplitude alone not sufficient
   - Change in sharpness without other change in morphology not adequate

Secondary criterion: After administration of a rapidly-acting AED:

- Significant **improvement in clinical state** *or*
- appearance of previously-absent **normal EEG patterns** (such as a posterior dominant rhythm)
- Not satisfactory: resolution of the “epileptiform” discharges leaving diffuse slowing without clinical improvement and without appearance of previously-absent normal EEG patterns

Chong et al, 2005 modification of Young et al 1996

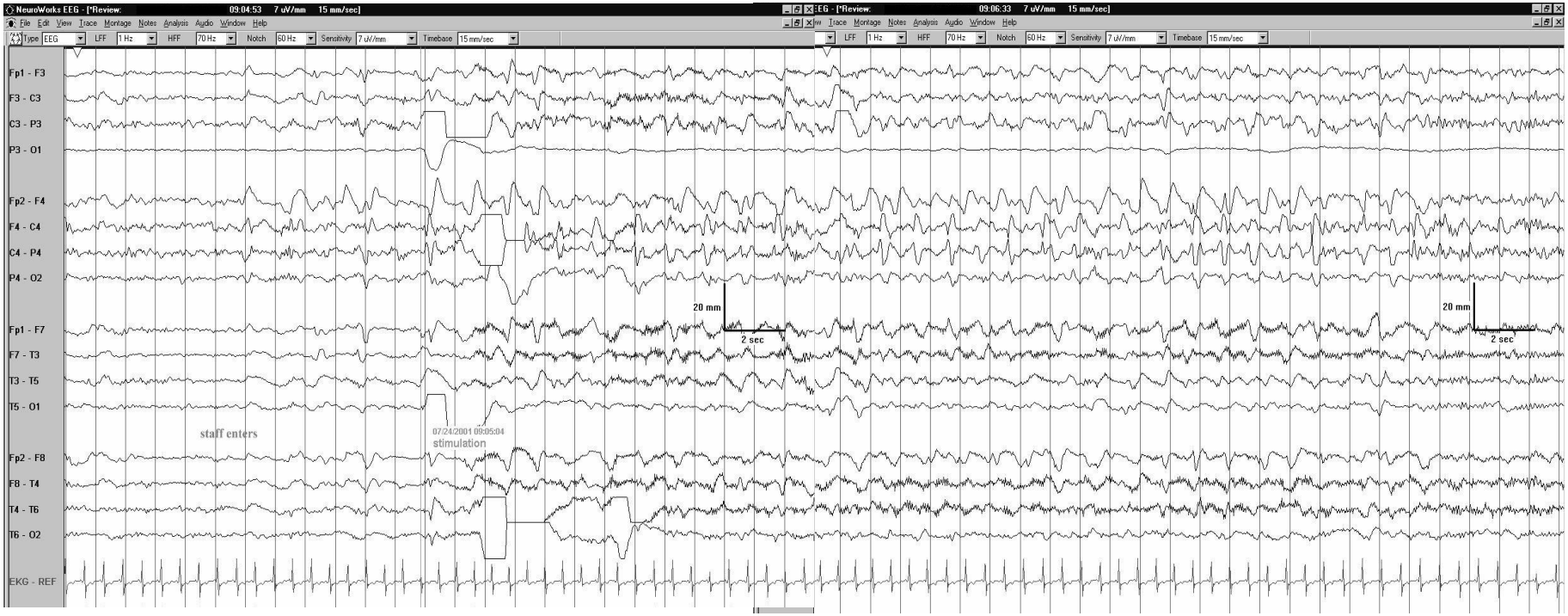
Strategies to support treatment decisions for patients in the ictal-interictal continuum: determine similarities to seizures

1. EEG signature:
   - Classify into PLEDs plus (low amplitude rhythmic discharge) and PLEDs proper (Reiher 91)
2. Physiologic measurements
   - Benzodiazepine trial
   - CBF and CBV (SPECT, CT perfusion, MR perfusion imaging, arterial spin labeling)
   - Cerebral metabolism (PET scanning)
   - Multimodality monitoring (PbtO2, hemodex for CBF, microdialysis for glutamate and GABA)
3. Quantify neuronal injury
   - Imaging studies (ADC, MR spectroscopy)
   - Serum markers (neuron specific enolase)
   - Microdialysis endpoints (LPR, glycerol)

Practical approach to patients with PEDs:

1. **Investigate the cause**: this may be guided by specific PED pattern (history, MRI, CSF, angio, brain biopsy)
2. Conventional **AED prophylaxis** for seizures: Levetiracetam (alternatives: oxcarbazepine, CBZ, DPH, VPA, TPM, GBP); at this point should not use cIV AEDs for PEDs without seizures
3. May do **benzo trial** to determine ictal nature
4. **Continue cEEG monitoring** for potential nonconvulsive seizures or status epilepticus.
5. **Long-term treatment**: individualize based on other EEG findings (e.g. epil discharges) and underlying brain injury
   - Acute PLEDs that resolved without seizures -> taper AEDs/one month after acute illness.
   - Acute PLEDs with seizures: AED treatment for 3-12 months
   - Consider DPH, phenobarbital, and benzos may adversely affect motor recovery after stroke (Camilo and Goldstein, 2004).

SIRPIDs: Stimulus-Induced Rhythmic, Periodic or Ictal Discharges



Staff enters

Stim

Prevalence: 22% (33/150) consecutive cEEG patients

Hirsch Epilepsia 2004 and 2007

Acknowledgements

Depart. of Biomedical Informatics

- **Adler Perotte, MD**
- **Samantha Kleinberg, PhD**
- **David Albers, PhD**
- **George Hripcsak, MD, MS**

Department of Neurosurgery

- **E Sander Connolly, MD**
- **Neurosurgery residents**

Division Critical Care Neurology

- J Michael Schmidt, PhD
- Stephan A. Mayer, MD
- NICU Fellows
- NICU nurses
- Neurology residents

Comprehensive Epilepsy Center

- **Bin Tu, MD**
- **EEG Technicians**
- **Epilepsy attendings**
- **Epilepsy fellows**