Brain Center
Rudolf Magnus

status epilepticus in children

Kees Braun
UMC Utrecht

status epilepticus in children

misleading EEG in SE

epidemiology
treatment
febrile SE

epileptic encephalopathies

nonconvulsive SE
ESES

status epilepticus in children: definition

old: seizure > 30 min or series of seizures with no recovery of consciousness

mean duration GTC seizure: 62 sec.

Theodore et al. Neurology 1994

if seizure duration > 5-10 min: chance of spontaneous termination is very low (<5%)

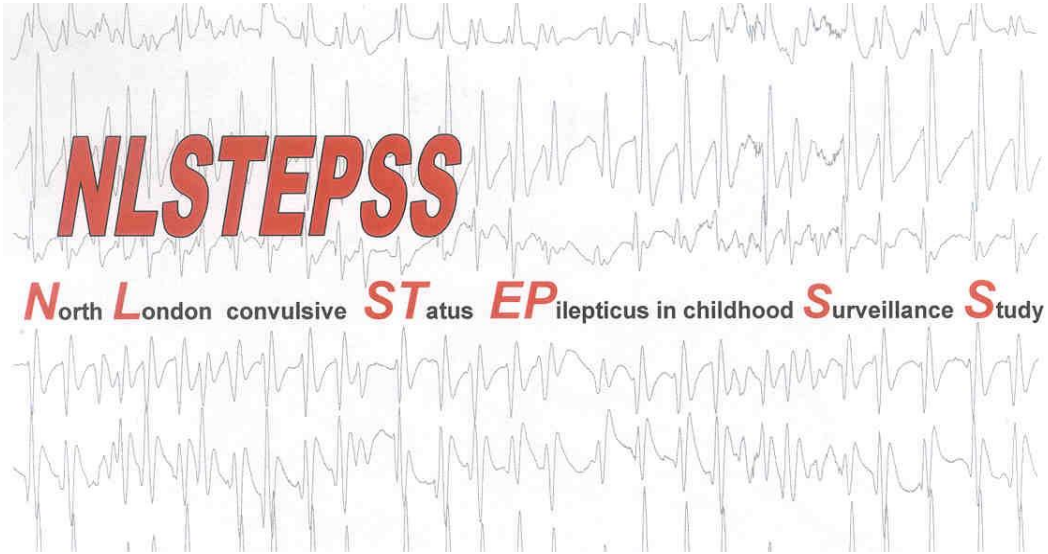
Shinnar et al. Ann Neurol 2001

status epilepticus in children: new definition

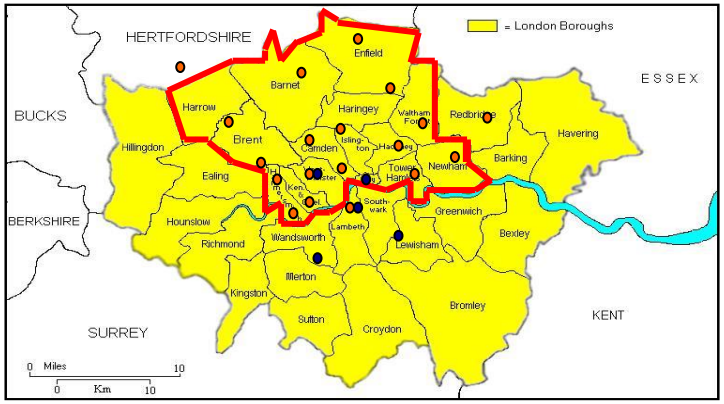
seizure > 5-10 min	‘early’ / ‘impending’ SE
seizure > 30 min	‘established SE’
seizure > 60 min	‘refractory SE’

Lowenstein et al. Epilepsia 1999
Shorvon et al. Epilepsia 2008
Meierkord et al. Eur J Neurol 2010
Brophy et al. Neurocrit Care 2012
Fernández et al. Seizure 2013

status epilepticus in children: epidemiology



Chin et al. Lancet 2006

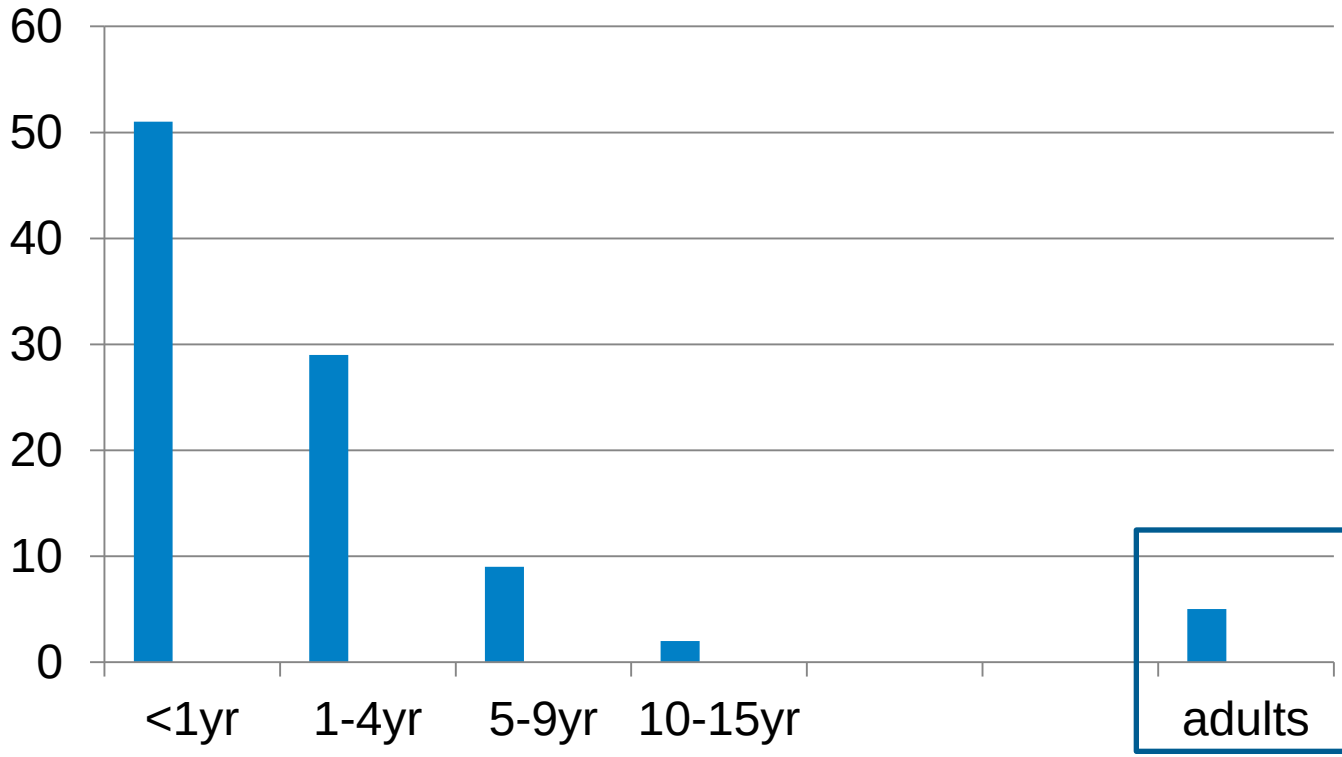


status epilepticus in children: epidemiology

convulsive SE >30 min, population based study

17-23/100.000/yr

Chin et al. Lancet 2006



Meierkord et al.
Eur J Neurol 2010

status epilepticus in children: epidemiology

Variable		Incidence Coefficient	*p*	95% CI
IMD 2004		1.03	0.007	1.01 – 1.06
Age				
	0-4	1.00 (reference)	-	-
	5-7	0.30	<0.0005	0.19 – 0.47
	8-9	0.16	<0.0005	0.08 – 0.32
	10-15	0.06	<0.0005	0.03 – 0.12
Ethnicity				
	White	1.00 (reference)	-	-
	Black	1.22	0.83	0.21-7.14
	Asian	6.62	0.002	2.0 – 21.9
	Other	1.37	0.72	0.25-7.5
IMD 2004 * Ethnicity				
	IMD 2004* White	1.00 (reference)	-	-
	IMD 2004* Black	1.00	0.97	0.95 - 1.05
	IMD 2004* Asian	0.97	0.05	0.93 – 1.00
	IMD 2004* Other	1.01	0.71	0.96 – 1.06

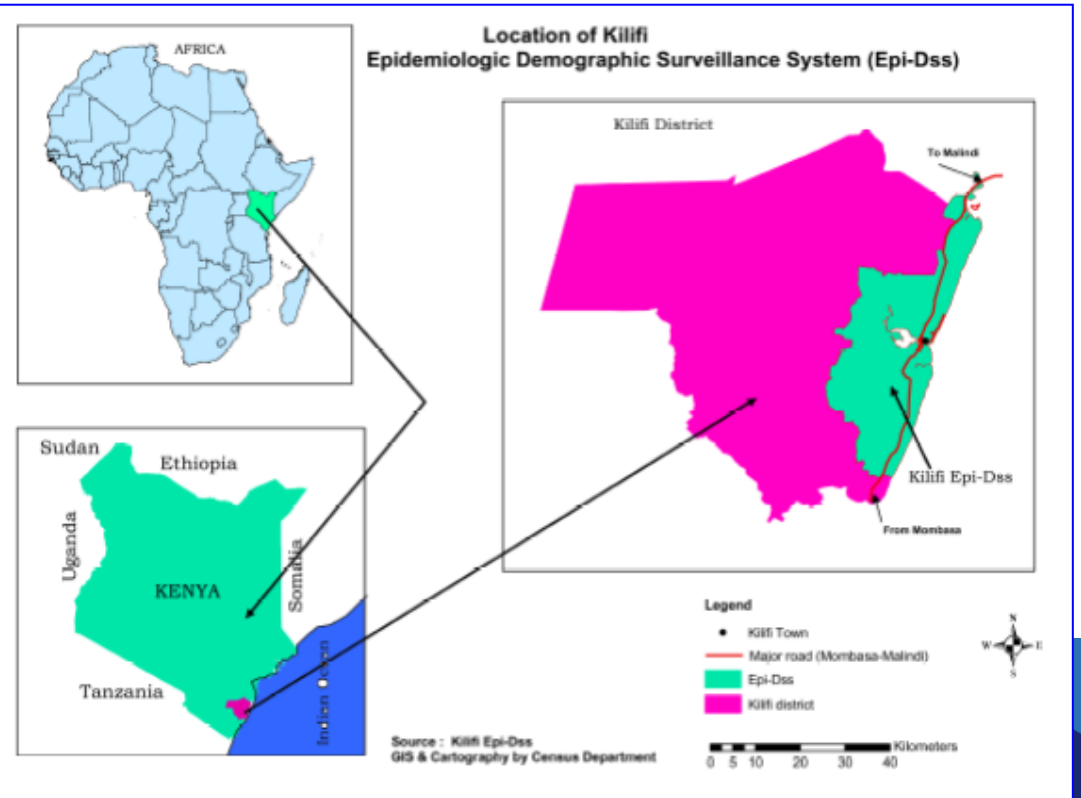
status epilepticus in children: epidemiology

convulsive SE >30 min, population based study

17-23/100.000/yr

Chin et al. Lancet 2006

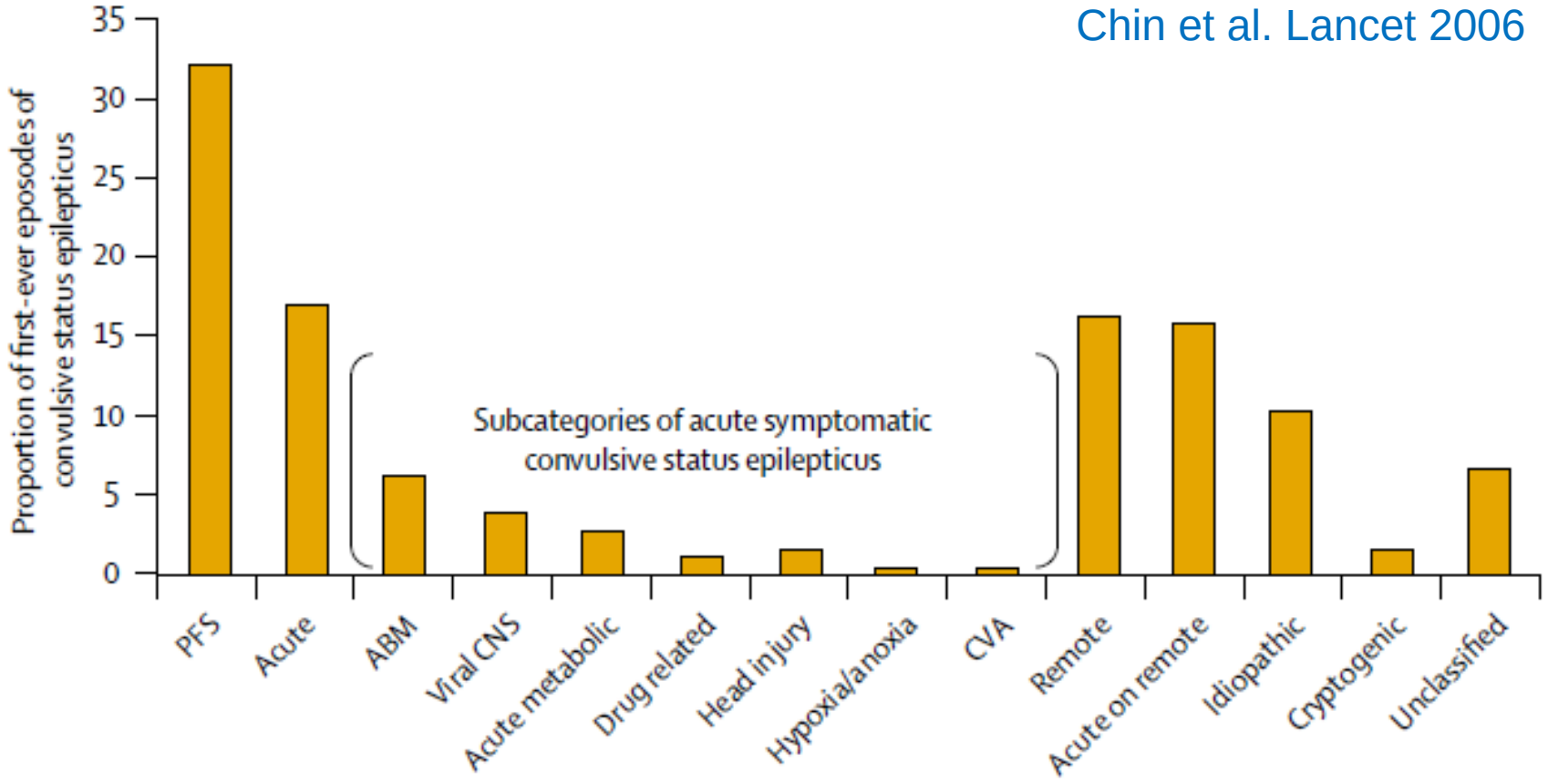
incidence = 189 (95% CI 158- 226) /100,000/yr



Sadarangani et al.
Lancet Neurol 2007

causes of first-ever childhood SE

Chin et al. Lancet 2006



status epilepticus in children: epidemiology

35%	focal onset only
5%	remained focal
86%	tonic-clonic
60%	> 1 hr
17%	recurrence (remote symptomatic: 47%)
3.4%	case fatality
78%	first-ever SE episode
	56% neurologically normal prior to SE

Chin et al. Lancet 2006

status epilepticus in children: treatment

outside hospital

midazolam (nasal, buccal) / diazapam (rectal), repeat once

benzodiazepines: general considerations

T_{max}	buccal/nasal MDZ < s.l. LZP or rectal DZP
receptor affinity	MDZ and LZP > DZP
% seizure/SE termination	rectal LZP > rectal DZP
	buccal/nasal MDZ > rectal DZP
	i.m. MDZ > i.v. LZP
	i.v. LZP = i.v. DZP
time to seizure termination	i.m. MDZ < i.v. LZP (NS)
	i.m. or nasal MDZ < i.v. DZP

benzodiazepines: general considerations

SE alters GABA and glutaminergic receptor numbers

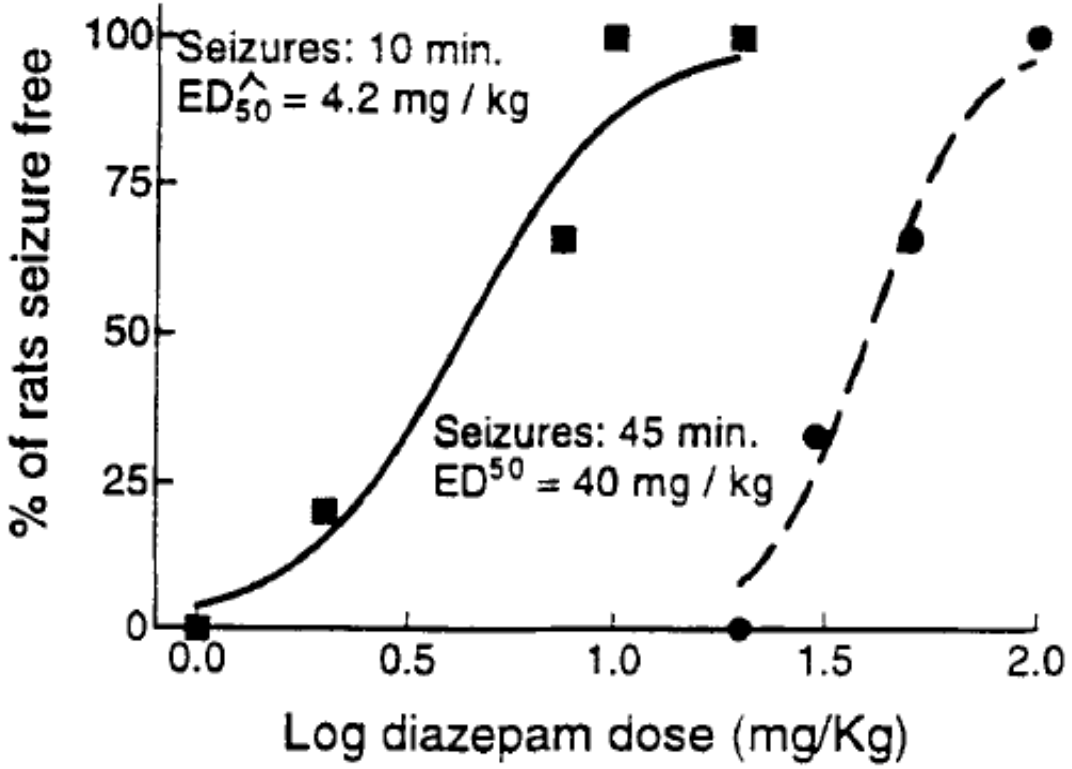
50% reduction in GABA receptors on neuronal membrane
within 1 hour of onset of SE1

- removes the receptors from the reach of benzodiazepines
- potential mechanism for loss of response to benzodiazepines

glutamate receptor numbers also increase
due to their migration to the cell membrane

Naylor et al. J Neurosci 2005

benzodiazepines: general considerations



Kapur et al. J Neurosci 1997

status epilepticus in children: treatment

outside hospital

midazolam (nasal, buccal) / diazapam (rectal), repeat once

in hospital: general measures

stabilization of vital functions, 100% O_2, i.v. access

check glucose

control hyperthermia

consider consultation intensivist

specific diagnostics by indication (lab, tox-screen, CT, CSF):

acute symptomatic causes!

status epilepticus in children: treatment

t=0, step 1	
if no i.v.:	midazolam i.m./nasal/buccal
once i.v.:	midazolam or lorazepam i.v.
t=5, step 2	
	repeat step 1
t=10, step 3	
	midazolam or lorazepam i.v.
t=15, step 4	
	phenytoin i.v. in 20 min. (or LEV or VPA)

refractory SE in children: treatment

definition: failure of initial benzodiazepine and another class of antiepileptic drug

incidence: of 193 children with convulsive SE: 26% > 1 hr

mortality up to 32%

Fernández et al. pSERG, Seizure 2013

refractory SE in children: treatment

PICU

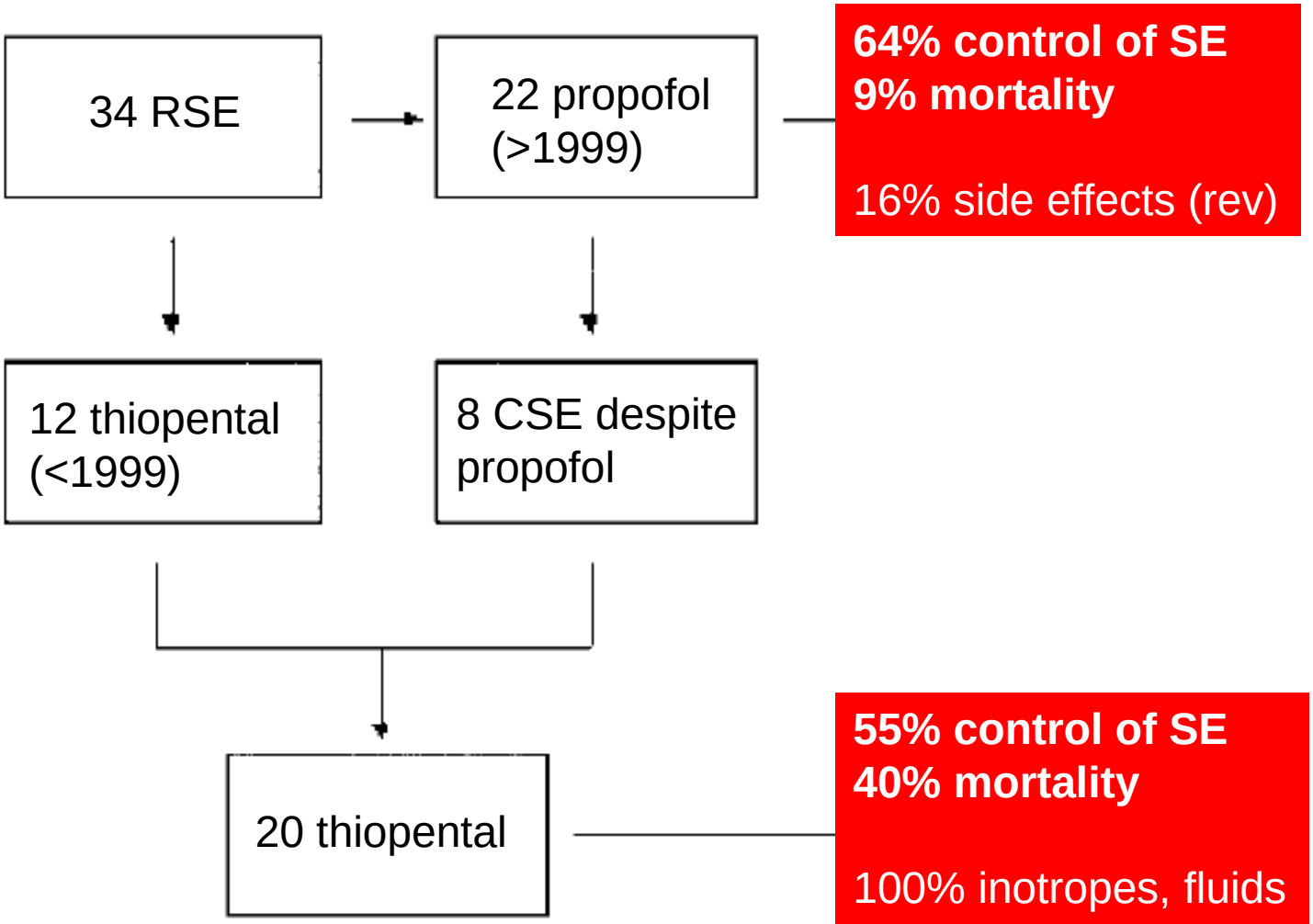
(before anesthetic treatment, after PHT: LEV? VPA? PHB?)

- continous midazolam i.v. (up to 1 mg/kg/hr)
- thiopental?
- propofol?

no controlled studies

NVN/NVK guidelines 2013

Fernández et al. pSERG, Seizure 2013



van Gestel et al. Neurology 2006

‘superrefractory’ SE in children: treatment

Therapy	Published cases in controlled or randomized studies (*n*)	Published cases in open series or as case reports (reports, *n*)
Pentobarbital/thiopental	9[a]	377 (32)
Midazolam	0	661 (29)
Propofol	14[a]	183 (34)
Ketamine	0	17 (8)
Inhalational anaesthetics	0	32 (11)
Hypothermia	0	10[c] (5)
Magnesium	0	11 (3)
Pyridoxine	0	14 (5)
Steroids/immunotherapy	0	50 (15)
Ketogenic diet	0	20 (6)
Transcranial magnetic stimulation	0	0
Vagal nerve stimulation	0	4 (4)
Deep brain stimulation	0	1[b] (1)
Resective neurosurgery	0	36 (15)
CSF drainage	0	1 (1)
Electroconvulsive therapy	0	8 (6)

SE that continues >24 hr after onset of anesthetic Tx

Shorvon and Ferlisi
Brain 2011

Fernández et al. pSERG
Seizure 2013

outcome of convulsive SE in children

systematic review

63 studies

short-term mortality 2.7-5.2%
morbidity other than epilepsy 15%
prognosis primarily determined by underlying cause
? effect of age and duration
? additional effect of CSE

Raspall-Chaure et al .
Lancet Neurol 2006

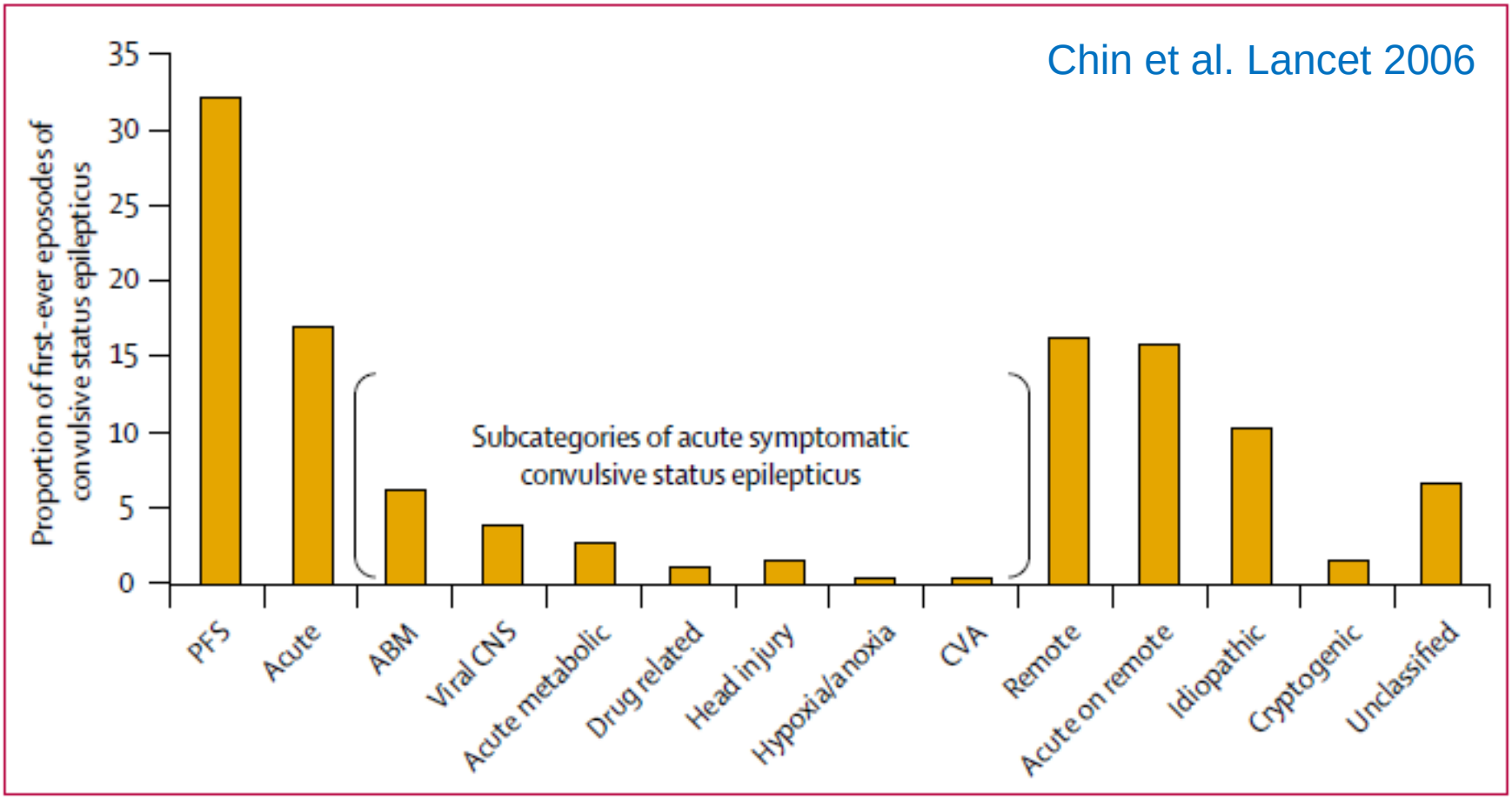
status epilepticus in children

convulsive SE

invisible SE

epidemiology
treatment
febrile SE

causes of first-ever childhood SE



25-40% = febrile SE

Fernández et al. pSERG, Seizure 2013

febrile SE in children

119 children with febrile SE (>30 min)

no CNS infection
no prior afebrile sz
no severe neurol disability

86% normal prior development
24% prior febrile seizures
25% family history FS (first-degree)

52% continuous SE
67% partial
99% convulsive
median age 1.3 yr, median duration 68 min

Shinnar et al. FEBSTAT, Neurology 2008

febrile SE in children

199 children with febrile SE (>30 min)

no CNS infection
no prior afebrile sz
no severe neurol disability

90% at least 1 AED
70% 2 or more AEDs
} required to terminate SE

48% required respiratory support

earlier AED initiation: shorter SE duration

Seinfeld et al. FEBSTAT, Epilepsia 2014

febrile SE in children - HHV

169 children with febrile SE (>30 min), HHV 6/7 serum PCR

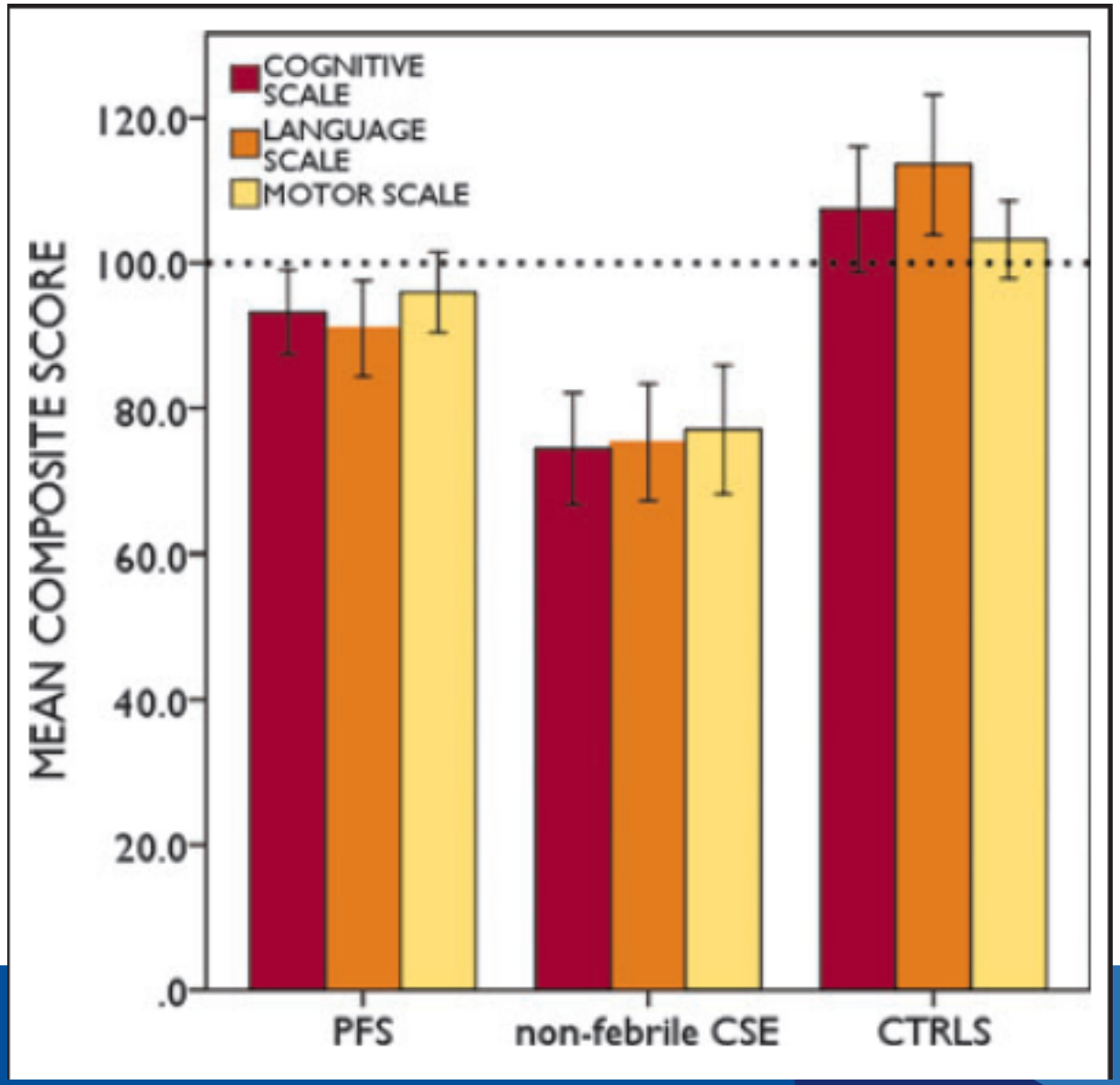
HHV-6B	32%	
HHV-7	7%	2/3 primary, 1/3 reactivation

- no pleocytosis
- CSF PCR –
- no differences in clinical characteristics
- proximate cause of fever or direct viral effect on brain?

Epstein et al. FEBSTAT, Epilepsia 2012

febrile SE in children

affects cognitive outcome



Martinos et al. Epilepsia 2013

febrile SE in children

febrile SE – TLE in adult life

2-5% of healthy children < 5 yrs have febrile seizures (FS)

5-10% of febrile seizures: febrile SE

50-80% of patients with refractory TLE and HS had FS

association febrile SE – hippocampal sclerosis

genetic predisposition?	2nd hit epileptogenic event febrile seizures status epilepticus	epileptogenesis latent period (8-11yrs)	TLE HS

neuronal loss (GABAergic > glutamatergic)
gliosis
mossy fibre sprouting

febrile SE – hippocampal abnormalities

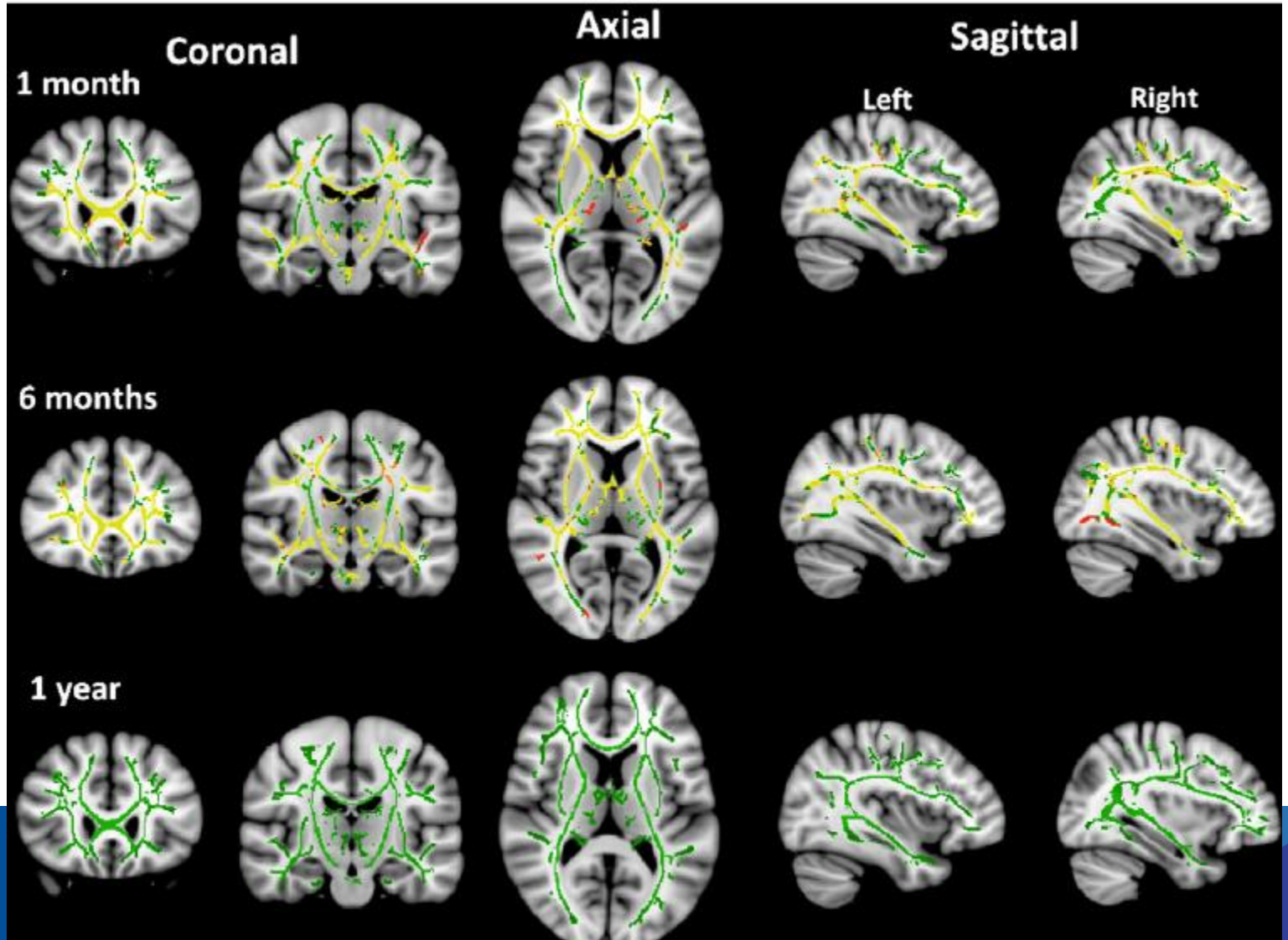
MRI <72 hrs following SE

	FSE (n = 191), n (%)			Simple FS, n (%)			
MRI finding	All	Definite	Suspect	All	Definite	Suspect	*p* Value
Any abnormality	63 (33.0)	46 (24.1)	17 (8.9)	17 (17.7)	9 (9.4)	8 (8.3)	0.0008
Hippocampal abnormality	40 (20.9)	30 (15.7)	10 (5.2)	2 (2.1)	2 (2.1)	0	<0.0001
Abnormal T2 signal	22 (11.5)	17 (8.9)	5 (2.6)	0	0	0	<0.0001
Developmental abnormality	20 (10.5)	16 (8.4)	4 (2.1)	2 (2.1)	2 (2.1)	0	0.0097
HIMAL	15 (7.9)	15 (7.9)	0	2 (2.1)	2 (2.1)	0	0.06
Other	5 (2.6)	0	4 (2.6)	0	0	0	0.17
Nonhippocampal abnormality	30 (15.7)	22 (11.5)	8 (4.2)	15 (15.6)	7 (7.3)	8 (8.3)	1
Temporal lobe/amygdala	15 (7.9)	8 (4.2)	7 (3.7)	1 (1.0)	1 (1.0)	0	0.015
Extratemporal	20 (10.5)	16 (8.4)	4 (2.1)	14 (14.6)	6 (6.3)	8 (8.3)	0.34

Shinnar et al. FEBSTAT, Neurology 2012

febrile SE – white matter abnormalities

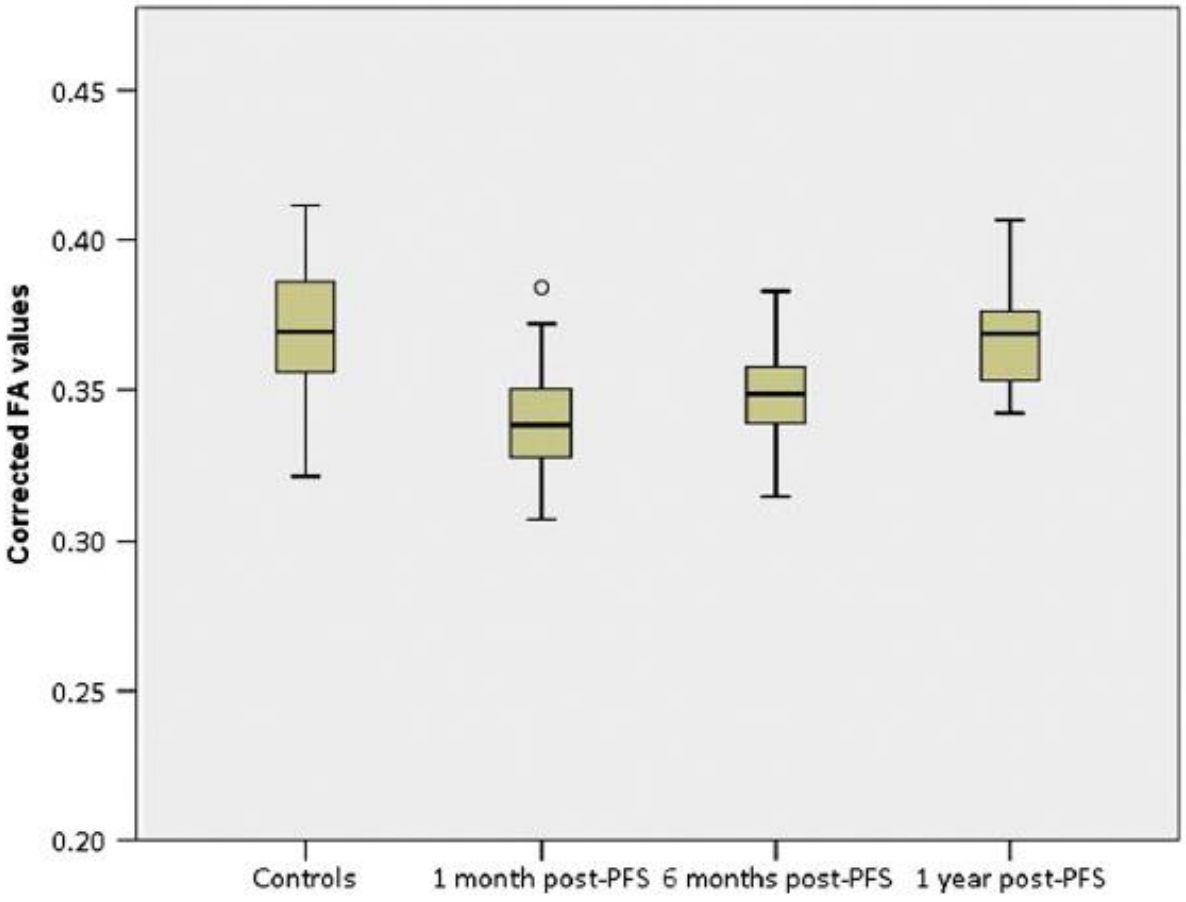
32 children with febrile SE, DTI/TBSS: 1, 6, 12 m



Yoong et al.
NeuroImage
2013

febrile SE – white matter abnormalities

32 children with febrile SE, DTI/TBSS: 1, 6, 12 m



temporary halting of normal white matter development?

Yoong et al. NeuroImage 2013

status epilepticus in children

convulsive SE

invisible SE

nonconvulsive SE
ESES

nonconvulsive / electrographic SE in children

“enduring epileptic disorder with altered consciousness, behavioural abnormalities, or merely subjective symptoms, without major convulsive movements”

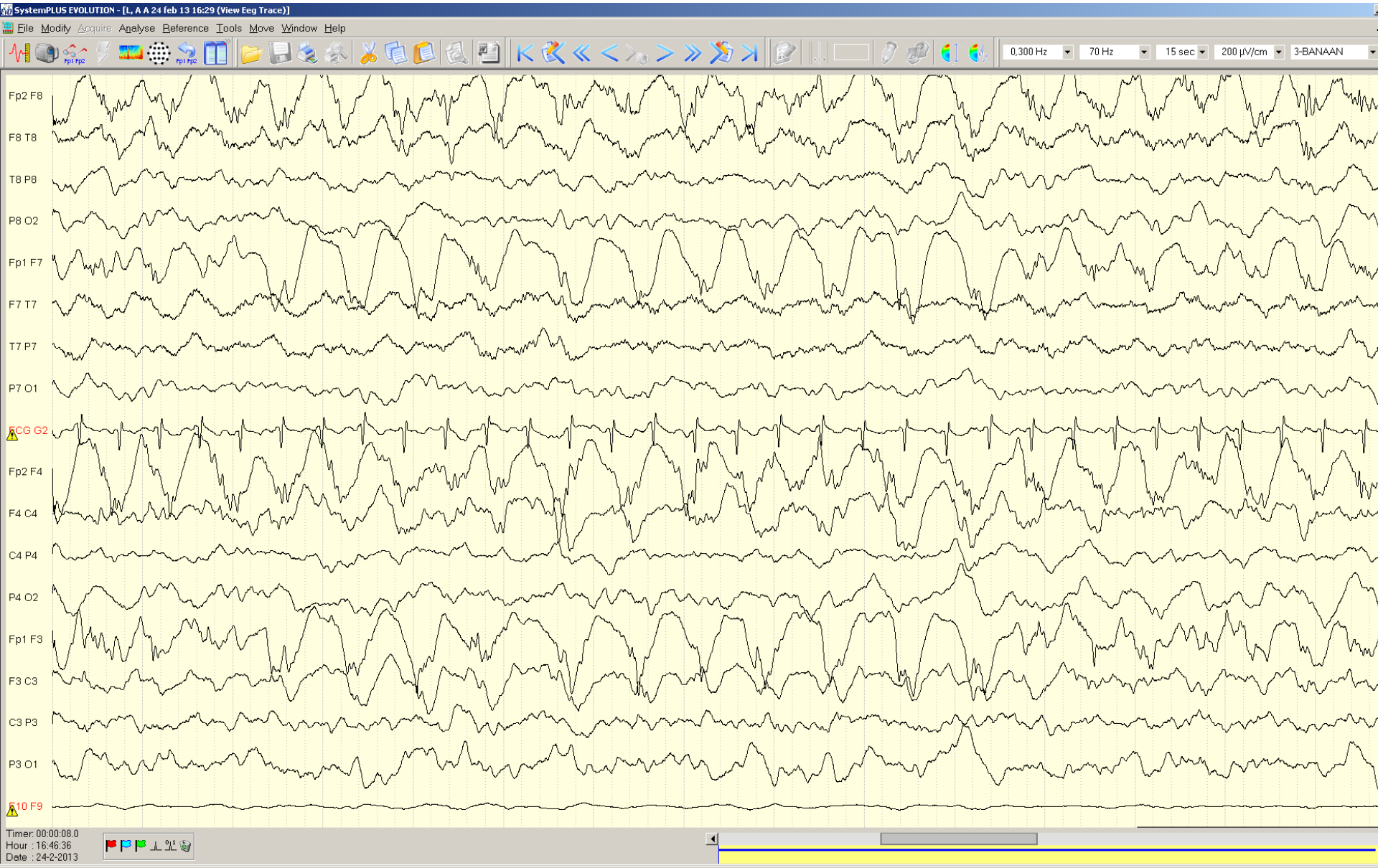
Abend et al. Lancet Neurol 2013

550 children, 11 US sites, continuous EEG on PICU:

162	29%	electrographic seizures (1/3 EEG only)
61	**11%**	**electrographic SE**
		continuous > 30 min: 46%
		intermittent sz > 30 min/1hr: 51%

Abend et al. Neurol 2013

nonconvulsive SE



electrographic seizures/SE after convulsive SE

98 children with convulsive SE on PICU
with subsequent continuous EEG monitoring

32 (33%) electrographic sz
17 (53%) *"some" clinical correlate*

15 (15%) electrographic SE

continuous 40%
intermittent 60%

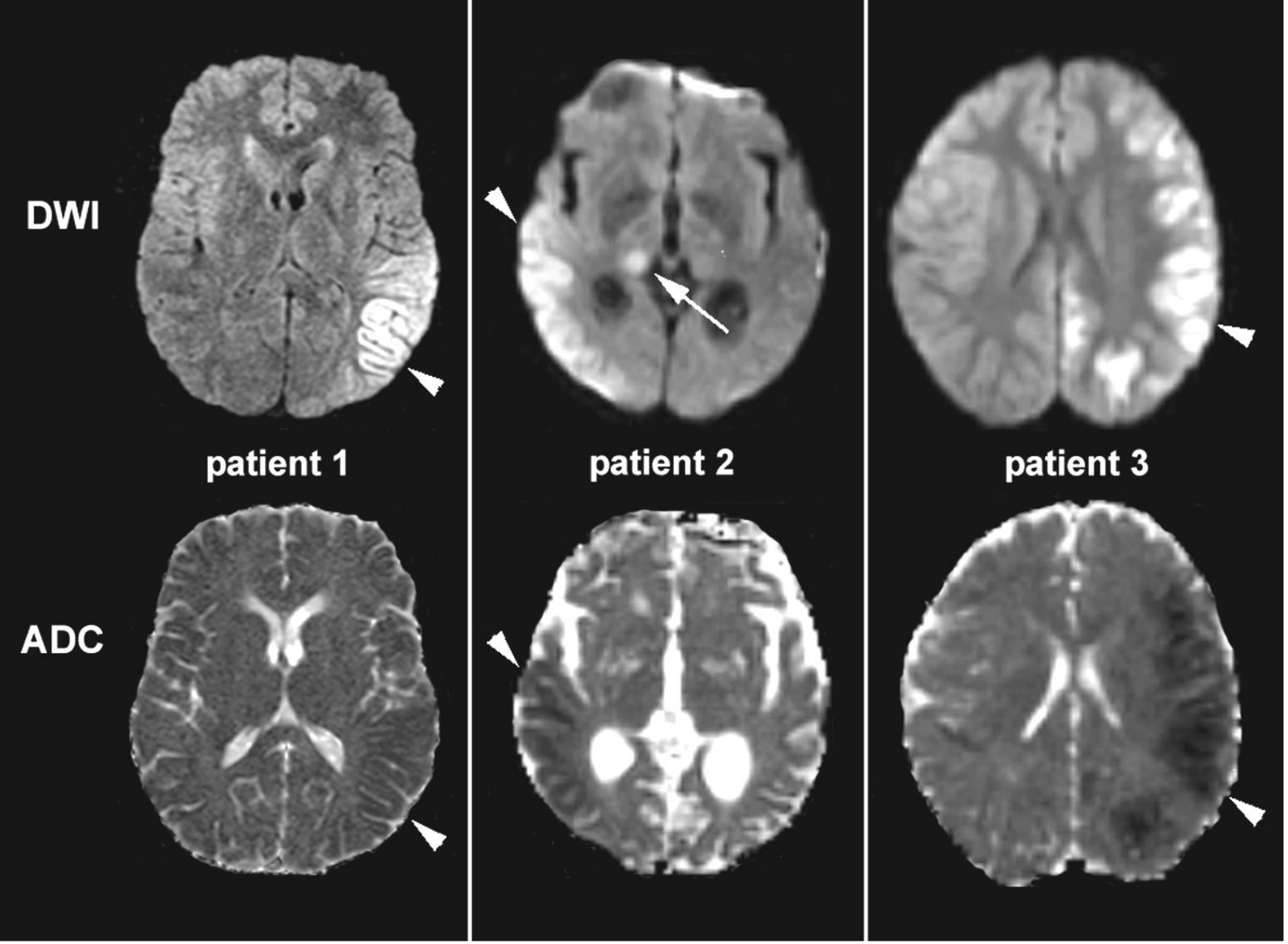
Fernández et al. J Pediatr 2013

outcome after electrographic sz / SE

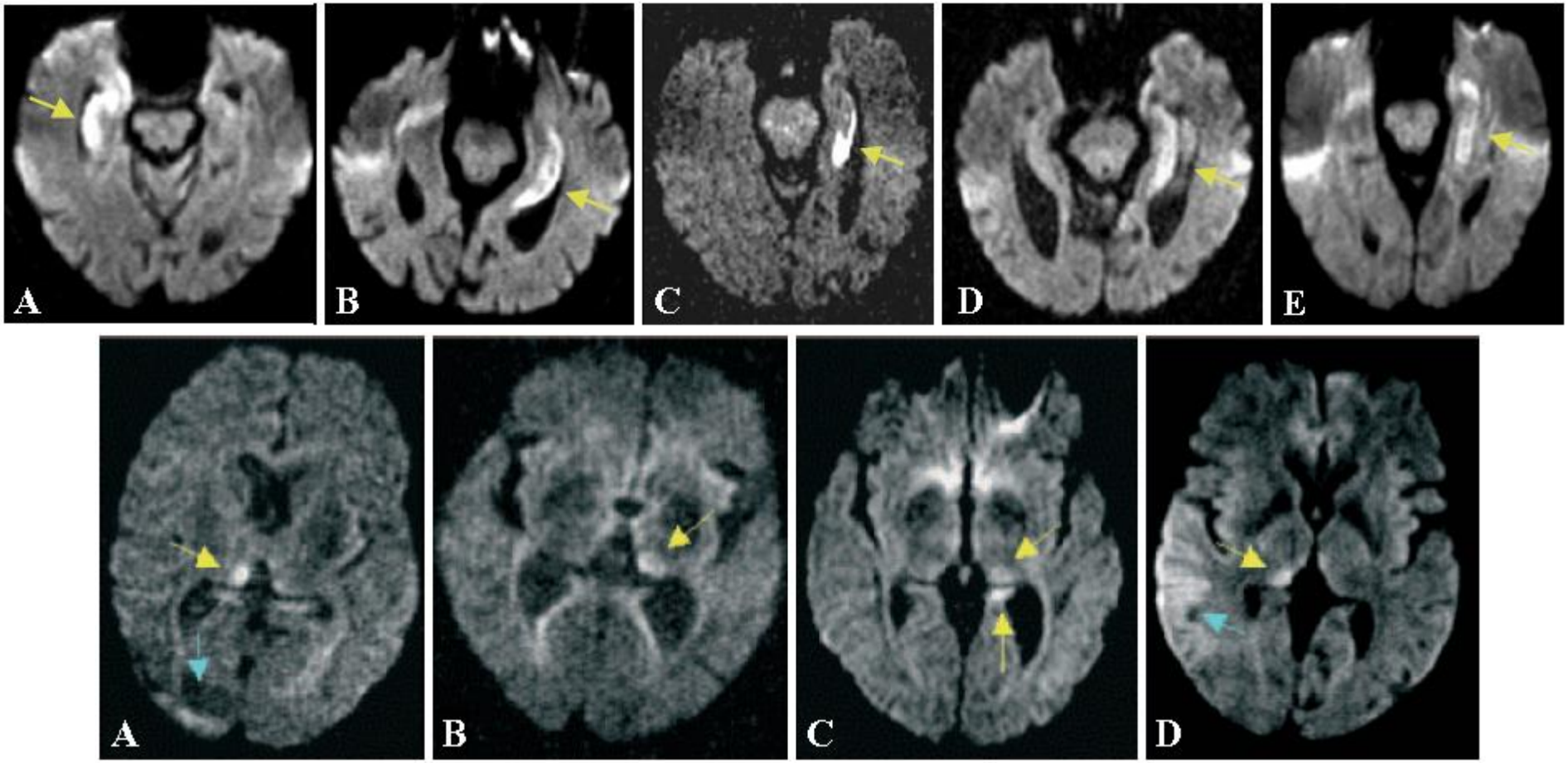
children on PICU	elctr sz	elctr SE
n=200	21%	22%
n=550	18%	11%

	mortality	neurol morbid
electrographic sz	no influence	no influence
electrographic SE	**OR 2.4 / 5.1**	**OR 17.3**

Abend et al. Lancet Neurol 2013



Lansberg et al. Neurology 2000

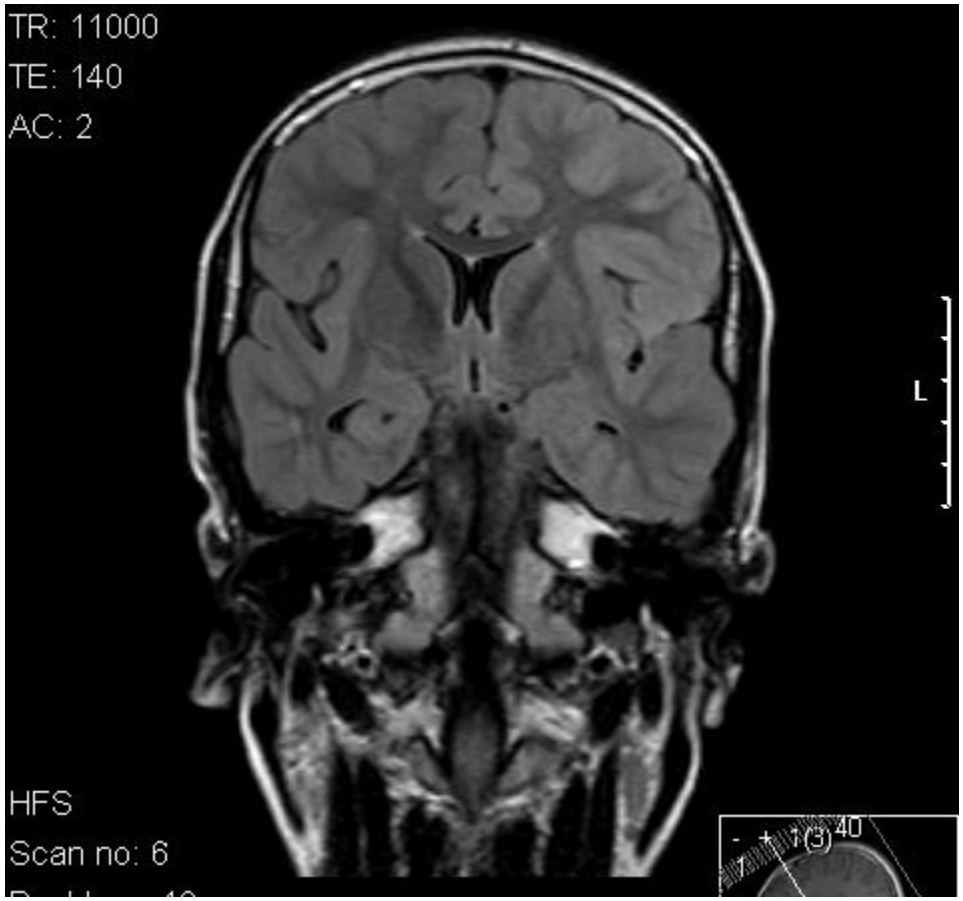


adults with partial complex SE
80% hippocampal diffusion abnormalities
31-90% pulvinar diffusion abnormality

Szabo et al. Brain 2005
Katramados et al. Epilepsia 2009

consequences of unrecognized hemi-SE

T2-FLAIR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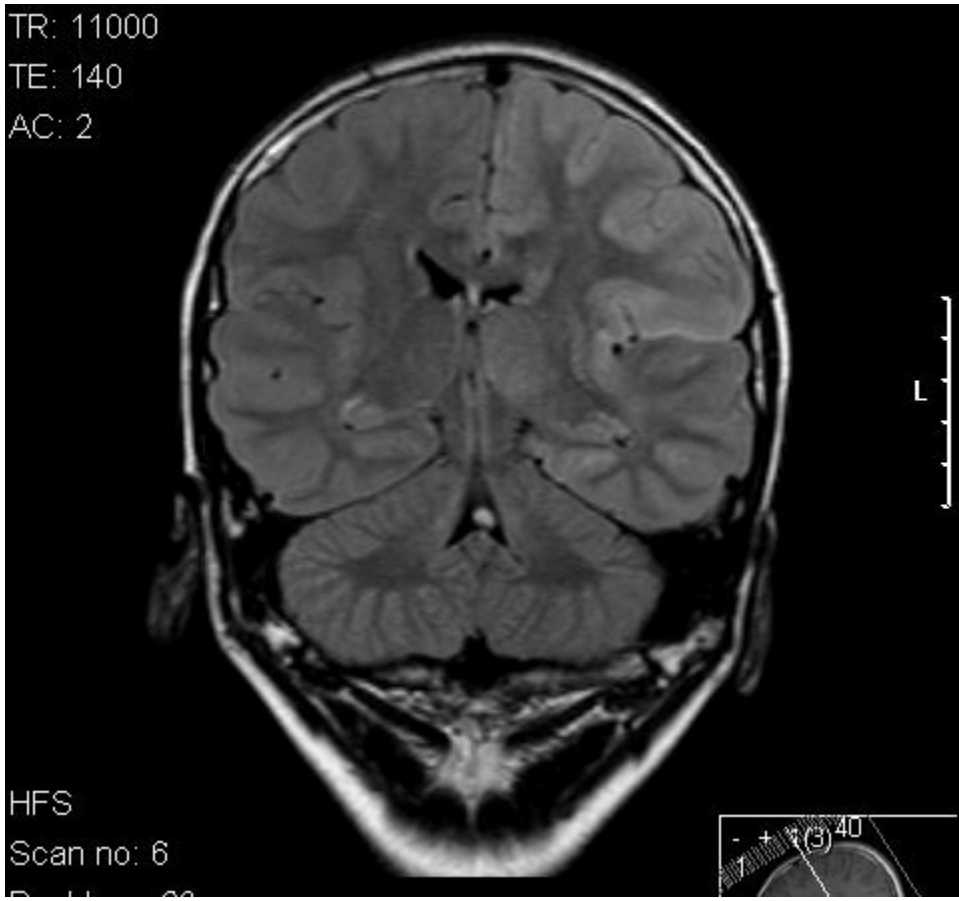
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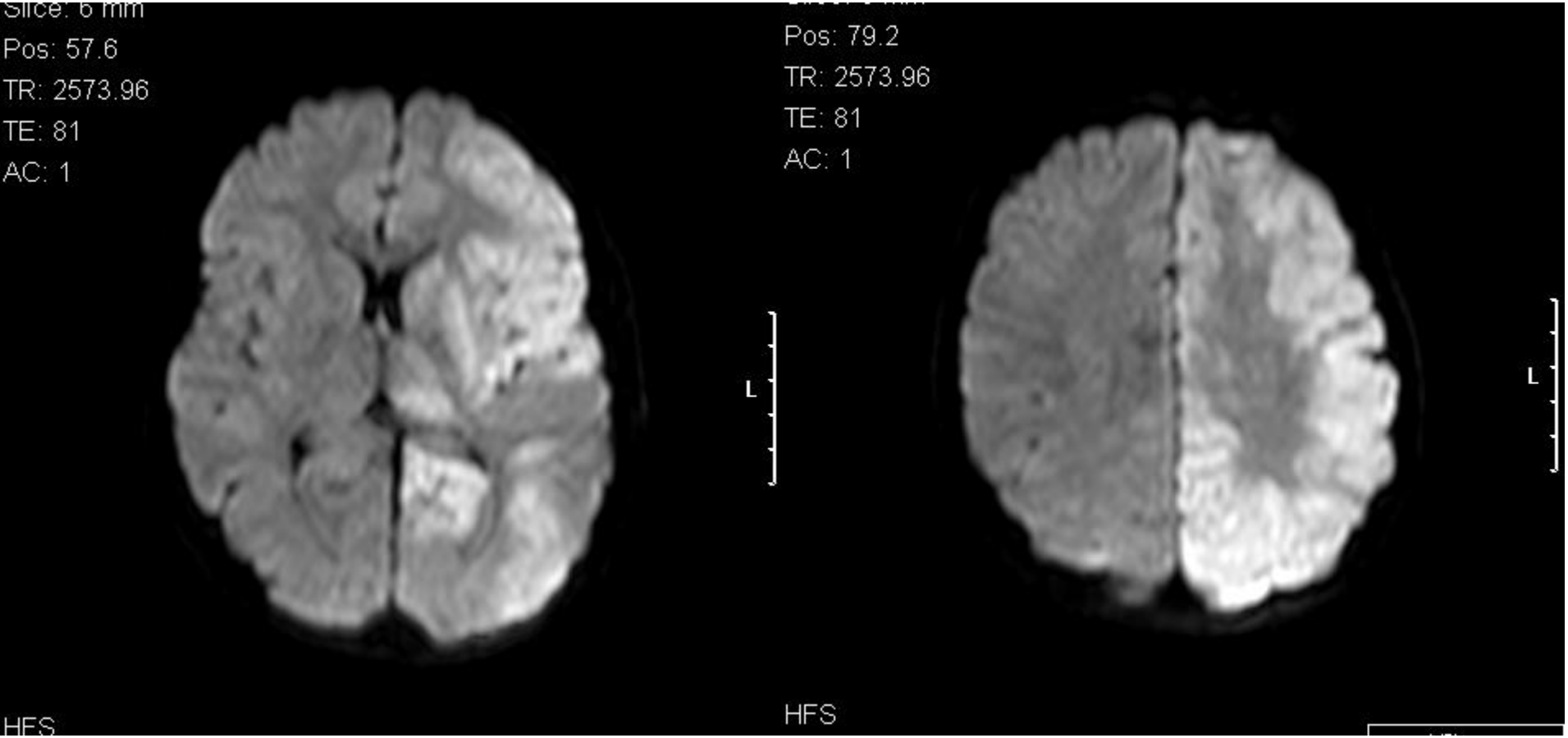
DWI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HFS
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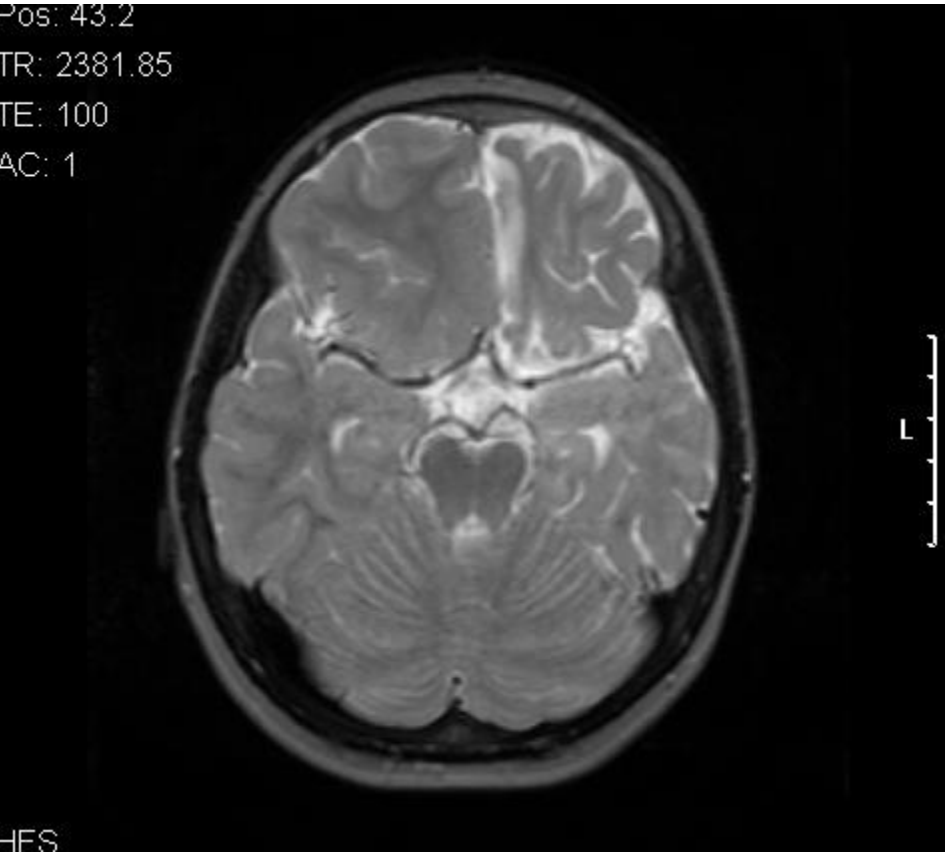
AC: 1
L
HFS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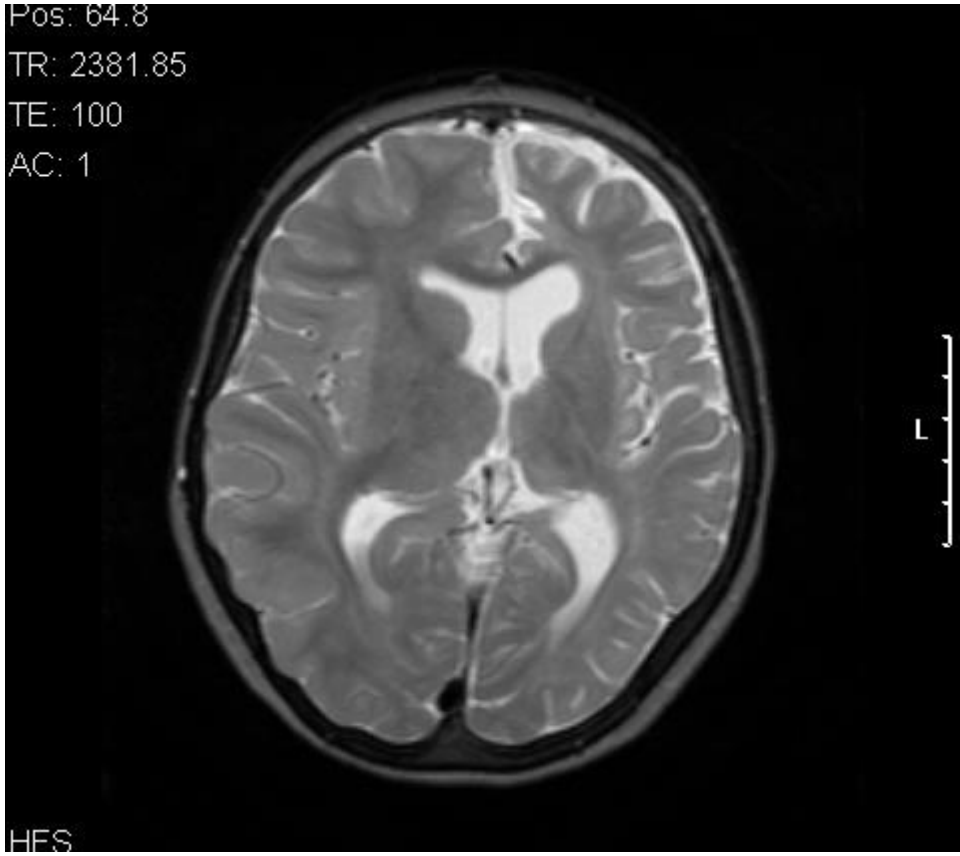
HFS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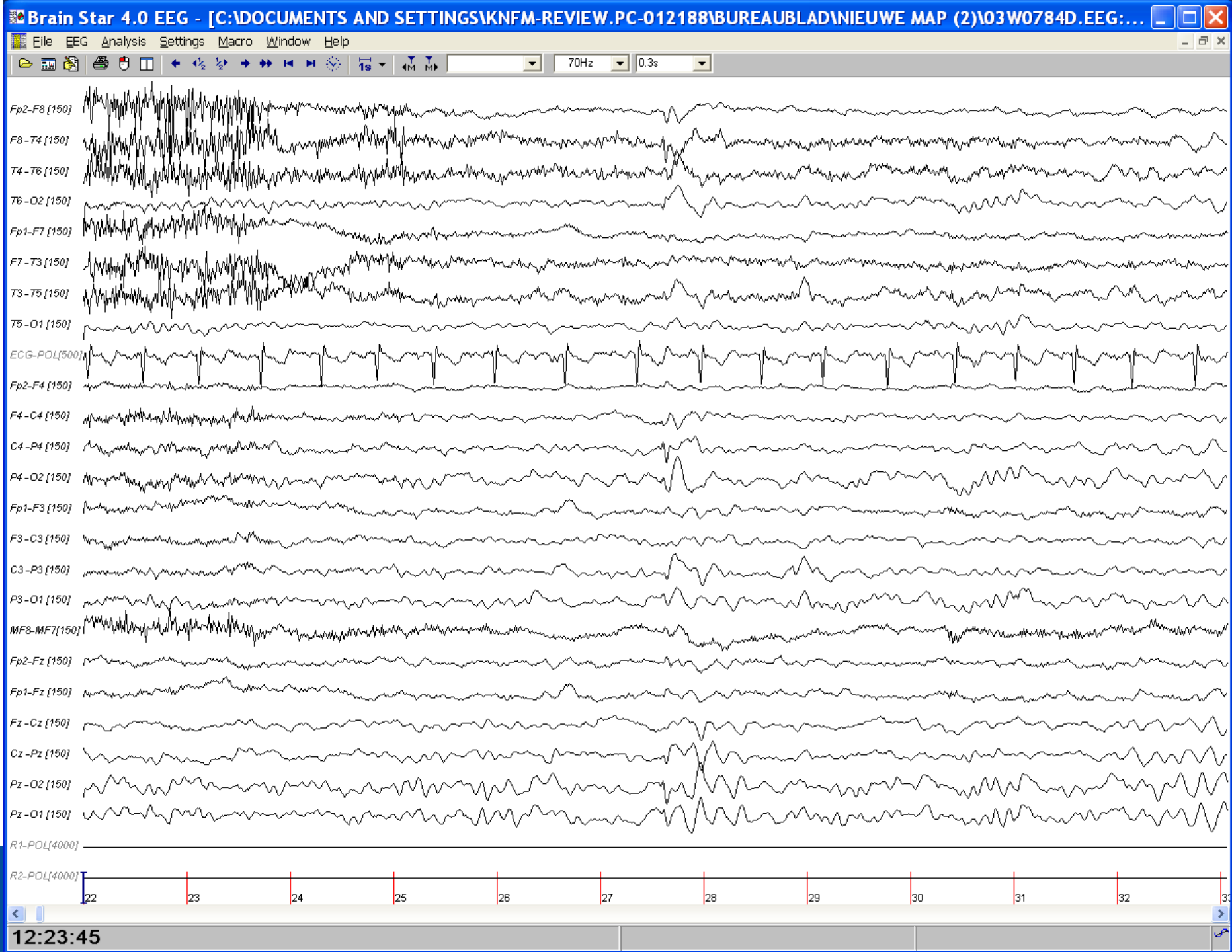
status epilepticus in children

convulsive SE

invisible SE

nonconvulsive SE
ESES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File EEG Analysis Settings Macro Window Help
70Hz
0.3s
Fp2-F8 [150]
F8-T4 [150]
T4-T6 [150]
T6-O2 [150]
Fp1-F7 [150]
F7-T3 [150]
T3-T5 [150]
T5-O1 [150]
ECG-POL[500]
Fp2-F4 [150]
F4-C4 [150]
C4-P4 [150]
P4-O2 [150]
Fp1-F3 [150]
F3-C3 [150]
C3-P3 [150]
P3-O1 [150]
MF8-MF7[150]
Fp2-Fz [150]
Fp1-Fz [150]
Fz-Cz [150]
Cz-Pz [150]
Pz-O2 [150]
Pz-O1 [150]
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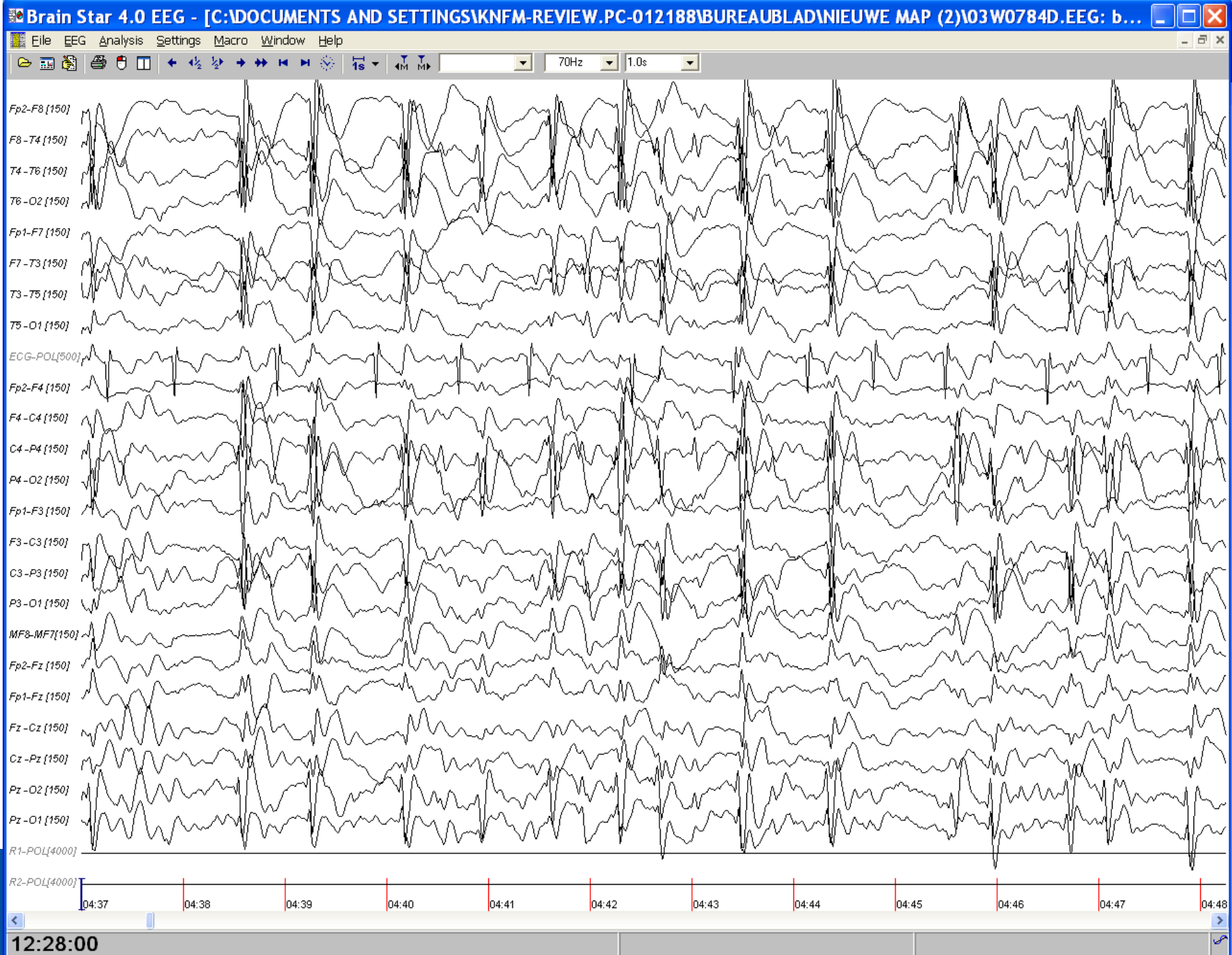
12:23:45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File EEG Analysis Settings Macro Window Help
70Hz
1.0s
Fp2-F8 [150]
F8-T4 [150]
T4-T6 [150]
T6-O2 [150]
Fp1-F7 [150]
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T3-T5 [150]
T5-O1 [150]
ECG-POL[500]
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F4-C4 [150]
C4-P4 [150]
P4-O2 [150]
Fp1-F3 [150]
F3-C3 [150]
C3-P3 [150]
P3-O1 [150]
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Fz-Cz [150]
Cz-Pz [150]
Pz-O2 [150]
Pz-O1 [150]
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R2-POL[4000]
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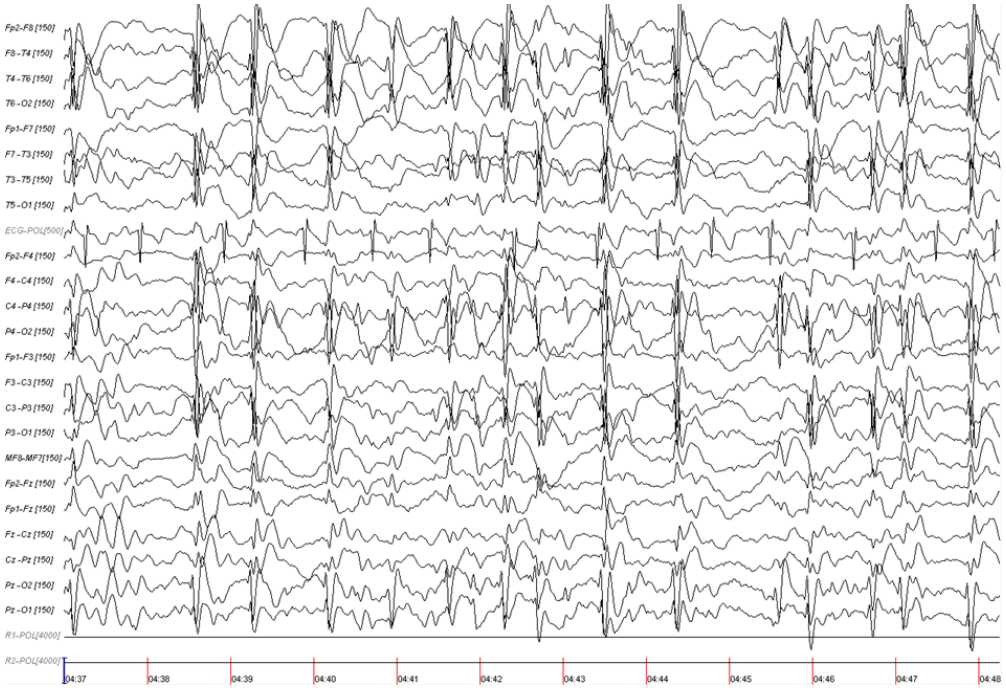
04:38
04:39
04:40
04:41
04:42
04:43
04:44
04:45
04:46
04:47
04:48
12:28:00

electrical status epilepticus in sleep

epileptic encephalopathy, *acquired* deterioration in:

- cognition
- language
- behavior



accompanied by ESES on EEG, **with or without seizures**

epilepsy syndromes with ESES

Landau-Kleffner syndrome (LKS)

epileptic encephalopathy with continuous spike-and-waves during slow wave sleep (CSWS)

atypical ‘benign’ focal epilepsy of childhood (ABFEC)

etiology

- structural
- genetic (GRIN2a, …)
- unknown

inflammation?

ESES

sleep induced epileptiform activity

> 85% non-REM sleep

absence of physiological sleep activity

age 1-14 years, median 4-8 y

impact of epileptic discharges

transient inhibition of brain networks

- functionally inappropriate synaptic cortico-cortical arrangements in a critical period for development of associative cortices

long lasting effects on brain function and plasticity

- interference with the sleep-dependent physiological processes of neuronal plasticity supporting memory consolidation for recently learned information

prognosis

- ESES resolves spontaneously during puberty
- cognitive sequelae often remain

→ early adequate treatment is mandatory

meta-analysis

- 114 papers: cognitive/EEG outcome of ESES
- authors contacted for additional patient data
- 575 patients (282 treated consecutively)

treatment	any effect (cognition and/or EEG)
AEDs	34%
Benzodiazepines	59%
Steroids	75%
Surgery	93%
Other	58%
Total	50%

van den Munckhof, Jansen et al. submitted

meta-analysis

- treatment with steroids and surgery (in suitable candidates) seems most effective
- benzodiazepines are an appropriate alternative
- AED are less effective

- pre-existent developmental delay is related to poorer treatment response

van den Munckhof, Jansen et al. submitted

meta-analysis

however:

- mostly small, retrospective studies
- publication bias
- no quantified outcome measures
- side-effects not included in analysis

a Randomized Controlled Trial is urgently needed!

Randomized European trial of Steroids versus Clobazam Usage for Encephalopathy with ESES

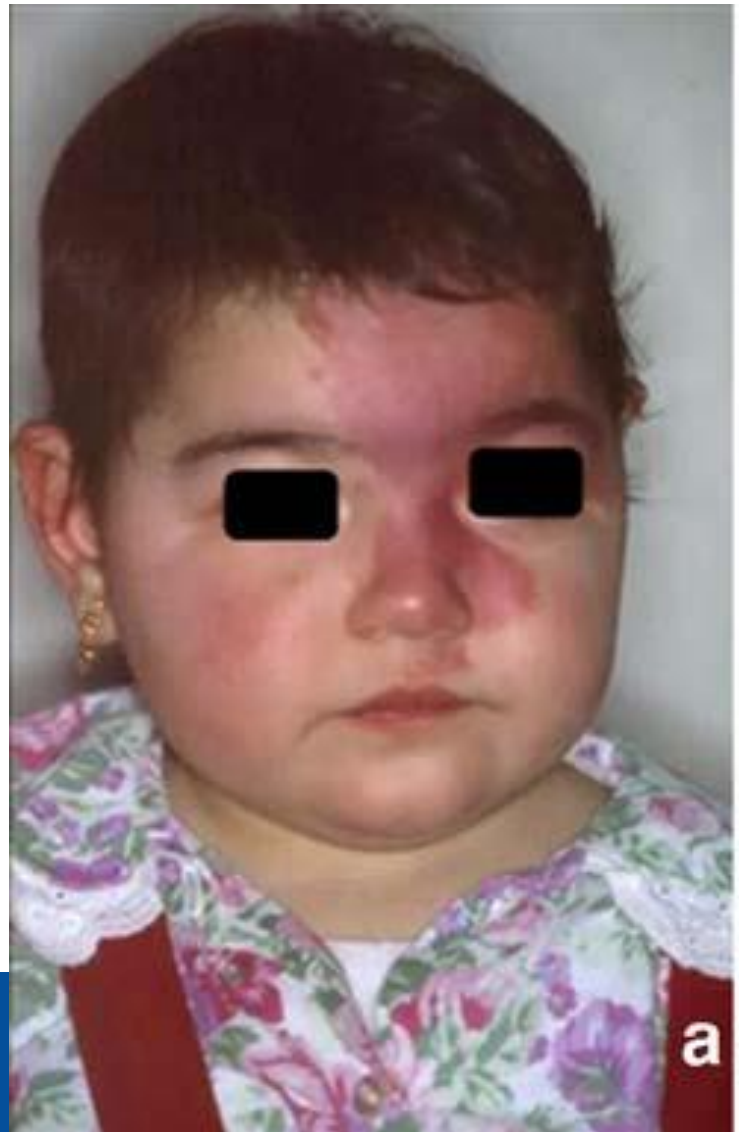
Epilepsiefonds
De Macht van het Kleine

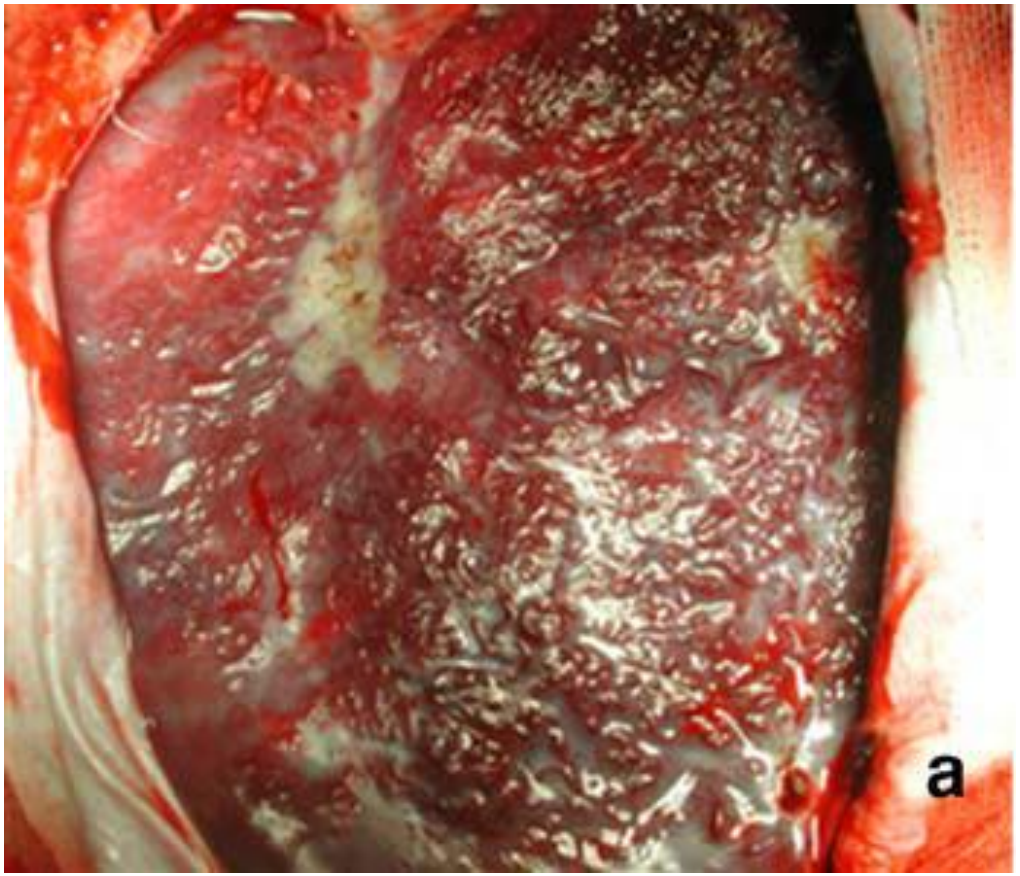
Brain Center
Rudolf Magnus

status epilepticus in children

misleading EEG in SE

Sturge-Weber syndrome





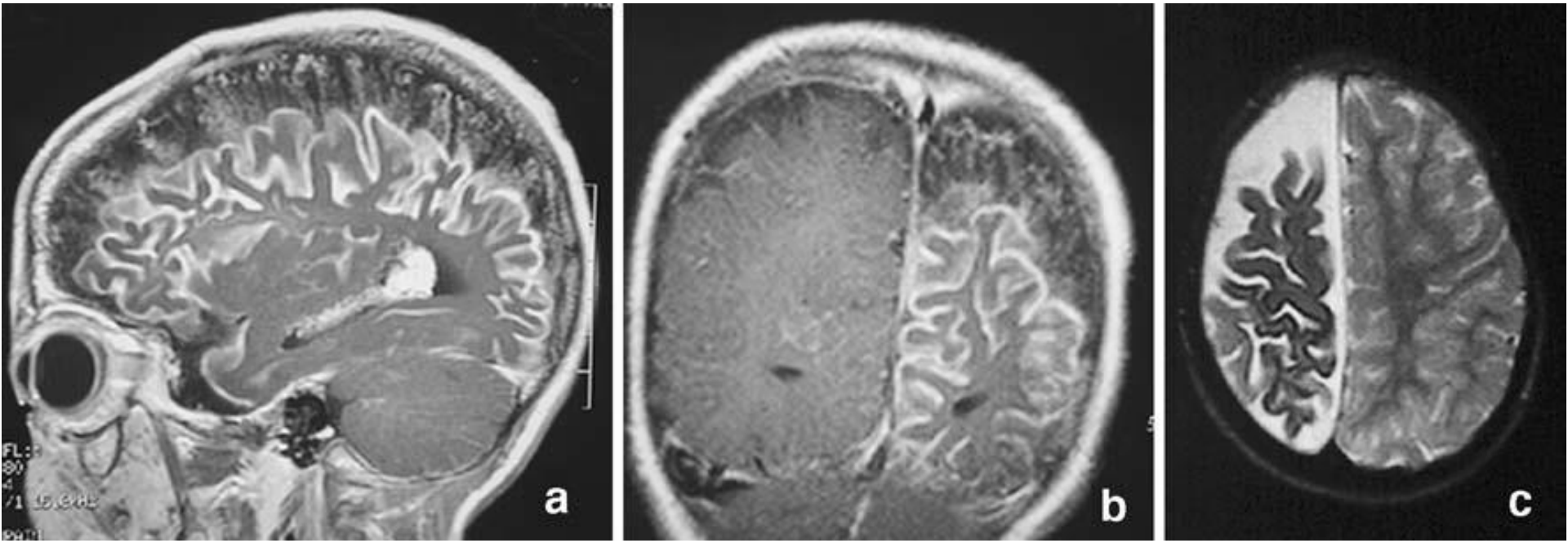
Di Rocco et al. CNS 2006

Sturge-Weber syndrome

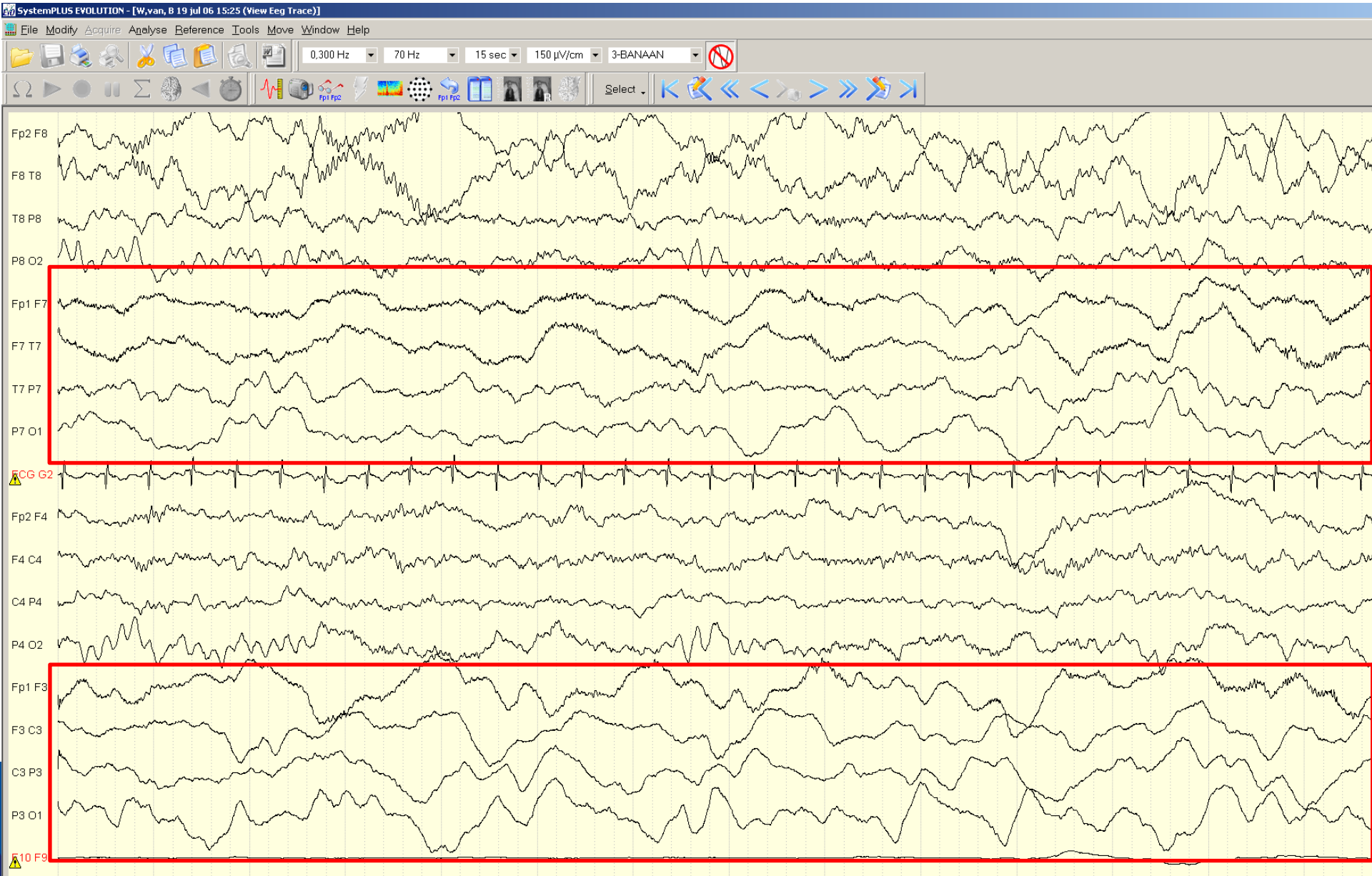
neurocutaneous syndrome
port-wine nevi n. V, pial angioma, glaucoma

MR: superficial cortical/meningeal enhancement
enlarged choroid plexus
venous congestion, hydrocephalus
progressive cerebral atrophy
progressive cortical calcifications
early in life: WM low T2 (“advanced myelination”)

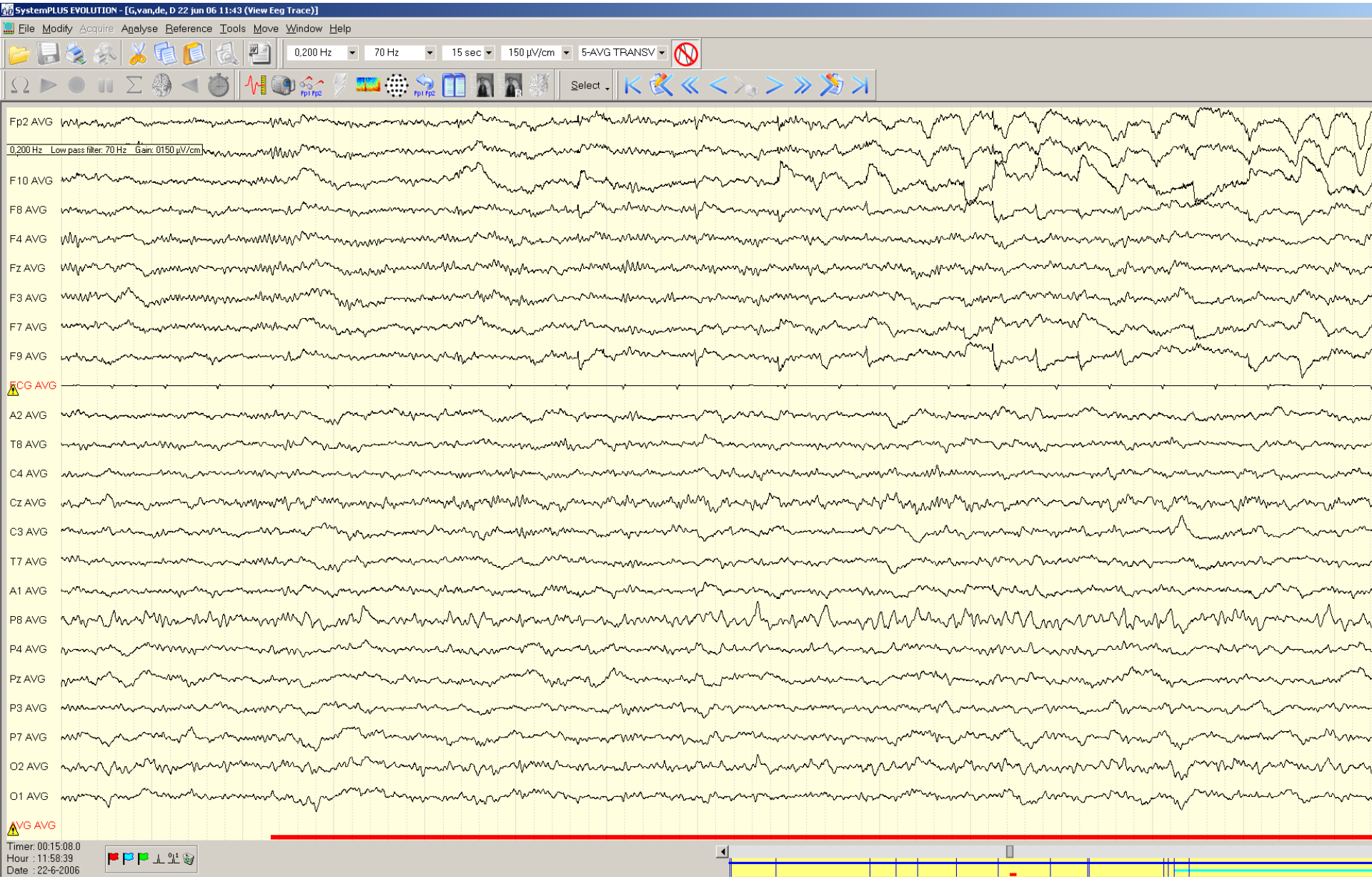
Sturge-Weber syndrome



Sturge-Weber syndrome L hemisphere



EPC


SystemPLUS EVOLUTION - [G,van,de, D 22 jun 06 11:43 (View Eeg Trace)]
File Modify Acquire Analyse Reference Tools Move Window Help
0,200 Hz
70 Hz
15 sec
150 µV/cm
5-AVG TRANSV
Select
Fp2 AVG
0,200 Hz Low pass filter: 70 Hz Gain: 0150 µV/cm
F10 AVG
F8 AVG
F4 AVG
Fz AVG
F3 AVG
F7 AVG
F9 AVG
ECG AVG
A2 AVG
T8 AVG
C4 AVG
Cz AVG
C3 AVG
T7 AVG
A1 AVG
P8 AVG
P4 AVG
Pz AVG
P3 AVG
P7 AVG
O2 AVG
O1 AVG
AVG AVG
Timer: 00:15:08.0
Hour : 11:58:39
Date : 22-6-2006

Epilepsia Partialis Continua

“spontaneous regular or irregular clonic muscular twitching affecting a limited part of the body, sometimes aggravated by action or sensory stimuli, occurring for a minimum of one hour, and recurring at intervals of no more than ten seconds”

Epilepsia Partialis Continua

Rasmussen encefalitis
POLG1 / Alpers
Sturge-Weber
MELAS
FCD
stroke
brain injury
DNKHC
tumor
meningo-encephalitis
CJD
Hashimoto

inflammatory	32%
tumor	19%
vascular	14%
traumatic	16%
other	19%

POLG

Tzoulis, Engelsen et al. Brain 2006, 2008

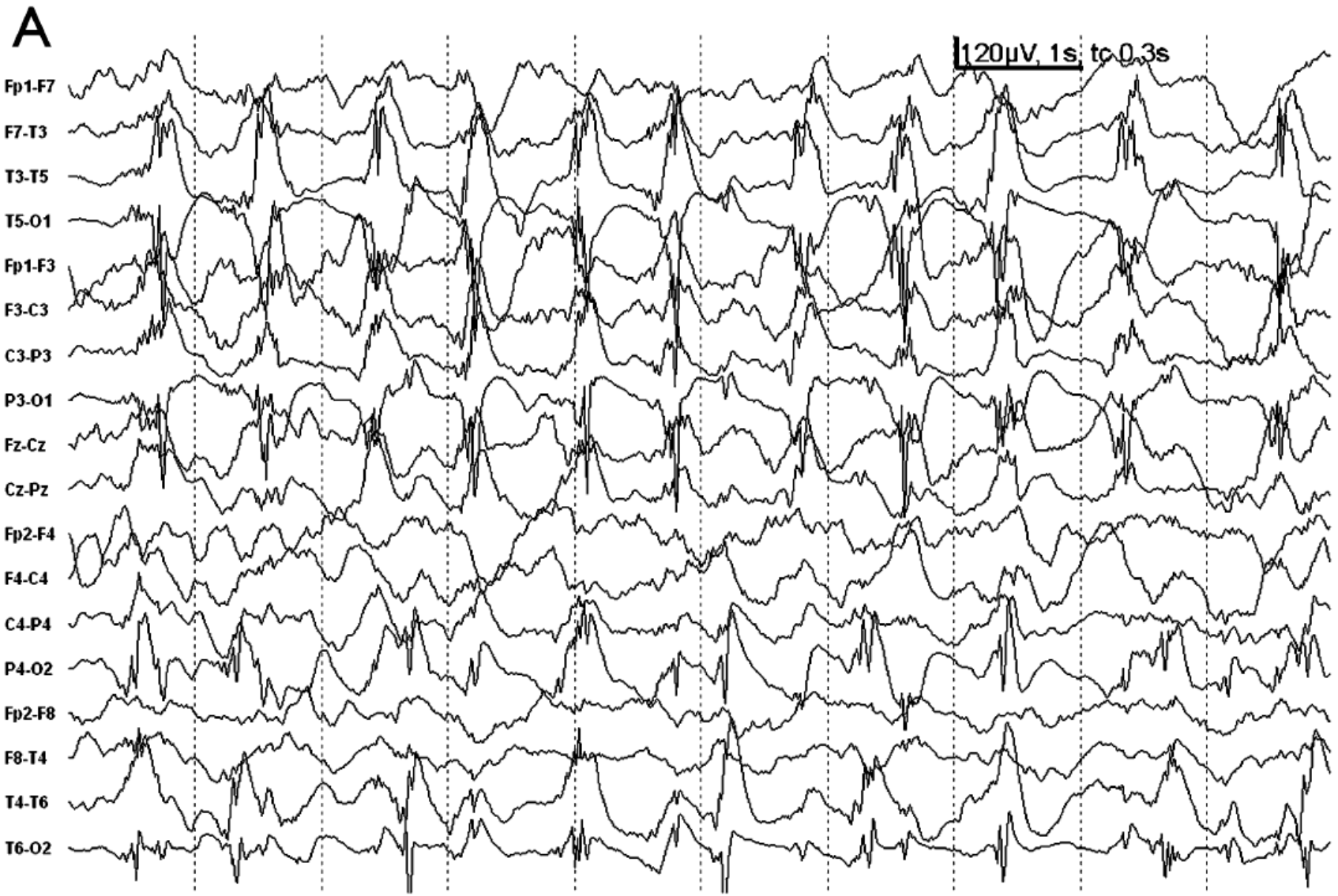
polymerase gamma mutations, AR (A467T W748S)
replication mtDNA

broad phenotype

Alpers syndrome, developmental regression
(VPA-induced) hepatic failure
occipital epilepsy, refractory SE, EPC, shifting foci
ataxia, polyneuropathy, ophthalmoplegia, myoclonus

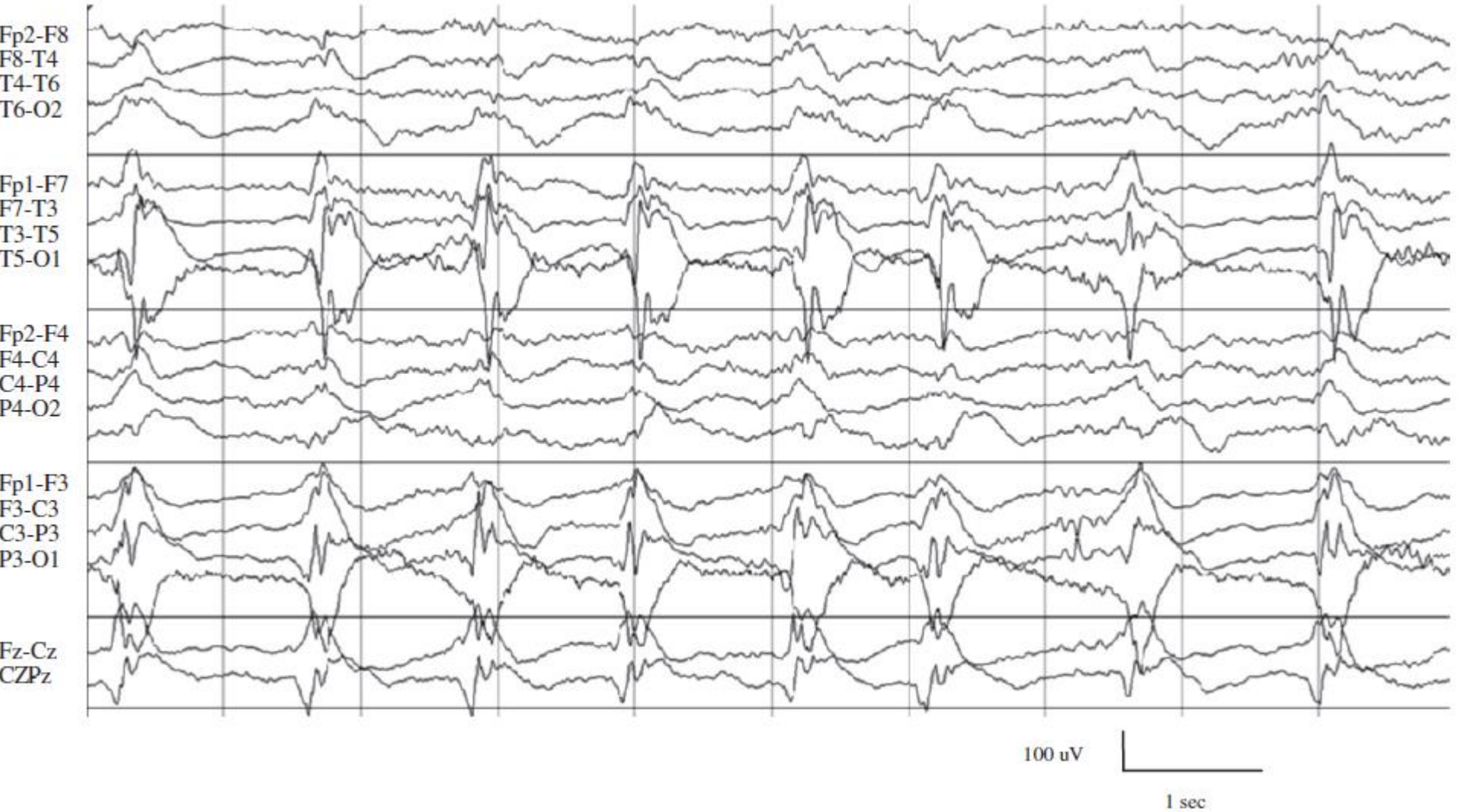
POLG – Alpers: RHADS

Wolf et al. Epilepsia 2009



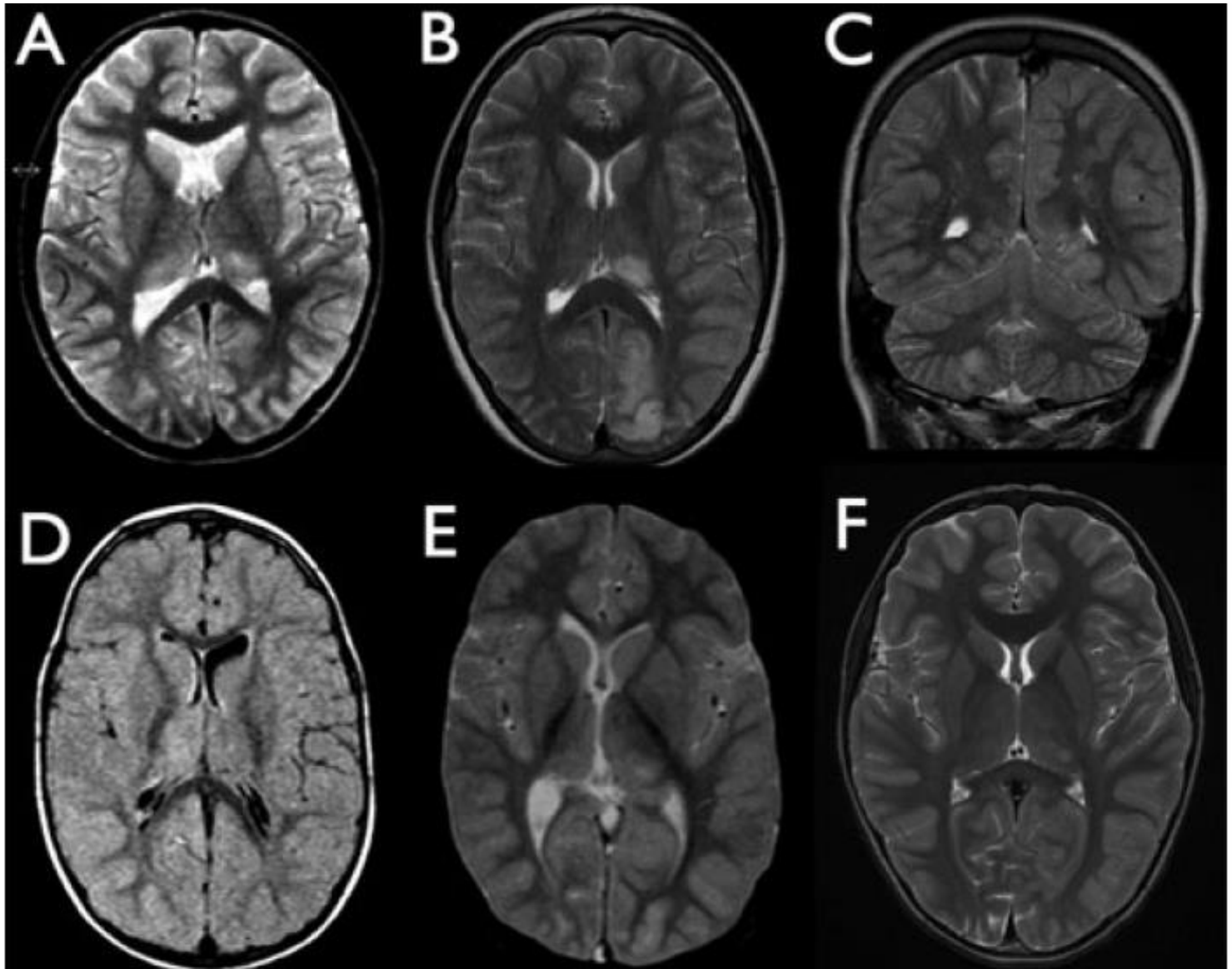
POLG – Alpers: RHADS

McCoy et al. Eur J Ped Neurol 2011

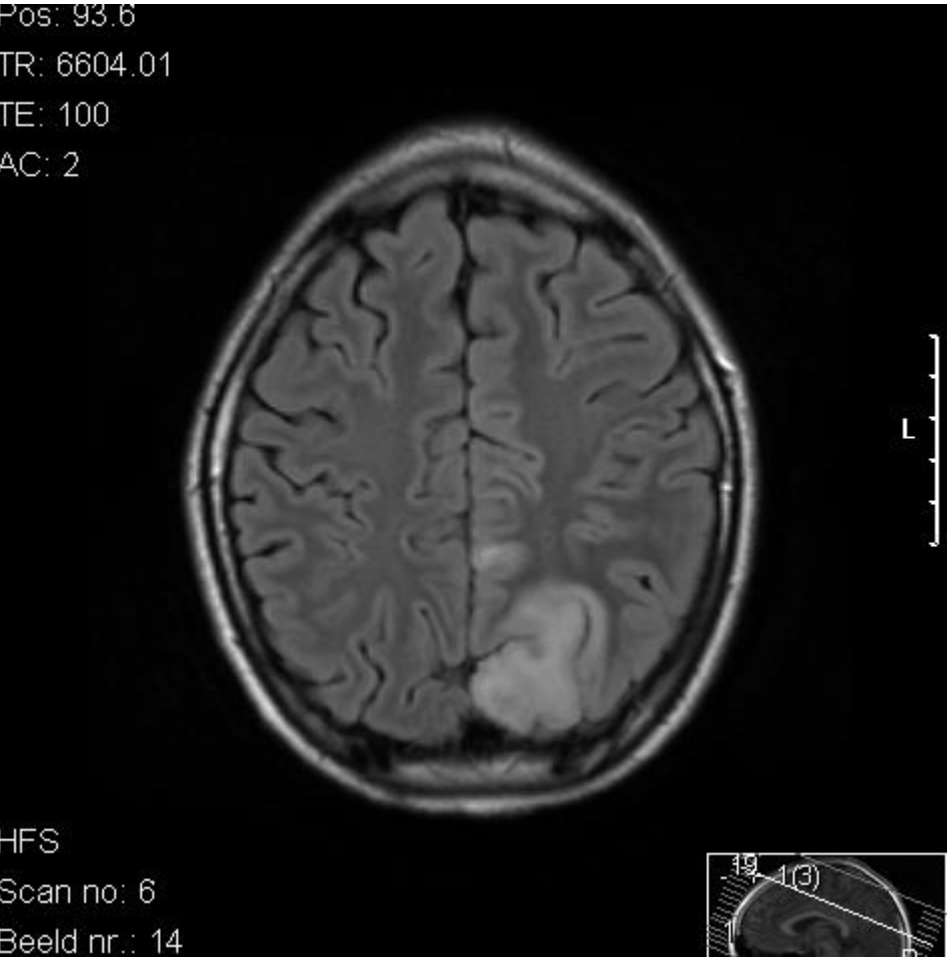


POLG - MRI

Wolf et al. Epilepsia 2009



T2-FLAIR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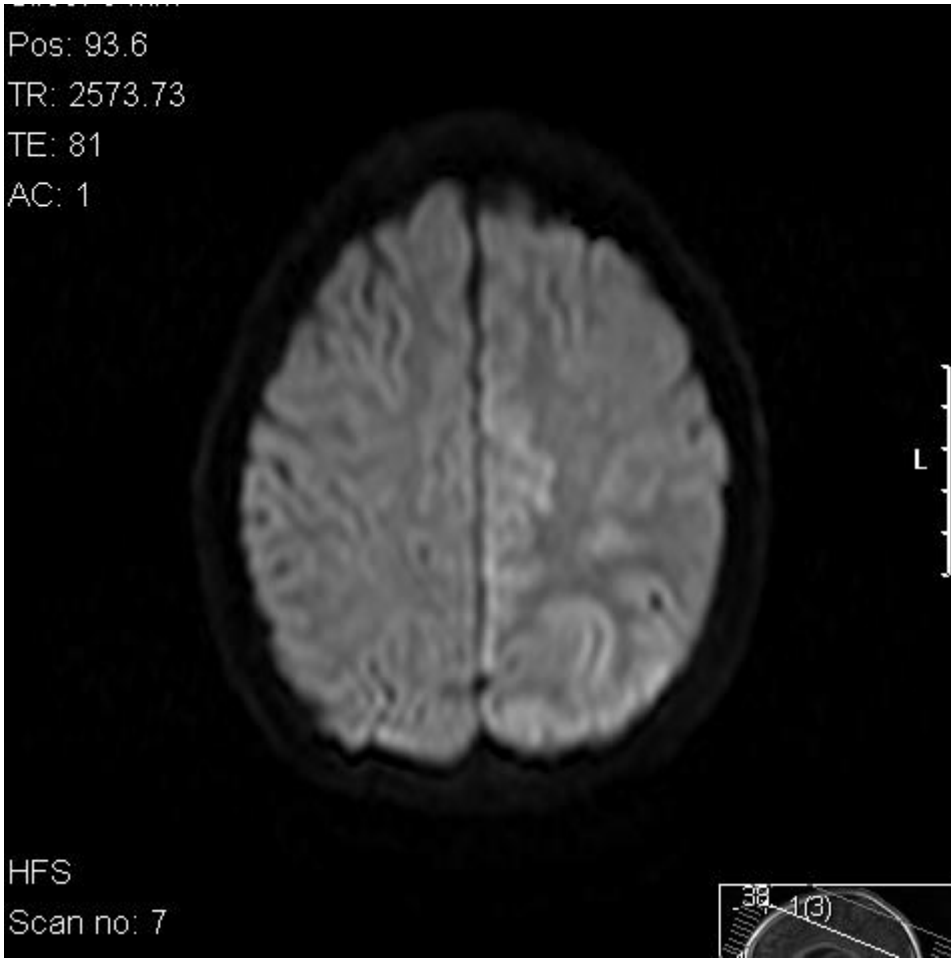
L
HFS
Scan no: 6
Beeld nr.: 14

DWI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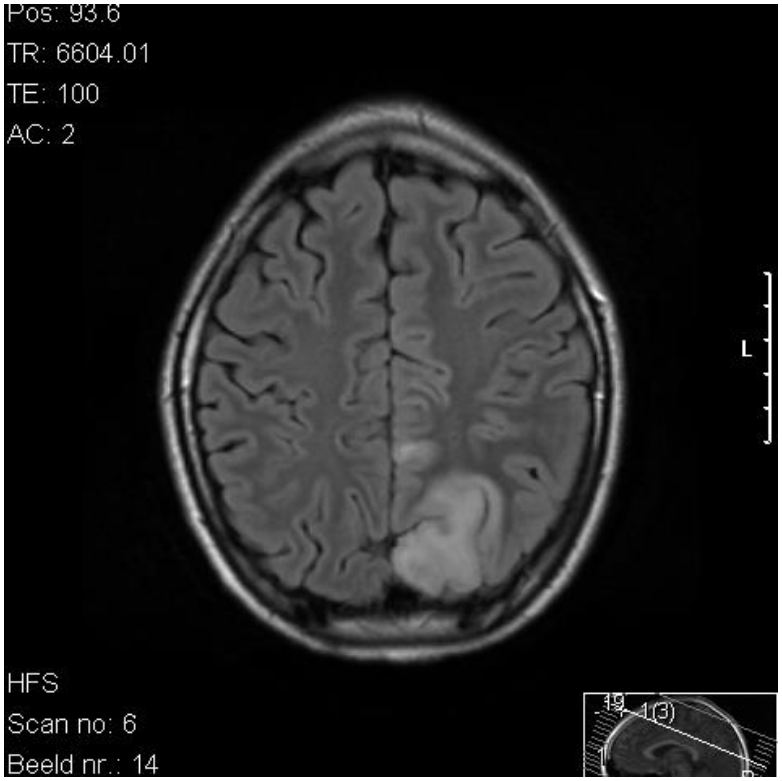
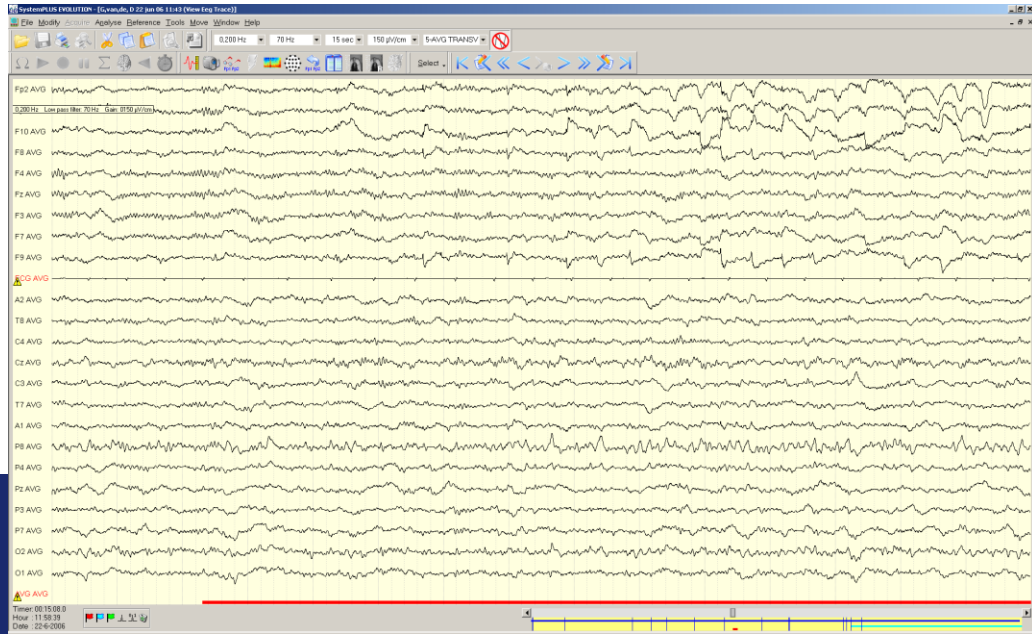
TE: 81
AC: 1
L
HFS
Scan no: 7

EPC – EEG invisible

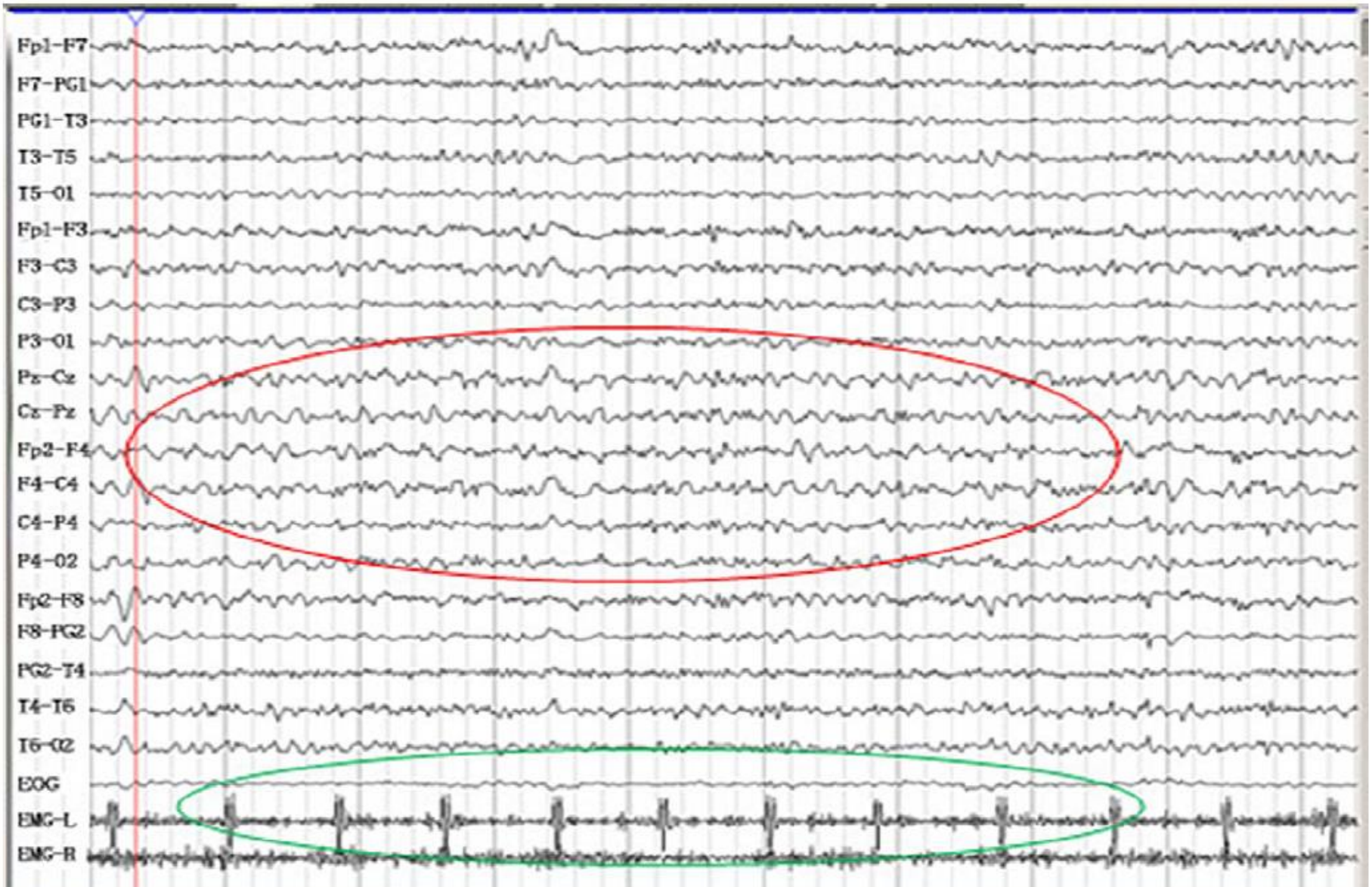




MRI may help!

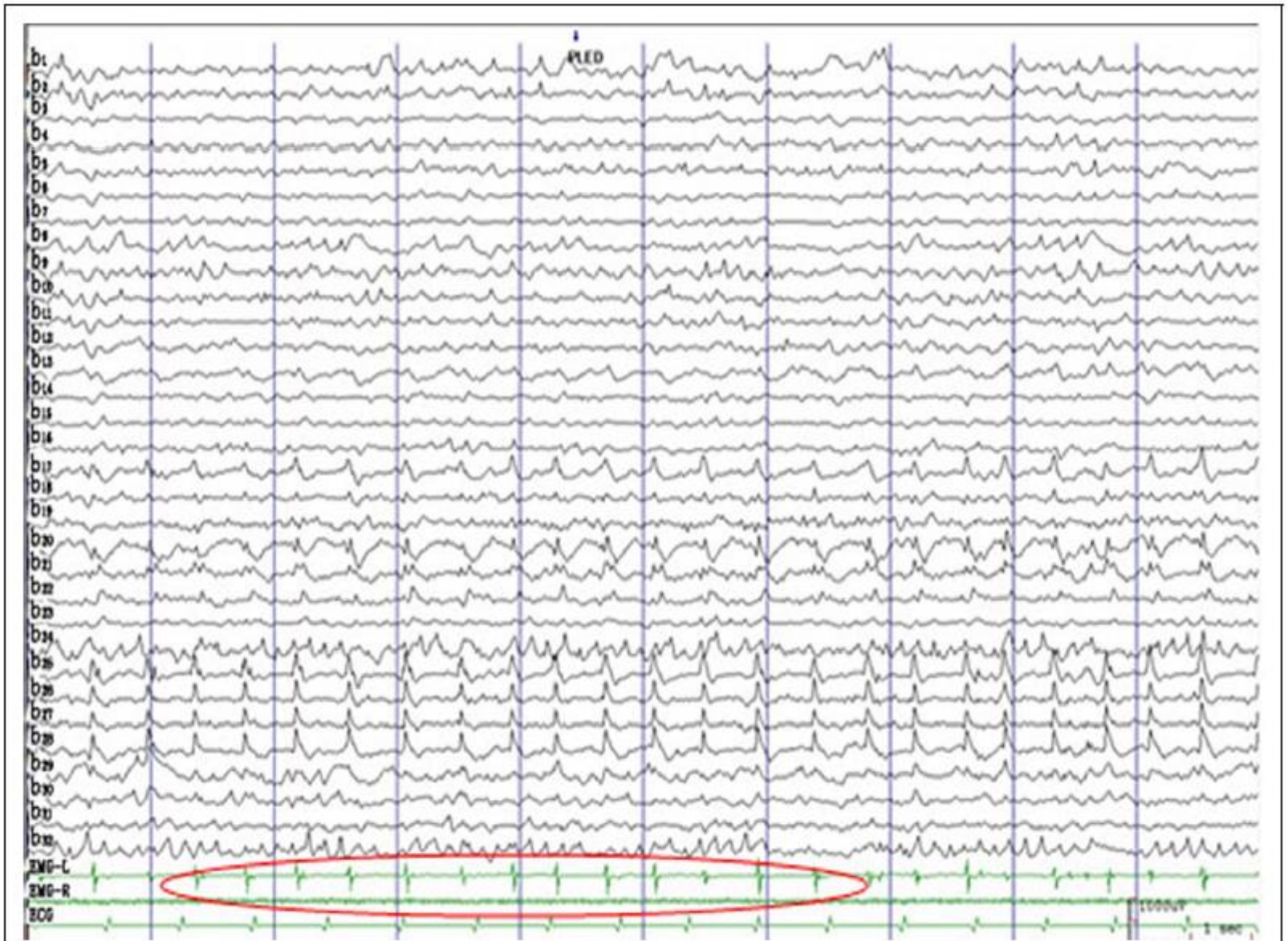
EPC – normal EEG, SE on iEEG

Lv et al. Clin EEG Neurosci 2013



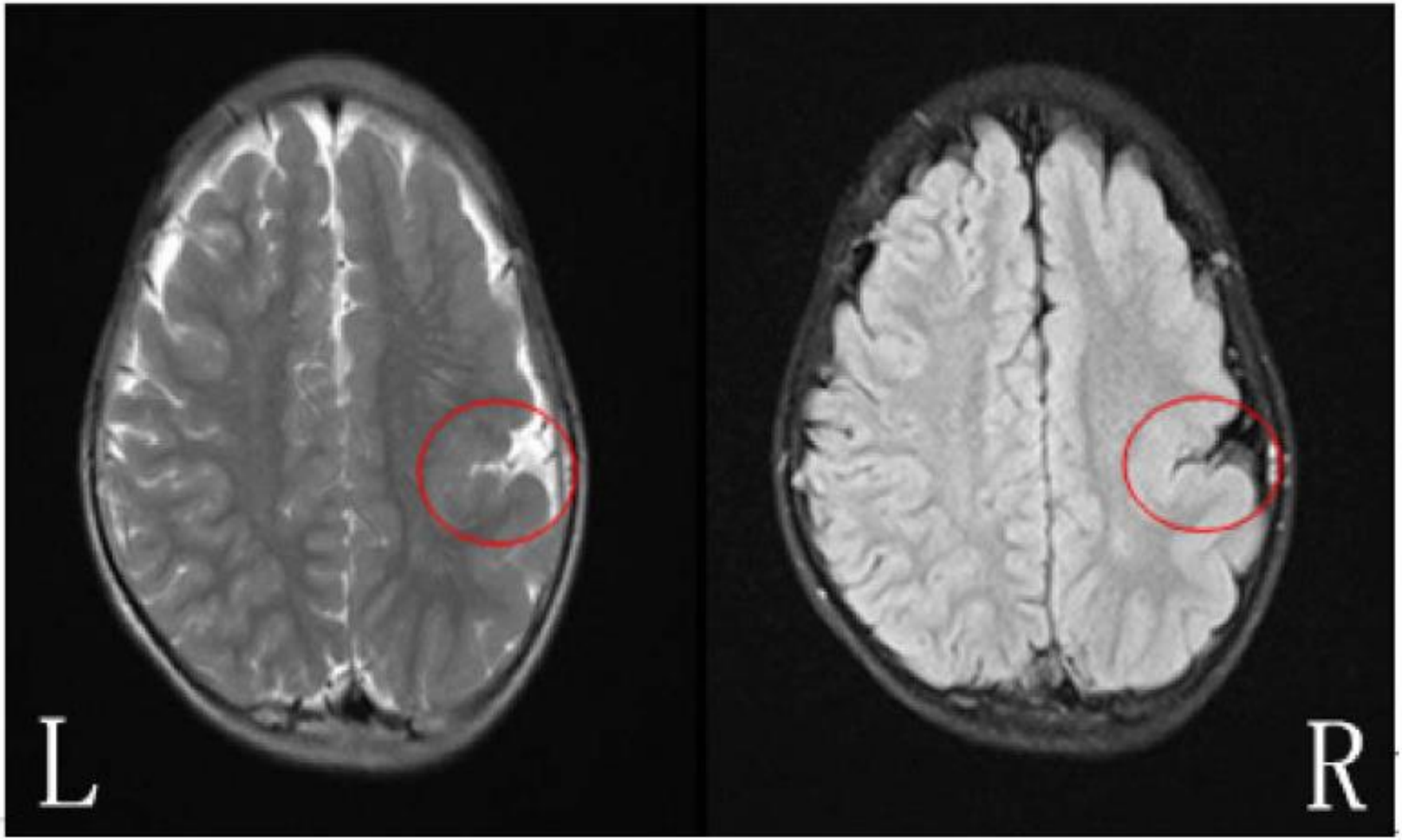
EPC – normal EEG, SE on iEEG

Lv et al. Clin EEG Neurosci 2013



EPC – normal EEG, SE on iEEG

Lv et al. Clin EEG Neurosci 2013



status epilepticus in children

epileptic encephalopathies

different shades of grey in SE

“furthermore, what appears to one interpreter as status epilepticus, is not to another reader, reflecting the “art” of EEG interpretation”

“seizures and epilepsy syndromes have undergone an evolution that has moved beyond a classification of focal or generalized conditions into a syndromic approach”

Sutter and Kaplan, Epilepsia 2012

criteria for NCSE in early life

- clear clinical change in behavior (cognition, memory, arousal, ataxia, motor learning/behavior) >30 min

- confirmation (clinical/neuropsych exam)

- (virtually) continuous paroxysmal episodes on EEG

- no continuous major seizures (tonic or clonic)

Sutter and Kaplan, Epilepsia 2012

epileptic encephalopathies in early life

“a condition where the epileptic activity itself may contribute to the severe neurological and cognitive impairment seen in severe epilepsy, over and above that which would be expected from the underlying pathology alone”

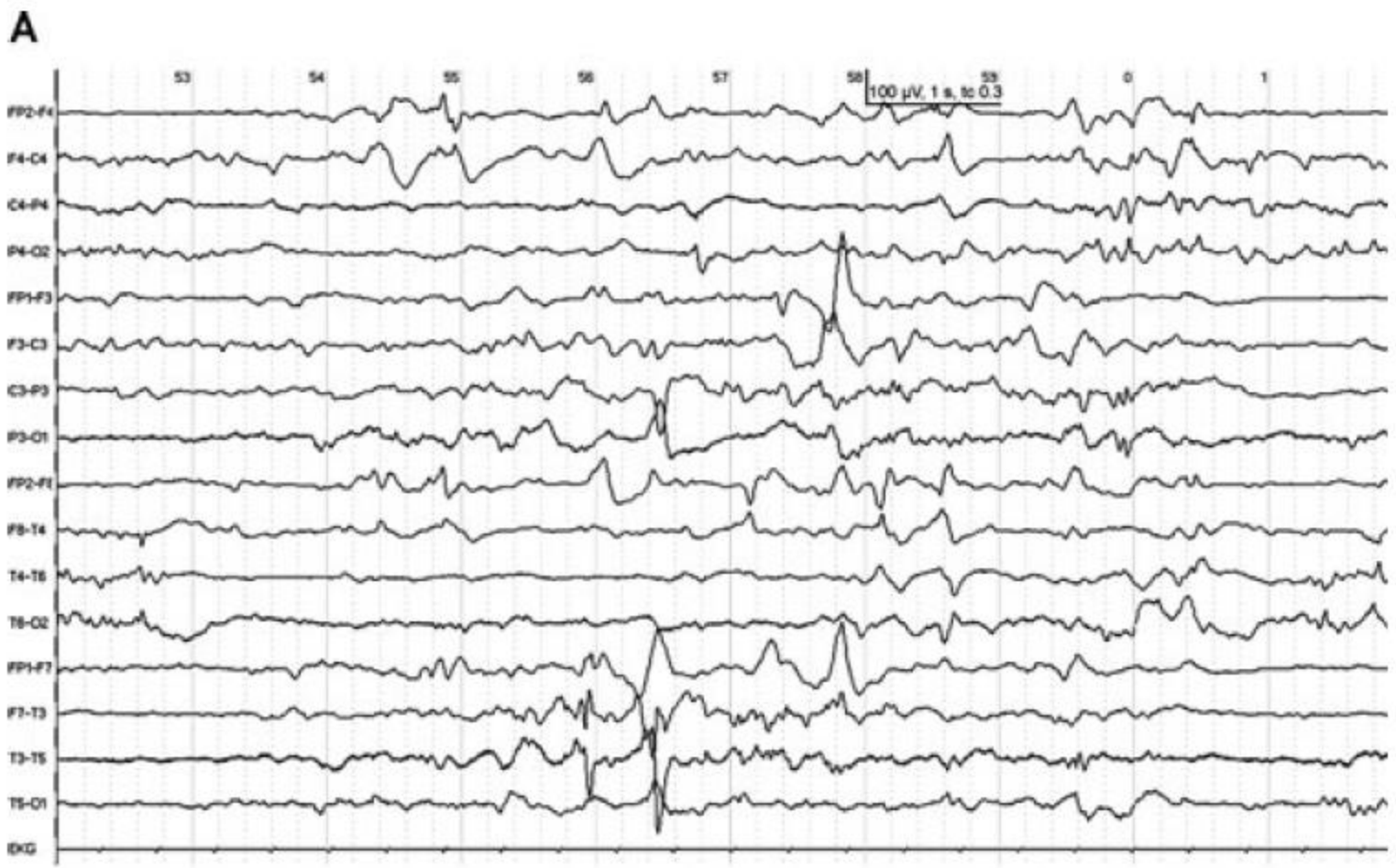
Berg et al. ILAE Epilepsia 2010
McTague and Cross, CNS drugs 2013

continous “interictal” epileptiform activity

may be reversible

may correlate with neurodevelopmental progress

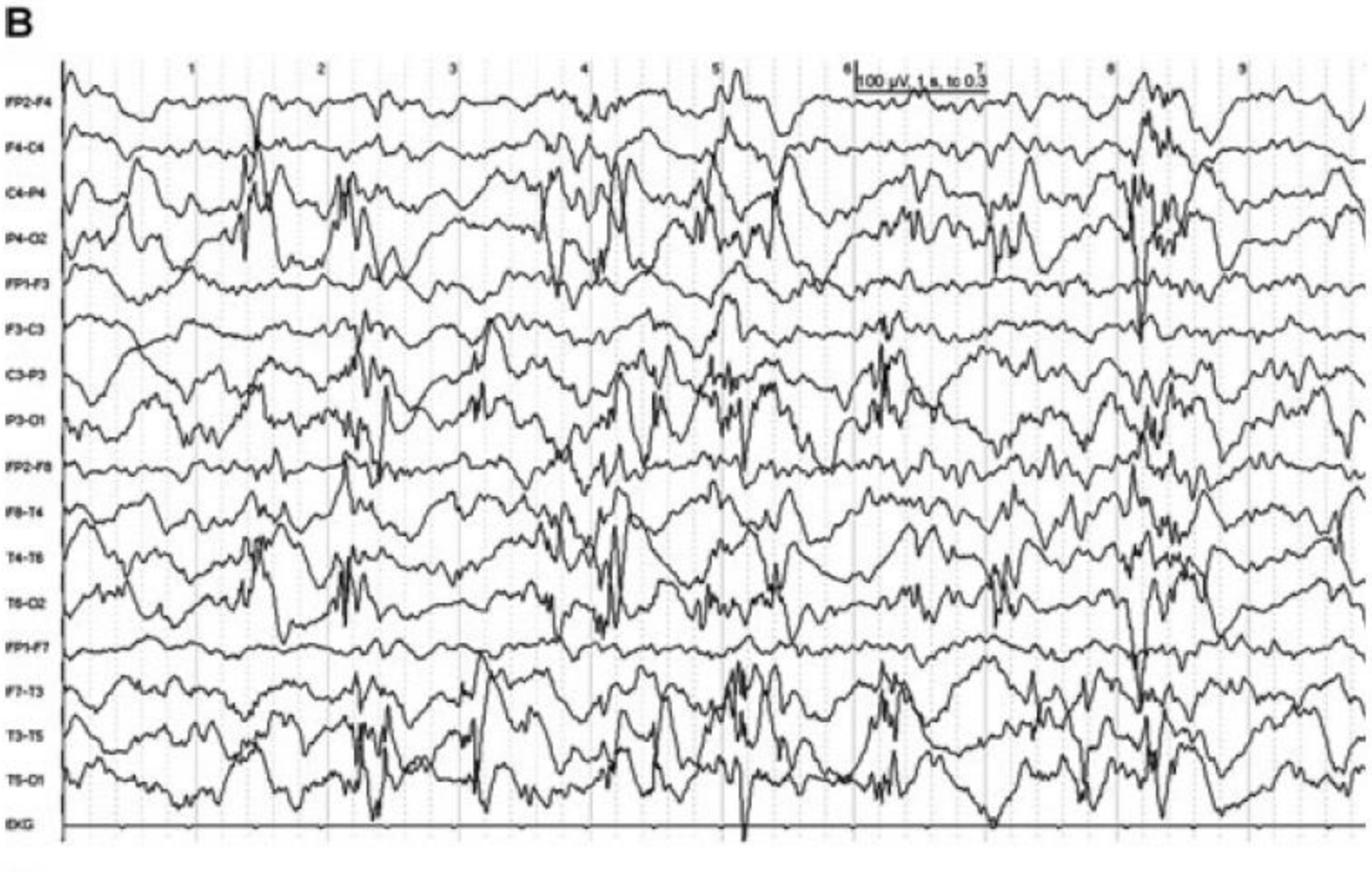
epileptic encephalopathies in early life - WS



"silent state"

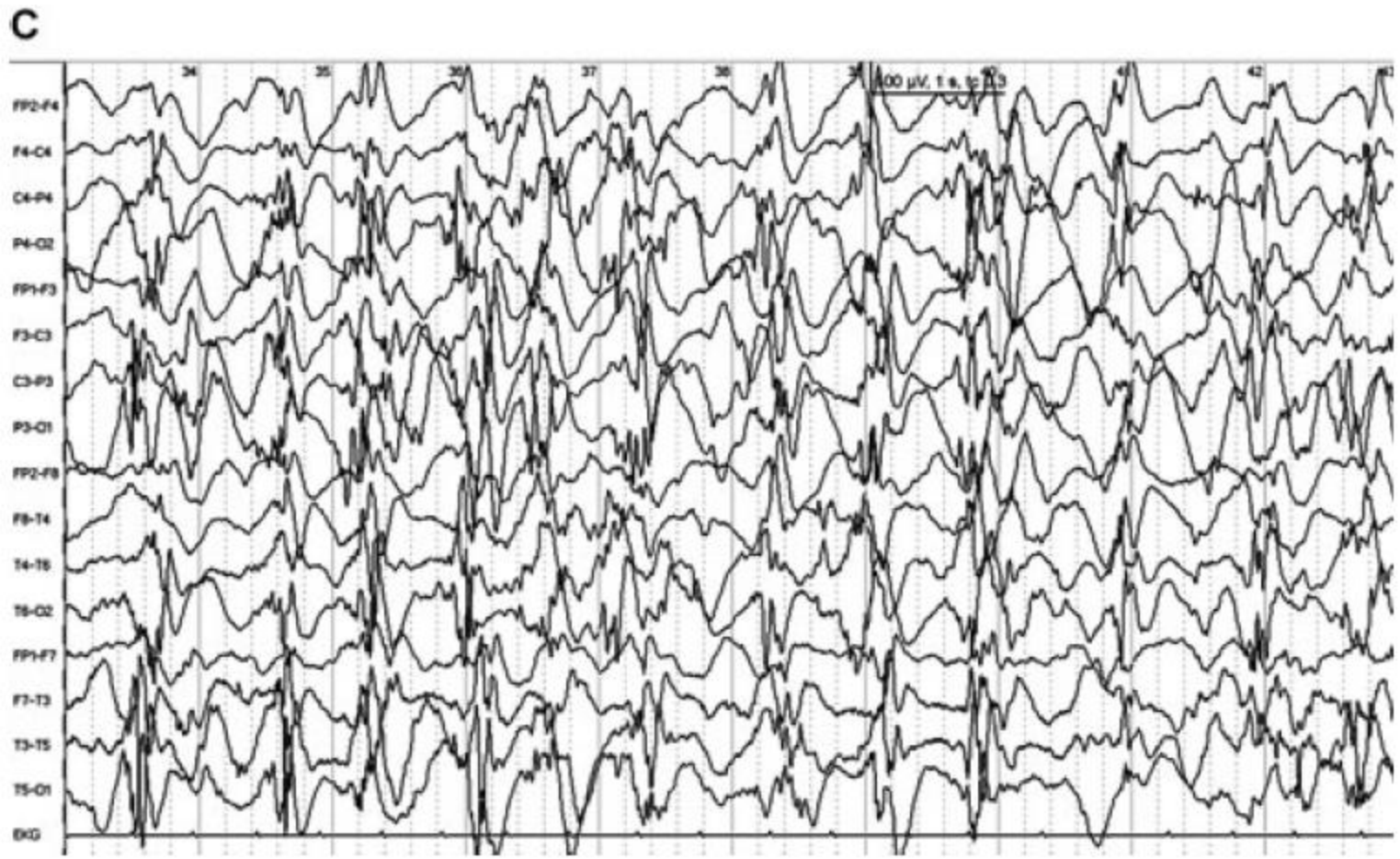
Philippi et al. Epilepsia 2008

epileptic encephalopathies in early life - WS



"mental deterioration" modified hypsarrhytmia Philippi et al. Epilepsia 2008

epileptic encephalopathies in early life - WS



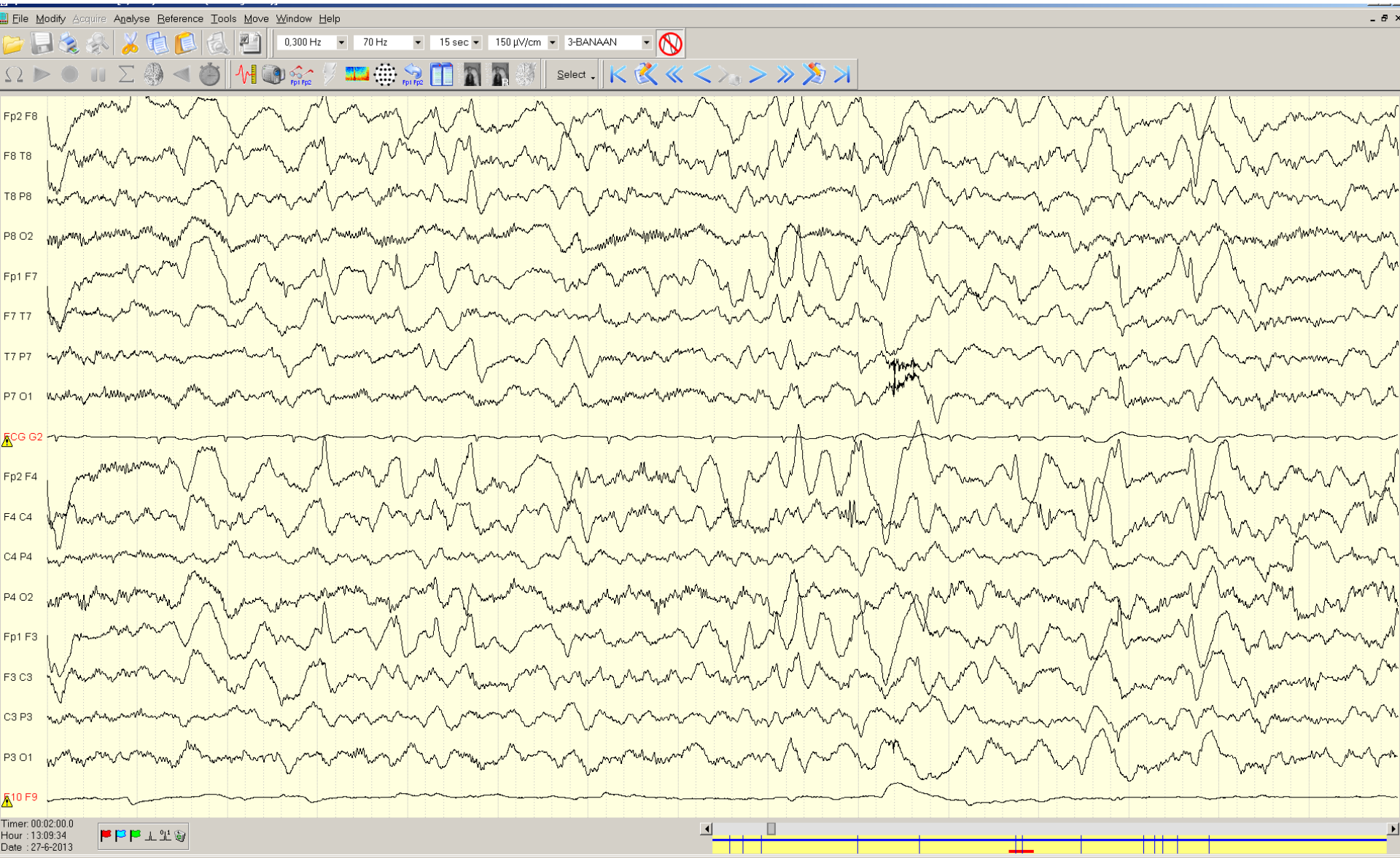
"severe mental deterioration" hypsarrhythmia Philippi et al. Epilepsia 2008

criteria for NCSE in early life – West syndrome

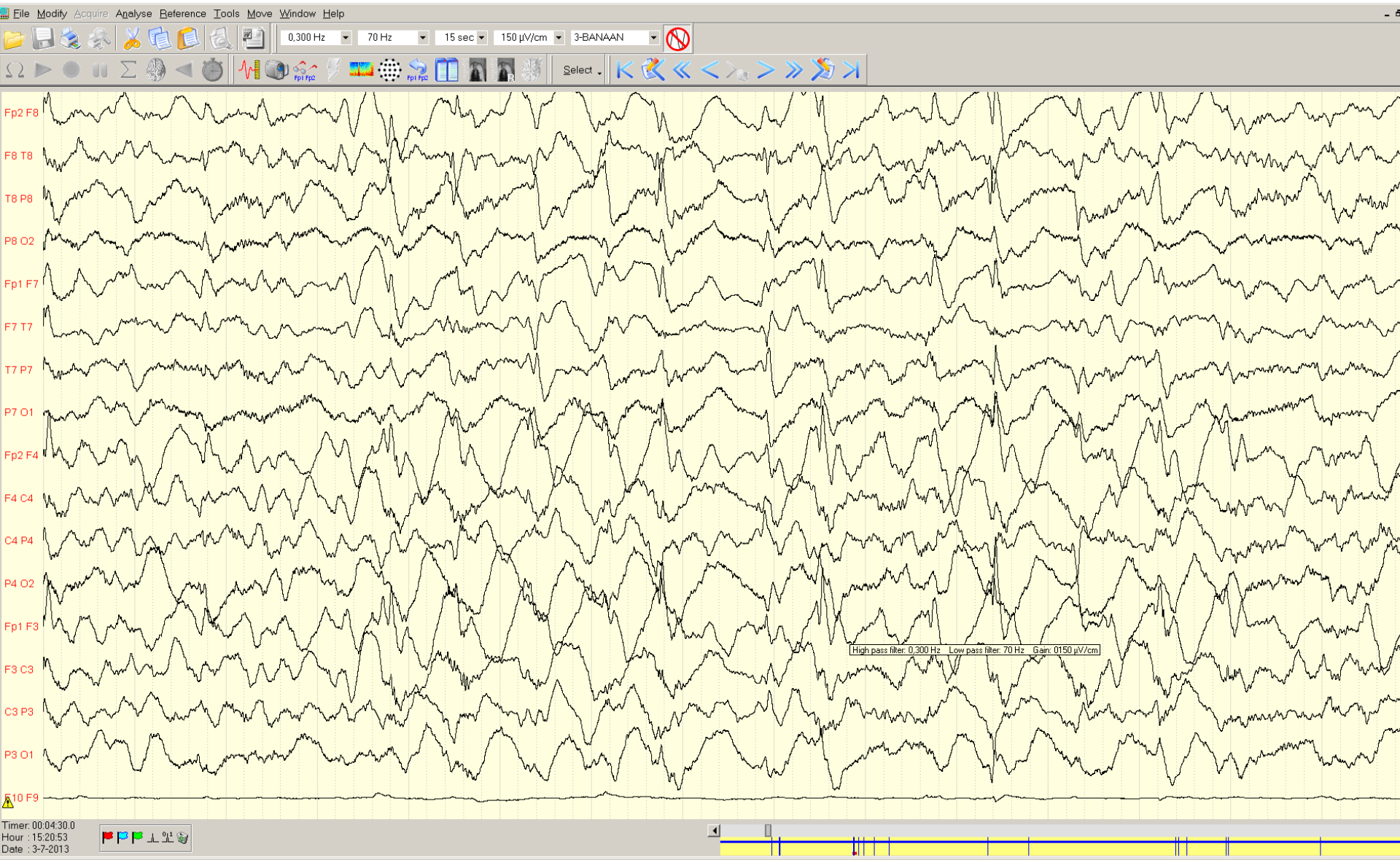
- clear clinical change in behavior (cognition, memory, arousal, ataxia, motor learning/behavior), >30 min
- confirmation (clinical/neuropsych exam)
- (virtually) continuous paroxysmal episodes on EEG
- no continuous major seizures (tonic or clonic)

Sutter and Kaplan, Epilepsia 2012

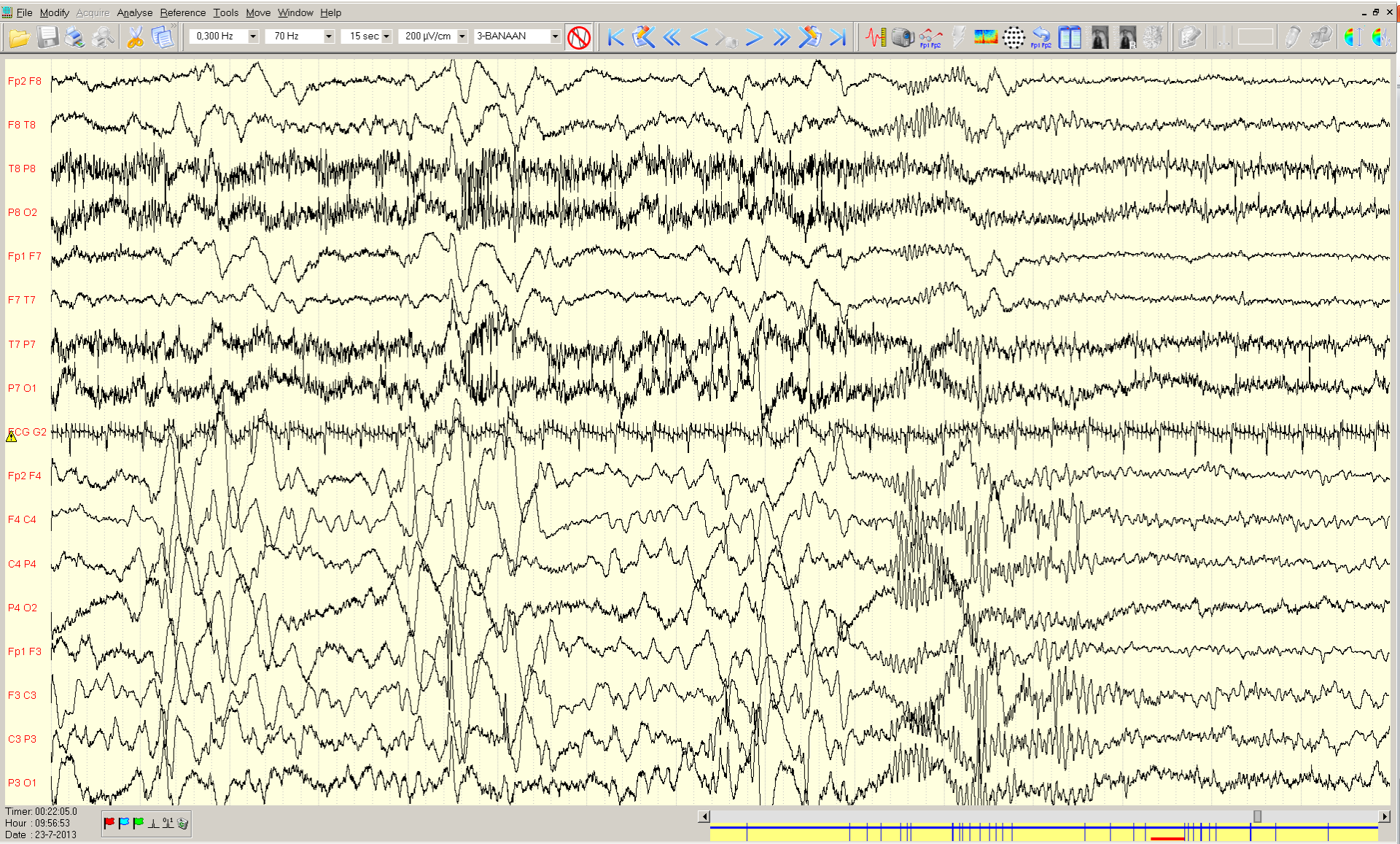
epileptic encephalopathies in early life - LGS



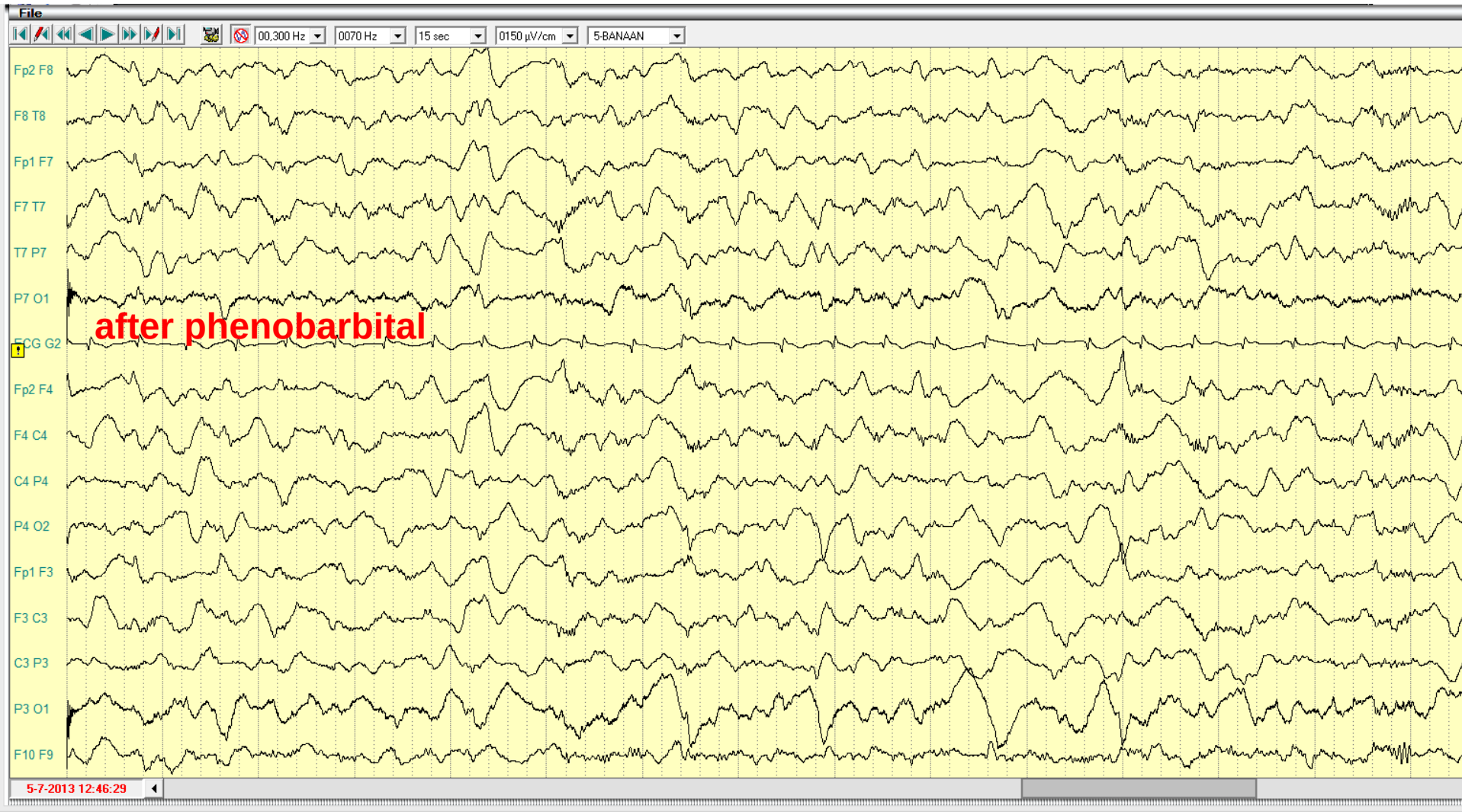
epileptic encephalopathies in early life - LGS



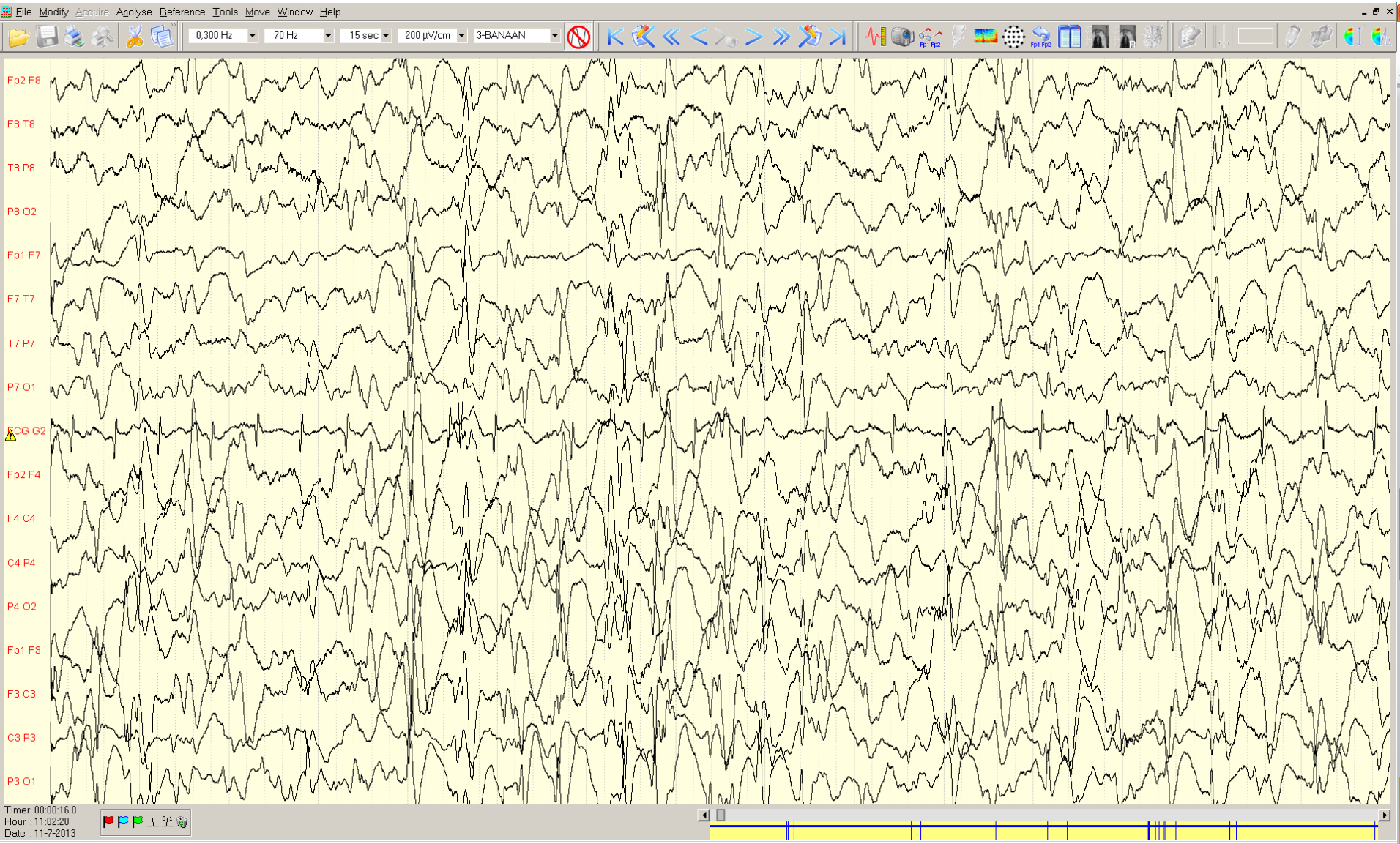
epileptic encephalopathies in early life - LGS



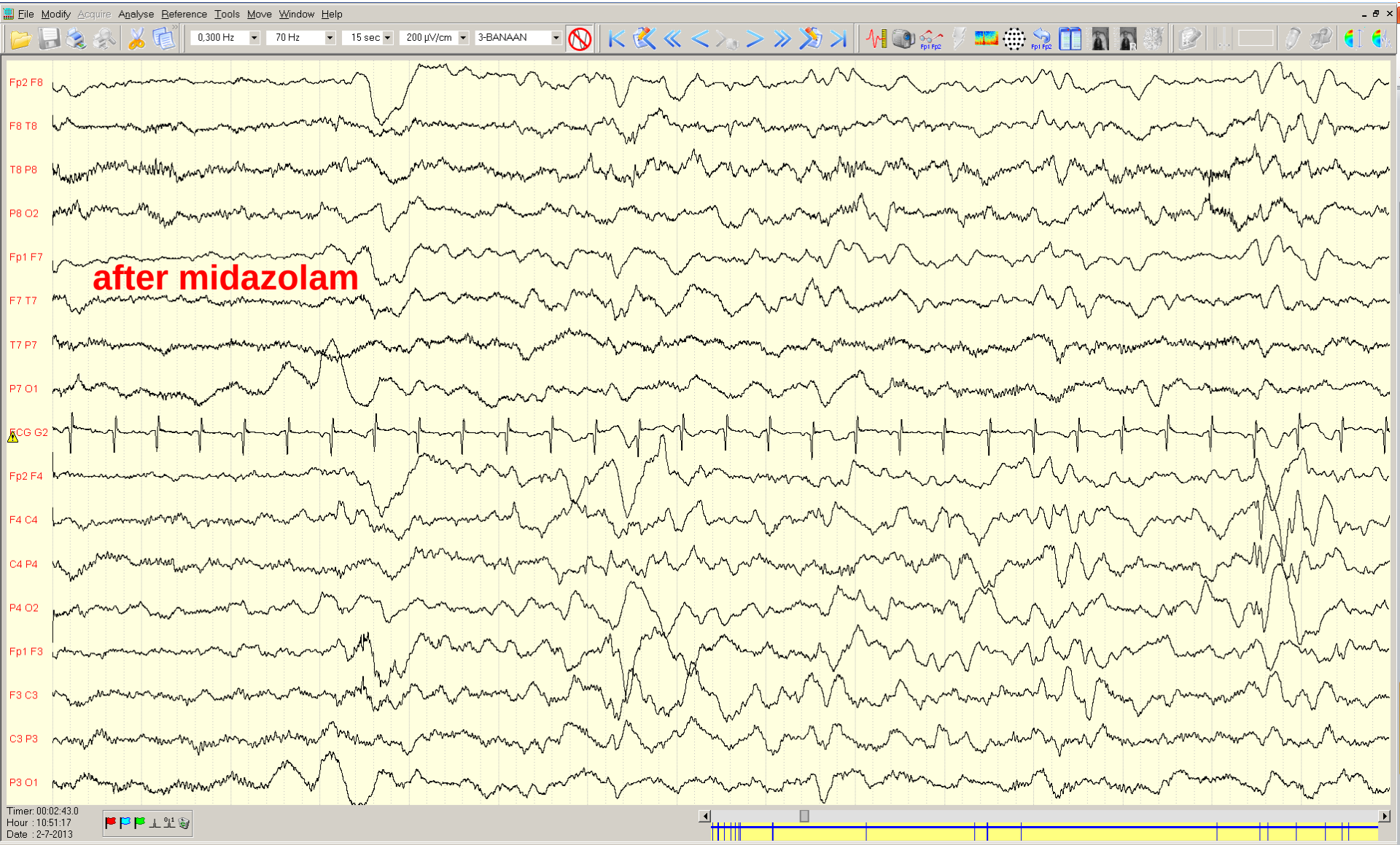
epileptic encephalopathies in early life - LGS



epileptic encephalopathies in early life - LGS



epileptic encephalopathies in early life - LGS



epileptic encephalopathies in early life

- Lennox-Gastaut syndrome: non-convulsive (atypical absence) SE is common
  - hard to differentiate from interictal EEG patterns
  - hard to treat

epileptic encephalopathies in early life

- Lennox-Gastaut syndrome: non-convulsive (atypical absence) SE is common
  - hard to differentiate from interictal EEG patterns
  - hard to treat

- West syndrome with developmental regression and full hypsarrhythmia; NCSE?
  - reversible EEG patterns with treatment
  - cognitive improvement

status epilepticus in children - conclusions

diagnosis / treatment
experienced team
child neurologist – neurophysiologist - intensivist

status epilepticus in children - conclusions

medical emergency
protocolized medicine
(super)refractory; expert opinion
treat underlying cause
febrile SE is frequent but not without risks

convulsive SE

invisible SE

status epilepticus in children - conclusions

convulsive SE

invisible SE

NCSE often follows CSE
NCSE affects outcome
ESES is a threat to cognitive development
optimal Tx not established

status epilepticus in children - conclusions

EEG may be non-epileptic in SE
Sturge-Weber
EPC
MRI may help

convulsive SE

invisible SE

status epilepticus in children - conclusions

convulsive SE

invisible SE

epileptic encephalopathies in early life:
formes frustes of NCSE?
clinical symptoms guide Tx

acknowledgements

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Brain Center
Rudolf Magnus

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