22nd Annual Scientific Meeting of the Epilepsy Society of Thailand
Main auditorium of Prasart Neurology Institute
Bangkok, July 19th and 20th, 2018

Epileptogenesis, glia and neurons : is it a paradigm shift?

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Kyoto, JAPAN

Disclosure Form

Company Name	Nature of Affiliation
• Eisai, Nihon-Kohden, Otsuka, UBC Japan	• Endowed Department
• Eisai, UBC Japan, Otsuka,	• Grants or Honorariums

Off-Label Product Usage
• None

Application of LFF and HFF

Time constant (TC)
to filter out slow components

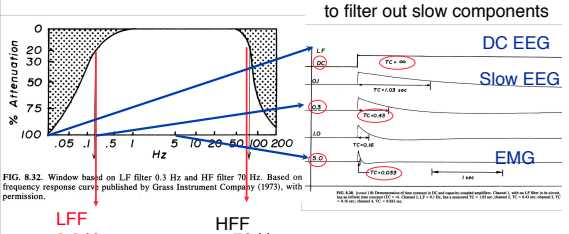


FIG. 8.32. Window based on LF filter 0.3 Hz and HF filter 70 Hz. Based on frequency response curve published by Grass Instrument Company (1973), with permission.

DC EEG
Slow EEG
EMG

LFF
0.3 Hz
(TC=0.5 s)

HFF
70 Hz

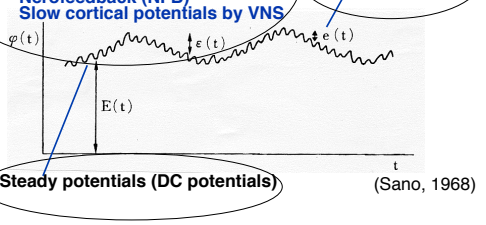
TC x LFF=0.16(1/2π)

0.1 sec	1.6 Hz
1 sec	0.16 Hz
10 sec	0.016 Hz

Schema of brain potentials

Slow potential shifts
ictal DC shifts
BP(MRCP)
CNV:
Nerofeedback (NFB)
Slow cortical potentials by VNS

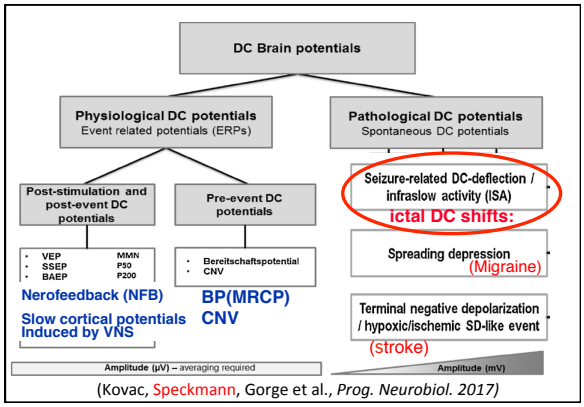
AC potentials



Steady potentials (DC potentials)

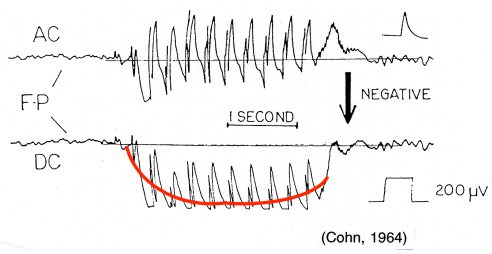
(Sano, 1968)

DC amplifier or long time constant(10sec) of AC amplifier needed



(Kovac, Speckmann, Gorge et al., *Prog. Neurobiol. 2017)*

Generalized spike and wave complex had also slow shifts



(Cohn, 1964)

FOCAL PERIODIC SLOW TRANSIENTS IN EPILEPSIA PARTIALIS CONTINUA: CLINICAL AND PATHOLOGICAL CORRELATIONS IN TWO CASES[1]

(Chatrian et al.,1964)

GIAN EMILIO CHATRIAN, M.D., CHENG-MEI SHAW, M.D.[2] AND FRED PLUM, M.D.

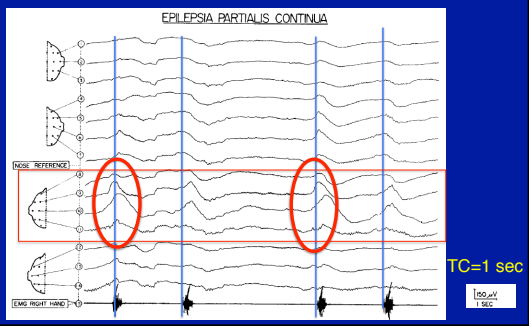
Electroenceph. clin. Neurophysiol., **1964,** *16*: 387–393

The first report of PLEDs with epilepsia partialis continua

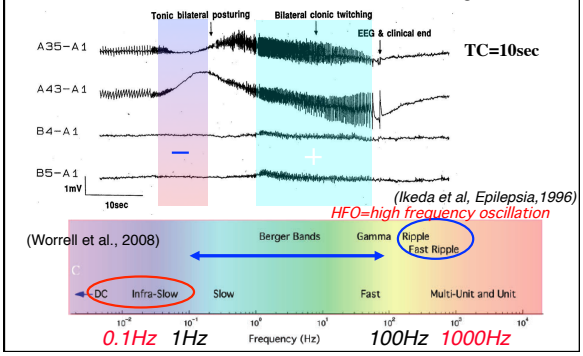
Periodic focal slow wave with focal seizure described in 2 cases
Time constants (TC) of 1 sec was employed, tin electrodes used

These slow transients may be the expression of local shifts of the steady potential (SP) of the cerebral cortex.

"The lack of any detectable epileptiform pattern in the EEG of some patients in the course of focal seizure activity is often adduced as an example of the limitations of EEG."

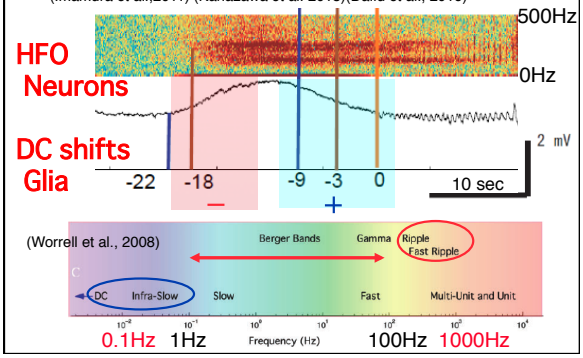


Wide-band EEG in clinical invasive recording

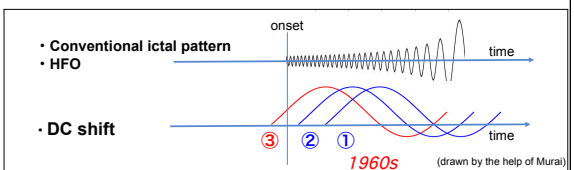


Ictal DC shift preceded HFO in invasive recording.

(Imamura et al.,2011) (Kanazawa et al. 2015)(Daifu et al., 2016)



Hypothesis of active vs. passive DC shift in the ictal period



		③Active DC shift	② ① Passive DC shift
Clinical state		Chronic epilepsy	Acute symptomatic seizure
Clinical	patients	Habitual seizures	Non-habitual seizures
Basic	animals	Chronic model	Acute model
		Chronic pilocarpine model LGi1 rat model NER(=Noda epilepsy rat model)	Acute pilocarpine model

(by Ikeda et al) (as the working hypothesis of AMED research team of Epilepsy and Glia, chaired by Maehara, Japan, 2015-2018)

Neuron, glia, and epilepsy: is it a paradigm shift?

1) Glia vs. neurons, i.e., active- vs. passive DC shifts
   AMED study in Japan
   Surgical outcome

2) Interictal red slow, i.e., co-occurrence of slow and HFO

3) 2 types of ictal DC shifts
   endorsed by TC10 sec vs. TC 2sec

4) Is it recorded by scalp EEG ?

5) Proposal of clinical practice parameter for recording and analysis of ictal DC shifts and HFO: invasive EEG

Expression of epileptogenicity by EEG

1) By conventional EEG

spikes, sharp waves (pyramidal neurons)

2) By wide-band EEG (surrogate marker?)

DC shifts, slow shifts (pyramidal neurons, glia)

HFO or fast ripple activity (pyramidal neurons, interneurons?)

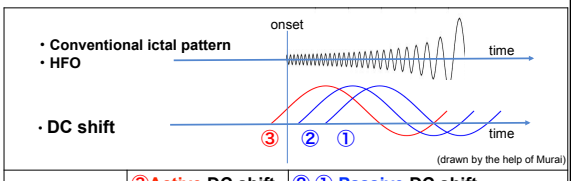
Terminology: Ictal DC (direct current) shifts

Also described as very slow, infra-slow, steady,

Recorded by

DC amplifier	DC shifts
AC (alternative current) amplifier	Slow shits
long time constant, i.e. 10 sec	
small low frequency filter (LFF) i.e., 0.016Hz	

Hypothesis of active vs. passive DC shift in the ictal period



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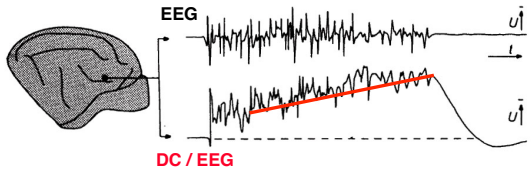
Ictal activity by pentylentetrazole

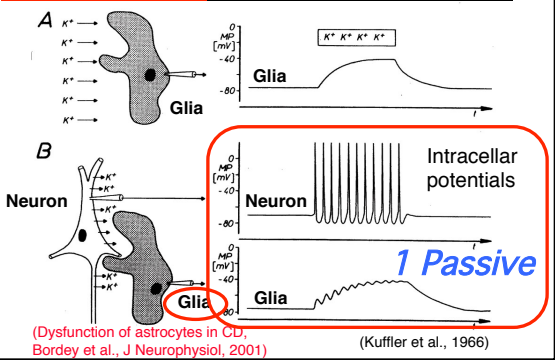
(acute animal model)



passive DC shifts?

(Speckmann & Elger, 1987)

Amplifying effects of glial cells on slow shifts

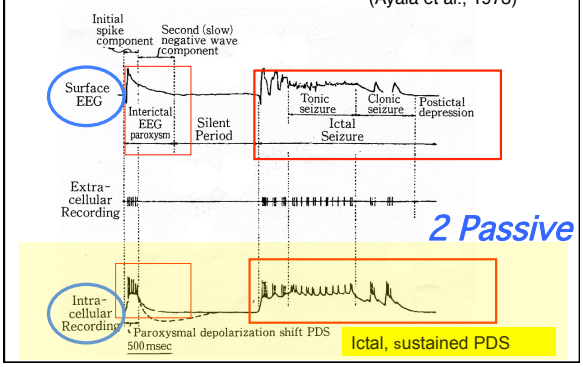


(Dysfunction of astrocytes in CD, Bordey et al., J Neurophysiol, 2001)

(Kuffler et al., 1966)

EEG and intracellular recording in interictal and ictal periods

(Ayala et al., 1973)



Impaired K^+ homeostasis is important both after seizure and before seizure, that may triggger seizure?

3 Active (?)

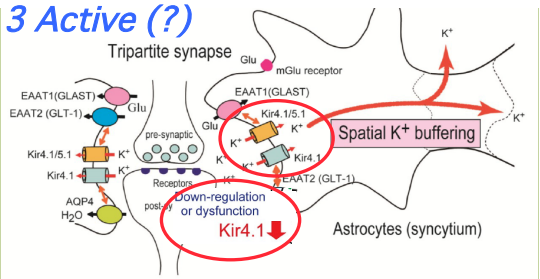


Figure 1. Astroglial spatial K^+ buffering and Kir4.1 channels. Astrocytes play a key role in controlling environmental K^+ concentrations at tripartite synapses via spatial K^+ buffering function, which also regulates extracellular glutamate concentrations. Kir4.1 channels, which consist of the homo-tetramer of Kir4.1 (Kir4.1) and the hetero-tetramer of Kir4.1 and Kir5.1 (Kir4.1/5.1), conduct K^+ buffering currents in astrocytes.

(Ohno et al. 2015)

Possible generator mechanism of Ictal DC shifts
Active vs. **Passive** mechanism

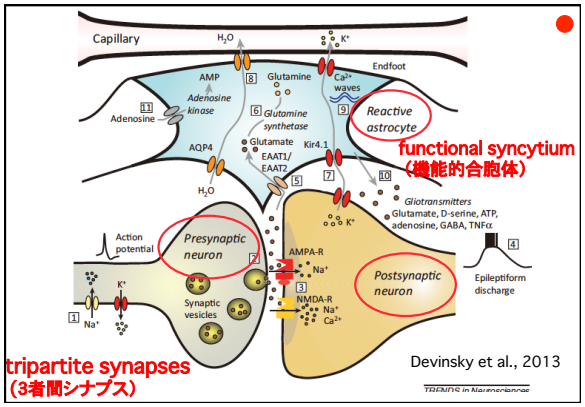
Passive generator mechanisms

1) Sustained paroxysmal depolarization shift (PDS) occurring in the epileptic neurons (1960s)

2) Augmented passive depolarization by increased $[K^+]$ of glia as the functional syncytium, associated with its dysfunction to salvage increased $[K^+]$ following seizure (1960s, 1990s)

Active generator mechanism

3) Active roles of glia: spontaneous slow oscillation of glia itself and decreased Kir4.1 channel in the astrocytes (after 2000)



Epilepsia, 37(7):662–674, 1996
Lippincott–Raven Publishers, Philadelphia
© International League Against Epilepsy

Subdural Recording of Ictal DC Shifts in Neocortical Seizures in Humans

Akio Ikeda, Kiyohito Terada, *Nobuhiro Mikuni, ‡Richard C. Burgess, §Youssef Comair, *Waro Taki, †Toshiaki Hamano, †Jun Kimura, ‡Hans O.Lüders, and Hiroshi Shibasaki

*Departments of Brain Pathophysiology, *Neurosurgery, and †Neurology, Kyoto University School of Medicine, Shogoin, Sakyo-ku, Kyoto, Japan; and Departments of ‡Neurology and §Neurosurgery, The Cleveland Clinic Foundation, Cleveland, Ohio, U.S.A.*

Brain (1999), 122, 827–838

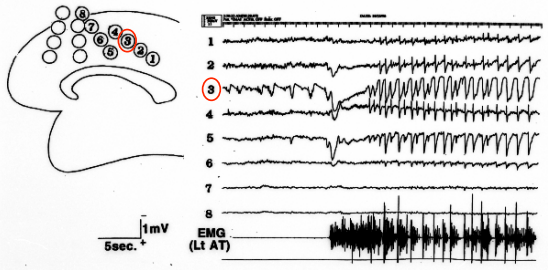
Focal ictal direct current shifts in human epilepsy as studied by subdural and scalp recording

Akio Ikeda,[1] Waro Taki,[2] Takeharu Kunieda,[2] Kiyohito Terada,[1] Nobuhiro Mikuni,[2] Takashi Nagamine,[1] Shogo Yazawa,[1] Shinji Ohara,[1] Tomokatsu Hori,[4] Ryuji Kaji,[3] Jun Kimura[3] and Hiroshi Shibasaki[1]

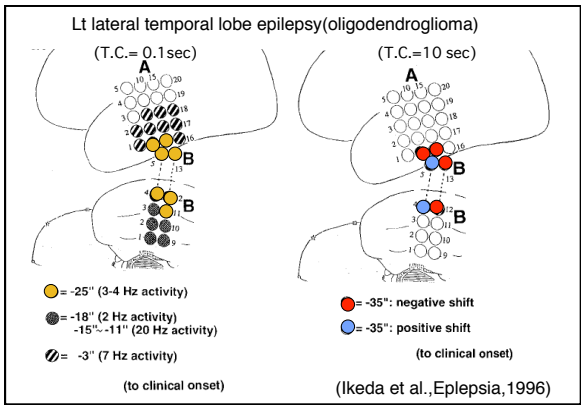
Departments of [1]Brain Pathophysiology, [2]Neurosurgery and [3]Neurology, Kyoto University School of Medicine, Kyoto and [4]Department of Neurosurgery, Tottori University School of Medicine, Tottori, Japan

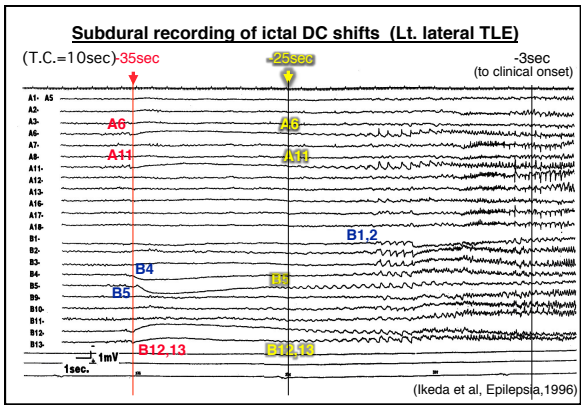
Correspondence to: Akio Ikeda, MD, Department of Brain Pathophysiology, Kyoto University School of Medicine, Shogoin, Sakyo-ku, Kyoto, 606, Japan
E-mail: akio@kuhp.kyoto-u.ac.jp

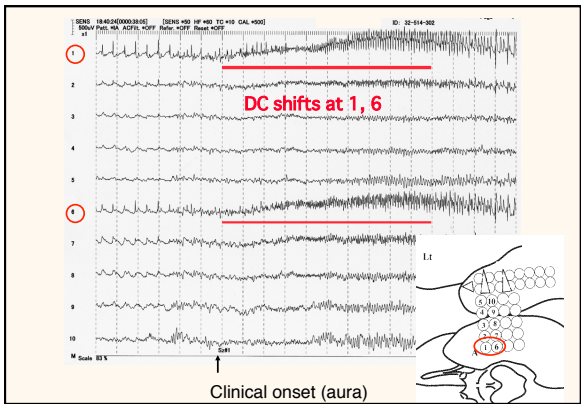
Subdurally recorded ictal EEG in Patient 1
TC=10sec, Focal, ictal slow shifts



(Ikeda et al, Brain,1999)





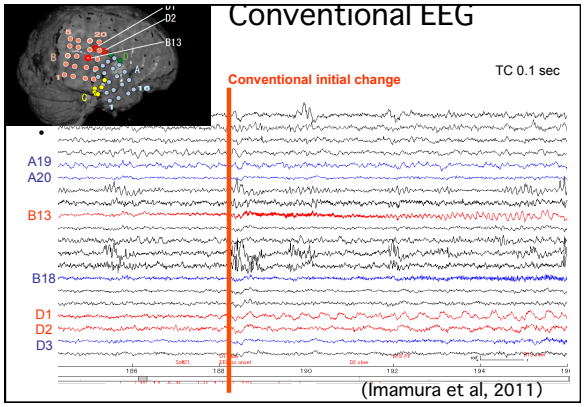


Ictal DC shifts (invasive recording): summary

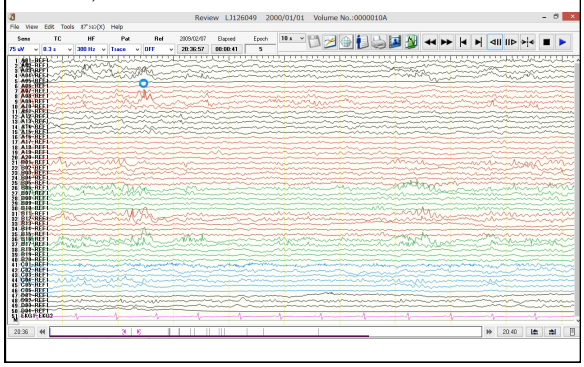
1) Ictal DC shifts recorded by invasive electrodes, especially subdural ones, in humans were almost invariably recorded regardless of underlying etiology or epilepsy type.

2) 96 % of patients showed ictal DC shifts, incidence rate being 42~100% (87%) of seizures in each patient.

2) Its more restricted localization could aid in delineating ictal onset zone clinically before surgery presumably as a core epileptogenic zone, if present.

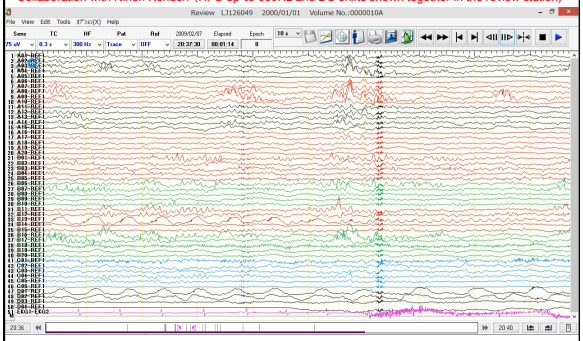


Sampling rate=2kHz, TC=10s, time window=20,30,60sec, 2m, 3m, HFF=300,1Hz

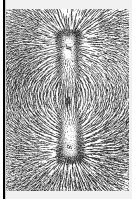


Time frequency analysis on the EEG review station (+-60sec)

Collaboration with Nihon Kohden (HFO up to 600Hz and DC shifts shown together in the review station)

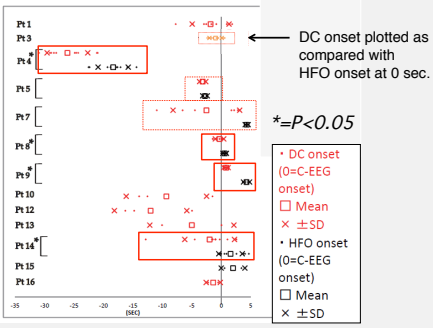


Ictal DC shifts occurred earlier than or as early as ictal HFO.



Alligned iron sand by the magnetic field.

Magnetic field= modified extracellular circumstances



(Kanazawa et al., Clin Neurophysiol, 2015)

Occurrence rate of ictal DC shifts and HFO

	DC shifts	HFO
Ikeda et al,1996,1999	96% of pts 87% of sz	
Imamura et al, 2010	100% of sz	100% of sz
Wu et al, 2014	94% of sz	84% of sz
Kanazawa et al, 2015	75% of pts 72% of sz	50% of pts 47% of sz
Nakatani (AMED) (2017)	95% of sz	77% of sz

Study group of Epilepsy and Glia by AMED (Japan Agency for Medical Research and Development)

Clinical approach= multi-institutional study of DC shifts in epilepsy surgery

Maehara T,MD (Tokyo), Inoue Y, MD (Shizuoka), Shirozu H, MD (Niigata), Watanabe Y, MD (Tokyo), Ikeda A, MD (Kyoto)

Pathology

Kakita Y, MD (Niigata)

Basic

Ohno Y, PhD (Osaka), Okada M, MD (Mie): pharmacology

Fukuda A, PhD (Hamamatsu), Koizumi S, PhD (Yamanashi): in vivo and in vitro analysis

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   Surgical outcome

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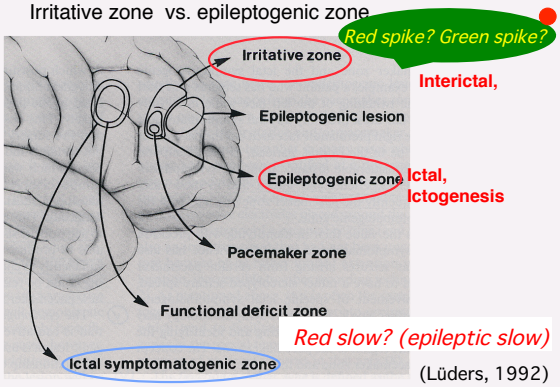
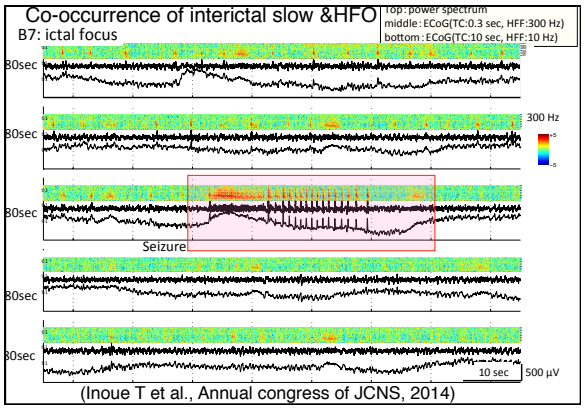
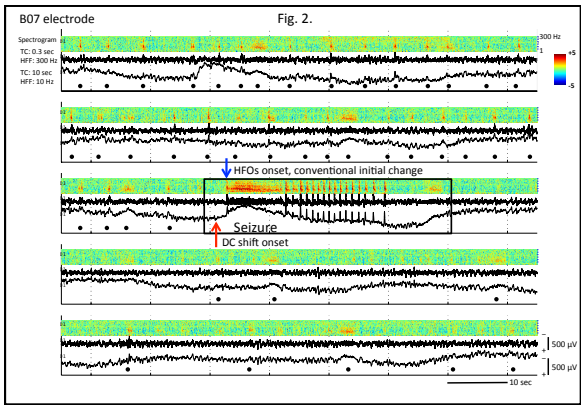
Irritative zone vs. epileptogenic zone



(Lüders, 1992)



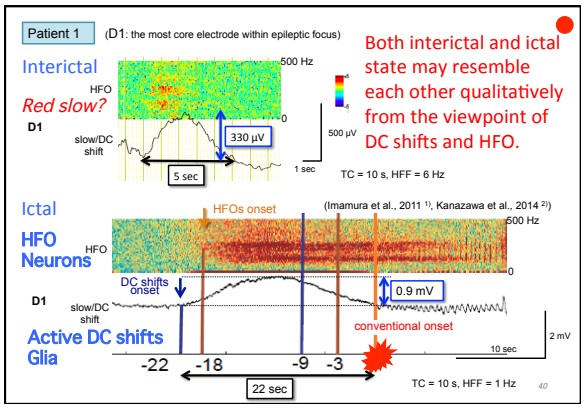
(Inoue T et al., Annual congress of JCNS, 2014)



Interictal slow shifts by macroinvasive electrodes

It could be defined as

- > 200 microV
- duration of 0.33-10sec
- always accompanied by HFO
- (>2SD of power at 80-200Hz from the baseline state)
- spikes or sharp waves excluded



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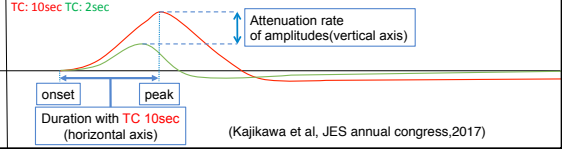
Methods

Subjects: 18 patients with intractable partial epilepsy
ECoG recording:
#1. band-pass filter of 0.016-600 Hz sampling rate of 2,000 Hz
#2. band-pass filter of 0.016-300 Hz sampling rate of 1,000 Hz
Analysis software: EEG review program (Nihon Kohden, Tokyo, Japan)
Selection of electrode: 1 electrode with the earliest ictal DC shifts with TC 10 sec
Parameters: #1. the amplitude and duration from onset to peak of ictal DC shifts with TC 10 sec and TC 2 sec superimposed TC 10 sec.
#2. the attenuation rate of the amplitudes
= (TC10sec-TC2sec)/TC10sec×100 (%)



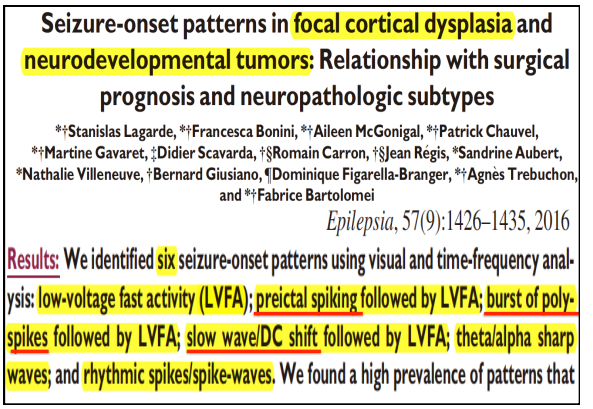
(Kajikawa et al, JES annual congress,2017)

Seizure-onset patterns in focal cortical dysplasia and neurodevelopmental tumors: Relationship with surgical prognosis and neuropathologic subtypes

*†Stanislas Lagarde, *†Francesca Bonini, *†Aileen McGonigal, *†Patrick Chauvel, *†Martine Gavaret, ‡Didier Scavarda, †§Romain Carron, †§Jean Régis, *Sandrine Aubert, *Nathalie Villeneuve, †Bernard Giusiano, ¶Dominique Figarella-Branger, *†Agnès Trebuchon, and *†Fabrice Bartolomei

Epilepsia, 57(9):1426–1435, 2016

Results: We identified six seizure-onset patterns using visual and time-frequency analysis: low-voltage fast activity (LVFA); preictal spiking followed by LVFA; burst of polyspikes followed by LVFA; slow wave/DC shift followed by LVFA; theta/alpha sharp waves; and rhythmic spikes/spike-waves. We found a high prevalence of patterns that



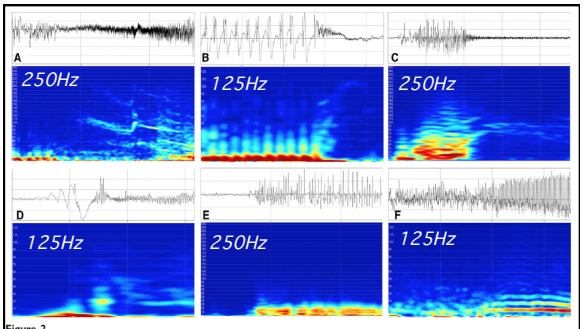


Figure 2.
The six patterns of seizure onset according to the time-frequency representation from SEEG trace. (**A**) Low-voltage fast activity (LVFA). (**B**) Preictal spiking with rhythmic spikes of low frequency followed by LVFA. (**C**) Burst of polyspikes of high frequency and amplitude followed by LVFA. (**D**) Slow wave or baseline shift followed by LVFA. (**E**) Rhythmic spikes or spike-waves, at low frequency and with high amplitude. (**F**) Theta/alpha sharp activity with progressive increasing amplitude.

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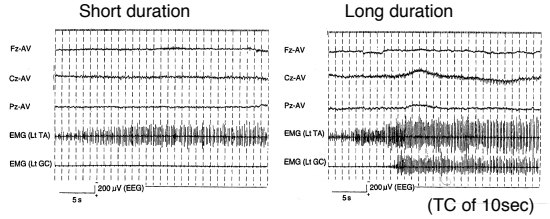
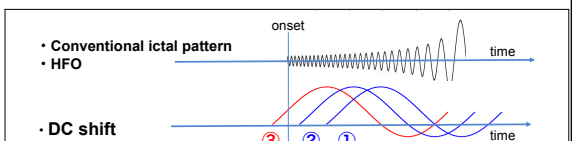
Scalp-recorded slow (DC) EEG with Lt focal motor seizures



Ictal DC shifts (scalp recording)
1) Incidence rate: 14~40% (22%) in 73 seizures.
2) Detected particularly when seizures were clinically intense, but not in small seizures. (Ikeda et al., 1999)

-> Future advancement in recording condition is warranted.

Hypothesis of active vs. passive DC shift in the ictal period



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Clinical	patients	Habitual seizures	Non-habitual seizures
Basic	animals	Chronic model	Acute model
		Chronic pilocarpine model LGi1 rat model NER(=Noda epilepsy rat model)	Acute pilocarpine model

(by Ikeda et al) (as the working hypothesis of AMED research team of Epilepsy and Glia, chaired by Maehara, Japan, 2015-2018)

Neuron, glia, and epilepsy: is it a paradigm shift?

1) Glia vs. neurons, i.e., active- vs. passive DC shifts
   AMED study in Japan
   Surgical outcome

2) Interictal red slow, i.e., co-occurrence of slow and HFO

3) 2 types of ictal DC shifts
   endorsed by TC10 sec vs. TC 2sec

4) Is it recorded by scalp EEG ?

5) Proposal of clinical practice parameter for recording and analysis of ictal DC shifts and HFO: invasive EEG

Standards as clinical practice parameters for recording and analysis of ictal DC shifts and HFO

Initially made by AMED research group in Japan
approved by JES, Japan Epilepsy Surgery Society
currently on the investigation by Japan Clinical Neurophysiology Society

てんかん研究　2017；35：3–13

難治部分てんかん患者の焦点検索における、発作時 DC 電位・HFO の記録および解析の標準化案

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Standards as clinical practice parameters for recording and analysis of ictal DC shifts and HFO

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Society

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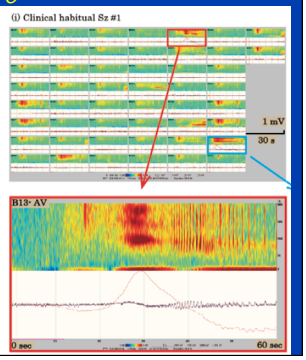
難治部分てんかん患者の焦



Conclusion

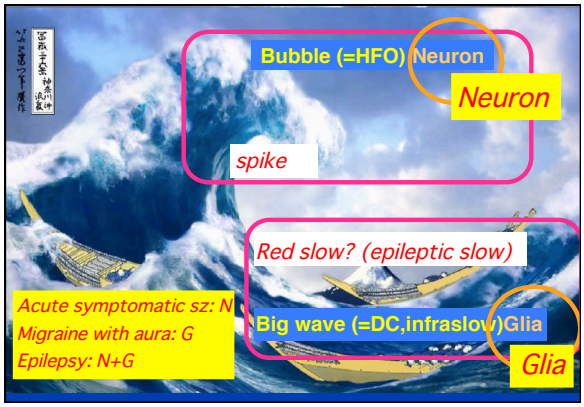
1) Subdurally recorded ictal DC shifts could represent humoral state of at least [K^+] immediately before seizure onset.

2) Active DC shifts were predominant in "chronic" epilepsy. Decreased Kir 4.1 channels of the astrocytes is responsible for DC shift generation.

3) Red slow, i.e., interictal slow with HFO may represent similar feature to ictal event.

4) Scalp EEG cold record both ictal DC shifts and HFO, but in a limited manner.

5) Proposal of clinical practice parameter for recoding and analysis of ictal DC shifts and HFO is warranted for further clinical application



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Special thanks to
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