February 14, 2025

AMED (Japan Agency for Medical Research and Development) Supports

International Collaboration

Implementation of wide band EEG in epilepsy care by digital EEG

Lecture:

Wide Band EEG Analysis

Now ready for clinical implementation

Akio IKEDA, MD, PhD, FACNS

Department of Epilepsy, Movement Disorders & Physiology

Kyoto University Graduate School of Medicine

Kyoto, JAPAN

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31st January 2025 (Friday)

Wide-band EEG from DC shifts to HFO 1

Moderator

Dr. Fitri Octaviana (Dr. Cipto Mangunkusumo Hospital, Indonesia)

Contents

- ✔ Mini lecture from Prof. Ikeda (Kyoto University, Japan) [30 min.]
- ✔ Presentation from Dr. Katsuya Kobayashi (Kyoto University, Japan) [30 – 60 min.]

14th February 2025 (Friday)

Wide-band EEG from DC shifts to HFO 2

Moderator

Dr. Aris Catur Bintoro (Central General Hospital Dr. Kariadi, Indonesia)

Contents

- ✔ Mini lecture from Prof. Ikeda (Kyoto University, Japan) [30 min.]
- ✔ Presentation from Dr. Masao Matsuhashi (Kyoto University, Japan) [30 – 60 min.]

India (New Delhi)	IST	2:30 PM –
Indonesia (Jakarta)	WIB	4:00 PM –
Thailand (Bangkok)	ICT	4:00 PM –
Taiwan (Taipei)	CST	5:00 PM –
Japan (Tokyo)	JST	6:00 PM –

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Disclosure Form

Company Name	Nature of Affiliation
• Sumitomo Pharma Co • Nihon-Kohden	• Industry-Academia Collaboration Courses • Collaboration study
• UCB Japan • Eli Lilly Japan • RICHO	• Collaboration study
Off-Label Product Usage	
• None	

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54th Annual congress of JSCN
October 24 ~ 26, 2024, Sapporo, Japan

Sapporo Super EEG
October 24 2024

Wide-band EEG from DC shifts to HFO
(invasive and scalp)
14:00 ～ 15:30

Lecture:

Wide Band EEG Analysis
Now ready for clinical implementation

Akio IKEDA, MD, PhD, FACNS
Department of Epilepsy, Movement Disorders

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RESEARCH ARTICLE

Epilepsia

Received: 16 February 2024 | Revised: 11 July 2024 | Accepted: 17 July 2024

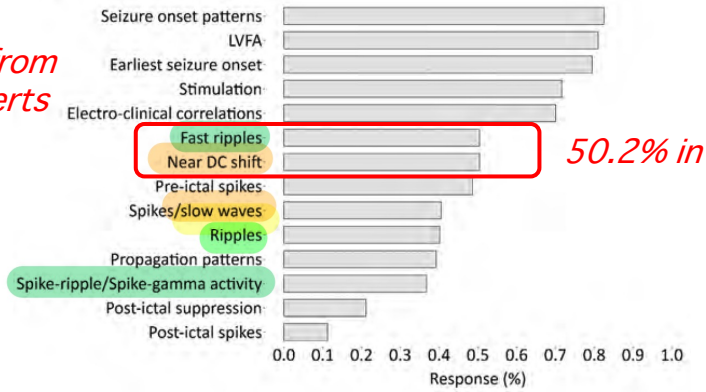
Investigating current clinical opinions in stereoelectroencephalography-informed epilepsy surgery

John Thomas[1,2] | Chifaou Abdallah[1] | Zhengchen Cai[1] | Kassem Jaber[1] | Jean Gotman[1] | Sandor Beniczky[3] | Birgit Frauscher[1,2,4]

Out of 14 ictal s-EEG features

(A)

Opinion from 321 experts



50.2% in each

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Wide-band EEG: a mysterious and very useful technique

1) What is the wide-band EEG?
2) Special machine? Special technique?
3) Is it useful? Is it redundant? Just only research?
4) Useful only in invasive EEG?
5) Is it recorded by scalp-EEG?
6) EEG technologist could analyze?

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Wide-band EEG: a mysterious and very useful technique

Long introduction

1) **active- vs. passive DC shifts**
   AMED study in Japan (Multi-institutional study)
   Surgical outcome

2) 2 types of ictal DC shifts, and pathology

3) Is it recorded by TC 2sec EEG ?

4) Is it recorded by scalp EEG ?

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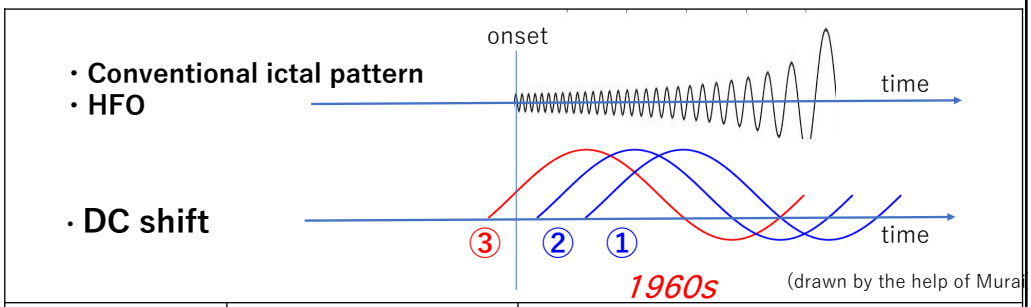
Hypothesis of active vs. passive DC shift in the ictal period



		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)

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Clinical neurophysiological features of epileptic seizures

1) PDS (paroxysmal depolarization shifts)

2) Impaired extracellular K homeostasis by deceased Kir4.1, related ictal DC shifts

Contents lists available at ScienceDirect

Neuroscience Research

journal homepage: www.elsevier.com/locate/neures

Review article

Neuroscience Research 156 (2020) 95–101

Active direct current (DC) shifts and "Red slow": two new concepts for seizure mechanisms and identification of the epileptogenic zone

Akio Ikeda[a,*], Hirofumi Takeyama[b], Christophe Bernard[c], Mitsuyoshi Nakatani[d,e], Akihiro Shimotake[a], Masako Daifu[d], Masao Matsuhashi[a], Takayuki Kikuchi[f], Takeharu Kunieda[f,g], Riki Matsumoto[h], Tamaki Kobayashi[f], Kazuaki Sato[d]

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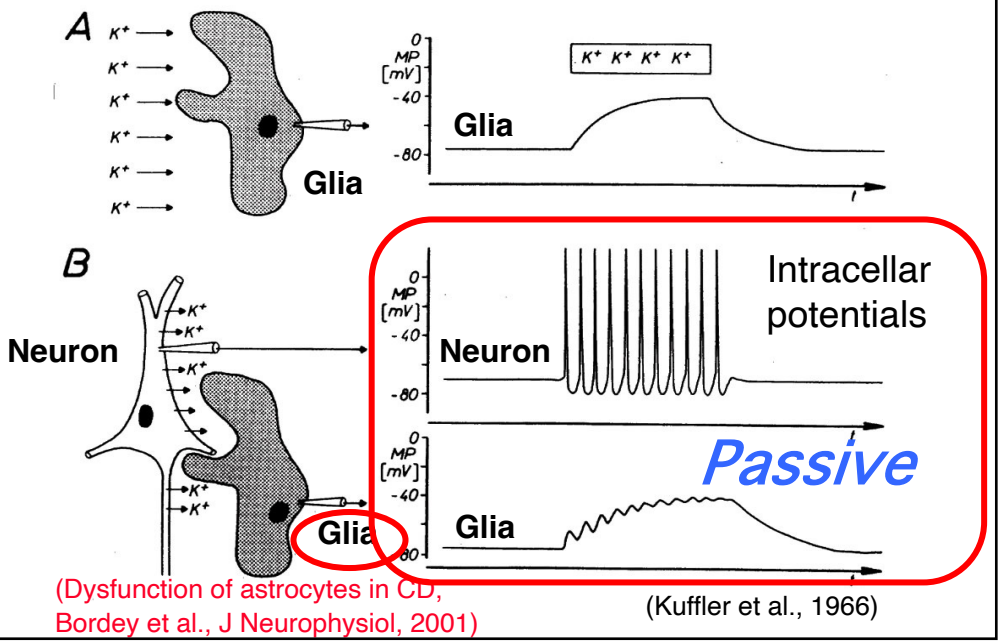
Amplifying effects of glial cells on slow shifts



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

(Kuffler et al., 1966)

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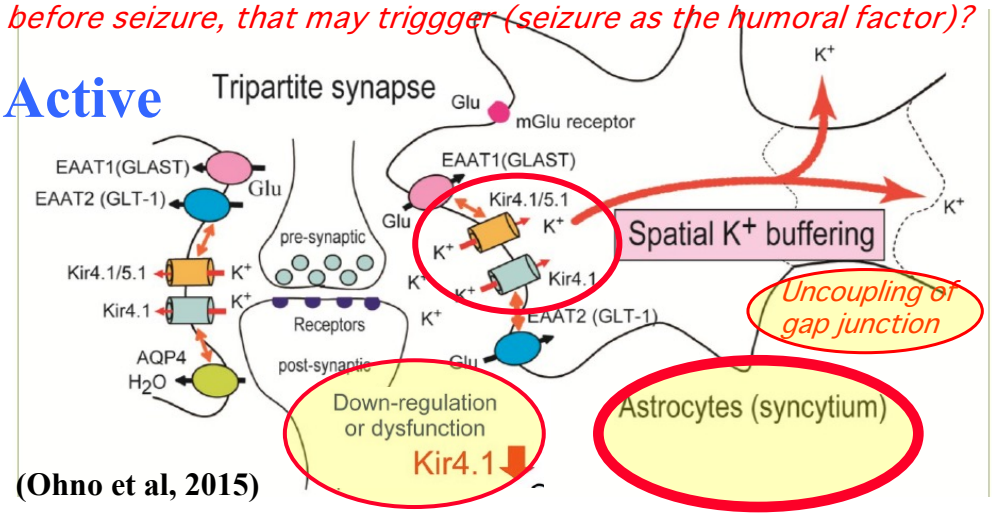
Impaired K^+ homeostasis is important both after seizure and before seizure, that may triggger (seizure as the humoral factor)?



(Ohno et al, 2015)

(recently shown by animal study, human sample from epiileptogenic zone generating ictal DC shifts)

Astrocyte depolarization (including DC shifts)
→ inhibition of astrocyte glutamate clearance
→enhancing neuronal activation by glutamate
(Armbruster et al, Nature Neurosciece, 2022)

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A comparison to epilepsy surgery outcome

	Retrospective study	Prospective study
Interictal HFO	•Jacobs J et al. Ann Neurol. 2010;67:209-220 •Akiyama T et al. Epilepsia 2011;52:1802–1811 • Van Klink NEC et al. Ann Neurol. 2017; 81: 664-676 others **Effective**	•Jacobs J et al. Neurology. 2018;91(11):e1040-e1052. 5 institutes •Zweiphenning W et al. Lancet Neurol. 2022; 21(11): 982–993 3 institutes **Non-effective**
Wide-band EEG (Ictal DC shifts ictal HFO)	• Nakatani M et al. Brain Commun. 2022; 4(5) : fcac222. doi: 10.1093/braincomms/fcac222 5 institutes in Japan **Effective**	SDG(subdural grid) → SEEG **Not yet**

(a table made by Prof. T Maehara, Tokyo, Japan)

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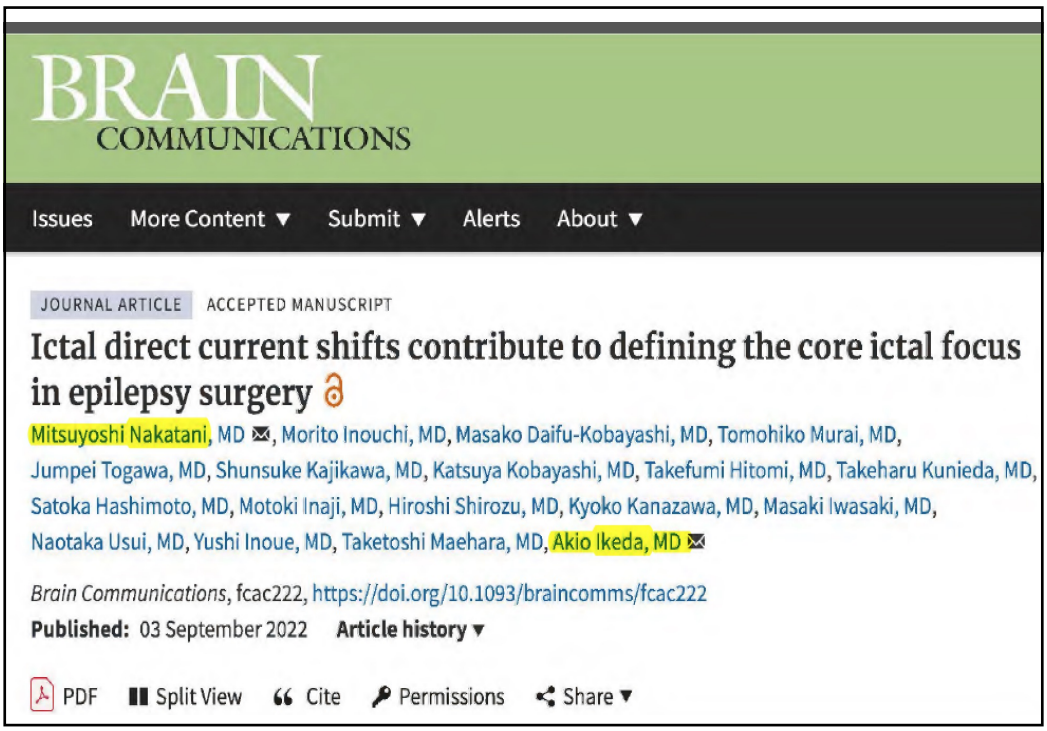

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Methods: patients and recording

AMED(Japan Agency for Medical Research and Development) study

5 institutes in Japan have participated in the study

Kyoto University Graduate School of Medicine, Kyoto
Tokyo Medical and Dental University, Tokyo
Nishi-Niigata Chuo National Hospital, Niigata
National Center Hospital, National Center of Neurology and Psychiatry, Tokyo
Shizuoka Institute of Epilepsy and Neurological Disorders, Shizuoka

Medically intractable focal epilepsy patients
- chronic placement of intracranial electrodes
- ECoG : sampling rate 1000 or 2000 Hz, time constant 10 sec

icDCs were defined as sustained negative and/or positive potentials longer than 3 sec, at least 200microV, preferentialy >1mV, viewed in a setting of a TC of 10 sec (Ikeda et al., 1999, Brain)

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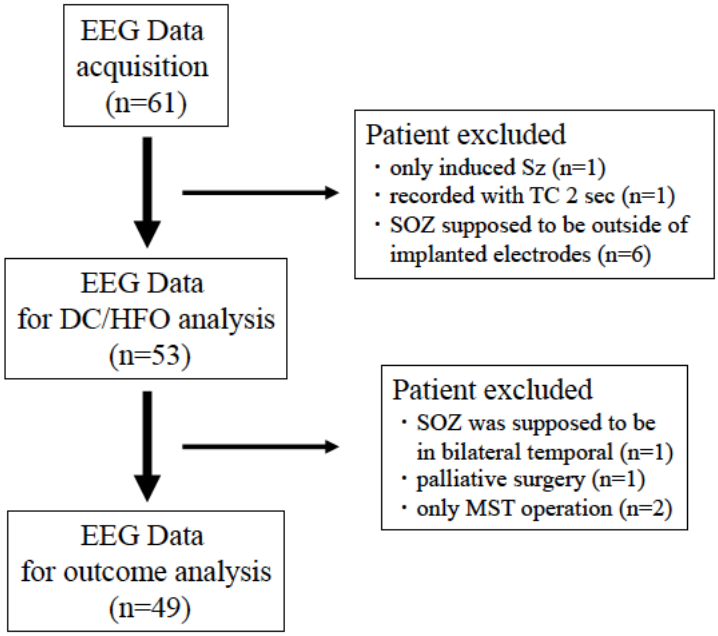
Large cohort studies on postoperative outcomes are still lacking.



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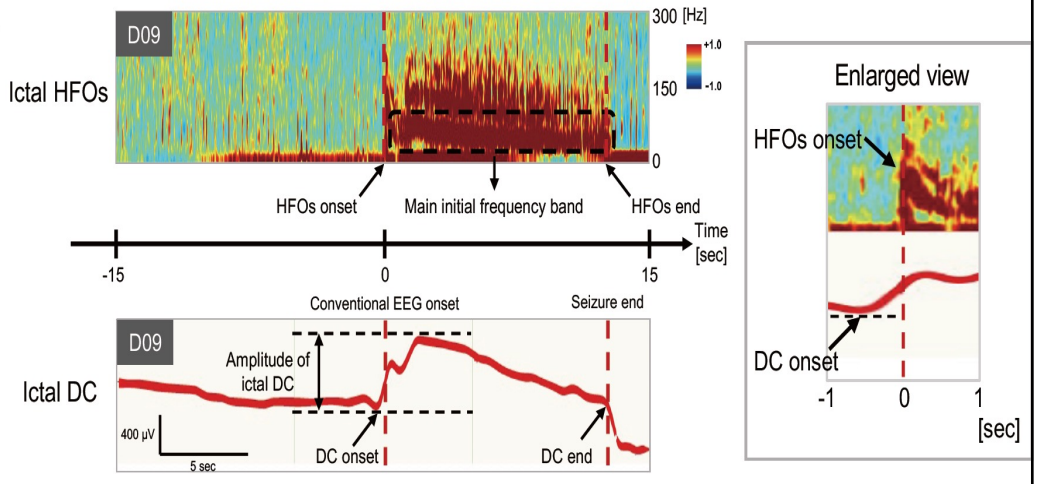
Analyzed by wide-band EEG analysis software (Nihon Kohden, Tokyo, Japan)



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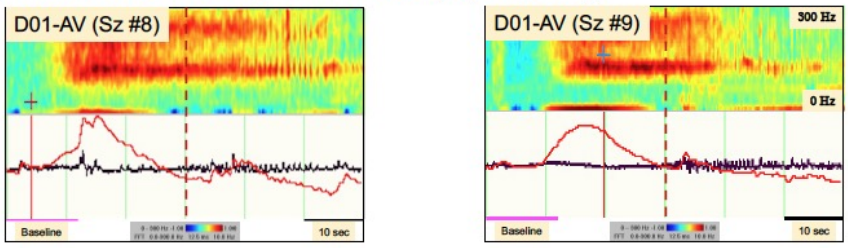
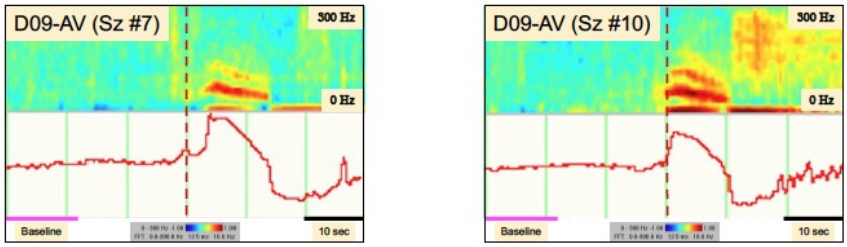
Reproducible, patient-specific patterns were identified.
Ictal HFO frequency band was either stable or became slower

A. Representative case in previous study (Patient 4)



B. Patient 10



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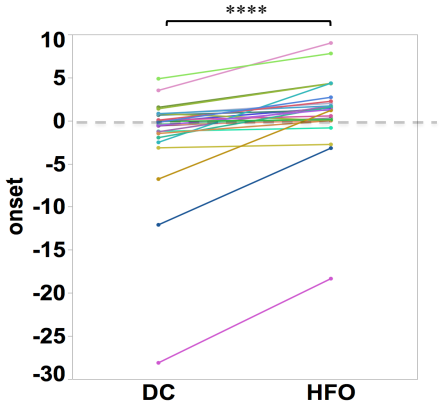
Results: onset time

In 27 out of 46 patients showing both ictal DC and ictal HFOs,
ictal DC onset time was statistically significantly earlier than ictalHFOs



conventional ECoG onset

ictal DC: -1.8 ± 6.0 (s)
ictal HFOs: +1.5 ± 5.5 (s)

(time 0: conventional ECoG seizure onset)

(Wilcoxon signed rank test, *****: $p < 0.001$)

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	Amplifier	Occurrence rate among patients (%)		Occurrence rate among seizures (%)		Correspondence of core electrodes of ictal DC and HFOs (%)	ictal DC amplitude (μV)	ictal DC duration (sec)	ictal HFOs frequency (Hz)	ictal HFOs duration (sec)
		ictal DC	ictal HFOs	ictal DC	ictal HFOs					
Nakatani et al., 2021 (n=61)	AC	92	71	86	62	39	1037 ± 570	15.8 ± 7.8 *	R (FR)	7.0 ± 4.1 *
Ikeda et al., 1999[18] (n=9)	AC	82 (subdural) 84 (scalp)	–	85 (subdural) 23 (scalp)	–	–	200 – (subdural) 50 – (scalp)	–	–	–
Modur et al., 2009[25] (n=1)	AC	100	100	100	75	10 – 75 ? (no detail)	–	– 25	R	Sustained (no detail)
Kim et al., 2009[41] (n=11)	DC	91	–	69.5	–	–	800 – 10,000	1 – 493	–	–
Wu et al., 2014[4] (n=15)	AC	100	67	91	81	19.3	1,700 ± 910	5 – 180	R, FR	–
Kanazawa et al., 2015[5] (n=16)	AC	75	50	71.3	46.3	–	903.1 ± 462.8	35.5 ± 15.6	R, FR	10.7 ± 9.7
Thompson et al., 2016[24] (n=15)	AC	100	–	100	–	–	300 – 8,500	– over 100	–	–

*: Long-lasting icDC or icHFOs beyond 30 sec analysis time-window after the seizure onset were excluded due to the limitation of the software.

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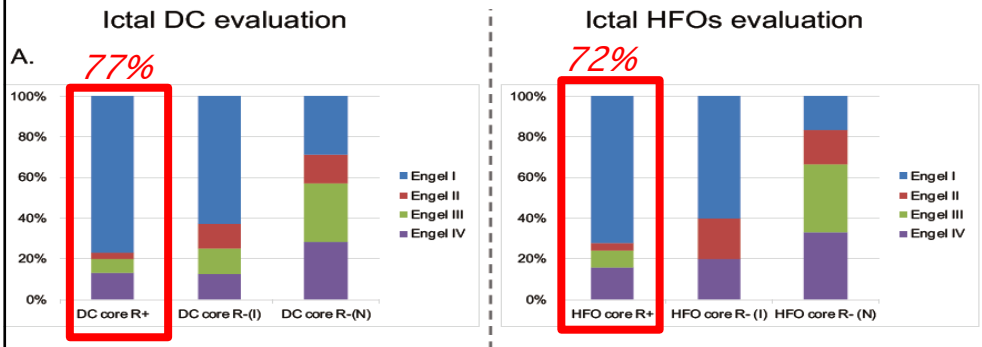
Results: surgical outcome

Complete resection of ictal DC and ictal HFOs 'core' areas significantly **correlates with good surgical outcome**.



B.

	Good	Bad
DC core R+	23	7
DC core R-	7	9

(p=0.044, Pearson's chi-square test)

	Good	Bad
HFOs core R+	18	7
HFOs core R-	4	7

(p=0.043, Pearson's chi-square test)

Overall, 66% in Engel I

Overall, 61% in Engel I

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Conclusion

1) It is the first large cohort multi-institutional study on wide-band EEG analysis and postoperative outcomes in Japan.

2) icDCs onset was statistically earlier than icHFOs onset in both MTLE and Neocortical epilepsy.

3) icDCs more frequently recorded than icHFOs among both patients (92% vs. 71%) and seizures (86% vs. 62%).

4) Complete resection of the core area of icDCs significantly correlated with favorable outcomes, similar to icHFOs outcomes.

5) The independent significance of icDCs and icHFOs should be considered as reliable biomarkers to achieve favorable outcomes in epilepsy surgery.

Wide-band EEG: a mysterious and very useful technique

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3) Is it recorded by TC 2sec EEG ?

4) Is it recorded by scalp EEG ?

Clinical Neurophysiology 137 (2022) 113–121

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Two types of clinical ictal direct current shifts in invasive EEG of intractable focal epilepsy identified by waveform cluster analysis

Shunsuke Kajikawa[a], Masao Matsuhashi[b], Katsuya Kobayashi[a], Takefumi Hitomi[c], Masako Daifu-Kobayashi[a], Tamaki Kobayashi[d,e], Yukihiro Yamao[e], Takayuki Kikuchi[e], Kazumichi Yoshida[e], Takeharu Kunieda[e,f], Riki Matsumoto[a,g], Akiyoshi Kakita[h], Takao Namiki[i], Ichiro Tsuda[j], Susumu Miyamoto[e], Ryosuke Takahashi[a], Akio Ikeda[b,*]

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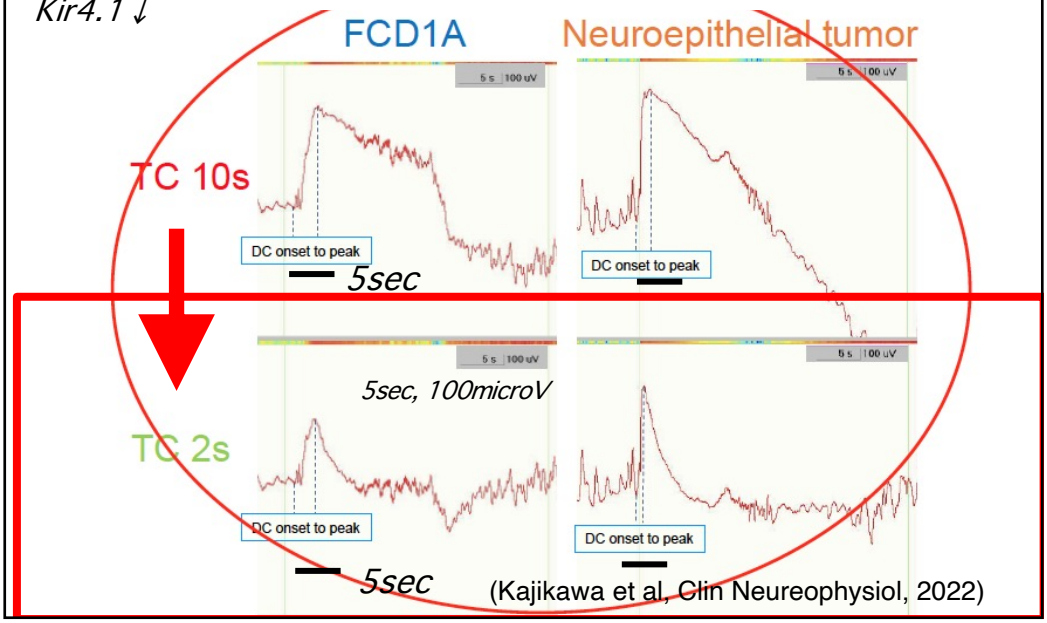
Type#1 DC shifts =rapid development, FCD1A

61%(Sz), 67%(pt)

Kir4.1 ↓



(Kajikawa et al, Clin Neureophysiol, 2022)

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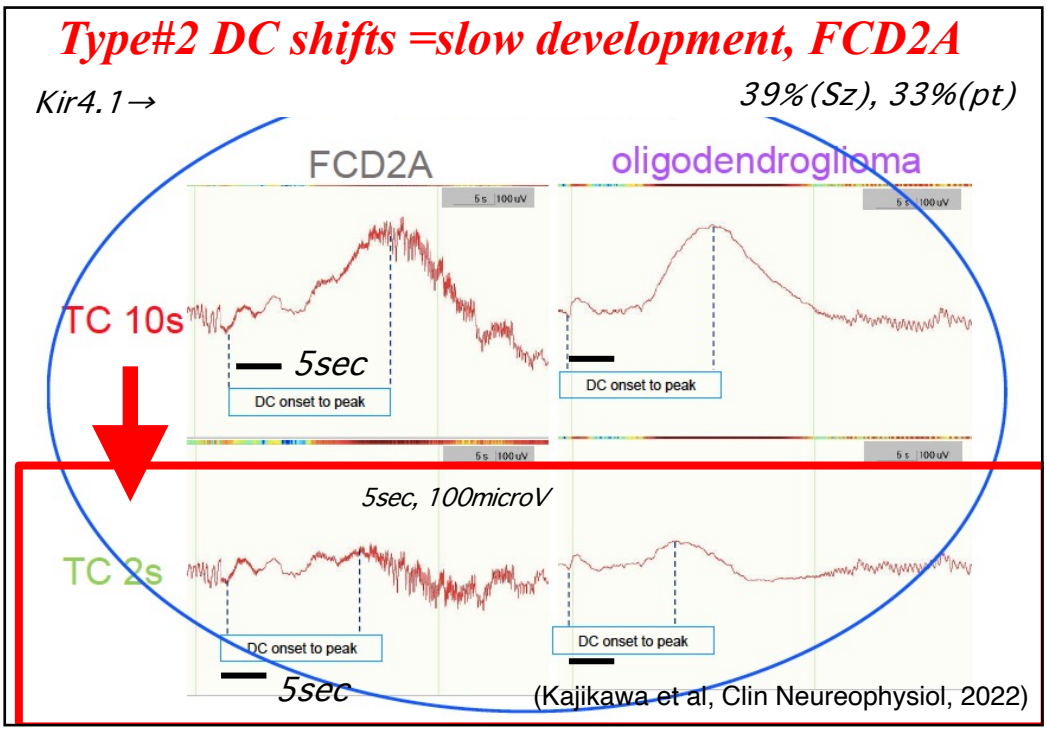
Type#2 DC shifts =slow development, FCD2A
Kir4.1→
39%(Sz), 33%(pt)
FCD2A
oligodendroglioma
TC 10s
5sec
DC onset to peak
5sec, 100microV
TC 2s
DC onset to peak
5sec
(Kajikawa et al, Clin Neureophysiol, 2022)

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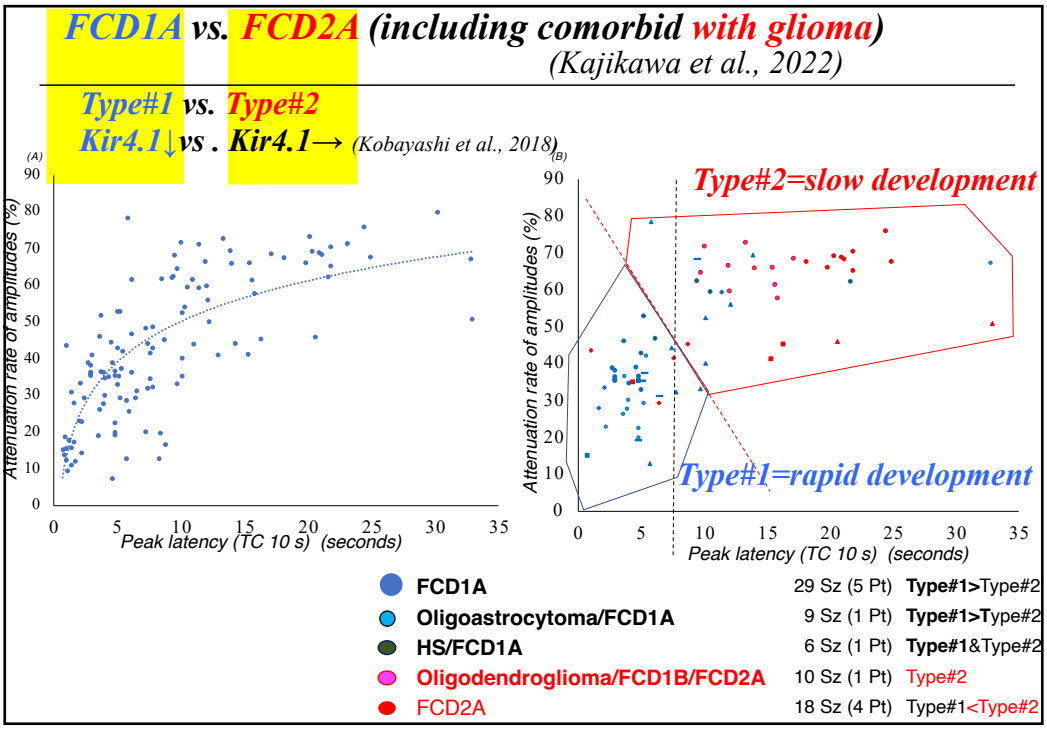
FCD1A vs. FCD2A (including comorbid with glioma)
(Kajikawa et al., 2022)
Type#1 vs. Type#2
Kir4.1↓vs . Kir4.1→ (Kobayashi et al., 2018)
Attenuation rate of amplitudes (%)
Peak latency (TC 10 s) (seconds)
Type#2=slow development
Type#1=rapid development
FCD1A 29 Sz (5 Pt) Type#1>Type#2
Oligoastrocytoma/FCD1A 9 Sz (1 Pt) Type#1>Type#2
HS/FCD1A 6 Sz (1 Pt) Type#1&Type#2
Oligodendroglioma/FCD1B/FCD2A 10 Sz (1 Pt) Type#2
FCD2A 18 Sz (4 Pt) Type#1<Type#2

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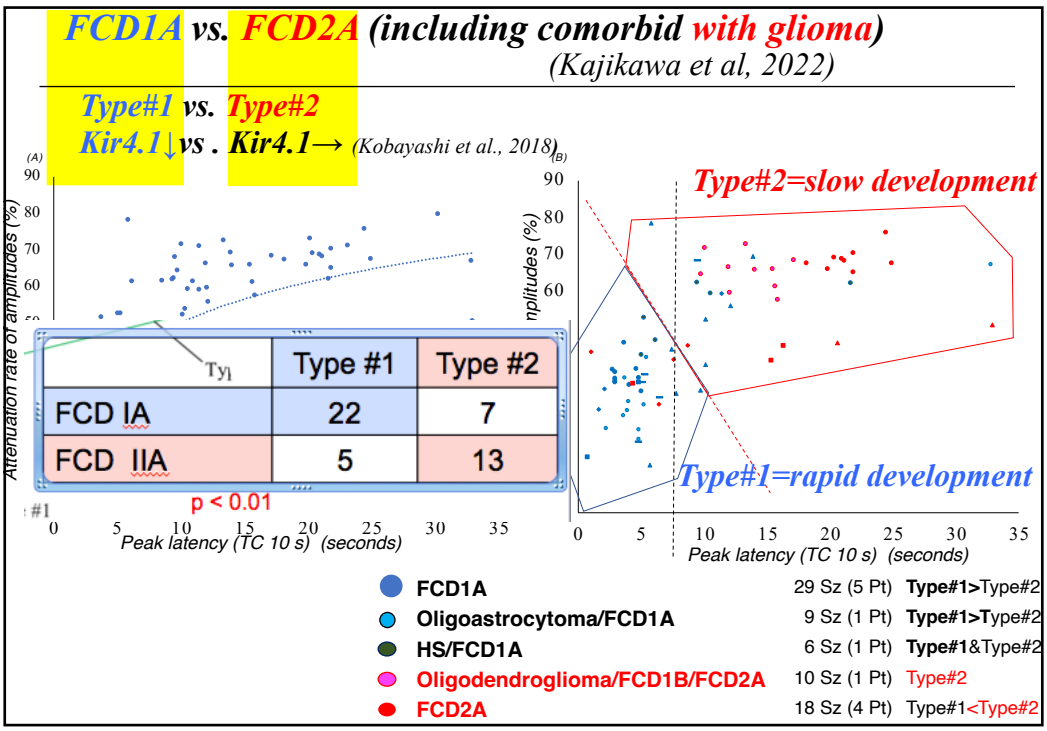

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61% (sz) 39%
67%(pt) 33%

表1　21患者120発作における発作時DC電位の2分類の比較

		Type #1 Rapid development（急峻勾配型DC電位）	Type #2 Slow development（緩徐勾配型DC電位）
発作回数（回）		73/120（60.8%）	47/120（39.2%）
患者数（人）		14/21（66.7%）	7/21（33.3%）
時定数10秒での評価項目			
TC 10sec	振幅（μV）	693.1±297.7	1,018.3±484.1
Latency at peak(sec)	頂点潜時（s）	4.5±2.4	15.8±6.6
時定数2秒での評価項目			
TC2sec	振幅（μV）	484.6±235.8	386.0±221.8
Latency at peak(sec)	頂点潜時（s）	2.8±2.1	10.2±6.1
時定数10秒から2秒に変換した際のAttenuation rate		小（36.4%）	大（65.3%）

DC：direct current．クラスター解析により同定された2群の発作時DC電位（type #1：急峻勾配型DC電位，type #2：緩徐勾配型DC電位）の各項目における比較を示した．Type #1は頂点潜時が短く振幅減衰率が低く，一方，type #2は頂点潜時が長く振幅減衰率が高い傾向にあった．（文献[30]の表1を日本語に訳して引用）

(Kajikawa et al, Clin Neurophysiol, 2022)

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Wide-band EEG: a mysterious and very useful technique

Long introduction

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4) Is it recorded by scalp EEG ?

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Received: 17 March 2023 | Revised: 26 September 2023 | Accepted: 26 September 2023

DOI: 10.1111/epi.17782

Epilepsia™

RESEARCH ARTICLE

Focal ictal direct current shifts by a time constant of 2 seconds were clinically useful for resective epilepsy surgery

Masaki Izumi[1,2] | Katsuya Kobayashi[3] | Shunsuke Kajikawa[4] | Kyoko Kanazawa[5] | Yutaro Takayama[6] | Keiya Iijima[7] | Masaki Iwasaki[7] | Yoji Okahara[2] | Seiichiro Mine[8] | Yasuo Iwadate[1] | Akio Ikeda[9]

Most commonly used digital EEG (TC of 2sec) in the world is available, being as good as EEG used lesser (long TC of 10 sec)

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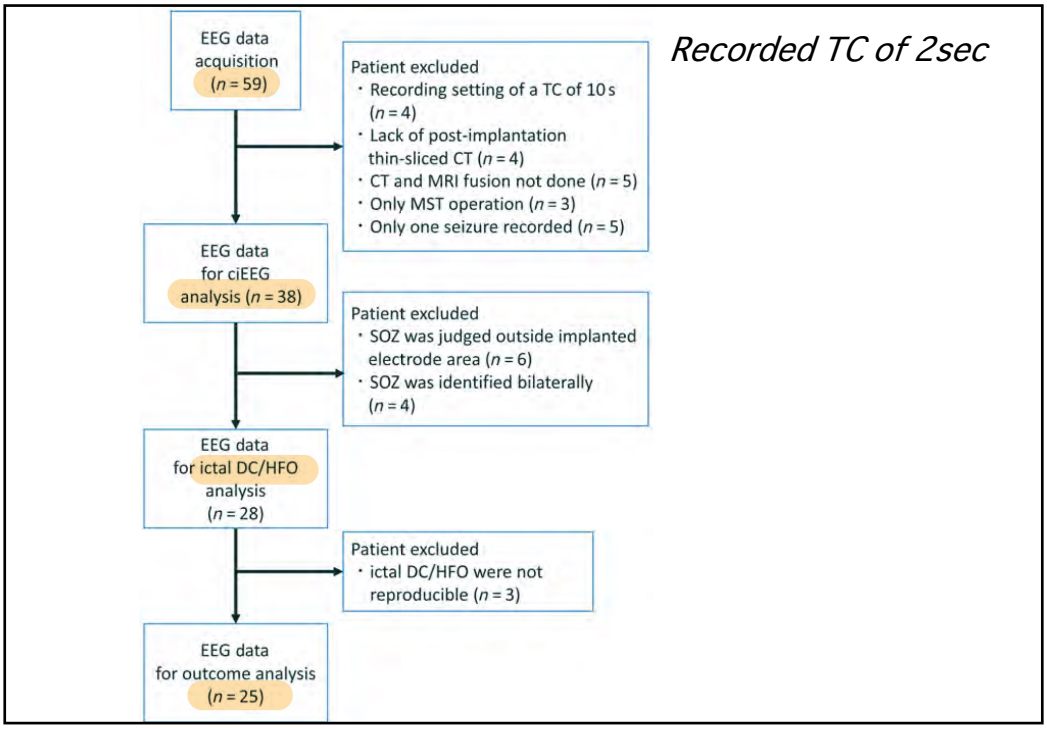
EEG data acquisition (n = 59)
Patient excluded
・Recording setting of a TC of 10 s (n = 4)
・Lack of post-implantation thin-sliced CT (n = 4)
・CT and MRI fusion not done (n = 5)
・Only MST operation (n = 3)
・Only one seizure recorded (n = 5)
EEG data for ciEEG analysis (n = 38)
Patient excluded
・SOZ was judged outside implanted electrode area (n = 6)
・SOZ was identified bilaterally (n = 4)
EEG data for ictal DC/HFO analysis (n = 28)
Patient excluded
・ictal DC/HFO were not reproducible (n = 3)
EEG data for outcome analysis (n = 25)
Recorded TC of 2sec

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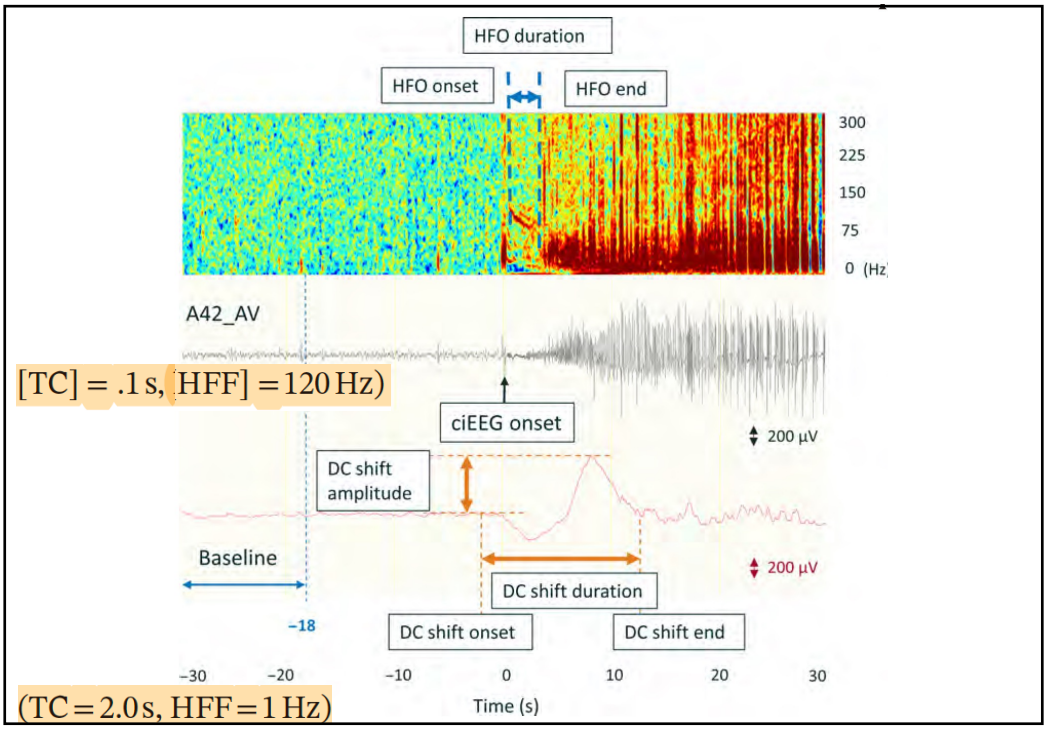
HFO duration
HFO onset
HFO end
300
225
150
75
0 (Hz
A42_AV
[TC] = .1 s, [HFF] = 120 Hz)
ciEEG onset
200 μV
DC shift amplitude
Baseline
200 μV
DC shift duration
−18
DC shift onset
DC shift end
−30
−20
−10
0
10
20
30
Time (s)
(TC = 2.0 s, HFF = 1 Hz)

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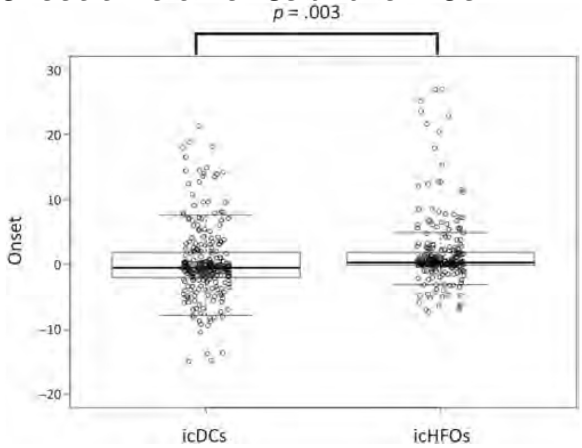
Onset time of icDCs and icHFOs



0.3 ± 5.5 s *1.7 ± 5.2 s*
(p < .005, t-test).

icDCs (142/147 seizures [96.6%]) and
icHFOs (135/147 seizures [91.8%]) occurred in all patients (100%).

1) TC is the attenuation marker for constant voltage activity

2) Brain DC (infraslow) activity is not constant, but dynamically changing with increment and decrement.

Application of LFF and HFF

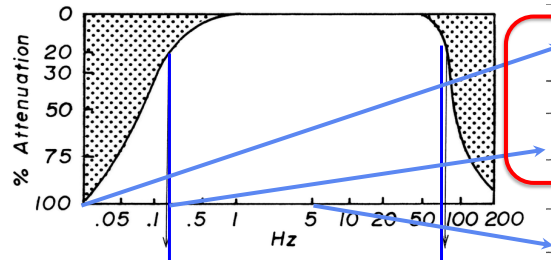


FIG. 8.32. Window based on LF filter 0.3 Hz and HF filter 70 Hz. Based on frequency response curve published by Grass Instrument Company (1973), with permission.

LFF
0.3 Hz
(TC=0.5 s)

HFF
70 Hz

Time constant (TC)
to filter out slow components

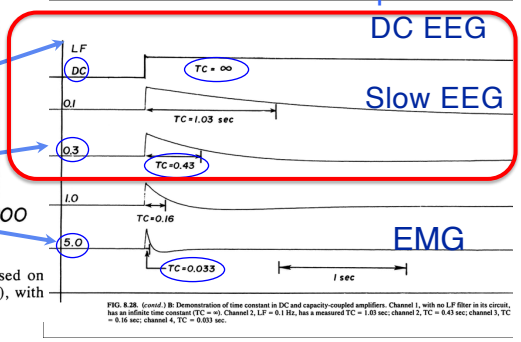


FIG. 8.28. (cont.) B: Demonstration of time constant in DC and capacity-coupled amplifiers. Channel 1, with no LF filter in its circuit, has an infinite time constant (TC = ∞). Channel 2, LF = 0.1 Hz, has a measured TC = 1.03 sec; channel 2, TC = 0.43 sec; channel 3, TC = 0.16 sec; channel 4, TC = 0.033 sec.

TC	x	LFF	=0.16(1/2π)
0.1 sec		1.6 Hz	
1 sec		0.16 Hz	
2 sec		0.08 Hz	
10 sec		0.016 Hz	

A comparison to epilepsy surgery outcome

	Retrospective study	Prospective study
Interictal HFO	•Jacobs J et al. Ann Neurol. 2010;67:209-220 •Akiyama T et al. Epilepsia 2011;52:1802–1811 • Van Klink NEC et al. Ann Neurol. 2017; 81: 664-676 others **Effective**	•Jacobs J et al. Neurology. 2018;91(11):e1040-e1052. 5 institutes •Zweiphenning W et al. Lancet Neurol. 2022; 21(11): 982–993 3 institutes **Non-effective**
Wide-band EEG (Ictal DC shifts ictal HFO)	• Nakatani M et al. Brain Commun. 2022; 4(5) : fcac222. doi: 10.1093/braincomms/fcac222 5 institutes in Japan **Effective**	SDG(subdural grid) → SEEG **Not yet**

(a table made by Prof. T Maehara, Tokyo, Japan)

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   AMED study in Japan (Multi-institutional study)
   Surgical outcome

2) 2 types of ictal DC shifts, and pathology

3) Is it recorded by TC 2sec EEG ?

4) **Is it recorded by scalp EEG ?**

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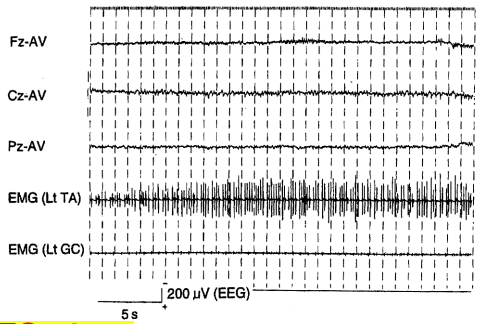
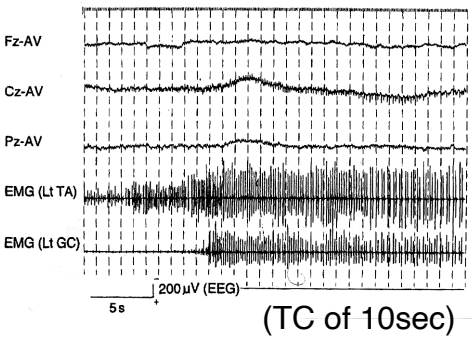
Scalp-recorded slow (DC) EEG with Lt focal motor seizures

Short duration



TC 10sec

Long duration



(TC of 10sec)

Ictal DC shifts (scalp recording):

Incidence rate: 14~40% (22%) in 73 seizures.

1) Detected particularly when seizures were clinically intense, but not in small seizures. (Ikeda et al., 1999)

-> Future advancement in recording condition is warranted.

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Currently now ready for DC shifts & HFO analysis for scalp EEG

1) 1990s, waveform analysis of HFO (SEPs, spikes) was introduced.
2) It was done by high value of LFF, but was not ideal method or rather skeptical because it would easily produce artifact mimicking HFO.

3) We now have strong tools and situation after 2000 ! as follows

1. **Wide-band EEG analysis**
2. **Basic and animal study HFO for epileptic activity**
3. **Wide frequency range time-frequency analysis program**
4. **TC 2sec is better to record DC shifts in scalp EEG than TC 10sec**

It is ready to apply DC shifts and HFO for scalp EEG

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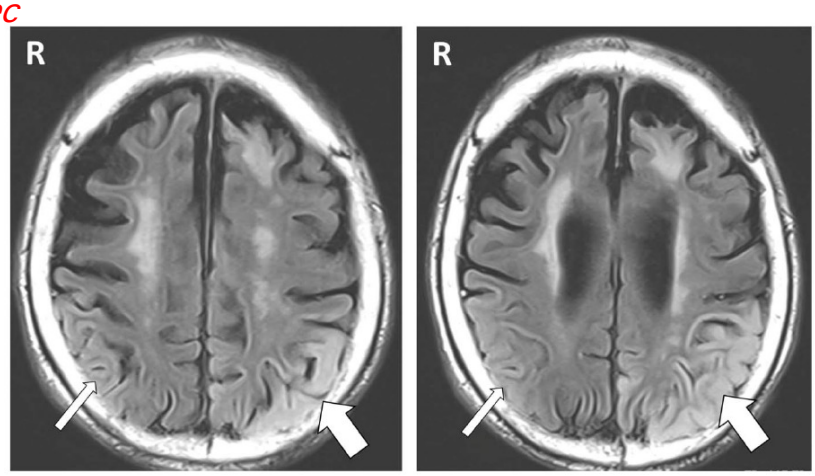
Scalp EEG Could Record Both Ictal DC Shift and HFO Together Even With a Time Constant of 2 Seconds (J Clin Neurophysiol 2020;37: 191–194)

Tomohiko Murai,* Takefumi Hitomi,*† Masao Matsuhashi,‡ Riki Matsumoto,* Yuki Kawamura,§ Masutaro Kanda,§ Ryosuke Takahashi,* and Akio Ikeda‡

TC 2sec



(Murai et al., 2020)

acute chronic

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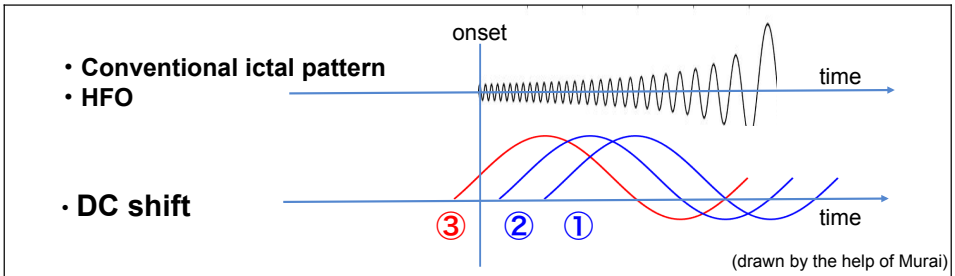
Hypothesis of active vs. passive DC shift in the ictal period



(drawn by the help of Murai)

		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	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)

(Ikeda et al., 2020)

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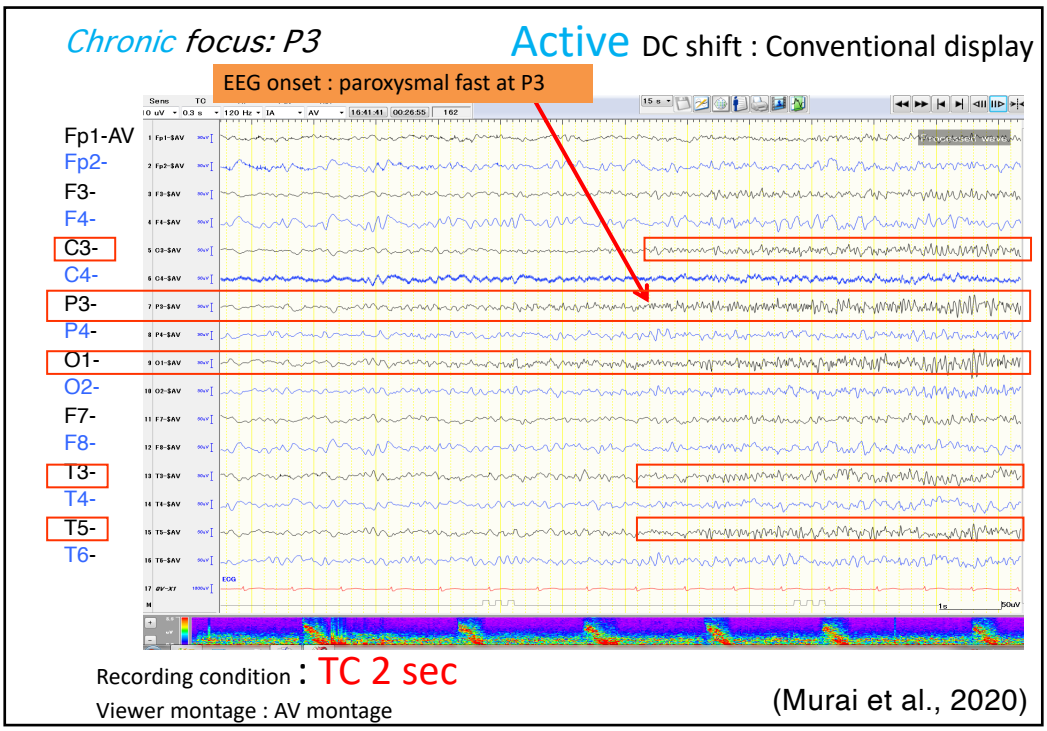
Chronic focus: P3
Active DC shift : Conventional display
EEG onset : paroxysmal fast at P3
Fp1-AV
Fp2-
F3-
F4-
C3-
C4-
P3-
P4-
O1-
O2-
F7-
F8-
T3-
T4-
T5-
T6-
Recording condition : TC 2 sec
Viewer montage : AV montage
(Murai et al., 2020)

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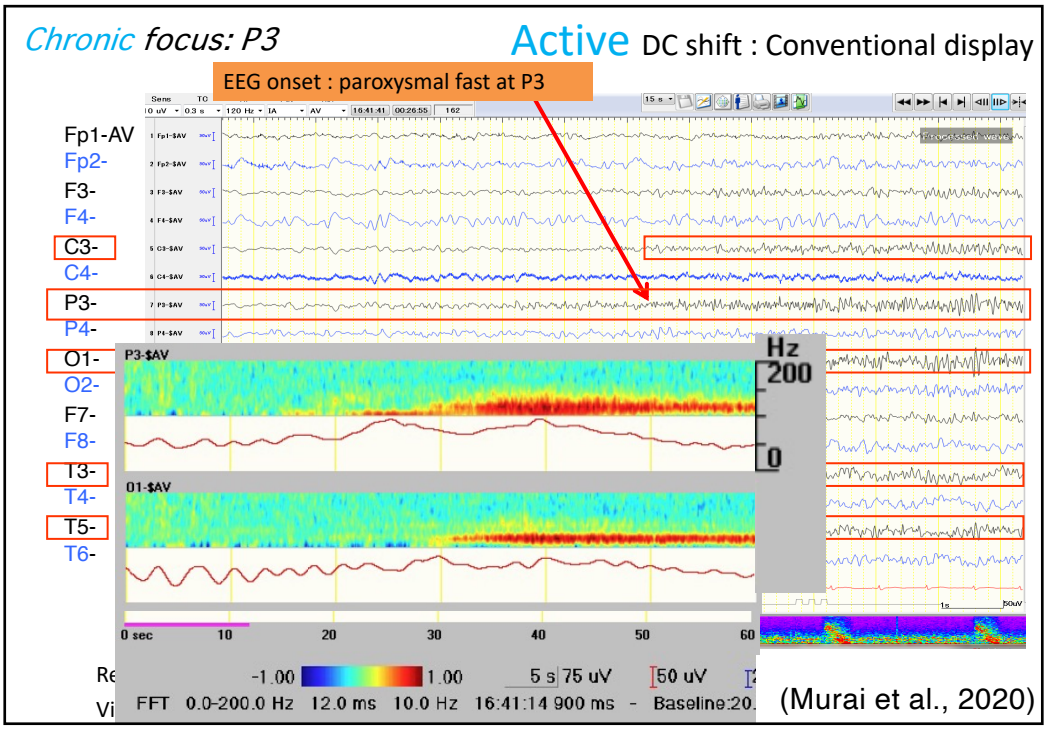
Chronic focus: P3
Active DC shift : Conventional display
EEG onset : paroxysmal fast at P3
Fp1-AV
Fp2-
F3-
F4-
C3-
C4-
P3-
P4-
O1-
O2-
F7-
F8-
T3-
T4-
T5-
T6-
P3-$AV
O1-$AV
Hz
200
0
0 sec
10
20
30
40
50
60
-1.00
1.00
5 s
75 uV
50 uV
FFT 0.0-200.0 Hz 12.0 ms 10.0 Hz 16:41:14 900 ms - Baseline:20.
(Murai et al., 2020)

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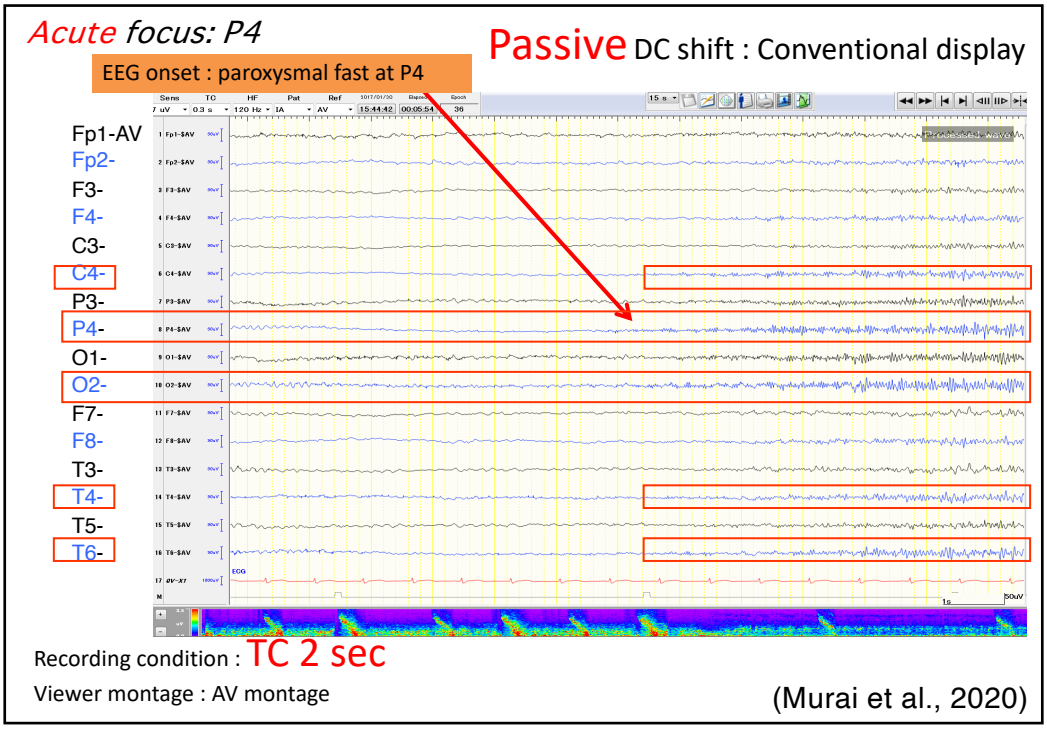
Acute focus: P4
EEG onset : paroxysmal fast at P4
Passive DC shift : Conventional display
Fp1-AV
Fp2-
F3-
F4-
C3-
C4-
P3-
P4-
O1-
O2-
F7-
F8-
T3-
T4-
T5-
T6-
Recording condition : TC 2 sec
Viewer montage : AV montage
(Murai et al., 2020)

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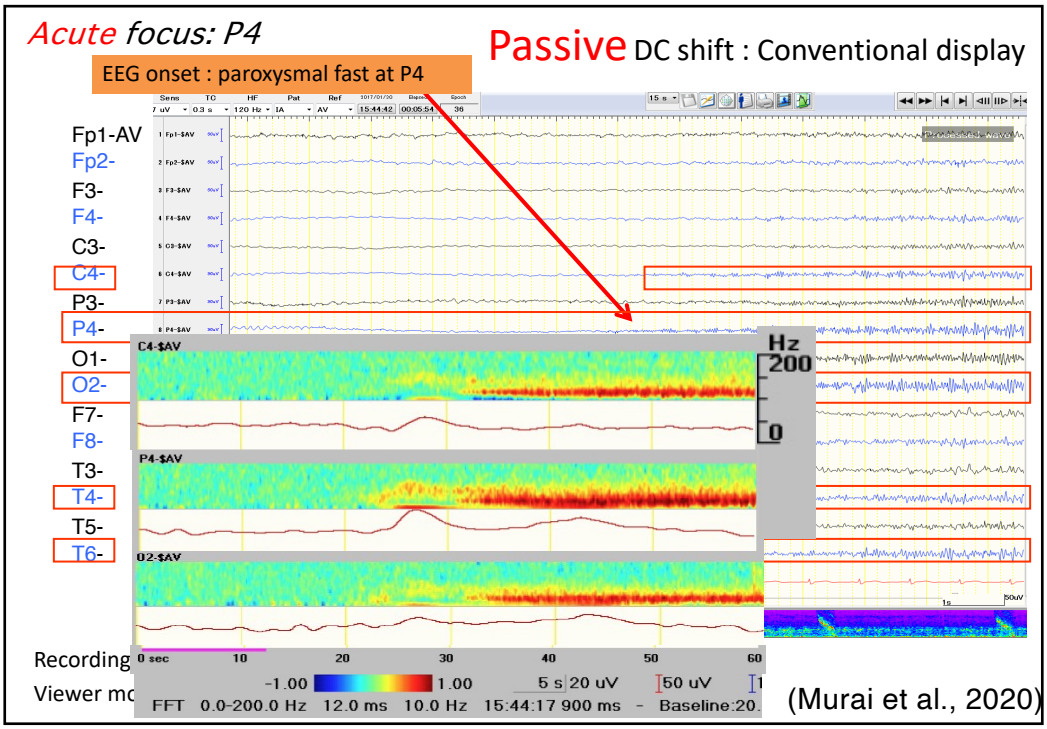
Acute focus: P4
EEG onset : paroxysmal fast at P4
Passive DC shift : Conventional display
Fp1-AV
Fp2-
F3-
F4-
C3-
C4-
P3-
P4-
O1-
O2-
F7-
F8-
T3-
T4-
T5-
T6-
C4-$AV
P4-$AV
O2-$AV
Hz
200
0
0 sec
10
20
30
40
50
60
-1.00
1.00
5 s 20 uV
50 uV
FFT 0.0-200.0 Hz 12.0 ms 10.0 Hz 15:44:17 900 ms - Baseline:20.
(Murai et al., 2020)

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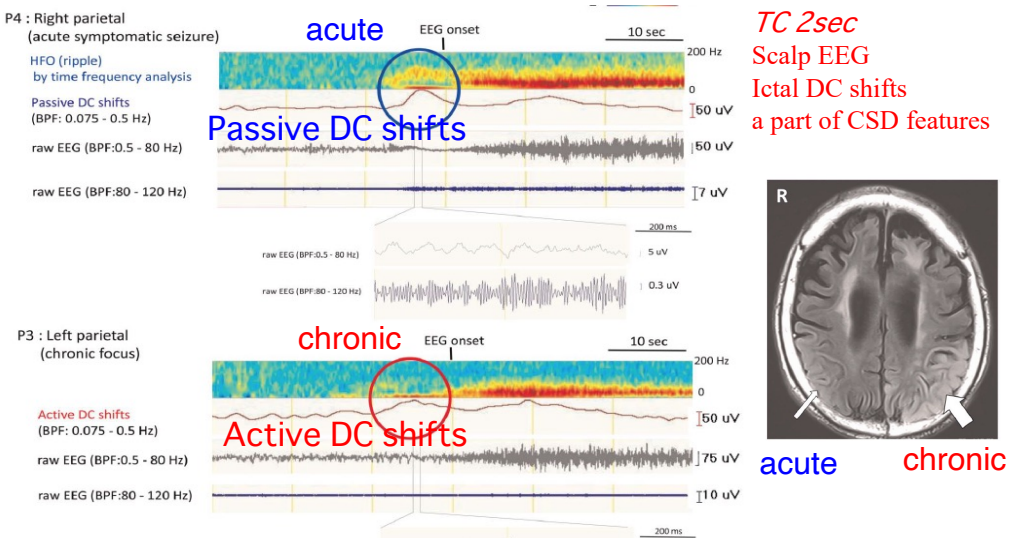

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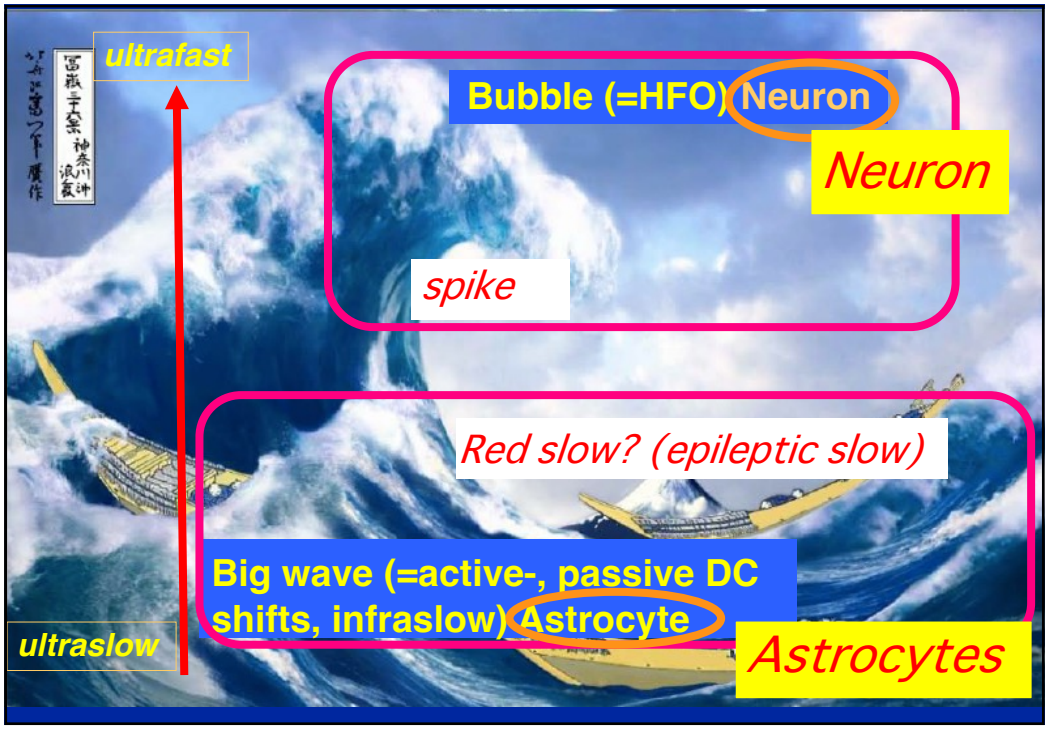

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