小動物用MRIを用いたてんかんモデルマウスにおけるけいれん発作発症に伴う脳内変化の評価

The Assessment of Brain Functions in the Proconvulsants-provoked Convulsive Seizure Model Mice using Magnetic Resonance Imaging

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徳島文理大・香川薬・薬物治療

（様式2－A）口頭発表におけるCOI状態の開示
申告すべきCOI状態がない場合

日本てんかん学会
COI 開示

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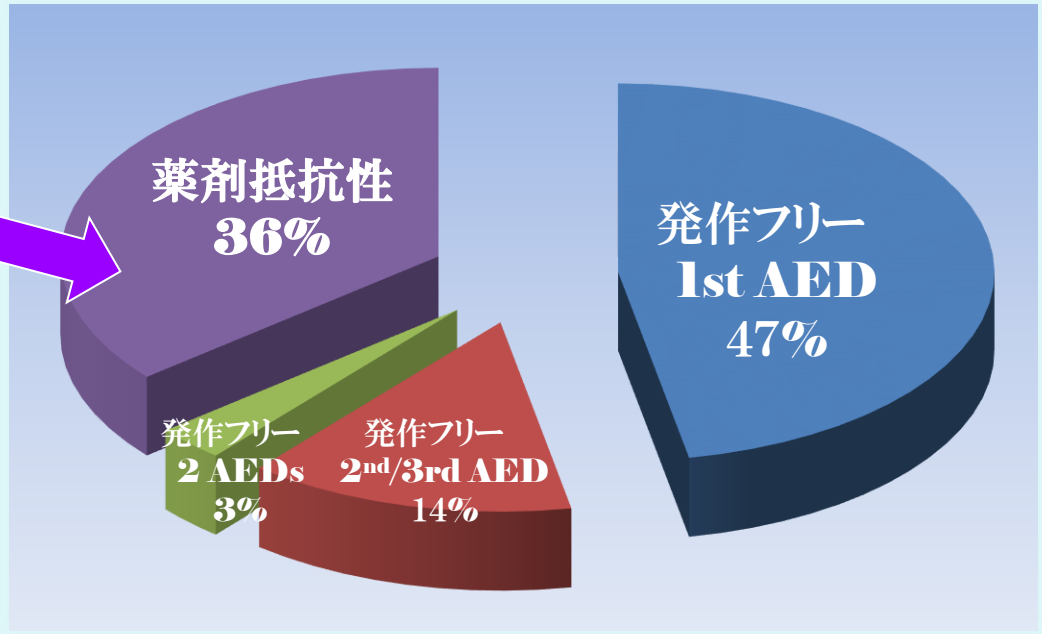
演題発表に関連し、開示すべきCOI 関係にある　企業などはありません。

薬剤治療抵抗性てんかん
Pharmacoresistant Epileptics

てんかん有病率　→　100人に 0.8～1人
(日本で 約100万人、全世界では6000万人)

新しい作用機序に基づく
新規治療薬の開発が必要！



てんかん発作発症機構および
発作抑制機構の解明

(症候性てんかん40%, 特発性てんかん26%)
AED: 抗てんかん薬
Kwan et al., 2000, 343:314-319, N Engl J Med

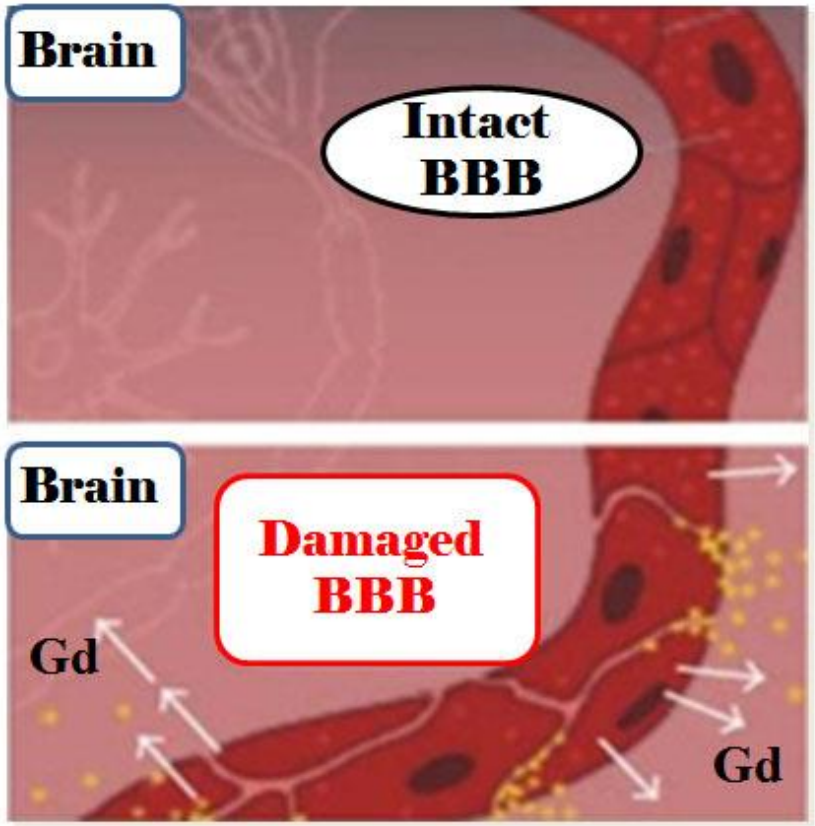
てんかんの病因とBBB
The Etiology of Epilepsy and BBB

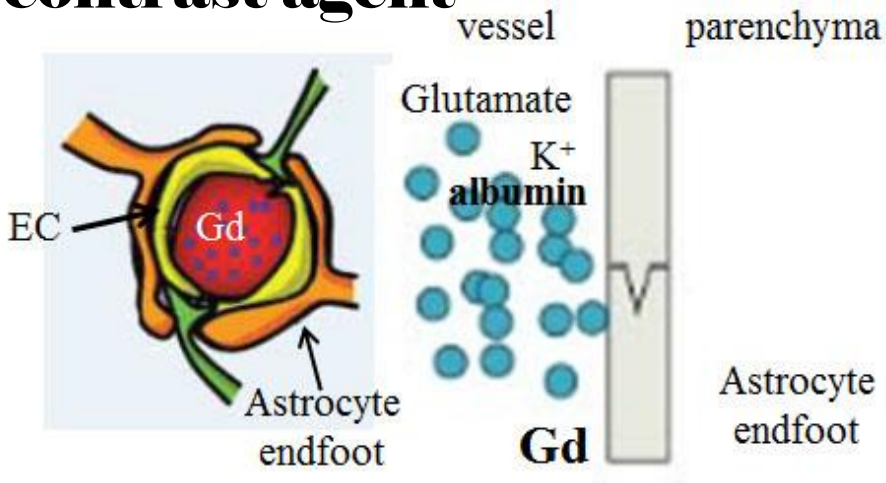
1. 血液脳関門（Blood-brain barrier; BBB）との関係
   - ✓ 薬物トランスポーター仮説
     BBBに存在する薬物トランスポーター（排泄機構）の異常活性
   - ✓ BBB機能不全仮説

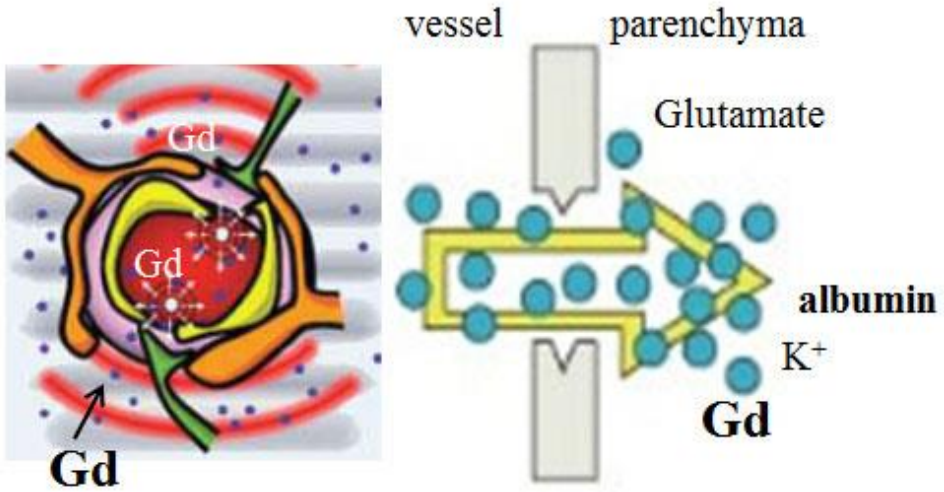
2. 抗てんかん薬（AED）妥当性
   - ✓ てんかん原性ネットワーク仮説
     同一分類されたてんかん・発作型でも発症メカニズムが異なる

Basic Principle of Gd-Enhanced Magnetic Resonance Imaging (GdEMRI)

✓ **Use BBB impermeable Gadolinium (Gd) as image MR contrast agent**



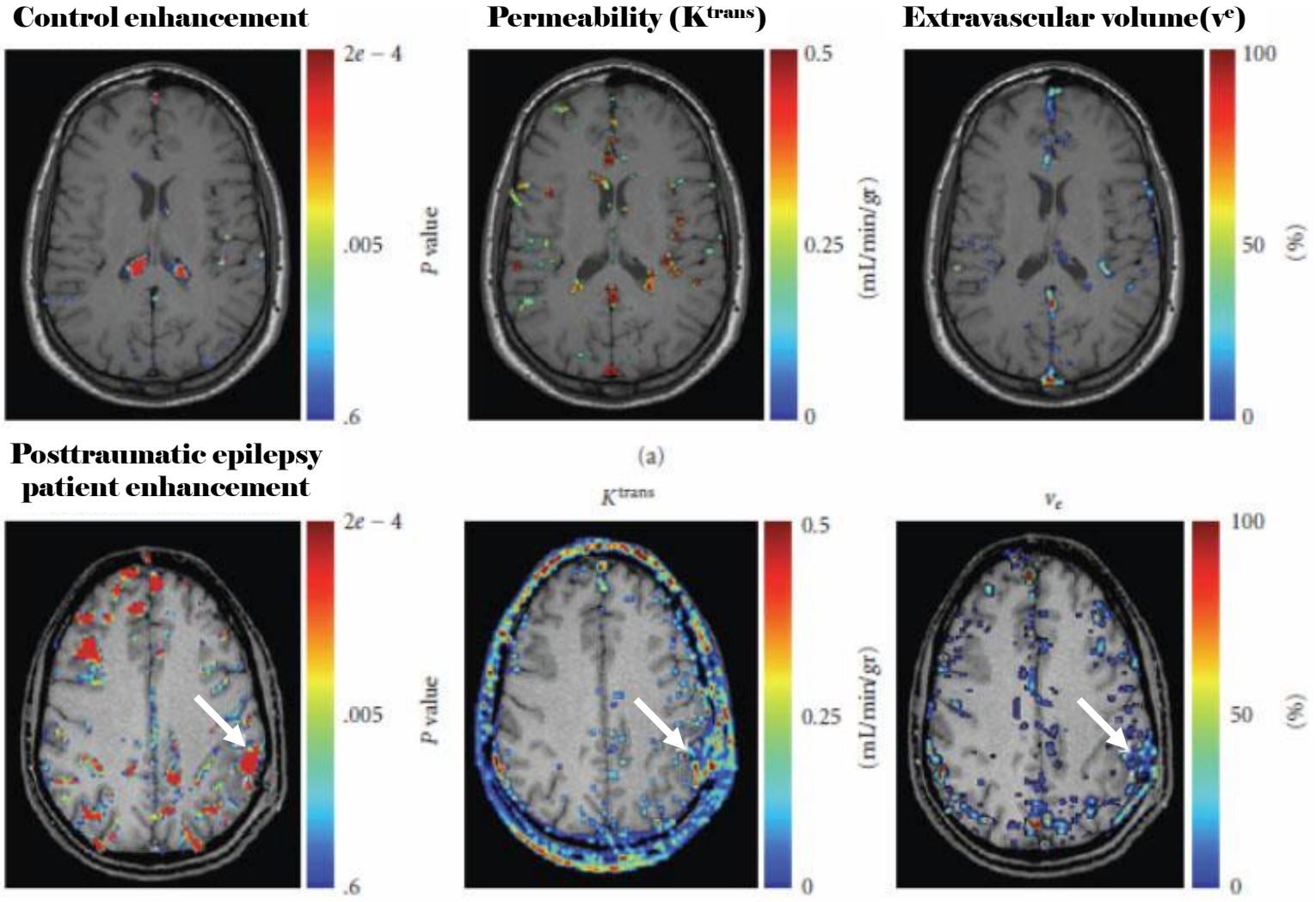




BBB Breakdown Following Traumatic Brain Injury

No BBB disruption in control subject

Increased BBB permeability in a 28-year-old PTE patient 10 days following TBI

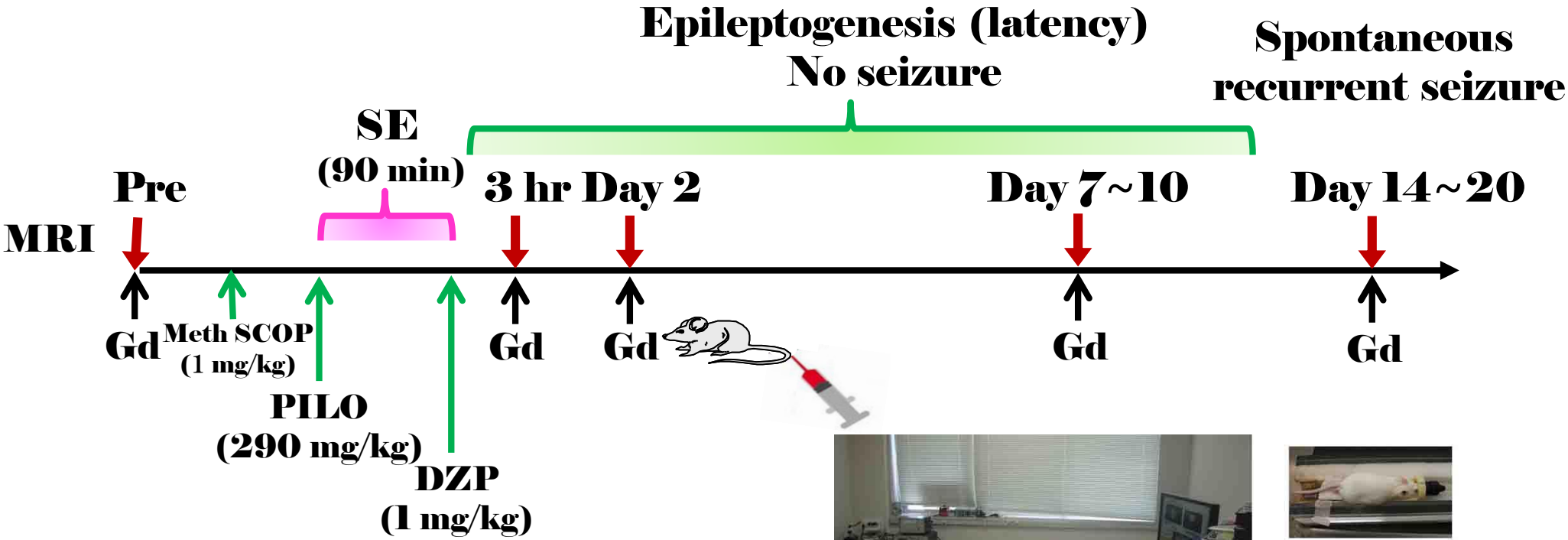


GdEMRI using Gd-DTPA（マグネビスト）

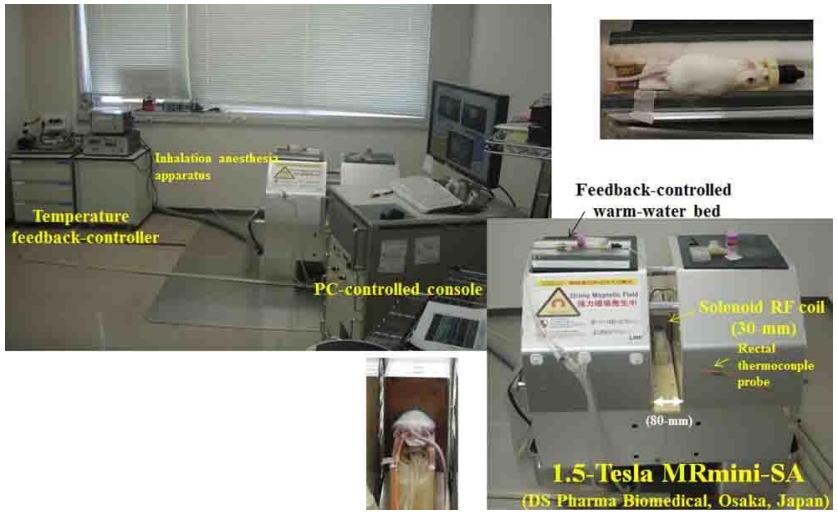
Cardiovascular Psychiatry and Neurology 2011

Epileptic Seizures in PILO-SE mice

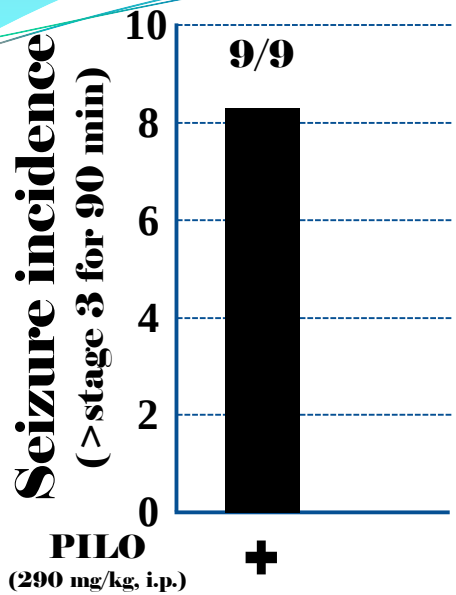
Experimental schedule

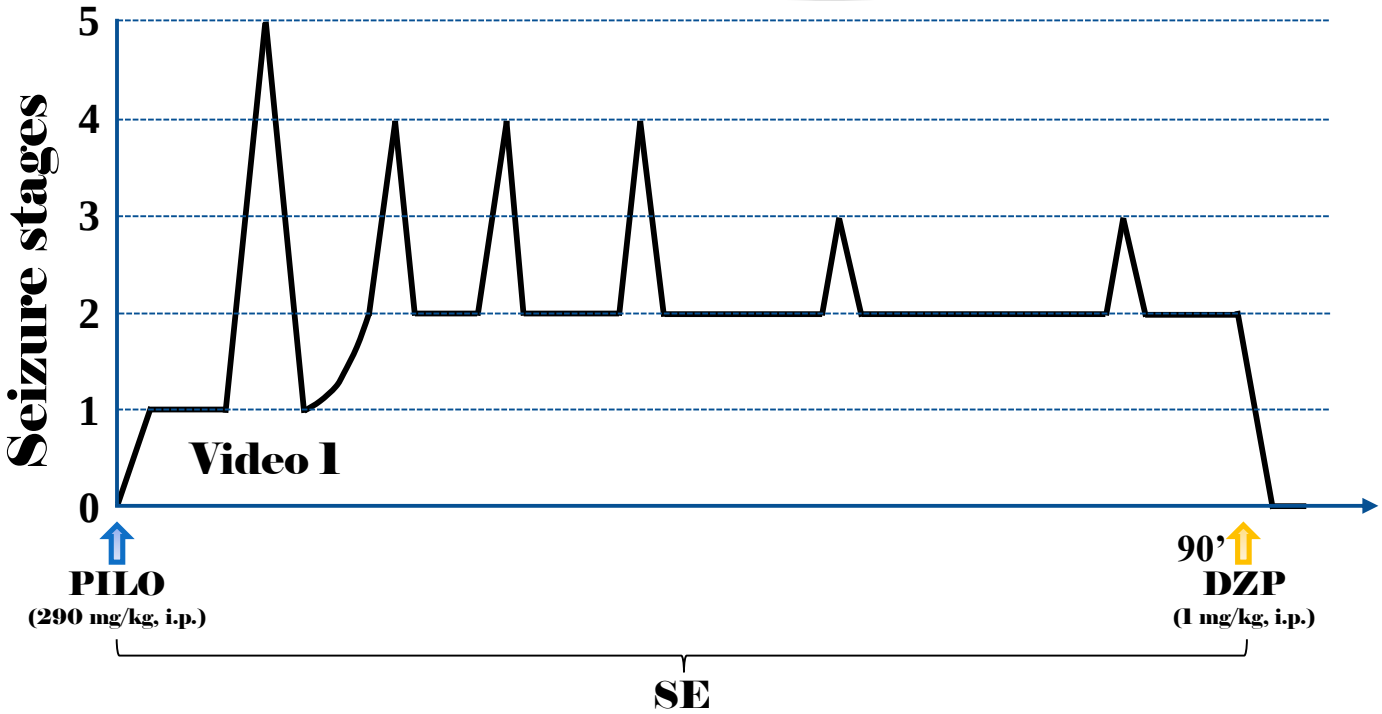


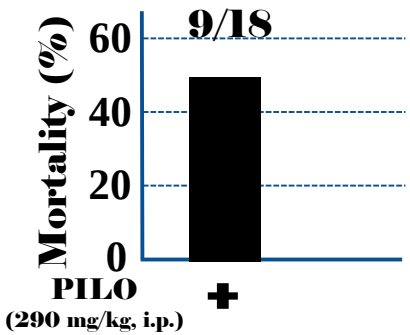
SE: Status Epileptics



Epileptic Seizures in PILO-SE mice

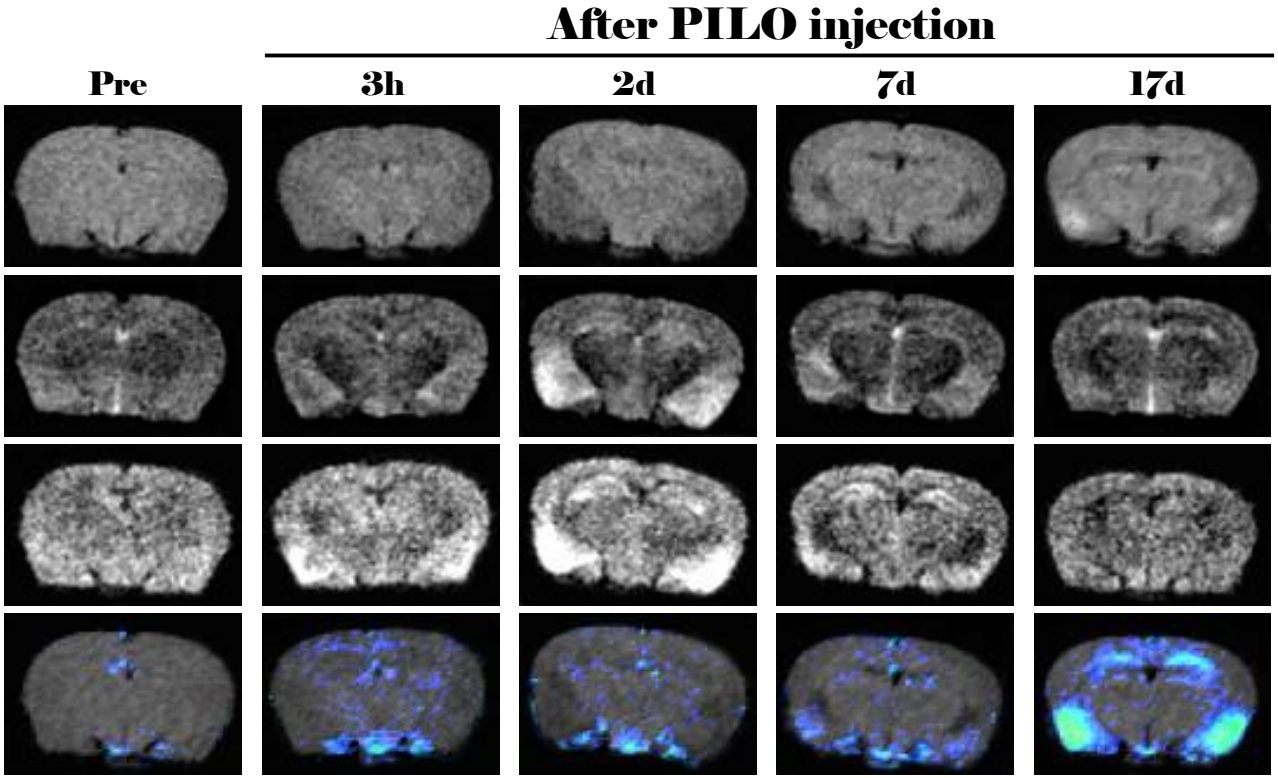


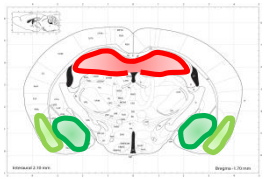




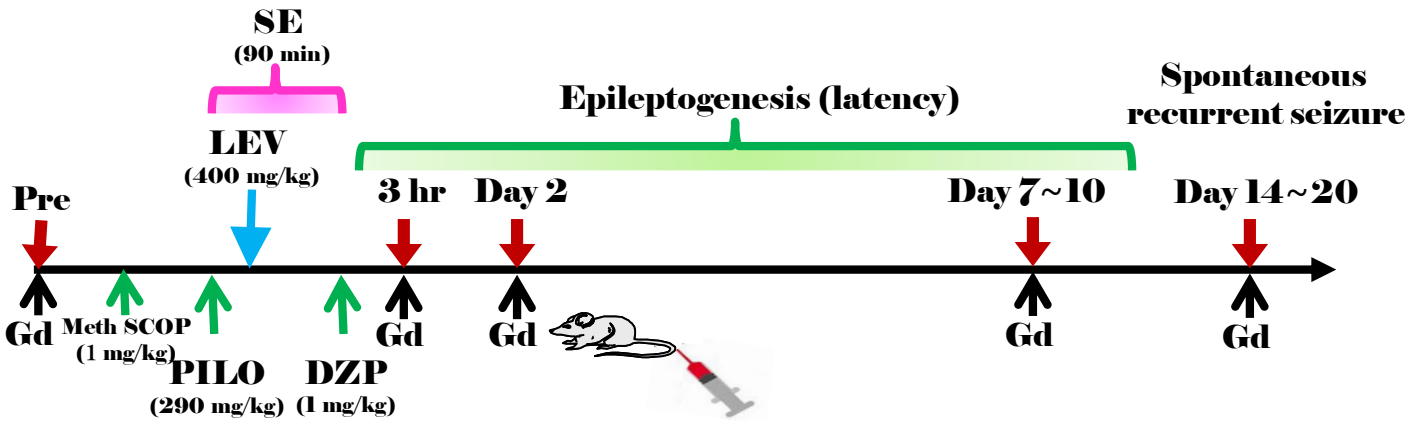
Stage	Seizures
0	normal
1	immobilization
2	facial, vibrissal and forelimb clonus (short myoclonic jerk)
3	myoclonic jerking consisted of a whole body jerk with or without irregular, bilateral forelimb movements
4	generalized clonic seizures (GCS) with kangaroo posture
5	generalized tonic–clonic seizures (GTCS) with loss of posture tone.

BBB Breakdown in PILO-SE mice





Hippocampus, amygdala and piriform cortex

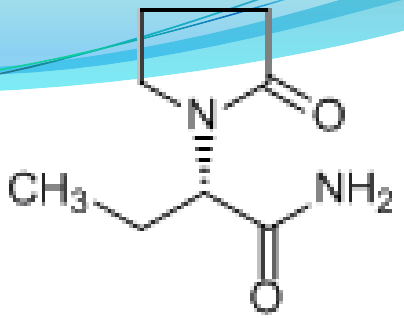


Changes in MR parameters following prolonged seizures

T_1WI	↑		Atrophy: Cell loss
	Edema: Vasogenic	Cytotoxic	
T_2WI	↑	↑	Gliosis
DWI	↓	↑	Gliosis?
GdEMRI (T_1WI)	↑		BBB leakage

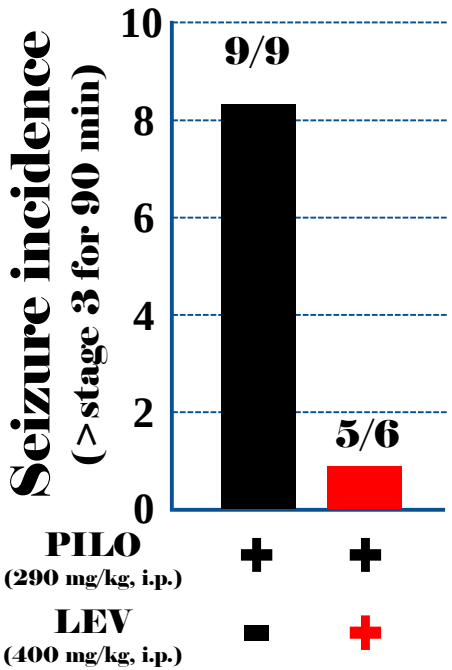
The underlying mechanisms of these changes are in most cases not well known.

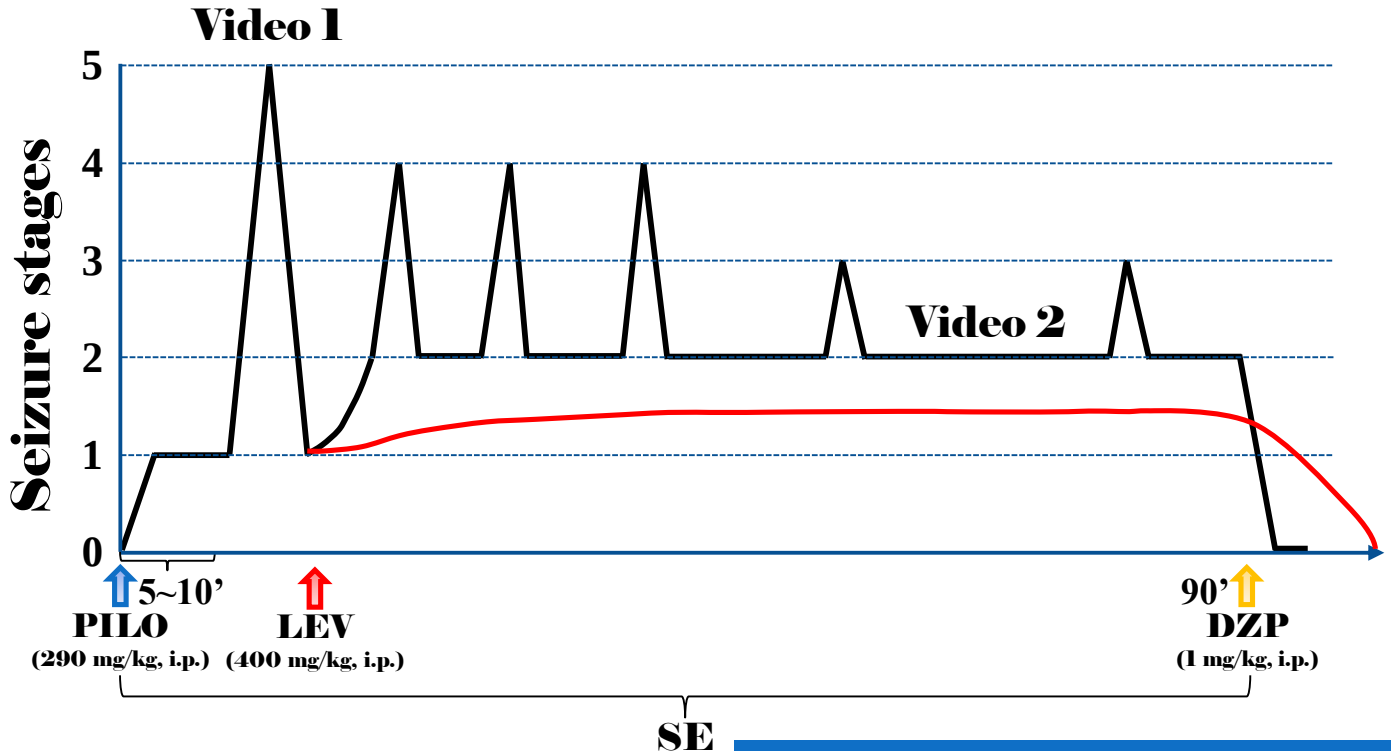
Levetiracetam (E Keppra®)

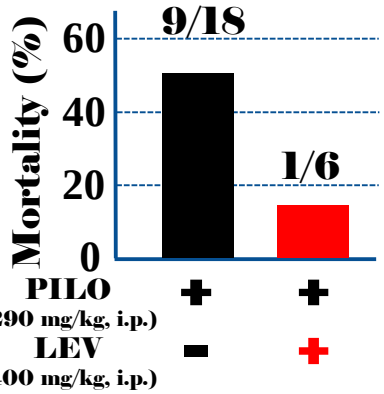


- **Levetiracetam (LEV) is approved for treatment of partial, myoclonic, and tonic-clonic seizures.**
- **LEV, add-on therapy, is also effective for refractory epilepsy.**
  (LEV improves memory in mild cognitive impairment?)
- **LEV binds to the synaptic vesicle protein SV2A, and inhibits presynaptic calcium channels to modulate of synaptic neurotransmitter release in the brain.**
- **The proposed therapeutic range for seizure control is 11 μg/mL (60 μM) (5-30 μg/mL, 30-180 μM).**
- **Pharmacokinetics of LEV are affected by renal function.**

Effect of LEV on PILO-induced Seizures during Status Epileptics



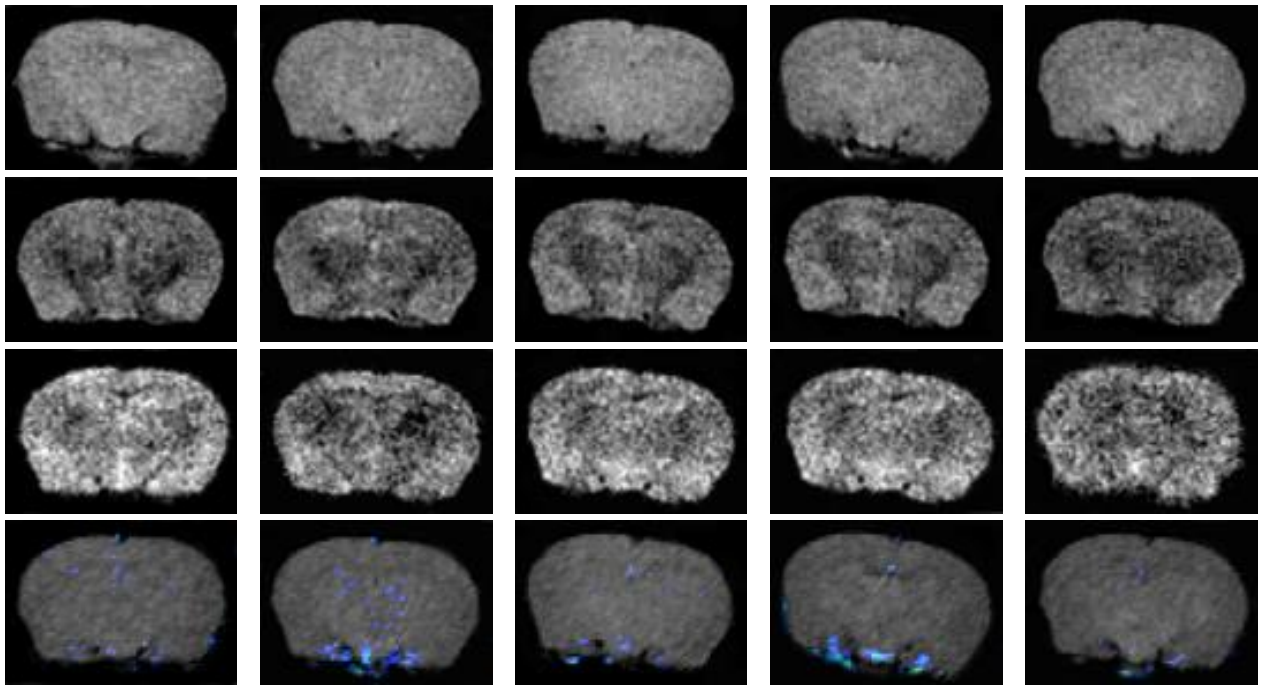




Video 2

Effects of LEV on BBB Breakdown in PILO-SE mice

Treatment with LEV after PILO injection

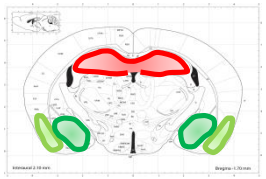


T_1WI
TR: 500 msec
TE: 9 msec
NEX=8

T_2WI
TR: 2500 msec
TE: 69 msec
NEX=4

DWI
TR: 2500 msec
TE; 69 msec
b-factor: 800 sec/mm²
NEX=4

GdEMRI
TR: 500 msec
TE: 9 msec
NEX=4



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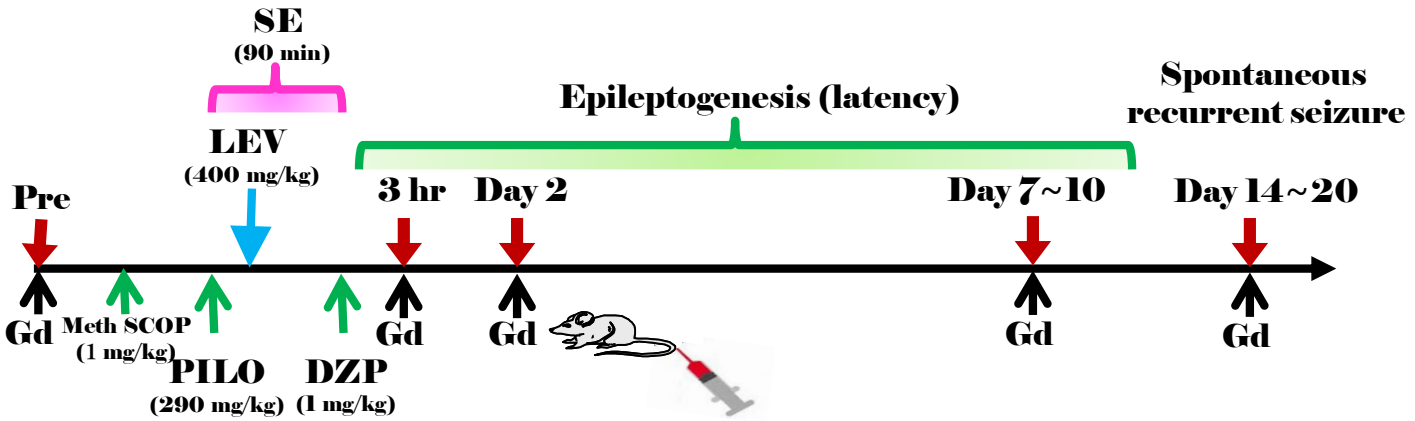
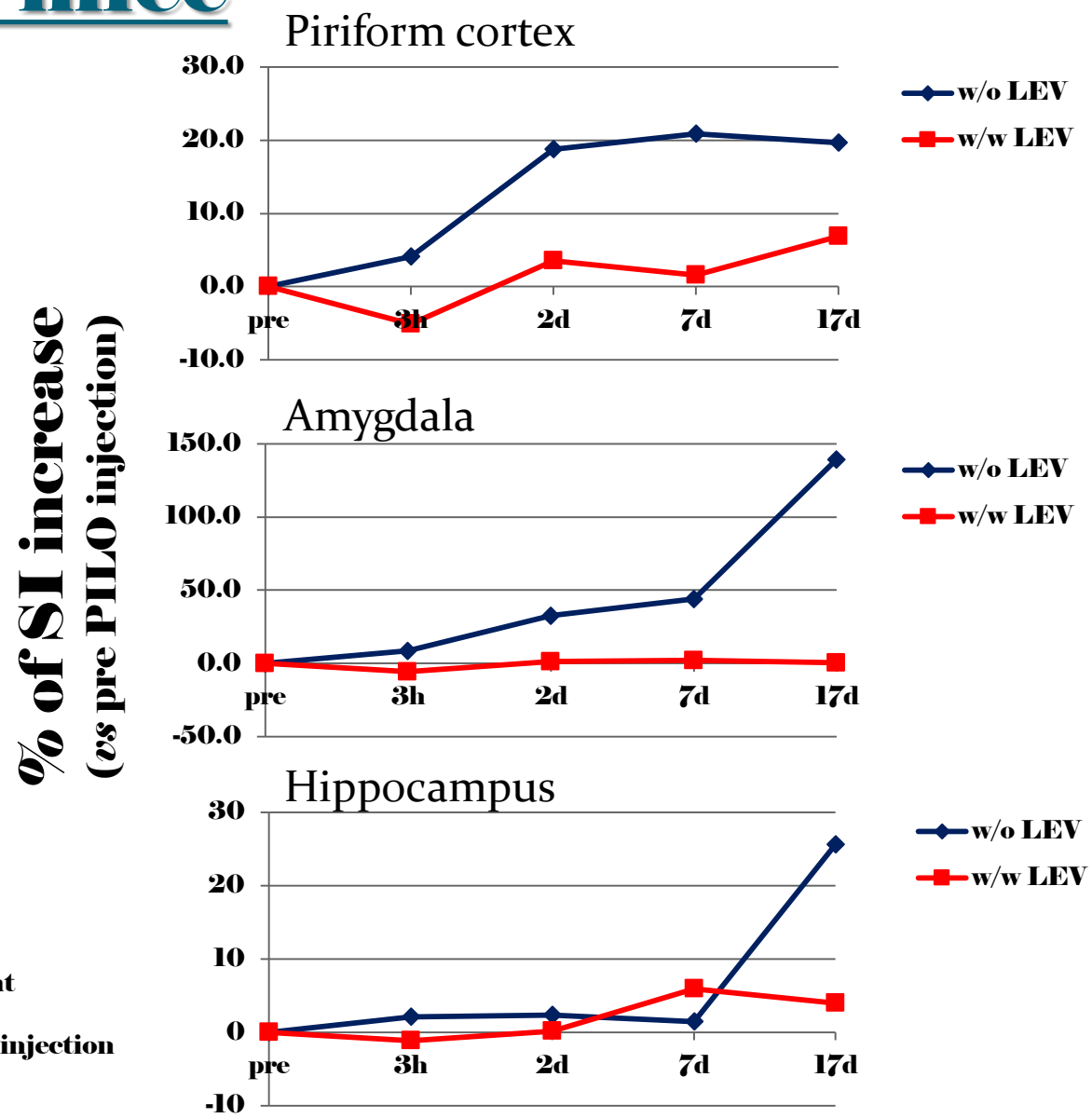


Effects of LEV on BBB Breakdown in PILO-SE mice

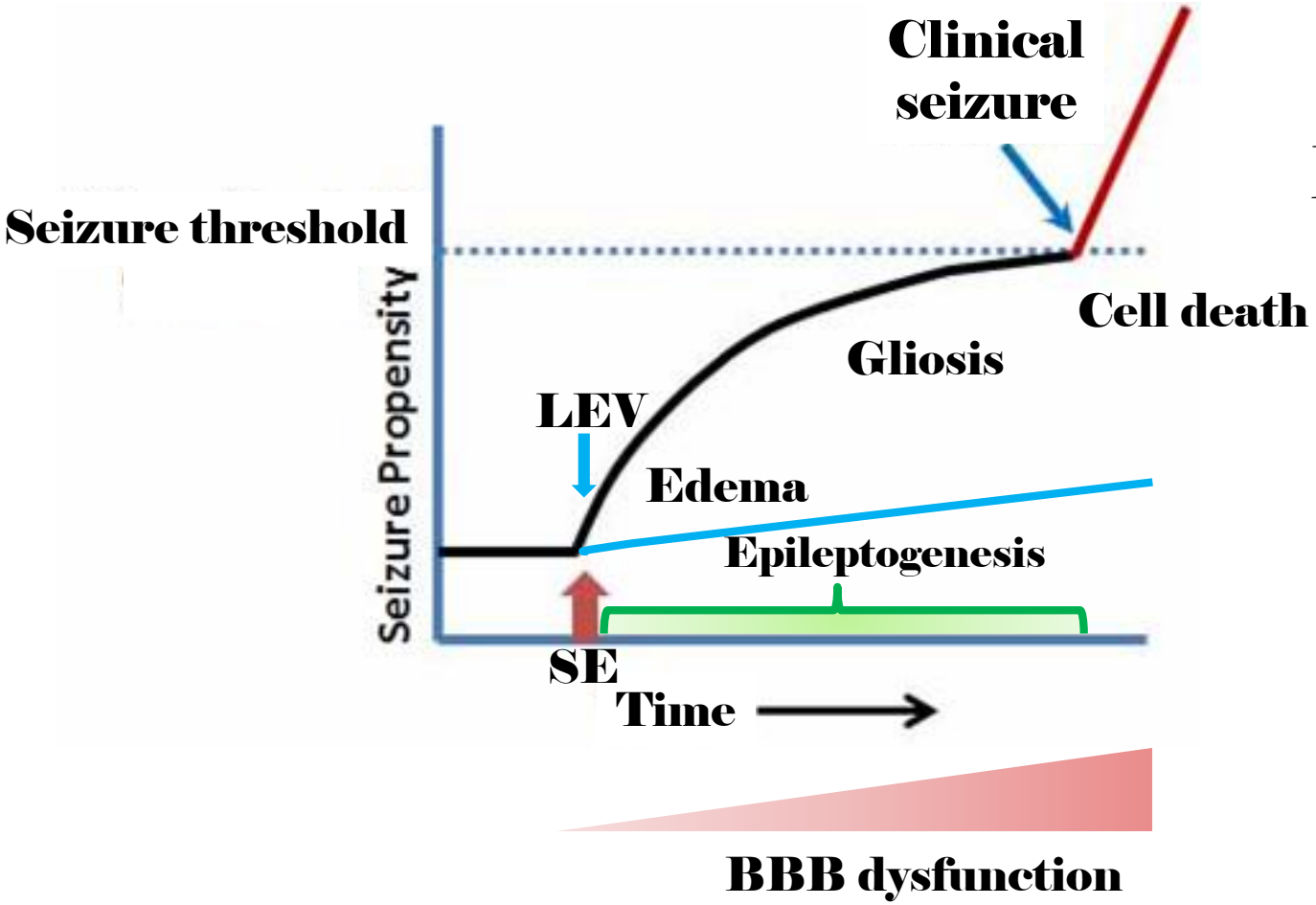


$$C_t(\%) = \frac{R_t - R_{pre}}{R_{pre}} X100$$

C_t: % of change at the time point
R_t: SI in ROI at the time point
R_{pre}: SI in ROI prior to PILO injection
SI: Signal Intensity

Hypothetical Epileptogenic Events and Treatment

PILO-SE model



LEV服用でSEを抑制

↕ ?

BBB保護

まとめ Take home massages

- PILO-SE後・・・
  - 2日目でHippocampus、AmygdalaとPiriform cortexでT_2WとDWの信号強度が上昇 ⟶ 細胞障害性浮腫
  - 17日目でAmygdalaとPiriform cortexでT_1Wの信号強度が上昇 ⟶ 細胞死
  - BBB透過性亢進
    - 内側側頭葉部位(Amygdala) から起きる
      - ✓潜在期(latent)から慢性期(chronic) に増悪
- 1st PILO誘発GTCS後LEV投与・・・
  - PILO-SEの発症を抑制
  - PILO誘発BBB透過性亢進を抑制
- LEV服用でけいれん準備性(seizure susceptibility)減弱または消失

  ⟶BBB保護作用？

Brain insults and BBB dysfunction