How does epilepsy get complicated?

altered molecules, cells and circuits

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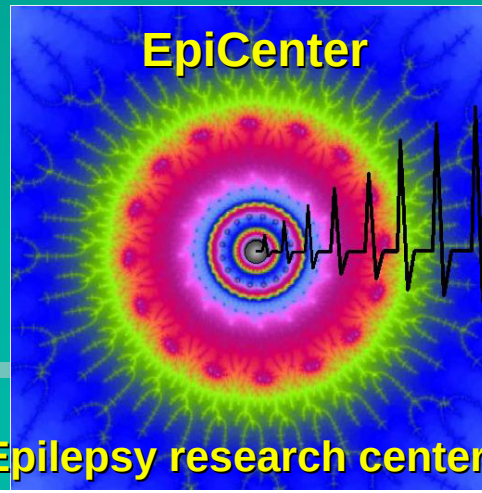

What is complicated epilepsy?

- Seizures become unresponsive to medications
- Seizures evolve, get worse….
- Epilepsy interferes with normal life:
  - Depression
  - Cognitive difficulties
  - Financial, social and other issues.

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~30% of people with epilepsy become resistant to medications

Early Identification of Refractory Epilepsy*

Patrick Kwan, M.D., and Martin J. Brodie, M.D.

***NEJM,* 342:314-319, 2000**

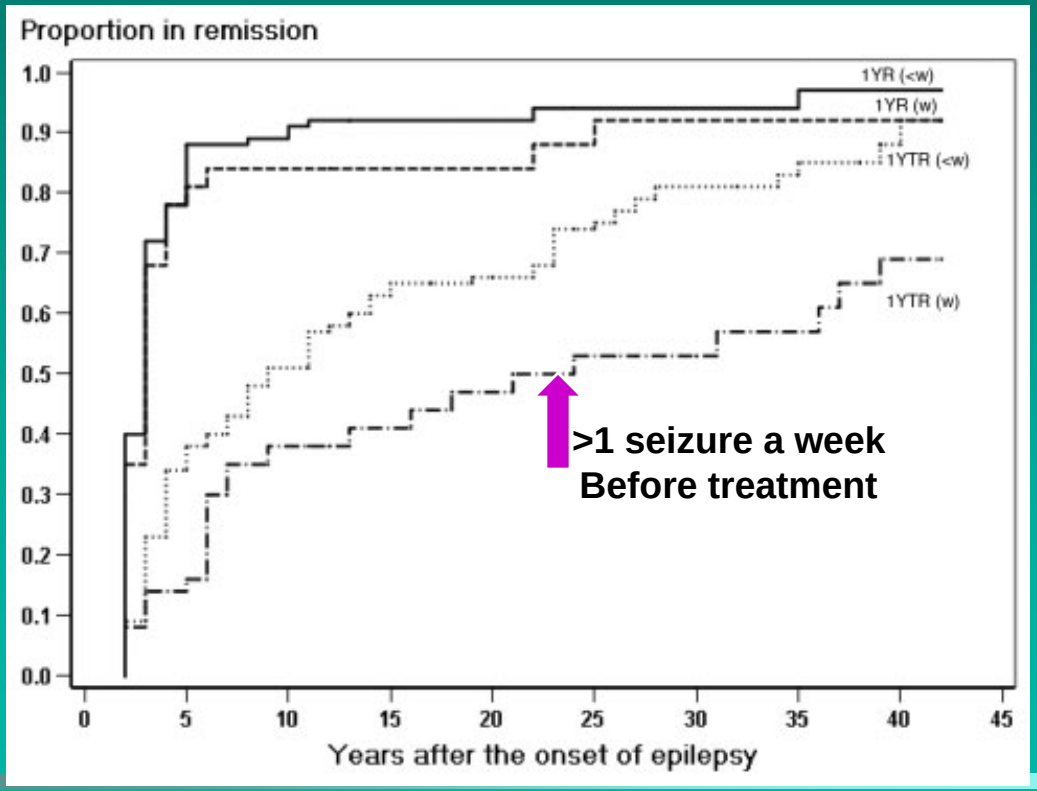
The prevalence of persistent seizures was higher in patients with:

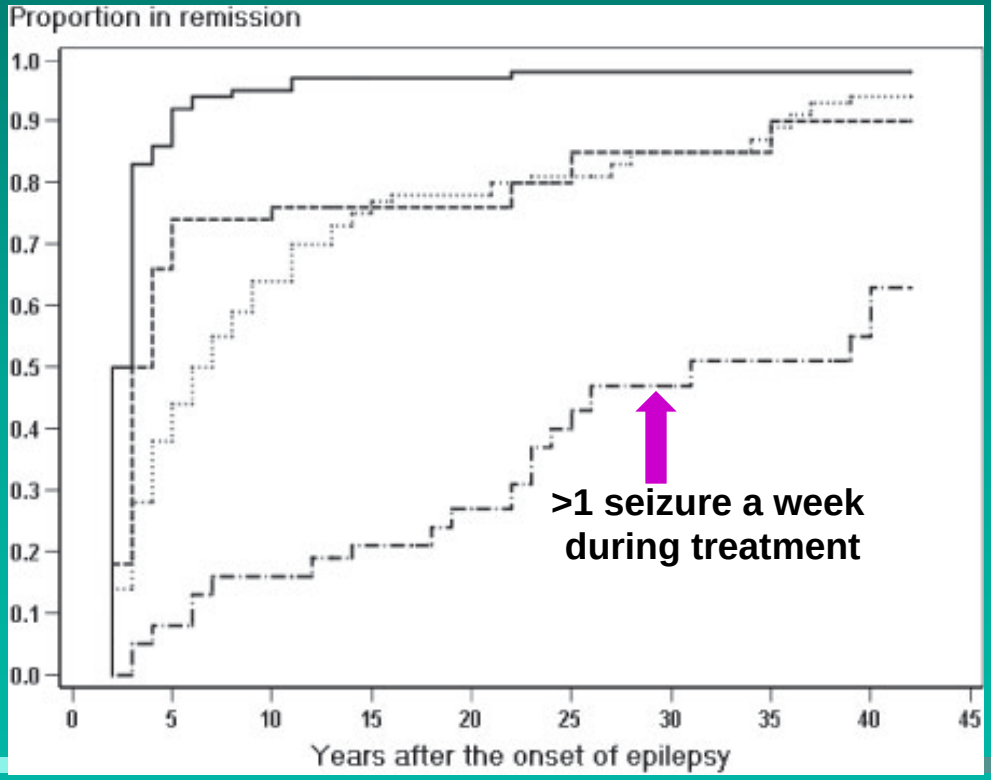
1. Symptomatic epilepsy rather than idiopathic epilepsy (P=0.004)
2. More than 20 seizures before starting treatment (P<0.001)

***Epilepsy that does not respond to treatment**

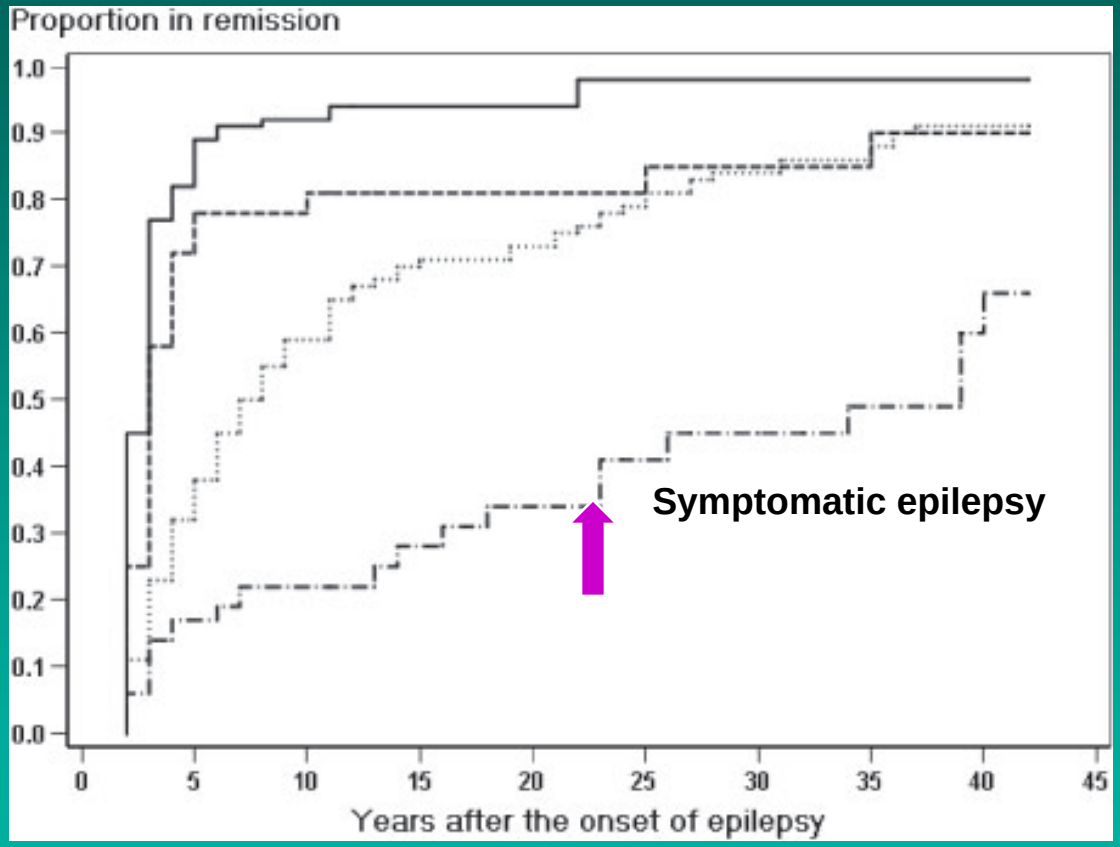
Early seizure frequency and aetiology predict long-term medical outcome in childhood-onset epilepsy

Matti Sillanpaa, Dieter Schmidt, Brain, 2009





Role of the basis (etiology) of the Epilepsy in determining if it gets complicated



All patients with: (a) idiopathic or cryptogenic epilepsy, and (b) having less than weekly pretreatment seizures entered 1YR

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  How does this happen?
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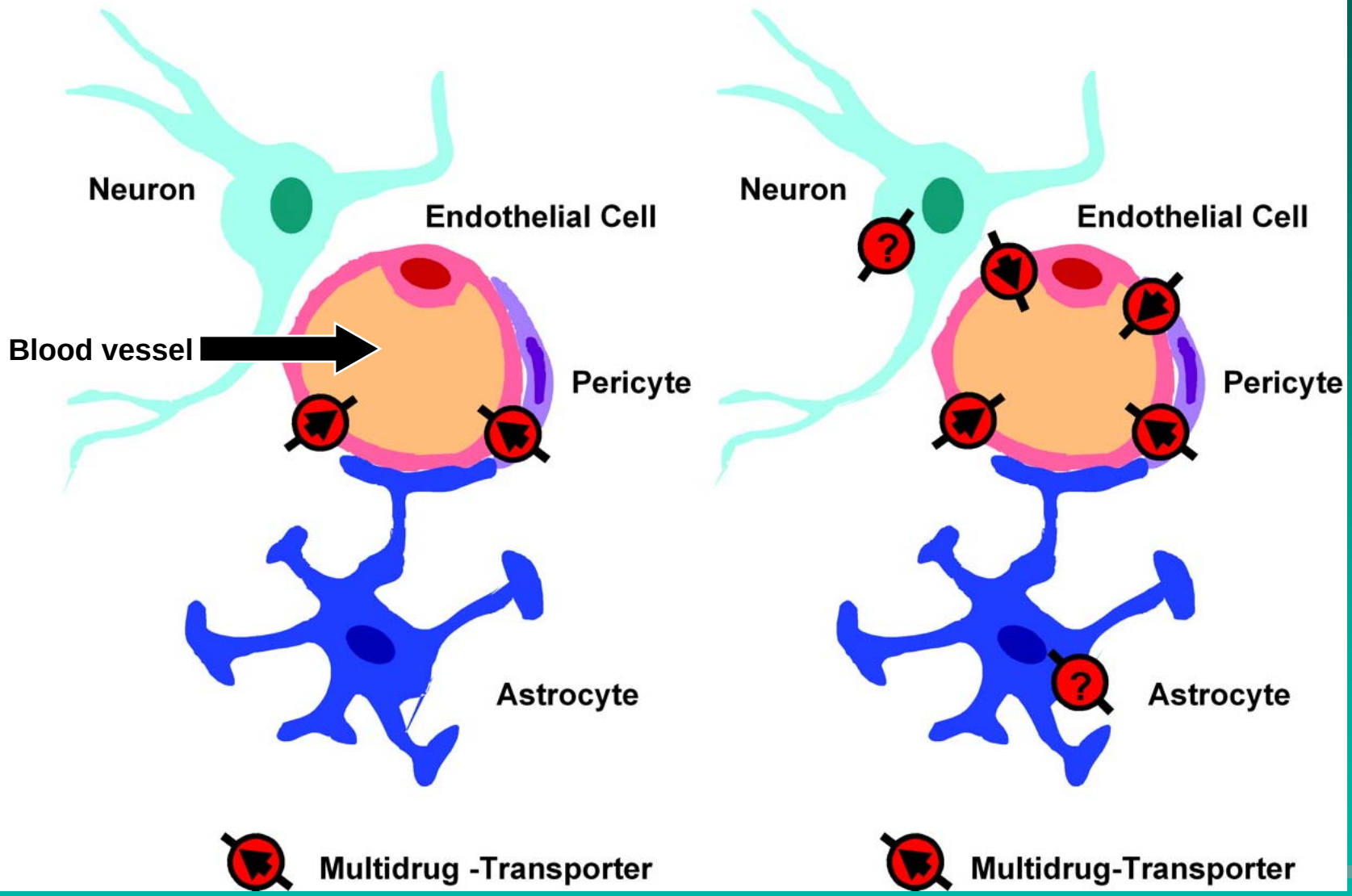
In the epileptic brain,"shuttles" that throw anticonvulsants out of brain cells are induced



Remy & Beck, 2006

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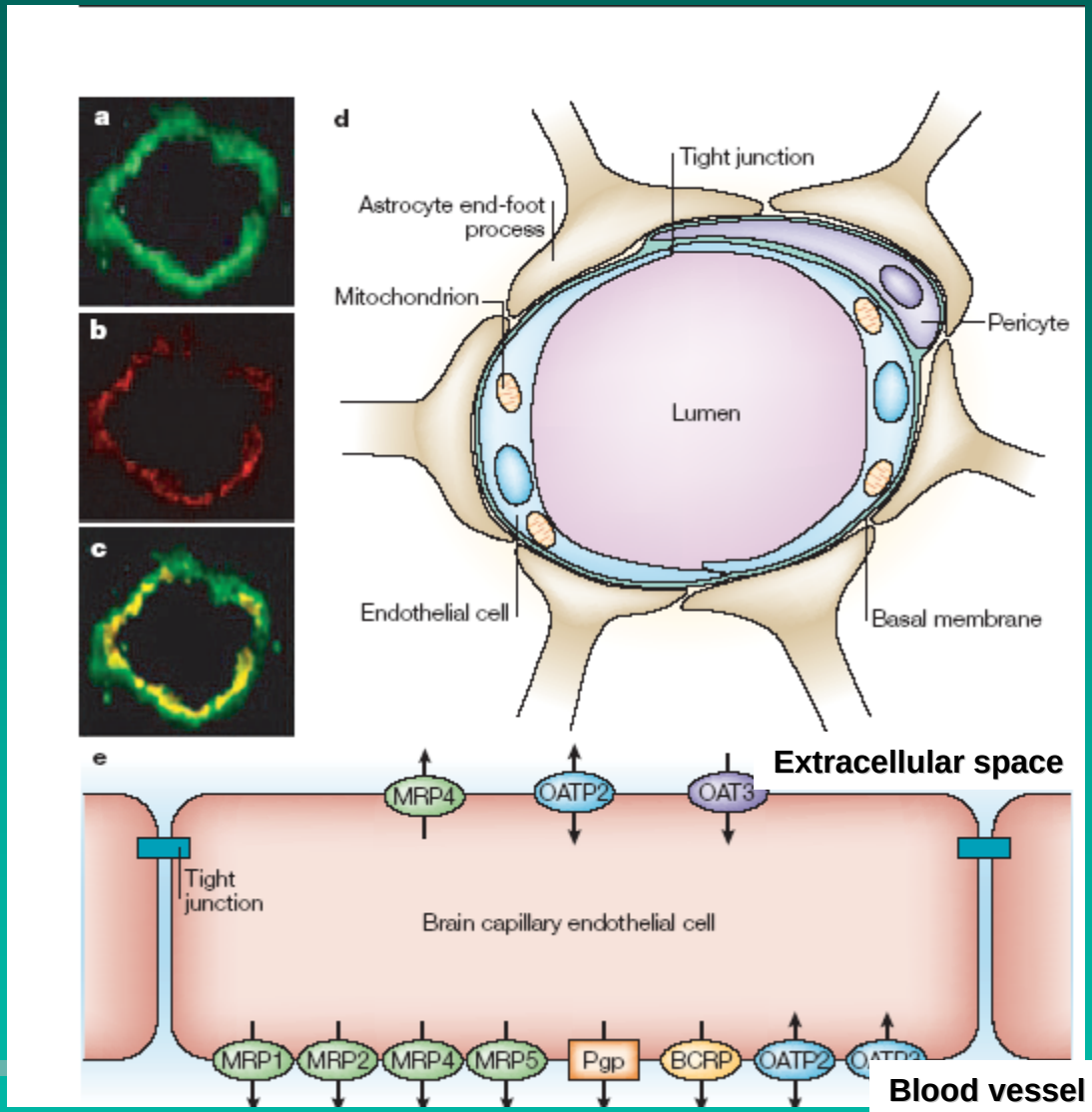
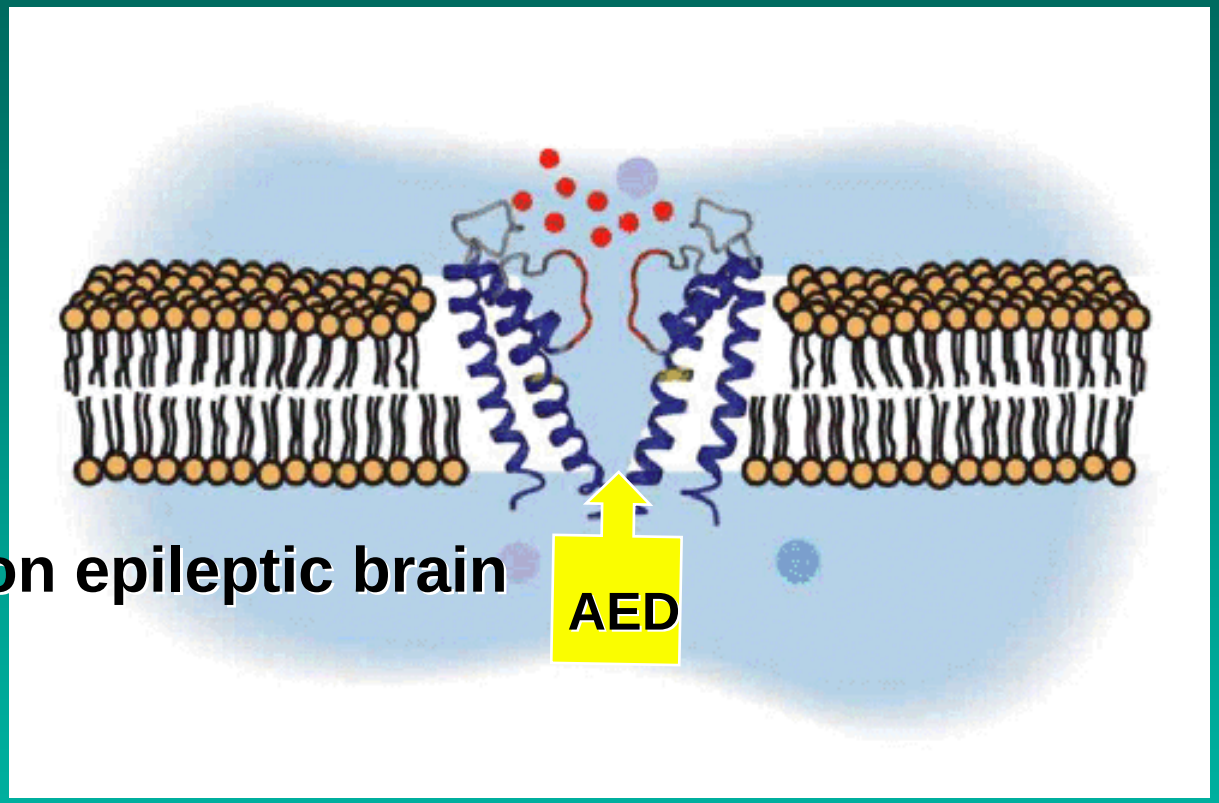


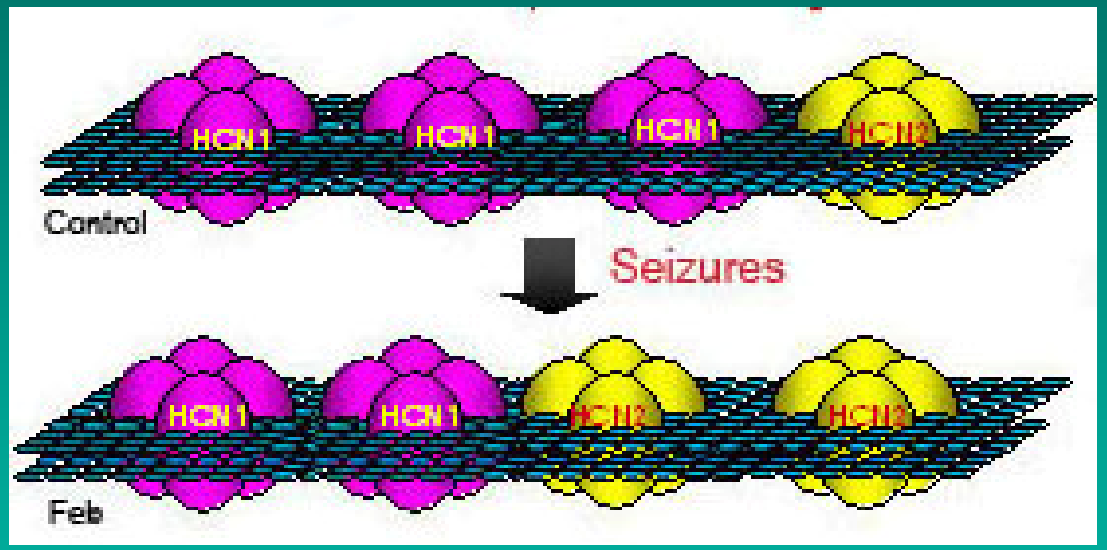
Multiple drug resistance
Glycoproteins
Transporters

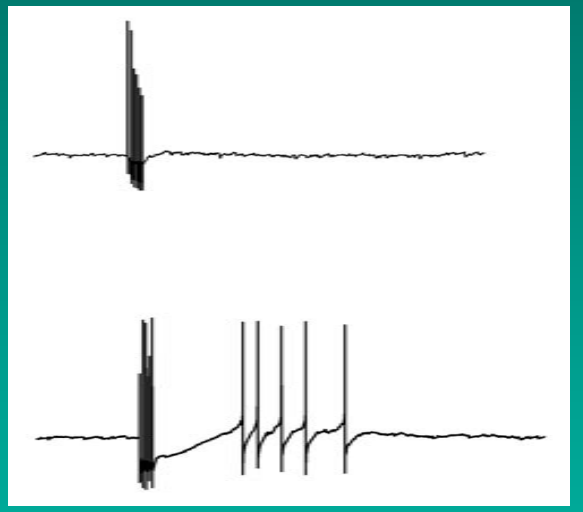
From Loscher & Potschka, 2005

Ion channels that govern excitability of brain cells become unresponsive to anticonvulsant medicines



Brain cells in epilepsy may make too much, too little or the wrong kind of ion channel





This generates hyper-excitable brain cells

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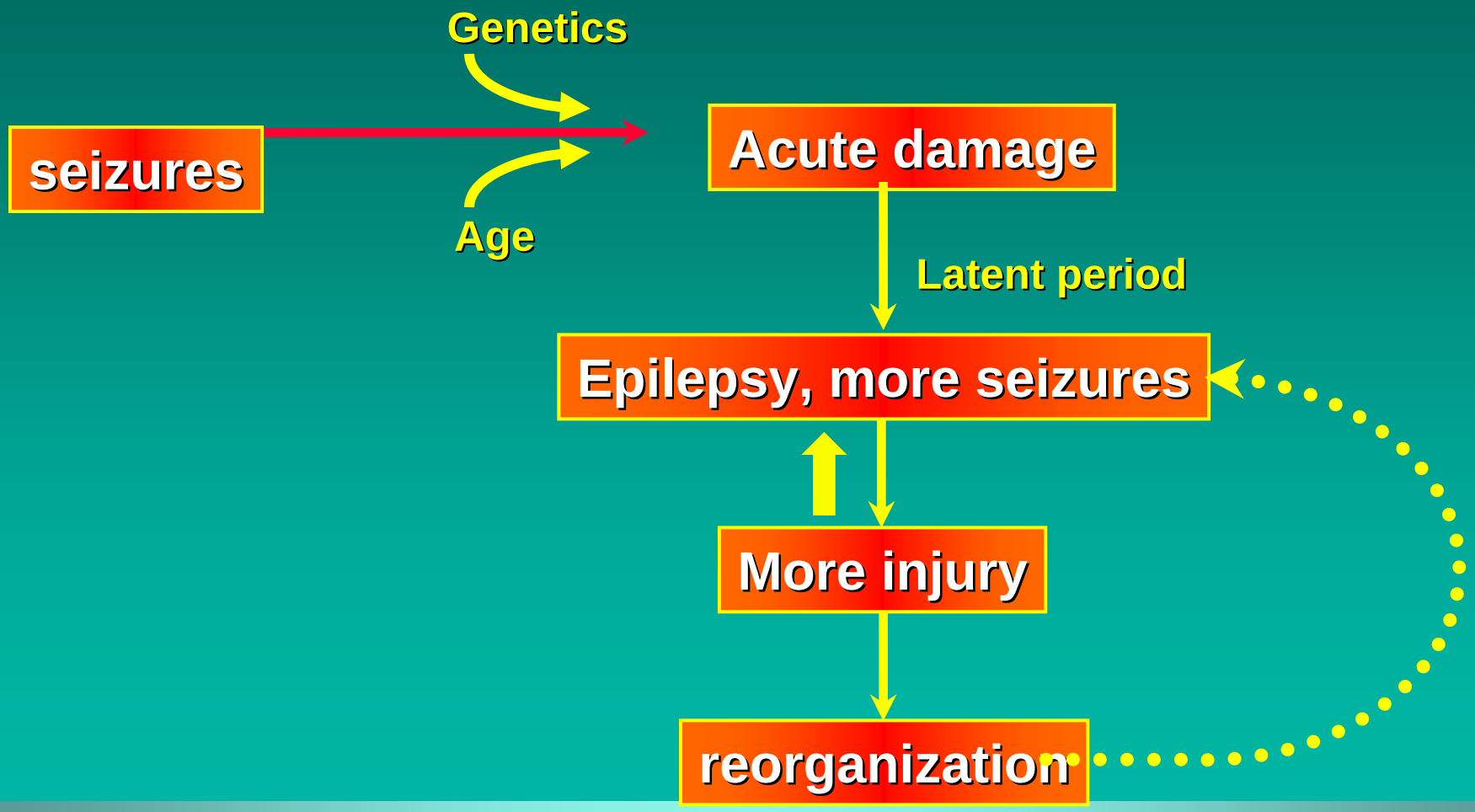
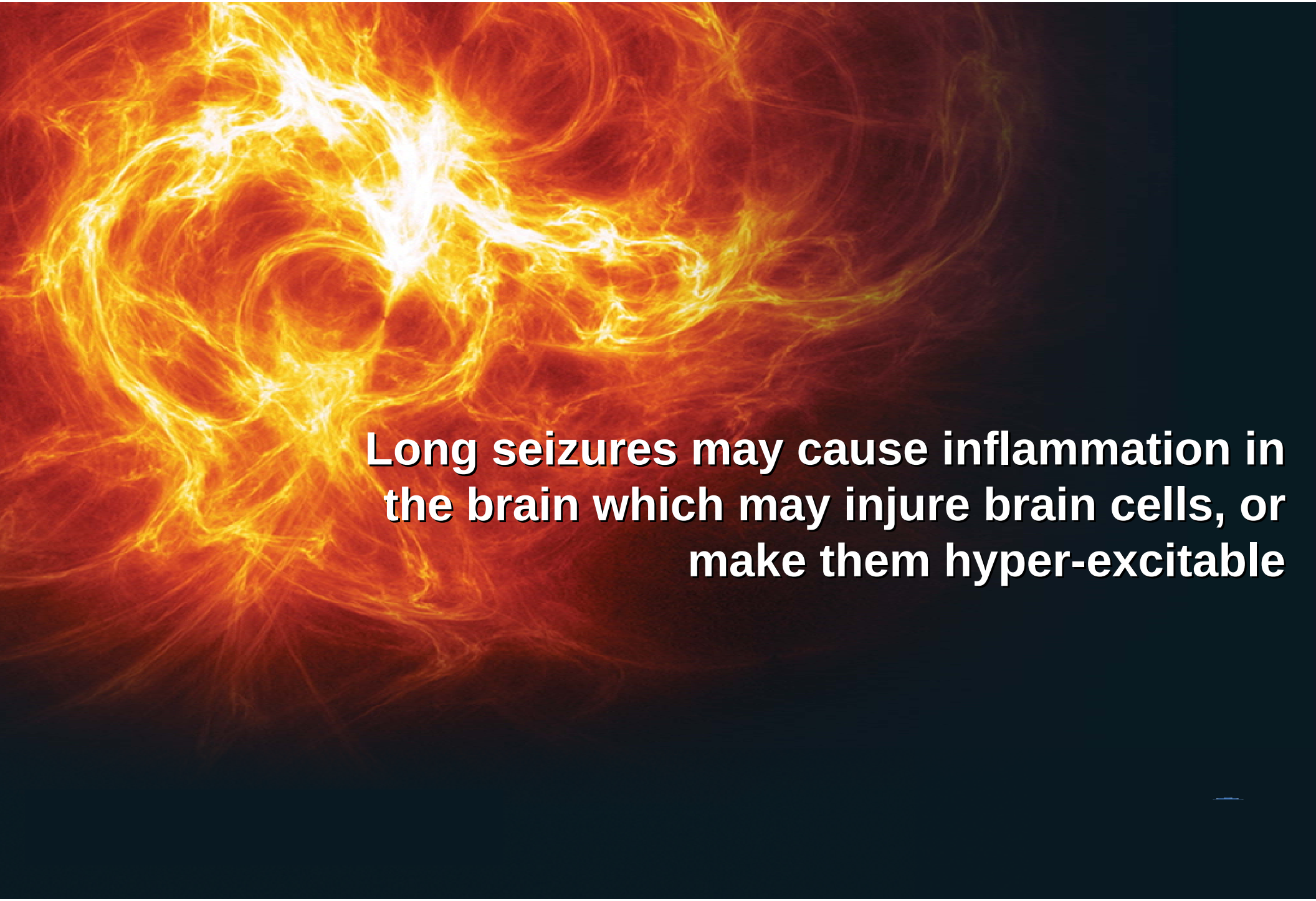
- Do the seizures themselves make future ones worse?
- This is known as **kindling,** and is found in animals.
- No evidence for kindling in humans.

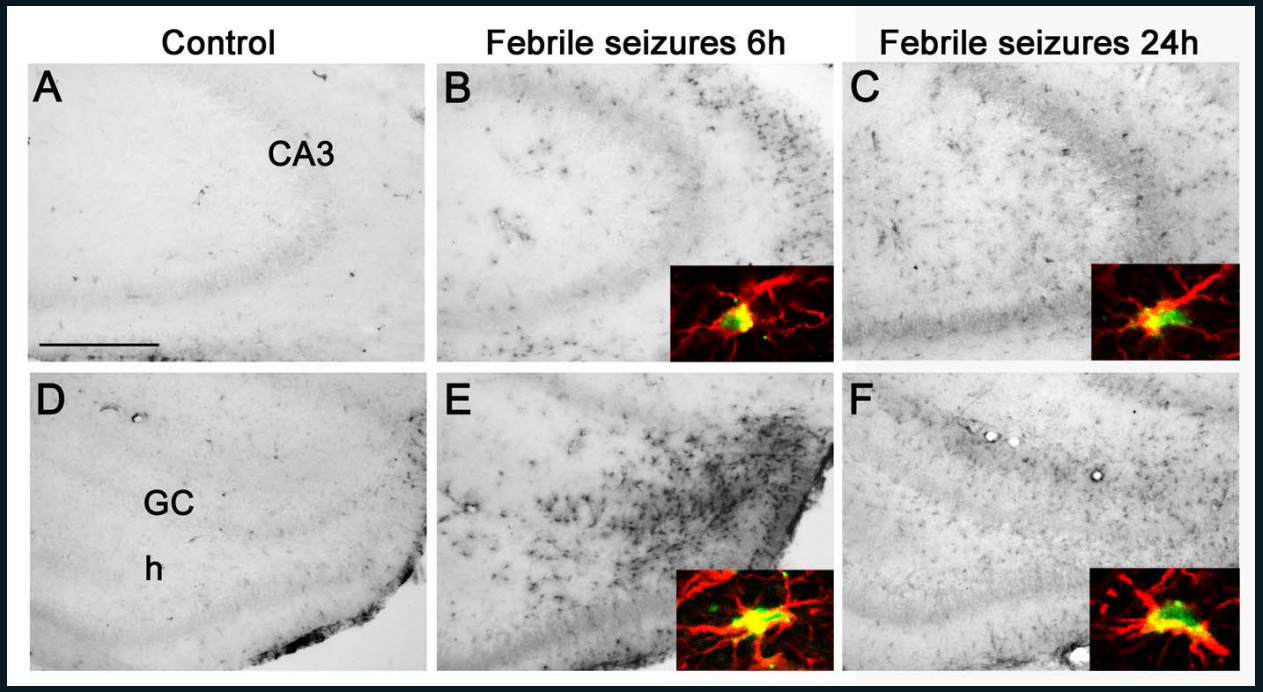
However, there are many ways in which seizures can change the brain, and make it more vulnerable to having worse future seizures

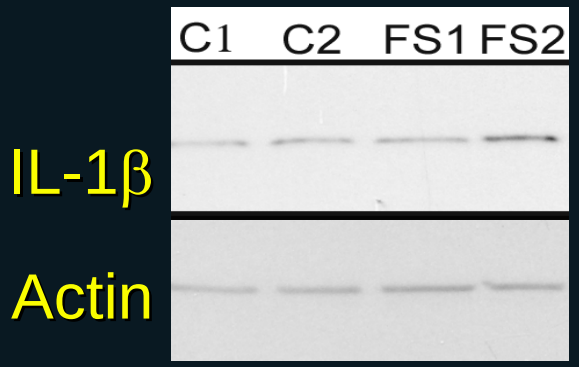
Long Seizures in adult brain can result in cell death, and the remaining cells can create abnormal circuits

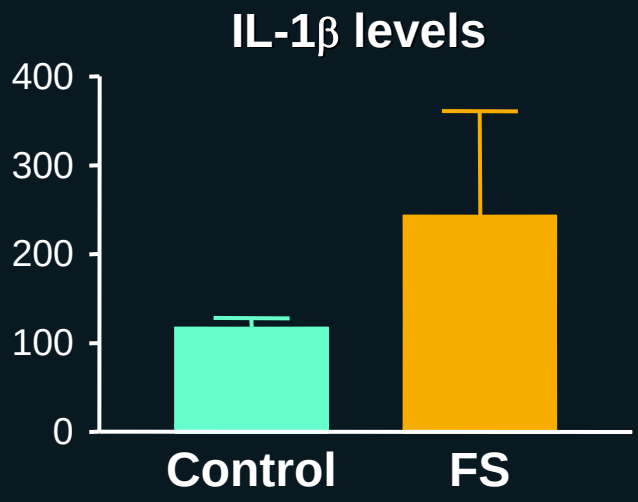



Long seizures may cause inflammation in the brain which may injure brain cells, or make them hyper-excitable

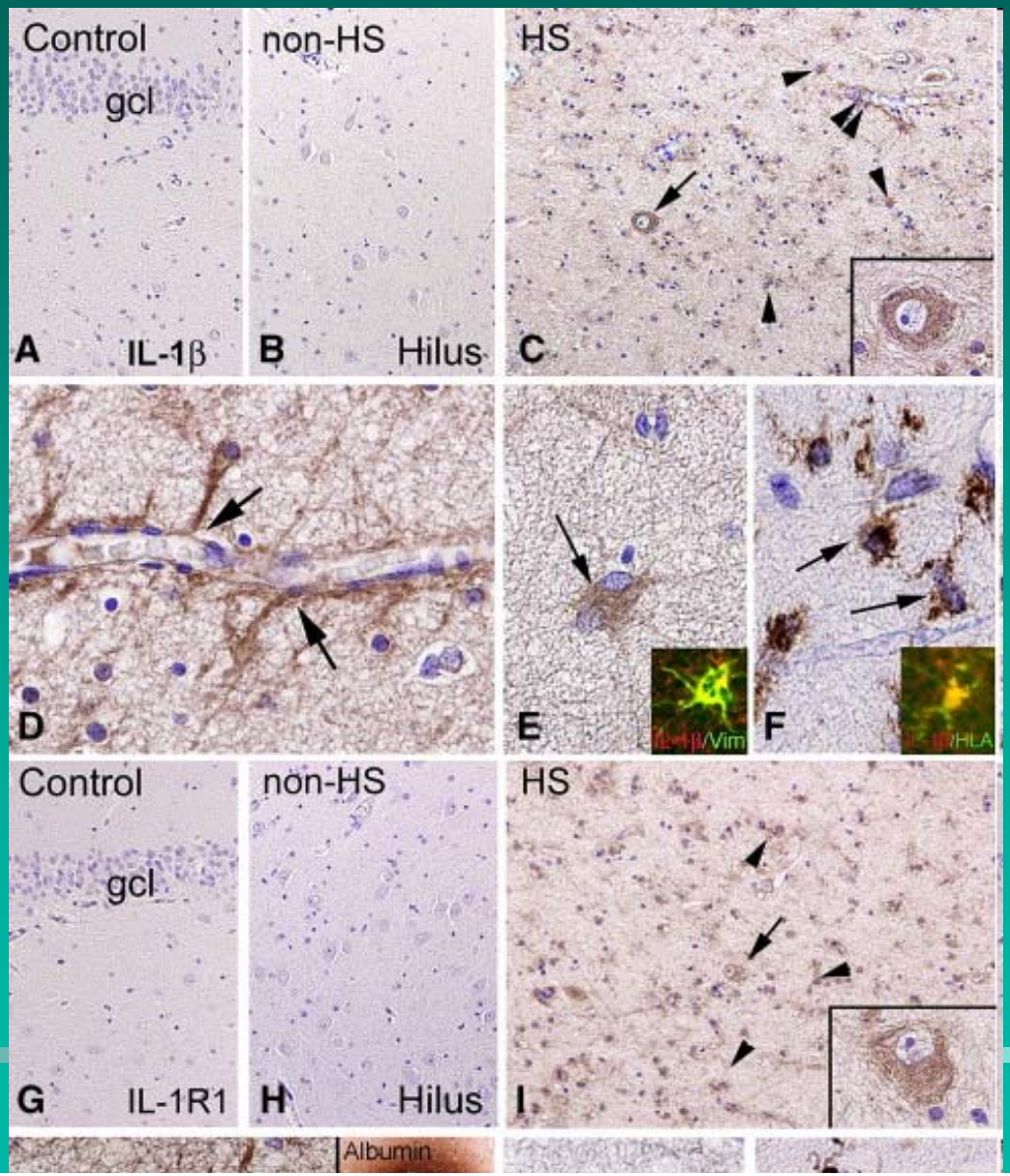
The inflammatory mediator interleukin 1β is increased by Long Febrile Seizures







Inflammation in resected human epileptic hippocampus



Ravizza et al., 2008

Inflammation may contribute to cell loss and other changes in brain activity

- Many cells that die during epilepsy are inhibitory
- Cell loss promotes the formation of abnormal excitatory connections in the brain: sprouting
- Inflammatory molecules can influence neurons, making them hyper-excitable.

Many changes in the brain which help make epilepsy complicated are still being discovered
(including here, at UCI…)

- Inflammation; gliosis, cell loss, hyper-excitability
- Cell loss: loss of inhibition, sprouting
- Even cells that survive are changed: receptors, ion channels
- Water content in the brain,
- Breakage of blood-brain barrier
- Altered ion and pH balance….etc, etc.

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The same brain regions that are involved in many epilepsies are responsible for learning and memory, emotion, decision making…

Why is it important to find out *how* epilepsy becomes complicated?

Because we hope to prevent the process in the future:

Anti-inflammatory drugs?

Neuroprotective?

Water balance?

Other?

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