What is the Clinical Evidence for Epileptogenesis in Humans?

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An alternative and accessible version of this presentation is available at 2:00 pm in the Videocast of Day One

Disclosure – Dr Shinnar

- Dr Shinnar has no significant financial conflicts of interest relating to this lecture or session.

High risk for developing epilepsy

- There are a number of conditions both acquired and genetic that are associated with a significantly increased risk of subsequent epilepsy in the human.
- In many of these acquired conditions, there is an early injury, sometimes associated with acute symptomatic seizures, followed by a “silent period” and then epilepsy may develop.

High risk for developing epilepsy (~10-50%)

- Acquired factors
  - Traumatic brain injury (penetrating missile wound, intracranial hematoma, depressed skull fracture, early seizure)
  - Status epilepticus
    - Febrile Status Epilepticus
  - Stroke
  - Brain tumor—resected
  - Encephalitis
  - Supratentorial craniotomy
  - Severe hypoxic ischemic insult at birth
- Mixed (genetic or acquired)
  - Cerebral palsy--especially with mental retardation
- **Genetic factors**
  - **Tuberous sclerosis**

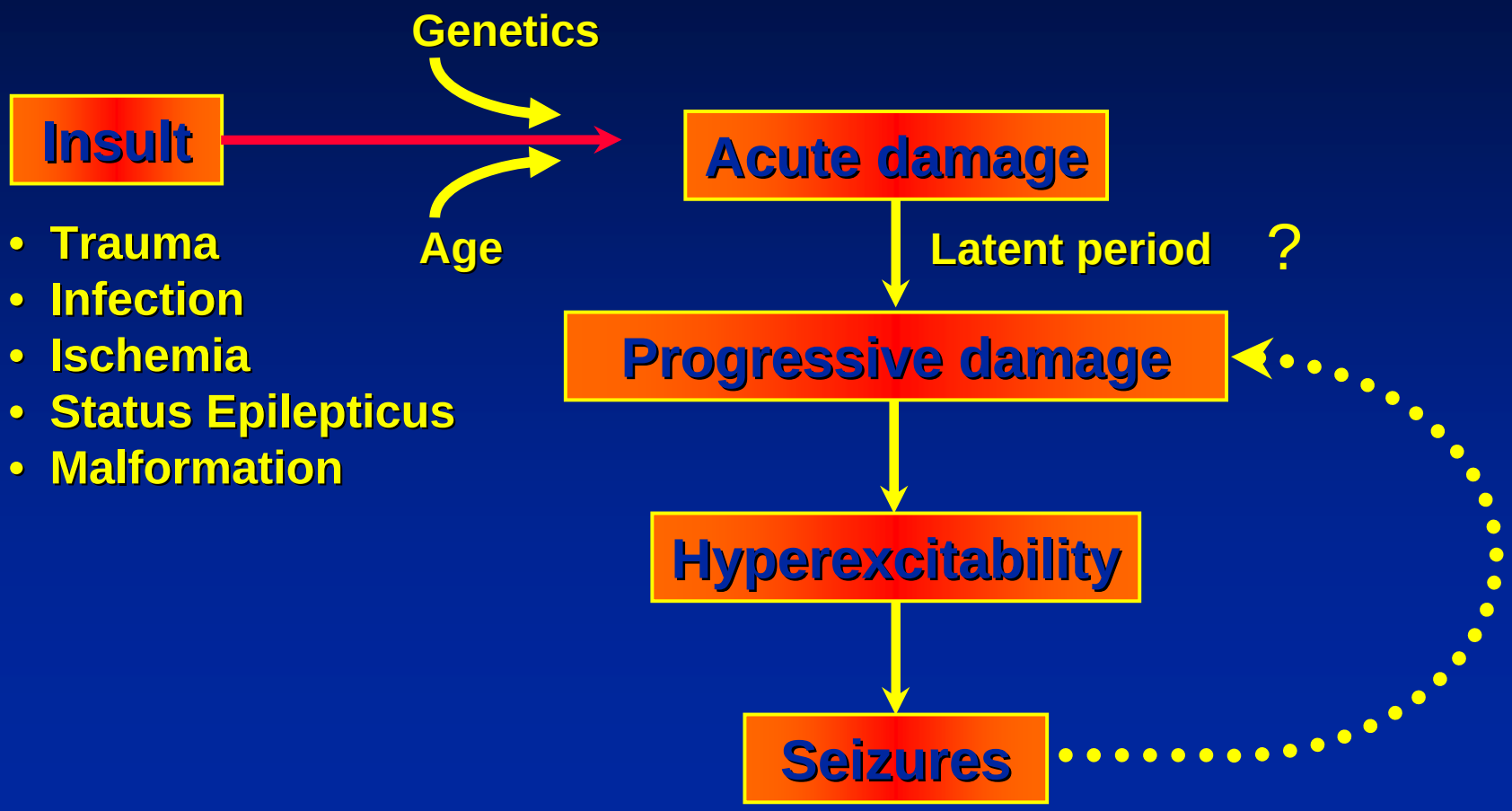
Common Themes

- Blood in brain
- Profound lack of oxygen
- Provoked seizures
- Inflammation

Epileptogenesis vs Evolution of Epilepsy Syndrome

- In some of these (ie brain insult) there is clearly a period of epileptogenesis
- In others (absence seizures, Rolandic) more likely that we are seeing delayed seizure expression as a function of brain maturation rather than epileptogenesis
- In a third set (dysplasia, tuberous sclerosis etc) may well be a combination of brain maturation and of epileptogenesis

Acquired Epileptogenesis



Biomarkers for Epileptogenesis with clear convincing proof in humans

- None
- We need these in order to study the period of epileptogenesis where clinical seizures are not yet present
- Two areas of promise in the study of epileptogenesis are
  - Prolonged febrile seizures
  - Head trauma

Epileptogenesis Following Prolonged Febrile Seizures

- Long latency period (mean 8-11 years)
- Effect not universal (30-40% risk following status)

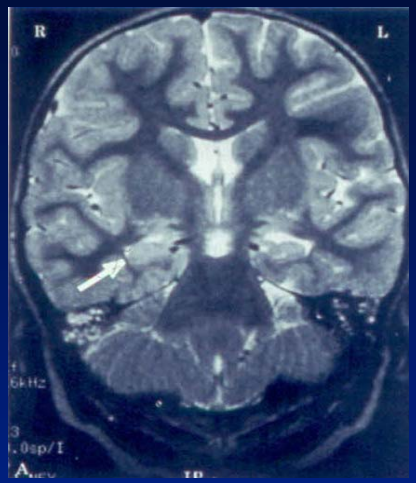
While temporal lobe epilepsy following prolonged febrile seizures is the human model with the most data, the same issues are present in post-traumatic epilepsy, epilepsy following stroke etc..

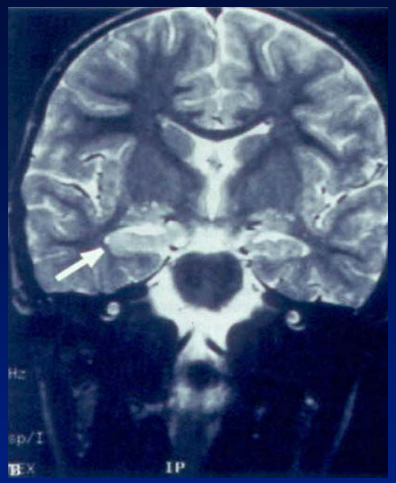
- There is therefore a need for noninvasive biomarkers in the human that can be correlated with epileptogenesis

Do Febrile Seizures Cause MTS?

Acute and Chronic MRI Changes

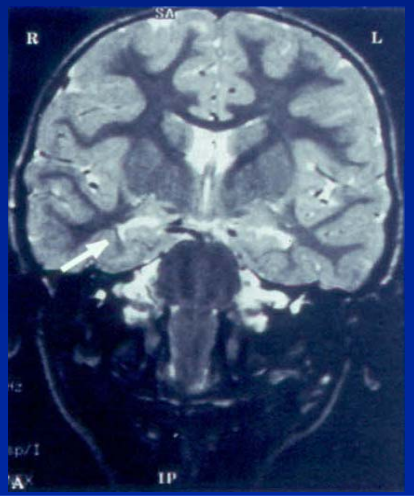
Acute

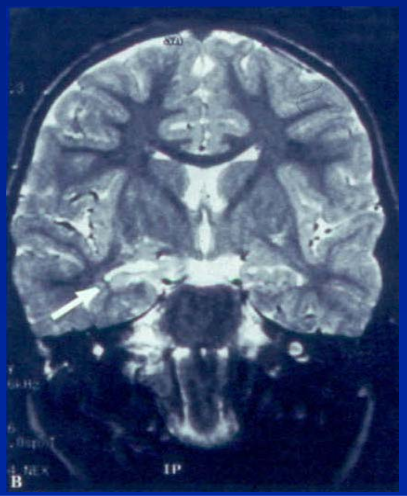




Case 7 Case 8

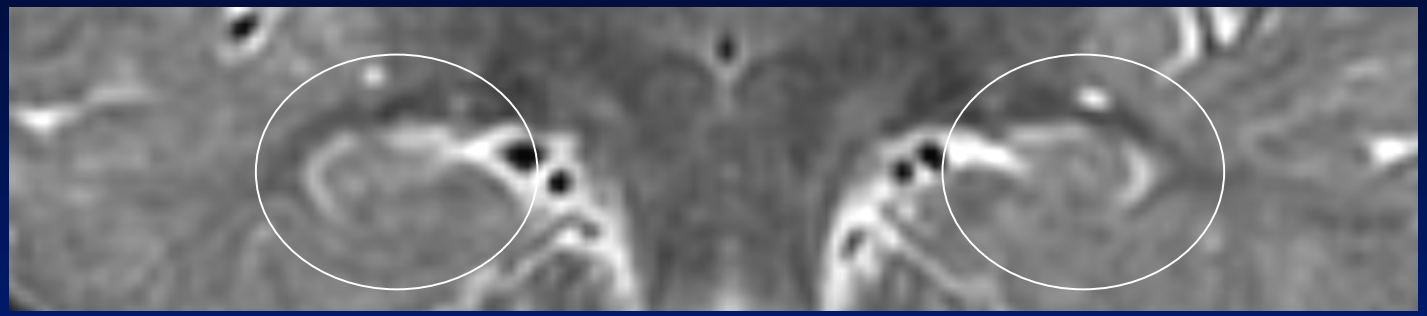
Chronic



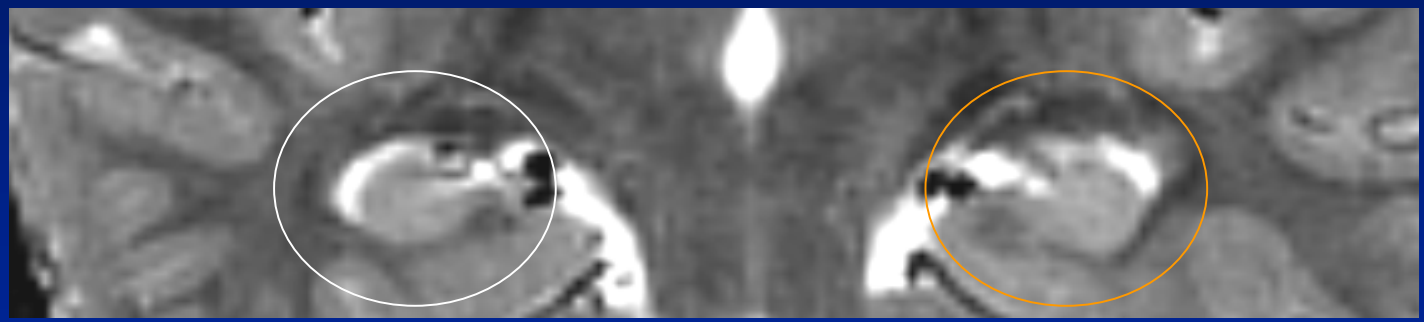


VanLandingham KE, et al.
Ann Neurol 1998;43:413-426.

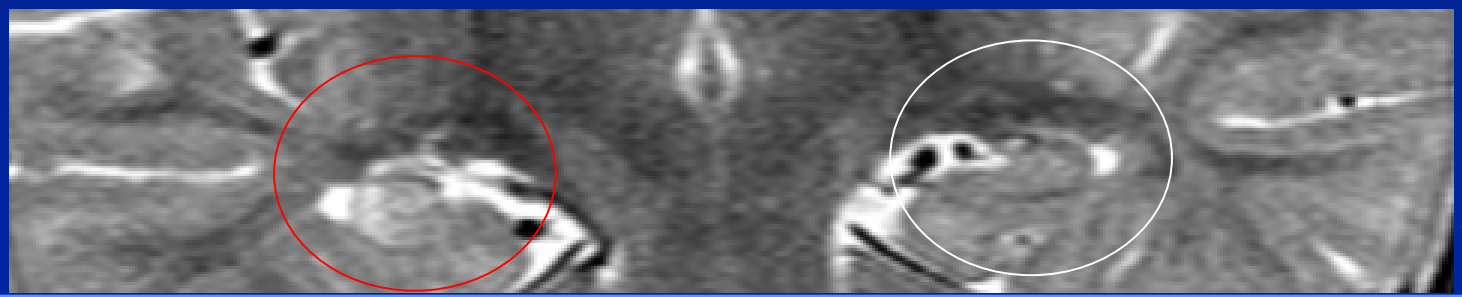
Shades of Gray: T2 Intensity in Hippocampi After Febrile SE



Both hippocampi have normal T2 Intensity

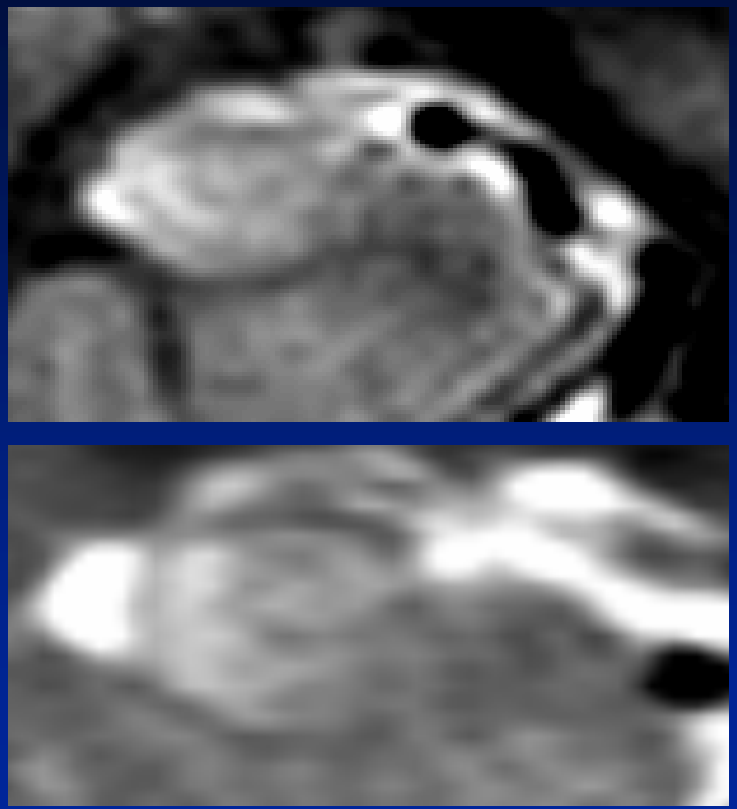


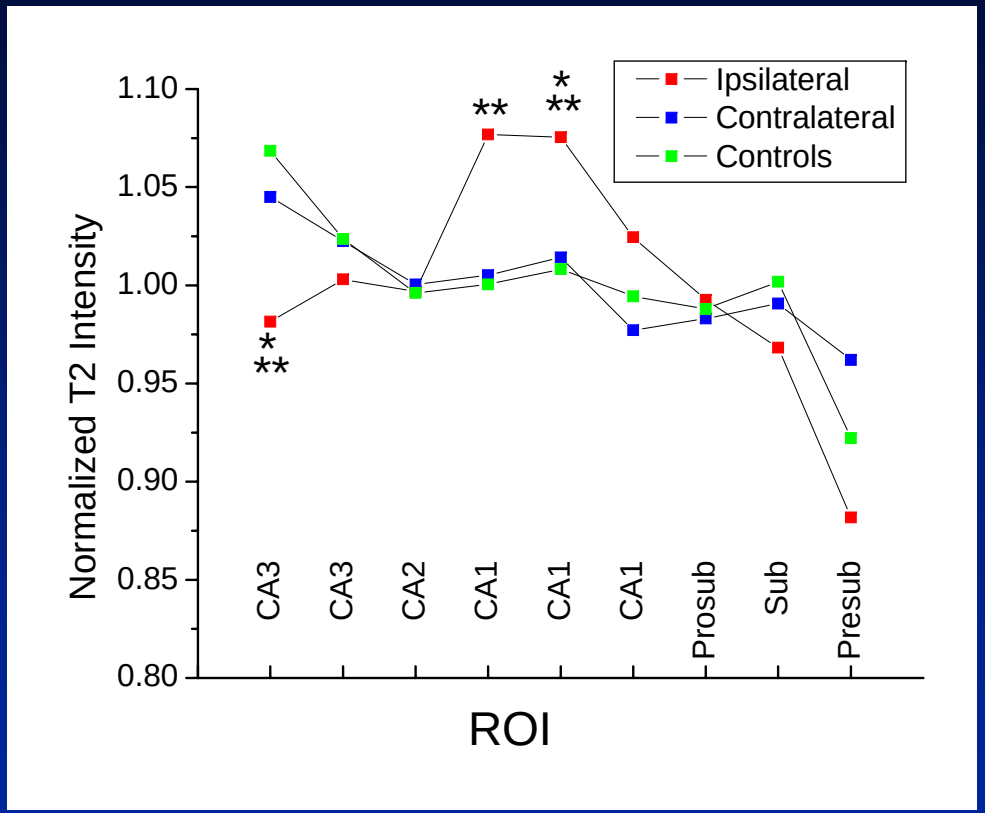
Left hippocampus slightly increased T2 and reduced anatomical landmarks.



Right hippocampus marked increase T2 in lateral inferior aspect, near CA1.

T2 Signal Increase Maximal in CA1 After FSE



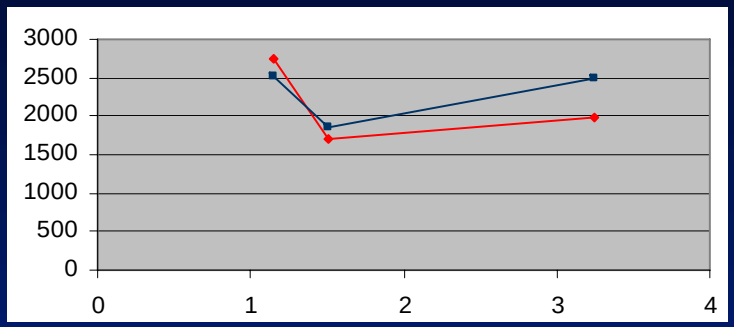


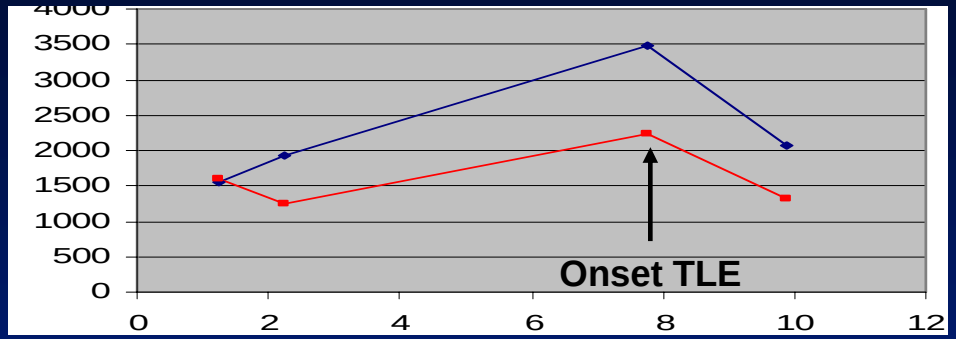
From FEBSTAT: "Consequences of Prolonged Febrile Convulsions in Childhood"
NINDS - R01 NS43209 PI S. Shinnar. As of 8/1/06

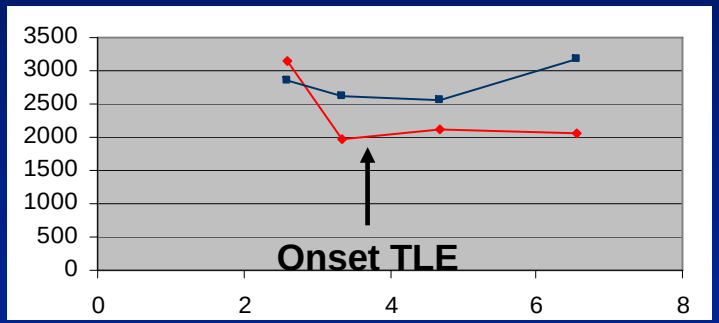
Bilateral Hippocampal Volume Loss After FSE

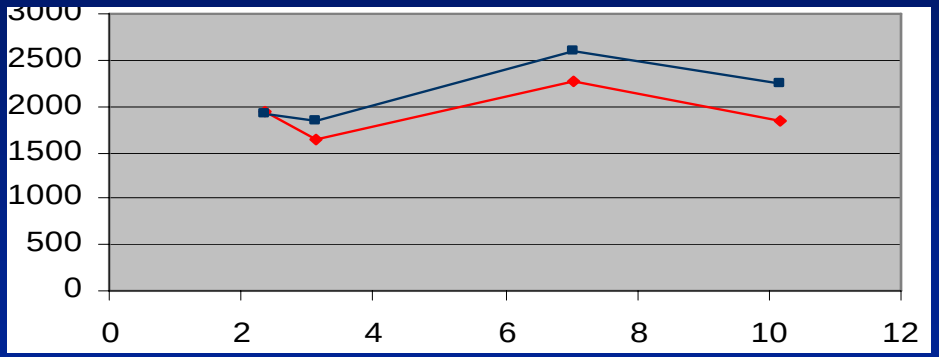
- Seen in 6 of 7 cases with adequate data
- Only one side has increased T2 but both lose volume
- Maximum volume loss on side with increased T2
- Clear volume loss on contralateral side as well
  - no evidence of increased T2 on acute or follow-up MRIs
  - subsequent growth is greater than side with increased T2

Examples of Hippocampal Volume Changes After FSE: Is this pattern a biomarker for TLE?









Initial Injury → Vol Loss *(Bilateral)* → Asymmetric Growth → Late Atrophy?

From FEBSTAT: "Consequences of Prolonged Febrile Convulsions in Childhood"
NINDS - R01 NS43209 PI S. Shinnar. As of 8/1/06

Examples of Negative Evidence for Epileptogenesis

- First Unprovoked Seizure
  - Treatment reduces recurrence risk but does not affect long term outcome
- Simple Febrile Seizures
  - Treatment reduces recurrence risk but does not affect long term outcome

Epileptogenesis Following Major Head Trauma

- In civilian head trauma significantly increeased risk (20-25%) if prolonged LOC, depressed skull fracture or intracranial hemorrhage
- In non civilian head injury risk can approach 50%
- There is again a latency period ofmonths to years
- Effect not universal
- Risk remains increased for life.

An issue with trauma, stroke and other types of injuries is distinguishing the progressive changes that reflect the injury, from those that more specifically reflect epileptogenesis.

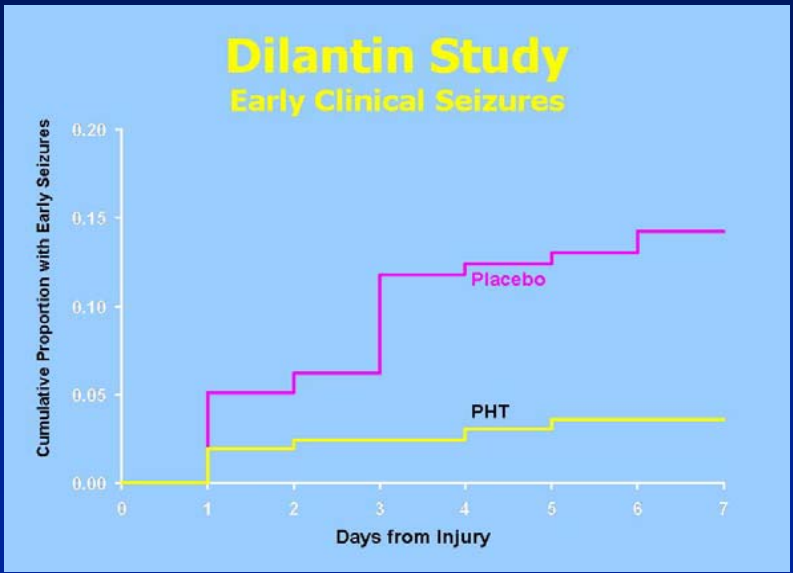
In head trauma significant advances are being made in part due to head trauma. In other settings this remains a major problem.

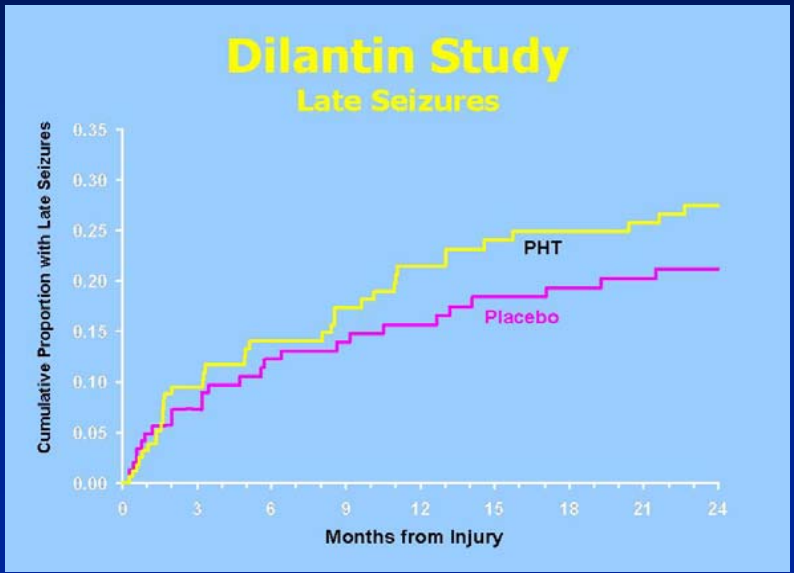
Epileptogenesis following Head Trauma

- Acute Post-traumatic Seizures
  - Treatment reduces risk of acute seizures but does not reduce risk of epilepsy
  - Recent data show that while Rx reduces risk of clinical seizures, there are frequent electrographic seizures occurring. THEREFORE NEW UNCERTAINTY
- Imaging Changes

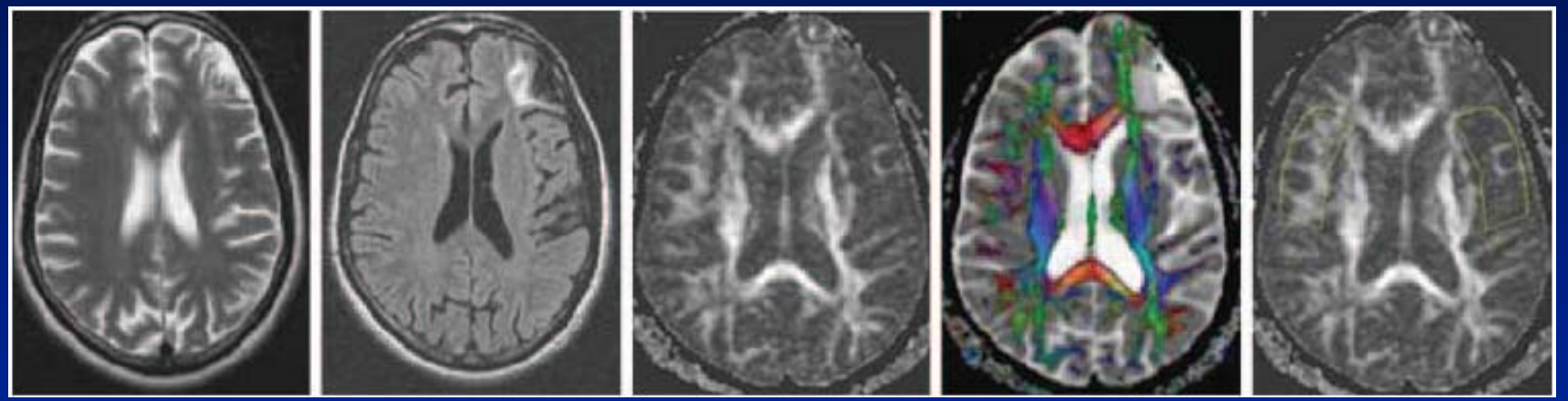
Probably not on the causal path

Early clinical seizures after TBI, craniotomy





Epileptogenesis Following Head Trauma



Gupta et al Epilepsia 2005

Epileptogenesis in the Human
What we need to do now

- Develop noninvasive techniques to study epileptogenesis in the human - BIOMARKERS
  - Imaging
  - EEG
  - Gene Expression
- Use animal models to better understand the epileptogenic process as can use invasive techniques and time frame is shorter.
- Develop therapies that can interrupt the epileptogenic process and prevent clinical epilepsy from developing.

Human Epileptogenesis

- We have made much progress and now have several human conditions where we may be able to study epileptogenesis using imaging, neurophysiological and genetic techniques
- Ultimately, the goal is to learn how to interrupt this process. There is still much to be done but there are some glimmers of light in the tunnel.