Challenges in the management of people with epilepsy after severe brain injury

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Disclosures

Company Name	Nature of Affiliation
• Novartis	• Honoraria, Consulting fees, expenses
• UCB	• Consulting fees, expenses
• EISAI, Bial	• Consulting fees
• GE	• Consulting fees
• **EU-FP7**	• **Research funding for “EURIPIDES”**

Definitions

Epilepsy:

*"disorder characterised by an **enduring predisposition** to generate epileptic seizures and by the neurobiological, cognitive, psychological and social consequences of this condition."*

Epileptogenesis:

*includes **both** the **development** of an epilepsy condition and **progression** after the condition is established.*

Biomarker – diagnostic / prognostic:

indicator of normal biologic or pathogenic processes

Surrogate endpoint – predicting treatment response:

measurement used in therapeutic trials as substitute for clinically meaningful endpoint of how patient functions and predicts effect of therapy.."

Risk factors for epilepsy

- Febrile convulsions
  - 3- 5% of children have FC
    3-5% of children with FC will develop epilepsy
- Head Injury
  - risk dependent on severity, highest risk with missile injuries
- CNS Infections
  - encephalitis, meningitis, abscess

Risk factors for epilepsy

• Learning disability	9 - 15 fold
• Cerebrovascular Diseases	3 - 5 fold
• Dementia	6 - 8 fold
• Alcohol	only risk factor in 1/3 of people 20 – 40 years
• Recreational drugs	cocaine, heroin
• Rural residence	higher in rural areas
• Socio-economic status	more in lower strata
• Race	more in Africans
• Male sex	more head trauma

Highest risk

- 50+ year old male
- African origin (grew up near a river)
- with a Hx of prolonged febrile convulsions
- Immigrant
- unemployed
- lives in rural area (Bovingdon)
- Is drug and alcohol dependent
- was in the gulf war or is member of a street gang and suffered from a serious head injury

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TBI and epilepsy

- **Intracerebral hematoma (exp subdural hematoma)**
- **Brain contusion**
  biparietal contusion (66%)
  dural penetration with metal fragments (62.5%)
  multiple intracranial operations (36.5%)
  multiple subcortical contusions (33.4%)
  subdural hematoma with evacuation (27.8%)
  Midline shift > 5 mm (27.8%)
  multiple/bilateral cortical contusion (25.8%)
- **Increased injury severity**
  LOC/amnesia > 24hrs
  GCS < 10
- **Early post-traumatic seizures**

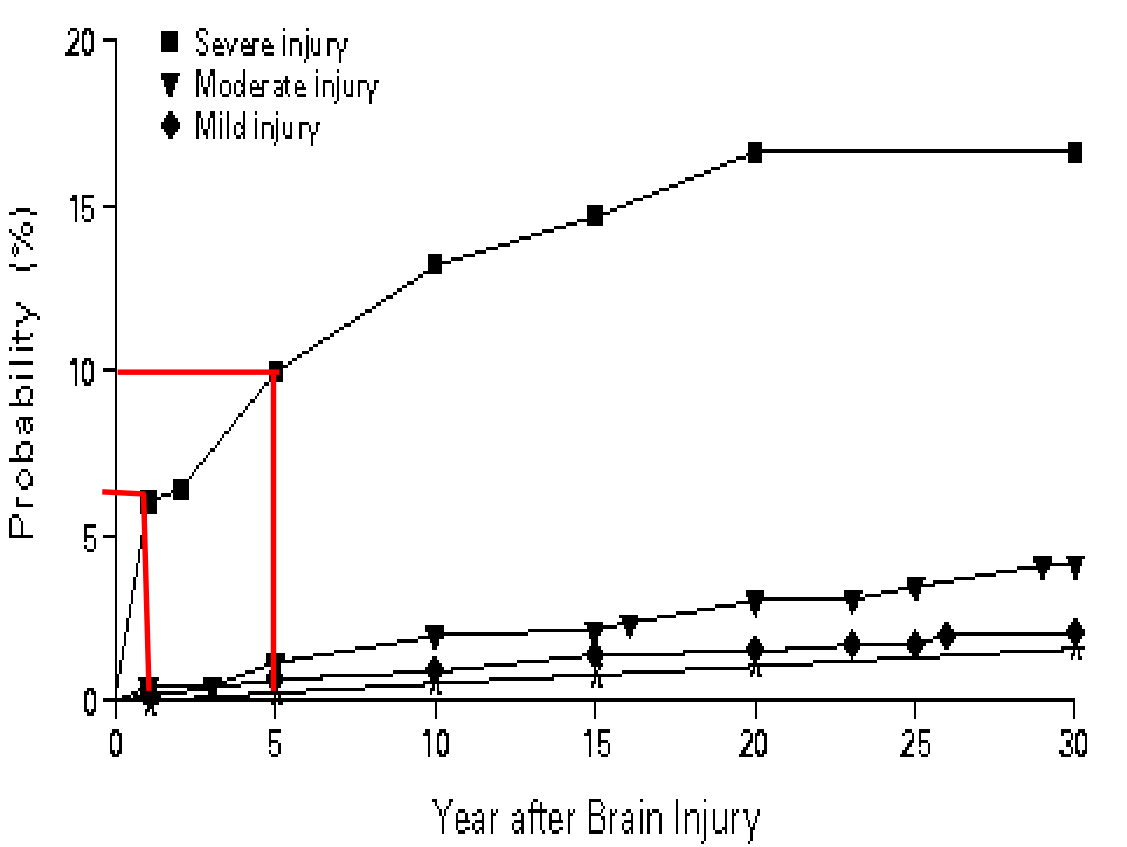
Immediate	1st 24h
Early seizures	1st 7d
Late seizures	>7d

- **> 50 years**

TBI and epilepsy

Annegers et al, NEJM 1998

- Cumulative 5-year probability
  - mild injury 0.5%
  - moderate 1.2%
  - severe 10%
- Highest risk:
  1st year after trauma
  decreasing progressively
- Risk increased up to ?? Years
  - moderate injury: up to 10yrs
  - mild injury: over 20 yrs



Prophylaxis

- Patient stratification WHO ?

Early studies: AED prevented early and late seizures, but often methodologically flawed

Later studies: prophylaxis only effective at prevention of early seizures

(Chang & Lowenstein 2003)

Risk factors for late seizures:

GCS<10
cortical contusion
depressed skull #
subdural haematoma, epidural haematoma, intracerebral haematoma
penetrating head wound
early seizures

Post-traumatic Epilepsy

Prophylactic treatment ?

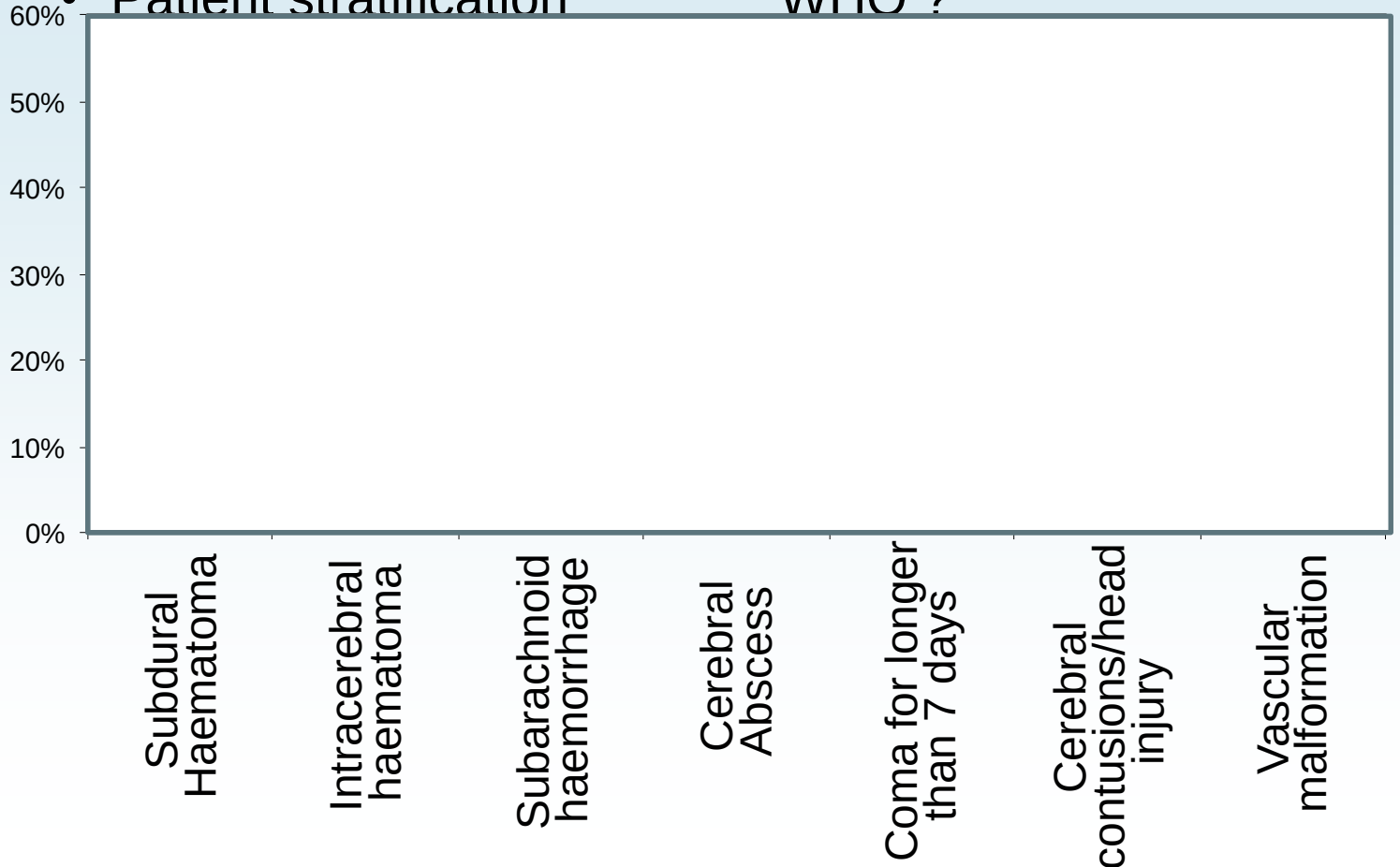
Questionnaire:

50 neurosurgeons from 21 neurosurgical centres

- Use of prophylaxis in various acute neurosurgical conditions ?
- Which AED and for how long ?

Prophylaxis

- Patient stratification WHO ?



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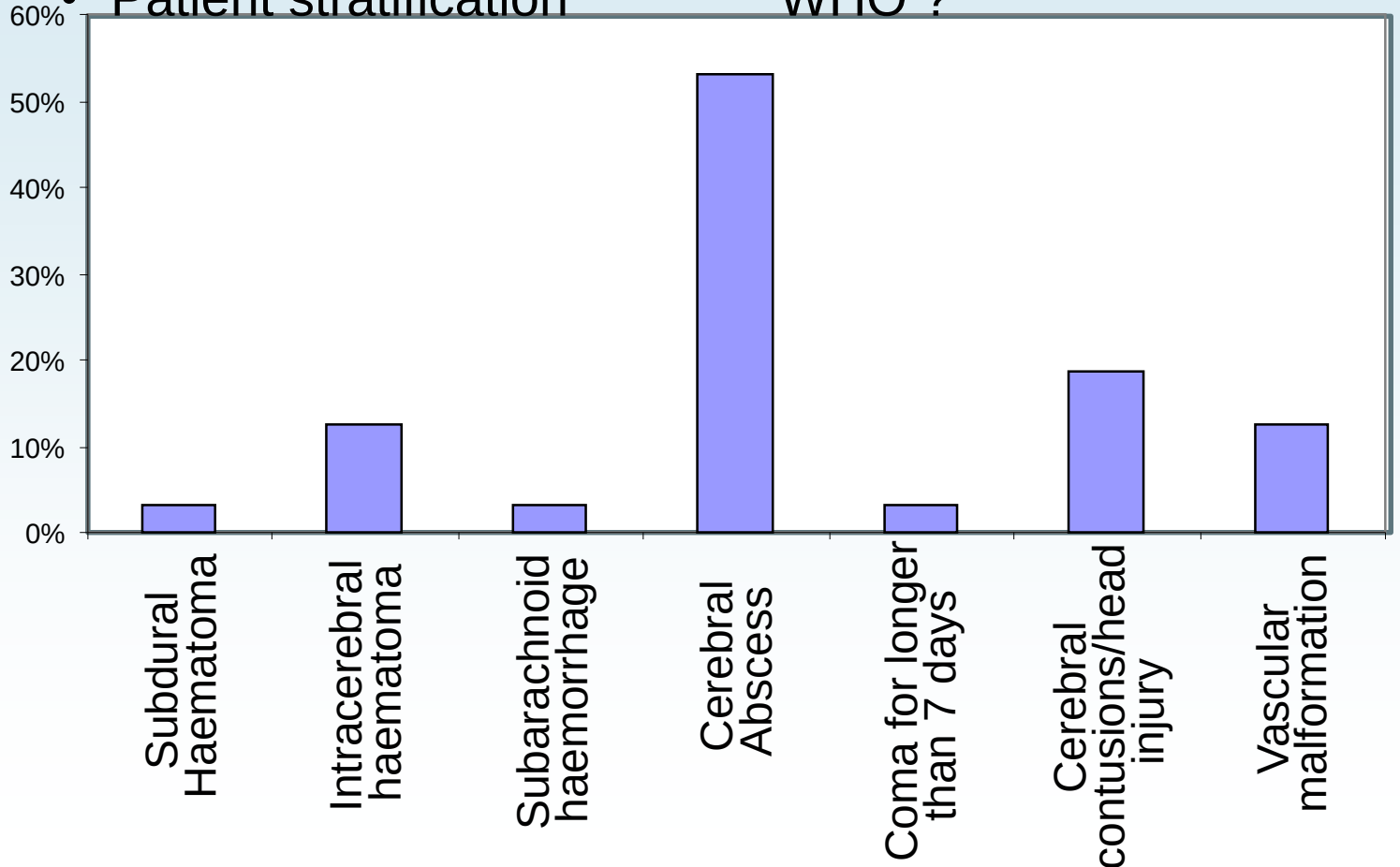
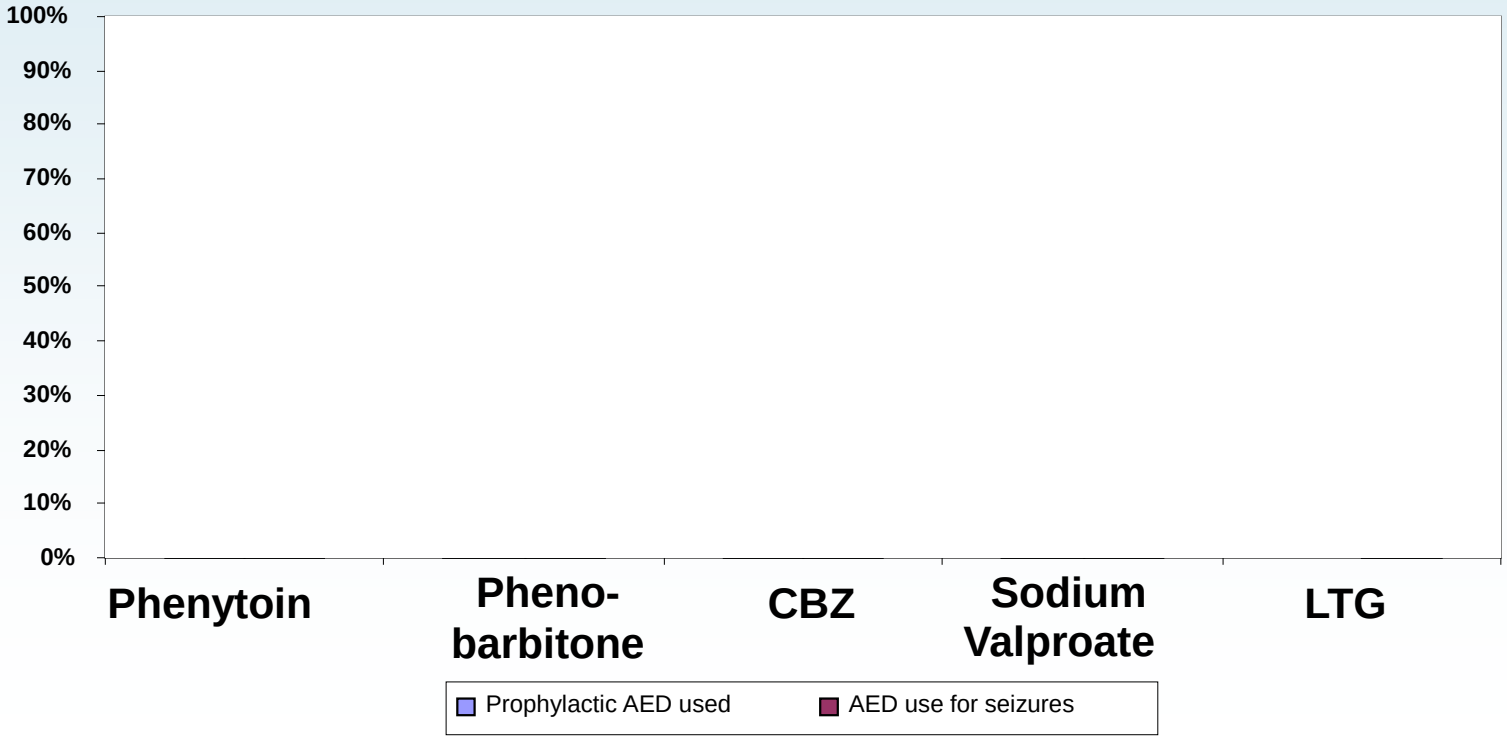


Prophylaxis

- Patient stratification — WHO ?
- Prediction of outcome — WHICH DRUG ?



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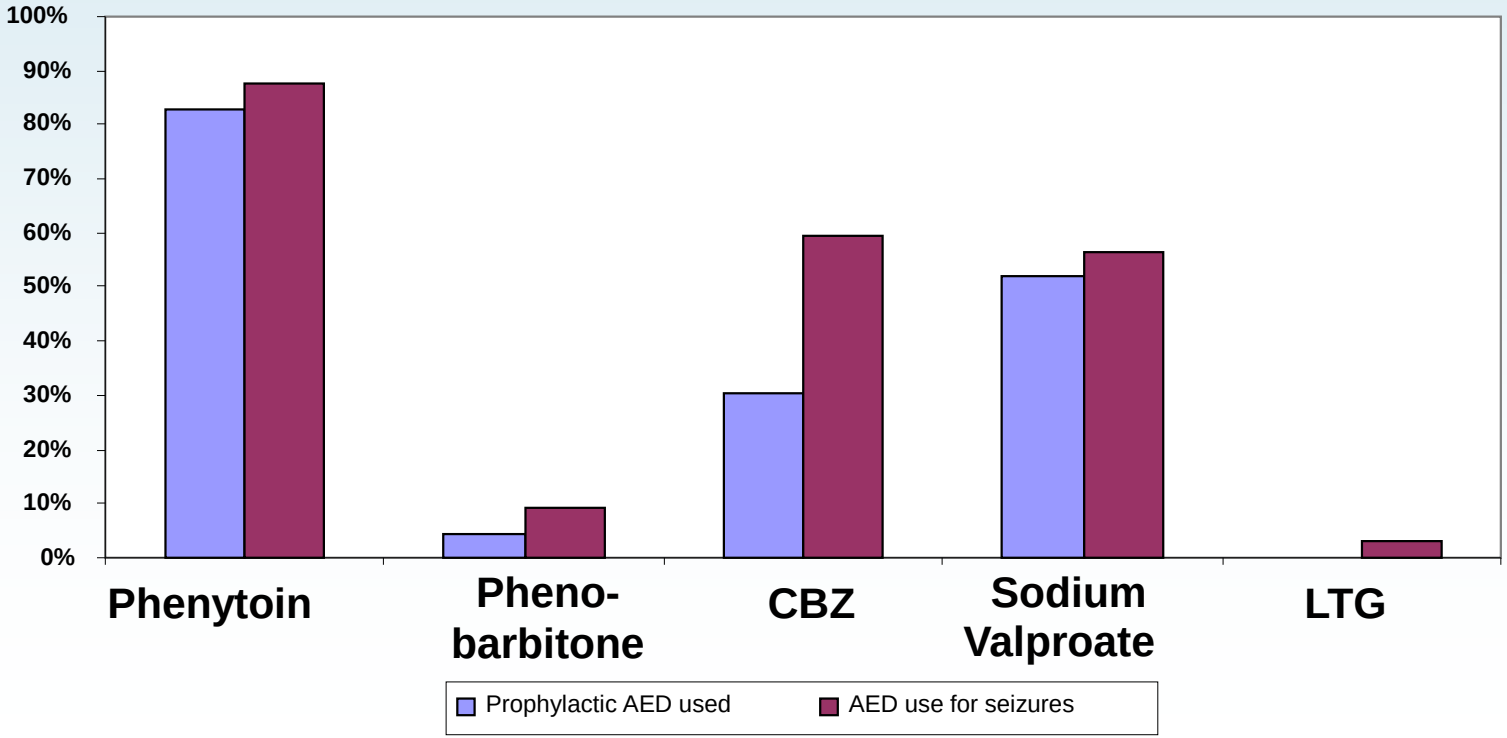


Prophylaxis

- Patient stratification — WHO ?
- Prediction of outcome — WHICH DRUG ?
- Monitoring of treatment — WHEN START / STOP?

Indefinitely

Withdrawn prior to discharge

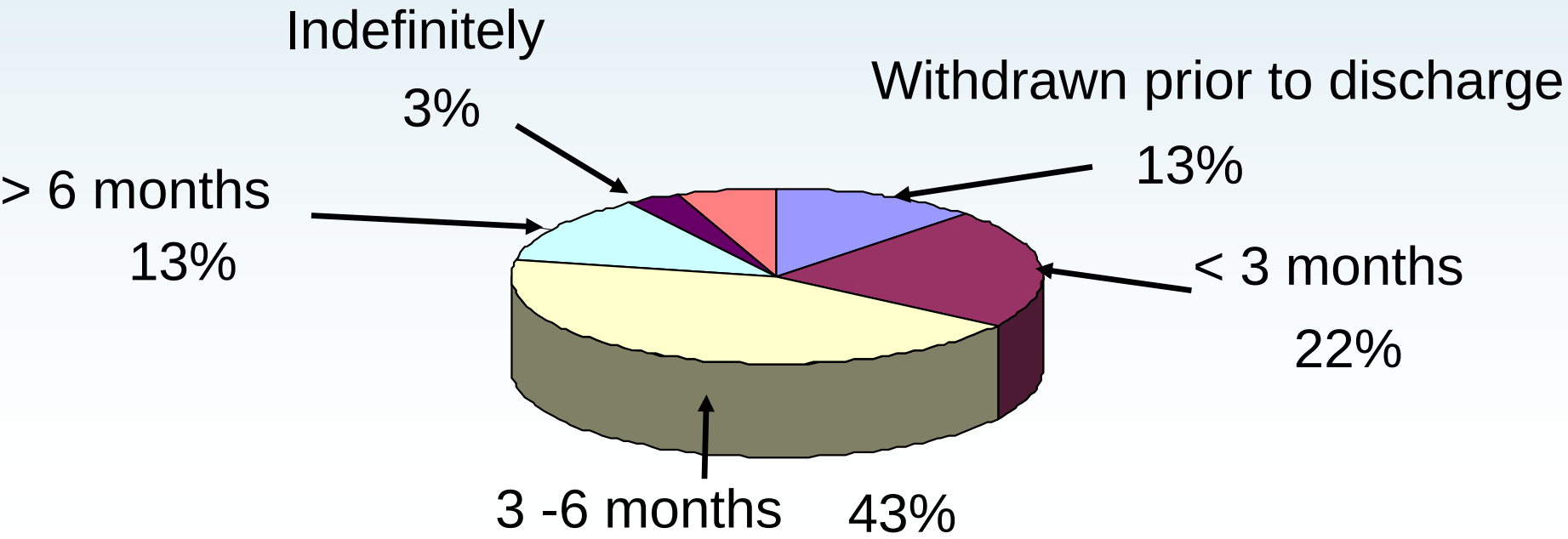
> 6 months

< 3 months

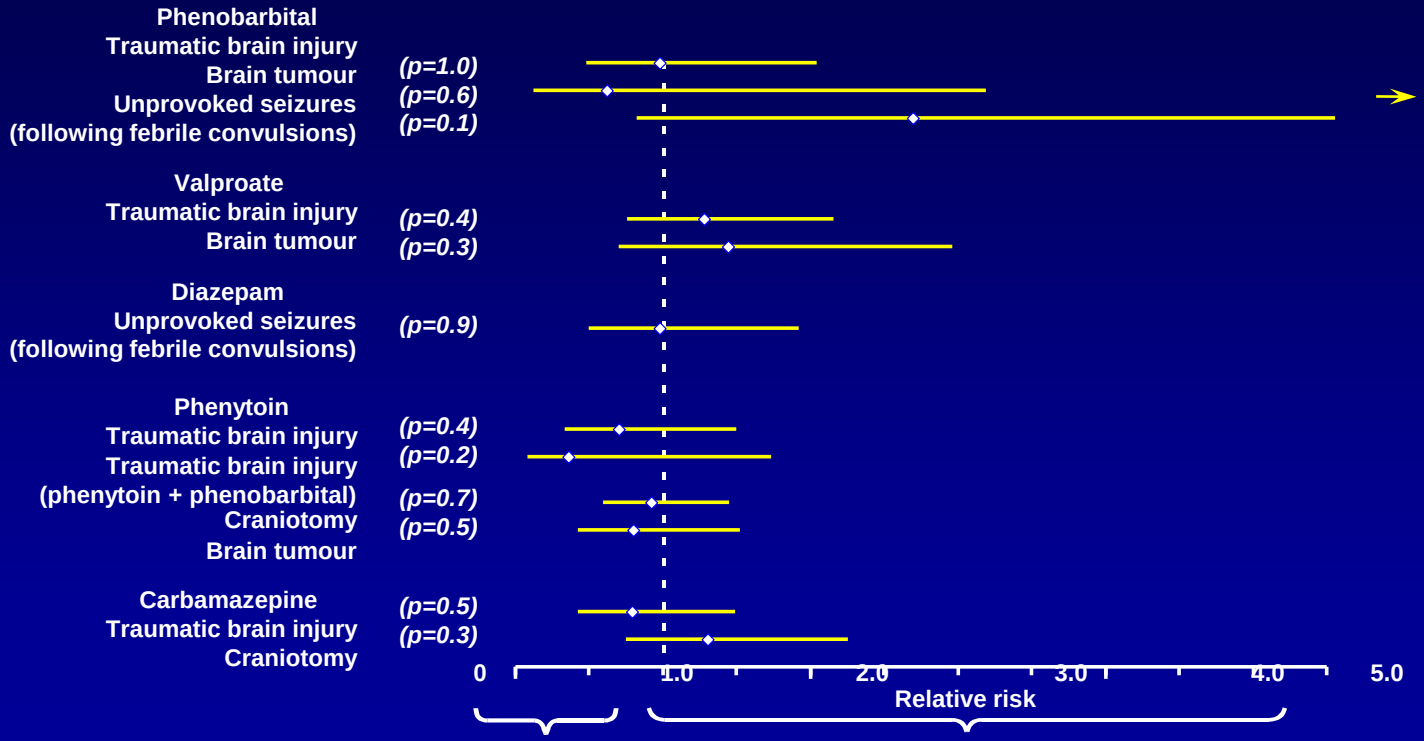
3 -6 months

Prophylaxis

- Patient stratification — WHO ?
- Prediction of outcome — WHICH DRUG ?
- Monitoring of treatment — WHEN START / STOP?



Post-traumatic Epilepsy
Evidence base for prophylactic treatment



Temkin NR. Epilepsia 2001;42(4):515–24

Post-traumatic Epilepsy
Prophylactic treatment

No place for this! – WHY?

- **Animal models used to screen for AED do not reproduce relevant epileptogenic mechanisms of human post-traumatic epilepsy**
- **AED tested devoid of antiepileptogenic properties**
  - **Valproate: antiepileptic property in animal models, but increases risk of post-traumatic epilepsy**
  - **Topiramate: lowers glutamate release after TBI**
- **suboptimal treatment**
  - **dosing too little**
  - **onset too late**
  - **duration too short**
- **erratic compliance**
- **Heterogenicity of study population**

Post-traumatic Epilepsy
Starting treatment

➢Clinical situations in which one may consider starting an AED for epilepsy:

- Prophylactic use
- Newly diagnosed epilepsy
  - Single Seizure
  - Recurrent Seizures
- Chronic epilepsy

Post-traumatic Epilepsy
Starting treatment after single seizure ?

- This is a controversial area
- A single unprovoked attack usually not treated
- General practice: defer treatment until 2 or more seizures, although patients perceived to be at high risk may be treated after a single attack
- AED treatment following a single seizure may reduce the risk of seizure recurrence in the short term although long term prognosis seems unchanged

Clinical treatment gaps

- Patient stratification — WHO ?
- Prediction of outcome — WHICH DRUG ?
- Monitoring of treatment — WHEN START / STOP?



all epilepsies begin with a 1st seizure

Clinical treatment gaps

- Patient stratification — WHO ?
- Prediction of outcome — WHICH DRUG ?
- Monitoring of treatment — WHEN START / STOP?



EEG: high specificity, but low sensitivity

MRI: high sensitivity, but low specificity

Anti-epileptogenesis trials

Post-traumatic epilepsy

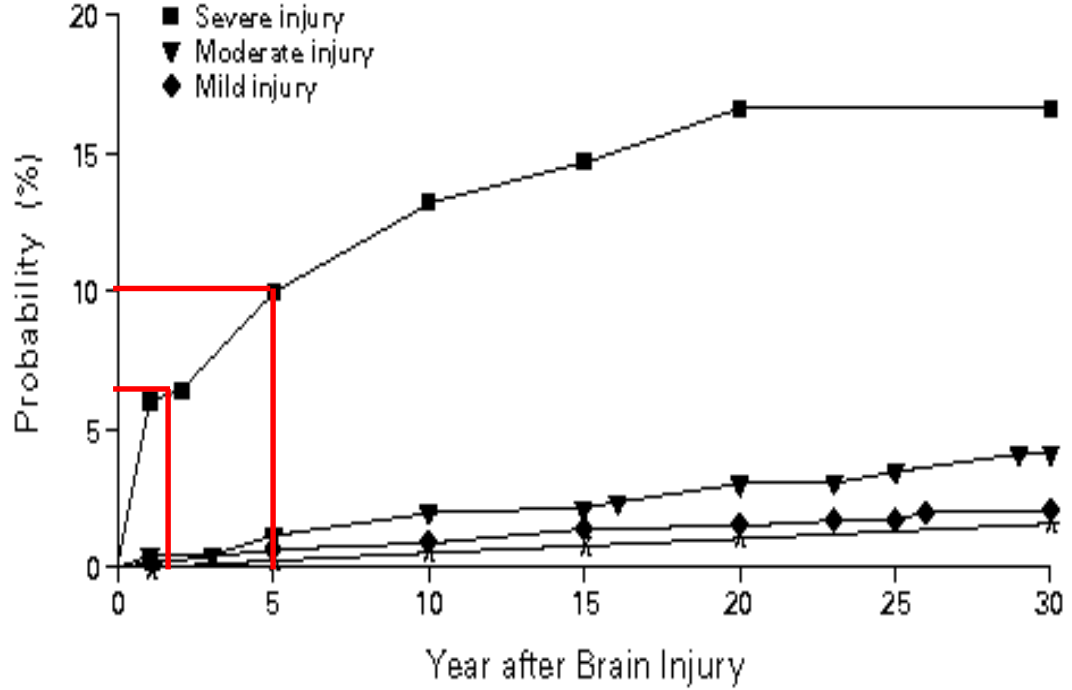
- Hospital admission for TBI:
  ~ 5M p.a. in Europe

- Cumulative 5-year probability:

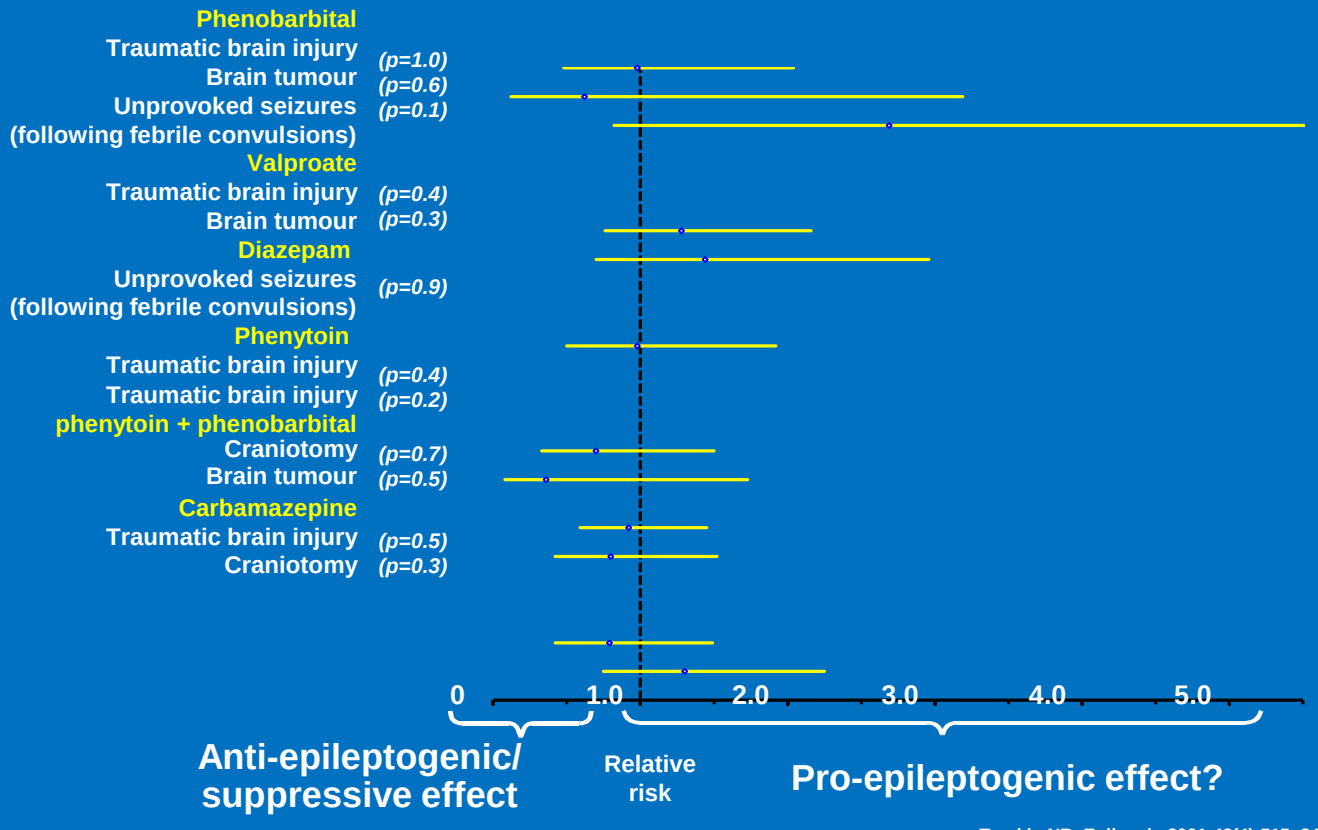
  mild injury (0.5%)

  moderate (1.2%)

  severe (10%)



Prophylactic treatment



Temkin NR. Epilepsia 2001;42(4):515–24

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Anti-epileptogenesis

"where the money is"

110.000 ischemic strokes per year in UK.

3.000 – 4.000 new vascular epilepsy cases per year in UK.

Anti-epileptogenesis-trials

"where the money is…spent"

Table 3. The required sample size to achieve α = 0.05 and π = 0.8 for selected values of P and τ.

P τ	0.01	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	0.99
0.03	1992458	19322	4656	1988	1070	652	428	294	208	147	99
0.1	554752	5393	1303	558	301	184	121	83	59	42	28
0.2	246672	2408	584	251	136	83	55	38	27	19	13
0.3	143979	1413	345	149	81	50	33	23	16	12	8
0.4	92632	915	225	98	54	33	22	15	11	8	5
0.5	61824	617	153	67	37	23	15	11	8	5	4
0.6	41285	418	105	47	26	16	11	8	6	4	3
0.7	26614	275	71	32	18	11	8	6	4	3	2
0.8	15611	168	45	21	12	8	5	4	3	2	1
0.9	7052	84	24	12	7	5	3	2	2	1	1

Friedman, A., Bar-Klein, G., Serlin, Y., Parmet, Y., Heinemann, U. & Kaufer, D. (2014).

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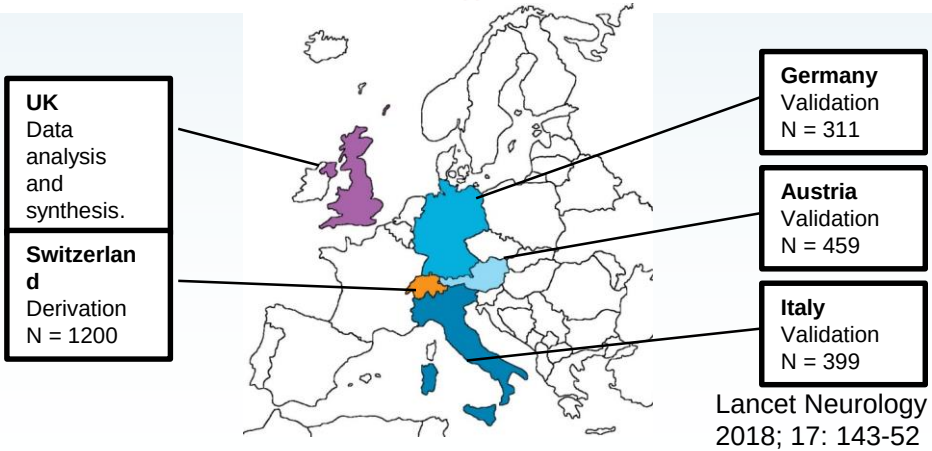
Prediction of late seizures after ischaemic stroke with a novel prognostic model (the SeLECT score): a multivariable prediction model development and validation study

Marian Galovic, Nico Döhler, Barbara Erdélyi-Canavese, Ansgar Felbecker, Philip Siebel, Julian Conrad, Stefan Evers, Michael Winklehner, Tim J von Oertzen, Hans-Peter Haring, Anna Serafini, Giorgia Gregoraci, Mariarosaria Valente, Francesco Janes, Gian Luigi Gigli, Mark R Keezer, John S Duncan, Josemir W Sander, Matthias J Koepp, Barbara Tettenborn

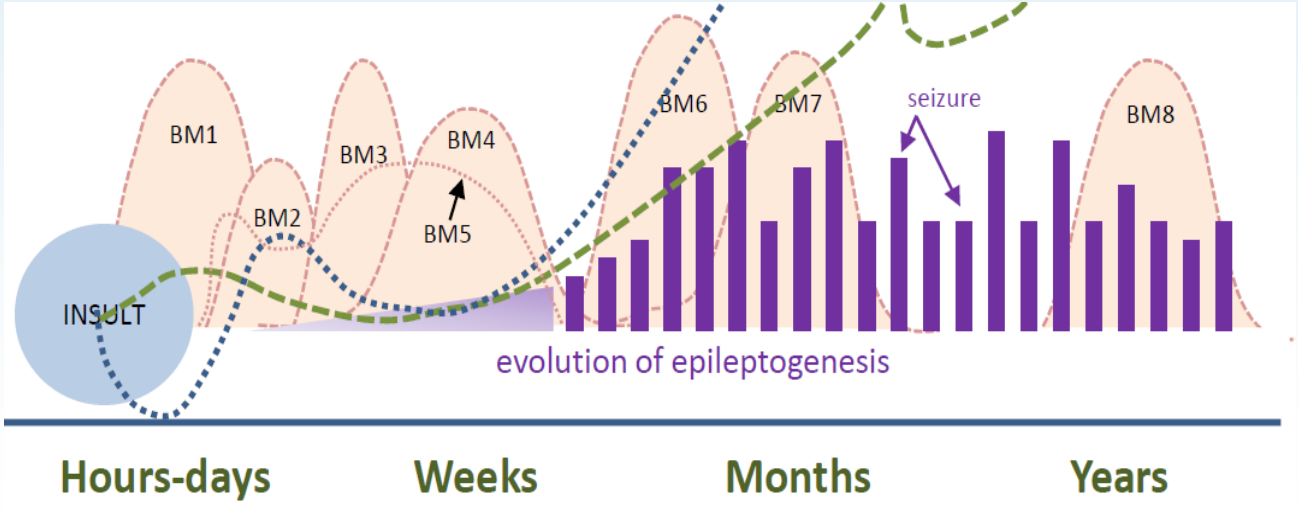


Lancet Neurology 2018; 17: 143-52

Feasibility of anti-epileptogenesis trials

"right treatment for the right person at the right time"

- **Who?** enriched population
- **How?** **thera**peutic targets relevant mechanism, early diag**nosis**



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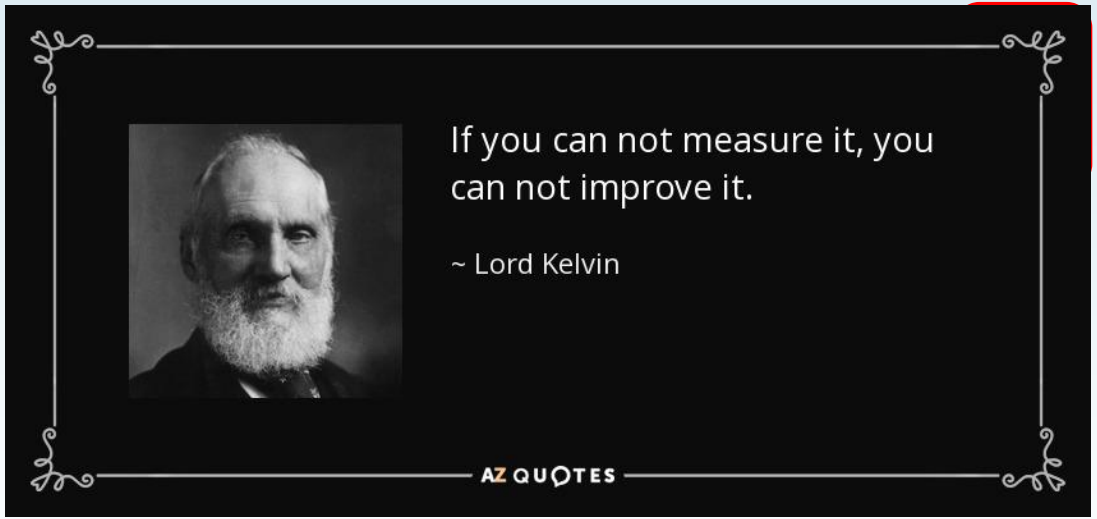


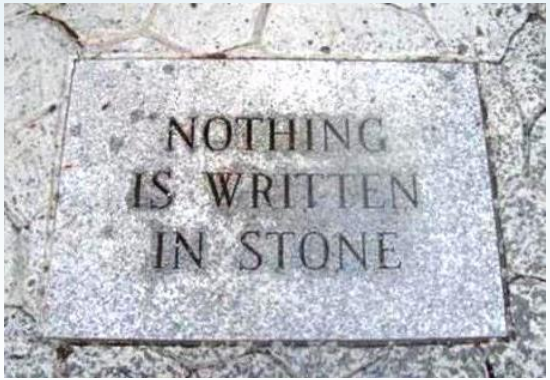
identify persistent measurable disturbances characterising the "enduring propensity"

Pitkanen et al., 2013

Key requirement for anti-epileptogenesis trials

Biomarker of disease activity (other than seizures)

- quantifiable
- objectively measured and evaluated
- reproducible
- cheap and easy to obtain
- results available quickly
- high accuracy
- good sensitivity
- good specificity



Prognostic Biomarkers of post-stroke epilepsy

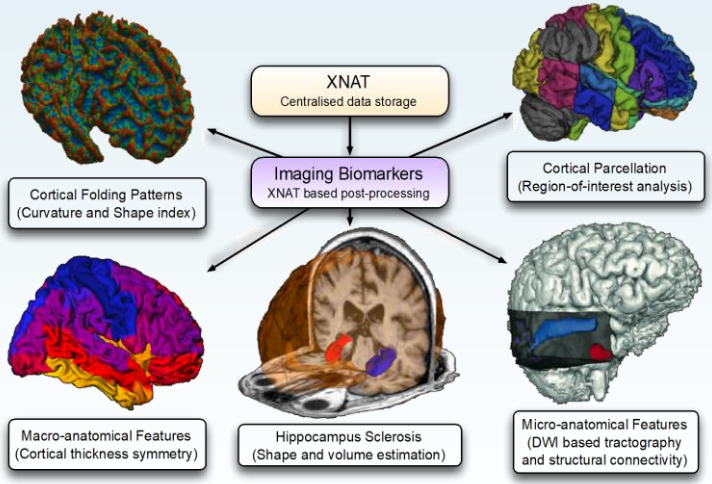
MRI

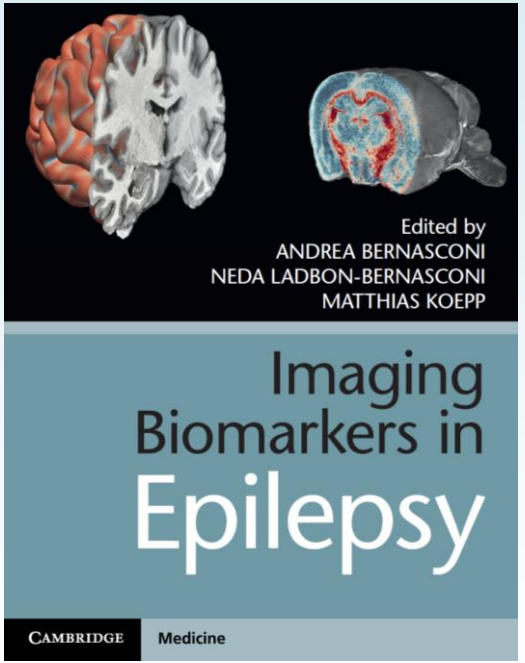
PET

EEG

Quantitative MRI:

- High sensitivity to detect abnormalities
- low specificity for epileptogenicity

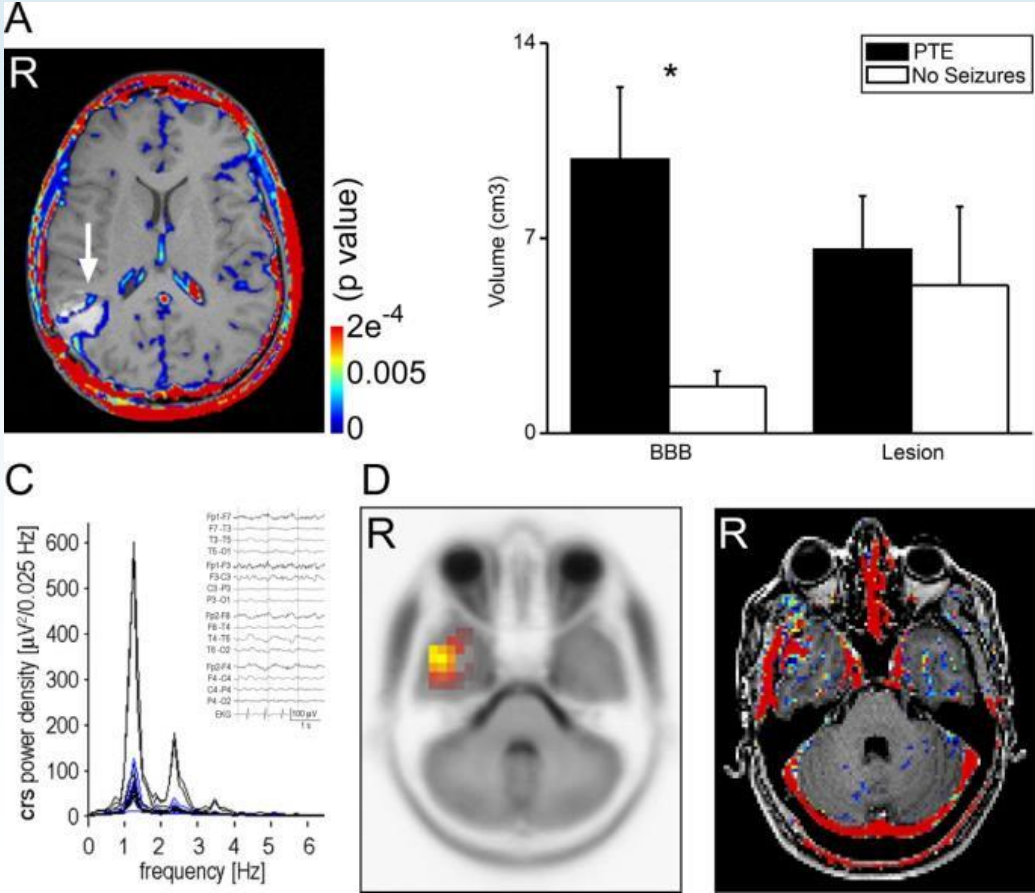




Imaging BBB dysfunction – too leaky

Dynamic contrast-enhanced imaging (DCE)

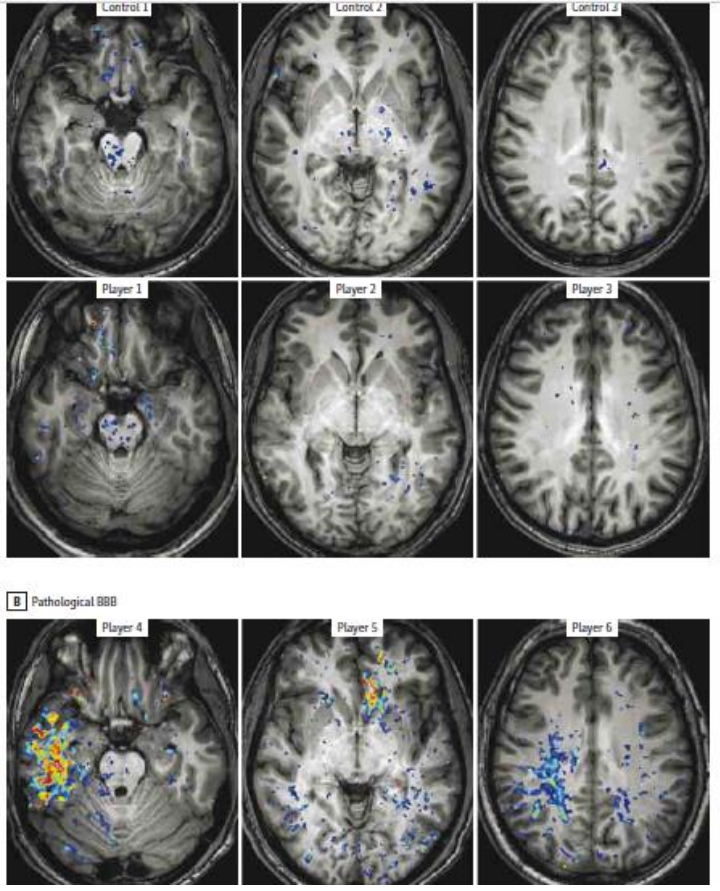
- BBB disruption after TBI
  82.4% PTE
  25% non-epileptic patients
- Volume of cerebral cortex with BBB disruption larger in PTE patients
- Slow wave EEG activity: localized to region of BBB disruption in 70%, correlated to volume of BBB disrupted cortex



Imaging BBB dysfunction – too leaky

Dynamic contrast-enhanced imaging (DCE)

- BBB disruption in
  - 16 amateur football players
  - 13 track and field athlete “controls”
- focal BBB lesions in different cortical regions including
  - temporal (player 4)
  - frontal (player 5)
  - parietal (player 6)
- No difference in concussion scores



Imaging BBB dysfur

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- No difference in concussion score

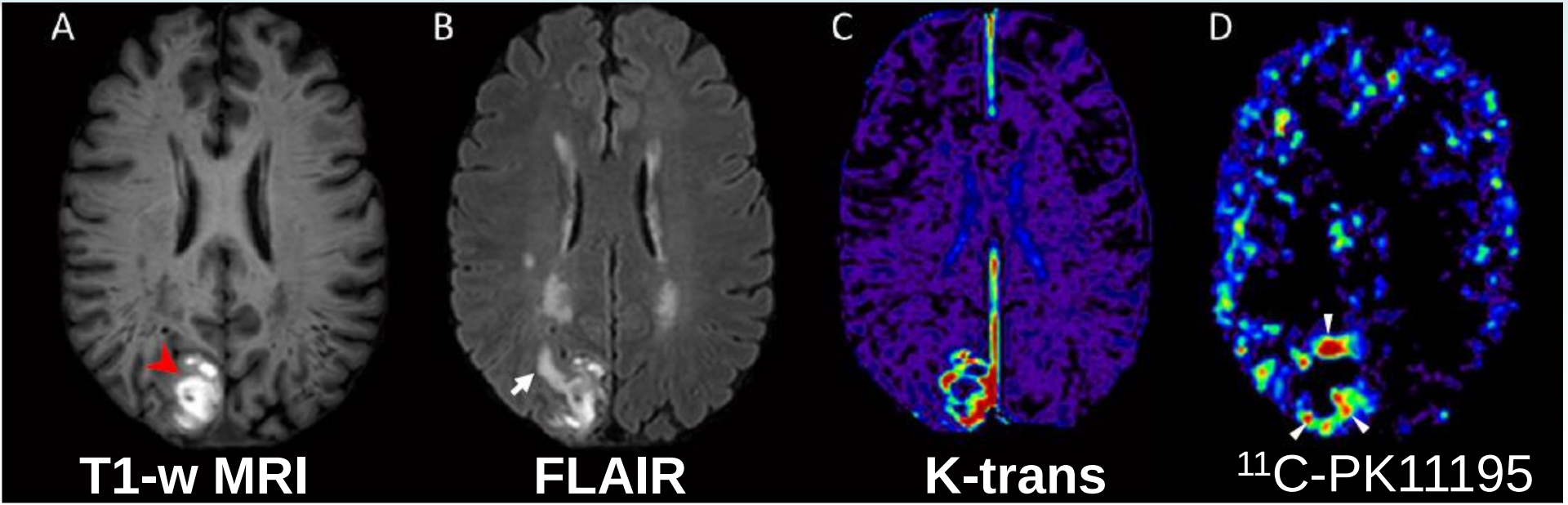
BBB dysfunction

Imaging biomarker

too leaky → 1st phase of epileptogenesis:

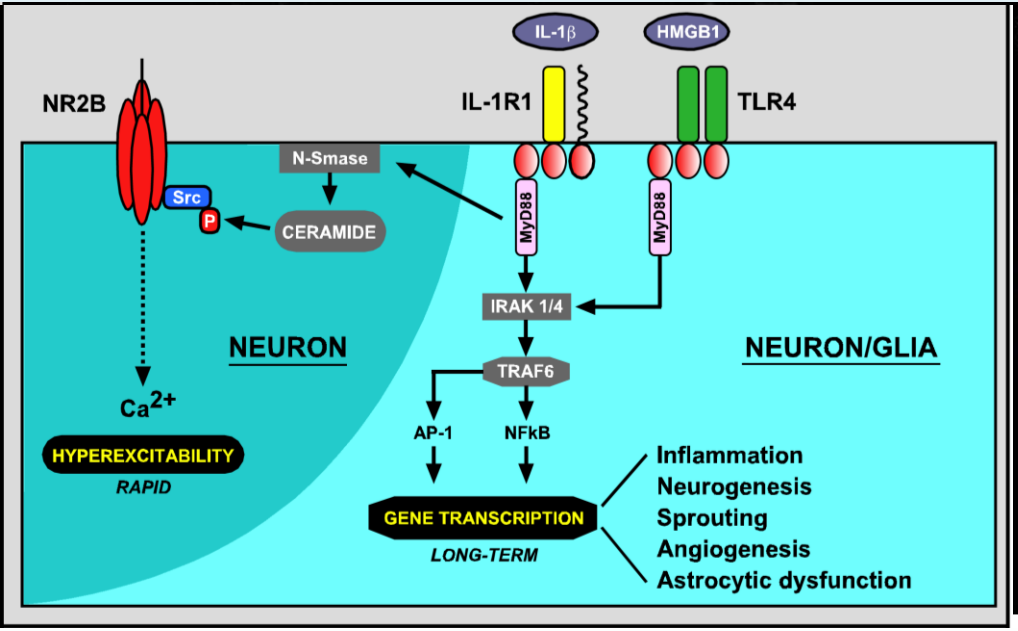
- Diffusion-weighted imaging (DWI)
- post-contrast FLAIR
- dynamic contrast-enhanced imaging (DCE)

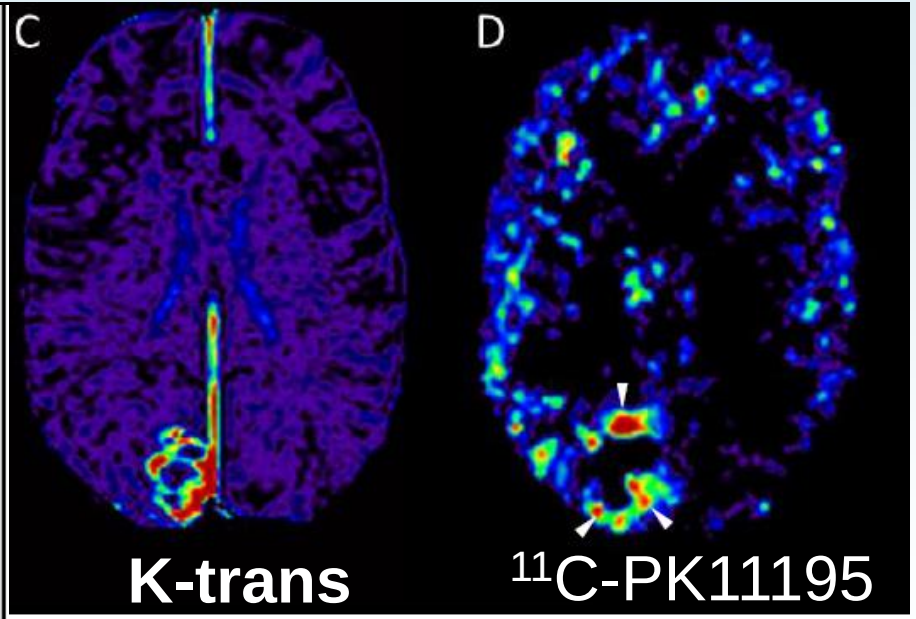
maging BBB dysfunction and inflammation



maging BBB dysfunction and inflammation

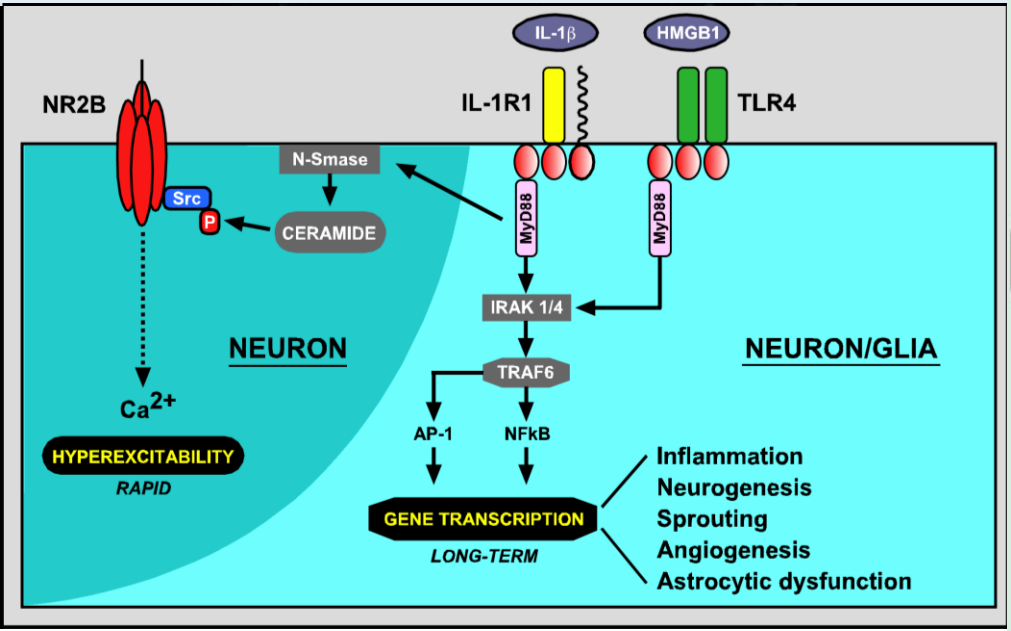
Therapeutic opportunities:
anakinra (AM Vezzani)

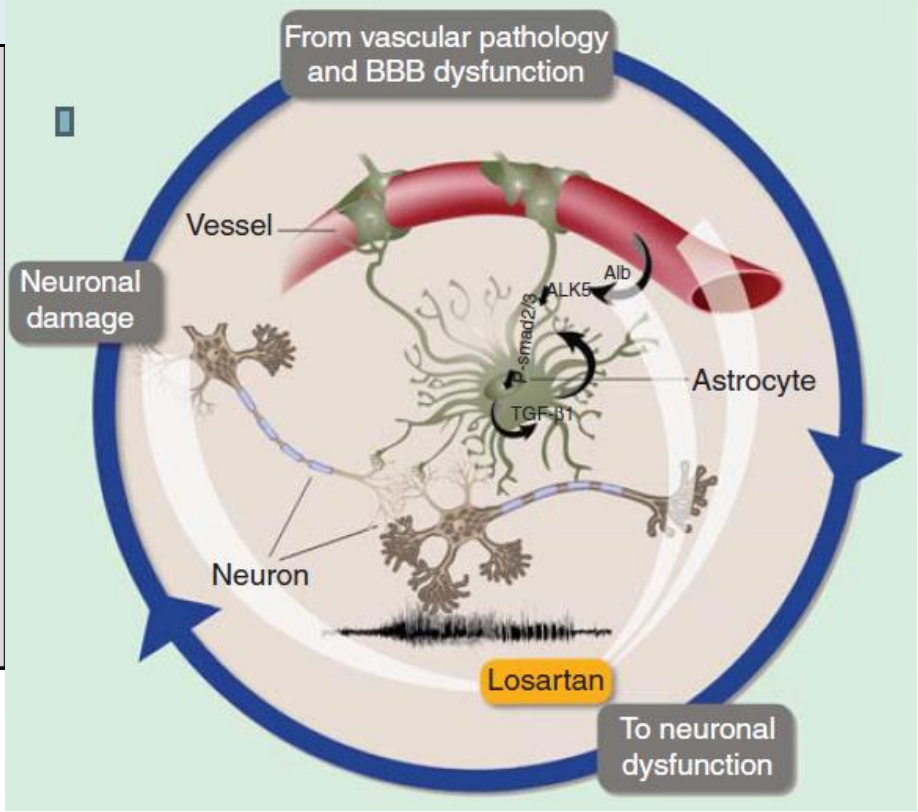




BBB dysfunction and inflammation

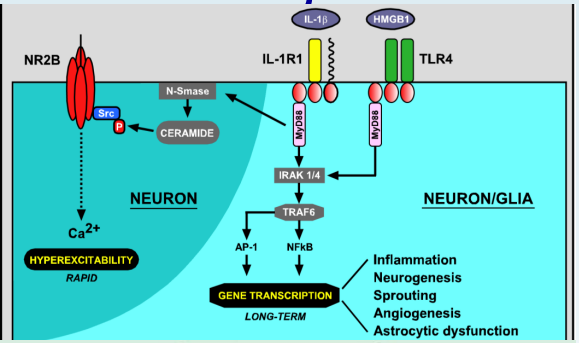
Therapeutic opportunities: anakinra, losartan (A Friedman)

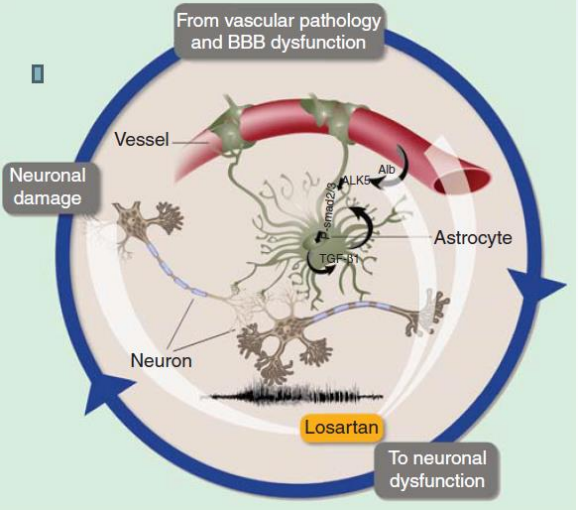


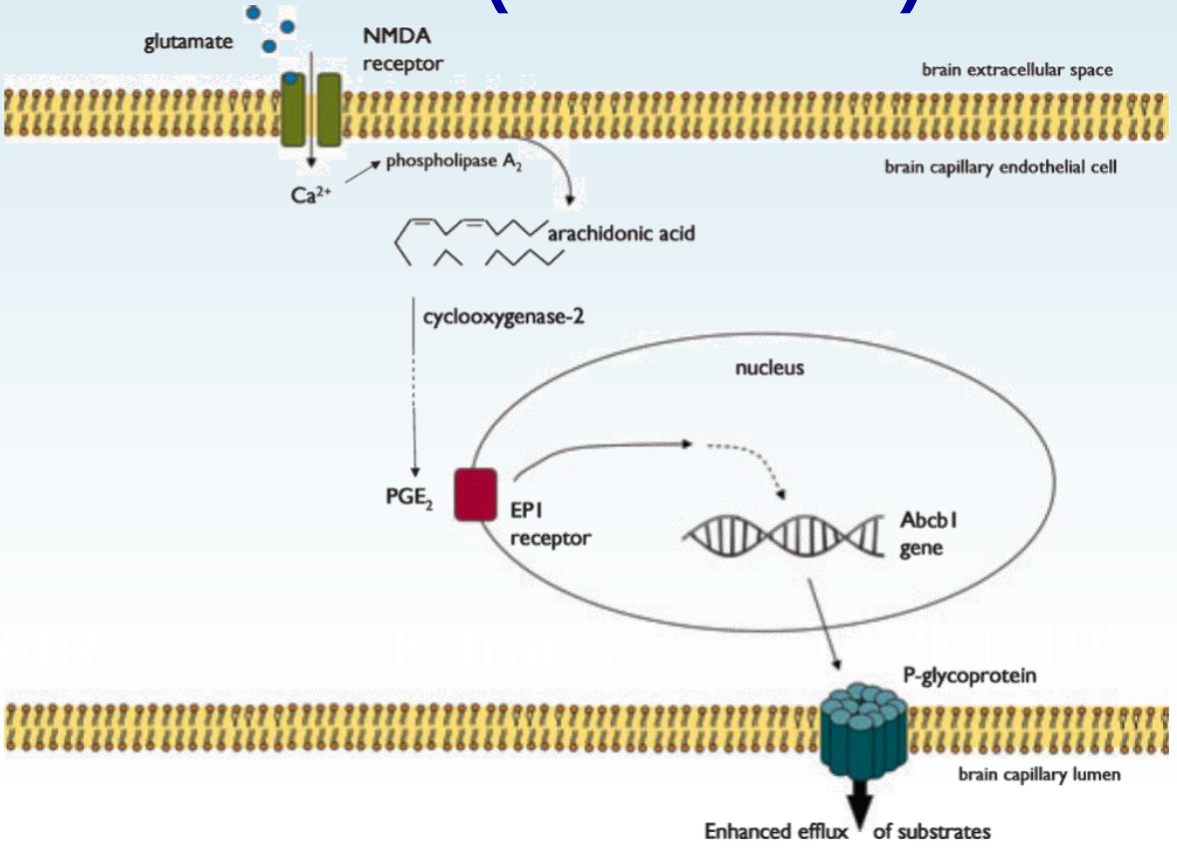


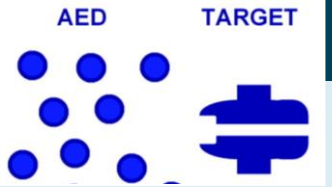
BBB dysfunction and inflammation

Therapeutic opportunities:
anakinra, losartan, Cox-2 inhibitors (H Potschka)







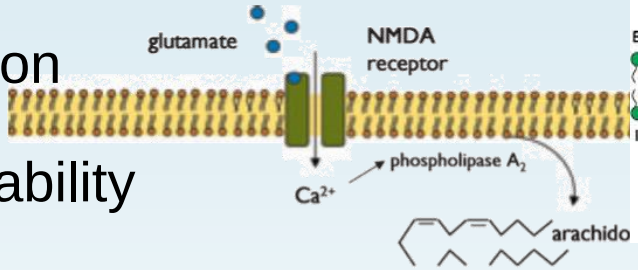


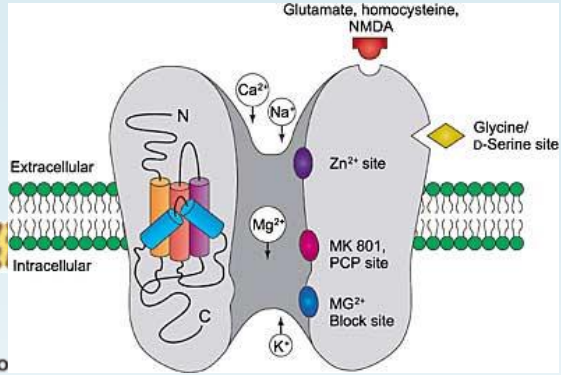
NMDA receptors

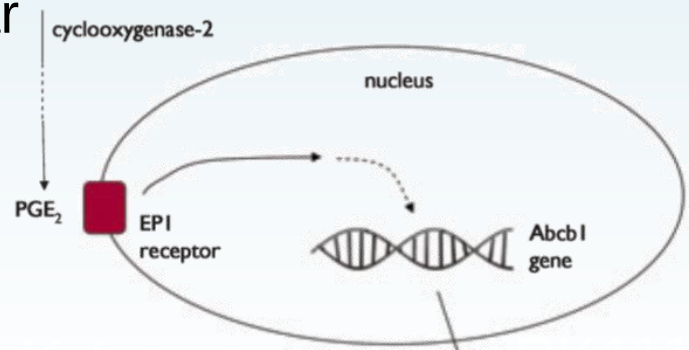
Therapeutic opportunities

“Target hypothesis”:

- Impaired GABAergic inhibition
- NMDA-receptor hyper-excitability
- Glutamate via NMDA activates intracellular inflammatory enzyme cascade that upregulates P-glycoprotein (P-gp)







Prognostic Biomarkers of post-stroke epilepsy

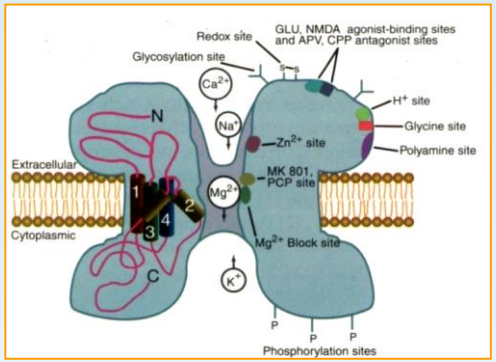
MRI

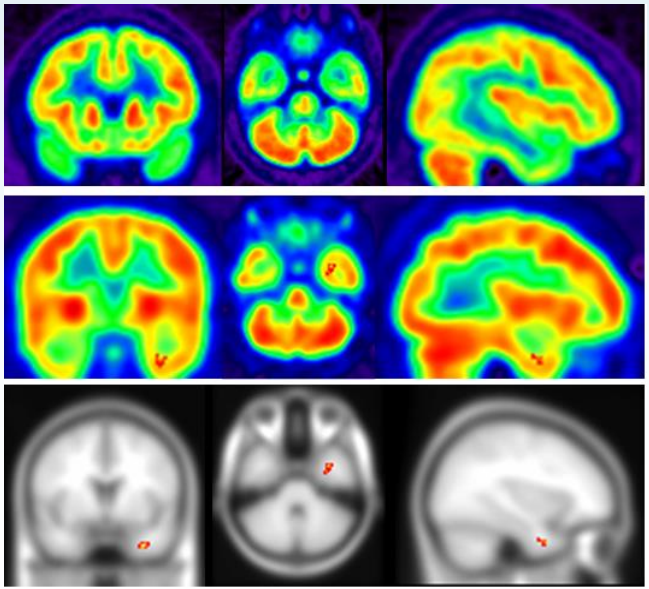
PET

EEG

GE-179 PET

- binds to open (activated) ion-channel (PCP-site)





Healthy control

R TLE

Increase of ^{18}F-GE179

Prognostic Biomarkers of post-stroke epilepsy

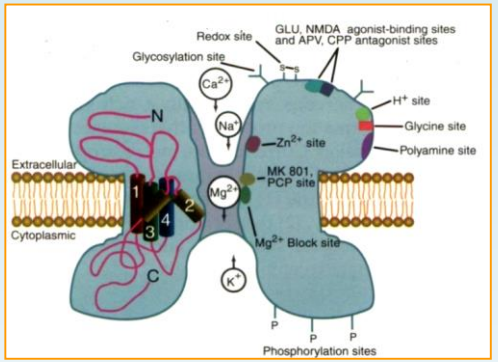
MRI

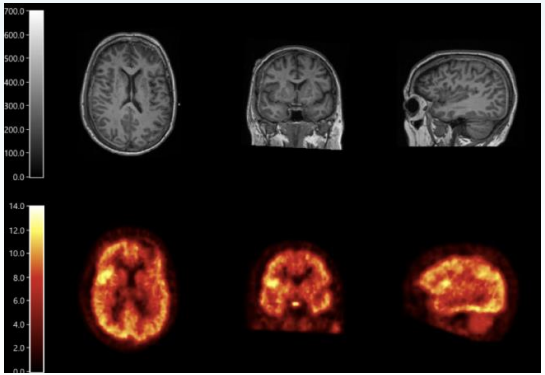
PET

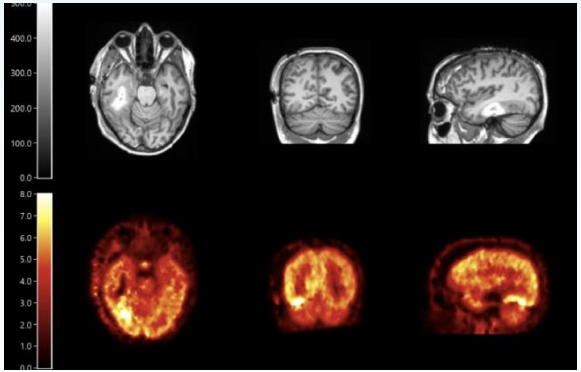
EEG

GE-179 PET

- binds to open (activated) ion-channel (PCP-site)
- Widespread changes post-TBI and stroke





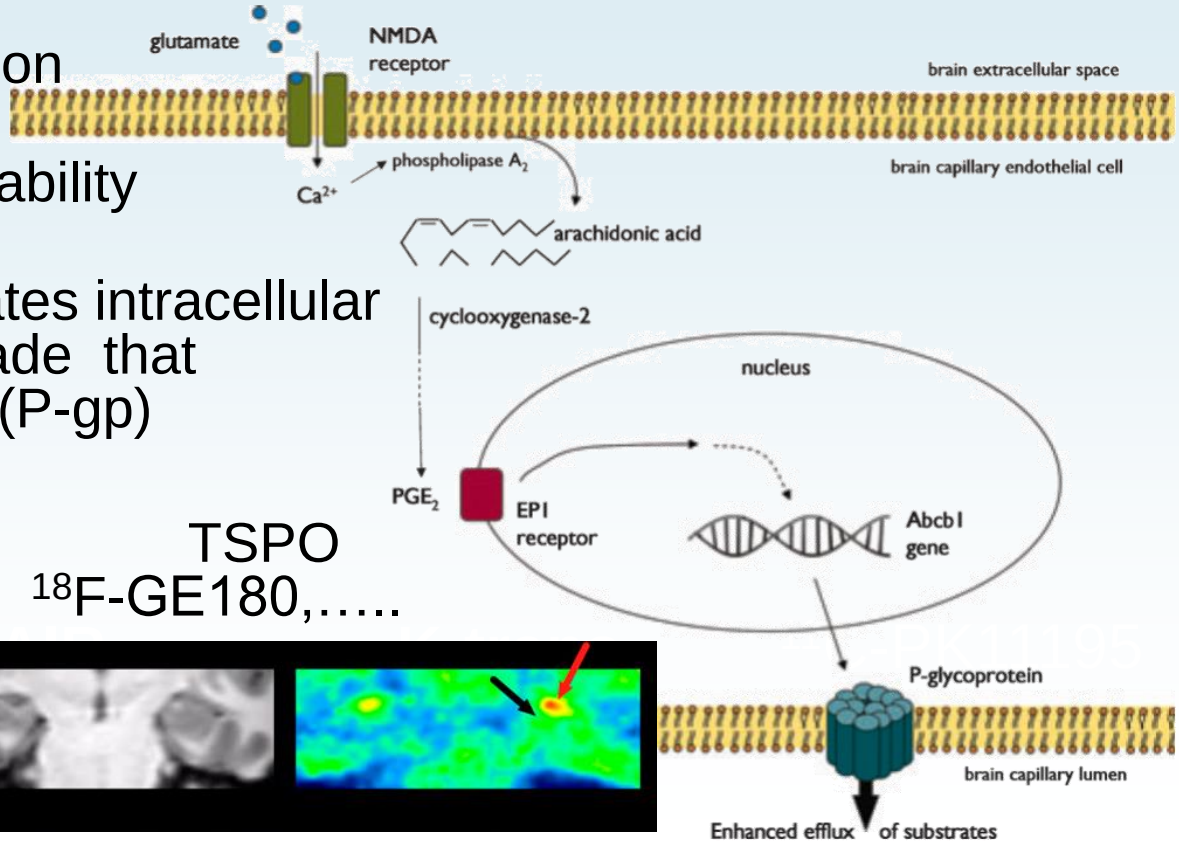


Inflammation

Therapeutic opportunities

"Target hypothesis":

- Impaired GABAergic inhibition
- NMDA-receptor hyper-excitability
- Glutamate via NMDA activates intracellular inflammatory enzyme cascade that upregulates P-glycoprotein (P-gp)



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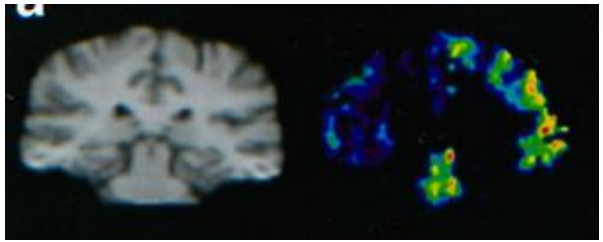
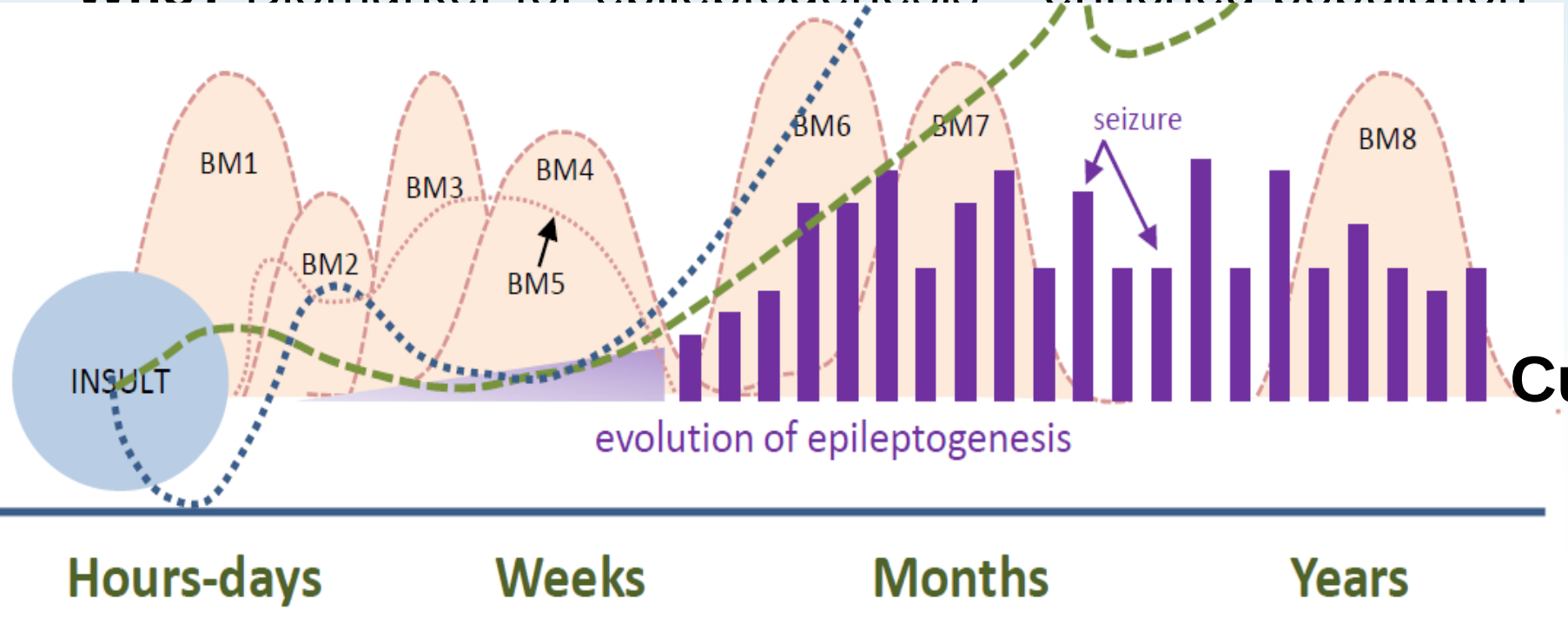


TSPO
^{18}F-GE180,…..

“Anti-epileptogenesis” trials

“right treatment for the right person at the right time”

- **How? thera**peutic targets relevant mechanism - early diag**nosis**
- **Who?** Biomarker for epileptogenesis – enriched population



Treatment of post-traumatic Epilepsy
Prediction of Treatment responder

Why bother?

Treatment of post-traumatic Epilepsy
Prediction of Treatment responder

Why bother?

- **Mortality**

  2 - 3x that of the general population

  Standardised Mortality Rates

Overall:	2 - 3
In the first 5 years:	4 – 5
20 - 40 years:	5 – 8
Chronic epilepsy:	8 - 15

Treatment of post-traumatic Epilepsy
Prediction of Treatment responder

Why bother?

- **Mortality**
- **The Burden of Epilepsy - NHS**
  - 0.25% of GP costs
  - 0.63% of hospital costs
  - 0.95% of pharmaceutical costs

  Over £585M per year direct costs

  Social costs up to 4 fold greater

Treatment of post-traumatic Epilepsy
Prediction of Treatment responder

How to define drug resistance?

- 30% patients (UK: 150.000 /)
- drug-treated history

  after two failed AED, only 3-4% chance of seizure freedom
  (Kwan & Brodie, NEJM 2000)

- Role of genetics

Post-traumatic Epilepsy
Role of genetics

- FH more common in late PTS, only in patients <16 years (Jennett et al)
- no increased risk amongst 1st degree relatives (Schaumann, Ottman)

- Best predictor for PTE: history of depression, even FH

- Only one genetic variant studied in any detail in any context

Post-traumatic Epilepsy
Role of genetics

- ApoE alleles: 3 common ε2, ε3, ε4
  Encode separate isoforms of protein
- Accepted role in Alzheimer's disease

- ε4 increases risk of poor outcome after TBI, and other acute injuries
- In TBI, ApoEε4 allele suggested roles:
  - No effect on outcome mild/moderate injury
  - Predicts risk of poor outcome after severe TBI
  - Increases risk of post-traumatic seizures

Outlook

In this section

- A - Z of epilepsy topics
- What is epilepsy?
- Blog
- Epileptic seizures
- First aid
- Just diagnosed
- Diagnosing epilepsy
- Treatment
- Living with epilepsy
- Parents, carers & teachers
- Personal stories
- Your epilepsy
- Associated conditions
- Epilepsy TV
- Glossary

Neurologist talks school rugby after son's concussion

Professor Matthias Koepp is a neurologist at Epilepsy Society. He is also father to two teenage boys, Noah, 16, (left, below) and Joshua, 13. Both of them are keen rugby players. Here he talks about the dilemma of being both a dad and a neurologist on the touchline and about his anxiety following Noah's recent concussion during a game.

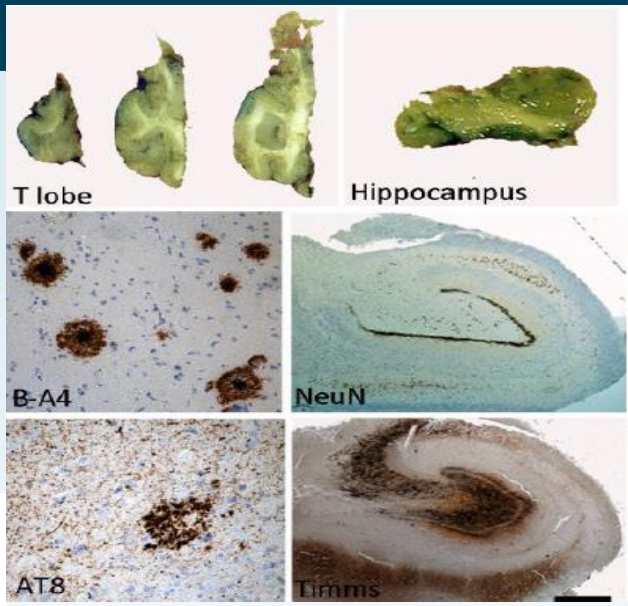
'Watching my two boys play rugby in their school teams has always concerned me as a neurologist. Of course you are on the touchline cheering them on, wanting them to win, but particularly by the age of 16 these boys are huge. They are heavy, they are fit, but their frontal lobes are not fully developed so they have no fear. They do not fully understand the consequences of their actions. They think they are invincible and the adrenaline is pumping.

Outlook

Prediction of treatment response

- generic tool for various disorders

Prediction of cognitive decline



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Outlook

Prediction of treatment response

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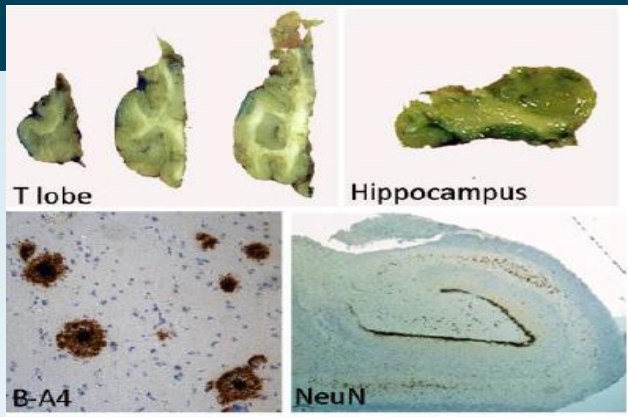

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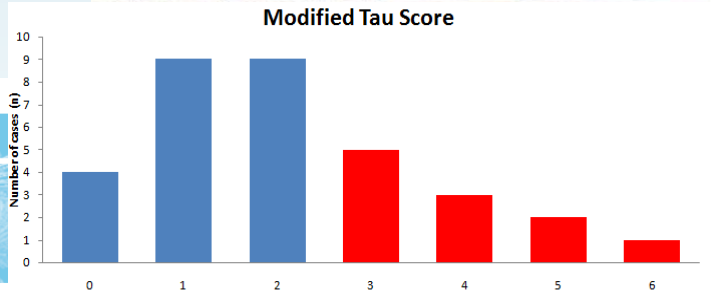

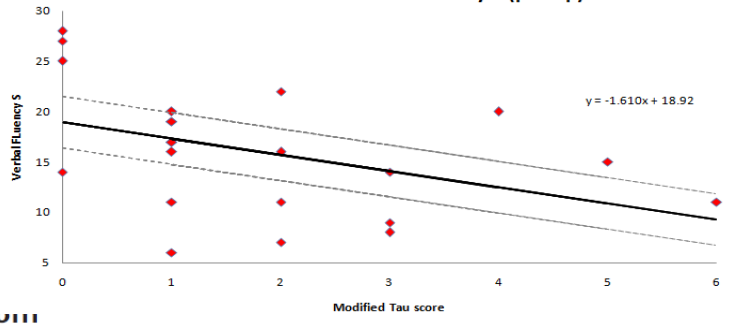

Conclusions

- Identify individuals at risk
- Treat before seizures develop
- Treat for defined period
- Start with reasonable time window after causative event
- Do not interfere with functional recovery from event
- Treatment is free of significant side effects