Does MTLE cause progressive neurocognitive damage?

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Do seizures beget seizures?

- "The tendency of the disease is toward self-perpetuation; each attack facilitates occurrence of another by causing instability of the nerve elements"
  - Gowers, 1881
- Is there evidence of epilepsy as a progressive disease?

Outline

- Temporal lobe epilepsy
- Animal models of limbic epilepsy
- Human evidence of progressive damage
  - MRI
- Human evidence of progressive neurocognitive damage

Temporal lobe epilepsy

- "Most common and most intractable form of epilepsy"
  - Engel, 2003, AES
- Previously defined by electroclinical syndrome
  - Potential for false localisation
- PET and MRI era
  - Better definition of cases
  - Bias toward lesional epilepsy in many series

Different forms of Temporal lobe epilepsy

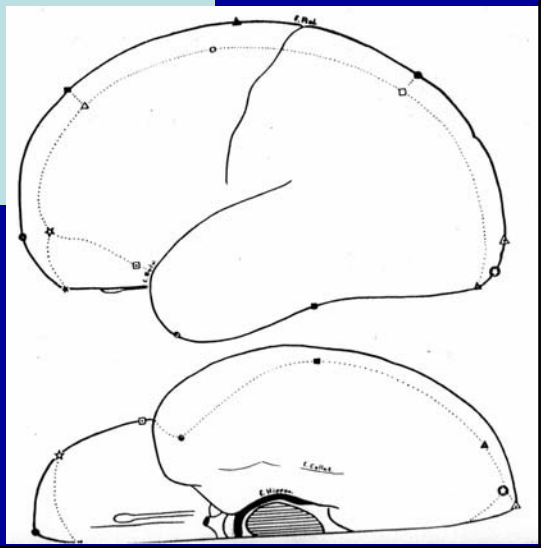
Mesial temporal lobe epilepsy with hippocampal sclerosis
- primary
- secondary ?dual pathology
- familial

Mesial temporal lesions
- tumours
- cavernomas

Benign non-familial TLE

Partial Epilepsy with auditory features

Neocortical TLE



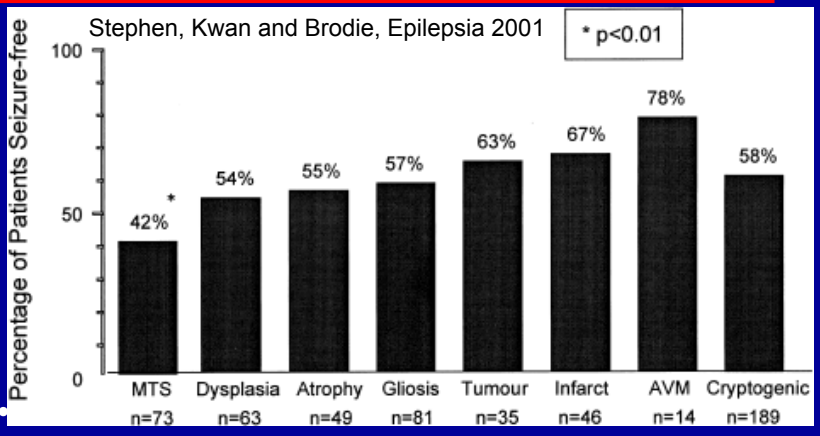
Temporal lobe CPS

- Epigastric sensation, fearfulness,
- Arrest in activity, usually don't fall
  - loss of awareness, oral and gestural automatisms
  - unresponsive and amnestic for events
- Duration 30s to 2 mins, postictal confusion
  - may progress to tonic clonic seizures (2nd GTCS)
- Majority of patients have 3-10 seizures/month
  - 2nd GTCS controlled on medication
- Prognosis for seizure control

"Temporal lobe epilepsy, most refractory partial epilepsy"

- 2,200 adult hospital-based outpatients
  - follow-up of 1 to 7 years
  - 62% partial epilepsy, 22% generalized epilepsy, 16% undetermined epilepsy
- Seizure control (>1 year without seizure)
  - 82% of idiopathic generalized epilepsy
  - 35-45% of symptomatic / cryptogenic partial epilepsy
  - 36% of extra-TLE patients
  - Temporal lobe epilepsy 20% seizure free
    - Only 11% in partial epilepsy with hippocampal sclerosis
      - Semah et al., Neurology 1998

Poor prognosis not uniform



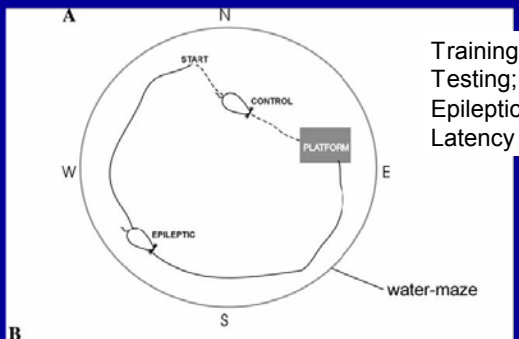
- Familial cases, further examples of better prognosis

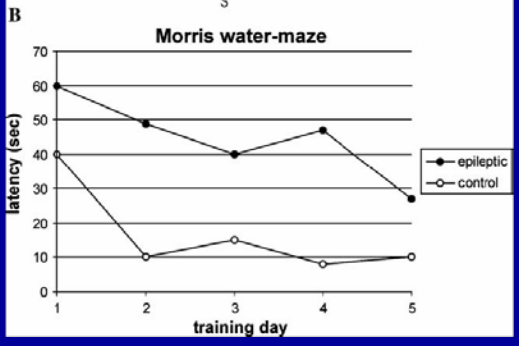
Mesial temporal lobe epilepsy

- Natural history
  - Surgical cases, mean 9 year to become intractable
  - remission $\geqslant$ 1 year in 26%, $\geqslant$ 5 yrs in 8.5%
    - Berg et al, Neurology 2003
- Duration of seizures
  - total time spent in seizures
- Follow up in medical series
  - decrease in seizure frequency, over 10 years
    - 26% of group had >75% reduction in seizures
      - Holmes et al., Epilepsia 1998
  - Medical group, 102 with TLE, median 52 months
    - 50% improved at follow up (12% seizures free, 38% >50% reduction)
      - Helmstaedter et al., Ann Neurol 2003

Animal studies

- Evidence for seizures causing irreversible cognitive damage
- Great variety of sources
  - Majak and Pitkänen, Epil Behav 2004
- Spatial learning and Morris water maze
  - setpal hippocampus
- Status epilepticus
- Brief seizures





Training; 5 trials/day for 5 consecutive days
Testing; 18 weeks after SE
Epileptic rat searches for the platform
Latency to find the platform longer

But what about brief seizures?

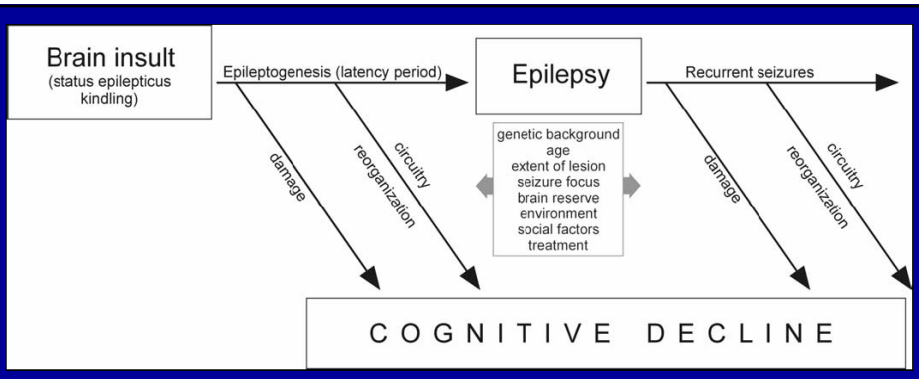
Kindling models
10-20 partial seizures
3 2nd GTCS

SE and spontaneous seizures

Impaired spatial learning
Relationship to number of seizures

Neuonal death and seizures

- Relationship to the number of seizures?
  - Full kindling vs. partial kindling
  - Following SE; <1 seizure per day vs. >1 seizure per day
- Problem of the relative contribution of the initial insult
  - more spontaneous seizures in more damaged brain after SE
  - SE continues to cause cell loss for weeks after the insult
- Seizures (repeated brief or SE) cause neuronal death in vulnerable subpopulations of neurons
  - Once these have died further seizures may not cause additional neuronal loss

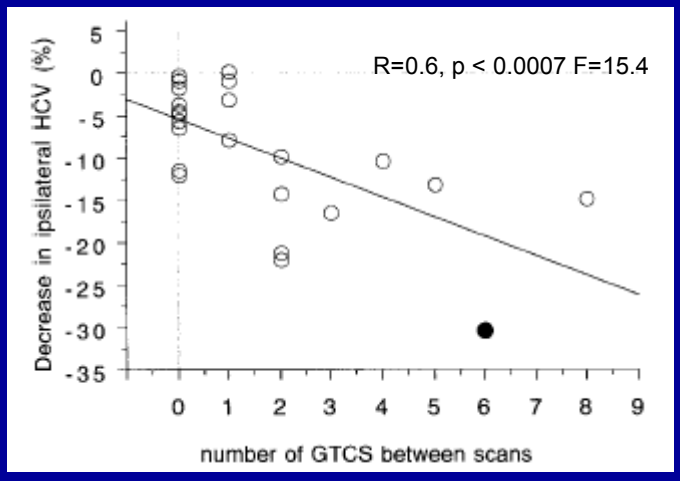


Majak and Pitkänen, Epil Behav 2004

Seizure-induced re-modeling of neuronal networks
Neuronal loss and damage
Neurogenesis
Axonal sprouting
Reduced dendritic branching and spine loss
Gliosis

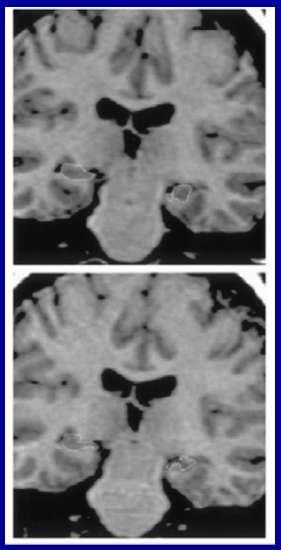
Human evidence

- Various cross-sectional studies have shown a positive correlation between the severity of epilepsy and the extent of hippocampal damage
  - MRI; positive correlation between the severity of epilepsy and the extent of hippocampal damage (Kalviainen et al., Neurology 1998)
  - Histology; Longer duration of TLE associated with more widespread reduction in neuronal densities in hippocampus (Mathern, Prog Brain Res 2002)
  - Both studies indicated slow progression



Patients from first seizure clinic, TLE but not HS
Correlation between hippocampal volume loss and 2nd GTCS

Briellmann et al., Ann Neurol 2002



12 patients with refractory TLE and HS
Surgical program
Seizure free patients
- no change in volume

Continued seizures
- Correlation between volume change and seizures

Fuerst et al., Ann Neurol 2003

Larger MRI studies

- 179 patients (66 with TLE)
- Reduced HV at baseline in TLE patients
- Similar rates of HV loss in patients with TLE, extratemporal focal epilepsy and controls
- No correlation with number of partial seizures or 2nd GTCS in TLE
  - Only extratemporal group correlation with 2nd GTCS
- Structural damage likely to be due to initial precipitating injury with age related volume loss
- Not by repeated seizures
- Subtle neocortical atrophy
  - Liu et al., Epilepsia 2005

Longitudinal MRI studies

- 103 patients with newly diagnosed focal epilepsy
- Serial MRI studies at diagnosis and after 1, 2 to 3, and 5 years
- No difference was observed in the mean HC volumes between controls and patients at baseline, after 1, 2 to 3, and 5 years of follow-up
- 8% of patients had HC damage at diagnosis
- 13% of patients developed HC volume decrease during 2 to 3 years of follow-up
  - longer duration of seizure disorder and larger seizure number before the epilepsy was diagnosed
    - Salmenpera et al., Neurology 2005

Problems in interpretation of data

- What is the cause of the volume loss?
  - Initial precipitating insults causing neuronal loss
    - greater with more severe epilepsy
  - Ongoing damage from initial insult
  - Recurrent seizures
- Hippocampal volume
  - Other regions need to examined
- Can have cognitive changes without significant atrophy

Cognitive studies

- What causes it?
  - Initial insult vs. continued spontaneous seizures
- All seizures?
  - Secondarily generalised tonic clonic vs. SPS/CPS
- All persons?
  - Subsets ≡ genetic influences
- Nature of seizure related damage
  - Neurogenesis, axonal and dendritic changes vs. neuronal death and atrophy
- Personality, psychosocial changes vs. cognitive decline

Cognitive function and epilepsy

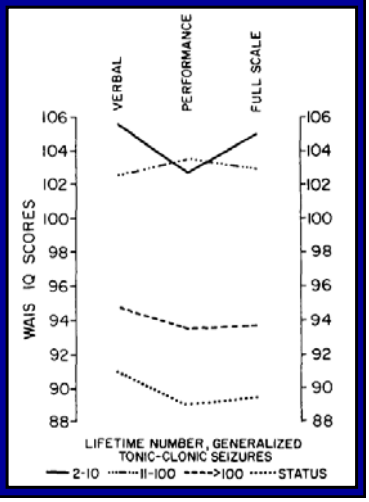
- Majority have normal IQ
  - But as a group more likely to have impaired cognitive performance
  - c/w age and education matched controls
- Will have poorer education, social circumstances and employment status
  - Sillanpaa et al., NEJM 1998
- Psychocsocial deficits despite normal IQ
  - Camfield et al., 1993

Site of neuropathology important

- Material specific memory dysfunction
  - Dominant temporal lobe - Verbal memory
  - Nondominant – Visuospatial/figural memory
- But deficits beyond memory function
- Most attention has been paid to outcome following temporal lobectomy
  - Extent of resection, dominant temporal lobe
  - Relationship to preoperative memory function

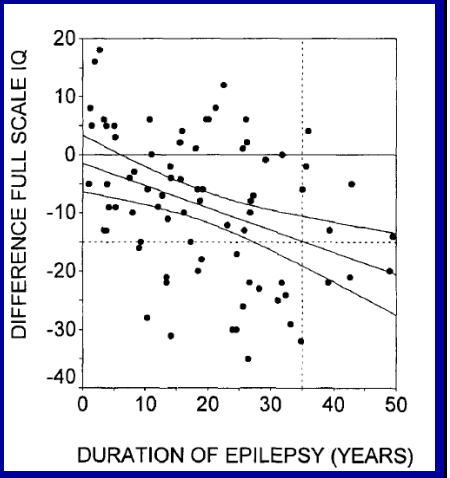
Cross sectional studies

- Dodrill, Prog Brain Res, 2002
  - Estimate of 2nd GTCS
  - Correlation with 2nd GTCS



Measures of IQ

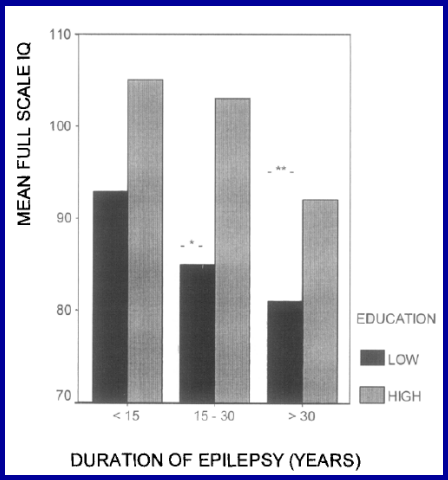
- Jokeit and Ebner
  - Prog Brian Res, 2002
  - Epilepsy surgery series
  - reduced intelligence



Cross sectional studies

- Helmstaedter and Elger, 1999
  - 63 Left MTLE cases vs 125 controls
  - No accelerated deterioration with age in MTLE
- Dodrill review of neuropsychology studies in adults
  - 8 cross sectional studies show strong relationship between seizures and cognitive decline
  - 8 longitudinal studies; 5 mild relationship, 3 none

- Benefit of higher IQ
  - Jokiet and Ebner
    - JNNP, 1999



Studies in MTLE

- Selwa et al., Epilepsia 1994
  - 28 patients with TLE (electroclinical plus)
    - Complex partial seizures, mean 8/mth
    - Retested after baseline 1-8 years
  - No change in memory scores
    - Increase in FSIQ 2.7, PIQ 4.4
- Holmes et al., Epilepsia 1998
  - 35 patients assessed not operated upon
    - 2-42 years of seizures, mean 9/mth, 10 years apart
    - No difference in verbal memory scores
      - Subsets examined, including 6 pts. With >100 2nd GTCS

Effect of AEDs

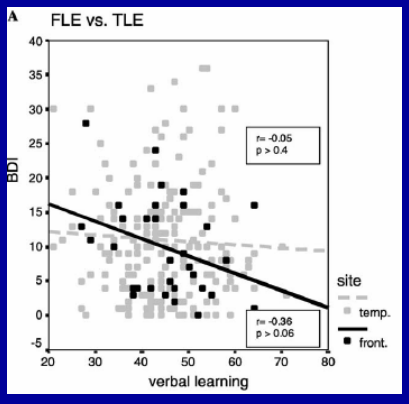
- The cognitive effects of most of the AEDs is relatively modest
  - Attention and concentration
  - Psychomotor speed
- Polypharmacy
- High serum levels of an AED

} Relevant to study groups

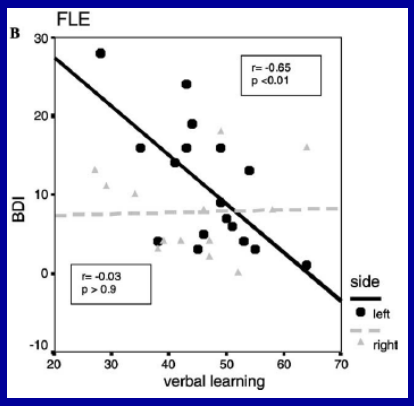
- Comparative studies
  - Phenobarbitone vs. carbamazepine, phenytoin and valproate
  - Gabapentin and lamotrigine better than carbamazepine
  - Topiramate has specific deficits
- Note the deleterious effects of AEDs may be offset by the benefit of seizue improvement or freedom

Psychiatric co-morbidity

- Major depression
  - Lifetime to date 39%
    - Altshuler et al. 1999
  - Intractable CPS 57%
    - Blumer et al., 1998
- Anxiety
  - Surgical series 32%
    - Victoroff, 1994
- Psychosis
  - 9%, Mendez et al., 1993



Depression and cognitive function
Helmstaedtar, Epil Behav 2004



Longitudinal study of cognition

- Attempt to determine if cognitive decline is progressive
- Does treatment, successful surgery, stop decline
- 147 patients with TLE – surgery
  - 63% seizure free
- 102 with TLE - medical treatment
  - 12% Seizure free
- Follow up mean 57 months
  - Helmstaedter et al., Ann Neurol 2003

Longitudinal study

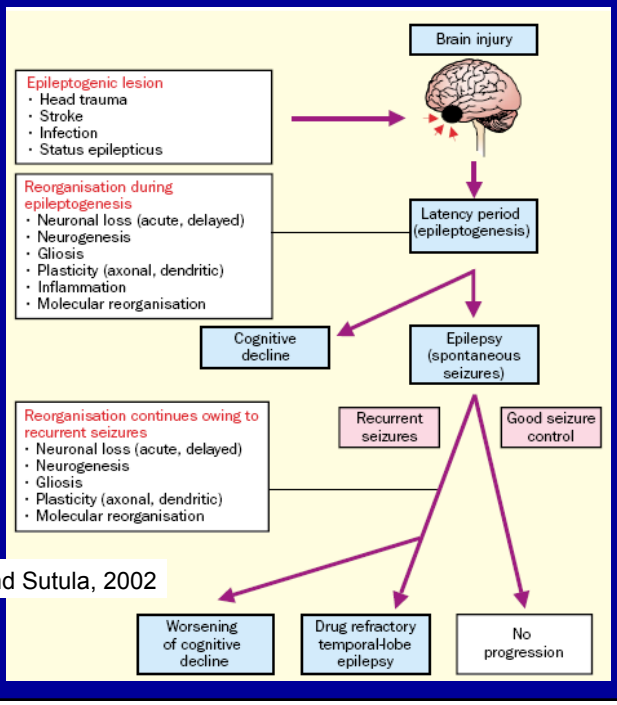
- Comprehensive measures of memory and non-memory function
- 50% of medical group had significant memory decline at repeat testing
  - Associated with frequency and severity of seizures
    - Helmstaedter et al., Ann Neurol 2003

Longitudinal study

- 60% of surgical group had memory decline
  - Successful surgery had potential to halt the deterioration
    - Non-memory function improved first, memory later
  - More severe decline than medical group
  - When surgery dominant, more extensive and unsuccessful
- "Reserve capacity"
  - Better long term outcome with higher baseline function
    - Helmstaedter et al., 2003

Problems with studies

- Cross sectional studies
  - Longer duration of epilepsy
  - But infer intra-individual changes for inter-individual differences
- Longitudinal not truly prospective
  - Many do not provide detailed seizure type and frequency during follow up period
  - AEDs not controlled for, not uniform
  - Duration of follow-up often not uniform
- Not long enough?, need >25 years



Pitkanen and Sutula, 2002

Conclusions

- MTLE will have neurocognitive deficits at diagnosis
- Risk factors for poorer baseline function
  - Hippocampal sclerosis
  - Polypharmacy
  - Frequent seizures
- Progressive neurocognitive decline
  - Frequent seizures, 2nd GTCS
  - Epilepsy surgery
- Future directions in research
  - Subsets of TLE
  - Children