The new Organization of the Epilepsies

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Disclosure

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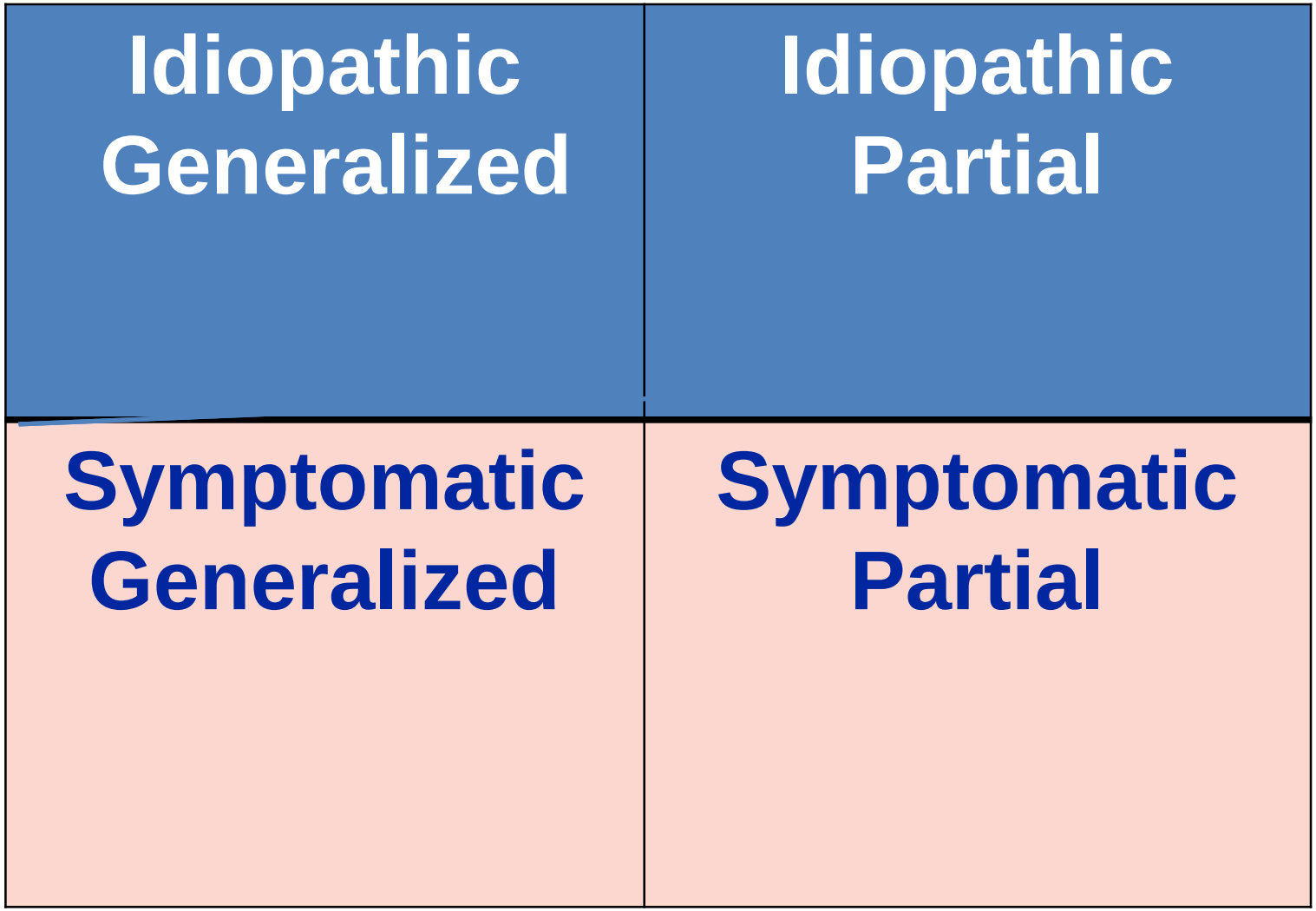
- NINDS, CURE, US DOD, NHMRC, ARC
- SAB: Dravet.org, *PCDH19* Alliance

Type of Financial Relationship

- UCB, Janssen-Cilag, Athena Diagnostics, Biocodex, GlaxoSmithKline

Classification – primarily clinical tool

1989 Classification seemed so simple….



But many patients could *not* be classified

Often it did work…

Idiopathic Generalized Childhood Absence	**Idiopathic Partial** Benign Centro-Temporal Epilepsy
Symptomatic Generalized Dravet	**Symptomatic Partial** TLE with HS

But often it did not work…

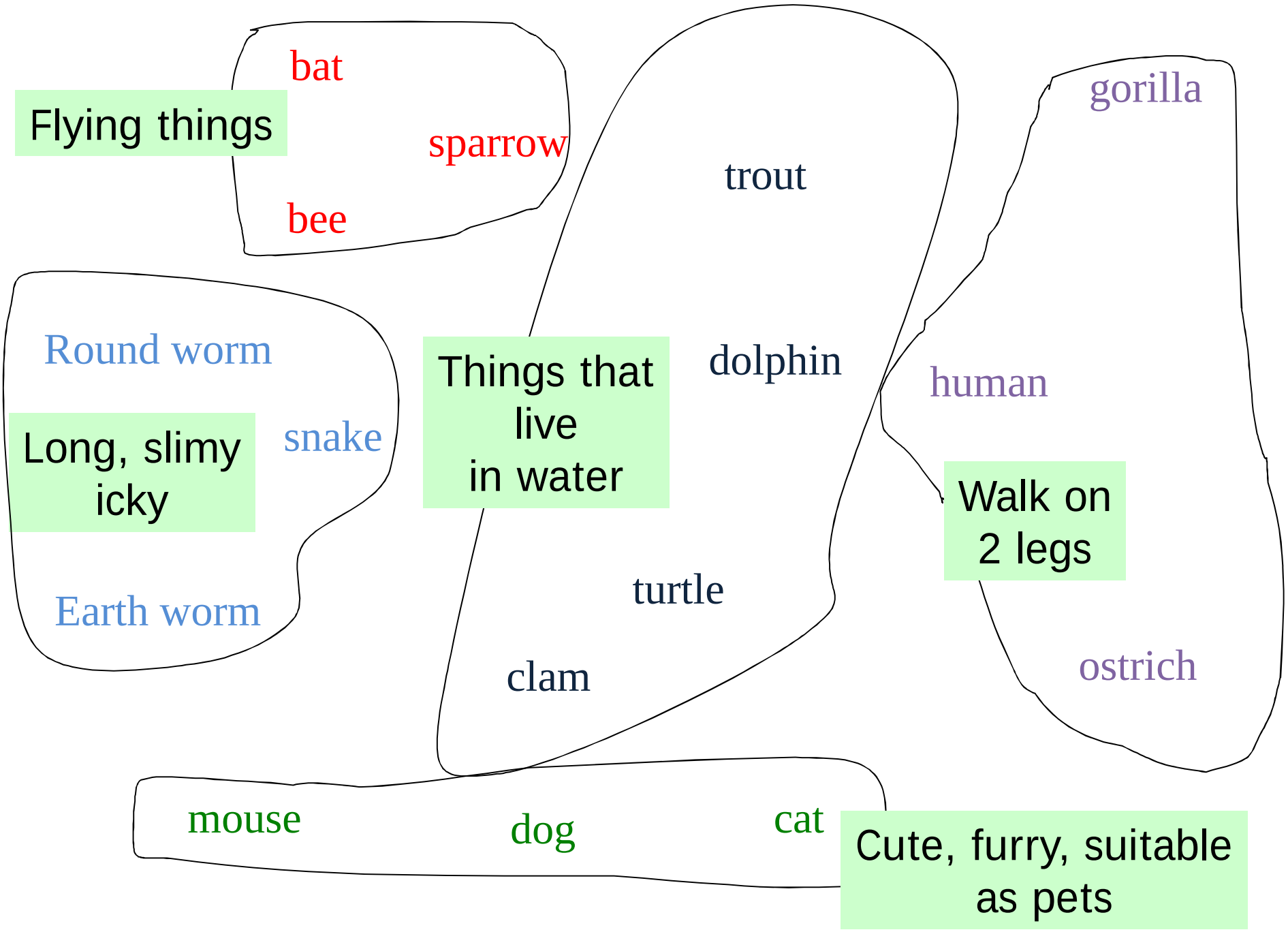
Idiopathic Generalized Childhood Absence	**Idiopathic Partial** Benign Centro Temporal Epilepsy
Symptomatic Generalized Dravet	**Symptomatic Partial** TLE with HS

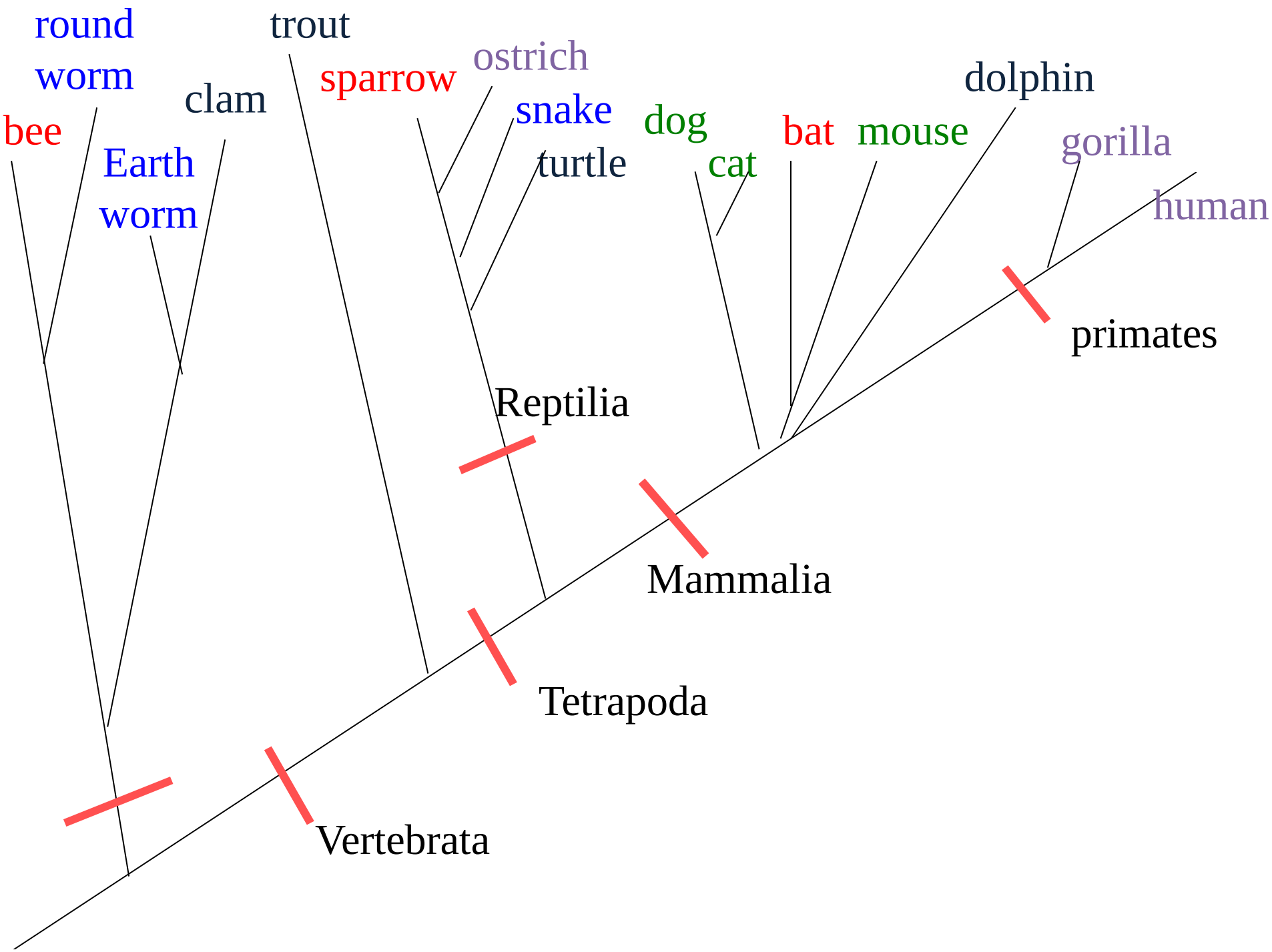
Too Difficult, Too Complicated…
…Too Arbitrary

- Dravet – 80% have *SCN1A* mutations
  - Not idiopathic?
- West - generalized
  - Arises from a focal pathology? Focal semiology?
- Atonic seizures - generalized ?
  - Callosotomy
- Lennox-Gastaut - generalized epilepsy?
  - Occurs with focal seizures?

Purpose of the International Classification of Seizures and Epilepsies

- To provide a common international terminology and classification
- Largely for clinical (treatment) purposes
- Purpose of classification: to organize items according to their fundamental relationships


Flying things
bat
sparrow
bee
Round worm
Long, slimy
icky
snake
Earth worm
Things that
live
in water
trout
dolphin
turtle
clam
gorilla
human
Walk on
2 legs
ostrich
mouse
dog
cat
Cute, furry, suitable
as pets


round
worm
bee
clam
Earth
worm
trout
sparrow
ostrich
snake
turtle
dog
cat
bat
mouse
dolphin
gorilla
human
primates
Reptilia
Mammalia
Tetrapoda
Vertebrata

2005-2009 Commission Report, Epilepsia 2010;51:676-685

SPECIAL REPORT

Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005–2009

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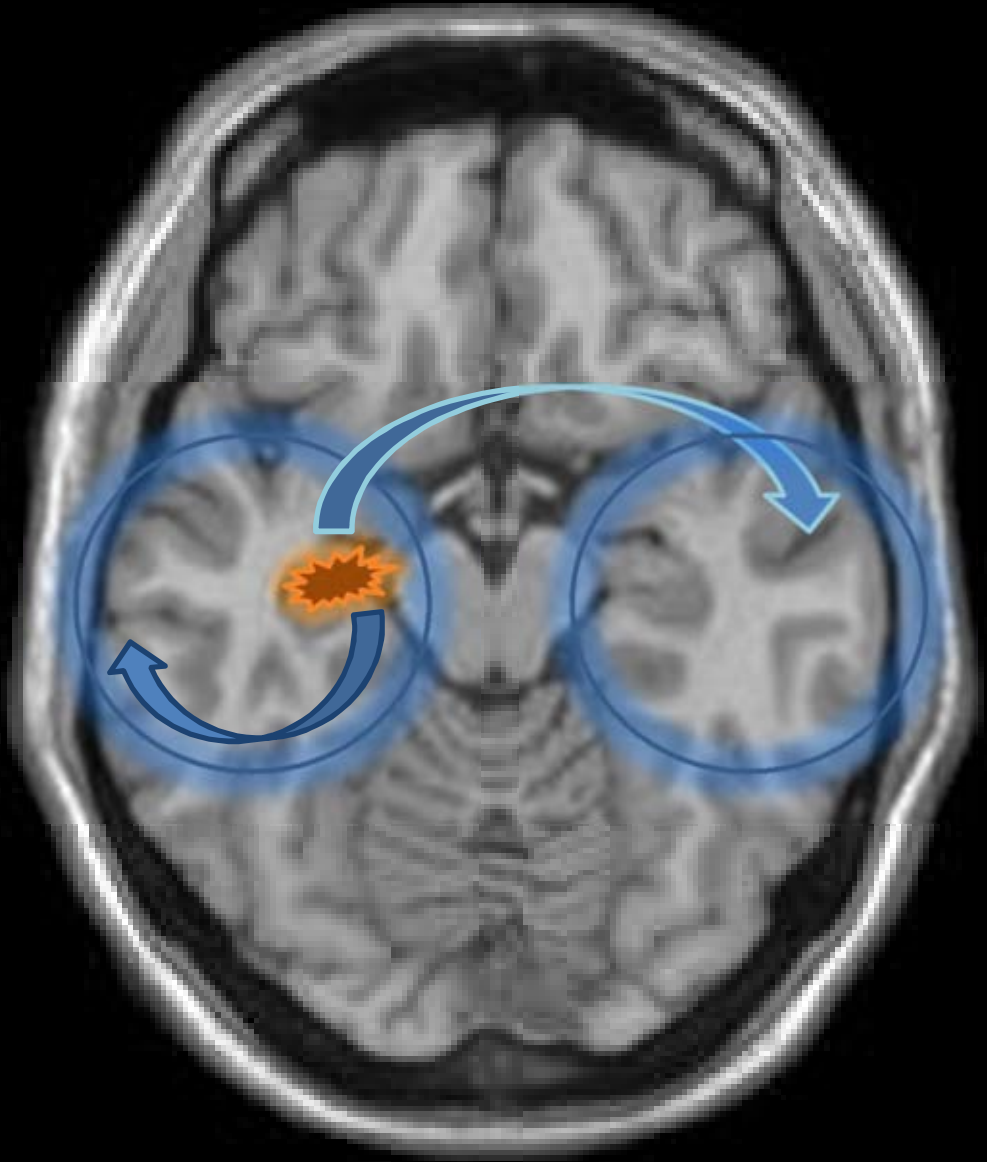
Focal seizures

- Originate within networks limited to one hemisphere
- May be discretely localized or more widely distributed….



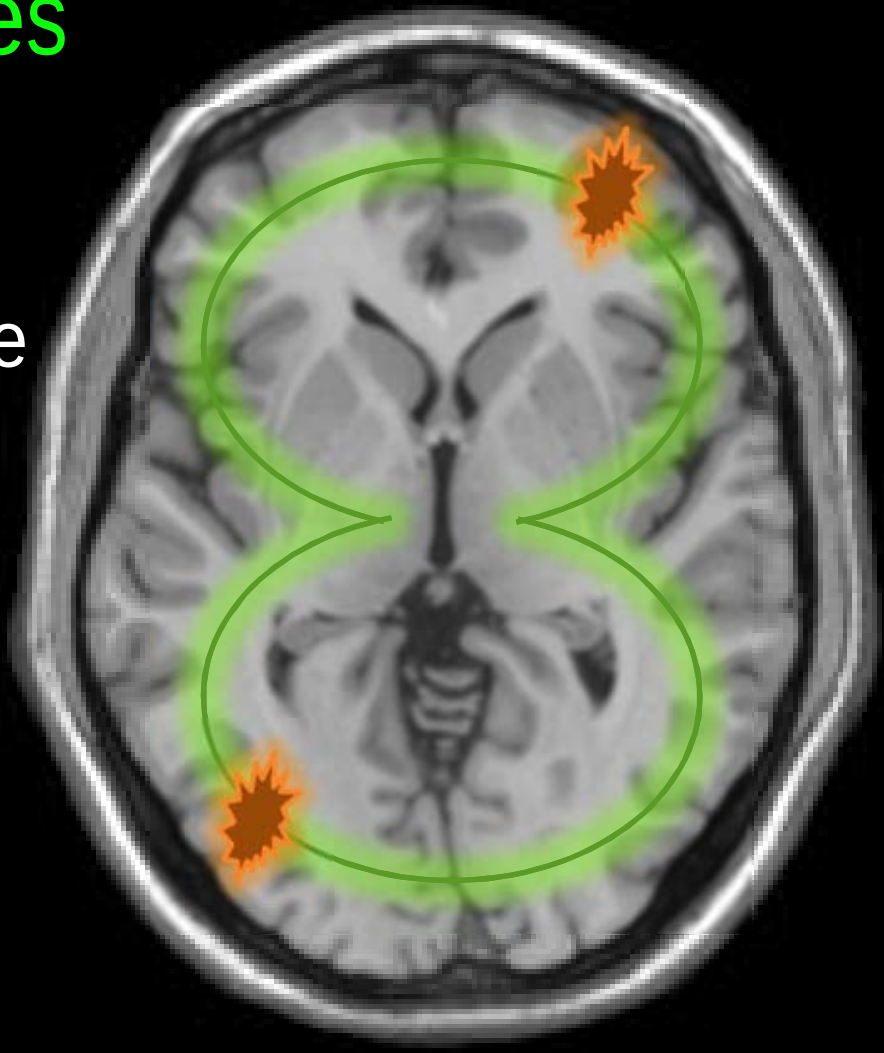
Focal seizures

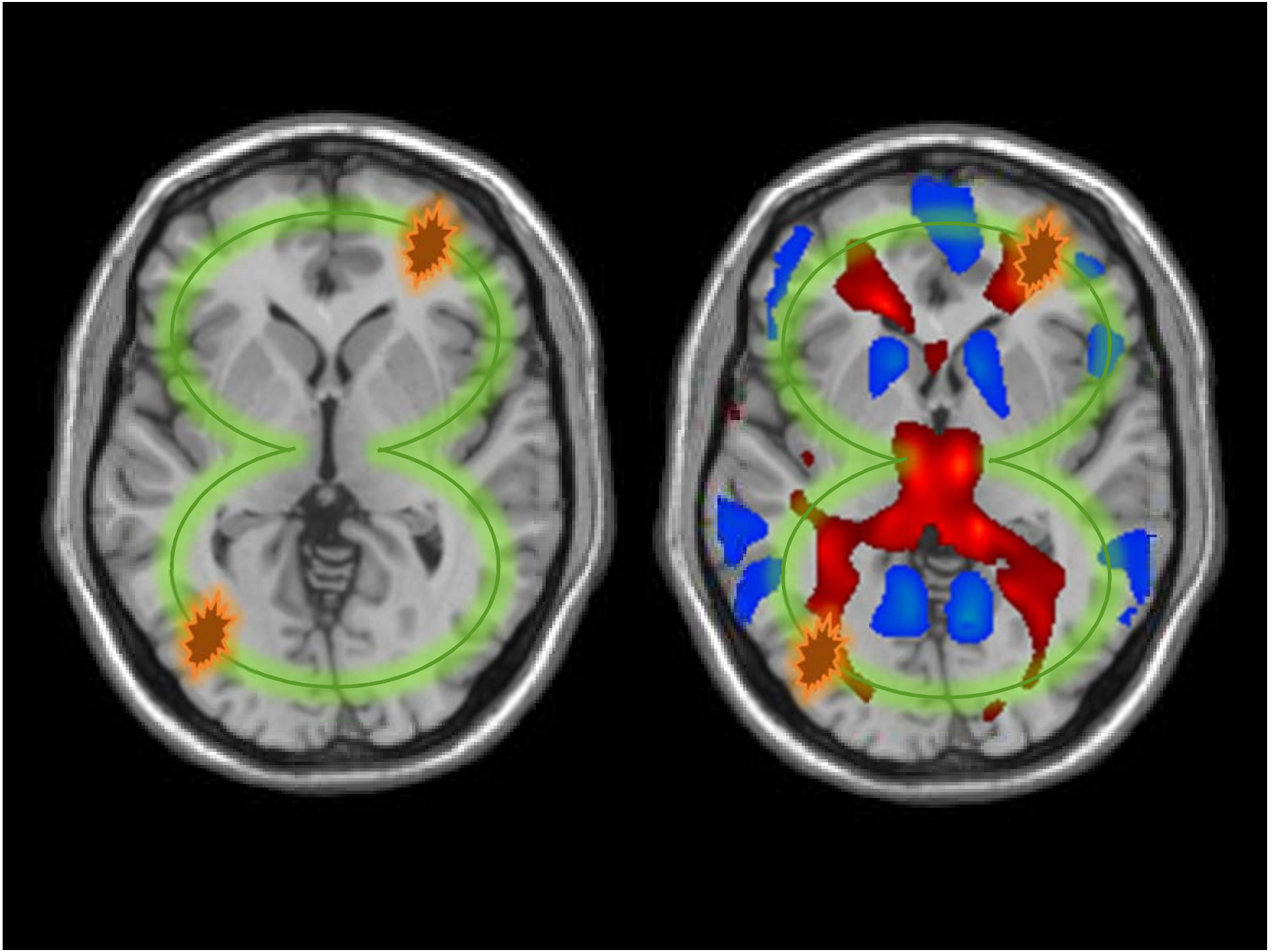
Blume et al Epilepsia 2001

- Previous term: simple partial
  - No impairment of consciousness or awareness
  - Motor or autonomic components eg. focal clonic
  - Subjective sensory or psychic features è Aura
- Previous term: complex partial
  - Altered cognition è Focal Dyscognitive
- Previous term: secondarily generalized
  - Evolving to bilateral, convulsive seizure
  - With tonic, clonic or tonic and clonic components

Generalized seizures

- Originate at some point within and rapidly engage bilaterally distributed networks
- Can include cortical and subcortical structures but not necessarily the entire cortex





Generalized seizures

Tonic-clonic (in any combination)

Absence

- Typical
- Atypical
- Absence with special features
  - Myoclonic absence
  - Eyelid myoclonia

Myoclonic

- Myoclonic
- Myoclonic atonic
- Myoclonic tonic

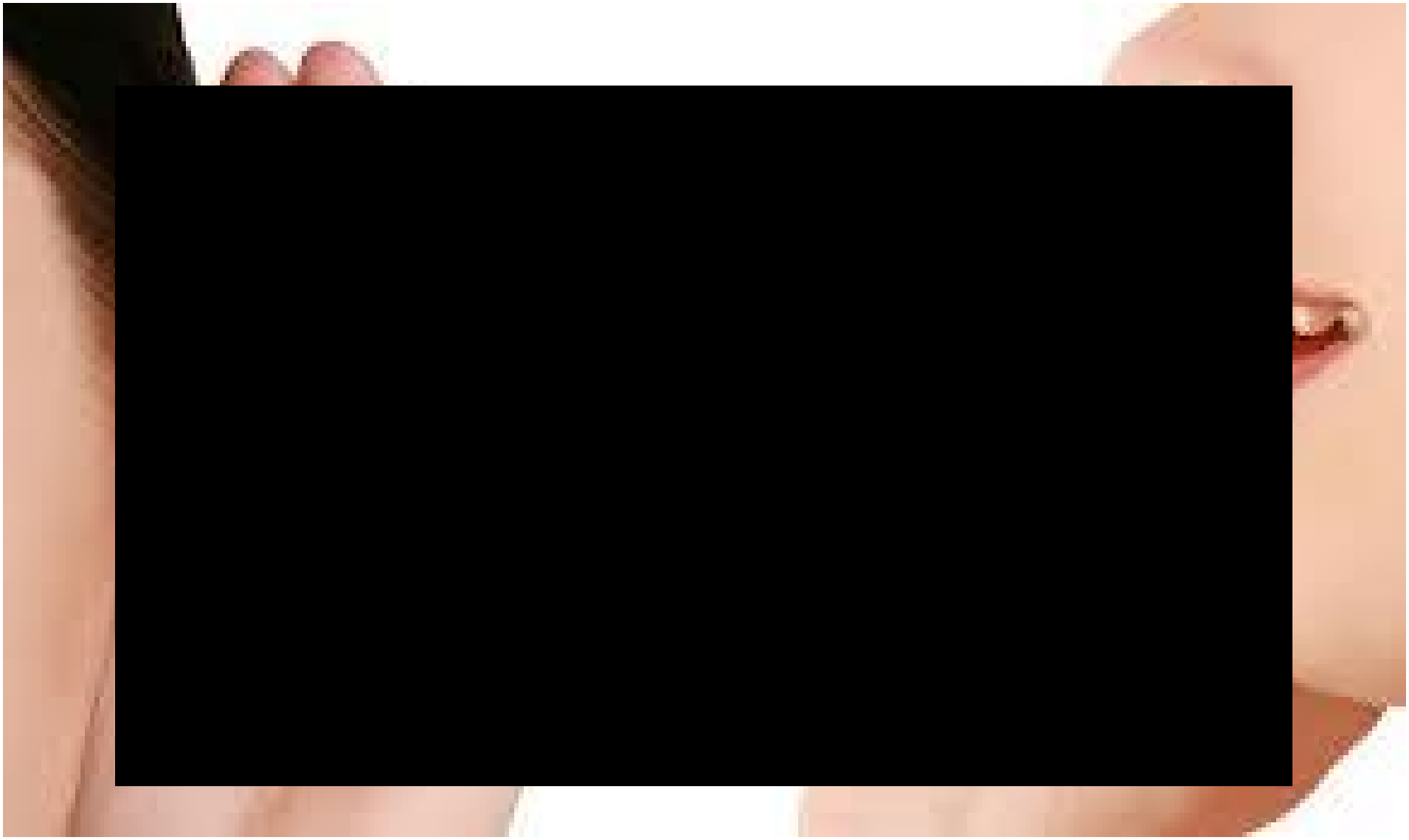
Clonic

Tonic

Atonic

Seizure types thought to occur within and result from rapid engagement of bilaterally distributed systems

Refinements to the Organization



Approaches to epilepsy diagnosis

Aetiology

Electroclinical syndromes

Unchanged!

- A dia sis can be made as previous
  - e. nox-Gastaut syndrom
  - Cl sence Epile
- A diagnosis is *not* the same as a classification

ILAE Proposal for Revised Terminology for Organization of Seizures and Epilepsies 2010

Electroclinical Syndromes and Other Epilepsies Grouped by Specificity of Diagnosis

Electroclinical syndromes

One example of how syndromes can be organized:
Arranged by typical age at onset*

Neonatal period
- Benign neonatal seizures^
- Benign familial neonatal epilepsy (BFNE)
- Ohtahara syndrome
- Early Myoclonic encephalopathy (EME)

Infancy
- Febrile seizures^, Febrile seizures plus (FS+)
- Benign infantile epilepsy
- Benign familial infantile epilepsy (BFIE)
- West syndrome
- Dravet syndrome
- Myoclonic epilepsy in infancy (MEI)
- Myoclonic encephalopathy in nonprogressive disorders
- Epilepsy of infancy with migrating focal seizures

Childhood
- Febrile seizures^, Febrile seizures plus (FS+)
- Early onset childhood occipital epilepsy (Panayiotopoulos syndrome)
- Epilepsy with myoclonic atonic (previously astatic) seizures
- Childhood absence epilepsy (CAE)
- Benign epilepsy with centrotemporal spikes (BECTS)
- Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)
- Late onset childhood occipital epilepsy (Gastaut type)
- Epilepsy with myoclonic absences
- Lennox-Gastaut syndrome (LGS)
- Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS)+
- Landau-Kleffner syndrome (LKS)

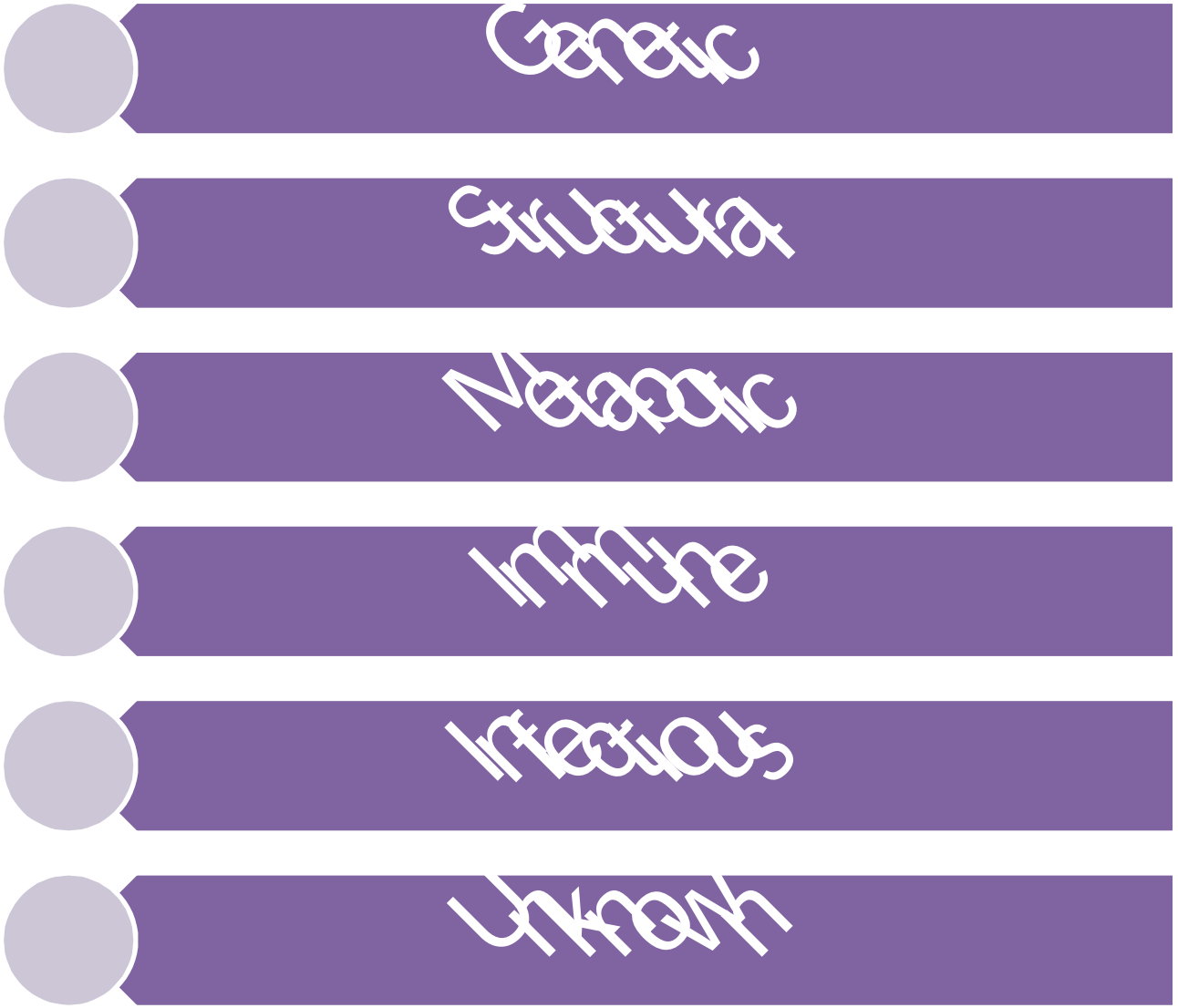
Adolescence – Adult
- Juvenile absence epilepsy (JAE)
- Juvenile myoclonic epilepsy (JME)
- Epilepsy with generalized tonic-clonic seizures alone
- Autosomal dominant epilepsy with auditory features (ADEAF)
- Other familial temporal lobe epilepsies

Variable age at onset
- Familial focal epilepsy with variable foci (childhood to adult)
- Progressive myoclonus epilepsies (PME)
- Reflex epilepsies

- Electroclinical syndromes unchanged
- Organise how you wish e.g. age of onset, EEG findings
- 2 page handout - clinical tool can download from ILAE Classification commission website in many languages

Aetiology

Aetiology


Genetic
Structural
Neoplastic
Immune
Infectious
Unknown

Aetiology >1 in many cases

Etiology

Genetic

Unknown

Structural

Infectious

Metabolic

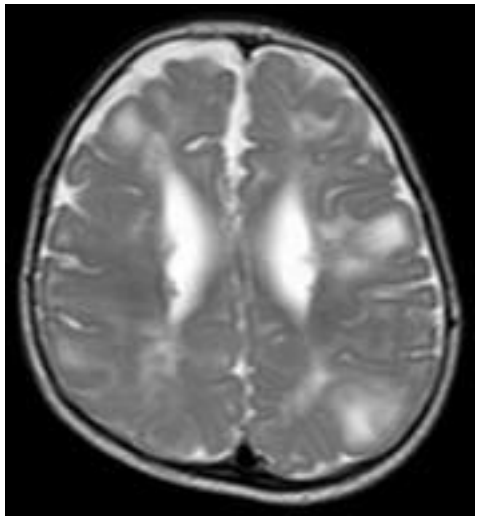
Immune

Genetic

- Concept:
  - Epilepsy is the direct result of a known or inferred genetic defect
  - Seizures are the core symptom of the disorder
- Evidence
  - appropriately designed family studies or
  - replicated molecular genetic studies

- Genetic does *not* exclude the possibility of environmental factors contributing

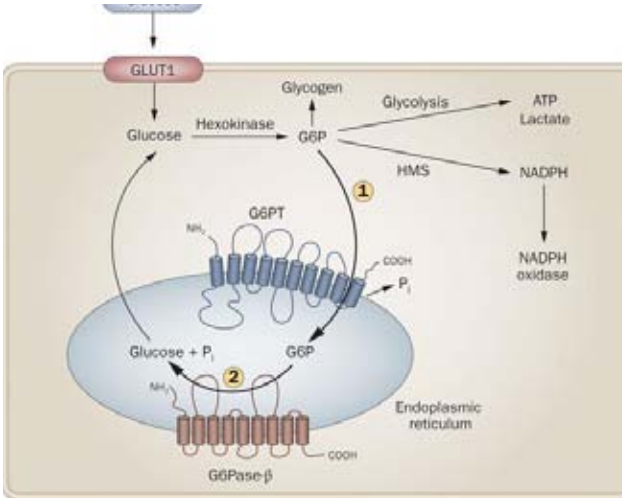
Structural



- Concept: epilepsy is the result of a distinct other structural condition or disease
  - eg. tuberous sclerosis

- Evidence: Must have a substantially increased risk of developing epilepsy with the condition

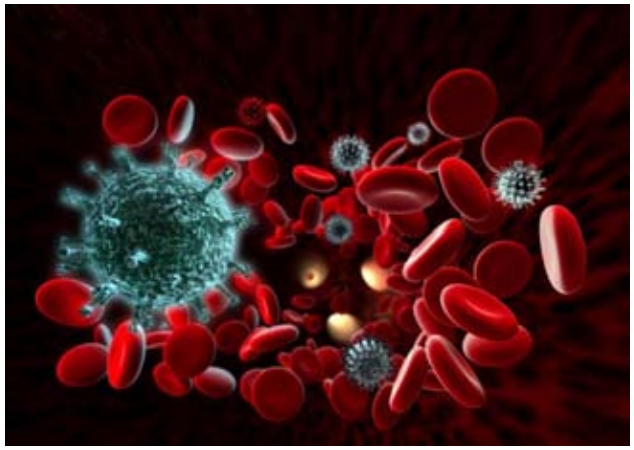
Metabolic



- Concept: epilepsy is the result of a metabolic condition or disease with widespread manifestations
  - eg. aminoacidopathies
  - pyridoxine-dependent seizures

- Evidence: Must have a substantially increased risk of developing epilepsy with the metabolic condition

Immune



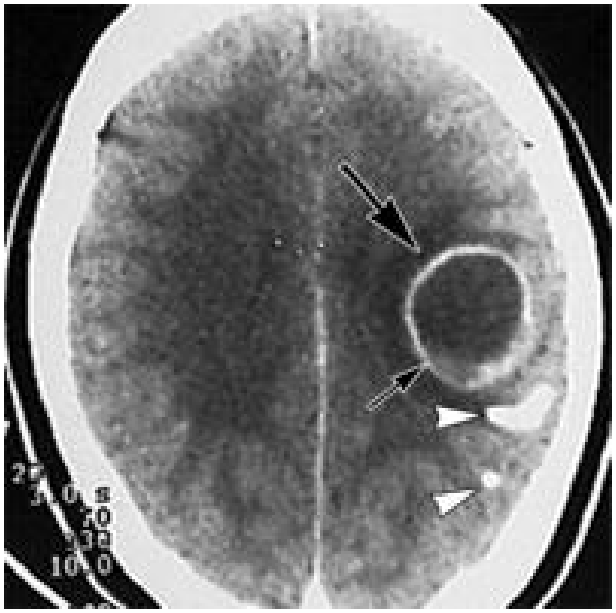
- Concept: epilepsy is the result of autoimmune mediated central nervous system inflammation

  eg. autoimmune encephalitides

  – anti-NMDA encephalitis

  – limbic encephalitis

- Evidence: Must have a substantially increased risk of developing epilepsy with the immune condition



Infectious

- Concept: epilepsy is the result of an infectious cause

  eg. tuberculosis, HIV, cerebral malaria, neurocysticercosis

- Evidence: Must have a substantially increased risk of developing epilepsy with the infectious condition

Unknown

- The underlying cause is unknown

Terms no longer recommended

- Catastrophic
  - Implication of this word is devastating for the child and his family
- Benign
  - Glosses over the burden of cognitive, behavioral, psychiatric disorders and SUDEP that accompany epilepsy

New recommended terminology

- Self-limited
  - high likelihood of spontaneous remission
- Pharmacoresponsive

- Syndrome names retain word “benign”

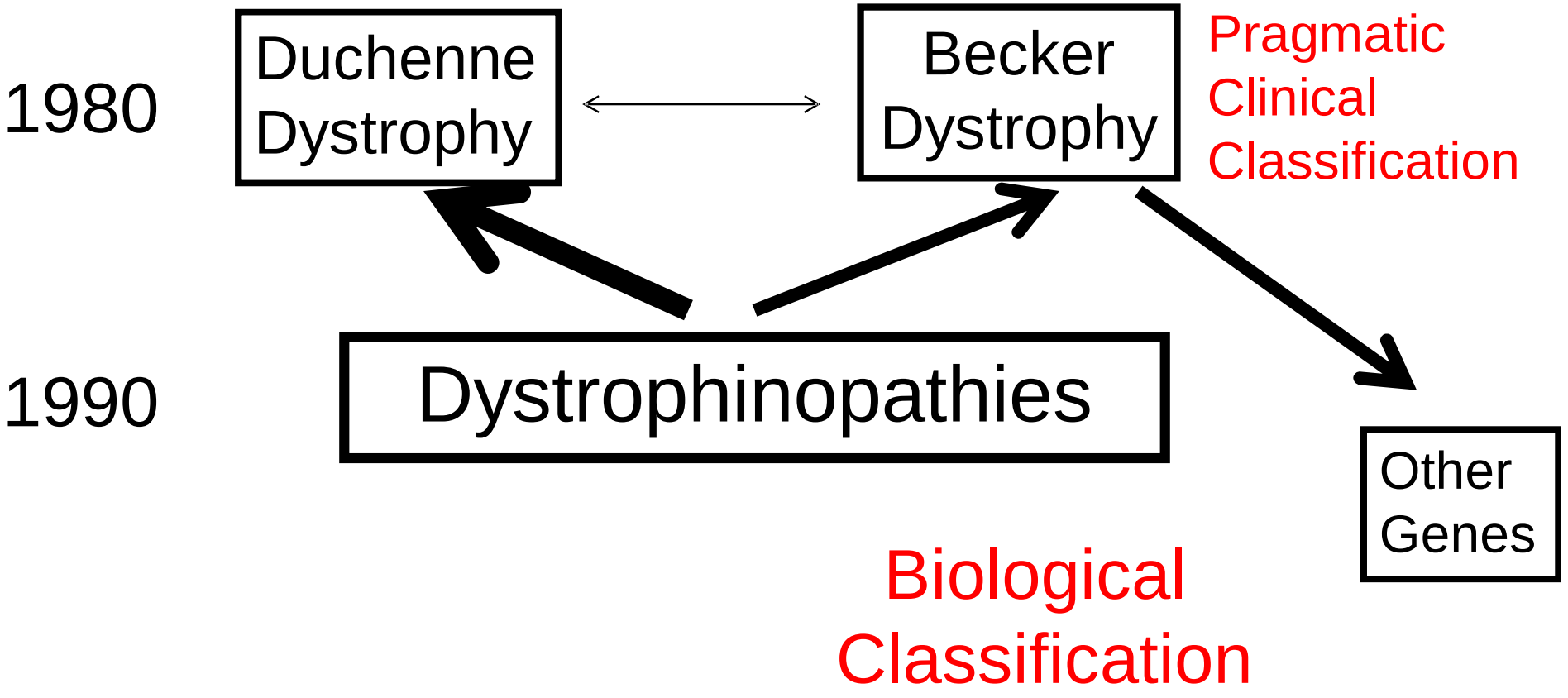
- Genetic generalized epilepsies replaces idiopathic generalized epilepsies

Epileptic encephalopathy
Modified concept

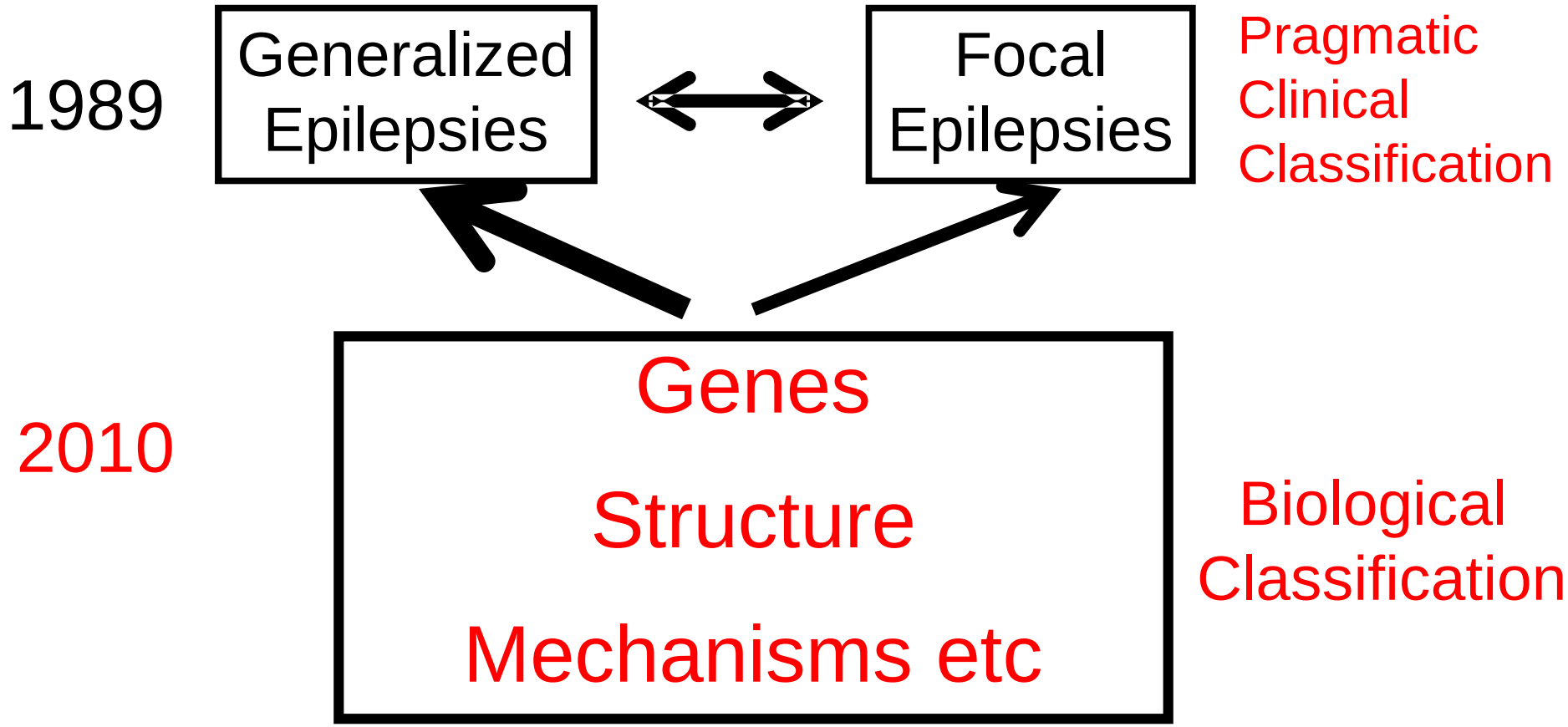
- *the epileptic activity itself contributes to cognitive and behavioral impairments beyond that expected from the underlying pathology alone (e.g. cortical malformation)*

- Group of syndromes (West, Dravet, etc)
  - Interference with developmental processes during critical periods
- Spectrum of severity
- Any age

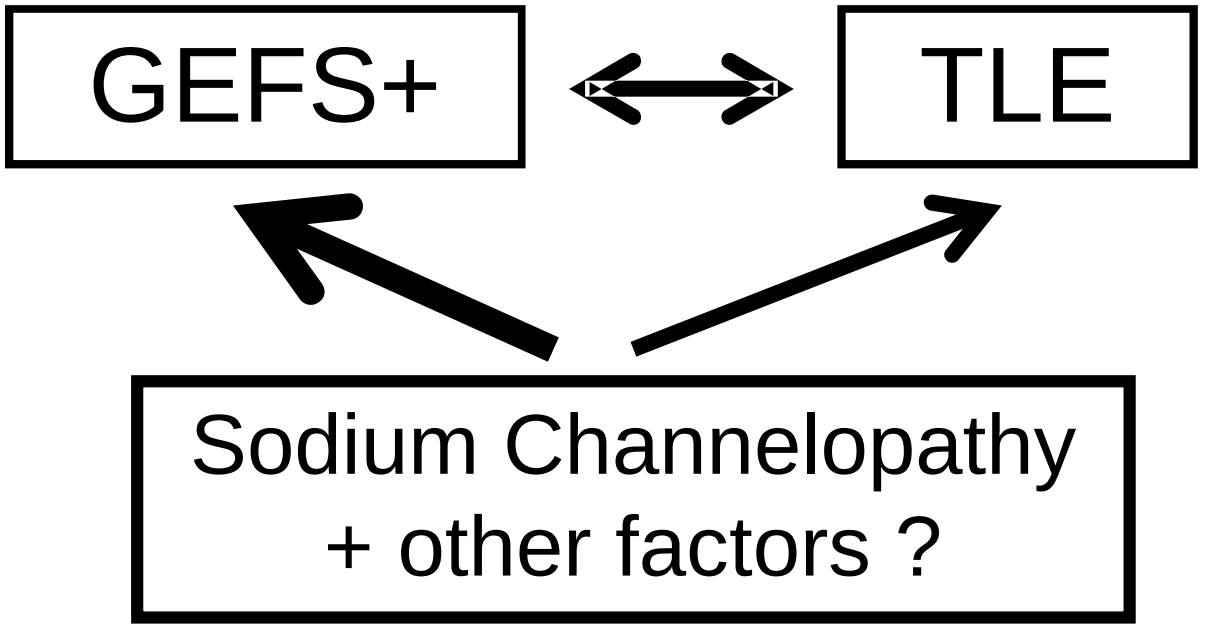
Towards a biological classification: Muscle disease



Towards a biological classification: Epilepsies

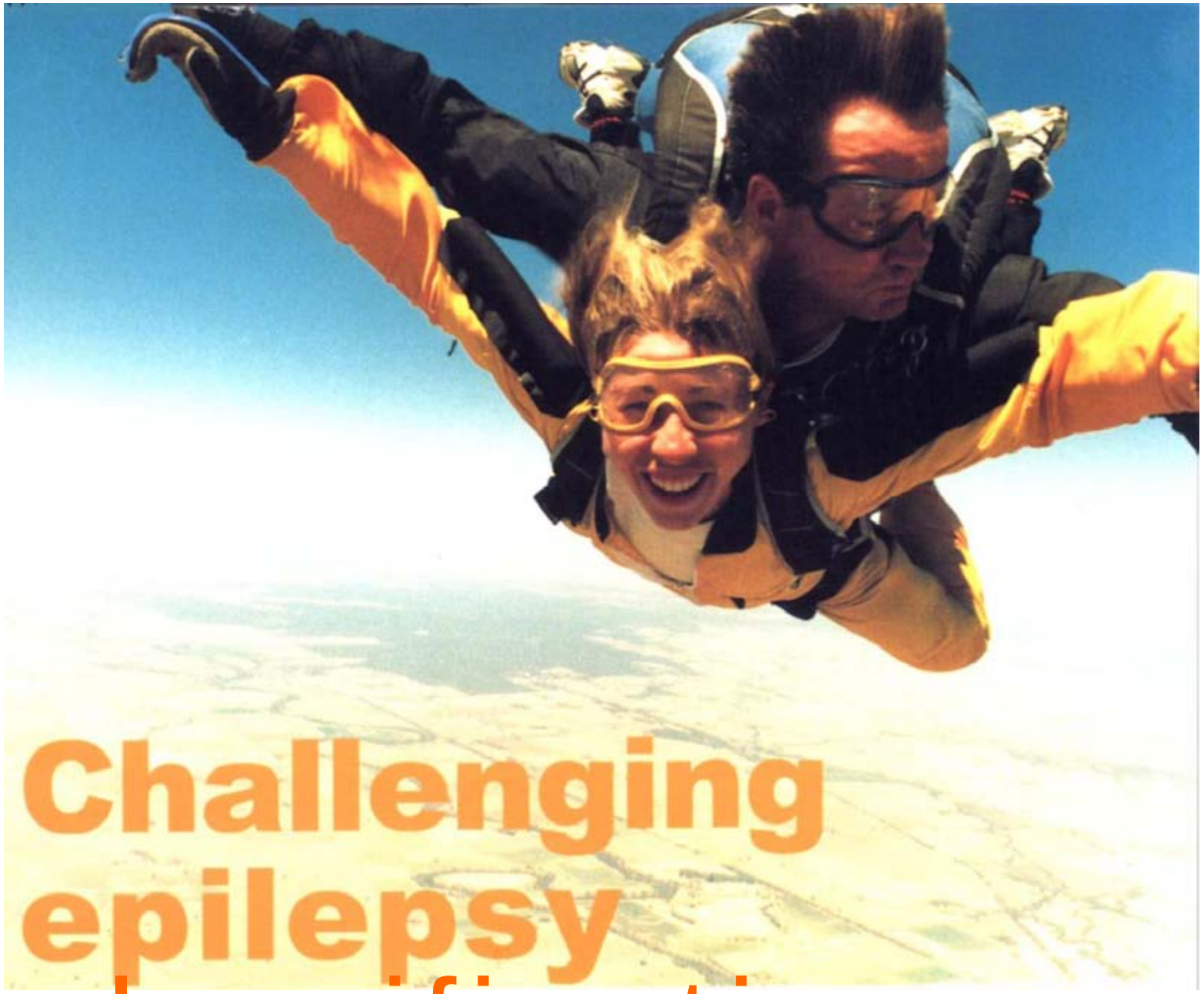


Towards a biological classification: Epilepsy example



Pragmatic
Clinical
Classification

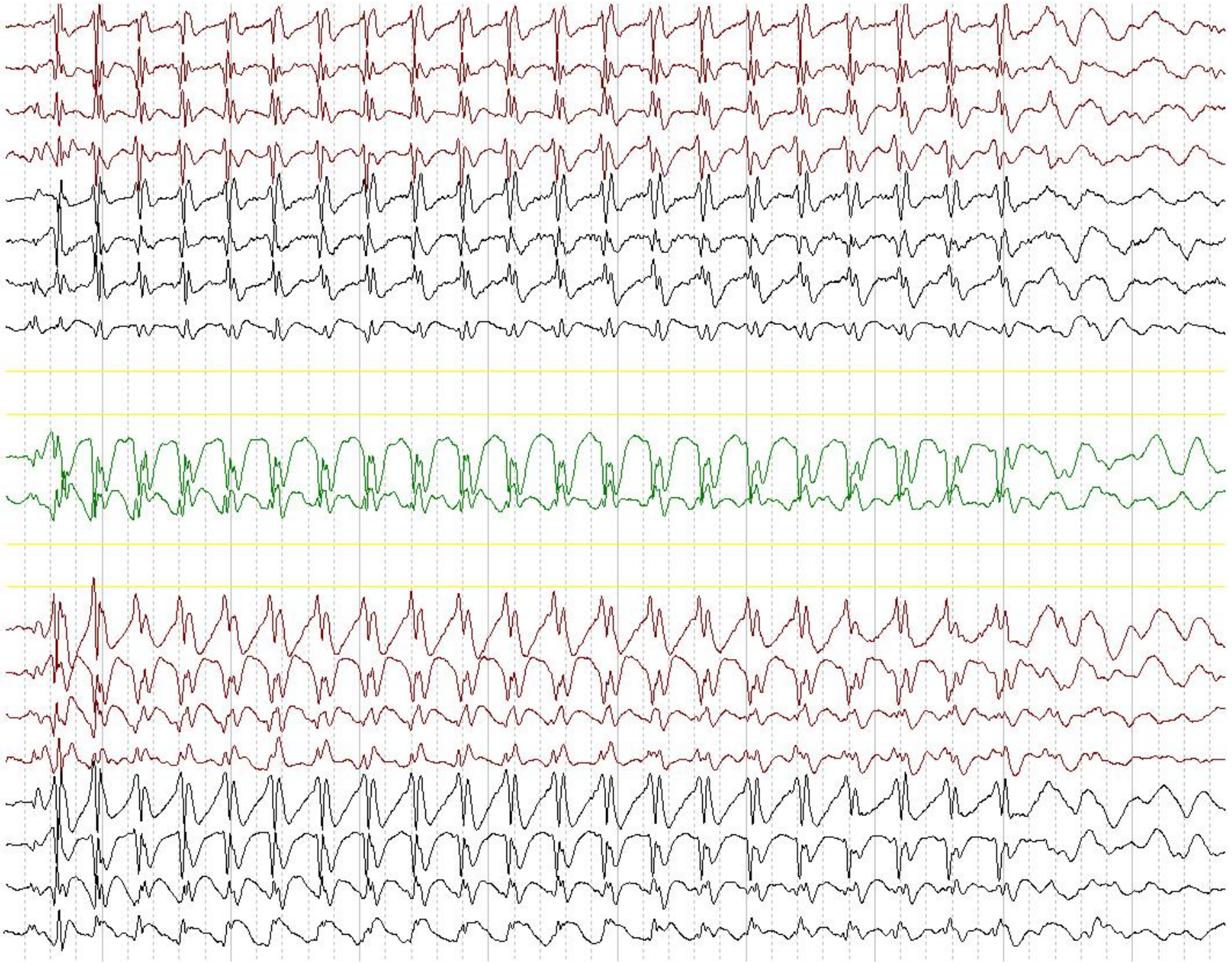
?? Biological
Classification



classification

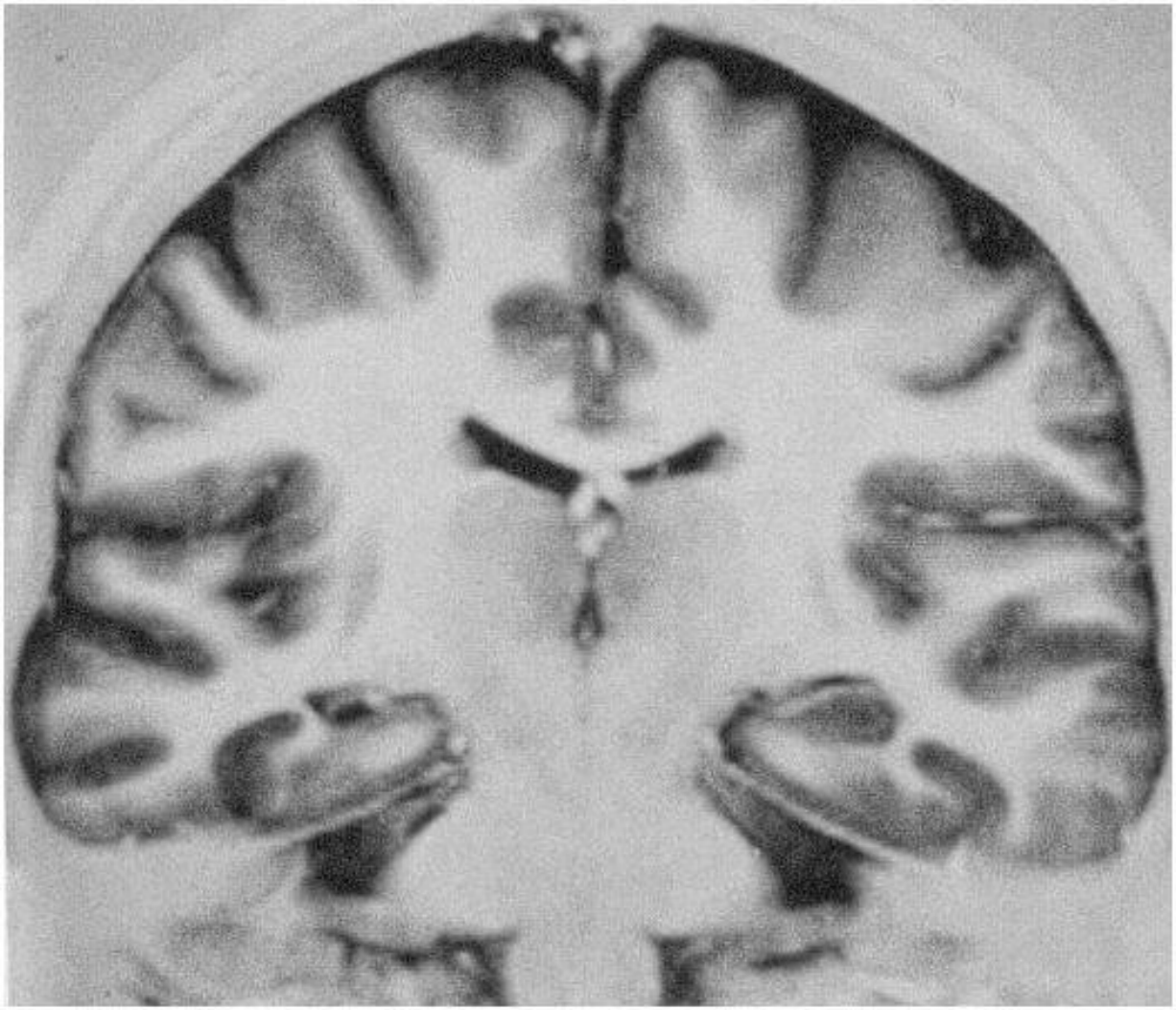
Lyndal, 17 year old student

- 3 minute febrile seizures at 18 mths and 7 yrs
- 8 years
  - absence seizures – stare for 10 seconds

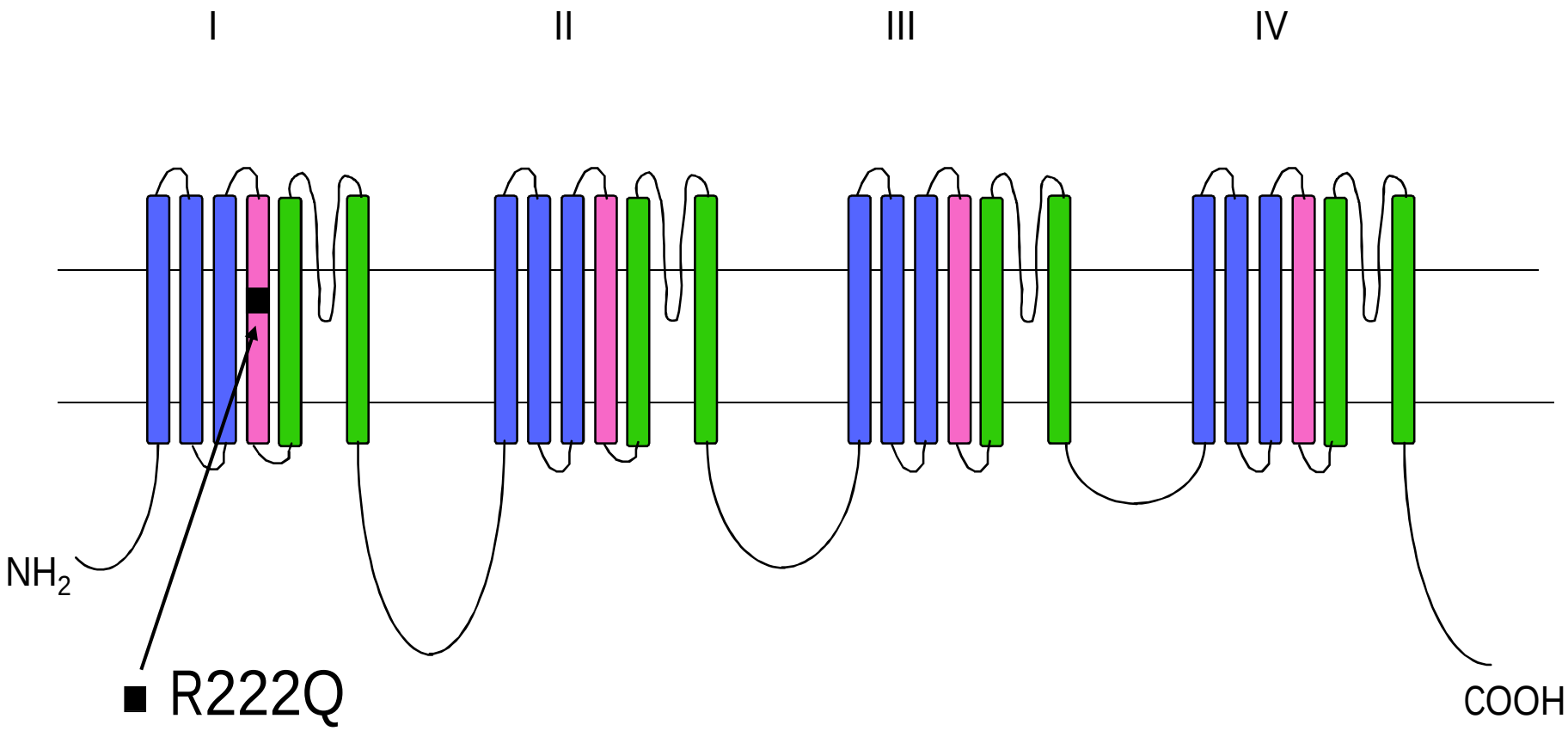


16 year old student

- 3 minute febrile seizure 18 mths and 7 yrs
- 8 years
  - absence seizures – stare for 10 seconds
  - 3 Hz generalized spike wave
- 14 years
  - focal dyscognitive seizures: déjà vu, head and eye deviation, pallor, altered awareness for 90 seconds
  - Rare convulsive seizures
  - EEG bitemporal discharges, generalized spike wave



SCN1A mutation



SCN1A gene encodes the α1 subunit of the sodium channel

Diagnosis?

1989

- Febrile convulsions
- Idiopathic Generalized Epilepsy
- Symptomatic Partial Epilepsy

2013

Electroclinical syndrome

- Febrile Seizures Plus
- Childhood Absence Epilepsy – Genetic Generalized Epilepsy syndrome
- Temporal lobe epilepsy with hippocampal sclerosis

Aetiologies

- Genetic - *SCN1A*
- Structural - HS
- Two therapies: Anti-epileptic and surgery

What are the components of a model or models for organizing epilepsies?

Whatever you choose……

- Age at onset
- Underlying cause
  - Channelopathy
    - Voltage gated
    - Ligand gated
  - mTOR-opathy
  - Glioma
    - Ganglio
    - Oligodendro
  - Malformation of cortical development
    - FCD type I
    - FCD type II
    - Hemimegalencephaly
    - Lissencephaly...

§EEG
- úGeneralized spike & wave
- úBurst suppression pattern...

§Seizures types

§Triggers
- §Nocturnal
- §Photic stimulation...

§Developmental course
- úPrior to onset
- úAfter onset
- úLanguage disturbance ...

Organize epilepsies to reflect our knowledge

- Electro-clinical syndromes BY AGE, other…

Neonatal	Benign familial neonatal seizures
Infancy	Epilepsy of infancy with migrating partial seizures
Childhood	Childhood absence epilepsy (CAE)
Adolescence	Juvenile absence epilepsy (JAE)

Less Specific Age Relationship

e.g. Familial focal epilepsy with variable foci childhood to adolescence

Organize epilepsies to reflect our knowledge

- Epilepsies with structural aetiology

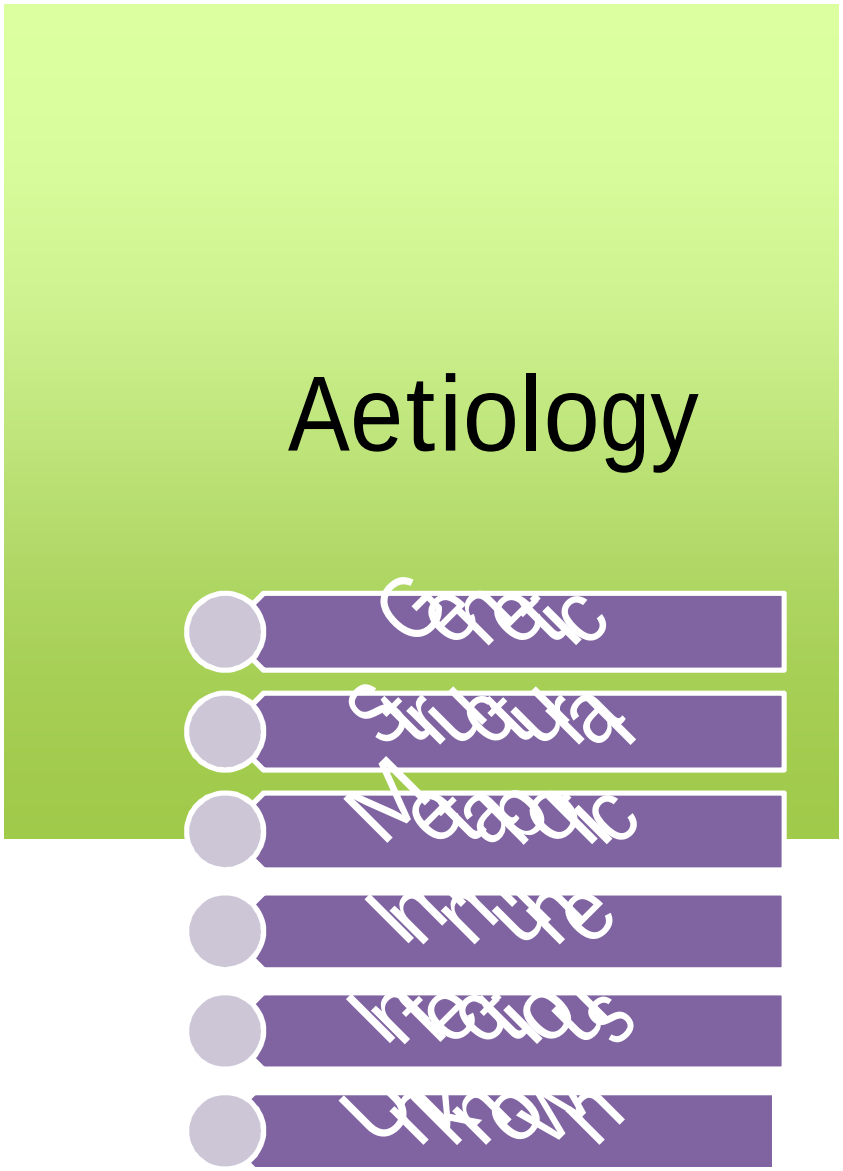
  e.g. Type of malformation
  Disorder – mTORopathy

- Epilepsies of unknown cause

  e.g. By age at onset

  By predominant seizure manifestations

Approaches to epilepsy diagnosis



Refinement of the Organization of the Epilepsies

- Changes to seizure concepts well accepted
- Changes to seizure terminology being implemented

- Etiological subgroups now separated: immune and infectious added
- Flexible – you can organize it how you wish
- Must remain a dynamic and evolving classification

The Future? - A scientific classification based on biological mechanisms