Overview of the epilepsies of childhood and comorbidities

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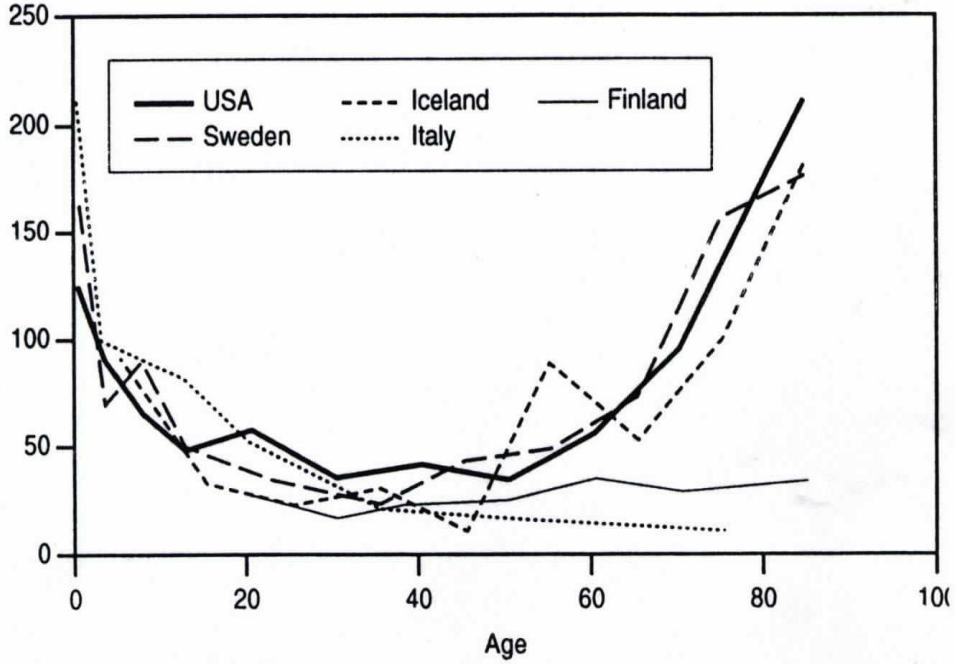
Epilepsy

- is a common condition – prevalence 0.5%
  - is not a single condition
  - can be difficult to diagnose
  - no single treatment
- misdiagnosis rate is high
- 25% resistant to medication
  - more likely if lesional
- surgical treatment may be an option if localised onset to seizures



Definition of epilepsy

ILAE, Fisher et al Epilepsia 2005, 2014

a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures.

Epilepsy: A disease of the brain

1. **At least two unprovoked (or reflex) seizures occurring more than 24 hours apart;**
2. **One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years**
3. **Diagnosis of an epilepsy syndrome.**

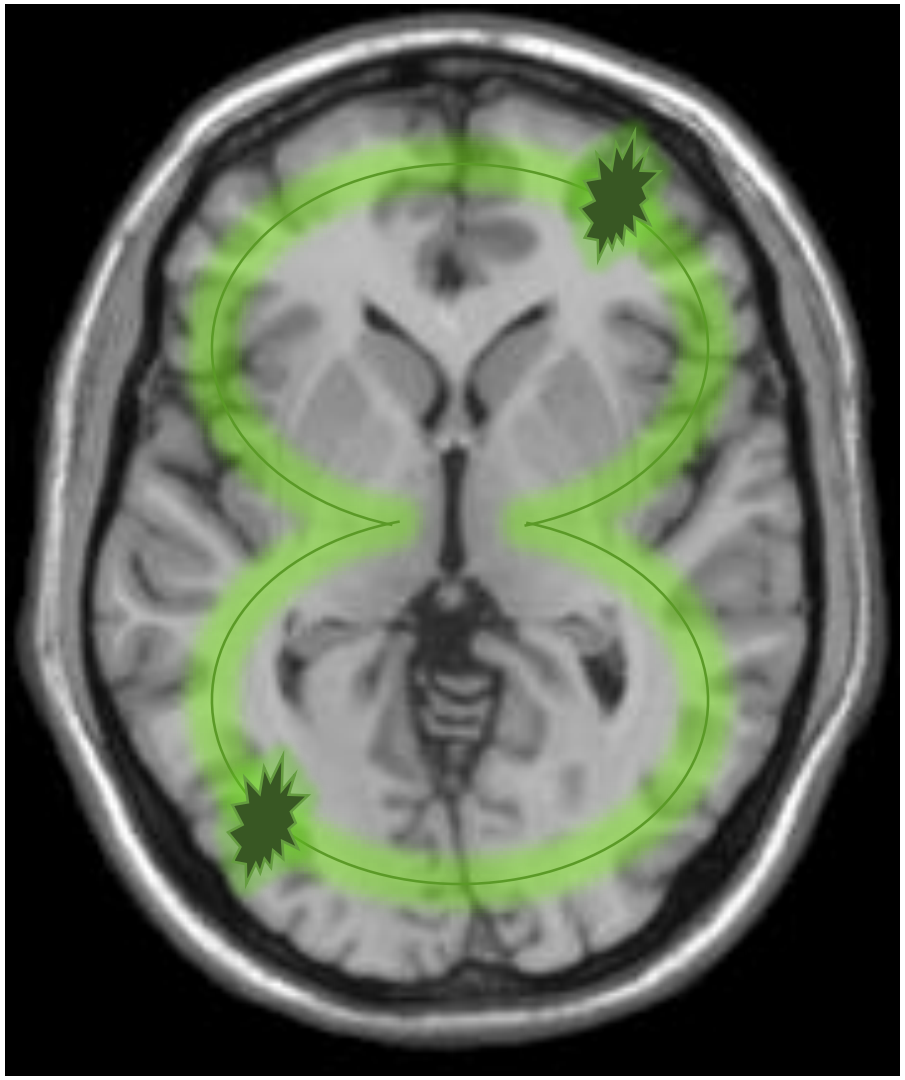
Definition of a seizure

A transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain

ILAE 2005

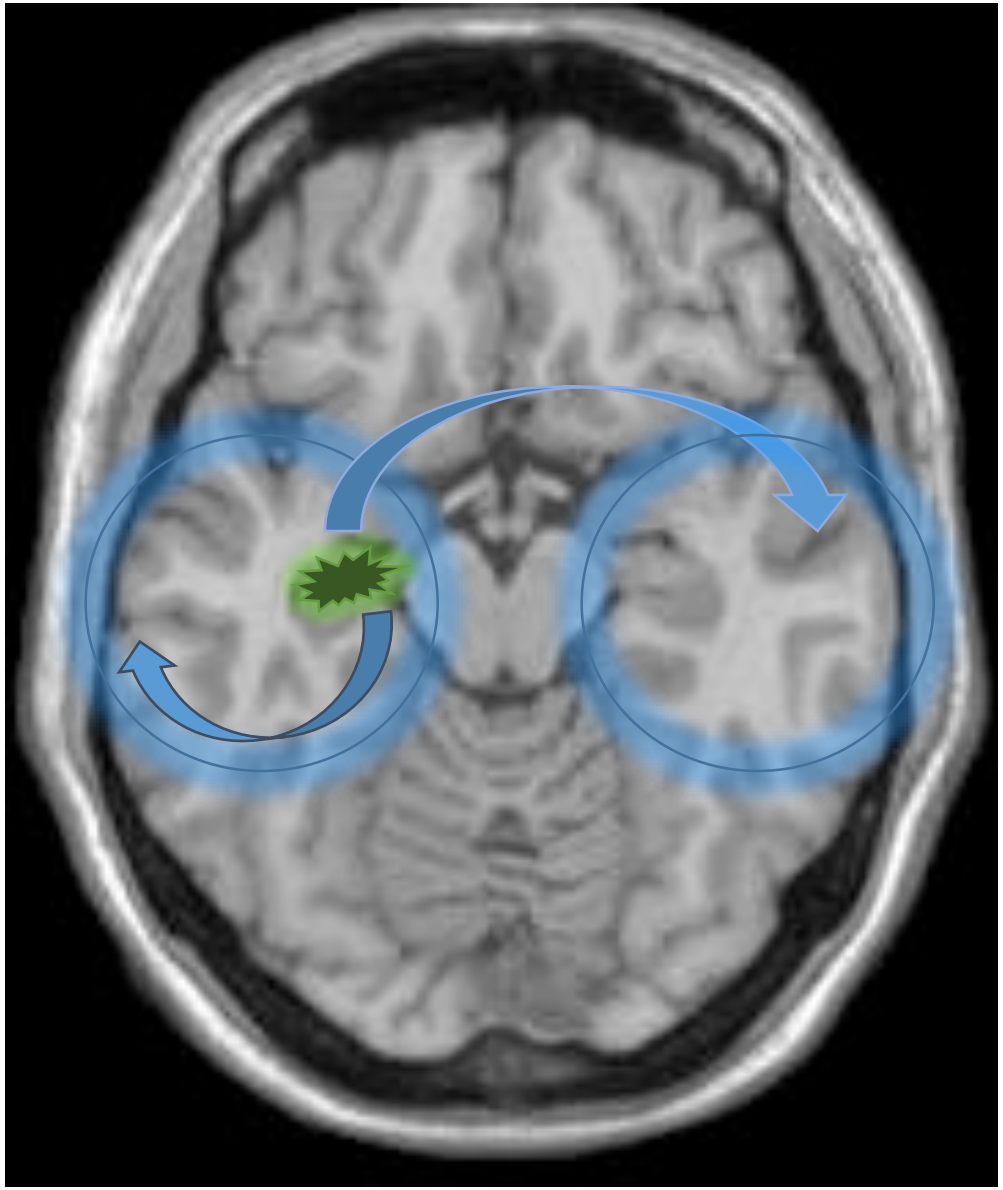
Generalised seizures

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

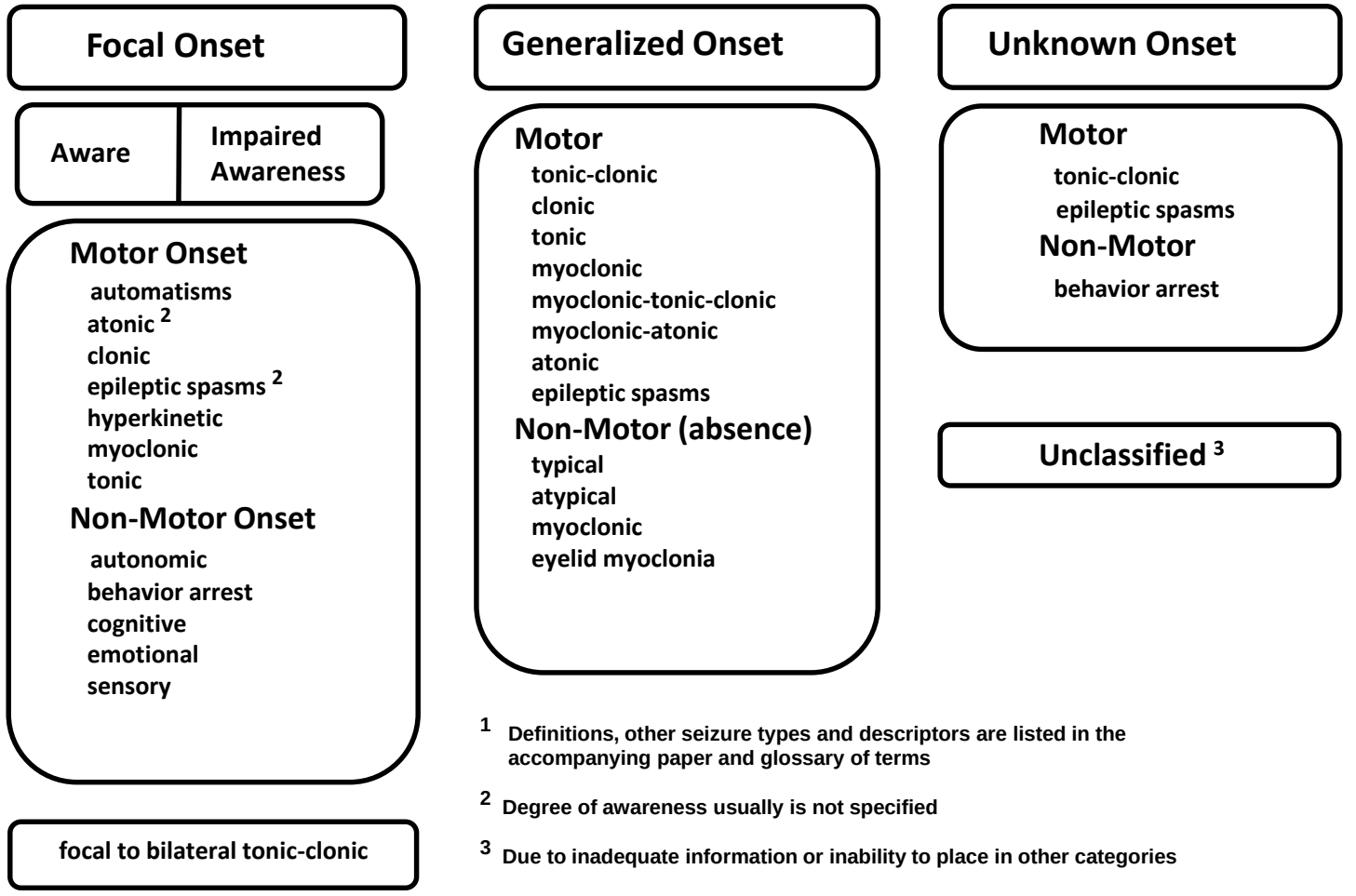


Focal seizures

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



ILAE 2017 Classification of Seizure Types Expanded Version [1]



1 Definitions, other seizure types and descriptors are listed in the accompanying paper and glossary of terms

2 Degree of awareness usually is not specified

3 Due to inadequate information or inability to place in other categories

Fisher et al Epilepsia in press (ILAE)

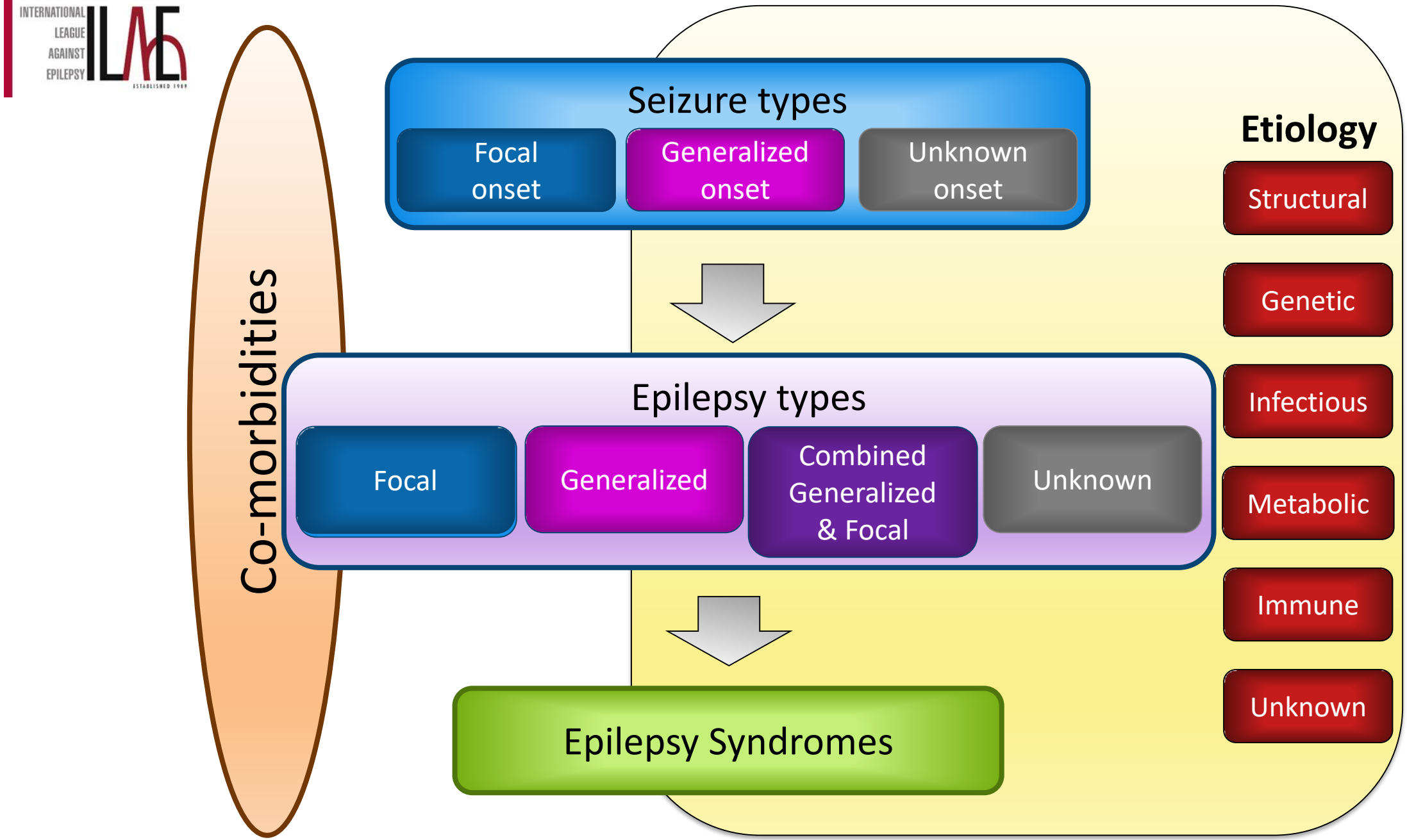
Role of investigation

EEG: type of epilepsy, unlikely to be diagnostic unless record event

- **should be performed on all children presenting with two probable epileptic seizures**

Determining cause

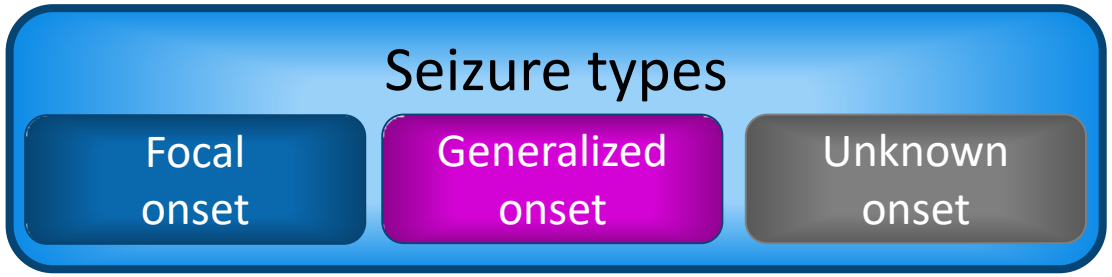
- **MRI: performed in all where no clear self limiting syndrome, specifically in children with likely focal onset**
- **Genetic evaluation: particularly children with early onset complex epilepsy**
- **Metabolic evaluation: dependent on clinical presentation eg pyridoxine dependency**



Scheffer et al Epilepsia 2017;58: 512-521

1. Seizure types

- **Certain that events are epileptic seizures – not referring to distinguishing epileptic versus non-epileptic**
- **In some settings → classification according to seizure type may be maximum level of diagnosis possible**
- **In other cases → simply too little information to be able to make a higher level diagnosis**
  - **eg. when a patient has only had a single event**



ILAE 2017 Classification of Seizure Types Basic Version [1]

Focal Onset

- Aware | Impaired Awareness
- Motor Onset
  Nonmotor Onset
- focal to bilateral tonic–clonic

Generalized Onset

- Motor
  - Tonic–clonic
  - Other motor
- Nonmotor (Absence)

Unknown Onset

- Motor
  - Tonic–clonic
  - Other motor
- Nonmotor

Unclassified [2]

ILAE 2017 Classification of Seizure Types Expanded Version [1]

Focal Onset

Aware | Impaired Awareness

Motor Onset
- automatisms
- atonic [2]
- clonic
- epileptic spasms [2]
- hyperkinetic
- myoclonic
- tonic

Nonmotor Onset
- autonomic
- behavior arrest
- cognitive
- emotional
- sensory

focal to bilateral tonic–clonic

Generalized Onset

Motor
- tonic–clonic
- clonic
- tonic
- myoclonic
- myoclonic–tonic–clonic
- myoclonic–atonic
- atonic
- epileptic spasms

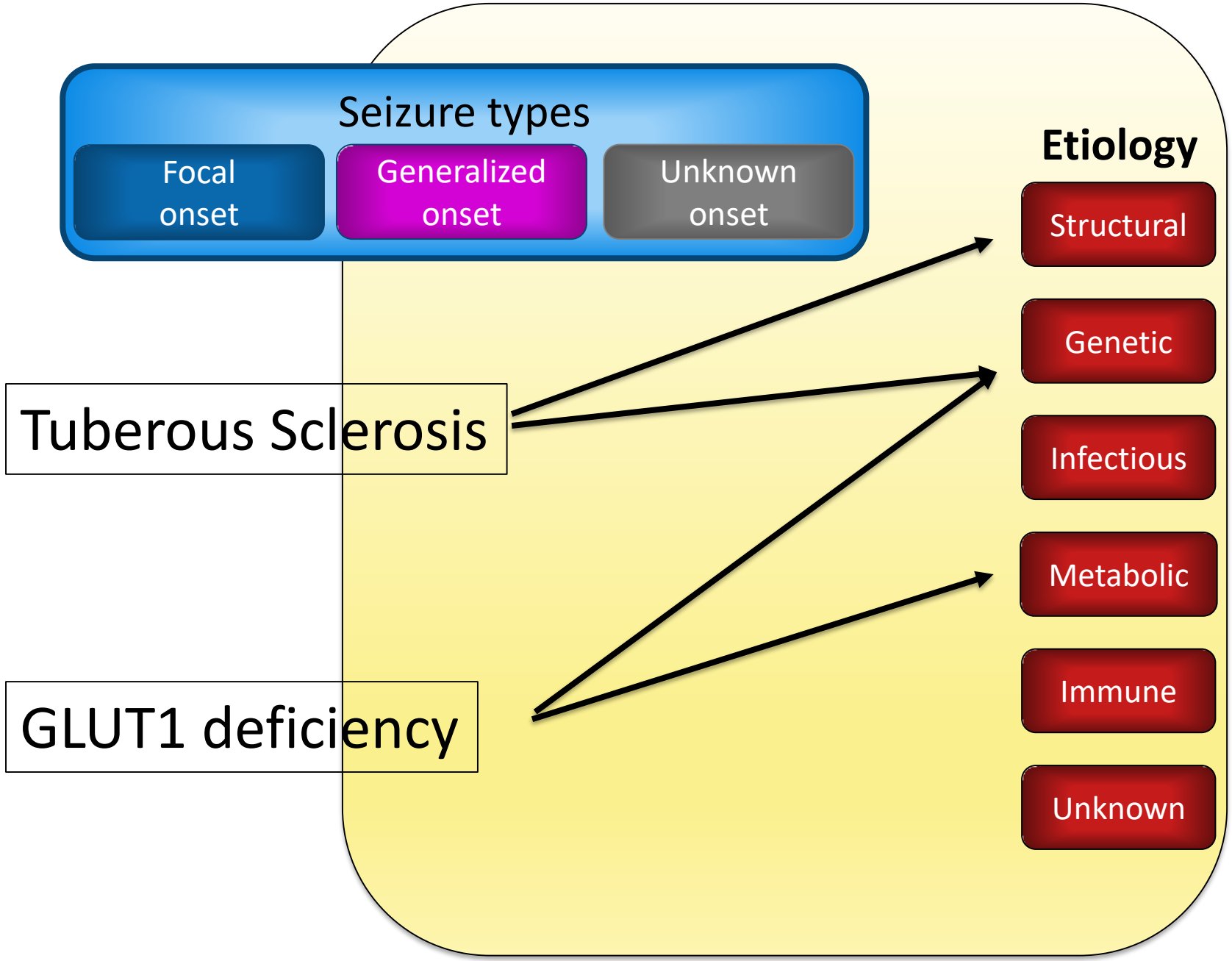
Nonmotor (absence)
- typical
- atypical
- myoclonic
- eyelid myoclonia

Unknown Onset

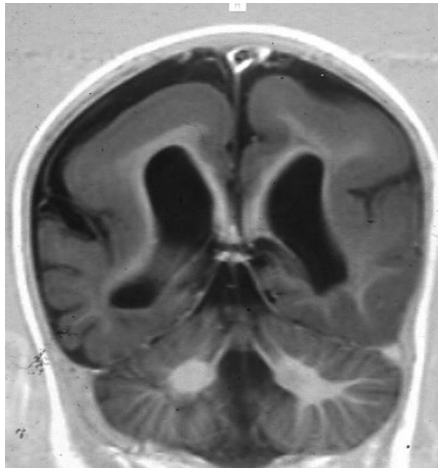
Motor
- tonic–clonic
- epileptic spasms

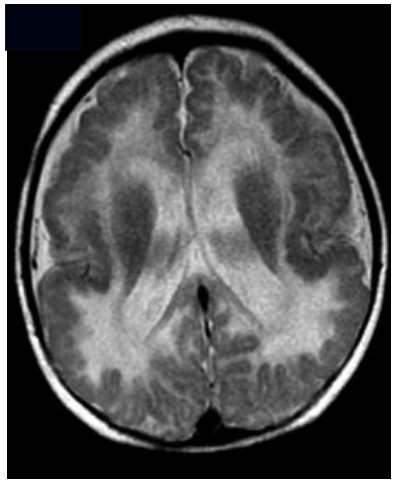
Nonmotor
- behavior arrest

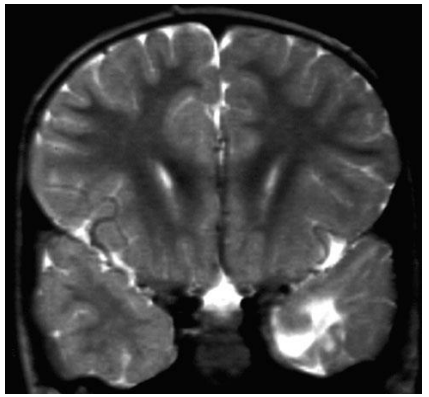
Unclassified [3]

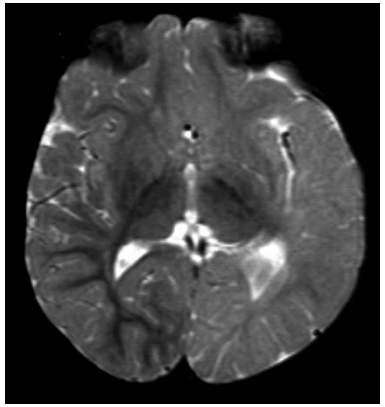

Seizure types
Focal onset
Generalized onset
Unknown onset
Etiology
Structural
Genetic
Infectious
Metabolic
Immune
Unknown
Tuberous Sclerosis
GLUT1 deficiency

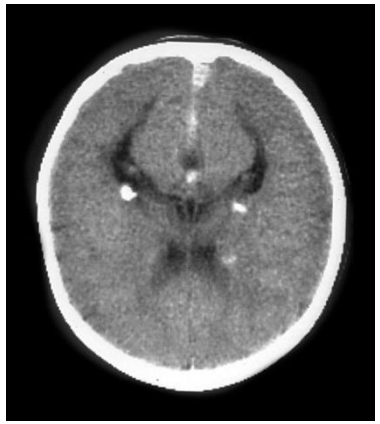
Structural

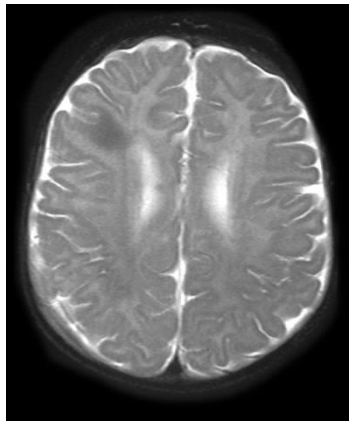


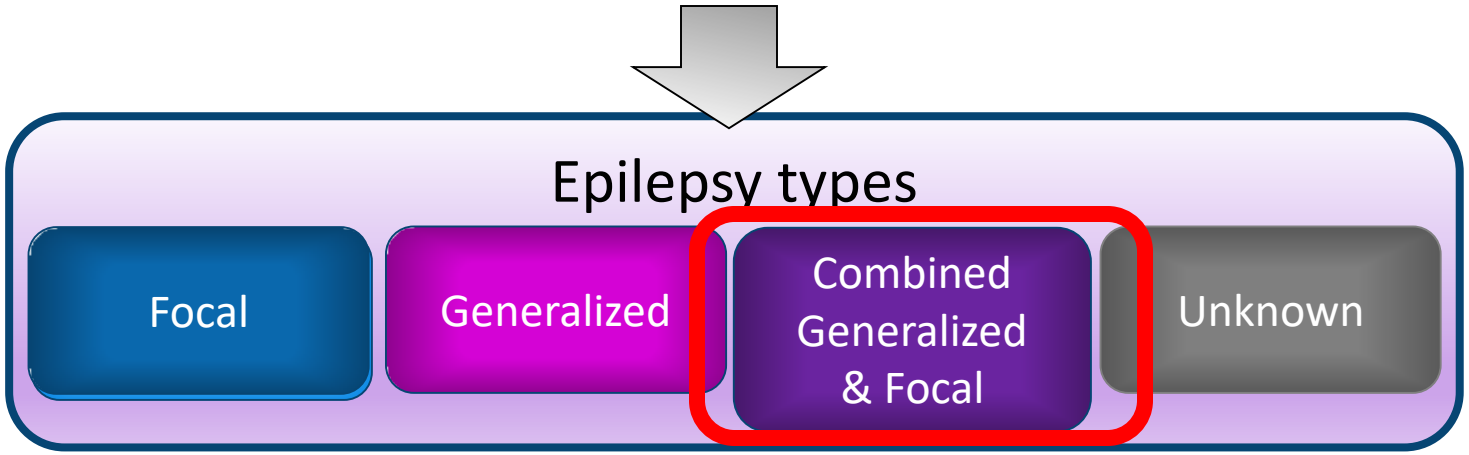




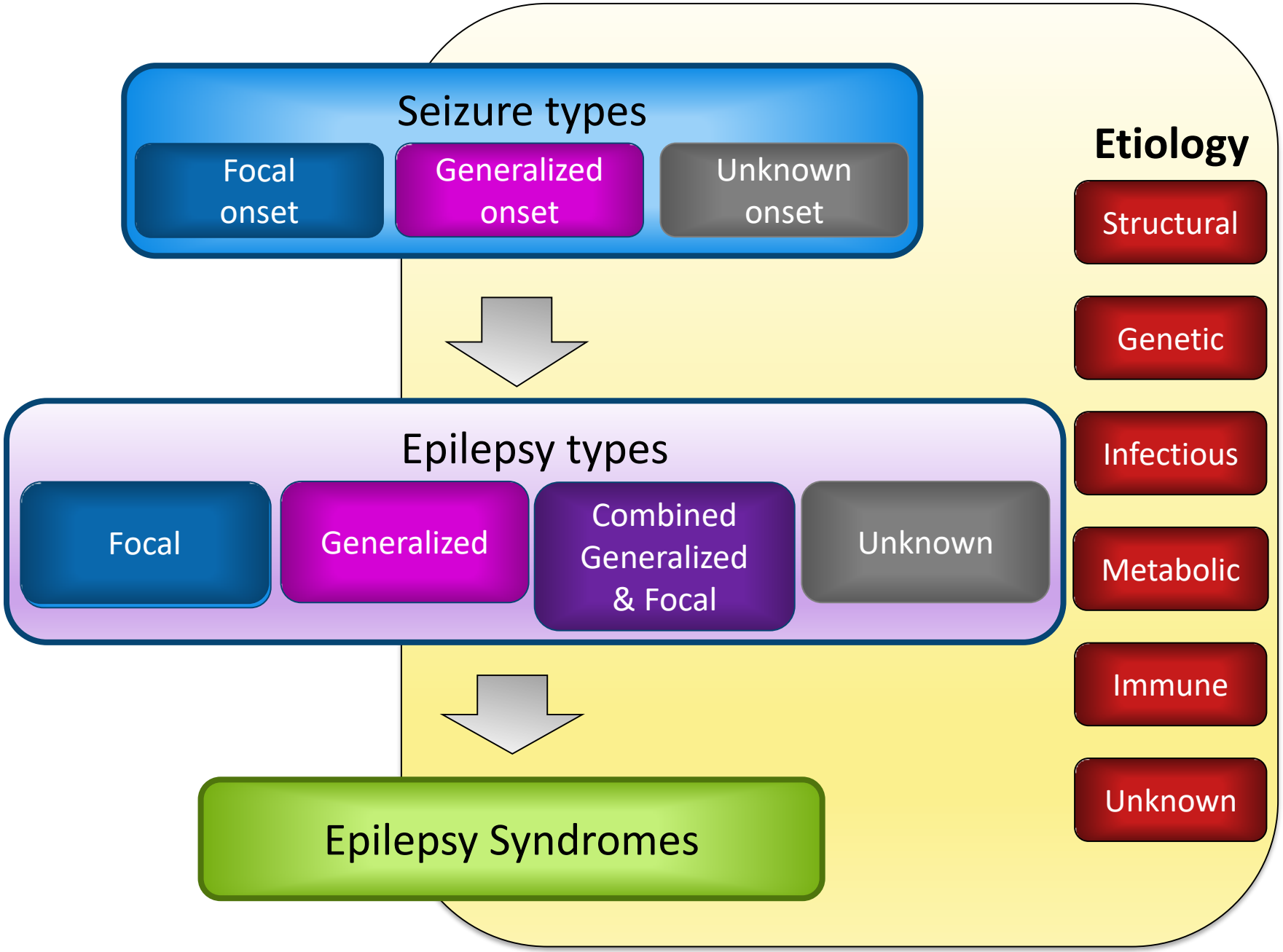








- **Where unable to make an Epilepsy Syndrome diagnosis or a diagnosis of Etiology**
- **Many examples**
  - **Temporal lobe epilepsy**
  - **Generalized tonic-clonic seizures in a 5 year old with generalized spike-wave**
  - **Both focal impaired awareness seizures and absence seizures in a patient**
  - **Cannot tell if tonic-clonic seizure is focal or generalized**

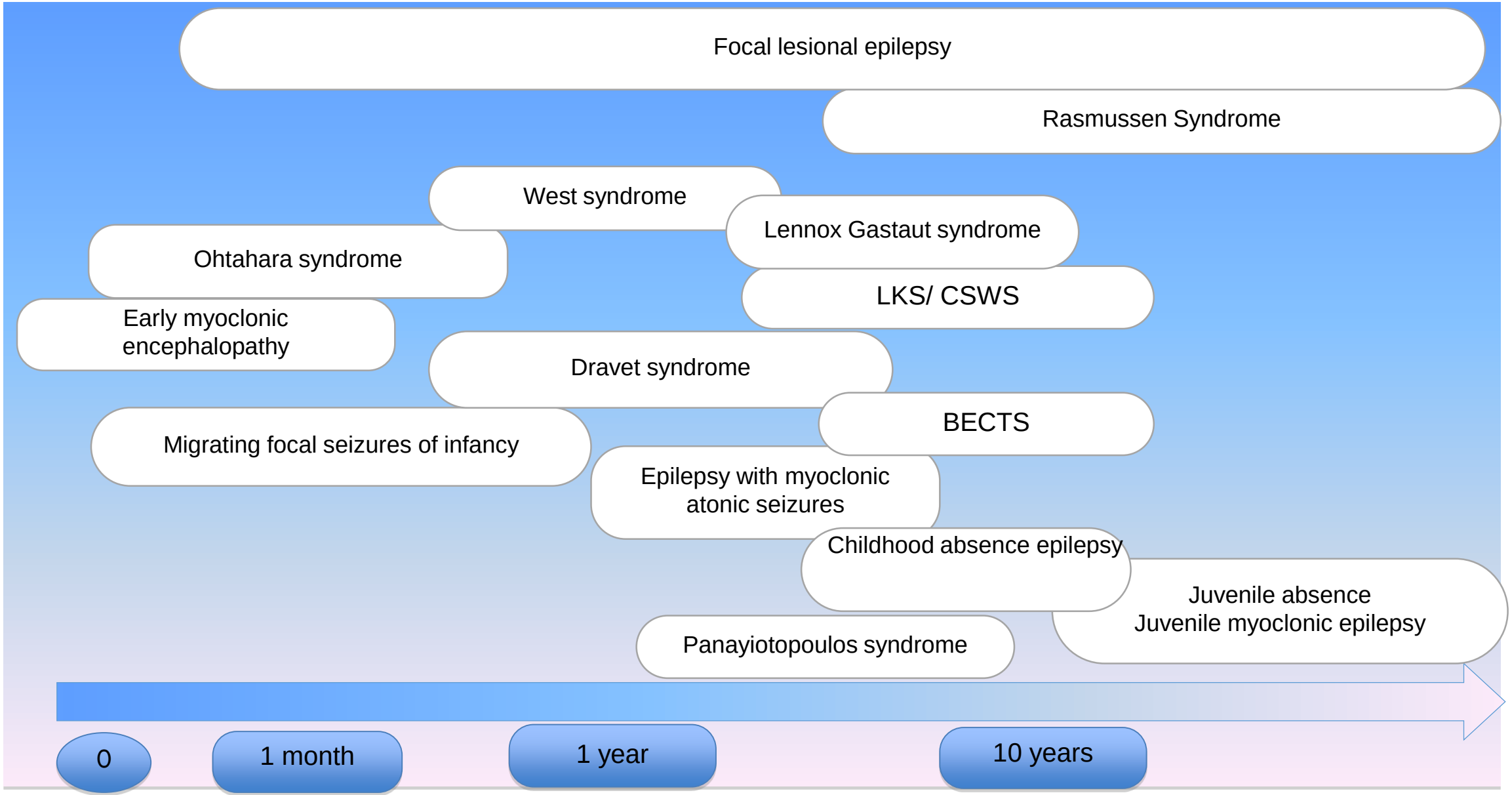

Seizure types
Focal onset
Generalized onset
Unknown onset
Epilepsy types
Focal
Generalized
Combined Generalized & Focal
Unknown
Epilepsy Syndromes
Etiology
Structural
Genetic
Infectious
Metabolic
Immune
Unknown

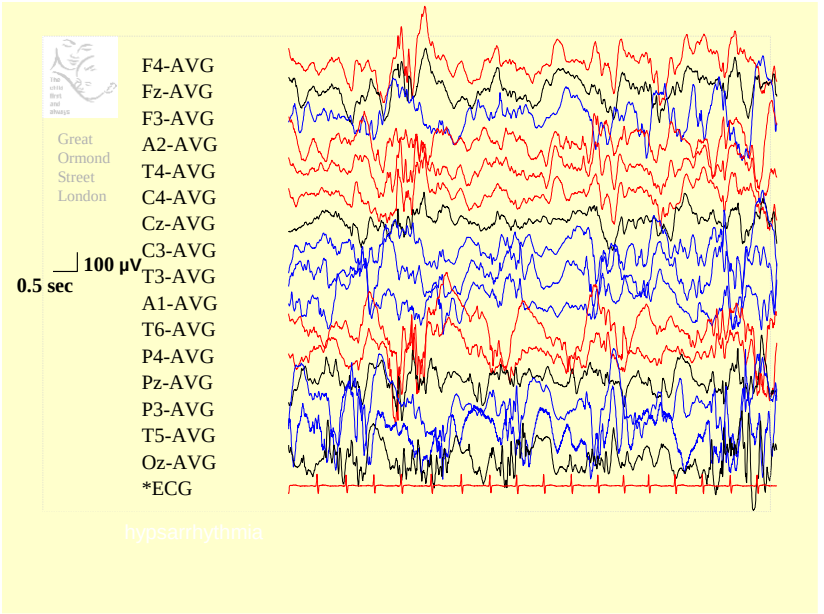
Diseases, syndromes and epilepsies

‘syndrome’

a group of clinical entities that are reliably identified by a cluster of electroclinical characteristics. Patients whose epilepsy does not fit the criteria for a specific syndrome can be described with respect to a variety of clinically relevant factors

Epilepsy syndromes





‘West Syndrome’

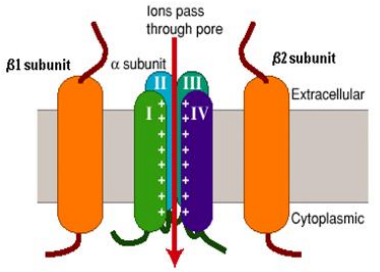
- *–Infantile Spasms*
- *–Hypsarrhythmia*
- *–Developmental plateau*

85% developmental compromise, 60% ongoing seizures

Improved outcome related to short treatment lag, prompt response to treatment & shorter duration of hypsarrythmia

Dravet syndrome

- 1% of the epilepsy population
- Normal early development/imaging
- Febrile and afebrile general and unilateral <u>prolonged clonic or tonic-clonic s. 1st year of life</u> (100%)
- Later appearance of myoclonus (80%), atypical absences (40%), focal seizures (46%)
- Developmental delay progressively apparent
- Prognosis always unfavorable, for seizures, cognitive development, high mortality rates (up to 15%)
- ***>80% mutation SCN1A***



Effective AEDs

Valproate

Clobazam

Topiramate

Levetiracetam

Ketogenic diet

Newer agents

Stiripentol

Chiron et al Lancet 2000

Seizure aggravation

Carbamazepine, phenytoin

Lamotrigine - *Guerrini*

Treatments on the horizon

Panayiotopoulos Syndrome

ictal vomiting

may be associated with pallor, pupillary changes, hypersalivation – may become flaccid and unresponsive mimicking syncope

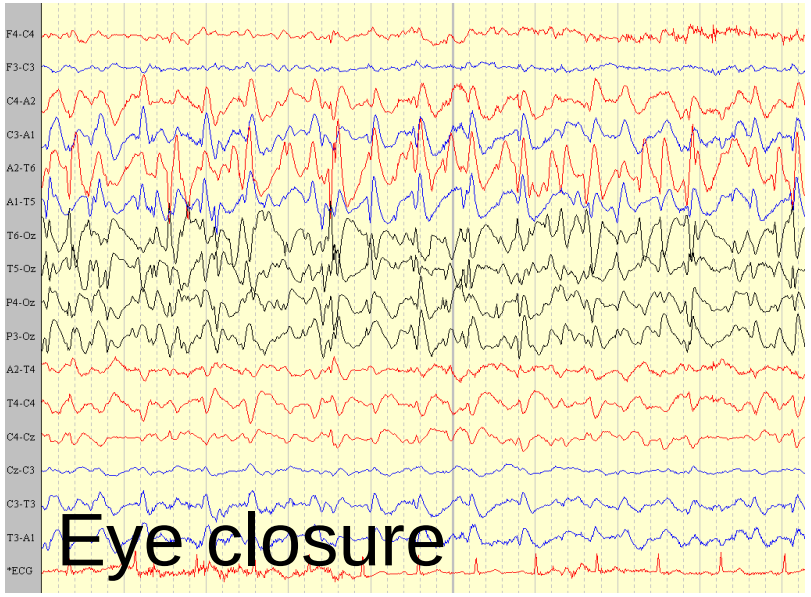
behavioural change, headache often occur at onset

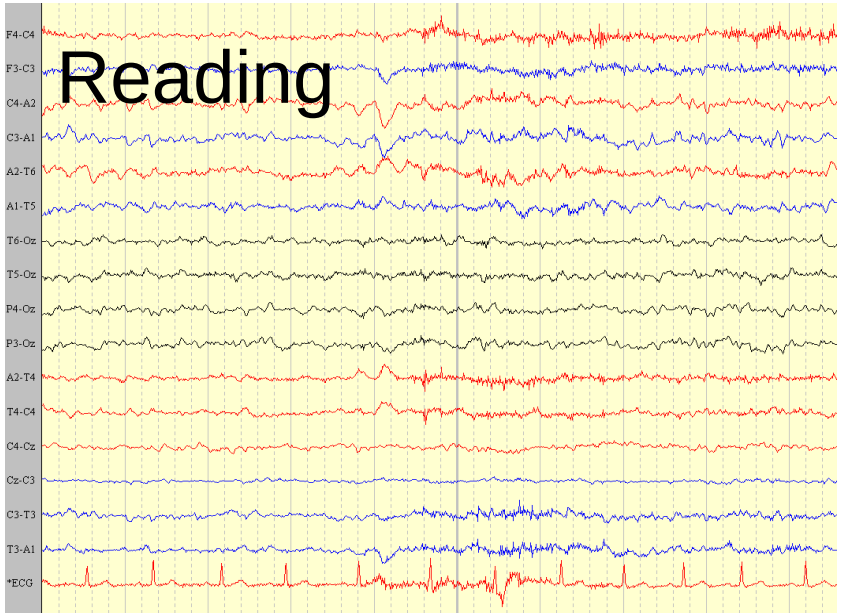
confusion, eye deviation, hemi or generalised szs may develop

= autonomic epilepsy

EEG may show multifocal or generalised spikes

occipital spikes predominate - seen in less than 40% in first EEG increasing to 75% in subsequent recordings





Myoclonic Astatic Epilepsy
(Doose syndrome)

- **Onset age 18m-60m**
- **Multiple seizure types**

  Myoclonic astatic, absence, tonic-clonic, eventually tonic

- **Initial T/C, increase in frequency**
- **One third present with stormy course**
- **Self limited, seizures abate within 3 years 50-89%**
- **Up to 58% normal cognitive outcome (22% SMR; *?associated with prepetitive NCS*)**
- **VPA, ESM, BNZ, LEV, steroids**

Lennox Gastaut Syndrome

Seizure types

- Tonic 74-92%
- Atypical absence 13-100%
- Atonic 14-36%
- Nonconvulsive status 50-75%
- *Myoclonus* *4-22.5%*

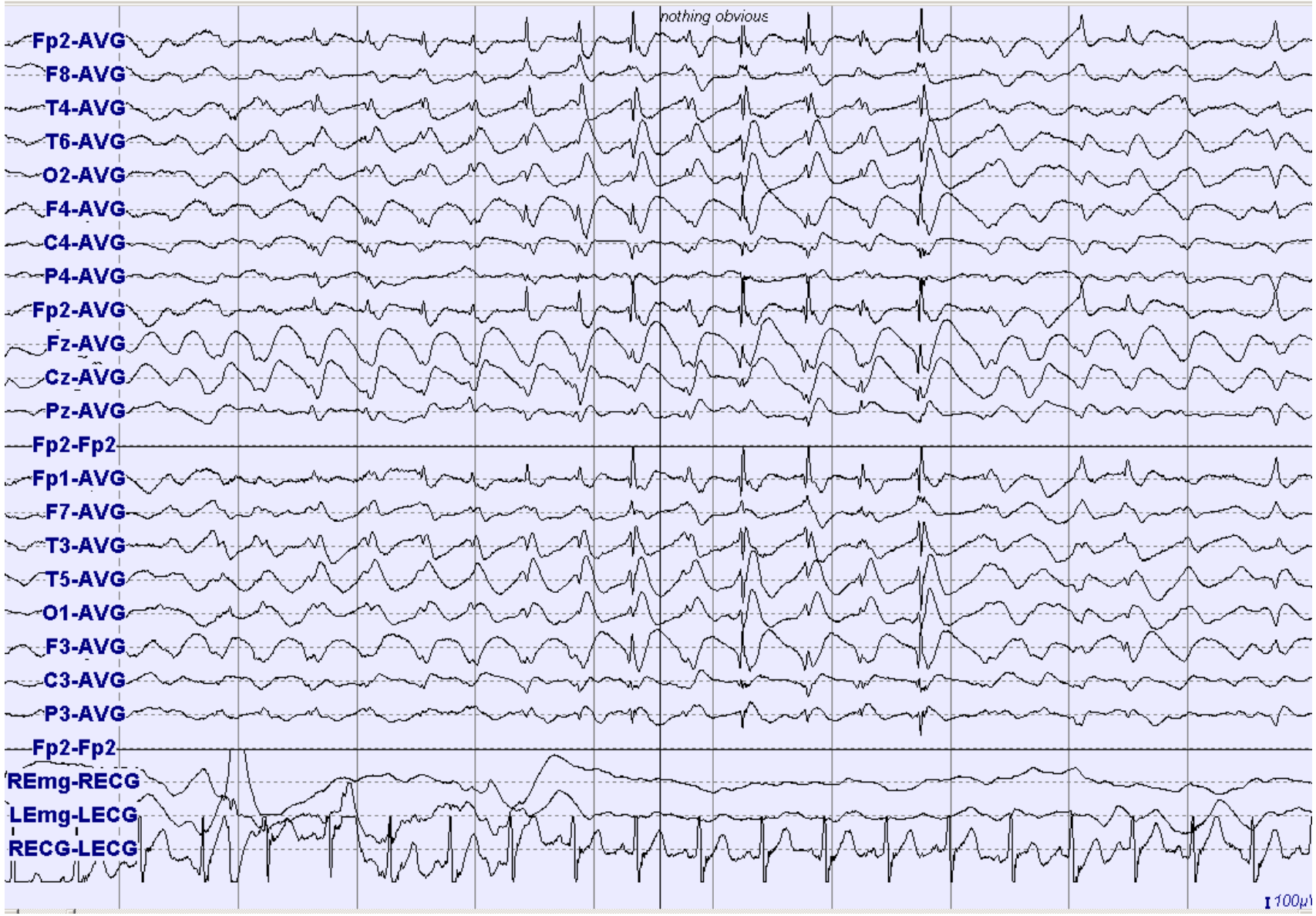
EEG

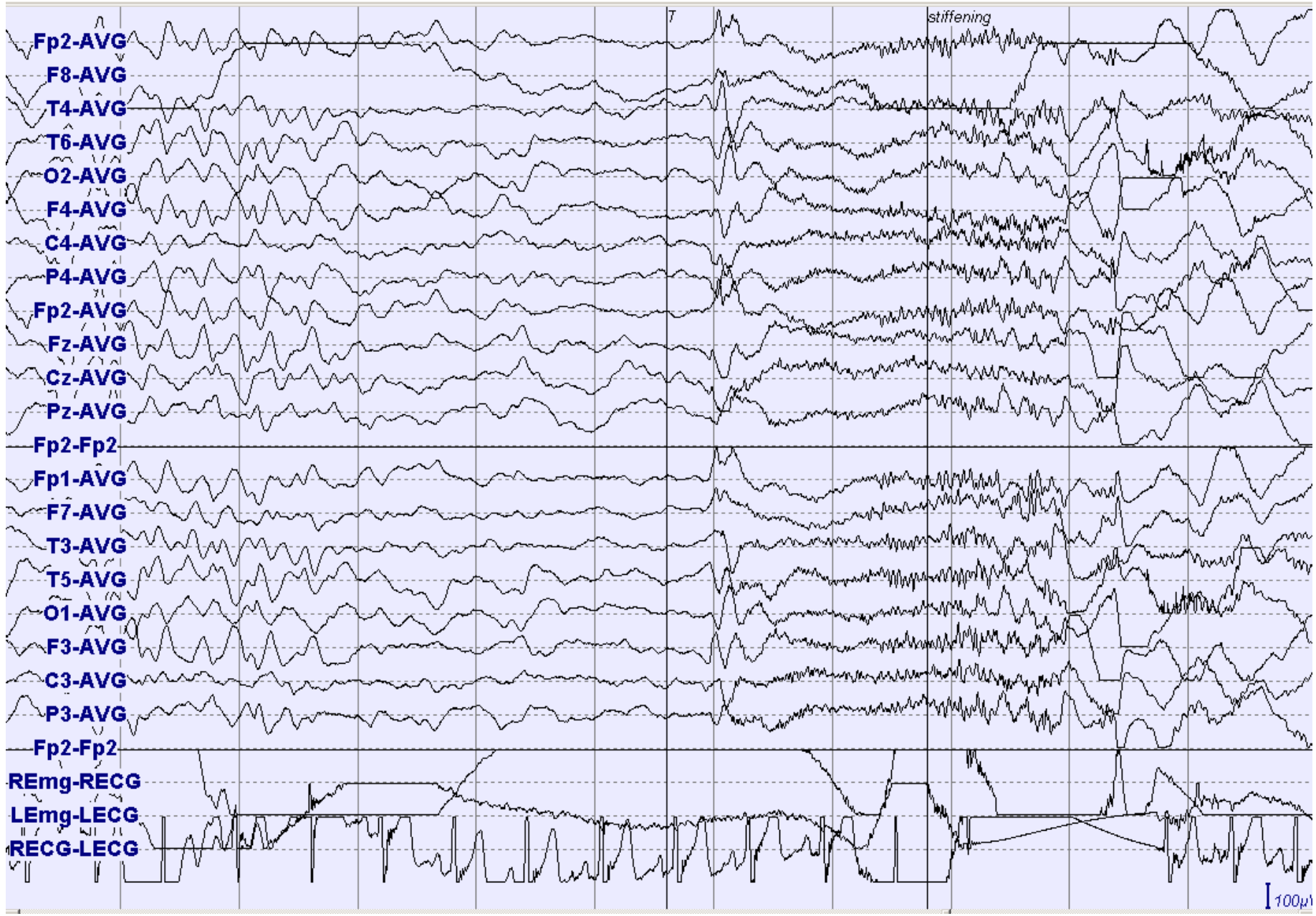
- Diffuse slowing
- Slow- spike wave
- Fast rhythms in sleep

Prognosis

- Medication resistant
  - VPA, LMT, TPM, CLB
- Remission 0-7%
- Characteristic seizures continue
- SSW may be replaced by multifocal independent spike foci

Beaumanoir & Blume 2005

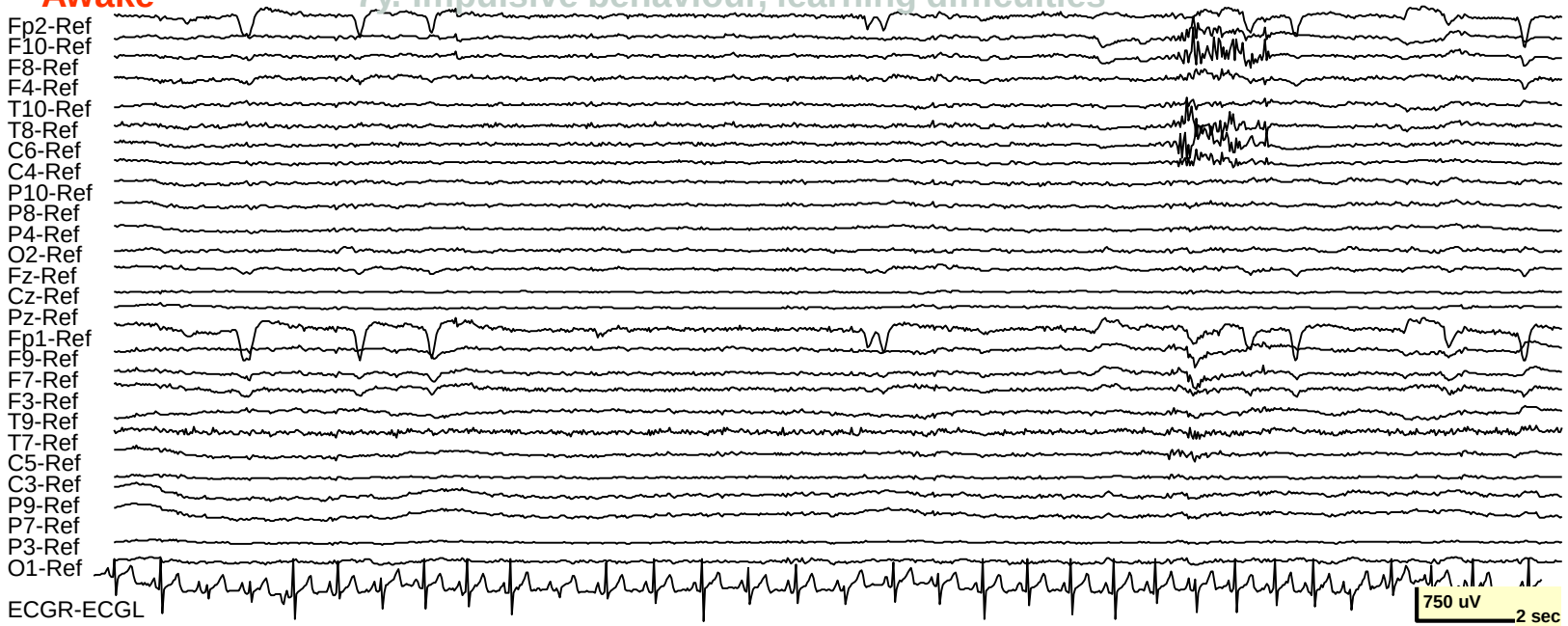

nothing obvious
Fp2-AVG
F8-AVG
T4-AVG
T6-AVG
O2-AVG
F4-AVG
C4-AVG
P4-AVG
Fp2-AVG
Fz-AVG
Cz-AVG
Pz-AVG
Fp2-Fp2
Fp1-AVG
F7-AVG
T3-AVG
T5-AVG
O1-AVG
F3-AVG
C3-AVG
P3-AVG
Fp2-Fp2
REmg-RECG
LEmg-LECG
RECG-LECG
100µV


T
stiffening
Fp2-AVG
F8-AVG
T4-AVG
T6-AVG
O2-AVG
F4-AVG
C4-AVG
P4-AVG
Fp2-AVG
Fz-AVG
Cz-AVG
Pz-AVG
Fp2-Fp2
Fp1-AVG
F7-AVG
T3-AVG
T5-AVG
O1-AVG
F3-AVG
C3-AVG
P3-AVG
Fp2-Fp2
REmg-RECG
LEmg-LECG
RECG-LECG
100µV

A

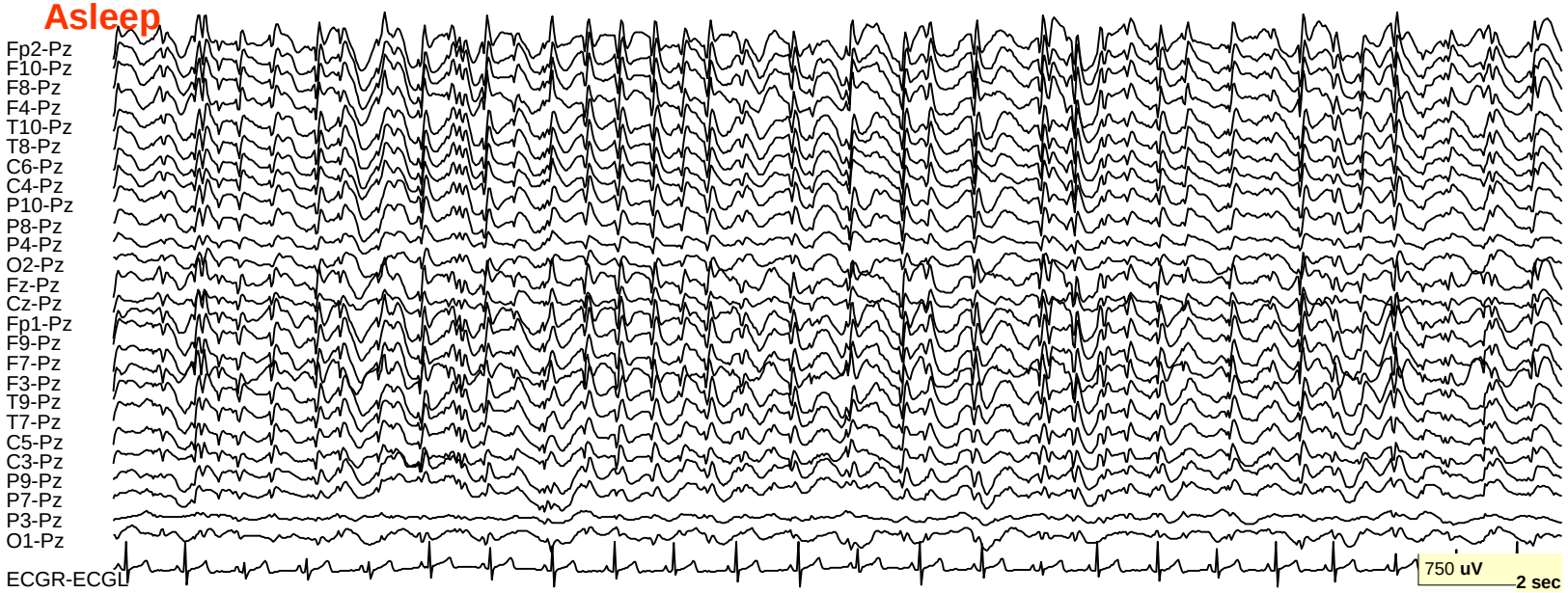
Awake

7y. Impulsive behaviour, learning difficulties



B

Asleep



Landau-Kleffner syndrome

- Normal early development and language
- Onset before 6 years
- Auditory agnosia
- Cognitive/behaviour/motor problems
- Seizures in 75%, but may be infrequent
- Epileptogenic activity affecting speech cortex
- Posterior temporal foci

Landau-Kleffner syndrome

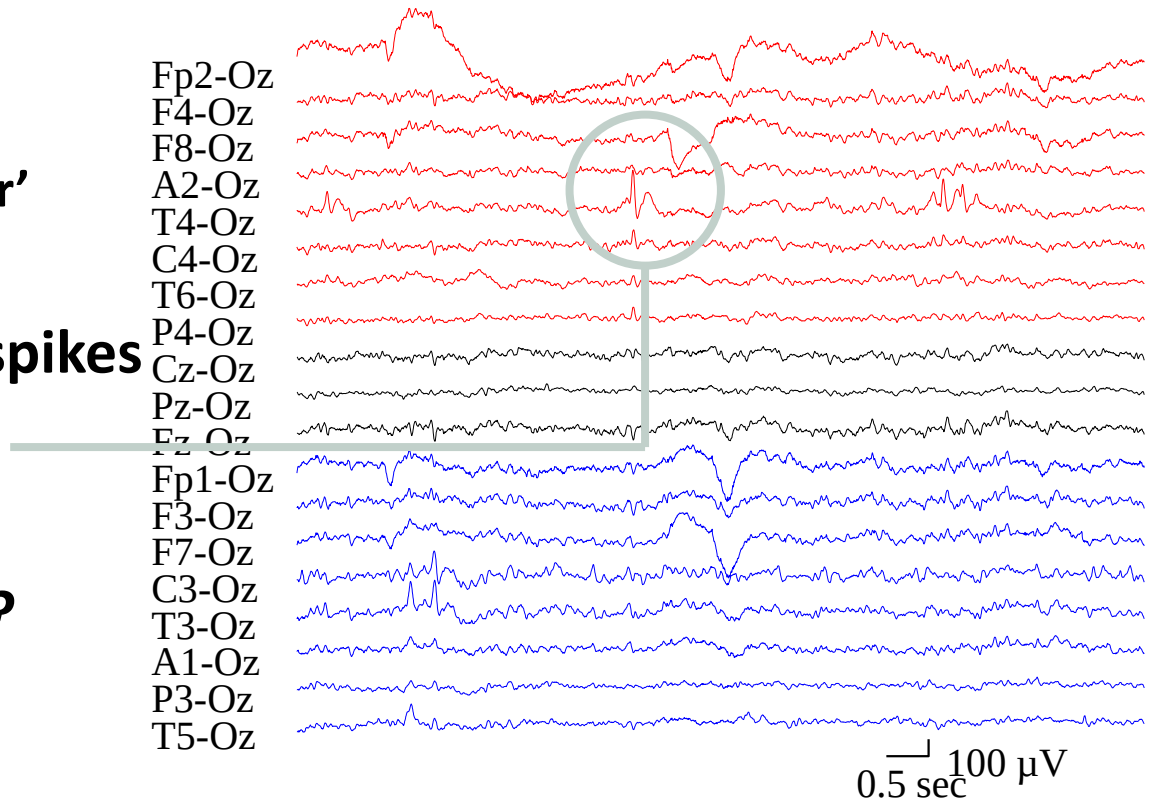
- **Seizures remit by 13-15 years of age in most**
- **Outcome for language less good:**

  10-20% acquire normal language
- **Medical treatment- sodium valproate, ethosuximide, clobazam, steroids**
- **Surgical treatment-multiple subpial transections**

Childhood Epilepsy with Centrotemporal Spikes

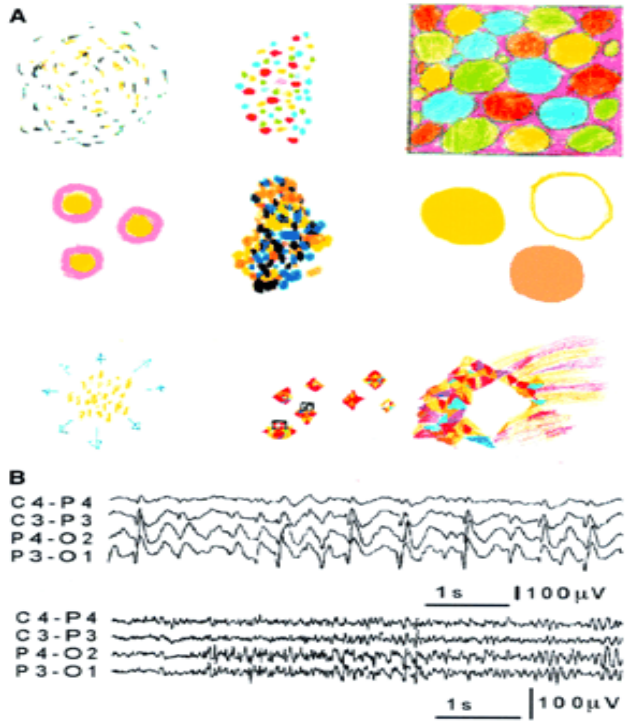
- Age 5-10 years
- Seizures from sleep
  - Rolandic ‘focal motor’
  - GTC
- Centrotemporal spikes on EEG

To treat or not to treat?



Late onset Benign Occipital Epilepsy (Gastaut)

- Age of onset mean 6years
- Visual seizures
  - Elemetary hallucinations, blindness or both
- Hemi (41%) or generalised convulsions (8%)
- Post ictal headache one third
- Treatment carabamazepine
- Full remission in >90% by 19 years



Childhood Absence Epilepsy

- Onset 4-8 years
- Seizure types
  - Absence seizures
    - Pyknolepsy = frequent
    - Frequent - many / day
  - Generalized Tonic-Clonic Seizures
    - 40%
    - Adolescence
- Normal intellect

EEG

- Generalized spike-wave activity
- 2.5-3.5 Hz

Aetiology **- Genetic > 1 gene**

Treatment

- Sodium Valproate
- Ethosuximide
- Lamotrigine

Prognosis good

Juvenile Myoclonic Epilepsy

- Onset 12 - 18 years
- Seizure types
  - Myoclonus
  - GTCS
  - Absences in 30%
- Photosensitive
- Sleep-wake cycle
- Normal intellect
- 4% evolve from CAE

EEG

Generalized spike-wave discharges
3.0 - 6.0 Hz
Polyspike-wave

Aetiology: Polygenic > 1 gene

- Rare genes identified
- Genetic heterogeneity

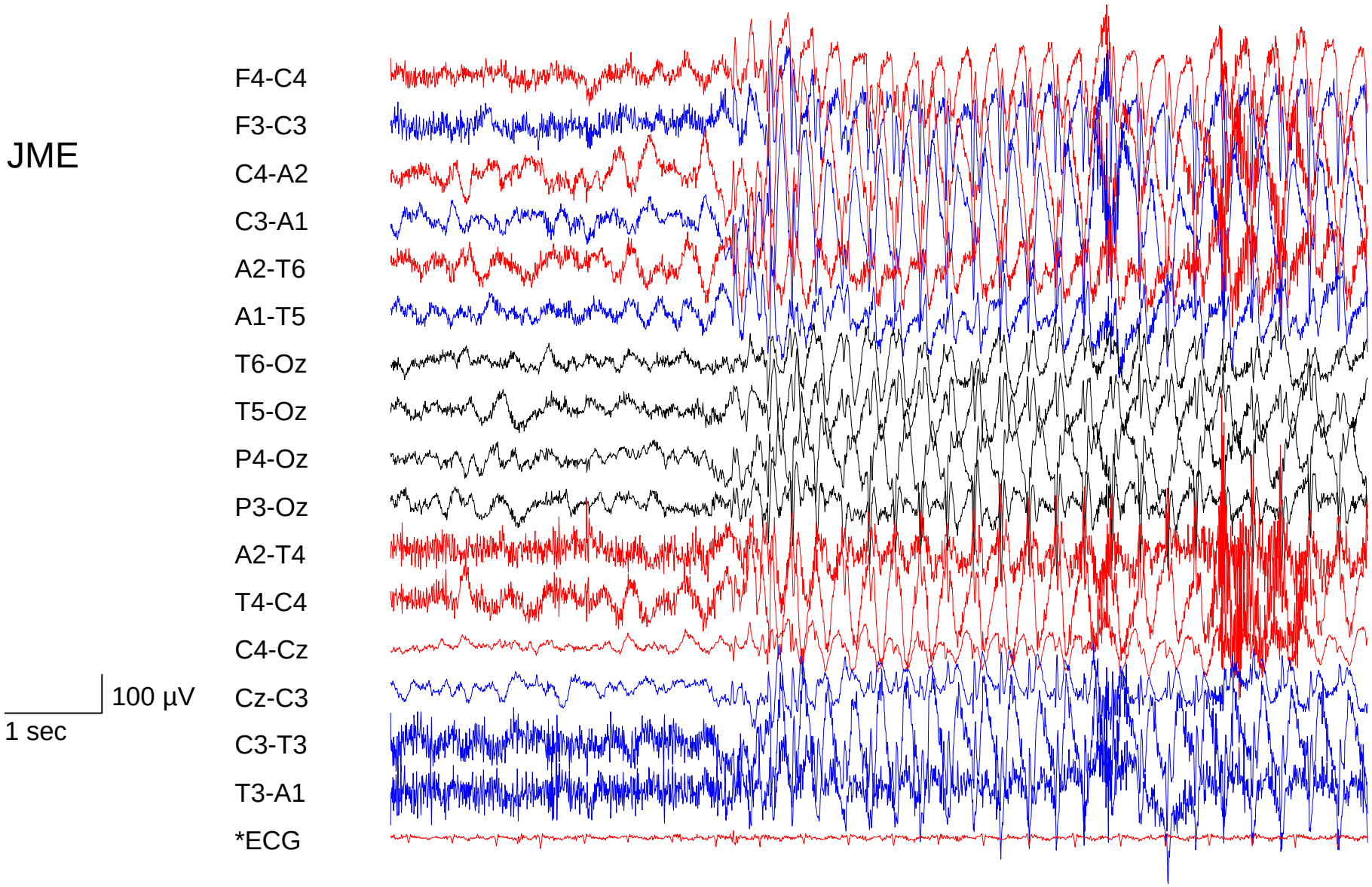
Treatment

VPA, LVT
Lifestyle factors are critical - *avoid*
Fatigue
Alcohol
Photic eg disco strobe lights

Prognosis

Good
Spontaneous remission rare

JME


F4-C4
F3-C3
C4-A2
C3-A1
A2-T6
A1-T5
T6-Oz
T5-Oz
P4-Oz
P3-Oz
A2-T4
T4-C4
C4-Cz
Cz-C3
C3-T3
T3-A1
*ECG
100 µV
1 sec

Goals of management

- **Accurate diagnosis**
- **Prompt and optimal investigation**
- **Accurate diagnostic & prognostic information for families**
- **Seizure freedom**
- **No adverse effects to treatment**
- **Ease and optimal timing of referral for complex patients**

Initial treatment

- **Antiepileptic medication**
  - **Similar drugs to adults**
  - **Data limited in children**
  - **Guided by epilepsy diagnosis**

- **Aim: seizure freedom**
  - **Awareness that medication can worsen seizures**

When to stop treatment

- **Related to epilepsy syndrome**
- **Benign syndromes;**
  - **predictability of age**
- **Evidence for consideration after two years seizure freedom**
- **Careful consideration**

  Risk of recurrence - underlying aetiology

  Timing of medication withdrawal

Psychiatric disorder in epilepsy

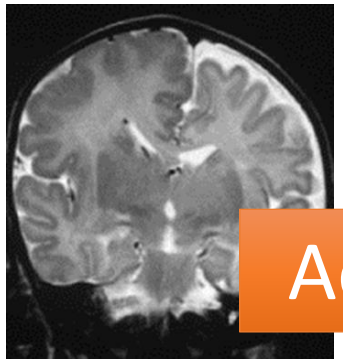
N=10438, age 5-15 years

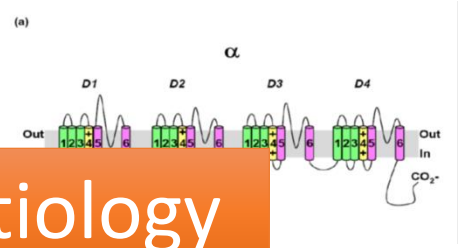
British Child and Adolescent Mental Health Survey

Group (N)	% with psychiatric disorder (N)					% SLD (N)
	Any	**Emot**	**Cond**	**ADHD**	**PDD**	
Epilepsy plus (25)	**56.0% (14)**	16.0% (4)	24.0% (6)	12% (3)	16.0% (4)	35.0% (7/20)
Pure epilepsy (42)	**26.2% (11)**	16.7% (7)	16.7% (7)	0	0	2.4% (1/41)
Diabetes (47)	**10.6% (5)**	6.4% (3)	8.5% (4)	2.1% (1)	0	2.2% (1/46)
All other (10,202)	9.3% (946)	4.2% (427)	4.7% (483)	2.2% (228)	0.2% (25)	0.5% (52/9974)

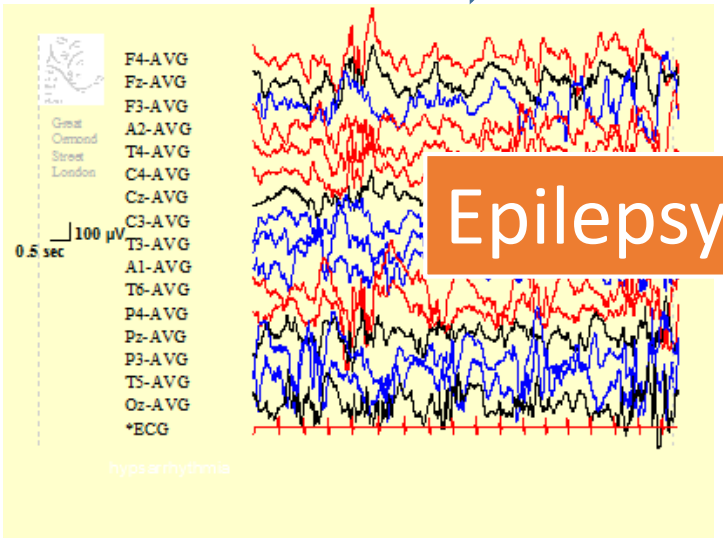
Any, any psychiatric disorder, not including learning disability; Emot, any emotional disorder; Cond, any conduct disorder, including oppositional defiant disorder; ADHD, any attention deficit/hyperactivity disorder; PDD, any pervasive developmental disorder (autistic disorder); SLD, severe learning disability

Davies S, et al. Dev Med Child Neurol 2003;45:292-5





Aetiology



Epilepsy

Cognitive/mental function

Medication

Epilepsy and cognition

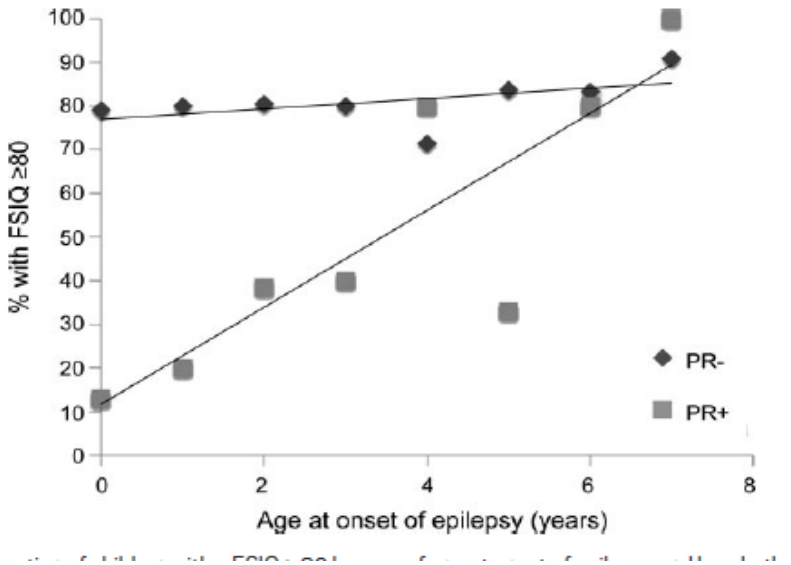
Cognitive deficits progress over time

Longitudinal study of a cohort with epilepsy onset < 3 years

TABLE 1. Mean Vineland Scores at Initial Study Entry and Over Time for the Full Study Sample (n = 172)

Domain	Baseline, Mean (SE)	1 Year, Mean (SE)	2 Years, Mean (SE)	3 Years, Mean (SE)	P Value for Trend
Composite	92.0 (1.5)	86.6 (2.0)	82.9 (2.4)	81.5 (2.7)	<.0001
Communication	93.4 (1.5)	90.4 (2.0)	87.2 (2.0)	85.2 (2.3)	.0003
Daily Living	89.6 (1.4)	79.0 (1.6)	76.5 (2.0)	74.6 (2.4)	<.0001
Motor	94.4 (1.7)	90.0 (2.2)	83.1 (2.5)	80.5 (3.3)	<.0001
Social	96.1 (1.7)	92.7 (2.0)	90.0 (2.2)	88.8 (2.4)	.0015

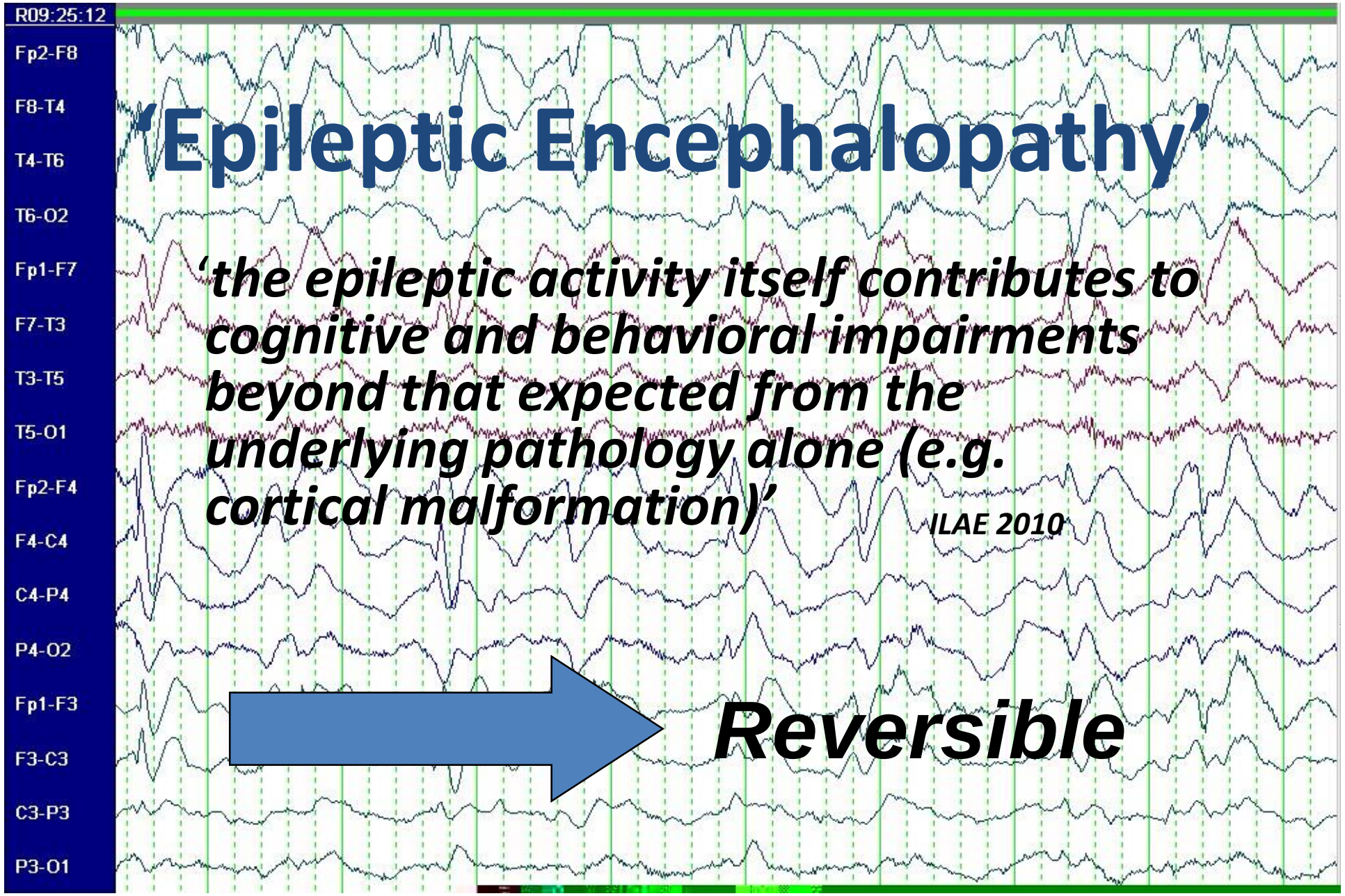
Berg et al Pediatrics 2004;114: 645-650



Longitudinal study to 8-9 years following seizure onset <8 years

Dichotomous IQ indicator strongly correlated with age at onset in pharmacoresistant group (p<0.0001) , not pharmacoresponsive group (p=0.61)

Berg et al Neurology 2012;79:1384-1391



'Epileptic Encephalopathy'

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

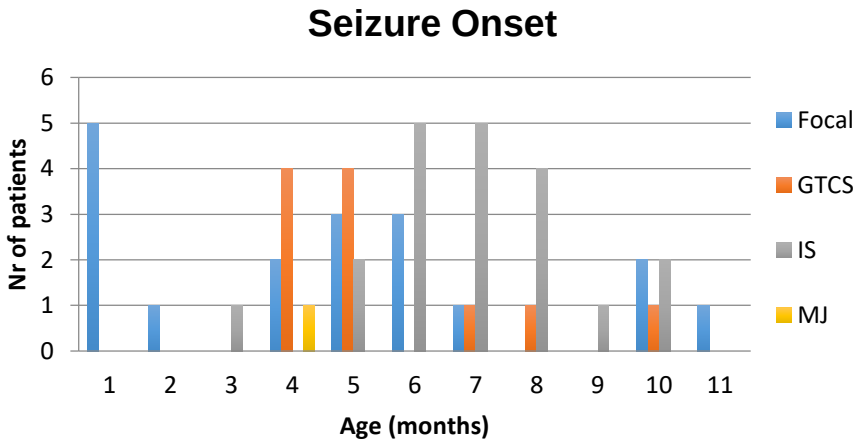
ILAE 2010

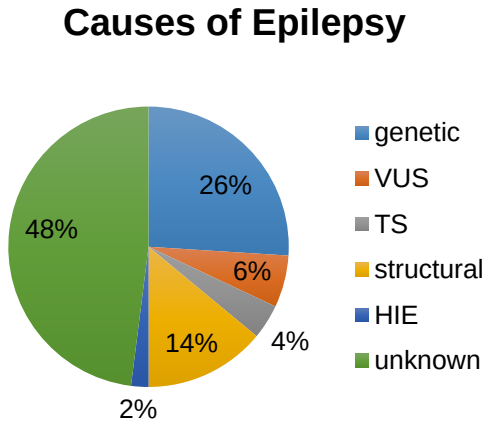
Reversible

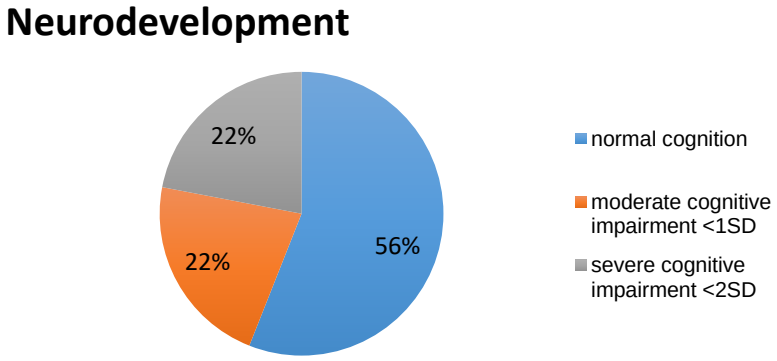
New onset epilepsy in infancy

EPIPEG

Design: prospective observational cohort study of all children presenting with infantile epilepsy in London and the South-East of England August 2016 - October 2017.







Mean Bayley scores (BS): cognition 84 (55-115, SD=17.67), motor 79.4 (46-124, SD=22.4), language 83 (47-115, SD=17.1).

Neurobehaviour in epilepsy

Cause or consequence?

- **Children with new onset 'idiopathic' epilepsies assessed prior to AED significant abnormalities**

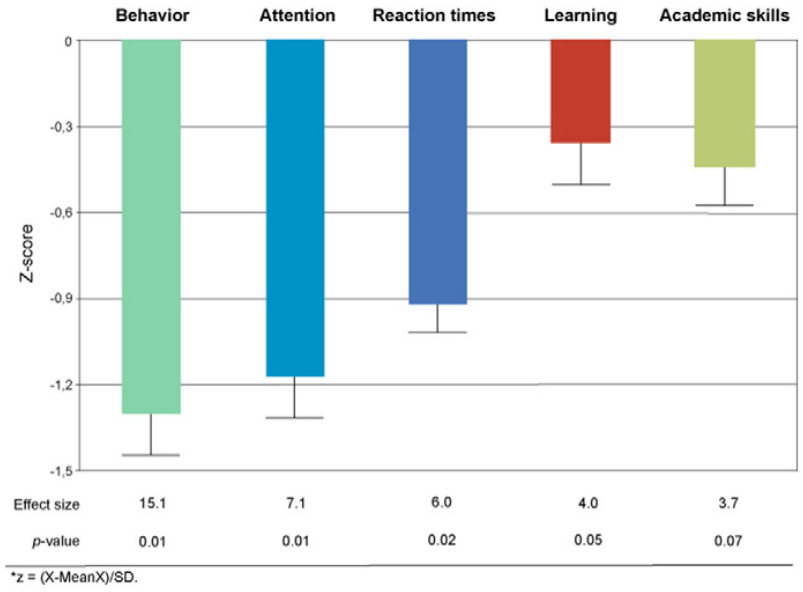
  Oostrom et al 2003

- **Academic problems antecedent to onset of epilepsy**

  Hermann et al 2006

- **Behaviour problems evident at diagnosis, & probably antecedent**

  Austin et al 2001



Oostrom et al Pediatrics 2003;112:1338-44

Concepts revisited

ILAE, Fisher et al Epilepsia 2014;55:475-482

Epilepsy: A disease of the brain

1. **At least two unprovoked (or reflex) seizures occurring more than 24 hours apart;**
2. **One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years**
3. **Diagnosis of an epilepsy syndrome.**

Epilepsies = a group of diseases

Not all due to epileptiform activity…

- **Many disorders *not* solely due to epileptiform activity**

  eg. developmental or behavioural deterioration

- **eg. Dravet syndrome- developmental slowing or regression occurs at 1-2 years when epileptiform activity not frequent**
  - **Suggests *both* a developmental and epileptic component**
  - ***Both* likely secondary to underlying *SCN1A* mutation**

- **Where both delayed development *and* frequent epileptiform abnormalities**

  →suggest term "developmental epileptic encephalopathy"

Scheffer et al Epilepsia 2017;58: 512-521

INTERNATIONAL LEAGUE AGAINST EPILEPSY ILAE ESTABLISHED 1909

CHildren with Epilepsy in Sussex Schools (CHESS)

- **To characterise the prevalance and spectrum of difficulties in 'active' epilepsy (children aged 5-15 years)**
  - ***Cognition (global and specific difficulties)***
  - ***Academic Achievement***
  - ***Behaviour (neurodevelopmental, psychiatric and motor)***
- **85 Children (74% of eligible population) underwent assessment.**
- **DSM-IV-TR consensus clinical diagnoses**

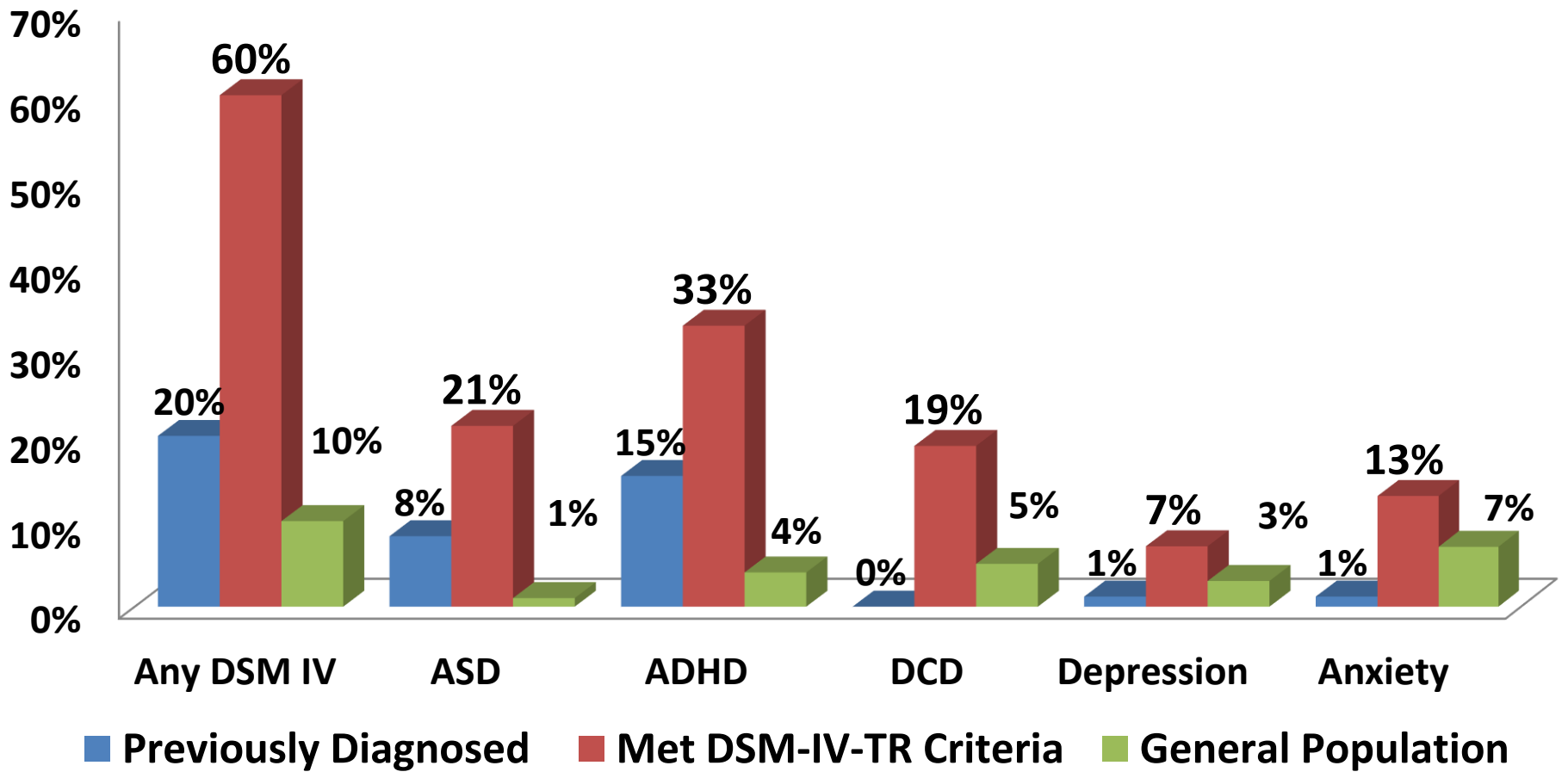
CHESS Study – Main Findings

- **Cognition/Academic Achievement**
  - **24% below IQ 50, 40% below IQ 70 (IDD) 55% below 85.**
  - **Memory + Processing Speed problems (approximately 50%)**
  - **42% displayed academic underachievement**

- **Behaviour/Psychiatric**
  - **60% had DSM-IV behavioural or motor disorder.**
  - **Only 33% of these had previously been diagnosed.**
  - **80% had at least one DSM-IV and/or or cognitive impairment.**
  - **34% had IQ below 85 and 1 or more DSM-IV disorder.**

Reilly et al Pediatrics. 2014 Jun 1;133(6):e1586-93

Behaviour/Psychiatric/Motor Diagnosis



Reilly et al Pediatrics. 2014 Jun 1;133(6):e1586-93

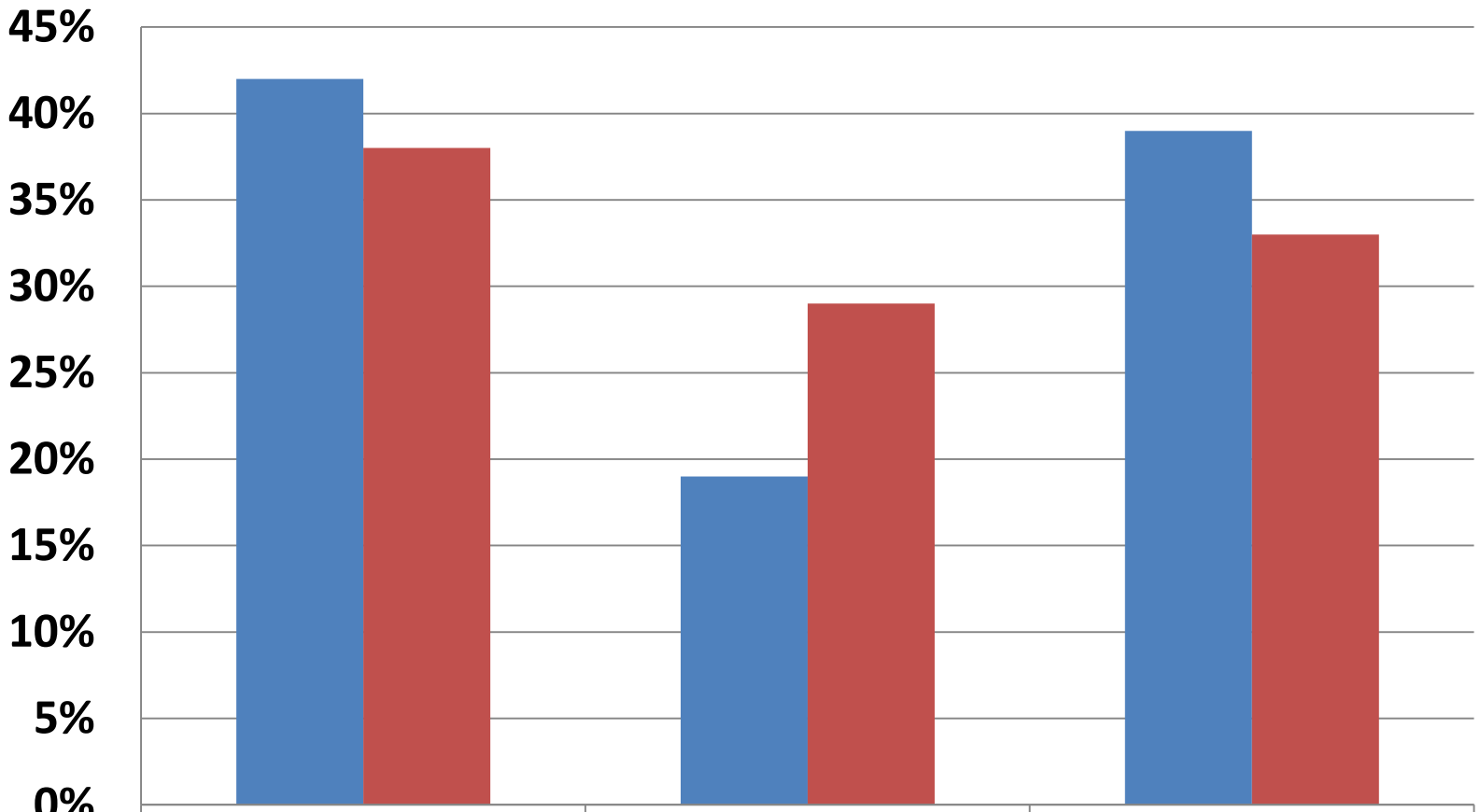
Sussex Early Epilepsy and Neurobehaviour (SEEN) study

Recruitment

- Children with epilepsy born between 2008 and 2014, resident in RH10 to RH14 between 31 August 2014 and 29 February 2016. Had to be at least one year of age at the time of assessment.
- 48 of 53 (91% of eligible children with epilepsy) with epilepsy took part
- A comparison group of 48 gender and age matched children with neurodisability (neurological/neurodevelopmental difficulties)
- ***Child Assessment***
  - Global development, adaptive behaviour, sleep, behaviour.
- ***Parent Assessment***
  - Depression anxiety, stress , sleep and maternal parenting stress
  - Interviews with parents of children with epilepsy

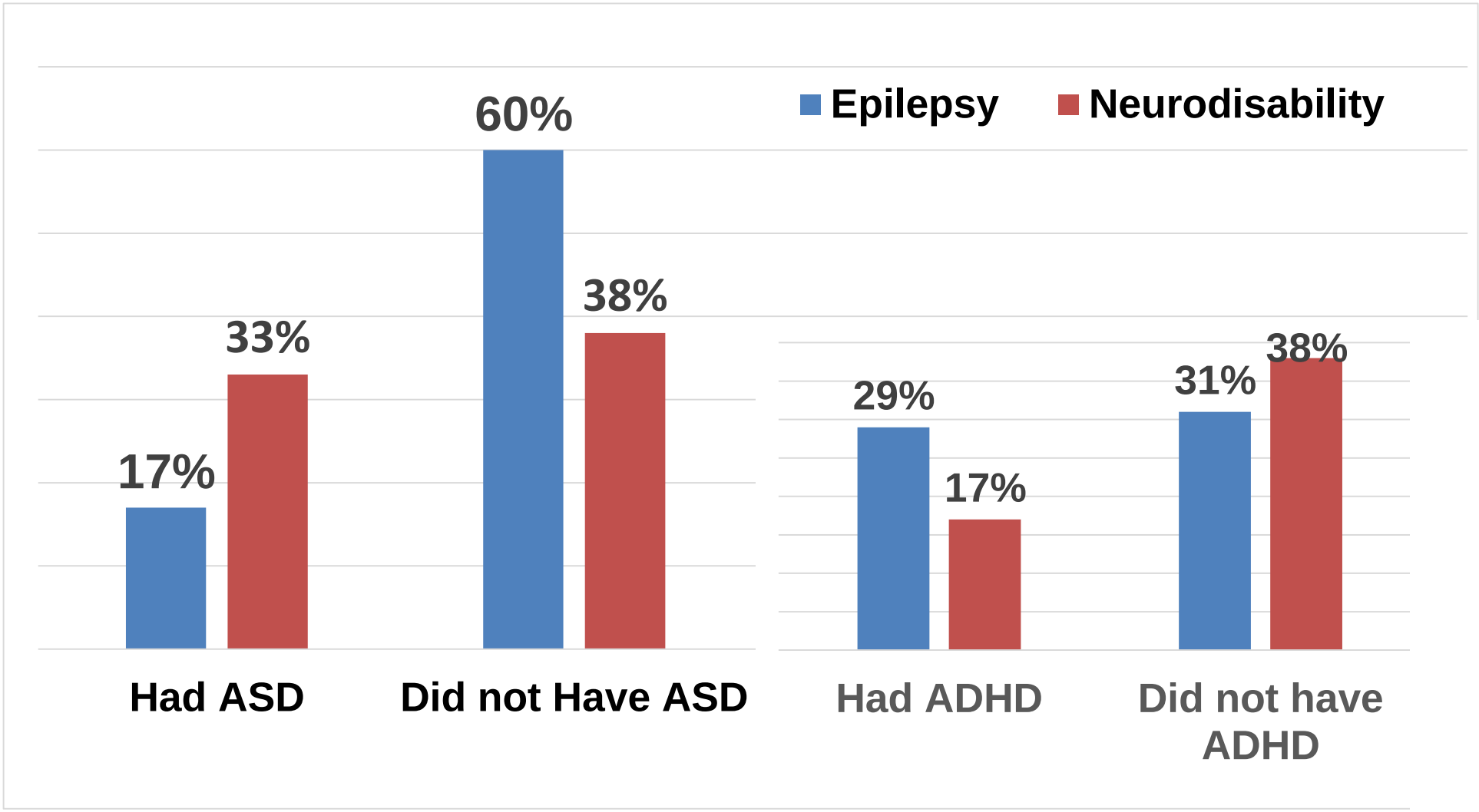
Reilly et al submitted

Child Development



	No significant delay	DQ 50-69	DQ<50
Epilepsy	42%	19%	39%
Neurodisability	38%	29%	33%

Autism Spectrum Disorder/ADHD



What is Epilepsy?

- Epilepsy should be understood as a Disability Complex (Neville, 1999) - Epileptic Seizures and an increased risk for
  - Cognitive difficulties (Global or Specific)
  - Symptoms of Neurodevelopmental Disorders – ADHD and ASD
  - Symptoms of Emotional Disorders (Anxiety and Depression)
  - A range of motor difficulties including DCD
  - Academic Underachievement
- The additional difficulties frequently constitute the major disability of children with epilepsy
- For many epilepsy is an Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations (ESSENCE) disorder

A role for intervention?

- ***Early recognition imperative for optimised outcome?***
- **Psychology/neurodevelopmental assessment should be available at diagnosis**
  - **Educational support**
  - **Mental health intervention**
  - **Sleep intervention**