Introduction to Phenotyping of Neurodevelopmental Disorders

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PHENOTYPING

- Remains a manual task
  - Efforts to make this a scalable task
  - e.g. HPO terminology, EHR data extraction

- Important to understand basic concepts of clinical data
  - What is actually entered into your data capture form?

OVERVIEW

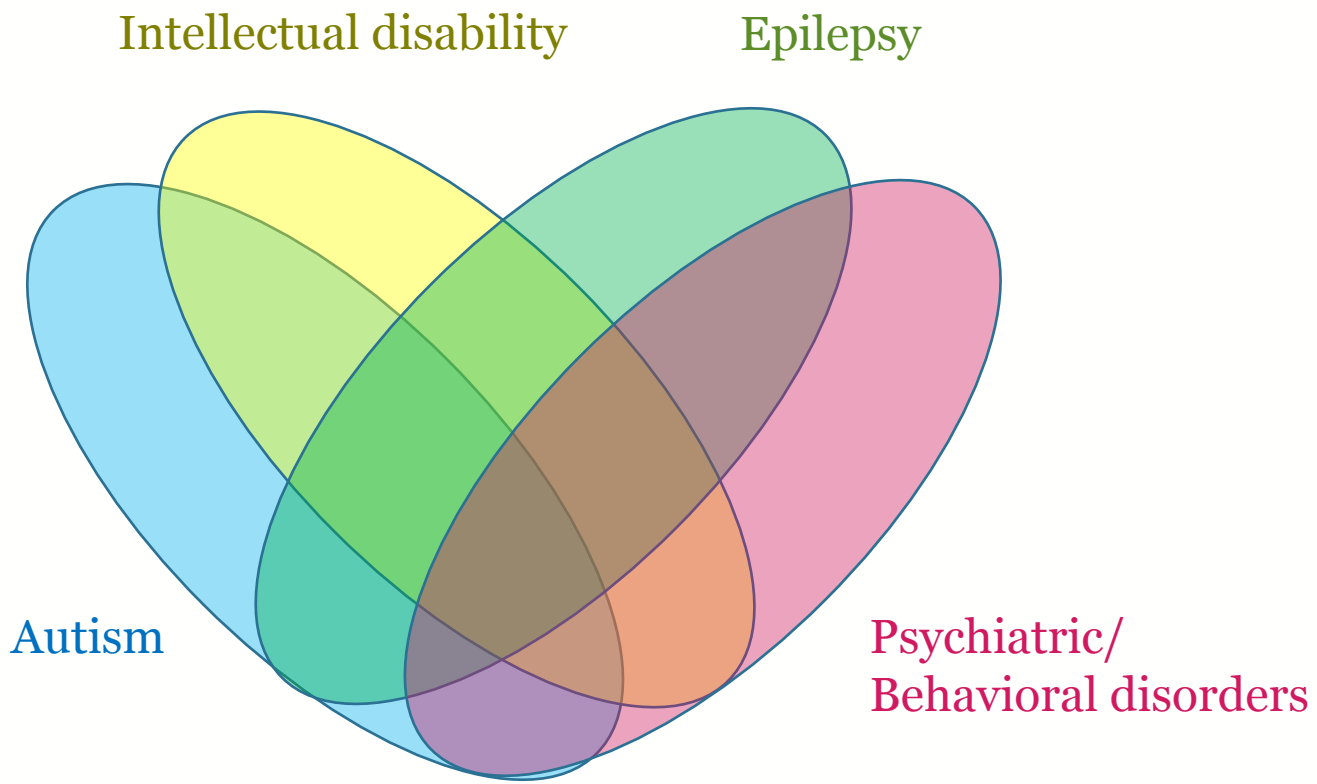
- Introduction to neurodevelopmental disorders
- Epilepsy as an example
- Tools for phenotyping

OVERVIEW

- **Introduction to neurodevelopmental disorders**
- Epilepsy as an example
- Tools for phenotyping

NEURODEVELOPMENTAL DISORDERS

- Group of disorders in which brain development is affected
- Shared risk factors and etiologies



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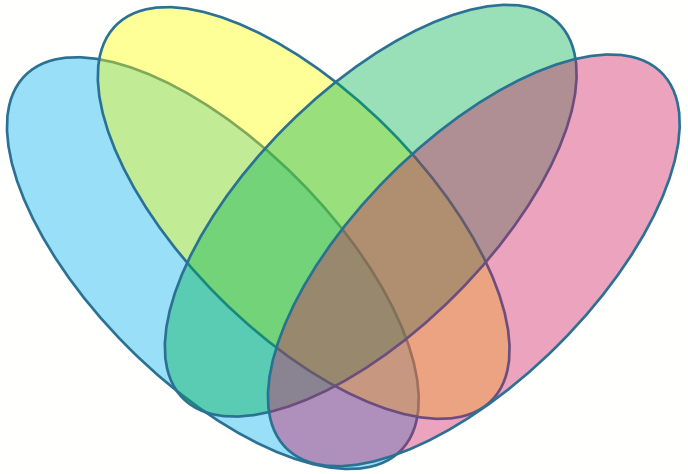
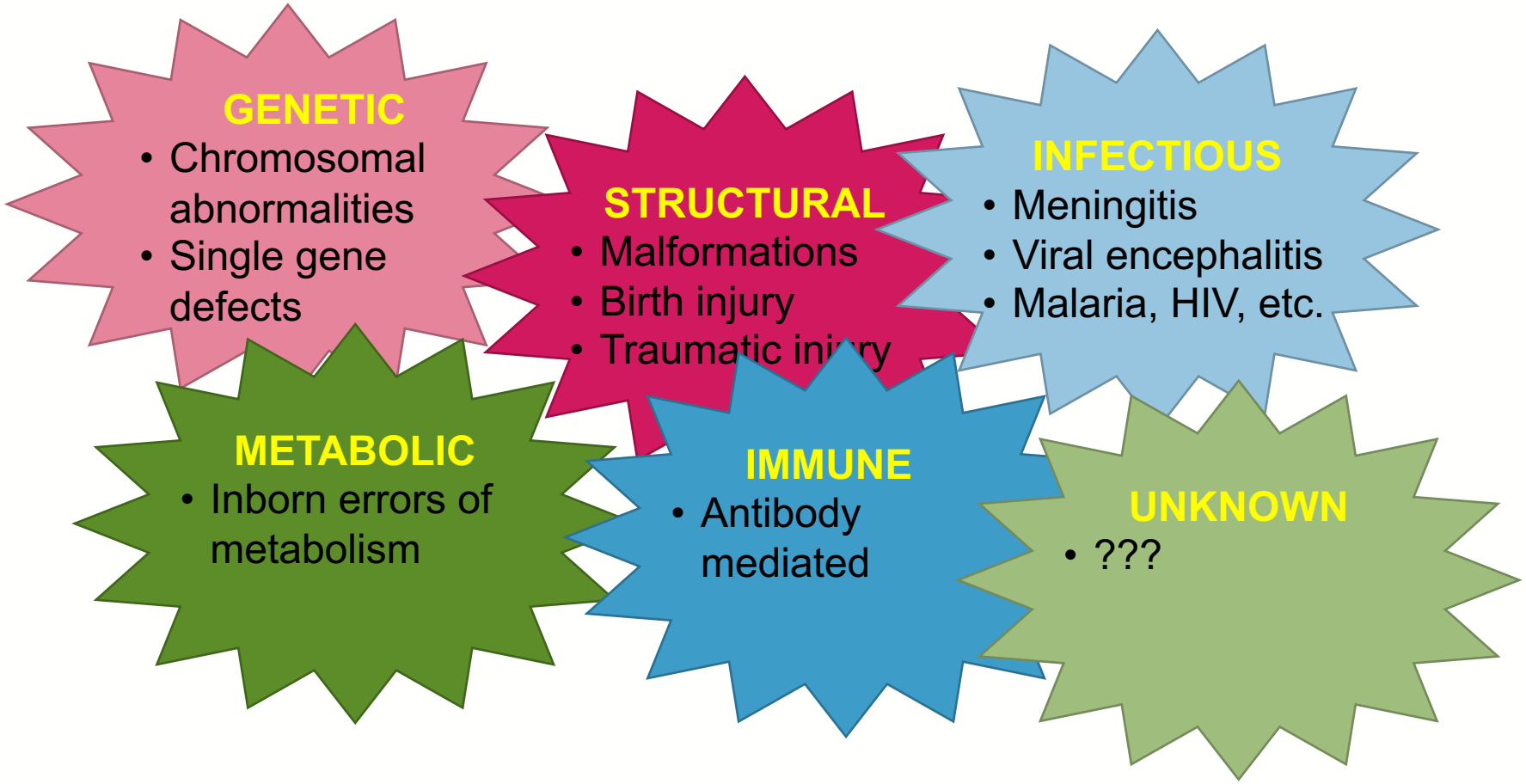
NEURODEVELOPMENTAL DISORDERS

- Lifelong conditions, often starting in childhood
  - Often overlap of several symptoms
  - Various symptoms with genetic etiology
- Not associated with permanent regression
- Examples:
  - Epilepsy
  - Autism spectrum disorders
  - Developmental delay and intellectual disability
  - Neuropsychiatric conditions
  - Childhood onset movement disorders



DIFFERENT ETIOLOGIES



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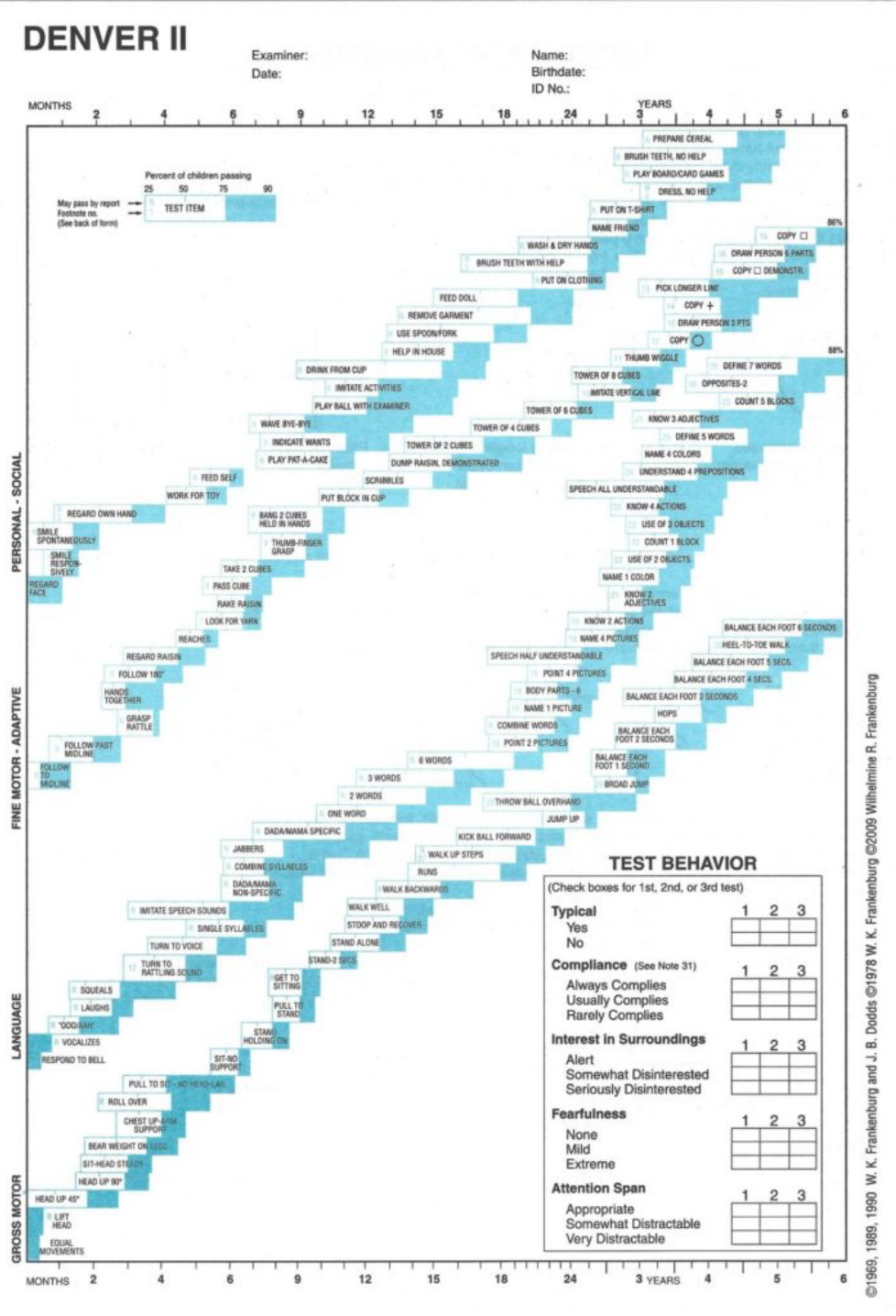
WHAT IS AGE-APPROPRIATE DEVELOPMENT?

- **Cognition:** Thinking, reasoning, problem-solving, understanding
- **Motor development:** Gross/fine motor skills, jumping, hopping, throwing/catching, drawing, stacking
- **Social interaction:** Initiating peer contact, group play
- **Language:** Speaking, understanding language
- **Adaptive:** Dressing, eating, washing



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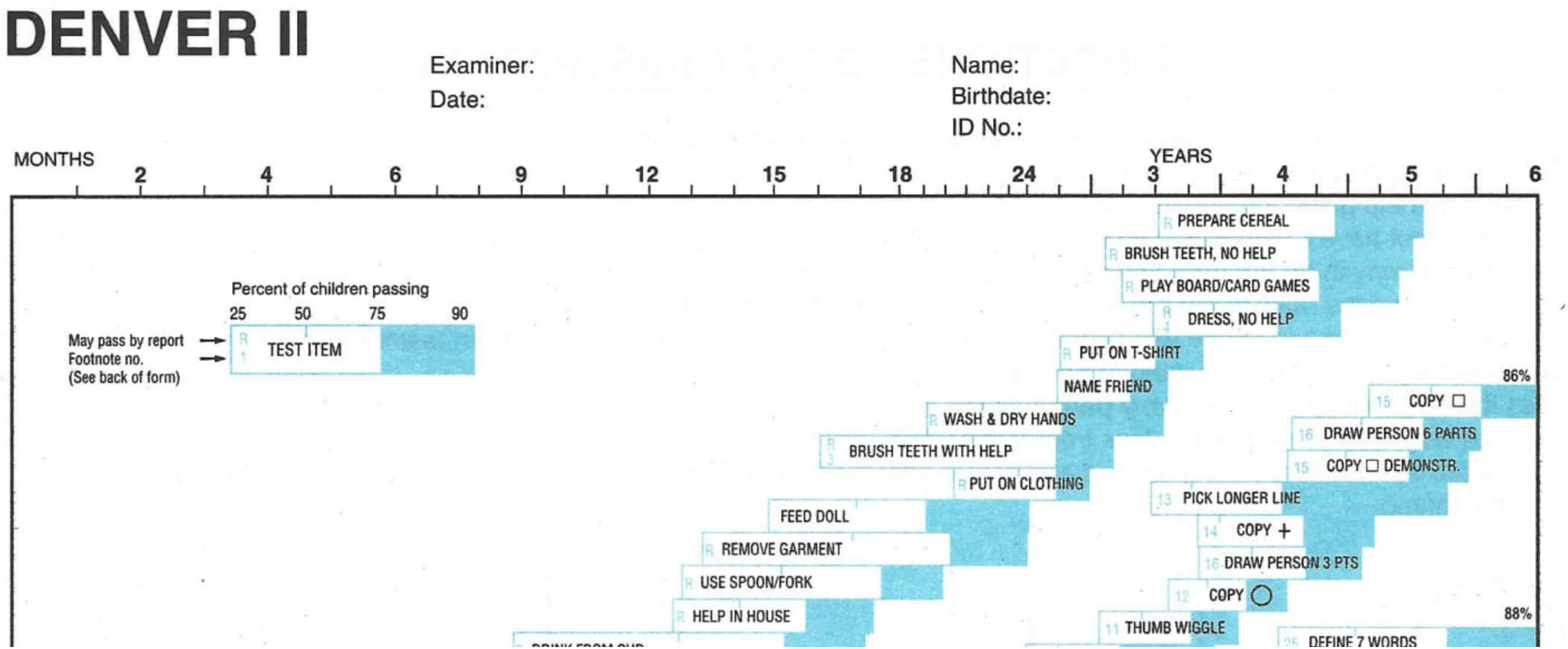
AGE-APPROPRIATE DEVELOPMENT



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WHAT IS AGE-APPROPRIATE DEVELOPMENT?

Category	Item	Typical Range (months)
Gross Motor	Rolls over	2.1 -5.4
	Sit without support	**5.4 - 6.8**
	Pull to sit,no head lag	2.8-6.2
	Pull to stand	7.8-9.7
	Gets to sitting	7.6-9.9
	Stand alone	10.4-13.7
	Walks well	**11.1-14.9**
	Walk up steps	14.1-21.6
	Kick ball forward	15.9-23.2
	Throw ball overhand	17.1-35
	Jump up	21.4-28
	Broad jump	28-38
	Heel-to-toe walk	4y- 5.7 y

WHAT IS AGE-APPROPRIATE DEVELOPMENT?

Category	Item	Typical Range (months)
Fine Motor	Hands together	2.2 - 4
	Grasp object	2.6-3.9
	Reach	4.3-5.6
	Transfer hand - hand	5.1-7.7
	Thumb finger grasp	7.2-10.2
	Pincer grasp	9 - 12
	Scribbles	11.7-16.3
	Copy circle	3.1y-4y

WHAT IS AGE-APPROPRIATE DEVELOPMENT?

Category	Item	Typical Range (months)
Language	Ooo – aah (vocalization)	0.6-2.7
	Laugh squeal	1.3-3.1
	Turn to voice	3.6 - 6.6
	Non-specific mama	5.7 - 9.1
	Specific mama	6.9-13.3
	One word	9.7-15
	Six words	13.7-21.4
	Combine words	**17.2-25**
Personal Social	Smile responsively	0.5 -1.5
	Put on t-shirt	2.3y-3.4y
	Brush teeth, no help	2.6y-5.0y
	Regard hand	0.8-4
	Feed self	4.8-6.5
	Wave bye	6.7-14
	Drink from cup	8.8-17.1
	Use spoon/fork	12.8-19.9

DEVELOPMENTAL IMPAIRMENT: DEFINITIONS

- Chronic condition
- Originates at birth or during childhood
- Expected to continue indefinitely
- Substantially restricts individual's functioning in several major life activities
- Likely to be lifelong

DEVELOPMENTAL IMPAIRMENT: DEFINITIONS

- **Global developmental delay**
  - Child **under 5 years** of age
  - Significant delays in several domains of development
  - At least 2 SD below mean with standardized testing

- **Intellectual disability**
  - Child **5 years of age or older**
  - Deficits in cognitive functions (e.g. reasoning, problem-solving, planning, abstract thinking, judgment, academic learning and learning from experience)
  - Limited functioning in ≥1 activities of daily life across multiple environments
  - Onset of deficits during the developmental period

DEGREES OF INTELLECTUAL DISABILITY

Level	IQ Range
Mild	IQ 52-69
Moderate	IQ 36-51
Severe	IQ 20-35
Profound	IQ 19 or below

*definition according to DSM-V

But what does this practically mean?

CLINICAL FEATURES OF ID

- **Mild ID:** ***Can live independently*** with minimum levels of support. Support may be needed during periods of transition or uncertainty. Individuals with mild ID are slower in all areas of development and daily living skills, but they are able to function in ordinary life with minimal support.

- **Moderate ID:** May be able to ***live independently with moderate levels of support*** (e.g. residential or group home settings). Individuals with moderate ID can take care of themselves, travel to familiar places in their community, and learn basic skills related to safety and health. Their self-care requires moderate support.

CLINICAL FEATURES OF ID

- **Severe ID:** ***Require daily assistance with self-care activities*** and safety. Typically can understand speech but often have limited communication abilities. May be able to learn simple routines but typically live in family or group care settings.

- **Profound ID:** Cannot live independently and ***require 24 hour supervision***. Typically have limited communication skills and physical limitations.

CLINICAL FEATURES OF ID

	Mild	Moderate	Severe	Profound
Living independently	Live independently with minimal support	May be able to live independently with moderate support	Cannot live independently	Cannot live independently
Ability to self-care	Independent	Requires moderate support	Requires daily assistance	Requires 24 hour supervision
Language skills	Typical	Limited	Basic	None
Reading/writing	Can read/write	Basic skills	Cannot read/write	Cannot read/write
Ability to work	Can work in semiskilled jobs	May be able to work unskilled jobs	Cannot work	Cannot work
Social interactions	Unaffected	Some impairment but can interact appropriately	Few	Few
Physical limitations	Rare	Sometimes	Common	Common

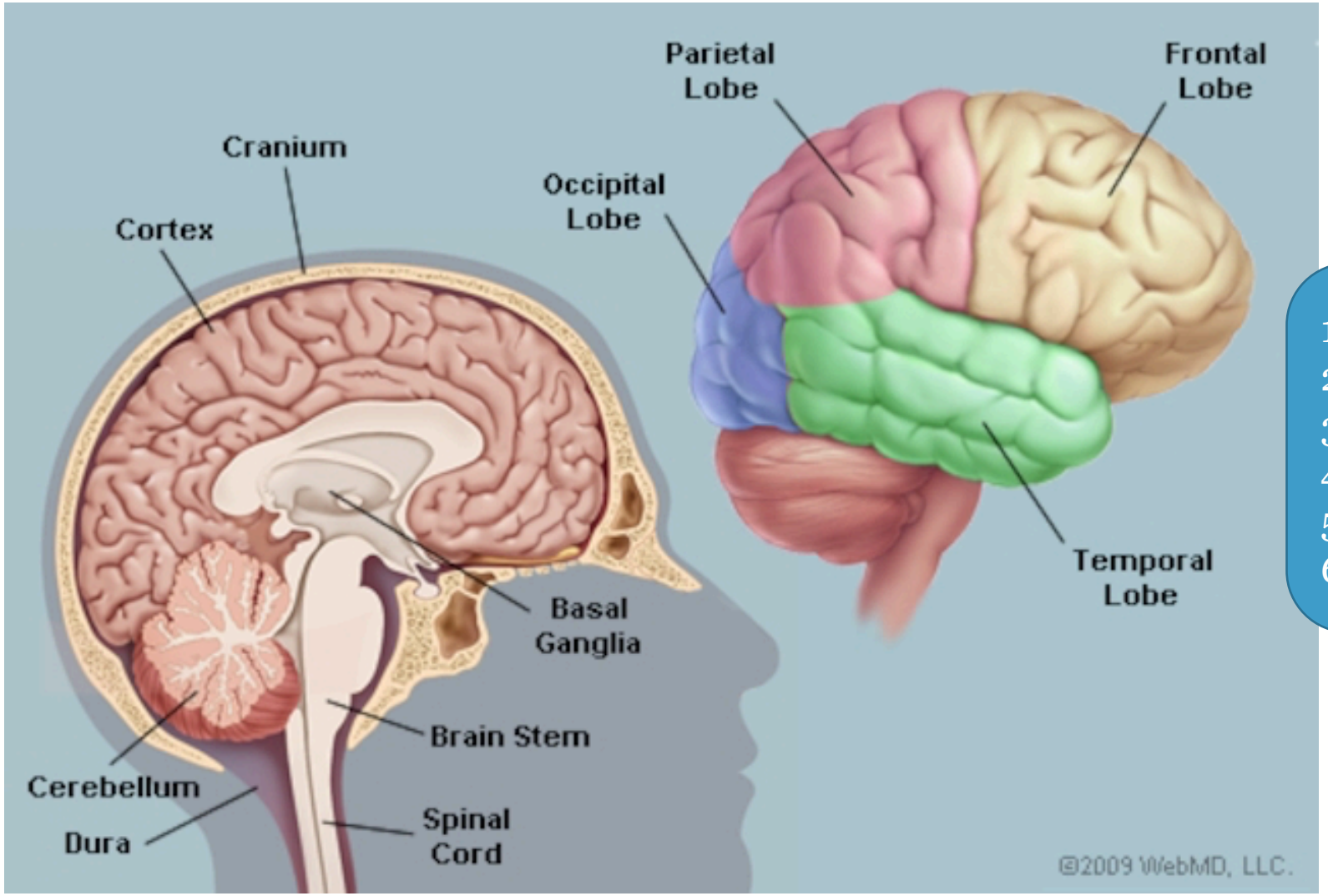
WHAT ABOUT LEARNING DISABILITY?

- Term used inconsistently
- May be used to mean:
  - Mild intellectual disability
  - Global developmental delay (< age 5y)

OR

  - Specific learning disability
    - Impairment in reading, impairment in the written expression, and impairment in mathematics
    - e.g. Dyslexia
  - DSM-V criteria for specific learning disability

BRAIN ANATOMY



1. Mental Status
2. Motor Examination
3. Cranial Nerves
4. Reflexes
5. Coordination/Gait
6. Sensory Examination

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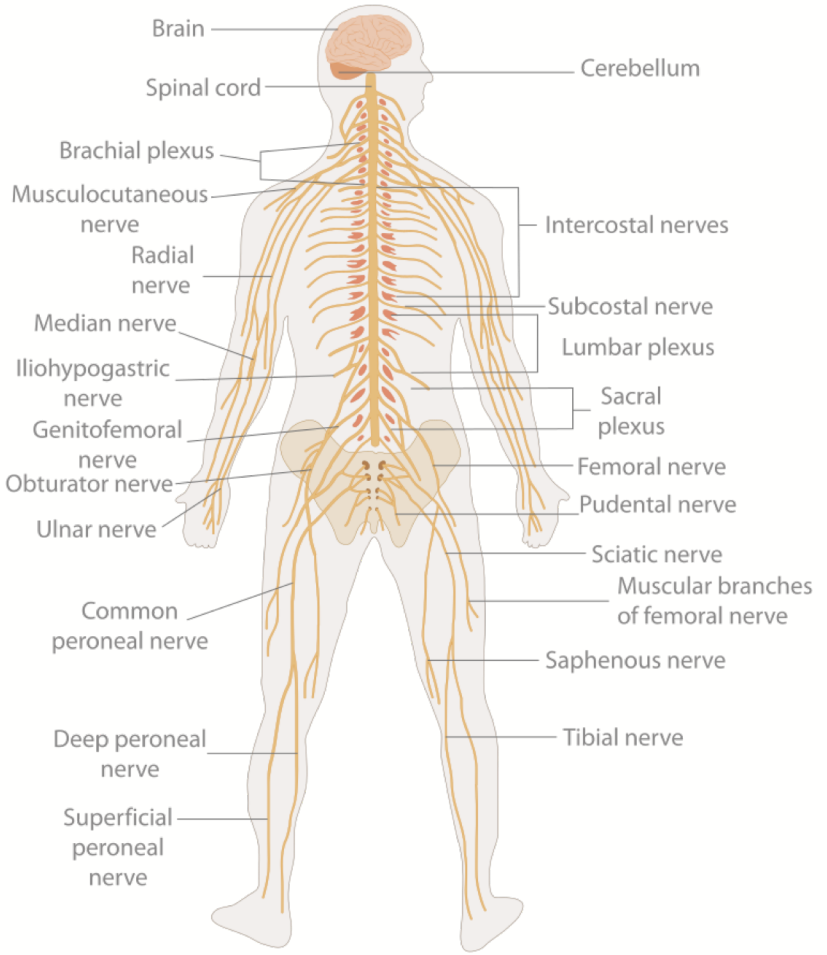
THE NEUROLOGICAL EXAMINATION

- **Mental status**
  - Watch infant or child interact with parent/caregiver
  - Ask older children to follow directions/answer questions
  - Assessing cognitive function
  - Levels of awareness
- **Motor examination**
  - Older children: push/pull against healthcare provider's hands
  - Muscle strength/tone (hypotonia/hypertonia)



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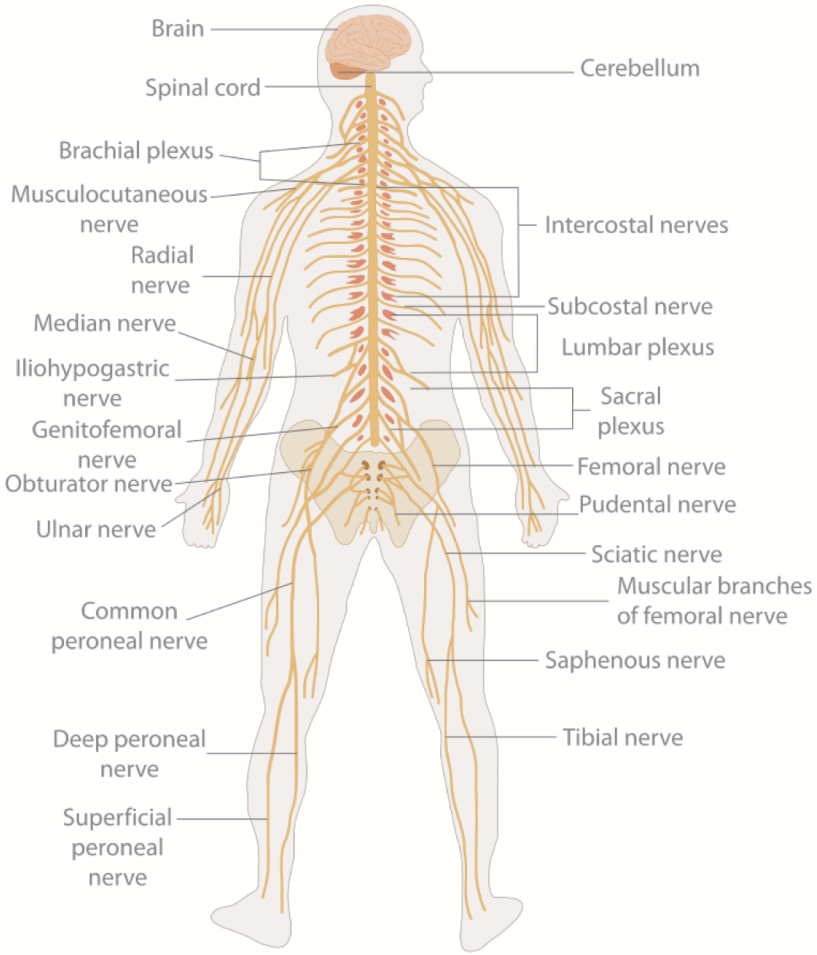
THE NEUROLOGICAL EXAMINATION

- **Newborn and infant reflexes (primitive)**
  - Blinking
  - Babinski (plantar reflex): abnormal >2y
  - Crawling
  - Moro's reflex (startle reflex): abnormal >6m
  - Tonic neck reflex
  - Palmar and plantar grasp

- **Muscle stretch reflexes (in older child)**
  - Formerly called deep tendon reflexes
  - Peripheral nerve impairment: reduced/absent (myopathy, neuropathy, motor neuron disease)
  - Spinal cord injured: exaggerated response (spasticity)



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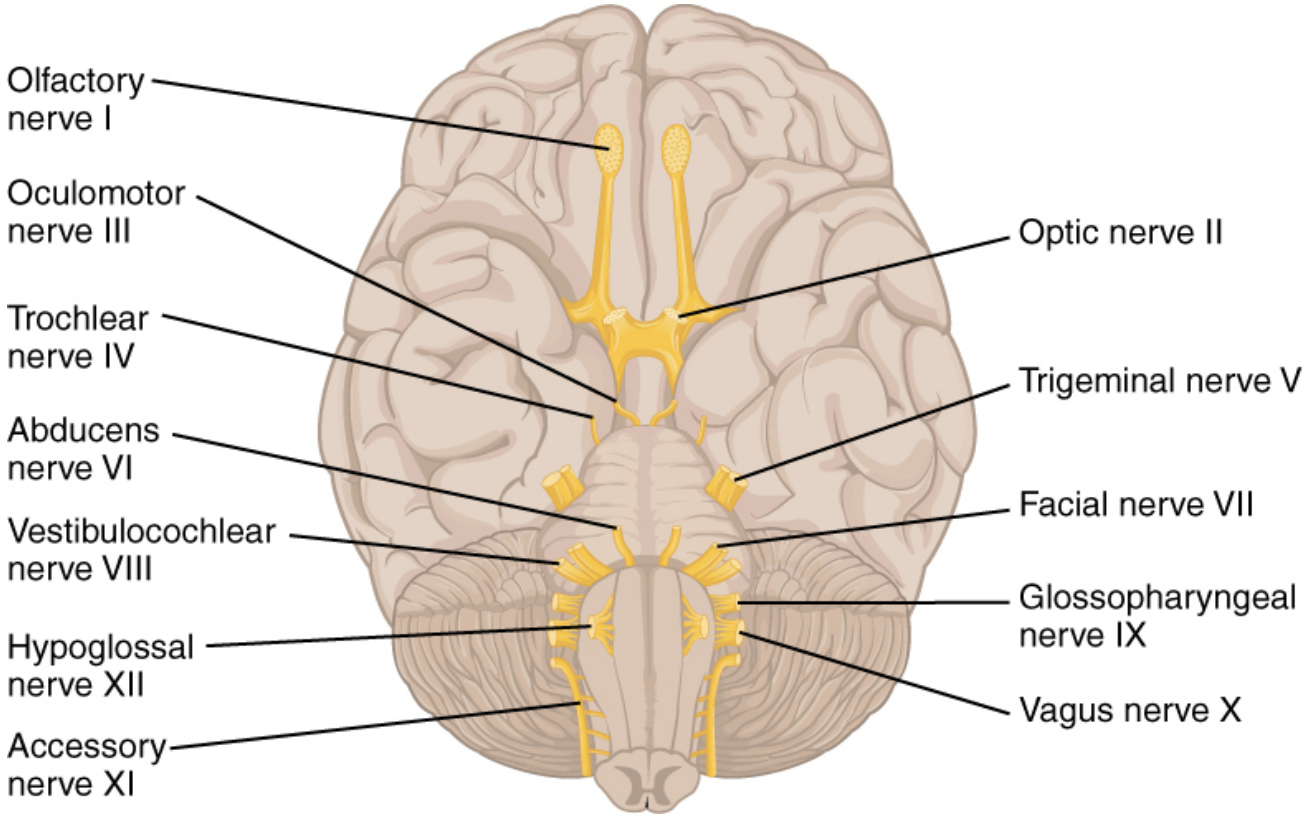
THE NEUROLOGICAL EXAMINATION

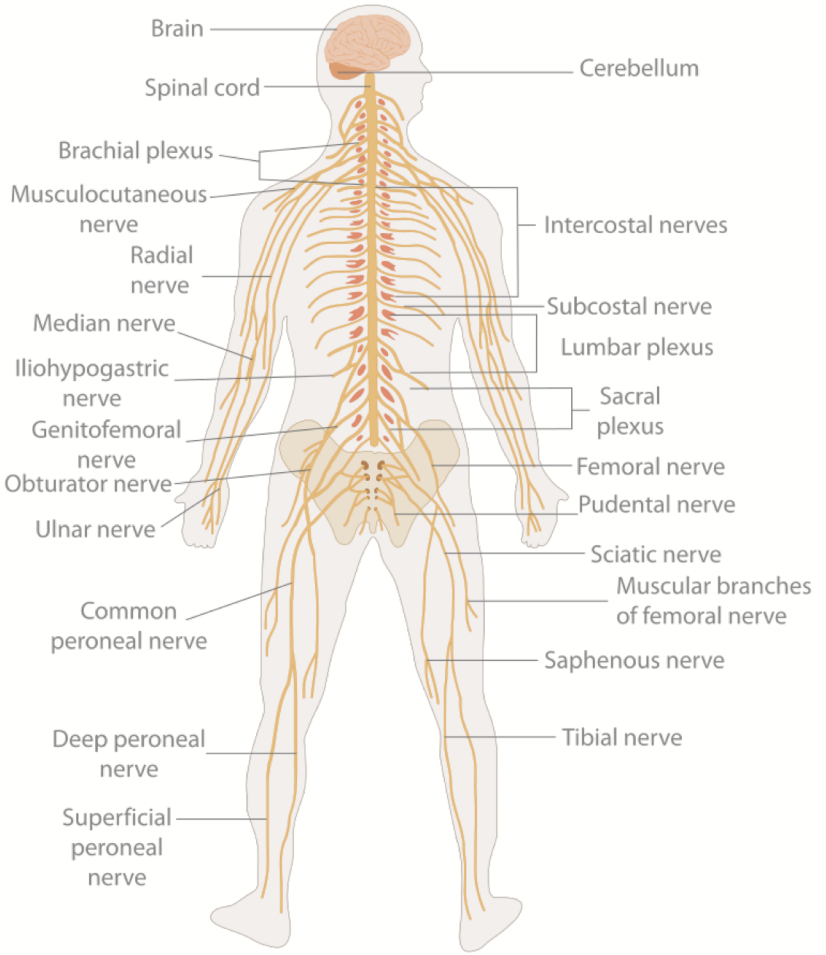
- **Evaluation of the cranial nerves**
  - Deficits/abnormalities based on function of cranial nerve



THE NEUROLOGICAL EXAMINATION

- **Coordination and gait**
  - Standing/walking (with eyes open or closed)
  - Problems with movement (ataxia)

- **Sensory examination**
  - Ability to feel, identify sensations (hot/cold, sharp/dull)
  - Sensory deficits (neuropathies)



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THE NEUROLOGICAL EXAMINATION

- **Mental status**: Patient cannot remember where she is due to dementia
- **Cranial nerves**: Patient has swallowing problems due to a neuromuscular disorder
- **Motor exam:** Patient has hemiplegia (half-sided weakness) after stroke
- **Reflexes:** Patient has spasticity with increased reflexes after brain injury at birth
- **Gait, coordination:** Patient has a ataxia due to a tumor in the cerebellum
- **Sensory exam:** Patient has loss of sensation in diabetic neuropathy

OVERVIEW

- Introduction to neurodevelopmental disorders
- Epilepsy as an example
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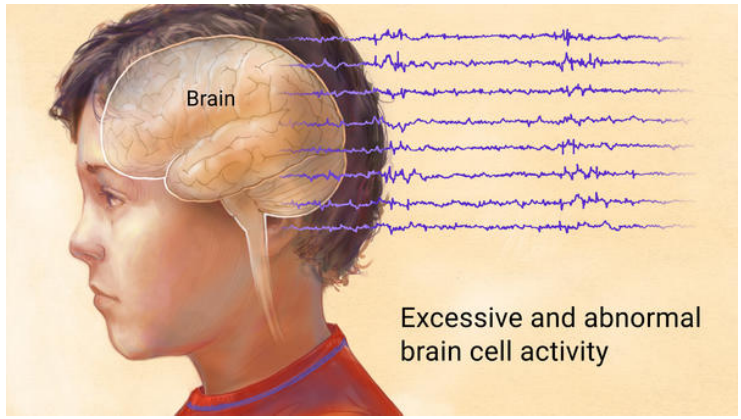
- Introduction to neurodevelopmental disorders
- **Epilepsy as an example**
- Tools for phenotyping

WHAT IS EPILEPSY?

- ≥2 unprovoked seizures; single seizure with predisposition for further seizures
- Abnormal, unregulated electrical discharges in brain
- Seizures can be controlled in ~80% of patients
  - Medications, surgery



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WHAT IS EPILEPSY?

- Affects 1:26 people in the United States
- 10% of people with have single unprovoked seizure
- Comorbidity with other neurodevelopmental disorders
  - 25% of people with intellectual disability have epilepsy
  - 20-25% of people with autism have epilepsy

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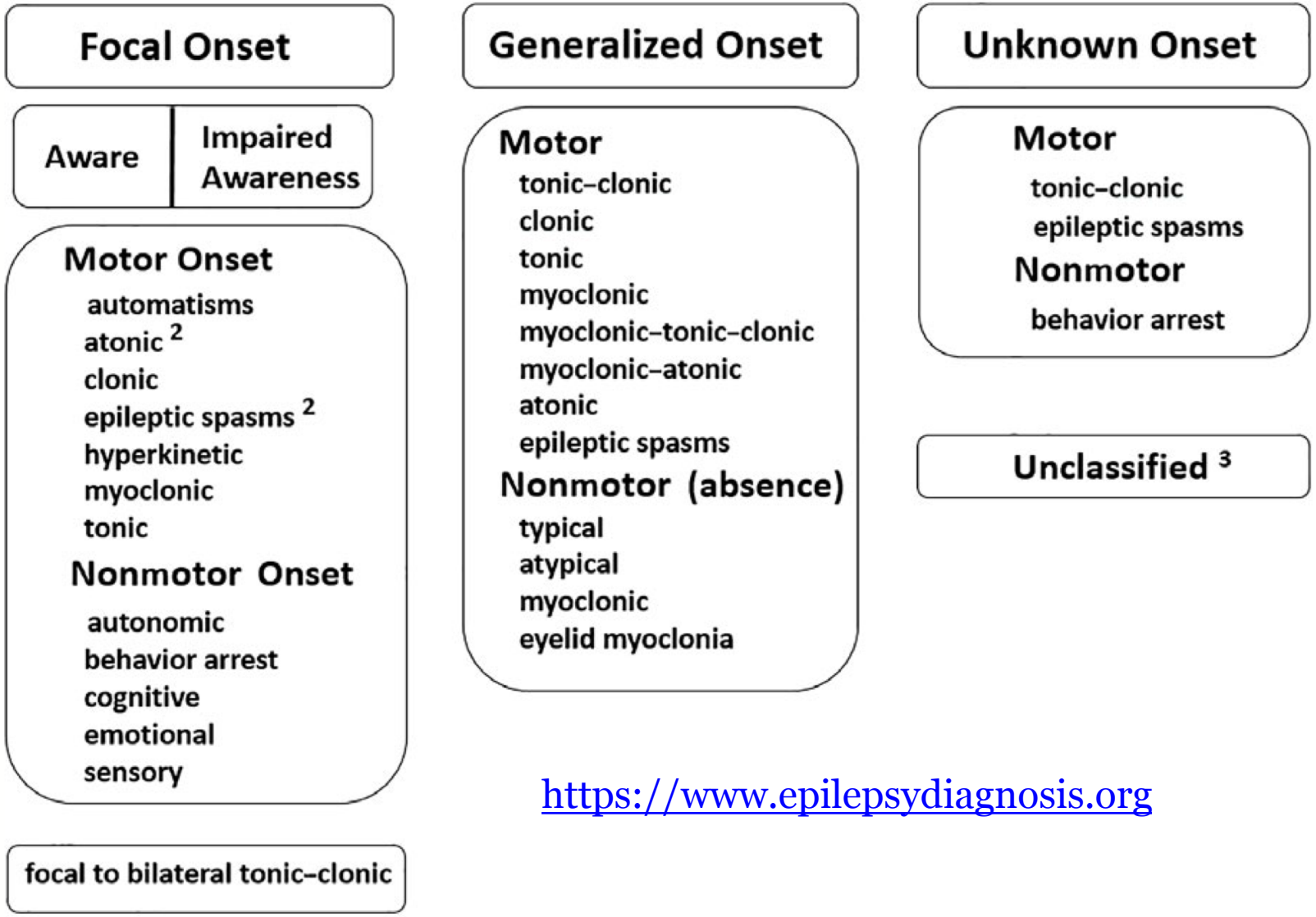
SEIZURE TYPES: ILAE CLASSIFICATION



https://www.epilepsydiagnosis.org

Fisher et al, *Epilepsia*, 58(4):522–530, 2017

SEIZURE TYPES VS. EPILEPSY SYNDROMES

- Epilepsy syndrome: group of features occurring together
  - Types of seizures commonly seen together
  - Age when seizures commonly begin
  - Part of the brain involved
  - EEG features
  - Usual course
  - Etiology
- Syndrome provides information about treatments/prognosis
- Syndrome takes into account information about underlying etiology

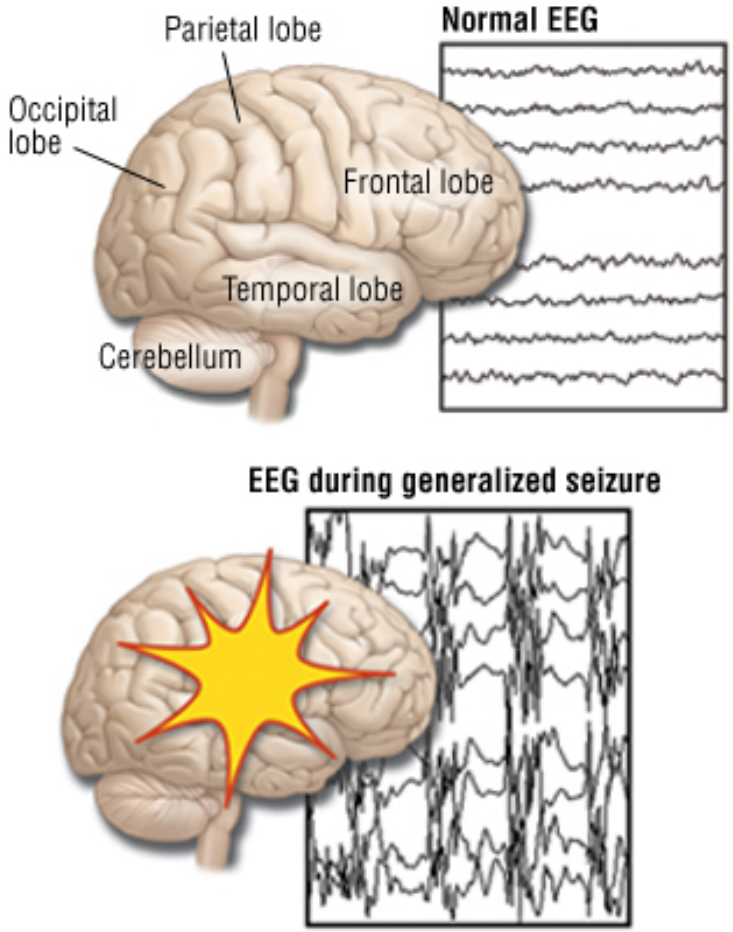
SEIZURE TYPES: GENERALIZED

Motor onset

- Convulsive (formerly grand mal)
  - Generalized tonic-clonic
  - Clonic
- Tonic
- Atonic
- Myoclonic
  - Myoclonic jerks
  - Myoclonic-atonic
  - Eyelid myoclonia ± absence

Non-Motor Onset

- Absence (formerly petit mal)
  - Atypical absence
  - Myoclonic absence



GENERALIZED TONIC-CLONIC SEIZURES

- Bilateral, symmetric generalized motor seizures
- Occur with loss of consciousness
- Tonic (bilateral increased tone, lasting seconds to minutes) and then a clonic (bilateral sustained rhythmic jerking) phase

SEIZURE VIDEOS

- Donated by patient to the ILAE, publicly available
- Special regulations for videos as videos can identify patients
- Take care and proper precautions when handling data from research participants

GENERALIZED TONIC-CLONIC SEIZURES

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TYPICAL ABSENCE SEIZURES

- Abrupt onset and offset of altered awareness, variable severity
- Onset often in childhood (primary school age)
- Memory for events during the seizures is usually impaired
- Clonic movements of eyelids, head, eyebrows, chin, perioral or other facial parts may occur
- Oral and manual automatisms are common
- Associated epilepsy syndromes:
  - Childhood absence epilepsy (CAE)
  - Juvenile myoclonic epilepsy (JME)
  - Juvenile absence epilepsy (JAE)
  - Genetic epilepsy with febrile seizure plus (GEFS+)
  - Dravet syndrome
  - Epilepsy with myoclonic-atonic seizures (Myoclonic-astatic epilepsy, Doose syndrome)
  - Epilepsy with myoclonic absences

TYPICAL ABSENCE SEIZURE

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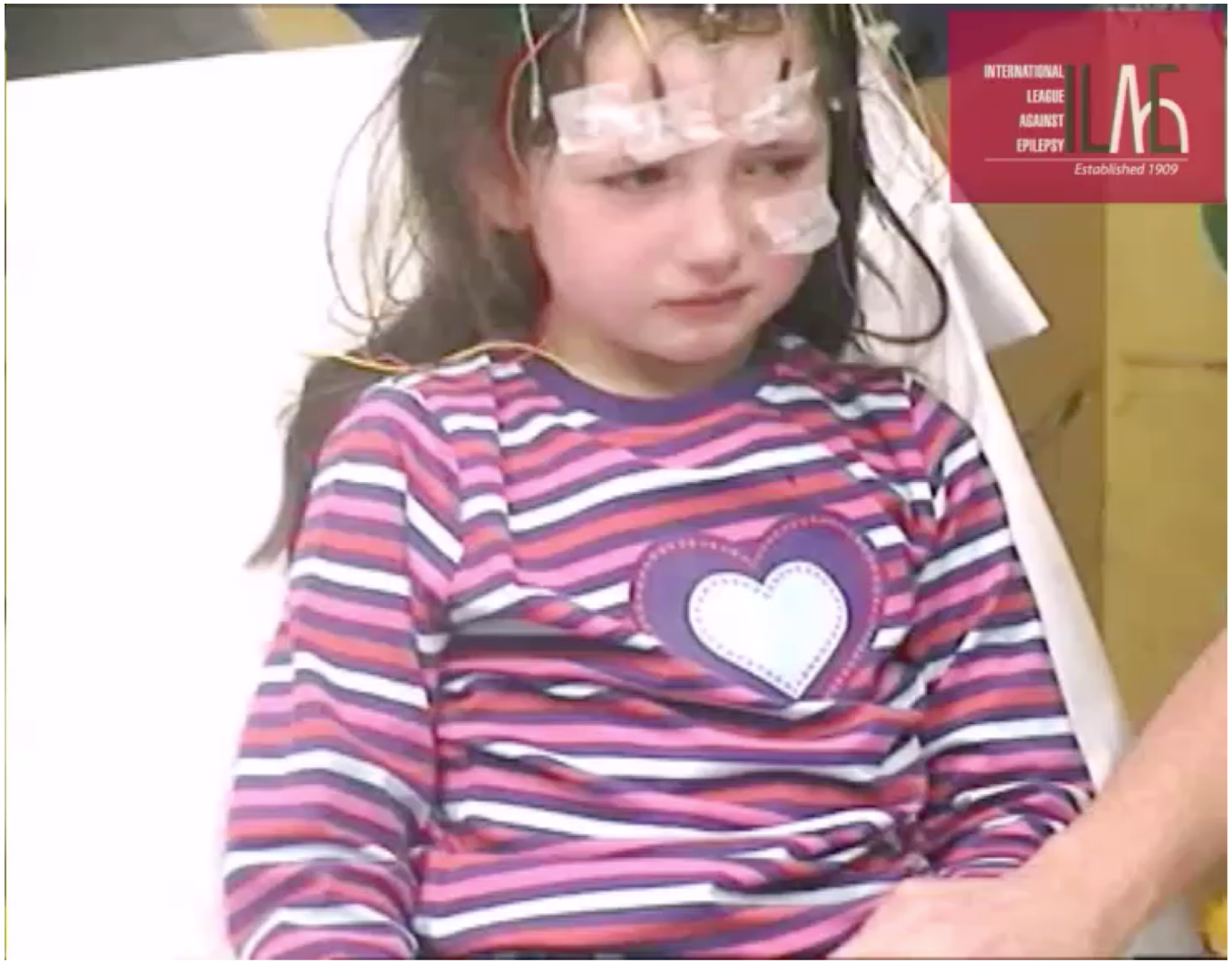
ATYPICAL ABSENCE SEIZURES

- Less abrupt onset/offset than typical absence seizures
- Often associated with loss of muscle tone of the head, trunk or limbs (e.g. gradual slump) and subtle myoclonic jerks
- Often occur in individuals with intellectual impairment
- Loss of awareness may be minimal
- Associated epilepsy syndromes:
  - Lennox-Gastaut syndrome
  - Dravet syndrome
  - Epilepsy with myoclonic-atonic seizures (Myoclonic-astatic epilepsy, Doose syndrome)
  - Epilepsy with myoclonic absences

ATYPICAL ABSENCE SEIZURE



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MYOCLONIC SEIZURES

- A single or series of jerks (brief muscle contractions)
- Each jerk is typically milliseconds in duration
- Myoclonic status epilepticus: ongoing (> 30 minutes) irregular jerking, often with partially retained awareness
- Associated epilepsy syndromes:
  - Juvenile myoclonic epilepsy
  - Progressive myoclonus epilepsies
  - Lennox-Gastaut syndrome
  - Dravet syndrome
  - Epilepsy with myoclonic-atonic seizures (Myoclonic-astatic epilepsy, Doose syndrome)

MYOCLONIC SEIZURE

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TONIC SEIZURES

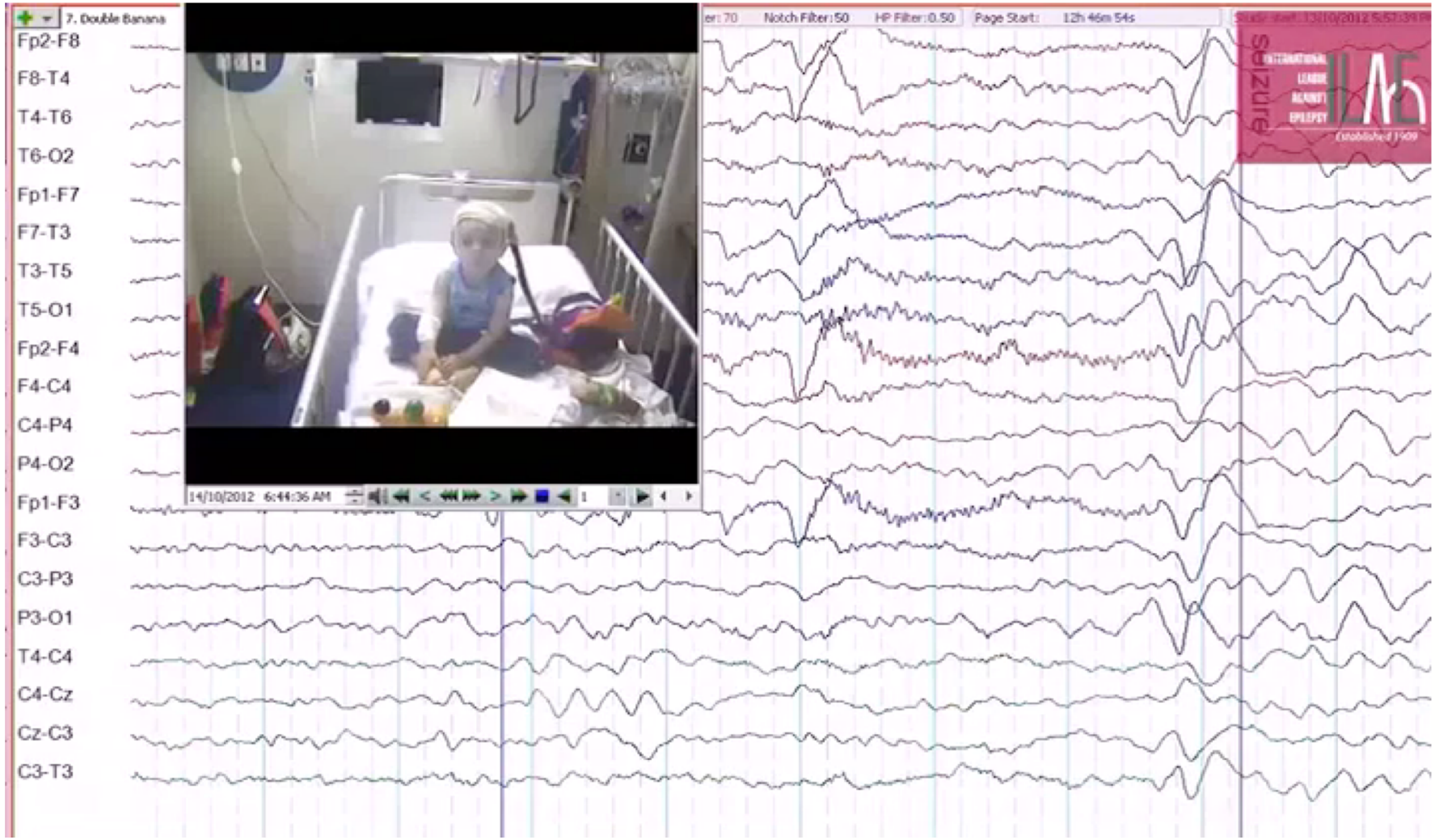
- Bilaterally increased tone of the limbs
- Typically lasts seconds to a minute
- Often occur out of sleep and in runs of varying intensity of tonic stiffening
- The individual is unaware during these events.
- Often occur in individuals with intellectual impairment
- May cause individual to fall to ground (“drop attack”)
- Associated epilepsy syndromes:
  - Lennox-Gastaut syndrome
  - Epilepsy with myoclonic-atonic seizures (Myoclonic-astatic epilepsy, Doose syndrome)

TONIC SEIZURE

ATONIC SEIZURES

- Sudden loss or diminution of muscle tone without apparent preceding myoclonic or tonic features
- Very brief (<2 seconds)
- May involve the head, trunk or limbs
- Often occur in individuals with intellectual impairment
- May cause individual to fall to ground (“drop attack”)
- Associated epilepsy syndromes:
  - Lennox-Gastaut syndrome
  - Epilepsy with myoclonic-atonic seizures (Myoclonic-astatic epilepsy, Doose syndrome)

ATONIC SEIZURE



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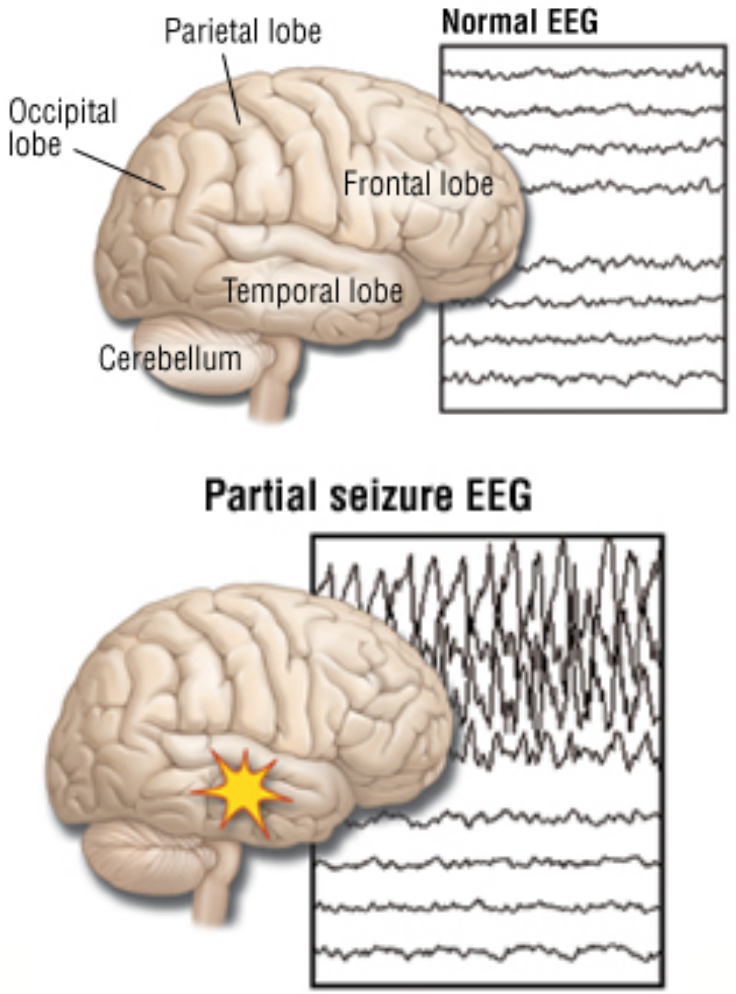
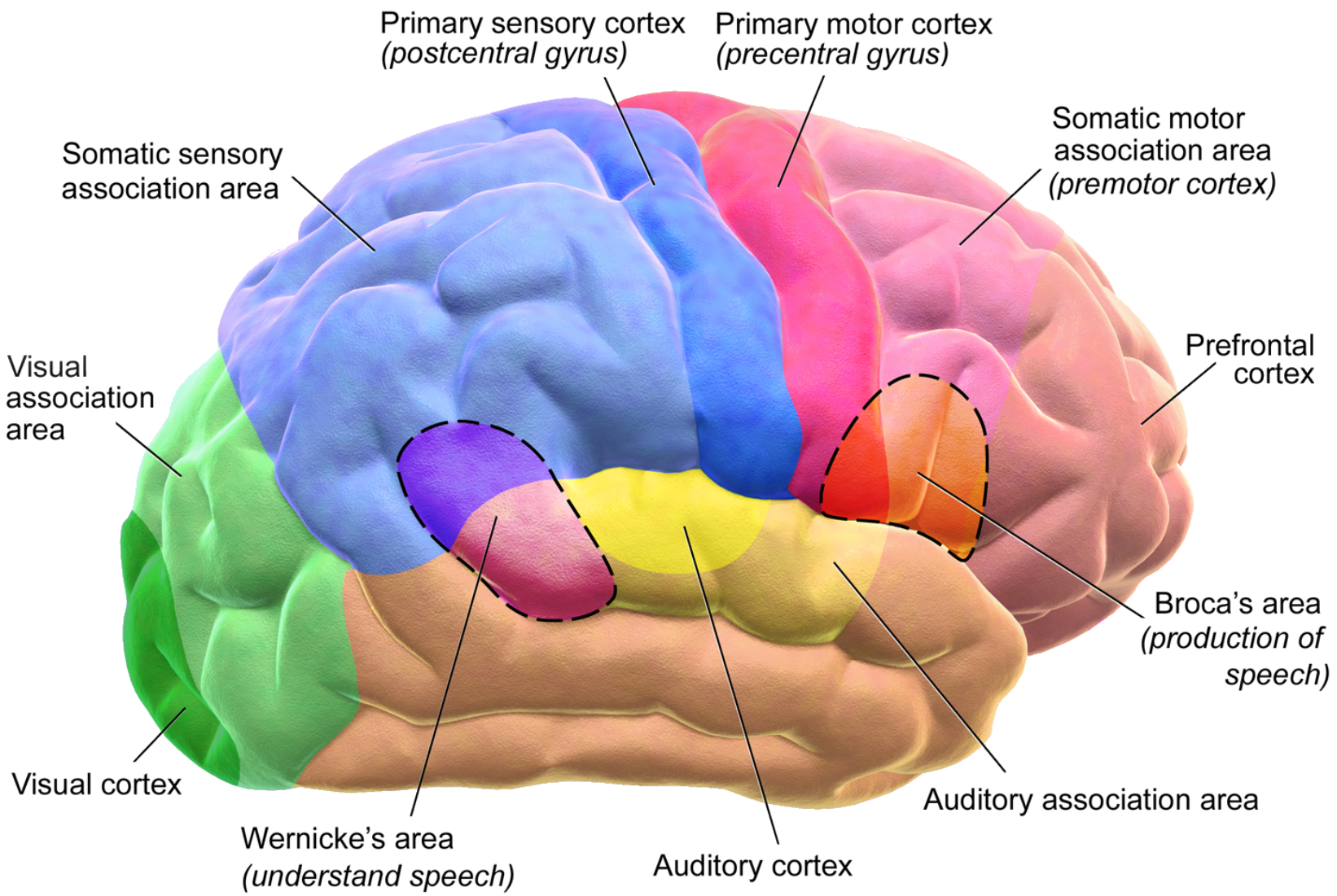
SEIZURE TYPES: FOCAL

- By features
  - Aware seizure
  - Autonomic
  - Cognitive
  - Sensory
  - Behavioral arrest
  - Motor
  - Impaired awareness

- By lobar localization
  - Frontal
  - Temporal
  - Parietal
  - Occipital



CEREBRAL CORTEX



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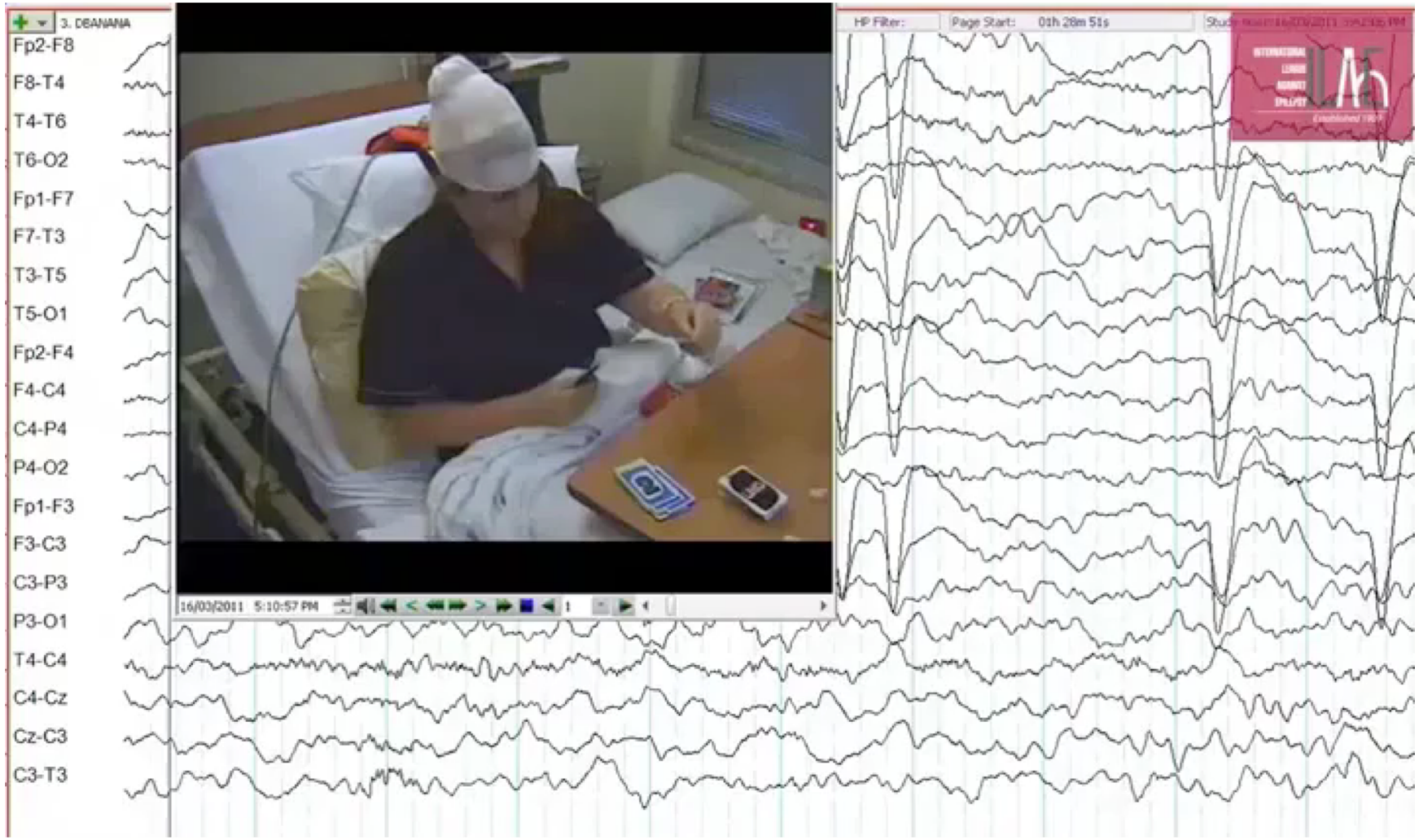
TYPES OF FOCAL SEIZURES

Name	Symptoms	Also Known As	Subtypes
Focal Aware	Full awareness retained May also be classified using other motor or non-motor onset features (e.g. focal aware sensory seizure, focal aware motor seizure)	Simple partial seizure	
Focal Autonomic	Alterations in systems controlled by the autonomic nervous system	Epileptic aura	Palpitations, epigastric sensation, hypo-/hyperventilation, etc.
Focal cognitive	Alteration in a cognitive function (a deficit or a positive phenomenon such as forced thought)	Epileptic aura	Déjà vu, jamais vu, aphasia, dyscalculia, forced thoughts, etc.
Focal emotional	Alterations in mood or emotion, or the appearance of altered emotion	Epileptic aura	Gelastic, dacrystic, fear, anxiety, anger, etc.

TYPES OF FOCAL SEIZURES

Name	Symptoms	Also Known As	Subtypes
Focal Sensory	Physical sensation being experienced at seizure onset	Epileptic aura	Somatosensory, visual, auditory, gustatory, olfactory, etc.
Focal Behavior Arrest	Decrease in amplitude and/or rate or arrest of ongoing motor activity		
Focal Motor	Involves motor activity; may be due to either an increase or decrease in contraction in a muscle or group of muscles	Some formerly called complex partial seizures	Hemiclonic, focal clonic, focal tonic, focal hyperkinetic, focal automatism, etc.
Focal Impaired Awareness	If awareness is impaired at any point during the seizure, the seizure is a focal impaired awareness seizure. The degree of loss of awareness may vary.	Complex partial seizure; focal dyscognitive seizure	

FOCAL IMPAIRED AWARENESS SEIZURE



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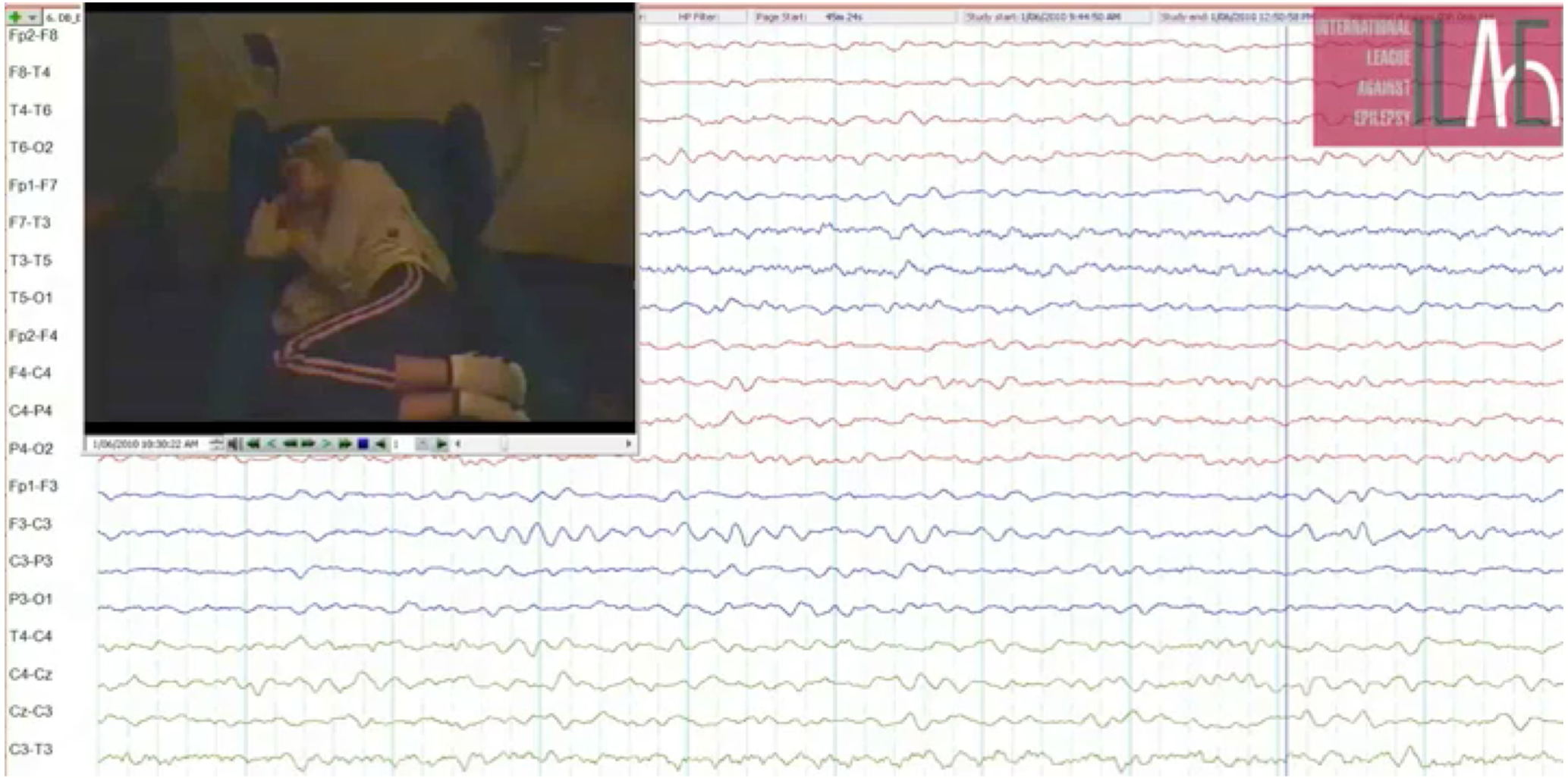
FOCAL MOTOR SEIZURE – FRONTAL LOBE



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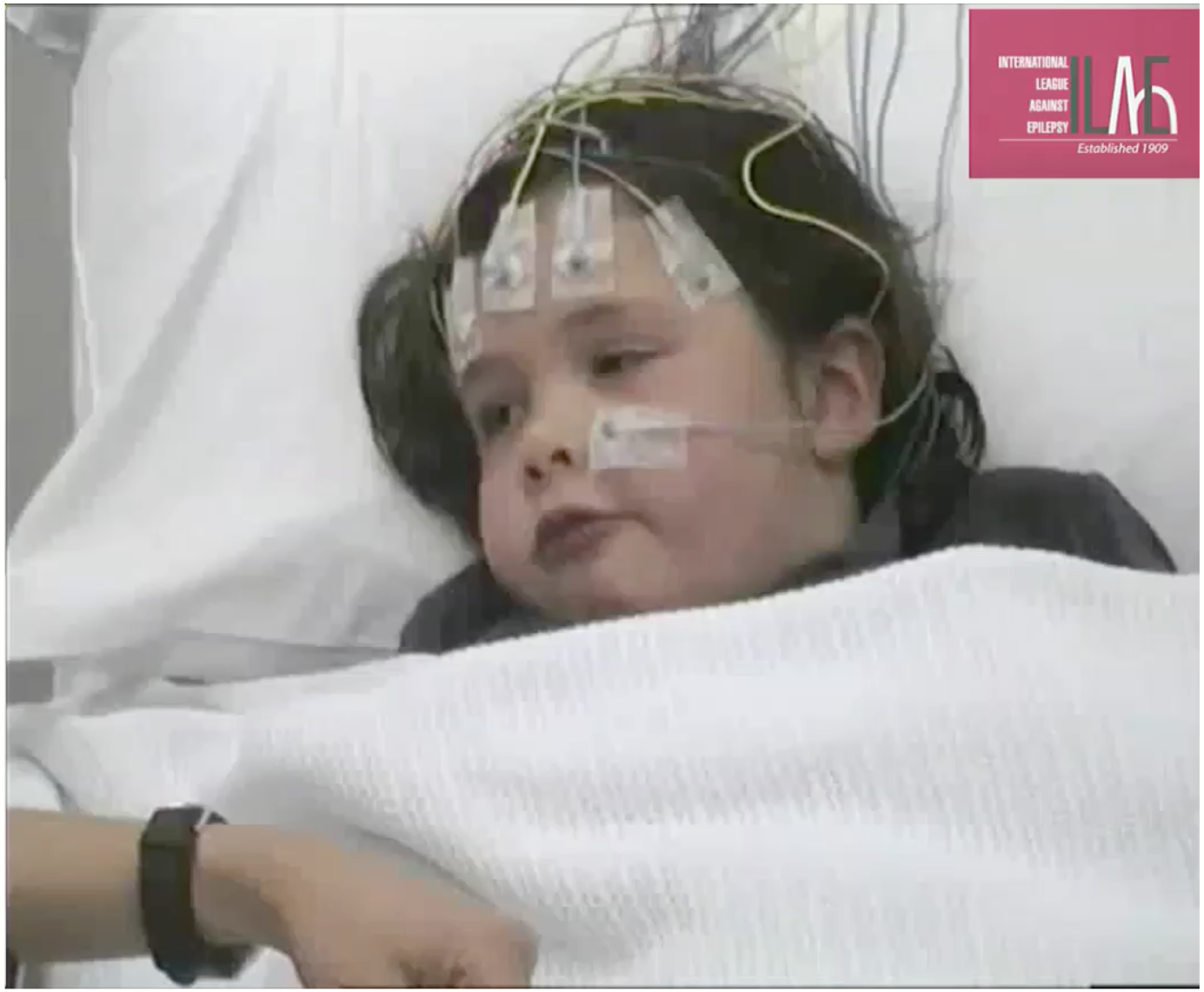
FOCAL AWARE SENSORY SEIZURE



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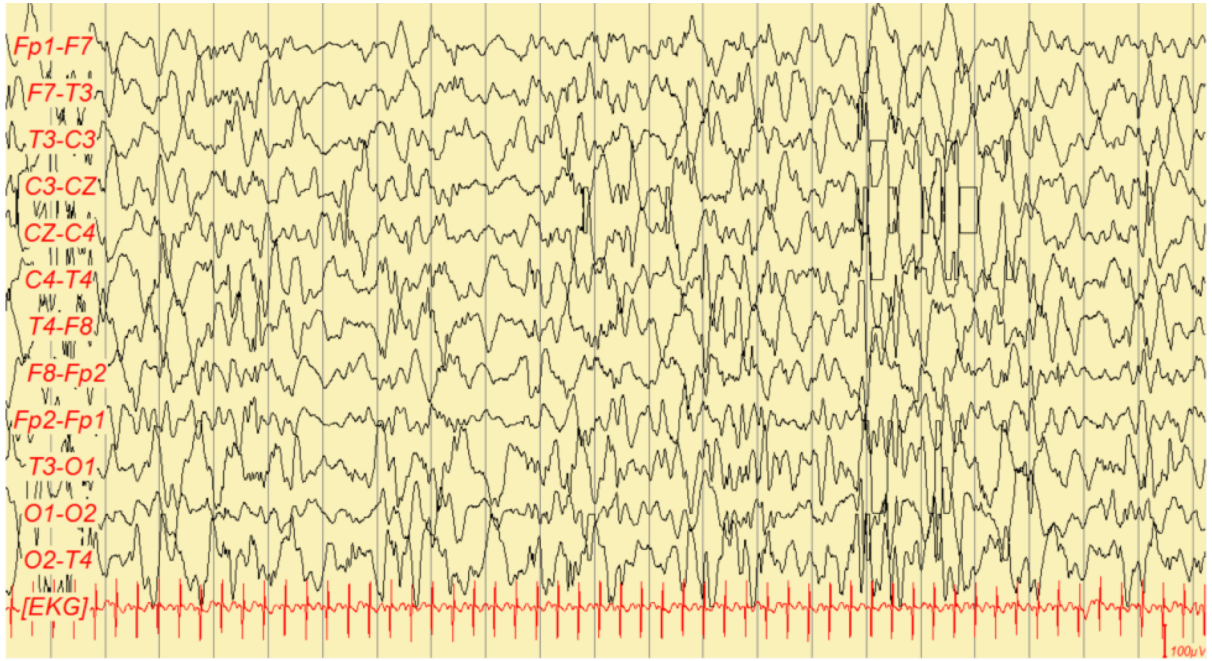
SEIZURE TYPES: EPILEPTIC SPASMS

- Formerly called infantile spasms
  - Average onset 4m (1m-2y)
  - 1:2500 children
  - May be very subtle
  - Clusters are common
  - Often associated with hypsarrhythmia on EEG (West Syndrome)
- Slight bobbing of head
- Flexor spasms
- Extensor spasms
- Related epilepsy syndromes:
  - West syndrome
  - Early myoclonic encephalopathy
  - Ohtahara syndrome
  - Lennox-Gastaut syndrome



EPILEPTIC SPASMS

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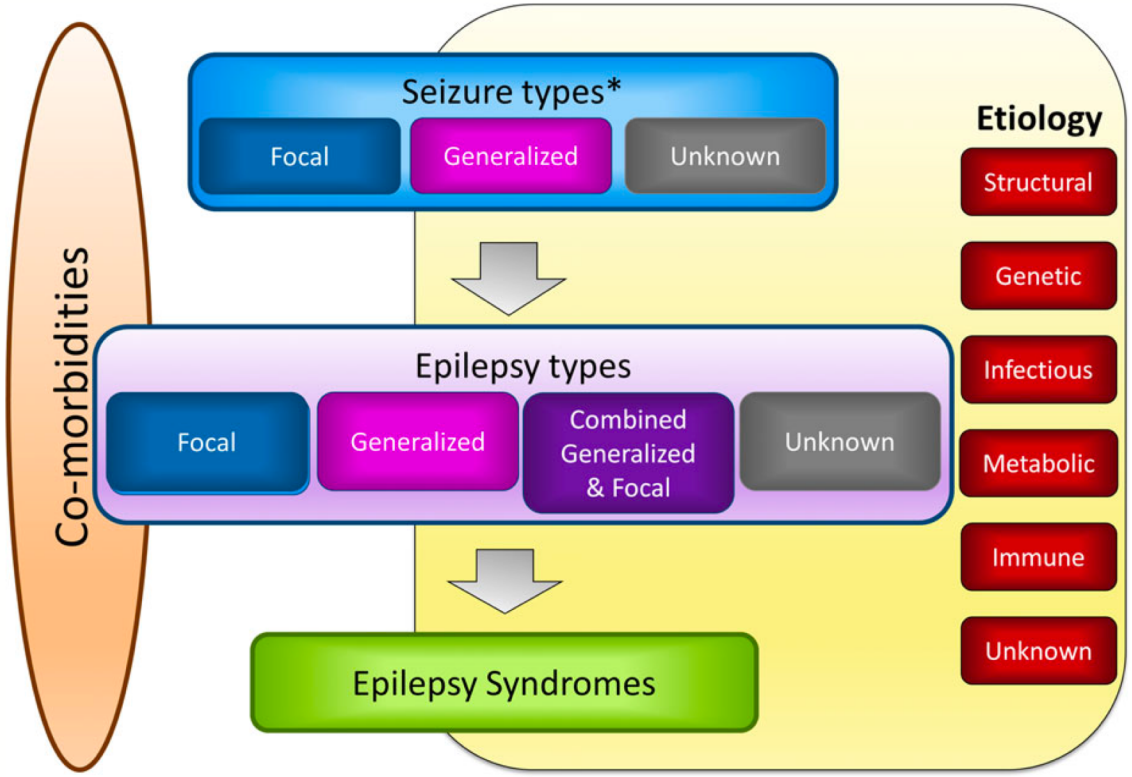
CLASSIFICATION OF EPILEPSY SYNDROMES

- International League Against Epilepsy (ILAE) – Updated 2017
- https://www.epilepsydiagnosis.org



Scheffer et al. *Epilepsia*, 58(4):512–521, 2017

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INTRODUCTION TO EPILEPSY SYNDROMES

- **Idiopathic/Genetic Generalized Epilepsies**
  - Childhood Absence Epilepsy
  - Juvenile Absence Epilepsy
  - Juvenile Myoclonic Epilepsy
  - Epilepsy with Generalized Tonic-Clonic Seizures Alone
- **Familial (Focal) Epilepsy Syndromes**
  - Autosomal dominant epilepsy with auditory features
  - Familial Focal Epilepsy with Variable Foci
  - Familial Temporal Lobe Epilepsy
  - Genetic Epilepsy with Febrile Seizures Plus (GEFS+)
- **Developmental and Epileptic Encephalopathies**
- **Self-Limited Neonatal/Infantile Epilepsies**
- Other epilepsies
  - Progressive Myoclonus Epilepsies
  - Pharmacoresponsive Childhood Focal Epilepsies

DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHIES

0-3 months	• **Ohtahara syndrome** (***STXBP1, KCNQ2, SCN2A***) ▪ Neonatal onset, tonic seizures, burst suppression on EEG • **Epilepsy of Infancy with Migrating Focal Seizures** (***KCNT1, SCN2A, TBC1D24***) ▪ Refractory focal seizures, migrate from one region to another

DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHIES

0-3 months	• **Ohtahara syndrome** (***STXBP1, KCNQ2, SCN2A***) ▪ Neonatal onset, tonic seizures, burst suppression on EEG • **Epilepsy of Infancy with Migrating Focal Seizures** (***KCNT1, SCN2A, TBC1D24***) ▪ Refractory focal seizures, migrate from one region to another
4 months – 2 years	• **West syndrome** (***CDKL5, STXBP1, ARX, DNM1)*** ▪ Epileptic spasms with hypsarrhythmia on EEG, developmental delay/regression • **Dravet syndrome** (***SCN1A***) ▪ Prolonged febrile/afebrile sz, focal (hemiclonic), regression

DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHIES

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2-10 years	• **Landau-Kleffner syndrome** (***GRIN2A***) ▪ Acquired aphasia, previously normal devt, +/- seizures ▪ Continuous spikes and waves during sleep (CSWS)

COMMON COMORBIDITIES

- Developmental impairment
- Autism spectrum disorders
- Hyperkinetic movement disorders
  - **Dystonia**: Sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both
  - **Choreoathetosis**
    - **Chorea**: ongoing random-appearing sequence of one or more discrete involuntary movements or movement fragments
    - **Athetosis**: a slow, continuous, involuntary writhing movement
  - **Stereotypies**: Repetitive, simple movements that can be voluntarily suppressed
  - **Tremor:** Rhythmic back-and-forth or oscillating involuntary movement about a joint axis

DIAGNOSTIC TOOLS: EEG

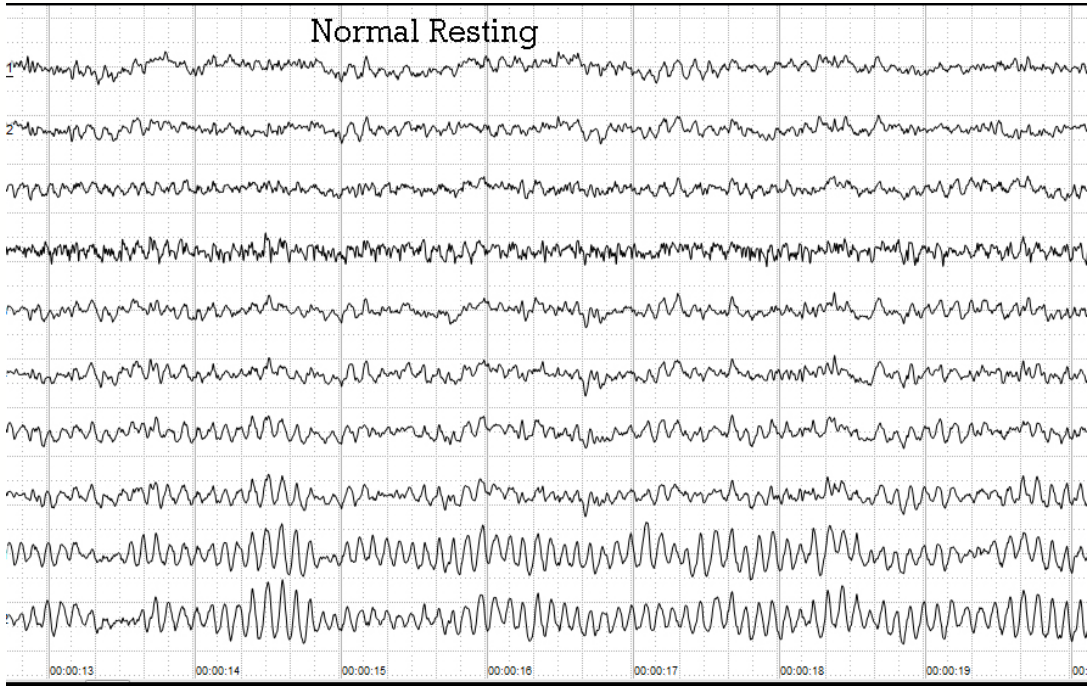
- Measures electrical brain activity via scalp electrodes
- Purpose: to diagnose and/or monitor epilepsy
- Types of EEGs:
  - Routine EEG
  - Prolonged EEG
  - Ambulatory EEG
  - EEG-video monitoring
  - Long-term monitoring
- A normal EEG does not exclude a diagnosis of epilepsy

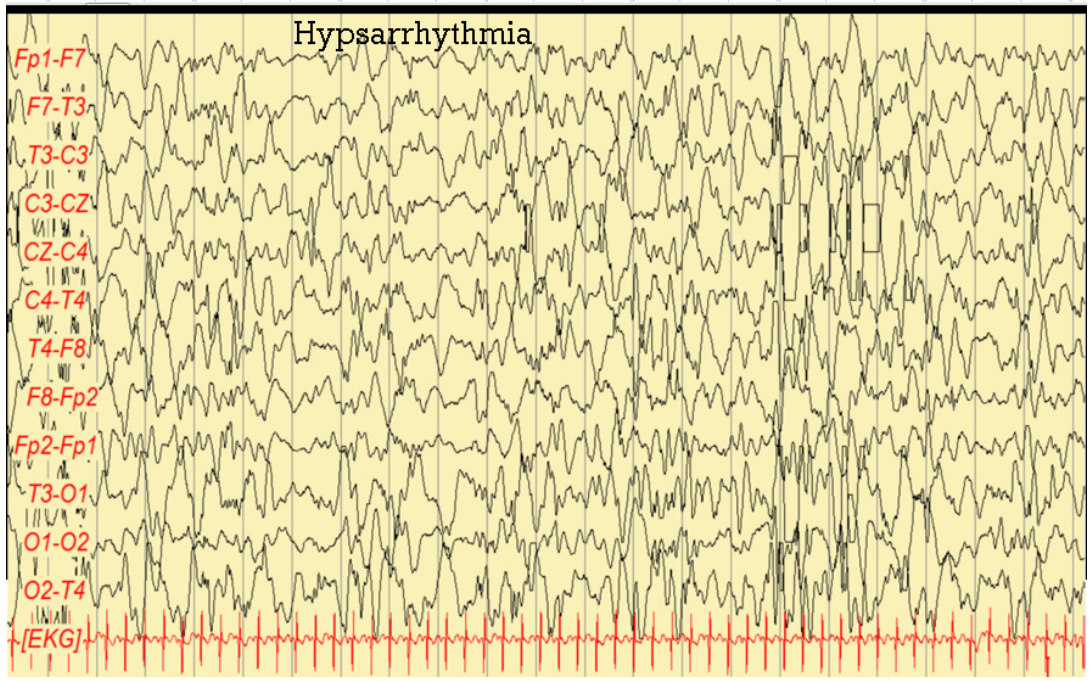
DIAGNOSTIC TOOLS: EEG

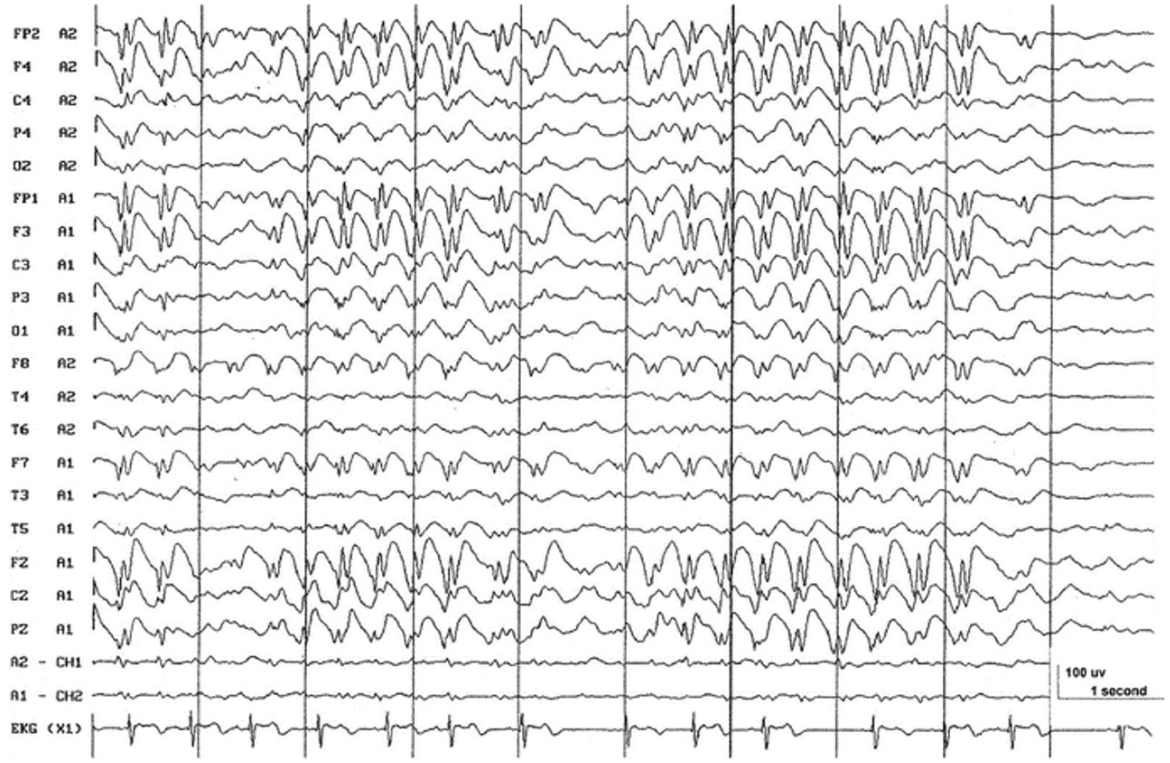
- **Routine EEG**
  - 20-30 minutes
  - Usually without video
  - Standard activation procedures: hyperventilation, sleep deprivation, intermittent photic stimulation
- **Prolonged EEG**
  - 1-2 hours, with or without video
- **Ambulatory EEG**
  - Done in outpatient setting or at home over 1-3 days
- **EEG-video monitoring**
  - Inpatient and prolonged
  - Done over several days
- **Long-term monitoring**
  - Refers only to length of testing
  - Does not necessarily include video

EEG: WHAT ARE WE LOOKING FOR?

- **Background**
  - Slow background typically associated with underlying encephalopathy
  - Not epileptiform in and of itself
- **Epileptiform discharges**
  - Focal discharges coming from specific seizure focus
  - Generalized discharges, as well as speed (e.g. slow vs. fast spike-wave)
  - Infants: hypsarrhythmia, multifocal epileptiform discharges
- **Response to activation procedures**
  - Hyperventilation often activates absence seizures with generalized spike-wave
  - Intermittent photic stimulation: epileptiform discharges, photosensitivity
- **Events of interest captured on video**
  - Is there an epileptiform EEG correlate? (i.e. Are events of interest seizures?)







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DIAGNOSTIC TOOLS: MRI

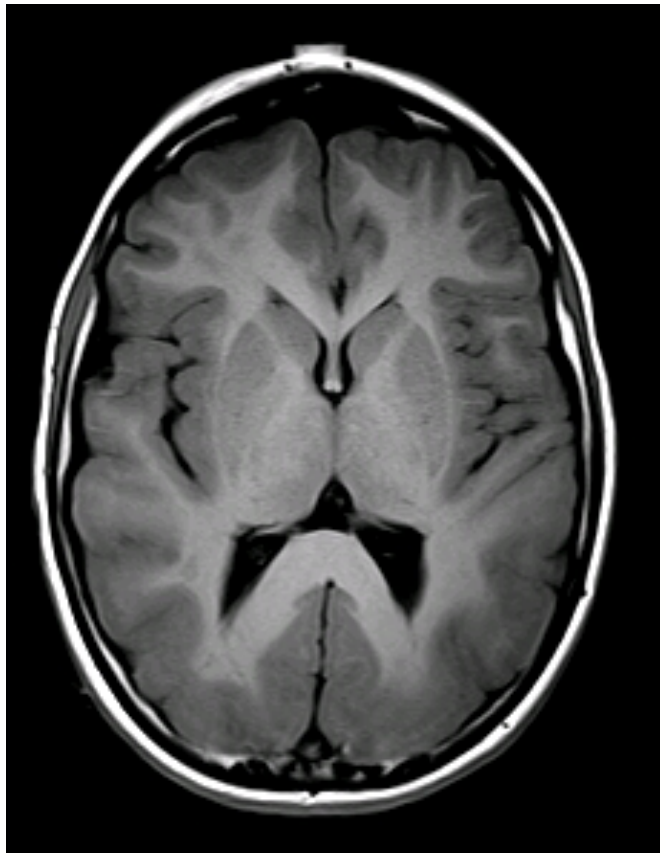
- Identifies structural changes in the brain that may cause seizures
- Produces accurate picture of brain's structure
- Generates computer images using magnetic field and pulses of radio waves
- Different strengths of MRI (Tesla)
  - e.g. 1.5T and 3T
  - Higher number providers higher resolution image
- Infants, younger children, individuals with developmental disabilities typically require sedation or general anesthesia

BRAIN MRI VS. HEAD CT

- Complementary techniques
- Head CT:
  - Faster and cheaper than MRI
  - Allows detection of calcification
  - Can be performed in patients with implantable medical devices
- Brain MRI:
  - Does not use ionizing radiation (better for children)
  - More detailed images of soft tissue, higher sensitivity to detect specific abnormalities in brain structure
  - Allows evaluation of structures that may be obscured by artifacts from bone in CT

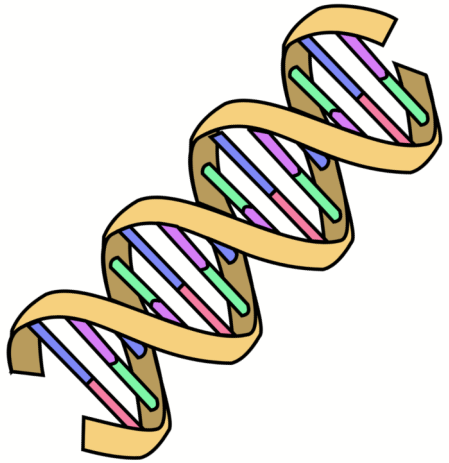
MRI: WHAT ARE WE LOOKING FOR?

- **Malformations of cortical development**
  - Disorders of neuronal migration during embryonic brain development
  - Some examples: cortical dysplasia, polymicrogyria, lissencephaly, etc.
- **Evidence of brain injury**
  - Hypoxic ischemia secondary to perinatal stroke
  - Other brain injuries due to infection, inflammation, trauma
  - Results in gliosis (atrophy and increased free water in tissues)
- **White matter abnormalities**
  - Abnormalities of corpus callosum
  - Abnormalities in myelination
- **Tumors (benign and malignant)**
- **Vascular malformations**
- **Mesial temporal sclerosis**
  - Hardening and atrophy of hippocampus
  - Often associated with temporal lobe epilepsy



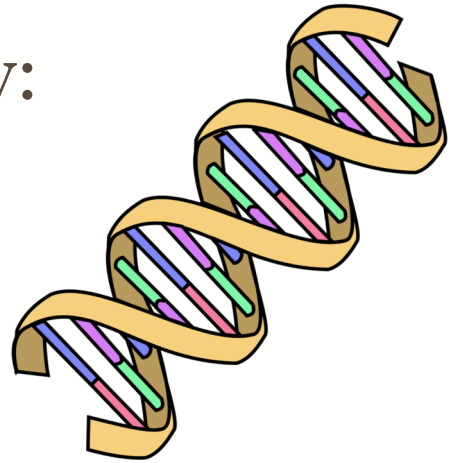
DIAGNOSTIC TOOLS: GENETIC TESTING

- Indicated for all children with developmental delay and/or autism
- **Chromosomal analysis**
  - Karyotype: number and appearance of chromosomes
  - Chromosomal microarray (SNP array or array CGH): higher resolution, copy number variants
- **Next generation sequencing (NGS) assays**
  - Panel-based tests
  - Whole exome sequencing
  - Whole genome sequencing
- **Single gene testing**



GENETIC TESTING: WHAT ARE WE LOOKING FOR?

- Underlying genetic etiology for individual's neurodevelopmental disorder
- >40% of children with early-life epilepsies have genetic cause (Berg et al. 2017)
- Be discriminating when attributing genetic etiology:
  - Look for words **likely pathogenic** or **pathogenic**
  - Evaluate in appropriate clinical context



OVERVIEW

- Introduction to neurodevelopmental disorders
- Epilepsy as an example
- Tools for phenotyping

OVERVIEW

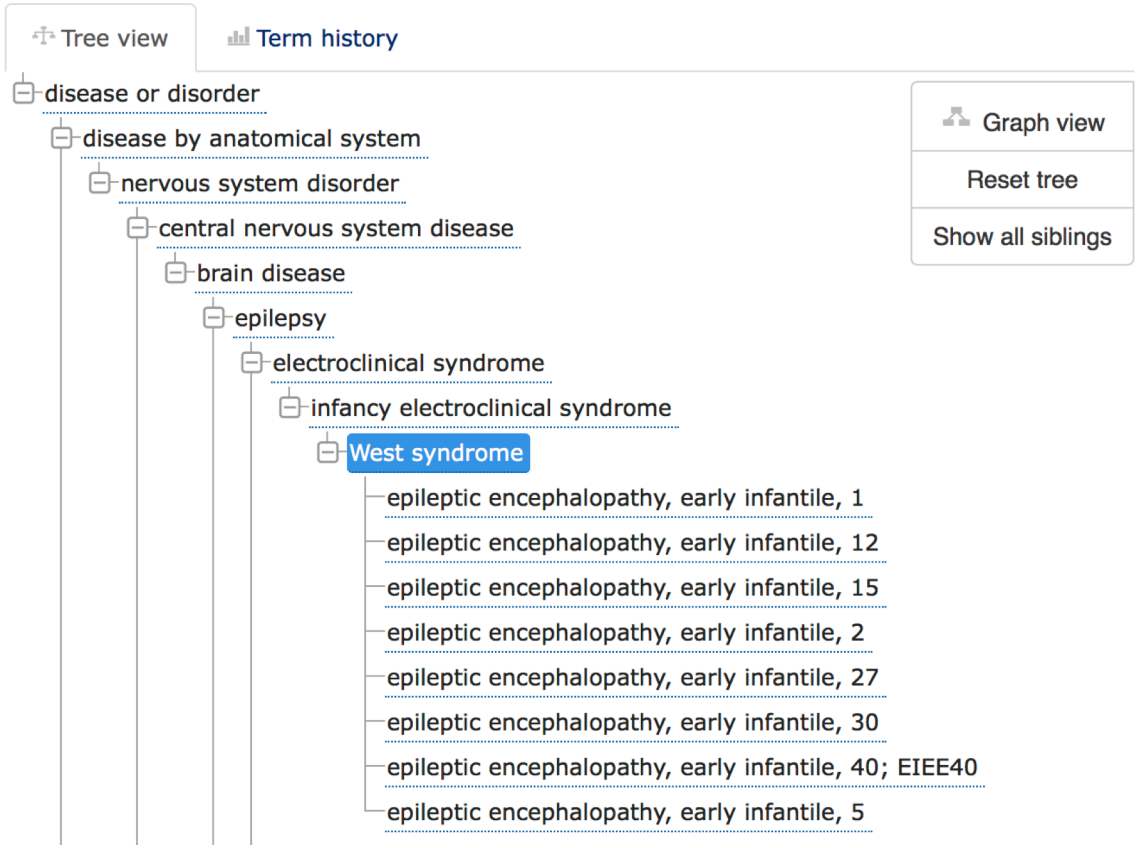
- Introduction to neurodevelopmental disorders
- Epilepsy as an example
- **Tools for phenotyping**

CLASSIFICATION ONTOLOGIES

- **Human phenotype ontology (HPO)**
  - Phenotypes rather than syndromes or diseases
  - Disease features (“What you can see or measure”, symptoms)
  - http://compbio.charite.de/hpoweb/#
- **Monarch Disease Ontology (MONDO)**
  - Ontology of human diseases (“Disease entities”, syndromes)
  - Does not take into account phenotypic features
  - https://www.ebi.ac.uk/ols/ontologies/mondo

CLASSIFICATION ONTOLOGIES

MONDO: West syndrome



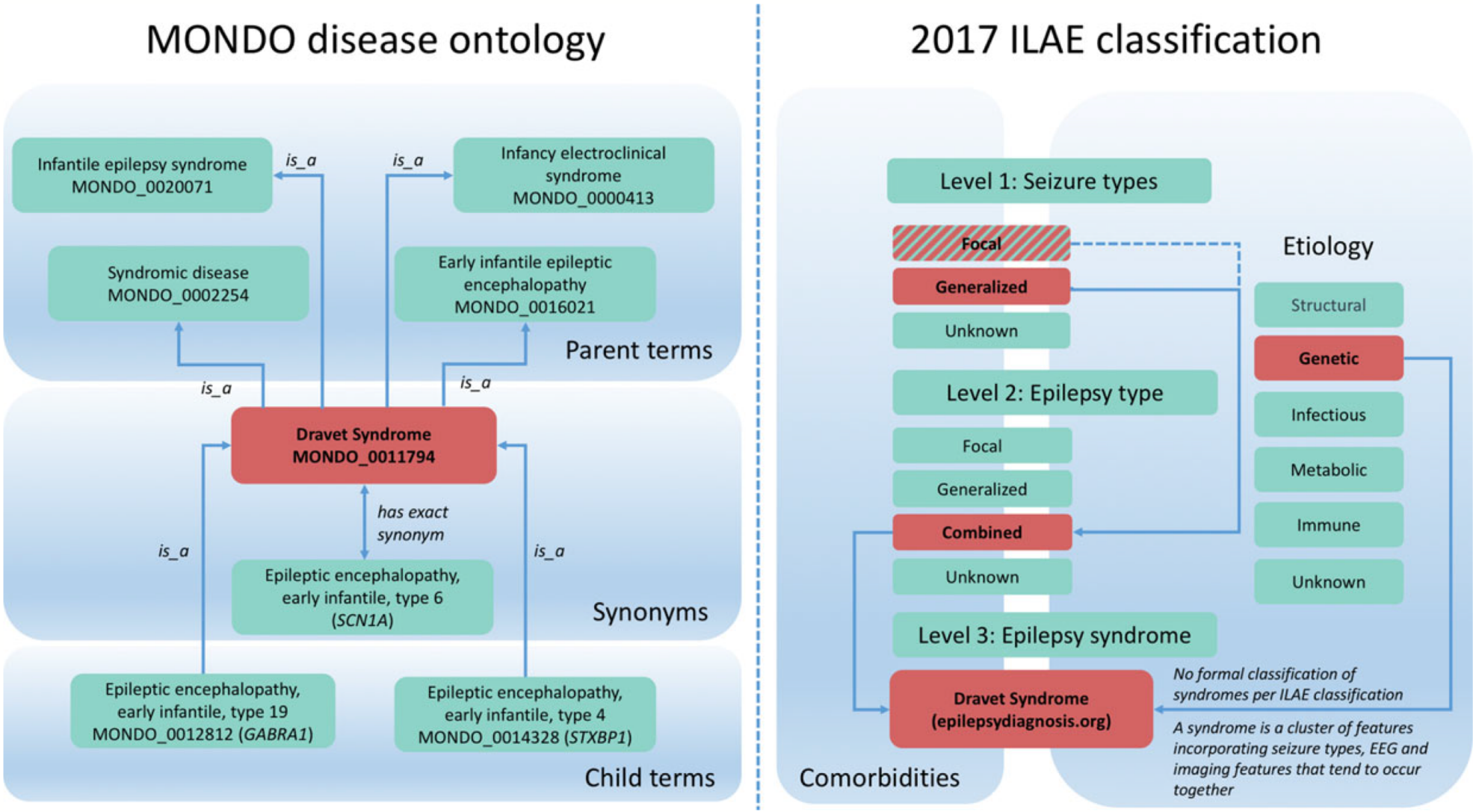
HPO:

HP:0011097: Epileptic spasms
HP:0001263: Global developmental delay
HP:0002521: Hypsarrhythmia

CLASSIFICATION ONTOLOGIES

- Different user groups have different needs/goals
- Large scale genomic studies/diagnostic genomic sequencing lab
  - HPO terminology
  - Useful in identifying undiagnosed patients with similar features
- Clinical Genome Resource (ClinGen)
  - MONDO terms used to curate validity of disease-gene relationships
- Neurologists and clinicians
  - Making diagnoses in individual patients
  - ILAE classification
  - ICD-10 (WHO, billing)

MONDO VS. ILAE



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DATA ENTRY FORMS

- Designed for needs of specific study

- Example: **Epi25 Collaborative**
  - Collaborative of >200 partners, >40 research cohorts
  - >14,000 exomes sequenced so far
  - Goal: identify genetic factors in human epilepsy
  - Phenotyping is crucial

Birth details and antecedents	
Gestational Age	
Head circumference at birth	
Birth weight	
Head trauma with skull fracture, intracranial bleeding	
CNS infection	
Neonatal seizures	
Normal neonatal period (other than seizures)	
Neonatal period comments	Expand

Other features	
Head size	
Tone	
Dysmorphic	
Movement disorder	
Other abnormalities	
Previous genetic analysis	
Conventional karyotype	
Copy number analysis	
Gene panel performed	
Individual gene testing	
Metabolic testing	

Seizure Types

	Yes	No	Unknown	
Febrile seizures Seizure of any type (or unknown type) provoked by a documented fever of >38?/100.4?	○	○	○	reset
Infantile/epileptic spasms See ILAE Definition	○	○	○	reset
Tonic See ILAE definition	○	○	○	reset
Atonic See ILAE definition	○	○	○	reset
Myoclonic See ILAE definition	○	○	○	reset
Absence See ILAE definition	○	○	○	reset
Atypical Absence See ILAE definition	○	○	○	reset
Generalized Tonic-Clonic See ILAE definition	○	○	○	reset

Age in months at first occurrence	
Age at first seizure (excluding classical febrile seizures	View equation Minumum of all seizure onsets (computed)
Age in months of onset correction	Overrides the age of onset in case type of seizure at onset is not known
Neurological examination	
Neurological examination	
Investigations	
EEG finding 1 * must provide value	
Neuroimaging	
Neuroimaging performed * must provide value	CT MRI Not done CT and MRI Unknown reset
Neuroimaging findings * must provide value	
Neuroimaging findings comments	Expand

Comorbidities

	Yes	No	Unknown	
Developmental delay prior to seizure onset	○	○	○	reset
Regression/plateau	○	○	○	reset
Intellectual Disability	○	○	○	reset
Autism spectrum disorder	○	○	○	reset
Psychosis	○	○	○	reset
Drug resistant Failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom (see Kwan, P. et al, Epilepsia 2010)	○	○	○	reset

Family History

Reported family history of consanguinity	
Family History	Family history of any seizures (including febrile) regardless of reported aetiology. Family history refers to any biological relative of the proband, including their offspring.

A FINAL NOTE…

WORDS MATTER

- Clinical research is a partnership of equal stakeholders
  - Researchers
  - Clinicians/healthcare providers
  - Participants and their family members
- Use “people first” language when talking with, to, and about research participants
- Use proper and respectful terminology

WORDS MATTER

✗ Do not say…	✓ Please use…
Mental retardation, mental handicap	Intellectual disability
Mentally retarded	Person with an intellectual disability
Epileptic, epilepsy patient	Person with epilepsy
Autistic	Person (diagnosed) with autism
The disabled	People with disabilities
Wheelchair-bound, confined to a wheelchair	Person who uses a wheelchair
Normal	Non-disabled, person without a disability
Suffers from/afflicted by (e.g. epilepsy)	Has epilepsy

WHY IS THIS IMPORTANT?

- Using person first language reminds you that you are working with people who have dignity, feelings, and rights.

- Our research participants are not a disability, disorder, or phenotype.
  - Puts the person before the disability

- It may require more words, but ultimately respect for our research participants is worth it.