Casual Friday Presents

Seizures and Related Activity

FM Strategies: Physiology, Pathology, Interventions.

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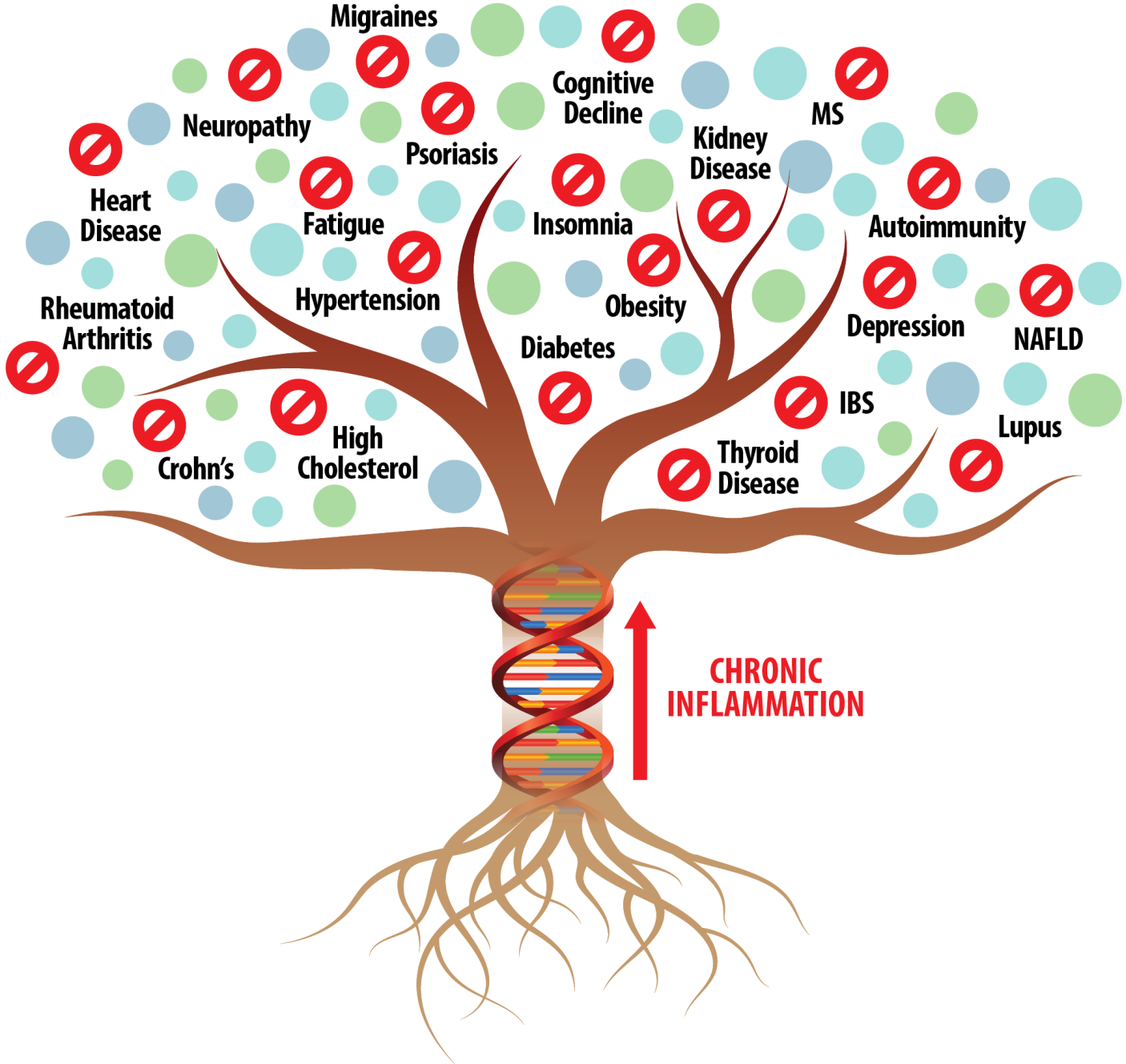
Migraines
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Cognitive Decline
MS
Kidney Disease
Heart Disease
Fatigue
Insomnia
Autoimmunity
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Obesity
Depression
NAFLD
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Diabetes
IBS
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High Cholesterol
Thyroid Disease
CHRONIC INFLAMMATION

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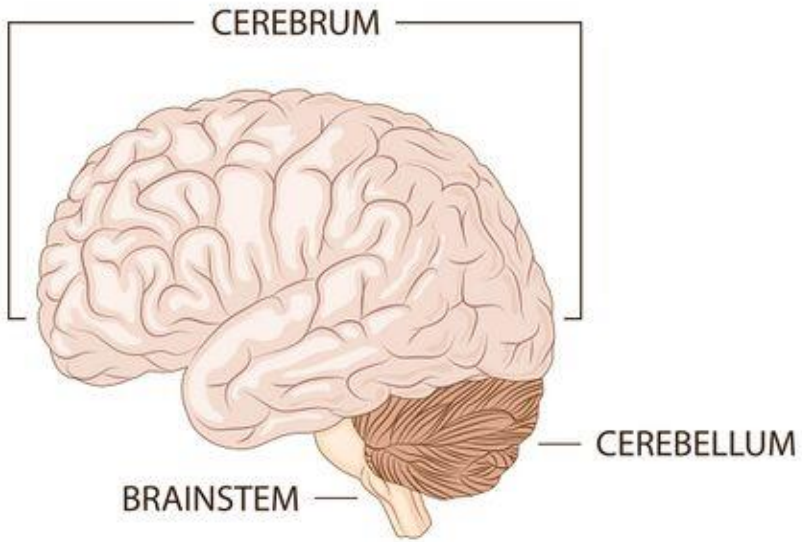
A seizure represents the uncontrolled, abnormal electrical activity of the brain that may cause changes in the level of consciousness, behavior, memory, or feelings. Convulsive concussion, convulsive syncope, movement disorders, rigors, sleep-related events, or psychogenic non-epileptic spells are all in the differential diagnosis of an event. Seizures can classify as partial or generalized. In a partial seizure, the most common seizure type in adults, one area of the cortex activates first and may manifest through simple symptoms such as a motor or sensory phenomena. Generalized seizures result from diffuse cortical activation at seizure onset or generalization of partial seizure activity.



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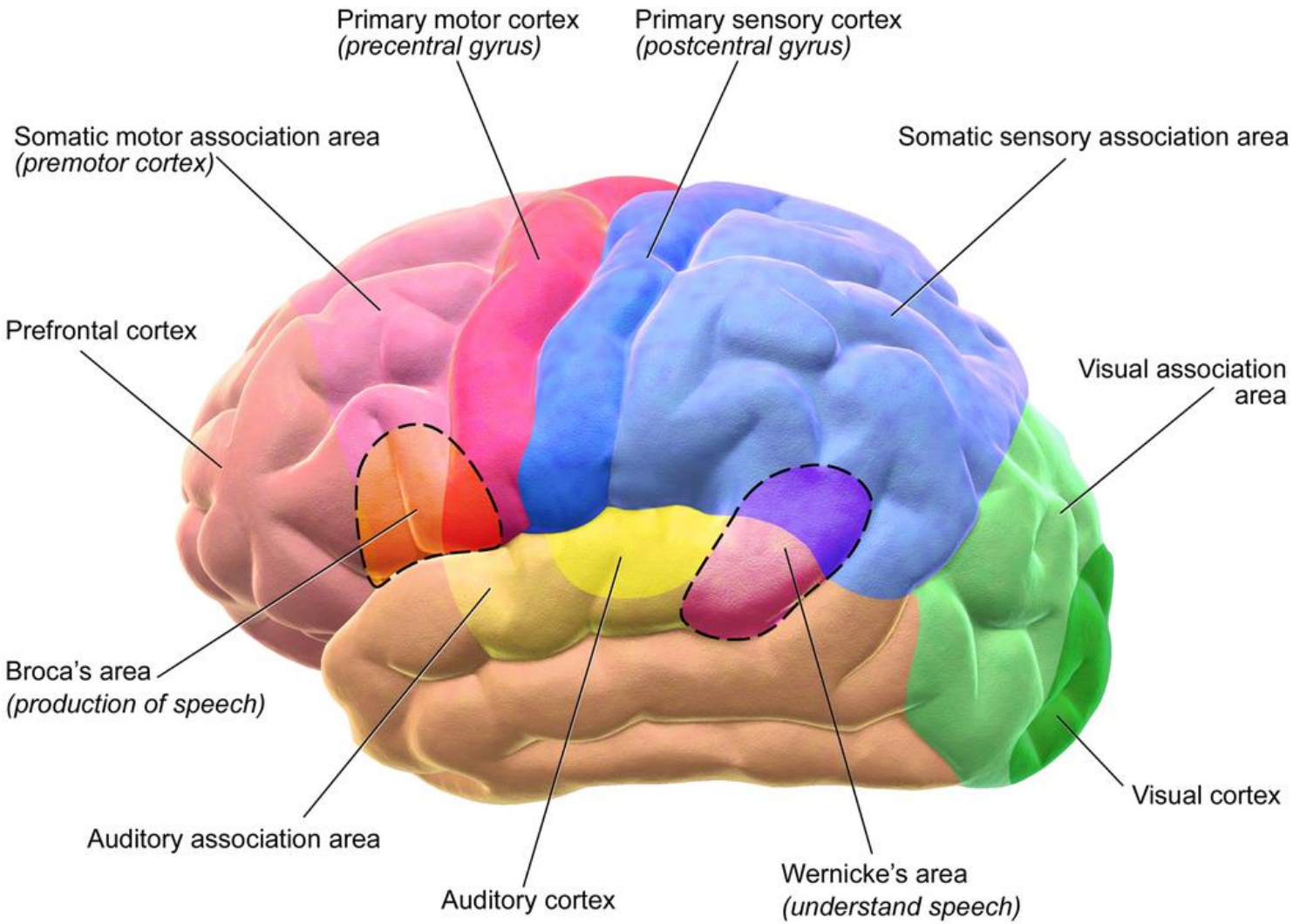
Motor and Sensory Regions of the Cerebral Cortex



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Paroxysmal spells may originate from the central nervous system, cardiac disturbances, psychiatric causes, or other etiologies. Syncope, convulsive concussion, convulsive syncope, rigors, movement disorders, sleep-related events, and psychogenic nonepileptic seizures are all in the differential diagnosis of a transient event with movements. Epileptic seizures constitute a type of paroxysmal event.[1]

An epileptic seizure is a transient occurrence with signs or symptoms due to abnormal, excessive, and synchronous neuronal activity in the brain. There are many different types of seizures. The current classification designates 2 large categories: partial or generalized. In a partial seizure, an area of the cortex is thought to be initially activated and may manifest simple symptoms, such as motor or sensory phenomena. Partial seizures may rapidly secondarily generalize and spread to involve all cortical areas. Generalized seizures result from diffuse cortical activation at seizure onset. See **Image.** Seizure From Cortical Changes and Porencephalic Cyst. The most common seizure type in adults is partial-onset seizures with rapid secondary generalization.[2]

Seizures with dyscognitive features, also known as complex partial seizures, are associated with altered awareness or consciousness. These may have minimal motor manifestations, such as lip-smacking or small-amplitude extremity movements, and may present as an isolated confusional state.

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Epilepsy, by definition, is a condition of recurrent unprovoked seizures. Determining whether a first seizure or recurrent seizures are provoked or unprovoked is fundamentally essential for diagnosis and treatment.

Epileptic syndromes serve to condense clinical information into useful nomenclature. Localization-related is used in this context to denote seizures arising from pathology in a localizable brain area. Idiopathic epilepsy is associated with no symptoms other than seizures. In symptomatic epilepsy, seizures reflect an underlying identifiable brain disease. Cryptogenic refers to seizure disorders suspected to be symptomatic of underlying brain disease, but without definitive proof of the underlying cause. Specialists usually diagnose an epileptic syndrome.[3]

Status epilepticus is defined as an enduring epileptic condition. There are as many types of status epilepticus as there are types of seizures. Generalized convulsive status epilepticus is a medical emergency. Current definitions define status epilepticus as a single generalized convulsion lasting greater than 5 minutes or a series of generalized seizures without full return of consciousness.[4]

Epilepsy occurs because of a predisposition to seizures from genetic susceptibility or a chronic pathologic process. By definition, unprovoked seizures occur in the absence of provocative causes or more than 7 days after an acute injury or insult such as stroke or brain hemorrhage. Recurrent unprovoked seizures define epilepsy.

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Seizures may be either provoked or unprovoked. Provoked seizures, also known as acute symptomatic seizures, may result from electrolyte disorders, toxins, head injury, infectious processes, vascular anomalies, tumors or other mass lesions, and many other causes. A listing of provoked causes of seizures is lengthy and could include complications of almost any disease process. Some common causes are listed below:

- Electrolyte disturbances (hypoglycemia, hyponatremia, hypernatremia, hypocalcemia, others)
- Acute toxic effects (antidepressants, sympathomimetics, others)
- Withdrawal syndromes (ethanol, benzodiazepines, others)
- Irregularity with prescribed antiepileptic medications
- Sepsis
- CNS infections
- Hypoxic brain injury
- Traumatic brain injury
- Stroke, ischemic or hemorrhagic
- Neoplasm
- Inflammatory (lupus cerebritis, anti-NMDA receptor encephalitis, others)
- Fever
- Sleep deprivation

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Pathophysiology

Everyone has some propensity to have seizures. The concept of a seizure threshold means that each individual exists on a seizure-susceptibility continuum, with multiple factors influencing susceptibility. Medications, genetic factors, electrolyte abnormalities, sleep state, infections, brain inflammation, or injury from many causes may lead to an individual crossing that threshold with a resulting seizure.

At the cellular level, seizures begin with the excitation of susceptible cerebral neurons, which leads to synchronous discharges of progressively larger groups of interconnected neurons. Neurotransmitters are undoubtedly involved. Glutamate is the most common excitatory neurotransmitter, and gamma-aminobutyric acid (GABA) is an important inhibitory neurotransmitter. An imbalance between excessive excitation and reduced inhibition initiates abnormal electrical activity. These electrical paroxysmal depolarization shifts (PDS) seem to trigger epileptiform activity. Increased activation or decreased inhibition of such discharges could result in seizures. The brain region affected often manifests as clinical signs or symptoms of the seizure.[3]

Generalized convulsive status epilepticus is accompanied by systemic changes of lactic acidosis, increased catecholamine levels, hyperthermia, respiratory compromise, and other systemic alterations.[8][9][10] However, the ongoing excessive electrical activity that occurs with status epilepticus is damaging to the brain.[11] There is an evolution of generalized convulsive status epilepticus from continuous or discrete seizures to a condition of minimal or no motor activity. The electrical activity reflected by the electroencephalography evolves as well.[12] The result may be a type of nonconvulsive generalized status epilepticus.

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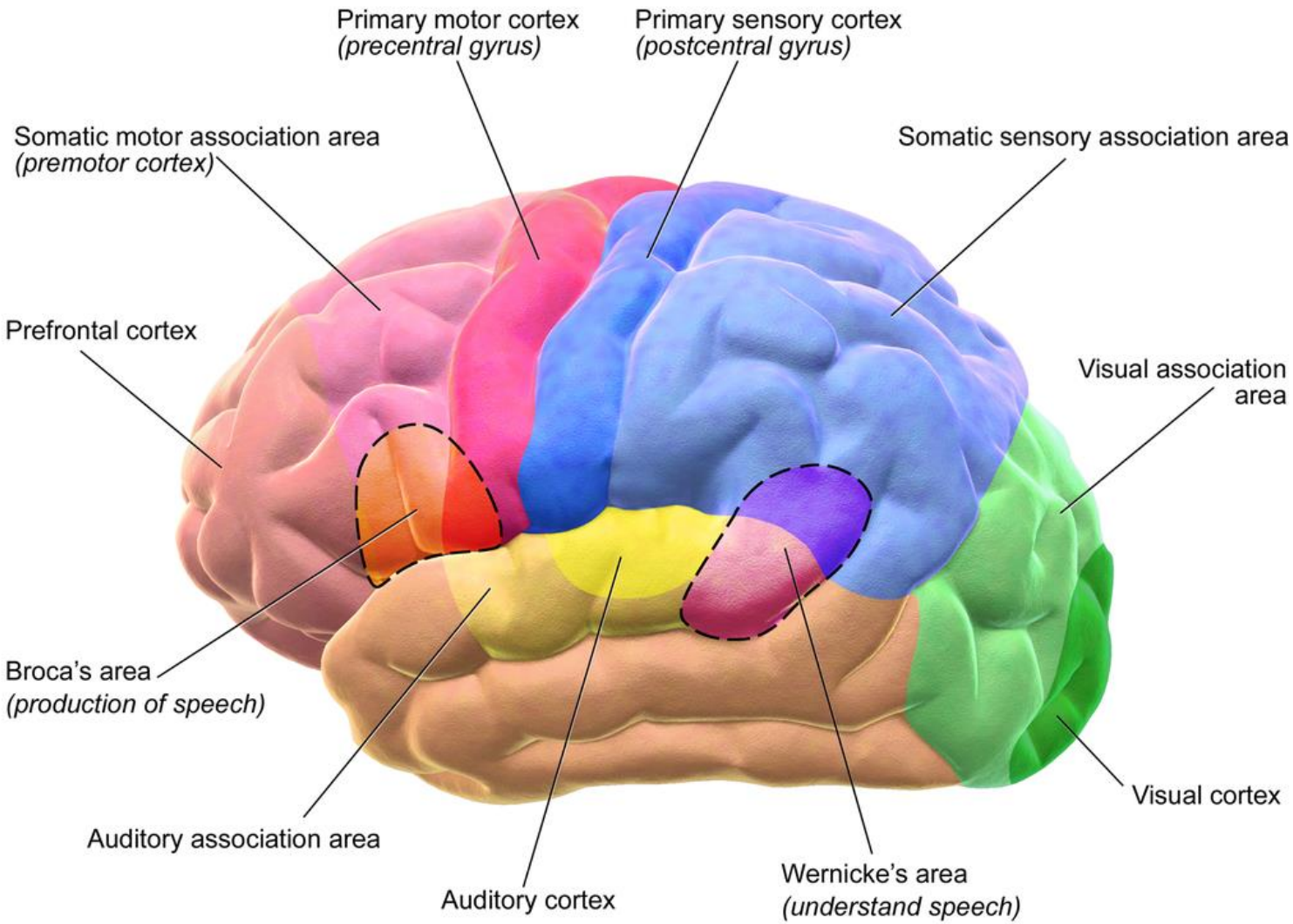
As with many medical conditions, history is key in assessment and guide further evaluations. The first question posed to the caregiver is whether the event was a seizure or some other type of transient event. A sudden alteration in consciousness with associated motor movements is the common description of a convulsive seizure. For generalized seizures with associated motor movements, the convulsion typically has a stiffening or tonic phase followed by clonic movements - rhythmic phase motor movements. There may be a noise or cry at the onset of the seizure. Some patients describe a prodrome or aura before the event. Urinary incontinence may or may not be present. Tongue biting, if present, is most frequently lateral. Following a generalized tonic-clonic seizure, patients have some transient alteration in consciousness referred to as the postictal state. There are many types of seizures other than generalized convulsions, and any transient alteration of consciousness, unusual behavior, or individualized perception might conceivably represent a type of seizure.

Key historical points include history with attention to the history of seizures, medication use, past medical history, and social history, especially any history of alcohol or illicit drug use. Any history of immunosuppression or malignancy is critical to discover. Frequently, there be a history of unresponsive spells that, in retrospect, might be seizures. Events leading up to the seizure are quite important, and friends, family, or coworkers may have crucial historical information. For the patient with known epilepsy, an obvious question would be to ask if there has been any irregularity with medication use.

Motor and Sensory Regions of the Cerebral Cortex



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Definitions

Ictal: happening during a seizure. [1]

The word comes from a Latin word meaning a blow or a stroke. In medicine, the **ictal phase** is the actual time of the seizure. It starts with the very first symptom or abnormal brain wave and lasts until the seizure stops. [1, 2]

Inter-ictal: space between events.

Post-ictal: space after event.

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Review

Seizure Semiology: Its Value and Limitations in Localizing the Epileptogenic Zone

Krikor Tufenkjian, ✉ and Hans O. Lüders

Epilepsy surgery has become an important treatment option in patients with medically refractory epilepsy. The ability to precisely localize the epileptogenic zone is crucial for surgical success. The tools available for localization of the epileptogenic zone are limited. Seizure semiology is a simple and cost effective tool that allows localization of the symptomatogenic zone which either overlaps or is in close proximity of the epileptogenic zone. This becomes particularly important in cases of MRI negative focal epilepsy. The ability to video record seizures made it possible to discover new localizing signs and quantify the sensitivity and specificity of others. Ideally the signs used for localization should fulfill these criteria; 1) Easy to identify and have a high inter-rater reliability, 2) It has to be the first or one of the earlier components of the seizure in order to have localizing value. Later symptoms or signs are more likely to be due to ictal spread and may have only a lateralizing value. 3) The symptomatogenic zone corresponding to the recorded ictal symptom has to be clearly defined and well documented. Reproducibility of the initial ictal symptoms with cortical stimulation identifies the corresponding symptomatogenic zone. Unfortunately, however, not all ictal symptoms can be reproduced by focal cortical stimulation. Therefore, the problem the clinician faces is trying to deduce the epileptogenic zone from the seizure semiology. The semiological classification system is particularly useful in this regard. We present the known localizing and lateralizing signs based on this system.

Ictal category	Examples	Commonly implicated region/network
Somatosensory	Tingling, numbness, burning, electric sensations	Contralateral primary sensory cortex; S2; posterior insula
Visual	Flashing lights, colored shapes, visual loss, distortion	Occipital cortex; visual association cortex
Auditory	Buzzing, ringing, distorted sound, occasionally voices	Superior temporal cortex
Olfactory/gustatory	Unpleasant smell or taste	Mesial temporal, amygdala, insula or operculum
Autonomic/visceral	Tachycardia, sweating, flushing, piloerection, nausea, throat constriction	Insula, amygdala, mesial temporal and autonomic networks
Abdominal	Rising epigastric sensation, butterflies, pressure or nausea	Often mesial temporal; also insular or frontal networks
Emotional	Sudden fear, dread, anxiety, joy or laughter	Amygdala, mesial temporal, cingulate or hypothalamic networks
Cognitive/experiential	Déjà vu, jamais vu, dreamlike state, forced thoughts, memory disturbance	Temporal and temporal-association networks
Language	Inability to speak, impaired comprehension, inability to name	Dominant frontal, temporal or parietal language networks
Motor	Tonic posturing, clonic jerking, myoclonus, automatisms, hypermotor movements	Primary motor, premotor, supplementary motor or frontal networks
Behavioral arrest	Sudden freezing, staring or cessation of activity	Frequently temporal or frontal network involvement
Awareness impairment	Reduced responsiveness or inability to recall the event	Usually bilateral network disruption rather than activation of one isolated location

The Genetics of Epilepsy

Piero Perucca[1,2,3], Melanie Bahlo[4,5] and Samuel F. Berkovic[6]

View Affiliations and Author Notes

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3.4.1. Genetic contributions to focal epilepsies: evidence from epidemiological, twin, and clinical studies.

Population-based epidemiological studies have found that the risk of seizures or epilepsy among first-degree relatives of probands with focal epilepsy is two to three times that of the general population (119). The familial risk varies according to the underlying etiology. It is increased among first-degree relatives of probands with focal epilepsy of unknown cause (more than twofold) or prenatal/developmental cause (almost fivefold) but not among first-degree relatives of probands with focal epilepsy of postnatal cause (118). Yet genetic influences may also play a role in this last group. In a Danish population-based study that included more than 1.6 million people, a positive family history of epilepsy carried more than a 10-fold-increased risk of developing epilepsy following a severe head trauma (20). Furthermore, although affected first-degree relatives of probands with focal epilepsy are also likely to have focal epilepsy, the risk of developing focal epilepsy is similar among relatives of probands with either focal epilepsy or generalized epilepsy (i.e., increased ~2.5-fold) (118), suggesting coexisting shared genetic influences.

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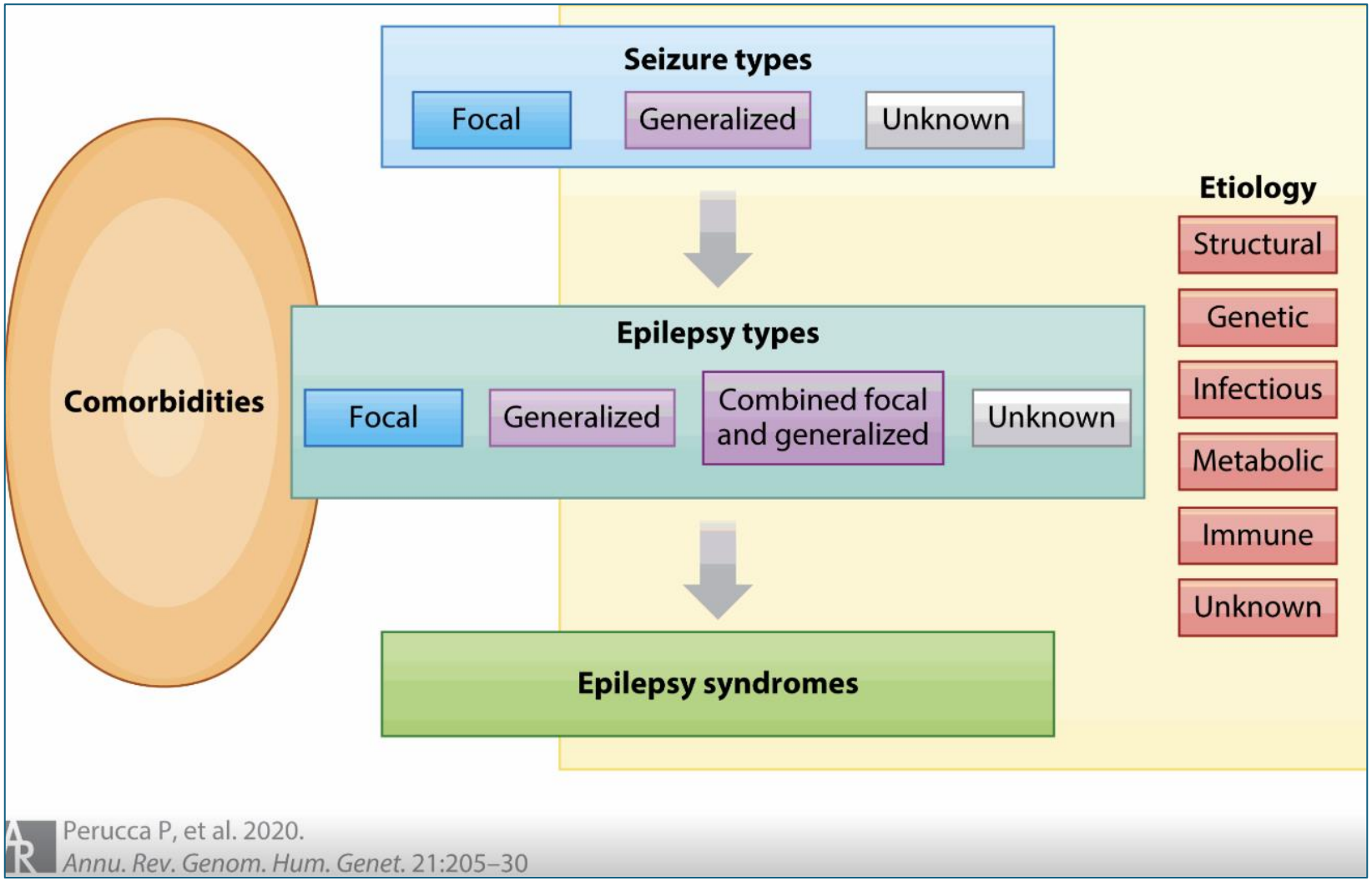

Perucca P, et al. 2020.
Annu. Rev. Genom. Hum. Genet. 21:205–30

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Second-hit mosaic mutation in mTORC1 repressor DEPDC5 causes focal cortical dysplasia–associated epilepsy

Théo Ribierre,[1] Charlotte Deleuze,[1] Alexandre Bacq,[1] Sara Baldassari,[1] Elise Marsan,[1] Mathilde Chipaux,[2] Giuseppe Muraca,[1] Delphine Roussel,[1] Vincent Navarro,[1,3] Eric Leguern,[1,4] Richard Miles,[1] and Stéphanie Baulac[1,4]

Published April 30, 2018 - More info

DEP domain–containing 5 protein (DEPDC5) is a repressor of the recently recognized amino acid–sensing branch of the mTORC1 pathway. So far, its function in the brain remains largely unknown. Germline loss-of-function mutations in *DEPDC5* have emerged as a major cause of familial refractory focal epilepsies, with case reports of sudden unexpected death in epilepsy (SUDEP). Remarkably, a fraction of patients also develop focal cortical dysplasia (FCD), a neurodevelopmental cortical malformation. We therefore hypothesized that a somatic second-hit mutation arising during brain development may support the focal nature of the dysplasia. Here, using postoperative human tissue, we provide the proof of concept that a biallelic 2-hit — brain somatic and germline — mutational mechanism in *DEPDC5* causes focal epilepsy with FCD. We discovered a mutation gradient with a higher rate of mosaicism in the seizure-onset zone than in the surrounding epileptogenic zone. Furthermore, we demonstrate the causality of a *Depdc5* brain mosaic inactivation using CRISPR-Cas9 editing and in utero electroporation in a mouse model recapitulating focal epilepsy with FCD and SUDEP-like events. We further unveil a key role of Depdc5 in shaping dendrite and spine morphology of excitatory neurons. This study reveals promising therapeutic avenues for treating drug-resistant focal epilepsies with mTORC1-targeting molecules.

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Autosomal Dominant Epilepsy with Auditory Features

Synonyms: ADEAF, Autosomal Dominant Lateral Temporal Lobe Epilepsy, Autosomal Dominant Partial Epilepsy with Auditory Features

Roberto Michelucci, MD, PhD, Elena Pasini, MD, and Emanuela Dazzo, PhD.

▸ Author Information and Affiliations

Initial Posting: April 20, 2007; Last Update: May 9, 2024.

Diagnosis/testing. The clinical diagnosis of ADEAF can be established in a proband with characteristic clinical features, normal brain imaging by MRI, and family history consistent with autosomal dominant inheritance. The molecular diagnosis is established in a proband with characteristic clinical features and a heterozygous pathogenic variant in *LGI1*, *MICAL1*, or *RELN* identified by molecular genetic testing.

Genetic counseling. By definition, ADEAF is inherited in an autosomal dominant manner. Most individuals diagnosed with ADEAF have an affected parent; the proportion of individuals with ADEAF caused by a *de novo* pathogenic variant is believed to be low. Offspring of an individual with ADEAF who is heterozygous for a pathogenic variant have a 50% chance of inheriting the pathogenic variant; the chance that offspring who inherit the pathogenic variant will manifest ADEAF ranges from 54% to 85% depending on the assumed penetrance. Once the ADEAF-related pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

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Piero Perucca[1,2,3], Melanie Bahlo[4,5] and Samuel F. Berkovic[6]

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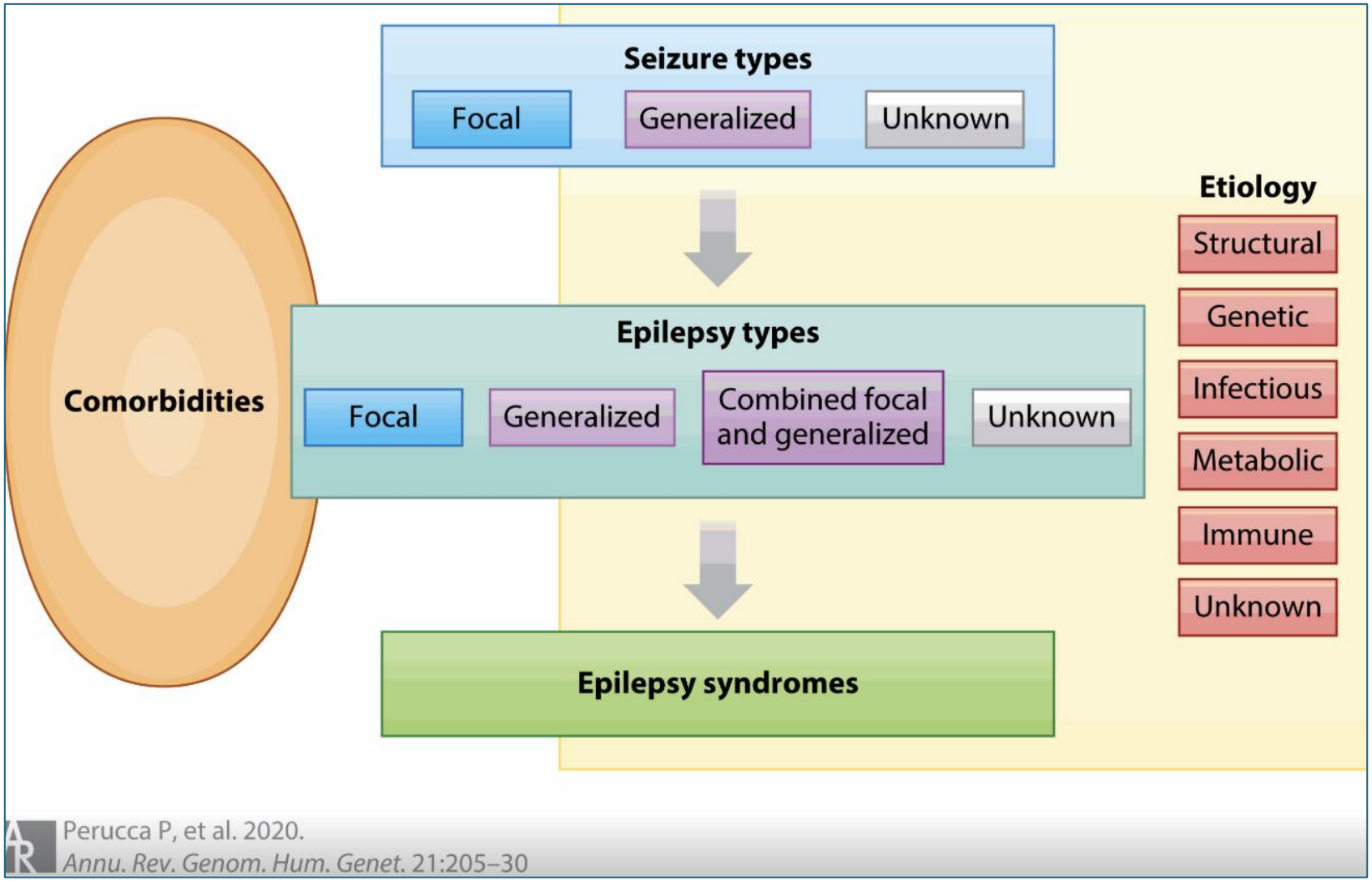

Perucca P, et al. 2020.
Annu. Rev. Genom. Hum. Genet. 21:205–30

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Review > J Integr Neurosci. 2023 Oct 17;22(6):137. doi: 10.31083/j.jin2206137.

Mold and Mycotoxin Exposure and Brain Disorders

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Affiliations + expand

PMID: 38176924 DOI: 10.31083/j.jin2206137

Free article

Abstract

Gene-environment interaction is an emerging hypothesis to explain the increased incidence of neurological disorders. In this context, the health and clinical effects of exposure to air pollutants have received increasing attention. One of these pollutants is the growth of fungi and molds in the form of multicellular filaments, known as hyphae. Fungi and molds not only grow in outdoor environments, but they also thrive indoors with excessive moisture, producing mycotoxins. Mold enters the body through the nose via the olfactory neurons, which directly communicate with the brain. Mycotoxins induce toxicological effects similar to those associated with brain disorders such as oxidative stress and inflammation. One mold species can produce several different mycotoxins, and one mycotoxin can be produced by several different molds. Even a small amount of mold growth in the air conditioners and their ducts or the panels inside the buildings and even the cars cause the occupants to be chronically exposed to and constantly inhaling spores and mycotoxins, which causes illness. In this review, we focused on mold and mycotoxin exposure and brain disorders.

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Methylmercury: A Potential Environmental Risk Factor Contributing to Epileptogenesis

Yukun Yuan [1]

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Abstract

Epilepsy or seizure disorder is one of the most common neurological diseases in humans. Although genetic mutations in ion channels and receptors and some other risk factors such as brain injury are linked to epileptogenesis, the underlying cause for the majority of epilepsy cases remains unknown. Gene-environment interactions are thought to play a critical role in the etiology of epilepsy. Exposure to environmental chemicals is an important risk factor. Methylmercury (MeHg) is a prominent environmental neurotoxicant, which targets primarily the central nervous system (CNS). Patients or animals with acute or chronic MeHg poisoning often display epileptic seizures or show increased susceptibility to seizures, suggesting that MeHg exposure may be associated with epileptogenesis. This mini-review highlights the effects of MeHg exposure, especially developmental exposure, on the susceptibility of humans and animals to seizures, and discusses the potential role of low level MeHg exposure in epileptogenesis. This review also proposes that a preferential effect of MeHg on the inhibitory GABAergic system, leading to disinhibition of excitatory glutamatergic function, may be one of the potential mechanisms underlying MeHg-induced changes in seizure susceptibility.

J Biochem Mol Toxicol. 2023 Mar;37(3):e23285. doi: 10.1002/jbt.23285. Epub 2022 Dec 16.

Biochemical responses as early and reliable biomarkers of organophosphate and carbamate pesticides intoxication: A systematic literature review

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Abstract

Inhibition of cholinesterase (ChE) activity has been long considered as the main diagnostic method of organophosphate (OP) and carbamate pesticides poisoning; however, it has been shown that ChE activity may also be altered due to exposure to other non-organophosphorus toxicants and variety of different medical conditions. Hence, to avoid misdiagnosis, we aimed to systematically review available documents to look for additional biomarkers of OP and carbamate poisoning. The electronic databases in addition to Google scholar were searched for eligible articles on March 2022 using "organophosphate," "carbamate," and "biomarker" including all their similar terms. After collecting the relevant documents, the data were extracted and described qualitatively. In total, data of 66 articles from 51 human and 15 animal studies were extracted. Findings demonstrated that enzymes such as β-glucuronidase, neuropathy target esterase, amylase, and lipase, in addition to hematological indicators such as CBC, CRP, lactate dehydrogenase, and CPK have high sensitivity and accuracy in the diagnosis of OP poisoning. Findings suggest that using various markers for diagnosis of OP intoxication is helpful for appropriate management, and early identifying the patients at risk of death. The suggested biomarkers also help to avoid misdiagnosis of OP poisoning with other similar conditions.

The Genetics of Epilepsy

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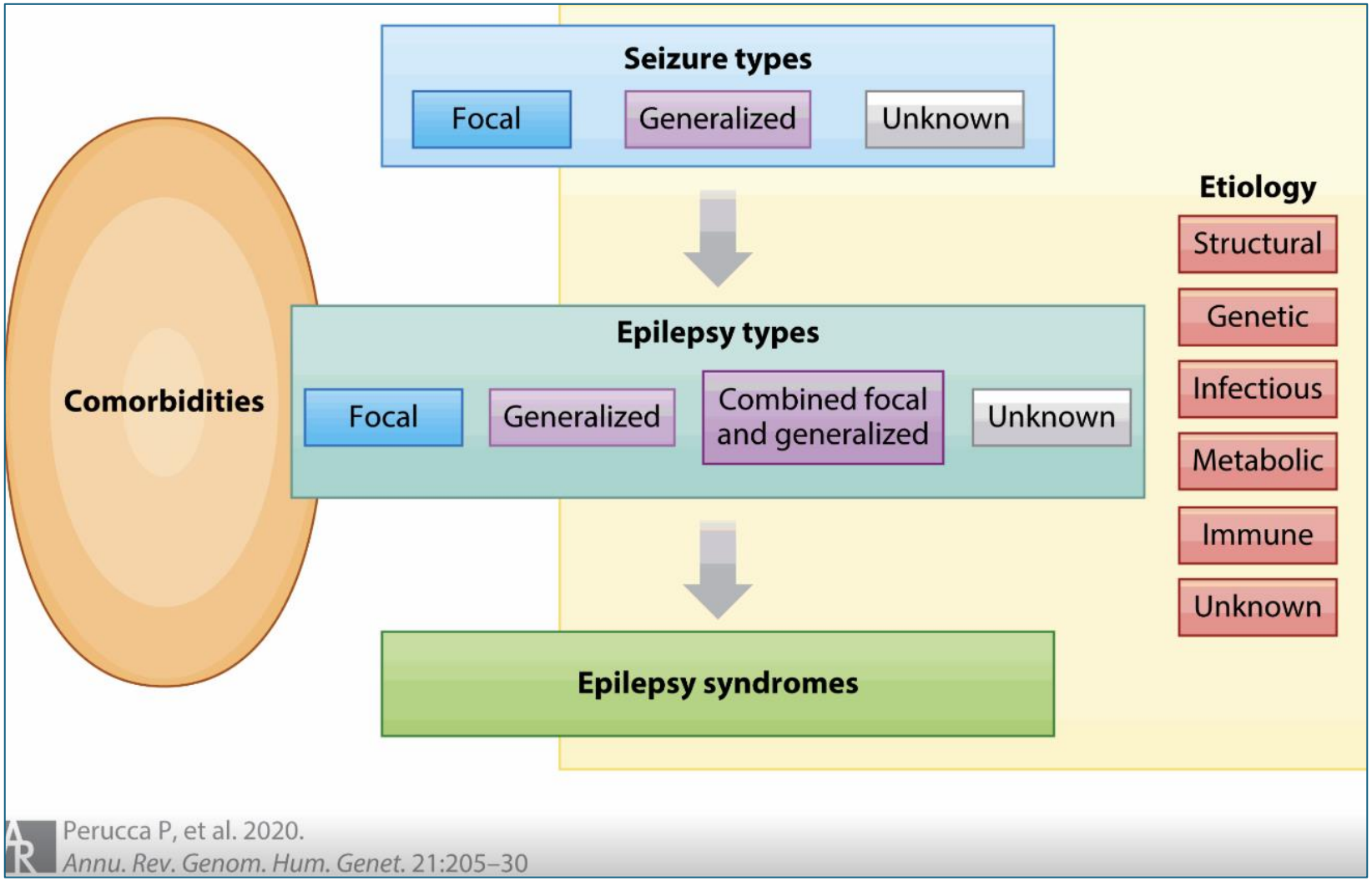

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