MODULES ON EPILEPSY

MODULE I

Anatomy, Physiology and Eiology of Epilepsy

CONTENT

1.	INTRODUCTION	6
2.	ANATOMY RELATED TO EPILEPSY	11
3.	PHYSIOLOGY OF EPILEPSY	20
4.	ETIOLOGY OF EPILEPSY	23
5.	REFERENCES	25

INTRODUCTION

Epilepsy is a chronic noncommunicable disease of the brain that affects people of all ages.

Around 50 million people worldwide have epilepsy, making it one of the most common neurological diseases globally. Nearly 80% of people with epilepsy live in low- and middle-income countries. It is estimated that up to 70% of people living with epilepsy could live seizure-free if properly diagnosed and treated. The risk of premature death in people with epilepsy is up to three times higher than for the general population. Three quarters of people with epilepsy living in low-income countries do not get the treatment they need. In many parts of the world, people with epilepsy and their families suffer from stigma and discrimination.

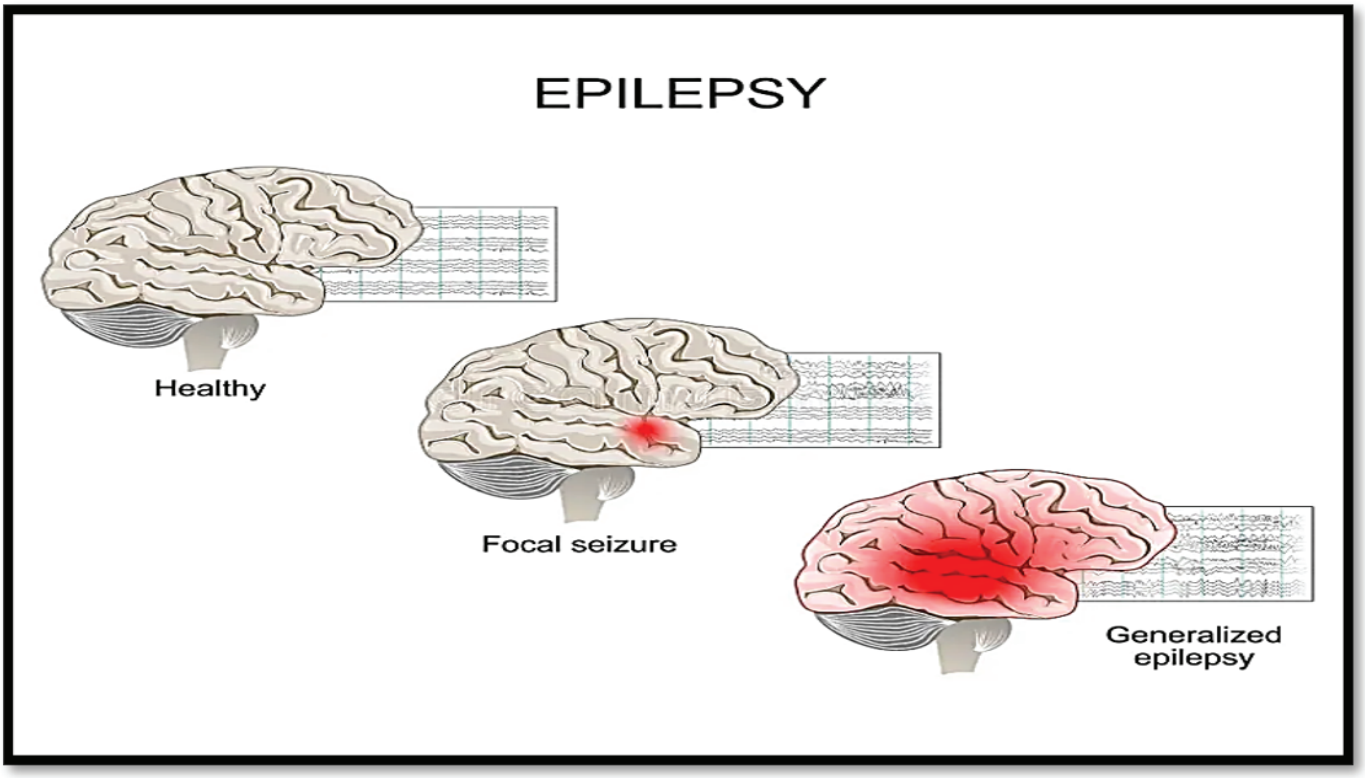

Figure 1: Healthy brain, focal seizure brain & Generalised Epilepsy Diagram

Epilepsy is a chronic, non-communicable brain disorder affecting approximately 50 million people globally. It is marked by recurrent seizures, which are short episodes of involuntary movements that can involve either a specific part of the body (partial) or the entire body (generalized),sometimes is accompanied by loss of consciousness and control over bowel or bladder functions.

These seizure episodes occur due to excessive electrical discharges in clusters of brain cells, and can originate in different areas of the brain. The nature of seizures can vary widely, from brief lapses in attention or muscle jerks to severe, prolonged convulsions. The frequency of seizures can also vary, ranging from less than one per year to several per day.

Experiencing one seizure does not necessarily mean a person has epilepsy (up to 10% of people worldwide experience a seizure at some point in their lives). Epilepsy is diagnosed when an individual has two or more unprovoked seizures. It is one of the oldest known medical conditions, with documentation dating back to 4000 BCE. Epilepsy has long been surrounded by fear, misunderstanding, discrimination, and social stigma, which persist in many parts of the world today, impacting the quality of life for those with the condition and their families.

Signs and Symptoms

Seizure characteristics vary depending on where in the brain the disturbance begins and how far it spreads. Temporary symptoms may include loss of awareness or consciousness and disturbances in movement, sensation (including vision, hearing, and taste), mood, or cognitive functions.

People with epilepsy are more prone to physical injuries (such as fractures and bruises from seizure-related falls) and have higher rates of psychological conditions, including anxiety and depression. Additionally, the risk of premature death is up to three times higher in people with epilepsy compared to the general population, with the highest rates in low- and middle-income countries and rural areas. Many causes of epilepsy-related deaths, especially in low- and middle-income countries, are potentially preventable, such as falls, drowning, burns, and prolonged seizures.

Prevalence

Epilepsy contributes significantly to the global disease burden, affecting around 50 million people worldwide. The proportion of the general population with active epilepsy (i.e., ongoing seizures or the need for treatment) is estimated to be between 4 and 10 per 1,000 people.

Globally, an estimated 5 million people are diagnosed with epilepsy each year. In high-income countries, the annual incidence is about 49 per 100,000 people, while in low- and middle-income countries, it can be as high as 139 per 100,000. This higher incidence is likely due to factors such as endemic conditions (e.g., malaria or neurocysticercosis), higher rates of road traffic injuries, birth-related injuries, and variations in medical infrastructure, availability of preventive health programs, and accessible care. Nearly 80% of people with epilepsy live in low- and middle-income countries.

Causes

Epilepsy is not contagious. Although various underlying mechanisms can lead to epilepsy, the cause remains unknown in about 50% of cases globally. Causes of epilepsy are categorized as structural, genetic, infectious, metabolic, immune, and unknown. Examples include:

Brain damage from prenatal or perinatal causes (e.g., oxygen deprivation or trauma during birth, low birth weight)

- Congenital abnormalities or genetic conditions associated with brain malformations
- Severe head injuries
- Strokes that reduce oxygen supply to the brain
- Brain infections such as meningitis, encephalitis, or neurocysticercosis
- Certain genetic syndromes
- Brain tumors

Treatment

Seizures can be managed effectively. Up to 70% of people with epilepsy could achieve seizure freedom with the appropriate use of antiseizure medications. Discontinuing these medications can be considered after 2 years without seizures, taking into account relevant clinical, social, and personal factors. Documented seizure etiology and abnormal EEG patterns are the most consistent predictors of seizure recurrence.

In low-income countries, about three-quarters of people with epilepsy do not receive the treatment they need, a phenomenon known as the "treatment gap." In many low- and middle-income countries, there is low availability of antiseizure medications, with recent studies indicating that the average availability of generic antiseizure drugs in the public sector is less than 50%. This limited availability can be a barrier to accessing treatment.

Diagnosis and treatment of most people with epilepsy can be done at the primary health-care level without sophisticated equipment. WHO pilot projects have shown that training primary health-care providers to diagnose and treat epilepsy can significantly reduce the treatment gap. Surgery might be beneficial for patients who respond poorly to drug treatments.

Prevention

Approximately 25% of epilepsy cases are potentially preventable. Effective measures include:

• Preventing head injuries through the reduction of falls, traffic accidents, and sports injuries to prevent post-traumatic epilepsy.

• Providing adequate perinatal care to reduce new cases caused by birth injuries.

• Using medications and other methods to lower fever in children to prevent febrile seizures.

• Preventing epilepsy associated with stroke by managing cardiovascular risk factors, such as high blood pressure, diabetes, obesity, and avoiding tobacco and excessive alcohol use.

• Reducing the incidence of central nervous system infections in tropical areas through parasite elimination and education on infection prevention, which can decrease epilepsy cases due to neurocysticercosis.

Social and Economic Impacts

Epilepsy accounts for over 0.5% of the global burden of disease, considering both years of life lost due to premature mortality and years lived with disability. The economic impact of epilepsy includes healthcare needs, premature death, and lost work productivity. Out-of-pocket expenses and productivity losses can place substantial financial burdens on households. An economic study in India found that public financing for epilepsy treatment is cost-effective and alleviates the financial burden on households.

The stigma and discrimination associated with epilepsy are often more challenging to address than the seizures themselves. People with epilepsy and their families may face prejudice and pervasive myths, such as beliefs that epilepsy is incurable, contagious, or a result of immoral behavior, which can isolate them and discourage treatment-seeking. Human Rights People with epilepsy often face reduced access to education, restrictions on obtaining driving licenses, barriers to certain occupations, and limited access to health and life insurance. In many countries, outdated laws reflect centuries of misunderstanding about epilepsy, such as permitting marriage annulment due to epilepsy or denying access to public places for people with seizures.

Legislation based on internationally accepted human rights standards can prevent discrimination, improve access to healthcare services, and enhance the quality of life for people with epilepsy.

WHO Response

The first global report on epilepsy, "Epilepsy: A Public Health Imperative," produced in 2019 by WHO and key partners, highlighted the burden of epilepsy and the necessary public health response at global, regional, and national levels.

ANATOMY REALTED TO EPILEPSY

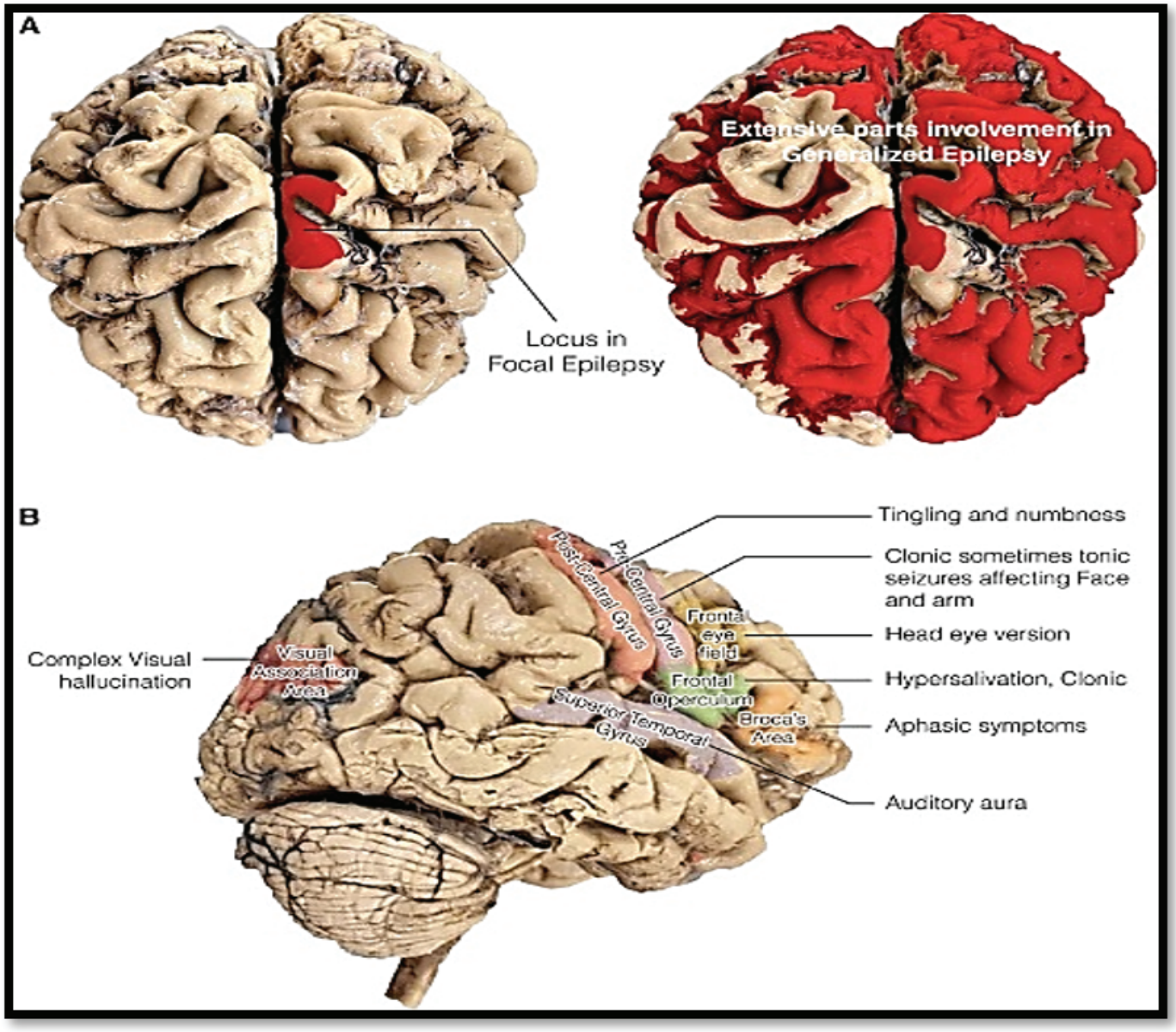

Figure 2 The anatomical basis of epilepsy. A, Structures (marked in red) affected in focal and generalized seizures. B, Semiological signs by symptomatogenic areas affected in seizure.

The anatomical regions associated with seizures play a crucial role in their classification and treatment. The revised classification by the International League Against Epilepsy aligns seizure semiology (clinical manifestation signs) with their anatomical origin (focal vs. generalized). Fayerstein et al. conducted a study where semiologic features were correlated with the localization of the seizure onset zone (temporal, prefrontal dorsolateral, prefrontal ventro-mesial, parietal, insular).

The study found that dystonia, integrated behavior, and bilateral or unilateral hyperkinetic movements were statistically significant based on localization and were indicative of seizures originating from the parietal, temporal, and prefrontal ventro-mesial regions, respectively.

Recently, epilepsy centers worldwide have resumed trials involving deep brain stimulation techniques such as vagus nerve stimulation and transcranial magnetic stimulation in various intracerebral structures, including the thalamus, hippocampus, and subthalamic nucleus, to treat patients with medically or surgically refractory epilepsy. The neuroanatomic circuitry is also implicated in the cardiovascular manifestations associated with seizures.

A seizure, characterized by excessive hypersynchronous neuronal discharge in the brain, results in a sudden and temporary alteration of neurological function. Non-epileptic seizures are brief, typically occur once, and are triggered by a reversible factor. In contrast, epilepsy is a neurological disorder marked by two or more unprovoked seizures. Epilepsy affects about 1% of the population, with approximately 75% of cases beginning in childhood, highlighting the developing brain's increased vulnerability to seizures.

Seizures are defined by hyperexcitability and hypersynchrony in neurons. Hyperexcitability indicates that a specific threshold of excitability must be surpassed for a seizure to occur, meaning that seizures arise when excitation outweighs inhibition. Hypersynchrony involves a group of neurons firing simultaneously and at a similar rate. Although individual neurons might experience hyperexcitability and emit rapid, repetitive, paroxysmal discharges, a seizure involves many neurons firing in a coordinated manner.

The development of seizures can be attributed to various mechanisms, but fundamentally, it can be explained by the loss or dysfunction of cells that typically inhibit excitatory cells and prevent the spread of electrical discharges, or by the overproduction of chemicals causing abnormal electrical discharges. Additionally, to understand the origin of the electrical activity, it is essential to examine the structure and function of the brain cells generating this activity.

The Hippocampus and Epilepsy

The hippocampus, located deep within the medial part of the thalamus, is crucial for memory processing, emotions, spatial navigation, and learning. The hippocampal formation includes the uncus, hippocampal proper, gyrus fasciolaris, longitudinal striae, and indusium griseum. This region plays a significant role in epilepsy, receiving sensory impulses from the posterior cingulate cortex, contralateral hippocampus, and the occipital, temporal, and parietal lobes through the lateral and medial perforant pathways. Seizures can lead to abnormal neurogenesis in the hippocampus, creating faulty circuits that impair its function.Hippocampal sclerosis (HS) and mesial temporal lobe epilepsy (MTLE) are terms often used interchangeably and are associated with epilepsy-related cognitive dysfunction. HS is characterized by shrinkage, hardening, selective neuronal loss, and secondary astroglial proliferation affecting various parts of the hippocampus.

According to the International League Against Epilepsy's 2004 criteria, MTLE-HS involves neuronal cell loss and gliosis in the CA1 and end-folium areas, with relative sparing of the transitional cortex at the mid-body of the anterior-posterior axis. This condition often extends to the amygdala, uncus, and parahippocampal gyrus.

Thom categorized hippocampal sclerosis into three types:

1.Classical: Neuronal loss and gliosis primarily in CA1, CA3, and end-folium.

2.Total: Severe neuronal loss across all hippocampal subfields and the dentate gyrus.

3.End-folium: Neuronal loss and gliosis confined to the hilum of the dentate gyrus.

The Temporal Lobe, Thalamus, Amygdala and Epilepsy

Approximately two thirds of instances of intractable epilepsy that are treated surgically are caused by temporal lobe epilepsy (TLE), the most prevalent kind of focal epilepsy. Neocortical temporal lobe epilepsy (nTLE), often referred to as extrahippocampal, nonlesional, or lateral neocortical epilepsy, and mesial temporal lobe epilepsy (mTLE) are two subtypes of TLE. The anterior thalamus and hippocampal regions exhibit volume reduction and cortical atrophy in mTLE. Both faulty white matter tracts and connections as well as abnormal grey matter abnormalities are seen in TLE. These abnormalities involve diffuse networks including the fronto-temporal, fronto-occipital, fornix, or temporo-occipital fasciculus.

It has been demonstrated that individuals with TLE have reduced baseline volumes in the anterior thalamus, which is involved in memory processing, spatial navigation, and communication with the hippocampus.

The nucleus of the mediodorsal thalamus is vital for goal-directed behavior, and the perifascicular thalamus and intralaminar thalamic nucleus for behavioral flexibility. Limbic system atrophy is linked to thalamic lesions in TLE.

Cortex of Olfactory and Epilepsy

Increased glial cell densities in the layers of the epileptogenic piriform cortex (primary olfactory cortex) have been seen in post-mortem epileptic cases. Olfactory cortex seizures are characterized by diminished olfactory functioning, confusion during testing, and unpleasant auras. In the pre-ictal stage, olfactory auras are linked to hyperresponsive neurons.

Epilepsy and The Frontal Cortex

The dorsolateral, medial orbital, and inferior orbital regions make up the frontal lobe. Primary motor, premotor, and prefrontal cortex are further divisions of the dorsolateral frontal lobe. Primary motor area-originating frontal lobe seizures lack the post-ictal phase, have early motor symptoms, and can happen while you are sleeping.

Speech arrest and unilateral spreading clonic activity that starts on the face and spreads to the arm are its main features. One of the most prevalent forms of focal epilepsy is frontal lobe epilepsy. The frontal eye field, secondary motor cortex, and Broca's language area are further divisions of the premotor cortex (Figure 2).

Lateral deviation of the eyes occurs when a seizure affects the frontal eye field. When aphasic seizures occur, Broca's language region is involved. Versive is represented by premotor area involvement. Versive seizures with forced head turns that are characterized by involuntary head deviation are indicative of premotor region involvement. In juvenile myoclonic epilepsy, frontal lobe disease may result in rostral corpus callosum atrophy. Complex automatism, unilateral or bilateral tonic activity, or contralateral clonic movement are symptoms of frontal lobe epilepsy. Paradoxical lateralization in frontal lobe epilepsy may be caused by loci foci in the medial frontal lobe. Idiopathic generalized epilepsies in children are characterized by abnormal volumes in the thalamus and frontal lobes.

Cerebellum and Epilepsy

Cerebellar atrophy is common in epileptic patients. Patients with intractable epilepsy have been observed to benefit from cerebellar stimulation in the anterior lobe. Cerebellar stimulation is based on the idea that pathologic facilitation or disinhibition of Purkinje cells might be used to prosthetically create changes in neurologic activity that is abnormally and undesiredly heightened. Cerebellar biopsies performed during the stimulation period revealed a decrease in Purkinje cells, stellate cells, and molecular layer.

Dendritic Pathology and Epilepsy

Dendritic spines are thin protrusions on the surface of neurons that serve as contact points between neurons. These postsynaptic structures form synaptic connections with axon terminals and are primary targets for excitatory synapses in the brain. The density of dendritic spines is indicative of cellular processes involved in neural plasticity and cognitive functions such as memory and learning. Pathological conditions can induce changes in dendritic spines, leading to hyperexcitability in neuronal circuits, which lowers seizure thresholds and contributes to progressive epileptogenesis. Neurons exhibit a variety of firing patterns and dendritic morphologies, which play a crucial role in modulating these patterns. Computational models of neocortical pyramidal cells have shown that the total length of the apical dendrite and its branching pattern significantly influence burst spike intervals, determining whether a cell exhibit burst firing. Modifying the dendritic tree's size or topology, without altering the total dendritic length, can change a cell's firing pattern from bursting to tonic firing. Changes in the size or structure of pyramidal cells in epilepsy can alter neuronal burst firing, thereby impacting information processing and cognition. Epilepsy is a neurological condition characterized by two or more unprovoked seizures. About 75% of epilepsy occurs during childhood, reflecting the heightened susceptibility of the developing brain to seizures. Brain regions specialized for learning and memory, particularly the neocortical regions and the hippocampus, are comparatively more prone to seizures.

Epilepsy is associated with anatomical changes in the hippocampus, amygdala, frontal cortex, temporal cortex, and olfactory cortex. Dendritic spines, which form synaptic contacts with axon terminals, are key to neural plasticity and cognitive functions. Alterations in dendritic structure or morphology can lead to hyperexcitability, affecting firing patterns and contributing to epileptogenesis.

PHYSIOLOGY OF EPILEPSY

The mechanisms that cause hyperexcitability and hypersynchrony in the neural networks of the brain must be examined in order to comprehend the physiology of epilepsy.

Neuronal Excitability and Inhibition

Balance Between Excitation and Inhibition: Normal brain function relies on a balance between excitatory and inhibitory signals. Excitatory neurotransmitters, such as glutamate, and inhibitory neurotransmitters, like gamma-aminobutyric acid (GABA), work together to regulate neuronal firing. In epilepsy, this balance is disrupted, leading to excessive excitatory activity or insufficient inhibitory control, resulting in hyperexcitability of neurons.

Ion Channels and Receptor Dysfunction: Ion channels play a crucial role in maintaining neuronal excitability by regulating the flow of ions (e.g., Na+, K+, Ca2+) across the cell membrane. Mutations or dysfunctions in these channels can lead to abnormal neuronal firing. Receptor dysfunction, including alterations in GABA receptors (leading to reduced inhibition) and glutamate receptors (leading to increased excitation), also contributes to seizure activity.

Mechanisms of Hyperexcitability

Abnormal Synaptic Transmission: Enhanced release of excitatory neurotransmitters or reduced release of inhibitory neurotransmitters can cause increased synaptic excitation. Malfunctioning synaptic vesicle proteins and neurotransmitter reuptake mechanisms can also contribute to prolonged excitatory signaling.

Neuronal Network Changes: Synaptic plasticity, including long-term potentiation (LTP) and long-term depression (LTD), can be abnormally regulated in epilepsy, leading to strengthened excitatory connections and weakened inhibitory connections. Structural changes in neurons, such as increased dendritic spine density, can increase the number of excitatory synapses.

Hypersynchrony and Network Connectivity

Synchronous Neuronal Firing: In epilepsy, large groups of neurons fire simultaneously in a highly coordinated manner, leading to the synchronous discharge observed in seizures. Abnormalities in gap junctions, which allow direct electrical communication between neurons, can contribute to this hypersynchrony.

Altered Brain Connectivity: Changes in the connectivity of brain networks, including the development of aberrant neural circuits, can predispose individuals to seizures.

This involves the formation of new synapses or the reorganization of existing ones in a way that promotes hyperexcitability. Regions such as the hippocampus, thalamus, and cortex are particularly involved in these network changes.

Pathophysiological Processes

Neuroinflammation: Inflammatory processes in the brain, involving glial cells (microglia and astrocytes), can contribute to the pathogenesis of epilepsy. Pro-inflammatory cytokines can alter neuronal excitability and synaptic function.

Genetic and Epigenetic Factors: Genetic mutations in ion channels, neurotransmitter receptors, and other proteins involved in neuronal excitability are well-documented in various forms of epilepsy. Epigenetic modifications, such as DNA methylation and histone acetylation, can influence gene expression patterns associated with epileptogenesis.

Metabolic Dysfunction: Mitochondrial dysfunction and altered energy metabolism can affect neuronal excitability and contribute to seizure generation. Energy deficits can impair the function of ion channels and neurotransmitter systems.

Structural and Functional Brain Abnormalities

Hippocampal Sclerosis: One of the most common pathological findings in temporal lobe epilepsy is hippocampal sclerosis, characterized by neuronal loss and gliosis in the hippocampus.

Cortical Malformations: Developmental malformations of the cortex, such as cortical dysplasia, can create an abnormal substrate for seizure generation

Seizure Propagation

Focal to Generalized Seizures: Seizures can begin in a specific area (focal onset) and spread to involve both hemispheres (generalized onset). The mechanisms of spread involve both synaptic and non-synaptic pathways, including extracellular ionic changes and ephaptic coupling (interaction between neurons through local electric fields).
Role of the Thalamus: The thalamus acts as a relay center, and its involvement is crucial in the propagation of seizures, particularly in generalized epilepsies. Abnormal thalamocortical oscillations can facilitate the spread of epileptic activity.

Functional Conncetivity

Various methods exist for measuring signals non-invasively (such as scalp EEG, MEG, or fMRI) or invasively using intracranial electrodes (iEEG). With the abundance of data from epilepsy monitoring protocols, numerous functional connectivity techniques have been developed and applied. It's crucial to highlight those studies, like those by Ansari-Asl et al. (2006) and Wendling et al. (2009), have compared these methods. They've concluded that there isn't a universally superior functional connectivity approach; instead, the choice should be tailored to the specific application.

Relationship between Structural and Functional Connectivity in Epilepsy

Advancements in diffusion tensor imaging (DTI) have greatly enhanced the analysis of structural connectivity in epilepsy patients, allowing the detection of abnormalities in white matter fiber structure. These abnormalities, particularly around seizure onset zones, have been identified using DTI technologies. However, accurately identifying small fiber bundles and crossing fiber tracts relies on probabilistic tractography, which presents challenges due to subjective threshold definitions.

Despite these challenges, understanding structural connectivity is crucial as it influences functional connectivity and potentially seizures. Recent studies have explored the relationship between brain structure and function. For instance, research combining resting-state fMRI (RS-fMRI) data with DTI scans in healthy individuals has revealed interconnected cortical brain regions forming resting-state networks, highlighting the neuroanatomical basis of interregional communication.

In epilepsy, Zhang et al. (2010) investigated the relationship between structure and function. They found a disconnect between whole-brain functional and structural networks in idiopathic generalized epilepsy. Utilizing network-based data analysis on DTI tractography and RS-fMRI, they observed deviations in topological organization in both functional and structural connectivity networks in patients compared to controls. These deviations were prominent in regions implicated in epilepsy pathogenesis. This decoupling could potentially serve as a biomarker for detecting subtle brain abnormalities in epilepsy, although intermittent disruptions by interictal discharges and motion artifacts should also be considered.

iEEG Functional Connectivity of Epileptic Networks

The exploration of how human brain activity synchronizes during seizures has a rich history dating back to studies by Brazier (1972), Gotman (1983), and Lieb et al. (1987). It's widely accepted that a focal seizure with secondary generalization involves a network phenomenon, starting in a specific region and spreading to other areas of the brain. Recent research has applied network theory concepts to investigate the relationship between functional connectivity and seizures in epilepsy, as discussed in the review by Kramer and Cash (2012). While ongoing research continues to identify network characteristics supporting epileptic seizures, some key findings have emerged. These include the prevalence of small-world topologies and hubs, although there are some diverging viewpoints in the literature. One consistent observation is the increased coupling of brain voltage activity at seizure onset and termination in both human and animal models.

For instance, Kramer et al. (2010) employed a functional network analysis approach using intracranial EEG (iEEG) data during seizures. They constructed binary networks where edges were formed between electrodes showing statistically significant cross correlations in their iEEG signals. Their findings, illustrated in Fig. 1, indicated an increase in network density at seizure onset and termination, returning to inter-ictal levels during the seizure itself.

This suggests that seizure maintenance is not characterized by hyper-synchrony and that brain regions may decouple during the seizure. It's worth noting that the seizure onset activities in this study encompassed both low-amplitude, high-frequency discharges.

Further investigation is needed to address several issues concerning the evolution of functional networks during seizures. Firstly, there's a need to comprehend how seizure onset patterns impact these networks and whether other brain state changes, such as transitions from sleep to wakefulness at seizure onset, influence network evolution. Burns et al. (2012) and Yaffe et al. (2012) took a different approach, examining the temporal evolution of functional connectivity network structures during seizures using intracranial EEG (iEEG) and stereotactic EEG (sEEG) data, respectively.

These studies analyzed the eigenvalue centrality of adjacency matrices computed using coherence in specific frequency bands. Eigenvalue centrality represents the importance or influence of nodes within a network. Tracking the evolution of the first eigenvector of the adjacency matrix over pre-ictal, ictal, and post-ictal periods, they observed consistent state transitions during seizures within individual patients. Interictal periods showed relatively stable states with minor fluctuations in the first eigenvector, implying that epileptic network functional connectivity progresses through a finite set of states. However, challenges persist in iEEG-based functional connectivity research. These include determining and applying suitable coupling measures to iEEG data, converting coupling statistics to network edges, understanding the impact of iEEG reference montage on network features, developing robust tools for network statistic assessment, and creating data analysis tools for assessing dynamic network evolution. The International Epilepsy Electrophysiology Portal is a valuable resource in advancing this research, facilitating data, tool, and expertise sharing among researchers aiming to understand epilepsy better.

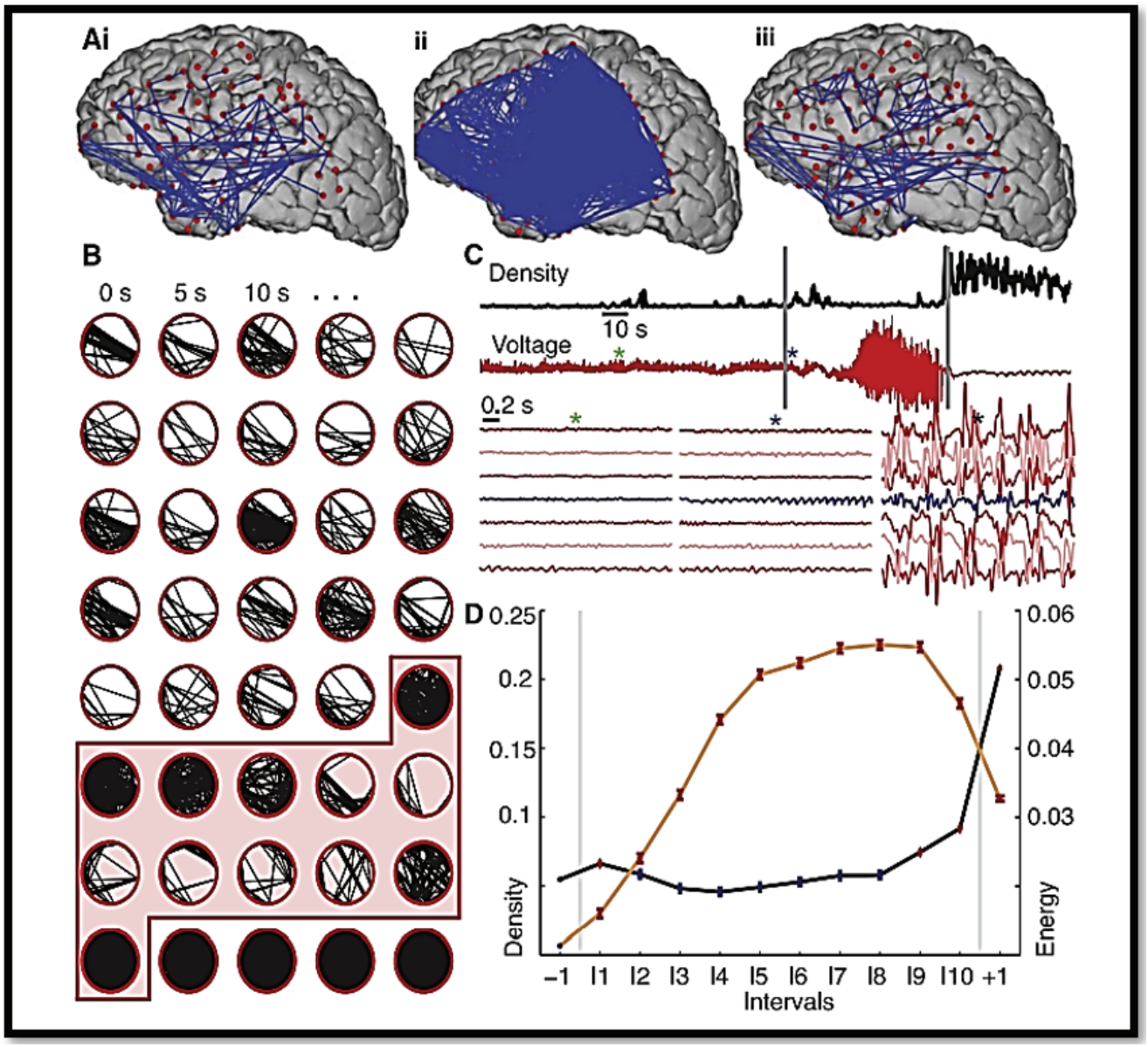

Figure 3Reprinted from Kramer et al. (2010) with permission from Society for Neuroscience (copyright 2010). Network synchronization increases at ictal onset and offset but falls to preictal values during the seizure. (A) Representative networks just before the seizure starts, (i) at seizure initiation, (ii) and in the middle of the seizure (iii) from an single seizure in a single patient. In this example, the electrode locations have been projected onto a reconstruction of this patient's cortical surface. Because some of the electrodes cannot be easily visualized in this two-dimensional representation, the data are displayed as circular networks containing all electrodes as individual nodes. (B) The networks progress from left to right, top to bottom, with a 5 s interval between networks. We arrange the electrodes in a circle (without reference to their physical locations) and indicate sufficiently strong coupling between electrode pairs with black lines. The shaded region denotes the ictal interval. Visual inspection of the evolving network topologies suggests increased network density (i.e., more edges) near ictal onset and termination. (C) The network density (black) and ECoG data from a single electrode (red, top) for the representative example. Signals were recorded using a common average reference. At ictal onset and termination, indicated with the vertical gray lines, the network density increases dramatically, whereas during the middle portion of the seizure, the Cog data exhibits large-amplitude fluctuations. The colored asterisks indicate the location of three 2 s intervals plotted for representative grid and strip electrodes below, including the activity of the presumptive onset electrode as identified by the clinical team (blue trace). (D) The density (black curve), averaged across all subjects and seizures and adjusted for differences in subjects, for 12 time intervals: one preictal (1), 10 ictal (I1, I2, ... , I10), and one postictal (+1). In each interval, the circle indicates the mean density (n = 9049 networks preictal, n = 939 networks per ictal interval, and n = 2817 networks postictal) and the vertical lines the SE. Statistically significant increases in density compared with preictal values are indicated in red and occur at ictal onset (interval I1) and near ictal offset (intervals I9, I10, +1). We also plot the normalized signal energy (orange curve) for each interval averaged across all subjects and seizures (n = 45,609 preictal, n = 3614 per ictal interval, and n = 10,842 postictal). Unlike the density, the signal energy increases significantly above preictal values for all ictal and postictal intervals

fMRI Functional Connectivity of Epileptic Networks

Biswal et al.'s (1995) description of brain functional connectivity using fMRI has resulted in an expansion of interest and studies of fMRI based brain connectivity. This approach relies upon correlation of spontaneous low frequency (<0.1 Hz) fluctuations in the blood oxygen level-dependent (BOLD) response and has been termed resting functional connectivity MRI (rfc-MRI). Accordingly, areas exhibiting spontaneous BOLD correlations are said to be functionally connected. Advances in this field include the description of the default mode network (DMN) (Raichle et al., 2001), the presence of anti-correlated networks (Greicius et al., 2003), a combination of multi-institutional databases to provide normative data on connectivity (Biswal et al., 2010), and the description of multiple brain networks that may be extracted by data-driven methods (Craddock et al., 2012). There has been a recent acceleration of studies investigating rfcMRI in epilepsy. Contingent upon the goals of the study, a given MRI volume serves as a network node or region of interest (ROI). Termed the "seed" region, it can either be correlated with all voxels in the brain (ROI-to-whole-brain) to explore global connectivity (Pereira et al., 2010; Negishi et al., 2011), or correlated with another ROI (ROI-to-ROI) to ascertain connectivity between areas of interest in a network (Bettus et al., 2010). Additional methods of analyzing rfc-MRI as it relates to epilepsy and/or functional connectivity include independent component analysis (Zhang et al.,2010), graph theory (Constable et al., 2013), temporal clustering analysis, regional homogeneity, and amplitude of low frequency fluctuation measures (Wurina et al., 2012).

rs-fmri, Temporal Lobe Epilepsy, and The Default Mode Network

The DMN is likely the most studied network by rfc-MRI. The DMN is characterized by regions of enhanced activity while the brain is at rest, and consists of the posterior cingulate cortex (PCC)/precuneus (PC), ventral anterior cingulate cortex/mesial prefrontal cortex (mPFC), angular gyrus, inferior temporal cortex (ITC), and mesial temporal lobe (mTL) (Raichle et al., 2007; Buckner et al.,2008; Zhang et al., 2010). Zhang et al. (2010) found that in patients with mTLE that presented with hippocampal sclerosis (HS), there were significant alterations in functional connectivity throughout the DMN, including decreased connectivity in the MTL, ITC, and dorsal mPFC bilaterally, and increased connectivity in the PCC. In contrast, McCormick et al. (2013) found functional connectivity between the hippocampus and PCC was decreased in the epileptogenic hemisphere, while connectivity to the contralateral PCC was increased. However, it is hard to directly compare these opposing trends since the McCormick group used ROI-to-ROI for analysis, while Zhang et al. (2010) used ICA. Nonetheless, these studies together suggest that physiological impairment to one node of the DMN can lead to network-wide alterations, including a possible compensatory response in the PCC in the case of HS.

In another study, increases in connectivity in mTLE were observed in the hippocampus and amygdala that were contralateral to the epileptogenic hemisphere, while decreased connectivity between the entorhinal cortex and anterior hippocampus was seen in the affected hemisphere (Bettus et al., 2010). This paradoxical trend in hippocampal connectivity contradicts findings by Pereira et al.(2010),

who determined that mTLE patients with left HS display bilateral decreases in hippocampal functional connectivity. However, the latter study was exclusive to subjects with HS, while the prior included subjects without cortical abnormalities and with non-HS malformations.

In addition, these studies determined connectivity through different methods, using ROI-to-ROI and ROI-to-whole-brain measures, respectively. Another study that was not exclusive to patients with HS, and evaluated functional connectivity with ROI-to-whole-brain methodology found that in patients with right or left TLE there is decreased connectivity between the hippocampus and PC in the DMN (Haneef et al.,2014). Thus, changes in DMN hippocampal connectivity in patients with TLE seem to vary, with possible causes being differences in histopathological abnormalities, analytical methodology, and individual patient brain dynamics.

The studies defined above provide a rough sketch of what is possible to derive regarding the network physiology of epilepsy using rfc-MRI. There has been great interest in characterizing the connectivity of the IOZ. Whole-brain analyses that are possible with noninvasive fMRI provide one potential advantage over invasive electrode analyses that may be subject to a sampling problem.

Rfc-MRI studies show evidence for both increased and decreased connectivity in the IOZ (Bettus et al., 2010; Stufflebeam et al., 2011). This mirrors the electrophysiological literature, showing hypersynchrony (Schevon et al., 2007), and fragmentation (Truccolo et al., 2011) of the IOZ as well as for its isolation from areas outside the IOZ (Warren et al., 2010). While rfc-MRI studies derive larger scale networks, their correspondence with electrophysiological measures of connectivity suggests that this line of research may be an important one to explore (He and Liu, 2008; Keller et al., 2011, 2013). Great strides have been made in analyzing the functional connectivity of epileptic networks, yet ultimately, we would like to apply this understanding to improve treatment of epilepsy, and efforts to achieve this are being explored. Negishi et al. (2011) showed patients with reduced contralateral connectivity in pathological regions to have better seizure freedom rates after unilateral resection.

The above-mentioned rfc-MRI IOZ abnormalities suggest that rfc-MRI can be developed into a useful biomarker for the IOZ, which can guide surgical treatment by selecting the site for resection as well as neurostimulation. Alternatively, insights into functional connectivity may suggest novel treatment strategies to stop seizures by partially isolating rather than removing (Ching et al., 2012) pathological brain areas responsible for seizure. While currently there is no generally accepted clinical use for rfc-MRI as applied to epilepsy, the studies outlined above demonstrate the possible potential for identifying the ictal onset zone.

In addition, proof of concept has been shown for defining functional zones as may be also required for epilepsy surgery. In patients with brain tumors, Zhang et al. (2009) showed electrical stimulation mapping of sensorimotor cortex to better correlate with rfc-MRI than task-based MRI, and Kokkonen et al. (2009) used an ICA-based analysis to show good correspondence between task based and resting fMRI. Mitchell et al. (2013) have recently showed in surgical patients implanted with electrodes that a classifier approach for defining language and resting networks correlates with results of electrical stimulation mapping.

Finally, the aforementioned study by McCormick et al. (2013) showed rfc-MRI between hippocampus and precuneus better predicted post-surgical memory deficits than Wada testing. The growing body of such results strongly suggests that functional connectivity analyses – most likely integrated with anatomical and effective connectivity – will provide useful clinical tools to aid both surgical and non-surgical treatment of epilepsy.

Effective connectivity

While functional connectivity aims to assess connectivity based on statistical dependencies in neuronal activity, effective connectivity aims to establish causal relationships between distinct regions. In other words, functional connectivity relies on disproving the null hypothesis that separate brain areas function independently of one another, while effective connectivity seeks to model these relationships by adding weighted directionality to them (Friston, 2011). This can be achieved by two approaches: interventional and non-interventional. Non-interventional methodologies rely on recordings of brain dynamic activity (e.g., fMRI or ECoG), and employ methods such as Granger causality and dynamic causal modeling to derive causal interactions (Brovelli et al., 2004; Kiebel et al., 2009). In contrast, interventional approaches measure evoked responses to stimulation applied directly to the human brain to achieve the same end (Matsumoto et al., 2004; David et al.,2010; Entz et al., 2014; Keller et al., 2014a, b). Here we will focus on the latter, as it facilitates direct evaluation of connectivity in the human brain in patients with epilepsy, and is thus a powerful tool in studying both connectivity and seizure electrophysiology.

This is highlighted by studies that have shown correspondence between connectivity measures using interventional effective connectivity measures and noninvasive MRI-based measures, including anatomic connectivity using DTI (Conner et al., 2011) and functional connectivity using resting fMRI (Keller et al., 2011).

CCEPs and the ictal onset zone

Cortico-cortical evoked potential (CCEP) mapping involves brief (<10 ms) electrical stimulation at a given location and recording an evoked potential at another site. CCEPs are typified by an early deflection (N1) that occurs before 50 ms, and a later one (N2) after 50 ms (Matsumoto et al., 2004; Keller et al., 2011).

CCEPs provide a unique opportunity to directly study differences in electrophysiology between normal and epileptogenic cortex in the human brain, and have shown potential as a diagnostic tool in epilepsy. Valentin et al. (2002) used single pulse electrical stimulation to stimulate the IOZ and recorded responses within and outside of it. They identified both early (<100 ms) and late evoked responses, and determined that while early responses showed a similar distribution in normal and pathological tissue, late responses, which presented like after-discharges, were linked to the IOZ in patients with temporal lobe epilepsy (TLE).

Notably, in TLE the distribution of delayed responses was nearly as reliable as studying seizure onset in localization of the IOZ. This suggests CCEPs may not only allow identification of seizure networks, but could also be clinically useful in corroborating the suspected IOZ.

Stimulation of the IOZ results in larger N1 responses than when normal cortex is perturbed (Iwasaki et al., 2010; Enatsu et al., 2012b).

Additionally, ictal onset patterns characterized by repetitive spiking show larger CCEPs amplitudes than those by focal paroxysmal fast activity. These results seem to contradict the conclusion by Lacruz et al. (2007) that ipsilateral and contralateral connections between normal and epileptogenic hemispheres were similar. These findings may be reconciled by considering that the latter study only looked for the presence or absence of CCEPs responses, while those that found differences between ictal and normal cortex assessed the amplitude of evoked potentials.

In addition to ictal onset, ictal propagation has also been explored using CCEPs. The topography of brain networks as determined by CCEPs is often partially inconsistent with seizure spread. For example, CCEPs carried out on the posterior cingulate gyrus in patients with posterior cingulate epilepsy revealed effective connections that did not completely correlate with seizure spread (Enatsu et al., 2014). Furthermore, in cases where focal epilepsy was associated with secondary generalization, the discrepancy between CCEPs distribution and ictal propagation patterns was larger than in those without secondary generalization. Ictal propagation to regions not generating evoked potentials after stimulation of the IOZ supports the notion of step-wise seizure propagation to regions that are not under the direct influence of the electrographically identified IOZ. At the same time, regions that respond to CCEPs but do not display ictal activity lend credence to the presence of inhibitory mechanisms that prevent ictal activity from spreading throughout entire neural networks (Enatsu et al., 2012a).

ETIOLOGY OF EPILEPSY

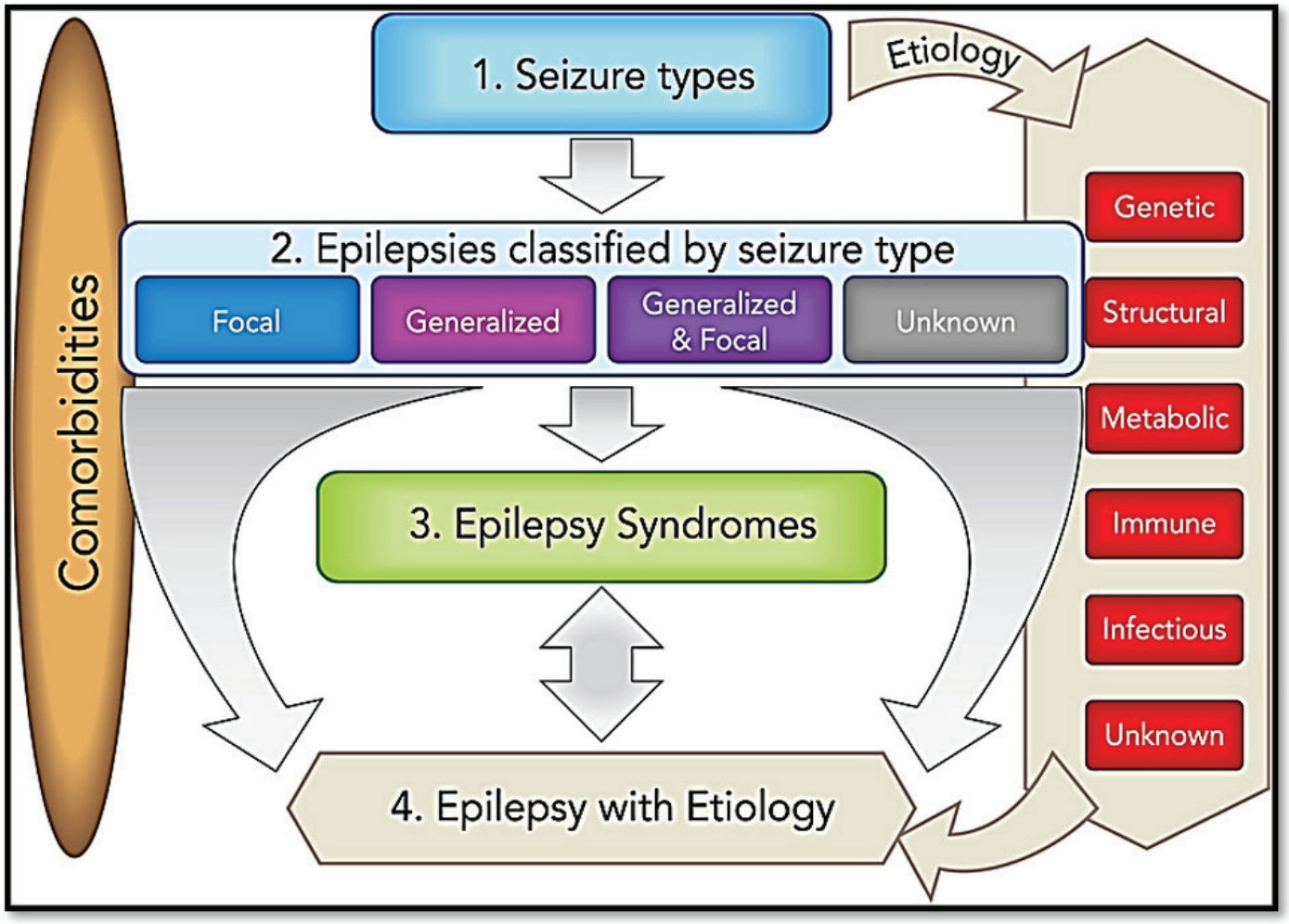

Figure 4 ETIOLOGY OF EPILEPSY

Epilepsy is a neurological disorder characterized by recurrent, unprovoked seizures, which are episodes of abnormal electrical activity in the brain.

Genetic Factors:

Genetics plays a significant role in epilepsy. Various genetic mutations and alterations can predispose individuals to epilepsy. Some forms of epilepsy have a clear genetic basis, while others may have a complex genetic component involving multiple genes interacting with environmental factors.

Structural Brain Abnormalities: Structural abnormalities in the brain are commonly associated with epilepsy. These abnormalities can result from prenatal factors (such as genetic mutations or developmental abnormalities), perinatal factors (such as birth trauma or hypoxia), or postnatal factors (such as traumatic brain injury or infections).

Common structural abnormalities linked to epilepsy include cortical dysplasia, hippocampal sclerosis, tumors, vascular malformations, and post-traumatic scars.

Metabolic and Neurotransmitter Imbalances:

Imbalances in neurotransmitters (chemical messengers in the brain) and metabolic disturbances can contribute to the development of epilepsy. For example, deficiencies in neurotransmitters like gamma-aminobutyric acid (GABA), which has inhibitory effects in the brain, can lead to increased excitability and seizure activity.

Infections and Inflammatory Conditions:

Certain infections and inflammatory conditions affecting the brain can trigger epileptic seizures. Examples include viral infections like herpes simplex encephalitis, bacterial meningitis, and autoimmune disorders such as autoimmune encephalitis.

Developmental Disorders:

Individuals with developmental disorders such as autism spectrum disorder or intellectual disability have a higher risk of developing epilepsy. The underlying neurological abnormalities associated with these developmental disorders may predispose individuals to seizures.

Traumatic Brain Injury:

Head trauma, such as that resulting from accidents, falls, or physical assaults, can cause damage to the brain and increase the risk of epilepsy. Post-traumatic epilepsy can develop immediately after the injury or months to years later.

Cerebrovascular Disease:

Conditions affecting the blood vessels in the brain, such as stroke, hemorrhage, or cerebral venous thrombosis, can disrupt blood flow and oxygen supply to brain tissue, leading to seizures.

Perinatal and Neonatal Factors:

Events occurring during pregnancy, labor, or shortly after birth can influence the risk of developing epilepsy later in life. Factors such as prenatal exposure to toxins, maternal infections, premature birth, or hypoxic-ischemic encephalopathy (lack of oxygen to the brain during birth) can increase the likelihood of epilepsy.

Environmental Factors:

Certain environmental factors, such as exposure to toxins, pesticides, or heavy metals, may contribute to the development of epilepsy, particularly in susceptible individuals.

Idiopathic Epilepsy:

In some cases, epilepsy may occur without an identifiable cause. This form of epilepsy, known as idiopathic epilepsy, is believed to have a strong genetic component, although specific genetic mutations may not always be identified.

Understanding the complex interplay of genetic, structural, environmental, and neurological factors contributing to epilepsy is essential for accurate diagnosis, treatment, and management of the condition. Advances in genetics, neuroimaging, and molecular biology continue to enhance our understanding of epilepsy etiology, paving the way for more personalized approaches to treatment and intervention.

REFERENCES

1. Entz L, Toth E, Keller CJ, Bickel S, Groppe DM, Fabo D, et al. Evoked effective connectivity of the human neocortex. Hum Brain Mapp 2014. http://dx.doi.org/ 10.1002/hbm.22581.

2. Fisher RS, van Emde Boas W, Blume W, Elger C, Genton P, Lee P, et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against

3. Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia 2005;46:470–2.

4. Friston KJ. Functional and effective connectivity in neuroimaging: a synthesis. Hum Brain Mapp 1994;2:56–78.

5. Friston KJ. Functional and effective connectivity: a review. Brain Connect2011;1:13–36.

6. Friston KJ, Frith CD, Liddle PF, Frackowiak RS. Functional connectivity: the principalcomponent analysis of large (PET) data sets. J Cereb Blood Flow Metab 1993;13:5–14.

7. Gomez-Gardenes J, Gomez S, Arenas A, Moreno Y. Explosive synchronization transitions in scale-free networks. Phys Rev Lett 2011;106:128701.

8. Gotman J. Measurement of small time differences between EEG channels: method and application to epileptic seizure propagation. Electroencephalogr Clin Neurophysiol 1983;56:501–14.

9. Greicius MD, Krasnow B, Reiss AL, Menon V. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. Proc Natl Acad Sci USA 2003;100:253–8.

10. Guye M, Regis J, Tamura M, Wendling F, McGonigal A, Chauvel P, et al. The role of corticothalamic coupling in human temporal lobe epilepsy. Brain 2006;129:1917–28.

11. Hagmann P. From diffusion MRI to brain connectomics [Ph.D. dissertation] Lausanne, CH: EPFL; 2005.

a. Haneef Z, Lenartowicz A, Yeh HJ, Levin HS, Engel Jr J, Stern JM. Functional connectivity of hippocampal networks in temporal lobe epilepsy. Epilepsia 2014;55:137–45.

12. He B, Liu Z. Multimodal functional neuroimaging: integrating functional MRI and EEG/MEG. IEEE Rev Biomed Eng 2008;1:23–40.

13. Hobbs JP, Smith JL, Beggs JM. Aberrant neuronal avalanches in cortical tissue removed from juvenile epilepsy patients. J Clin Neurophysiol 2010;27:380–6.

14. Honey CJ, Kotter R, Breakspear M, Sporns O. Network structure of cerebral cortex shapes functional connectivity on multiple time scales. Proc Natl Acad Sci USA 2007;104:10240–5.

15. Iwasaki M, Enatsu R, Matsumoto R, Novak E, Thankappen B, Piao Z, et al. Accentuated cortico-cortical evoked potentials in neocortical epilepsy in areas of ictal onset. Epileptic Disord 2010;12:292–302.

16. Keller CJ, Bickel S, Entz L, Ulbert I, Milham MP, Kelly C, et al. Intrinsic functional architecture predicts electrically evoked responses in the human brain. ProcNatl Acad Sci USA 2011;108:10308–13.

17. Keller CJ, Bickel S, Honey CJ, Groppe DM, Entz L, Craddock RC, et al.

18. Neurophysiological investigation of spontaneous correlated and anticorrelated fluctuations of the BOLD signal. J Neurosci 2013;33:6333–42.

19. Keller CJ, Honey CJ, Entz L, Bickel S, Groppe DM, Toth E, et al. Corticocortical evoked potentials reveal projectors and integrators in human brain networks. J Neurosci 2014a;34:9152–63.

20. Keller CJ, Honey CJ, Mégevand P, Entz L, Ulbert I, Mehta AD. Mapping human brain networks with cortico-cortical evoked potentials. Philos Trans R Soc B 2014. http://dx.doi.org/10.1098/rstb.2013.0528.

21. Kiebel SJ, Garrido MI, Moran R, Chen CC, Friston KJ. Dynamic causal modeling for EEG and MEG. Hum Brain Mapp 2009;30:1866–76.

22. Kokkonen SM, Nikkinen J, Remes J, Kantola J, Starck T, Haapea M, et al. Preoperative localization of the sensorimotor area using independent component analysis of resting-state fMRI. Magn Reson Imaging 2009;27:733–40.

23. Kramer MA, Cash SS. Epilepsy as a disorder of cortical network organization.

24. Neuroscientist 2012;18:360–72

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