Chapter

Clinical Neurophysiology of Epileptogenic Networks

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Abstract

Current theories and models of brain rhythm generation are based on (1) the excitability of individual neurons and whole networks, (2) the structural and functional connectivity of neuronal ensembles, (3) the dynamic interaction of excitatory and inhibitory network components, and (4) the importance of transient local and global states. From the interplay of the above, systemic network properties arise which account for activity overdrive or suppression, and critical-level synchronization. Under certain conditions or states, small-to-large scale neuronal networks can be entrained into excessive and/or hypersynchronous electrical brain activity (epileptogenesis). In this chapter we demonstrate with artificial neuronal network simulations how physiological brain oscillations (delta, theta, alpha, beta and gamma range, and transients thereof, including sleep spindles and larger sleep waves) are generated and how epileptiform phenomena can potentially emerge, as observed at a macroscopic scale on scalp and intracranial EEG recordings or manifested with focal and generalized, aware and unaware, motor and nonmotor or absence seizures in man. Fast oscillations, ripples and sharp waves, spike and slow wave discharges, sharp and rhythmical slow waves, paroxysmal depolarization and DC shifts or attenuation and electrodecremental responses seem to underlie key mechanisms of epileptogenesis across different scales of neural organization and bear clinical implications for the pharmacological and surgical treatment of the various types of epilepsy.

Keywords: epilepsy, seizure, epileptogenic networks, epileptogenesis, focal and generalized epilepsies, epileptic syndromes, cortico-thalamo/ganglio-cortical networks (primary generalized tonic-clonic seizures, myoclonic jerks, photoparoxysmal responses, typical and atypical absences), focal neocortical and allocortical or limbocortical networks (focal [auto]motor, aware or unaware seizures with secondary propagation, bilateral spreading and/or generalization), nerve action potential, depolarization and repolarization, excitatory and inhibitory postsynaptic potentials, neuronal and network excitability, structural and functional network connectivity, physiological brain oscillations (delta, theta, alpha, beta and gamma oscillations, sleep spindles, sleep waves), fast oscillations and synchronization, ripples and sharp waves, paroxysmal depolarization and DC shifts, spike and slow wave discharges, sharp and rhythmical slow waves, electrodecremental responses and desynchronization, stochastic resonance, phasic and tonic inhibition, critical-level synchronization, depolarization block, critical global and local transient brain states, decreased network inhibition or defective activation of GABAergic transmission,

increased network excitation (glutamatergic, cholinergic and monoaminergic transmission) or excitability and synchronization, biological and artificial neuronal networks, excitatory and inhibitory network components, recurrent neuronal networks with inhibitory feedback, pulse-coupled neural networks and neuronal spiking models, cerebral cortex, neocortex and allocortex, thalamus and basal ganglia, hippocampus, entorhinal cortex and limbic system, brainstem, ascending reticular activation system, intracellular and extracellular recordings, local-field potentials, intracranial and scalp-surface electroencephalography, antiseizure or antiepileptic medications, epileptogenesis-modifying medications, pharmacological, neurostimulation, neurosurgical treatments of epilepsy

1. Introduction

A seizure is the clinical manifestation of an abnormal, excessive or hypersynchronous discharge of a population of neurons [1]. Epileptogenesis is the sequence of underlying processes and/or events that can turn a neuronal network into an epileptogenic (hyperexcited or hypersynchronous) one [1–6].

Generalized epileptic seizures are considered to originate at some point within, and rapidly engage bilaterally distributed networks, including cortical (not necessarily the entire cortex) and subcortical structures (diencephalon/thalamus, basal ganglia, limbic system). Even if individual seizure onsets appear localised or asymmetric, the location and lateralisation may not be consistent from one seizure to another [1–6].

Focal epileptic seizures are considered to originate primarily within networks limited to one cerebral hemisphere. These are more discretely localised or distributed, and can originate or involve cortical and subcortical structures independently in either hemisphere. Ictal onset is consistent from one seizure to another with preferential propagation patterns, usually slower when compared to generalized epilepsies, which can potentially evolve and spread to the contralateral hemisphere or eventually engage bilateral hemispheres (bilateral spreading or secondary generalisation). In cases where there are more than one local epileptogenic networks involved corresponding to more than one seizure types, each individual seizure type has a consistent site of onset [1–6].

The fundamental principle of causality implies that both processes, 'focal' and 'generalized', start somewhere locally in the brain. The particular propagation pathways, how rapidly they spread and engage bilateral cortical networks are crucial for the distinction of 'focal' and 'generalized' epileptogenic networks, which may be more of an operational rather than a pragmatic dichotomy.

All diverse clinical patterns of seizures with either focal or generalized underlying pathomechanisms can be classified into a few categorical types of stereotypical epileptic features: seizures with preserved, impaired or lost *awareness* or *consciousness* and with predominantly *motor* (clonic/myoclonic, tonic/myotonic/dystonic, hyperkinetic/paretic or spasms), *limited-motor* (subtle automatisms, negative myoclonus, atonia, behavioural changes) or *non-motor* (sensory, autonomic, perceptual, behavioural arrest or absences) manifestations (**Table 1**) [1–6].

Seizure propagation takes preferential faster or slower pathways through the same neural/cerebral substrate in terms of neocortical structural connections (short-range and long-range association fibers: arcuate fasciculus, uncinate fasciculus, superior and inferior fronto-occipital fasciculi, etc. and interhemispheric association fibers: corpus

I. Generalized onset - usually compromised consciousness/awareness with variable degrees of motor manifestations, as a result of rapid bilateral hemispheric spread from the very beginning of the seizure and involvement of key (not necessarily all) *neocortical and subcortical structures (diencephalon, basal ganglia and limbic system, brainstem and cerebellum)*
A. Seizures with tonic and/or clonic manifestations (tonic-clonic, clonic or tonic seizures) **B. Absences** (typical, atypical or myoclonic absences) **C. Myoclonic seizure types** (myoclonic seizures, myoclonic-astatic seizures or eyelid-myoclonia) **D. Epileptic spasms** (myotonic seizures) **E. Atonic seizures**
II. Focal onset – may or may not (to a variable extent) compromise consciousness/awareness, and show variable degrees of motor and sensory manifestations implying more focal involvement, at least initially confined only to one cerebral hemisphere, of key *neocortical [frontal, temporal, insular, parietal, occipital] and/or subcortical structures (diencephalon, basal ganglia and limbic system, brainstem and cerebellum)*, with potential for ipsilateral, contralateral and/or bilateral hemispheric spreading and/or secondary generalisation
A. Localised to: **1.** ***Neocortical*** **- without local spread** (focal clonic, myoclonic or inhibitory-motor seizures, focal sensory seizures with elementary symptoms) or **with local spread** (jacksonian march-seizures, focal tonic [asymmetric] seizures, dysphasic/aphasic seizures or focal sensory seizures with experiential symptoms) **2.** ***Limbic-system*** **predominantly** (hippocampal, parahippocampal)
B. With ipsilateral propagation to: **1.** ***Neocortical areas*** (includes hemi-tonic, hemi-clonic or hemi-atonic seizures) **2.** ***Limbic areas*** (insula, amygdala, hypothalamus, including gelastic seizures)
C. With contralateral spreading to: **1.** ***Neocortical areas*** (hyperkinetic seizures) **2.** ***Limbic areas*** (dyscognitive seizures with or without automatisms [psychomotor])
D. With bilateral spreading or secondarily generalized: **1. Tonic-clonic seizures** **2. Absence seizures** **3. Epileptic spasms (from focal lesions)**

Table 1.
Basic seizure categorization scheme [1–6].

callosum, anterior and posterior commissures) and functional network connectivities (sensorimotor, central-executive, default-mode, salience, visuospatial attention, language, visual networks, etc.), as well as subcortical structures (thalamus, limbic system and ascending reticular activating system [ARAS]) or subcortical network connections and functional connectivities (thalamocortical, limbic system fibers [cingulum, fornix, medial forebrain bundle, etc.]) [7].

Across diverse seizure patterns the following fundamental seizure types emerge with fairly distinct pathomechanisms in the underlying epileptogenic networks (**Table 2**) [1–5].

Based on further patient and epilepsy characteristics, in particular age at onset and remission (where applicable), seizure triggers, diurnal variation, distinctive comorbidities such as intellectual, neurological and psychiatric abnormalities, evolution and progression of the condition or not, correlated with the underlying brain pathology, aetiology and pathophysiology, electroclinical, neuroimaging and genetic investigations, epilepsies can be organized into more complex clinical diagnostic entities, so-called epilepsy syndromes. Such syndromes have a typical age of seizure onset,

Focal motor aware or unaware (more extended local networks involved)	Focal motor with ipsilateral or contralateral propagation, bilateral spreading or secondary generalized	Primarily generalized (originate within and rapidly engage bilaterally distributed networks), involving cortical and subcortical structures	Absence seizures	Myoclonic jerks	Epileptic Spasms

Table 2.
Fundamental seizure types emerging from seizure semiology and distinct pathophysiological processes.

specific seizure types and EEG characteristics and other electroclinical and neuroimaging features which, when taken together, allow the specific syndromic epilepsy diagnosis [8, 9]. The identification of an epilepsy syndrome is useful as it provides information on which underlying aetiologies should be considered, what is the current and future prognosis, which pharmacological anti-seizure medications and/or neurosurgical or neurostimulation interventions might be most useful. Certain epilepsy syndromes may manifest seizure exacerbation, modification or ineffective control with particular anti-seizure medications, which can be avoided and seizure-control outcomes can be optimized through early syndromic diagnosis [2–6, 8–11]

The differential effectiveness of antiepileptic drugs across seizure types highlights likely distinct seizure pathomechanisms and the underlying pathophysiological processes of different epileptic syndromes (**Table 3**) [8–11].

Antiseizure medications in *italics* are generally avoided or contraindicated for the treatment of idiopathic (genetic) generalized epilepsies (**Table 3**). **Carbamazepine, Oxcarbazepine, (Fos)Phenytoin** (mainly voltage-dependent sodium channel blockers binding in the inactivated sodium channels and preventing high-frequency action potentials) may be used in the rare pure forms of primarily generalized tonic-clonic seizures (GTCS) but are not indicated as first-line for idiopathic generalized epilepsies, either because they are ineffective or may exaggerate/exacerbate certain types of seizures. Carbamazepine may treat manic and depressive symptoms in bipolar disorder by increasing dopamine turnover and GABA transmission. **Eslicarbazepine** has lower affinity for inactive voltage-gated sodium channels in the resting state compared to Carbamazepine and Oxcarbazepine, thereby selectively inhibits repeated neuronal firing in the epileptic focus, as well as T-type calcium channels in vitro. **Lacosamide** may be selective for inhibiting depolarized neurons (slow inactivation gating of sodium channels), affecting only those neurons (at the epileptic focus) which are depolarized or active for long periods of time. **Lamotrigine** (acting as voltage-gated inactivated sodium channel and R-type calcium channel blocker, suppressing glutamate release and stabilising membranes) may exaggerate myoclonic jerks in juvenile myoclonic epilepsy and some progressive myoclonic epilepsies. **Ethosuximide** (T-type calcium channel blocker) is only effective for absences and may be effective in negative myoclonus. **Levetiracetam** is an inhibitor of synaptic vesicle protein 2A (SVP2A) and presynaptic neurotransmitter release in high-frequency firing neurons and inhibitor of N-type calcium channels. It may indirectly enhance GABAergic neurotransmission via GABA-A receptors and decrease glutaminergic excitation via modulation of NMDA and AMPA receptors or upregulation of glial glutamate transporters. **Brivaracetam** is the racetam derivative of Levetiracetam with 20 times higher affinity for binding SVP2A, while also inhibiting sodium channels and impairing epileptogenesis through modulation of

AEDs	Focal seizure motor or not, aware or unaware	Focal seizure secondarily generalized GTCS	Primarily generalized GTCS	Myoclonic jerks	Absence seizures
Valproate	Effective	Effective	Effective	Effective	Effective
Ethosuximide	Ineffective	Exaggerates?	Exaggerates?	Effective in negative myoclonus	Effective
Zonisamide	Effective	Effective	Effective	Effective	Effective?
Topiramate	Effective	Effective	Effective	Effective	Effective?
Levetiracetam Brivaracetam	Effective Effective (adjunct)	Effective Effective (adjunct)	Effective Unknown	Effective Unknown	Effective Unknown
Lamotrigine	Effective	Effective	Effective	Exaggerates	Effective
Phenytoin	*Effective*	*Effective*	*Effective*	*Ineffective*	*Exaggerates*
Carbamazepine	*Effective*	*Effective*	*Effective*	*Ineffective*	*Ineffective, Exac of atypical absences?*
Oxcarbazepine	*Effective*	*Effective*	*Effective*	*Exacerbates*	*Exacerbates*
Eslicarbazepine	Effective	Effective	Effective	Ineffective	Ineffective
Lacosamide	Effective	Effective	Effective (adjunct)	Unknown	Unknown
Cenobamate	Effective (adjunct)	Effective (adjunct)	Unknown	Unknown	Unknown
Perampanel	Effective (adjunct)	Effective (adjunct)	Effective (adjunct)	Unknown	Unknown
Phenobarbital	Effective	Effective	Effective	Effective	Exaggerates?
Clobazam	Effective	Effective	Effective?	Effective?	Effective?
Clonazepam	Effective?	Effective?	Ineffective?	Effective	Effective
Tiagabine	*Effective (adjunct)*	*Effective (adjunct)*	*Ineffective*	*Exaggerates*	*Exaggerates*
Vigabatrin	*Effective (adjunct)*	*Effective (adjunct)*	*Ineffective* *Effect for Epl.Spasms*	*Exaggerates*	*Exaggerates*
Gabapentin *Pregabalin*	*Effective* *Effective (adjunct)*	*Effective* *Effective (adjunct)*	*Ineffective* *Ineffective*	*Exaggerates* *Exaggerates*	*Exaggerates* *Exaggerates*

Table 3.
Adapted from Panayiotopoulos [5] and adjusted based on updated publicly available information from https://www.medicines.org.uk/emc and https://www.fda.gov/drugs and https://go.drugbank.com/drugs and https://bnf.nice.org.uk/

synaptic GABA. **Zonisamide** (blocking repetitive firing of voltage-gated sodium channels, reducing T-type calcium channel currents or binding allosterically to GABA receptors inhibits the uptake of GABA and enhances the uptake of glutamate) and **Topiramate** (voltage-dependent sodium channel blocker, allosteric stimulator of GABA-A receptors and inhibitor of AMPA and Kainate glutamate receptors) are effective in all types of epilepsy. **Cenobamate** reduces repetitive neuronal firing in the epileptic focus by enhancing the inactivation of sodium channels and inhibiting the persistent component of the sodium current and acts as a positive allosteric modulator

of GABA-A ion channel subtypes. **Gabapentin** (presynaptic voltage-dependent calcium channel inhibitor and dose-dependent inducer of L-glutamic acid decarboxylase that enhances GABA synthesis) and **Pregabalin** used as adjunctive for focal seizures may have pro-myoclonic effects. **Clonazepam** (1,4-benzodiazepine, full agonist of GABA-A receptors resulting in increase in the frequency of chloride-channel opening) is mainly used for myoclonic jerks, but it may not suppress GTCS of juvenile myoclonic epilepsy. **Clobazam** (1,5-benzodiazepine, partial agonist of GABA-A receptors) licensed as adjunctive therapy may be more efficacious in focal than generalized epilepsies. **Phenobarbital** is a potentiator agonist of GABA-A receptors resulting in increased duration of chloride-channel opening and may also act on Glutamate receptors. **Perampanel** (non-competitive AMPA glutamate receptor antagonist) is mostly used for focal epilepsies and only as adjunctive for primary generalized ones. **Valproate** (directly suppresses voltage-gated sodium channel activities and influences many other channels and neurotransmitters and indirectly enhances GABAergic neurotransmission as inhibitor of succinic semialdehyde dehydrogenase [GABA transaminase]) is effective against all types of epilepsy [5, 8–11]. **Fenfluramine** (a serotonin-releasing agent that stimulates multiple 5-HT receptor subtypes) is used as an adjunctive treatment in Dravet syndrome. **Rufinamide** (prolonging the inactive state of voltage-gated sodium channels and inhibiting mGluR5 subtype receptors at high concentration) is used as an adjunctive treatment of seizures in Lennox-Gastaut syndrome. **Stiripentol** potentiates GABAergic transmission by elevating the levels of GABA and acting as a positive allosteric modulator of GABA-A receptors and is used as an adjunctive treatment in Dravet syndrome. **Cannabidiol** (**CBD Oil)**, the major component of the resin of *Cannabis sativa* plant (marijuana), is devoid of the psychoactive, euphoric or intrusive effects and abuse liability of the tetrahydrocannabinol (THC) component. Endocannabinoid receptors regulate cognition, pain sensation, appetite, memory, sleep, immune function, fear, emotion or mood and are mostly localized in the hippocampus and amygdala. Cannabidiol may have low affinity for endocannabinoid receptors but may indirectly modulate these receptors by blocking the breakdown of Anandamide. It could also activate the transient receptor potential of Vanilloid type-1 (TRPV1), antagonise the G protein-coupled receptor 55 (GPR55), target abnormal sodium channels, block T-type calcium channels, modulate adenosine receptors or adenosine reuptake, voltage-dependent anion selective channel protein (VDAC1) or tumor necrosis factor alpha (TNFa) release. It has been licenced as adjunctive treatment in Tuberous Sclerosis and (together with Clobazam) in Lennox-Gastaut and Dravet syndromes. (publicly available information at: https://go.drugbank.com/drugs and https://bnf.nice.org.uk/).

2. Physiological brain networks

From individual neurons to dynamic neuronal networks

In the following, embarking from the Hodgkin-Huxley neuronal membrane model we endeavour to create biologically realistic and computationally efficient models of spiking neurons and further on to generate a local spiking neuronal network of a 1000 excitatory and inhibitory neurons. Our aim is to study the behaviour of this simple network under different structural and functional constraints, and critical network parameters, in order to understand the rich network dynamics that emerge, and gain insight into the physiology of cortical neuronal networks and pathophysiology of seizures [12].

2.1 Modeling the neuron

The Hodgkin-Huxley biological neuron model

The Hodgkin-Huxley type models [13] represent the biophysical properties of cell membranes and ionic conductances (current flows) that help determine at any time the neuronal resting and action membrane potentials (for mathematical details [14]). The lipid bilayer is represented as a capacitance (Cm). Voltage-gated and leak ion channels are represented by nonlinear (gn) and linear (gL) conductances, respectively. The electrochemical gradients driving the flow of ions are represented by batteries (E), and ion pumps and exchangers are represented by current sources (Ip) (**Figure 1**) [12, 15].

If the integration of Excitatory Postsynaptic Potentials (EPSP) and Inhibitory Postsynaptic Potentials (IPSP) at the long somatodendritic processes of pyramidal neurons (thousands of synaptic contacts) [16] is sufficient to shift the resting membrane potential at the axon hillock closer to threshold (around −55 mV, inside negative), voltage-gated fast Na-channels open up allowing an influx of Na^+ and depolarization current sufficient to turn the inside of the membrane positive, resulting in the generation of an action potential (up to +40 mV, the inside positive). The local reversal of the membrane potential during the upstroke makes the Na^+ channels rapidly turn into an inactivated (non-conducting absolute refractory) state, while different voltage-gated channels open up allowing together with leaky K^+ channels for the early repolarisation and late after-hyperpolarisation phases of the membrane potential (prolonged relative refractory state). This is a very simplified *integrate-and-fire model* of a neuron and accounts for the action potential generated in a neuron (**Figures 2** and **3a** and **b**) [19].

The processing of post-synaptic potentials is much more than a simple algebraic summation, most likely a geometrical (vectorial) spatiotemporal integration with very

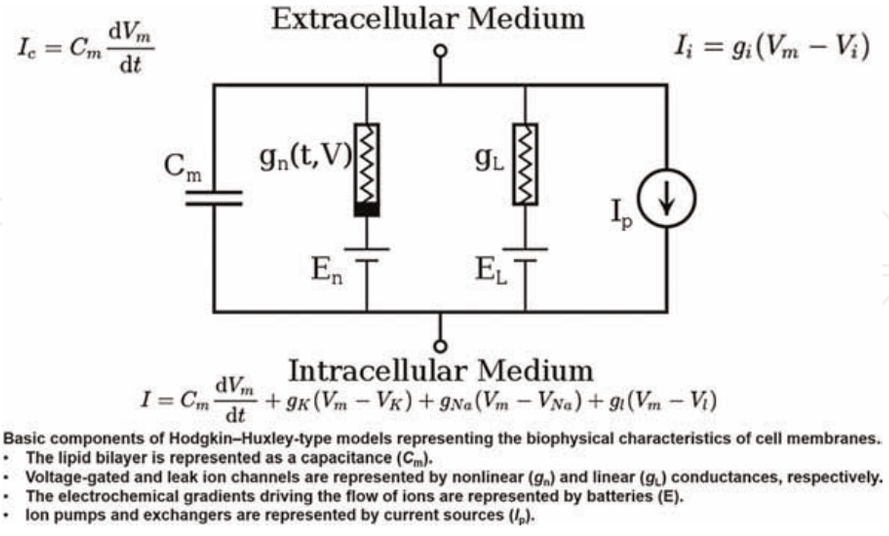

Figure 1.
The electronic circuit equivalent of the Hodgkin-Huxley biological neuronal model [14] from https://commons.wikimedia.org/wiki/File:Hodgkin-Huxley.svg By Krishnavedala via Wikimedia Commons—Own work, CC0, https://commons.wikimedia.org/w/index.php?curid=21725464 with added-on fundamental equations for current flowing through the lipid bilayer (I_c), current through a given ion channel (I_i) and total current through the membrane (I) for a cell with potassium (K^+) and sodium (Na^+) channels. V_m is the membrane potential, V_i is the reversal potential of the i*-th ion channel,* V_K *and* V_{Na} *are the potassium and sodium reversal potentials, respectively,* g_K *and* g_{Na} *are the potassium and sodium voltage-gated (nonlinear) conductances per unit area, respectively and* g_l *and* V_l *are the leak (linear) conductance per unit area and leak reversal potential, respectively.*

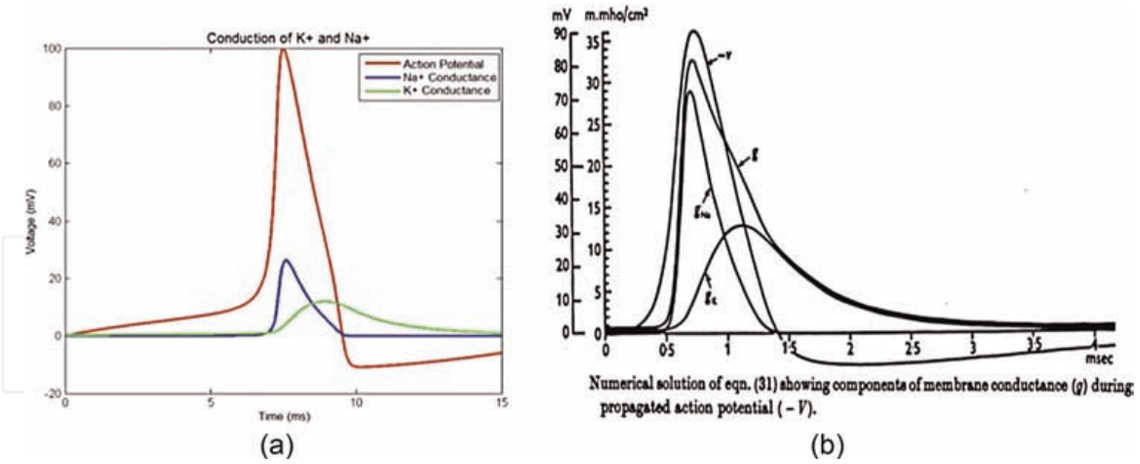

Figure 2.
(a) Main sodium and potassium conductance/current giving rise to the action membrane potential, reproduced under CC BY 4.0 from: Figure 6 of Johnson M & Chartier S (2017). Spike neural models (part I): The Hodgkin-Huxley model. The Quantitative Methods for Psychology [17]. (b) A graph of the sodium and potassium conductances (GNa and GK), their sum (Gm), and the membrane voltage (Vm) during a propagating nerve impulse, which is basically a numerical solution of the Eq. 4.32 published by Hodgkin AL & Huxley AF. A quantitative description of membrane current and its application to conduction and excitation in nerve. The Journal of Physiology [18].

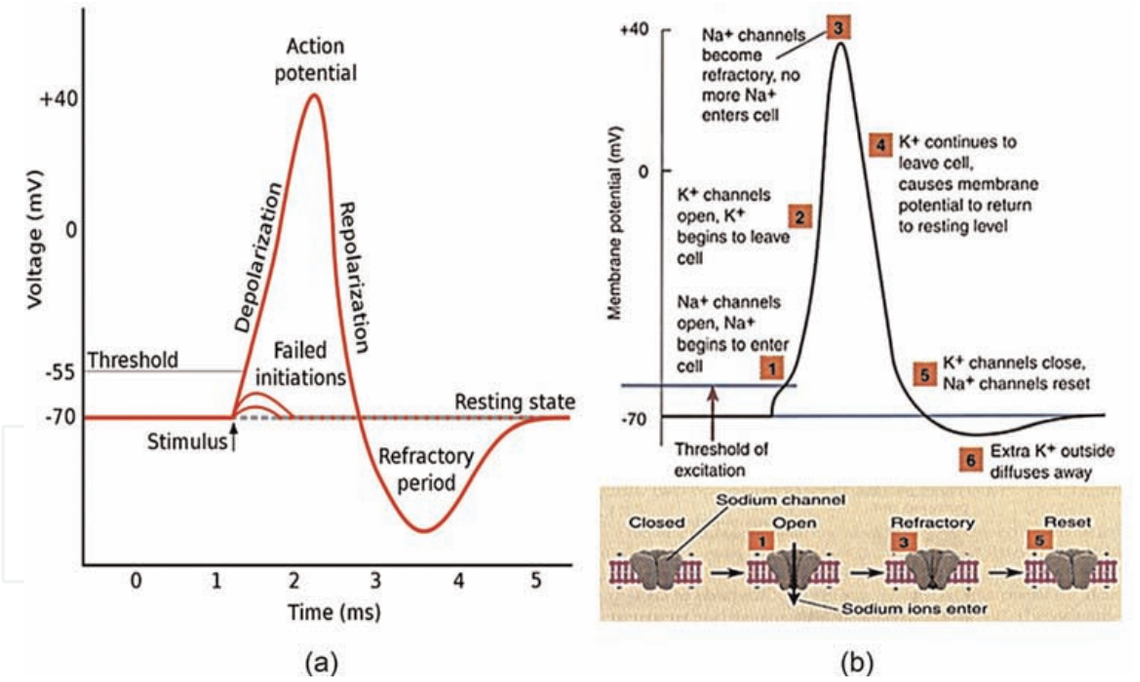

Figure 3.
(a) Approximate plot of a typical action potential shows its various phases as the action potential passes a point on a cell membrane. The membrane potential starts out at approximately −70 mV at time zero. A stimulus is applied at time = 1 ms, which raises the membrane potential above −55 mV (the threshold potential). After the stimulus is applied, the membrane potential rapidly rises to a peak potential of +40 mV at time = 2 ms. Just as quickly, the potential then drops and overshoots to −90 mV at time = 3 ms, and finally the resting potential of −70 mV is reestablished at time = 5 ms. By Original by en:User:Chris 73, updated by en:User:Diberri, converted to SVG by tiZom —Own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=2241513 (b) ion movements during an action potential, showing when channels open or close during the action potential. Bottom image shows the corresponding sodium channel states at specific points of the action potential. The diagram was created by: If Only and was retrieved online from: scioly.org/wiki/index.php/File:Image12.jpg (publicly available).

complex feature-extracting properties. Many pyramidal neurons with long/extensive arborization processes geometrically integrate in time all postsynaptic EPSP and IPSP on their somatodendrites into a postsynaptic amplitude-modulated potential (analogue signal) which is translated at the axon hillock via an *all-or-none* generated response to an action potential (digital signal). This is fundamentally a nonlinear process [20–22]. Neurons essentially communicate with each other via *all-or-nothing* action potentials (a binary code of 1 or 0). The code of this digital communication lies either in the instantaneous or average firing rates (frequency modulation) or in the critical timing or phase of the firing (time/phase modulation) [23–25]. The postsynaptic potential amplitude-modulation (AM) is basically converted into an instantaneous or average firing rate of cortical pyramidal neurons, a frequency-modulation (FM) code, often seen in primary sensory/visual or motor and other neocortical or allocortical areas. The majority of cortical neurons though seem to rely on a critical-timing and phase-modulation (PM) code for information processing. Furthermore, the firing frequency or firing rate patterns observed may reflect the level of synchrony or synchronization in the underlying spiking neurons [26–29].

2.2 Modelling postsynaptic potentials of neuronal networks

The highest contribution to Local Field Potentials (LFP) and the Electroencephalogram (EEG) signal comes from the postsynaptic membrane potentials of pyramidal

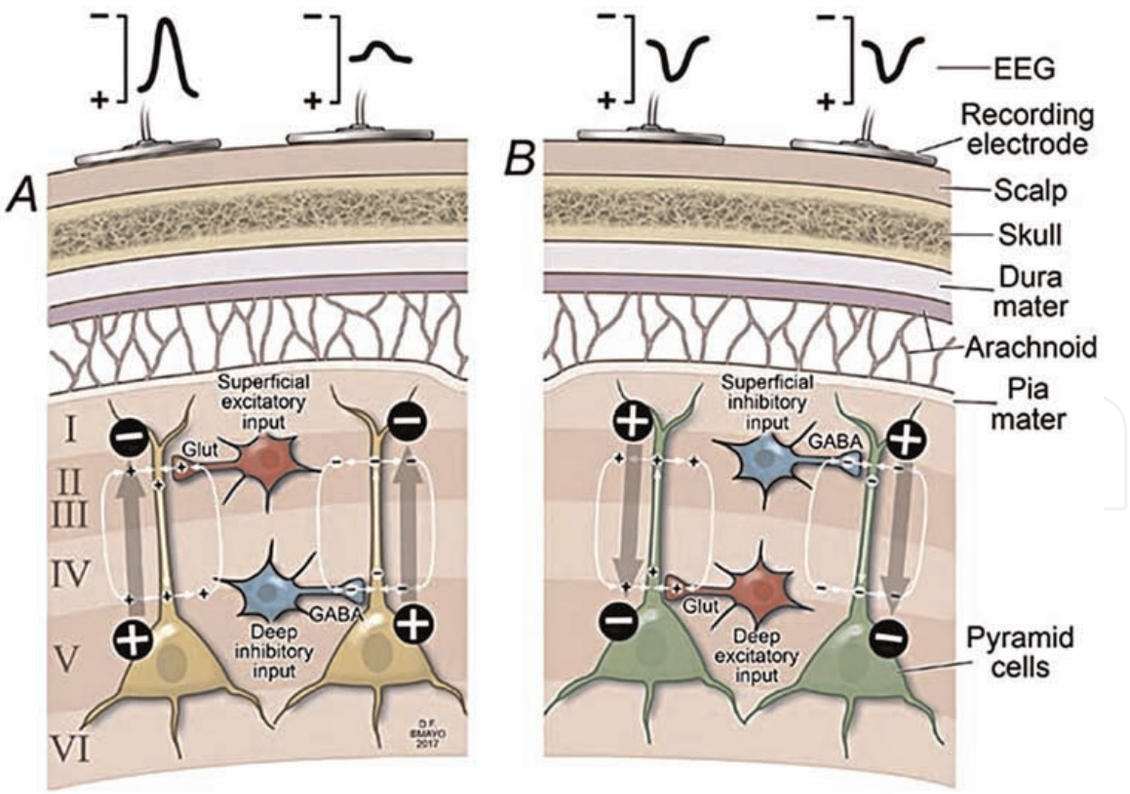

Figure 4.
Neurophysiological basis of the EEG potentials recorded on the scalp surface from the geometrical summation of minute current dipoles of millions of pyramidal cortical neurons with variable magnitude, polarity and orientation depending on the local dominant circuitries implicated each time. Reproduced with permission from Tatum et al. [30].

cells of cortical layer V creating a local current sink or rise, equivalent to a minute electrical dipole pointing at variable directions, depending on the local geometry (infoldings with gyri and sulci) and local circuitry of the cortical region, cortical neurons implicated and their spatial relationship with the scalp sensor (**Figure 4**) [29–32]. In addition, there is volume conducted electrical activity from every other region of the brain picked up at all scalp sensors, which is difficult to disentangle from the particular region in question, especially when other sources dominate the background (known as the reverse problem of EEG source localisation). To make things worse, the scalp and all the layers of tissue that intervene between the cerebral cortex and the scalp surface sensors act as low-pass filters, filtering out most of the high-frequency (mostly gamma range) activities of the EEG and severely contaminating the recorded EEG with muscle activity, eye or movement and other artefacts. The extracranial EEG may have excellent temporal resolution (down to the millisecond scale), but has fairly poor spatial resolution [29, 30, 32].

In principle, for an electrical signal deflection to be detected on the scalp sensor as an electrical potential difference between the underlying cortical region and a less active reference electrode, activities of millions of cortical/pyramidal neurons need to be spatiotemporally summated over an area of about 4–9 (2^2–3^2) cm^2 of cerebral cortex [30, 32]. The larger the numbers of cortical/pyramidal neurons and the more synchronous their depolarization (corresponding to firing rates or bursts of action potentials), the greater the deflection on the scalp EEG (if at right angles to the cortical surface and current lines are traveling in the same direction). Although there are asymmetries between the depolarizing and repolarizing regions of the pyramidal neurons as reflected in current lines and waveform morphologies, current lines are mainly created by the depolarizing wave front and fan out away from the current sink, reflecting the volume conductive properties of that brain region. In essence every depolarization wave-front creates a minute electrical dipole and depending on the direction of that (negative at the apical dendrites vs. positive at the somata or vice versa), the radial components of that to the cortical surface will constructively contribute towards a positive or respectively negative deflection on the scalp EEG signal (**Figure 4**) [29, 30, 32].

None of the shortfalls of scalp EEG is a limiting factor with the use of in-depth electrodes robotically implanted (with accurate coordinates) in the human brain for epilepsy surgery purposes, which can reach even the deepest regions of the brain and record intracranial stereo-EEG from about 1 mm^3 voxels of brain tissue (the issue is which specific points in the brain these multiple depth contacts should target) [29].

The hallmark of epilepsy on the EEG is the interictal epileptiform spike or sharp wave, excessive or hypersynchronous discharges and paroxysmal rhythmical activities or attenuation changes in the background EEG activity before, during and after the seizure. The paroxysmal or synchronous depolarisation of millions of cortical neurons (converted in bursts of spikes or tonic neuronal firing) allows for spatiotemporal summation of the electrical activity of millions of cortical neurons and underlies the excessive or hypersynchronous discharges and other epileptiform phenomena we detect on scalp EEG. The cellular neurophysiological correlate of the interictal and ictal epileptiform discharges is the paroxysmal depolarization shift (PDS) of individual cortical neurons. The PDS is a prolonged (calcium-dependent) neuronal depolarization that results in multiple sodium-channel (inward) current-mediated action potentials during depolarization,

followed by a prominent after-hyperpolarization phase beyond the baseline resting membrane potential, mediated by calcium-dependent potassium-channel (outward) currents and/or gamma-aminobutyric acid (GABA)-activated chloride (Cl^-) currents [33–36].

2.3 Modelling action potentials of neuronal networks

Using biophysically accurate Hodgkin-Huxley-type models for action potentials of neuronal networks would be computationally so demanding [37] that we could simulate only few neurons in real time. Using an integrate-and-fire model is computationally very effective, but the model is unrealistically simple and incapable of producing the rich spiking and bursting dynamics exhibited by cortical neurons. On balance, we adopted the simple spiking model proposed by Izhikevich [38], which is as biologically plausible as the *Hodgkin-Huxley* model, yet as computationally efficient as the *integrate-and-fire* model.

The spiking model developed by Izhikevich [38] essentially represents the complex integration of depolarising forces (voltage-gated and leaky sodium channels/inward currents) and repolarising forces (voltage-gated and leaky potassium channels/outward currents) by determining few key parameters: (a) the rate of decay of the action potential, (b) the sensitivity threshold for triggering the action potential, (c) the reset level of the depolarisation potential of the membrane and (d) the reset level of the repolarisation potential of the membrane. Depending on these four parameters, the model reproduces spiking and bursting behavior of different known types of cortical neurons as shown in **Figure 5**, and allows for dynamic functional connectivity and emergence of waves and rhythms at different scales of neural organization [39].

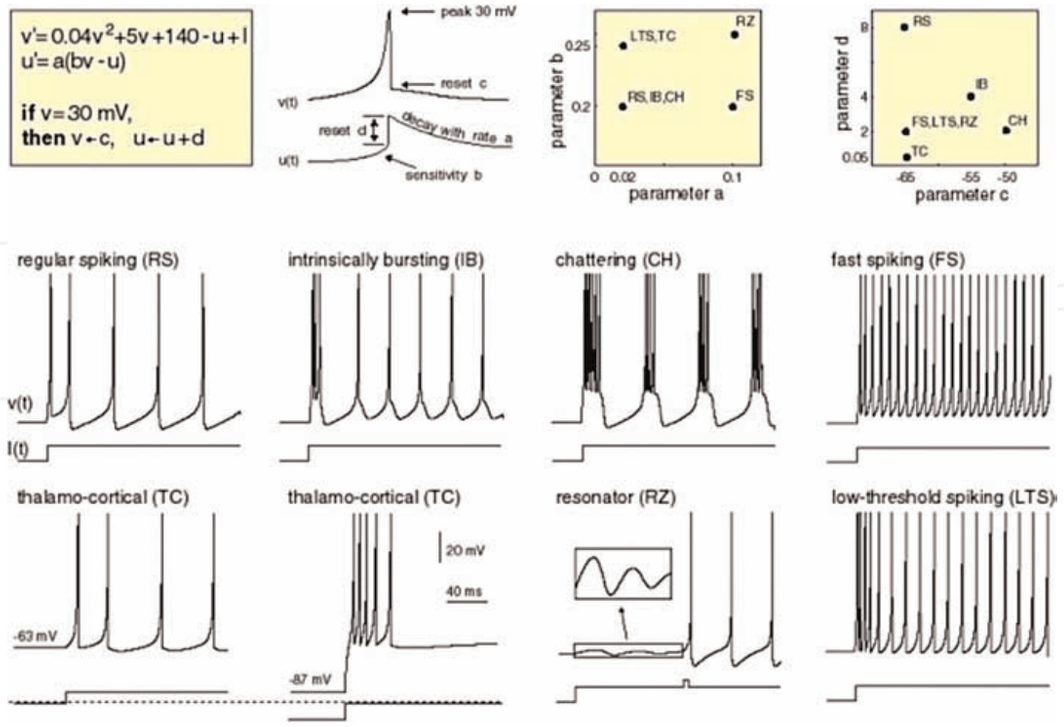

Figure 5.
Known types of cortical neurons correspond to different values of the parameters a, b, c, d in the model described by the equations in the left upper box. RS, IB, and CH are cortical excitatory neurons. FS and LTS are cortical inhibitory interneurons. Each inset shows a voltage response of the model neuron to a step of dc-current I = 10 (bottom). Time resolution is 0.1 ms. This figure has been reproduced with permission from Izhikevich [37–42].

2.4 Cortical neuronal spiking model

Neocortical neurons in the mammalian brain are classified into several types according to the pattern of spiking and bursting seen in intracellular recordings [38]. **Excitatory** cortical cells are divided into 4 different classes, with *RS (regular spiking)* neurons being the most typical neurons of the cortex. Upon a prolonged stimulus (injected DC-current, equivalent in a particular neuron to spatial convergence and temporal summation of more EPSP vs. IPSP) the neurons fire a few spikes with short interspike period and then the period increases (*spike frequency adaptation*). Increasing the strength of the injected DC-current increases the *interspike frequency*, though this can never become too fast because of large spike-after hyperpolarizations. **Inhibitory** cortical cells are usually divided into two classes, the most common being the *FS* (*fast spiking*) neurons that can fire periodic trains of action potentials with extremely high frequency, practically without any adaptation (slowing down). The other type of cortical inhibitory interneurons is the *LTS* (*low threshold spiking*) neurons that start spiking when a minimum low-threshold has been reached [37–42].

The best way to simulate the different dynamics of different neurons, is to assign for each excitatory cell $(a_i, b_i) = (0.02, 0.2)$ and $(c_i, d_i) = (-65, 8) + (15, -6)\, r_i^2$, where r_i is a random variable uniformly distributed on the interval [0, 1], and i is the neuron index. Thus, $r_i = 0$ corresponds to regular spiking (RS) cell, while $r_i = 1$ corresponds to the chattering (CH) cell. We use r_i^2 to bias the distribution toward RS cells. Similarly, each inhibitory cell has $(a_i, b_i) = (0.02, 0.25) + (0.08, -0.05)\, r_i$ and $(c_i, d_i) = (-65, 2)$ [38].

In addition, the Izhikevich model [39] can reproduce the behavior of **thalamocortical neurons**, which provide the major input to the cortex. *TC (thalamo-cortical)* neurons have two firing regimes: When at rest (v is around −60 mV) and then get depolarized, they exhibit tonic firing. However, if a negative current step is delivered and the membrane potential gets hyperpolarized (v is around −90 mV), the neurons fire a rebound burst of action potentials (bursting firing). The dynamics of other neuronal types, including those in **hippocampus**, basal ganglia, brainstem, and olfactory bulb, can also be simulated by this model [41].

The proposed Izhikevich simulation model [42] belongs to the class of pulse-coupled neural networks (PCNN). The synaptic connection weights among the neurons are described by a matrix $S = (s_{ij})$. Firing of the jth neuron instantaneously changes the variable v_i by s_{ij} [38]. Although the network is connected randomly and there is no synaptic plasticity included, the neurons tend to self-organize into assemblies that exhibit collective rhythmical behavior in a frequency range corresponding to that of the awake mammalian cortex. Changing the relative strength (weights) of synaptic connections (excitatory and inhibitory) and the strength of the thalamic drive can produce other types of collective behavior, including spindle waves and larger slow sleep oscillations [39]. Therefore, our spiking model is fairly adaptable and can reproduce the dynamics of many different known types of neocortical and allocortical neurons (biological plausibility), while its high computational efficiency allows us to observe and study collective cortical states at a global neuronal network level [37–42].

3. Epileptogenic brain networks

3.1 Cortico-thalamocortical neuronal networks

The reticular nucleus of the thalamus is part of the ascending reticular activating system (RAS) that modulates thalamocortical pathways and helps to synchronize and

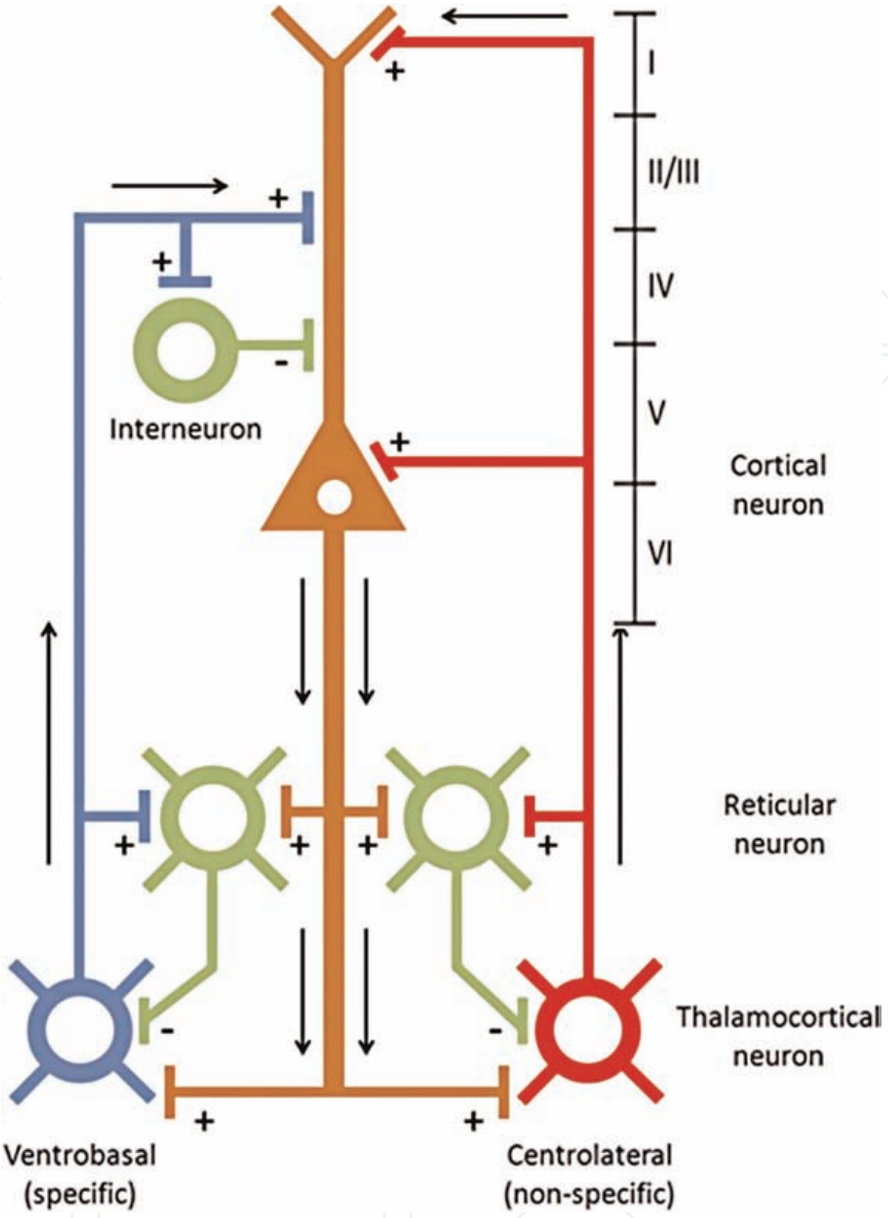

Figure 6.
The thalamocortical network. Please note the projection of specific and association thalamic nuclei project to layers III and IV of the neocortex and the projection of nonspecific thalamic nuclei to more superficial layers as well, layer I and II, allowing a temporal binding and integrative processing of information via cortical coincidence detection of specific and nonspecific thalamocortical inputs. By Zacharybarry (talk)—self-made, Public Domain, https://en.wikipedia.org/w/index.php?curid=33934402.

desynchronize the EEG. Typically, the EEG is synchronized when thalamic relay neurons are in burst mode, and desynchronized when they are in tonic mode. Stimulation of the RAS suppresses slower activity (e.g. delta or theta) and stimulates faster activity (e.g. beta and gamma) and vice versa. This modulation leads to remarkable changes in cerebral electrical activity during wakefulness and sleep [43].

Most regions of cortex receive converging inputs from both specific (or association) nuclei and nonspecific thalamic nuclei (**Figure 6**). Specific and association thalamic nuclei project most commonly to layers III and IV of the neocortex, whereas nonspecific thalamic nuclei may reach more superficial layers, including layer I and II. This arrangement allows for regions such as the reticular formation to alter cortical

excitability levels by modulating the responsiveness of cortical neurons to inputs from specific or association thalamic nuclei. Furthermore, specific/association and nonspecific thalamic nuclei share reciprocal connections with the cerebral cortex. These provide a feedback mechanism from the cortex to the thalamus, which serves to control the amount of input that reaches a specific region of cortex at any moment (**Figures 6** and 7) [44–46].

Intracranial recordings in experimental animals and humans for brain surgery (including epilepsy surgery) suggest that gamma (30–70 Hz) rhythms are mostly generated in the superficial somatosensory cortical layers II/III, while high beta rhythms (20–30 Hz) are mostly generated in deep layer V mainly in association with activity in the fast-spiking interneurons (**Figure 6**) [47]. The majority of cortical pyramidal cells are firing at a lower frequency range (usually <25 Hz) and their information coding may be based more on instantaneous firing rates or the critical timing and phase of their activation (timing or phase modulation code). Certain neurons in primary sensory (e.g. in early visual cortical areas) [48] and other neocortical or allocortical areas (e.g. in the hippocampus) can fire at higher frequencies and

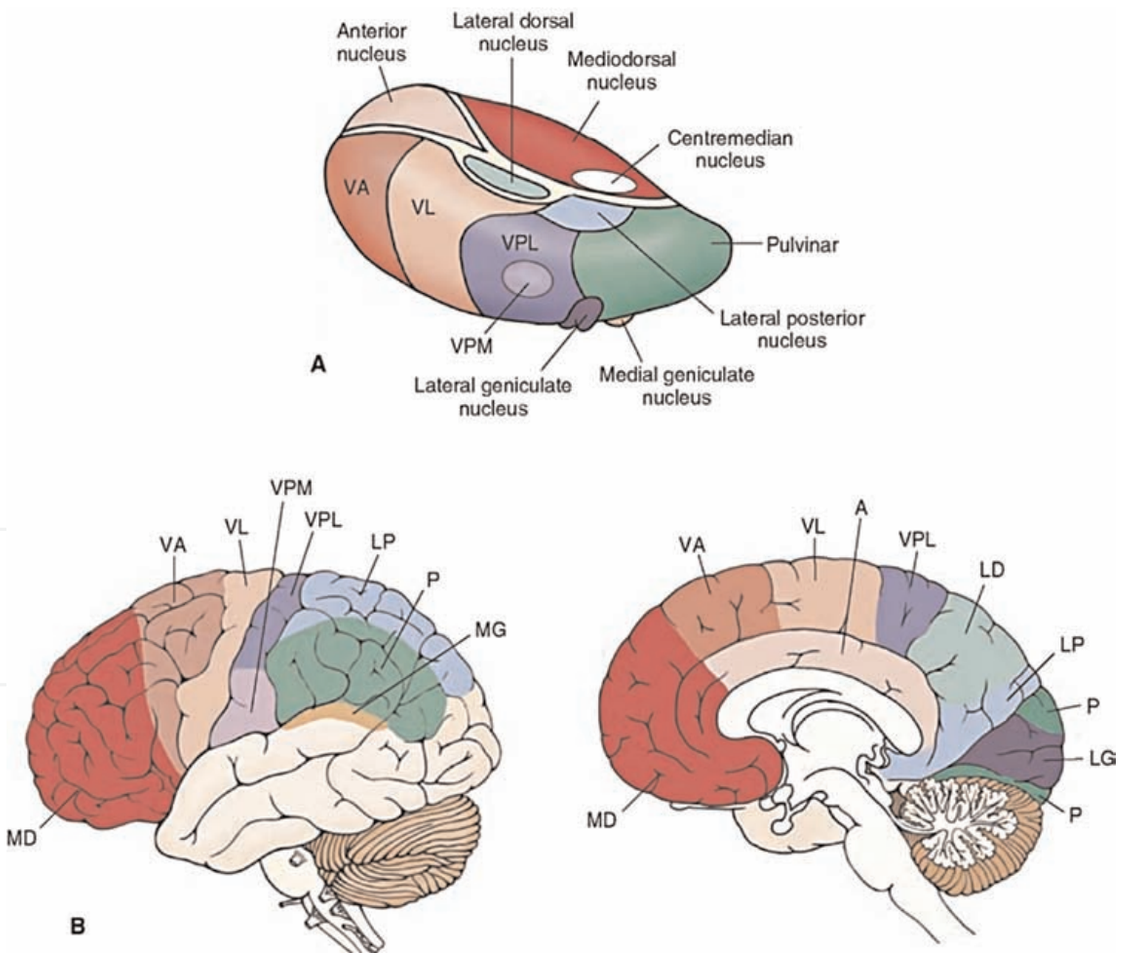

Figure 7.
Thalamocortical relationships. (A) The relative positions of thalamic nuclei. (B) Lateral (left) and medial (right) views of the cerebral cortex that demonstrate the projection targets of thalamic nuclei. Color-coding is to facilitate visualization of the reciprocal connections between thalamic nuclei and the cerebral cortex. VPM = ventral posteromedial nucleus; VPL = ventral posterolateral nucleus; VA = ventral anterior nucleus; VL = ventrolateral nucleus. Reproduced from http://what-when-how.com/neuroscience/the-thalamus-and-cerebral-cortex-integra tive-systems-part-2/.

their information coding may be also based on the average firing rates (frequency modulation code) [46–49].

Gamma oscillations probably reflect a general rapid mechanism that 'synchronizes' neuronal networks in spatially disparate cortical areas to enable fast processing or coherent binding of visual, sensory or perceptual information across cortical and subcortical networks [50–52]. The integration of EPSP and IPSP into firing an action potential in a single neuron is essentially a nonlinear amplitude-modulation postsynaptic process and the majority of pyramidal neurons rely on an instantaneous or burst firing, critical-timing and phase-modulation code for information processing. Looking at neuronal networks from a macroscopic perspective (where intracranial LFP/EEG represents a collective mean-field measure), increased amplitude in higher-frequency oscillations may be considered as an index of neuronal spiking synchrony. That is, on a large scale there may be a quasi-linear relationship between the mean frequencies of oscillatory activities from postsynaptic integration of EPSPs and IPSPs on somatodendritic processes and the coordinated or synchronized firing rates of pyramidal cells, even if on the neuronal-cell microscale a non-linear relationship is seen through random or regular, bursting or tonic firing patterns of pyramidal cells [23, 25, 28, 29, 32, 37].

Although gamma oscillatory activities are also present during sleep and under anesthesia, fast oscillations are mainly associated with increased levels of alertness/wakefulness, in keeping with activity in cholinergic neurons of the brainstem and basal forebrain [50, 53]. Increase of beta activity has been demonstrated after finger or foot movement when the muscles relax, while increase of gamma activity (greater than 30 Hz) immediately preceding the finger movement is thought to be associated with activation of cortical motor neurons. Sometimes on the scalp EEG we record equivalent sensorimotor cortical mu-rhythms which undergo suppression (desynchronization) upon performing a motor action or motor imagery, even observing another person performing a motor action or abstract motion [54].

Light sleep transition is characterized by alpha drop-out and appearance of V-sharp waves, spindles (alpha and beta range) and K-complexes (represent a depolarizing–hyperpolarizing sequence within an oscillatory cycle) before further transition to the less organised large slow wave oscillations of sleep (down to 1 Hz). Sleep spindles must be generated within the thalamus as they persist in the thalamus after decortication and high brainstem transection. Sleep spindles must be driven by the reticular nucleus of the thalamus (GABAergic neurons), as they are abolished in the dorsal thalamus after disconnection from the reticular nucleus but are preserved in the rostral part of the reticular nucleus severed from the dorsal thalamus [55].

At the onset of sleep decreased activity of brainstem cholinergic neurons contributes to the overall hyperpolarization of thalamocortical cells, thus bringing their membrane potential in the range where bursting discharges can occur. Such clusters of high-frequency action potentials excite the dendrites of neurons in the reticular nucleus, and trigger a dendrodendritic avalanche leading to synchronization of the entire reticular nucleus. Bursting of reticular neurons causes powerful GABAergic inhibitory postsynaptic potentials in thalamocortical neurons which promote cortical deafferentation (slow wave oscillations). The end of this inhibitory cycle a rebound low threshold spike (LTS) is triggered, crowned by a high-frequency burst of action potentials, which in turn excites the target reticular cells (**Figure 6**) [56–58]. Although previously thought that the main functional correlate of sleep spindles was to block incoming sensory stimuli from the thalamus to the cortex, today we believe that sleep spindles also serve a process of memory consolidation during sleep [59].

3.2 Cortico-limbocortical neuronal networks

Theta activity in hippocampal networks (**Figure 8**) seems to represent a dynamic state emerging from engaging in the task of spatial navigation and memory retrieval processes. Larger theta activity has been seen in the left anterior hippocampus and parahippocampal cortex during goal-directed navigation compared to purposeless movements. Theta oscillations are also frequent during memory processing and more so during recall than learning tasks [60].

The major input to the Hippocampus is from the Entorhinal Cortex (EC) which is strongly and reciprocally connected with many cortical and subcortical structures. Different thalamic nuclei (anterior and midline groups), the medial septum (medial septal nucleus and diagonal band of Broca), the supramammillary nucleus of the hypothalamus, the raphe nuclei and locus coeruleus of the brainstem, are connected with the entorhinal cortex which serves as the interface between neocortical (e.g. parahippocampal gyrus and perirhinal cortex) and subcortical structures, and the hippocampus (**Figure 9**) [61].

The direct perforant pathway (axons from EC layer III) forms synapses on the very distal apical dendrites of CA1 neurons (monosynaptic circuit). The indirect perforant pathway (axons from EC layer II) reaches CA1 via the trisynaptic circuit: Granule cells in the Dentate Gyrus (first synapse), via the mossy fibers to pyramidal neurons in CA3 (second synapse), and via the Schaffer collaterals to pyramidal neurons in CA1 (third synapse). The major output of the Hippocampus is axons from CA1 projecting back directly and via the Subiculum to the Entorhinal Cortex, completing the trisynaptic circuit (**Figure 8**) [62]. The trisynaptic circuit of the hippocampus is organized transversely along the hippocampus. Association and commissural fibers are organized along the anteroposterior axis [63].

Hilar mossy cells and CA3 pyramidal cells give rise to ipsilateral hippocampal association fibers (to the dendrites of granule cells and GABAergic interneurons of the inner molecular layer of the dentate gyrus) and contralateral commissural fibers

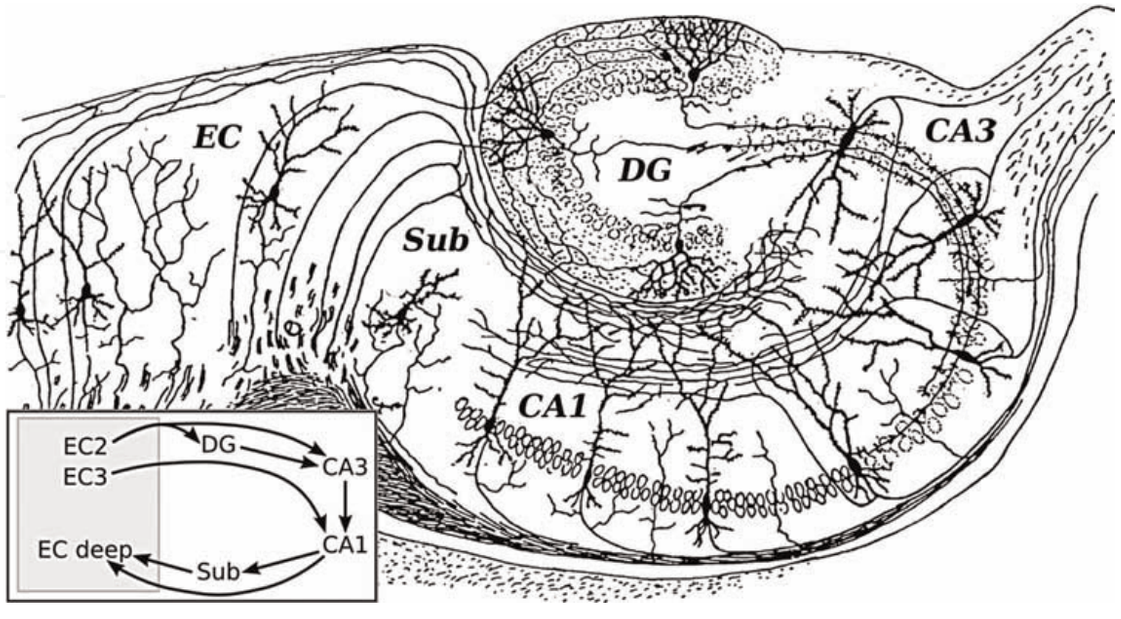

Figure 8.
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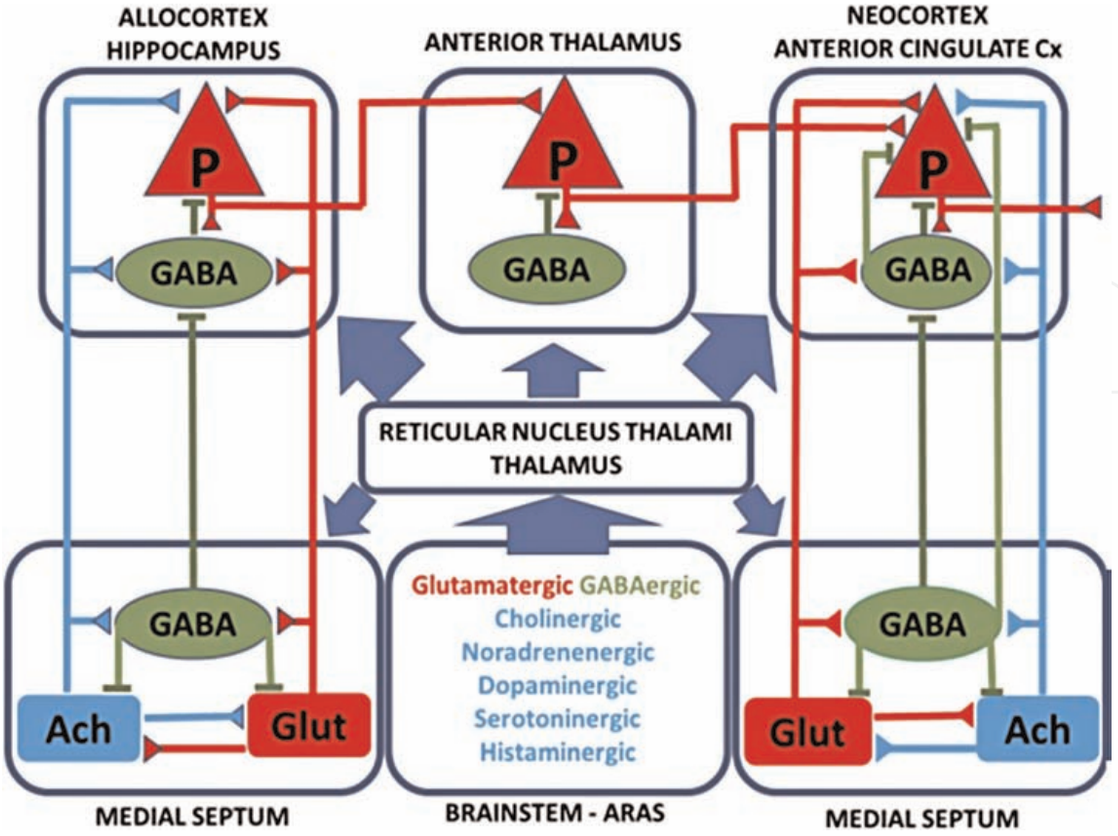

Figure 9.
The septal-hippocampal-thalamo-cortical axis. Overview of the complex interactive circuitry of excitatory, inhibitory and modulatory components, underlying some of the structural and functional connectivity of the limbo-cortical networks with clinical implications for the pharmacological and neurosurgical/neurostimulation treatment strategies of epilepsy.

(terminating on principal cells and interneurons of CA3, CA2 and CA1 regions), passing through the dorsal and ventral hippocampal commissures to reach the contralateral hippocampus and dentate gyrus. Hippocampal commissural connections are mainly excitatory and seem to be less abundant and evolutionary declined in monkey and humans [64].

Schaffer collaterals are axon collaterals from the CA3 pyramidal cells of the ipsilateral and contralateral hippocampi and project information to the pyramidal neurons of the CA1 hippocampal area. The Schaffer collateral synapses represent excitatory (positive feedback) glutamatergic synapses that assist activity-dependent plasticity and development of memory processing and formation [65]. Basket cells in CA3 receive excitatory input from the pyramidal cells and provide inhibitory feedback to the pyramidal cells. This recurrent inhibition is a powerful feedback circuit that can dampen excitatory responses and shape up the oscillatory activity of the hippocampus [66]. The hippocampal trisynaptic loop with so extensive feedforward and feedback projections constitutes a fundamental mechanism of recurrent controlled excitation underpinning memory, learning and emotion in the limbocortical networks (Papez circuit) (**Figure 10**).

There are many brain structures that transmit information to and from the trisynaptic circuit and their activity can be directly or indirectly modulated by the activity of the trisynaptic loop. A major output goes via the fornix to the lateral septal area and to the mammillary body of the hypothalamus and additional output pathways go to other cortical areas including the anterior cingulate and prefrontal cortex.

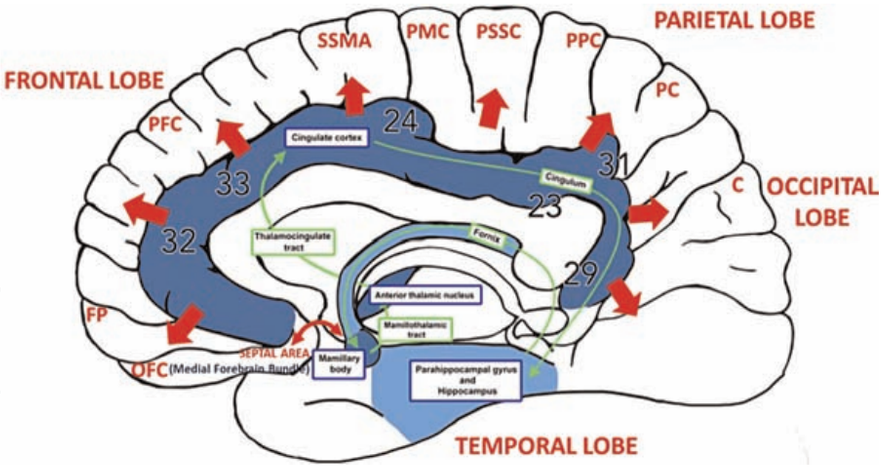

Figure 10.
Limbic system or circuit of Papez. Modified with permission from Weininger et al. [67]. OFC: orbitofrontal cortex, FP: frontopolar, PFC: prefrontal cortex, SSMA: supplementary sensorimotor area, PMC: primary motor cortex, PSSC: primary somatosensory cortex, PPC: posterior parietal cortex, PC: precuneus, C: cuneus.

The crura of the fornix form connections through the corpus callosum and the hippocampal commissures with bilateral hippocampal formations. The CA3 is connected to the lateral and medial septum via the alveus and the fimbria fornix. The CA1 and the subiculum are connected to parahippocampal regions, the entorhinal cortex and nucleus accumbens, and project to septal nuclei, preoptic nuclei, ventral striatum, orbital cortex and anterior cingulate cortex (via the precommissural fornix) and to the anterior and lateral dorsal nuclei of the thalamus, the mammillary bodies, and ventromedial hypothalamus (via the postcommissural fornix) [68].

The mammillary bodies receive information from the hippocampal formation via the fornix and relay information to the anterior nuclei of the thalamus and the anterior cingulate cortex (Brodmann 24, 32, 33) via the mammillothalamic tract. The subiculum relays information to the posterior cingulate cortex (Brodmann 23). Via the cingulate gyrus and the thalamic nuclei primary sensory and association cortical areas can be reached which integrate information at a higher level attending to complex stimuli in the external and internal environments (**Figure 10**). The temporal association cortex identifies the nature of stimuli (perception), while the frontal association cortex plans responses to the stimuli (behaviour). The association cortex projects to other association cortical areas and to subcortical structures including the hippocampus, thalamus, basal ganglia, cerebellum and brainstem [33]. The hippocampus receives modulatory input from the serotoninergic, noradrenergic and dopaminergic systems, the amygdala, the nucleus reuniens of thalamus and the medial septum. The supramammillary nucleus of the hypothalamus is strongly connected via the medial forebrain bundle to the medial septum, diencephalon and brainstem. The medial septum (medial septal nucleus and diagonal band of Broca) sends cholinergic (65%) and GABAergic fibers to CA1 and glutamatergic fibers to all parts of the hippocampus (**Figure 9**) [34].

Theta (4–12 Hz) high amplitude oscillations of the hippocampal CA1 pyramidal cells emerge during active exploration, voluntary movements, rapid eye movement (REM) sleep and certain brain states related to arousal [69]. Type 1 (fast theta oscillations) associated with spatial navigation and movement are driven by atropine-resistant inputs on the distal dendrites, whereas Type 2 (slow theta oscillations) associated with arousal and anxiety on sensory salience are driven by atropine-sensitive inputs on the somata, and chloride (Cl^-)-mediated inhibitory postsynaptic potentials

on pyramidal cells. Although in vitro experiments suggest that theta oscillations can be intrinsically generated in the hippocampal excitatory—inhibitory networks, in vivo studies suggest that the supramammillary-septal-hippocampal loop is crucial for the generation and modulation of theta local-field potential oscillations in the hippocampus [70]. The hippocampus is a highly epileptogenic structure and part of an extensive network (limbic system) that involves all 4 neocortical lobes, the dienceph-alon/thalamus and the brainstem (**Figure 10**). The medial septum and the anterior nucleus of the thalamus could critically influence and/or allow propagation of seizures from and into the neocortex (**Figure 9**) and therefore have both been studied as a site of neurostimulation in human [71] and in animals with optogenetics [72].

3.3 Neuronal network physiological dynamics

We start by simulating a rudimental recurrent neuronal network of randomly connected 1000 neurons in real time (**Figure 11**). In the raster plots of network neurons, every excitatory neuron is represented by a black dot and every inhibitory neuron is represented by a red dot. The neuronal activity is manifested between 200 ms and 700 ms (within a 0.5 s interval). The graphs below the raster plots depict the cumulative spiking activity of all neurons (mV vs. ms) during the same time interval; the spikes of the excitatory neurons are depicted with blue and the spikes of the inhibitory neurons are depicted with red.

In our initial recurrent neuronal network (the first raster plot and cumulative spikogram below on the left of **Figure 12**), we omitted all inhibitory neuronal activity; this resulted in a very unstable network which rapidly went out of control, with all

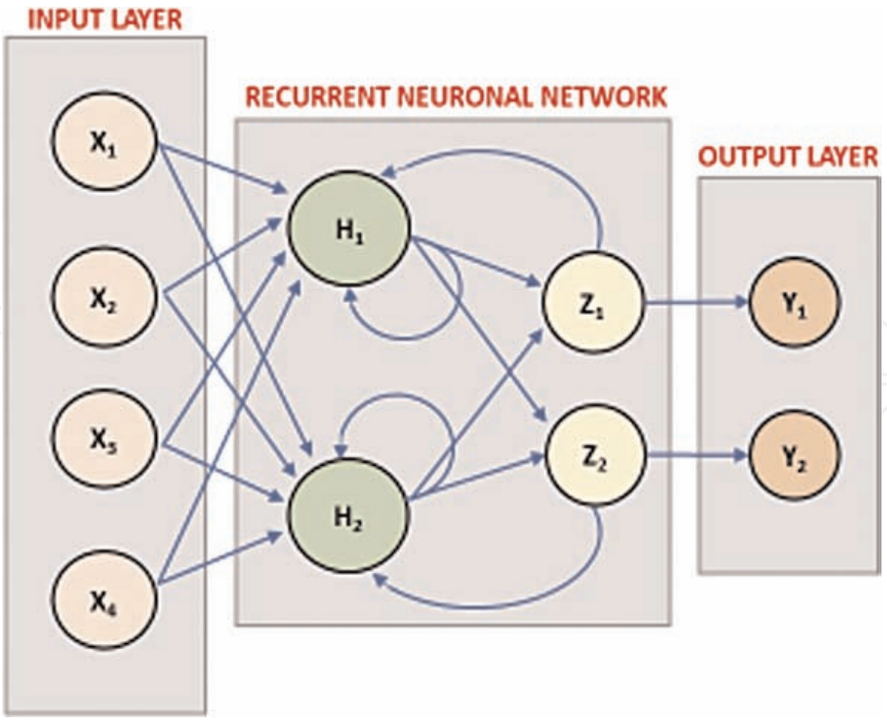

Figure 11.
Abstract state-space representation of the components of a recurrent neuronal network across different layers. The letters X, H, Z and Y represent sets of input [X], output [Y] and state variables [H, Z] in the form of state vectors related by differential or difference equations, whose values evolve over time depending on the values they have at any given time and the externally imposed values of input variables. The values of output variables depend on the state variables.

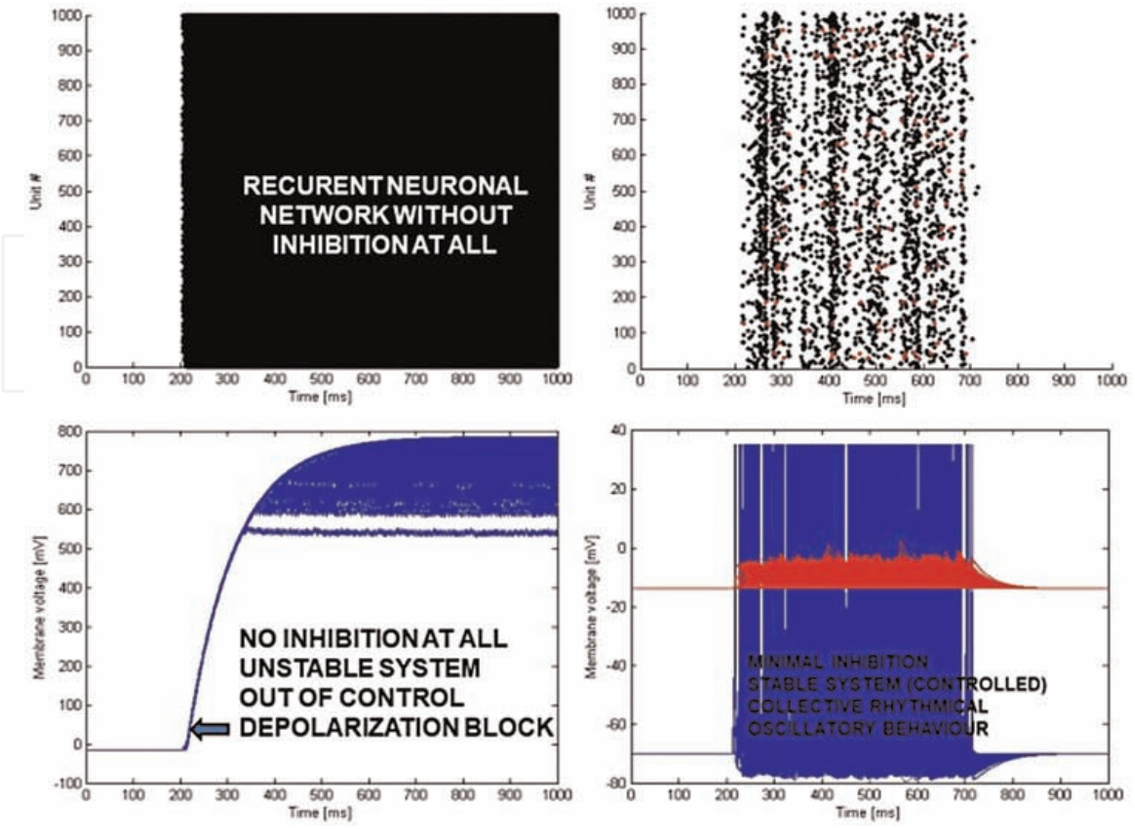

Figure 12.
Recurrent neuronal network without inhibition (on the left) and with inhibition (on the right). As soon as a tiny amount (1%) of recurrent inhibitory neurons were introduced into our random network, not only the spiking neuronal network gets effectively stabilized under such small inhibitory control, but starts also displaying quite complex rhythmical patterns and collective oscillatory behavior of self-organized neuronal assemblies. This is what we would describe as order emerging out of chaos*. At the meso/macroscopic level, quasi-linear phenomena (oscillations of delta, theta, alpha, beta and gamma range and the harmonics thereof) can emerge on the large scale of neuronal networks despite the complex non-linear and stochastic dynamics that govern the behavior of single neurons at the microscopic level.*

excitatory neurons depolarising up to hundreds of millivolts: with such high voltages a small volume of cortex would literally thermocoagulate!

Biologically this is of course not plausible. In vivo when the membrane potential of any excitatory cell shoots up and remains above −25 mV without returning to its resting baseline level of −65 mV, the cell goes into a so-called *depolarization block* where Na^+ channels enter an inactivated state equivalent to the absolute refractory state of neurons (**Figure 3**). If there is sufficient Na-K-ATPase activity, energy supply and adequate time, allowing the electrochemical gradients to be restored over time, the neuron enters a relative refractory period and the Na+ channels resume an active state in which they can open up again upon critical fluctuations in the membrane potential that reach/surpass threshold level. Therefore, ongoing *repolarization* of excitatory pyramidal cells (facilitated by inhibitory interneurons) is essential in maintaining the critical membrane potential fluctuations that drive both physiological and epileptogenic network oscillations.

Motivated by the anatomy of the mammalian cortex [28], we choose the ratio of excitatory to inhibitory neurons to be 4 to 1, and we make the inhibitory synaptic connections stronger about 4 times. Besides the synaptic input, each neuron receives a noisy external (thalamic) input. In principle, one can use *Regular Spiking* (RS) cells to

model all excitatory neurons and *Fast Spiking* (FS) cells to model all inhibitory neurons [37]. Based on the *Izhikevich* model, our neuronal spiking network exhibits rich cortical-like asynchronous spiking dynamics (**Figure 5**); neurons fire Poisson spike-trains with random firing rates varying from 0 to 25 Hz (similar to the firing-rate range of most cortical pyramidal neurons). Darker vertical linear areas emerge in our raster plots (on the right of **Figure 12**) that indicate that there are episodes of synchronized firing in the alpha and gamma frequency range (around 10 and 40 Hz, respectively). Although the network is connected randomly without any synaptic plasticity, the neurons, whether excitatory or inhibitory, when firing tend to self-organize into assemblies and exhibit rather collective rhythmical behavior across a wide range of frequencies corresponding to physiological rhythmical EEG activities (delta, theta, alpha, beta and gamma range) in the awake and sleep state of the mammalian cortex.

As the number of external input neurons varies from 1 to 500 (external drive increases), so does the number of oscillatory cycles (**Figures 13** and **14**). For example, for <10 neuron input no collective rhythmical activity is generated, for 10–25 input neurons a 2 Hz (slow delta) oscillatory activity is generated, for 25–50 input neurons a 2–4 Hz (delta) oscillatory activity is generated, for 50–100 input neurons a 4–6 Hz (slow theta) oscillatory activity is generated, for 100–150 input neurons a 6–8 Hz (fast theta) oscillatory activity is generated, for 150–250 input neurons a 8–10 Hz (lower alpha) oscillatory activity is generated, for 250–400 input neurons a 10-12 Hz (higher alpha) oscillatory activity is generated, for 350–500 input neurons a 12–18 Hz (fast/beta) oscillatory activity is generated.

As we keep varying a few critical conditions in the continuous parameter space of our neuronal network model, a vast amount of variation can be introduced under scale transformation in the complex oscillatory behavior of the neuronal network. Our neuronal spiking network model can also simulate an allocortical septal-hippocampal network. The external driving input in a limbocortical neuronal network would be coming from the medial septum (integral part of the supramammillary-septal-hippocampal loop). Such a simulation requires a different ratio of excitatory to inhibitory neurons with perhaps stronger synaptic strengths, reflecting the strong perisomatic inhibition by parvalbumin-positive basket cells (generating Sharp-Wave Ripples and Gamma Oscillations in hippocampal models) [34, 49, 66, 68, 70].

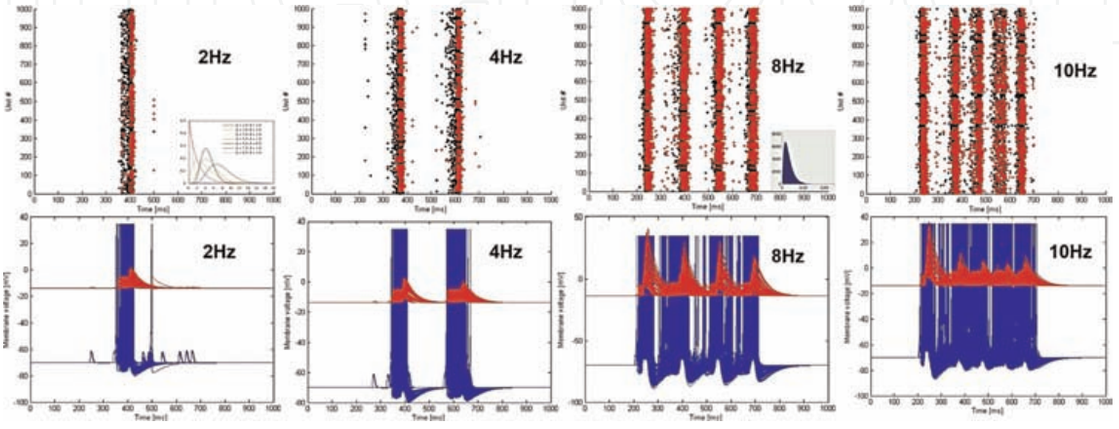

Figure 13.
Complex rhythmical patterns and collective oscillatory behaviour of self-organised neuronal assemblies (oscillations of delta, theta, and alpha range).

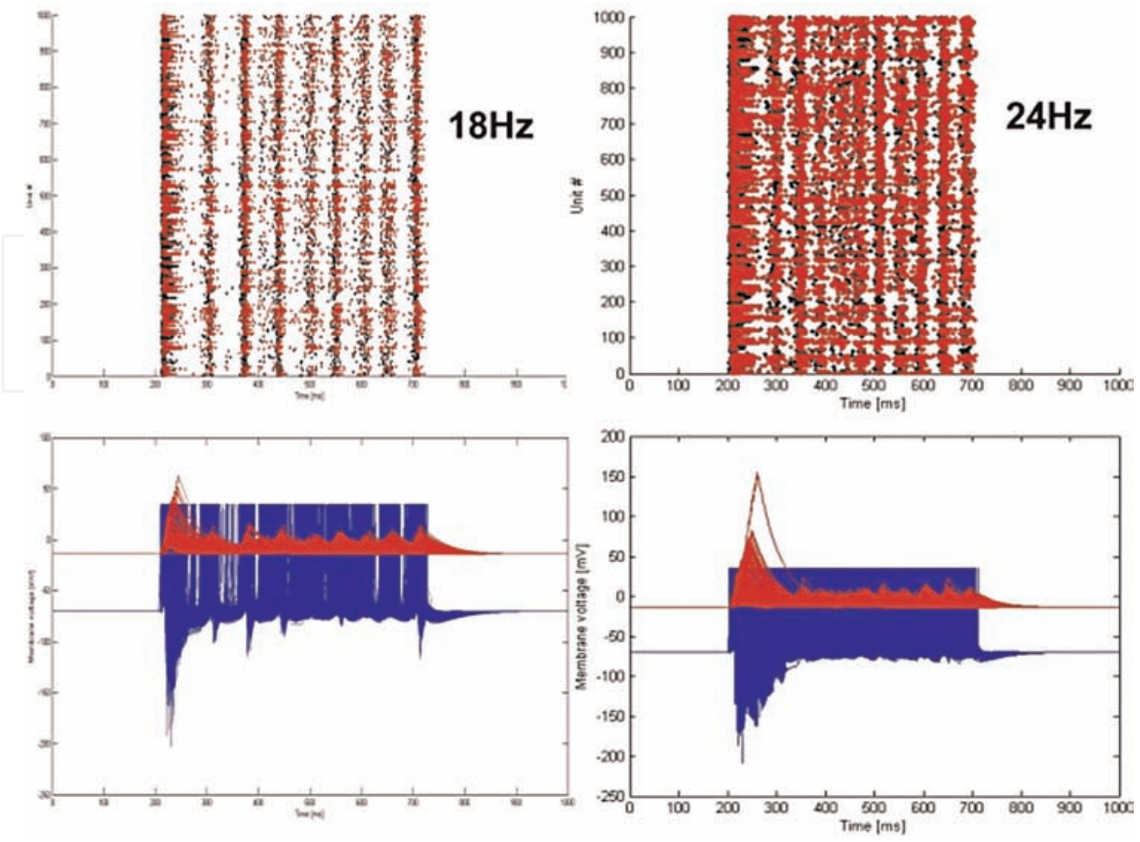

Figure 14.
Complex rhythmical patterns and collective oscillatory behavior of self-organized neuronal assemblies (oscillations in the beta and low gamma frequency range).

3.4 Neuronal network epileptogenic dynamics

While varying the aforementioned network parameters in our *local neocortical or allocortical* network simulation, the most interesting and unexpected behaviour of our network model was the emergence of erratic stochastic bursting of transient (spiking) neuronal activity outside the anticipated interval of 200-700 ms. This was initially an isolated event, quickly brought under control by a concomitant surge of local inhibitory activity (please see raster plot on the left and cumulative spikogram under in **Figure 15**). This stochastic type of bursting activity was reminiscent of an isolated and fairly limited paroxysmal depolarization [73] that died out as a result of sufficient or effective *local inhibitory control* [74]. On a macroscopic scale a *paroxysmal depolarization shift* could appear like an *interictal epileptiform discharge* on intracranial (iEEG) [74] and extracranial (scalp EEG) recordings [73].

At that stage the thalamic or septal input into our network was random noise or a Poisson train-like noise input. Slightly tuning the network further in the critical parameter space as follows: 200 *thalamo-cortical* or *septo-hippocampal* neuron input, overall synaptic weight/strength constant at 0.14, gamma probability distribution for the inhibition of scale-factor $\theta = 2.0$ and shape-parameter $k = 0.015$, and intrinsic membrane excitability with resting membrane potential at −75 mV, sensitivity threshold at −65 mV and resting membrane recovery threshold at −15 mV, were sufficient to trigger the most remarkable and unpredictable behaviour observed in our neuronal network.

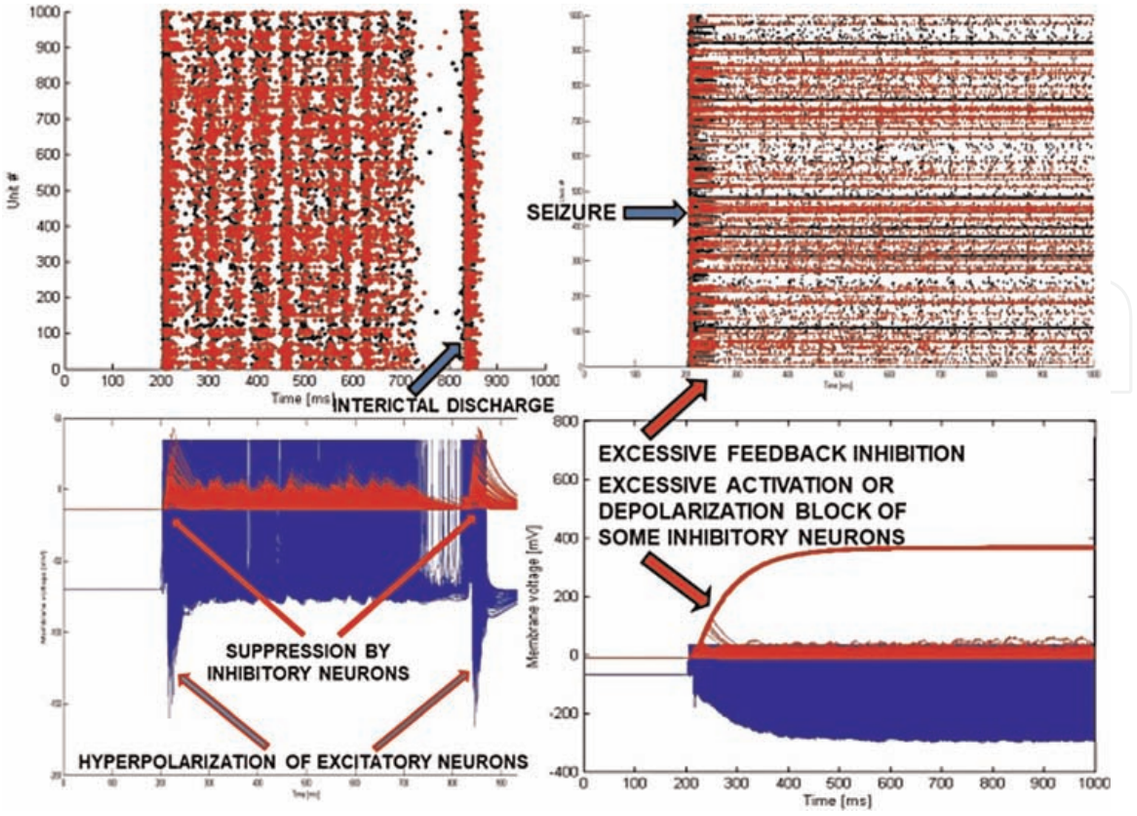

Figure 15.
Interictal and ictal paroxysmal depolarization shifts for critical parameters of our neuronal network (200 neuron input, overall synaptic weight/strength constant at 0.14, gamma probability distribution for the inhibition with scale-factor θ = 2.0 and shape-parameter k = 0.015, intrinsic membrane excitability with resting membrane potential at −75 mV, sensitivity threshold at −65 mV and resting membrane recovery threshold at −15 mV).

This was the generation of sustained *pathological high frequency oscillatory activity* that emerged from stochastic or random noise like other previously described physiological high frequency (beta/gamma range) oscillatory activities [75]. This was amplified in amplitude and frequency beyond any limit. It could not be checked upon by the local inhibitory network and eventually went completely out of control in what could be the equivalent of a *seizure*. The model allows for incredible predictions of the underlying processes taking place during epileptogenesis/ictogenesis (the process of seizure generation and development).

As can be appreciated from the figure above (raster plot and cumulative spikograms at the bottom on the right of **Figure 15**) ictogenesis starts with a *hyperexcitation wave-front* through an initial process of *stochastic resonance* [75] similar to previously described high-frequency oscillatory generation processes [76]. This is immediately followed by a massive feedback burst of inhibitory activity (*phasic inhibition*) [77] that desynchronizes or brings the underlying unit oscillators to a transient halt, resulting on a network scale in transient attenuation/suppression of background rhythms (**Figure 16**). Depending then on the level of sustained or effective background inhibition (*tonic inhibition*) [78] a process of *synchronization* [35] starts and recurrent cycles of alternating excitation and inhibition go on to entrain larger and larger ensembles of unit oscillators into a common resonating high frequency [36]. This maximizes the amplitude of the oscillation and recruits a massive number of unit oscillators into excessive and hypersynchronous oscillatory activity.

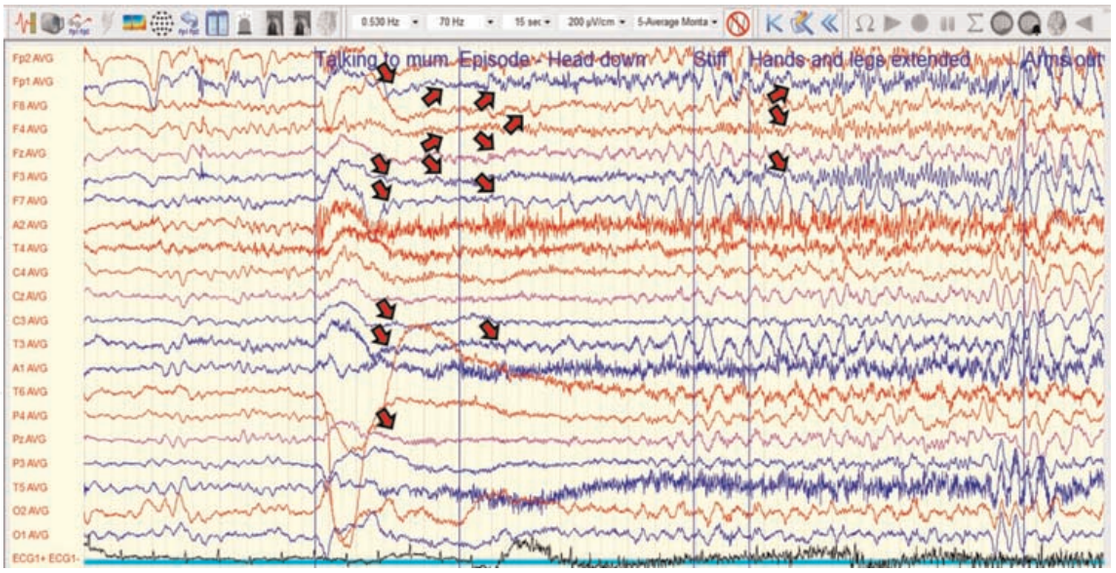

Figure 16.
Initial background rhythm attenuation (intermixed with muscle artefact on some channels) followed by rapid build-up of fast oscillatory activities. This is likely the result of widespread, initial phasic and then tonic inhibition through an extensive cortico-ganglio/thalamo-cortical (left > right) network. This focal-onset left mesial frontal/sylvian tonic seizure manifested suddenly and evolved rapidly (secondary generalized).

In both physiological and pathological high-frequency activities modelled, there was always a massive inhibitory response to the initial overexcitation wave front, something that is of note as it suggests that for any organized large-scale oscillatory activity to develop a critical level of *synchronization* of unit oscillators is required through recurrent cycles of excitation and inhibition [79]. This is achieved with the early excessive feedback wave of inhibition that follows the initial huge wave of excitation, resulting in an excessive hyperpolarization of the excitatory neurons. This is pivotal in uniformly suppressing or phase-resetting all unit oscillators and synchronously restarting them or coupling/forcing them into a *synchronization process* [78] that gradually entrains larger and larger neuronal ensembles. Excessive *afterhyperpolarization potentials* [80–82] are also crucial in shifting a huge number of inactivated sodium channels from the inactivated to the closed state, rendering them available again for repeated waves of overexcitation during a sustained *paroxysmal depolarization shift* [83, 84].

Resonance is an oscillation of maximal amplitude with all unit oscillators oscillating in a synchronous or synchronized manner, observed when the frequency of a periodically applied *depolarization force* (or a Fourier component of it) is equal or close to a natural frequency of the system. When a small oscillating or periodic *depolarization force* is applied near a resonant frequency of a dynamic system, the system will oscillate at a higher amplitude than when the same force is applied at other, non-resonant frequencies [35]. Obviously, the resonant frequencies of local neocortex or allocortex are defined by the critical combination of local structural and functional connectivity, periodic thalamic or septal input, synaptic weights, interaction of excitatory (recurrent excitatory synapses) and inhibitory (loss of inhibition or disinhibition) components and intrinsic neuronal excitability (endogenous bursting) [78, 79].

The inhibitory oscillatory components of our neuronal network manifest another interesting phenomenon. Driven by the initial overdepolarization of pyramidal cells, some of the inhibitory interneurons excessively 'depolarized' to hundreds of

millivolts, a rather unique prediction of our model (right bottom of **Figure 15**). Translating this early abnormality in a critical subpopulation of inhibitory cells in biological terms, raises two possibilities. These would allow an initial wave of over-excitation due to stochastic noise and critical time coincidences in a potentially hyperexcitable system of unit oscillators to rapidly or progressively attain an oscillation of maximal amplitude (resonance) in depolarizing and hyperpolarizing directions while going through consecutive synchronization cycles of excitation and inhibition [85–89]. One possibility is that some of the inhibitory interneurons can go into an actual *depolarization block*, leaving effectively unchecked the excitatory oscillators (unopposed EPSPs on pyramidal cells) to rapidly or progressively evolve into a paroxysmal depolarization (this is likely to occur towards the end of a seizure due to metabolic depletion). The other possibility is that excessive initial phasic inhibitory GABAergic activity, sometimes in combination with GABA transporter (GAT-1) malfunction in astrocytes, releases too much extrasynaptic GABA which facilitates concurrent extrasynaptic $GABA_BR$ activation. This results in enhanced/sustained tonic $GABA_A$ currents that persistently hyperpolarize and increase membrane Cl^- conductance causing bursts of IPSPs to override the depolarizing currents in thalamocortical [85, 86] or pyramidal neurons [90]. Such rhythmical bursts of IPSPs can entrain thalamocortical/gangliocortical (**Figure 16**) and limbocortical (**Figures 17-19**) networks to paroxysmal and/or hypersynchronous activity.

The neuronal network attains a paroxysmal depolarization state when the different excitatory and inhibitory oscillatory components reach maximal

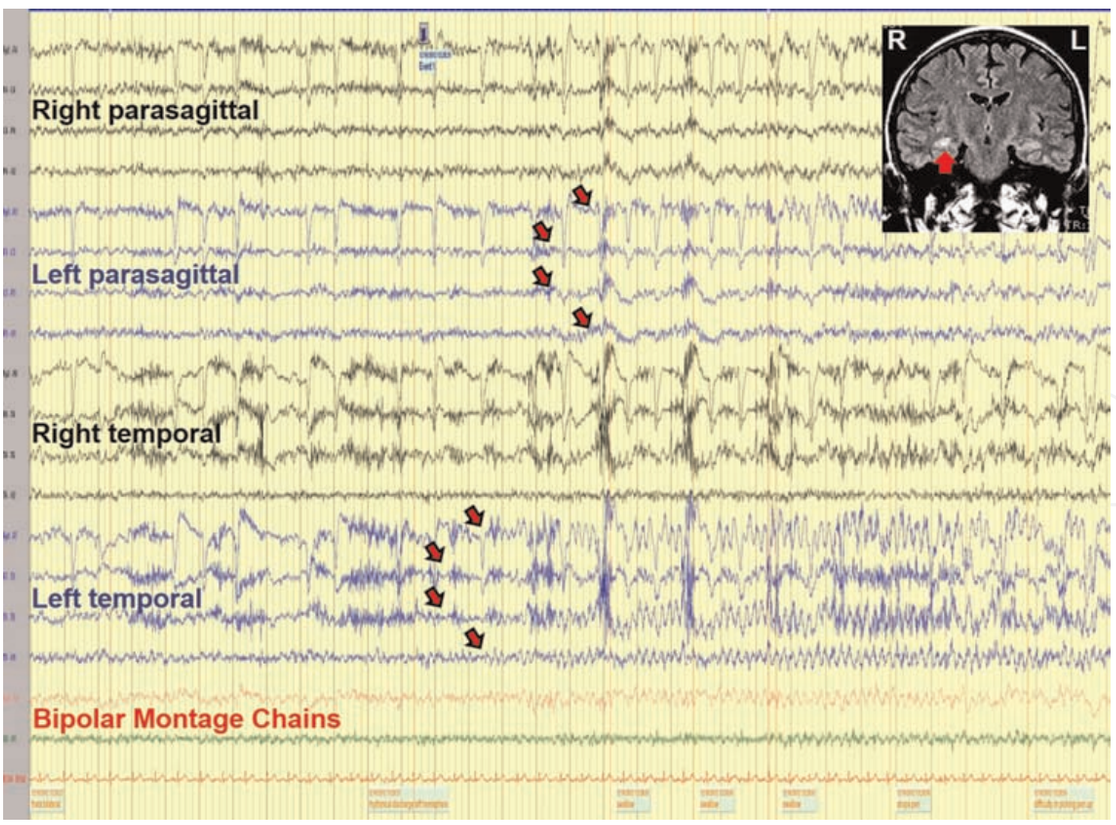

Figure 17.
A left-side mesial temporal onset seizure on the EEG with a rhythmical theta activity build-up over the left temporal region. The MRI scan at the right top corner of the figure indicates severe right mesial temporal lobe sclerosis. Because of lack of concordance between scalp Electroencephalography and MR imaging, we had to undertake intracranial iEEG recordings in this case to determine the exact ictal-onset (potential epileptogenic zone).

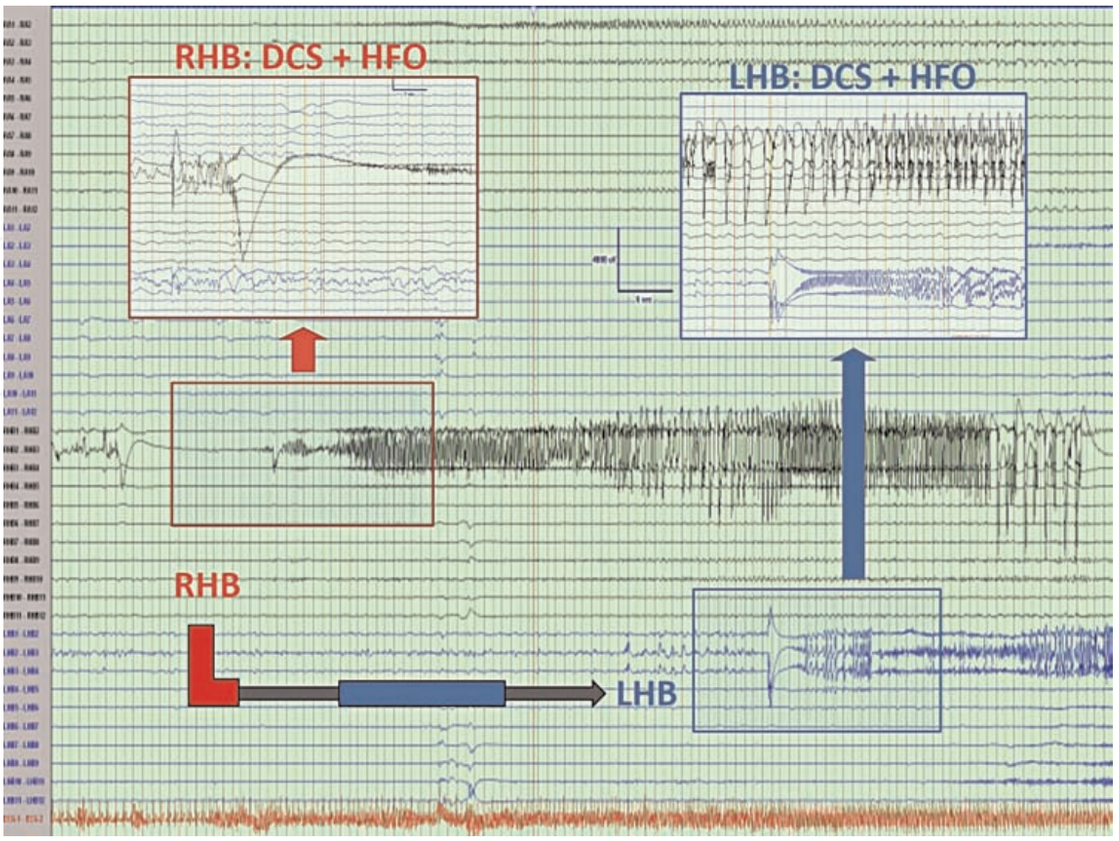

Figure 18.
Human intracranial EEG recordings of bilateral hippocampi to demonstrate baseline (DC) shifts and high-frequency oscillations (HFOs) as surrogate markers of the ictal onset zone. In this patient they always started from the most atrophic and sclerotic (burnt out) right hippocampus and subsequently spread to the left hippocampus. Resection of the right hippocampus in this case conferred seizure freedom and confirmed the epileptogenic zone.

depolarization and hyperpolarization potentials or when excitatory and inhibitory oscillatory units synchronize via depolarizing and hyperpolarizing currents into an oscillation of maximal amplitude. Epileptogenic depolarizing currents can emerge from abnormal or excessive ionic Na^+ [91] and Ca^{++} [92] channel-conductances or excessive excitatory (Glutamate) and neuromodulatory (Acetylcholine, Noradrenaline, Dopamine, Serotonin, etc) neurotransmitter release and receptor function [87–89]. Epileptogenic afterhyperpolarizing currents can emerge from abnormal, insufficient or excessive ionic Cl^- [93] and K^+ [94–96] channel-conductances or abnormal, insufficient or excessive inhibitory (GABA) neurotransmitter release and receptor function [85, 86]. Multiple combinations of the above epileptogenic mechanisms are plausible.

Critical synchronization, resonant oscillation and massive depolarization of excitatory and inhibitory neurons seem to account for a massive release of potassium ions (K^+) from the principal (pyramidal) and supportive glial cells [97]. These shift the resting electrochemical/equilibrium gradients of the cell membrane from −65 mV probably closer to −50 mV, where voltage-gated Na^+ channels are still active and much more likely to open (they are also less likely to be inactivated because of increased Cl^- conductance and sustained tonic GABAergic currents). The membrane conductances essentially change to levels that allow for a massive sustained depolarization shift of the principal/pyramidal cells (massive influx of Na^+ and slower Ca^{2+} inward currents) to take place [83, 84]. Paroxysmal depolarization shifts manifest

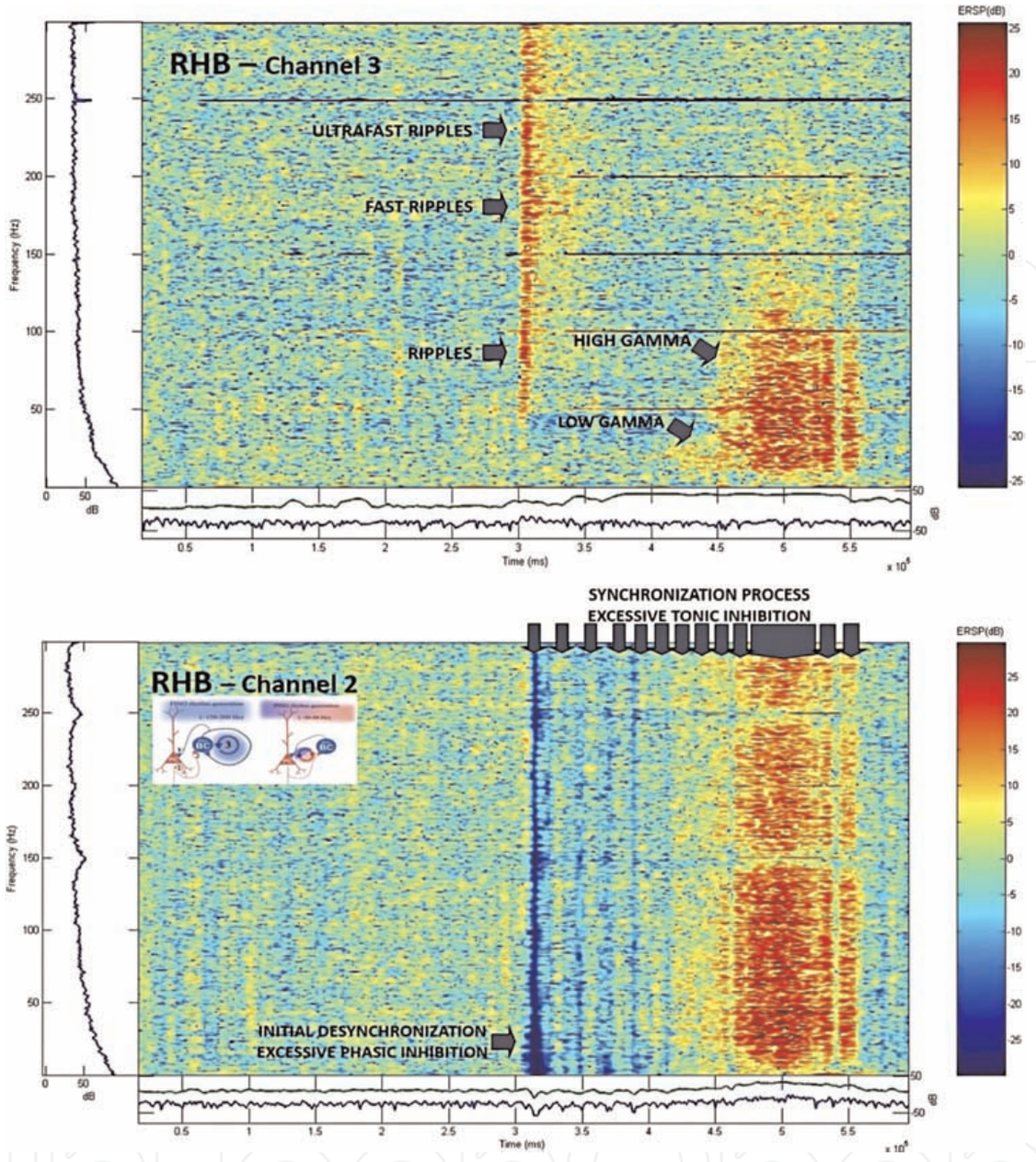

Figure 19.
Within the right posterior hippocampus (Channel 3 Spectrogram) an initial wave of over-excitation (high-frequency ripple synchronization) with ripples/fast ripples followed by excessive feedback inhibition and brief period of attenuation (broadband suppression/desynchronization or phase-resetting of unit oscillators) of the right middle hippocampus (Channel 2 Spectrogram) and recurrent excitation-inhibition oscillatory cycles (synchronization process) before a sustained paroxysmal depolarization shift develops with pathological low/high gamma, ripple and fast ripple oscillations. The inset figure shows the interaction of hippocampal pyramidal cells with parvalbumin-positive basket-cells (interneurons) generating high-frequency gamma-oscillations (PING mechanism) and ripple-frequency phase-modulations (FINO mechanism), reproduced from [66].

electrophysiologically with huge baseline (DC) shifts and very high amplitude pathological high-frequency oscillations (pHFOs) known as pathological beta/gamma oscillations (15–80 Hz), (fast) ripples (80–150 Hz) and (ultra)fast ripples (150–500 Hz) (**Figures 18–20**) [66, 98–100].

Obviously, as this excessive and hypersynchronous overdrive of excitatory and inhibitory neurons goes on, the membrane depolarization shifts towards a more 'toxic'

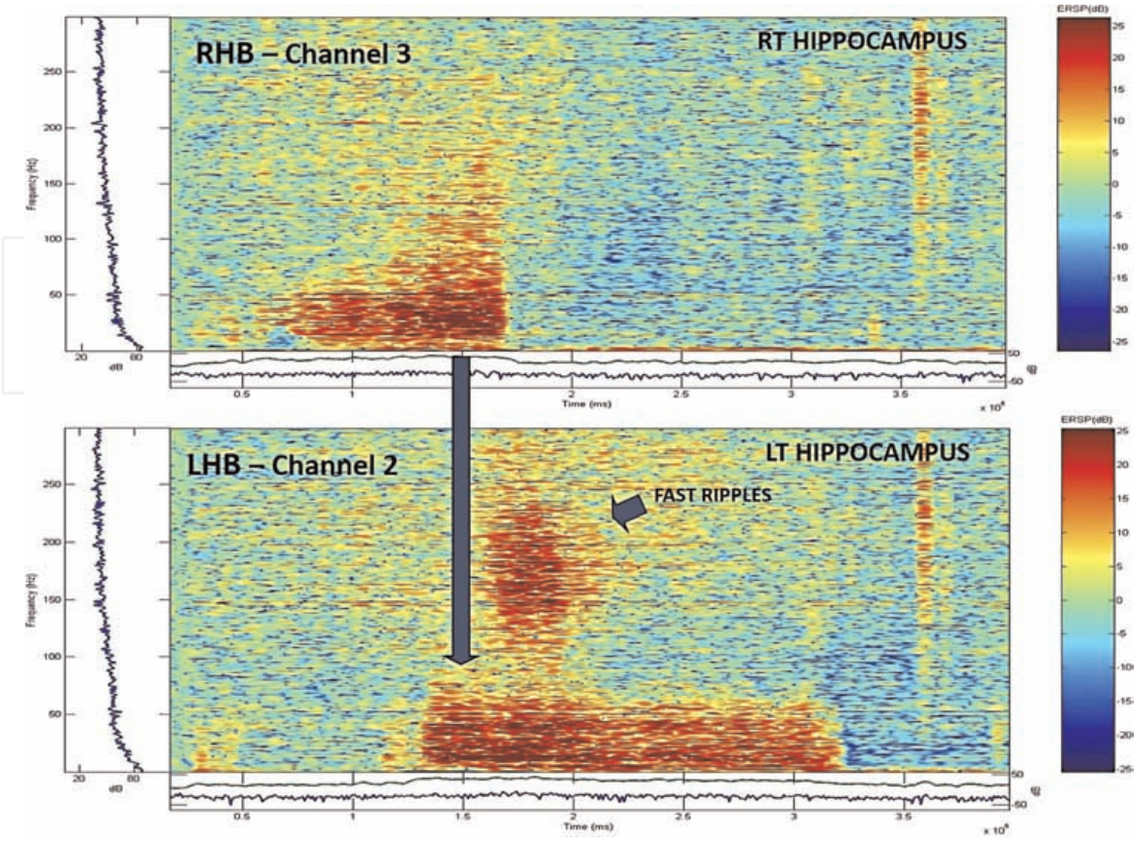

Figure 20.
Spreading of pathological/epileptogenic gamma oscillatory activity in man from the right hippocampus (top spectrogram) to the left hippocampus (bottom spectrogram) with subsequent fast ripples in the left hippocampus. Hilar mossy cells and CA3 pyramidal cells give rise not only to ipsilateral associational hippocampal fibers but also some contralateral commissural fibers (terminating on principal cells and interneurons to CA3, CA2 and CA1 regions), passing through the posterior and anterior hippocampal commissures to reach the contralateral hippocampus and dentate gyrus. More extensive polysynaptic pathways via the entorhinal and perirhinal cortex integrate the hippocampus with the ipsilateral and contralateral hemispheres and homologous hippocampal network. This particular focal motor unaware seizure died out in the right hippocampus/hemisphere but propagated and continued in the left hippocampus/hemisphere, declaring itself on the scalp EEG as seen in ***Figure 15****.*

range of less negative potentials (around −35 mV or above) which will eventually render all voltage-gated Na-channels inactivated. At that point, as the Na-K-ATPase pumps and ion-transporters require sufficient energy and time to restore the electrochemical membrane gradients, a combination of inactivated Na-channels and metabolic depletion will bring the activity of the excitatory and inhibitory cells to sub physiological levels or to a halt (depolarization block and metabolic depletion) during the postictal phase (**Figure 21**) [73, 74].

4. Epileptogenic networks: Aetiology, pathogenesis, pathophysiology and clinical implications

4.1 Epileptogenic cortico-thalamo/ganglio-cortical networks (pathophysiology of typical absences, myoclonic jerks, primary generalized tonic-clonic seizures and photoparoxysmal responses)

Idiopathic (genetic) generalized epilepsy is the prototypical phenotype of primary generalized epilepsies manifesting with a variable combination of absence, myoclonic

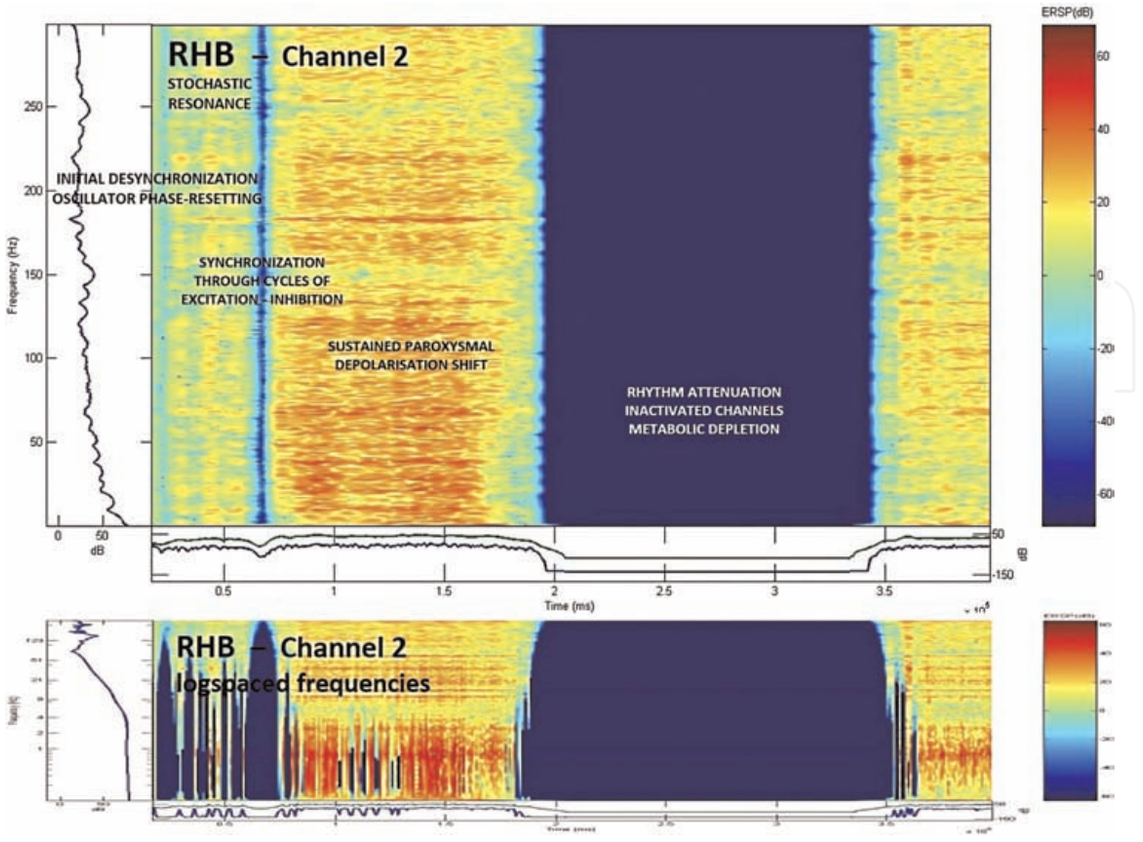

Figure 21.
This particular seizure started in the right hippocampus with a brief period of broadband attenuation (desynchronization or phase-resetting of unit oscillators). After an initial synchronization phase (through recurrent cycles of depolarization and repolarization) it transitioned to a sustained broadband paroxysmal depolarization shift and lasted altogether for about 2 min and 15 s. It ended with a prolonged postictal period of broadband suppression of background rhythms for another 2.5 min. The spectrogram at the top shows the power per 1 Hz individual frequency component from 1 to 300 Hz (nonorthogonal continuous 3-cycle wavelet decomposition) versus time in x10^5 ms, while the spectrogram at the bottom shows log-spaced frequencies (pseudo-orthogonal decomposition) to help appreciate the concentration of power which is mostly <4 Hz but more sustained over time between 12 and 64 Hz (beta and low/high gamma range).

and generalized tonic-clonic seizures, and photoparoxysmal responses (PPR) in the young population (<25 years). Absence epilepsy is one of the most common generalized epilepsies of childhood. It has a unique endo-phenotype based on perturbed cortico-thalamocortical circuitry with genetic and developmental features. It can appear in childhood (CAE) or juvenile ≥10 years (JAE) and can modify or improve its phenotype in adolescence. Typical absences can be triggered in more than >80% of patients with hyperventilation. CAE can even regress with or without treatment, while JAE that is more likely to present with generalized tonic-clonic seizures (up to 80% GTCS) compared to CAE (up to 20%) may also be more resistant to treatment [101].

Another relative endophenotype is that of juvenile myoclonic epilepsy (JAE) and of epilepsy with GTCS seizures alone or on awakening (EGTCS-a, Janz) with perhaps more permanent or pharmaco-resistant features, characterised more by motor myoclonic seizures (MJ) and generalized tonic-clonic seizures (GTCS) with or without absences and perhaps different engagement or imbalance of fronto-central (thalamo-basoganglio-cortical) networks. Photosensitivity (PS) may coexist in roughly 1/5 of CAE, 1/4 of JAE or 1/3 of JME epilepsies [101].

The EEG hallmark of this wide spectrum of genetic/developmental epilepsies varying from less motor manifestations (absences) to more motor manifestations

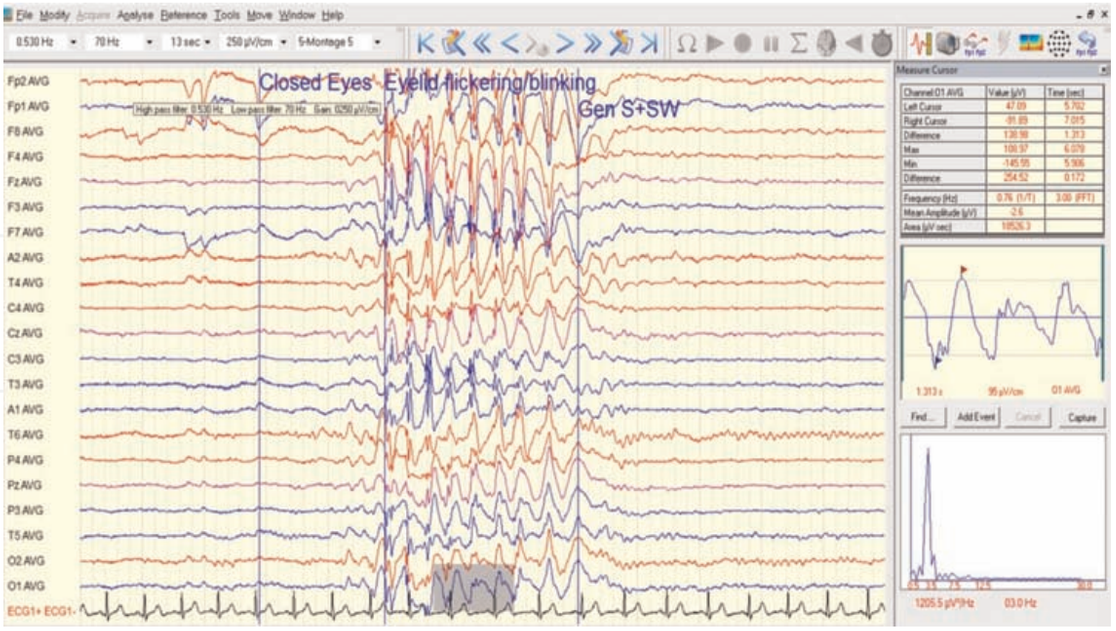

Figure 22.
Spike/polyspike and slow wave discharges in a patient with Juvenile Myoclonic Epilepsy. The spike is a recruiting wave associated with excitatory postsynaptic potentials (EPSPs) and the slow wave is an inhibitory wave associated with hyperpolarizing postsynaptic potentials (IPSPs) in cortical cells, essentially preventing the development of a generalized convulsive seizure.

(myoclonic and generalized tonic-clonic seizures) is the epileptiform generalized spike-and-wave discharges (GSWD) (**Figure 22**). These can also vary in morphology across the different subtypes from a typical regular 3 Hz spike-and-slow-wave (often seen in CAE albeit some variations) to more irregular 3–6 Hz spikes/polyspikes-and--slow-wave patterns (often seen in JAE, JME and EGTCS-a) against a fairly normal background EEG (perhaps with some exceptions occasionally of more focal spikes, sharp waves, slow waves, OIRDA, etc.). The spike is a recruiting wave associated with excitatory postsynaptic potentials (EPSPs) from thalamic relay neurons on cortical cells and consequent phasic inhibition of the thalamic relay neurons. The slow wave is associated with tonic inhibition and hyperpolarizing postsynaptic potentials (IPSPs) on thalamic relay neurons resulting in secondary tonic inhibition of cortical cells (deafferentation), overriding cortical excitation and entraining pyramidal cortical neurons and thalamo-cortical networks in hypersynchronous paroxysmal activity.

The thalamocortical interaction implicated in primary or idiopathic (genetic) generalized epilepsies is one of the most studied epileptogenic networks. The basic thalamocortical circuitry is composed of pyramidal neocortical neurons, thalamic relay neurons, and neurons from the reticular nucleus of the thalamus (NRT) (**Figure 6**). The thalamic relay neurons receive ascending inputs from the Reticular Activation System (ARAS) and project to neocortical pyramidal neurons. Cholinergic pathways from the forebrain and ascending serotonergic, noradrenergic, and cholinergic brainstem pathways regulate the excitability of the thalamic relay neurons and the thalamocortical circuitry (**Figure 9**) [102]. As a result, thalamic relay neurons manifest oscillations in their resting membrane potential, which increase the probability of synchronous activation of neocortical pyramidal neurons (EPSPs) during depolarization states and lower the probability of neocortical activation (IPSPs) during hyperpolarization states. This generates thalamocortical oscillatory rhythms and

induces slow coherent oscillations in the cortex (resonance phenomena), characterised by periods of relatively increased excitation (up-states) and periods of relatively increased inhibition (down-states), such as the fast oscillations in sleep spindles and larger slower oscillations observed in sleep [103, 104].

Within a potential cortical area (sensorimotor cortex) medium-amplitude 5–9 Hz oscillations secondary to decreased phasic ($GABA_AR$) inhibition [105–107] may entrain other cortical areas and the thalamus leading to a strong and synchronous cortical output that excites the GABAergic neurons of the Nucleus Reticularis of the Thalamus (NRT). The thalamic relay neurons have GABA-B receptors and receive GABAergic tonic inhibition from the neurons of the Nucleus Reticularis of the Thalamus (NRT) [108]. Also increased ambient (extrasynaptic) GABA levels around thalamic relay neurons due to reduced GABA uptake by GAT-1 (malfunction of thalamic astrocytes GABA transporter), may further enhance extrasynaptic $GABA_AR$ tonic inhibition [78]. Enhanced tonic inhibition persistently hyperpolarizes thalamic relay neurons and increases their membrane Cl^- conductance.

The hyperpolarization of thalamic relay neurons due to excessive or sustained GABAergic tonic inhibition of thalamic relay neurons shifts the T-calcium channels from the inactivated to the closed state and permits the synchronous opening of a large population of the T-calcium channels (about every 100 milliseconds). The rhythmic IPSP bursts on thalamic relay neurons, driven by a transient low-threshold calcium channel (transient T-calcium current) with intrinsic bursting behaviour, induce a widespread burst of excitation on neocortical pyramidal cells giving rise to the spike and secondary tonic cortical inhibition (following excessive excitatory bursting) which causes widespread cortical deafferentation, a phenomenon we macroscopically observe on scalp EEG as generalized slow wave complexes following the spike(s) (**Figure 22**) and as *absences* in patients' behaviour [85, 86, 90, 97]. A functional mutation in the CACNA1H gene encoding the Cav3.2 low-voltage activated Ca^{+2} channel has been found in the Genetic Absence Epilepsy Rats from Strasbourg (GAERS animal model of absence epilepsy) [109]. Alterations or mutations in the chloride channel subunits or molecules that regulate their function can increase membrane conductance of Cl^-. Increased Cl^--mediated hyperpolarizing currents (IPSPs) increase the number of T-calcium channels available for activation, resulting in imbalanced networks of excitatory and inhibitory components with increased synchronization in the thalamocortical circuit and decreased seizure-threshold [94, 101–117]. Animal models of absence seizures have demonstrated that GABA-B receptor antagonists can suppress absence seizures, whereas GABA-B agonists can worsen them [111].

This explains why antiepileptic medications such as Ethosuximide, Valproic acid, Lamotrigine, Levetiracetam and Zonisamide, by blocking or suppressing the T-calcium channel currents, are more effective in preventing absence seizures. On the other hand, antiepileptic medications that indiscriminately increase GABA levels (e.g. Tiagabine, Vigabatrin) or Phenobarbital (prolongs Cl^--channel opening duration) are associated with worsening of absence seizures. The effect of benzodiazepines (Diazepam, Lorazepam, Clonazepam and partial agonist: Clobazam) may be slightly more selective (increased frequency of Cl^--channel opening), also manifested on the EEG often with increased fast cortical oscillatory activity (increased intracortical inhibition and synchronization) with more variable effects on the degree of synchronization (usually desynchronization) of the thalamocortical circuit [101–111].

4.2 Epileptogenic focal neocortical and allocortical/limbocortical networks (pathogenesis and pathophysiology of focal-onset, aware or unaware, seizures with secondary propagation, bilateral spreading or generalization

Focal seizures manifesting with a variable combination of auras, sensory, motor, limbic or autonomic, aware or unaware seizures with secondary unilateral or bilateral propagation and generalization represent the collective phenotype of focal-onset, propagated or secondarily generalized epilepsy. They can occur at any age, but would be more common among the adult-onset epilepsies or in patients with an apparently normal brain development, who have never had previously any seizures in young life. Although there are no obvious neurological deficits or abnormal brain development, thorough investigations may reveal a range of subtle focal brain abnormalities or insults (structural, ischaemic/vascular, inflammatory, infectious, metabolic, autoimmune, neoplastic, degenerative, epigenetic, etc) which could be part of localised or more widespread epileptogenic networks [1–6]. On the other hand, focal/multi-focal or generalized symptomatic epilepsies are usually associated with some kind of focal or generalized brain dysfunction, injury or developmental abnormality. People with symptomatic epilepsies have neurological or cognitive deficits and a higher chance of intellectual disability, cerebral palsy, Lennox-Gastaut syndrome and other neurodevelopmental conditions/problems. Nowadays, as a result of widespread applications of epilepsy surgery with direct intracranial EEG recordings, focal neocortical and allocortical/limbocortical epileptogenic networks have been more thoroughly studied and better understood [1–6].

Please see the example below of a focal-onset musicogenic seizure with progressive ipsilateral propagation, bilateral spreading and secondary generalization in a patient who turned out to have an autoimmune (GAD65 + ve antibody-mediated) limbic encephalitis (**Figures 23–25**).

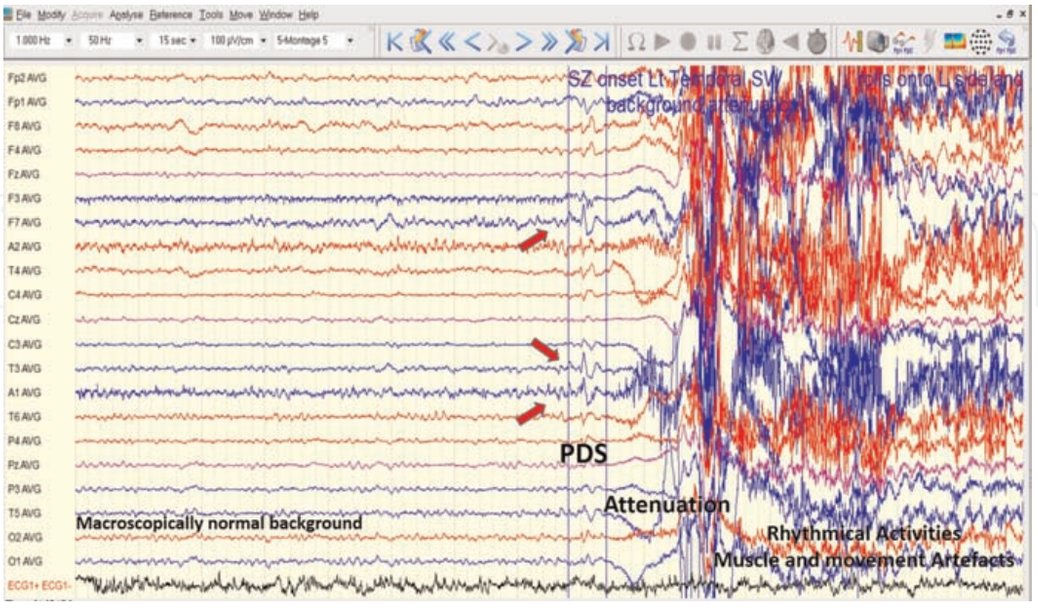

Figure 23.
Against a normal background upon the patient listening to one of her favourite songs from her childhood (previously she had been exposed to all sort of different music styles, including the most dysharmonic/atonality scales of Schoenberg's dodecaphony) a single high-amplitude sharp wave appeared over the left frontotemporal (maximum at anterior temporal F7 electrode) region, followed by a widespread desynchronization/attenuation of the EEG for 1–2 s.

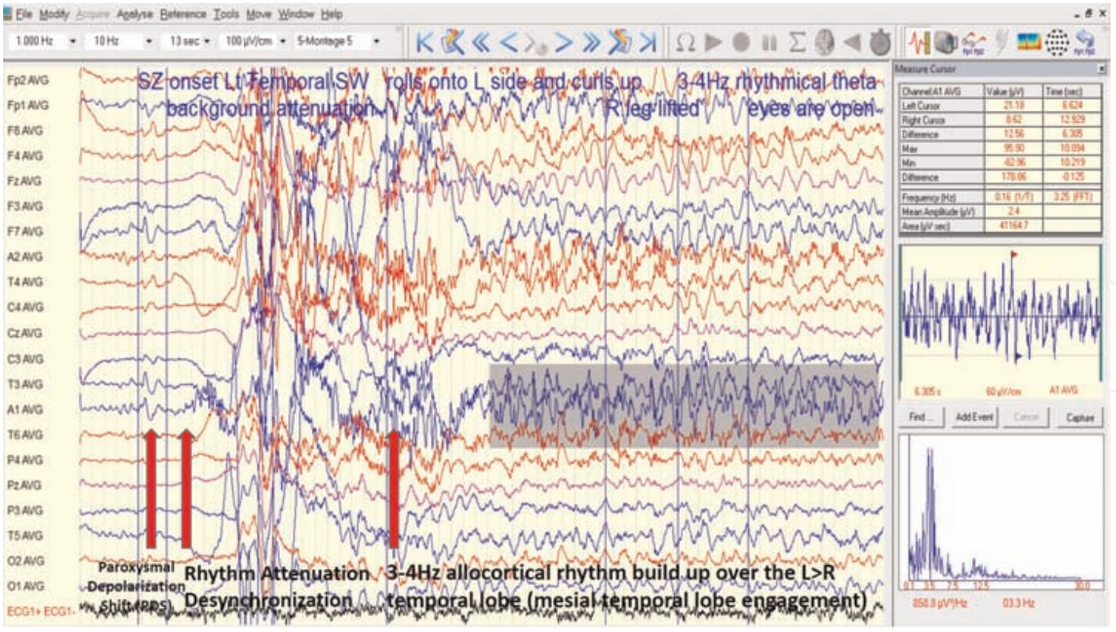

Figure 24.
Following the background EEG attenuation lasting for 1–2 s, a widespread frontotemporal (maximum at mid-temporal A1 electrode) rhythmical 3–4 Hz theta-range activity (with opening of her eyes), started building up indicating engagement of left limbo-cortical networks (left hippocampus and limbic system).

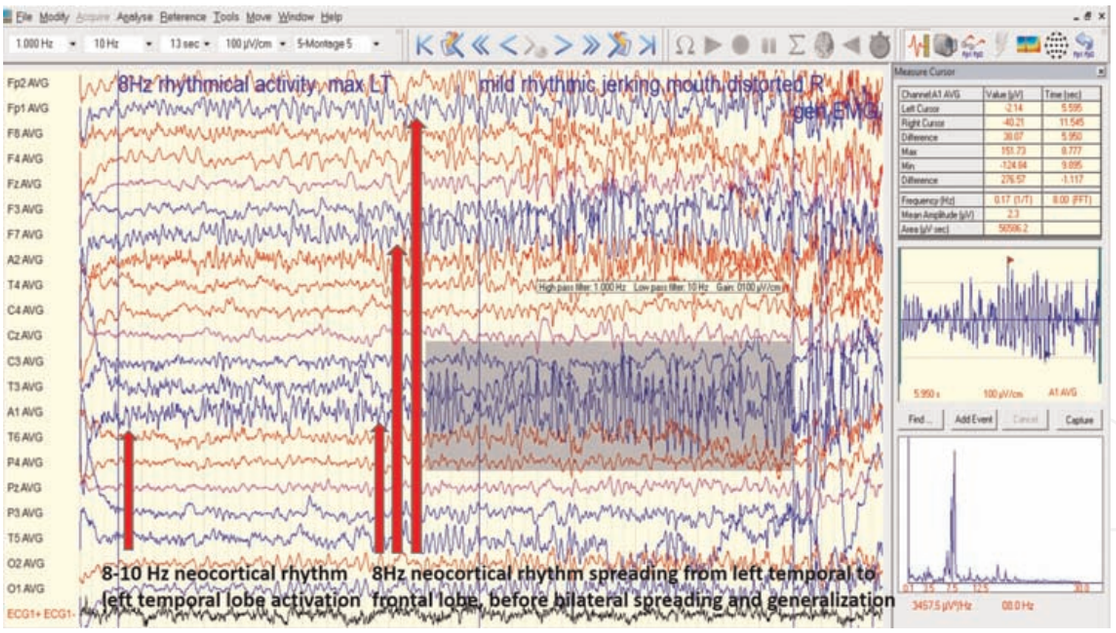

Figure 25.
Following the engagement of left limbo-cortical networks, there is an acceleration of the background activity over the left hemisphere into a rhythmical 8–9 Hz alpha-range (neocortical) activity predominantly over the left frontotemporal (maximum at A1 temporal electrode) region, before spreading to bilateral frontal regions and clinically manifesting with a generalized tonic-clonic seizure (the EEG gets obscured by muscle and movement artefact).

In the focal type of epilepsies, there is either decreased inhibition and/or increased excitation and/or structural and functional connectivity changes (acquired or cumulated through life) in the local network that can alter the dynamic interaction of excitatory and inhibitory network components and/or result in increased network

synchronization processes [118]. The following fundamental mechanisms in different combinations can alter the dynamic interaction of excitatory and inhibitory network components resulting in focal-onset seizures:

- Decreased inhibition or defective activation of GABAergic neurons
- Increased excitation or increased network synchronization processes

4.2.1 Mechanisms leading to decreased inhibition

The release of γ-amino-butyric acid (GABA), the main inhibitory brain neurotransmitter, from presynaptic neuron terminals binds to GABA-A and GABA-B receptors and inhibits the postsynaptic neuron either by direct induction of an inhibitory postsynaptic potential (IPSP) via GABA-A receptor-mediated chloride currents, or by indirect inhibition of the release of excitatory neurotransmitter in the presynaptic afferent projection, with a GABA-B receptor-mediated potassium current [119].

GABA-A receptors (made of 2 alpha, 2 beta and 1 gamma subunits) are coupled to chloride channels which are modulated by several mechanisms, such as changes in the 3-dimensional conformation of subunits/proteins or phosphorylation at different sites of the channel. For example, chloride channels are modulated by benzodiazepines (e.g. diazepam, lorazepam, clonazepam, clobazam), barbiturates (e.g. phenobarbital, pentobarbital), Topiramate or Cenobamate or Stiripentol. Benzodiazepines increase the frequency of chloride channels opening, whereas barbiturates increase the duration of channels opening. Topiramate or Cenobamate or Stiripentol also increase the frequency of chloride channel opening, but they bind to a different site from benzodiazepines (allosteric modulators) [120].

The chloride equilibrium potential is roughly the same as the resting membrane potential equilibrium, about −70 mV. Therefore, the electromotive force for net chloride flux during the resting potential is minimal. As the summation of excitatory postsynaptic potentials (EPSPs) results in depolarization of the membrane potential, the influence of inhibitory postsynaptic potential (IPSP) mediated chloride currents on the membrane potential becomes even more crucial, as only these can increase the threshold for firing an action potential and decrease neuronal excitability [80–82, 85, 86, 90, 121].

4.2.1.1 Defective GABA-A inhibition

Mutations or lack of expression of appropriate GABA-A receptor complex subunits, their assembly molecules or the molecules that modulate their electrical properties can cause decreased inhibition [120, 122]. For example, hippocampal pyramidal neurons may not be able to assemble alpha-5, beta-3, gamma-3 receptors because of deletion of chromosome 15 (i.e. Angelman syndrome) [123]. Animal models of focal-onset epilepsy based on pilocarpine models, electrical or chemical kindling, have shown changes in the distribution of subunits of the GABA-A receptor complex [124].

4.2.1.2 Defective GABA-B inhibition

The GABA-B receptor complex, often located in the presynaptic excitatory nerve terminals, consists of 2 subunits (with 7 transmembrane domains each),

coupled to potassium channels modulated via G proteins. Upon activation it drives a potassium current with longer latency and duration of action compared to the chloride current generated by activation of the GABA-A receptor. Thus, alterations in the GABA-B receptor complex may be crucial for ictal transformation [108, 125].

4.2.1.3 Defective network function of GABAergic interneurons

As we have demonstrated, in complex neuronal networks with recurrent feedforward and feedbackward projections from excitatory to inhibitory neurons, feedforward and feedbackward inhibition emerge from the critical time activation of GABAergic inhibitory neurons relative to the output of the Glutamatergic excitatory neurons of the network [35, 76–78, 126, 127]. The hippocampal model has been extensively investigated as the prototype neuronal network of focal epileptogenesis. Schaffer collateral axons from the CA3 pyramidal neurons (main afferent input) activate the CA1 principal neurons (hippocampal pyramidal cells). At the same time collateral feedforward projections to GABAergic inhibitory interneurons activate their somata, before or during activation of the apical dendrites of the CA1 pyramidal neurons [66, 79–82, 100, 128].

As a result of this crucial structural and functional connectivity, during passive transmission of the excitatory postsynaptic potential (EPSP) from the apical dendrites to the axon hillock of the CA1 pyramidal neurons, a concurrent GABAergic inhibitory postsynaptic potential (IPSP) inhibits the soma or axon hillock of the CA1 pyramidal neurons. This feedforward inhibitory projection simultaneously hinders pyramidal cell depolarization and firing of an action potential [129]. Recurrent axon collaterals from the CA1 pyramidal neurons activate GABAergic interneurons after the pyramidal neurons have fired an action potential. This creates a feedbackward inhibitory system (multiple inhibitory circuits with built-in time-lags) that allows GABAergic cells to control repetitive firing in principal neurons (CA1 pyramidal cells) and also inhibit the surrounding hippocampal pyramidal cells. The critical timing of these excitatory-inhibitory cycles (push-and-pull mechanism) accounts for the generation of normal gamma-oscillatory and hippocampal sharp-wave ripples, or abnormal fast ripples and ultra-fast ripples [35, 36, 66, 76–79, 98–100, 126, 127, 130, 131].

The mossy cells of the hilar polymorphic region of the dentate gyrus of the hippocampus (which receive feedforward input from the Entorhinal Cortex and feedback activation from CA3) appear to activate GABAergic neurons and gate-control the inhibitory tone of the network. The mossy cells may be susceptible to seizure-related neuronal death [132, 133]. The loss of mossy cells results not only in impairment of GABAergic interneuron activation (deafferentation), but also in synaptic reorganization and changes in network plasticity, with formation of newly sprouted circuits of excitatory and inhibitory cells in an attempt to restore inhibition. However, with epilepsy progression the sprouted synaptic contacts also create recurrent excitatory circuitries that permanently alter the balance between excitatory and inhibitory tone in the hippocampal network [133, 134].

4.2.1.4 Defective intracellular buffering of calcium

In rodent hippocampal experiments, recurrent seizures can result in progressive loss of hyperpolarized resting membrane potentials in the hilar polymorphic region of

the dentate gyrus and eventually loss of interneurons that lack the calcium-binding proteins parvalbumin and calbindin [135, 136]. Further experiments showed the critical role of adequate concentrations of calcium-binding proteins for neuronal survival in settings with sustained increases in intracellular calcium under neuronal cellular stress [137], such as in status epilepticus, febrile convulsions, brain hypoxia and other metabolic, toxic, ischaemic and inflammatory brain insults. Interindividual differences in these calcium-binding proteins may explain the variable susceptibility of different patients and with advancing age to epileptogenesis via the premature loss of critical interneurons, a process that alters inhibitory controls of local neuronal networks in favour of excitation [138–140].

4.2.2 Mechanisms leading to increased excitation

Similar concepts of structural and functional organisation to the chloride channels, with crucial electrophysiological implications, also hold for the voltage-gated sodium, potassium and calcium channels. Alterations or mutations in the chloride, potassium or sodium and calcium channel subunits or in the molecules that regulate their function may increase or decrease the membrane permeability and conductance of chloride, potassium or sodium and calcium ions forming the chloride-mediated and potassium-mediated hyperpolarizing currents (IPSPs) that counterbalance the sodium-mediated and calcium-mediated depolarizing currents created by the summation of EPSPs [94, 112–114]. The overall network balances and imbalances attained in excitatory and inhibitory components critically modulate the seizure-threshold or the tendency to seizures [33, 35, 36, 66, 69, 76–79, 85–90, 93, 97, 115].

A lower seizure-threshold and thus increased epileptogenesis may result from inappropriate activation of fast or long-acting NMDA channels or reduced intracellular calcium-buffering proteins (parvalbumin and calbindin), increasing the vulnerability of neurons to cellular stress-injury and death [134, 137, 140]. The release of the excitatory amino acid Glutamate from presynaptic neuron terminals mediates excitatory potentials (EPSPs) in the postsynaptic neuron membrane via: N-methyl-D-aspartic acid (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)/Kainate, and Metabotropic Glutamate receptors. These receptors are coupled by means of different postsynaptic membrane mechanisms to several depolarizing channels [33, 66, 69, 87–89, 116].

4.2.2.1 Increased activation of NMDA receptors

Fast glutamatergic neurotransmission is based on activation of AMPA/Kainate and NMDA receptors. The AMPA/Kainate receptors are coupled to channels that create currents of monovalent cations (sodium and potassium), whereas the NMDA receptors open channels that allow also divalent cations to pass through (calcium). Slow glutamatergic neurotransmission is also possible via metabotropic receptors, which alter postsynaptic membrane excitability with late-onset and more prolonged postsynaptic changes in phosphorylation and gene expression by means of a second-messenger system which uses calcium as a catalyst for various intracellular reactions. Normal NMDA receptor function is thought to be associated with learning and memory, whereas increased activation has been observed in several animal models of focal epilepsy, such as kindling, kainic acid, pilocarpine, etc. [116, 117, 141, 142].

4.2.2.2 Increased synchronization induced by ephaptic phenomena

Widespread electrical fields emerging from synchronous activation of many pyramidal neurons in laminar hippocampal structures or local changes in extracellular ionic concentrations of potassium and calcium [97] or increased neuronal coupling due to more permanent changes in functional gap junctions [143] may further increase the excitability of neuronal assemblies by nonsynaptic (ephaptic) interactions, predisposing to focal-onset seizures or status.

4.2.2.3 Increased synchronization and/or activation from recurrent excitatory collaterals

Intractable focal-onset epilepsies are frequently accompanied by abnormalities in the limbic system, particularly in the hippocampal formation. Hippocampal atrophy and sclerosis are common lesions associated with neuronal loss and gliosis, particularly affecting the hilar polymorphic region and CA1 pyramidal regions, with relative sparing of the CA2 pyramidal region and only intermediate severity lesions in the CA3 pyramidal region and dentate granule neurons. About 2/3 of patients with intractable temporal-lobe epilepsy have marked hippocampal sclerosis, while animal models with >100 brief convulsions or epileptic status showed similar changes, suggesting that epileptogenesis or hippocampal/limbic system kindling can be a self-perpetuating process [132, 138, 139].

Perhaps subtler and more common than overt hippocampal sclerosis may be Mossy-fiber sprouting. The mossy fibers are the axons of the dentate granule neurons that mostly project to the hilar polymorphic region and CA3 pyramidal neurons. Progressive loss of neurons in the hilar polymorphic region and degeneration of their synaptic projections on dentate granule neurons, induce sprouting of the neighbouring mossy-fiber axons and formation of recurrent excitatory collaterals, with an overall increase in the excitatory drive of dentate granule neurons [133, 134, 140].

4.3 Epileptogenicity: critical conditions and clinical implications

As we have demonstrated in previous sections, epileptogenicity seems to be intricately related to the mechanisms that vary the level of consciousness and transition through sleep (cortico-thalamocortical circuits) and the processes of learning, memory, emotion and complex behaviour (cortico-limbocortical circuits). In our simulations of neocortical, thalamocortical and allocortical neuronal networks the following parameters or processes have emerged as most critical for epileptogenesis:

4.3.1 Excitability of individual neurons and entire networks

The intrinsic/inherent cell membrane and synaptic membrane excitability properties, influence the electrochemical ionic gradients/equilibriums and ionic transmembrane conductances (presynaptic, synaptic, extrasynaptic and postsynaptic receptors, ionic channels and ligands/neurotransmitters, transporters, ion pumps and exchangers, channelopathies and antiepileptic drug effects). These ultimately determine the intrinsic excitability and oscillatory dynamics of the individual neuron and its interactions with other structurally/functionally interconnected neurons.

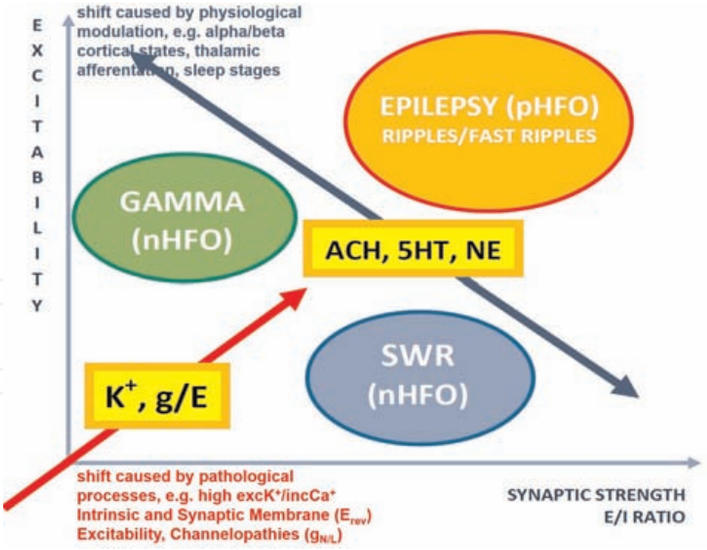

Figure 26.
A summary of the interaction of multiple neurophysiological epileptogenic mechanisms.

The membrane excitability characteristics and shortening of time integration constant (via a "push-and-pull" mechanism) of synchronized, coincidental or critically interacting excitatory (EPSP) and inhibitory (IPSP) postsynaptic potentials can increase or decrease the excitability of the entire network (**Figure 26**) [79, 85–97].

The intrinsic excitability of the neuron directly increases excitation or the number of fast or transient oscillations by reducing the relative refractory period of the firing neurons and/or increase the probability of spatiotemporal summation or integration of synchronous/coincidental EPSPs and/or IPSPs. These mechanisms can drive the firing rates of neurons broadband, the amplitude of the postsynaptic oscillations high and the time/phase dynamics of their firing complex. They can thus generate a range of physiological transient and rhythmical cortical neuronal activities (in delta, theta, alpha, beta and gamma frequencies as reflected in extracellular recordings, local field potentials, intracranial and scalp surface EEG) and can drive local or widespread networks in paroxysmal/hypersynchronous activity [85–97, 126, 127].

4.3.2 Structural connectivity of neuronal networks

The structural connectivity (spatial network geometry) of neurons is critical for the dynamic interaction of excitatory and inhibitory network components. The spatial distribution of excitatory and inhibitory neurons reflects how sharpened or spread out the inhibition may be around excitatory neurons. Changing the relative distribution of the inhibition, that is, how locally vs. widespread the inhibition acts, shapes up and critically determines individual neuronal and collective oscillatory network behavior, generating a range of physiological transient and rhythmical cortical neuronal activities and can drive local or widespread networks in paroxysmal or hypersynchronous activity (**Figures 13–15**) [76, 79, 126, 127, 144].

Early developmental and life-long brain changes induce progressive small-to-large scale structural changes in cortical networks (and thus in epilepsies with age) via migration and branching-off patterns of neurons, plasticity changes via sprouting or pruning of neuronal processes, reinforcement or attenuation of synaptic contacts.

Cortical network development and life-long plasticity changes determine long-term episodic memory formation or retrieval and operational learning memory, and may be responsible for the development of thalamocortical (e.g. idiopathic/genetic generalized epilepsies) or build-up of neocortical and limbocortical epileptogenic networks (e.g. abnormal excitatory recurrent collaterals) [1–6, 101, 126, 127, 144].

4.3.3 Functional connectivity of neuronal networks

The functional connectivity (synaptic strengths/weights) of the network is critical for the dynamic interaction of excitatory and inhibitory network components. Changing the relative strength of synaptic connections, critically determines the oscillatory behavior of the network, and can produce a range of physiological transient and rhythmical cortical neuronal activities and collective behaviors, from local spatiotemporal to systemic synchronization phenomena. These can sustain the excitatory up-states of cortical neurons, shape and enhance plasticity, memory, structural and functional connectivity of thalamocortical, limbocortical and neocortical neuronal networks (**Figures 13–15**) [43–53, 126, 127, 144].

Memory and learning (new memory formation and retrieval, short-term working memory and operational learning), diurnal variations in brain function (spindle waves and slow sleep oscillations) and longer lasting plasticity changes emerge from the short to long-term potentiation and/or depression of synaptic connections. Developmental brain changes are also associated with progressive plasticity changes, affecting brain rhythms and epilepsies with age including the build-up (e.g. through abnormal excitatory recurrent collaterals) or shape up of epileptogenic networks (e.g. through recurrent seizures, high firing-rate and/or hypersynchronous synaptic activations) [1–6, 126, 127, 144].

4.3.4 Critical global and local transient brain states (microstates)

Neocortical activation is driven by thalamic/reticular input and the level of consciousness rises or drops with a varying reticular, thalamic, septal or neocortical drive. As higher numbers of thalamic input neurons engage larger numbers of cortical neurons, this physiologically brings about thalamocortical arousal, thalamosensory afferentation and amplifies cortical cognitive processing upon multi-modal sensory stimulation of the cortex. Cortical rhythms speed up and modulate from slow oscillatory (delta and theta range) activities during sleep and low consciousness states to faster oscillatory activities (alpha with closed eyes and beta/gamma with open eyes) in the awake and alert brain (**Figures 13–15**) [43–53].

In a similar fashion, limbocortical activation is externally driven by varying septal, reticular, thalamic, or neocortical input. While internally limbocortical activation is driven by CA3/modulatory Mossy-fiber input into CA1/Subiculum and further into entorhinal cortex that interfaces with the neocortical parahippocampal gyrus and perirhinal cortex, anterior nucleus of the thalamus, the posterior and anterior cingulate cortex, temporal association cortex (for stimulus perception) and frontal association cortex (for planning behavioural responses) and other subcortical structures. This gives rise to physiological high-frequency gamma oscillations (nHFO) and sharp-wave ripples (SWR) for memory storage/retrieval and arousal respectively (**Figure 26**) [33, 34, 49, 60–66, 68, 69].

When critical local and global conditions are met, transitions across different global and local brain states (microstates) become a powerful modulator of small-to-

large scale neocortical, ganglio-thalamocortical and/or limbocortical networks that elicit or unmask epileptogenic network activity in the form of pathological gamma-oscillations (pHFO), ripples and fast ripples, paroxysmal depolarizations and DC shifts at the microscopic/mesoscopic level (extracellular and local-field potentials) or spike-and-waves discharges, sharp and rhythmical fast and slow waves or attenuation/electrodecremental responses at the macroscopic level (EEG) (**Figure 26**) [33, 34, 60–66, 68, 69, 98–100, 126, 127]

4.3.5 Epileptogenicity and clinical implications

The above have crucial clinical implications for our current practice and future approach to epileptic disorders. We need to identify focal lesions or more widespread abnormalities of structural and/or functional connectivity (focal cortical dysplasias, developmental dysplasias/malformations, previous or perinatal brain injuries, hypoxic or metabolic and toxic insults, ischaemic or vascular lesions and malformations, tumours, space-occupying lesions, infiltrative, (para)neoplastic, inflammatory, infective/postinfective, autoimmune, vasculitic, (epi)genetic, neurodegenerative, etc) and modify the local and global, structural and/or functional connectivity and network excitability [1–6, 98–100, 127].

A common approach to modifying the local and global functional connectivity and network excitability is by means of antiepileptic medications (**Figure 27**). For this

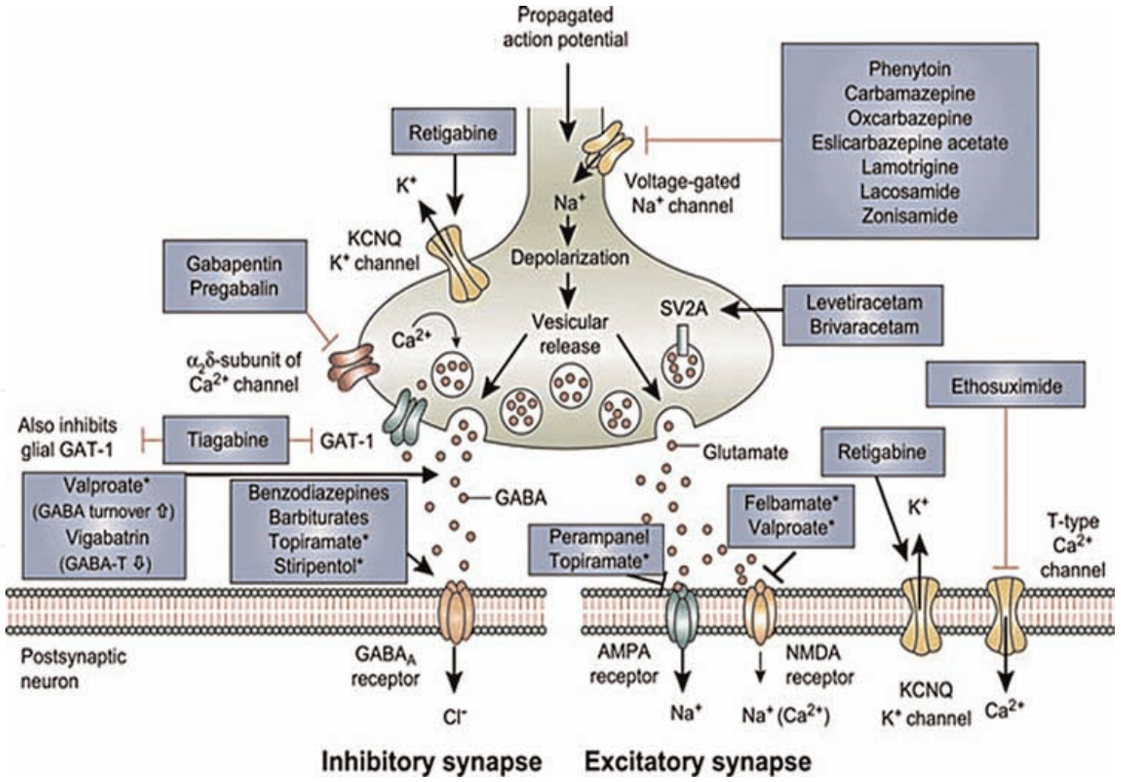

Figure 27.
Mechanism of action of clinically approved anti-seizure drugs. Published in Löscher et al. [145] under CC BY-NC 4.0 license. The updated and modified figure has been reproduced with permission from Löscher and Schmidt [146]. The initial figure was modified with permission from Macmillan Publishers Ltd © Bialer, M. & White, H. S. Nat. Rev. Drug Discov. 9, 68–82 (2010). Drugs marked with asterisks indicate that these compounds act by multiple mechanisms (not all mechanisms shown here). GABA-T: GABA aminotransferase, GAT: GABA transporter, SV2A: synaptic vesicle protein 2A, GABA: gamma-aminobutyric acid, NMDA: N-methyl-D-aspartate, AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, KCNQ: a family of voltage-gated potassium channels (also known as the Kv7 family).

purpose, we employ different antiseizure medications as monotherapy or in various optimal combinations (polytherapy):

1. fast voltage-gated Na^+-channel blockers (e.g. Carbamazepine, Eslicarbazepine, Oxcarbazepine, Phenytoin, Lamotrigine acting also on L-type Ca^{+2}-channels, Zonisamide acting also on T-type Ca^{+2}-channels, Cenobamate acting also on GABA-A receptors, Valproate acting also on Ca^{+2} and K^+ channels and having anti-NMDA and indirect GABAergic effects, etc.) and/or slow voltage-gated Na^+-channel blockers (e.g. Lacosamide)

2. SVPA2 receptor inhibitors (e.g. Brivaracetam, Levetiracetam acting also on N-Type Ca^{+2}-channels)

3. AMPA glutamate receptor antagonists (e.g. Perampanel, Topiramate acting also on GABA-A receptors), with all the above used to control/suppress the intrinsic local and global network excitability

4. GABA-A receptor agonists (e.g. Clobazam, Clonazepam, Midazolam, Lorazepam, Diazepam, Phenobarbitone, Primidone, Stiripentol, etc) used to enhance local and global network inhibition (**Table 3**) [1–11].

An alternative approach to modifying the local and global, structural and functional network connectivity and excitability is by means of neurosurgery (with resection or thermocoagulation of highly epileptogenic lesions/zones and disruption or disconnection of epileptogenic networks, etc) [98] and neurostimulation (vagus nerve, electrical/magnetic or optogenetic cortical stimulation or deep brain stimulation of the thalamus [anterior, centromedian, subthalamic nuclei]/basal ganglia, hippocampus, etc.) [71].

Current antiseizure medications (**Figure 27**) are mostly effective at preventing initiation, propagation, spreading or generalization of epileptic seizures. Modelling epileptogenesis across all scales of neuronal organization will further our understanding of the mechanisms of epileptogenesis, leading to better pharmacological and neurosurgical or neurostimulation treatment strategies and the development of new antiepileptic and epileptogenesis-modifying medications [1–11, 71, 98].

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