Chapter 1

Pathophysiology of Epilepsy

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1.1 Introduction and Definitions

A *seizure* is a situational clinical event that may be instigated by any number of extrinsic or intrinsic precipitating factors and that results in an excessive, hypersynchronous discharge of a cortical neuronoglial population and manifests in the brain in either a localized or widespread manner. This abnormal activity takes over the normal functioning of one or more brain networks to result in seizures that characterize over 40 recognized epileptic syndromes.[1]

Epilepsy, is a central nervous system disorder characterized by recurrent seizures that manifest over a duration of time, even perpetually, and may occur spontaneously.

Epileptogenicity refers to the expression of the epilepsy as it may appear in electrographic recordings while *epileptogenesis* identifies the mechanism by which it comes about and is then perpetuated as a result of changes in cellular properties, gene expression, neuronoglial interactions and network reorganization.[2,3]

Brain function involves several incongruent parallel networks, cortical and subcortical, that align in a variety of ways to achieve different ends (e.g., cognition, language, sensory integration, locomotor execution). Epilepsy, once established, occasionally subsumes and, at times, overtakes some or most of these in often reproducible patterns in the form of seizures.

1.2 Cerebrocortical Anatomy

1.2.1 Cerebral Microstructure

The human cerebral cortex comprises 82% of total brain mass, while containing only 19% of the neurons in the brain. The greater relative cortical size, therefore, does not reflect an increased relative number of cortical neurons compared with other primates. The ratio of cerebrocortical glial cells to neurons (3.76:1) remains similar to that in other primates, despite astrocytes increasing progressively in size and number throughout evolution. Since Cajal, the brain has been primarily considered in a neuronal context, but it has become increasingly evident that glial cells, particularly astrocytes, serve a much greater role than once thought, so that it is important for us to consider the brain more as a neuronoglial entity in the context of functional expression, as well as in its disorders.

The neuronal cytoarchitecture of the human cerebral cortex varies by region and was originally mapped in detail and reported by Brodmann in 1908–9. Its width is upwards of 5 mm and it contains 16.34 billion neurons and 60.84 billion astrocytes spread throughout its considerable, highly-convoluted mantle.[4] A distinct stratification is noted with three to six layers that are differently constituted by region. The neopallium or neocortex, with its six cellular layers, occupies the majority of the surface area, while the archipallium

or archicortex, represented by the hippocampus and dentate gyrus situated in the mesial temporal lobe, with their three layers, is the phylogenetically oldest part of the cerebral cortex. A transitional cortex or paleocortex, represented by the piriform area and entorhinal cortex, with its five layers, bridges the neocortex and archicortex.

The mesial temporal lobe, well known for its propensity toward epileptogenicity, is composed of the uncus, including the amygdala, the piriform area, the parahippocampal gyrus with its subicular complex and entorhinal cortex, the hippocampus, and the dentate gyrus. The hippocampus is composed of four subregions, CA1–4, with a layered structure that varies, to a degree, by subregion (Figure 1.1). CA3 has the following strata – lacunosum-moleculare,

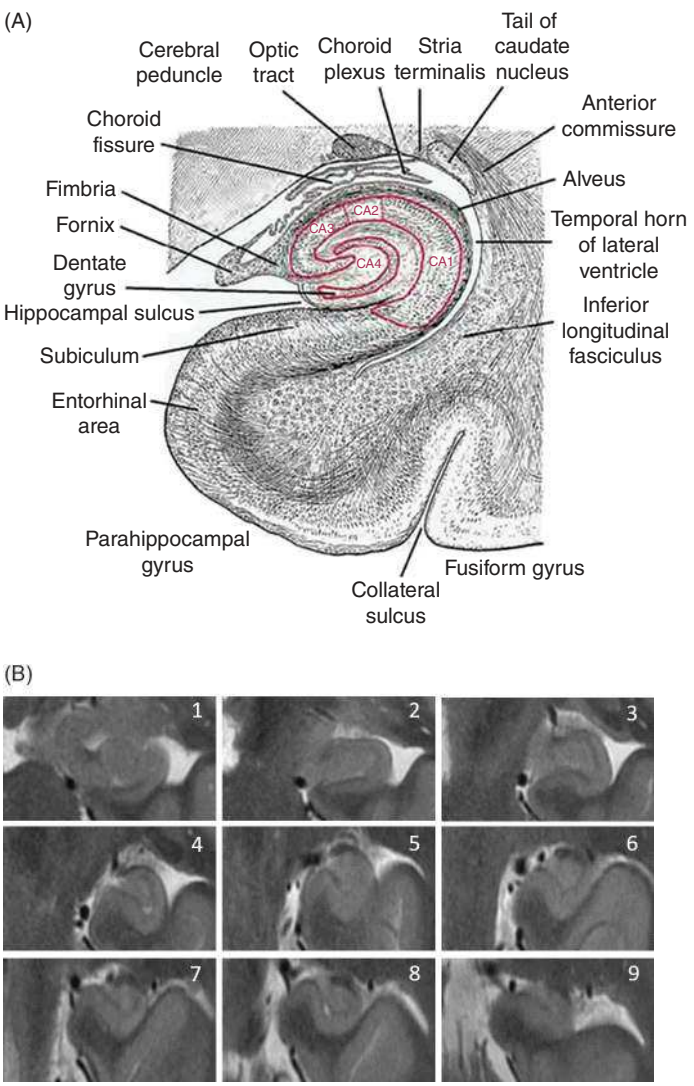

Figure 1.1 (A) Schematic representation of the right hippocampus and parahippocampal gyrus. (B) T2-weighted magnetic resonance images of the left hippocampus shown sequentially from anterior (1) to posterior (9). The most posterior image is immediately beyond the level of the midbrain tectum.

radiatum, lucidum, pyramidal, and oriens – while CA1 and CA2 lack the lucidum stratum. CA4 extends into the hilum of the dentate gyrus, which itself is composed of layers – the molecular, inner molecular, and granular – arranged in two blades joined in a V-shape containing the hilum. The primary input is from the entorhinal cortex (EC) via the perforant pathway, which also provides some reciprocal connections. The EC is widely and reciprocally connected to cortical and subcortical areas and therefore provides a conduit for input from a diversity of sources, initially to the dentate gyrus, which serves as a gatekeeper for the remainder of the hippocampus. The perforant pathway originates in layer II of the EC and extends to the dentate granular layer with some axons also extending to CA3 and fewer to CA1. Axons of dentate granule cells (e.g., mossy fibers) synapse with hilar and CA3 pyramidal cell dendrites, and the corresponding pyramidal axons extend to other CA3 neurons via immediate collaterals, to the contralateral hippocampus and to CA1 neurons (e.g., Schaffer collaterals) which, in turn, will synapse upon neurons of the subicular complex that will project back to the entorhinal cortex. Other projections to the prefrontal cortex, lateral septal area, and mammillary body extend the influence of the hippocampus upon functionally distinct areas.

In hippocampal sclerosis, neuronal loss and gliosis occur primarily in the dentate hilus (i.e., CA4 subregion) and CA1 subregion with less change in the CA3 subregion. The resulting loss of hilar interneurons and CA1 pyramidal neurons induces a synaptic reorganization (e.g., mossy fiber sprouting) with aberrant innervation of the dentate gyrus itself. Ostensibly, this results in a recurrent hyperexcitable situation that may be triggered by a yet undefined mechanism. Several initial events may bring about a relatively selective injury to this vulnerable area of the brain, including such events as trauma,[5,6] early protracted fever,[7] and hypoxia.[8]

The neocortex has primary areas that subserve the various sensory modalities and both locomotor and oculomotor action, and these lie adjacent to association areas that undertake more complex functions such as abstraction, creativity, and integrative aspects of locomotor function. The six layers are characterized by the different neuronal shapes, sizes, density, and distribution of nerve fibers. They constitute the following, from outer to inner layer:

I molecular layer
II external granular layer
III external pyramidal layer
IV internal granular layer
V internal pyramidal layer
VI multiform layer.

These may be organized functionally into three areas according to their projections:

1. *Supragranular (layers I–III):* origins and terminations of intracortical connections identified as associational (i.e., within the same hemisphere) or commissural (i.e., interhemispheric); most highly developed in humans
2. *Internal granular (layer IV):* termination of thalamocortical fibers, particularly evident in the sensory cortex
3. *Infragranular (layers V, VI):* primarily origin of subcortical projections with layer V comprising principal efferent projections to basal ganglia, brainstem, and spinal cord, and layer VI projecting to thalamus; motor areas bear very small to absent granular layers.

The interneuronal population of the cerebral cortex is characterized by morphology and includes, but is not limited to, basket cells, Martinotti cells, chandelier cells, bouquet cells,

bipolar cells, and neurogliaform cells.[9] The molecular layer (layer I) is an important synaptic field of the cortex, with most dendrites originating in pyramidal cells and axons from elsewhere in the ipsi- and contralateral hemispheres and thalamus.[10] Martinotti cells in the deeper cortical layers also contribute axons to the molecular layer, where horizontal Retzius–Cajal cells and stellate cells may be found. Basket cells constitute 5–10% of cells in the cerebral cortex and are found in layers II–VI.[11] They form extensive axosomatic connections with pyramidal neurons. The external granular layer contains both small pyramidal and stellate cells from which dendrites extend into the molecular layer and axons into the deeper layers for intracortical distribution. The external pyramidal layer contains progressively larger pyramidal cells whose apical dendrites extend into the molecular layer and axons project to other cortical destinations. Stellate (i.e., granule) cells are most prominent in layer IV (internal granular layer). Their axons remain within the cortex and synapse with en passage dendrites from layers V and VI, other stellate and Martinotti cells. Layers V and VI are considered phylogenetically older than the more superficial layers. The internal pyramidal layer contains pyramidal cells that intermingle with stellate and Martinotti cells. The giant Betz cells reside here in the primary motor area. The multiform layer contains predominantly fusiform cells.

Approximately 80–90% of cerebrocortical neurons are glutamatergic while 10-20% are GABA-ergic interneurons, which exert inhibitory control and influence rhythmic network oscillations.[12] About 40% of interneurons, largely basket cells, express parvalbumin (PV), while 30%, largely Martinotti cells, express somatostatin, and the remaining 30%, largely bouquet and neurogliaform cells, express the serotonergic receptor, 5HT3A.[13,14] PV-expressing basket cells are fast-spiking, showing high-frequency spike trains exceeding 200 Hz, and have been implicated in the development of epilepsy in both genetic and lesional models.[15] Martinotti cells participate in a disynaptic surround inhibition of pyramidal cells.[16] The nicotinic acetylcholine receptor α2 subunit specifically marks layer V Martinotti cells projecting to layer I, where they target certain pyramidal cells, synchronizing them in a frequency-dependent manner.[17] Loss of this important central mechanism may bias the local circuitry toward excitability, as was seen in a mouse model of Dravet syndrome wherein excitability in both fast-spiking, PV-expressing basket cells and somatostatin-expressing Martinotti cells resulted in a disinhibition of cortical output.[18]

1.2.2 Cerebral Connectivity

For over a century, the neuron and its connectivity has been regarded, quite rightly, as the primary structural entity underlying function. The study of local non-neuronal cellular and extracellular compartmental influences upon its behavior has introduced a greater complexity to our still incomplete understanding of both normal and abnormal expression. This section will therefore review both the traditional synapse-mediated connectivity that has been identified and the nonsynaptic influences that have been more recently investigated.

1.2.2.1 Large-Scale Connectivity

The cerebral white matter contains three types of axons that constitute association, commissural, and projection fibers. Association fibers connect parts of one hemisphere over short intergyral distances via subcortical arcuate fibers and more longitudinally oriented interlobar bundles. The cingulum services the limbic lobe and interconnects the cingulate and parahippocampal gyri and the septal area. The superior longitudinal fasciculus, situated above the insula, interconnects all the lobes and includes the arcuate fasciculus that

descends into the temporal lobe. Processed visual and proprioceptive signals pass anteriorly to the frontal cortex to execute appropriate locomotor responses when needed. Similarly, receptive and expressive language areas of the temporal and frontal cortices are interconnected by arcuate fibers. The much smaller inferior longitudinal fasciculus lies beneath the insula interconnecting the occipital and temporal cortices. The inferior occipitofrontal and uncinate fasciculi are part of the same association bundle lying beneath the insula and striatum with the shorter uncinate fasciculus passing along the stem of the Sylvian fissure interconnecting the temporal pole and the orbitofrontal cortex. The superior occipitofrontal fasciculus interconnects the frontal with the parieto-occipital cortices dorsally and mesially.

Commissural fibers largely traverse the corpus callosum with the forceps frontalis drawing fibers from the frontal lobes into the genu of the callosum anteriorly, which tapers inferiorly into the rostrum, and the forceps occipitalis connecting the occipital lobes through the splenium posteriorly. Direct connections are made between topographically and functionally similar regions of both hemispheres. Indirect connections exist for the hand area of the primary sensory cortex and parts of the primary visual cortex via callosal fibers passing from their respective association cortices to which they are primarily connected. The anterior commissure interconnects the middle and inferior gyri and the uncus of both temporal lobes. The fornices are symmetric bundles that originate along each hippocampus, leaving its posterior end to connect the hippocampal formation from each side with the hypothalamus and septal area. The forniceal or hippocampal commissure connects the two hippocampi across the midline.

Projection fibers connect the cerebral cortex with subcortical structures, appearing as the corona radiata in both hemispheres, and are afferent or efferent in relation to the cortex. Most afferent or corticofugal connections arise in the thalamus, with a few originating in the hypothalamus and brainstem. The thalamic radiations – anterior, middle, posterior, and inferior – are reciprocal and distribute between prefrontal, parietal, occipital, and temporal cortices, respectively. The corticofugal motor projection fibers do not constitute an integral aspect of the epileptogenic network, although they constitute the means by which some semiological features manifest.

1.2.2.2 Nonsynaptic Features

The Extracellular Space

The promotion of excitability and neuronoglial synchrony may be initiated and perpetuated by alterations in the extracellular space. Interference with Na^+-K^+ pump function by hypoxia or ischemia in hippocampal CA1 pyramidal neurons, known to be sensitive to changes in membrane K^+ currents,[19] can induce a transition to a state of excitability. Likewise, the transmembrane Cl^- gradient may be compromised by alteration of the Cl^--K^+ cotransport mechanism resulting in a compromise of GABA-activated inhibitory Cl^- currents.[20] Shrinkage of the extracellular space alone through changes in osmolality have also been shown to induce epileptiform bursting among hippocampal CA1 neurons.[21] Ephaptic transmission is enhanced by such circumstances, promoting wider field activation.[22] Spontaneous synchronous field bursts among these same neurons have been reported in hippocampal slice models exposed to a low Ca^{2+} environment designed to block chemical synaptic activity.[23] The extrasynaptic space can also be considered a medium for diffusion of neurotransmitters that affect extrasynaptic receptors and transporters to influence cells without mediation by frequency-coded neurotransmission.[24] Extrasynaptic nicotinic acetylcholine receptors, in

particular, provide a fast form of transmission through ligand-gated ion channels and can interfere with dendritic signal integration after synaptic activation has occurred.[25]

Gap Junctions

These membrane channels, composed of connexin proteins, vary widely in distribution throughout the cerebral cortex and ostensibly underlie the functional organization of the neuronoglial environment in different areas.[26] There is some indication that gap junctions are up-regulated in epilepsy and that seizure duration may be influenced by gap-junction blockade, [27] although mRNA and protein expression of constituent glial connexins appears not to be altered.[28] Faster propagation may promote the hypersynchronous activity that characterizes ictal expression. Although different connexin protein subunits of gap-junction hemichannels predominate in neurons and glia, heterologous junctions have been identified and, indeed, glutamate release from neurons has been shown to evoke calcium waves in astrocytes, spreading via gap junctions, that may, in turn, activate neurons at a distance.[29] Moreover, the same syncytial junctional arrangement of astrocytes may serve to buffer excess extracellular K^+ to reduce excitability in a limited area of the cerebral cortex by creating a more efficient voluminous sink.[30] Hence, disturbance of such an arrangement by trauma or ischemia may alter its capacity and render a particular site more susceptible to the induction and maintenance of epileptogenicity.

Neuronal gap junctions appear predominantly in inhibitory interneurons. The two patterns of expression are identified between parvalbumin-positive multipolar bursting (Pb^+MB) cells,[31,32] and calretinin-positive multipolar ($Calr^+M$) cells and Pb^+MB cells. The Pb^+MB cells synapse upon the soma and proximal dendrites of cortical pyramidal cells.[31] Gap junctional blockade of these inhibitory interneurons may lead to pyramidal cell excitation, either by interfering with the timing of inhibition of pyramidal cells,[33] or releasing inhibition of pyramidal cells through blockade between Pb^+MB and $Calr^+M$ cells.[34] Fast ripples, field potentials of hypersynchronous pyramidal cell activity with frequencies of 250–600 Hz, are implicated in ictogenesis,[35] and are thought to be partly a product of inhibitory interneuronal behavior adversely influenced by altered gap junctional communication.[36] Likewise, hippocampal pyramidal axoaxonal gap junctional connections have been identified and modeling studies have implicated these in generating fast ripples as well.[37]

1.3 Cerebrocortical Biochemistry and Electrophysiology

Our understanding regarding the biochemical basis of epileptic seizures remains rooted in the early idea that they reflect an imbalance of inhibitory and excitatory influences in the brain, resulting in an increase in excitation and/or a decrease in inhibition. Consistent with this view are now well-established seizure-associated changes in synaptic communication mediated by glutamate and gamma-aminobutyric acid (GABA), the main excitatory and inhibitory neurotransmitters in the mammalian brain, respectively.[38]

Intracellular glutamate is synthesized primarily from glucose through glycolysis and the Kreb's cycle. Upon depolarization of the presynaptic terminal, opening of voltage-gated calcium channels and the resultant influx of calcium ions facilitates vesicular release of glutamate into the synaptic cleft. Glutamate can bind to multiple receptors, including both ionotropic and metabotropic varieties. Ligand-gated ion channels activated by glutamate include alpha-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA), *N*-methyl-D-aspartate (NMDA), and kainate receptors. AMPA activation mediates fast

synaptic transmission and causes a rapid and transient depolarization of the postsynaptic cell. If sustained, depolarization of the postsynaptic cell by AMPA activation causes the expulsion of magnesium ions from coactivated NMDA receptors, permitting the movement of sodium, potassium, and calcium ions down their concentration gradients and depolarizing the cell. NMDA receptors are the primary means by which calcium ions enter the postsynaptic cell, a critical step in the initiation of secondary messenger systems involved in synaptic plasticity.[39]

Metabotropic glutamate receptors are divided into three groups: Group I (mGLuR1, 5), Group II (mGluR2, 3), and Group III (mGluR4, 6, 8). Group I receptors are primarily postsynaptic and their activation is both excitatory and inhibitory, modulating the conductance of sodium, potassium, and voltage-gated calcium channels. Group II and III are primarily presynaptic and their activation inhibits adenylate cyclase and decreases cyclic adenosine monophosphate (cAMP) concentrations, limiting the presynaptic release of glutamate. AMPA-mediated neurotransmission at certain synapses on principal cells in the neocortex, hippocampus, and striatum can also induce mGLuR-dependent long-term potentiation (LTP), particularly following strong repeated stimulation protocols.[40]

Removal of glutamate from the extracellular space is an active process involving glia and postsynaptic neuronal uptake via excitatory amino acid transporters (EAATs), of which there are five subtypes. Replenishing glutamate in the presynaptic terminal is achieved by shuttling glutamate back to the original cell via the glutamate–glutamine cycle. Within glia, glutamine synthetase converts intracellular glutamate to glutamine, which is then released into the intracellular space. Glutamine is then transported into the presynaptic cell, where it is converted back to glutamate by glutaminase and transported into vesicles by vesicular glutamate transporters (VGLUTs).[41]

GABA is synthesized within presynaptic terminals by the enzyme glutamic acid decarboxylase (GAD), which removes a carboxyl group from the α carbon of L-glutamate. Upon depolarization of the presynaptic terminal, opening of voltage-gated calcium channels and the resultant influx of calcium ions facilitates vesicular release of GABA into the synaptic cleft. Binding of GABA to $GABA_A$ receptors on the post-synaptic membrane facilitates the influx of chloride ions into the postsynaptic cell resulting in hyperpolarization, whereas binding to metabotropic $GABA_B$ receptors facilitates a G-protein-mediated activation of adenylate cyclase. This results in a cAMP-mediated increase in potassium channel conductance and the release of potassium ions from the cell, again resulting in hyperpolarization. GABA is removed from the extracellular space by GABA transporters (GATs) located on perisynaptic glia and the presynaptic neuron. GABA transport is accompanied by the influx of two sodium ions and one chloride ion. Reversal of GATs has also been implicated as a nonsynaptic mechanism of GABA receptor activation.[42,43]

Prolonged depolarization of neurons within epileptic foci can result in a paroxysmal depolarization shift (PDS), characterized by the repetitive firing of sodium-dependent action potentials. These represent the intracellular correlate of epileptiform discharges measured extracellularly via the EEG. Burst activity associated with PDS is commonly followed by GABA-mediated hyperpolarization, which suppresses seizure activity. However, if this inhibition fails, PDS can propagate to affect multiple brain regions and may generalize to the entire brain. The most common form of epilepsy associated with focal seizures is mesial temporal lobe epilepsy (mTLE). mTLE is frequently linked to mesial temporal sclerosis (MTS), characterized by neuronal loss and astrogliosis within the hippocampus and other neighboring structures, including the entorhinal cortex and amygdala.

Other hippocampal pathologies associated with mTLE include loss of hilar mossy cells and somatostatin-expressing GABAergic interneurons in the hilus, dispersion of the granule cells layer, and aberrant sprouting of granule cell axons. These pathologies are known to disrupt glutamate and GABA transmission within these networks and are widely believed to be pathophysiological.[44]

In contrast to the localized imbalance of GABAergic and glutamergic neurotransmission and seizure propagation characteristic of focal epilepsies, seizures associated with generalized epilepsies typically arise in multiple brain areas simultaneously and are caused by an abnormal activation of thalamocortical circuits. This reflects a dysregulation of GABAergic thalamic relay neurons, which project broadly throughout neocortex to influence the activity of glutamergic pyramidal neurons. Such seizures are characterized by a "spike and wave" pattern of ictal activity, which is also seen during absence epilepsy.[45]

In addition to the prominent roles of glutamate and GABA neural transmission in epileptogenesis, catecholamine neurotransmitters have also been implicated as modulators of epileptogenic pathophysiology within the brain. Abnormalities of dopaminergic neural transmission have been implicated in temporal lobe epilepsy, juvenile myoclonic epilepsy, and autosomal dominant nocturnal frontal lobe epilepsy. The nigrostriatal dopamine pathway has been implicated in modulating thalamocortical loops involved in generalized epilepsies. The mesocorticolimbic dopamine projection from the ventral tegmental area to the frontal cortex has been implicated in motor and behavioral symptoms associated with epilepsy.[46,47] Among the various noradrenergic brainstem nuclei, ascending pathways from the locus coeruleus (LC) have been implicated as having antiepileptic modulatory effects. These pathways branch extensively to innervate the entire cerebrum, where they exert an inhibitory influence on seizure activity. Common antiepileptic drugs, including phenobarbital, carbamazepine, valproic acid, and phenytoin, produce an increase in noradrenaline in some brain regions. Similarly, increased noradrenaline has been implicated in the antiepileptic effects of vagal nerve stimulation, perhaps in combination with galanin, neuropeptide Y, and adenosine, which are coreleased with noradrenaline.[48]

As illustrated by the kindling model of epilepsy, pathophysiological behavior in otherwise normal brain networks can result from aberrant induction of synaptic plasticity within these networks via a LTP-like phenomenon. Kindling results from repetitive seizure activity induced by either chemical or electrical stimulation of a discrete locus within the brain, which spreads with increasing efficiency to associated brain structures via established synaptic pathways. As the propagation of seizure activity via these networks expands, the electrographic activity and accompanying behavioral manifestations become increasingly complex. Once established, the kindled state persists for many months and pathophysiological behavior re-emerges rapidly if additional stimulation is applied to the kindled focus. The progression of seizure propagation associated with the kindling model has given rise to the assertion that seizure activity alone may be sufficient to promote epileptogenesis, that seizures beget seizures. While this is certainly true in the case of status epilepticus resulting in diffuse brain injury, it remains controversial whether brief clinical seizures analogous to those produced during the kindling process are sufficient to promote epileptogenesis.[49,50]

1.4 Genomics

The past two decades have witnessed an acceleration in our understanding of the role of genetics in rendering vulnerability toward various categories of epileptogenicity. Several

linkage analyses and association studies have contributed to the wealth of information, now supplemented by chromosome microarrays and next-generation sequencing. Upwards of 80% of epilepsy cases are thought to be related to genetic factors.[51] Epilepsy has been grouped into three broad classes defined as genetic generalized epilepsy (GGE), focal epilepsy (FE), and epileptic encephalopathy (EE), with specific syndromes assigned to each group according to specific manifestations, EEG features, age of onset, and manner of progression.[52] A 22q11.2 deletion appears to lower seizure threshold in nonepileptic patients but has also been shown to manifest in patients with GGE and with FE.[53] Many of the current discoveries of genes involved in epileptogenesis support a channelopathy hypothesis, although a host of others are involved in transcriptional regulation, trafficking of synaptic vesicles, and mammalian target of rapamycin (mTOR) signaling suggesting a considerable genetic heterogeneity.

1.4.1 Genetic Generalized Epilepsies

Juvenile myoclonic epilepsy and childhood absence epilepsy exemplify this category and are early-life onset conditions with bihemispheric expression. Large recurrent deletions at chromosomes 15q13.3, 16p13.11, and 15q11.2 have been identified in GGE patients,[54,55] but with variable inheritance patterns and incomplete penetrance.[56] An association with autism and schizophrenia has also been found with these same three deletions. A severe early myoclonic epilepsy with hypotonia and developmental delay has been shown to bear a de novo mutation in *EEF1A2*,[57] which encodes the α2 subunit of eukaryotic elongation factor 1 and is also involved in actin cytoskeletal remodeling via protein kinase B.[58] Exome-sequencing has failed to provide statistically relevant genetic risk factors, despite several candidate sequence variants in affected patients.[59]

1.4.2 Focal Epilepsies

Heritable conditions such as familial mesial temporal lobe epilepsy (FMTLE), autosomal dominant lateral temporal epilepsy (ADLTE), autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), genetic epilepsy with febrile seizure plus (GEFS+), and autosomal dominant partial epilepsy with auditory features (ADPEAF) represent linkages in a number of chromosomes. FMTLE is not associated with hippocampal sclerosis or with febrile seizures and shows an autosomal dominant inheritance with incomplete penetrance.[60] Only one linkage has been identified on 4q13.2-21.3 in a four-generation family with 12 patients.[61] Linkage analysis in a three-generation family with 11 patients with ADLTE or ADPEAF provided a localization onto 10q.[62] Mutations of the *leucine-rich glioma-inactivated 1* (*LGI1*) gene at the 10q24 locus were subsequently identified.[63] Likewise, mutations in *CHRNA4*, encoding the α4 subunit of the pentameric nicotinic acetylcholine receptor, have been shown to cause ADNFLE. The gene is mapped to 20q13 and found in all layers of the frontal cortex.[64] Both 15q11.2 and 16p13.11 deletions have been found in patients with focal and other epilepsies.[59] The *NDE1* gene inhabits the latter deletion site and encodes a protein important for cell-positioning during cortical development. Neuropathological review of two cases of mesial temporal epilepsy with the same heterozygous *NDE1*-containing 16p13.11 deletion were found not to have evidence of cortical dyslamination or abnormality in cytoarchitectonics, although a cortical hamartia was present in one and hippocampal sclerosis in the other.[65] Mutations in *DEPDC5* on 22q12.2 have been implicated in familial FE with variable foci (FFEVF),[66,67] childhood FE,[68] and ADNFLE.[69]

Unlike the situation with *NDE1* deletion, brain malformations have been identified with *DEPDC5* mutations in the form of bottom of sulcus and focal cortical dysplasias, heterotopias, and hemimegelencephaly.[70] The *DEPDC5* gene is responsible for a protein belonging to the GATOR1 complex which regulates the mTOR pathway through its inhibition of mTOR complex 1 and, through this, cell growth, division, and plasticity. Dysregulation gives rise to several disorders, including tuberous sclerosis, focal cortical dysplasia, and hemimegelencephaly[71] and an accompanying intractable epilepsy.

1.4.3 Epileptic Encephalopathies

Early notions of ion-channelopathies resulting from gene mutations and giving rise to epilepsy came from studies that identified *KCNQ2* in benign familial neonatal epilepsy,[72] *SCN2A* in benign familial infantile epilepsy,[73] and *SCN1A* in Dravet syndrome.[74] Different mutational sites are found for these conditions from either GGE or FE.[75] Other genes clearly implicated in EE include *STXBP1* and *CDKL5*. These more severe disorders are attributable to highly penetrant single gene or copy number variant mutations.[52] Exome sequencing has proven to be of great value in confirming the presence of de novo mutations and drawing attention to the genetic heterogeneity of conditions such as Dravet syndrome or severe myoclonic epilepsy of infancy. Such studies have identified *HCN1* involved with hyperpolarization-activated, cyclic-nucleotide-gated channels,[76] *GABRA1* encoding the α1 subunit[77] and *GABRB3* encoding the β3 subunit[78] of the $GABA_A$ receptor, *STXBP1* encoding the syntaxin-binding protein required for presynaptic vesicle fusion,[77] and *KCNB1* encoding a voltage-gated potassium channel,[79] all of which are critical for neuronal transmission and regulating excitability.

Encoding of proteins involved in chromatin remodeling and transcriptional regulation has been perturbed by deletions and duplications of variable lengths of DNA (i.e., copy number variants), as with de novo mutation in *CHD2* that encodes a chromatin remodeling factor[80] in both EE[81] and GGE.[82]

1.5 Neuronoglial Migrational Disorders

Both genetic and developmental aspects of cellular organization of the cerebral cortex constitute an important consideration regarding epileptogenesis, as disorganization, whether micro- or macroscopic, is a familiar substrate for epileptogenic expression. A number of genes regulating microtubular function (i.e., *LIS1*, *TUBA1A*, *TUBB3*, *DCX*) and actin (i.e., *FilaminA*) have been implicated in cerebrocortical disorganization and a resultant intractable epilepsy.[83] Periventricular heterotopia (PVH) itself has been shown to result from mutations in the filamin 1 gene which prevent cellular migration.[84,85] Doublecortin (DCX), a microtubule-associated protein that regulates radial and tangential migration of neurons in cortical development, shows a characteristic expression pattern in focal cortical dysplasia Ia suggesting abnormal cortical maturation.[86] Neuroimaging often readily identifies lissencephaly, pachygyria, subcortical band heterotopia, and periventricular nodular heterotopias, and may overlook minor focal failures of cellular migration (e.g., microdysgenesis) because of limits of resolution. Associated cortical network hyperexcitability may arise from singular or multiple anomalous sites,[87] with both increased postsynaptic glutamate and decreased $GABA_A$ receptors.[88]

Tuberous sclerosis complex (TSC) is a genetic disorder caused by mutations in one of two tumor suppressor genes, *TSC1* and *TSC2*, resulting in disordered neuronal migration.