

The Developing Brain and Neonatal Seizures: Neuroanatomical and Neurophysiological Mechanisms of Seizure Susceptibility

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<https://doi.org/10.58624/SVOAPD.2026.05.033>

Received: September 01, 2026

Published: September 30, 2026

Citation: Palić I, Rakić O. The Developing Brain and Neonatal Seizures: Neuroanatomical and Neurophysiological Mechanisms of Seizure Susceptibility. *SVOA Paediatrics* 2026, 5:5, 218-233. doi: 10.58624/SVOAPD.2026.05.033

Abstract

Neonatal seizures represent a distinctive manifestation of neurological dysfunction arising within a rapidly developing and highly excitable brain. Their increased occurrence during the neonatal period reflects not only the high incidence of acute cerebral insults but also unique neuroanatomical and neurophysiological characteristics of immature neuronal networks. Transient cortical structures, evolving thalamocortical and corticocortical connectivity, intense synaptogenesis, and incomplete myelination provide a developmental substrate fundamentally different from that of the mature brain. At the cellular level, developmental regulation of GABAergic and glutamatergic neurotransmission, chloride homeostasis, voltage-gated ion channels, and excitatory–inhibitory balance contributes to enhanced neuronal excitability. These intrinsic characteristics interact with disturbances of cerebral energy metabolism, ionic gradients, and neuroinflammatory pathways following hypoxic–ischemic injury, perinatal arterial ischemic stroke, intracranial hemorrhage, infection, metabolic abnormalities, and structural brain disorders. The convergence of developmental susceptibility and superimposed cerebral pathology facilitates the transition from neuronal hyperexcitability to pathological synchronization and recruitment of immature neuronal networks. This review summarizes the neuroanatomical and neurophysiological foundations of neonatal seizure susceptibility and integrates them with the major pathophysiological mechanisms through which cerebral injury promotes seizure generation and propagation. Understanding neonatal seizures within this developmental framework provides a mechanistic perspective on why the immature brain is uniquely vulnerable to seizure activity.

Keywords: Neonatal Seizures; Developing Brain; Neuroanatomy; Neurophysiology; Brain Maturation; Neuronal Hyperexcitability

Introduction

Neonatal seizures represent the most common neurological emergency during the neonatal period and constitute a distinct, developmentally determined form of cerebral dysfunction. Their incidence is substantially higher during the neonatal period than at later stages of childhood, reflecting both the high frequency of acute cerebral insults in neonates and the intrinsic susceptibility of the developing brain to seizure generation. In contrast to seizures occurring later in life, most neonatal seizures are acute provoked events arising in the context of an identifiable cerebral or systemic disturbance. Hypoxic–ischemic brain injury, perinatal arterial ischemic stroke, intracranial hemorrhage, central nervous system (CNS) infection, metabolic disturbances, and structural brain abnormalities constitute the major acquired causes, while a smaller proportion are related to genetic or metabolic epilepsies [1,2].

The increased susceptibility of the neonatal brain to seizures cannot be explained solely by the frequency of perinatal brain injury. Rather, it reflects a unique developmental state in which neuronal proliferation, migration and differentiation, cortical organization, synaptogenesis, axonal growth, and the establishment of functional neuronal networks are occurring simultaneously. During fetal and early postnatal development, transient neuronal structures and circuits, including the subplate and developing thalamocortical connections, contribute to patterns of neuronal activity that differ fundamentally from those of the mature cerebral cortex. Consequently, the anatomical substrate through which abnormal electrical activity is generated, synchronized, and propagated is continuously changing throughout the preterm and term periods [3,4].

These neuroanatomical characteristics are accompanied by profound developmental differences in neuronal physiology. The immature brain is characterized by a dynamic imbalance between excitatory and inhibitory neurotransmission, developmental regulation of glutamatergic and γ -aminobutyric acid (GABA) signaling, distinctive expression of voltage-gated ion channels, and immature mechanisms of intracellular and extracellular ionic homeostasis. In particular, developmental regulation of neuronal chloride transport influences the effects of GABA_A receptor activation, while the composition and functional properties of glutamate receptors favor strong excitatory signaling during critical periods of brain maturation. Although the concept that GABA is uniformly excitatory throughout the human neonatal brain is an oversimplification, developmental differences in chloride gradients and inhibitory network maturation remain important components of the increased excitability of immature neuronal networks [3,5].

Seizure susceptibility therefore emerges from the interaction between an intrinsically excitable developmental substrate and pathological processes capable of disrupting neuronal homeostasis. Energy failure, membrane depolarization, extracellular potassium accumulation, excessive glutamate release, intracellular calcium loading, inflammation, and alterations in synaptic transmission can shift immature neuronal networks from physiological activity toward pathological hypersynchronization. The same cerebral insult may therefore have different electrophysiological consequences depending on gestational age, regional brain maturation, cellular composition, and the developmental state of local and long-range neuronal networks [3,5].

Understanding neonatal seizures consequently requires a developmental rather than exclusively etiological perspective. The neonatal brain should not be regarded simply as a smaller version of the mature brain; its transient anatomical structures, evolving connectivity, neurotransmitter systems, ion transport mechanisms, and metabolic requirements create a distinctive biological environment for seizure initiation and propagation. This developmental framework is particularly relevant when considering the different patterns of brain injury encountered in preterm and term neonates, in whom the anatomical substrate and predominant mechanisms of injury differ substantially [1,4].

The aim of this review is to examine the neuroanatomical and neurophysiological mechanisms that underlie the particular susceptibility of the developing neonatal brain to seizures. Emphasis is placed on cortical and network maturation, transient developmental circuits, excitation–inhibition balance, GABAergic and glutamatergic neurotransmission, ion-channel expression, and ionic homeostasis, followed by an analysis of how hypoxic–ischemic, vascular, hemorrhagic, inflammatory, metabolic, and structural cerebral disturbances interact with these developmental characteristics to initiate and propagate seizure activity. By integrating developmental neurobiology with the pathophysiology of neonatal brain injury, this review seeks to provide a mechanistic framework for understanding why seizures arise so readily during this unique period of brain maturation [1,3,5].

Developmental Neuroanatomy of the Neonatal Brain

The neuroanatomical substrate of neonatal seizures is determined by the highly dynamic organization of the developing brain. During fetal and early neonatal life, the cerebral cortex undergoes a sequence of partially overlapping processes that include neuronal proliferation, migration, differentiation, cortical lamination, axonal growth, synaptogenesis, and progressive establishment of functional connectivity. Importantly, these processes occur within transient anatomical compartments that are absent or substantially reorganized in the mature brain. Consequently, the preterm and term neonatal brain should be considered a continuously changing neural system in which the anatomical pathways available for generation, synchronization, and propagation of pathological neuronal activity depend strongly on developmental stage [4,6,8].

Cortical Development and Neuronal Organization

Development of the human cerebral cortex begins with proliferation of neural progenitor cells within the ventricular and subventricular zones, followed by migration of postmitotic neurons toward the developing cortical plate.

Excitatory projection neurons migrate predominantly along radial glial scaffolds, whereas cortical interneurons follow largely tangential migratory routes before integrating into cortical circuits. Successive waves of neuronal migration contribute to the characteristic inside-out organization of the neocortex, in which later-generated neurons migrate beyond earlier-born neurons to occupy progressively more superficial cortical layers. These processes establish the cellular architecture upon which subsequent synaptic and network organization depends [4,8].

During fetal development, however, cortical organization differs fundamentally from the mature six-layered cortex. The developing cerebral wall contains transient compartments, including the ventricular zone, subventricular zone, intermediate zone, subplate, cortical plate, and marginal zone. These compartments have distinct cellular compositions and connectivity patterns and undergo substantial changes across gestation. Transient laminar organization is therefore not merely an intermediate morphological stage but provides the structural framework within which early neuronal communication and cortical circuit formation occur [4,9].

The late fetal period is particularly important because it corresponds to the developmental stage encountered clinically in very and extremely preterm neonates. During this interval, neuronal migration is approaching completion in many cortical regions while dendritic differentiation, synaptogenesis, axonal growth, and organization of cortical connectivity accelerate. At the same time, transient fetal circuits coexist with emerging permanent cortical networks. The simultaneous presence of these two organizational systems is a distinctive characteristic of the developing brain and may influence how local pathological neuronal activity becomes integrated into larger functional networks [4,8].

Abnormalities occurring during neuronal proliferation, migration, or cortical organization can permanently alter cortical architecture. Misplaced neurons, abnormal cortical lamination, and disturbed formation of local neuronal circuits may produce regions in which excitatory and inhibitory connectivity is atypically organized. This developmental principle provides the neuroanatomical basis for the epileptogenic potential of malformations of cortical development and demonstrates how disturbances of normal fetal corticogenesis can create intrinsically hyperexcitable neuronal substrates [8].

The Subplate and Transient Developmental Circuits

One of the most distinctive features of the fetal and preterm cerebral cortex is the subplate zone, a transient but highly developed compartment located beneath the cortical plate. The subplate reaches particular prominence during the second half of gestation and contains differentiated subplate neurons, growing cortical afferents, extracellular matrix, glial elements, and migrating neurons. During the mid- and late fetal periods, it represents a major site of early synaptogenesis and serves as a temporary functional interface between incoming afferent pathways and the developing cortical plate. Thalamocortical axons reach the developing cortex relatively early but do not immediately establish their mature pattern of termination within cortical layer IV. Instead, many afferent fibers accumulate temporarily within the subplate, where they form functional synaptic contacts with subplate neurons. These transient circuits allow thalamic input to interact with the developing cortex before mature thalamocortical connectivity has been established. From approximately the late second to third trimester, thalamocortical fibers progressively penetrate the cortical plate, and between approximately 29 and 32 postconceptional weeks increasingly establish their definitive cortical connections [4,8,10].

The subplate therefore functions as an important developmental hub through which spontaneous and sensory-driven neuronal activity contributes to maturation of cortical networks. Subplate neurons participate in the organization of thalamocortical connectivity, maturation of cortical columns, development of inhibitory circuits, and coordination of early cortical activity. During the preterm period, transient subplate circuitry coexists with progressively developing permanent cortical circuitry, creating a network architecture fundamentally different from that of the mature brain. This transient organization may also be relevant to seizure susceptibility. Subplate neurons are highly differentiated and synaptically active at a developmental stage when overlying cortical circuits remain immature. Experimental evidence indicates that these neurons express functional glutamatergic receptors and participate in spontaneously active neuronal networks. Their strategic location at the interface between incoming afferent systems and the developing cortical plate provides a potential anatomical substrate through which abnormal neuronal activity may influence broader cortical networks. Moreover, disruption of subplate organization can interfere with subsequent development of cortical connectivity and inhibitory circuitry [4,7,10,11].

Synaptogenesis and Maturation of Neuronal Networks

Synaptogenesis in the human brain begins well before birth and follows a regionally and temporally heterogeneous trajectory. Early synapses are prominent within transient compartments such as the marginal zone and subplate before extensive synaptic organization develops within the cortical plate. During the late fetal and neonatal periods, synaptic density increases rapidly as dendritic arborization expands and thalamocortical, corticocortical, and commissural pathways progressively establish functional connections. Importantly, the formation of excitatory and inhibitory synapses does not occur synchronously. Glutamatergic and GABAergic circuits undergo distinct developmental trajectories, and their functional properties continue to change during the neonatal period. Thus, increasing synaptic density does not necessarily imply mature network stability. Instead, developing cortical networks combine high plasticity and rapidly evolving connectivity with incompletely established inhibitory control, creating conditions in which physiological synchronization and pathological hypersynchronization may be separated by a relatively narrow functional margin [7,10,11].

Long-range connectivity also undergoes major reorganization during late gestation. Thalamocortical fibers progressively establish mature cortical targets, while associative and commissural pathways expand and interhemispheric connectivity becomes increasingly organized. Between approximately 33 and 35 postconceptional weeks, increasing interhemispheric synchronization accompanies progressive reorganization of the subplate, while later gestation is characterized by further maturation of long intrahemispheric and callosal connections. These developmental changes have important implications for neonatal seizure organization. In an immature brain, pathological activity arises within networks whose local connectivity may already support synchronization but whose long-range pathways remain incompletely developed. The developmental architecture may therefore favor relatively localized or multifocal seizure initiation rather than the rapid engagement of widely distributed bilateral networks characteristic of some seizure types in the mature brain. The predominantly focal organization of neonatal seizures can thus be understood, at least partly, within the context of immature corticocortical and interhemispheric connectivity [4,10].

White-Matter Development and Myelination

White-matter development is equally dynamic during the preterm and neonatal periods. Axonal growth occurs in parallel with maturation of oligodendroglial lineage cells and progressive myelination. Oligodendrocyte precursor cells differentiate through pre-oligodendrocyte and immature oligodendrocyte stages before becoming mature myelin-forming cells. During approximately 23–32 weeks of gestation, premyelinating oligodendrocytes represent a prominent oligodendroglial population within developing cerebral white matter, while extensive myelination occurs predominantly later in gestation and during postnatal development [11,12].

Myelination does not proceed uniformly throughout the brain. Sensory and motor pathways generally mature earlier than many associative pathways, and the process continues extensively after birth. Consequently, axonal conduction properties and the temporal coordination of activity across distributed neuronal populations differ substantially between the preterm, term neonatal, and mature brain. The immature state of white-matter pathways therefore contributes to the developmental characteristics of neuronal network communication [9,11]. Developing white matter is also anatomically intertwined with growing thalamocortical, corticocortical, and callosal axons. During the preterm period, these pathways traverse regions that are particularly vulnerable to hypoxic–ischemic and inflammatory injury. Damage to developing axons, oligodendroglial cells, or transient connectivity compartments can therefore alter not only white-matter integrity but also the subsequent organization of cortical networks [10–12].

Taken together, developmental neuroanatomy provides a critical structural foundation for understanding neonatal seizure susceptibility. The neonatal cerebral cortex contains transient neuronal compartments, rapidly evolving synaptic networks, immature long-range connectivity, and incompletely myelinated axonal pathways. These characteristics do not themselves constitute pathological abnormalities; rather, they define the developmental substrate within which alterations in neurotransmission, membrane excitability, ionic homeostasis, or cerebral metabolism can more readily produce abnormal neuronal synchronization. The functional consequences of this developmental architecture become particularly apparent when considered together with the distinctive neurophysiology of the immature brain [4,8,10].

Neurophysiological Characteristics of the Developing Brain

The distinctive neurophysiology of the developing brain reflects the functional requirements of rapid neuronal growth, synaptogenesis, circuit refinement, and activity-dependent plasticity. During fetal and early postnatal development, neuronal networks must remain sufficiently excitable to generate spontaneous activity patterns that guide migration, differentiation, synaptic stabilization, and establishment of functional connectivity. The same properties that facilitate normal brain maturation, however, reduce the margin between physiological excitation and pathological hypersynchronization. Developmental regulation of inhibitory and excitatory neurotransmission, ion-channel expression, and transmembrane ionic gradients therefore represents a fundamental biological substrate for the increased seizure susceptibility of the neonatal brain [10,13,14].

Developmental Excitation–Inhibition Balance

Normal neuronal function depends on a continuously regulated balance between excitatory and inhibitory influences. In the mature cortex, this balance is maintained by coordinated activity of glutamatergic principal neurons, GABAergic interneurons, voltage- and ligand-gated ion channels, and homeostatic mechanisms that stabilize membrane potential and extracellular ion concentrations. During development, however, these components mature asynchronously. Excitatory synaptic mechanisms become functionally prominent at a stage when inhibitory networks, chloride regulation, and long-range cortical connectivity remain incompletely developed. This developmental bias toward excitation is not simply an immature or defective version of adult physiology. Increased neuronal excitability has important physiological functions during brain development. Spontaneous depolarization and synchronized network activity participate in neuronal differentiation, dendritic growth, synaptogenesis, refinement of sensory pathways, and stabilization of developing neuronal circuits. Consequently, mechanisms that increase excitability are temporarily advantageous for normal maturation, even though they simultaneously create a neuronal environment in which relatively modest pathological disturbances may facilitate seizure generation. The relationship between excitation and inhibition is also strongly dependent on developmental stage, brain region, cell type, and subcellular compartment. The concept of a globally “excitable neonatal brain” therefore represents a useful framework but should not imply uniform neurophysiological properties throughout the neonatal central nervous system. Rather, seizure susceptibility emerges from multiple temporally and spatially heterogeneous developmental processes that converge to reduce network stability [10,13–15].

GABAergic Neurotransmission

γ -Aminobutyric acid is the principal inhibitory neurotransmitter in the mature cerebral cortex, where activation of GABA_A receptors typically increases chloride conductance and drives the membrane potential toward a relatively negative chloride equilibrium potential. The functional effect of GABA_A receptor activation, however, depends fundamentally on the transmembrane chloride gradient. This gradient changes substantially during neuronal maturation and is regulated predominantly by developmentally expressed cation–chloride cotransporters [15–17].

Two transport systems are particularly important: the Na⁺–K⁺–2Cl[−] cotransporter NKCC1, which promotes intracellular chloride accumulation, and the K⁺–Cl[−] cotransporter KCC2, which extrudes chloride from neurons. In many immature neuronal populations, relatively high intracellular chloride concentrations shift the chloride equilibrium potential toward more positive values. Under these conditions, opening of GABA_A receptor-associated chloride channels can produce chloride efflux or reduced inward chloride flux, resulting in membrane depolarization rather than the robust hyperpolarization characteristic of mature neurons. With maturation, increasing functional expression of KCC2 and changes in chloride transport progressively lower intracellular chloride concentration and strengthen hyperpolarizing GABAergic inhibition [15–18].

The developmental transition in GABAergic signaling is nevertheless considerably more complex than a simple universal switch from “excitatory GABA” to “inhibitory GABA.” The polarity and functional consequences of GABA depend on neuronal subtype, brain region, developmental stage, resting membrane potential, chloride microenvironment, and the relative contribution of shunting inhibition. Furthermore, much of the mechanistic evidence originates from experimental animal preparations, and direct extrapolation of developmental timing to the human neonatal cortex requires caution. Human studies nevertheless demonstrate substantial maturation of cortical GABAergic neurons and GABA_A receptor organization during late gestation and early infancy. Development of the human cortical GABAergic system continues throughout the second half of gestation. GABAergic interneurons continue to populate and mature within the cerebral cortex, while GABA_A receptor distribution and enzymes involved in GABA synthesis undergo marked developmental changes.

Thus, both preterm and term neonates possess an inhibitory system that remains structurally and functionally dynamic. The incomplete maturation of this system is particularly relevant because efficient inhibition requires not only GABA release and receptor activation but also appropriate chloride gradients, interneuronal connectivity, and temporal synchronization of inhibitory inputs [15,19]. Developmental chloride homeostasis therefore provides an important mechanistic link between brain maturation and seizure susceptibility. Experimental studies have shown that NKCC1-mediated chloride accumulation can facilitate epileptiform activity in immature neuronal networks, whereas maturation of KCC2-dependent chloride extrusion contributes to stabilization of inhibitory signaling. Importantly, pathological neuronal activity itself can alter chloride homeostasis, suggesting that the relationship between impaired inhibition and seizures may become bidirectional once sustained network hyperexcitability develops [16–18].

Glutamatergic Neurotransmission

Glutamate is the principal excitatory neurotransmitter of the central nervous system and acts through ionotropic N-methyl-D-aspartate (NMDA), α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate receptors, as well as metabotropic glutamate receptors. During development, glutamatergic signaling has essential roles in neuronal migration, synapse formation, activity-dependent plasticity, and refinement of cortical circuits. The expression, subunit composition, localization, and functional properties of glutamate receptors change markedly during fetal and neonatal brain development. NMDA receptor-mediated transmission is particularly prominent during early brain development. Developmental differences in NMDA receptor subunit composition can result in prolonged synaptic currents and altered sensitivity to voltage-dependent magnesium blockade, thereby increasing the duration and magnitude of excitatory postsynaptic signaling. These properties facilitate activity-dependent synaptic plasticity but can also promote neuronal depolarization and calcium entry when glutamatergic activity becomes excessive [18-20].

AMPA receptors also undergo important developmental changes. Early in development, AMPA receptor populations may contain a greater proportion of receptors with increased calcium permeability, depending on their subunit composition and RNA editing. Calcium-permeable AMPA receptors can amplify depolarization and intracellular calcium signaling and may cooperate with NMDA receptor activation in sustaining excitatory network activity. As the brain matures, changes in receptor composition modify calcium permeability and synaptic kinetics [19,20].

The developmental abundance and functional characteristics of glutamate receptors therefore provide an important physiological counterpart to immature inhibitory control. Enhanced glutamatergic responsiveness supports normal synaptic development, but in the setting of energy failure, ischemia, inflammation, or other cerebral insults, excessive extracellular glutamate can transform this physiological developmental mechanism into a major driver of pathological depolarization and excitotoxicity. This interaction becomes particularly important in the pathophysiology of acute provoked neonatal seizures [10,20].

Developmental Expression of Voltage-Gated Ion Channels

Neuronal action potential generation and propagation depend on the coordinated activity of voltage-gated sodium, potassium, and calcium channels. The expression and biophysical properties of these channels change throughout brain development, producing developmental differences in resting membrane potential, action potential threshold, firing patterns, neurotransmitter release, and repetitive neuronal activity. Ion-channel maturation therefore contributes directly to the evolving excitability of neonatal neuronal networks [12,20].

Voltage-gated sodium channels are responsible for the rapid inward sodium current underlying action potential initiation and propagation. Different sodium-channel α -subunits exhibit distinct developmental and cellular expression patterns. Their distribution between excitatory and inhibitory neuronal populations is particularly important because altered sodium-channel function can either enhance excitatory neuronal firing or impair inhibitory interneuronal activity. The clinical importance of these mechanisms is illustrated by neonatal-onset epilepsies associated with pathogenic variants affecting sodium-channel genes, although genetic epilepsies represent an extreme manifestation of mechanisms that normally participate in developmental regulation of membrane excitability [20].

Potassium channels provide a major counterbalance to depolarizing currents by regulating membrane repolarization, resting membrane potential, action potential duration, and repetitive firing. Developmental changes in potassium-channel expression therefore influence neuronal firing thresholds and the capacity of networks to terminate sustained depolarization.

The importance of potassium conductances in neonatal network stability is particularly evident from neonatal epilepsies associated with KCNQ2 dysfunction, in which reduced M-current markedly increases neuronal excitability [12,21].

Voltage-gated calcium channels contribute to membrane excitability, neurotransmitter release, intracellular signaling, and activity-dependent gene expression. Calcium influx is essential for normal synaptic development, but excessive intracellular calcium represents a central pathway linking prolonged depolarization to cellular injury. In immature neurons, the interaction between voltage-gated calcium currents, calcium-permeable glutamate receptors, and intracellular calcium stores can therefore amplify excitatory signaling during pathological network activation [12,18].

Ionic Homeostasis and Cellular Excitability

Stable neuronal activity requires maintenance of steep transmembrane gradients of sodium, potassium, chloride, and calcium. These gradients determine resting membrane potential, action potential generation, synaptic responses, and neuronal recovery following depolarization. Their maintenance is energetically demanding and depends particularly on Na⁺/K⁺-ATPase activity, which uses ATP to extrude intracellular sodium while importing potassium. The close relationship between ionic homeostasis and cellular energy metabolism is therefore fundamental to understanding the vulnerability of neonatal neurons to acute cerebral injury [10,21].

During repetitive neuronal firing, extracellular potassium concentration increases as potassium exits neurons during action potential repolarization. Under physiological conditions, Na⁺/K⁺-ATPase activity, astrocytic potassium buffering, and extracellular diffusion restore ionic equilibrium. If these mechanisms are overwhelmed or compromised, extracellular potassium accumulation depolarizes neighboring neurons, bringing their membrane potentials closer to firing threshold and facilitating further synchronized activity. This creates a positive feedback mechanism through which initially localized hyperexcitability can recruit surrounding neuronal populations [21].

Chloride homeostasis is similarly critical because intracellular chloride concentration determines the efficacy and polarity of GABA_A receptor-mediated signaling. Any process that increases intracellular chloride or impairs chloride extrusion can weaken hyperpolarizing inhibition and, under some circumstances, render GABAergic currents depolarizing. Importantly, intense neuronal activity itself can challenge chloride extrusion mechanisms, meaning that inhibitory efficacy may progressively deteriorate during sustained pathological activity [13-16].

Calcium occupies a unique position at the interface between physiological neuronal signaling and pathological excitability. Transient increases in intracellular calcium regulate neurotransmitter release, synaptic plasticity, gene transcription, and neuronal differentiation. Excessive or prolonged calcium accumulation, however, activates proteases, phospholipases, nitric oxide pathways, mitochondrial dysfunction, and other processes contributing to cellular injury. NMDA receptors, calcium-permeable AMPA receptors, and voltage-gated calcium channels therefore provide convergent pathways through which excessive excitation can be translated into both sustained neuronal activity and excitotoxic injury [18,19].

The dependence of ionic gradients on cellular energy availability makes the developing brain particularly sensitive to conditions that impair oxidative metabolism. Hypoxia–ischemia, hypoglycemia, and other metabolic disturbances can reduce ATP production, compromise Na⁺/K⁺-ATPase activity, disrupt membrane potentials, increase extracellular potassium and intracellular sodium and calcium, and promote excessive neurotransmitter release. Thus, disturbances of ionic homeostasis provide a crucial mechanistic bridge between acute neonatal brain injury and the emergence of neuronal hyperexcitability [10,21].

Collectively, the neurophysiological characteristics of the developing brain demonstrate that neonatal seizure susceptibility cannot be attributed to a single neurotransmitter, receptor, or ion channel. Rather, it emerges from the convergence of developmentally regulated GABAergic signaling, strong glutamatergic excitation, evolving voltage-gated conductances, immature inhibitory networks, and metabolically dependent mechanisms of ionic homeostasis. These physiological characteristics are essential for normal brain maturation but create a relatively narrow homeostatic reserve when the neonatal brain is exposed to hypoxic–ischemic, metabolic, inflammatory, hemorrhagic, or structural insults. Their integration provides the mechanistic basis for understanding why the neonatal brain is particularly susceptible to seizure generation [10,13,21].

From Brain Injury to Neonatal Seizures: Pathophysiological Mechanisms

The intrinsic excitability of the developing brain provides a permissive substrate for seizure generation, but most neonatal seizures arise in association with an acute cerebral insult. Hypoxic–ischemic encephalopathy (HIE), perinatal arterial ischemic stroke, and intracranial hemorrhage represent the predominant causes of acute symptomatic neonatal seizures, while central nervous system infection, metabolic disturbances, and structural brain abnormalities constitute additional important etiologies [1,22,23]. Although these conditions differ substantially in anatomical distribution and primary mechanism of injury, they converge on several common cellular pathways: energy failure, membrane depolarization, disruption of ionic gradients, excessive glutamatergic transmission, intracellular calcium accumulation, neuroinflammation, and impairment of glial and vascular homeostasis. Within developmentally excitable neuronal networks, these disturbances facilitate the transition from cellular dysfunction to pathological synchronization and seizure generation [10,22,24].

Hypoxic–Ischemic Brain Injury

Hypoxic–ischemic encephalopathy is the most common cause of acute symptomatic seizures in term neonates. The pathophysiological cascade begins with reduced oxygen and substrate delivery to cerebral tissue, leading to impaired oxidative phosphorylation and declining ATP production. As cellular energy stores become depleted, ATP-dependent ion pumps—particularly Na^+/K^+ -ATPase—can no longer maintain transmembrane ionic gradients. Intracellular sodium and calcium concentrations increase, potassium accumulates extracellularly, and neuronal membranes undergo progressive depolarization [22,24,25].

Membrane depolarization promotes excessive release of excitatory amino acids, particularly glutamate, while energy failure compromises energy-dependent glutamate uptake by neurons and astrocytes. The resulting increase in extracellular glutamate causes sustained activation of NMDA and AMPA receptors. NMDA receptor activation further enhances calcium entry, whereas calcium-permeable AMPA receptors and voltage-gated calcium channels provide additional routes for intracellular calcium accumulation. Because glutamatergic signaling is particularly prominent in the developing brain, this excitatory cascade can strongly amplify neuronal depolarization and facilitate seizure generation [10,18,24].

The acute phase of hypoxic–ischemic injury is followed by partial recovery of cerebral energy metabolism after resuscitation and reperfusion. This latent interval may subsequently progress toward secondary energy failure, characterized by mitochondrial dysfunction, oxidative and nitrosative stress, excitotoxicity, inflammation, and activation of cell-death pathways. Seizures commonly emerge during this evolving phase of injury, when partially injured but electrically viable neuronal networks coexist with disturbed ionic and metabolic homeostasis [24,25].

Mitochondrial dysfunction occupies a central position in this process. Excessive intracellular calcium loading impairs mitochondrial function, promotes formation of reactive oxygen species, and reduces the capacity for ATP regeneration. At the same time, oxidative stress can modify ion channels, membrane transporters, and neurotransmitter receptors, further destabilizing neuronal membrane potential. Thus, neuronal hyperexcitability and cellular injury are not independent phenomena: both arise from overlapping disturbances of energy metabolism, ionic homeostasis, and excitatory neurotransmission. Inflammatory responses further modify the post-hypoxic neuronal environment. Activated microglia, astrocytes, endothelial cells, and infiltrating immune cells release cytokines and other inflammatory mediators that can alter synaptic transmission, blood–brain barrier integrity, and neuronal excitability. The developing brain therefore enters a dynamic state in which excitotoxic, metabolic, inflammatory, and vascular processes interact to lower seizure threshold [24–26].

From a mechanistic perspective, HIE illustrates particularly clearly the interaction between developmental physiology and acquired pathology. Developmentally enhanced glutamatergic signaling, incompletely mature inhibitory control, and limited capacity to compensate for severe disturbances of ionic equilibrium provide the substrate; energy failure and excitotoxicity provide the trigger. Seizures are therefore an integrated manifestation of evolving cellular and network dysfunction rather than an isolated electrical consequence of hypoxia [10,24].

Perinatal Arterial Ischemic Stroke

Perinatal arterial ischemic stroke represents another major cause of neonatal seizures and differs from HIE primarily in the focal distribution of cerebral injury. Occlusion of a cerebral artery produces an ischemic core in which profound reduction in blood flow rapidly causes severe energy failure and irreversible cellular injury.

Surrounding this core is tissue exposed to less severe perfusion impairment, where neurons may remain structurally viable while experiencing substantial metabolic and electrophysiological instability [22,27].

Within ischemic tissue, ATP depletion compromises Na^+/K^+ -ATPase activity and produces loss of transmembrane ionic gradients. Extracellular potassium increases, intracellular sodium and calcium accumulate, and neurons become depolarized. Excessive glutamate release and impaired glutamate clearance amplify depolarization through NMDA and AMPA receptor activation. These mechanisms resemble those occurring in global hypoxia–ischemia but are spatially concentrated within and around the vascular territory affected by arterial occlusion. The interface between severely ischemic and relatively preserved tissue may be particularly relevant to seizure generation. Neurons within the infarct core may rapidly lose the capacity to sustain organized electrical activity, whereas neurons in surrounding metabolically compromised tissue can remain electrically active but hyperexcitable. Local ionic disequilibrium, excitatory neurotransmitter accumulation, inflammatory signaling, and altered interactions between injured and relatively preserved neuronal populations create conditions favorable for focal pathological synchronization. Inflammation is an integral component of neonatal arterial ischemic injury. Activation of microglia and cerebral endothelial cells, recruitment of peripheral immune cells, and changes in blood–brain barrier function occur after neonatal stroke. Importantly, the inflammatory response of the developing brain differs from that of the mature brain and may exert both injurious and reparative effects depending on cell population and temporal phase. In the acute setting, however, inflammatory signaling may further modify neuronal excitability and the extracellular environment surrounding the infarct [27].

The focal anatomical nature of perinatal arterial ischemic stroke therefore provides a clear explanation for its strong association with focal neonatal seizures. A localized region of metabolically unstable but electrically active cortex can act as an ictogenic substrate, while the developmental state of surrounding cortical and subcortical connections determines how abnormal activity is subsequently recruited and propagated [22,27].

Intracranial Hemorrhage

Intracranial hemorrhage constitutes an important cause of acute symptomatic seizures in both preterm and term neonates, although the anatomical patterns of hemorrhagic injury differ substantially with gestational age. In preterm infants, germinal matrix–intraventricular hemorrhage (GMH–IVH) predominates because of the vascular and structural vulnerability of the germinal matrix, whereas term neonates may present with intraparenchymal, subdural, subarachnoid, or other forms of intracranial hemorrhage. The relationship between hemorrhage and seizures depends strongly on the location and extent of injury. Blood confined predominantly to the ventricular system does not necessarily create a direct cortical epileptogenic focus. In contrast, parenchymal involvement, hemorrhagic venous infarction, associated ischemic injury, or secondary distortion of cerebral tissue can directly disturb cortical and subcortical neuronal networks. Therefore, the mechanism of seizure generation following neonatal hemorrhage should not be reduced to nonspecific “cortical irritation” by blood [22,23].

Hemorrhagic injury initiates multiple biochemical processes capable of modifying neuronal excitability. Breakdown of erythrocytes releases hemoglobin and heme-derived products, while iron-dependent oxidative reactions promote formation of reactive oxygen species. Thrombin and other coagulation-associated molecules can activate inflammatory signaling, and tissue injury promotes microglial and astrocytic responses. Edema, local perfusion abnormalities, and secondary disturbances of ionic homeostasis may further destabilize neurons adjacent to the hemorrhage [29].

In the preterm brain, these processes occur within a particularly vulnerable developmental environment containing immature oligodendroglial cells, growing axons, transient subplate circuits, and incompletely established cortical connectivity. Severe GMH–IVH may therefore influence neuronal networks not only through the immediate effects of hemorrhage but also through associated periventricular hemorrhagic infarction, white-matter injury, inflammation, and disruption of developing connectivity [4,28].

The propensity for seizures after intracranial hemorrhage is consequently determined by the interaction among hemorrhage location, parenchymal involvement, secondary ischemia, inflammatory responses, and developmental network organization. This distinction is especially important when considering the different pathoanatomical substrates of hemorrhage in preterm and term neonates [22,23].

Infection and Neuroinflammation

Central nervous system infection can generate seizures through direct neuronal injury and through inflammatory modification of neuronal excitability. Bacterial meningitis, viral encephalitis, and congenital or perinatally acquired infections can activate innate immune pathways within the developing brain. Microglia, astrocytes, endothelial cells, and neurons participate in this response and produce cytokines, chemokines, prostaglandins, reactive oxygen species, and other mediators that alter the neuronal microenvironment. Proinflammatory cytokines can directly influence synaptic function. Interleukin-1 β and related inflammatory pathways can enhance glutamatergic neurotransmission and reduce the effectiveness of inhibitory mechanisms, thereby shifting neuronal networks toward excitation. Inflammatory signaling can also modify receptor phosphorylation, ion-channel function, and neurotransmitter release. Consequently, inflammation does not merely accompany neuronal injury; it can actively change seizure threshold [30,31].

Blood–brain barrier dysfunction represents another important component of inflammation-associated hyperexcitability. Inflammatory activation of cerebral endothelial cells and disruption of tight-junction organization can increase barrier permeability and permit plasma proteins and circulating inflammatory mediators to interact with neural tissue. Experimental neonatal hypoxic–ischemic models demonstrate an association between seizure activity, inflammatory cytokine expression, and blood–brain barrier disruption, emphasizing the close interaction among vascular, inflammatory, and neuronal processes in the injured neonatal brain [26]. Microglial activation is particularly relevant during early development because microglia have physiological roles in synaptic remodeling, neuronal maturation, and regulation of developing circuits. Pathological activation can alter these functions and modify excitatory–inhibitory network relationships. The effects of inflammation in the neonatal brain are therefore strongly development dependent: the same cellular systems involved in normal circuit formation can participate in pathological hyperexcitability when excessively activated [30].

Infection-associated seizures should therefore be understood as the consequence of convergent mechanisms involving direct cellular injury, inflammatory modulation of neurotransmission, blood–brain barrier dysfunction, altered ionic homeostasis, and, in severe disease, secondary disturbances of cerebral perfusion and energy metabolism [30,31].

Metabolic and Electrolyte Disturbances

Metabolic and electrolyte disturbances can provoke neonatal seizures by directly altering neuronal energy availability, membrane potential, neurotransmitter function, or ion gradients. Unlike structural cerebral lesions, some metabolic causes can produce predominantly functional neuronal disturbances before irreversible anatomical injury develops. This makes rapid recognition and correction particularly important [23,32].

Hypoglycemia is a major example of the close relationship between cerebral metabolism and neuronal excitability. The neonatal brain has substantial glucose requirements, while endogenous energy reserves may be limited. Severe or prolonged reduction in glucose availability compromises ATP production, which in turn impairs energy-dependent ion pumps and membrane stability. Neuronal depolarization promotes release of glutamate and aspartate, producing excitotoxic signaling and intracellular calcium accumulation. Severe neonatal hypoglycemia can therefore cause both acute seizures and characteristic cerebral injury, with posterior cortical regions frequently demonstrating particular vulnerability [32].

Hypocalcemia alters the stability of neuronal membranes because extracellular calcium influences voltage-gated sodium-channel activation and neuronal firing threshold. Reduced extracellular calcium facilitates membrane excitability and repetitive neuronal discharge. Hypomagnesemia may contribute both independently and through its relationship with calcium homeostasis; magnesium also modulates NMDA receptor function, providing another potential link between electrolyte imbalance and enhanced glutamatergic activity. Disturbances of sodium concentration modify extracellular osmolality and transmembrane electrochemical gradients. Both severe hyponatremia and hypernatremia can cause neurological dysfunction and seizures, although through different mechanisms. Hyponatremia promotes water movement into the brain and cerebral edema, while rapid or severe hypernatremia produces cellular dehydration and can be associated with vascular and hemorrhagic complications. Rapid changes in sodium concentration may be particularly destabilizing because the brain requires time to adapt its intracellular osmolyte composition [23].

Metabolic seizure generation therefore illustrates a broader principle: stable neuronal electrical activity depends on intact energy metabolism and precisely regulated extracellular ionic composition. The developmentally excitable neonatal brain may become rapidly unstable when either of these conditions is disrupted [10,32].

Structural Brain Abnormalities

Structural abnormalities of the developing brain represent a fundamentally different pathophysiological substrate because the abnormality may be present before birth and may directly alter the architecture of neuronal networks. Malformations of cortical development arise from disturbances of neuronal proliferation, migration, differentiation, or cortical organization and include a broad spectrum of abnormalities ranging from focal cortical dysplasia to lissencephaly, polymicrogyria, and other disorders of cortical formation. Abnormal cortical architecture can disrupt the normal spatial relationship between excitatory projection neurons and inhibitory interneurons, alter dendritic and axonal organization, and produce atypical local connectivity. Ectopic or dysmorphic neurons may exhibit abnormal membrane properties and receptor expression, while disorganized cortical layers can facilitate recurrent excitatory connections. The result is the formation of neuronal networks with an intrinsically reduced threshold for pathological synchronization [7,33].

The timing of the developmental disturbance is important because different stages of corticogenesis generate different structural phenotypes. Abnormalities of early proliferation differ anatomically and functionally from disorders of neuronal migration or later cortical organization. As described previously, the fetal brain contains transient structures and connectivity patterns that guide subsequent cortical maturation; disruption of these developmental processes can therefore alter both local cortical architecture and long-range network formation [6,7].

In neonates with structural malformations, seizure generation may consequently arise without the acute metabolic collapse characteristic of HIE or stroke. Instead, the anatomical network itself provides an enduring hyperexcitable substrate. Superimposed physiological stress, metabolic disturbance, or additional genetic abnormalities affecting ion channels or synaptic proteins may further lower seizure threshold [7,33].

Network Mechanisms of Neonatal Seizure Generation and Propagation

Neonatal seizure generation represents a transition from increased excitability of individual neurons to coordinated pathological activity within neuronal networks. The cellular disturbances described in the preceding sections—including membrane depolarization, altered chloride gradients, excessive glutamatergic signaling, extracellular potassium accumulation, impaired energy metabolism, and reduced inhibitory efficacy—can increase the probability that individual neurons will discharge repetitively. A seizure, however, requires more than enhanced neuronal firing. It emerges when sufficiently large populations of interconnected neurons become recruited into temporally organized and self-sustaining activity. The developmental architecture of the neonatal brain strongly influences each stage of this process, from local synchronization to recruitment and subsequent propagation [3,5,10,21].

Transition From Neuronal Hyperexcitability to Seizure Generation

Neuronal hyperexcitability refers to an increased probability that neurons will generate action potentials in response to synaptic or intrinsic membrane events. This state may result from increased excitatory conductances, reduced inhibitory restraint, extracellular potassium accumulation, altered chloride homeostasis, or changes in voltage-gated ion channels. Hyperexcitability alone, however, does not necessarily produce a seizure. Pathological seizure activity requires recruitment of interconnected neuronal populations and the development of synchronized or otherwise highly organized network dynamics capable of sustaining repetitive activity [5,21].

In the neonatal brain, the transition toward ictal activity occurs within networks already characterized by spontaneous synchronized activity. During normal development, coordinated neuronal events contribute to synaptic refinement, establishment of sensory pathways, and formation of cortical circuits. Immature neurons and neuronal networks demonstrate a relatively high capacity for synchronization, reflecting the developmental abundance of excitatory mechanisms, evolving inhibition, electrical coupling, and transient network architecture [3,21,34].

Acute cerebral injury can shift these physiological mechanisms toward pathological activity. Membrane depolarization brings neurons closer to firing threshold, while extracellular potassium accumulation further depolarizes neighboring cells. Increased extracellular glutamate strengthens recurrent excitatory transmission, and impaired chloride regulation may reduce the capacity of GABAergic inhibition to oppose recruitment. Once a critical population of interconnected neurons becomes sufficiently excitable, recurrent synaptic and nonsynaptic interactions can produce a self-reinforcing transition from isolated or irregular firing to organized ictal activity [5,10,16,21].

Hypersynchronization of Immature Neuronal Networks

Synchronization is a fundamental property of developing neuronal networks. Before mature cortical circuits are established, spontaneous synchronized activity participates in activity-dependent development and provides temporal signals required for circuit formation. Experimental studies of immature cortex demonstrate that developing neuronal populations can generate coordinated network events through combinations of synaptic transmission, gap-junction coupling, intrinsic membrane properties, and transient developmental circuits. Gap junctions may be particularly relevant during early development because electrical coupling provides a direct pathway for rapid communication between neighboring cells. Experimental neonatal cortical networks can exhibit coordinated activity in which electrical coupling contributes substantially to synchronization. Although the relative contribution of individual mechanisms differs according to brain region and developmental stage, these observations illustrate that immature networks possess several mechanisms capable of coordinating neuronal activity before mature chemical synaptic organization has been fully established [3,34].

Chemical synaptic transmission subsequently becomes increasingly important as cortical circuits mature. Strong glutamatergic signaling can recruit neighboring neurons, whereas GABAergic mechanisms regulate the spatial and temporal extent of this recruitment. When inhibitory restraint is insufficient relative to recurrent excitation, activity can spread through local networks and produce increasingly coherent population discharges. Developmental alterations in chloride homeostasis may further influence this process by changing the functional effect of GABAergic signaling [14,21]. Thus, the same capacity for coordinated activity that is essential for normal developmental plasticity may facilitate pathological hypersynchronization when the extracellular environment or excitation–inhibition balance is disrupted. This dual role of developmental network activity is central to understanding why seizures occur so readily during the neonatal period [3,21].

Seizure Initiation and the Ictal Core

Contemporary models of focal seizure generation distinguish between tissue that is fully recruited into ictal activity and surrounding regions exposed to intense synaptic input but not yet recruited. Human intracranial recordings in older patients have demonstrated sharply demarcated territories of intense hypersynchronous neuronal firing—the ictal core—surrounded by an ictal penumbra in which neurons receive substantial synaptic drive while local inhibitory mechanisms continue to restrain full recruitment. Direct evidence establishing an identical core–penumbra organization in human neonates remains limited. Nevertheless, this model provides a useful conceptual framework for understanding how a localized region of injured neonatal cortex may generate an initially focal seizure. A region affected by ischemia, hemorrhage, structural malformation, or localized metabolic dysfunction may contain electrically viable neurons exposed to abnormal ionic and neurotransmitter conditions. If recurrent excitation becomes sufficiently strong to overcome local inhibitory restraint, this population may become the first network territory recruited into ictal activity [27,35].

Within the recruited region, intense neuronal firing further modifies the local extracellular environment. Potassium accumulates, glutamate release increases, intracellular chloride may rise during repetitive GABA_A receptor activation, and metabolic demand increases. These changes can reinforce depolarization and reduce inhibitory efficacy, producing a positive-feedback process that helps sustain the ictal state [14,16,35].

The ictal core should therefore not be regarded simply as a fixed anatomical “seizure focus.” Rather, seizure initiation reflects a dynamic interaction between intrinsically or secondarily hyperexcitable tissue and surrounding neuronal networks. This distinction is particularly relevant in neonates, in whom the functional architecture of cortical and subcortical connectivity is rapidly changing with gestational and postnatal maturation [4,9].

Recruitment of Surrounding Neuronal Networks

For a seizure to propagate beyond its site of initiation, adjacent neuronal populations must cross the threshold from receiving ictal synaptic input to becoming actively recruited into the seizure. Experimental and human studies indicate that inhibitory interneurons can initially restrain propagation despite substantial excitatory input. When this inhibitory restraint fails or is overwhelmed, surrounding neurons become recruited and the ictal territory expands. Several mechanisms may promote recruitment in the developing brain. Repetitive excitatory synaptic input can progressively depolarize neighboring neurons, while extracellular potassium accumulation reduces the distance between resting membrane potential and action potential threshold. Increased intracellular chloride during sustained neuronal activity may reduce the hyperpolarizing effectiveness of GABA_A receptor-mediated currents. Simultaneously, increasing metabolic demand can compromise ATP-dependent restoration of ionic gradients, particularly in tissue already affected by hypoxia or ischemia [14,16,35].

Recruitment is therefore a dynamic process rather than passive electrical spread. Each newly recruited neuronal population becomes an additional source of synaptic excitation and ionic disturbance, facilitating subsequent recruitment of connected regions. This process provides a mechanistic explanation for the spatial evolution characteristic of an ictal event [5,35].

In the neonatal brain, however, recruitment occurs within networks whose inhibitory circuitry and long-range connectivity remain immature. The relative contribution of recurrent local excitation, GABAergic restraint, transient developmental connections, and nonsynaptic mechanisms is therefore likely to differ from that in the mature cortex. This developmental context must be considered when adult-derived models of seizure recruitment are applied to neonatal seizures [3,9,21].

Propagation Through Immature Cortical and Subcortical Networks

Once local neuronal populations have been recruited, seizure activity may propagate through anatomically and functionally connected pathways. In the mature brain, propagation can involve corticocortical association fibers, commissural pathways, thalamocortical circuits, and other distributed networks. In neonates, many of these pathways are present but remain structurally and functionally immature, while transient developmental circuits continue to contribute to network organization [4,9].

The subplate is particularly relevant during fetal and preterm development. It temporarily receives thalamocortical afferents and participates in the organization of cortical activity before mature thalamocortical connections are fully established. Experimental studies demonstrate that subplate neurons can participate in coordinated network events and influence activity in the developing cortical plate. The subplate may therefore contribute to the pathways through which neuronal activity is organized in the immature cortex, although its specific role in human neonatal seizure propagation remains incompletely defined [4,34].

Thalamocortical connectivity undergoes substantial maturation during the late second and third trimesters. Thalamic axons progressively establish definitive cortical targets while reciprocal corticothalamic pathways and the thalamic reticular system continue to mature. Consequently, the contribution of thalamocortical loops to network synchronization is likely to differ considerably between an extremely preterm infant, a late-preterm infant, and a term neonate. Interhemispheric and long-range intrahemispheric connectivity also mature progressively during late gestation. The developing corpus callosum and association pathways provide increasingly effective communication between distant cortical regions, but their functional organization remains incomplete during much of the neonatal period. Seizure propagation is therefore constrained and shaped by the connectivity available at a particular developmental stage [4,9].

Influence of Developmental Connectivity on Seizure Propagation

The anatomical pathways through which seizures propagate cannot be separated from the developmental stage of the brain. At very preterm ages, transient fetal compartments and local circuits remain prominent, while long-range cortical connectivity is relatively immature. With advancing gestation, regression of the subplate is accompanied by increasing maturation of thalamocortical, corticocortical, and commissural pathways. The network substrate available for seizure propagation therefore changes substantially across the neonatal period. This developmental principle may help explain why seizure organization differs with gestational age. A seizure arising in an extremely preterm brain encounters a markedly different structural and functional network from one arising at term. The number, strength, conduction properties, and spatial distribution of available connections influence whether abnormal activity remains localized, spreads contiguously through neighboring cortex, recruits remote ipsilateral regions, or reaches the contralateral hemisphere [4,9].

Incomplete myelination may additionally influence the temporal characteristics of long-range propagation. Myelination increases conduction velocity and temporal precision of axonal signaling; therefore, immature white-matter pathways are expected to support different patterns of interregional communication than mature pathways. However, myelination alone does not determine seizure spread, which also depends on synaptic efficacy, axonal connectivity, inhibitory restraint, and the excitability of target neuronal populations. Developmental connectivity should consequently be viewed as a dynamic anatomical framework within which seizure propagation occurs. As the brain matures, the same pathological trigger may generate different network behavior because the pathways available for recruitment have changed [4,9,28].

Developmental Basis of the Predominantly Focal Nature of Neonatal Seizures

Neonatal seizures are predominantly focal in onset, even when they occur in the context of diffuse cerebral injury. This characteristic reflects both the focal nature of many neonatal brain lesions and the developmental organization of neuronal networks. Perinatal arterial ischemic stroke and focal hemorrhagic or structural lesions provide obvious localized substrates, but focal seizure initiation is also common in more globally distributed conditions such as HIE [1,22].

One possible explanation is that diffuse cerebral disturbances do not affect all neuronal populations identically. Regional differences in maturation, perfusion, metabolic demand, receptor expression, connectivity, and severity of injury can create localized areas with particularly low thresholds for ictal recruitment. Seizures may therefore begin within the most vulnerable or hyperexcitable network territory even when the initiating insult is systemic or widespread [10,21].

Immaturity of long-range corticocortical and interhemispheric connections may further limit immediate bilateral synchronization. Local neuronal networks can support seizure initiation before distant cortical territories are efficiently recruited. As connectivity matures, increasingly organized long-range pathways provide a broader substrate for seizure propagation, but during the neonatal period these networks remain developmentally heterogeneous [4,9].

The focal character of neonatal seizures therefore provides an important illustration of the relationship between developmental anatomy and seizure physiology. It is not merely a descriptive feature of neonatal seizure expression but may reflect the underlying architecture of the immature brain: highly excitable local neuronal networks embedded within incompletely mature long-range connectivity [4,9,10].

Conclusion

The high susceptibility of the neonatal brain to seizures reflects the convergence of developmental neuroanatomical and neurophysiological characteristics. Transient cortical circuits, evolving connectivity, strong glutamatergic signaling, immature GABAergic regulation, developmental ion-channel expression, and limited ionic and metabolic homeostatic reserve create a neuronal environment in which the threshold for pathological synchronization is relatively low. Acute cerebral insults further destabilize this developmentally excitable substrate. Hypoxic–ischemic injury, stroke, hemorrhage, inflammation, metabolic disturbances, and structural abnormalities converge on common mechanisms involving energy failure, altered ionic gradients, membrane depolarization, excitotoxicity, and impaired inhibitory control. These processes facilitate the transition from cellular hyperexcitability to coordinated network seizure activity. Neonatal seizures should therefore be understood as the product of an interaction between brain maturation, cerebral pathology, and developing neuronal networks. A developmental perspective provides the most coherent framework for understanding why the neonatal brain is uniquely susceptible to seizure generation and propagation.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgement

None.

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