Review

Developmental Neuroscience

Dev Neurosci 2018;40:417–436
DOI: 10.1159/000497471

Received: October 12, 2018
Accepted after revision: February 4, 2019
Published online: April 4, 2019

How Early Can a Seizure Happen? Pathophysiological Considerations of Extremely Premature Infant Brain Development

Melisa Carrasco Carl E. Stafstrom

Division of Pediatric Neurology, Department of Neurology, The Johns Hopkins University School of Medicine, Baltimore, MD, USA

Keywords
Neonatal seizure · Prematurity · Brain development · Neurophysiology · Electroencephalogram · Spontaneous neuronal activity

Abstract
Seizures in neonates represent a neurologic emergency requiring prompt recognition, determination of etiology, and treatment. Yet, the definition and identification of neonatal seizures remain challenging and controversial, in part due to the unique physiology of brain development at this life stage. These issues are compounded when considering seizures in premature infants, in whom the complexities of brain development may engender different clinical and electrographic seizure features at different points in neuronal maturation. In extremely premature infants (<28 weeks gestational age), seizure pathophysiology has not been explored in detail. This review discusses the physiological and structural development of the brain in this developmental window, focusing on factors that may lead to seizures and their consequences at this early time point. We hypothesize that the clinical and electrographic phenomenology of seizures in extremely preterm infants reflects the specific pathophysiology of brain development in that age window.

Introduction

Our understanding of the mechanisms contributing to neonatal seizures has increased markedly over the past decade [1–3]. However, the questions of how early the premature brain can give rise to a seizure and whether different pathophysiological mechanisms pertain to seizures in extremely premature infants (defined as <28 weeks gestational age [wga]) have not been addressed extensively in the literature. In this commentary, we explore pathophysiological considerations related to seizures in such extremely premature infants, as such considerations may help to identify potential targets for therapeutic intervention in this vulnerable population.

Seizures in Term and Preterm Infants

Neonatal seizures constitute a neurological emergency, requiring prompt recognition and treatment. Yet, the definition and identification criteria for neonatal seizures in full-term infants are not uniformly accepted, and the problem is even more acute for premature infants [4, 5]. A seizure involves abnormal (excessive, hypersynchronous) neuronal firing that disrupts normal brain functioning. On the electroencephalogram (EEG), a neonatal seizure is characterized as rhythmic electrical activity of acute onset, lasting 10 s or more [6]. To meet this defini-

KARGER

E-Mail karger@karger.com
www.karger.com/dne

Carl E. Stafstrom
Division of Pediatric Neurology, The Johns Hopkins University School of Medicine
Rubenstein Bldg 2157, 200 N. Wolfe Street
Baltimore, MD 21287 (USA)
E-Mail cstafst1@jhmi.edu

tion, an EEG seizure must have a definitive beginning, evolution of amplitude and frequency over the course of the episode, and clear resolution [7, 8]. In full-term infants, an electrographic seizure may consist of rhythmic sharp waves or spikes. In preterm infants, electrographic seizures may be marked by rhythmic slow or sharp waves superimposed on a discontinuous baseline EEG [9–14]. Ictal discharges in preterm neonates tend to be of low frequency (often <1 Hz) [15], focal, and restricted to small areas of the cortex [16–18]. A diagnosis of an electrographic seizure must be made cautiously, as some rhythmic activity is normal and numerous potential artifacts and technical confounders must be excluded [19]. Clinically, seizures in full-term infants can be electroclinical (observable clinical changes accompanying an ictal EEG pattern) or "electrographic only" (also called subclinical or electrically decoupled). In extremely premature infants, seizures are almost always electrographic only, meaning that ictal EEG patterns are seen without observable clinical manifestations [17, 20, 21]. Due to this "electroclinical dissociation," EEG monitoring is pivotal in the critical care of sick premature infants and essential for clinical treatment trials [22].

Seizure incidence is highest in early postnatal life among term newborns, affecting 1–5 neonates per 1,000 live births [23, 24]. Clinical and basic science studies confirm that seizures clearly can occur in preterm infants, but there is wide variation among studies reporting seizure incidence rates in the extremely premature population [25]. The discrepancies between reports on preterm neonates are likely related to the difficulty of identifying seizures in this population of very ill babies, from both clinical and EEG perspectives [26]. It also seems to take longer to detect and diagnose seizures in extremely premature infants [27]. The diagnostic uncertainty is compounded by the variable sensitivity and specificity of the various recording techniques to detect seizures, ranging from full-montage conventional EEG to reduced-channel montage EEG to amplitude-integrated EEG (aEEG). Full-montage conventional video-EEG is considered the current gold standard for neonatal seizure detection [28–31]. To date, there has been no prospective study reporting the incidence of electrographic seizures among continuously monitored premature infants, making determination of the true seizure incidence in this developmental period tentative. A few selected studies are described below.

In a retrospective analysis of 77 infants born <28 wga, only 1 baby was found to have an ictal pattern when monitored by 2-channel EEG for the first 72 h after birth [32]. Another study, which included extremely and very preterm infants (<32 wga), reported that 5% of the infants in a cohort with a median gestational age of 29 weeks had seizures when monitored with multichannel EEG for 72 h after birth [18]; the clinical seizure types included tonic, clonic, myoclonic, and subtle (e.g., pedaling or chewing movements). Other studies of infants <32 wga have reported electrographic seizures in 0.9–8.7% [9, 13, 15, 33, 34] and clinical seizures in 5–10% [26, 35], and an aEEG study reported a 48% seizure incidence in a group of 95 infants <32 wga [36]. Another aEEG study, comparing seizures in premature newborns <30 wga as part of a caffeine dose exposure trial, found a 40% seizure incidence among neonates receiving standard-dose caffeine [37]. A recent report using the Neonatal Seizure Registry (from 7 US pediatric centers) determined that 12 of 18 subjects <28 wga (67%) had subclinical seizures shortly after birth, as early as 23 wga, with ictal activity confirmed on EEG; the etiology of the seizures in the majority of these neonates was intracranial hemorrhage [5, 15]. Finally, a retrospective secondary analysis of more than 8,000 deliveries of infants <37 wga examined "major" morbidities including grade III or IV intraventricular hemorrhage, hypoxic-ischemic encephalopathy, and seizures [38]. Among 342 infants born between 23 and 28 wga with major morbidities, seizures were reported in 18 babies (5.2%), but there was no consistent trend in seizure incidence over those 5 gestational weeks.

Neonatal seizures are associated with significant morbidity and mortality, worse behavioral, cognitive and language outcomes, and an increased incidence of epilepsy later in life [36, 39, 40]. Compared with term and late premature infants, children born extremely prematurely later exhibit higher rates of cognitive and motor impairments [41]. They remain at a high risk for death and disability, with 30–50% mortality and 20–50% of the survivors going on to have morbidities, including neurocognitive difficulties [42–48]. Those with a more tenuous early course are at particular risk [49], and neurocognitive outcomes are worse in those born at the youngest gestational ages [50].

Understanding the pathophysiology of seizures early in gestation, including the question of when during ontogeny a definitive seizure can occur, would provide useful information to the clinician at the bedside. Such knowledge could aid in clinical decision-making (e.g., whether to pursue continuous EEG monitoring of an extremely preterm newborn) and could also provide guidance as to whether to initiate an anti-seizure medication, a decision that must be balanced against potential detrimental effects of anti-seizure drugs on the developing

Table 1. Seizure features in extremely preterm infants that require pathophysiological explanation

Observation	Physiological correlate	Selected Ref.
Reported incidence varies	Different methods of recording, varied populations studied	5, 18, 32
Focal onset of seizures Occipital > frontal	Limited ability to propagate seizure activity Earlier maturation of occipital region	17, 18
Most seizures are subclinical (>50%) Subtle differences from normal movements Neurophysiological differences	Inadequate coupling of discharges to motor system Effects of GABAergic drugs	9, 15, 17
Shorter seizures	Limited ability to sustain seizure activity	9, 13, 17
Higher mortality	Multifactorial; sicker infants	5, 15
Delayed diagnosis	Less protocolized evaluations Sickest infants get EEGs Limited knowledge about seizures at this age Lower accuracy of aEEG	5, 27, 33
Etiology: ICH, infection > HI	Fragility of cerebral vasculature	5, 15, 53

GABA, γ-aminobutyric acid; ICH, intracerebral hemorrhage; HI, hypoxia-ischemia; EEG, electroencephalogram; aEEG, amplitude-integrated EEG.

brain [51, 52]. It is critical to determine whether or not to treat EEG or clinical manifestations sometimes described as "seizure-like." To address these questions, we here discuss the cellular mechanisms that may contribute to the emergence of seizures during extremely premature brain development (Table 1).

Brain Development and Seizures

To understand seizures in early brain development, it is necessary to consider the specifics of the brain's physiology and structure as a function of age. While electrographic seizures certainly occur in extremely preterm infants, their brains may lack sufficient neural circuitry necessary to produce hypersynchronous electrical discharges and effectively generate a clinical seizure. A seizure at such an early time point usually reflects a response of the developing brain to an acquired dysfunction, and its etiology is a critical determinant of seizure occurrence and outcome. Among extremely preterm infants, intraventricular hemorrhage and associated complications (ventriculomegaly and periventricular hemorrhagic infarction) [29, 53] is the most common seizure etiology, followed by infection, whereas among term babies, hypoxia-ischemia is the most common cause [5, 10, 14, 53]. Metabolic derangements, genetic mutations, and cortical dysplasia are less common etiologies among preterms. EEG in this setting can be helpful to guide effective treatment of seizures and to avoid overtreatment [54]. In addition, EEG is a useful tool to determine patients at higher risk for a specific brain pathology contributing to seizures, such as intraventricular hemorrhage [55]. Newer techniques such as automated approaches to lessen observer variability [56] and combining EEG with functional magnetic resonance imaging hold promise for improved seizure discharge localization in preterm infants [57].

What Is Required for a Seizure?

At any gestational age, a seizure represents a pathological insult superimposed on ongoing developmental processes (Fig. 1). The capacity of the brain to generate and propagate a seizure is reliant on several key developmental milestones. First, a sufficient number of neurons, whether in the neocortex, hippocampus, or another brain area, must develop and express electrical excitability, which requires the formation and operation of ion channels, axons, dendrites, and synapses. A seizure can only occur when a network of neurons fires excessively and synchronously; a single neuron or a few neurons can be hyperexcitable, but a clinical or electrographic seizure emerges only when a sufficient network is activated. Synchronized neuronal bursts will be represented on EEG as rhythmic slow waves, sharp waves, or spikes. For a seizure

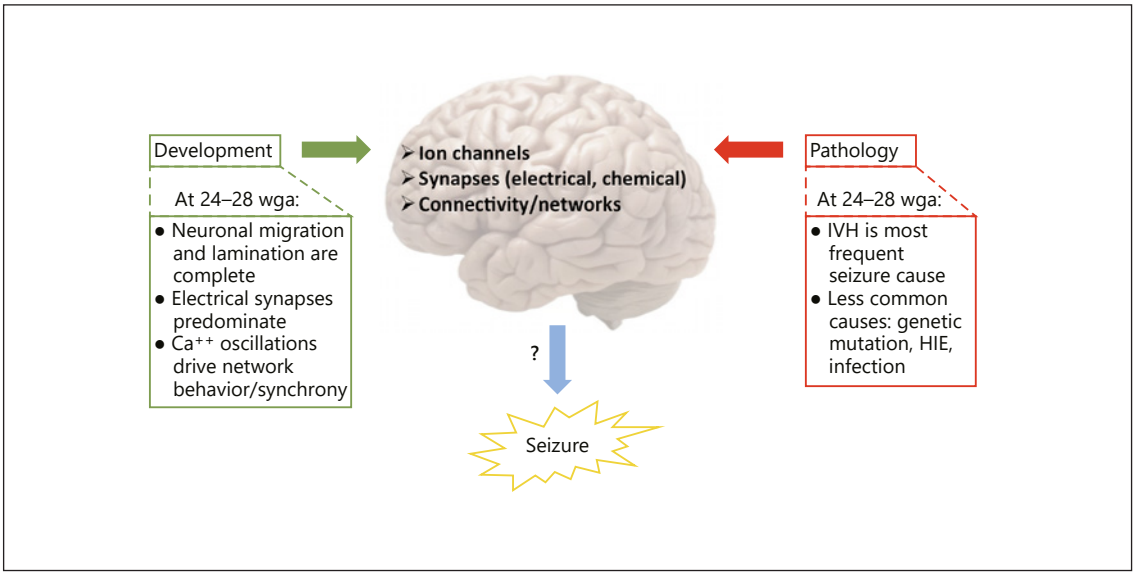

Fig. 1. Interaction of normal brain developmental processes with superimposed pathological insults. During normal development, ion channels, electrical and chemical synapses, and neural networks develop to ensure the normal operation of the brain. At any given developmental age, however, a superimposed pathology can affect one or more of these functions to engender seizures. During extreme prematurity (<28 wga), neuronal migration and lamination are complete, electrical synapses predominate and chemical synapses have not yet formed, and neuronal activity is driven by random calcium transients. The most common seizure etiology at this age, intracerebral/intraventricular hemorrhage, might alter these developmental physiological processes and cause seizure generation. wga, weeks gestational age; IVH, intraventricular hemorrhage; HIE, hypoxic-ischemic encephalopathy; Ca^{++}, calcium.

to propagate beyond its initiation site, the synchronous neuronal firing must overcome local inhibition and activate adjacent or distant neuronal regions, which requires synapse integrity, myelination, and axonal transmission. The white matter must be sufficiently mature and healthy to allow faithful transmission of impulses from the central nervous system (CNS) to the peripheral nervous system (PNS). For example, for a motor seizure to be observed clinically, corticospinal tracts must be present and connect the motor cortex to the spinal cord and subsequently transmit discharges to peripheral nerves, neuromuscular junctions, and muscles.

Seizures can also originate in the limbic system, especially among late preterm and term infants, as well-established connections between the hippocampus, diencephalon, and brainstem can give rise to seizures presenting as apnea, behavioral arrest, or oral-buccal-lingual movements [58–60]. These "subtle seizures" must not be confused with normal newborn activity; the EEG aids in determining which clinical signs correlate with ictal electrographic activity, as similar-appearing events may or may not have associated paroxysmal discharges [61]. Yet, at very young gestational ages, caution must be exercised before concluding that an EEG pattern is indeed ictal.

Comparison of Brain Development in Rodents and Humans

Animal models, especially rodents, have been informative for studying the mechanisms underlying early brain development and seizure vulnerability, making it imperative to compare, to the degree possible, brain development in rodents or other models with that in humans. This topic has been addressed from several perspectives, and while correlations remain approximate, the mechanisms and timing of various normal and abnormal developmental processes appear to be comparable [62–69]. Despite differences in gestational lengths, the sequence and overall patterns of development are similar between different mammals [70]. With respect to factors such as brain growth by weight, neurogenesis, neurochemical maturation, oligodendrocyte formation, and myelination, brain development in rodents from birth (postnatal day [P] 0) until P10 roughly corresponds to human brain development in the 3rd trimester (~27–40 wga). Numerous studies have suggested that brain development in rodents at P7 resembles that at 32–36 wga in humans, and P10 approximates term gestation in humans (Table 2) [68, 70–73]. Continuous aEEG patterns observed in P10–

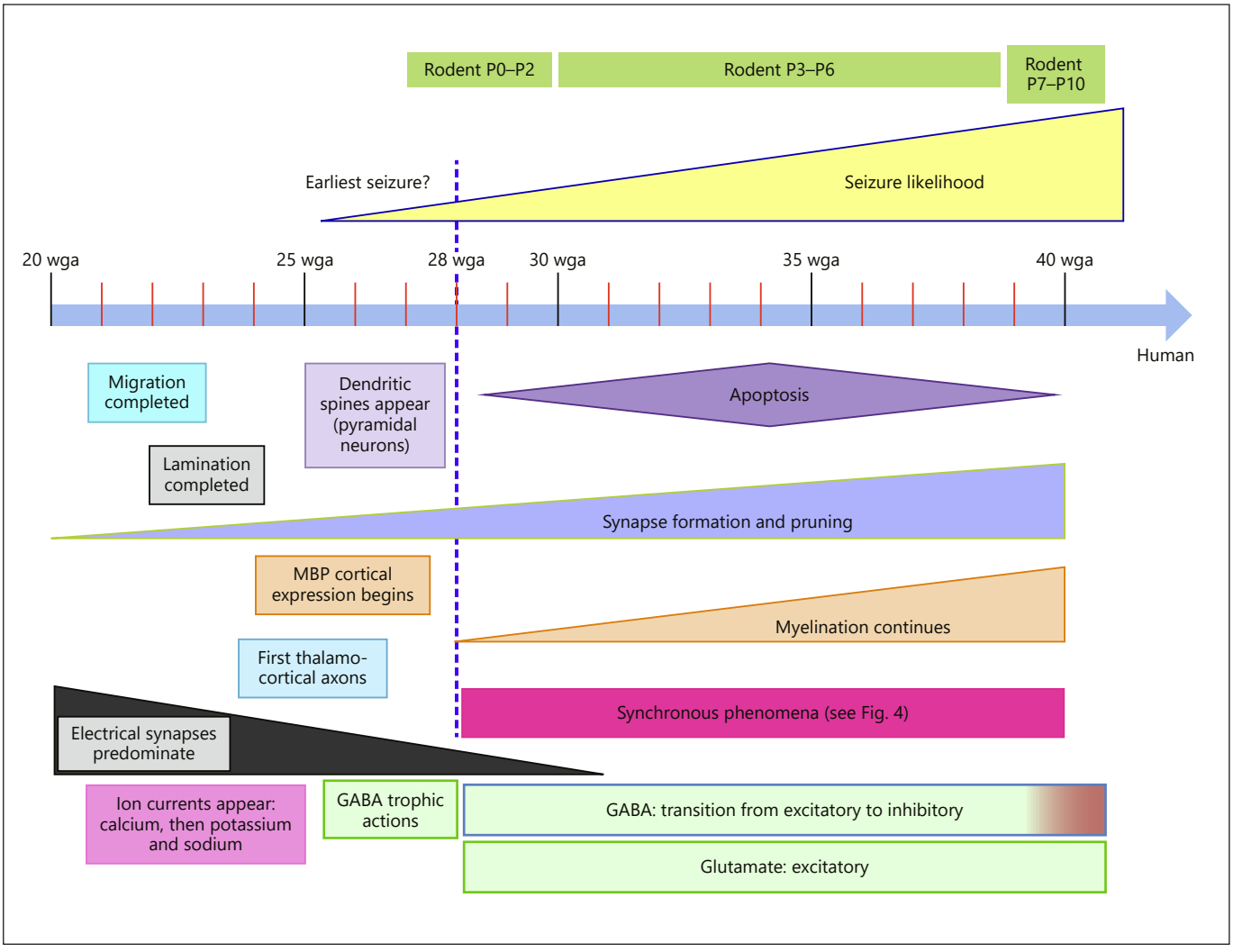

Fig. 2. Major developmental events during premature brain development. The rodent timeline (green bar) is above the human timeline (blue bar). Multiple processes occur simultaneously. During extreme prematurity (<28 wga), structural and physiological developmental aspects suggest that seizure generation might be less likely than during later preterm and postnatal development. The gestational age at which a seizure can first occur is uncertain. Specifically, before 28 wga, synapse formation is not robust, synchronized activity and neuronal oscillations have not yet developed, and excitation via glutamate and GABA synaptic activity has not yet become engaged. Comparisons between rodent and human brain development are approximate. wga, weeks gestational age; P, postnatal day; MBP, myelin basic protein; GABA, γ-aminobutyric acid.

Table 2. Comparison of rodent and human early brain development

Rodent	Human	Major physiological milestones
P0–7	Early-to-mid 3rd trimester	Ca^{++} transients (unsynchronized) → synchronized activity via gap junctions → synchronized firing via excitatory GABAergic and glutamatergic activity
P7–10	Late 3rd trimester to birth	Synchronized firing via excitatory GABAergic and glutamatergic activity persists → desynchronized firing → GABA becomes inhibitory

P, postnatal day; GABA, γ-aminobutyric acid.

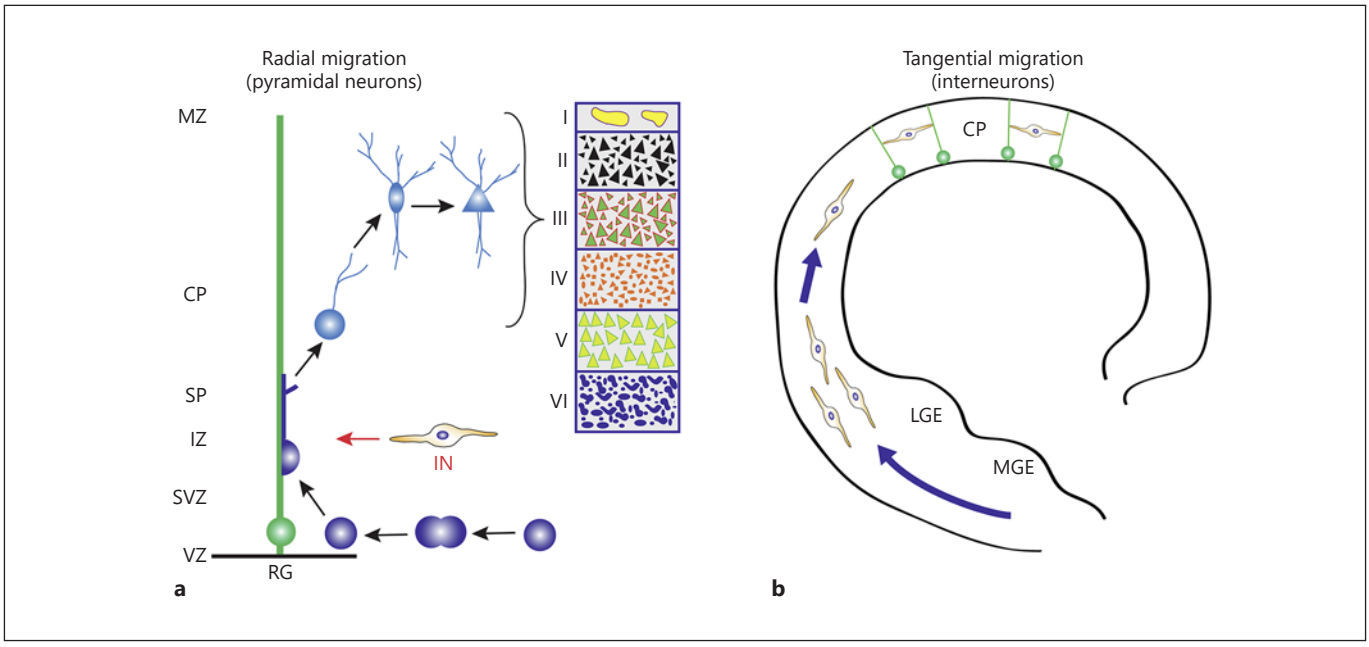

Fig. 3. Neuronal migration. **a** Excitatory pyramidal neurons are born in the VZ. Division of these neuroblasts forms RG cells (green) that extend their processes to the pial surface (MZ) and form a scaffold along which future neurons travel to the CP. Once at the CP, neurons develop extensive dendritic branches, axons, and synaptic connections, eventually laminating into a 6-layered cortex (I–VI; **inset**). GABAergic INs migrate tangentially from the ganglionic eminences (see **b**). **b** Inhibitory INs originate in the MGE and LGE and migrate in a tangential fashion into the developing CP. Disruption of either radial or tangential migration can result in a neural circuit prone to seizure generation. RG, radial glia; VZ, ventricular zone; SVZ, subventricular zone; IZ, intermediate zone; SP, subplate; CP, cortical plate; MZ, marginal zone; IN, interneuron; MGE and LGE, medial and lateral ganglionic eminences; GABA, γ-aminobutyric acid.

12 rat pups approximate those in term human neonates, supporting the maturational studies cited above [63, 74].

Larger animal models may be valuable for exploring premature brain pathophysiology. For example, preterm ("0.7" gestation) sheep, approximating human 28–32 wga [75], develop electroclinical seizures after hypoxia-ischemia induced by umbilical cord occlusion, and these seizures are ameliorated by therapeutic hypothermia [76, 77]. Therefore, fetal sheep could potentially be used to study mechanisms of neuronal and network hyperexcitability.

Overview of Brain Development

Brain development can be summarized as a series of sequential but overlapping steps, each governed by a complex set of molecular, genetic, and environmental influences: formation of the neural tube; proliferation of neuronal stem cells; neuron differentiation and migration; and cortical organization including axon and dendrite growth, synaptogenesis, and myelination [78]. It is important to recognize that human brain development occurs over a protracted duration of several months; thus, at any particular time point, the degree of maturation will differ between different brain areas and even between cortical layers in the same region [79]. Any consideration of seizure generation must take into account the precise timing of each developmental stage (Fig. 2).

Neuronal Migration and Cortical Lamination

Neurons and glia are generated from progenitor cells that proliferate in vast numbers in the ventricular zone (VZ) and adjacent subventricular zone (SVZ), then migrate to the cortical plate of the cerebral cortex and hippocampi in layers, a process that is tightly regulated and essential for proper development of a normal brain architecture (Fig. 3) [80]. Cells destined to become cortical pyramidal neurons migrate from the VZ and SVZ to their final location along radial glia cells [81, 82]. The SVZ is a

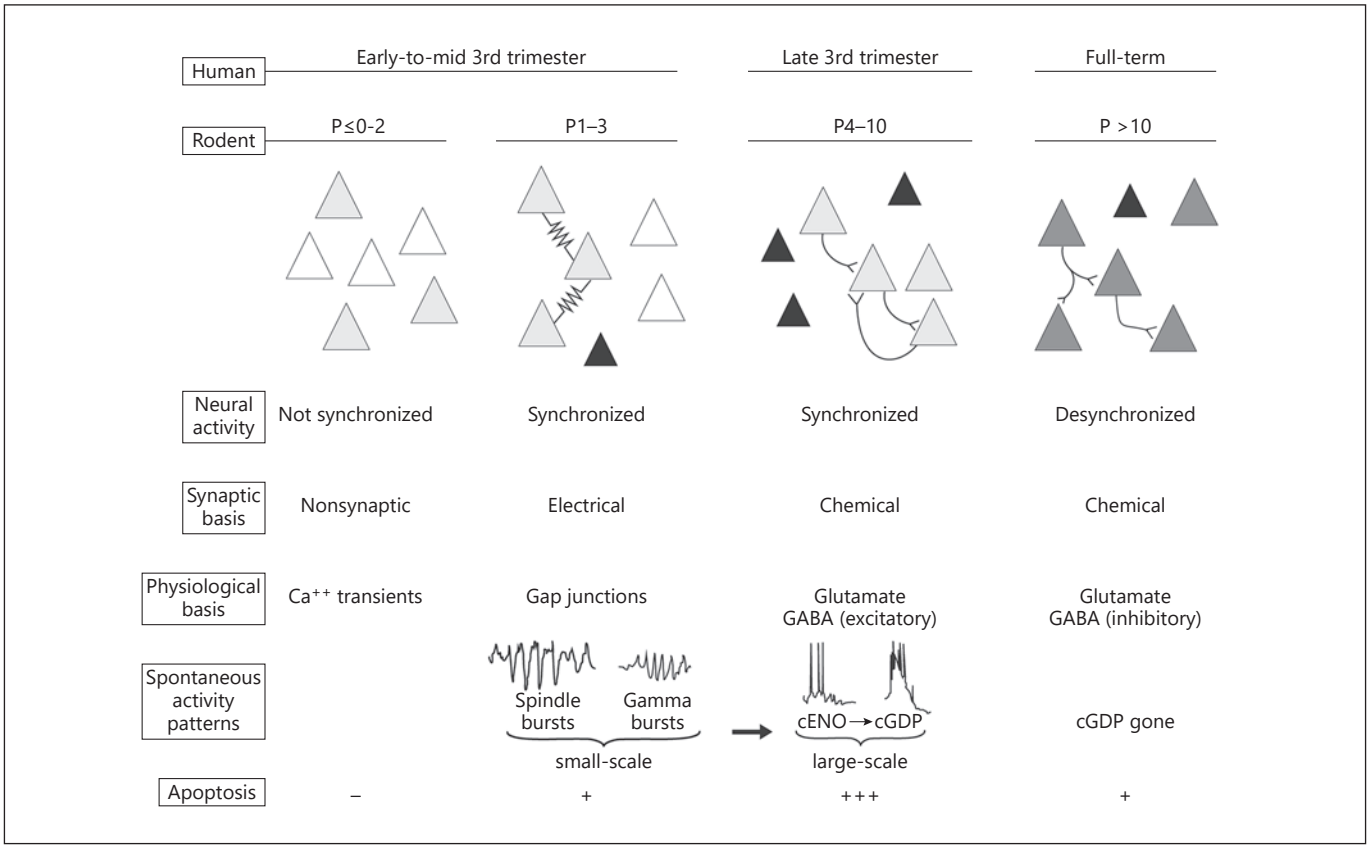

Fig. 4. Time course of development of synchronized neural activity in the premature brain. Data are derived from rodent studies and extrapolated to humans. At P0–2 and earlier, neurons are immature with regard to membrane properties and ion channels and do not yet exhibit synchronized activity. Rather, their neural activity is random and spontaneous, derived from voltage-gated calcium channels. Light-gray triangles depict immature neurons involved in such spontaneous calcium transients, while white triangles are immature neurons that do not produce calcium transients. By P1–3, some cells are interconnected via gap junctions (resistor symbols) and therefore are capable of synchronized neural activity. In addition, at this age, some cells undergo apoptosis (black triangles); apoptosis peaks between P4 and P10. By P4–10, chemical synapses are forming, mediated by both glutamate and GABA; GABA is excitatory at this stage. This time point also represents peak seizure incidence and susceptibility in rodents and humans (i.e., term gestational age). Finally, after P10, neurons and circuits are more mature (dark gray): GABA is hyperpolarizing and inhibitory, and neural firing is desynchronized. Spontaneous activity patterns, as described in the text and Table 3, are hand-drawn from literature examples. These waveforms have different time and amplitude scales. Field potential recording of spindle bursts has a peak amplitude of ~100 μV and duration of ~200 ms. Field potential recording of gamma bursts has a peak amplitude of ~200 μV and duration of ~500 ms. Intracellular recording of cENOs has a duration of ~5 s. Intracellular recording of cGDPs has a duration of ~0.5 s. The concepts are derived from a number of sources [including 88, 102, 103, 114, and 205]. The cartoon is modified with permission from Elsevier [88]. P, postnatal day; GABA, γ-aminobutyric acid; cENO, cortical early network oscillation; cGDP, cortical giant depolarizing potential.

transient layer that disappears over fetal development yet plays the critical role of containing neurons that receive the initial projections from the thalamus. Neurons are laid down in the cortical plate in an inside-first, outside-last fashion – first-arriving neurons compose the deepest cortical layers (V and VI) and later-born neurons localize in more superficial layers (II, III, and IV). Neurons bound to become inhibitory interneurons migrate tangentially (rather than radially) from their birthplace in the ganglionic eminences of the forebrain [83].

In rodents, migration proceeds until around birth (embryonic day [E] 19–21). In humans, migration begins around 18 wga [67]; by the gestational age at which infants are viable (and hence seizures might be documented), around 23 wga, neuronal migration is essentially finished and brain development has progressed to the stage of corti-

cal organization, i.e., cellular orientation, alignment, and lamination. Lamination is complete in the rodent cortex by P4–5 and in humans by ~24 wga. Inaccurate organization or lamination due to aberrant cell migration can result in cortical dysgenesis (e.g., lissencephaly and heterotopias), which greatly increases the risk for seizures [84–86]. Apoptosis (programmed cell death) is also an integral process in brain development and occurs in parallel with migration and organization, peaking in the 3rd trimester [87, 88].

Synapse Formation

Full synaptic function requires both structural and functional elements – synapses must form, synthesize neurotransmitters, and be able to package, release and metabolize neurotransmitters; appropriate receptors must also develop. These processes occur at different times and rates in different brain areas.

The earliest intercellular communication in the developing brain occurs via electrical synapses (gap junctions) [89]. Gap junctions are observed by P5 in rodents [90]. In humans, connexins (gap junction channels) can be observed as early as the blastocyst stage (1–2 wga), and different connexins peak embryologically or in the early postnatal period, depending on their specific function [89, 91]. Gap junctions precede chemical synapses and facilitate very fast electrical transmission, permitting rapid synchrony of a neural network. In addition, gap junctions allow the passage of small molecules such as second messengers and ions between neurons as well as between neurons and glia. The profusion of electrical synapses in various brain regions during prenatal development facilitates a variety of oscillatory activities (discussed below), both normal and pathological (Fig. 4).

In rodents, chemical synapse formation peaks during postnatal weeks 2–3 [67]. In humans, synaptogenesis begins in some brain regions around the 3rd month of gestation [92] and accelerates around 20–24 wga [93]. γ-Aminobutyric acid (GABA) is the initial active neurotransmitter, and prior to the development of inhibitory synapses, GABA is released in a paracrine fashion and exerts trophic actions [79], facilitating the formation of both glutamate and GABA synapses [94]. Dendritic spines begin to appear on pyramidal neurons (~24–27 wga). A period of rapid dendritic arborization and exuberant synaptogenesis ensues, extending through the remainder of gestation. The number of synapses and dendritic spines increases around birth and then peaks in the first few postnatal months to years [1, 95]. Therefore, the bulk of synapse development occurs after mid-gestation, which is why sufficient connections may not be available to support seizure generation much before 24 wga. During early cortical organization, many synaptic connections are transient, and it is important to recognize that the presence of synaptic structures does not necessarily mean that they are functional.

Glia begin developing somewhat later than neurons [96]. Astrocytes are especially important for synapse formation, as they secrete factors that enhance synapse maturation, promote neuronal expression of synaptic proteins, and reinforce appropriate synaptic contacts [97] while at the same time diminishing extraneous contacts, a process known as activity-dependent pruning [98]. Glia are also critical for regulating neuronal metabolism and providing energy to the developing brain in both normal and abnormal conditions (e.g., hypoxia-ischemia) [99]. Glial dysfunction, inflammation, or injury during development clearly predisposes to seizure generation [100, 101].

Onset of Spontaneous Activity and Development of Brain Connectivity

The ability of neurons to generate spontaneous activity is an early and critical step in brain development, and it occurs prior to network activity that is driven by sensory input. The general sequence is: (1) unsynchronized, random neural activity in the form of calcium (Ca^{++}) transients; (2) synchronized neural activity across small neural networks driven by electrical synaptic transmission; and (3) synchronous activity via chemical neurotransmission, permitting activation of larger neural networks (a prerequisite for seizure propagation) [102, 103]. Each of these steps is elaborated below and summarized in Figure 4.

Spontaneous neuronal activity evolves over the course of gestation. The earliest neocortical spontaneous activity (P0–2 in rodents) consists of Ca^{++} transients, observed in the VZ around E14–18 [104], corresponding to mid-gestation in humans; at that stage, synaptogenesis and myelination are beginning to accelerate. Ca^{++} transients are also observed in the cortical plate, where they rely on electrical activity for generation, since they do not occur when neuronal activity is prevented by sodium channel blockade [105]. These Ca^{++} transients are critical for maturation of excitatory neurons, neuronal migration, and dendrite development [106]. They occur randomly in an unsynchronized pattern and are probably not sufficient to give rise to a seizure.

The next stage (P1–3 in rodents) involves highly synchronized bursts of neuronal activity in small neural networks, dependent on electrical synaptic transmission.

Voltage-dependent ion channels begin to appear at this stage, but they are not yet sufficiently mature to generate propagated activity. In rodents, forms of transient activity have been recorded that mediate local synchronization within cortical columns and local neural networks; this activity is dependent on emerging glutamatergic and perhaps cholinergic synaptic activity and includes spindle bursts and spontaneous gamma oscillations (Table 3; Fig. 4) [103, 107]. Spindle bursts are observed in the visual and somatosensory cortices beginning around P0 and are thought to arise from subplate neurons [108, 109]. The subplate is a transient layer in the developing cerebral cortex located between the intermediate zone and the cortical plate (Fig. 3a) [110, 111]. Subplate neurons receive synaptic input from the thalamus and modulate many aspects of cortical development and plasticity; they are also quite vulnerable to injury [112]. Spontaneous gamma oscillations (25–100 Hz) start around P3 and are generated by thalamocortical pathways and in cortical supragranular layers [113]. Both spindle bursts and gamma oscillations can occur spontaneously or in response to sensory stimulation [114].

Over time, other mechanisms emerge that allow the synchronization of larger neocortical areas (P4–10). Early postnatal cortical neurons in rodents develop cortical early network oscillations (cENOs), activated by glutamatergic synapses (including N-methyl-D-aspartate [NMDA] and α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid [AMPA] receptors) [115, 116]. cENOs propagate diffusely but gradually across the cortex from their initial preponderance in posterior regions to more anterior areas by P1–6 [117], a period that parallels the human early-to-mid 3rd trimester, when substantial neurogenesis, synaptogenesis, and myelination are occurring. cENOs are eventually replaced by cortical giant depolarizing potentials (cGDPs) around P4–5 in rodents [118], approximating the mid 3rd trimester in humans. cGDPs consist of membrane depolarizations lasting hundreds of milliseconds. They occur about 10 times more frequently than cENOs and are mostly driven by excitatory GABAergic transmission [118, 119] in association with persistent sodium current activation [120, 121] and some NMDA receptor contribution [71, 73], allowing more rapid synchronization of larger neocortical networks. The net effect of cGDPs on network physiology is initial excitation, modulated by inhibition at the peak of the cGDP (thereby constraining seizure generation) [122]. The cGDP represents one of the initial synapse-driven neuronal patterns observed in the hippocampus and neocortex [123, 124]. cGDPs disappear when GABA becomes hyperpolarizing (late in the 1st week of life in rodents, around term in humans).

The sources of spontaneous activity described above are thought to modulate developmental processes including cell migration and differentiation, synaptogenesis, and regional connectivity in rodents [107]; in humans as well, spontaneous activity transients are required for brain growth [125]. Genetic factors precisely govern the emergence of the various oscillations in the developing brain; germline mutations, present since conception, can alter oscillatory behaviors and all subsequent developmental steps [126]. In humans, spontaneous activity transients begin as early as 24 wga as focal events, become more widespread with hemispheric synchrony by 30 wga (via brainstem activation), and attain even more synchrony by 34 wga as the corpus callosum matures [11, 127]. The human EEG equivalents of cENOs, cGDPs, spindle bursts, spontaneous gamma oscillations, and other sources of spontaneous neuronal activity are not known with certainty (Table 3) [128]. The human premature EEG pattern called "delta brushes" (or "delta-beta complexes," a marker of the quiet sleep stage) has been proposed as the in vivo EEG correlate of spindle bursts [129].

EEG activity in very preterm infants is characterized by long discontinuous periods of voltage attenuation punctuated by intermittent bursts of high-voltage, irregular activity [130]. Interburst durations decrease progressively with gestational age [12, 131], and as GABA becomes inhibitory, spontaneous activity transients disappear and the EEG becomes continuous [11]. Persistence of discontinuous EEG activity in preterm infants could disrupt network development, especially that of frontal cortical networks, and may account for some of the neurodevelopmental sequelae of prematurity [132]. If early postnatal spontaneous neuronal activity in humans were to follow a similar developmental course as in rodents, it would be reasonable to conclude that synchronous activity would not be present in humans until the 3rd trimester, representing one reason why seizures are not even more prevalent prior to ~28 wga.

Cortical Burst Dynamics in Extremely Preterm Infants

The prominent discontinuous activity recorded on EEGs of infants <28 wga (tracé discontinu) consists of high-amplitude, irregular, nonrhythmic bursts. Burst frequency and duration increase as gestation progresses, and the discontinuous periods (interburst intervals) decrease. In extremely premature infants, the symmetry and sharpness of bursts at 72 h of life were found to predict cognitive and motor outcomes at the age of 2 years [133]. Furthermore, the bursts exhibited "scale-free" properties, meaning that fluctuations in neural activity did not con-

Table 3. Activity patterns in early brain development

		Characteristics	Ref.
Spontaneous Ca^{++} transients	VZ transients	– E14–18 – Independent of electrical activity (connexin dependent) – Dependent on Ca^{++} release from intracellular stores – Synchrony in pairs of adjacent precursor cells – Role in proliferation and differentiation of VZ precursor neurons and coordination of cell cycle entry	206, 207
	CP transients	– Synchronous between neurons – TTX sensitive (rely on electrical activity for generation) – Rely on voltage-gated calcium channels	105
Local synchronous events (small scale)	Spindle bursts	– ~P0–3 – Approximately every 10 s – Subplate neurons – Require gap junctions – Can occur spontaneously or in response to sensory stimulation – Under control of glutamate and GABA – Involved in promotion of cortical synapses and connectivity (intracortical and thalamocortical); involved in development of the barrel cortex (rodents) – Equivalent to delta brushes in humans	86, 107, 109, 208, 209
	Gamma oscillations	– P >3 – 25–100 Hz – Approximately every 10–30 s – In postnatal models can occur spontaneously or in response to sensory stimulation – Localization in local thalamocortical pathways, supragranular layers – Can continue into adulthood	113, 210
Widespread synchronous events (large scale)	cENOs	– Peak approximately between birth and P3 – Glutamate dependent – Low frequency (0.01–0.05 Hz) – Propagate from posterior to anterior areas by P1–6 – Allow gradual synchronization of larger cortical areas	98, 100, 118, 205
	cGDPs	– May overlap in time with cENOs P4–5 – Peak P6–8, disappear ~P10 – Driven by depolarizing GABA – Higher frequency (0.5–1 Hz) – Duration hundreds of milliseconds – Allow rapid synchronization of larger cortical areas	118, 123, 211

Data obtained mainly from rodents. E, embryonic day; P, postnatal day; VZ, ventricular zone; CP, cortical plate; cENOs, cortical early network oscillations; cGDPs, cortical giant depolarizing potentials; TTX, tetrodotoxin; GABA, γ-aminobutyric acid.

form to a specific temporal or spatial scale. Rather, scale-free behavior results in paroxysmal EEG bursts thought to arise from a dynamic balance between excitation and inhibition in developing neural circuits. The constant interplay between the excitation and inhibition states may predispose to seizures (if excitation predominates) or may afford protection from seizures (if inhibition predominates). We speculate that the limited occurrence of seizures in extremely premature infants may be related to the chaotic, discontinuous activity seen on EEG; that is, the alternation between excitation and inhibition activity generates EEG bursts that may impede the pathological synchrony of activity required to generate seizures among neonates <28 wga.

Excessive Brain Excitation Favors Increased Seizure Occurrence in Moderate-to-Late Preterm and Term Newborns, but Less So in Extremely Premature Infants

During gestation, the immature brain exists in a state of excitation/inhibition imbalance, with a relative excess of excitation manifest in several physiological factors [134]. Early increased excitation is necessary for numerous activity-dependent developmental processes, including neurogenesis, cell migration, differentiation, synapse formation, and neural circuit development, but it also renders the immature human brain overly susceptible to seizures, especially close to term [73, 135]. During this period of excessive excitation, the amount of chemoconvulsant necessary to induce seizures experimentally in rodents as young as P0–5 is much lower than that required to induce seizures in adult animals using the same agents [136, 137].

Electrophysiological Maturation

Two broad mechanisms govern a neuron's firing: (1) intrinsic membrane properties (input resistance and the membrane time constant) determined by cell morphology and ion channel properties and (2) synaptic transmission [138]. Immature neurons are electrically compact – they have high input resistances, long membrane time constants, and low resting potentials; action potentials in these neurons are broad and slow [139]. Over the 2 weeks following birth, coincident with the arrival of neurons in the cortical plate, these membrane properties change markedly, with a dramatic decrease in input resistance and time constant and an increase in membrane potential [140]. These factors correspond to the waning of electrical synaptic transmission and emergence of chemical synaptic transmission [141], combining to enable a neuron to fire action potentials readily and in prolonged bursts. Therefore, the likelihood of seizure generation is lower at P0 than after a week or two of postnatal development in rodents. When extrapolated to humans, the evolution of membrane properties would suggest that early in the 3rd trimester, neurons are less capable of the rapid firing associated with seizures. Similarly, synaptic currents can be evoked in rat neurons at very young ages, certainly by P3, but their amplitude and duration increase markedly over the next 2 weeks [79]. All of these factors favor increased excitability at and after term in rodents.

Ion Channel Development

In the developing brain, ion channel and neurotransmitter receptor activity is regulated developmentally and contributes to the excitation/inhibition balance [142, 143]. The sequence of ion channel development is complex and not fully understood. The expression of specific channels and currents changes as a neuron differentiates, migrates, and finally arrives at its cortical location (~P4–6). The presence and type of specific ion channels govern the ability of a neuron to fire action potentials, and determine their amplitude and mode of firing (i.e., single or repetitive). Calcium channels mediating excitatory inward currents develop earliest, with later emergence of excitatory sodium currents and excitability-stabilizing potassium currents. Until arrival at the cortical plate, neurons maintain a low but steady level of potassium channel expression and a very small but steadily increasing expression of voltage-gated sodium channels [140]. Once at the cortical plate, expression of both potassium and sodium channels increases markedly. These and other ion conductance changes, such as the hyperpolarization-activated cation current I_h [140, 144], confer the ability to fire repetitively and therefore permit the rapid, hypersynchronous firing characteristic of seizure discharges.

Glutamate Receptors

Excitatory glutamatergic neurons are expressed abundantly during development (Fig. 2). Glutamate binds to one of three types of postsynaptic receptor: NMDA, AMPA, and kainate; each receptor type is composed of subunits that govern the excitatory current flow. NMDA and AMPA receptor subunit configurations confer relative hyperexcitability around mid-to-late preterm gestation. In human white matter, expression of the NMDA receptor subunits GluN1 and GluN2B increases over the course of preterm life, up until 37 wga [145, 146]. At this point in development, GluN2B is expressed widely across multiple brain regions, including the hippocampus. GluN2B subunits enhance Ca^{++} influx and thus confer longer excitatory postsynaptic currents. Meanwhile, the GluN1 subunit, required for all functional NMDA receptors, also favors excitation during this period.

In the resting state, magnesium ions (Mg^{++}) block the pore of NMDA receptors and prevent their excitation. For NMDA receptors to function, two concurrent events need to happen: (1) glutamate must bind to the NMDA receptor and (2) membrane depolarization (from simultaneously activated nearby AMPA receptors) must extrude Mg^{++} from the NMDA channel pore. The voltage-dependent

Mg^{++} block of NMDA receptors is present to some extent as early as 26 wga [147], but it becomes increasingly operational later in preterm life and postnatally, supporting the conclusion that excitation is higher around term than earlier in gestation [148, 149]. Mg^{++} block is weakly present at P1–4 in rats (equivalent to extreme prematurity in humans), so at this age, membrane depolarization would not be as likely to extrude Mg^{++}, preventing NMDA receptor overactivation and seizure generation [149]. One mechanism by which exogenously administered Mg^{++} (in the form of $MgSO_4$) may work to reduce excitability, such as in the treatment of preeclamptic seizures, is by enhancing Mg^{++} blockage of NMDA receptors. In rodents, $MgSO_4$ ameliorates seizures by binding to NMDA receptors [150]; in a fetal sheep model, $MgSO_4$ did not prevent seizures but *did* reduce the total number and duration of seizures [77]. Maturational profiles of the AMPA receptor subunits GluA1, GluA3, and GluA4 in the perinatal human brain suggest that AMPA receptors are overexpressed late in gestation and are initially largely deficient in GluA2. GluA2 deficiency enhances excitation as it allows increased permeability to calcium influx [151, 152].

GABA Receptors Mediate both Excitation and Inhibition during Development

Cortical inhibition also follows a developmental profile, contributing to an increased seizure risk among neonates 34 wga and older [153]. While the subunit composition of NMDA and AMPA receptors confers additional excitability at term and in the early postnatal period, the inhibitory substantia nigra system has yet to fully develop its ability to suppress excessive cortical excitation in extremely premature neonates [154, 155].

Moreover, $GABA_A$ receptors mediate excitation rather than inhibition early in gestation, beginning in the early postnatal period in rodents and persisting until about P14 [73]. Excitatory GABA action is important for several physiological functions and contributes to neurogenesis, cell differentiation, synapse formation, and cortical columnar architecture development [156, 157]. During the 1st postnatal week, GABAergic interneurons and pyramidal cells form circuits that promote network oscillations [158]. In addition, GABA-mediated depolarization contributes to NMDA receptor activation and in this way potentiates excitatory synapse function [159, 160].

GABA can mediate excitation or inhibition depending on the intracellular versus extracellular chloride (Cl^-) concentration, which sets the Cl^- equilibrium potential and which varies over development (Fig. 5). In late pregnancy and around birth, $GABA_A$ receptors primarily mediate depolarization due, at least in part, to the relative expression of cation chloride cotransporters: the early expression of sodium-potassium-chloride cotransporter 1 (NKCC1; imports Cl^-) and the delayed expression of potassium-chloride cotransporter 2 (KCC2; exports Cl^-) [161–163]. Although present since P4 in neocortical layer II and III neurons in rats, the expression of NKCC1 does not peak in the hippocampus until P7, or roughly late preterm gestation in humans [164]. In the cortex and hippocampus, NKCC1 expression peaks between P3 and P14 in rats [162]; in humans, this coincides with the late preterm and early postterm period. During extreme prematurity, GABA does not yet mediate synaptic function, either excitatory or inhibitory; rather, GABA at this stage exerts trophic actions and therefore is not likely to contribute to seizure occurrence so early in development.

When NKCC1 predominates, GABA binding to its postsynaptic receptor will engender depolarization and excitation due to Cl^- efflux; this will also trigger inward Ca^{++} currents and remove the voltage-dependent Mg^{++} block from NMDA receptors, promoting Ca^{++} entry and activation of second messengers that enhance neuronal depolarization, thus increasing brain excitability and the seizure risk [73, 165, 166]. As postnatal development progresses, KCC2 expression increases and NKCC1 expression decreases, eventually resulting in GABAergic inhibition (~P10) [166, 167]. The developmental transition from excitatory to inhibitory GABA signaling begins gradually in late preterm humans, corresponding to the relative preponderance of NKCC1 versus KCC2 [162]. While the transition from GABAergic depolarization to inhibition is partly explained by Cl^- cotransporters, recent data suggest a more complex situation. Specific distributions of impermeant anions with fixed negative charges on intracellular proteins (ribosomes, tubulin, etc.) as well as on extracellular glycoproteins also regulate the Cl^- distribution and concentration in immature neurons [168]. The ontogeny of these mechanisms must be elucidated as clinical translation trials are designed [169].

It is important to recognize that the transition from GABA-mediated excitation to GABA-mediated inhibition does not occur instantaneously or in every brain region at the same time. Rather, this transition is gradual, not all-or-none, as evidenced by the fact that GABAergic agonists such as phenobarbital and benzodiazepines are often effective as anticonvulsants in term neonates [170] even when significant GABA-mediated depolarization is present [171]. At the same time, GABA agonists can cause neonatal myoclonus [172, 173]. That is, GABA excitation and inhibition coexist at term and near term in humans and other precocial species [166, 174].

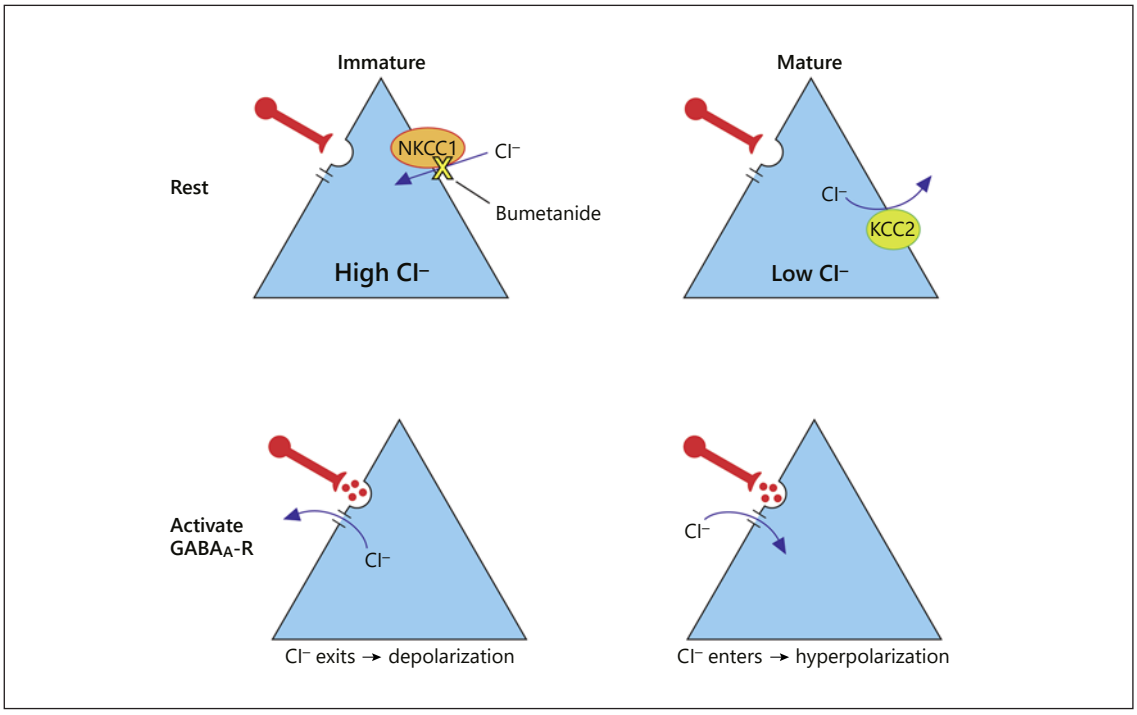

Fig. 5. Simplified cartoon illustrating GABA responses as a function of age. Neurons (blue triangles) illustrate the role of intracellular chloride (Cl^-) concentration as a function of age in neuronal responses to GABA (red dots). At early developmental stages (left), the intracellular chloride concentration is high due to the activity of a membrane transporter (NKCC1; orange oval) that imports chloride; activation of $GABA_A$ receptors at this age (lower left) causes chloride efflux and depolarization. In the mature brain (right), NKCC1 expression is much reduced, but another chloride transporter (KCC2; light-green oval) is highly expressed and extrudes chloride, keeping the intracellular chloride concentration relatively low. Therefore, in the mature brain, activation of $GABA_A$ receptors (lower right) results in chloride influx and hyperpolarization of the neuron. The relative intracellular chloride concentrations at the two ages are indicated by the sizes of the Cl^- lettering. Bumetanide (upper left) blocks NKCC1 action, reducing the depolarizing action of GABA at immature ages; it has been proposed as an age-specific anti-seizure treatment for neonatal seizures (see text). $GABA_A$-R, γ-aminobutyric acid type A receptor; KCC2, potassium-chloride cotransporter 2; NKCC1, sodium-potassium-chloride cotransporter 1.

Furthermore, the magnitude of the depolarization driving force caused by glutamate receptor activation far exceeds the magnitude of the depolarization mediated by GABA (due to the much larger driving force of glutamate). Finally, even during early development, when GABA exerts an excitatory action, it also mediates some inhibition by a "shunting" mechanism, increasing membrane conductance and countering the depolarizing conductance changes from nearby AMPA receptors. This protective inhibition may represent a mechanism for preventing runaway excitation and continuous seizures [175].

Much optimism has been generated regarding the possibility that altering the Cl^- gradient could represent a novel treatment for neonatal seizures [176]. For example, there is considerable evidence that bumetanide, a diuretic drug, blocks NKCC1 and hence opposes the depolarizing action of GABA and suppresses seizures in experimental models [177, 178]. Clinical trials have not yet proven any clear efficacy [179], but it still holds promise [180; but see 181]. Other novel approaches to neonatal seizure therapy are being pursued as well [174, 182]. It is not certain whether these approaches will have a beneficial effect on seizures in extremely premature infants, before the GABA depolarizing response develops.

In summary, multiple, converging mechanisms can increase excitability and therefore contribute to a predisposition to seizures in moderate-to-late preterm infants and term infants. Many of these mechanisms are not yet fully operative during very early brain development (<28 wga), though seizures do occur in extremely premature neonates.

Myelination Begins at Mid-Gestation and Continues until Middle Age

Myelin provides the substrate for rapid axonal conduction by restricting action potentials to nodes of Ranvier (saltatory conduction) [183]. CNS myelination, the process of enveloping axons with a myelin sheath, is governed by oligodendrocytes and controlled directly by glutamatergic neuronal activity [184]. Oligodendrocyte precursor cells first appear in humans at 9 wga in the ganglionic eminences; over the next few weeks, oligodendrocytes migrate to the cortical plate [185]. Myelin basic protein (MBP) is not expressed until oligodendrocytes reach full maturity, at mid-gestation (Fig. 2). MBP is first found around 18 wga in the human thalamus and 21 wga in the internal capsule, with myelination progressing in a caudal-to-rostral pattern. Cortical expression of MBP is not likely until after 24 wga [185]. Thereafter, myelination continues until at least young adulthood and even into middle age [186]. The brains of extremely premature infants lack sufficient myelination to propagate seizures, which is partly why electrographic seizures in premature infants are invariably focal or multifocal rather than generalized [18]. Moreover, oligodendrocytes can be readily damaged by hypoxia or seizure activity [187].

Peripheral Nerve Development

Spinal cord and peripheral nerve development is necessary for the clinical expression of motor seizures. The PNS is derived primarily from neural crest precursor cells that give rise to myelinating and nonmyelinating Schwann cells that are involved in myelination or in the support of unmyelinated peripheral axons, respectively. Motor neurons project axons across varying extracellular milieus and over large distances to synapse onto muscles [188]. This process occurs as follows. At the tip of each axon, a protrusion known as the growth cone is a dynamic, motile structure that assumes the shape of filopodia (finger-like projections). Both the growth cone and filopodia actively explore their environment for cues to guide axons to target muscles [189].

Motor neurons are born centrally and exit the CNS and into the PNS, binding to muscle (forming neuromuscular junctions) with the assistance of axon guidance cues. While little is known about the specific mechanisms of the anterograde signaling between neurons and muscle that lead to neuromuscular junction formation, early outgrowth of pathways of the cranial nerves and spinal plexus occurs around 4–7 weeks postconception, resulting in rudimentary limb activation as early as 8–10 wga in humans [190]. Further functional maturation of these pathways takes several additional weeks, which may explain why convulsive activity with clonic limb movements is not prominent early in gestation [102].

Effects of Seizure Activity on Developmental Processes

Efforts to understand the effects of seizures at various early stages on subsequent development are gaining momentum. The hippocampus appears to be at an especially high risk, with early seizures contributing to the inappropriate enhancement of the synaptic connections in the period immediately following ictal activity, which may alter normal synaptogenesis and contribute to later cognitive deficits [191]. Recent studies on neonates have identified an association between increasing seizure burden and poorer outcomes, likely driven by seizure-associated injury leading to loss of neuron integrity and deficits in energy metabolism [192]. Poorer neurological outcome also appears to be associated with longer seizure duration, as evidenced by the degree of brain injury on brain MRI scans of full-term newborns with hypoxic-ischemic encephalopathy and subsequent seizures [193]. Because the seizures themselves may impair synapse proliferation and synaptic plasticity [69, 194], it may be fortuitous that the extremely premature brain has a limited propensity for seizures [195]. In addition, ongoing seizures may adversely affect ion channel and synapse function [191, 196, 197], myelination [198], dendritic branching [199], and overall brain development [200], from which extremely premature infants may be somewhat shielded [201]. Clinical and electrographic seizures can be elicited in newborn rodents (even at P0) by a number of convulsant stimuli, including 4-aminopyridine, which blocks potassium channels [137], flurothyl [202], kainate [203], and hypoxia [204], among others; subsequent behavioral and cognitive deficits, seizure-induced cell damage, and subsequent predisposition to seizures vary inversely with age at seizure induction.

Conclusions

Multiple complex, dynamic, interacting factors come into play to determine the time course, clinical manifestations, and electrical expression of seizure activity during early brain development. We hypothesize that seizure occurrence at various gestational ages is a direct consequence of definable physiological factors that change dur-

ing fetal life, thereby conferring different seizure manifestations, consequences, and treatment opportunities over development.

Several pivotal steps in brain development must take place prior to seizure onset, as addressed above, including the proliferation, differentiation, and migration of neuronal stem cells, followed by organization of the CNS and PNS into mature structures. At a microscopic level, synaptogenesis and myelination allow neuronal signal generation and transmission. Development of spontaneous and oscillatory activity may contribute to seizure initiation. Tipping the excitation/inhibition balance towards pathological excitation and seizure generation does not likely occur until the 3rd trimester, when multiple mechanisms converge to render the brain susceptible to seizures. By that age, factors promoting excitation include membrane properties, excitatory GABA action, and glutamate receptor subunit compositions. Scale-free activity recorded on EEG eventually evolves into more synchronized brain activity after 28 wga, when the occurrence of seizures becomes more plausible.

There is no doubt that seizure activity can occur in extremely premature infants and in animal models approximating that developmental stage. However, seizures in that age range appear to have less severe clinical manifestations, are primarily electrographic, and propagate less widely, all factors related to definable pathophysiological considerations below 28 wga. The documented predisposition of extremely premature infants to seizures might be even higher if the hyperexcitability mechanisms discussed above were already fully operational in this age window. This hypothesis requires rigorous further experimental and clinical assessment.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding was involved in the preparation of this review.

Author Contributions

Both authors were equally involved in conceptualizing, writing, and editing this review.

References

1 Jensen FE. Neonatal seizures: an update on mechanisms and management. Clin Perinatol. 2009 Dec;36(4):881–900.
2 Nagarajan L. Neonatal seizures: current management and future challenges. London: Mac Keith Press; 2016.
3 Sands TT, McDonough TL. Recent advances in neonatal seizures. Curr Neurol Neurosci Rep. 2016 Oct;16(10):92.
4 Petrini JR, Dias T, McCormick MC, Massolo ML, Green NS, Escobar GJ. Increased risk of adverse neurological development for late preterm infants. J Pediatr. 2009 Feb;154(2):169–76.
5 Glass HC, Shellhaas RA, Tsuchida TN, Chang T, Wusthoff CJ, Chu CJ, et al.; Neonatal Seizure Registry study group. Seizures in preterm neonates: a multicenter observational cohort study. Pediatr Neurol. 2017 Jul;72:19–24.
6 Abend NS, Wusthoff CJ. Neonatal seizures and status epilepticus. J Clin Neurophysiol. 2012 Oct;29(5):441–8.
7 Clancy RR, Legido A. The exact ictal and interictal duration of electroencephalographic neonatal seizures. Epilepsia. 1987 Sep-Oct;28(5):537–41.
8 Husain AM. Review of neonatal EEG. Am J Electroneurodiagn Technol. 2005 Mar;45(1):12–35.
9 Scher MS, Aso K, Beggarly ME, Hamid MY, Steppe DA, Painter MJ. Electrographic seizures in preterm and full-term neonates: clinical correlates, associated brain lesions, and risk for neurologic sequelae. Pediatrics. 1993 Jan;91(1):128–34.
10 Patrizi S, Holmes GL, Orzalesi M, Allemand F. Neonatal seizures: characteristics of EEG ictal activity in preterm and fullterm infants. Brain Dev. 2003 Sep;25(6):427–37.
11 Vanhatalo S, Kaila K. Development of neonatal EEG activity: from phenomenology to physiology. Semin Fetal Neonatal Med. 2006 Dec;11(6):471–8.
12 Vecchierini MF, André M, d'Allest AM. Normal EEG of premature infants born between 24 and 30 weeks gestational age: terminology, definitions and maturation aspects. Neurophysiol Clin. 2007 Oct-Nov;37(5):311–23.
13 Okumura A, Hayakawa F, Kato T, Itomi K, Maruyama K, Kubota T, et al. Ictal electroencephalographic findings of neonatal seizures in preterm infants. Brain Dev. 2008 Apr;30(4):261–8.
14 Pavlidis E, Lloyd RO, Boylan GB. EEG – a valuable biomarker of brain injury in preterm infants. Dev Neurosci. 2017;39(1-4):23–35.
15 Shah DK, Zempel J, Barton T, Lukas K, Inder TE. Electrographic seizures in preterm infants during the first week of life are associated with cerebral injury. Pediatr Res. 2010 Jan;67(1):102–6.
16 Gillam-Krakauer M, Carter BS. Neonatal hypoxia and seizures. Pediatr Rev. 2012 Sep;33(9):387–96.
17 Janáčková S, Boyd S, Yozawitz E, Tsuchida T, Lamblin MD, Gueden S, et al. Electroencephalographic characteristics of epileptic seizures in preterm neonates. Clin Neurophysiol. 2016 Aug;127(8):2721–7.
18 Lloyd RO, O'Toole JM, Pavlidis E, Filan PM, Boylan GB. Electrographic seizures during the early postnatal period in preterm infants. J Pediatr. 2017 Aug;187:18–25.e2.
19 Tolonen M, Palva JM, Andersson S, Vanhatalo S. Development of the spontaneous activity transients and ongoing cortical activity in human preterm babies. Neuroscience. 2007 Mar;145(3):997–1006.

20 Mizrahi EM, Kellaway P. Characterization and classification of neonatal seizures. Neurology. 1987 Dec;37(12):1837–44.
21 Boylan GB, Stevenson NJ, Vanhatalo S. Monitoring neonatal seizures. Semin Fetal Neonatal Med. 2013 Aug;18(4):202–8.
22 Stevenson NJ, Vanhatalo S. Designing a trial for neonatal seizure treatment. Semin Fetal Neonatal Med. 2018 Jun;23(3):213–7.
23 Hauser WA. Epidemiology of epilepsy in children. Neurosurg Clin N Am. 1995 Jul;6(3):419–29.
24 Vasudevan C, Levene M. Epidemiology and aetiology of neonatal seizures. Semin Fetal Neonatal Med. 2013 Aug;18(4):185–91.
25 Ishii N, Kono Y, Yonemoto N, Kusuda S, Fujimura M; Neonatal Research Network, Japan. Outcomes of infants born at 22 and 23 weeks' gestation. Pediatrics. 2013 Jul;132(1):62–71.
26 Jacobs J, Spelbrink EM. Seizures in preterm infants. J Clin Neurophysiol. 2016 Oct;33(5):382–93.
27 Pisani F, Facini C, Pelosi A, Mazzotta S, Spagnoli C, Pavlidis E. Neonatal seizures in preterm newborns: a predictive model for outcome. Eur J Paediatr Neurol. 2016 Mar;20(2):243–51.
28 Hellström-Westas L. Amplitude-integrated electroencephalography for seizure detection in newborn infants. Semin Fetal Neonatal Med. 2018 Jun;23(3):175–82.
29 Pisani F, Pavlidis E. The role of electroencephalogram in neonatal seizure detection. Expert Rev Neurother. 2018 Feb;18(2):95–100.
30 Rakshasbhuvankar A, Rao S, Palumbo L, Ghosh S, Nagarajan L. Amplitude integrated electroencephalography compared with conventional video EEG for neonatal seizure detection: a diagnostic accuracy study. J Child Neurol. 2017 Aug;32(9):815–22.
31 Shellhaas RA, Chang T, Tsuchida T, Scher MS, Riviello JJ, Abend NS, et al. The American Clinical Neurophysiology Society's guideline on continuous electroencephalography monitoring in neonates. J Clin Neurophysiol. 2011 Dec;28(6):611–7.
32 Weeke LC, van Ooijen IM, Groenendaal F, van Huffelen AC, van Haastert IC, van Stam C, et al. Rhythmic EEG patterns in extremely preterm infants: classification and association with brain injury and outcome. Clin Neurophysiol. 2017 Dec;128(12):2428–35.
33 Le Bihannic A, Beauvais K, Busnel A, de Barace C, Furby A. Prognostic value of EEG in very premature newborns. Arch Dis Child Fetal Neonatal Ed. 2012 Mar;97(2):F106–9.
34 Pisani F, Copioli C, Turco EC, Sisti L, Cossu G, Seri S. Mortality risk after neonatal seizures in very preterm newborns. J Child Neurol. 2012 Oct;27(10):1264–9.
35 Kohelet D, Shochat R, Lusky A, Reichman B; Israel Neonatal Network. Risk factors for neonatal seizures in very low birthweight infants: population-based survey. J Child Neurol. 2004 Feb;19(2):123–8.
36 Vesoulis ZA, Inder TE, Woodward LJ, Buse B, Vavasseur C, Mathur AM. Early electrographic seizures, brain injury, and neurodevelopmental risk in the very preterm infant. Pediatr Res. 2014 Apr;75(4):564–9.
37 Vesoulis ZA, McPherson C, Neil JJ, Mathur AM, Inder TE. Early high-dose caffeine increases seizure burden in extremely preterm neonates: a preliminary study. J Caffeine Res. 2016 Sep;6(3):101–7.
38 Manuck TA, Rice MM, Bailit JL, Grobman WA, Reddy UM, Wapner RJ, et al.; Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Preterm neonatal morbidity and mortality by gestational age: a contemporary cohort. Am J Obstet Gynecol. 2016 Jul;215(1):103.e1–14.
39 Ronen GM, Buckley D, Penney S, Streiner DL. Long-term prognosis in children with neonatal seizures: a population-based study. Neurology. 2007 Nov;69(19):1816–22.
40 Douglass LM, Heeren TC, Stafstrom CE, DeBassio W, Allred EN, Leviton A, et al. Cumulative incidence of seizures and epilepsy in ten-year-old children born before 28 weeks' gestation. Pediatr Neurol. 2017 Aug;73:13–9.
41 Kuban KC, Joseph RM, O'Shea TM, Allred EN, Heeren T, Douglass L, et al.; Extremely Low Gestational Age Newborn (ELGAN) Study Investigators. Girls and boys born before 28 weeks gestation: risks of cognitive, behavioral, and neurologic outcomes at age 10 years. J Pediatr. 2016 Jun;173:69–75.e1.
42 Hintz SR, Kendrick DE, Wilson-Costello DE, Das A, Bell EF, Vohr BR, et al.; NICHD Neonatal Research Network. Early-childhood neurodevelopmental outcomes are not improving for infants born at <25 weeks' gestational age. Pediatrics. 2011 Jan;127(1):62–70.
43 Vohr BR. Neurodevelopmental outcomes of extremely preterm infants. Clin Perinatol. 2014 Mar;41(1):241–55.
44 Glass HC, Costarino AT, Stayer SA, Brett CM, Cladis F, Davis PJ. Outcomes for extremely premature infants. Anesth Analg. 2015 Jun;120(6):1337–51.
45 Jarjour IT. Neurodevelopmental outcome after extreme prematurity: a review of the literature. Pediatr Neurol. 2015 Feb;52(2):143–52.
46 Stoll BJ, Hansen NI, Bell EF, Walsh MC, Carlo WA, Shankaran S, et al.; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993–2012. JAMA. 2015 Sep;314(10):1039–51.
47 Anderson JG, Baer RJ, Partridge JC, Kuppermann M, Franck LS, Rand L, et al. Survival and major morbidity of extremely preterm infants: a population-based study. Pediatrics. 2016 Jul;138(1):e20154434.
48 Zegers MJ, Hukkelhoven CW, Uiterwaal CS, Kollée LA, Groenendaal F. Changing Dutch approach and trends in short-term outcome of periviable preterms. Arch Dis Child Fetal Neonatal Ed. 2016 Sep;101(5):F391–6.
49 Logan JW, Dammann O, Allred EN, Dammann C, Beam K, Joseph RM, et al. Early postnatal illness severity scores predict neurodevelopmental impairments at 10 years of age in children born extremely preterm. J Perinatol. 2017 May;37(5):606–14.
50 Joseph RM, O'Shea TM, Allred EN, Heeren T, Hirtz D, Jara H, et al.; ELGAN Study Investigators. Neurocognitive and academic outcomes at age 10 years of extremely preterm newborns. Pediatrics. 2016 Apr;137(4):e20154343.
51 Bittigau P, Sifringer M, Ikonomidou C. Antiepileptic drugs and apoptosis in the developing brain. Ann N Y Acad Sci. 2003 May;993(1):103–14.
52 Al-Muhtasib N, Sepulveda-Rodriguez A, Vicini S, Forcelli PA. Neonatal phenobarbital exposure disrupts GABAergic synaptic maturation in rat CA1 neurons. Epilepsia. 2018 Feb;59(2):333–44.
53 Sheth RD, Hobbs GR, Mullett M. Neonatal seizures: incidence, onset, and etiology by gestational age. J Perinatol. 1999 Jan;19(1):40–3.
54 Jan S, Northington FJ, Parkinson CM, Stafstrom CE. EEG monitoring technique influences the management of hypoxic-ischemic seizures in neonates undergoing therapeutic hypothermia. Dev Neurosci. 2017;39(1-4):82–8.
55 Iyer KK, Roberts JA, Hellström-Westas L, Wikström S, Hansen Pupp I, Ley D, et al. Early detection of preterm intraventricular hemorrhage from clinical electroencephalography. Crit Care Med. 2015 Oct;43(10):2219–27.
56 O'Toole JM, Boylan GB, Vanhatalo S, Stevenson NJ. Estimating functional brain maturity in very and extremely preterm neonates using automated analysis of the electroencephalogram. Clin Neurophysiol. 2016 Aug;127(8):2910–8.
57 Arichi T, Whitehead K, Barone G, Pressler R, Padormo F, Edwards AD, et al. Localization of spontaneous bursting neuronal activity in the preterm human brain with simultaneous EEG-fMRI. eLife. 2017 Sep;6:e27814.
58 Acharya JN, Wyllie E, Lüders HO, Kotagal P, Lancman M, Coelho M. Seizure symptomatology in infants with localization-related epilepsy. Neurology. 1997 Jan;48(1):189–96.
59 Evans D, Levene M. Neonatal seizures. Arch Dis Child Fetal Neonatal Ed. 1998 Jan;78(1):F70–5.
60 Nordli DR Jr. Diagnostic difficulty in infants and children. J Child Neurol. 2002 Jan;17(Suppl 1):S28–35.
61 Pinto LC, Giliberti P. Neonatal seizures: background EEG activity and the electroclinical correlation in full-term neonates with hypoxic-ischemic encephalopathy. Analysis by computer-synchronized long-term polygraphic video-EEG monitoring. Epileptic Disord. 2001 Sep;3(3):125–32.
62 Dobbing J, Sands J. Quantitative growth and development of human brain. Arch Dis Child. 1973 Oct;48(10):757–67.

63 Romijn HJ, Hofman MA, Gramsbergen A. At what age is the developing cerebral cortex of the rat comparable to that of the full-term newborn human baby? Early Hum Dev. 1991 Jul;26(1):61–7.
64 Clancy B, Finlay BL, Darlington RB, Anand KJ. Extrapolating brain development from experimental species to humans. Neurotoxicology. 2007 Sep;28(5):931–7.
65 Galanopoulou AS, Moshé SL. In search of epilepsy biomarkers in the immature brain: goals, challenges and strategies. Biomarkers Med. 2011 Oct;5(5):615–28.
66 Biran V, Verney C, Ferriero DM. Perinatal cerebellar injury in human and animal models. Neurol Res Int. 2012;2012:858929.
67 Pressler R, Auvin S. Comparison of brain maturation among species: an example in translational research suggesting the possible use of bumetanide in newborn. Front Neurol. 2013 Apr;4:36.
68 Semple BD, Blomgren K, Gimlin K, Ferriero DM, Noble-Haeusslein LJ. Brain development in rodents and humans: identifying benchmarks of maturation and vulnerability to injury across species. Prog Neurobiol. 2013;106-107:1–16.
69 Katsarou AM, Moshé SL, Galanopoulou AS. Interneuronopathies and their role in early life epilepsies and neurodevelopmental disorders. Epilepsia Open. 2017 Sep;2(3):284–306.
70 Molnár Z, Clowry G. Cerebral cortical development in rodents and primates. Prog Brain Res. 2012;195:45–70.
71 Ben-Ari Y. Basic developmental rules and their implications for epilepsy in the immature brain. Epileptic Disord. 2006 Jun;8(2):91–102.
72 Cuaycong M, Engel M, Weinstein SL, Salmon E, Perlman JM, Sunderam S, et al. A novel approach to the study of hypoxia-ischemia-induced clinical and subclinical seizures in the neonatal rat. Dev Neurosci. 2011;33(3-4):241–50.
73 Nardou R, Ferrari DC, Ben-Ari Y. Mechanisms and effects of seizures in the immature brain. Semin Fetal Neonatal Med. 2013 Aug;18(4):175–84.
74 Tucker AM, Aquilina K, Chakkarapani E, Hobbs CE, Thoresen M. Development of amplitude-integrated electroencephalography and interburst interval in the rat. Pediatr Res. 2009 Jan;65(1):62–6.
75 Barlow RM. The foetal sheep: morphogenesis of the nervous system and histochemical aspects of myelination. J Comp Neurol. 1969 Mar;135(3):249–62.
76 Bennet L, Dean JM, Wassink G, Gunn AJ. Differential effects of hypothermia on early and late epileptiform events after severe hypoxia in preterm fetal sheep. J Neurophysiol. 2007 Jan;97(1):572–8.
77 Bennet L, Galinsky R, Draghi V, Lear CA, Davidson JO, Unsworth CP, et al. Time and sex dependent effects of magnesium sulphate on post-asphyxial seizures in preterm fetal sheep. J Physiol. 2018 Dec;596(23):6079–92.
78 Silbereis JC, Pochareddy S, Zhu Y, Li M, Sestan N. The cellular and molecular landscapes of the developing human central nervous system. Neuron. 2016 Jan;89(2):248–68.
79 Ben-Ari Y. The developing cortex. Handb Clin Neurol. 2013;111:417–26.
80 Marín O, Valiente M, Ge X, Tsai LH. Guiding neuronal cell migrations. Cold Spring Harb Perspect Biol. 2010 Feb;2(2):a001834.
81 Nadarajah B, Alifragis P, Wong RO, Parnavelas JG. Neuronal migration in the developing cerebral cortex: observations based on real-time imaging. Cereb Cortex. 2003 Jun;13(6):607–11.
82 Wu Q, Liu J, Fang A, Li R, Bai Y, Kriegstein AR, et al. The dynamics of neuronal migration. Adv Exp Med Biol. 2014;800:25–36.
83 Chu J, Anderson SA. Development of cortical interneurons. Neuropsychopharmacology. 2015 Jan;40(1):16–23.
84 Raymond AA, Fish DR, Stevens JM, Cook MJ, Sisodiya SM, Shorvon SD. Association of hippocampal sclerosis with cortical dysgenesis in patients with epilepsy. Neurology. 1994 Oct;44(10):1841–5.
85 Barkovich AJ, Kuzniecky RI. Gray matter heterotopia. Neurology. 2000 Dec;55(11):1603–8.
86 Pang T, Atefy R, Sheen V. Malformations of cortical development. Neurologist. 2008 May;14(3):181–91.
87 Dekkers MP, Nikoletopoulou V, Barde YA. Cell biology in neuroscience: Death of developing neurons: new insights and implications for connectivity. J Cell Biol. 2013 Nov;203(3):385–93.
88 Blanquie O, Kilb W, Sinning A, Luhmann HJ. Homeostatic interplay between electrical activity and neuronal apoptosis in the developing neocortex. Neuroscience. 2017 Sep;358:190–200.
89 Belousov AB, Fontes JD. Neuronal gap junctions: making and breaking connections during development and injury. Trends Neurosci. 2013 Apr;36(4):227–36.
90 Peinado A, Yuste R, Katz LC. Gap junctional communication and the development of local circuits in neocortex. Cereb Cortex. 1993 Sep-Oct;3(5):488–98.
91 Hardy K, Warner A, Winston RM, Becker DL. Expression of intercellular junctions during preimplantation development of the human embryo. Mol Hum Reprod. 1996 Aug;2(8):621–32.
92 Huttenlocher PR, De Courten C, Garey LJ, Van der Loos H. Synaptic development in human cerebral cortex. Int J Neurol. 1982-1983;16-17:144–54.
93 Tau GZ, Peterson BS. Normal development of brain circuits. Neuropsychopharmacology. 2010 Jan;35(1):147–68.
94 Oh WC, Lutzu S, Castillo PE, Kwon HB. De novo synaptogenesis induced by GABA in the developing mouse cortex. Science. 2016 Sep;353(6303):1037–40.
95 Rakic P, Bourgeois JP, Eckenhoff MF, Zecevic N, Goldman-Rakic PS. Concurrent overproduction of synapses in diver se regions of the primate cerebral cortex. Science. 1986 Apr;232(4747):232–5.
96 Molofsky AV, Deneen B. Astrocyte development: a guide for the perplexed. Glia. 2015 Aug;63(8):1320–9.
97 Chung WS, Allen NJ, Eroglu C. Astrocytes control synapse formation, function, and elimination. Cold Spring Harb Perspect Biol. 2015 Feb;7(9):a020370.
98 Barker AJ, Ullian EM. New roles for astrocytes in developing synaptic circuits. Commun Integr Biol. 2008;1(2):207–11.
99 Brekke E, Morken TS, Sonnewald U. Glucose metabolism and astrocyte-neuron interactions in the neonatal brain. Neurochem Int. 2015 Mar;82:33–41.
100 Devinsky O, Vezzani A, Najjar S, De Lanerolle NC, Rogawski MA. Glia and epilepsy: excitability and inflammation. Trends Neurosci. 2013 Mar;36(3):174–84.
101 Koh S. Role of neuroinflammation in evolution of childhood epilepsy. J Child Neurol. 2018 Jan;33(1):64–72.
102 Luhmann HJ, Sinning A, Yang JW, Reyes-Puerta V, Stüttgen MC, Kirischuk S, et al. Spontaneous neuronal activity in developing neocortical networks: from single cells to large-scale interactions. Front Neural Circuits. 2016 May;10:40.
103 Kirischuk S, Sinning A, Blanquie O, Yang JW, Luhmann HJ, Kilb W. Modulation of neocortical development by early neuronal activity: physiology and pathophysiology. Front Cell Neurosci. 2017 Nov;11:379.
104 Weissman TA, Riquelme PA, Ivic L, Flint AC, Kriegstein AR. Calcium waves propagate through radial glial cells and modulate proliferation in the developing neocortex. Neuron. 2004 Sep;43(5):647–61.
105 Corlew R, Bosma MM, Moody WJ. Spontaneous, synchronous electrical activity in neonatal mouse cortical neurones. J Physiol. 2004 Oct;560(Pt 2):377–90.
106 Bando Y, Irie K, Shimomura T, Umeshima H, Kushida Y, Kengaku M, et al. Control of spontaneous Ca2+ transients is critical for neuronal maturation in the developing neocortex. Cereb Cortex. 2016 Jan;26(1):106–17.
107 Kilb W, Kirischuk S, Luhmann HJ. Electrical activity patterns and the functional maturation of the neocortex. Eur J Neurosci. 2011 Nov;34(10):1677–86.
108 Khazipov R, Sirota A, Leinekugel X, Holmes GL, Ben-Ari Y, Buzsáki G. Early motor activity drives spindle bursts in the developing somatosensory cortex. Nature. 2004 Dec;432(7018):758–61.
109 Yang JW, Reyes-Puerta V, Kilb W, Luhmann HJ. Spindle bursts in neonatal rat cerebral cortex. Neural Plast. 2016;2016:3467832.
110 Luhmann HJ, Kilb W, Hanganu-Opatz IL. Subplate cells: amplifiers of neuronal activity in the developing cerebral cortex. Front Neuroanat. 2009 Oct;3:19.
111 Kostović I, Jovanov-Milosević N. The development of cerebral connections during the first 20-45 weeks' gestation. Semin Fetal Neonatal Med. 2006 Dec;11(6):415–22.

112 Luhmann HJ. Cajal-Retzius and subplate cells: transient cortical neurons and circuits. In: Rubenstein JLR, Rakic P, editors. Cellular migration and formation of neuronal connections. Comprehensive Developmental Neuroscience. Elsevier; 2013. Chapter 45, p. 843–56.
113 Bitzenhofer SH, Ahlbeck J, Wolff A, Wiegert JS, Gee CE, Oertner TG, et al. Layer-specific optogenetic activation of pyramidal neurons causes beta-gamma entrainment of neonatal networks. Nat Commun. 2017 Feb;8:14563.
114 Luhmann HJ, Khazipov R. Neuronal activity patterns in the developing barrel cortex. Neuroscience. 2018 Jan;368:256–67.
115 Garaschuk O, Linn J, Eilers J, Konnerth A. Large-scale oscillatory calcium waves in the immature cortex. Nat Neurosci. 2000 May; 3(5):452–9.
116 McCabe AK, Chisholm SL, Picken-Bahrey HL, Moody WJ. The self-regulating nature of spontaneous synchronized activity in developing mouse cortical neurones. J Physiol. 2006 Nov;577(Pt 1):155–67.
117 Namiki S, Norimoto H, Kobayashi C, Nakatani K, Matsuki N, Ikegaya Y. Layer III neurons control synchronized waves in the immature cerebral cortex. J Neurosci. 2013 Jan; 33(3):987–1001.
118 Allène C, Cattani A, Ackman JB, Bonifazi P, Aniksztejn L, Ben-Ari Y, et al. Sequential generation of two distinct synapse-driven network patterns in developing neocortex. J Neurosci. 2008 Nov;28(48):12851–63.
119 Sipilä ST, Huttu K, Soltesz I, Voipio J, Kaila K. Depolarizing GABA acts on intrinsically bursting pyramidal neurons to drive giant depolarizing potentials in the immature hippocampus. J Neurosci. 2005 Jun;25(22): 5280–9.
120 Sipilä ST, Huttu K, Voipio J, Kaila K. Intrinsic bursting of immature CA3 pyramidal neurons and consequent giant depolarizing potentials are driven by a persistent Na+ current and terminated by a slow Ca2+-activated K+ current. Eur J Neurosci. 2006 May;23(9):2330–8.
121 Stafstrom CE. Persistent sodium current and its role in epilepsy. Epilepsy Curr. 2007 Jan-Feb;7(1):15–22.
122 Khalilov I, Minlebaev M, Mukhtarov M, Khazipov R. Dynamic changes from depolarizing to hyperpolarizing GABAergic actions during giant depolarizing potentials in the neonatal rat hippocampus. J Neurosci. 2015 Sep;35(37):12635–42.
123 Garaschuk O, Hanse E, Konnerth A. Developmental profile and synaptic origin of early network oscillations in the CA1 region of rat neonatal hippocampus. J Physiol. 1998 Feb; 507(Pt 1):219–36.
124 Griguoli M, Cherubini E. Early correlated network activity in the hippocampus: its putative role in shaping neuronal circuits. Front Cell Neurosci. 2017 Aug;11:255.
125 Benders MJ, Palmu K, Menache C, Borradori-Tolsa C, Lazeyras F, Sizonenko S, et al. Early brain activity relates to subsequent brain growth in premature infants. Cereb Cortex. 2015 Sep;25(9):3014–24.
126 Reid CA, Rollo B, Petrou S, Berkovic SF. Can mutation-mediated effects occurring early in development cause long-term seizure susceptibility in genetic generalized epilepsies? Epilepsia. 2018 May;59(5):915–22.
127 Selton D, Andre M, Hascoët JM. Normal EEG in very premature infants: reference criteria. Clin Neurophysiol. 2000 Dec; 111(12):2116–24.
128 Thomason ME. Structured spontaneity: building circuits in the human prenatal brain. Trends Neurosci. 2018 Jan;41(1):1–3.
129 Khazipov R, Milh M. Early patterns of activity in the developing cortex: focus on the sensorimotor system. Semin Cell Dev Biol. 2018 Apr;76:120–9.
130 Shany E, Berger I. Neonatal electroencephalography: review of a practical approach. J Child Neurol. 2011 Mar;26(3):341–55.
131 Biagioni E, Frisone MF, Laroche S, Kapetanakis BA, Ricci D, Adeyi-Obe M, et al. Maturation of cerebral electrical activity and development of cortical folding in young very preterm infants. Clin Neurophysiol. 2007 Jan;118(1):53–9.
132 Tokariev A, Stjerna S, Lano A, Metsäranta M, Palva JM, Vanhatalo S. Preterm birth changes networks of newborn cortical activity. Cereb Cortex. 2019 Feb;29(2):814–26.
133 Iyer KK, Roberts JA, Hellström-Westas L, Wikström S, Hansen Pupp I, Ley D, et al. Cortical burst dynamics predict clinical outcome early in extremely preterm infants. Brain. 2015 Aug;138(Pt 8):2206–18.
134 Stafstrom CE, Rho JM. Neurophysiology of seizures and epilepsy. In: Swaiman K, Ashwal S, Ferriero D, Schor N, Finkel R, Gropman A, et al., editors. Swaiman's pediatric neurology. 6th ed. Amsterdam: Elsevier; 2017. p. 506–12.
135 Miller SM, Goasdoue K, Björkman ST. Neonatal seizures and disruption to neurotransmitter systems. Neural Regen Res. 2017 Feb; 12(2):216–7.
136 Stafstrom CE, Thompson JL, Holmes GL. Kainic acid seizures in the developing brain: status epilepticus and spontaneous recurrent seizures. Brain Res Dev Brain Res. 1992 Feb;65(2):227–36.
137 Luhmann HJ, Dzhala VI, Ben-Ari Y. Generation and propagation of 4-AP-induced epileptiform activity in neonatal intact limbic structures in vitro. Eur J Neurosci. 2000 Aug;12(8):2757–68.
138 Zhang ZW. Maturation of layer V pyramidal neurons in the rat prefrontal cortex: intrinsic properties and synaptic function. J Neurophysiol. 2004 Mar;91(3):1171–82.
139 McCormick DA, Prince DA. Post-natal development of electrophysiological properties of rat cerebral cortical pyramidal neurones. J Physiol. 1987 Dec;393(1):743–62.
140 Picken Bahrey HL, Moody WJ. Early development of voltage-gated ion currents and firing properties in neurons of the mouse cerebral cortex. J Neurophysiol. 2003 Apr; 89(4):1761–73.
141 Valiullina F, Akhmetshina D, Nasretdinov A, Mukhtarov M, Valeeva G, Khazipov R, et al. Developmental changes in electrophysiological properties and a transition from electrical to chemical coupling between excitatory layer 4 neurons in the rat barrel cortex. Front Neural Circuits. 2016 Jan;10:1.
142 Moody WJ, Bosma MM. Ion channel development, spontaneous activity, and activity-dependent development in nerve and muscle cells. Physiol Rev. 2005 Jul;85(3):883–941.
143 Spitzer NC. Electrical activity in early neuronal development. Nature. 2006 Dec;444 (7120):707–12.
144 Noam Y, Bernard C, Baram TZ. Towards an integrated view of HCN channel role in epilepsy. Curr Opin Neurobiol. 2011 Dec;21(6): 873–9.
145 Monyer H, Burnashev N, Laurie DJ, Sakmann B, Seeburg PH. Developmental and regional expression in the rat brain and functional properties of four NMDA receptors. Neuron. 1994 Mar;12(3):529–40.
146 Jantzie LL, Talos DM, Jackson MC, Park HK, Graham DA, Lechpammer M, et al. Developmental expression of N-methyl-D-aspartate (NMDA) receptor subunits in human white and gray matter: potential mechanism of increased vulnerability in the immature brain. Cereb Cortex. 2015 Feb; 25(2):482–95.
147 Marret S, Gressens P, Gadisseux JF, Evrard P. Prevention by magnesium of excitotoxic neuronal death in the developing brain: an animal model for clinical intervention studies. Dev Med Child Neurol. 1995 Jun;37(6):473–84.
148 Burgard EC, Hablitz JJ. Developmental changes in NMDA and non-NMDA receptor-mediated synaptic potentials in rat neocortex. J Neurophysiol. 1993 Jan;69(1):230–40.
149 Kirson ED, Schirra C, Konnerth A, Yaari Y. Early postnatal switch in magnesium sensitivity of NMDA receptors in rat CA1 pyramidal cells. J Physiol. 1999 Nov;521(Pt 1): 99–111.
150 Hallak M, Hotra JW, Custodio D, Kruger ML. Magnesium prevents seizure-induced reduction in excitatory amino acid receptor (kainate and alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid) binding in pregnant rat brain. Am J Obstet Gynecol. 2000 Oct;183(4):793–8.
151 Kumar SS, Bacci A, Kharazia V, Huguenard JR. A developmental switch of AMPA receptor subunits in neocortical pyramidal neurons. J Neurosci. 2002 Apr;22(8):3005–15.
152 Sanchez RM, Koh S, Rio C, Wang C, Lamperti ED, Sharma D, et al. Decreased glutamate receptor 2 expression and enhanced epileptogenesis in immature rat hippocampus after perinatal hypoxia-induced seizures. J Neurosci. 2001 Oct;21(20):8154–63.

153 Briggs SW, Galanopoulou AS. Altered GABA signaling in early life epilepsies. Neural Plast. 2011;2011:527605.
154 Moshé SL, Brown LL, Kubová H, Velísková J, Zukin RS, Sperber EF. Maturation and segregation of brain networks that modify seizures. Brain Res. 1994 Nov;665(1):141–6.
155 Dehorter N, Vinay L, Hammond C, Ben-Ari Y. Timing of developmental sequences in different brain structures: physiological and pathological implications. Eur J Neurosci. 2012 Jun;35(12):1846–56.
156 Young SZ, Platel JC, Nielsen JV, Jensen NA, Bordey A. GABA(A) increases calcium in subventricular zone astrocyte-like cells through L- and T-type voltage-gated calcium channels. Front Cell Neurosci. 2010 Apr;4:8.
157 Luhmann HJ, Kirischuk S, Sinning A, Kilb W. Early GABAergic circuitry in the cerebral cortex. Curr Opin Neurobiol. 2014 Jun;26:72–8.
158 Pelkey KA, Chittajallu R, Craig MT, Tricoire L, Wester JC, McBain CJ. Hippocampal GABAergic inhibitory interneurons. Physiol Rev. 2017 Oct;97(4):1619–747.
159 Ben-Ari Y. Excitatory actions of gaba during development: the nature of the nurture. Nat Rev Neurosci. 2002 Sep;3(9):728–39.
160 Cherubini E, Griguoli M, Safiulina V, Lagostena L. The depolarizing action of GABA controls early network activity in the developing hippocampus. Mol Neurobiol. 2011 Apr;43(2):97–106.
161 Dzhala VI, Staley KJ. Excitatory actions of endogenously released GABA contribute to initiation of ictal epileptiform activity in the developing hippocampus. J Neurosci. 2003 Mar;23(5):1840–6.
162 Dzhala VI, Talos DM, Sdrulla DA, Brumback AC, Mathews GC, Benke TA, et al. NKCC1 transporter facilitates seizures in the developing brain. Nat Med. 2005 Nov;11(11):1205–13.
163 Khazipov R, Tyzio R, Ben-Ari Y. Effects of oxytocin on GABA signalling in the foetal brain during delivery. Prog Brain Res. 2008;170:243–57.
164 Plotkin MD, Snyder EY, Hebert SC, Delpire E. Expression of the Na-K-2Cl cotransporter is developmentally regulated in postnatal rat brains: a possible mechanism underlying GABA's excitatory role in immature brain. J Neurobiol. 1997 Nov;33(6):781–95.
165 Dzhala VI, Kuchibhotla KV, Glykys JC, Kahle KT, Swiercz WB, Feng G, et al. Progressive NKCC1-dependent neuronal chloride accumulation during neonatal seizures. J Neurosci. 2010 Sep;30(35):11745–61.
166 Ben-Ari Y, Khalilov I, Kahle KT, Cherubini E. The GABA excitatory/inhibitory shift in brain maturation and neurological disorders. Neuroscientist. 2012 Oct;18(5):467–86.
167 Sedmak G, Jovanov-Milošević N, Puskarjov M, Ulamec M, Krušlin B, Kaila K, et al. Developmental expression patterns of KCC2 and functionally associated molecules in the human brain. Cereb Cortex. 2016 Dec;26(12):4574–89.
168 Glykys J, Dzhala V, Egawa K, Balena T, Saponjian Y, Kuchibhotla KV, et al. Local impermeant anions establish the neuronal chloride concentration. Science. 2014 Feb;343(6171):670–5.
169 Khanna A, Walcott BP, Kahle KT. Limitations of current GABA agonists in neonatal seizures: toward GABA modulation via the targeting of neuronal Cl(–) transport. Front Neurol. 2013 Jun;4:78.
170 Painter MJ, Scher MS, Stein AD, Armatti S, Wang Z, Gardiner JC, et al. Phenobarbital compared with phenytoin for the treatment of neonatal seizures. N Engl J Med. 1999 Aug;341(7):485–9.
171 Khazipov R, Esclapez M, Caillard O, Bernard C, Khalilov I, Tyzio R, et al. Early development of neuronal activity in the primate hippocampus in utero. J Neurosci. 2001 Dec;21(24):9770–81.
172 Lee DS, Wong HA, Knoppert DC. Myoclonus associated with lorazepam therapy in very-low-birth-weight infants. Biol Neonate. 1994;66(6):311–5.
173 Ozcan B, Kavurt S, Yucel H, Bas AY, Demirel N. Rhythmic myoclonic jerking induced by midazolam in a preterm infant. Pediatr Neurol. 2015 Jun;52(6):e9.
174 Yawno T, Miller SL, Bennet L, Wong F, Hirst JJ, Fahey M, et al. Ganaxolone: a new treatment for neonatal seizures. Front Cell Neurosci. 2017 Aug;11:246.
175 Khazipov R, Valeeva G, Khalilov I. Depolarizing GABA and developmental epilepsies. CNS Neurosci Ther. 2015 Feb;21(2):83–91.
176 Pressler RM, Mangum B. Newly emerging therapies for neonatal seizures. Semin Fetal Neonatal Med. 2013 Aug;18(4):216–23.
177 Dzhala VI, Brumback AC, Staley KJ. Bumetanide enhances phenobarbital efficacy in a neonatal seizure model. Ann Neurol. 2008 Feb;63(2):222–35.
178 Cleary RT, Sun H, Huynh T, Manning SM, Li Y, Rotenberg A, et al. Bumetanide enhances phenobarbital efficacy in a rat model of hypoxic neonatal seizures. PLoS One. 2013;8(3):e57148.
179 Pressler RM, Boylan GB, Marlow N, Blennow M, Chiron C, Cross JH, et al.; NEonatal seizure treatment with Medication Off-patent (NEMO) consortium. Bumetanide for the treatment of seizures in newborn babies with hypoxic ischaemic encephalopathy (NEMO): an open-label, dose finding, and feasibility phase 1/2 trial. Lancet Neurol. 2015 May;14(5):469–77.
180 Thoresen M, Sabir H. Epilepsy: neonatal seizures still lack safe and effective treatment. Nat Rev Neurol. 2015 Jun;11(6):311–2.
181 Pressler RM, Boylan GB, Marlow N, de Vries LS, Blennow M, Chiron C, et al.; NEMO consortium (NEonatal seizure treatment with Medication Off-patent). Bumetanide for neonatal seizures-back from the cotside. Nat Rev Neurol. 2015 Dec;11(12):724–5.
182 Dzhala V, Staley K. Treatment of drug-resistant seizures with chloride extrusion enhancer CLP257. Amer Epil Soc Abstr. 2018:3.050.
183 Nave KA, Werner HB. Myelination of the nervous system: mechanisms and functions. Annu Rev Cell Dev Biol. 2014;30(1):503–33.
184 Demerens C, Stankoff B, Logak M, Anglade P, Allinquant B, Couraud F, et al. Induction of myelination in the central nervous system by electrical activity. Proc Natl Acad Sci USA. 1996 Sep;93(18):9887–92.
185 Jakovcevski I, Filipovic R, Mo Z, Rakic S, Zecevic N. Oligodendrocyte development and the onset of myelination in the human fetal brain. Front Neuroanat. 2009 Jun;3:5.
186 Bartzokis G. Age-related myelin breakdown: a developmental model of cognitive decline and Alzheimer's disease. Neurobiol Aging. 2004 Jan;25(1):5–18.
187 Back SA. White matter injury in the preterm infant: pathology and mechanisms. Acta Neuropathol. 2017 Sep;134(3):331–49.
188 Wu H, Xiong WC, Mei L. To build a synapse: signaling pathways in neuromuscular junction assembly. Development. 2010 Apr;137(7):1017–33.
189 Dent EW, Gupton SL, Gertler FB. The growth cone cytoskeleton in axon outgrowth and guidance. Cold Spring Harb Perspect Biol. 2011 Mar;3(3):a001800.
190 de Vries JI, Fong BF. Normal fetal motility: an overview. Ultrasound Obstet Gynecol. 2006 Jun;27(6):701–11.
191 O'Leary H, Bernard PB, Castano AM, Benke TA. Enhanced long term potentiation and decreased AMPA receptor desensitization in the acute period following a single kainate induced early life seizure. Neurobiol Dis. 2016 Mar;87:134–44.
192 Pinchefsky EF, Hahn CD. Outcomes following electrographic seizures and electrographic status epilepticus in the pediatric and neonatal ICUs. Curr Opin Neurol. 2017 Apr;30(2):156–64.
193 van Rooij LG, Toet MC, van Huffelen AC, Groenendaal F, Laan W, Zecic A, et al. Effect of treatment of subclinical neonatal seizures detected with aEEG: randomized, controlled trial. Pediatrics. 2010 Feb;125(2):e358–66.
194 Zhou C, Lippman JJ, Sun H, Jensen FE. Hypoxia-induced neonatal seizures diminish silent synapses and long-term potentiation in hippocampal CA1 neurons. J Neurosci. 2011 Dec;31(50):18211–22.
195 Trevelyan AJ. Do cortical circuits need protecting from themselves? Trends Neurosci. 2016 Aug;39(8):502–11.
196 Isaeva E, Isaev D, Khazipov R, Holmes GL. Selective impairment of GABAergic synaptic transmission in the flurothyl model of neonatal seizures. Eur J Neurosci. 2006 Mar;23(6):1559–66.
197 Lippman-Bell JJ, Zhou C, Sun H, Feske JS, Jensen FE. Early-life seizures alter synaptic calcium-permeable AMPA receptor function and plasticity. Mol Cell Neurosci. 2016 Oct;76:11–20.

198 Dwyer BE, Wasterlain CG. Electroconvulsive seizures in the immature rat adversely affect myelin accumulation. Exp Neurol. 1982 Dec;78(3):616–28.
199 Casanova JR, Nishimura M, Swann JW. The effects of early-life seizures on hippocampal dendrite development and later-life learning and memory. Brain Res Bull. 2014 Apr;103:39–48.
200 Holmes GL, Gairsa JL, Chevassus-Au-Louis N, Ben-Ari Y. Consequences of neonatal seizures in the rat: morphological and behavioral effects. Ann Neurol. 1998 Dec;44(6):845–57.
201 Thibeault-Eybalin MP, Lortie A, Carmant L. Neonatal seizures: do they damage the brain? Pediatr Neurol. 2009 Mar;40(3):175–80.
202 Karnam HB, Zhou JL, Huang LT, Zhao Q, Shatskikh T, Holmes GL. Early life seizures cause long-standing impairment of the hippocampal map. Exp Neurol. 2009 Jun;217(2):378–87.
203 Stafstrom CE, Chronopoulos A, Thurber S, Thompson JL, Holmes GL. Age-dependent cognitive and behavioral deficits after kainic acid seizures. Epilepsia. 1993 May-Jun;34(3):420–32.
204 Jensen FE, Holmes GL, Lombroso CT, Blume HK, Firkusny IR. Age-dependent changes in long-term seizure susceptibility and behavior after hypoxia in rats. Epilepsia. 1992 Nov-Dec;33(6):971–80.
205 Egorov AV, Draguhn A. Development of coherent neuronal activity patterns in mammalian cortical networks: common principles and local hetereogeneity. Mech Dev. 2013;130(6-8):412–23.
206 Owens DF, Kriegstein AR. Patterns of intracellular calcium fluctuation in precursor cells of the neocortical ventricular zone. J Neurosci. 1998 Jul;18(14):5374–88.
207 Uhlén P, Fritz N, Smedler E, Malmersjö S, Kanatani S. Calcium signaling in neocortical development. Dev Neurobiol. 2015 Apr;75(4):360–8.
208 Minlebaev M, Ben-Ari Y, Khazipov R. Network mechanisms of spindle-burst oscillations in the neonatal rat barrel cortex in vivo. J Neurophysiol. 2007 Jan;97(1):692–700.
209 Tolner EA, Sheikh A, Yukin AY, Kaila K, Kanold PO. Subplate neurons promote spindle bursts and thalamocortical patterning in the neonatal rat somatosensory cortex. J Neurosci. 2012 Jan;32(2):692–702.
210 Minlebaev M, Colonnese M, Tsintsadze T, Sirota A, Khazipov R. Early γ oscillations synchronize developing thalamus and cortex. Science. 2011 Oct;334(6053):226–9.
211 Ben-Ari Y, Cherubini E, Corradetti R, Gaiarsa JL. Giant synaptic potentials in immature rat CA3 hippocampal neurones. J Physiol. 1989 Sep;416(1):303–25.