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The Brain, Seizures and Epilepsy Throughout Life: Understanding a Moving Target

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The human brain is a tremendously complex and still enigmatic three-dimensional structure, composed of countless interconnected neurons and glia. The temporal evolution of the brain throughout life provides a fourth dimension, one that influences every element of the brain's function in health and disease. This temporal evolution contributes to the probability of seizure generation and to the type and the nature of these seizures. The age-specific properties of the brain also influence the consequences of seizures on neuronal structure and behavior. These, in turn, govern epileptic activity and cognitive and emotional functions, contributing to the diverse consequences of seizures and epilepsy throughout life.

The Scope of the Problem

The incidence of seizures and of epilepsy varies throughout life, peaking in neonates and children and increasing again after the age of 50 (1–4). In addition to the quantitative measure of the incidence of seizures, the type of seizures (and of epilepsy syndromes) varies with age: for example, febrile seizures take place in infants and children (1, 5–7), whereas the incidence of post-stroke epilepsy increases in adults compared with children (1, 3, 8). What is the basis of these age-dependent variations? What are the age-specific properties of the brain that contribute to the probability of seizure generation and to the nature of the resulting seizure?

A second, reciprocal aspect of the interaction of the age of the brain and seizures involves the effects of a seizure on the structure and function of neurons and neuronal networks. Here, again, clinical evidence suggests that the consequences of a seizure might vary with age. For example, the consequences of status epilepticus (SE) in young children seem to depend on the inciting etiology (9, 10), and, in general, mortality and cognitive outcomes are more favorable than in the adult and elderly individual (11–14). In contrast, status epilepticus in adult and aging individuals can have major detrimental effects on cognitive function and even survival (14–16). What is the basis of these age-dependent variations? What are the age-specific properties of the brain that modulate the effects of seizures on neuronal integrity and function?

These questions are of paramount clinical importance because they should provide clues for developing age-specific diagnostic tools, prognostic models, and intervention strate-

gies. Thus, while the answers to these questions are not fully elucidated, the questions provide a framework for discussing the salient elements of the evolving interaction between the brain and seizures throughout life.

The following paragraphs highlight a few of the many facts that influence age-specific seizures and the age-specific consequences of seizures. Because most of the direct information about seizures throughout the life-span often derives from animal models, these are discussed. The author regrets that this overview is not comprehensive and likely omits a number of important publications. Nonetheless, this review serves to illustrate crucial features of the topic.

Age-Specific Brain Properties Influence Seizures That Are Generated During Each Age

Whereas brain development from embryonic life to senescence is a continuum, here it is divided into four stages: the neonatal, childhood, adulthood, and aging epochs.

The Neonatal Brain and Age-Specific Neonatal Seizures

The neonatal brain is in a stage of rapid flux from both structural and functional perspectives. Neurons are still being born, circuits are being formed, and synapses are being established (17, 18). Synaptic currents are often slower (19), neurotransmitters play trophic roles (20), and circuits are not fully mature (21). These facts predict that seizures may propagate poorly and may thus remain subclinical, or manifest as fragmented motor activity (22, 23).

From a molecular standpoint, there are developmental changes in both excitatory and inhibitory neurotransmission (24–34) excitatory and inhibitory components of synaptic transmission do not develop concurrently (33, 35). GABAergic synapses seem to be the first to function (36). In addition, GABA receptor subunit expression is developmentally regulated and is relatively low during development (30), whereas



glutamate receptor expression is high, favoring robust neurotransmission in excitatory synapses.

Indeed, both presynaptic and postsynaptic elements of glutamatergic synapses undergo developmental changes that favor hyperexcitability in the neonatal period: glutamate transporter expression is low, increasing glutamate levels at synapses. In addition, the developmental characteristics of all three types of the major glutamate receptors, NMDA, AMPA, and metabotropic, favor augmented glutamatergic neurotransmission (31–33). Together, all of the facts described above contribute to the observed facility in which insults such as hypoglycemia or hypoxia generate seizures in the neonate, and to the fragmentary nature of many neonatal seizures.

The Child's Brain and Age-Specific Seizures

Animal models have been instrumental in elucidating the changes in excitability and seizure vulnerability during the developmental transition from the neonatal to the childhood periods. In this context, it is helpful to note the complexity of comparing developmental status of human and rodent brain. A useful approach is to focus on a single region or circuit and assess multiple developmental processes, such as neurogenesis, synaptogenesis, dendritic growth, and functional maturity across species (see table in Avishai-Eliner et al. [37] for such comparison of rat, monkey, and human hippocampus). This approach enables studying the role of specific stages of maturation of a given brain region on the susceptibility to seizures and the generation of specific seizure types (38–42). Insight from non-human work has suggested that the child's limbic circuit is characterized by an overshoot of axons in some hippocampal pathways (43), and an accompanying overshoot of excitatory synapses and glutamate receptors (31, 32). This apparent augmented excitability is combined with the susceptibility of young children to sustain fever and febrile seizures as well as trauma and infections. Hence, typical seizures in the child include febrile (5, 44, 45) and traumatic (46) seizures, as well as other reactive or provoked seizures. Increasing maturation of neuronal circuits supports rapid propagation and often severe seizures in this age group (41, 42).

The Mature Brain: Sex-Specific Properties and Seizures

The spurt in the release of sex hormones that accompanies puberty and adolescence contributes to structural and functional neuronal changes and further maturation of neuronal circuits. Sex-dependent dimorphism further arises in numerous brain regions and circuits (47–49). In addition to the arrival of sex hormones from the gonad and other peripheral sources, sex hormones are also synthesized within brain regions including the hippocampus (50). The effects of the female sex hormones on neuronal excitability are complex. Estrogen is generally believed to promote excitability (51) as well as augmented synaptic plasticity (e.g., [52]). In contrast, progesterone-derived neurosteroids augment GABA_A receptor function (48, 53, 54). The cyclical nature of hormonal release during the menstrual cycle in women promotes cyclical or catamenial seizures and epilepsy, often complicating the management of seizures in women (47, 51). In analogy to the female sex hormones, the effects of testosterone—directly and indirectly—on neuronal excitability are complex (55, 56).

How Aging Influences Seizures

The incidence of seizures increases in the middle-aged and the elderly (57, 58). This is a result, in part, of the increased incidence of tumors and cerebrovascular diseases including stroke (3). In addition, there are likely intrinsic processes within the aging brain that might promote susceptibility to seizures. For example, an increasingly recognized source of the increased incidence of seizures in the aging brain may derive from increased accumulation of the molecules Tau and amyloid beta. It has been shown that these compounds may interact to influence excitability at several levels (59, 60), thus influencing excitability in both normal and dementing aging individuals. Much more work remains to be done to explain and hopefully prevent the human observational studies on increased seizure susceptibility during aging (61). The nature of seizures in the elderly might differ from those observed earlier in the life cycle. Partial complex seizures may be confused with “senior” moments, and a number of additional factors contribute to the complexity of diagnosing seizures in the elderly (62).

Age-Specific Brain Properties Influence the Consequences of Seizures at Different Ages

The Neonatal Brain: Specific Vulnerabilities to the Effects of Seizures

The neonatal brain is in a stage of rapid flux from both a structural and a functional perspective. As mentioned above, neurons are still being born, circuits are being formed, and synapses continue to be established and mature. Many of these processes are activity dependent, in that they are influenced by synaptic communication. For example, activation of certain synapses is believed to strengthen them at the expense of nonactive synapses that are pruned (63, 64). Clearly, then, a burst of abnormal neuronal activity (a seizure) has the potential to disrupt this activity-dependent process, leading to aberrant hyperexcitable or hypo-excitable circuit. At the structural level, excitatory synapses reside on dendritic spines (65); spine size and integrity, as well as the integrity of the dendrites that carry the spines, are activity dependent (66–69). These observations suggest that seizures might influence the structure of spines and dendrites during development, resulting in stunted, dysfunctional neurons (70–73).

At the molecular level, seizures during the neonatal and infancy periods modify neurotransmission through several mechanisms. Neonatal seizures may directly influence the effects of activation of GABA-A receptors (74–77) and alter receptor expression at both excitatory and inhibitory synapses. For example, such seizures modify the expression of glutamate receptors of various types (78–81), GABA receptors (82), and a number of additional important ion channels (83–86). Notably, both the structural and molecular changes provoked by neonatal seizures might be persistent (87, 88).

Excitotoxicity Throughout the Life Cycle

In both human and animal models, prolonged seizures and status epilepticus appear to result in loss of specific neuronal populations in hippocampus and the hilus of the dentate gyrus (89–94), as well as other vulnerable brain regions (for examples, see Cavalheiro et al. [90], Motte et al. [93], Pitkänen



et al. [95], and Kubová et al. [96]). However, the majority of evidence suggests that even prolonged seizures and SE are less likely to provoke cell death during development (70, 71, 97–102). Reorganization of neuronal connectivity is another common outcome of seizures in the mature brain. Typical is axonal “sprouting” and the formation of new synapse (103–107). This process, which might be driven in part by the loss of neuronal targets of the affected axons, is also more attenuated during development (108, 109). Subtle changes in neuronal structure, including loss of dendritic spines and synapses (70, 110), with potential loss of hippocampal volume (111) are found. Thus, during the developmental stages of infancy and childhood, rodent brain seems more resilient to seizure-induced excitotoxicity. However, the age-specific mechanisms responsible for this relative resilience are not fully understood.

Understanding why neurons in hippocampus and other vulnerable regions do not die, when the inciting seizures are prolonged and severe is of paramount clinical importance. The underlying mechanisms might enable future protection of neurons in the adult brain from seizure-provoked death. One potential mechanism for this resilience of neurons in immature brain to long seizures and status epilepticus is the relatively mild inflammation in response to seizures during development (112, 113). This is in contrast to the adult, where cytokines and related mediators are both released from injured cells and contribute to neuronal death (113). A second mechanism might involve the resilience of mitochondria in the immature brain to accumulation of reactive oxygen species (ROS), which promotes mitochondrial injury and cell death (114, 115). During adult SE, metabolic demand in neurons results in the formation of ROS and overwhelming of mitochondrial function. In contrast, mitochondria in immature brain are partially uncoupled due to the high basal expression of the mitochondrial uncoupling protein 2 (UCP2). This protein reduces mitochondrial membrane gradient, prevents ROS accumulation, and protects from seizure-induced cell loss (116, 117). Other properties of the developing brain, potentially including higher levels of BDNF and other growth factors might protect neurons from excitotoxic injury.

Notably, the paucity of cell loss does not indicate that seizures during infancy or childhood do not have significant sequelae. Indeed, a large body of existing and emerging literature suggests that functional (45, 118) as well as structural changes in neurons may be induced by seizures throughout life, and may contribute to cognitive deficits and emotional dysfunction (119).

Cognitive Vulnerability During Aging

An important correlate (comorbidity) of seizures and epilepsy involves cognitive deficits (110, 120–122). In humans, it is more difficult to discern the relationship of the epilepsy and the cognitive defects (122). Temporal lobe or limbic seizures propagate through the same neuronal pathways that are engaged in learning and memory processes (111). Thus, seizures might directly cause such problems; alternatively, the abnormalities that result in the seizures might independently provoke cognitive dysfunction. Work in experimental animal models demonstrated that seizures, and even interictal activity, reduce cognitive performance (118). Indeed, in both humans and ani-

mals, rapid seizure-induced injury to dendritic spines and the synapses that they carry might underlie some of the cognitive effects of epileptic activity (123).

During aging, whereas there does not seem to be a major reduction in the numbers of hippocampal neurons, spine density is reduced in pyramidal cells. This finding, reported in aging monkeys, suggests that the number of synapses is also reduced (124). This loss of functional excitatory synapses might be a basis for reduced cognitive reserve in the aging brain. The aging brain may thus be more vulnerable to seizure-induced loss of additional synapses. Other factors that contribute to vulnerability to cognitive loss that might be provoked by seizures include an established, age-dependent accumulation of mitochondrial injury (125). In addition, there is an accumulation of beta amyloid and tau, as described above. These factors, and probably many additional ones that are as yet unknown, combine to exacerbate the potential consequences of seizures on the aging brain.

Summary

The brain evolves throughout life, and this evolution contributes to the probability of the occurrence of seizures, as well as to their type. In addition, the consequences of seizures are significantly influenced by age-specific properties of the brain. Understanding the unique features of the neonatal, child, adult, and aging brain is crucial for optimal diagnosis and treatment of both seizures and their consequences.

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