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Hoyer Lecture Epilepsy in Children: Listening to Mothers

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Abstract

The incidence of epilepsy is significantly higher in children than adults. When faced with the diagnosis of epilepsy, parents have many questions regarding cause, treatment and prognosis. While the majority of children with epilepsy have an excellent prognosis and respond well to therapy, some children are refractory to therapy and suffer from cognitive decline. Animal models are now providing insights into the mechanisms responsible for the high incidence of seizures during development and age-dependent seizure-induced damage. One of the causes of the increased susceptibility of the young brain to seizures is the depolarizing effects of GABA secondary to high intracellular concentrations of chloride in young neurons. While cell loss is not a feature of seizures in the young brain, recurrent seizures do result in aberrant sprouting of mossy fibers, reduce neurogenesis, and alter excitatory and inhibitory neurotransmitter receptor structure and function. Behavioral consequences of early-life seizures include impaired spatial cognition, which now can be assessed using single cell recordings from the hippocampus. Antiepileptic drugs have had a tremendous positive influence in epilepsy management although there are now a number of studies demonstrating that antiepileptic drugs at therapeutic concentrations can impair cognition and result in increased apoptosis. While clinical judgment and experience is paramount when discussing the consequences of seizures and their treatment, awareness of studies from animals can provide the clinician with guidance in addressing these important issues with parents.

Introduction

"Your child has epilepsy"

This is one of the most frightening phrases a parent can hear from their physician. To many parents, the term epilepsy carries serious negative connotations and raises serious concerns about their child's future. While many of the parents' fears are unfounded, there is no question that a child with epilepsy has profound effects on the entire family. Epilepsy is a chronic disorder and parents have to deal with the condition 24 hours a day, seven days a week. Because we live in a society where the father often works and is out of the home for much of the day mothers often assume the primary responsibility for the medical care of their child. The child's healthcare worker therefore spends a considerable amount of time talking to mothers about their child.

In this review article I will address a few of the many questions mothers ask, emphasizing where basic neuroscience research can help provide answers. These questions include: 1. Why

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does my child have seizures?; 2. Are seizures harmful to my child's brain?; and 3. Are antiepileptic drugs harmful?

1. Why does my child have seizures?

There is a high incidence of seizures during the first months and years of life [2]. The highest risk period occurs at the time of birth. The infant is at considerable risk for a number of insults during the birthing process including trauma, hypoxic-ischemic insults, intracranial hemorrhages, and infection. In addition, a large number of pathological processes occurring in neonates may present initially with seizures. For example, congenital brain anomalies, inborn errors of metabolism, and genetic conditions may lead to recurrent seizures during the neonatal period.

The enhanced risk of seizures in the young brain is not only related to environmental insults, but also to a propensity for the immature brain to have a lower seizure threshold than the mature brain. Animal models have paralleled the clinical situation demonstrating that the immature brain is quite susceptible to seizures elicited by a number of chemoconvulsants and electrical stimulation (reviewed in [3]).

While there are likely multiple factors responsible for increasing the susceptibility of the young brain to seizures, a considerable focus has been on excitatory and inhibitory neurotransmission as a factor of age. It is likely that the enhanced excitability of the immature brain relates to the sequential development and expression of excitatory and inhibitory signaling pathways. In the adult brain, glutamate is the primary excitatory neurotransmitter and γ-amino-butyric acid (GABA), the principal inhibitory transmitter. Excitatory synaptic transmission is mediated by glutamate that is released from the pyramidal neurons and depolarizes and excites the target neurons via ionotropic receptors N-methyl-D-Aspartate (NMDA), α-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid (AMPA), and kainic acid (KA). Fast inhibition is through $GABA_A$ activation while $GABA_B$ provides a slower and longer inhibition.

During fetal development GABAergic synapses develop before glutamatergic synapses [4]. During the early postnatal period, at a time when the immature brain is highly susceptible to seizures [5,6], GABA exerts a paradoxical excitatory action [5,7] in the immature brain because of a larger intracellular concentration of Cl^- in immature neurons than mature ones [8-10] (Fig. 1). The shift from a depolarizing to a hyperpolarizing Cl^- current occurs in an extended period depending on the age and developmental stage of the structure. The shift is mediated by an active Na^+-K^+-$2Cl^-$ co-transporter (NKCC1) that facilitates the accumulation of Cl^- in neurons and a delayed expression of a K^+-Cl^- co-transporter (KCC2) that extrudes Cl^- to establish adult concentrations of intracellular Cl^- [11]. The depolarization by GABA of immature neurons is sufficient to generate Na^+ action potentials and to remove the voltage dependent Mg^{2+} blockade of NMDA channels and activate voltage-dependent Ca^{2+} channels, leading to a large influx of Ca^{2+} that in turn triggers long term changes of synaptic efficacy. The synergistic action of GABA with NMDA and Ca^{2+} channels is unique to the developing brain and has many consequences on the impact of GABAergic synapses on the network. In addition, agents that interfere with the transport of Cl^- exert an anti-epileptogenic action [11]. With maturation there is increasing expression of KCC2 and decreasing function of NKCC1, a transporter that brings Cl^- into the cell which results in an inhibitory effect of GABA. The lack of an efficient time-locked inhibition, the delayed maturation of postsynaptic $GABA_B$ mediated currents and the high input resistance of immature neurons will facilitate the generation of action potentials and synchronized activities [12,13].

Another cause of the increased susceptibility of the immature brain to seizures is overabundance of excitatory neurotransmission receptors [14-16]. With maturation, axonal collaterals and attendant synapses regress [17].

N-methyl-D-aspartate NMDA receptors are heteromeric with an obligate NR1 subunit. In the immature brain the predominant NR2 subunit is the NR2B subunit [18]. The NMDA receptor is a complex one which has characteristics of both ligand- and voltage-gated channel. The ion Mg^{2+} lies in the pore of the channel, preventing permeability of Na^{+} and Ca^{2+} ions. When Mg^{2+} is released from the pore by membrane depolarization, the flow of Na^{+} and Ca^{2+} ions can occur. Compared to the NR2A subunit, which is highly expressed on mature neurons, NR2B units have a reduced Mg^{2+} sensitivity, resulting in enhanced excitability [19]. The NR2C, NR2D, and NR3A subunits also are increased in the first two postnatal weeks [20]. The ontogeny of the postsynaptic density (PSD), a cytoskeleton specialization at the synapse composed of glutamate receptors, molecular scaffolding and cell adhesion molecules, parallels the ontogeny of NMDA receptors with substantial decreases in NR2B and increases in NR2A and PSD during development [21].

The AMPA receptor is primarily responsible for fast excitatory neurotransmission. The AMPA receptor rapidly responds to glutamate with opening of the channel to allow Na^{+} to enter the cell and depolarize the membrane. This influx of Na^{+} is sufficient to allow the displacement of Mg^{2+} from the NMDA channel and allow Na^{+} and Ca^{2+} ions to enter the cell through the NMDA receptor. AMPA receptors are heteromeric and made up of four subunits, including combinations of the GluR1-4 subunits [19]. In the immature rodent and infant human brain AMPA receptors lack the GLuR2 subunit and are Ca^{2+} permeable [22-24]. Enhanced Ca^{2+} permeability enhances excitability and results in an increase in the likelihood of seizures.

In summary, the immature brain's high susceptibility for seizures can be explained by the morphological and physiological events occurring during early life. The overabundance of synaptic connections, the increased intracellular Cl^{-} resulting in a depolarizing effect of GABA, and the over-expression of AMPA and NMDA receptors with a composition that enhances excitability of neuronal networks, and the lack of developed inhibitory networks leads to a situation were the immature brain is at high risk for seizures.

2. Are seizures harmful to my child's brain?

Because the etiology of epilepsy can result in both seizures and cognitive impairment, it is not surprising that IQ scores of children with epilepsy are lower than the IQs in a control population of children [26,27]. In addition, the number of children experiencing difficulties in school because of learning disabilities is substantially greater than in the normal population [28-31]. However, some children with epilepsy slow in their mental development over time [27] or even have progressive declines of IQ on serial intelligence tests [32]. Children with medically refractory epilepsy are at particularly high risk for cognitive impairment [33-35].

Determining the pathophysiological basis for cognitive impairment in children has been a challenge because it is difficult to distinguish between the many variables that could contribute to the cognitive impairment. Genetics, etiology, age of onset, seizure frequency, duration, and severity, and antiepileptic drug therapy may all play a role in cognitive dysfunction. Since these variables are very difficult to control clinically, animal studies can be used to tease out which factors are responsible for seizure-related cognitive impairment.

In adult animals, prolonged or frequent seizures cause neuronal loss in hippocampal fields CA1, CA3, and the dentate hilus [36-39] and subsequent sprouting of mossy fibers [39,40]. As discussed above, the threshold for seizure generation is lower in immature brains than in adults. However, developing neurons are less vulnerable, in terms of neuronal damage and cell loss, than mature neurons. It takes a longer anoxic episode to irreversibly kill cells in young animals than older animals [41]. Likewise, young animals are far less vulnerable to cell loss in the hippocampus following a prolonged seizure [42-46] or recurrent seizures, particularly during the first two weeks of life [47-49].

While neonatal seizures do not result in cell loss, recurrent seizures result in spine loss in CA3 pyramidal cells [50] and sprouting of mossy fibers [47,51-53]. The mossy fiber sprouting differs significantly from the sprouting seen after status epilepticus in adult rats, occurring primarily in the CA3 pyramidal cell layer [54]. Neurogenesis also can be reduced by early-life seizures [55].

Recurrent early-life seizures have been shown to result in immunohistological alterations of glutamate [53,56] and GABA subunit expression [57]. Neonatal seizures can result in reductions in glutamate receptor 2 (GluR2) mRNA expression and protein levels [58], selective reduction in the membrane pool of glutamate receptor 1 subunits, decreases in the total amount of NMDA receptor 2A [59], and reductions in the excitatory amino acid carrier 1 (EAAC1) [58].

Early life seizures may also alter GABAergic neurotransmission. Rats subjected to lithium-pilocarpine-induced seizures at postnatal day 10 show long-term $GABA_A$ receptor changes including a two-fold increase in the alpha1 subunit expression (compared with lithium-injected controls) and enhanced type I benzodiazepine augmentation, findings that are different from the adult animal where status epilepticus results in reductions of the α1 subunit [60]. Persistent decreases in GABA current amplitudes in the hippocampus in rats also occur following neonatal seizures [61].

Effects of Neonatal Seizures on Cognition

In addition to these morphological changes, animal studies have shown that recurrent seizures result in cognitive impairment. Using a variety of techniques to induce seizures investigators have found that rats subjected to a series of seizures during the first weeks of life have considerable cognitive impairment when the animals are studied during adolescence or adulthood [47,48,51-54,59,62,63].

Long-term potentiation of synaptic transmission in the hippocampus is the primary experimental model for investigating the synaptic basis of learning and memory in vertebrates [64]. In experimental models LTP is induced by a high frequency (titanic) stimulation. Following this stimulation the post-synaptic response increases substantially compared to before the tetanic stimulation. Such an enhancement in synaptic efficiency can last for hours. Recurrent early-life seizures using either flurothyl [65] or kainic acid [59] have previously been shown to result in reduced LTP. The opposite of LTP, long-term depression (LTP) has been shown to be enhanced by recurrent neonatal seizures [59].

Rats with neonatal seizures show impairment of spatial memory in the water maze with longer times to find the platform than controls [47,48,51,66]. These deficits are present when the rats are tested either during adolescence or when fully mature. Likewise, recurrent pentylenetetrazol [52] and hyperthermic [62,67] seizures during early development result in subsequent impairment in visual-spatial memory. Impairment of auditory discrimination following early-life seizures has also been reported [68].

The cellular concomitants of spatial memory impairment can be studied using firing patterns of single hippocampal neurons. Certain cells are activated selectively when the animal moves through a particular location in space (the ‘place field’) (Fig. 2). Firing fields are stable over days to weeks as long as the environment remains constant, suggesting that place cells retain information about location rather than creating it *de novo* each time the rat enters the environment [69-72]. The hippocampus is proposed to function as a spatial map [73]. As shown by studies showing the association between place cell firing patterns and spatial performance [1,67,74,75], place cell function appears to be a robust surrogate biological marker for spatial memory.

We recorded the activity of place cells from hippocampal subfield CA1 in freely moving rats subjected to 100 brief flurothyl-induced seizures during the first weeks of life and then tested them in the Morris water maze followed by place cell testing [66]. Rats with recurrent seizures had marked impairment in the Morris water maze when compared to control rats. In parallel, there were substantial deficits in action potential firing characteristics of place cells with two major defects: i) The coherence, which provides a measure of the precision of the firing field, firing rate, and field size were reduced compared to control cells (Fig. 3); and ii) The fields were less stable than those in control place cells. These results show that recurrent seizures during early development are associated with significant impairment in spatial learning and that these deficits are paralleled by deficits in the hippocampal map.

This study thus provides a cellular explanation for how recurrent seizures during early development lead to cognitive impairment and adds to the increasing evidence that seizures during early development have long-term adverse effects on cognitive function and these cognitive changes are reflected at the single cell level. This study, and others [1,74-77], confirms that abnormalities in place cell firing patterns are predictive of deficits in spatial cognition.

While place cells are a powerful single cell surrogate marker for spatial cognition, they do not fire in isolation. Information from multiple areas of the cortex, including visual and somatosensory cortex send afferent fibers to the hippocampus. Information is transferred through hippocampal oscillations. The oscillatory modulation of place cell firing is crucial for temporal coding information. Oscillations in brain structures provide temporal windows that bind cooperating neuronal assemblies for the representation, processing, storage and retrieval of information. Theta rhythm (4-10 Hz) is critically involved in memory function of the hippocampus [78,79]. Information arriving with theta oscillations is stored in the hippocampus, whereas information arriving in the absence of theta is not encoded, or encoded with less precision [78,80,81]. Likewise, gamma oscillations (30-100 Hz) have been implicated in complex function including the processing or perceiving of sensory information [82,83], consciousness [84,85] and storage of immediate memories [86-88].

Hippocampal, pyramidal cells are characterized by their precise temporal firing relationship with hippocampal theta oscillations [1,87,89-91]. When the firing field is entered by the rat, place cells will fire preferentially on the peak of the CA1 recorded theta cycle (Fig. 4). As the rat crosses the field, the cells fire earlier on successive theta peaks (Fig. 4C and 4D). This phenomenon is called phase precession [91,92]. Because of this characteristic, two cells with partially overlapping fields will fire at a specific, but different phase of the ongoing theta cycle. Their relative firing interval will be constant and directly related to the distance separating their fields (Fig. 5). As a result, the sequence of events experienced by the animal, as well as its timing is encoded: the time difference between action potentials is observed on a large time scale (the time it takes to get from field A to field B) and also in the order of tens of milliseconds. The firing sequences of cell assemblies are compressed in a time window short enough to induce LTP-like synaptic changes [93,94]. Using these measurements, a time compression index can be defined, for all possible pairs of cells, as the ratio of two spike timing measures: 1) The time necessary for the animal to go from one field to the other; and 2) The equivalent compressed time in the theta domain, i.e., the time lag between the spikes of the two corresponding place cells within one theta cycle [95]. We have previously shown that adult rats subjected to status epilepticus have aberrant phase precession and impaired time compression of firing among pairs of neurons [1], together with marked deficits in the Morris water maze.

In summary, seizures during early development in rodents result in long-standing cognitive impairment, aberrant mossy fiber sprouting in the CA3, reduced neurogenesis, alterations in

the expression and distribution of glutamate and GABA receptors, and physiological evidence for enhanced excitability. How these alterations in synaptic organization, neurogenesis, and receptor function result in cognitive impairment is not clear.

3. Are antiepileptic drugs harmful?

A major concern of mothers is what the antiepileptic drugs do to their child. While there are a host of animal studies examining the effects of various antiepileptic drugs (AEDs) in adult animals, there is remarkably little data regarding the effects of AEDs on the developing brain.

Phenobarbital—Because of its long history, phenobarbital is one of the oldest AEDs available and one of the most studied drugs. The drug has been given both prenatally to pregnant dam and postnatally to rat pups. The offspring of pregnant mice treated with phenobarbital are more hyperactive [96,97], habituate less rapidly than control offspring to the open field [96] and have impaired performance in operant behavior [98]. When studied as adults, mice exposed to phenobarbital have deficits in the hippocampal eight-arm maze, spontaneous alternations, and water maze performance [99].

To examine the long-term effects of phenobarbital following status epilepticus Mikati and colleagues [100] administered phenobarbital or saline chronically to animals that had undergone kainic acid-induced status epilepticus at postnatal day (P) 35. Therapy with daily phenobarbital administered at therapeutic concentrations was started directly before or one day after the status epilepticus and was continued for four months. Rats receiving phenobarbital had therapeutic concentrations during most of the 24-hour dosing period. The animals were subsequently tested using the water maze (a measure of spatial memory), open field (a measure of activity level), and handling tests (a measure of emotionality). Rats that received phenobarbital prior to status epilepticus had a shorter and less severe status epilepticus as compared to the rats given kainic acid alone. Rats starting phenobarbital immediately before kainic acid was administered did not differ from control rats on behavioral testing and had no subsequent spontaneous recurrent seizures and no histological lesions. Rats receiving kainic acid alone had significantly poorer performance than did control rats in the water maze, were more aggressive, had histological lesions, and manifested spontaneous recurrent seizures. Compared to the group treated only with kainic acid, rats receiving kainic acid followed by phenobarbital had even greater disturbances in memory, learning, and activity level.

Administration of phenobarbital to rat pups results in significant decreases in brain weight, DNA, RNA, protein, and cholesterol concentrations [97,101] and reduced neuronal number [102-104]. Chronic exposure of cultured mouse spinal cord neurons to phenobarbital leads to reduced cell survival, and decreased length and number of dendrite branches [105,106]. Brain concentration of dopamine and norepinephrine was reduced and the uptake of dopamine, norepinephrine, serotonin and GABA into synaptosomal preparations of brain tissue were greater for offspring of pregnant mice treated with phenobarbital [107]. Phenobarbital given to rat pups prenatally [108,109] or postnatally [110] result in apoptosis and subsequent cognitive impairment.

Phenytoin—Surprisingly little is known about its effects on cognitive function in animals [111]. Phenytoin given to pregnant mothers can produce vestibular dysfunction, hyperactivity, impaired startle responses, and deficits in learning and memory in the offspring [112-114]. The AED-induced dysfunction in rats is related both to the dose and duration of phenytoin exposure with greater deficits with exposure to higher doses for a longer duration. Phenytoin results in apoptosis when administered to rat pups [110].

Valproate acid—Valproate appears to have beneficial effects following status epilepticus. To study the long-term effects of valproate on the developing brain following status epilepticus, Bolanos et al. [115] administered a convulsant dose of kainic acid to rats on P35. From P36-75 rats received daily injections of phenobarbital, valproate or saline, and spontaneous seizure frequency was monitored with video recordings. After tapering of the drugs, the rats were tested in the water maze and handling tests. In the phenobarbital and saline-treated groups, there was impaired learning in the water maze, increased emotionality, recurrent seizures, and histological lesions in the hippocampal areas CA3, CA1, and dentate hilus. However, VPA-treated rats had no spontaneous seizures, abnormalities in handling, or deficits in spatial learning, and had fewer histological lesions than animals receiving kainic acid alone. The study demonstrated that VPA treatment after kainic acid-induced status epilepticus in young rats prevented many of the neurological sequelae typically seen after kainic acid administration. In addition, rats without a history of status epilepticus treated with valproate did not differ from control rats in any of the behavioral tests or histological examination. Like a number of other drugs, valproate results in apoptosis when given to rat pups [110].

Gabapentin—Gabapentin has been shown to have beneficial effects on learning and behavior. Following kainic acid-induced status epilepticus in prepubescent rats (P35) gabapentin was administered twice daily from P36-P75 [116]. Following tapering of the drugs, the rats were tested in the water maze and open-field, a test that measures activity level. In animals treated with gabapentin following status epilepticus there was a reduced incidence of spontaneous recurrent seizures and reduced status epilepticus-associated hyperactivity compared to saline-treated controls. No differences in performance in the water maze or injection test were found between the gabapentin-treated and saline-treated animals chronically following status epilepticus. This study demonstrated that gabapentin had a beneficial effect on behavior and seizure susceptibility following status epilepticus, but did not contribute to impairment or enhancement in learning in these animals. Gabapentin given to control rats had no effect on behavior or histological examination.

Topiramate—Topiramate has a negative modulatory effect on the α-amino-3-hydroxy-5-methyl-4 isoxazol propionic acid (AMPA)/kainate (KA) subtype of glutamate receptors [117]. Because of its effects on excitatory neurotransmission, there have been concerns raised about the long-term cognitive effects of topiramate. To assess the effects of topiramate on cognitive function in the immature brain Cha et al. [118] gave topiramate, 80 mg/kg, or saline for 4 weeks following a series of 25 neonatal seizures or lithium-pilocarpine-induced status epilepticus in P20 rats. Age-matched control rats without a history of seizures were administered topiramate or saline. Following completion of the topiramate injections, animals were tested in the water maze for spatial learning and the brains examined for cell loss and sprouting of mossy fibers. While there was a trend for improved visual-spatial performance in the water maze following topiramate therapy in rats with neonatal seizures, no differences were found in the histological examination of the hippocampus. Neonatal rats exposed to 4 weeks of topiramate did not differ from non-treated controls in water maze performance or histological examination. These findings demonstrated that chronic treatment with topiramate following status epilepticus had a mild beneficial effect on cognitive function. Of equal importance, long-term administration of high-dose topiramate in the normal developing rat brain did not impair cognitive performance.

In a study whether topiramate had any neuroprotective effects in rats with neonatal seizures, Zhao and colleagues [119] administered topiramate or saline chronically during and following a series of 25 neonatal seizures. After completion of the topiramate treatment, animals were tested in the water maze for spatial learning and the open field for activity level. Rats treated with topiramate performed better in the water maze than rats treated with saline. Topiramate

also reduced the amount of seizure-induced sprouting in the supragranular region. No differences between topiramate- and saline-treated rats were seen in the open field test.

Topiramate has also been found to be effective in blocking hypoxia-induced seizures and reducing the damage associated with a second epileptic insult [120,121]. Koh et al. [120] used a “two-hit” rodent seizure model to study the long-term effect of perinatal hypoxia on later kainate seizure-induced neuronal damage. The authors investigated the therapeutic efficacy of a post-seizure treatment protocol using topiramate in reversing the conditioning effect of early-life seizures. Hypoxia at P10 induced seizures without cell death, but caused an increase in susceptibility to second seizures induced by kainic acid. Repeated doses of topiramate given for 48 hours after hypoxia-induced seizures prevented the increase in susceptibility to kainic acid seizure-induced hippocampal neuronal injury. No adverse effects of topiramate were seen.

There are significant limitations to how much the information from the animals studies described above can be translated to the human condition. The studies varied in the animal species, age treatment commenced, durations of treatment, dosages, and outcome measures. The pharmacokinetics and phamacodynamics of AEDs differ across species and none of the studies have employed dams with epilepsy. Most importantly, because of the limited behavioral repertoire of rodents extrapolation to humans is tenuous. Animal models obviously can not model many of the skills that distinguish humans from other species. Abilities such as speech, language and abstract thinking require human studies.

Pathophysiological Mechanisms Responsible for AED Adverse Effects on Brain Development

In humans, AEDs administered during gestation may have teratogenic effects in the offspring [122-125] and lead to neuropsychological deficits [123,126-130]. Study of the neurological consequences of these treatments has largely been limited to patients suffering from severe malformations so that subtle changes in brain architecture and function have not been investigated thoroughly. Koch et al. [123] prospectively studied 67 children or adolescents born to mothers with epilepsy (treated or not). Abnormal EEG patterns and lower IQ levels positively correlated with AED therapy. Children exposed *in utero* to polytherapy had worse outcomes than children exposed to monotherapy.

Since the fetus is typically exposed to AEDs throughout gestation, AEDs could have an effect at many stages of brain development: proliferation, migration, cell growth and differentiation, connectivity and cell death. As described above, there is some data indicating cell proliferation can be impaired with AEDs [97,101]. More recent studies have demonstrated that AEDs can effect brain development by adversely effecting neuronal migration and enhancing apoptosis [109,110,131].

Neuronal migrational disorders

Construction of the brain is a highly coordinated process, leading to the genesis of specific cell types and to their precise movement and settlement into their correct target layers [3]. Neuronal migration disorders are among the most common causes of developmental neurological defects. As immature neurons migrate through the cerebral tissue they are influenced by several factors that modulate their journey. Among these factors, neurotransmitters have been shown to play an important role. The neurotransmitters have a crucial modulatory effect on migrating neuroblasts, acting as motility-promoting signals, acceleratory signals, or even stop signals. Neuronal migration may be influenced not only by genetic alterations [132] but also by teratogenic (e.g., alcohol or cocaine), physical (e.g., irradiation), infectious, and pharmacological agents acting during the period of cell migration [133,134]). GABA and

glutamate affect cortical cell migration [135], thus supporting the idea that environmental cues may influence the definitive numbers and positions of cortical neurons. It also raises the possibility that drugs acting on these types of receptors can modify the migration pattern, but this issue has been poorly investigated. Blockers of GABA or NMDA receptors can retard neuronal migration *in vitro* [136]. These effects are of particular relevance for the *in utero* developmental phases during which neurons mature and extend dendrites and axons, and start forming synapses. Thus, crucial processes including neuronal migration can be adversely affected by AEDs.

Neuronal migration can be altered by GABAergic drugs. Manent and colleagues [136] administered carbamazepine, vigabatrin and valproate to pregnant rats from embryonic days 14 to 19 at doses similar to those used clinically. Rat pups exposed to AEDs *in utero* were analyzed postnatally. In addition, animals born to untreated pregnant animals that had experienced one generalized convulsive seizure per day during the same gestational period were analyzed in parallel. Prenatal exposure to vigabatrin and valproate resulted in hippocampal and cortical dysplasias, which were likely to result from a neuronal migration defect and neuronal death. However, the offspring of rats with convulsive seizures or rats exposed to carbamazepine showed no clear-cut evidence of dysplasia.

Apoptosis

Studies by Ikonomidou [109,137], Bittigau et al. [110,138], and Olney et al. [134] demonstrate that phenytoin, phenobarbital, diazepam, clonazepam, sulthiame, vigabatrin and valproate cause apoptotic neurodegeneration in the developing rat brain at plasma concentrations relevant for seizure control in humans. In these studies drugs have been administered to either the fetus or the rat pups. The period of vulnerability to AEDs is during a period of intense synaptogenesis. In contrast, therapeutic dosages of levetiracetam and topiramate did not lead to apoptosis [138,139].

There is also a relationship between AED-induced apoptosis and cognitive function. Jevtovic-Todorovic and colleagues [140] administered midazolam, nitrous oxide and isoflurane to 7-day-old infant rats and observed widespread apoptotic neurodegeneration and impaired LTP in hippocampal slices obtained from these animals three weeks later. Persistent deficits in memory and learning could be demonstrated when the rats were tested subsequently using the Morris water maze or the radial arm maze.

Whether there is a direct causal relationship between apoptosis and impaired learning can not yet be determined. It is also not known whether a similar process occurs in humans. Nevertheless, these studies raise concern about the effects of AEDs on the developing brain.

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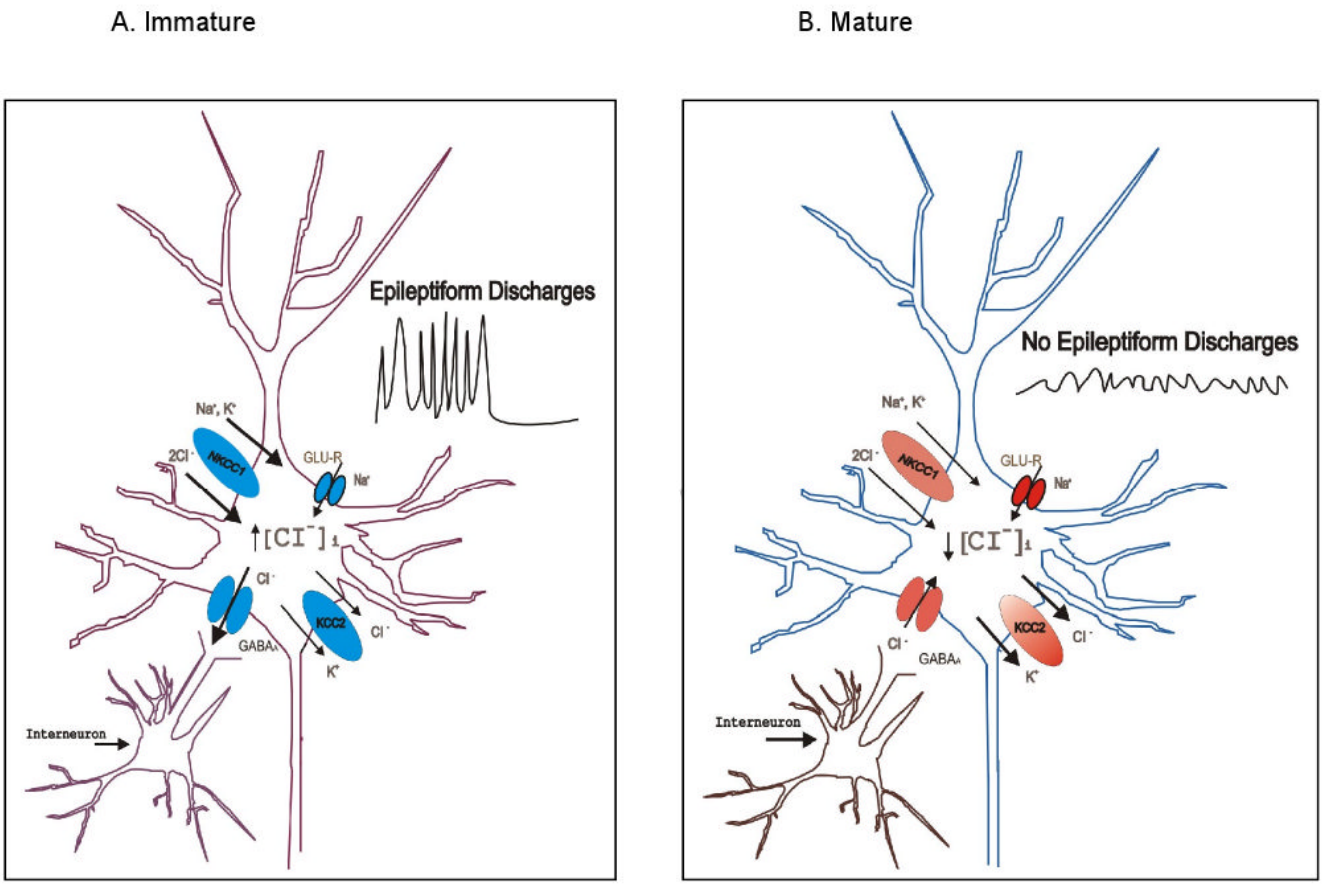

Figure 1.

Cartoons of immature (A) and mature (B) neuron. The immature neuron (A) is in a more excitable state than the mature neuron (B). Because NKCC1 develops and functions sooner than KCC2 there is an increase of chloride within immature neurons compared to mature neurons (A). The increase in intracellular chloride results in a depolarized chloride equilibrium potential. When the GABA channel is activated by GABA there is a flow of chloride from inside the cell to outside the cell. Since chloride carries a negative charge the exodus of chloride served to depolarize the cell, making it more likely to discharge when sodium enters the cell. In the mature neuron (B) KCC2 is functional and balances the increase of chloride through NKCC1 with an outward flow of chloride. Because of lower intracellular chloride levels when the GABA receptor is activated chloride enters the cell carrying a negative charge thus resulting in hyperpolarization.

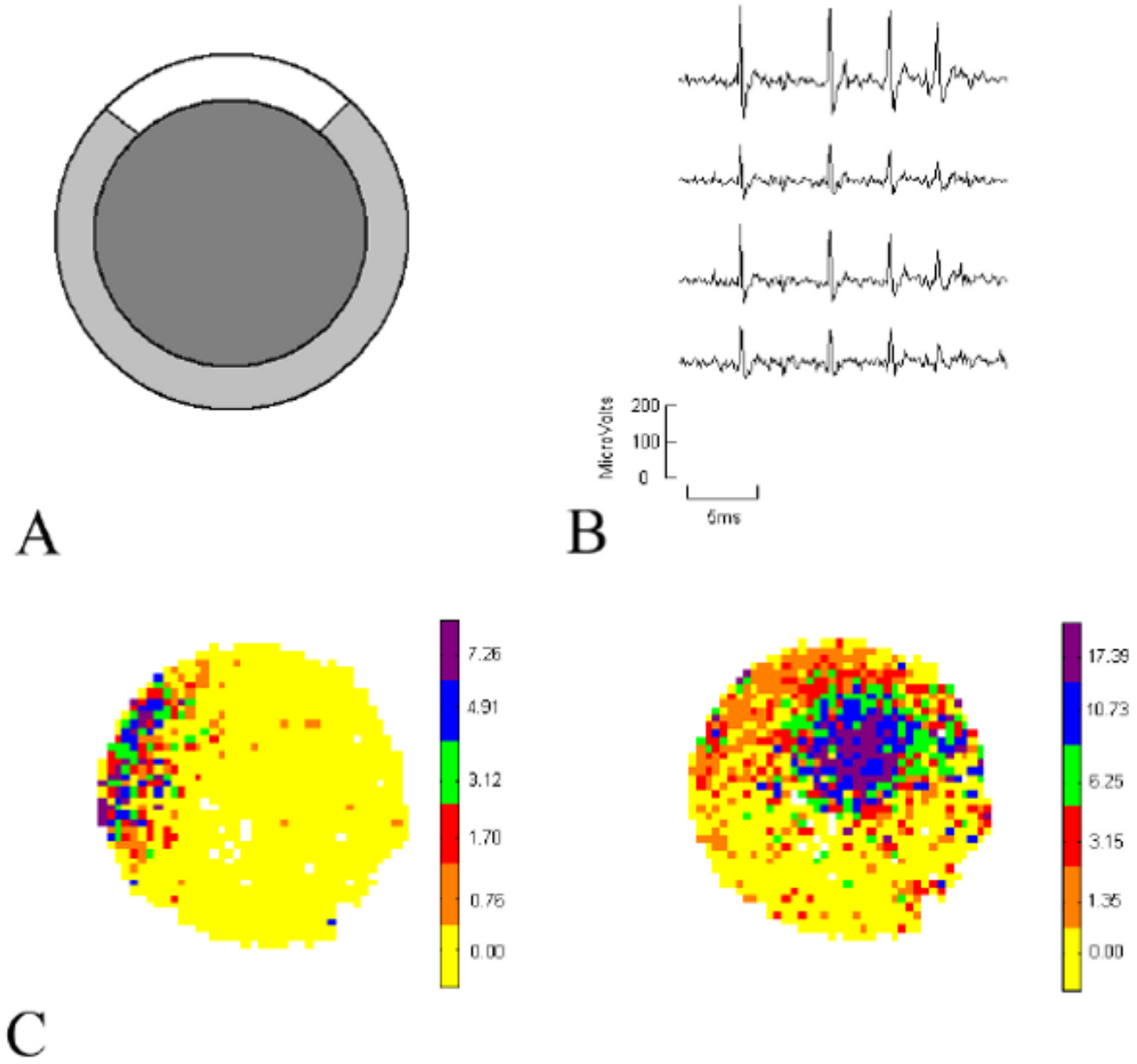

Figure 2.

Example of place cell recording chamber, color-coded representation of spatial firing of two pyramidal cells (B,D) and an interneuron. A. The rat's headstage contains a diode allowing tracking of position. An orienting card is on the wall of the cylinder. The intracranial electrodes are attached to a cable with preamplifier in place. Food pellets are scattered randomly about the cylinder causing the rat to visit the entire apparatus. B. Color-coded firing rate maps were used to visualize firing distributions. Pixel rates were coded in the sequence: yellow, orange, red, green, blue and purple. The firing rate was exactly zero for yellow pixels. Unvisited pixels in the cylinder and pixels outside the cylinder were coded white. The maximum firing field is at 5 o'clock. AP traces from the tetrode are shown on the right. C. Is an example of an interneuron with no place preference firing and a much higher firing rate than the place cells

in B and D. The maximum firing rate of the place cell in D is at 12 o'clock. From Zhou et al. [25] with permission.

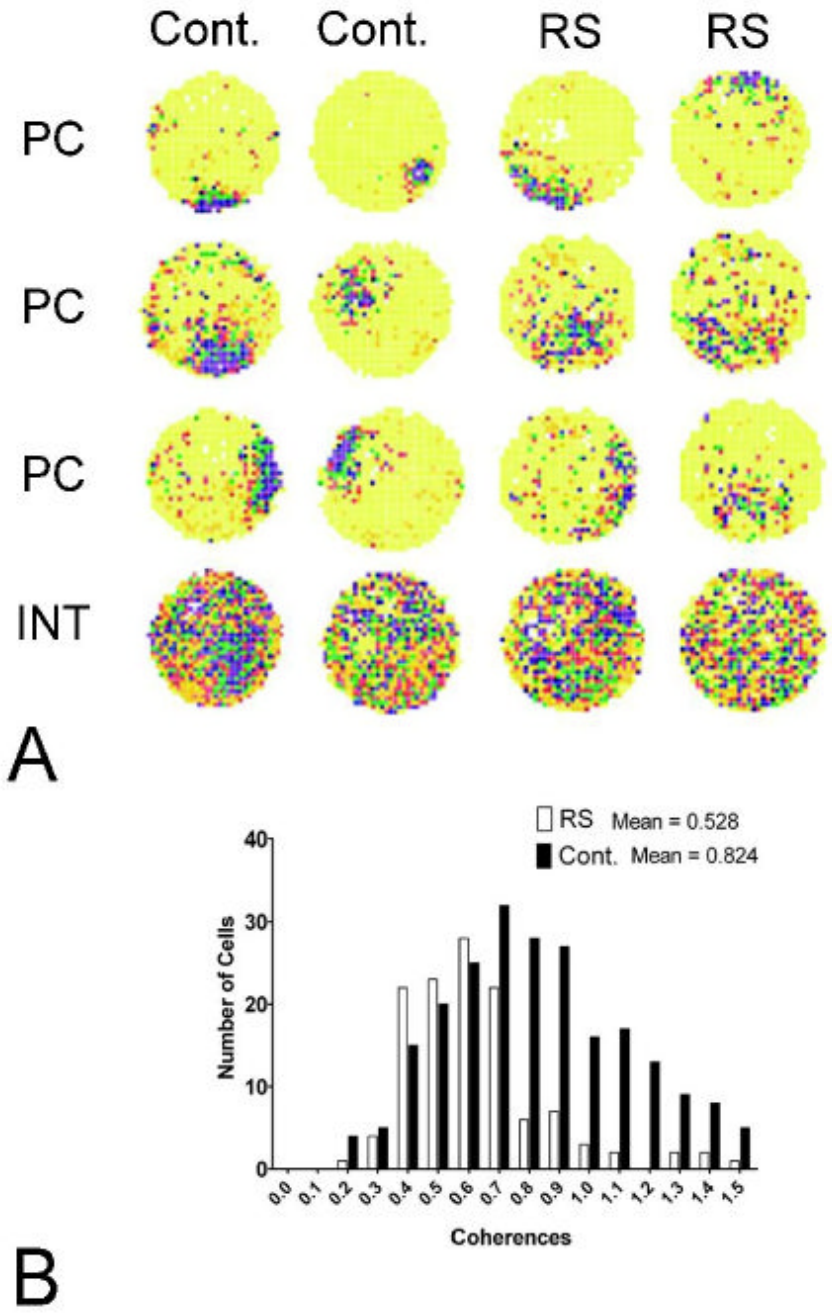

Figure 3.

A. Examples of place cells and interneurons from controls (Cont.) and recurrent seizure (RS) rats. Color-coded firing rate maps were used to visualize firing distributions. Note that the place cell firing fields were smoother and more precise in the controls as evidenced by higher coherences than in the recurrent seizure rats. Cells from the recurrent seizure groups were "noisier" with greater out of field firing than the controls. The interneurons did not show preferential place firing. B. Histogram of coherences in the recurrent seizure and control groups. Note the distributions were different with the recurrent seizure groups having lower coherences than the controls. From [66] with permission.

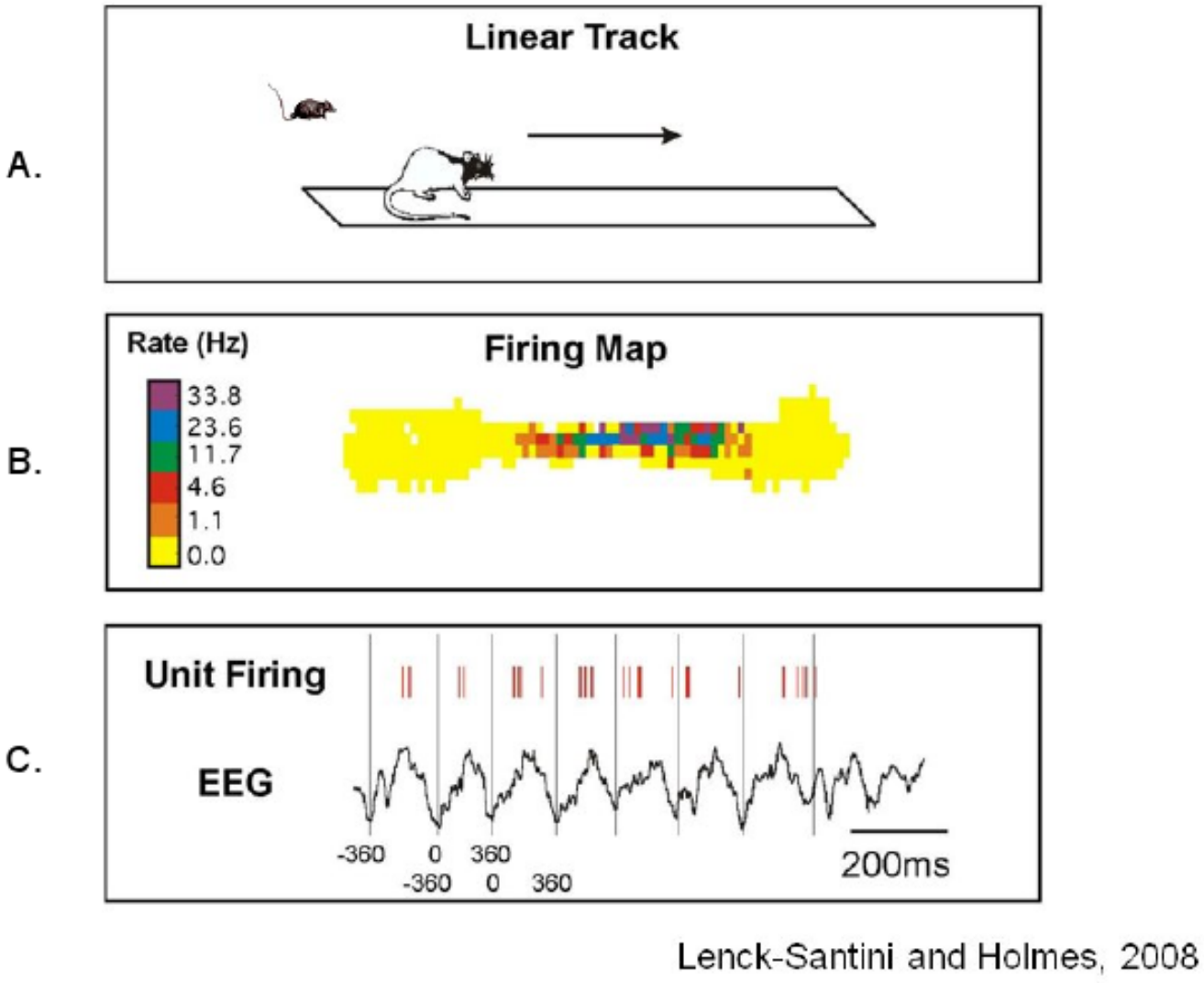

Figure 4.

Phase precession of hippocampal place cells. A. Place cells are recorded in rats while they were running back and forth on a linear track. B. Top-view spatial firing map of a cell for the entire session. C. Hippocampal EEG and firing activity of the same cell (red bars) during a single firing field crossing. As the rat crosses the field, the cell bursting activity occurs at a slightly higher frequency than the theta EGG signal. On successive cycles AP appear in advance (precess) to the peak of the theta wave. Long vertical bars represent the 0° theta phase, i.e., the trough of the theta wave. Phase precession of hippocampal place cells. From [1] with permission.

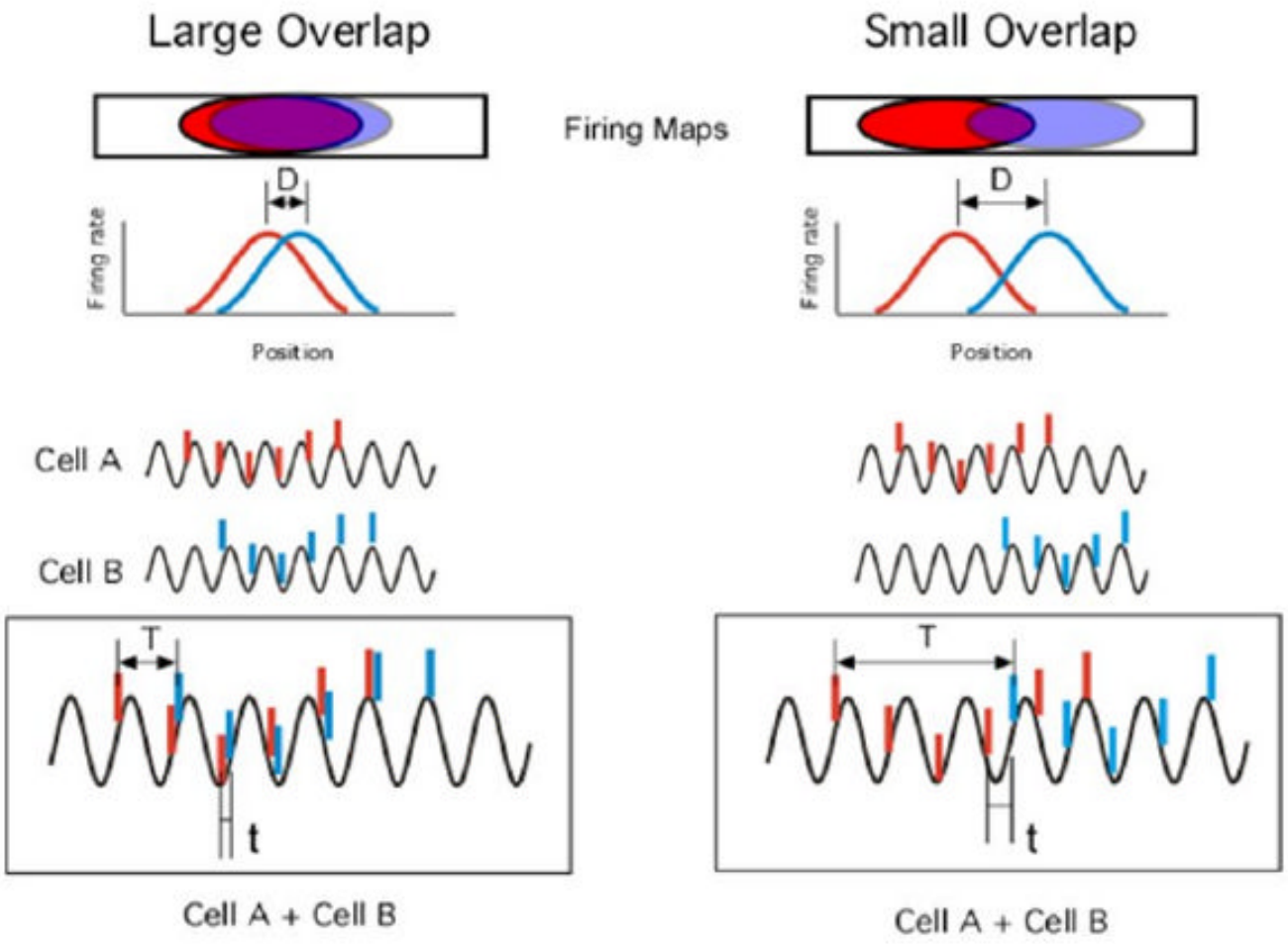

Figure 5.

Schematic representation of the compression of temporal sequences phenomenon. Place cells with partially overlapping fields (red and blue) have different firing relationship depending on whether the field centers are adjacent (A) or distant (B). There is a linear relationship between the inter-field distance (D) and the time required to go from field center to another (running time: T). There is also a relationship between the running time (T) and the time interval between action potentials in the same theta cycle (t). Cells with adjacent fields fire at a short time interval whereas cells with distant fields fire at long time intervals. Black traces: EEG during the crossing of both place fields. Red and blue vertical lines: action potentials. From [1] with permission.