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Why are Children with Epileptic Encephalopathies Encephalopathic?

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Abstract

The epileptic encephalopathies are devastating conditions characterized by frequent seizures, severely abnormal EEGs and cognitive slowing or regression. The cognitive impairment in the epileptic encephalopathies may be more concerning to the patient and parents than the epilepsy itself. There is increasing recognition that the cognitive co-morbidity can be both chronic, primarily due to the underlying etiology of the epilepsy and dynamic or evolving because of recurrent seizures, interictal spikes and antiepileptic drugs. Much of our understanding of the neurophysiological underpinnings of cognitive dysfunction in the epileptic encephalopathies comes from rodent studies. Frequent seizures and interictal EEG discharges in rats lead to considerable spatial and social-cognitive deficits. Paralleling these cognitive deficits are dyscoordination of dynamic neural activity within and between the neural networks that subserve normal cognitive processes.

Keywords

oscillations; theta rhythm; phase; coherence; voltage correlations; active avoidance; water maze; interictal spikes

While the majority of children with epilepsy maintain stable IQ scores, there is now strong evidence that some children with epilepsy slow, or even regress, in their mental development¹⁻³. While etiology of the epilepsy is the most important factor in cognitive development, there are indications that early-life seizures independent of etiology can lead to cognitive impairment^{4;5}.

Cognition is of particular concern in children with epileptic encephalopathies⁶⁻⁸, defined by the International League Against Epilepsy (ILAE) as a condition where the “epileptic activity itself may contribute to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone (e.g., cortical malformation), and that these can worsen over time”⁸. The epileptic encephalopathies are characterized by slowing or regression of development due to seizures, abnormal interictal cortical and subcortical EEG activity, or both, rather than the underlying etiology of the epilepsy⁶. While all of the epilepsy syndromes have an underlying etiology that could lead

to the cognitive impairment, the observation that individuals with epileptic encephalopathies who are successfully treated with medications or surgery can improve cognitive function is a demonstration that seizures and an abnormal EEG play an important role in cognitive impairment⁹⁻¹³.

Understanding the neurophysiological underpinnings of the epileptic encephalopathies is essential to developing targeted therapies to prevent or improve cognitive function in this vulnerable group of children. Trying to determine those factors that lead to cognitive decline is difficult in children because of the variability in etiology, age of seizure onset, seizure frequency, duration and intensity, interictal EEG abnormalities and antiepileptic drug therapy. Rodent models have therefore been invaluable in understanding cognitive impairment in the epileptic encephalopathies since the investigator can control the majority of these variables.

Unfortunately, there have been few animal models of the epileptic encephalopathies that lend themselves to study of cognition. The best studied genetic model of the epileptic encephalopathies has been the Dravet model in which a knock-out of the SCN1A gene in inhibitory interneurons causes frequent seizures and a high mortality rate¹⁴⁻¹⁷. Cognitive studies in this model have been limited in scope and have been inconsistent¹⁸⁻²⁰. Importantly, there is now evidence that the mutation of the sodium channel can result in cognitive deficits independent of seizures^{21,22}. Acquired models of the epileptic encephalopathies, such as infantile spasms²³⁻²⁵, have not been well studied in regards to cognitive function.

Our laboratory has also taken the approach of teasing apart the components of the epileptic encephalopathies, namely seizures and interictal discharges, in normal rats. Seizures are induced with chemoconvulsants allowing us to control the duration and number of seizures and interictal discharges in rat pups that are otherwise normal. While we do not create a model of the epileptic encephalopathies, this approach allows us to determine the effects of recurrent seizures and interictal spikes during early development separately from the underlying etiologies that cause the encephalopathy.

Effect of Recurrent Early-Life Seizures on the Developing Brain

Using the recurrent flurothyl seizure and the experimental febrile status epilepticus (FSE) model of recurrent early-life seizures (ELS), we and others have shown cognitive impairment when animals are tested as adolescents or adults^{26-29;29-42}. Cognitive deficits seen following ELS include deficits of spatial cognition in the Morris and radial-arm water maze^{28;32;34;43}, non-match to sample task²⁶, and active avoidance task³³ as well as impaired auditory discrimination³⁷ and reduced behavioral flexibility²⁶. While we found that ELS does not result in cell death^{31;44;45}, there is evidence of synaptic reorganization as indicated by sprouting in CA3^{36;46} and reduced neurogenesis⁴⁷. We have also demonstrated that ELS lead to persistent decreases in GABA currents in the hippocampus⁴⁸ and neocortex^{49;50}, enhanced excitation in the neocortex⁵⁰, impairment in spike frequency adaptation⁵¹, enhanced short-term plasticity⁵², alterations in LTP^{27;53}, and a lower seizure threshold⁴⁴. All of the physiological findings are indicative of altered excitatory:inhibitory

(E/I) balance in the brain. Alterations in E/I balance have pronounced effects on inhibitory and excitatory synaptic currents (EPSPS and IPSPS) that ultimately result in the generation of delta, theta, alpha, beta and gamma oscillatory rhythms.

The theta frequency is the most prominent oscillation in the rat hippocampus. Theta is associated with exploratory behavior and is principally generated by entorhinal cortical inputs onto the distal apical dendrites of pyramidal cells⁵⁴. Gamma oscillations are locally generated by the ongoing interaction of pyramidal cells and fast discharging interneurons in which pyramidal cells excite basket cells which then in turn inhibit pyramidal cells⁵⁵. Theta is necessary for spatial memory performance⁵⁶ and is associated with the segmenting of spatial experience and modulated by behavior and cognitive demand⁵⁷ as well as the formation and segregation of neuronal assemblies⁵⁴. Moreover, “fast” gamma oscillations have been hypothesized to “route” information flow in CA1⁵⁸ while “slow” gamma is strongly coupled to CA3 and believed to be essential for memory storage⁵⁹. The roles for oscillations in other frequencies (delta, alpha and beta) have not been well characterized.

Hippocampal theta oscillations have also been shown to influence the timing of place cell action potentials^{60;61} (Fig. 1). Hippocampal place cells fire only when the animal is in a specific position in the environment, the so-called “firing field.” In the hippocampus, place cells are characterized by their location-specific firing as well as their precise temporal firing relationship with hippocampal theta^{62;63}. When the rat enters the cell’s firing field, action potentials fire preferentially on the rising phase of the CA1 recorded theta cycle. As the rat enters and crosses the firing field, the cells fire earlier on successive theta peaks, a phenomenon called phase precession^{60;64}. The hypothesis that place cells provide a cognitive map of the environment that allows for accurate navigation within a given space⁶⁵ has received much experimental support and has been shown to have a close relationship with spatial behavior⁶⁶⁻⁶⁸. To this end, the cognitive map may serve as a surrogate for spatial memory^{69;70}.

Following pilocarpine-induced status epilepticus in adult rats, place cells become less precise in their firing fields and have less stability from session to session⁷¹. Recurrent seizures during the first weeks of life cause impairment in spatial cognition with poor performance in the water maze and radial-arm water maze as well as substantial deficits in place cell precision and stability²⁸.

ELS heavily influences the microcircuitry that regulates synaptic excitation and inhibition within and between key cognitive circuits, particularly the hippocampus. While a model of FSE in rat pups is not associated with hippocampal cell loss⁷²⁻⁷⁴, FSE have been found to persistently modify inhibitory h-channels⁷⁵ and alter GABAergic inhibition⁷⁶. FSE have been shown to lead to long-term increases in network hyperexcitability^{77;78}. The long-term effects of such post-FSE network modifications on hippocampal network oscillations in freely moving animals are still unknown. We have recently shown that a subset of FSE animals have difficulty learning an active avoidance task (Fig. 3). In this task rats have to use cues outside a rotating arena to avoid a stationary shock zone. Rats that have difficulty learning this task after FSE tend to have larger and more hyperexcitable CA1 place cells than control animals or FSE animals that are able to learn the task³³. Small errors in the

timing of oscillations and positional firing can propagate across networks. It is possible that such timing errors are even more detrimental in developing animals where oscillations drive circuit formation and stabilization.

The physiological capacity to coordinate dynamic neural activity within and between neural networks is believed to underlie normal cognitive processes⁷⁹. Moreover, several studies have proposed that the coordination of neuronal firing occurs with respect to local oscillations within specific circuits, such as theta oscillations in the hippocampus⁸⁰ that have correlated with learning and memory⁸¹⁻⁸³. Both modeling and experimental work suggest that the dynamic phase relationships of synaptic current as well as the timing of action potentials during theta rhythm are critical in processes underlying both the encoding and retrieval of memory. These key features of memory are coordinated by theta phase, which temporally organizes the transfer of neural information between the hippocampus and neocortex and within the hippocampal circuit^{83;84}. In accordance with this body of work, we have recently shown the translational relevance of the “temporal coordination hypothesis”, which simply states that the dynamic temporal coordination of neurons within and between relevant circuits underpins learning and memory⁴⁰. We have shown that levels of temporal coordination among neurons in the hippocampal circuit by theta oscillations depend on levels of cognitive demand, and reflect cognitive outcome post febrile status epilepticus. Specifically, control and FSE rats were trained to simply forage for food pellets or perform an active avoidance spatial task on the same open arena. FSE rats were sorted by those that were able to reach task criterion (FSE-L) and those that could not (FSE-NL). FSE-NL CA1 place cells did not exhibit phase preference within local theta oscillations in either context and exhibited poor cross-theta interaction between CA1 and CA3. FSE-L and control CA1 place cells exhibited phase preference at peak theta that shifted during active avoidance to the same static phase preference observed in CA3. These results therefore imply that the dynamic organization of CA1 neurons within theta enable communication within the hippocampal circuit that is necessary for the performance of a complex spatial task⁴⁰.

To illustrate the importance of synchronization of neural information CA1 firing patterns can be examined. The activity of CA1 place cells is organized by inputs to synapses from CA3 at the stratum radiatum and inputs from the entorhinal cortex at stratum lacunosum, both along the apical dendrite of CA1 pyramidal cells. The organization of excitation and inhibition at these synapses is organized by hippocampal theta oscillations. Inhibition at these synapses is mediated by specific interneuron types, oriens-lacunosum molecular (O-LM) cells at the stratum lacunosum and bistratified cells at the radiatum. A third interneuron type, the basket family of interneurons, fires rhythmic bursts in register with theta oscillations and thereby produces critical inhibitory currents in the region of the pyramidal cell bodies^{85;86}. Seizure-induced changes to either part of this circuit, either changes to the excitability of the CA1 pyramidal cell dendrite, the inhibitory regulation of the entorhinal or CA3 inputs from their respective interneuron types, will dramatically affect the timing and coordination of these inputs. This will ultimately affect the temporal coordination of cellular action potentials within CA1 and between CA1 and CA3. This is important for cognition as the direct inputs from entorhinal cortex have been implicated in the firing specificity of CA1 place fields⁸⁷ as well as the encoding of information⁸⁴. In addition, the inputs from CA3 are believed to

be critical for retrieval of spatial information⁸⁴ as well as serve as temporary memory store that allows for spatial pattern completion⁸⁸. The timing of either component in this circuit could make calculation of current and projected position difficult, particularly in the active avoidance task where position is constantly changing and needs to be updated at regular intervals.

Oscillations may therefore have a major role in modulating neuronal firing within brain regions as well as components of neural circuits that are separated by great distances. Coherence is a measure of “coupling” oscillations and therefore provides a dynamic link between brain areas required for the integration of distributed information^{89;90} (Fig. 2). High coherence values are taken as a measure of strong connectivity between the brain regions that produce the compared EEG signals. Firing of action potentials across distant sites is coordinated through phase, i.e. when two signals from distant structures are in phase, correlated firing of action potentials in the two structures is selectively enhanced. A significant portion of neurons in the medial prefrontal cortex (PFC) of freely behaving rats are phase locked, a process in which the phase of two oscillators have a constant relationship, to the hippocampal theta rhythm with action potentials occurring at specific phases of the hippocampal theta. Phase preference provides temporal ordering of the excitability windows of neurons, thereby enhancing the flow of information from one region to the other. Repeated regulation of neuronal spike-timing within a circuit could also result in an action potential-dependent plasticity and selective strengthening of synapses^{91;92}.

As with theta oscillation, coherences of gamma oscillations have also been shown to have an important role in learning in rodents. Gamma phase synchrony between the entorhinal cortex and CA1 region predicted correct versus incorrect trials in a delayed non-matching-to-place T-maze task⁹³. In this test rats have to learn to alternate arms in the T-maze to receive a reward. When the animal reached the decision point in the maze, there was a transient burst of synchronous high gamma (65-140 Hz) before correct, but not incorrect trials.

State changes coupled across networks that are driven by neuromodulatory systems can also be measured by voltage correlations⁹⁴. Unlike coherence, which is a measure of phase between two signals, voltage correlations do not consider phase and are based on the amplitude of the EEG signal across networks. If the voltage correlations are high the amplitude is similar in the two neural structures sampled whereas if the voltages correlation is low, the amplitudes differ between the structures. Voltage correlations can provide a measure of large-scale interactions between cortical areas that are indirectly connected through polysynaptic pathways^{95;96}. The association between EEG amplitude from two sources over a time interval provides a distinctly different measure of connectivity from coherence, which does not take voltage into account. Voltage correlations allow for informative inferences regarding the large-scale oscillatory interactions between brain regions that mediate cognition. If voltage correlations are high, they indicate there is a greater co-modulation of frequency between two signals. Oscillations that have antithetical patterns will tend to exhibit negative voltage correlations.

ELS have been associated with marked increases in coherences within the hippocampus and between the hippocampus and PFC^{44;97}. In rat pups with ELS, field recordings from the

dorsal and ventral hippocampus and PFC have marked increases in coherence as well as decreases in voltage correlation at all bandwidths compared to controls while there are minimal differences in total power and relative power spectral densities⁴⁴. ELS rats exhibited autistic-like impairments in sociability and social novelty tests⁴⁴. These findings suggest that ELS can have long-standing effects on neuronal circuit development, inter-regional communication and ultimately, sociability behavior.

Remarkably, oscillatory activity is malleable and has been shown to be modified with experience. Kleen et al.²⁶ showed that following ELS rats were initially impaired in a delayed-non-match-to-sample task. While performing the memory task, dynamic oscillation patterns revealed that PFC theta power was increased among seizure-exposed rats. This enhancement appeared after the first memory-training steps using short delays and plateaued at the most difficult steps, which included both short and long delays. Further, seizure rats showed enhanced CA1-PFC theta coherence in correct trials compared with incorrect trials when long delays were imposed, suggesting increased hippocampal-PFC synchrony for the task in this group when memory demand was high. Seizure-exposed rats also showed heightened gamma power and coherence among all three structures during the trials. These results demonstrated hippocampal-PFC enhancements with training following ELS. These compensatory network changes between interconnected circuits may lend support to physiological changes that are necessary for cognitive rehabilitation following neurological insults to higher cognitive systems.

However one must be cautious when attempting to correlate changes in oscillatory activity with behavior. As with many biological processes there is likely a “sweet spot” for oscillatory parameters. It is likely that in some tasks increased coherence is detrimental while in others decreased coherence is harmful. As previously discussed, when compared to control rats, ELS have marked increases in coherence between the hippocampus and PFC along with sociability deficits⁴⁴. Thus, increased coherence could be related to improved spatial cognition while resulting in impaired social cognition.

Effect of Interictal Spikes (IS) on Cognition

In addition to seizures, there is compelling evidence that IS in both animals and humans can result in cognitive impairment. In both children and adults IS can cause transitory cognitive impairment⁹⁸⁻¹⁰⁴. Aarts et al.¹⁰² found that IS can briefly disrupt neural processes affecting localize function within the brain region where they occur. The authors studied the effects of IS on both verbal and non-verbal short-term memory in patients with epilepsy but without clear clinical manifestations during the IS. In right-handed individuals right hemisphere IS were associated with errors in a non-verbal task whereas left hemisphere IS resulted mainly in errors in verbal tasks. EEG discharges interfered primarily when occurring simultaneously with the presentation of the stimulus, corresponding with the encoding phase of the task. Shewmon and Erwin in a series of carefully performed studies⁹⁸⁻¹⁰¹ found that occipital IS could disrupt visual perception. IS in the occipital region caused transitory deficits with stimuli presented in the contralateral visual field. Deficits were most pronounced when they occurred during the slow wave following the IS.

To study the effects of IS on memory and reaction time Kleen et al.¹⁰⁵ studied rats that developed chronic IS following intrahippocampal pilocarpine in a hippocampal-dependent operant behavior task, delayed-match-to-sample. Hippocampal IS that occurred during memory retrieval strongly impaired performance while IS that occurred during memory encoding or memory maintenance did not affect performance in those trials. There is a significant and sustained reduction of action potentials for up to two seconds following an IS in rats; when occurring in flurries, IS reduced action potential firing for up to six seconds¹⁰⁶. In addition to affecting action potentials, the widespread inhibitory wave immediately after IS can dramatically reduce the power of gamma oscillations and other oscillatory signals in the hippocampus¹⁰⁷. Since as described above, oscillations are intimately linked to ongoing learning and memory functions, this disruption in oscillations would likely contribute to cognitive deficits^{105;108}.

Patients with temporal lobe epilepsy and IS have also been shown to have declines in working memory during periods of IS¹⁰⁹. Using similar methodology to that used in rats, Kleen et al.¹¹⁰ investigated whether IS in patients with temporal lobe epilepsy resulted in memory impairment. Ten patients with intra-hippocampal depth electrodes were studied during a simple memory task, the Sternberg test, where 4 letters are presented and after a delay the patient has to determine whether a single letter was one of the 4 letters shown. Hippocampal IS occurring in the memory retrieval period decreased the likelihood of a correct response when the IS was contralateral to the seizure focus or bilateral. This study provided biological validity to the use of animal models in the study of IS-related transient cognitive impairment.

In addition to the transient effects of IS on behavior and cognition, IS can cause long-standing sequelae in developing animals. In studies of the effects of IS on striate cortex in rabbits, IS were elicited by epidural focal application of either penicillin^{111;112} or bicuculline^{113;114} in the striate cortex. IS were elicited for 6-12 hours following each drug application and drug applications were given daily from ages 8-9 days to 24-30 days. None of the rabbits had behavioral seizures. In single-unit recordings from the lateral geniculate nucleus, superior colliculus and occipital cortex ipsilateral to the hemisphere with IS there was an abnormal distribution of receptive field types whereas normal recording were found from the contralateral hemisphere. This finding was age-dependent as adult rabbits with similarly induced interictal spikes had normal development of cells. These studies showed that disruption of neuronal activity in the geniculostriate system by interictal spikes, during critical developmental periods, have a detrimental effect on the formation of receptive fields in the occipital cortex.

IS have also been elicited in young rats with flurothyl inhalation¹¹⁵. Rat pups were given a low dose of flurothyl for four hours for 10 days during continuous electroencephalographic monitoring. Rats developed IS without seizures while age-matched controls under similar testing conditions had few IS. When rats were tested as adults, there was impairment in reference memory in the probe test of the Morris water maze, reference memory impairment in the four-trial radial-arm water maze and impaired long-term potentiation. Early-life IS resulted in impaired neurogenesis in the dentate but did not cause an increase in apoptosis. This study demonstrated that IS in rat pups without seizures can result in long-standing

spatial cognitive impairment. These findings suggest that IS may be even more detrimental to the developing brain than seizures. Whereas seizures are discrete events, IS are typically present 24 hours a day.

In summary, there is now considerable information as to why children with epileptic encephalopathies are encephalopathic. Frequent seizures beginning early in life are a major component of the epileptic encephalopathies and there is now abundant clinical and animal data showing that recurrent seizures during development can have severe consequences on cognition. Children with epileptic encephalopathies always have severely abnormal EEGs with frequent multifocal and/or generalized interictal discharges and background slowing and disorganization. As with recurrent seizures, the evidence suggests that interictal spikes and neuronal network dyscoordination contribute to the child's encephalopathy. While there is still much to be learned about the basic neurobiology of cognitive impairment in the epileptic encephalopathies, there is urgent need now to use what is known to develop therapeutic interventions.

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Fig. 1. Place cell recording. A) Rat with head stage for electrodes with attached light-emitting diode. B) Recording chamber with cue card marked with a “X”. Rat is tethered to cable connecting head stage to the amplifier. C) Example of a place cell firing rate map with corresponding color code for firing rate at right. The yellow signifies areas of the chamber where the rat visited but the cell did not fire action potentials. D) Example of a phase map where the phase of the theta in which the action potential fires is shown.

Fig. 2.

Conceptual illustration of the relationship between action potential firing and local oscillations. There are strong neural connections between the hippocampus (Hipp) and PFC. As shown in the bottom two traces, when coherence of the theta rhythm in the PFC and Hipp is high and there is no difference in phase action potentials in both structures are closely aligned. When coherence is low with large differences in phase the action potentials are not aligned and action potentials coming from hippocampus arrive in the PFC at an inopportune time.

Fig. 3.

Synaptic integration of spatial information indicated by CA1 theta phase preference and implications for cognitive outcome post FSE. A) CA1 place cell with cell body indicated in the pyramidal cell layer (purple), CA3 inputs indicated at stratum radiatum (red) and entorhinal cortex (blue) inputs indicated at stratum lacunosum molecular (SLM). During foraging on the stable arena, this particular CA1 place cell (field shown on far right) tends to fire action potentials toward the peak of local theta oscillations (middle), suggesting that it is innervated by inputs from the entorhinal cortex (solid blue line at left). B) During active avoidance on the rotating arena, the same CA1 place cell (remapped place field shown on far right) now tends to fire action potentials toward the trough of local theta oscillations (middle), suggesting that it is now innervated by inputs from the CA3 (solid red line at left). C) Illustration of baseline network states during foraging in relation to cognitive outcome defined by performance in the active avoidance task. The top portion illustrates the mean phase preference of individual CA1 place cells (black lines) of a subset of FSE animals that are unable to learn the active avoidance task (FSE-NL). These cells tend to exhibit preferred phases of firing at different phases of theta that may represent changes in the microcircuitry that underpin phase preference and the routing of spatial information between brain regions. The bottom portion illustrates phase preference of CA1 place cells from FSE animals that are able to learn the active avoidance task (FSE-L). Collectively, these cells tend to prefer to fire toward the peak of theta oscillations (conceptual illustration of corresponding Rayleigh vectors are shown at right). This tendency may improve the coincidence of CA1 cell activity with inputs from the entorhinal cortex in a manner that may improve the underlying cellular

mechanisms of learning. Ultimately, this alteration of temporal organization could offset the effects of FSE and increase the probability of learning the active avoidance task.