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## Effect of Seizures on the Developing Brain and Cognition

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### Abstract

Epilepsy is a complex disorder, which involves much more than seizures, encompassing a range of associated comorbid health conditions that can have significant health and quality-of-life implications. Of these comorbidities, cognitive impairment is one of the most common and distressing aspects of epilepsy. Clinical studies have demonstrated that refractory seizures, resistant to antiepileptic drugs, occurring early in life have significant adverse effects on cognitive function. Much of what has been learned about the neurobiological underpinnings of cognitive impairment following early-life seizures has come from animal models. While early-life seizures in rodents do not result in cell loss, seizures do result in changes in neurogenesis and synaptogenesis and alteration of excitatory/inhibitory balance, network connectivity and temporal coding. These morphological and physiological changes are accompanied by parallel impairment in cognitive skills. This increased understanding of the pathophysiological basis of seizure-induced cognitive deficits should allow investigators to develop novel targets for therapeutic interventions.

### Introduction

Although seizures are the most striking clinical manifestation of childhood epilepsy, children with epilepsy are at risk not only for seizures, but also for a myriad of co-morbid health problems that occur at a higher rate than would be expected by chance<sup>1</sup>. Among the co-morbidities associated with epilepsy in children, cognitive abnormalities are among the most common and troublesome<sup>2,3</sup>. The distribution of intelligence quotient (IQ) scores of children with epilepsy is skewed toward lower values<sup>4,5</sup> and the number of children with epilepsy experiencing difficulties in school because of learning disabilities is greater than children without epilepsy<sup>6–11</sup>.

While most children with epilepsy maintain stable IQ scores, there is now strong evidence that some of them slow, or even regress, in their mental development<sup>5,12,13</sup>. In a community-based cohort study, Berg et al<sup>14</sup> assessed and prospectively followed 198 children (aged <8 years) with new-onset epilepsy for 8–9 years. In this cohort refractoriness to antiepileptic

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drugs (AEDs) was associated with an 11.4 point lower full scale IQ. There were substantial age-resistance to treatment interactions for IQ, indicating a lessening impact of recurrent seizures with increasing age. The authors appropriately concluded that uncontrolled seizures impair cognitive function with effects being most severe in infancy. Cognition is of particular concern in children with an epileptic encephalopathy<sup>15-17</sup>, a condition characterized by the slowing or regression of development due to seizures, abnormal interictal cortical and subcortical EEG activity, or both, rather than the underlying etiology of the epilepsy<sup>15</sup>.

Much of the cognitive impairment that occurs in people with epilepsy is related to its underlying etiology. Both acquired disorders such as trauma, hypoxic-ischemic insults, and mesial temporal sclerosis secondary to prolonged febrile seizures and genetic disorders, including tuberous sclerosis, fragile X, Rett, and Dravet syndromes, can lead to significant cognitive impairment in addition to causing epilepsy. While etiology of the epilepsy clearly plays a major role in cognitive development, there are indications that early-life seizures independent of etiology can lead to cognitive impairment<sup>18,19</sup>. For example, in a study of neuropsychological function in children with focal cortical dysplasia by Korman et al.<sup>19</sup> it was found that age of onset of epilepsy and extent of the dysplasia each contributed independently to cognitive dysfunction indicating that early onset of epilepsy disrupted critical periods of development leading to poor cognitive outcomes.

In order to prevent, limit and reverse cognitive comorbidities, it is essential to understand the neurobiological basis of cognitive dysfunction of seizures in children. While studies have indicated that children with seizures occurring early in life, particularly when frequent and resistant to therapy, are at highest risk for cognitive deficits, it is difficult to ascertain the neurobiological disturbances that lead to cognitive impairment. In the clinic it is difficult to differentiate the effects of the number, duration and seizure type, EEG abnormalities and antiepileptic drug therapy from the etiology of the epilepsy (Fig. 1). For this reason, many of the advances in our understanding of the long-term effects of early-life seizures come from rodent studies in which the investigator has control over the etiology and treatment of the seizures.

## Genetic Models

Animal models of early-life seizures include genetic and acquired models. The discovery of multiple genetic mutations associated with human epileptic encephalopathies and advances in genetic techniques have resulted in the generation of multiple models in animals carrying the human equivalent of these genes. Mutations in the gene coding for the type-1 alpha subunit of the Nav1.1 sodium channel in neurons, *SCN1A*, has been linked to the epileptic encephalopathies, especially Dravet syndrome and generalized epilepsy with febrile seizures plus (GEFS+). Models of Dravet syndrome have thermally-induced and spontaneous seizures that develop during the animal's maturation<sup>20-23</sup>. Likewise, models of generalized epilepsy + (GEFS+) mimic the clinical features of the condition with increased susceptibility to thermally-induced seizures and generalized tonic-clonic seizures<sup>24-27</sup>.

There is some evidence that the current Dravet syndrome models have social and spatial cognitive impairment when compared to control animals. Animals with some of them have performed poorly in a social recognition and social novelty task compared to controls<sup>28–30</sup>. Others, however, have shown similar performance to control animals<sup>31</sup>. Regarding animal models' ability to mimic the cognitive decline seen in this disorder, few examples of behavioral testing specific for spatial memory have been reported. However, those that have had such testing have shown significant impairments. This includes Ohmori et al.'s work<sup>31</sup> showing impaired performance of mice on a Barnes maze, a cognitive task assessing spatial learning in rodents. Similar results have been repeated in at least one other animal model specific for the SCN1A mutations thought to underlie Dravet syndrome.<sup>30</sup> Additional assessments of cognition have shown deficits in the memory requiring components of context-dependent fear conditioning.<sup>29,30</sup> Behavioral tests in the GEFS+ model have been similar to those seen in the Dravet models, including hyperactivity, impaired social performance, and deficits in spatial memory<sup>32</sup>. In addition deficits in cued fear conditioning and risk assessment have also been reported in this model<sup>32</sup>.

Discerning if the cognitive impairments associated with genetic models of early-life seizures are a result of the seizures seen in the other models, or a result of the mutated protein itself and resultant physiologic changes is important. Bender et al.<sup>33</sup> caused a similar decrease in the expression of Nav 1.1 protein seen in the genetic models of Dravet syndrome featuring SCN1A mutations, but through injection of specific small interfering RNA (siRNA) into the medial septum and diagonal band of Broca (MSDB), a brain region important for spatial cognition through its regulation of theta oscillations in the hippocampus, of adult Sprague-Dawley rats. This allowed for an evaluation of the effect of less SCN1A expression on cognition without affecting development of the rats or inducing the spontaneous seizures seen in the Dravet syndrome models. Rats with siRNA-induced firing of interneurons had spatial memory impairment compared to controls indicated by a comparative behavioral lack of response to a change in object location during a reaction-to-novelty task. This specific finding would suggest that the mechanistic changes underlying Dravet syndrome may also play a role in the cognitive impairment seen in the disorder that could be compounded by the effect of the associated developmental seizures.

In general, there has been limited work on the cognitive effects of seizures in the genetic disorders. In addition, the genetic models currently used only affect one specific gene/protein, when multiple genetic changes likely underlie the pathophysiology of many of the epileptic encephalopathies. Finally, while many advances have been made regarding the generation of models of specific syndromes such as West syndrome, Dravet syndrome or GEFS+, there remain few models that exhibit most qualities of the other encephalopathies, like Ohtahara syndrome, beyond the early repetitive seizure models. There are also no animal models that consistently exhibit the characteristics that match some of the syndromes like Lennox-Gastaut syndrome, indicating that further work must be done in order to fully understand the processes behind such disorders.

## Acquired Models

Acquired models of early-life seizures have been more extensively studied than the genetic models. With acquired models the investigator has control of age of seizure onset and seizure frequency in normal developing rats and thus can distinguish the effects of seizures from etiology of the seizures. Far more work on the cognitive effects of seizures on the developing brain have been done in the acquired models rather than the genetic models. For that reason, this review deals primarily with the two models of early-life seizures (ELS), experimental febrile status epilepticus<sup>34–38</sup> and recurrent flurothyl-induced seizures.

In the febrile status model rat pups are placed in a glass container and their core temperature, which is highly correlated with brain temperature, increased to approximately 40.5°C as a simulation of high fever. Manifested as a set of characteristic behaviors, hyperthermic seizure onset is heralded by sudden freezing, followed by oral automatisms and forelimb clonus. Seizures progress to body flexion and one or more tonic-clonic seizures. To accurately model prolonged febrile seizures in humans, hyperthermia (maximum temperature: 41.5–42.9°C) is maintained for approximately 40 minutes, which results in seizures lasting 36–40 minutes.<sup>37</sup> In the repeated flurothyl-induced seizure model, a 10% flurothyl solution (Bis(2,2,2-trifluoroethyl) ether), an inhaled convulsive agent, is delivered to the pups, which are placed in a plastic container located in an airflow hood<sup>39–41</sup>. Flurothyl (0.1 ml) is injected slowly onto filter paper placed on the inside of the container where it evaporates. Although the behavioral features of the seizures are age-related, the typical sequence of the seizures consists of myoclonic jerks followed by forelimb clonus, wild running, loss of posture and severe tonic posturing.

## Effects of Seizures on the Developing Brain

Using the flurothyl model of recurrent ELS in rat pups to human mimic neonatal seizures, we have shown cognitive impairment when the animals are tested during adolescence or adulthood<sup>39,42–47</sup>. Cognitive deficits seen following ELS include deficits of spatial cognition in the water maze<sup>43,48</sup>, non-match to sample task<sup>40</sup>, impaired auditory discrimination<sup>49</sup> and reduced behavioral flexibility<sup>42</sup>. While ELS do not result in cell death<sup>46,50</sup>, there is evidence for synaptic reorganization as evidenced by sprouting in CA3<sup>51,52</sup> and reduced neurogenesis<sup>53</sup>. Functionally, we have demonstrated that ELS lead to persistent decreases in GABA currents in the hippocampus<sup>54</sup> and neocortex<sup>55,56</sup>, enhanced excitation in the neocortex<sup>56</sup>, impairment in spike frequency adaptation<sup>57</sup>, marked reductions in after hyperpolarizing potentials following spike trains<sup>57</sup> and alterations in short-term<sup>58</sup> and long-term plasticity<sup>39,59</sup>.

One of the major difficulties in deciphering the complex issue of cognitive outcomes following ELS in children is the gulf between the behavioral/mental spheres in which these deficits are substantiated and the underlying physiological/developmental domains that are both the cause of these deficits and the most likely domain for therapy and intervention. While these descriptive studies have added to the body of work describing the effects of ELS on the neurophysiology of the developing brain, there remains a major gap in determining how these myriad of morphological and functional changes result in cognitive impairment.

To understand the electrophysiological basis of early-life seizures, investigators have used *in vivo* electrophysiological techniques to record local field potentials (LFPs) and single cell activity in animals actively engaged in behavioral testing. One of the strongest techniques is the recording of place cells, which fire action potentials (APs), also called units, based on where the animal is within its environment.<sup>60,61</sup> (Fig. 2) Specifically, these hippocampal pyramidal neurons selectively discharge (rate coding) when the animal enters certain locations of the environment, called the cells' firing fields. Field location, size and shape are specific to each cell and each environment and fields tend to cover the surface of the environment homogeneously when a large number of neurons are being recorded simultaneously. Since there is a relationship between place cell activity and the ongoing spatial behavior of rats<sup>62,63</sup>, such signals provide the animal with a spatial representation in order to navigate efficiently within the environment. Adult rats that experienced status epilepticus (SE) and have impaired learning in the water maze have defective place cells<sup>64,65</sup>, with imprecise and stable firing fields<sup>65</sup>. Likewise, flurothyl-induced seizures during the first weeks of life cause impairment in spatial cognition with poor performance in the water maze and radial-arm water maze and have substantial deficits in AP firing with impaired place cell precision and reduced place cell stability<sup>43</sup>. In the febrile status epilepticus model, rats have spatial cognition deficits and impaired place cell firing field<sup>34</sup>, indicating that rate coding can be impaired in multiple models of ELS. Furthermore, these findings suggest that abnormalities in single cell firing contribute to impaired spatial cognition.

Network oscillations underlie the temporal binding of spatially distributed neuronal populations, enabling information processing for cognition<sup>66,67</sup>. Theta frequency (5–12 Hz), the largest amplitude oscillation in the hippocampus, is associated with exploratory behavior and has been found to be necessary for spatial memory performance<sup>68,69</sup>. Gamma oscillations (30–90 Hz) have been hypothesized to “route” information flow in CA1<sup>70</sup> with slow gamma (20–50 Hz) coupled to CA3 and believed to be essential for memory storage<sup>71</sup>. There is a slowing of hippocampal CA1 theta in animals with spatial cognition deficits in both the flurothyl<sup>50</sup> and hyperthermia<sup>34</sup> induced seizures model.

Oscillations are dynamic events that can be modulated by experience. In a study measuring oscillatory activity in the hippocampus and medial prefrontal cortex of adult rats that had experienced flurothyl-induced seizures in the first weeks of life, and were remedially trained on a delayed-nonmatch-to-sample memory task, power was increased among ELS rats<sup>42</sup>. 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, ELS rats showed enhanced CA1-Prefrontal Cortex (PFC) theta coherence in correct trials compared with incorrect trials when long delays were imposed, suggesting hippocampal-PFC enhancements for the task in this group when memory demand was high. ELS rats also showed heightened gamma power and coherence among all three structures during the trials. These results provided the first evidence that training of rats after ELS can dynamically alter oscillatory activity of hippocampal-PFC circuitry.

## Effects of Interictal Spikes on the Developing Brain

In addition to seizures, interictal spikes (IIS) can result in cognitive impairment in both rats and humans. Following intrahippocampal pilocarpine infusion, rats develop IIS that result in transient impairment in the delayed-match-to-sample test, a hippocampal-dependent operant behavior task<sup>72</sup>. Hippocampal IIS that occur during memory retrieval strongly impairs performance. However, IIS that happen during memory encoding or memory maintenance do not affect performance. In a similar study of people with temporal lobe epilepsy (TLE) who have bilateral depth electrodes implanted into their hippocampi for preoperative seizure localization, IIS cause transient memory impairment<sup>73,74</sup>. Hippocampal IIS occurring during the memory retrieval period decrease the likelihood of a correct response on a short-term memory test, the Sternberg task, when they arise bilaterally in both temporal lobes or in the temporal lobe contralateral to the seizure focus<sup>73</sup>. Because patients with TLE often have impaired memory in the epileptic hippocampus and require the non-epileptic hippocampus for memory, IIS arising from the damaged epileptic hippocampus have little effect on memory while IIS involving the intact non-epileptic hippocampus interfere with memory retrieval. As with rodents with TLE, patients with TLE and IIS have specific deficits in retrieval of memory while sparing other forms of memory.

IIS in rodents, similar to seizures, result in a sustained reduction of action potentials (APs) in the hippocampus for up to two seconds following IIS<sup>75</sup>. Furthermore, when occurring in flurries, defined as four or more IIS occurring within 10 sec, IIS can reduce APs firing for up to six seconds. The widespread inhibitory wave immediately following IIS can also reduce the power of gamma (>30 Hz) oscillations and other oscillatory signals in the hippocampus<sup>76</sup>. As will be discussed further, since gamma oscillations are closely coupled with ongoing learning and memory function, disruption in oscillations may contribute to cognitive deficits.

In adults with IIS, the cognitive effects are typically transient and may have little long-term consequences in cognitive function, unless they occur very frequently. However, in the immature brain, the effects of IIS also have long-term adverse effects on developing neural circuits. In interesting studies from the 1980's, IIS were elicited by either penicillin<sup>77</sup> or bicuculline<sup>78</sup> through focal application on the striate cortex of the occipital lobe of immature rabbits. IIS occurred for 6–12 hours following each drug application which was given daily starting from postnatal day 8–9 and continued for 3–4 weeks. None of the rabbits had behavioral or electrographic seizures. In single-unit recordings from the lateral geniculate nucleus, superior colliculus and occipital cortex ipsilateral to the occipital lobe with the IIS, an abnormal distribution of receptive field types was seen, whereas normal recording was present in the contralateral hemisphere. Remarkably, this finding is age-dependent. Adult rabbits with similarly induced IIS have a normal distribution of receptive field types, highlighting the vulnerability of critical developmental periods to cumulative IIS effects over time. Likewise, focally-induced IIS by stereotaxic injections of bicuculline in the prefrontal cortex (PFC) in rat pups for several days result in long-standing increases in short term plasticity in the PFC and marked inattentiveness during a spatial memory task, when the rats are tested as<sup>79</sup>.

To further study the effect of recurrent multifocal IIS during development, rat pups were given a low dose of flurothyl for four hours for 10 days during continuous EEG monitoring<sup>80</sup>. Rats developed IIS without seizures while age-matched controls under similar testing conditions had few IIS. When the rats were tested as adults, there was impairment in reference memory in the Morris water maze, working memory impairment in the four-trial radial-arm water maze and impaired long-term potentiation. Early-life IIS resulted in impaired new cell formation and decreased cell counts in the hippocampus but did not cause an increase in apoptosis. This study, for the first time, demonstrates that IIS in rat pups without seizures can result in long-standing spatial cognitive impairment. These findings suggest that suppressing IIS may be as important as treating seizures during brain development.

## Conclusions

In summary, while etiology of the seizures is the primary factor in cognitive outcome, rodent models of childhood epilepsy have shown that both seizures and IIS can be detrimental to brain development. With further refinement of our knowledge of the pathophysiological underpinnings of seizure-related cognitive deficits it is hoped that future therapies will target cognition as much as seizures. While not covered in this review, AEDs can also contribute to cognitive impairment in both children and animals. While suppressing seizures and IIS is an important goal, clinicians should be cognizant of the potentially detrimental effects of AEDs on the developing brain when making treatment decisions.

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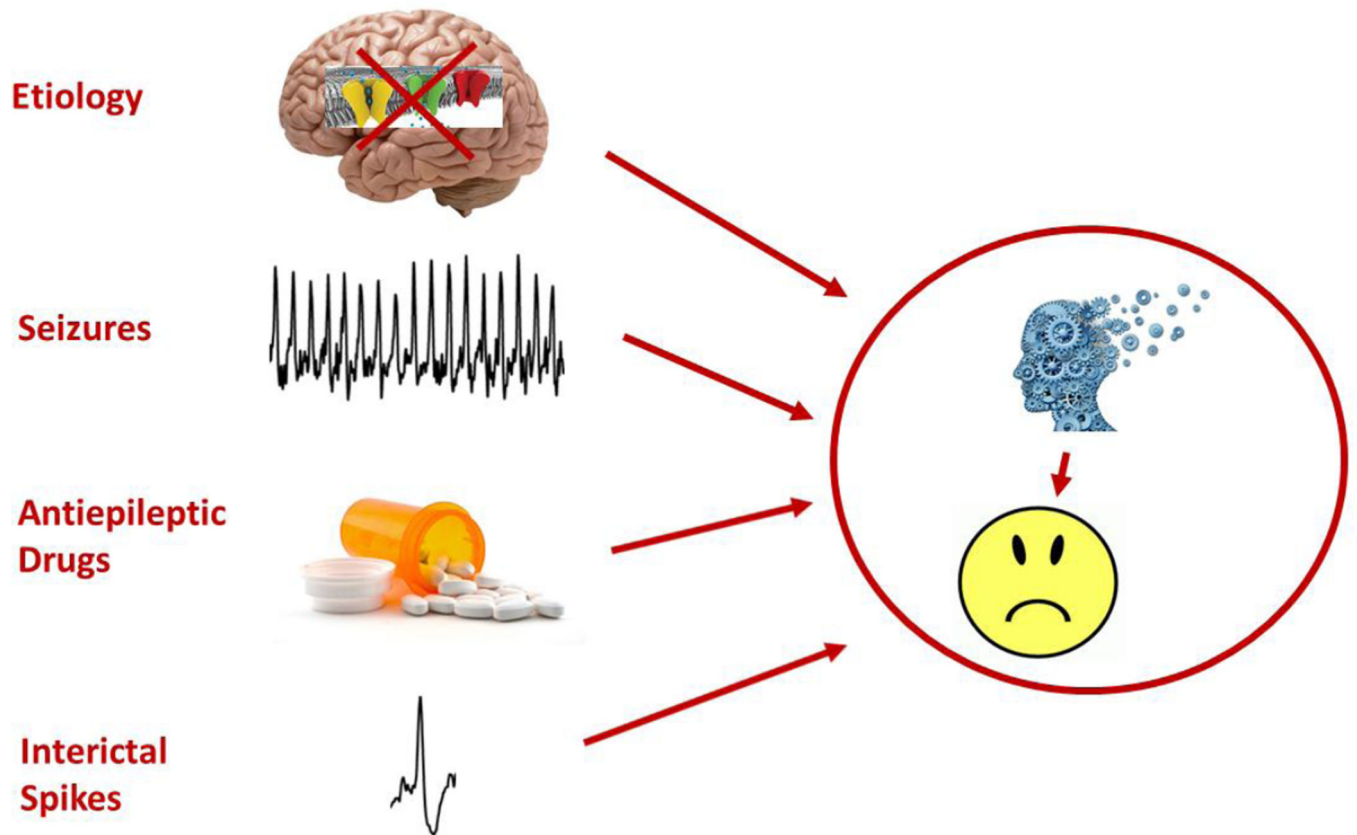
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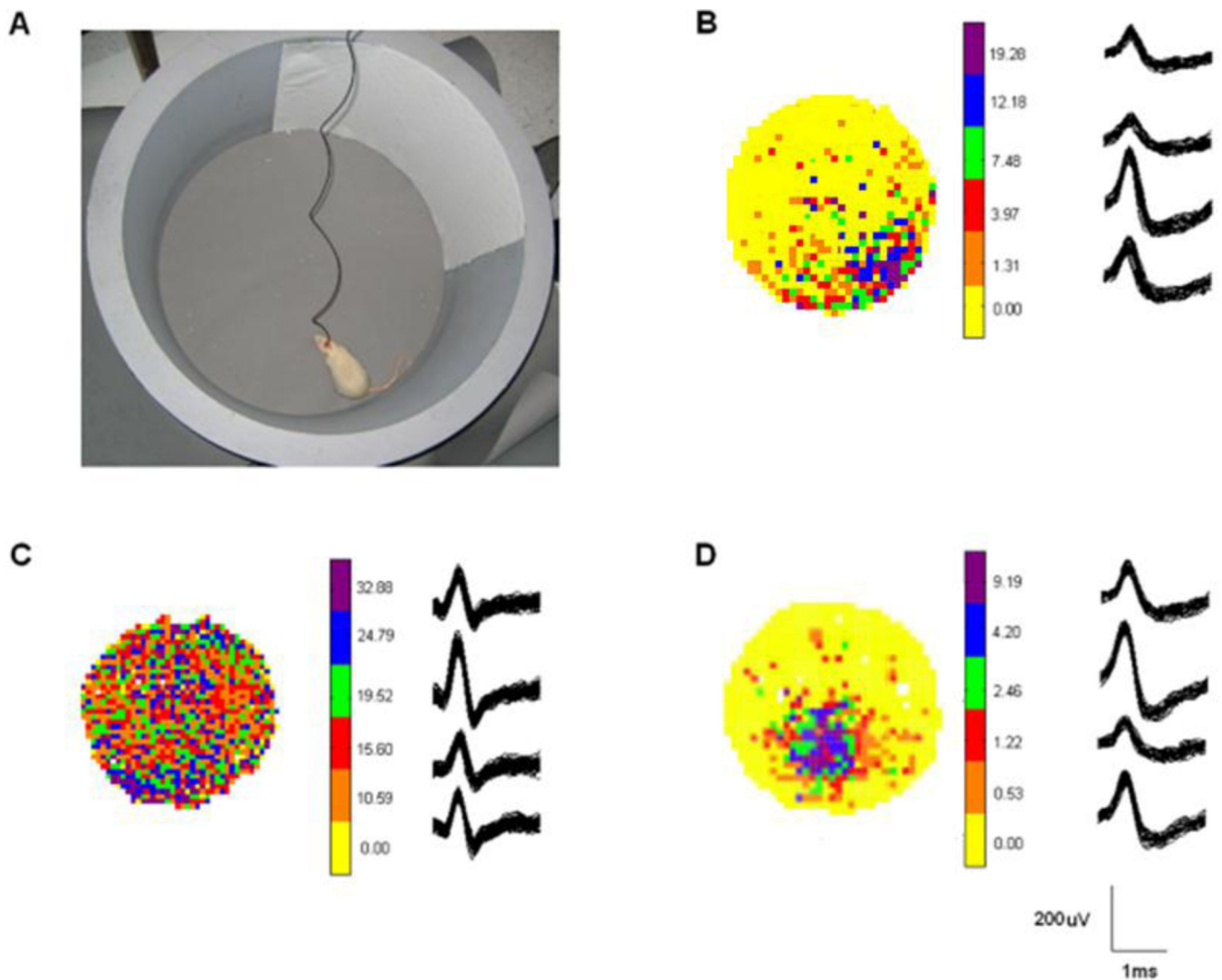
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**Fig. 1.**

There are many factors that determine cognitive outcome with early-life seizures. Etiology is the primary determinant of cognitive outcome. For example, channelopathies, such as occur in Dravet syndrome, may have major effects on cognition. Likewise, seizures, antiepileptic drugs and interictal spikes contribute to cognitive impairment.



**Fig. 2.**

Place cell recordings. The recording cylinder with cue card is shown in A. Examples of place cells (B,D) and an interneuron (C) are shown. The place cell in B is at approximately 5 o'clock while the place cell in D is at approximately 7 o'clock but is closer to the center of the cylinder than the cell depicted in B. Firing frequency is color coded. Yellow shows areas of the cylinder in which the cell did not fire while the green, blue and purple colors show high firing rates in the place firing field. Waveforms from the tetrodes are shown next to the color coded firing rates. The neuron recorded in C is an interneuron which shows a higher firing rate but no clear place preference.