Published in final edited form as:

Brain Dev. 2012 June ; 34(6): 469–477. doi:10.1016/j.braindev.2011.08.009.

Maturation of EEG Oscillations in Children with Sodium Channel Mutations

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Abstract

Dravet syndrome (DS) is a severe epileptic encephalopathy beginning in infancy in which children have difficulty to control seizures and cognitive impairment. The majority of children with DS carry mutations of the gene *Scn1a*, which codes for the α subunit of the type 1 voltage-gated sodium channel and is important for the function of interneurons. Interneurons have a critical role in the generation of brain rhythms involved in cognitive processing. We hypothesized that children with DS with *Scn1a* mutations would have abnormal oscillatory activity. To address this hypothesis, we used EEG power spectral analysis during the waking to determine if frequency and power are altered in 23 EEGs from 12 children with DS compared to 18 age-matched controls. While there were few differences between the EEG power spectra in DS and controls in children under 2 years, in older children group differences were apparent. In DS children between 3-5 years there were significant decreases in percentage of alpha power compared to controls and in DS children over age 6 years there was a marked increase of theta and decrease of alpha compared to controls. Developmental status paralleled the power spectral analysis with an increasing likelihood of having severe cognitive problems with increasing age. These results demonstrate that *Scn1a* mutations result in an age-dependent alteration in oscillatory process. Such abnormalities in developmental progression of oscillations may play an important role in poor cognitive development in children with DS.

Keywords

Dravet syndrome; *Scn1a* mutation; age-dependent alteration; brain oscillation; spectral analysis; Severe Myoclonic Epilepsy in Infancy

Introduction

Dravet syndrome (DS), also referred to as Severe Myoclonic Epilepsy in Infancy, is a severe epileptic encephalopathy in which children have medically intractable epilepsy and cognitive impairment [1, 2]. The condition often begins with atypical febrile seizures and progresses to include generalized myoclonic, clonic, tonic-clonic and atypical absences [3,

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4]. The electroencephalogram (EEG) is often normal in the first year of life but eventually evolves into a pattern with spikes and spike-wave discharges during the interictal period [5].

Typically, infants develop normally during the first year of life, prior to the onset of medically intractable epilepsy. However, beginning in the second year of life a progressive decline is observed in multiple domains of cognitive function, including psychomotor and visuospatial abilities [1, 6, 7]. While early-life seizures are perhaps the most striking feature of DS, the most debilitating consequences of the syndrome are the associated cognitive and behavioral impairments. In most patients, normal development is halted in the first few years of life and rarely improves, despite a tendency for seizures to decrease with increasing age [6-8].

Approximately 80% of patients with DS carry mutations of the gene *Scn1a*, which codes for the type I voltage-gated sodium channel (Nav1.1) [9, 10]. There is evidence that *Scn1a*-associated epileptic disorders are caused by selective impairments of firing in inhibitory interneurons [11-13]. Nav1.1 has been found to colocalize with parvalbumin (PV)[14], a marker for interneurons that are predominantly basket, chandelier and axo-axonic cells in morphology [15]. PV positive interneurons are characterized as fast-spiking GABAergic cells that play critical roles in the spatiotemporal patterning of neural networks, especially during cognitive processes [16].

Brain rhythms have a major influence on brain function. In rodents, theta rhythm (4-10 Hz) is critically involved in mnemonic function of the hippocampus [17, 18]. Information arriving in the hippocampus with theta oscillations is stored in the hippocampus whereas information arriving in the absence of normal theta activity is not encoded or not encoded with the same degree of precision as when theta is present [18-20]. Phase of theta is critical in learning and memory: tetanic stimulation in CA1 produces long-term potentiation (LTP) when administered at the peak of theta and long-term depression (LTD) when delivered at the trough [21]. Temporarily suppressing hippocampal theta during a spatial memory task markedly impairs performance which can be reversed when the precise frequency of theta is restored to the animal [22]. Gamma oscillations (30-100 Hz) are also instrumental in the processing or perceiving of sensory information [23, 24], consciousness [25, 26] and storage of immediate memories [27-29]. Human data have also demonstrated the importance of brain oscillations and cognition, particularly memory [30-32].

As *Scn1a* plays a role in brain oscillations and alterations in brain oscillation patterns have been associated with developmental delay [33]), we hypothesized that children with DS would have altered brain oscillations when compared to similarly aged children without DS. A secondary hypothesis was that with age, oscillatory patterns in children with DS would mature differently from controls and parallel the deterioration in cognitive abilities. We report here that power spectral analysis (PSA) in children with DS showed age-related differences in percentage of alpha and theta power and that these alterations in PSA paralleled developmental status.

Methods

Twelve children with DS with a total of 23 EEGs performed between ages 1-9 yrs and 18 similarly aged controls made up the study population. All children with DS had *Scn1a* mutations. Controls consisted of children referred to the laboratory for evaluation of possible seizures. All of the controls had normal EEGs. EEGs and developmental assessments were analyzed retrospectively. The study was approved by the Institutional Review Board of Dartmouth College.

Digital EEGs were recorded during the fully awake, drowsy and sleep states using the 10-20 System of Electrode placement. Investigators blinded to the developmental assessment evaluated two, 30 second epochs of artifact-free EEG during the awake states for spectral analysis. Wakefulness was assessed by detection of eye blinks and technologist observations. If there was any question about possible drowsiness the epoch was not evaluated. EEG segments were taken at a time when there was no generalized epileptiform activity.

PSA was conducted using Twin® EEG software (Grass Telefactor) using an average reference montage. Frequencies from 0-25 Hz were analyzed using a Fast Fourier Transform (FFT) with Hamming windowing, a sampling rate of 200 Hz, and epoch size of 256 Hz with a frequency resolution 0.781 Hz. Edge (defined as the frequency below which 90% of the power in the EEG was located), mean, and peak frequency and percentage of total power in the delta (0-4 Hz), theta (4-7 Hz), alpha (8-12) and beta (13-25) bandwidths for each channel were calculated.

Because of age-related changes in frequency and power of oscillations, the infants were arbitrarily stratified into three age groups at the time they had the EEG: 1-2 yrs: n = 5; 3-5 yrs: n = 10; 6-9 yrs: n = 8. The EEGs at these time points were compared to 18 similarly aged controls: 1-2 yrs: n = 6; 3-5 yrs: n = 6; 6-9 yrs: n = 6. Based on review of the medical records, developmental profiles were classified as normal, moderate and severe.

Assessments were made using the Denver Development Screening Test, a method for screening cognitive and motor performance in preschool children. Tasks were grouped into four categories (social contact, fine motor skill, language, and gross motor skill). Children with deficits in only one domain were classified as having moderate abnormalities while children with deficits in more than one domain were classified as having profound delays. All of the children in the study were evaluated by a pediatric neurologist (RPM or GLH) at Dartmouth-Hitchcock Medical Center.

EEGs were also assessed for epileptiform activity. Records were coded as having generalized epileptiform discharges, focal or multifocal discharges or no epileptiform discharges. Developmental assessments and PSA were compared in the children with and without generalized epileptiform discharges.

Developmental Assessments

All DS children in the study were evaluated at least once by a pediatric neurologist. Developmental assessments utilized portions of the Denver Screening evaluations [34]. This scale reflects what percentage of a certain age group is able to perform a certain task and groups abilities into four categories (social contact, fine motor skill, language, and gross motor skill). Children were considered delayed if they were unable to perform a task (direct observation or parental report) compared to age norms. Children were arbitrarily classified as having severe impairment if they were delayed 6 months or more in two or more categories and mild to moderate impairment if they were delayed in only one measure. For example a 17 month who had delayed language skills but was otherwise meeting age-normed developmental milestone in the other areas would be considered mildly/moderately impaired. In children over the age of six years IQ was obtained through either neuropsychological assessment with full scale IQ (moderate to profound impairment IQ < 50, mild intellectual impairment IQ 50-70). If the child was considered untestable because of cognitive status the child was classified as having profound impairment. All children used as controls were also evaluated by a neurologist and all were described as developmentally normal.

Statistical analysis

All data was assessed to determine if the data came from a Gaussian distribution using the D'Agostino and Pearson omnibus normality test. While the majority of the data had a Gaussian distribution, because of unequal group size we evaluated the data using non-parametric statistics. Edge, mean, and peak frequencies and relative percentage of power accounted for by delta, theta, alpha and beta frequencies were calculated and were compared between the two groups (DS and controls) using the Mann-Whitney U test (MWU). Because there were no differences in frequency or power of homologous electrodes placed over the left and right hemispheres, the data for right and left electrodes was combined. Data is presented as means $\pm$ SE and a p value of <0.05 was considered statistically significant.

Results

All of the children with DS had seizures, with the most common types being myoclonic, generalized tonic-clonic or clonic-tonic-clonic and atypical absence. All of the children were on one or more antiepileptic drugs (AEDs). A total of 13 different AEDs were used in addition to the vagal nerve stimulator and the ketogenic diet. The most commonly used AEDs at the time of the EEG included levetiracetam (12/23, 52.1%), valproate (10/23, 43.5%), topiramate (6/23, 26.1%) and clobazam (6/23, 26.1%). None of the control children were taking AEDs.

The mean age of the children in the three age groups did not differ between the DS and controls (1-2 yrs: DS -1.4 ± 0.3 , Cont. -1.7 ± 0.2 ; 3-5 yrs: DS -4.2 ± 0.3 , Cont. -4.3 ± 0.3 ; 6-9 yrs: DS -7.5 ± 0.4 , Cont. -7.3 ± 0.5 , all $p > 0.1$).

Figure 1 compares edge, mean and peak frequencies between children with DS and controls between 1-2 years old. There were few differences in the controls and DS children at most electrode locations. At some electrodes edge and mean frequencies were higher in the DS children than the controls. Figure 2 compares percentage delta, theta, alpha and beta in DS and control children between 1-2 years old. At a few electrodes pairs percent delta, alpha and beta frequency were higher in the DS group than the controls.

Figure 3 compares edge, mean and peak frequencies in children with DS and controls between 3-5 years old. Other than a statistically significant increase in edge frequency in the controls compared to the DS children in C3/C4, no significant differences between groups were seen. Figure 4 compares percentage delta, theta, alpha and beta in DS and control children between 3-5 years old. At a few electrodes pairs per cent alpha and beta frequency were higher in the DS patients than the controls but this was not consistent across all electrodes.

Marked differences were seen in the DS children and controls after age 6 years. Increases in mean and peak frequencies were seen in a number of electrode pairs in the controls compared to the DS children (Fig. 5). Figure 6 compares percentage of delta, theta, alpha and beta in DS and control children between 6-9 years old. Compared to the controls the DS children had marked increases in percent theta and decreases of alpha activity.

To assess broad changes in PSA, the average percent of delta, theta, alpha and beta power were calculated by averaging data from each electrode for each EEG recording. Figure 7 shows that in children between 1-2 years no group differences were seen. Decreases in alpha power in the DS children compared to controls were present in the 3-5 age group and increases in theta and decreases in alpha in the 6-9 age group. For illustrative purposes, Figure 8 illustrates changes in delta, theta, alpha and beta activity as a function of age in the

DS and control groups. Percentage of alpha increased with age and theta decreased with age in the controls but not the DS children.

Epileptiform activity

Spikes, sharp waves and spike-wave discharges were seen in 20 out of 23 EEG recordings (87.0%) from the DS children. There was not a relationship between age and presence or absence of generalized discharges (1-2 years, no generalized spikes = 4; generalized spikes = 1; 3-5 years, no generalized spikes = 4; generalized spikes = 6; 6-9 years, no generalized spikes = 4; generalized spikes = 4).

Developmental assessments

Developmental assessments were obtained on 12 children with DS. Five of the 12 children with DS were evaluated more than once, e.g. a child may have been evaluated once between 3-5 years and again after age six years. Within each of the age groups only one evaluation per child was used. There was a relationship between age and developmental status. Of four children with DS studied at 1-2 years of age one was normal and three had mild to moderate delay; of seven children between 3-5 years none were normal, four had mild to moderate delays and two had severe delays; of six children 6-9 years, none were normal, one had mild delays and five had severe delays (Chi square = 10.07, $p=0.039$). There was no relationship between developmental status and presence of generalized spike-wave on the EEG ($p > 0.1$; data not shown).

Discussion

In this study we found that PSA of short epochs of waking EEG in children with DS showed age-related alterations in background rhythms. Whereas EEGs from children with DS differed little from controls in children studied under 2 years of age, there was a failure of alpha to proportionally increase and theta to decrease with age. Compared to controls, children with DS between 6-9 years of age had marked increases in theta and decreases in alpha power. The PSA findings reflected development. Children with DS below the age of 6 years were less likely to have severe developmental delay than children 6 years of age or older. While epileptiform activity was present in the majority of the records, there was not a relationship between generalized discharges and cognitive status.

Other studies have demonstrated the relationship of background frequencies with cognitive function. For example, in a study of 95 children with epilepsy (mean age = 10.41 years) who had both EEGs and neuropsychological batteries performed, Koop et al. [35] showed that the presence of slow-wave activity, but not epileptiform activity, was related to memory impairment ($p < 0.01$). In a study of PSA in 200 infants between 6-24 months of age who were evaluated for seizures it was found that compared with the normal infants, children with developmental delay had lower mean frequencies and greater delta and less theta and alpha power [33]. In DS presence or absence of alpha activity was statistically related to whether the patient had severe or less severe mental deficits [36]. Of interest, Akiyama et al. [36] did not find a relationship between either generalized or focal spikes or episodes of convulsive status epilepticus and outcome.

As a retrospective, observational study, there are a number of limitations in the interpretation of the findings. Developmental assessments were gleaned from the medical record and the children were not evaluated in a systematic fashion. The number of patients evaluated was small and only group comparisons were made. It was not possible to make correlations between degree of PSA abnormalities and developmental status. The observation that children with marked abnormalities in PSA were more severely affected

than those without abnormalities does not necessarily mean that the abnormal oscillations cause the cognitive deficits. Rather the intellectual disability and altered PSA may be caused by other factors that influence both cognition and the EEG. Only if restoring normal oscillatory activity resulted in improved development could a causal relationship be more firmly proposed. It is possible that an underlying abnormality in Nav1.1, through impaired function of interneurons, causes epileptic discharges and abnormal oscillations, which contribute to impaired intellectual development in a parallel or additive manner. An important question that has not yet been addressed in human patients is whether restoring oscillatory activity would result in improved development of cognitive functions. Such a result would support a causal relationship between the two and offer new directions for therapy.

An important observation in this study was that alterations in oscillatory activity (in the theta and alpha bands) developed over the first 6-9 years rather than being markedly different at the time of early symptom onset. One interpretation is that this observation reflects an increasing deviation from controls during a time when development of oscillations in DS is halted and oscillations in the normal brain are still developing. Consistent with this interpretation, the initial signs of the DS phenotype in transgenic rodent models appear (by postnatal week 2) before other changes in interneuron physiology and oscillations normally fully mature (postnatal weeks 3 to 4)[12, 37, 38]. Although it is unclear precisely how the developmental time-course of these processes correlates to that in humans, we can speculate that an abnormality in Nav1.1 may impair the normal maturation of some developmental processes, including the development of oscillatory activity as observed during the first 6 to 9 years in children with DS in this study.

In summary, we found that children with DS have age-related alterations in oscillatory activity and that such changes in oscillations paralleled developmental status. Future challenges will be to determine if correcting the abnormal rhythms can improve cognitive status in these children.

Acknowledgments

This work was supported by the National Institutes of Health grant R01NS044295 (G.H).

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Fig. 1.

Comparison of edge, mean and peak frequencies in children with DS and controls between 1-2 years old. There were little differences in the controls and DS children at most electrode locations. At some electrodes edge and mean frequencies were higher in the DS children than the controls. ($p < 0.05 = *$).

Fig. 2.

Percentage delta, theta, alpha and beta in DS and control children between 1-2 years old. At a few electrodes pairs percent delta, alpha and beta frequency were higher in the DS group than the controls. ($p < 0.05 = *$)

Fig. 3.

Comparison of edge, mean and peak frequencies in children with DS and controls between 3-5 years old. Other than a statistically significant increase in edge frequency in the controls compared to the DS children in C3/C4, no significant differences between groups were seen. ($p < 0.05 = *$)

Fig. 4.

Percentage delta, theta, alpha and beta in DS and control children between 3-5 years old. At a few electrodes pairs percent alpha and beta frequency were higher in the controls than the controls. ($p < 0.05 = *$; $p < 0.01 = **$; $p < 0.0001 = ****$)

Fig. 5.

Comparison of edge, mean and peak frequencies in children with DS and controls between 6-9 years old. Increases in mean and peak frequencies were seen at some electrode pairs in the controls compared to the DS children. ($p < 0.05 = *$; $p < 0.01 = **$)

Fig. 6. Percentage delta, theta, alpha and beta in DS and control children between 6-9 years old. Compared to the controls the DS children had markedly increases in percent theta and decreases of alpha activity. ($p < 0.05 = *$; $p < 0.01 = **$; $p < 0.001 = ***$; $p < 0.0001 = ****$)

Fig. 7.

Changes in total delta, theta, alpha and beta activity as a function of age in the children with DS and controls. Note decreases in alpha power in the DS children compared to controls in the 3-5 age group and increases in theta and decreases in alpha in the 6-9 age group. No group differences were seen in children between 1-2 years ($p < 0.01 = **$)

Fig. 8.

Illustration of changes in delta, theta, alpha and beta activity as a function of age in the children with DS and controls. Percentage of alpha increased with age and theta decreased with age in the controls but not the DS children.