The possible role of GABAergic interneurons in EEG phase relationships: an exploratory case study of Dravet's Syndrome

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Abstract

Background: Dravet's Syndrome is an intractable epilepsy of infancy (ISIE) that typically occurs in Dravet's Syndrome is linked to a mutation in the SCN1A gene. This mutation leads to an alteration of Na_+ 1.1 channels, which is known to control the firing of thalamocortical structures and is linked to seizure activity in Dravet's Syndrome.

Methods: An 11-year-old subject with Dravet's Syndrome who also presented with Autism Spectrum Disorder (ASD) symptoms was examined. EEG data was collected on a Cadwell EASY11 system using the linked ear referenced 10-20 system montage. EEG phase z-score analyses using Neuroguide™ were used to assess deviations from normal neural functioning.

Results: Abnormal characteristics of phase shift and phase lock were clearly evident.

Conclusions: Deviant EEG phase relationships have been proposed as a descriptor of dis connectivity in ASD and now for Dravet's Syndrome. This may account for the similarity of Dravet's behavior to ASD. Further research on the exact manipulation of the phase relationships by methods of neural stimulation and/or pharmacological influence may not only prove the proposed model but yield a successful clinical protocol to treat Dravet's syndrome.

Case history

The subject of this case study is an 11-year-old male. He had a normal birth and development until he first onset of seizures around 8 months. Several pharmacological attempts failed including Phenobarbital, Tegretol, Keppra, Zonagen, Lamictal, Dilantin, and Flexerol. Seizures continued lasting 10 min to 2 hours. The subject reached developmental milestones until age 3 at which point he regressed to age 2 development. At age 3 a vague seizure stimulus was inserted, and it was turned off at age 8 when declared ineffective. Scheduled brain surgery was cancelled after results of genetic testing gave a diagnosis of Dravet's Syndrome at age 8.5.

Current Diagnosis: Dravet's Syndrome, ASD, ADHD, combined type, seizure type:
Developmental Disorder, 100 mg BID, Myoclonic jerks noted
Mixed Recepetive/Expressive Language Disorder
• Axis II: Severe Mental Retardation
• Axis III: Dravet's Syndrome

Background Information

Role of the SCN1A gene in Dravet's Syndrome and GABA: Mutations in the SCN1A gene on chromosome two are strongly associated with Dravet's Syndrome and thought to be a primary component of the disorder via effects on GABAergic mechanisms. Hypoactivity in the SCN1A gene (especially one copy of the gene) and knock-out (i.e., having no copies of the gene) of SCN1A has been shown to reduce current in Na_+ 1.1 channels, thereby inhibiting GABAergic interneurons in the hippocampus of mice (Yu et al. 2006).

GABA, EEG Phase Reser and Epilepsy: Thatcher et al. proposed that GABA (N-2,6-dihidroxy-N-methylglycine) is the most critical factor in controlling phase shift and phase lock. They identified specific characteristics in phase reset and termed them GABA. This phase involvement was defined as a necessity for normal brain function because inactivations of phase could lead to multiple disorders including Autism and epilepsy (Thatcher et al. in press 2008). Walker and Kozlowski (2007) further investigated GABAergic function with epilepsy and related the "evidence of epilepsy" that is a product of dysregulation of the hypothalamic structures.

Methods

• Cadwell EASY11 system on 19-channels using the 10-20 system with a linked ear montage was used.
• Data was collected via EEG phase z-score analyses using Neuroguide™
• EEG data was collected on 07/17/09, 08/07/09, 08/26/09, 09/07/09, 09/08/09, 08/26/09 and 08/28/09.

Results

Data were collected on 07/17/09, 12 min before myoclonic seizures were observed. Z-scores less than zero were consistently observed in all locations for phase shift duration in all bands except theta, regardless of medication dosage, day or presence/absence of myoclonic seizures (as shown in Figure 1). Theta phase shift (see figure 2) maintained an anterior/posterior imbalance regardless of day, medication dosage or presence/absence of myoclonic seizure activity. Data phase lock was inconsistent (see figure 3). Figure 4 describes a general pattern of phase difference among all the data collected. Figure 5 describes the most consistent observed phase lock interval for the data collected.

Discussion/Conclusions

This subject demonstrates consistencies in EEG phase relationships including phase shift and theta phase lock. With the exception of theta, all frequency bands had global Z<0 phase shift. Theta had Z<0 phase shift values along short distance connections but not along long distance connections. Phase lock was found to be Z>3 globally. These phase shift and phase lock findings are congruent with other findings in ASD as reported in in press 2008. The present study is also consistent with the correlation of Z<0 phase shift and Z>3 phase lock with lower IQ scores in in press 2008. Phase lock exhibited Z<0 or a mix of phase connectivity (especially Delta) scores and did not match the model proposed in Thatcher et al. in press 2008.

Thatcher et al. (in press 2009) investigated phase characteristics in Autism to GABA (A) and B) in the thalamus in controls and the thalamic network in GABA in the hippocampus region of mice as influenced by loss of current in Na_+ 1 channels. Yu et al. (2008) further go on to suggest that other genes controlling GABA are also strongly suspected to be components of the manifestations of Dravet's Syndrome.

The common thread in a general model of epilepsy, Dravet's Syndrome and ASD is GABA. This phase reset data indicates possible abnormalities in GABA in this subject. This subject's age-regressive symptoms associated with Dravet's also mimic that of a Pervasive Developmental Disorder. This matching of symptoms and phase characteristics of the model of Thatcher et al. (in press 2008) along with the known influence of the SCN1A gene on GABA further suggests that the model of GABA exists as a component of both these disorders and that GABA might be a contributing factor to the manifestation of symptoms in both disorders. This similarity of a GABA driven change may also explain the similar behaviors associated with ASD and Dravet's Syndrome.

Not all phase characteristics found in this subject with Dravet's Syndrome match previous findings in Autism (Thatcher et al. in press 2008). In the model of Thatcher et al. (in press 2008), sodium channels are responsible for the mechanism of GABA-mediated phase reset characteristics. Thatcher et al. (in press 2008) also focused on the thalamic network in their model while Yu et al. (2006) only explored the hippocampal region.

This study has several limitations. The sample size is not the largest, the data collected is only eyes-open. The data collected was task-oriented with specific stimulus (watching a movie), and the normative database used does not have such conditions among recorded. All data collected while the subject was taking numerous medications to what extent they are distorting the results here remains uncertain. However, medication changes did not affect some of the EEG phase characteristics.

Future research might include a greater sample size, a collection of eyes-closed data as well as the subjects who have Dravet's Syndrome but aren't under the influence of medication. Eyes-open data with the addition or removal of stimulus would allow for more accurate data as compared to norm. Manipulation of phase relationships via methods of neural stimulation and/or pharmacological mechanisms could serve to validate the proposed model. Furthermore such exploration could yield a reduced functional analysis of Dravet's Syndrome and ASD.

References


Figure 1: Phase shift values for (a) 1‐4 Hz, black outline, (b) 8‐12 Hz, gray outline, (c) 12‐25 Hz, green outline) and high beta (25‐30 Hz, orange outline). As seen in legend below, colors within each panel correspond to standard deviations from normal.

Figure 2: Theta phase shift (red outline) as observed on multiple days and times. Seizure presence is indicated by a red lightning bolt. Phase shift value for short distances was Z<0. See color legend in figure one.

Figure 3: Inconsistencies in Delta z-score average phase locking interval. No consistent pattern matched with seizure occurrence, medication, or day.

Figure 4: Overall phase difference values maintained continually throughout data collection. See color legend in figure one.

Figure 5: The most consistent observed element was theta z-scored phase lock interval which was universally Z<3 on all EEG data collected. See color legend in figure one.