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

Daniel M.Tuttle, LCSW
Psychological Sciences Institute, John's Creek GA

Abstract

Background: Dravet's Syndrome or Severe Myoclonic Epilepsy of Infancy (SMEI) is a form of intractable epilepsy developing during the first year of life and thereafter. Psychomotor delay and a variety of cognitive impairments typically occur. Dravet 's Syndrome is linked to a mutation of the SCN1A gene. This mutation leads to an alteration of $Na_v1.1$ channels, which is known to impair GABAergic inhibitory interneurons and is linked to seizure activity in Dravet's Syndrome.

Method: 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 EASY-II system using the linked ear referenced 10-20 system montage. EEG phase z-score analyses using Neuroguide™ was used to assess deviations from normal neural functioning.

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

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

Case history

The subject of this case study is an 11-year-old male. He had a normal birth and development until febrile onset of seizures around 8 months. Several pharmacological attempts failed including Phenobarbitol, Tegretol, Keppra, Zonegran, Lamictal, Dilantin, and Felbatol. 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 5 a vagus nerve stimulator 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:
•**Axis I:** Pervasive Developmental Disorder, NOS. ADHD, combined type, severe.
Mixed Receptive/Expressive Language Disorder.
Developmental Coordination Disorder.
•**Axis II:** Severe Mental Retardation
•**Axis III:** Dravet's Syndrome

Medications:
Data collected 07/14/09 to 08/07/09
•Depakote 500 mg AM and 625 mg PM
•Topomax 100 mg BID
•Clobozam 5 mg BID
•Triple Bromide 344 mg daily
Changes for data collected 08/26/09
•Depakote 250 mg AM and 375 mg PM
•Topomax 50 mg AM and 100 mg PM
•Banzel 100 mg BID
•Changes for data collected 08/28/09
•Banzel 200 mg BID

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 interneurons. Haploinsufficiency (i.e. having only one copy of the gene) and knockout (i.e. having no copies of the gene) of SCN1A has been shown to reduce current in the $Na_v1.1$ channels, thereby affecting GABAergic interneurons in the hippocampus of mice (Yu et al. 2006).

GABA , EEG Phase Reset and Epilepsy: Thatcher et al. proposed that GABA (A) & (B) localized to the thalamus control phase shift and phase lock. They identified specific characteristics in phase reset and linked them to GABA. This phase involvement was defined as a necessity for normal brain function because imbalances of phase could lead to multiple disorders including Autism and epilepsy (Thatcher et al. in press 2008). Walker and Kozlowski (2007) further instigated GABAergic deficiencies with epilepsy and also referenced the "body of evidence" that epilepsy is a product of dysregulation of the thalamocortical structures.

Methods

•A Cadwell EASY II system on 19-channels using the 10/20 system with a linked ears montage was used.
•Neural functioning was evaluated via EEG phase z-score analyses using Neuroguide™
•Eyes-open data was collected 01/13/09, 05/20/09,07/14/09, 07/17/09, 08/05/09, 08/07/09, 08/26/09 and 08/28/09.
•At least 60 seconds of artifact-free eyes open data was collected in each analysis. Due to the inability of the subject to keep his eyes closed and not move, eyes-open data was task oriented with the subject watching a movie on the TV screen directly in front of him, allowing for a stationary posture and minimized eye movement.

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 (see 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 . Delta phase lock was inconsistent (see figure 3). Figure 4 describes a general pattern of phase difference/lag seen throughout the data collected. Figure 5 shows the most consistent z-scored phase lock value of theta phase lock greater than three.

Figure 1: Phase shift values for delta (1-4 Hz, black outline), alpha (8-12 Hz, grey outline), beta (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.

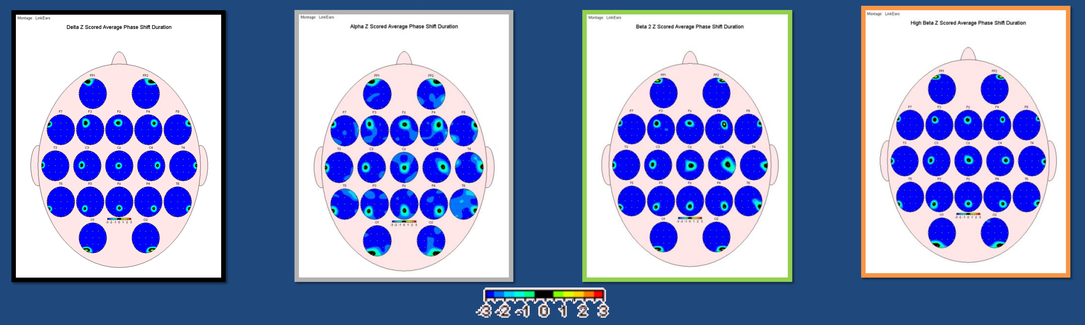
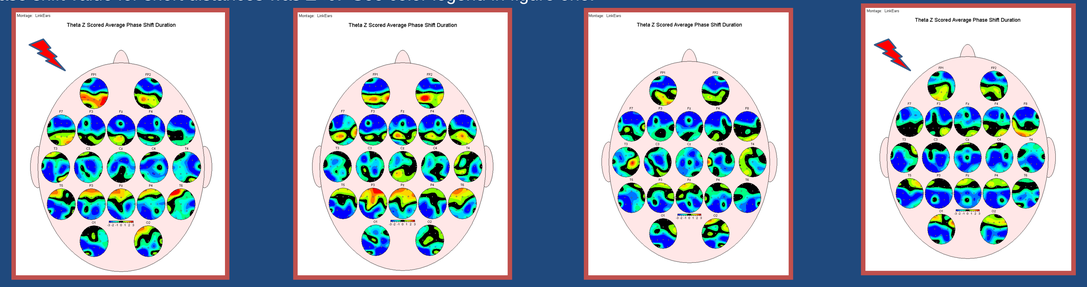


Figure 2: Theta phase shift (red outline) as observed on multiple days and times. Seizure presence is indicated by a red lightning bolt. Phase shift value for short distances was Z<0. See color legend in figure one.



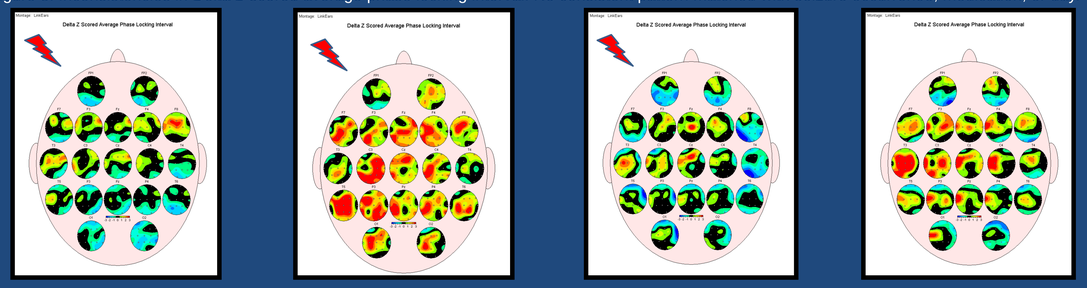
•08/07/09
•10 minutes into recording
•Myocolinics noted in right arm

•08/07/09
•17 minutes into recording
•No seizure noted

•08/28/09
•6 minutes into recording
•No seizure noted

•08/26/09
6 minutes into recording
•Multiple myoclonic seizures

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

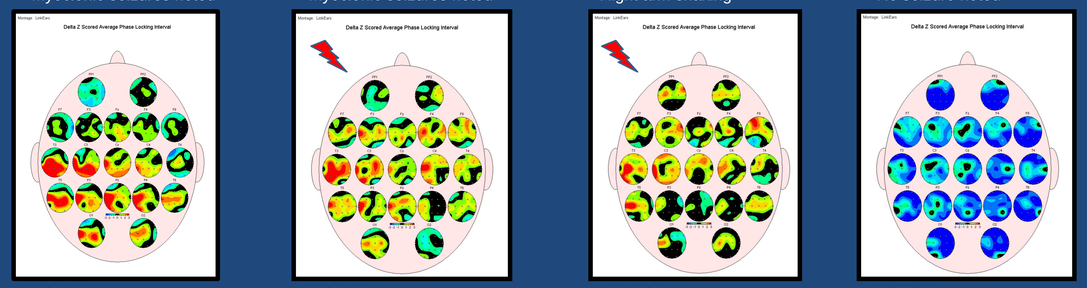


•07/14/09
•10 minutes into recording
• Myoclonic seizures noted

•07/17/09
•14 minutes into recording
•Myoclonic seizures noted

•08/07/09
•10 minutes into recording
•Right arm shaking

•08/07/09
•17 minutes into recording
•No seizure noted



•08/21/09
•17 minutes into recording
•No seizure noted

•08/26/09
•9 minutes into recording
•Myoclonic seizures noted

•08/26/09
•16 minutes into recording
•Multiple myoclonic seizures

•08/28/09
•6 minutes into recording
•No seizure noted

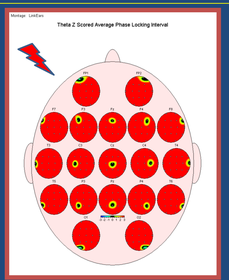
Figure 4: Overall phase difference values maintained continuity throughout data collection. See color legend in figure one.

•08/07/09
•10 minutes into session
•Myoclonic jerks noted

•08/07/09
• 17 minutes into session
• No seizure noted

•08/28/09
•6 min
• No seizure noted

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



Discussion/Conclusions

This subject demonstrates consistencies in EEG phase reset 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 in short distance connections but in only some long distance connections. Phase lock in theta was found to be Z>3 globally. These phase shift and phase lock findings are congruent with other findings in Autism (Thatcher et al. in press 2008). The present study is also consistent with the correlation of Z<0 phase shift and Z>0 phase lock with lower IQ (Thatcher et al. in press 2008). Phase lock in other bands exhibited Z<0 or a mix of phase connectivity (especially Delta) scores and did not match the model proposed by Thatcher et al. (in press 2008).

Thatcher et al. (in press 2008) attributed phase characteristics in Autism to GABA (A) and (B) in the thalamus. Yu et al. (2006) explored the influence of the SCN1A gene on GABAergic interneurons in the hippocampal region of mice as influenced by loss of current in $Na_v1.1$ channels. Yu et al. (2006) further go on to suggest that other genes controlling GABA are also strongly suspected to be components of the manifestation 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 alterations 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 with the model of Thatcher et al. (in press 2008) alongside the known influence of the SCN1A gene on GABA further enhances an argument that 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 influence might also explain the similarity in the 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 not suggested as instigators of GABA abnormalities and resultant phase reset characteristics. Thatcher et al. (in press 2008) also focused on the thalamus in their model while Yu et al. (2006) only explored the hippocampal regions.

This explorative study has multiple limitations. The sample size is n=1. The data collected is only eyes-open. The data collected was task-oriented with specific stimulus (watching a movie), and the normative database used did not have such conditions when being recorded. All data was collected while the subject was taking numerous medications and to what extent they are distorting the results here remains unknown. However, medication changes did not affect some of the EEG phase characteristics.

Future investigations might include a greater sample size, a collection of eyes-closed data as well as subjects who have Dravet's Syndrome but aren't under the influence of medication. Eyes-open data with the omission of video stimulus would yield more accurate data as compared to norms.

Manipulation of phase relationships via methods of neural stimulation and/or psychopharmacological methods could serve to validate the proposed model. Furthermore such exploration could yield a successful clinical protocol to treat Dravet's Syndrome symptoms.

References

Thatcher, R. W., North, D. M., Neubrander, J., Biver, C. J., Cutler, S., and DeFina, P. (in press): Autism and EEG phase reset: deficient GABA mediated inhibition in thalmo-cortical circuits. 2008.

Walker, J.E. and Kozlowski, G.P. (2005): Neurofeedback treatment of epilepsy. *Child and Adolescent Psychiatric Clinics of North America*. 163-176.

Yu F.H., Mantegazza, M., Westenbroek, R., Robbins, C.A., Kalume, F., Burton, K.A., Spain, W.J., McKnight, G.S., Scheuer, T. & Catterall, W.A. (2006, September): Reduced sodium current in GABAergic interneurons in a mouse model of severe myoclonic epilepsy of infancy. *Nature Neuroscience, 9*,1142-1146.