## Quantitative EEG in Pediatric Epilepsies

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## Quantitative EEG-Spectral Analysis

- Every wave is a mixture of different frequencies
- Spectral analysis is used to separate the wave into different frequencies
- Fourier Transform analysis

$$f(\xi) = \int_{-\infty}^{\infty} f(x) e^{-2\pi i x\xi} dx$$







alfa

beta

teta

delta

5 -0

10 20 Hz

30

## **Dravet** Syndrome

- An epileptic encephalopathy of early childhood with ominous course
- Unusually severe febrile seizures developing during the first year of life
- Towards the second year of life, various kinds of seizures appear (myoclonic, generalized tonic clonic, partial with generalization, partial complex and atypical absences)
- Towards the end of the second year of life developmental delay becomes evident
- Cognition continues to deteriorate and will ultimately lead to mental retardation, usually in the mild to moderate range

# SCN1A gene mutations- nonsense vs. missense

- SCN1A gene, encoding for the Nav.1.1. voltage gated sodium channel
- Hundreds of mutations have been described, some of them (nonsense or frameshift) leading to premature truncation of protein and severe clinical phenotype, while missense mutations may lead to milder clinical picture



### Brain oscillation in DS

- As was presented by Gregory L. Holmes (2012) the oscillatory activity in DS is slower, and the continuous alteration is age- dependent.
- Such abnormalities in developmental progression of oscillations may play an important role in poor cognitive development in children with DS.
- In our work we show the impact of nonsense mutations vs. missense on background activity in DS.

### Methods

- 12 children with SCN1A mutations (truncating/missense) on the DS/GEFS+ spectrum between the ages of 3-16
- Patients files were collected to sort out age/gender/mutation/drugs treated
- 52 EEGs collected from 10 of the 12 children with DS
- Sampling of 30 sec epochs of artifact-free during awake/eyes closed/sleep
- Power spectral analysis of the samples was done. Recordings obtained form standard F3,FZ, F4, C3, Cz, C4 electrodes was imported to Matlab 6.5 for Windows (Mathworks Inc.)be digitally and subsequently lowpass filtered with cut-off frequency ~ 40 Hz. Power spectrums was generated utilizing Welch algorithm. Data between 1 and 40 Hz was subjected to further analysis by Fourier Transform analysis.
- Calculation of alfa/beta/delta/teta and mean frequencies

#### Results

10 patients, 5 missense , 5 truncating mutations

Age: 7.91667 ±4.23102 (3-16)

AED: 2.34 (2.23 vs. 2.57, NS) Both groups were treated by the same AED, with no significant relief or control of seizures

52 EEG recordings: Eyes open, awake: 20, Eyes closed, awake:7, Sleep: 25

#### Spectral analysis of sleep EEG epochsstatistical results

	Fz_S	SLEEP		F3_S	SLEEP		F4_S	SLEEP	
	Missense	Nonsense	P (T Test)	Missense	Nonsense	P (T Test)	Missense	Nonsense	P (T Test)
Mean	11.76±1.8	5.94±0.7	* p<0.01	11.5±2.5	10.06±0.2	, , , , , , , , , , , , , , , , , , ,	11.9±1.8	10.64±1.3	, ,
Delta	0.2923±0.6	0.4676±0.003	* p<0.01	0.2966±0.08	0.3548±0.03		0.2814±0.06	0.3297±0.05	
Theta	0.1626±0.04	0.2657±0.06	* p<0.05	0.1725±0.04	0.1817±0.01		0.1699±0.04	0.1882±0.03	
Alpha	0.2523±0.03	0.2211±0.05		0.2461±0.03	0.2453±0.04		0.2461±0.02	0.2337±0.02	
Beta	0.2926±0.08	0.0456±0.003	* p<0.01	0.2846±0.1	0.218±0.003		0.3024±0.08	0.2483±0.05	

	Cz_SLEEP			C3_SLEEP			C4_SLEEP		
	Missense	Nonsense	P (T Test)	Missense	Nonsense	P (T Test)	Missense	Nonsense	P (T Test)
Mean	11.73±2.04	7.005	* p<0.05	11.53±2.5	10.61±0.9		12.38±1.6	11.16±1.9	
Delta	0.2854±0.07	0.4605	* p<0.05	0.289±0.08	0.3195±0.01		0.2621±0.05	0.289±0.06	
Theta	0.1678±0.03	0.2023		0.1752±0.04	0.1885±0.03		0.1641±0.02	0.1933±0.05	
Alpha	0.2567±0.02	0.2415		0.2517±0.02	0.2506±0.01		0.2508±0.02	0.249±0.02	
Beta	0.2898±0.09	0.0957		0.2839±0.1	0.2413±0.04		0.3229±0.07	0.2686±0.08	

Hypothesis Test Summary								
	Null Hypothesis	Test	Sig.	Decision				
85	The distribution of Meanfr_SLEEP_fz is the same across categories of 1-m, 2- truncating.	Independent- Samples Mann- Whitney U Test	.036 <sup>1</sup>	Reject the null hypothesis.				
87	The distribution of Delta_SLEEP_ is the same across categories of 1 m, 2-truncating.	Independent- fzSamples Mann- Whitney U Test	.0361	Reject the null hypothesis.				
90	The distribution of Beta_SLEEP_ is the same across categories of 1 m, 2-truncating.	Independent- fzSamples - Mann- Whitney U Test	.0361	Reject the null hypothesis.				

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Asymptotic significances are displayed. The significance level is .05.

<sup>1</sup>Exact significance is displayed for this test.

Slower background activity for truncating mutations vs missense mutations in sleep samples



Mean Frequency Sleep

Nonsense Missense









#### Theta % Sleep

#### Discussion

- This study manage to show how PSA of short epochs EEG in children with DS have worse alterations in background rhythms of nonsense mutations.
- We found that patients with nonsense mutations show an increase in Delta power and a decrease in Alpha and Beta power in Fz, Cz electrodes.
- The Mean frequency in patients with truncating mutations was lower.
- The PSA findings reflect development. As presented in former studies, presence of slow-wave activity, but not epileptiform activity, was related to cognitive impairment.



## Vagal Nerve Stimulator





- Antiseizure drugs are the primary treatment modality for patients with epilepsy.
- One-third of patients with epilepsy have refractory or drug-resistant seizures.
- When medications are not enough to control seizures, physicians often turn to nonpharmacologic options, such as VNS.



- The VNS transmitter is placed subcutaneously wile the wire is attached to the cervical part of the Vagus nerve.
- Electrical pulses reach the Vagus and as a result neurotransmitters decrees in their action in a desensitization mechanism.

#### Brain oscillation in VNS patients

- VNS have been shown to be associated with improvement of cognitive functions, mood and alertness in patients with refractory epilepsy.
  (Rizzo 2004)
- This improvement is associated with the background activity, showing higher mean frequency and an increase in Theta rhythm. (Marrosu 2005)
- Using the same quantitative EEG SA, we compared the background activity of our patients before the VNS transplant and after.
- Our goal was to find out if changes in the background activity are visible.

#### Methods

- 17 children with VNS (102 Pulse <sup>™</sup> and 103 Demipulse <sup>™</sup>) ages of 5-17
- Patients files were collected to sort out age/gender/drugs treated
- 17 EEGs collected from all children with VNS, before and after the transplant (total of 34 EEGs)
- Sampling of 30 sec epochs of artifact-free during awake/eyes closed/sleep
- Power spectral analysis of the samples was done. Recordings obtained form standard F3, F4, T3, T4 electrodes was imported to Matlab 6.5 for Windows (Mathworks Inc.) be digitally and subsequently lowpass filtered with cut-off frequency ~ 40 Hz. Power spectrums was generated utilizing Welch algorithm. Data between 1 and 40 Hz was subjected to further analysis by Fourier Transform analysis.
- Calculation of alfa/beta/delta/teta and mean frequencies

#### Results

10 patients with proper EEGs recordings were analyzed at this point.

Age before VNS: 12.42 ±3.87 Age after VNS: 14.23 ± 4.35

AED: 2-3

30 EEG recording samples: Eyes open- awake: 12 Eyes closed- awake: 8 Sleep: 10

#### Spectral analysis of Eyes open EEG epochs

	T3 Eyes	s Open		T4 Eyes		
	pre vns	post vns	Р	pre vns	post vns	Р
mean	10.50±2.99	10.19±2.32		11.03±1.8	10.36±1.8	
delta	0.2850±0.09	0.2626±0.07		0.2676±0.06	0.2635±0.06	
theta	0.2098±0.04	0.2184±0.03		0.2059±0.04	0.2161±0.03	
alpha	0.2669±0.01	0.3024±0.05		0.2688±0.02	0.2990±0.05	
beta	0.2382±0.14	0.2167±0.1		0.2578±0.08	0.2214±0.08	

	F3 Eye	es Open		F4 Eye		
	pre vns	post vns	Р	pre vns	post vns	Р
mean	10.53±1.4	10.47±2.4		11.29±1.8	8.72±1.9	<0.05
delta	0.2930±0.05	0.2768±0.08		0.2558±0.05	0.3243±0.07	
theta	0.2197±0.004	0.2208±0.02		0.2007±0.05	0.2175±0.07	
alpha	0 2480+0 02	0 2692+0 005		0 2695+0 01	0 2912+0 05	
beta	0.2393±0.06	0.2333±0.1		0.2740±0.1	0.1670±0.07	<0.05

Nonparametric- Wilcoxon signed-rank test was preformed.

✤ No conclusive results.











## Our next goals

#### Dravet syndrome:

Find controls for our DS patients. We believe that in comparison to controls DS patients will show even a more significant alteration in background activity.

#### VNS:

A new model of VNS (106 AspireSR™) has been transplanted in our patients. Although no conclusive results were found, comparing background activity before and after transplant, we hypothesize that in comparison to the new VNS, alteration will show.

## Grateful for the opportunity...



