CHANGES IN VEP INDICES OF CORTICAL LATERAL INTERACTIONS WITH EPILEPSY TREATMENT

Mary M. Conte, Anastasiya Ashurova, Laura Ponticello, Erik J. Kobylarz, Douglas R. Labar, and Jonathan D. Victor

Department of Neurology and Neuroscience, Weill Medical College of Cornell University, New York, NY 10021

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PURPOSE

Vagus nerve stimulation (VNS) is a neurostimulation therapy for refractory epilepsy. The purpose of this study was to determine the effects of long-term VNS treatment on cortical lateral interactions reflected in the steady-state VEP, and to compare these effects with those previously seen in epilepsy patients treated with gabapentin. Both treatments are believed to modulate cortical GABAergic inhibition.

Vagus nerve stimulation (VNS) is delivered through a pacemaker-like pulse generator surgically implanted into a subcutaneous pocket in the left chest area below the left clavicle or in the left axilla.

METHODS

VNS PATIENTS - 11 patients with epilepsy. All had clinical benefit with VNS treatment (5M, 6F; mean age: 39 yrs).

Inclusion Criteria
- VNS treatment > 1 year
- Stable seizure medications > 1 month
- VA corrected to 20/40 or better OU

Exclusion Criteria
- Photosensitive seizures
- Seizures within 24 hrs prior to VEP testing
- Evidence of occipital lesions on imaging studies
- Ophthalmological disease that might affect VEPs

CONTROLS - 22 age-matched normal subjects (15M, 7F; mean age: 34 yrs).

VNS Patient Characteristics

Pt.	Sex	Age	Epilepsy Class	Seizure Type(s)	Seizure Medications
01	M	51	Localized	CPS	Topamax
02	F	31	Localized	CPS	Tegretol
03	F	46	Localized	CPS	Topamax, Dilantin
04	M	31	Localized	CPS + SG	Tegretol, Keppra
05	M	27	Localized	CPS + SG	Keppra, Zonegran
06	F	23	1° Generalized	PGTC, Myoclonic	Depakote, Trileptal
07	M	48	1° Generalized	PGTC, Myoclonic	Dilantin, Klonopin, Keppra
08	M	54	Localized	CPS	Dilantin
09	F	41	Localized	CPS + SG	Tegretol, Mysoline
10	F	26	Localized	CPS	Tegretol, Keppra
11	F	47	Localized	CPS + SG	Tegretol, Lamictal

VNS Therapy - Device Settings

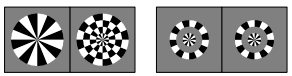
Pt.	Duration(yrs)	VNS Dose[1]	On/Off Cycle (sec)	Current (mA)	Freq (Hz)	Pulse Width (μs)
01	7.0	0.962	30 / 48	2.50	30	500
02	6.0	0.192	30 / 48	0.50	30	500
03	5.0	0.092	7 / 12	0.25	30	500
04	3.5	0.326	30 / 108	1.50	30	500
05	6.5	0.096	7 / 66	1.00	30	750
06	4.5	0.276	7 / 12	0.75	20	500
07	10.3	0.461	7 / 12	1.25	30	500
08	8.0	0.645	7 / 12	1.75	30	500
09	7.0	0.045	30 / 300	0.50	20	250
10	2.9	0.184	7 / 12	0.50	20	500
11	4.7	0.184	7 / 12	0.50	30	750

CPS: complex partial seizures
SG: secondary generalized seizures
PGTC: primary generalized tonic-clonic

VNS Dose[1] = Duty Cycle x Current (Harden, C. et.al., *Epilepsy & Behavior* 1, 93-99 (2000))

STIMULI – These consisted of contrast-reversal checkerboards and the radial windmill/dartboard pattern (Zemon & Ratliff, *PNAS*, 1982) shown on the right.
Modulation rate: 4.19 Hz., Contrast:0.3.
Binocular viewing at 1 m.
Field size: 8.8 x 8.8 deg.

Windmill/Dartboard Stimuli



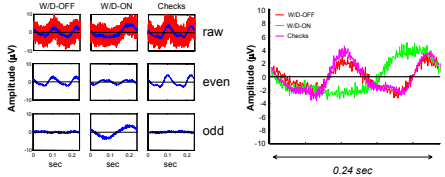
The modulated regions are identical in the W/D-ON and W/D-OFF configurations, but the static region is present only in the W/D-ON configuration. Thus, interactions between these regions may result in differences between the VEPs that the two stimuli elicit.

PROCEDURE - For the patients, single channel (Oz-Cz; grd: mastoid) steady-state VEPs were recorded with the VNS stimulator on (STIM-ON) and off (STIM-OFF) in recording sessions separated by approximately one hour. The order of the recording sessions was counterbalanced across patients. Two surface electrodes were placed over the sternocleidomastoid muscle near the surgical scar, to detect the activity of the VNS stimulator. In the STIM-ON condition, trials (duration: 30 sec) were initiated when the stimulator cycled off as evidenced in the neck recordings or in the EEG tracing. For patients whose off-cycle duration was less than 48 sec, the off-cycle duration was extended to allow for VEP recording. A total of 3 minutes (6 trials) of responses to each stimulus were collected for STIM-ON and STIM-OFF. Each 30 sec trial was divided into 10 sec epochs. We excluded all epochs in which there were artifacts or in which the device cycled on.

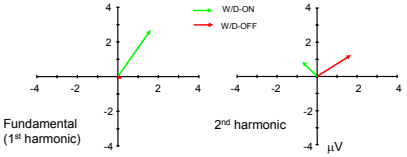
Procedures for controls were identical, except that only one set of 6 trials for each stimulus was collected, and no neck electrodes were placed.

ANALYSIS & RESULTS

CONTROL SUBJECT



Raw VEP waveforms from each valid epoch were averaged and Fourier analyzed to obtain even and odd harmonic response components (above). Fourier components are represented as vectors, whose magnitude indicates amplitude and whose direction indicates phase (below).



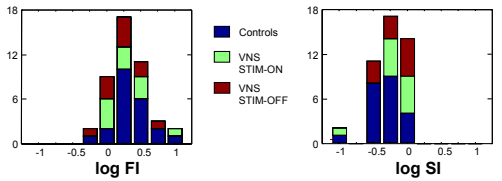
We observed two differences between the VEP waveforms elicited by W/D-ON and W/D-OFF stimuli, as measured by their Fourier components. The fundamental response is absent in W/D-OFF (since it is a contrast-reversing pattern, like a checkerboard), but present in W/D-ON. Its normalized size is quantified by a "Facilitation Index." The second harmonic response is attenuated in the W/D-ON configuration compared to the W/D-OFF configuration, as quantified by a "Suppression Index." These indices reflect lateral interactions between nearby neurons in visual cortex.

Facilitation Index

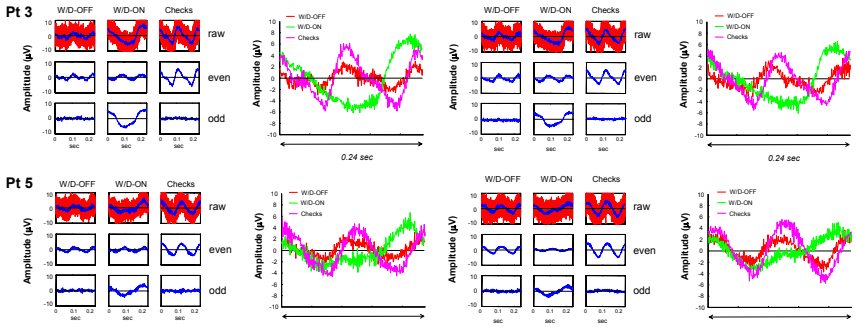
$$FI = \frac{\text{fundamental (W/D-ON)}}{\text{2nd harmonic (W/D-ON)}}$$

Suppression Index

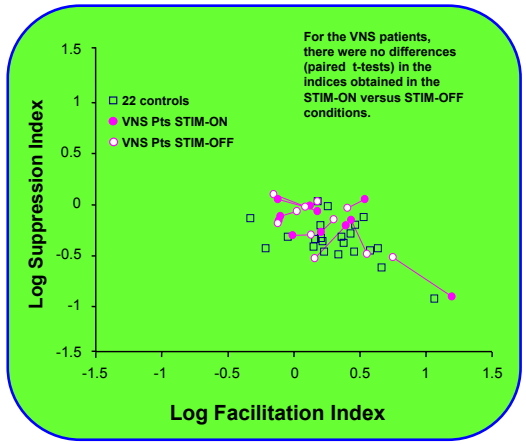
$$SI = \frac{\text{2nd harmonic (W/D-ON)}}{\text{2nd harmonic (W/D-OFF)}}$$



VNS PATIENTS



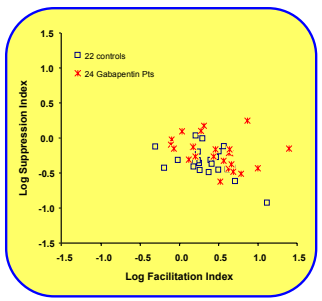
There was no difference in VEP waveforms or waveform variability obtained during STIM-ON and STIM-OFF sessions (above).



Summary Statistics

	log FI	log SI
22 Controls	.34 +/- .21	-.33 +/- .15
11 VNS Pts		
STIM - ON	.27 +/- .28	-.17 +/- .17
STIM - OFF	.21 +/- .22	-.19 +/- .19
24 Gabapentin Pts	.43 +/- .29	-.20 +/- .17

For both patient groups, the FI did not differ from that of controls. However, there is significantly less ($p < .05$) suppression than in controls for the patients on gabapentin therapy. For VNS patients, there was a trend in the same direction ($p = 0.06$ for STIM-ON, $p = 0.07$ for STIM-OFF).
There was no significant dependence of FI or SI on age, or, for the VNS patients, on VNS dose or treatment duration.



SUMMARY & CONCLUSIONS

- **Steady-state VEPs can be reliably recorded during VNS neurostimulation. Responses were not significantly different from responses obtained when the stimulator is turned off for an hour.**
- **Compared to normal controls, patients showed no difference in the facilitation index, but less lateral suppression ($p<0.05$ for gabapentin patients, $p=0.07$ for VNS patients).**
- **The similarity between the VEP measures obtained in the two patient groups is consistent with a similar mechanism of action of gabapentin and VNS on cortical lateral interactions.**

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http://www-users.med.cornell.edu/~jdvicto/vps.html