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Neurophysiological investigations of drug resistant epilepsy patients treated with Vagus Nerve Stimulation to differentiate responders from non-responders

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Abstract

Background: In patients treated with vagus nerve stimulation (VNS) for drug resistant epilepsy (DRE), up to 1/3 of patients will eventually not respond to the therapy. As VNS therapy requires surgery for device implantation, prediction of response prior to surgery is desirable. We hypothesized that

neurophysiological investigations related to the mechanisms of action of VNS may help to differentiate VNS responders from non-responders prior to the initiation of therapy.

Methods: In a prospective series of DRE patients, polysomnography (PSG), heart rate variability (HRV) and cognitive event related potentials (ERPs) were recorded. PSG and HRV were repeated after one year of treatment with VNS. PSG, HRV and ERPs were compared between VNS-responders (≥ 50% reduction in seizure frequency) and non-responders.

Results: 15/30 patients became VNS responders after 1 year of VNS treatment. Prior to treatment with VNS, the amount of deep sleep (NREM 3), the HRV high frequency (HF) power and the P3b amplitude were significantly different in responders compared to non-responders ($p=0.007$; $p=0.001$; $p=0.03$).

Conclusion: We found three neurophysiological parameters, NREM 3, HRV HF and P3b amplitude, to be significantly different in DRE patients who became responders to VNS treatment prior to initiation of their treatment with VNS. These non-invasive recordings may be used as characteristics for response in future studies and help avoid unsuccessful implantations. Mechanistically these findings may be related to changes in brain regions involved in the so-called vagal afferent network.

INTRODUCTION

Vagus nerve stimulation (VNS) (VNS Therapy Systems, Livanova, Houston, Texas, USA) is indicated for treatment of drug resistant epilepsy (DRE) patients who are unsuitable candidates for resective epilepsy surgery. Since its approval in 1997, over 100,000 patients have been implanted worldwide. The chances of > 50% seizure reduction range from 25-55% with a tendency for increased seizure control with time.(1, 2) An important drawback of the therapy in clinical practice is that predictors for response have not been identified while up to one third of patients do not respond to VNS. Retrospective studies with large sample sizes investigating the correlation between patient characteristics and outcome have been disappointing. Studies on age and duration of epilepsy, etiology and ictal onset zone in correlation to VNS response show inconsistencies and none of these described 'predictors' for VNS response allow to make predictions on an individual basis. (3-5)

Investigation of patients based on the current knowledge of the mechanism of action (MOA) of VNS may provide a more rational approach to identify patients' characteristics for response. Research on the underlying neurobiology of VNS indicates that the seizure suppressing effects are attributed to bottom-up targeting of crucial central nervous system structures through the afferent projections of the cervical vagus nerve, the so-called 'vagal afferent network' previously described in mechanistic reviews.(6, 7) Vagal afferents primarily project to the brainstem nucleus tractus solitarius (NTS), which in turn sends fibers among others to the hypothalamus and other brainstem nuclei such as the locus coeruleus (LC) and the parabranchial nucleus; these nuclei are important in modulating the activity of subcortical and cortical epileptic circuitry involving the thalamus and limbic structures. The LC is the main noradrenergic nucleus of the central nervous system and implied in the arousal promoting system of the brain. (8) Preclinical and clinical studies have demonstrated a crucial role of the LC-noradrenergic (LC-NE) system in the seizure suppressive effects of VNS.(9-11) We previously demonstrated that ≥

18 months of VNS treatment induced a significant increase of the P3 event related potential amplitude in VNS responders compared to non-responders. (12) The P3 reflects attentional and memory processes and the P3b component is correlated to LC-NE activity, whereas the P3a component reflects dopaminergic/frontal processes. (13) The timing and variability of the heart beat is controlled and modulated by sympathetic and parasympathetic inputs from the brain. The brain areas involved in this cortical control mechanism of heart rate variability (HRV) (anterior cingulate, amygdala, LC) belong to the 'vagal afferent network'. (14) An impaired HRV has already been described in DRE patients for more than 25 years.(15) HRV can be measured in time domain, quantifying the amount of variability, and frequency domain, estimating the distribution of HRV by assessing the low frequency (LF power) and high frequency (HF power) spectral content. (16) The anterior hypothalamus where the ventrolateral preoptic (VLPO) nucleus is situated is responsible for the induction and maintenance of sleep.(17) During non rapid eye movement (NREM) sleep stages the LC-NE system, a wakefulness promoting area is still active but on a decreased level. (18) The LC provides direct input to the hypothalamus and to thalamo-cortical connections, where a decreased connectivity is described during sleep in healthy individuals. (19, 20)

The LC, amygdala, hypothalamus and thalamo-cortical circuit are brain regions both involved in generation and regulation of P3, HRV and sleep and belonging to the 'vagal afferent network'. (Figure 1) Therefore we prospectively performed investigations of P3, HRV and sleep prior to and one year following VNS implantation and correlated this with long-term VNS response. We hypothesized that these non-invasive neurophysiological investigations related to the MOA of VNS may help to differentiate VNS responders from non-responders prior to implantation and therefore serve as clinical characteristics for response prediction.

MATERIALS AND METHODS

Subjects and VNS

Forty-four adult DRE patients were implanted with VNS between 09/2013 and 01/2017 at the Reference Center for Refractory Epilepsy in Ghent University Hospital, Belgium. Inclusion criteria for this prospective study were adult DRE patients and selection for VNS treatment after pre-surgical evaluation. Exclusion criteria were severe mental impairment, VNS implantation complications, VNS as a part of status epilepticus treatment. Patients were informed about the study and they or their caregiver signed informed consent. This prospective study was approved by the ethics committee of Ghent University Hospital (EC UZG 2013/094).

From 09/2013 to 09/2016 Demipulse Model 103 and from 10/2016 Aspire Model 106 were implanted subcutaneously below the left clavicle with stimulation of the left vagus nerve. Two/four weeks later, patients were admitted for a 48 hours video-electroencephalogram (EEG) monitoring with polysomnography (PSG) in the first night of admission (= baseline). After the first night, VNS was started with the following parameters: output current 0.25mA (0.5mA if tolerated), signal frequency 30Hz, pulse-width 500μs, duty cycle: 30s ON and 5-10min OFF-time. During the first year of treatment (every 6-8 weeks), current output was ramped up (steps of 0.25mA) to the maximum tolerable stimulation (max 3mA) then the duty cycle was adjusted. Stimulation parameters in VNS responders were: current output (0.75mA - 2.5mA), duty cycle (10min - 5 min OFF), stimulation duration 30 sec. (Table 1) VNS response based on the seizure frequency reported by patient or caregiver at baseline (mean of 1 - 3 months before implantation) and after one year (mean of 11 - 13 months after implantation). The patients were divided into one group with a seizure reduction of ≥ 50% (VNS responders) and one group with a seizure reduction < 50% (VNS non-responders).

The P3 potential was measured via a 3-stimulus auditory oddball task with low-probability target stimuli ('oddballs'), trains of high-probability stimuli ('standards') and low probability white noise stimuli ('distractors'). The signal can be divided into two components: the P3b component is evoked when the subject is responding to the target stimuli and reflects LC-NE activity, (13) whereas the P3a component appears as reaction to the distractor stimuli.

The P3b component was investigated in this study only at baseline in two conditions (VNS ON and VNS OFF). The test was conducted two times (randomized order), each lasted 20 minutes. Before initiating a task, the patient received either 20 min of VNS ON (current output 0.25-0.5mA, signal frequency 30Hz, pulse width 500μs, duty cycle: 7s ON-time and 18s OFF-time) or VNS OFF. The patients were seated in front of a computer screen and presented a series of auditory stimuli by running an E-Prime 2.0 script (Psychology Software Tools, Pittsburgh, PA, USA). Patients were instructed to press a button when the target sound was played, the standard sound and distractor were to be ignored. P3b amplitudes (μV) and latencies (ms) were calculated for all patients and analyzed in BRAIN VISION ANALYZER 2.0®.

HRV

HRV was calculated at baseline and after one year of treatment via electrocardiogram (ECG) registration during a resting position of five minutes without ectopic beats or artefacts. Two time-domain parameters, the standard deviation of all N-N intervals (SDNN) and the root mean square of the successive N-N differences (RMSDD) and two frequency domain parameters (LF and HF power) were evaluated in MATLAB®. The SDNN reflects the standard deviation of 'normal' sinus beats, both sympathetic and parasympathetic power contribute to SDNN.(16) The RMSDD reflects beat-to-beat variance in heart rate and measures the vagal mediated changes of HRV. (21) The LF power (0.15Hz and 0.4Hz) reflects both sympathetic and parasympathetic activity, the HF power (0.15Hz to 0.4Hz) reflects parasympathetic activity.(22) The Pan Thompkins algorithm was used for time domain analysis and the wavelet transformation (WT) with a Morlet mother wavelet for frequency domain analysis in the HF and LF spectrum. The Morlet mother wave technique

has been described by Addison et al and is known to reflect a good time and frequency resolution for high and low frequency spectral components in HRV analyses.(23)

Video-EEG recording /PSG

Video-EEG recording (48 hours) and PSG (first night) were performed at baseline and after one year of treatment. PSG signals recorded: airflow, abdominal and thoracic respirogram, oxygen saturation, EEG with 23 electrodes, ECG 2 electrodes under left and right clavicle, electro-oculogram (EOG) 2 electrodes, chin electromyogram (EMG) 2 electrodes, position, video and microphone. American Academy of Sleep Medicine (AASM) recommended EEG montage was applied for PSG scoring.(24) Video-EEG monitoring (International 10-20 System, 23 electrodes, sampling rate 256Hz) allowed to detect seizures during the PSG night. The PSG data were analyzed via Analyse Manager (REMBRANDT, MICROMED®), video-EEG monitoring recordings were analyzed in SYSTEMPLUS, MICROMED®. Scoring /analysis of PSG and video-EEG monitoring was performed by a neurologist experienced in sleep medicine and epilepsy (SH), blinded to VNS response after one year. Sleep stages (NREM 1, NREM 2, NREM 3 and REM sleep) in percent of total sleep time (TST) and apnea/hypopnea index (AHI) (events/hour) were evaluated at baseline and after one year of VNS.

Statistics

A linear mixed model analysis compound symmetry was performed via SPSS 25 with patient number as a random effect. As fixed variables and covariates, time (baseline/one year after treatment), VNS response after one year, sleep influencing medication (benzodiazepines, antidepressants, neuroleptics and barbiturates), changes in AED, seizures during PSG night and age at implantation were considered. Sleep stages, AHI, HRV and P3b parameters were dependent variables. A p-value of 0.05 was regarded as statistically significant. 95% confidence interval was included.

RESULTS

Subjects and VNS

Thirty adult DRE patients selected for VNS treatment were included in the study. Fourteen patients could not be included: VNS as status epilepticus treatment (one patient), local infection post VNS implantation (one patient), two patients died (one POLG 1 mutation, one unknown reasons), 10 patients did not participate or chose to be removed from the study. Mean age at implantation was 39.57 years (17 to 69 years, 14 female). Fifteen/30 patients were VNS responders one year following start of VNS. Detailed information on the subjects can be found in Table 1.

P3

In a subset of 13 patients (5/13 VNS responders) P3b was recorded and analyzed at baseline. **The P3b amplitude in the VNS OFF condition was significantly lower at baseline in VNS responders (p=0.025) compared to VNS non-responders.** VNS responders had a mean P3b amplitude of 3.5μV (95% CI 0.9-6.0), whereas VNS non-responders had a mean P3b amplitude of 7.3μV (95% CI 5.3-9.3). (Figure 2) (Table 2) The P3b amplitude in the VNS ON condition was not significantly different in VNS responders compared to VNS non-responders and the change of P3b amplitude between VNS OFF and VNS ON condition was not significant.

- **Figure 2**: P3b amplitude and VNS response. Means +/- 95% CI.

HRV

The HF power was significantly lower in VNS responders compared to VNS non-responders, both at baseline (p=0.03) and after one year of VNS (p=0.021). VNS responders had a mean HF power of 0.25Hz (95% CI 0.21-0.28) at baseline / 0.24Hz (95% CI 0.21-0.28) after one year and VNS non-responders had a mean HF power of 0.31Hz (95% CI 0.27-0.34) at baseline / 0.29Hz (95% CI 0.25-0.32) after one year. (Figure 3) (Table 2) No significant difference was found in time domain (SDNN and RMSSD) and frequency domain (LF and HF power) variables between baseline and one year of VNS.

- **Figure 3**: HF power baseline/one year of VNS and VNS response. Means +/- 95% CI.

PSG

The amount of NREM 3 was significantly higher in VNS responders at baseline (p=0.007) and after one year of treatment (p=0.001). VNS responders had a mean NREM 3 of 29% (95% CI 23.17-34.87) at baseline / 29% (95% CI 25.00-33.93) after one year and VNS non-responders had a mean NREM 3 of 17% (95% CI 11.49-23.19) at baseline / 18% (95% CI: 13.56–22.49) after one year. (Figure 4)

Other sleep stages did not differ significantly between VNS responders and VNS non-responders and did not change significantly due to VNS treatment. (Table 2) The AHI was significantly increased after one year of VNS treatment compared to baseline (p=0.04). Twenty-two/30 patients had an increase in AHI. Four patients developed mild obstructive sleep apnea syndrome (OSAS with AHI 5 - 15/hour). (Table 2)

- **Figure 4**: NREM 3 baseline and VNS response. Means +/- 95% CI.

AED change

Thirteen/30 patients had a change of their AED treatment in the year following VNS implantation due to AED-related side effects or seizure exacerbation. (Table 1) A change in AEDs within the first year after start of VNS had a statistically significant influence on the increase in AHI observed after a year of VNS treatment (p=0.03).

Sleep influencing medication/seizures during PSG

Detailed information on drug changes and seizures can be found in Table 1. A significant decrease in NREM 2 due to change in sleep influencing medication could be observed (p=0.04). Seizures during the PSG led to a significant decrease of REM sleep (p=0.006).

DISCUSSION

Although VNS treatment is a well-established therapy for DRE, responsiveness to the therapy is unpredictable. Given the typical heterogeneity both in the characteristics of VNS candidates and the effectiveness of VNS therapy, there is an urgent need for individualized response prediction.

In this prospective study we provide novel results on neurophysiological parameters chosen based on the MOA of VNS, that were significantly different in VNS responders prior to therapy initiation. VNS responders were characterized by a significantly lower P3b amplitude, a significantly lower HF power and significantly more NREM 3. This suggests the existence of a differential state of the 'vagal afferent network' in responders, making a subgroup of DRE patients responsive to the seizure suppressing effect of VNS.

The P3b component is linked to LC activity but also reflects the temporo-parietal junction integrity involving structures like the hippocampus with essential functions in memory storage procedures.(25) Murphy et al described that LC noradrenergic activity is reflected by the P3b component (26) and the reduced or absent integrity of the temporal-parietal junction leads to a severe decrease or loss of the P3b amplitude. (27, 28) The HF power of HRV reflects the activity of the vagus nerve ie. the parasympathetic influence on the heart. Several neuroimaging studies have described that the medial

prefrontal cortex, anterior cingulate, putamen and amygdala are involved in the cortical control of HRV. (14, 29) Sakaki et al described that higher functional connectivity between amygdala and medial prefrontal cortex are correlated with a higher HRV. (14) A recent neuroimaging study showed that high MRI contrast (neuromelanin-sensitive-weighted) in the LC, due to increased activity and reflecting a higher sympathetic tone is correlated with a lower HF power. (30) HF power is therefore correlated both to LC activity and limbic circuit brain structures.

For the regulation of sleep the VLPO in the anterior hypothalamus plays a crucial role. (17) Experimental studies showed that lesions of the VLPO lead to a reduction of NREM and REM sleep of more than 50%. (31) The VLPO receives afferents from the LC, where noradrenaline has an inhibiting effect on VLPO neurons and induces wakefulness. (32) Intact thalamo-cortical functioning plays an important role during sleep and is mainly decreased during NREM sleep stadia. (19, 20, 33) The LC is still active at a decreased level during NREM 3 and only falls silent prior to each sleep spindle and during REM sleep (18); it provides direct input to the thalamo-cortical circuit. The unusual high amount of NREM 3 with a mean amount of 29% of TST in VNS responders compared to about 20% in healthy individuals might be linked to a decreased LC activity but also a disturbed functional connectivity of the thalamo-cortical circuit might lead to this phenomenon. Functional and structural alterations of the thalamo-cortical connections are known to be involved in seizure generation and propagation and therefore believed to represent an important substrate of VNS responsiveness. (34-36) Recent neuroimaging studies on resting-state fMRI prior to VNS implantation in children found an enhanced connectivity of the thalami to the anterior cingulate cortex and left insula in VNS responders, stating that network connectivity differs in between epilepsy patients and is associated with treatment response.(37) Stereo-electroencephalography (SEEG) and high-density (HD) EEG studies have demonstrated that epileptic subcortico-cortical networks differ among epilepsy patients and some patterns may be associated with response to treatments affecting these networks such as VNS. (38, 39) The results of two of the three neurophysiological parameters investigated in this study (NREM 3, P3b) could be explained by a decreased LC activity, whereas the HF power results either reflect an increase in LC activity suggesting a more complex network connectivity pattern involving other structures of the vagal afferent network in this subpopulation. This complex network is also mentioned in major depression disorder (MDD), another approved indication for VNS treatment, where the target key structures (prefrontal cortex, cingulate cortex) belong to the vagal afferent network and stimulation of these regions is associated with

improvement of MDD. (40) Low HRV parameters, which normalize after neuromodulation treatment have been observed in MDD and provide a potential target engagement mechanism for optimizing neuromodulation treatments in depression. (41-43)

These three non-invasive, easy to perform neurophysiological tests provide additional strength in clinical practice supplementary to neuroimaging, HD EEG and SEEG to guide decision making in VNS treatment. We are aware of the fact that making individual decisions towards a selection of patients for VNS implantation based on these neurophysiological parameters alone is not feasible in current clinical practice due to the overlapping confidence intervals. A larger amount or an optimal combination of different characteristics involving different investigations may be required to create a successful predictive model for VNS response.

P3 amplitude, HRV HF power and NREM 3 were not affected after one year of VNS treatment. It is known that several polymorphisms in NA-related genes predispose to the development of neuropsychiatric disorders or correlate with treatment response.(44) A variability in noradrenaline receptors or the efficacy of the noradrenaline reuptake transporter may underlie the association between P3, HRV, NREM3 and clinical response. We hypothesize that these neurophysiological parameters are individually determined characteristics that might predispose to VNS responsiveness but cannot necessarily be altered by the treatment.

As described in several other studies, we found a significant increase of the AHI after one year of VNS (45, 46) in 22/30 patients. Four patients developed mild OSAS. A screening PSG for sleep disordered breathing before VNS treatment and follow-up PSG investigations in high-risk patients should be considered.

LIMITATIONS OF THE STUDY

Following the initiation of VNS therapy, 1/3 of patients had a change in their AED treatment and 1/3 in sleep influencing medication. Although these drug changes may have played a role both on the long-term seizure control after one year of combined VNS and AED therapy and on sleep quality in

these patients, the changes itself did not affect our primary findings namely that a lower P3b amplitude, lower HRV HF power and more NREM 3 at baseline characterizes future responders to VNS therapy.

It is known that VNS therapy tends to improve with longer treatment duration reaching a plateau phase around 18 months.(47) In this prospective study we investigated neurophysiological parameters at start of VNS and after one year of treatment as this was a time point feasible for a prospective trial including neurophysiological investigations and considered long enough to distinguish clinical responders from non-responders. Prospective studies with even longer follow-up times may be required to corroborate our findings in the stage of the plateau phase. Our finding that responders and non-responders are different at onset of therapy should however not be affected by longer treatment periods. Analysis of larger groups of VNS treated patients in whom baseline data such as sleep and ECG are available from pre-surgical video-EEG monitoring sessions could be of added value here.

CONCLUSION

This study is to our knowledge the first where easy to perform, non-invasive clinical tests, chosen based on the MOA of VNS, provide clinical characteristics of VNS responders that are significantly different from VNS non-responders. Prediction of response prior to implantation surgery is highly desirable in clinical practice. These non-invasive neurophysiological parameters add clinical value to neuroimaging, HD EEG and SEEG characteristics of VNS responders and should be implemented in decision making to guide neurostimulation strategies in DRE patients.(3)

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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FIGURE LEGENDS

Figure 1: Neurophysiological parameters linked to the VAN. HRV linked to prefrontal cortex (PFC), anterior cingulate cortex (ACC), amygdala (amyg), and Locus coeruleus (LC); Event related potential (ERP) P3b linked to LC; NREM 3 linked to thalamus (thal), hypothalamus (hyp), and LC; insula (ins), primary somatosensory cortex (S1), parabrachial nucleus (PB), dorsal raphe nucleus (DRN), nucleus tractus solitarius (NTS). Kate Campbell, Medical & Scientific Visualizations.

Figure 2: P3b amplitude and VNS response. Means +/- 95% CI.

Figure 3: HF power baseline/one year of VNS and VNS response. Means +/- 95% CI.

Figure 4: NREM 3 baseline and VNS response. Means +/- 95% CI.

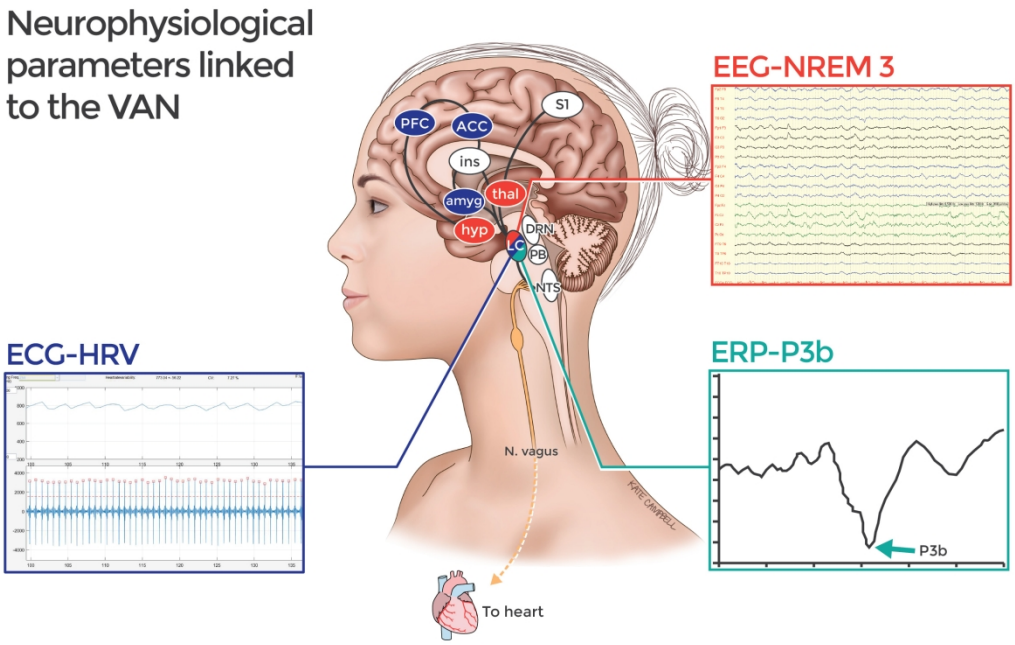
Patient	Age (years) at implantation	Sex	VNS model	Type of Epilepsy	Sleep influencing medication at baseline	Antiepileptic drugs at baseline	Change in AED within 1 year	Change in sleep influencing medication just before baseline /within 1 year	Seizures during PSG night (PSG 1/PSG 2)	AHI increase after 1 year	VNS parameters after one year Current/duty cycle
1	56	F	103	Focal	BZ/NL/ATD	LEV/CBZ	CBZ increase	no/yes	no/no	yes	1mA/30sec ON/3min OFF
2	40	F	103	Focal	none	OXC/LAC/VPA	no	no/no	no/no	yes	1.25mA/30sec ON/10min OFF
3	59	F	103	Multifocal	BZ	LEV/LAC	no	no/yes	no/no	yes	1.25mA/30sec ON/10min OFF
4	25	M	103	Focal	BZ	LEV/CBZ/LAC	no	no/no	no/no	yes	2mA/30sec ON/10min OFF
5	19	F	103	Focal	BZ/NL/ATD	CBZ/VGB	no	no/yes	no/yes	no	1.75mA/30sec ON/5min OFF
6	55	F	103	Focal	BZ/NL/ATD	LTG/LAC	no	no/yes	no/no	yes	1mA/30sec ON/10min OFF
7	36	M	103	Focal	ATD	VPA/PER/LEV	PER stop, LTG start	no/no	no/no	yes	2.75mA/30sec ON/5min OFF
8	43	M	103	Focal	BZ	TPM/LTG/LAC/OXC	no	no/no	no/no	yes	1.5mA/30sec ON/3min OFF
9	69	M	103	Focal	BZ	CBZ/LEV/VPA/LAC	VPA increase, LAC decrease	no/yes	no/no	yes	2mA/30sec ON/ 5min OFF
10	40	M	103	Focal	BZ	CBZ/LAC	no	no/no	no/no	yes	2.5mA/30sec ON/5min OFF
11	29	M	103	Multifocal	none	VPA/TPM/LAC	no	no/no	no/no	yes	1.75mA/30sec ON/ 1.8min OFF
12	36	F	103	Focal	none	LEV/PHT/TPM	LEV decrease	no/no	no/no	yes	2.25mA/30sec ON/ 5min OFF
13	69	F	103	Multifocal	BZ	CBZ/LEV/TPM	CBZ decrease	no/no	no/no	no	0.75mA/30sec ON/ 10min OFF
14	46	M	103	Multifocal	BZ/NL	CBZ/VPA/PHT/PB	no	no/yes	no/no	no	0.75mA/ 30sec ON/10min OFF
15	38	F	103	Focal	BZ	CBZ/LEV/LTG/LAC	LAC decrease	no/no	no/no	yes	1.25mA/30sec ON/5min OFF
16	38	F	103	Multifocal	BZ	LEV/LAC/TPM	LAC increase	yes/yes	no/no	no	2.25mA/30sec ON/5min OFF
17	45	F	103	Focal	BZ/ATD	PGB/LAC	LAC stop, CBZ start	no/yes	no/no	yes	2mA/ 30sec ON/ 10min OFF

18	28	F	103	Focal	BZ	LEV/PGB/LAC	LAC decrease, PGB increase	no/no	no/no	yes	2.75mA/30sec ON/ 5min OFF
19	41	M	103	Focal	BZ	VPA/CBZ/TPM	no	no/yes	no/no	yes	1mA/ 30sec ON/ 5min OFF
20	28	F	106	Focal	BZ	CBZ/RTG	CBZ increase, start BRV,RTG stop	no/no	yes/yes	yes	0.75mA/30sec ON/ 5min OFF
21	27	M	106	Focal	BZ/ATD	CBZ/LAC/TPM/LEV	no	no/no	yes/yes	no	1.25mA/30sec ON/ 5min OFF
22	54	M	103	Multifocal	BZ/ATD	LEV/VPA	LEV decrease	no/no	yes/no	yes	2mA/30sec ON/10min OFF
23	44	M	103	Focal	BZ/ NL	LAC/VPA/LEV	LEV increase, LAC stop	no/yes	no/no	yes	1.5mA/30sec ON/ 10min OFF
24	17	M	103	Multifocal	BZ	LEV	no	no/no	yes/yes	yes	2.25mA/30sec ON/ 5min OFF
25	30	M	103	Focal	none	VPA/LAC/TPM	no	no/no	no/no	yes	1.75mA/30sec ON/5min OFF
26	34	F	103	Multifocal	none	LEV/TPM/OXC	OXC increase	yes/no	yes/yes	yes	1.375mA/ 30 sec ON/5 min OFF
27	39	M	106	Focal	BZ	VPA/LEV/PGB/OXC	no	no/no	yes/yes	yes	1.75mA/ 30 sec ON/5min OFF
28	59	F	106	Focal	none	CBZ	no	no/no	no/no	no	1.875mA/ 30sec ON/5min OFF
29	20	M	106	Focal	BZ	PHT/LEV/CBZ/LAC	no	no/no	yes/no	no	2mA/30sec ON/5min OFF
30	23	M	106	Multifocal	BZ	LEV/VPA/LAC/TPM	no	no/yes	no/yes	no	2mA/30sec ON/5min OFF

Patients	NREM 1 (% of TST) baseline	NREM 1 (% of TS) after 1 year VNS	NREM 2 (% of TST) baseline	NREM 2 (% of TST) after 1 year VNS	NREM 3 (% of TST) baseline	NREM 3 (% of TST) after 1 year VNS	REM (% of TST) baseline	REM (% of TST) after 1 year VNS	AHI baseline	AHI after 1 year VNS	HF power (Hz) baseline	HF power (Hz) after 1 year VNS	P3b amplitude (µV) baseline
1	9.1	7.0	51.7	43.5	27.1	23.6	12.1	25.9	.3	2.1	0.27	0.3	
2	16.3	5.6	57.3	47.1	5.9	29.6	20.5	17.7	5.5	3.7	0.3	0.25	
3	2.4	5.3	78.5	57.8	7.5	17.2	11.5	19.7	.2	.9	0.26	0.17	6.41
4	2.2	5.0	45.3	51.6	38.4	29.4	14.1	14.0	.5	.8	0.15	0.15	
5	5.0	3.4	53.6	54.9	20.7	21.3	20.7	20.4	.4	.1	0.28	0.3	6.53
6	16.6	1.9	59.9	55.4	7.1	36.0	16.5	6.6	.5	1.5	0.3	0.34	7.58
7	3.8	2.9	66.1	71.2	18.6	8.2	11.6	17.7	.8	2.0	0.28	0.26	6.97
8	2.8	2.4	69.6	86.6	19.2	2.3	8.4	8.7	.0	1.3	0.26	0.29	
9	4.3	4.2	38.4	37.2	35.7	36.4	21.6	22.1	3.5	14.7	0.34	0.15	0.36
10	3.2	3.8	47.3	59.2	34.8	32.4	14.7	4.6	3.0	6.5	0.15	0.37	
11	8.8	2.6	45.5	37.5	33.9	31.6	11.7	28.3	2.7	4.7	0.35	0.3	2.96
12	2.6	2.2	58.7	57.8	8.7	17.1	30.1	22.9	.8	1.2	0.32	0.29	
13	5.1	2.3	44.5	43.2	37.2	45.1	13.2	9.3	1.2	2.9	0.25	0.24	
14	2.4	2.2	41.5	27.8	39.6	42.4	16.5	27.6	10.6	4.3	0.26	0.29	2.86
15	2.0	3.9	52.0	57.0	13.8	18.1	32.1	21.0	.8	1.1	0.15	0.24	
16	3.7	6.4	66.7	67.1	12.6	7.3	17.0	19.3	1.8	.5	0.29	0.28	
17	5.5	2.9	56.0	42.4	27.2	38.2	11.3	16.5	6.8	7.8	0.15	0.15	5.02
18	.3	2.6	73.4	84.8	3.3	12.7	22.9	.0	1.9	6.2	0.37	0.35	6.14
19	5.8	8.3	27.5	31.6	41.3	38.9	25.4	21.2	.8	3.5	0.38	0.33	2.66
20	4.7	2.9	59.7	78.9	19.3	12.5	16.3	5.7	1.2	5.4	0.35	0.31	10.79
21	6.1	4.9	59.0	63.3	29.9	31.7	5.0	.0	1.4	1.0	0.17	0.17	
22	3.0	3.2	40.8	60.8	30.1	9.4	26.1	26.5	.3	7.3	0.27	0.28	
23	2.4	1.9	73.2	43.4	6.3	35.4	18.1	19.3	1.5	2.3	0.21	0.16	
24	.8	9.2	52.0	62.5	43.7	28.2	3.5	.0	.7	4.0	0.32	0.27	

25	3.7	2.1	54.3	54.3	25.8	6.5	16.2	37.1	1.0	1.2	0.31	0.38	6.26
26	5.3	5.1	61.4	53.9	10.7	20.1	22.6	20.8	.0	.7	0.37	0.19	
27	1.4	3.5	65.7	63.3	33.0	24.8	.0	8.4	1.8	2.3	0.17	0.19	
28	1.3	1.6	52.7	45.2	30.7	37.3	15.3	15.9	2.4	.8	0.33	0.33	11.75
29	1.8	.6	67.4	56.8	18.3	20.3	12.4	22.3	1.6	.6	0.32	0.33	
30	2.1	1.7	67.0	78.9	15.0	15.3	15.9	4.1	.8	.4	0.39	0.32	

>50% reduction in seizure frequency after one year of treatment



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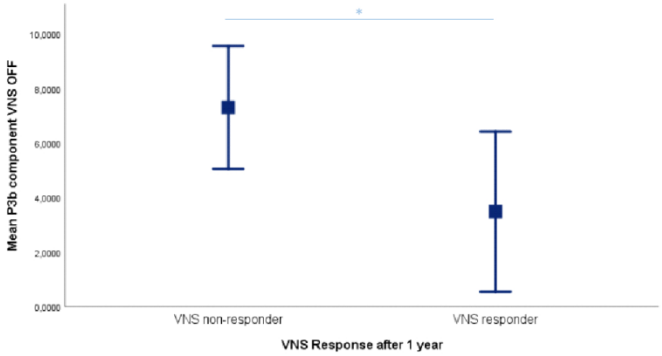

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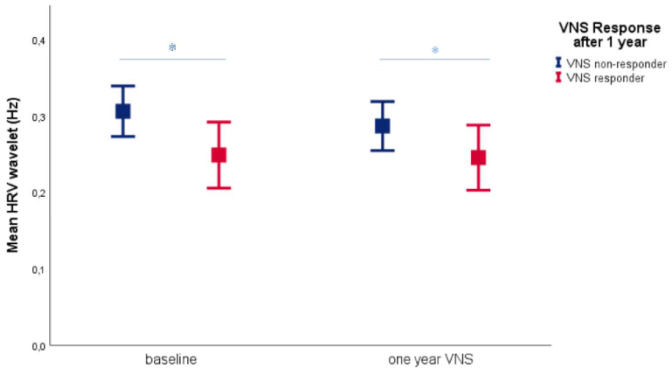

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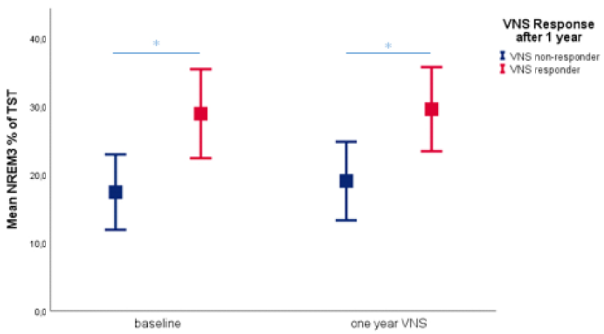

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