Neuromodulation: Technology at the Neural Interface

Received: December 30, 2024 Revised: February 21, 2025 Accepted: March 17, 2025

https://doi.org/10.1016/j.neurom.2025.03.068

Effect of Vagus Nerve Stimulation on Electroencephalogram Synchronization: A Longitudinal Study Using a Clinical-Research Response Scale

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ABSTRACT

Objectives: No reliable biomarkers exist for predicting and assessing vagus nerve stimulation (VNS) response. While VNS induces acute electroencephalography (EEG) desynchronization after implantation, longitudinal evaluations of EEG synchronization changes are lacking. This study constitutes the first prospective investigation evaluating EEG synchronization before and after VNS device implantation and correlating it with the clinical response to VNS.

Materials and Methods: High-density EEG recordings were obtained from 12 adults with drug-resistant epilepsy before and after VNS device implantation (one, three, and six months). EEG resting state (180 seconds), with eyes open and eyes closed (EC), was recorded in VNS ON and OFF conditions. The global weighted phase lag index (wPLI) was computed as an EEG phase-synchronization measure and correlated with the VNS response using various assessment methods, including binary classification (>50% or <50% seizure frequency reduction), percentage of seizure reduction, and the newly developed Clinical-Research Response Scale (CRRS).

Results: We observed a progressive decrease of wPLI in the delta band during the EC VNS OFF condition, which correlated with the VNS response over time, particularly when assessed using the new CRRS compared with other assessment methods. Additionally, a higher preimplant global wPLI predicted a better outcome of VNS, as did an early magnet response.

Conclusions: Overall, VNS may positively influence specific brain states, with a time-dependent evolution of EEG synchronization reflecting therapeutic efficacy. Preimplantation EEG synchronization and an early magnet response may predict VNS response. Moreover, the CRRS could constitute a more sensitive method for characterizing VNS response compared with traditional assessment methods.

Keywords: Biomarkers, electroencephalography, functional connectivity, refractory epilepsy, vagus nerve stimulation

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Source(s) of financial support: This work is supported by the Fund for Scientific Research and Fonds de la Recherche Scientifique with a Fund for Research Training in Industry and Agriculture grant. Riëm El Tahry is funded by the Walloon Excellence in Life Sciences and Biotechnology (WELBIO) department of the WEL Research Institute (X.2001.22).

INTRODUCTION

Vagus nerve stimulation (VNS) has been used as a palliative treatment for patients with drug-resistant epilepsy (DRE) for decades. Up to 60% of patients become responders (Rs) (>50% seizure reduction after implantation) as opposed to nonresponders (NRs) (<50% seizure reduction), with increasing effectiveness over time.[1–3] The VNS device also enables patients to use a magnet to activate the stimulator when they sense an incoming seizure, delivering a predefined electrical pulse to help manage the episode.[4] Various reviews found that approximately half of the patients using magnet stimulation experienced additional benefits, including reduced seizure severity and duration, improved postseizure recovery, and, in some cases, preventing the onset of seizures.[2,5]

Over the past decade, interest in understanding functional interconnections between brain regions has grown, with various functional connectivity measures available to assess the relationships between neurons and neural networks.[6] Altered brain functional organization has been implicated in several neurological disorders, including epilepsy.[7,8]

Among these metrics, phase synchronization measures specifically focus on signal phase coupling.[9] Previous studies have demonstrated that phase difference–based connectivity measures are particularly sensitive to the acute effects of VNS on electroencephalography (EEG).[10–12]

Bodin et al[11] found that during wakefulness, Rs exhibited a lower global phase lag index (PLI) compared with NRs, and showed reduced PLI during VNS ON vs OFF periods (mean duration of VNS therapy: 25.3 months, SD: 18). Using PLI and phase-locking value, another study demonstrated a significantly lower EEG synchronization with VNS ON compared with VNS OFF in Rs only (mean duration of VNS therapy: 7 years).[12] Vespa et al[10] expanded these findings by correlating VNS response with the weighted phase lag index (wPLI) measured during wakefulness and sleep. They found that Rs exhibited greater theta ratio (OFF/ON) desynchronization during sleep.

Before VNS device implantation, only a few EEG studies classified potential Rs and NRs, aiming to avoid any unnecessary procedures and optimize candidate selection. One study developed a predictive model using EEG phase synchronization metrics and clinical features, achieving 75.5% accuracy in the discovery cohort ($n = 70$) and 61.1% in the validation cohort ($n = 18$).[13] While wPLI did not significantly differ between Rs and NRs, a higher PLI was observed in the beta band for Rs. A retrospective study showed a trend toward higher preimplantation wPLI in the alpha band during sleep in patients with lower VNS efficacy.[14] Another study using the Directed Transfer Function found that future Rs had brain connectivity similar to that of healthy controls, unlike NRs who showed increased nodal strength in various regions.[15]

Despite these advances, methods for classifying patients' VNS responses still need to be improved.[16] Currently, researchers mainly use a simple binary classification (Rs/NRs) or percentages of seizure reduction, which are easy to use but do not capture the full spectrum of VNS effects. Conversely, the McHugh classification[17] covers a broader range of responses but complicates statistical investigations because of its numerous classes. To date, none of these methods have demonstrated overall superiority. As research on VNS mechanisms progresses, the classification methods for patient response may also require adaptation.

The present study investigated EEG phase synchronization metrics in patients with DRE before VNS device implantation and their evolution over time after the implantation. In this context, both the acute and chronic effects of VNS on EEG synchronization are evaluated, with the ultimate goal of introducing a new clinical scale that more accurately reflects patients' true VNS response.

MATERIALS AND METHODS

Patient Selection

Twelve patients followed up at University Hospital Saint-Luc in Brussels were prospectively recruited between March 1, 2022, and January 1, 2024. Inclusion criteria were 1) diagnosis of DRE, 2) planning of cervical VNS device implantation (SenTiva DUO® Model 1000-D, LivaNova, Houston, TX), 3) patients aged between 18 and 70 years, and 4) patients with an IQ >55 on the Wechsler scale (normal or mild cognitive impairment). Exclusion criteria included 1) a history of another neuromodulation device and 2) dementia/neurodegenerative diseases. This study was approved by the local ethics committee (Comité d'éthique hospitalo-facultaire of University Hospital Saint-Luc/UCLouvain; Approval No. 2022/10JAN/009) in accordance with guidelines established by the Declaration of Helsinki. All participants provided informed consent before any research activities.

Data Acquisition

Recording Method

EEG was recorded using a 64-channel system (Biosemi B.V., Amsterdam, Netherlands) following the 10–20 system, with a 1024 Hz sampling rate. Data processing was performed in MATLAB R2021a (MathWorks, Natick, MA) using custom scripts and the Letswave 6 toolbox (UCLouvain, Brussels, Belgium).[8] EEG segments exceeding 500 μV were rejected, along with epochs containing eye blinks or major interictal discharges, identified through semi-automatic independent component analysis in Letswave 6 and reviewed by a neurologist.

The EEG was subsequently rereferenced to the common average[18] of the 64 channels, and a second-order Butterworth band-pass filter (0.5–30 Hz) was applied. Additionally, four external electrodes recorded electrocardiogram and VNS artifacts, with two placed bilaterally on the laryngeal prominence to confirm VNS ON periods.

Protocol

Patients were scheduled for four EEG recording sessions. Visit 1 (V1) referred to the baseline visit, conducted within one month before VNS device implantation. V2, V3, and V4 were conducted at one, three, and six months after implantation, respectively. During each visit, a resting-state EEG was recorded with 180 seconds of eyes open (EO) and 180 seconds of eyes closed (EC). For the postimplantation visits, each condition (EO and EC) was recorded with VNS ON and OFF, ensuring equal amounts for each VNS condition.

After implantation, VNS parameters were adapted every two weeks following the scheduled programming, with the intensity increased in increments of 0.25 mA up to a maximum of 1.75 mA, if the titration was tolerated by patients.[19] All experiments were conducted using the clinical parameters specific to each patient, except for the duty cycle, which was adapted to minimize the experimentation duration. The scheduled programming was set back to the initial clinically programmed intensity and duty cycle after the experiment in all patients.

Patient Response Establishment

At V1, patients provided the average number of seizures they experienced over a three-month period before the implantation

and, if possible, the weekly frequency. Seizure frequency data, including all types of seizures reported by the patients, were collected from seizure diaries kept by the study participants or their caregivers. VNS responses were subsequently categorized using different assessment methods. First, a binary response classification after six months categorized patients as Rs or NRs (>50% or <50% of seizure diminution, respectively). Second, at each visit, the percentage of seizure reduction was calculated on the basis of the number of seizures (all types included) before implantation and at the different postimplantation visits. Additionally, a McHugh classification stage was assigned to each patient on the basis of the information available from the patient at each visit.[17]

Further, we developed a new rapid and easy tool for response evaluation called the Clinical-Research Response Scale (CRRS). We based the score on the chronic but also the acute response (ie, the response to the magnet). The chronic response is evaluated on the basis of four factors that are frequently reported in VNS response: seizure frequency, seizure intensity, seizure duration, and postictal recovery.[20,21] The acute response to the magnet was also taken into account because >50% of patients reported positive outcomes, including seizure abortion, reduced seizure duration, decreased intensity, and shorter postictal recovery time.[4,5]

The scores of chronic and acute responses were then combined into a final numeric score (evaluated at each visit: V2, V3, and V4) ranging from 0 (no response in any category) to 15 (maximal response in both acute and chronic effects) (Table 1).

Data Analysis: EEG Synchronization Measure

Functional connectivity is defined as the statistical dependencies between ≥two distinct brain regions.[22,23] wPLI was selected among different connectivity metrics as a phase-synchronization measure[9,14,24] because it effectively reduces volume conduction bias[24,25] and is useful for characterizing VNS-induced desynchronization.[10–12] Additionally, it has shown stability across different reference types, facilitating comparison across studies.[26]

This measure is based on the cross-spectrum between EEG signals, representative of a frequency domain cross-correlation, and computed as follows:

$$X = x(t)y(t)e^{\Delta\Phi(t)},$$

where $\Delta\Phi(t)$ is the phase difference between the signals at time t.

Table 1. Clinical-Research Response Scale.

Response type	VNS effect	Criterion	Score computation				Total score
Acute – magnet response							0–5
	Seizure-suppressing effect of magnet	>50%	+5				
		<50%	+4	Seizures not suppressed	Seizure duration ↘	Yes / No	If at least one "yes": +1
					Seizure intensity ↘	Yes / No	
					Postictal duration ↘	Yes / No	
		0%	+0		Seizure duration ↘	Yes / No	If "yes": +1
					Seizure intensity ↘	Yes / No	If "yes": +1
					Postictal duration ↘	Yes / No	If "yes": +1
Chronic							0–10
	Seizure frequency reduction	>80%	+10				
		>50%	+8				If at least one "yes": +1
		=50%	+7	Seizure duration ↘		Yes / No	
		>30%	+6	Seizure intensity ↘		Yes / No	
		=30%	+3	Postictal duration ↘		Yes / No	
		<30%	+0	Seizure duration ↘		Yes / No	If "yes": +1
				Seizure intensity ↘		Yes / No	If "yes": +1
				Postictal duration ↘		Yes / No	If "yes": +1
Total							0–15

Acute response: Patients rated how often the magnet stopped seizures (>50% = +5, ≤50% = +4) and described its effects on seizure duration, intensity, and postictal duration, scoring +1 for each observed effect if efficacy was <50%.
Chronic response: Patients reported weekly seizure frequency changes since the last visit, categorized by reductions of >80% (+10), >50% (+8), and >30% (+6). For 50% or 30% reductions, scores were adjusted to +7 or +3, respectively. Additional effects on seizure duration, intensity, and postictal duration were recorded for reductions <80%, with +1 for each observed effect if the reduction is <30%.

Table 2. Demographic and Clinical Characteristics of the Study Population.

ID	Age	Sex*	Epilepsy type and etiology	Epilepsy duration (years)	ASM	IQ range
1	24	M	Focal epilepsy, structural etiology	16	LCM, BVR, CBD	>70
2	40	M	Focal epilepsy, structural etiology	27	LCM, BVR	>70
3	37	F	Focal epilepsy, unknown etiology	4	TPM, CBM, LTG	84
4	34	M	Adult Lennox–Gastaut syndrome, unknown etiology	21	LEV, LTG, OXA	56
5	53	F	Generalized epilepsy, idiopathic	32	LCM, TPM	>70
6	66	F	Focal epilepsy, unknown etiology	58	LEV, LCM	100
7	41	F	Generalized epilepsy, idiopathic	34	VPA, LCM	84
8	25	F	Generalized epilepsy, idiopathic	14	LTG	72
9	28	M	Focal epilepsy, structural etiology	6	VPA, BRV	>70
10	47	F	Generalized epilepsy, idiopathic	33	LTG, VPA	84
11	33	F	Focal epilepsy, structural etiology	10	BVR, LCM	72
12	35	M	Focal epilepsy, unknown etiology	22	VPA, LTG, LCM	88

ASM, antiseizure medication; BVR, brivaracetam; CBD, cannabidiol; CBM, cenobamate; CBZ, carbamazepine; F, female; ID, patient's number; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine; M, male; OXC, oxcarbazepine; TPM, topiramate; VPA, sodium valproate.
*Sex assigned at birth.

The wPLI was computed over 1-second time windows using the following equation:

$$wPLI = \frac{|E[|Im(X)|.sgn(Im(X))]|}{E[|Im(X)|]},$$

where:

- *E[]* is the expectation operator over time
- *Sgn* is the signum function
- *Im()* is the imaginary component.

The wPLI was evaluated in the traditional narrow frequency bands of interest, including delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), and broadband (0.5–30 Hz). Analyses were conducted using a custom-developed script in MATLAB (version R2023a; MathWorks). The wPLI was averaged over all possible pairwise combinations of EEG signals among the 64 investigated electrodes to consider the entire brain. For each patient, the wPLI was evaluated under different conditions: VNS ON/OFF, without VNS, and EC/EO.

Statistical Analysis

Statistical analyses were performed using R® (version 4.1.2; R Core Team, Vienna, Austria). The Shapiro test was applied to each band to verify the normality of data and residuals. The variance inflation factor (VIF) was calculated to address potential multicollinearity issues for the predictors in each model. Values <5 indicate a low correlation between predictors. A Pearson correlation was performed for VIF values between 5 and 10, and only *p*-values <0.8 were considered.

For each EEG frequency band and each condition, statistical comparisons were performed over time. Three different linear mixed models (LMMs) were constructed, incorporating the three classification responses (binary, percentage of seizure reduction, and CRRS), with wPLI as the dependent variable. These models were implemented using the *lmer()* function in R, within the *lme4* package (v1.1.34) (Bates 2015). Visits (V1, V2, V3, and V4) and the classification of VNS response, as well as their interaction, were used as predictor variables, while the random effect of each patient was added to the model using the subject ID as a random variable. The general model used was "$wPLI_{delta}$ ~ *VNS response* + *Visits* + *VNS_resp:Visits* + *(1|ID)*" and it was controlled for each covariate (age, sex, number of antiseizure medications [ASM], epilepsy duration, type of epilepsy, and intensity of VNS stimulation at each visit).

Additionally, a linear regression based on the model "*VNS response* ~ $wPLI_{delta}$" was conducted to determine whether the VNS response—once accurately established (six months after implantation)[2]—could be predicted by baseline wPLI, limited to the state and frequency bands identified as significant in previous LMM analysis. To account for potential outliers and minimize their influence, the *lmrob* function from the *Robustbase* package (v0.99.2) was applied for the linear regression. To identify additional predictive clinical features for VNS response at V4, linear regressions were conducted using the *lm* function from the *stats* package (R Core Team; version 4.2.2), incorporating the above-mentioned covariates and the early magnet response at one month after implantation. For each linear regression, suitability of the fit was assessed through visual inspection, R^2 values, and root mean squared error. In all analyses, results were deemed significant at $p < 0.05$.

Table 3. VNS Parameters of Experimentation.

ID	V2 (16 ± 7 days*)				V3 (83 ± 12 days*)				V4 (178 ± 12 days*)			
	I. (mA)	Freq. (Hz)	Duty cycle	Pulse width (μs)	I. (mA)	Freq. (Hz)	Duty cycle	Pulse width (μs)	I. (mA)	Freq. (Hz)	Duty cycle	Pulse width (μs)
1	0.325	30	41%	250	1.75	30	57%	250	1.75	30	57%	250
2	0.5	30	41%	250	1.5	30	41%	250	1.75	30	41%	250
3	0.325	30	41%	250	1.25	20	41%	250	1.875	20	41%	250
4	0.5	30	41%	250	1.5	30	41%	250	1.75	30	57%	250
5	0.75	30	57%	250	1.75	30	41%	250	1.75	30	41%	250
6	0.5	30	41%	250	1.5	30	41%	250	1.5	20	41%	250
7	0.5	30	41%	250	NA	NA	NA	NA	1.75	30	41%	250
8	0.5	20	41%	250	1.75	20	41%	250	1.75	20	41%	250
9	0.5	30	41%	250	1.25	30	41%	250	1.75	30	41%	250
10	0.75	20	41%	250	NA	NA	NA	NA	1	20	41%	250
11	0.5	30	41%	250	1.5	30	41%	250	1.75	30	41%	250
12	0.5	30	41%	250	1.5	30	41%	250	1.75	30	41%	250

The VNS intensities, frequency, and pulse width used in the experiments were identical to those used in the clinic, except for the intensity of PAT1 and PAT3 in V1. The duty cycle was adjusted for all patients during the experiments and reverted to its clinical value at the end of each session. Duty cycle 41% = 14 seconds ON–30 seconds OFF; duty cycle 57% = 30 seconds ON–30 seconds OFF.
Freq., frequency; I., intensity; ID: patient's number; NA, not applicable, lacking data.
*Referring to the number of days after first VNS stimulation.

RESULTS

Study Population: Clinical Characteristics

Twelve patients (five male and seven female) with an average age of 38.5 ± 12 years were prospectively included in the study. The demographics and clinical characteristics of the patients are detailed in Table 2. Medication regimens remained unchanged for all patients between V1 (14 ± 10 days before implantation) and V4 (178 ± 12 days after first stimulation).

No patient dropped out during the follow-up, although two patients missed V3 (PAT7 and PAT10).

Clinical parameters, including frequency, pulse width, and duty cycle, were generally maintained at 30 Hz, 250 μs, and 30 seconds ON/5 minutes OFF, respectively, and remained consistent between visits unless modifications were necessary because of side effects or insufficient response (Supplementary Data 1).

Exceptionally, if patients experienced side effects due to the change in duty cycle, the experiment was conducted at 0.125 mA below the normal stimulation intensity to increase tolerability (experimental parameters are provided in Table 3). All patients reached the target dose of 1.75 mA within 14 weeks (98 days) after stimulation initiation, assuming the programming schedule remained unchanged.

Study Population: Clinical Responses

Clinical response at six months (V4) was summarized in Table 4 for each assessment method (ie, binary classification, percentage of seizure reduction, McHugh classification, and CRRS), highlighting the differences between these classification approaches. When considering both magnet and chronic response, CRRS assigned the same score to PAT6 and PAT7, while binary classification

Table 4. Clinical Response Classifications at Last Visit (V4).

ID	Binary response (R-NR)	Seizure diminution (%)	McHugh classification	CRRS		
				Chronic (0–10)	Acute (0–5)	Final (0–15)
1	R	80	IB	10	5	15
2	R	55	IIB	8	5	13
3	NR	17	IIIA	1	4	5
4	NR	14	IV	0	1	1
5	R	94	IB	10	5	15
6	NR	50	IIB	7	5	12
7	R	67	IIB	8	4	12
8	NR	13	IIIA	2	5	7
9	R	60	IIB	8	1	9
10	NR	0	V	0	0	0
11	NR	46	IIIA	6	5	11
12	NR	0	V	0	0	0

Comparison of the Binary Response Scale, the percentage of seizure diminution, and McHugh classification with the CRRS. Details of CRRS (acute, chronic, and final score) are provided for each patient.

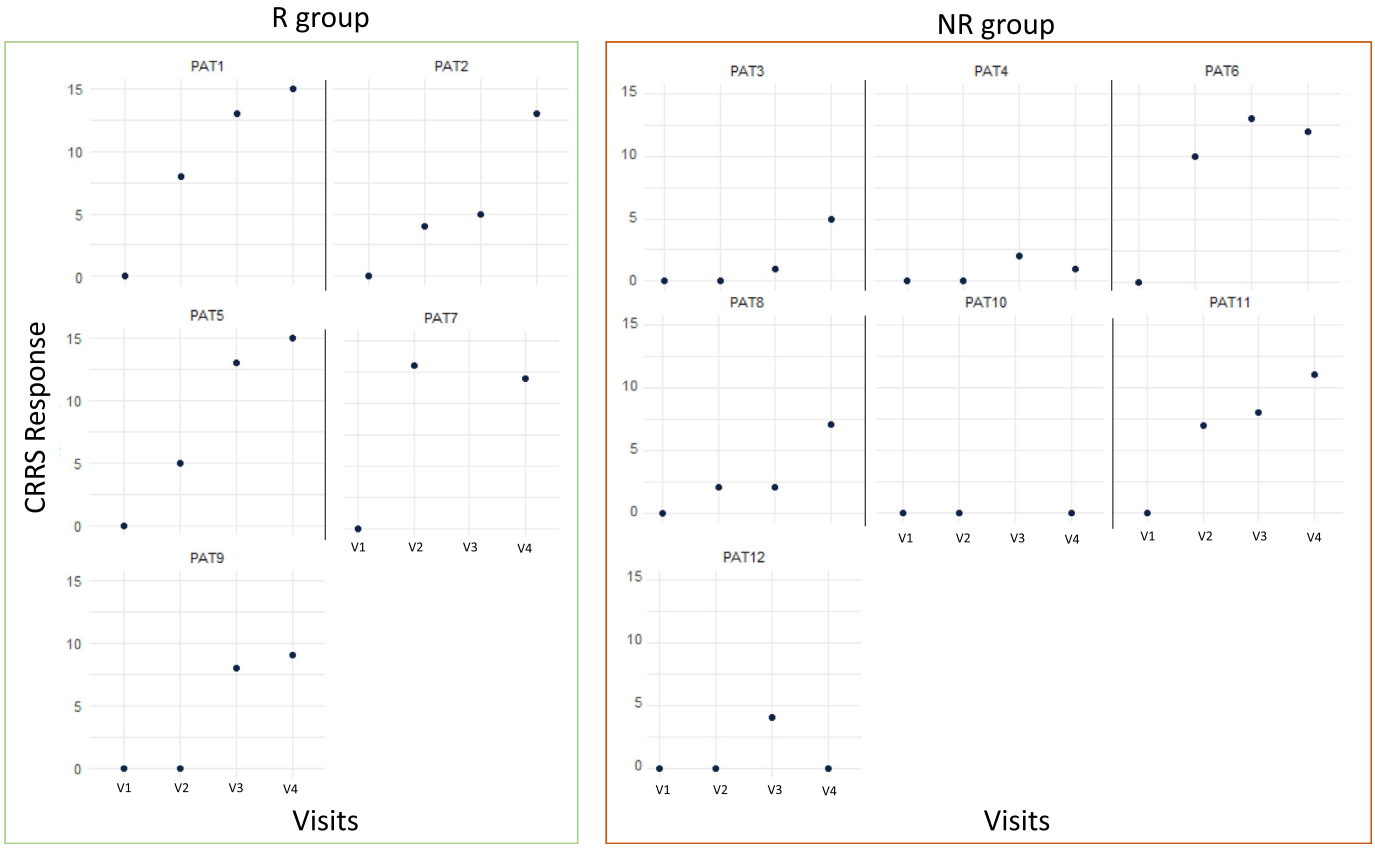

Figure 1. CRRS over time in VNS patients. Each point represents the final CRRS score at baseline (V1), one month (V2), three months (V3), and six months (V4) for each patient. Patients are classified as responders (Rs) or nonresponders (NRs) on the basis of binary classification. [Color figure can be viewed at www.neuromodulationjournal.org]

categorized them as NRs and Rs, respectively, despite the actual response of PAT6. Similarly, McHugh classified patients PAT3, PAT8, and PAT11 as IIIA, while CRRS highlighted differences among them (scores of 5, 7, and 11, respectively), and binary classification grouped them all as NRs.

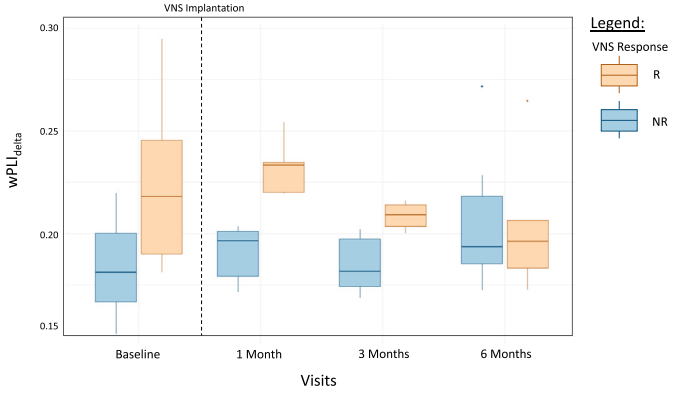

Figure 2. Variation in wPLI within the delta band with eyes closed during VNS OFF over time, using a binary scale. The median is represented as a horizontal line, the interquartile range (IQR) as the box's boundaries, and the whiskers indicate the 1.5 × IQR limit. Delta-band wPLI is displayed for each patient at baseline (preimplantation) and at one, three, and six months after implantation. In responders (Rs), wPLI decreased over visits, while nonresponders (NRs) showed no significant change in the binary model. [Color figure can be viewed at www.neuromodulationjournal.org]

The progression of the patient's response (CRRS) over time is shown in Figure 1 and reflects an increased response following implantation, as clinically expected.

Averaged Whole-Brain Synchronicity

Normality was confirmed for all data. LMMs were conducted for each response assessment method. A summary of the results can be found in Supplementary Data 2. LMMs with covariates are detailed in Supplementary Data 3. VIF was calculated for all covariates and remained <5, except for *Intensity* in the model with the percentage of seizure reduction (VIF = 5.03) and CRRS (VIF = 5.17). Pearson correlation analysis revealed no p values >0.8 ($p = 0.62$ and $p = 0.58$, respectively). All findings presented in the following sections are related to the delta band, EC, and VNS OFF condition. No significant results were observed in the other bands or conditions.

Binary Scale

Using binary classification, we observed a significant difference in wPLI between Rs and NRs to VNS, regardless of visit timing. This was indicated by the significant effect of the VNS response in our LMM ($p = 0.011$*) (Fig. 2), with decreased wPLI in Rs, while wPLi remained constant in NRs. However, no other significant effects were found (Supplementary Data 2), suggesting that the visits themselves do not influence wPLI in this model, nor does the combination of response status and visit

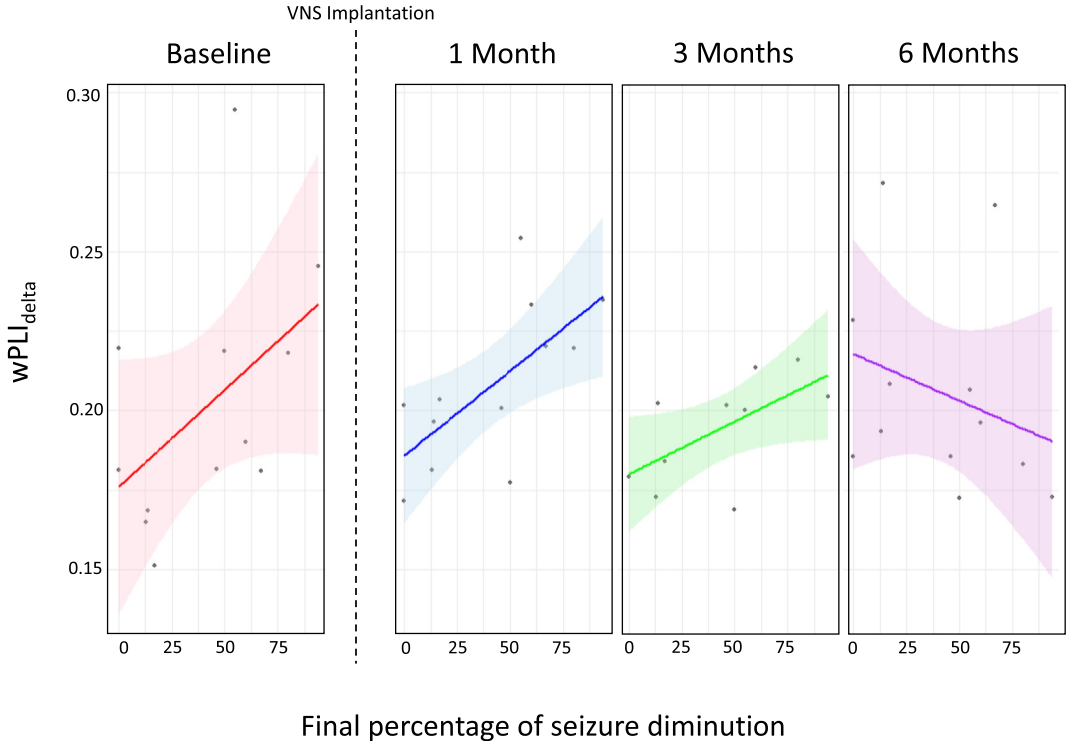

Figure 3. Variation in wPLI in the delta band with eyes closed in VNS OFF over time, using the percentage of seizure reduction. A significant interaction is found between the variation of delta-band wPLI over time and the final percentage of seizure diminution, with a diminution of wPLI over time in patients with a higher percentage of seizure diminution. [Color figure can be viewed at www.neuromodulationjournal.org]

timing. Therefore, while these findings need to be confirmed in further investigations, they highlight the limitations of binary classification in accurately reflecting the evolution of wPLI over time after implantation. When intensity was included as a covariate, no significant effect of intensity on wPLI was found ($p_I = 0.37$). However, an increased interaction between response and delta-band wPLI variation from baseline to V4 was reported ($p_{iV4} = 0.045$*).

Percentage of Seizure Reduction

Figure 3 shows the variation of delta-band wPLI over time, before and several visits after VNS device implantation, in relation to the clinical response, measured by the percentage reduction in seizures. After six months of therapy, the seizure reduction percentage was inversely correlated with the variation of global wPLI over time, with greater seizure reduction associated with lower global wPLI. Notably, in addition to the VNS response ($p = 0.028$*) or the timing of the last visit ($p_{V4} = 0.033$*), the combination of the percentage of seizure reduction and the timing of the visits significantly affected wPLI ($p_{iV4} = 0.019$*).

No significant results were found for other visits or their interactions (Supplementary Data 2). When the intensity was added as a covariate to the model, the effect of V4 on VNS response was no longer significant ($p_{V4} = 0.883$). However, the effect of the response and the interaction between V4 and response remained significant ($p = 0.028$* and $p_{iV4} = 0.013$*, respectively).

Clinical-Research Response Scale (CRRS)

Figure 4 illustrates the variation of wPLI over time in the delta band, from baseline to multiple visits after VNS device implantation, in relation to the final clinical response measured by CRRS. Similar to the percentage of seizure reduction, a better VNS response—indicated by a higher CRRS score—was associated with a decrease in wPLI over time relative to baseline, albeit with higher *p*-values. The CRRS score in an LMM model confirmed a significant effect of V4 on wPLI ($p_{V4} = 0.01$*) and a significant effect of response on wPLI ($p = 0.025$*). More importantly, our results show that higher CRRS score correlated with a decrease in global wPLI over time, which was reflected by a significant interaction between V4 and the response ($p_{iV4} = 0.006$**), highlighting that the combined effect of clinical response over time most affects the evolution of wPLI. When the intensity of the therapy was added as a covariate, the previously significant effect of V4 on wPLI disappeared ($p_{V4} = 0.855$), indicating that the intensity might be influencing the observed effect of V4. However, the significant effect of the clinical response on wPLI remained ($p = 0.023$*), and the significance of the interaction between response and V4 increased ($p_{iV4} = 0.003$**), suggesting a robust relationship between clinical response and wPLI at V4, independent of therapy intensity.

Regarding potential predictive characteristics, we found that at V1, a relationship can be observed between the wPLI at baseline and the final CRRS score, with a higher global baseline wPLI in the delta band in future Rs. When considering all patients, the regression was not significant ($p = 0.1$, $R^2 = 0.2$). However, examining the residuals (Supplementary Data 4) revealed that two patients (PAT10 and PAT12) had extreme values in all graphs. Interestingly, response assessment in these two patients was more complicated compared with the rest of the population included in the present study (Table 4). Indeed, PAT10 did not reach the

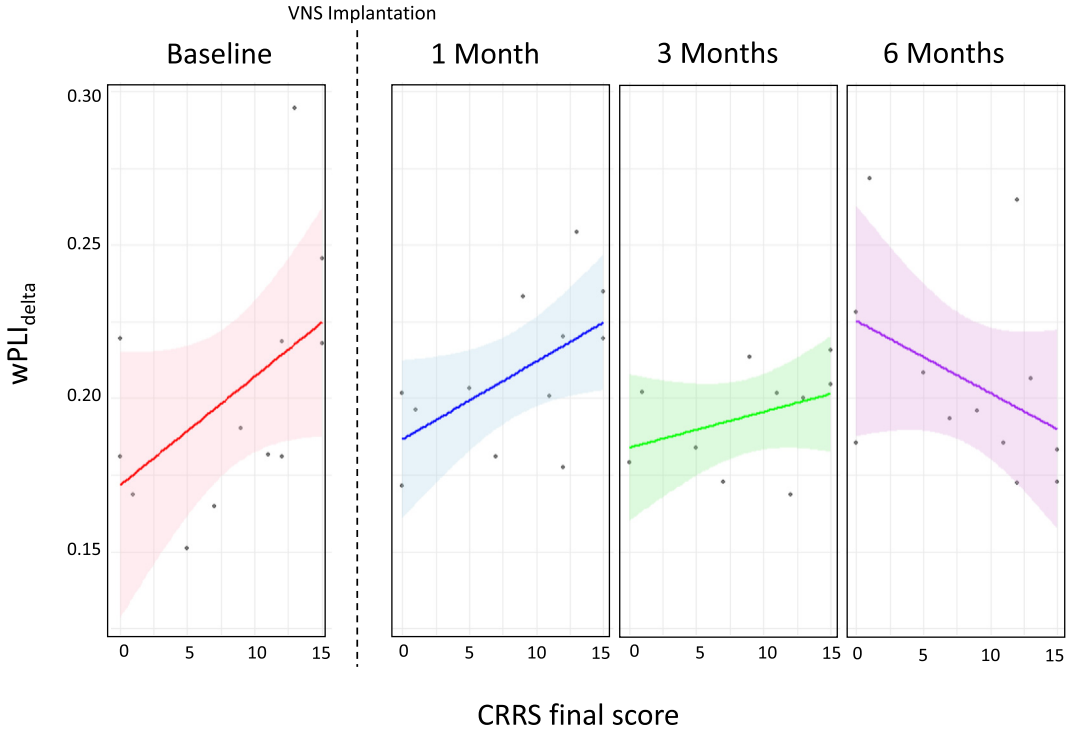

Figure 4. Variation in wPLI in the delta band with eyes closed in VNS OFF over time, using CRRS. A significant interaction is found between the variation of delta-band wPLI over time and the final CRRS score at six months, with patients who respond better to VNS showing a decrease in wPLI over the visits. This interaction is stronger than those observed with the other classification methods ($p_{iv4binary}$ = 0.056, $p_{iV4\%}$ = 0.019, $p_{iv4CRRS}$ = 0.006). [Color figure can be viewed at www.neuromodulationjournal.org]

optimal response intensity. PAT12 experienced one seizure per month and managed it with clobazam, making it difficult to assess seizure severity, duration, and postictal duration. Using a robust correction for managing extreme values, the regression revealed a significant positive linear correlation between wPLI at V1 and VNS response (p_{rob} = 0.01, R^2= 0.18).

Predictive Clinical Characteristics for VNS Response

Linear regression models were constructed to predict the response before VNS device implantation based on clinical features (age, sex, ASMs, epilepsy duration, type of epilepsy). None of these clinical features were significant (Supplementary Data 5). However, after implantation, patients reported an early effect of the magnet on seizures, typically preceding the chronic effect of the stimulation. Eight out of 12 patients used the magnet within the first month after implantation. The results of the linear regression demonstrated a significant positive association between the magnet effect at V2 and the chronic response at V4 (p = 0.003**, R^2 = 0.75) (Fig. 5). The mean magnet intensity at V2 was 0.73 mA (median = 0.75, minimum = 0.5, maximum = 1) and the mean intensity of clinical stimulation at V4 was 1.68 mA (median = 1.75, minimum = 1, maximum = 1.875).

DISCUSSION

Although VNS has been used for many years as an adjunct treatment for patients with DRE, no clear predictive marker of clinical response has been identified to date. In addition, clinical response to VNS is currently typically assessed in a binary fashion in the literature. However, additional benefits of VNS, such as reduced seizure severity or improved postictal recovery,[2,27] are not easily captured by binary classification. In this study, we prospectively followed 12 patients with DRE who underwent VNS device implantation. We studied EEG synchronization derived from a 64-channel EEG recording performed in controlled conditions while keeping all ASMs stable throughout the study. In addition, the

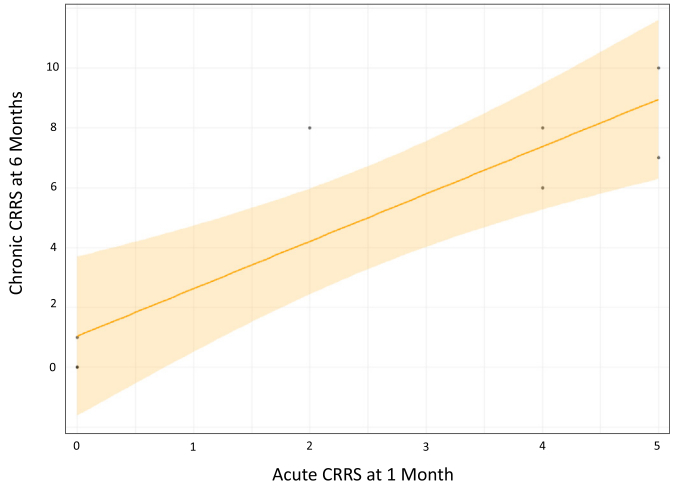

Figure 5. Relationship between magnet response at one month and chronic response at six months. Data are available for 8 out of 12 patients. Two patients share the same data point (Acute CRRS at V2 and Chronic CRRS at V4 both equal 0). [Color figure can be viewed at www.neuromodulationjournal.org]

effects of VNS on EEG synchronization were correlated with different types of clinical assessments of VNS outcome, including the traditional binary classification (Rs/NRs), the percentage reduction in seizure frequency, and most notably, the CRRS. Our results show that 1) preimplant wPLI in the delta band during EC condition may predict the clinical outcome of VNS, 2) a decreased wPLI over time in the delta band during the EC, VNS OFF condition is correlated with the final response, and 3) the magnet response at one month is correlated with VNS response at six months. In addition, our findings indicate that the evolution of VNS-triggered desynchronization over time is more closely associated with the CRRS than other response assessment methods.

EEG Synchronization Measures

In our study, patients with higher delta-band wPLI before VNS device implantation exhibited a higher future VNS response. Other studies using different EEG-connectivity measures or magnetic resonance imaging–derived functional and structural metrics have suggested that Rs may exhibit brain characteristics closer to those of healthy participants than NRs.[15,28,29] Moreover, one study comparing EEG between patients with DRE and healthy controls revealed that the latter showed a higher wPLI.[30] Another preimplantation study using scalp EEG–derived entropy, another connectivity measure reflecting levels of brain rhythm irregularity, found that Rs tended to exhibit lower entropy levels before VNS, indicating a more synchronized state. The authors concluded that patients with lower entropy and thus higher synchronization before VNS device implantation could benefit more from VNS,[31] which aligns with our findings. This may reflect brain states in Rs closer to those of healthy participants, indicating less pathological brain activity compared with patients with poorer VNS responses. It can be hypothesized that, in these patients, neural networks are more likely to be modulated by VNS through neural desynchronization.

In addition, our study demonstrated a significant effect of both VNS response and time (visits) on delta-band wPLI. Given that medication regimens remained consistent throughout the study, the observed effect of visits likely reflects the chronic impact of VNS over time. Previous studies using various connectivity measures have consistently reported lower connectivity during VNS ON periods compared with OFF periods,[11,32] particularly in Rs.[10,12,33] Additionally, reduced connectivity has been observed in the postimplantation period compared with the preimplantation period,[32] especially in Rs.[34] In line with this previous research, the significant interaction between VNS response and visits in our results suggests that the variation in wPLI over time is influenced by the patient's final response to VNS. Rs appear more affected by VNS over time, leading to a progressive decrease in wPLI.

Overall, our findings align with these studies, supporting the notion that VNS induces desynchronization, as indicated by decreased wPLI in Rs over time, while NRs exhibit minimal changes.

Clinical Classification Assessments

A reliable classification for VNS response may be challenging in many studies because of their retrospective nature, data availability issues, and difficulties in accurately reporting seizure counts. Moreover, the variable response to VNS further complicates treatment assessment response, potentially biasing studies.[16] Binary classification imperfectly distinguishes patients with marginally different seizure reductions (eg, 49% vs 51%). Moreover, the binary classification and the classification using the percentage of seizure reduction omit factors such as ictal/postictal duration, intensity, or magnet effects.[12,14] While clinically useful for including seizure reduction percentage and magnet effects, the McHugh classification is rarely used in research because of its complexity and the large number of groups that it creates, complicating the statistical comparisons. Considering these limitations, our results suggest that the CRRS scale emerges as a more representative and practical measure of VNS response.

Notably, our results indicate that while VNS appears to decrease wPLI in Rs, the binary classification showed no interaction between response status and visits. This suggests that more nuanced or alternative methods of classification and analysis might be needed to better understand the evolution of wPLI over time. Indeed, using the percentage of seizure reduction led to a stronger interaction between VNS and visits, and using CRRS further increased the significance of this interaction. Including the clinical intensity in our LMM reinforces the robustness of our findings, as the relationship between VNS response and wPLI, as well as the interaction between response and V4, were strengthened and further enhanced for the CRRS compared with other classification methods.

This highlights the complexity of VNS responses across patients and emphasizes the need for tools that can more accurately characterize individual responses, ultimately improving our ability to understand and predict VNS outcomes on a patient-by-patient basis.

Acute Magnet Response

Assessing the chronic VNS effects within the first three months after implantation is difficult because of the natural fluctuations occurring in epilepsy and the known long-term neuroplastic effects of VNS.[35] However, the acute magnet response could serve as an early predictor of chronic VNS efficacy. Indeed, our study suggests that the magnet response may be an initial marker of VNS effectiveness, potentially predicting long-term outcomes after implantation (Fig. 5). This aligns with previous findings wherein, using single-photon emission computed tomography, the degree of activation in the left limbic areas following an initial 0.25-mA VNS was correlated with long-term (six months) clinical VNS efficacy in 12 patients.[36] Moreover, studies in rats showed that VNS response is strongly linked to the norepinephrine (NE) and serotonin (5-HT) systems, with the locus coeruleus (LC) and dorsal raphe nucleus (DRN) playing key roles. It has been shown that LC reactivity increases directly and rapidly after short-term and long-term VNS administration, while DRN activity increases only after prolonged stimulation.[37] Additionally, elevated NE levels in the hippocampus after short-term VNS correlated with reduced seizure severity in rats,[38,39] and lesioning of serotoninergic and adrenergic neurons may reduce VNS efficacy.[40,41]

In this context, previous studies demonstrated that acute VNS increases NE release, which in turn could affect α1-adrenoreceptors in the DRN, leading to increased 5-HT neuron firing over time.[37,42,43] These studies suggest that the magnet may significantly modulate the LC specifically (acutely and chronically), although other mechanisms of VNS action exist.

Limitations and Future Perspectives

The primary limitation of this study is the small number of participants. While 46 pre- and post-VNS visits across four visits per participant provide sufficient data for the main analysis, they may limit subgroup analysis such as a wPLI regional brain subanalysis. Indeed, the small sample size may hinder the interpretation of

post-VNS visits, leading to potential nonsignificant results, specifically in VNS ON conditions, or for wPLI OFF/ON ratio calculations. Furthermore, previous studies typically include patients with longer implantation periods. An extended follow-up could help to observe further VNS effects, which typically increase over time in the literature (≥two years).[2,3,44] However, longer follow-up is difficult to achieve while maintaining all medication regimens stable.

Additionally, although wPLI allows for more precise characterization of VNS desynchronization (consistent with the proposal that VNS acts as a network therapy),[33,45] using only wPLI as a connectivity measure may have led to underestimation of the results. Comparing and combining multiple connectivity (eg, phase synchronization, correlation, coherence, Granger causality, etc.) or network measures (eg, global efficiency, average clustering coefficient, modularity, etc.) based on different mathematical principles could provide a more comprehensive representation of physiological functioning and improve the understanding and prediction of VNS response. Moreover, exploring aperiodic components of the EEG could also assess potential correlation between EEG background change and clinical outcome of VNS.

A common limitation in neuromodulation studies is assessing VNS response in some patients. While the CRRS provides a more precise evaluation, it does not account for nonresponse due to stimulation parameters. Indeed, some patients may not receive optimal stimulation because of side effects, or may not accurately report seizures, complicating the assessment of their response.

Finally, while the CRRS has proven useful in our data set, validation of this scale is warranted in a larger cohort. Incorporating a quality of life questionnaire may help validate our scale, and developing a version for children could extend its applicability. Additionally, the linearity of our scale might be an issue, as score differences may not reflect the same response differences across patients. Nevertheless, this limitation is quite common across various types of clinical classifications, including those used in pain research.[46]

CONCLUSIONS

VNS modulates brain states through a time-dependent evolution of EEG synchronization, possibly reflecting improvement in therapeutic efficacy over the course of treatment. While validation is needed, CRRS demonstrated a better characterization of VNS response compared with already existing classifications.

Acknowledgements

This research was supported by a statistical consultancy service provided by the Statistical Methodology and Computing Service technical platform at UCLouvain.

Data Availability

Anonymized data not published within this article are available from the corresponding author upon reasonable request or on this link: https://doi.org/10.14428/DVN/SBAGWH.

Authorship Statements

Venethia Danthine was responsible for the study conceptualization, data curation, formal analysis, project administration, funding acquisition, resources, investigation, methodology, visualization, and writing-original draft. Enrique Ignacio Germany Morrison was responsible for the methodology, software, validation, formal analysis, and writing–original draft. Lise Cottin was responsible for the methodology, software, validation, formal analysis, and writing–review and editing. Giulia Liberati was responsible for the conceptualization, investigation, supervision, methodology, and writing-review and editing. Inci Cakiroglu was responsible for the conceptualization, methodology, and writing-review and editing. Vincent Joris was responsible for the conceptualization, methodology, and writing-review and editing. André Mouraux was responsible for the conceptualization, methodology, and writing-review and editing. Roberto Santalucia was responsible for the conceptualization, methodology, and writing-review and editing. Alexane Fierain was responsible for the conceptualization, methodology, and writing-review and editing. Pascal Vrielynck was responsible for the conceptualization, methodology, and writing-review and editing. Susana Ferrao Santos was responsible for the conceptualization, methodology, funding acquisition, and writing-review and editing. Antoine Nonclercq was responsible for the conceptualization, investigation, supervision, methodology, and writing-review and editing. Riëm El Tahry was responsible for the conceptualization, funding acquisition, investigation, methodology, visualization, supervision, and writing-original draft. All authors approved the final version of the manuscript.

Conflict of Interest

The authors reported no conflict of interest.

How to Cite This Article

Danthine V., Germany Morrison E.I., Cottin L., Liberati G., Cakiroglu I., Joris V., Mouraux A., Santalucia R., Fierain A., Vrielynck P., Santos S.F., Nonclercq A., El Tahry R. 2025. Effect of Vagus Nerve Stimulation on Electroencephalogram Synchronization: A Longitudinal Study Using a Clinical-Research Response Scale.
Neuromodulation 2025; ■: 1–11.

SUPPLEMENTARY DATA

To access the supplementary material accompanying this article, visit the online version of *Neuromodulation: Technology at the Neural Interface* at www.neuromodulationjournal.org and at https://doi.org/10.1016/j.neurom.2025.03.068.

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COMMENT

This is a worthwhile and interesting topic, and one of particular interest to me. I would like to see more research that investigates biomarkers and factors leading to response vs nonresponse with neurostimulation. The manuscript is well-written and the methods are sound. I appreciated the CRRS tool and think it could be useful to help capture acute and chronic effects of VNS as well as seizure severity. It's interesting that both Phase Lag Index and magnet response could be potential early indicators of response to VNS. In future research, it would be useful to do a larger study with more patient and have balanced numbers of patients with generalized epilepsy, focal epilepsy, and Lennox Gastaut syndrome.

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