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The Immediate Effects of Vagus Nerve Stimulation in Intractable Epilepsy: An Intra-operative Electrocorticographic Analysis

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Abstract

The purpose of this study was to investigate whether and how vagus nerve stimulation (VNS) reduces the epileptogenic activity in the bilateral cerebral cortex in patients with intractable epilepsy. We analyzed the electrocorticograms (ECoGs) of five patients who underwent callosotomy due to intractable epilepsy even after VNS implantation. We recorded ECoGs and analyzed power spectrum in both VNS OFF and ON phases. We counted the number of spikes and electrodes with epileptic spikes, distinguishing unilaterally and bilaterally hemispherically spread spikes as synchronousness of the epileptic spikes in both VNS OFF and ON phases. There were 24.80 ± 35.55 and 7.20 ± 9.93 unilaterally spread spikes in the VNS OFF and ON phases, respectively (P = 0.157), and 35.8 ± 29.21 and 10.6 ± 13.50 bilaterally spread spikes in the VNS OFF and ON phases, respectively (P = 0.027). The number of electrodes with unilaterally and bilaterally spread spikes in the VNS OFF and ON phases was 3.84 ± 2.13 and 3.59 ± 1.82 (P = 0.415), and 8.20 ± 3.56 and 6.89 ± 2.89 (P = 0.026), respectively. The ECoG background power spectra recordings in the VNS OFF and ON phases were also analyzed. The spectral power tended to be greater in the high-frequency band at VNS ON phase than OFF phase. This study showed the reduction of epileptogenic spikes and spread areas of the spikes by VNS as immediate effects, electrophysiologically.

Key words: vagus nerve stimulation, electrocorticogram analysis, immediate effect

Introduction

Vagus nerve stimulation (VNS) is a palliative therapy for drug-resistant, intractable epilepsy that restrains an epileptic seizure by providing intermittent electric stimulations to the cervical vagus nerve. The clinical application of VNS was started based on the fundamental researches in an animal model in the United States in 1988, and health insurance coverage for VNS was applicable in Japan in 2010.[1,2] Several large clinical trials have demonstrated the results of VNS; thus, there is no room for doubt in terms of its effectiveness in the treatment of intractable epilepsy.[3,4] In addition, improvement of the cognitive function and emotional disorder has been known as a parallel effect associated with the restraint of epileptic seizures using VNS.[5] VNS has been used in clinical practice for the treatment of refractory depression since it was approved by the Food and Drug Administration (FDA) in the United States in 2005. Furthermore, it has been suggested as a treatment option for chronic migraine[6,7] and the aftereffects of cerebral infarction due to its anti-inflammatory action; therefore, VNS should be applied in the treatment of more diseases in the future.[8,9]

The responder ratio of the VNS treatment is 25%, 37%, and 50% at 3 months, 1 year, and 5 years during a treatment period, respectively.[10,11]

Although the mechanisms of the VNS treatment are still unclear, it has been suggested that its long-term effect is due to the modification of the extensive cerebrocortical activation by the deep brain nuclei, such as the thalamus, through the neurotransmitters, including the noradrenaline system.[12–14] However, few studies have been performed to analyze the immediate effect of VNS on the brain. It has been suggested in a prior study that the effect of VNS was associated with a direct or indirect influence on the electrophysiological modulation and/or the broad spread of the epileptogenic activity, from the nuclei of the solitary tract to the bilateral cortices

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in the acute phase.[15,16] In this study, we analyzed and compared the electrocorticogram changes before and after VNS stimulation during operations.

Materials and Methods

Patient population

The study subjects were five patients with intractable epilepsy who underwent an additional craniotomy (callosotomy) as a multistage-palliative treatment in our department between 2014 and 2018 because the effect of the preceded VNS therapy was insufficient or their satisfaction was poor. There were three males and two females, with an age range between 14 and 39 years (mean 26.2). These five patients were all poor-responder of VNS therapy. The patients' characteristics are summarized in Table 1. The mean period between the VNS surgery and callosotomy was 35 months.

This study was approved by the Ethical Committee of Sapporo Medical University Graduate School of Medicine, and written informed consent was obtained from all patients. When children were involved in this study, the permission of their parents was obtained.

Electrocorticogram recordings

All patients were administered general anesthesia by anesthesiologists, with the end-tidal sevoflurane concentration maintained at 2% during the electrocorticogram (ECoG) recording. The ECoG data were recorded using an MEE-1232 machine (Nihon Kohden, Tokyo, Japan), using a preamplifier bandwidth of 0.5–100 Hz and a sampling rate of 500 Hz. Two 1 × 6 or 2 × 8 subdural electrodes grids [10 mm intercontact distance, each contact distant with 3 mm diameter (Unique Medical, Tokyo, Japan)] were placed on the bilateral frontal cortices intraoperatively (Fig. 1); the reference electrode was placed on the earlobe, and the earth electrode was placed on the nasion. To precisely differentiate the VNS OFF and ON phases, an electrocardiogram was recorded at the same time to capture the stimulation artifact. During the VNS ON phases, the stimulation was associated with a 30 Hz activity detected on the electrocardiogram (Fig. 2).

The ECoG recordings consisted of discontinuous 180 s added consecutive 60 s three times each in the VNS ON and OFF phases before the start of the corpus callosotomy. A normal mode of VNS was turned off before the operations, and only a magnet mode was used for the recordings in the VNS ON phases, of which duration was 60 s. In order to avoid the influence of the VNS, the ECoG recordings were performed at least 60 s apart from the stimulation

Table 1 Patients' characteristics

Case	Age, gender	Seizure type	Epilepsy type	Etiology	Medication	McHugh classification	VNS duration	VNS parameter (intensity, pulse width)	Magnet mode parameters (intensity, pulse width, on time)
1	17 years, Male	GA, GM, GTC	LGS	rt. temporal tumor polymicrogyria	ESM, VPA, ZNS,	Class III	29 months	2.0 mA, 500 μs	2.25 mA, 750 μs, 60 s
2	14 years, Female	GA, GTC	LGS	Cortical dysplasia	CBZ, CZP, LEV, TPM	Class III	33 months	2.0 mA, 750 μs	2.25 mA, 750μs, 60 s
3	33 years, Female	FIA, GA, PNE	LGS	Cortical dysplasia	LEV, PHT, TPM, VPA	Class II	26 months	2.25 mA, 500 μs	2.5 mA, 500 μs, 60 s
4	28 years, Male	FIA, GA, GTC	LGS	Viral infection	PB, PHT, VPA	Class II	23 months	2.0 mA, 750 μs	2.25 mA, 750 μs, 60 s
5	39 years, Male	FIA, GA, GTC	Unknown	None	CZP, LEV, LTG	Class III	63 months	1.625 mA, 500 μs	1.875 mA, 750 μs, 60 s

GA: generalized atonic, GM: generalized myoclonic, GTC: generalized tonic–clonic, FIA: focal impaired awareness, PNE: psychogenic non-epileptic, LGS: Lennox–Gastaut syndrome, CBZ: clobazam, CZP: clonazepam, ESM: ethosuximide, LEV: levetiracetam, LTG: lamotrigine, PB: phenobarbital, PHT: phenytoin, TPM: Topiramate, VPA: valproic acid, ZNS: zonisamide.

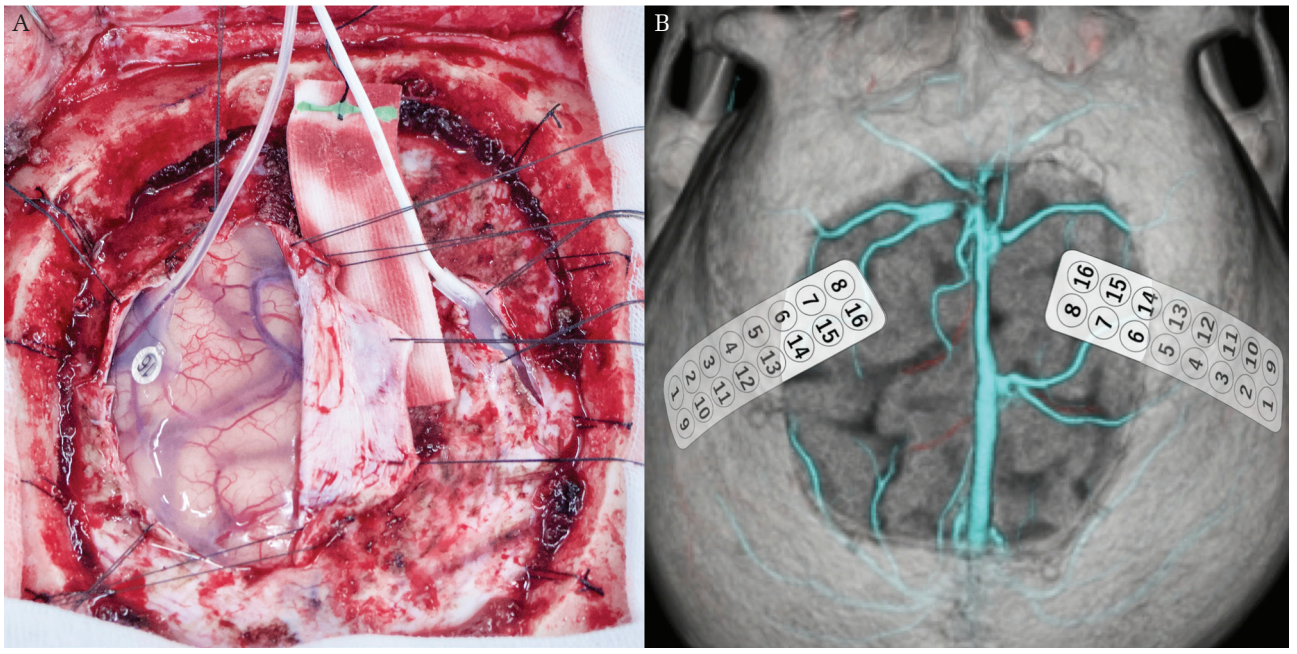

Fig. 1 (A) An intraoperative factual image of case 4. Two 2 × 8 subdural electrodes grids were placed on the bilateral frontal cortices. (B) A fusion image of 3D computed tomography and schematic electrodes grids.

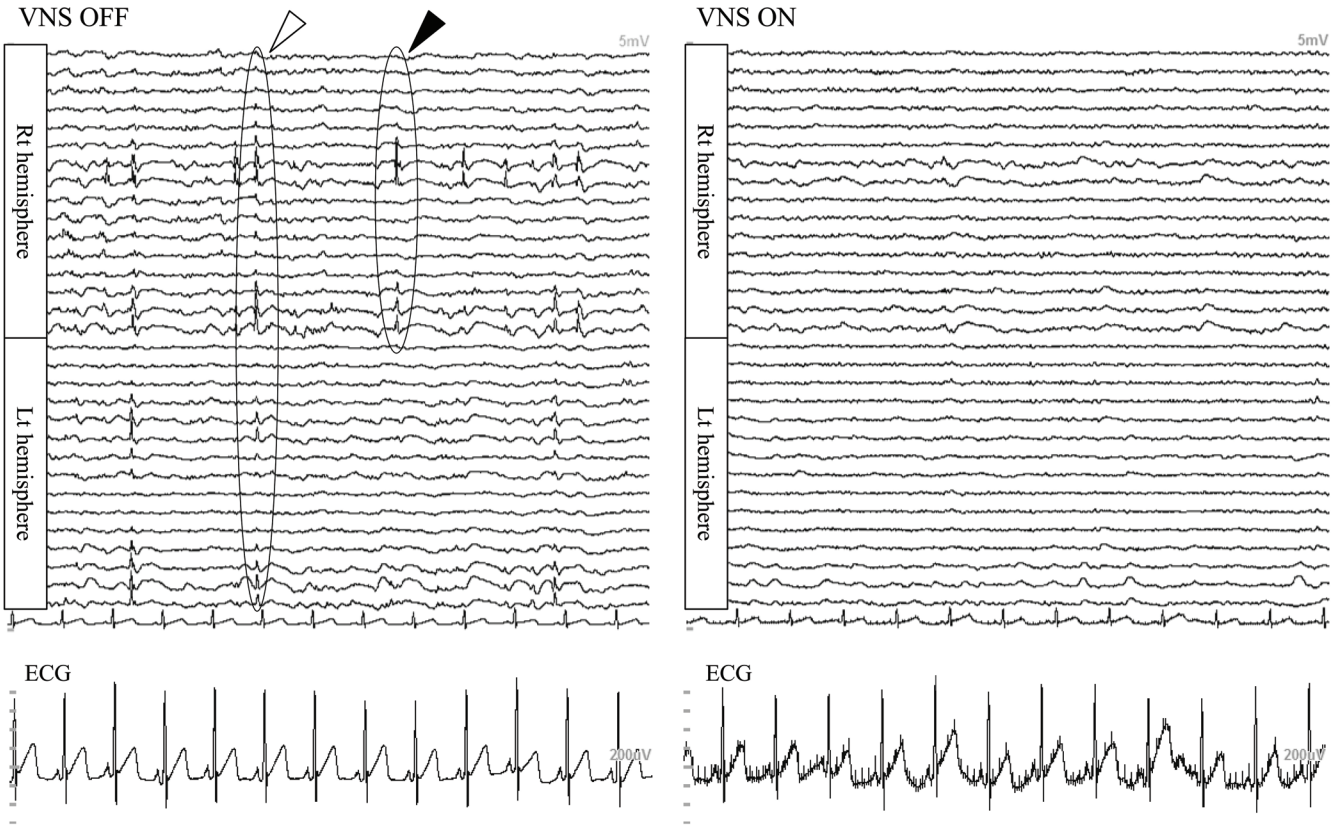

Fig. 2 An example of ECoG recordings of the bilateral hemispheres in case 3 during the vagus nerve stimulation (VNS) ON and OFF phases. The artifact of VNS stimulation is recorded on the ECG during the VNS ON phases. The unilateral spikes were defined as discharges spreading unilaterally hemispherically (*black arrowhead*), and also the bilateral spikes were defined as discharges spreading bilaterally hemispherically with synchronousness (*white arrowhead*). ECoG: electrocorticogram.

during the VNS OFF phases. In each patient, the usual VNS parameters were recorded (Table 1).

ECoG analysis

The records were reviewed and annotated by two neurosurgeons, board-certified members of the Japanese Epilepsy Society, who were blinded to the VNS ON and OFF phases. We analyzed the spikes that they both matched and excluded the ones with an amplitude of <400 μV. We counted a spike and wave complex as one spike.

We analyzed the number of spikes, the maximum amplitude of the spikes, and the number of electrodes where the spikes were shown. The power spectrum was then analyzed and compared between the VNS OFF and ON phases. The power spectrum was calculated by a fast Fourier transform range 1–60 Hz using MATLAB (Mathworks, Natick, MA, USA), and the number of points in the fast Fourier transform was configured to 500. We used all the electrodes of each patient for this analysis except ones containing artifacts or noise obviously caused by electronic devices and motion.

Statistical analysis

The data are expressed as means ± standard deviations. We used the Wilcoxon paired samples test to identify the group differences. Repeated measure analysis of variance was used to analyze the spectral power in each frequency.

All statistical analyses were conducted using the SPSS software package (version 12; SPSS Inc., Chicago, IL, USA). P <0.05 was considered to indicate statistical significance.

Results

Patients' characteristics

We observed five consecutive patients with intractable epilepsy despite multiple anti-epileptic drugs and even VNS implantation, who were scheduled to undergo callosotomy in our institution. The subjects' age ranged between 14 and 39 years (mean 26.2).

All patients were diagnosed with a generalized onset as seizure type and generalized epilepsy as epilepsy type, according to the International League Against Epilepsy (ILAE) classification of the epilepsies 2017.[17,18] The seizure types in all patients are described in Table 1, as follows: generalized atonic (GA), generalized myoclonic (GM), and generalized tonic–clonic (GTC) in case 1; GA and GTC in case 2; focal impaired awareness (FIA), GA, and psychogenic non-epileptic in case 3; and FIA, GA, and GTC in cases 4 and 5. The epilepsy types were West syndrome (WS) and Lennox–Gastaut syndrome (LGS) in case 1, LGS in cases 2–4, and unknown in case 5; McHugh Classification class III in cases 1, 2, and 5, and class II in cases 3 and 4 (Table 1).

In all cases, except for case 1, the frequency of the seizure attacks (FSA) had dramatically decreased soon after VNS implantation; however, after 1–2 years, the FSA gradually increased and the symptoms deteriorated. In case 1, although the complex seizure attacks had decreased after the VNS implantation, the drop attack had not decreased. Accordingly, the patients were scheduled to undergo callosotomy 23–63 months after the VNS implantation.

ECoGs recordings

During the callosotomy, we evaluated and compared the ECoGs between the VNS OFF and ON phases using subdural electrodes on both sides of the brain. The mean values of each of the following parameters VNS OFF phases versus ON phases, respectively. We counted the number of spikes, distinguishing the unilaterally hemispherically spread and the bilaterally hemispherically spread spikes as synchronousness of the epileptic spikes in both the VNS ON and OFF phases.

The number of unilaterally spread spikes in the VNS OFF and ON phases was 2–78 (mean 24.80 ± 35.55) and 0–23 (mean 7.20 ± 9.93), respectively; the difference was not statistically significant (P = 0.157). In contrast, the number of bilaterally spread spikes in the VNS OFF and ON phases was 5–83 (mean 35.8 ± 29.21) and 1–34 (mean 10.6 ± 13.50), respectively; the difference was statistically significant (P = 0.027).

The number of electrodes with unilaterally spread spikes in the VNS OFF and ON phases was 1–13 (mean 3.84 ± 2.13) and 1–8 (mean 3.59 ± 1.82), respectively; the difference was not statistically significant (P = 0.415). In contrast, the number of electrodes with bilaterally spread spikes was 2–18 (mean 8.20 ± 3.56) and 2–15 (mean 6.89 ± 2.89) in the VNS OFF and ON phases, respectively; the difference was statistically significant (P = 0.026).

The maximum amplitude (mV) of the unilaterally spread spikes in the VNS OFF and ON phases was 0.41–1.72 (mean 1.03 ± 0.27) and 0.41–1.58 (mean 1.06 ± 0.24), respectively; the difference was not statistically significant (P = 0.391). The maximum amplitude (mV) of the bilaterally spread spikes in the VNS OFF and ON phases was 0.42–1.88 (mean 1.04 ± 0.33) and 0.42–1.58 (mean 0.99 ± 0.30), respectively; the difference was also not statistically significant (P = 0.438). A significant reduction in both the number of spikes and electrodes were shown in the VNS ON phases. This effect was more pronounced for the bilaterally than for the unilaterally spread spikes (Table 2).

Table 2 The difference among the five cases in the number of spikes, the maximum amplitude of spikes, and the number of spike-positive electrodes in the VNS ON and OFF phases

		Case1		Case2		Case3		Case4		Case5	
	VNS status	Unilateral	Bilateral	Unilateral	Bilateral	Unilateral	Bilateral	Unilateral	Bilateral	Unilateral	Bilateral
Number of spikes (*n*)	OFF	32	2	38	2	21	8	83	78	5	34
	ON	7	0	9	0	1	2	34	23	2	11
Number of electrodes (*n*) (mean ± SD)	OFF	3.1 ± 1.2	9.5 ± 1.5	2.7 ± 1.5	4.5 ± 0.50	3.9 ± 1.9	12 ± 2.7	4.7 ± 2.3	8.0 ± 3.4	2.6 ± 1.0	7.9 ± 3.8
	ON	1.6 ± 0.73	0	4.0 ± 1.5	0	8.0 ± 0	10 ± 1.0	3.8 ± 1.6	6.0 ± 1.6	2.5 ± 0.50	8.2 ± 4.0
Maximum amplitude of spikes (mV) (mean ± SD)	OFF	0.70 ± 0.12	0.95 ± 0.25	1.2 ± 0.16	1.3 ± 0	1.1 ± 0.33	1.5 ± 0.39	1.1 ± 0.12	1.2 ± 0.16	0.43 ± 0.014	0.59 ± 0.098
	ON	0.75 ± 0.13	0	1.3 ± 0.093	0	1.6 ± 0	1.3 ± 0.30	1.2 ± 0.12	1.1 ± 0.13	0.45 ± 0.035	0.60 ± 0.11

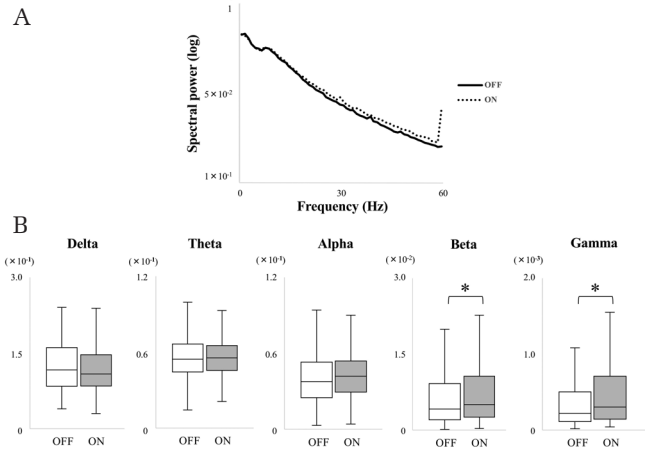

Fig. 3 (A) The mean electrocorticographic spectral power in the VNS OFF phases (*solid line*) and VNS ON phases (*dotted line*). In the VNS ON phases, the high-frequency spectral power, including beta and gamma bands, was greater than in the VNS OFF phases. Power spectrum (μV^2log). (B) Power spectra of δ, θ, α, β, and γ bands in the frontal lobe before and after VNS. Power spectrum (μV^2/s ± SD). Statistical significance: *P <0.05.

The ECoG background power spectra recordings were also analyzed in the VNS ON and OFF phases. We classified the frequency bands as δ: 1–3 Hz, θ: 4–7 Hz, α: 8–13 Hz, β: 14–30 Hz, and γ: more than 31 Hz. The mean values of each spectral band in the VNS OFF and ON phases were as follows: δ, 0.13 ± 0.45 and 0.12 ± 0.44 (P = 0.002); θ, 0.58 ± 0.20 and 0.57 ± 0.17 (P = 0.920); α, 0.41 ± 0.25 and 0.43 ± 0.21 (P = 0.068); β, 0.066 ± 0.0702 and 0.078 ± 0.075 (P <0.001); and γ, 0.0041 ± 0.0053 and 0.0059 ± 0.0078, respectively (P <0.001) (Fig. 3). The spectral power tended to be greater in the high-frequency bands and in the VNS ON phases. VNS may induce an increase of the spectral power in the high-frequency bands, particularly in the β and γ bands.

Discussion

Vagus nerve stimulation is a palliative therapy for refractory epilepsy that restrains an epileptic seizure by providing intermittent electric stimulations to the cervical vagus nerve. The aim of this study was to evaluate the effectiveness of VNS for suppression of the epileptic seizure using electrocorticography with subdural electrodes. Previous studies have analyzed the effect of VNS using electroencephalography (EEG) on the scalp, and demonstrated a decrease in the epileptic spikes and de-synchronousness as a long-term effect of VNS.[19–21]

As stated above, the mechanisms of the epileptic seizure suppression with VNS is unclear. Various

possibilities have been suggested, such as the change in the neurotransmitters' concentration,[22–24] expression of a new protein,[25,26] and change in the local brain blood flow.[27–29] Most of the previous studies demonstrated the VNS long-term effects using the trans-scalp EEG recording.[19–21] Bartolomei et al.[30] reported an evaluation with an intracranial electrode for the first time using stereotactic EEG (SEEG), and mentioned the possibility that the functional connectivity between the corticocortical neurons may be changed by VNS. Although subdural electrocorticography has many advantages including the sensitivity, preciseness, and spatial resolution, there are also some disadvantages compared with the transcranial electroencephalography, such as invasiveness and area coverage.[31,32] Some recent studies have reported on a non-invasive stimulation of other cranial nerves, such as trigeminal nerve stimulation[33] and that percutaneous VNS could have effects similar to those of the conventional VNS.[34,35]

In this study, interestingly, the VNS effects of decreased epileptic spikes and spread area were more pronounced in the bilaterally spread spikes than in the unilaterally spread spikes. Previous studies have suggested that patients with generalized seizure subtypes improved better in response to VNS than those with focal seizures.[36–39] Moreover, the seizure-free rate in patients undergoing VNS therapy was also described to be higher in the patients with primarily generalized seizures.[36] Although it is not fully understood why the VNS effects are more pronounced in patients with generalized than in those with focal seizures, our data might provide one explanation for it. Some authors showed that VNS may induce a decrease in the synchronization of the epileptic spikes.[19,40–42] This suggests that our findings can support the results of the past studies.

The spectral power tended to be greater in the high-frequency bands in the VNS ON phases than in the VNS OFF phases. This power spectral finding suggests that the frontal cortex cells were electroneurophysiologically affected by VNS. Gamma activity has previously been found to be increased in patients with epilepsia.[43,44]

According to past reports, the action potential caused by the electrical stimulation of the vagus nerve is conducted afferently to the cerebral cortex through the nuclei of the solitary tract of the brainstem, suppressing the cerebrocortical electric activity in both sides through the thalamus, limbic system, putamen, and other regions.[45,46] Notably, in this study, we found a reduction of the epileptogenic spikes in the inter-ictal phases in both hemispheres as an immediate effect of VNS using the subdural electrodes. Because the VNS effect in this study occurred soon after its activation as an immediate effect, the electrophysiological mechanism may have directly or indirectly affected the cerebral cortex, which was supported with the ECoGs.

The limitations of this study are as follows. First, all subjects were clinically non- or poor-responders to VNS because of the study design. The mechanism of the VNS effect may be further elucidated by evaluating patients who respond to VNS using an ECoG analysis. Second, the electrocorticography evaluation could be performed for only a short period and in a limited area. An evaluation of a broader area of the cortex can provide a more precise analysis in terms of the epileptic seizures' spread in the brain. Finally, in this study, we could compare the profiles of the epileptogenic spikes in both the VNS OFF and ON phases only during the inter-ictal phases. It is much more important to evaluate the spikes in the ictal phases; however, that was impossible to do during the craniotomy surgery.

We would like to emphasize that the results of this study proved the hypothesis that VNS adjusts, modifies, and controls an abnormal epilepsy-related network.

Conclusion

In this study, we found that VNS induced a reduction in the epileptogenic spikes and the spread areas of the spikes in the inter-ictal period as immediate effects, which suggested that VNS can restrain the neurophysiologic activity of an abnormal epilepsy-related network in the cerebral cortex through the nuclei of the solitary tract even in non- or poor-responding patients. Nonetheless, further investigation is necessary.

Conflicts of Interest Disclosure

The authors have no competing interests to disclosure.

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