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Secondary epileptogenesis on gradient magnetic-field topography correlates with seizure outcomes after vagus nerve stimulation

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ABSTRACT

Objective: To determine the correlation between secondary unilateral or bilateral spreading on gradient magnetic-field topography (GMFT) before and after vagus nerve stimulation (VNS), and postoperative seizure outcomes.
Methods: We analyzed pre- and post-VNS magnetoencephalography (MEG) in 15 patients with VNS implants. We applied McHugh classification to evaluate seizure outcomes. GMFT visualized the spatiotemporal spread of the gradient magnetic field from MEG (>300 fT/cm) before and after the spike peak. We compared the proportion of bilaterally spreading (PBS) MEG spikes and seizure outcomes. We also compared the interhemispheric time difference (ITD) between patients with and without corpus callosotomy.
Results: We allocated patients with favorable seizure outcomes of class I and II to group A (9 patients) and poor outcomes of class III–V to group B (6 patients). The number of post-VNS MEG spikes was significantly reduced compared to pre-VNS MEG spikes in group A, but not in group B. Group A showed significantly higher preoperative PBS than group B. Postoperative ITD significantly decreased in 5 patients who underwent corpus callosotomy compared to 10 patients without.
Conclusion: GMFT can detect the inter- and intrahemispheric spreading of spikes with high spatiotemporal resolution on the brain surface. Frequent interictal MEG spikes propagating bilaterally on GMFT may reflect a favorable seizure outcome after VNS. GMFT can identify dependent secondary epileptogenic spikes responding to VNS, which may be used to control generalized seizures in a subset of patients with pharmaco-resistant epilepsy.

1. Introduction

1.1. Vagus nerve stimulation

In current epilepsy surgery, vagus nerve stimulation (VNS) is an option for a subset of patients with refractory epilepsy. Since the introduction of VNS in the United States in 1988, neurosurgeons worldwide have performed VNS as a palliative therapy for reducing seizures in patients with pharmaco-resistant epilepsy (Englot et al. 2011, 2016). VNS can gradually produce therapeutic effects after the start of stimulation. Two years after VNS implantation, 43.3% to 63.0% of patients eventually reached 50% seizure reduction (Morris and Mueller 1999; Englot et al. 2016). After 3 or 4 years of having a VNS implant, 7.0% to 9.0% of patients achieved seizure free status (Vonck et al. 2004; De Herdt et al. 2007).

Although VNS has been established in clinical practice, we do not yet have a clear understanding of the specific mechanism of action behind VNS treatment of pharmaco-resistant seizures. Several mechanisms have been proposed to play a pivotal role in the efficacy of VNS, such as effects on the thalamus and limbic system via glutamate transmission in

Abbreviations: VNS, vagus nerve stimulation; AAS, atypical absence seizure; AS, atonic seizure; DA, drop attack; FBTCS, focal to bilateral tonic-clonic seizure; FIAS, focal impaired awareness seizure; GMS, generalized motor seizure; HD, head drop; MS, myoclonic seizure; PNES, psychogenic nonepileptic seizures; TCS, tonic-clonic seizure; TS, tonic seizure; Bil, bilateral; F, frontal; FSW, focal spike and wave; Lt, left; P, parietal; Rt, right; T, temporal.

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the nucleus of the solitary tract (NST) (Ruffoli et al. 2011), and whole-brain effects on the monoaminergic systems through the NST and locus coeruleus (Katagiri et al. 2019; Vonck et al., 2008).

1.2. Gradient magnetic-field topography and temporal signal-space separation

Conventional equivalent current dipole analysis shows efficiency for focal resection in patients with pharmaco-resistant focal onset seizures. Most patients who require VNS are not candidates for focal resection, because of their generalized onset seizures or unknown onset seizures (Iida et al. 2005). Gradient magnetic-field topography (GMFT) has been developed to avoid solving the mathematically complex problems for a unique solution for the epileptic foci. GMFT can visualize the dynamic changes in brain magnetic fields from the epileptic source on a three-dimensional brain surface (Hashizume et al. 2007). The magnetic field generated from VNS impacts the adoption of magnetoencephalography (MEG) analysis for patients with VNS implants. Taulu et al. developed a temporal signal-space separation (tSSS) algorithm to solve this problem (Taulu and Hari, 2009).

1.3. Corpus callosotomy and vagus nerve stimulation

Corpus callosotomy (CC) is a palliative surgical procedure used to treat generalized seizures in patients with pharmaco-resistant epilepsy (Spencer et al. 1985; Oguni et al. 1991; Kagawa et al. 2016). CC is known to be effective for drop attacks caused by myoclonic, tonic, or atonic seizures (Tanriverdi et al. 2009; Maehara and Shimizu 2001; Oguni et al. 1991; Rossi et al. 1996). In children with infantile spasms and hypsarrhythmia, the function of the corpus callosum in the chaotic bilateral fast and slow oscillations of hypsarrhythmia has been reported to be an essential part of the modulation of interhemispheric discharges (Baba et al. 2019). In our present study, we evaluated patients for whom CC did not improve seizure control and further VNS was required. The intra- and inter-hemispheric spreading of multiple spikes before and after VNS was first measured by MEG to identify the occurrence and time difference of spike spreading in the brain cortex using GMFT.

1.4. Hypothesis

We studied GMFT for pre- and post-VNS MEG in patients who required VNS for their pharmaco-resistant epilepsy. We evaluated the dynamic changes in MEG spike spreading over the unilateral and bilateral hemispheres by GMFT. We hypothesized that spike spreading on GMFT could predict the seizure outcomes of VNS; thus, bilateral spreading is a potential biomarker of seizure control by VNS.

2. Methods

2.1. Patients

We retrospectively reviewed the clinical records and MEG findings in patients who underwent VNS implantation and MEG pre-/post- (>6 months) VNS at Hiroshima University Hospital between March 2011 and January 2016. Our criteria for VNS implantation included patients who were not candidates for focal resection based on presurgical evaluations, those who were not candidates for further cortical resection after failed resective surgery, or those in which they or their families did not request focal resection. If patients had drop attacks, we preferentially performed CC before VNS. The presurgical evaluations included scalp video-electroencephalography (EEG) and magnetic resonance imaging (MRI). Further diagnostic modalities, i.e., positron emission tomography (PET) with fluorine-18 fluorodeoxyglucose ([^{18}F]-FDG) and iodine-123 iomazenil single-photon emission computed tomography (IMZ-SPECT) were also performed if necessary. All patients and their caretakers provided their informed consent before the surgery. 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.

We excluded the patients from this study if their raw MEG data or processed data with tSSS showed artifacts that did not allow spikes to be distinguished by visual inspection.

2.2. Vagus nerve stimulation (VNS)

Each patient was implanted with a model 103 or 105 vagus nerve stimulation (VNS) Therapy System (LivaNova, Houston, TX, USA). The VNS system was implanted in a standard manner under general anesthesia (Reid, 1990). The device was activated 2–3 weeks after implantation.

At the first visit, the stimulation was started with the following parameters: output current, 0.25 mA; magnet current, 0.50 mA; pulse width, 500 ms; signal on time, 30 s; signal off time, 5 min. The output current and magnet current intensity were increased by 0.25 mA, as tolerated, up to 2.25 mA output current. After reaching an output current of 1.5 mA, the off time was adjusted from 5 to 1.8 min if seizure control was insufficient. Each new setting was maintained for at least 1 month. If the patient and/or caregiver were satisfied with the results, they were reviewed every 3 months. Seizure frequency, side effects, and other significant information reported by patients and their caretaker were collected at the postoperative visits.

2.3. MEG recording before and after VNS

A Neuromag System (a whole-head 306-channel type, Elekta-Neuromag, Helsinki, Finland) digitally generated the MEG data at 600.615 Hz. Each MEG recording consisted of 3 epochs of 10 min with a simultaneous electrocardiogram, electro-oculogram, and international 10–20 system EEG recording. The patients rested with closed eyes while seated.

The VNS system included a Pulse Generator 103 or 105 (LivaNova). During the MEG following the VNS system implant, we temporarily stopped stimulation with the VNS device to reduce magnetic artifacts, then we removed any artifacts using the tSSS algorithm.

2.4. Spike selection and artifact removal

We identified interictal epileptiform MEG spikes with reference to an EEG that was recorded simultaneously (Fig. 1). MEG data were band-pass filtered at 14–50 Hz. Furthermore, we visually selected the interictal epileptiform MEG spikes with more than 300 fT/cm, which appeared after more than a 0.5 s spike-free interval. We counted the number of MEG spikes from pre- and post-VNS MEG recordings.

The tSSS algorithm was applied to remove VNS-derived artifacts in the post-VNS MEG study. Principal component analysis (PCA) was also applied, if necessary, to remove relatively mild artifacts, such as those from blinks and heart beats.

2.5. Gradient magnetic-field topography

We generated GMFT with 10 ms steps for 100 ms before and after the peak of selected MEG spikes from a planar gradiometer. We defined areas with spikes over 300 fT/cm as being an activated zone on GMFT (Fig. 2). Based on the spike spreading area, we classified them into 2 categories: unilaterally-spreading spikes (USS), defined as the spread of epileptic activity confined within one hemisphere; and bilaterally-spreading spikes (BSS), which are epileptic activity propagating to the contralateral hemisphere (Fig. 2).

For each patient, we calculated the proportion of bilaterally spreading spikes (PBS) by dividing the BSS by the BSS plus USS for each patient. We also measured the interhemispheric time difference (ITD) from the time of spike onset with activated GMFT spreading to the

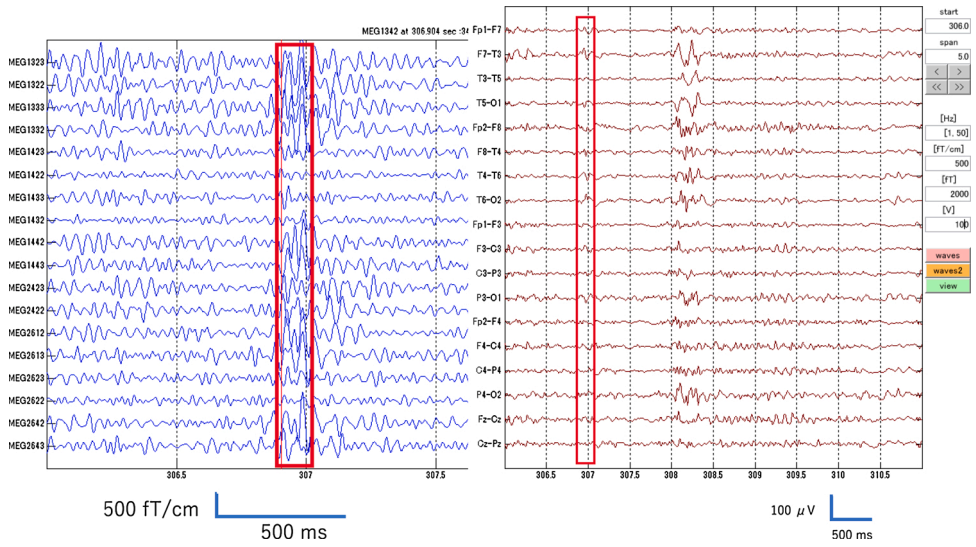

Fig. 1. An example of preoperative MEG and EEG for bilaterally spreading spikes. (A) The 1.5 second expanded and regional 18 MEG channels. (B) The bilateral temporal spikes corresponding to the MEG.

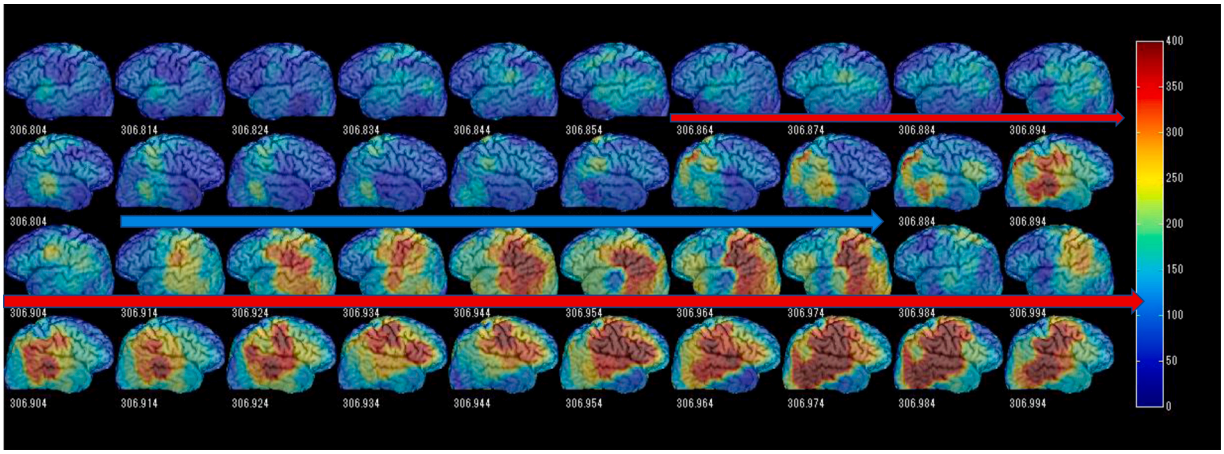

Fig. 2. An example of bilateral spreading spike on gradient magnetic field topography (GMFT) in Case 3. GMFT analysis visualized epileptic activity (> 300 fT/cm). The epileptic activity originating from the right parietal lobe starts at 306.864 s (red arrows). In the left hemisphere, the activity spreads to the left parietal lobe at 306.914 s and continues until 306.974 sec (blue arrow). The interhemispheric time difference reached 50 ms.

contralateral hemispheric spikes as we previously reported (Kagawa et al. 2016).

2.6. Patient classification based on seizure outcomes

The seizure reduction rate was calculated from the average number of seizures during the 3 months before the last follow-up. We applied the VNS-specific outcome scale proposed by McHugh et al. (McHugh et al. 2007): Class I, 80%–99% reduction in seizure frequency; Class II, 50%–79% reduction in seizure frequency; Class III, <50% reduction in seizure frequency; Class IV, magnet benefit only; and Class V, no improvement. Patients were classified as responders if they had a ≥50% total seizure reduction rate (group A = Class I and II) and as nonresponders if they had a <50% total seizure reduction rate (group B = Class III, IV, and V). Considering the cumulative therapeutic effect of VNS, we excluded patients with less than 2 years of follow-up after VNS implantation (Morris and Mueller 1999; Vonck et al. 2004; De Herdt et al. 2007; Englot et al. 2011; Englot et al. 2016).

2.7. Comparison of clinical parameters

Between the responders and nonresponders, we compared age at onset of epilepsy, age at VNS implantation, duration of seizure, sex, the number of preoperative AEDs, postoperative AEDs, the period of preoperative MEG to operation, the period of operation to postoperative MEG, and surgical clinical outcomes, spikes, PBS, and ITD.

We compared the number of MEG spikes, PBS, and ITD pre- and post-VNS. We also compared ITD between patients with and without corpus callosotomy. If patients presented with drop attacks associated with epileptic spasms, tonic or atonic seizures, we preferentially performed CC prior to VNS. We performed total CC for patients younger than 11 years, or older patients with severe mental retardation. We sectioned the anterior two-thirds during CC for patients aged 11 years or older with mild mental retardation to normal intelligence. We then performed VNS to palliate residual seizures following CC.

2.8. Statistical analyses

We used R version 3.6.1 (https://www.r-project.org/) for the statistical analyses. To test the proportion of category variables, we used a

Table 1
Patient characteristics and seizure outcomes.

No	Sex	Age (years)		Seizure types	Epilepsy surgery before VNS	Seizures	Video EEG findings before VNS	EEG findings after VNS		Follow-up (months)	Reduction rate of seizures	McHugh classification	Group
		at seizure onset	at VNS				Ictal EEG fidnings	Locations of interictal epileptiform discharges	Locations of interictal epileptiform discharges				
1	Female	3	53	FIAS, TS		FIAS	Diffuse flattening -> fast activities	Bil. F, T	Bil. F	78	FIAS >80%, TS = 100%	I	A
2	Female	6	36	FIAS, TS, PNES	Lt. Frontal corticotomy	No seizure	No seizure	Bil. F	Bil. F	72	FIAS = 100%, FTS > 80%	I	A
3	Male	9	53	GTCS, AS (DA)		GTCS	Diffuse flattening -> slow activities	Bil. T	Rt. T	25	GTCS = 100%, AS > 50%	I	A
4	Female	3	9	AAS	Total callosotomy	AAS	Sudden burst of high amplitude	Multifocal	Lt. T	67	AAS > 80%	I	A
5	Female	0.6	30	HD, TS (DA), MC	Anterior callosotomy	HD	Generalized slow activities	Bil. P, T	Rt. F, P, T	48	HD > 50%, TS < 50%, MC > 50%	II	A
6	Male	2	44	GTCS, TS (DA), PNES		GTCS	Diffuse slow spike and waves, PNES	Rt. F, T	Lt. F	50	Seizure free	I	A
7	Female	15	45	FBTCS		FBTCS	Diffuse rhythmic theta activities	Bil. F, T	Rt. T	27	FBTCS > 50%	II	A
8	Male	10	25	FIAS, FBTCS, AAS	Anterior callosotomy	FIAS, FBTCS	Diffuse rhythmic spikes	Bil. F, T	Bil. F, T	45	FIAS > 80%, FBTCS = 100%, AAS = 100%	I	A
9	Male	7	10	FIAS, FBTCS	Total callosotomy	FIAS, FBTCS	Diffuse rhythmic spikes	Multifocal	Multifocal	51	FIAS > 80%, FBTCS > 80%	I	A
10	Female	4	34	GTCS		GTCS	Diffuse slow activity	Bil. F, T	Bil. F	63	GTCS < 50%	III	B
11	Female	6	9	GMS, TS, MC		GMS, TS	Fast activities over Bil. F	None	Multifocal	53	GMS < 50%, TS < 50%, MC < 50%	III	B
12	Male	0.3	14	GTCS, MC, AAS	Total callosotomy	GTCS	Alpha like activities over Rt. hemisphere	Rt. F, T	Bil. F, T	51	GTCS = 0%, MC = 100%, AAS = 100%	III	B
13	Female	12	24	FIAS, AS		FIAS	Lt. spikes -> Diffuse flattening	Bil. F, T	Lt. F, T	48	Magnetical benefit only	IV	B
14	Male	11	23	FBTCS		No seizure	No seizure	Bil. T	Lt. T	55	FBTCS < 50%	III	B
15	Male	21	41	FIAS, AS (DA)		FIAS	Slow activities over Bil. F	Bil. F	Lt. T	24	No seizure reduction	V	B

VNS: vagus nerve stimulation, F: female, M: male, AAS: atypical absence seizure, AS: atonic seizure, DA: drop attack, FBTCS: focal to bilateral tonic-clonic seizure, FIAS: focal impaired awareness seizure, GMS: generalized motor seizure, HD: head drop, MC: myoclonic seizure, PNES: psychogenic nonepileptic seizures, TCS: tonic-clonic seizure, TS: tonic seizure. Bil: bilateral, EEG: electroencephalogram, F: frontal, Lt: left, P: parietal, Rt: right, SW: spike and wave, T: temporal, VEEG: viedo-electroencephalogram. Outcome = A: McHugh class I & II (≥ 50% seizure-frequency reduction), B: McHugh class III-V (<50% seizure-frequency reduction).

Fisher exact test. To test differences between 2 samples of continuous variables, we performed a Shapiro–Wilk normality test, followed by a paired *t* test or Wilcoxon signed rank test; alternatively, it was followed by a Welch 2 sample *t* test or Wilcoxon rank sum test. We set the level of significance at $p < 0.05$. We performed linear single regression analysis to find the coefficient of determination for the identified prognostic factors and surgical outcomes.

We applied receiver operating characteristic (ROC) curve analysis to evaluate the relationship between the sensitivity and specificity of PBS pre-VNS for seizure outcomes. We detected optimal PBS using the Youden index, which maximizes the sum of the sensitivity and the specificity.

3. Results

3.1. Clinical profiles

During the study period, 16 patients underwent VNS implantation. One patient was excluded because the follow-up period was less than 2 years. We analyzed MEG before VNS and clinical profiles in the remaining 15 patients (8 female). Table 1 describes the clinical profiles of these 15 patients. The age at seizure onset ranged from 0.3 to 21 years old with a median of 6.0 years. The duration of seizures ranged from 3 to 50 years with a median of 22.0 years. The age of patients at the time of VNS system implantation ranged from 9 to 53 years with a median age of 30.0 years. Seizure types recorded in the patient history consisted of focal impaired awareness seizure (FIAS) in 6 patients, tonic seizure (TS) in 5 patients, drop attack (DA), focal to bilateral tonic-clonic seizure (FBTCS) and tonic-clonic seizure (TCS) in 4 patients each, atypical absence seizure (AAS), atonic seizure (AS) and myoclonic seizure (MC) in 3 patients each, and generalized motor seizure (GMS), and head drop (HD) in 1 patient each. Two patients presented psychogenic nonepileptic seizures (PNES) captured during video EEG. Previous surgeries had been performed in 6 patients, these consisted of CC in 5 patients (patient Nos. 4, 5, 8, 9, and 12) and left frontal corticectomy in 1 patient (No. 2) before VNS. The number of preoperative antiepileptic drugs ranged from 2 to 6 (median 4.0). Video EEG captured seizures in 13 of 15 patients. The seizures consisted of FIAS in 5 patients, TCS in 4 patients, FBTCS in 2 patients, AAS, GMS, HD, PNES, and TS 1 patient each. Two patients showed multiple types of seizures. Ictal EEG showed diffuse ictal discharges in 7 patients, multifocal or bilateral discharges in 3 patients, and generalized discharges in one patient. Single focal ictal discharges were found in 1 patient (No. 12) and bilateral interictal epileptiform discharges in 14. None of the analysis based on seizure type reached statistical significance.

The preoperative MEG was performed from 1 to 6 months before VNS system implantation, with a median of 3.0 months, around the same time as video EEG. The postoperative MEG follow-up period ranged from 6 to 39 months with a median of 20.0 months. The postoperative clinical follow-up period ranged 24 to 78 months with a median of 51.0 months.

After VNS implantation, >80% seizure reduction (McHugh classification, I) occurred in 7 patients (Nos. 1, 2, 3, 4, 6, 8, and 9), >50% seizure reduction (II) was found in 2 patients (Nos. 5 and 7), and <50% seizure reduction (III) was found in 4 patients (Nos. 10, 11, 12, and 14). Magnetic benefit only (IV) was seen in 1 patient (No. 13). Patient No. 15 showed no improvement in seizures (V). Nine patients (Nos. 1–9) with McHugh classifications of I and II were categorized as VNS responders in group A. The remaining 6 patients (Nos. 10–15) with McHugh classifications of III, IV, and V were categorized as VNS nonresponders in group B. The postoperative EEG showed bilateral epileptiform discharges during interictal periods in 7 patients. The postoperative antiepileptic drugs ranged from 2 to 7 (median 4). There was no significant difference in clinical profiles between the group of responders and nonresponders.

Table 2
Number of MEG spikes before and after VNS

No. of spikes	All (n = 15)		Group A (n = 9)		Group B (n = 6)		
	median	range	median	range	median	range	*p*
Before VNS	34	4-575	32	6-131	43	4-575	0.64
After VNS†	23	0-59	18.5	9-30	43.5	0-59	0.13
p	0.042*		0.023*		> 0.99		

MEG, magnetoencephalography; VNS, vegus nerve stimulation
†In patient No. 9, MEG after VNS could not be analyzed using tSSS
*p < 0.05

3.2. Number of MEG spikes before and after VNS

Before VNS, the number of MEG spikes ranged from 4 to 575 with a median of 34 among the 15 patients (Table 2, Fig. 3). The BSS on GMFT ranged from 0 to 77 with a median of 8. The USS on GMFT ranged from 1 to 561 with a median of 12. One patient (No. 9 in group A) had excessive VNS-related artifacts obscuring MEG data despite applying tSSS for artifact removal. After VNS implantation, the number of MEG spikes ranged from 0 to 59 with a median of 23 among 14 patients. The BSS on GMFT ranged from 0 to 17 with a median of 5. The USS on GMFT ranged from 0 to 48 with a median of 14. There were significant decreases in the number of MEG spikes from pre-VNS to post-VNS ($p = 0.042$).

Prior to VNS, 10 of the 11 cases with BSS showed two-way propagation. One case (No.11) showed one-way propagation from right to left in each of their two BSS. After VNS, eight of the 10 cases with BSS showed two-way propagation. The remaining two cases (No. 2 and 14) showed only one-way propagation. One-way propagation was observed in cases with less than four BSS.

3.3. Number of spikes before and after VNS between responders and nonresponders

In the 9 responders of group A, the number of MEG spikes ranged from 6 to 131 with a median of 32 before VNS (Table 2). After VNS implantation, the number of MEG spikes ranged from 9 to 30 (median 18.5). There was a significant decrease in the number of MEG spikes in group A ($p = 0.023$). In the 6 nonresponders of group B, the number of MEG spikes ranged from 4 to 575 with a median of 43. After VNS implantation, the number of MEG spikes ranged from 0 to 59 with a median of 43.5. There was no significant decrease in the number of MEG spikes in group B ($p > 0.99$).

3.4. Number of GMFT spikes with bilateral or unilateral spreading before and after VNS

In 15 patients, the BSS on GMFT ranged from 0 to 77 with a median of 22 before VNS (Table 3). After VNS in 14 patients, the BSS on GMFT ranged from 0 to 17 with a median of 5. The BSS decreased after VNS although the difference was borderline ($p = 0.05$). In 15 patients, the USS on GMFT ranged from 1 to 561 with a median of 12 before VNS. After VNS in 14 patients, the USS on GMFT ranged from 0 to 48 with a median of 14. The unilateral spreading spikes did not decrease significantly ($p = 0.49$).

3.5. Number of GMFT spikes with bilateral or unilateral spreading before and after VNS between responders and nonresponders

In the 9 responders of group A, the number of BSS on GMFT ranged from 0 to 77 with a median of 22 before VNS (Table 3). After VNS, the number of BSS on GMFT ranged from 0 to 17 with a median of 5. The number of BSS of group A decreased significantly ($p = 0.03$). The number of USS on GMFT ranged from 1 to 54 with a median of 10 before VNS. After VNS, the number of USS on GMFT ranged from 1 to 22 with a median of 11.5. The number of USS of group A did not decrease

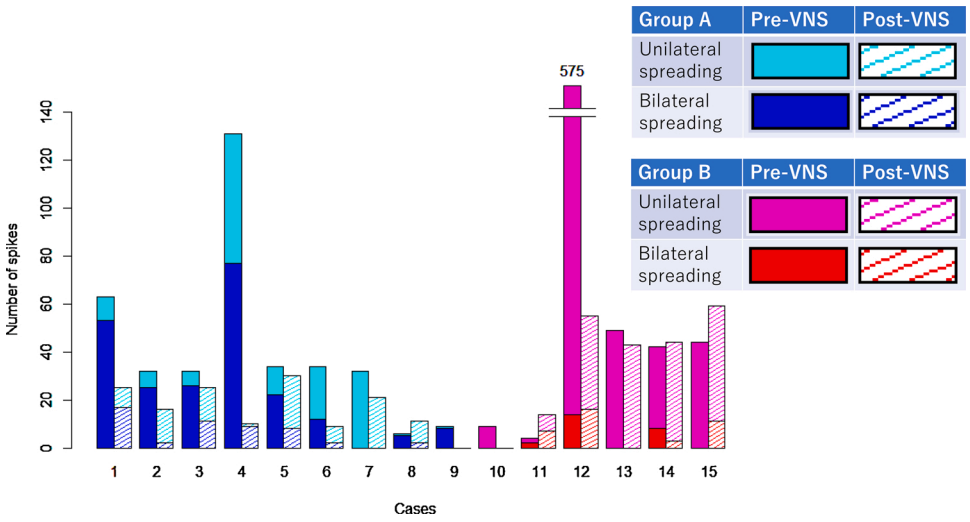

Fig. 3. The number of MEG spikes pre- and post-VNS between groups A (responders) and B (nonresponders). The number of MEG spikes decreased significantly from pre-VNS to post-VNS ($p = 0.042$). The number of MEG spikes in group A decreased significantly ($p = 0.023$).

Table 3
Number of GMFT spikes with bilateral spreading and unilateral spreading before and after VNS

No. of spikes	All (n = 15)				Group A (n = 9)				Group B (n = 6)			
	Bilateral		Unilateral		Bilateral		Unilateral		Bilateral		Unilateral	
	median	range	median	range	median	range	median	range	median	range	median	range
Before VNS	8	0-77	12	1-561	22	0-77	10	1-54	1	0-14	39	2-561
After VNS†	5	0-17	14	0-48	5	0-17	11.5	1-22	5	0-16	40	0-48
p	0.05		0.49		0.03*		0.45		0.45		0.56	

MEG, magnetoencephalography; VNS, vegus nerve stimulation
†In patient No. 9, MEG after VNS could not be analyzed using tSSS
*p < 0.05

significantly ($p = 0.45$).

In the 6 nonresponders from group B, the number of BSS on GMFT ranged from 0 to 14 with a median of 1 before VNS. After VNS, the number of BSS on GMFT ranged from 0 to 16 with a median of 5. The number of BSS of group B did not decrease significantly ($p = 0.45$). The number of USS on GMFT ranged from 2 to 561 with a median of 39 before VNS. After VNS, the number of USS on GMFT ranged from 0 to 48 with a median of 40. The number of USS of group B did not decrease significantly ($p = 0.56$).

3.6. Proportion of bilateral and unilateral spreading before and after VNS

In all patients, the proportion of bilateral spreading did not decrease from the pre-VNS MEG spikes ranging from 0 to 0.89 (median 0.50) to the postoperative proportion of bilateral spreading ranging from 0 to 0.90 (median 0.22) ($p = 0.22$; Table 4). The preoperative proportion of bilateral spreading was significantly different ($p = 0.013$) between groups A (median 0.78; range 0–0.89) and B (median 0.01; range 0–0.5). The postoperative proportion of bilateral spreading was not significantly different ($p = 0.33$) between groups A (median 0.24; range 0–0.9) and B (median 0.19; range 0–0.5). There were no significant differences in the proportions of bilateral and unilateral spreading between pre- and post-VNS in either group A or B.

Fig. 4 shows the ROC curve of the proportion of bilateral spreading before VNS and seizure outcomes between groups A and B. The area under the ROC curve (AUC) was 0.898. The Youden index indicated the optimal PBS as 0.50 with a sensitivity of 0.78 and specificity of 1.00. The proportion of bilateral spreading before VNS was significantly related to good seizure outcomes after VNS.

3.7. Interhemispheric time difference and corpus callosotomy

In all 15 cases, ITD pre- and post-VNS did not show any differences (Fig. 5). The ITD post-VNS reached a significant difference in 5 patients with CC (median, 15.0 ms; range, 14–17 ms) and 10 patients without CC (median, 22.0 ms; range, 17–33 ms; $p < 0.01$). In the 5 patients with CC, ITD decreased significantly compared with that in the 10 patients without CC. The change in ITD from pre-VNS to post-VNS was different between groups A and B ($p = 0.07$). In group A, ITD decreased from 25.5 ms to 17.0 ms. In group B, ITD increased from 16.0 ms to 21.0 ms. There

Table 4
Proportion of bilateral spread of MEG spikes before and after VNS

	All (n = 15)		Group A (n = 9)		Group B (n = 6)		
Proportion of bilateral spread	median	range	median	range	median	range	*p*
Before VNS	0.50	0-0.89	0.78	0-0.89	0.01	0-0.50	**0.013***
After VNS	0.22	0-0.90†	0.24	0-0.90**	0.19	0-0.50	0.33
p	0.22		0.076		0.42		

*p < 0.05
†In patient No. 9, MEG after VNS could not be analyzed using tSSS

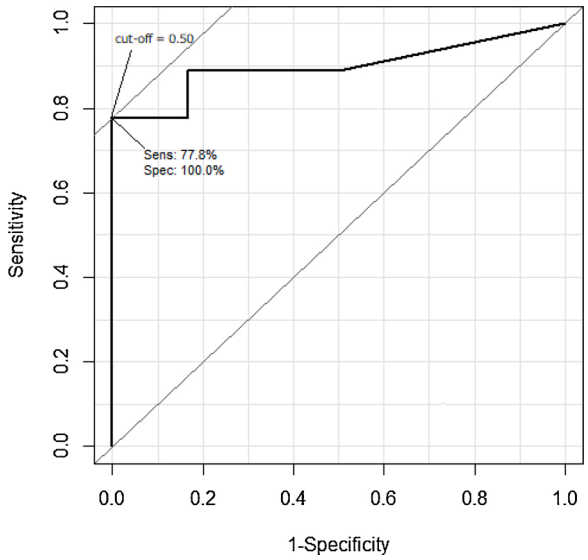

Fig. 4. Receiver operating characteristic curve of the proportion of bilateral spreading before VNS, and seizure outcomes between groups A and B. The area under the curve (AUC) was 0.898. The Youden index indicated the optimal PBS as 0.50 with a sensitivity of 0.78 and specificity of >0.99. The proportion of bilateral spreading before VNS was significantly related to good seizure outcomes after VNS.

was no difference between ITD pre- and post-VNS between groups A and B with and without CC.

4. Discussion

4.1. Summary of findings

We evaluated 2 groups that were followed-up for more than 2 years after VNS: group A consisted of favorable class I and II seizure outcomes in 9 patients, and group B consisted of poor class III–V outcomes in 6 patients. The number of post-VNS MEG spikes was reduced significantly compared with the number of pre-VNS MEG spikes in all patients. The total number of preoperative MEG spikes did not differ between groups A and B. The number of post-VNS MEG spikes was reduced significantly compared with the number of pre-VNS MEG spikes in group A, but not in group B. Group A showed significantly higher preoperative PBS than group B. The ROC curve analysis showed that preoperative PBS was significantly associated with good seizure outcomes after VNS. The postoperative ITD of BSS became significantly shorter in patients with CC than those without.

4.2. Bilateral spreading on GMFT related to dependent spikes

Group A showed a significantly higher preoperative PBS than group B; 13 of 15 patients showed interictal bilateral independent spikes including 2 patients with multiple independent spike foci on scalp EEG before VNS. GMFT was developed to analyze dynamic changes of epileptic spikes in the brain cortex using the magnetic field detected by a planner gradiometer (Hashizume et al. 2007). The most valuable thing GMFT established was demonstrating the inter- and intrahemispheric spreading of spikes. The secondary epileptogenesis spread from the primary epileptogenesis could be dependent or independent from the primary.

Mirror focus was first proposed by Lourie and Uemura (Lourie and Uemura 1965). Morrell continued to study mirror focus to understand secondary epileptogenesis in experimental seizures and human epilepsies (Morrell, 1989). A single EEG focus could develop into bilateral, independent interictal discharges in homologous regions. The mirror foci could be either dependent or independent from the original epileptic focus. In the group of patients with dependent spike discharges, if the primary focus is resected, the seizures terminate. For patients with independent spike discharges, excision of the primary focus does not result in cessation of either electrographic or clinical seizures emanating from the secondary focus (Morrell, 1985).

Here, we targeted the bilateral and unilateral spreading of a single spike on GMFT. The bilateral spreading on GMFT could represent the temporary proximity of spike discharges spreading to the contralateral focus. A higher proportion of bilateral spreading in the interictal discharges likely indicates that the epileptogenesis is secondary to the original epileptic focus. In patients with dependent secondary epileptogenesis, bilateral spreading was demonstrated; thus, their seizures responded well to VNS. By contrast, a higher proportion of unilateral spreading on GMFT might indicate independent bilateral epileptogenesis in patients with multiple/bilateral spike discharges, multiple types of seizures, or patients refractory to medications. Seizures with independent epileptogenesis did not respond well to VNS. Thus, VNS might not work individually for independent seizure foci.

4.3. Bilateral spreading after CC on GMFT

The post-VNS interhemispheric time difference of BSS was significantly shorter in patients with CC than in those without. The corpus callosum is a modulator of the secondary generalized discharges (Wada

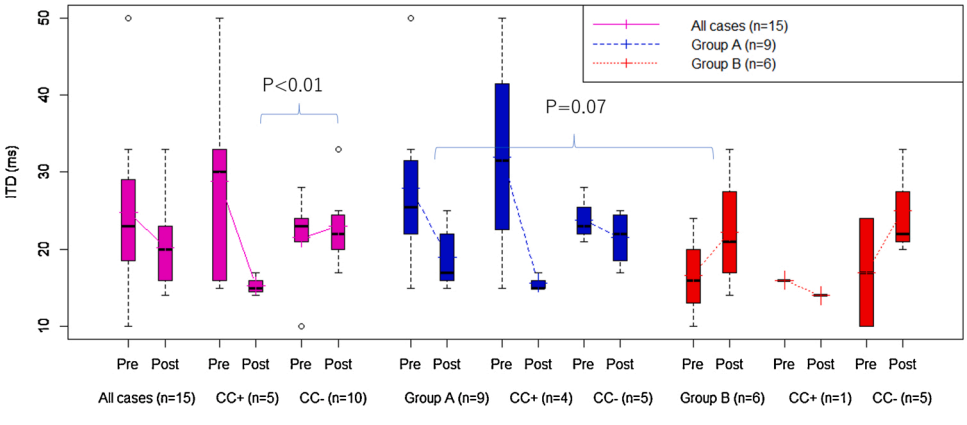

Fig. 5. Interhemispheric time difference (ITD) of bilaterally spreading spikes on gradient magnetic field topography (GMFT) between pre- and post-VNS, groups A and B, with and without corpus callosotomy.
The ITD post-VNS between 5 patients with corpus callosotomy (median, 15.0 ms; range, 14–17 ms) was significantly different from that in the 10 patients without corpus callosotomy (median, 22.0 ms; range, 17–33 ms; $p < 0.01$). In the 5 patients with corpus callosotomy, ITD decreased significantly compared with that in the 10 patients without corpus callosotomy. Between groups A and B, the change in ITD from pre-VNS to post-VNS was different between groups A and B ($p = 0.07$). In group A, ITD decreased from 25.5 ms to 17.0 ms. In group B, ITD increased from 16.0 ms to 21.0 ms. There was no difference between ITD pre- and post-VNS between groups A and B with and without corpus callosotomy.

2005). After CC, the generalized discharges often disappear. In patients with hypsarrhythmia, which represents the most chaotic generalized/multifocal epileptic discharges, the interictal epileptiform discharges become either bilateral independent discharges or unilateral discharges, or none after CC (Baba et al. 2019). In our present series, 5 patients required further VNS for their remaining generalized onset seizures. They presented bilateral epileptiform discharges. However, ITD significantly decreased in the 5 patients with CC, compared with that in 10 patients without. In patients without a corpus callosum, the bilateral spreading in the remaining epileptiform discharges might be modulated by the thalamus.

4.4. Bilateral spreading on GMFT modulated by the thalamus

REM sleep is known to reduce interictal epileptic discharges (Frauscher et al. 2016; Okanari et al. 2015; Sakuraba et al. 2016; Sammaritano et al. 1991). During REM sleep, although the number of the epileptic spikes and high frequency oscillations decrease, they accumulate in the epileptogenic zone. During NREM sleep, the spindles are well known to be modulated by the thalamus (Steriade et al. 1993). The continuous spike and waves during slow wave sleep (CSWS) or electrographical status epilepticus during sleep (ESES) in children were classified as having age-related epileptic encephalopathy (Scheffer et al. 2017). In a subset of patients with a thalamic lesion, the dysfunction of the thalamus could cause continuous spike and waves (Halász et al. 2019).

In a preceding experimental study, Katagiri et al. determined that the midline of the thalamus is activated in both the acute and chronic phase of VNS in a rat model (Katagiri et al. 2019). In another clinical study, Kagawa et al. speculated that the thalamus plays a pivotal role in ITD in patients who underwent CC (Kagawa et al. 2016). Based on the current investigation of ITD, we propose that bilateral spreading in the remaining epileptiform discharges could be modulated by the thalamus in patients following CC.

Shirozu et al. reported that GMFT could identify the spike onset zone for focal cortical dysplasia (Shirozu et al. 2019). Focal cortical dysplasia is an intrinsic epileptogenic lesion (Otsubo et al. 2005; Palmini et al. 1995). The early spike source in the cortex before the appropriate inverse solution of the dipole at the spike peak indicates either a discrete or extensive epileptogenic zone among the 3 types of focal cortical dysplasias: I, IIa, and IIb.

In patients who required VNS for pharmaco-resistant generalized onset seizures and multifocal spikes, the spike onset zones on GMFT are inconsistent. Inter- and intra-hemispheric spreading patterns were often seen. In the current study, unilateral spreading on GMFT was more often seen than bilateral spreading, but bilateral spreading was seen significantly more often in group A. In addition, post-VNS GMFT showed significantly decreased bilateral spreading spikes in group A. The spikes with bilateral spreading might be a target of VNS relating to the cessation of seizures.

4.5. Limitations and future directions

This study has several limitations. (1) the number of cases was inevitably limited in the number of patients with VNS that had pre- and post-MEG. We routinely performed MEG prior to VNS. However, the majority of patients with VNS did not participate in our study because their VNS device was metallic, limiting MEG. (2) the timing of post-VNS MEG was inconsistent.

Further study of post-VNS MEG to collect more cases and improve our analysis is warranted. Moreover, the timing of post-VNS MEG evaluation could be performed uniformly at the 2 year follow-up, when the effects of VNS are stabilized.

5. Conclusions

Frequent interictal MEG spikes propagating bilaterally on GMFT may reflect a favorable seizure outcome after VNS. GMFT can evaluate the epileptic spikes responding to VNS over the bilateral hemispheres on MEG before and after VNS, which may target the dependent secondary epileptogenesis to control generalized seizures in a subset of patients with pharmaco-resistant epilepsy.

In the analysis of MEG before and after VNS implantation, GMFT successfully determined epileptic activity spreading in both hemispheres. High preoperative PBS may serve as a favorable postoperative outcome factor.

Declaration of Competing Interest

The authors report no declarations of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eplepsyres.2020.106463.

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