Analysis of VNS Effect on EEG Connectivity with Granger Causality and Graph Theory

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***Abstract*—Vagus Nerve Stimulation (VNS) is treatment of refractory epilepsy; however, its physiological mechanism has not been fully understood. The effectiveness of VNS for each patient cannot be predicted preoperatively. Thus, the mechanism of VNS needs to be investigated in order to avoid ineffective operations. Because an epileptic seizure is caused by the spread of excessive discharge from neurons in the cerebrum, analyzing effects of VNS on electroencephalogram (EEG) would be useful for VNS mechanism investigation. In the present work, the EEG data of epileptic patients with VNS were analyzed by using Granger Causality (GC) and the graph theory. Since GC is an index which expresses the intensity of a causal relation between two time series, it may illustrate information interactions between EEG channels. In addition, a directed graph constructed from those GC values would express neural connection. The analysis was carried out with the EEG data of two patients with frontal lobe epilepsy receiving the VNS therapy. The result supported the existing hypothesis indicating the bilateral asymmetry of the VNS effect on the brain, and furthermore, it suggested that VNS would increase neural connection between the frontal lobe and other brain regions, and that should control epileptic seizures by keeping patients awake.**

I. Introduction

Epilepsy is a neurological disorder caused by abnormal discharge on the cerebrum, and it causes various types of seizures like spasm and disturbance of consciousness. 1% of population worldwide has epilepsy regardless of age and sex [1]. Epileptic seizures are categorized into some groups depending on the epileptic focus. For example, the frontal lobe epilepsy causes various symptoms like the spasm of the arms or the spasms in the whole body. The generalized epilepsy whose epileptic focus is not localized will cause the patients various symptoms like disturbance of consciousness.

A brain region from which abnormal discharge emerges is called an epileptic focus, and electroencephalogram (EEG) is used for epileptic focus identification.

Although epileptic seizures are controlled with anti-epileptic drugs, about 30% of epileptic patients cannot control their seizures even if they select the best drug, which is called refractory epilepsy [2]. The resection of an epileptic focus is a candidate of refractory epilepsy treatment; however, it is difficult to identify the epileptic focus precisely. In addition, there is the risk that resection damages important brain functions.

This work was partially supported in part by AMED SENTAN # 171122, the SECOM science and technology foundation, and JSPS KAKENHI # JP15H05719.

Fig. 1. schematic diagram of VNS [3]

The vagus nerve stimulation (VNS) therapy is another option for refractory seizure treatment; however, the effectiveness of VNS on each patient is unpredictable prior to its operation because physiological mechanisms of VNS have not been fully understood. This may lead to ineffective implants.

This work analyzes the EEG data recorded from epileptic patients with VNS in order to clarify the mechanisms of VNS, in which Granger Causality (GC) and the graph theory are used for EEG analysis to investigate the differences of functional neural network before and during the VNS therapy.

II. Vagus Nerve Stimulation

Vagus Nerve Stimulation (VNS) is palliative treatment for refractory epilepsy, in which a device implanted in the left breast gives stimuli to the vagus nerve. The schematic diagram of VNS is shown in Fig. 1. VNS implant operations were treated for over 80,000 patients worldwide by the end of 2014 [4]. Although the VNS stimuli may reduce the frequency and the intensity of seizures, about 50% of patients with VNS do not get seizure frequency reduction [5]. Since the mechanisms of VNS have remained to be unknown, it should be investigated for avoiding ineffective VNS operations.

III. Method

This section explains EEG analysis methods used for VNS mechanism investigation in this work.

A. EEG

The 10 - 20 electrode system shown in Fig. 2 is a typical electrode allocation for EEG recording. Since the EEG voltage is in the order of microvolts, the EEG recording is intolerable to artifacts caused by various sources like motion and blinks [6]. Thus, appropriate filters are needed before EEG analysis. EEG is classified into the five frequency bands listed in Table I: the δ wave, the θ wave, the α wave, the β wave, and

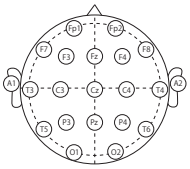


Fig. 2. 10 - 20 international electrode system

the γ wave. It is assumed that each frequency bands contain different types of information, for example, the α wave is useful for sleep stage scoring.

B. Laplacian filter

Because an EEG electrode records the potential emerged by nerve cells surrounding the electrode, applying a spatial filter to the recorded data would improve signal-to-noise ratio of the data. The Laplacian filter is a kind of spatial filters, which is expressed as follows [7]:

$$V_i^{LAP} = V_i^{ER} - \sum_{j \in S_i} g_{ij} V_j^{ER} \tag{1}$$

where V_i^{LAP} is the filtered potential of the i-th electrode, V_i^{ER} is the potential between the i-th electrode and the ear reference, and S_i is the set of electrodes located around the i-th electrode. g_{ij} is a weighting coefficient depending on the distance between the electrodes, and it is defined as follows:

$$g_{ij} = \frac{1/d_{ij}}{\sum_{j \in S_i} 1/d_{ij}} \tag{2}$$

where d_{ij} is the distance between the i-th and j-th electrodes.

C. Connectivity

The connectivity is a concept of physical or functional connection between brain regions. In this work, the functional connectivity based on the Granger Causality (GC) and the graph theory are adopted.

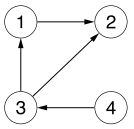
D. Granger Causality

GC is an index that illustrates the causal relation between two time series [8]. The present value of a time series $x_j(t)$ would be represented by the linear combination of its past values:

$$x_j(t) = \sum_{k=1}^{q} a_j(k) x_j(t-k) + e_j(t). \tag{3}$$

TABLE I
EEG BANDWIDTHS

Class	Frequency [Hz]		
δ wave	0.5	–	4
θ wave	4	–	8
α wave	8	–	13
β wave	13	–	40
γ wave	40	–	80



$$\begin{bmatrix} 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \end{bmatrix}$$

Fig. 3. directed graph D and its adjacency matrix A

In addition, $x_j(t)$ can be represented by the linear combination of its past values and another time series $x_i(t)$ as

$$x_j(t) = \sum_{k=1}^{q} a_j(k) x_j(t-k) + \sum_{k=1}^{q} a_i(k) x_i(t-k) + e_{ij}(t) \tag{4}$$

where $a_j(k)$ and $a_i(k)$ are the regression coefficients, and q is the model order. $e_j(t)$ and $e_{ij}(t)$ are the errors, respectively. Using these errors, GC from $x_i(t)$ to $x_j(t)$ is defined as follows:

$$\mathrm{GC}_{i \to j} = \ln \left(\frac{var[e_j(t)]}{var[e_{ij}(t)]} \right) \tag{5}$$

where $var[\cdot]$ denotes variance.

When the GC between the two time series is large, there may be a strong causal relation between them. The model order can be determined by the Akaike Information Criterion (AIC) [9].

E. Directed Graph and Adjacency Matrix

A directed graph D consists of a set of vertices V and a set of directed edges connecting vertex pairs E. To express the connection in a graph, an adjacency matrix A is used. In an unweighted directed graph, $A(i,j)$ is defined as follows:

$$A(i,j) = \begin{cases} 1 & \text{if there is an edge from vertex } i \text{ to vertex } j, \\ 0 & \text{otherwise.} \end{cases} \tag{6}$$

In a directed graph, the in- and out-degrees can be defined at each vertex, which are the numbers of edges coming from other vertices and edges going out from the vertex, respectively. Fig. 3 shows an example of a directed graph D and its corresponding adjacency matrix A. Since there is an edge from vertex 1 to vertex 2 in D, $A(1,2)$ has 1. The in-degree of vertex 2 is 2 because there are two edges from vertices 1 and 3.

In EEG connectivity analysis, the graph vertices denote the EEG electrodes, and directed edges illustrate their functional connection. When a vertex has a large in-degree, there would be a large information flow coming from other brain regions.

For example, Fallani et al. analyzed the functional connectivity during moving the feet and lips simultaneously [10]. They generated directed graphs with GC from the β wave of EEG and analyzed the functional connectivities. Large out-degree values were observed around the vertices corresponding to the cingulate motor area, which indicated that the cingulate motor area works as a hub of the functional neural network during the task.

IV. RESULT

This section reports an analysis procedure of the EEG data recorded from patients with VNS and its result.

TABLE II
PATIENT PROFILE

Subject	Sub1	Sub2
Age	42	27
Sex	M	F
Epileptic focus	Frontal lobe	Frontal lobe
EEG sampling rate [Hz]	512	512
VNS period [s]	138	330

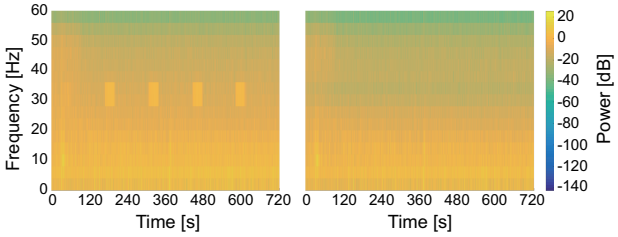


Fig. 4. original EEG spectrogram (left) and EEG spectrogram after filtering (right)

A. Analysis Process

The present work collected the EEG data from two epileptic patients with VNS Sub1 and Sub2, whose profiles are shown in Table II. The data collection and the analysis were approved by the ethics committee of the faculty of Medicine and Health Sciences, Yamaguchi University.

The Laplacian filter was applied to the EEG data. In this research, S_i was determined as a set of electrodes located within 0.98 times the scalp radius from the i-th electrode.

Fig. 4 shows examples of spectrograms of the EEG data collected from Sub1. In this figure, the horizontal axis represents time and the vertical axis represents frequency, and the color represents the magnitude of the power. The left figure shows spectrogram calculated from the original EEG data, in which the power around 30Hz increased for 30 seconds periodically in every 138 seconds due to the stimuli of the VNS therapy. Thus, notch filters were applied to the EEG data in order to reduce artifacts of the VNS stimuli. A spectrogram of the filtered EEG is shown in the right figure, in which the stimuli of the VNS therapy were not observed.

After the filtering with the Laplacian filter and notch filters, the EEG data were decomposed into the five frequency bands listed in Table I by applying bandpass filters. Then, the GCs among the EEG electrodes were calculated while VNS was on and off, respectively.

The degrees of the regression models were determined by AIC. Fig. 5 shows changes in mean AIC values of all electrode pairs by model degrees. Based on Fig. 5, the model orders were determined to be 25 for all patients and frequency bands.

A matrix M was generated so that $M(i, j)$ stores GC from the i-th to the j-th electrodes. The elements in M whose values were ranked in the top some proportions among all M elements were replaced by 1, and the other components were replaced by 0. Although the computation was executed with threshold proportions of 30%, 50%, and 70%, only the results

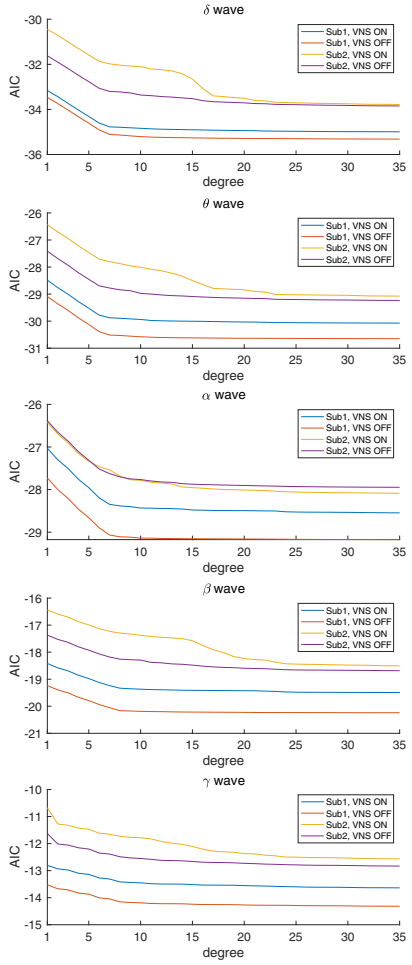


Fig. 5. changes in mean AIC values of all electrode pairs by model degrees

with the 30% threshold were shown here. This manipulation formed a binary matrix A, and a directed graph D was constructed by A. The in-degree and the out-degree of all vertices of D were displayed on a scalp map that is a head-shaped figure which contains electrode positions. An example of a scalp map is shown in Fig. 6. Red and blue represents high and low values, respectively. Because the number of the electrodes used in this analysis was 19, the highest value and the lowest value in scalp maps were 18 and 0, respectively.

B. Analysis Result

Figs. 7 and 8 are scalp maps which show characteristic patterns of in-degree distribution. Fig. 7 shows the in-degree of Sub1. While VNS was on, some vertices on the left hemisphere had particularly large in-degree especially in the δ bandwidth. The previous research indicated that the EEG power between 20Hz and 50Hz increased on the right hemisphere during the VNS stimuli [11]. The present result agrees with the existing hypothesis in terms of the bilateral asymmetry of the VNS effect on the brain.

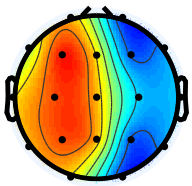


Fig. 6. scalp map

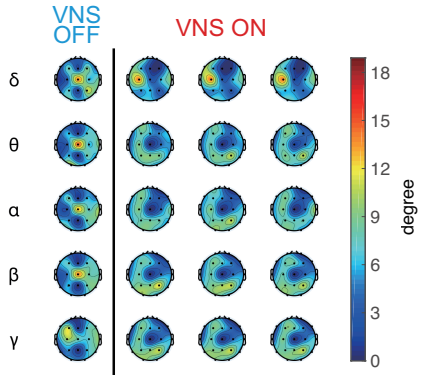


Fig. 7. in-degree of Sub1

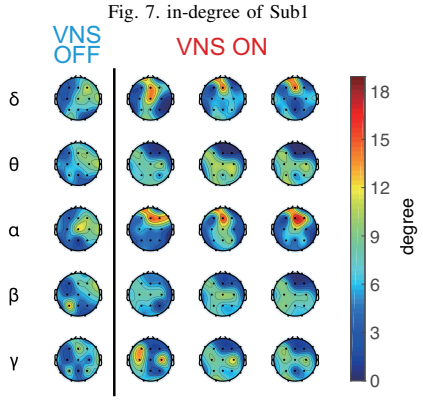


Fig. 8. in-degree of Sub2

Fig. 8 shows the in-degree of Sub2. During the VNS stimuli, high values were observed around the frontal lobe in the δ wave and the α wave. It was reported that the VNS therapy enhanced the recognition memory [12]. In addition, it was also reported that the EEG power of the δ wave increased during the working memory task [13]. In consequence, it was suggested that the VNS therapy would increase the functional connection from the frontal lobe to other brain regions, and would keep a patient awake. Therefore, VNS may control absence seizures which occur accompanied by the lack of consciousness. Malow et al. performed polysomnography and multiple sleep latency tests (MSLT) on refractory epileptic patients with VNS [14]. They compared mean sleep latency (MSL) recorded before and after 3 months of VNS, and concluded that the VNS treatment at low stimulus would improve daytime sleepiness.

V. Conclusion and Future Work

In this work, the effect of the VNS therapy on the EEG connectivity was analyzed in order to clarify the mechanisms of VNS. GCs among the EEG electrodes were computed, and the functional connectivity was expressed as a directed graph constructed from GC, whose in-degrees and out-degrees were visualized with scalp maps.

The analysis results supported the existing hypothesis of the bilateral asymmetric effect of the VNS therapy on the brain. In addition, the result suggested that the VNS therapy would increase the functional neural connection from the frontal lobe into other brain regions. This may contribute to epileptic seizure control through keeping patients awake.

In the future work, additional EEG data will be collected from patients with VNS in order to discuss the effectiveness change of the VNS therapy depending on the epileptic foci.

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