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A hypothesis of series resonance in the white matter for understanding the mechanism of spike-wave seizures

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ABSTRACT

Generalized epilepsy is accompanied by large-amplitude synchronized spike-wave discharges on electroencephalography. The condition rapidly and synchronously involves most regions of the brain, but the mechanism underlying this global involvement remains unclear. Here I attempt to clarify this phenomenon by hypothesizing a series resonance in an equivalent electric circuit for the white matter. This hypothesis is based on the ideas that the electric conduction along an axon is due to the displacement current, and the unit structure composed of a node of Ranvier and the next node can be regarded as a capacitor or an inductor, depending on the geometry and the substance around the nodes. The flash-visual evoked potentials at various flash repetition rates were measured in generalized epilepsy patients, and compared with those for healthy controls and focal epilepsy patients. The P_{100} amplitude plotted against the flash repetition rate had a maximum peak at a certain flash repetition rate only for each of the generalized epilepsy patients. The observation of a peak in the P_{100} amplitude was inferred to reflect the series resonance phenomenon in the white matter. I speculate that patients with generalized epilepsy have large regions of white matter with similar resonance frequencies.

1. Introduction

What are the precise differences between focal epilepsy and generalized epilepsy? In the case of generalized epilepsy, it is considered that there is some epileptogenic focus in the centrencephalic system (or the brainstem and thalami, in the current nomenclature), as suggested by Penfield [1]. However, it remains uncertain whether this is a truly representative model for generalized epilepsy, or indeed, whether a focus such as a tumor or an infarction in the brainstem will induce generalized epilepsy, as the model predicts.

Animal models have provided evidence that absence seizures, which are one of the forms of generalized epilepsy, are initiated by a cortical focus with a secondary involvement of the thalamus [2,3]. Similar results have been observed in human patients with absence seizures [4]. However, if there is an onset focus in the cortex, how different is generalized epilepsy from secondary generalized focal epilepsy? Moreover, the onset focus of spike-wave discharges is likely to vary in the cortex [2–6].

Carbamazepine, which is recommended as the first-line medicine for focal epilepsy, can worsen seizures if it is given to patients with certain types of generalized epilepsy [7]. This suggests that there are essential differences between focal epilepsy and generalized epilepsy.

Generalized epilepsy is accompanied by large-amplitude synchronized spike-wave discharges on electroencephalography (EEG). A typical spike-wave discharge is a 2–5 Hz periodic wave complex which has much larger amplitude than that of the background activities. In the normal brain, the thalamus is believed to play the role of a pacemaker supplying the periodic wave on EEG [8–11].

Despite the prior efforts, it remains unknown how most parts of the brain are synchronously and rapidly involved in epileptic spike-wave discharges in patients with generalized epilepsy.

Here I present a hypothesis that may explain how spike-wave discharges occur. The essence of my proposal is that the large amplitude of spike-wave discharges in generalized epilepsy is based on the resonance phenomenon of the electric circuits in the white matter.

2. Theory

2.1. The mechanism of electric conduction along an axon

Hodgkin-Huxley's model can explain how an action potential occurs [12–14], but this model does not address the phenomenon of the signal propagation along the axon. That is, when the voltage-gated sodium channels on the axon membrane open, the sodium ions flow from the

Abbreviations: VEP, visual evoked potential; EEG, electroencephalography; CK, creatine kinase; AED, anti-epileptic drug; VNS, vagus nerve stimulation; VPA, sodium valproate; CBZ, carbamazepine; LEV, levetiracetam; LTG, lamotrigine; PB, phenobarbital; JS, Jeavons syndrome

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outside to the inside of the axon through the ion channels in the cell membrane. This brings about the action potential, but it does not necessarily mean that the signal is propagated along the axon by the charged particles.

Most of the pertinent textbooks describe that propagation of the action potential is caused by a "local circuit" of current flow from the depolarized areas of the membrane to the adjacent resting membrane areas [15,16]. Many researchers seem to believe that this current flow is carried by the positive ions. However, if this model is accurate, does the current flow carried by the positive ions initiate the action potential at the next node of Ranvier in the case of myelinated fibers?

Signal propagation in the brain system is an electric phenomenon. It thus seems useful to adapt the principles of electromagnetics to the signal conduction in the brain. Maxwell's equation (i.e., rot $\mathbf{H} = \mathbf{i} + \partial\mathbf{D}/\partial t$, where $\mathbf{H}$, $\mathbf{i}$, and $\mathbf{D}$ denote the magnetic field, the electric current carried by the charged particles, and the electric flux density, respectively) shows us that an electric current is not only transferred with such charged particles as electrons or ions ($\mathbf{i}$), but also with the time-derivative of the electric flux density ($\partial\mathbf{D}/\partial t$), which is called the displacement current [17].

In this investigation, I assume that the electric conduction along an axon is not mediated by $\mathbf{i}$, but by $\partial\mathbf{D}/\partial t$. With this assumption, it is easy to understand why the saltatory conduction is faster than the continuous conduction. This is because the conduction of $\partial\mathbf{D}/\partial t$ along an axon is much faster than the conduction of ions.

The electric current from a node of Ranvier to the next node can be compared to the current through a capacitor in an electric circuit. A capacitor has a structure consisting of an insulator between two electrodes (Fig. 1A, *left*). Only variable current can be conducted through a capacitor, because $\partial\mathbf{D}/\partial t$ is zero for constant current. Even if the upper electrode in Fig. 1A (*left*) is revolved to the position next to the lower electrode, it is still expected to work as a capacitor (Fig. 1A, *middle*). This structure is considered to be a depolarized node of Ranvier and the next node, although the displacement current $\partial\mathbf{D}/\partial t$ between the two nodes is conducted through the curved path in the insulator outside and even inside of the axon (Fig. 1A, *right*). When an action potential occurs at a node of Ranvier, the density of the sodium ions is decreased on the outside of the axon and increased on the inside. This density change makes $\partial\mathbf{D}/\partial t$ non-zero and enables the current to conduct to the next node of Ranvier. This displacement current opens the voltage-dependent sodium channels of the next node, and the depolarization process continues periodically with the periodic current supplied by the thalamus.

The "curved" capacitor is also regarded as an inductor, because the path for the current is curved and the paths outside and inside of the axon form a complete loop (Fig. 1A, *right*). Whether the unit structure is regarded as a capacitor or an inductor depends on the capacitance of the capacitor C and the self-inductance of the inductor L, and the angular frequency of the electric current ω, as follows.

Assuming the current is a sine wave; i.e.,

$$I = I_0 \sin \omega t,$$

the voltage for the capacitor V_C is expressed as

$$V_c = \frac{1}{C}\int Idt = -\frac{I_0}{\omega C}\cos \omega t,$$

and the voltage for the inductor V_L is expressed as

$$V_L = \mathrm{L}\frac{\mathrm{dI}}{\mathrm{dt}} = \omega \mathrm{L} I_0 \cos \omega t.$$

The unit structure is regarded as a capacitor, if

$$|V_L| < |V_C| \quad \text{i. e. ,} \quad \omega \mathrm{L} < \frac{1}{\omega C}.$$

And it is regarded as an inductor, if

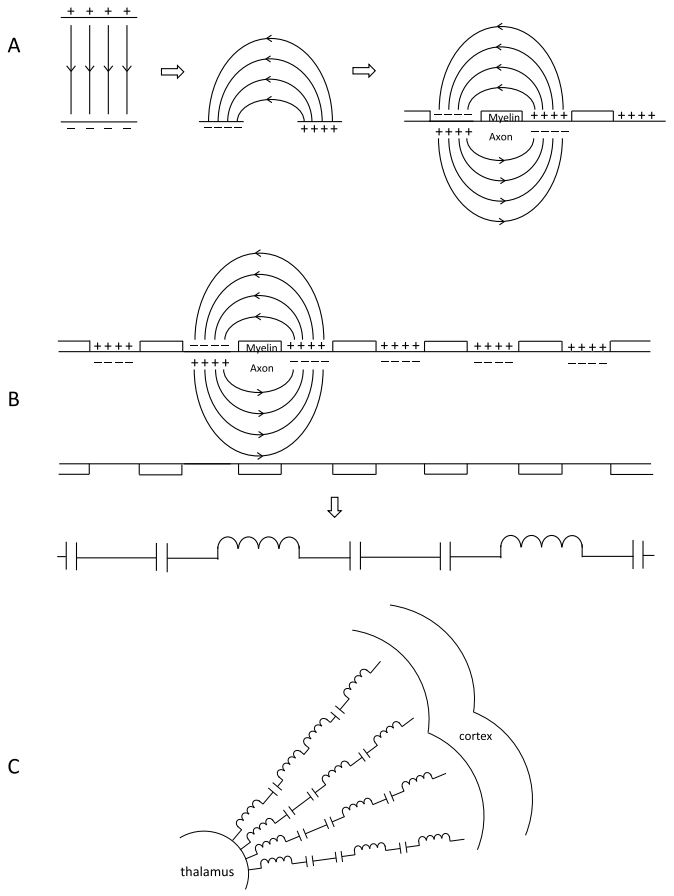

Fig. 1. Equivalent circuits for axons and the white matter. A: *Left*: A schematic of a capacitor. The upper horizontal line shows the positive electrode and the lower horizontal line shows the negative electrode. The vertical lines with arrows show the displacement current $\partial\mathbf{D}/\partial t$. *Middle*: The upper electrode of the *left* capacitor is revolved toward the right side of the lower electrode. The displacement current runs through the curved path. *Right:* A unit structure on a myelinated axon with the depolarized node of Ranvier at the left side. The displacement current through the curved path can be found not only outside but also inside the axon. This is also regarded as an inductor as well as a capacitor. **B:** A myelinated axon (*upper*) and its equivalent electric circuit (*lower*). Depolarization is found at the second-from-the-left-end node of Ranvier. **C:** A schematic of white matter with the thalamus and the cortex. Similar but slightly different equivalent electric circuits are found between the thalamus and the cortex in a certain brain area.

$$|V_L| > |V_C| \quad \text{i. e. ,} \quad \omega \mathrm{L} > \frac{1}{\omega C}.$$

The magnitude of C or L is determined by aspects of the geometry and the substantial characteristics around the nodes—specifically, the geometrical relation between the two adjacent nodes as well as the dielectric constant and the magnetic permeability in the extracellular and cytoplasmic sides of the nodes.

The behavior of a capacitor and that of an inductor for the alternative (variable) current are known to be opposite in a sense. That is, the phase of voltage is retarded compared to that of the current by $\pi/2$ for a capacitor and advanced by $\pi/2$ for an inductor, because $(-\cos \omega t)$ is retarded by $\pi/2$ compared to $(\sin \omega t)$, and $(\cos \omega t)$ is advanced by $\pi/2$ compared to $(\sin \omega t)$. In other words, the unit structure with the nearest two nodes can be regarded as a capacitor when the voltage phase is retarded, and it can be regarded as an inductor when the voltage phase is advanced.

An axon has many nodes of Ranvier, each of which plays the role of an electrode. Therefore an axon can be equivalent to an electric circuit with many capacitors and inductors chained in a serial manner (Fig. 1B). In this article, I call this hypothesis the "displacement current model".

Another model, the cable model, has been well established as a means of conceptualizing the propagation process of action potential. This model includes resistance along the interior of an axon and parallel resistance and capacitance across the axon membrane [16,18]. In this model, both the extracellular and cytoplasmic internode spaces are considered to be conductors. However, the displacement current model considers both these spaces to be insulators, which means that the electric current between the nodes is not carried by ions but by electric flux. Because the displacement current does not need to carry ions, the conduction is much faster than that of ion current. Indeed, in practical terms, the internode conduction time can be considered zero.

The displacement current model does not deny that the equivalent circuit for the membrane includes a resistor and a capacitor arranged in a parallel fashion. Therefore the current and voltage are expected to follow an exponential fall-and-rise pattern, but this is just because the rate-limiting process is the passage of the sodium ions through the sodium channels in the membrane. It does not mean that the displacement current follows the exponential fall-and-rise pattern in itself.

According to the reviews on the determinants of conduction velocity in myelinated nerve fibers, conduction velocity is nearly proportional to axon diameter, to which myelin thickness and internode distance are also linearly related [19–21]. With the displacement current model, conduction velocity must be proportional to internode distance. This is apparent from the following thought experiment. As the conduction time between the two nodes is practically zero, the practical conduction time for the whole axon is a summation of the passage time of the sodium ions through the sodium channels. If the internode distance is twice as long, then the nodes of Ranvier along the axon are half as many, which means the conduction time is half as long—that is, the conduction velocity is twice as high. As well, if the internode distance is *N* times as long, the nodes of Ranvier along the axon are one *N*th as many, and the conduction velocity is *N* times as high. Thus the conduction velocity is proportional to the internode distance. As long as the internode distance is linearly related to the axon diameter, the conduction velocity is also expected to be proportional to the axon diameter. This brings the same result as the cable model, although the explanation is quite different from the explanation using the length constant determined by the membrane resistance, axial resistance, and membrane capacitance in the cable model.

In the case of continuous conduction (i.e., unmyelinated conduction), the contribution of the displacement current to the whole conduction path is small, because the current across the ion channels in the membrane occupies a large portion of the whole path and the “internode” portion is small. Therefore, the conduction velocity predicted by the displacement current model is not expected to be highly different from that predicted by the cable model. Actually, even in the unmyelinated axons, it has been reported that the clustered sodium ion channels enable micro-saltatory conduction [22]. According to that report, the conduction velocity in the case with clustering sodium channels did not differ from that without clustering. This is consistent with the inference above.

2.2. A series resonance model with the idea of displacement current

It is well known that a series circuit that includes a capacitor and an inductor shows the so-called series resonance phenomenon, which means that the electric current has a maximum value at an inherent frequency determined by the inductor L and the capacitor C. The resonance frequency f is calculated as follows [17].

The differential equation for the series circuit including the resistor R, the inductor L, and the capacitor C is expressed as

$$\mathrm{RI} + \mathrm{L}\frac{\mathrm{dI}}{\mathrm{dt}} + \frac{1}{C}\int I dt = \mathrm{ZI}$$

with the common electric current I and the whole impedance Z.

If we assume the periodic wave for the current, we can express the current as $\mathrm{I} = \mathrm{I}_0 \, \mathrm{e}^{\mathrm{i}\omega t}$ for the current angular frequency ω. With this expression, Z is calculated as

$$\mathrm{Z} = \mathrm{R} + \mathrm{i}\omega\mathrm{L} + \frac{1}{i\omega C} = \mathrm{R} + \mathrm{i}\left(\omega\mathrm{L} - \frac{1}{\omega C}\right)$$

That is,

$$|Z| = \sqrt{R^2 + \left(\omega L - \frac{1}{\omega C}\right)^2}.$$

This means $|Z|$ has the minimum value for

$$\left(\omega L - \frac{1}{\omega C}\right) = 0, \quad \text{i.e.,} \quad \omega = \frac{1}{\sqrt{LC}}.$$

This also means that the current has the maximum value for

$$\omega = \frac{1}{\sqrt{LC}}.$$

That is, the resonance frequency f is expressed as

$$\mathrm{f} = \frac{1}{2\pi\sqrt{LC}}.$$

In addition, if there are many capacitors and inductors arranged in a serial manner, the corresponding equation is expressed as

$$\mathrm{RI} + \left(\sum \mathrm{L}\right)\frac{\mathrm{dI}}{\mathrm{dt}} + \left(\sum \frac{1}{C}\right)\int I dt = \mathrm{ZI}.$$

Therefore, we can get the resonance frequency of

$$\mathrm{f} = \frac{1}{2\pi}\sqrt{\frac{1}{\sum \mathrm{L}}\sum \frac{1}{C}},$$

using $\sum \mathrm{L}$ instead of L and $\sum \frac{1}{C}$ instead of $\frac{1}{C}$.

In other words, an axon has its own resonance frequency that is determined by its geometry and its substantial characteristics.

The thalamus is thought to supply the periodic current of various frequencies [23]. If the frequency generated by the thalamus happens to be the same as the resonance frequency of the axon, the electric current conducted along the axon will have the maximum value. In addition, as the human brain develops, the nearby axons will grow in a similar fashion. So the nearby axons are expected to have a similar geometry and similar substantial characteristics. The nearby axons are thus expected to have a similar resonance frequency. An area of the brain that has similar resonance frequencies is expected to behave in a similar way for a given frequency provided by the thalamus.

Thus, when the thalamus provides the white matter with its resonance frequency, the amplitude of the electric current for a certain white matter area will have the maximum value. I therefore hypothesized that the brain of a generalized epilepsy patient has similar resonance frequencies in a widespread area of his/her brain and that the resonance frequencies are in the range of approx. 2–5 Hz (Fig. 1C).

As long as the current frequency provided by the thalamus is the same as the resonance frequency for the white matter area, the current is expected to have the maximum value independent of the phase. That is, both the spike and wave phases are expected to have the maximal amplitude.

3. Methods

To test the validity of the hypothesis described above, I made use of the visual evoked potential (VEP). To the best of my knowledge, the VEP technique is the only evoked potential technique available at this time that enables evaluations of brain circuits while eliminating the contribution of the thalamus.

The modified flash-VEP method was performed with flash repetition rates varying from approx. 1 to 5 Hz instead of a fixed repetition rate. A recording electrode was placed on the occipital scalp, 5 cm above the inion, and a reference electrode was connected to the bilateral ears.

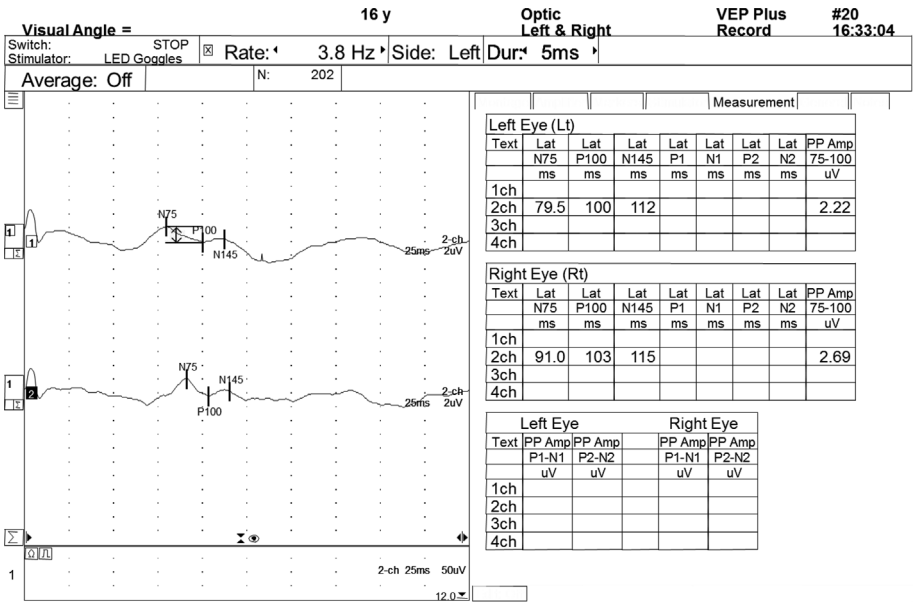

Fig. 2. Definition of the P_{100} amplitude. A VEP signal at 3.8 Hz of the flash repetition rate for Patient 1 with the stimulation of her left eye (*upper* wave) and that of her right eye (*lower* wave), respectively. The P_{100} amplitude is defined as the voltage difference between N_{75} and P_{100}.

Two hundred VEP signals were averaged for each repetition rate for each eye. The analysis time for each signal was 250 msec. I defined the positive peak of the VEP signal with the latency around 100 msec as P_{100}, and the negative peak next to it with the shorter latency as N_{75}. The P_{100} amplitude was estimated as the voltage difference between N_{75} and P_{100} (Fig. 2).

After the protocol was approved by the institutional review board and explained to the subjects, and after they had provided their consent to undergo the protocol, these modified flash-VEPs with the various flash repetition rates were used to examine four patients with generalized seizures, two patients with focal seizures, and two healthy controls. The P_{100} amplitude was then plotted against the flash repetition rate for each patient and control.

4. Results

No steady-state-VEPs were observed for any of the repetition rates used in this study. The P_{100} amplitude plotted against the various flash repetition rates for each patient with his/her clinical features are provided below.

4.1. Patient 1

Patient 1 was a 16-year-old Japanese female who, over the previous year, had often experienced myoclonus of her left or right arm just after getting up. She was admitted to our emergency room (ER) after her mother discovered her having a generalized seizure with her eyes open after taking a nap. When the patient arrived at our hospital, she was completely alert and had no neurological deficits. The findings of both her brain MRI and ECG were normal, and the laboratory data were all in the normal range except for high levels of creatine kinase (CK) and prolactin. Her inter-ictal EEG findings included 3–5 Hz diffuse spike-wave discharges dominant at her frontal area (Fig. 3A). I made the diagnosis of generalized epilepsy and prescribed sodium valproate (VPA).

The modified flash-VEP described above was then performed for the patient at flash repetition rates from 1.3 to 5.8 Hz. Her VEP waveforms showed a drastic change at the flash repetition rate around 4.6 Hz, whereas the VEP waveforms of her age-matched healthy control (18-year-old Japanese female) showed no such change at any flash repetition rate (Fig. 4). The patient's P_{100} amplitude plotted against the flash repetition rate was compared with those of the healthy controls (18-y-o Japanese female and 21-y-o Japanese male) and the focal epilepsy patients. Her P_{100} amplitude had a sharp peak around 4.6 Hz, whereas no obvious peak was observed in the healthy controls or in focal epilepsy patients (Fig. 5).

4.2. Patient 2

Patient 2 was an 18-year-old Japanese male who was admitted to our hospital to confirm a diagnosis. He had experienced left, right or bilateral arm myoclonus for a few seconds followed by a loss of consciousness for a few seconds once or twice a month since he was 5 years old. When he was 13, brain MRI was performed at another hospital and revealed no particular fault. General convulsions were observed when he was 14 and again when he was 15.

At his admission to our hospital, he did not show any neurological abnormalities. His brain MRI was normal, and his EEG included a number of generalized slow spike-waves with a frequency of approx. 4 Hz; the number of these waves was greater during sleep. I made a diagnosis of generalized epilepsy and prescribed VPA. Since the diagnosis, the patient has experienced no myoclonus or seizures. During his admission, the modified VEP technique was performed at the flash repetition rates from 0.3 to 4.8 Hz. His P_{100} amplitude had a sharp peak around 4 Hz (Fig. 5).

4.3. Patient 3

Patient 3 was a 32-year-old Japanese female who, at the age of 30 years, had been given a prescription of the anti-epileptic drugs (AEDs) carbamazepine (CBZ; 400 mg/day) and lamotrigine (LTG; 200 mg/day) by her former doctor. She had experienced her first general convulsion, which lasted a few minutes with a loss of consciousness and subsequent drowsiness, when she was 13 years old. Thereafter she had suffered from the same type of seizure approx. twice a year. She did not experience any seizures after she began to take the AEDs. I did not detect any focal neurological signs upon her examination at our hospital. Her cerebral MRI was normal, and her EEG included approx. 3 Hz generalized spike-wave discharges (Fig. 3B). I made a diagnosis of generalized epilepsy and stopped prescribing CBZ.

The modified VEP technique at the flash repetition rates from 0.8 to 5.3 Hz was performed; the results are shown in Fig. 5. There seemed to

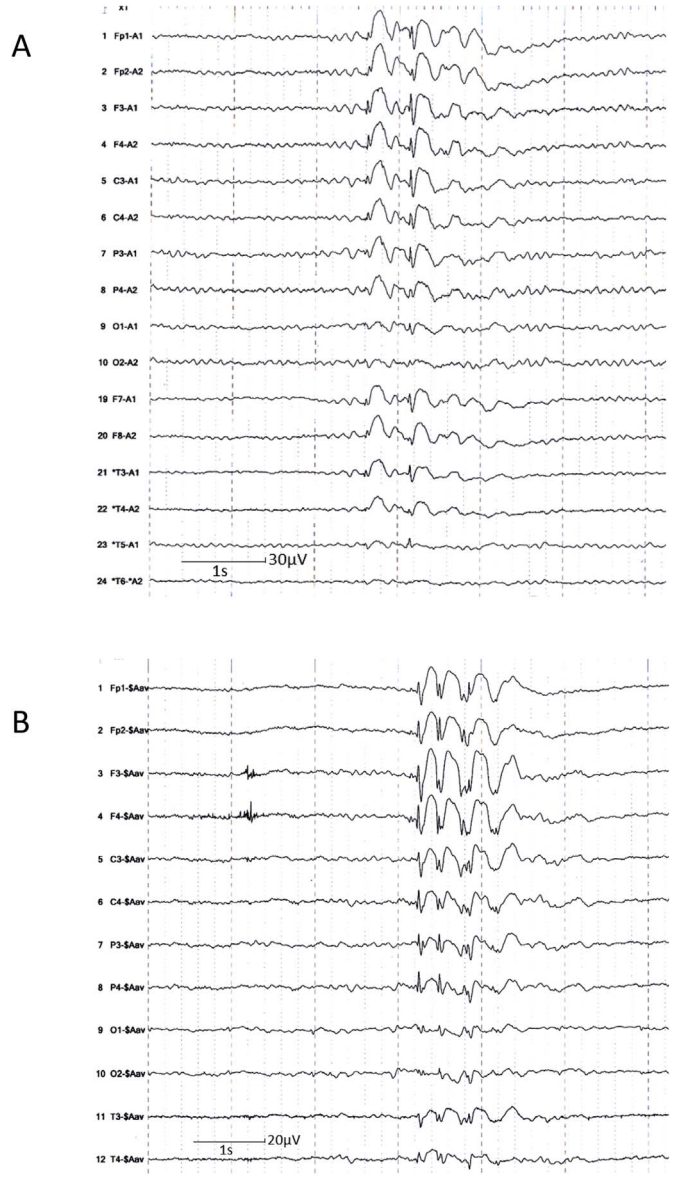

Fig. 3. Examples of the spike-wave discharges. A: A common reference electrode montage EEG for Patient 1 shows a generalized spike-wave around 3 Hz (high frequency filter, 30 Hz). **B:** An average montage EEG for Patient 3 shows a generalized spike-wave around 3 Hz (high frequency filter, 30 Hz).

be a P_{100} amplitude peak at the rate around 3 Hz, although the peak was rather broad compared with those of the younger Patients 1 and 2.

4.4. Patient 4

Patient 4 was a 32-year-old Japanese male who was admitted to our hospital. After tumbling from a chair in his office, he was discovered on the floor by a colleague at about 9:00 a.m. and brought to our ER. The colleague reported that the patient could say only “huh” when he was found, and that approx. 10 min later, he was able to reply to some easy questions. At approx. 4:00 p.m. on the same day, his consciousness was clear and he showed no neurological deficits. His brain MRI and ECG findings were normal and his blood data were all within normal limits except for the high serum prolactin level at his admission. His EEG showed 2–5 Hz spike-wave discharges, and the number of these discharges increased during photic stimulation and hyperventilation.

The patient had experienced similar seizures five times prior to his admission (most of them in the daytime) since the age of 17. I made a diagnosis of generalized epilepsy and prescribed him VPA. His modified VEP at the various flash repetition rates had a P_{100} peak around 4 Hz, although the peak was rather broader than those for the younger Patients 1 and 2 (Fig. 5).

4.5. Patient 5

Patient 5 was a 36-year-old Japanese male who had experienced a loss or change of consciousness for approx. 10 min to 2 days at a time on three separate occasions since the age of 31. Prior to his admission to our hospital, he went to bed after having worked all night. Two hours later, he had a minute-long generalized clonic seizure; his wife reported that he groaned and kept his eyes open during the seizure. He then walked around in his house without saying a word. His wife called an ambulance which brought him to our ER.

Upon admission, he showed no neurological deficits except for a mild consciousness disturbance. His brain MRI showed a cavernous hemangioma in his left frontal lobe, and his EEG included a small number of 1–2 Hz sharp waves in his frontal lobe area. I made a diagnosis of symptomatic focal epilepsy. The modified VEP method performed using various flash repetition rates showed no prominent P_{100} amplitude peaks (Fig. 5).

4.6. Patient 6

Patient 6 was a 65-year-old Japanese male brought to our ER after being observed having a generalized tonic clonic seizure while working outside at 9:00 a.m. During the seizure, his eyes were open and he gazed toward his right side. His colleagues called for an ambulance. The seizure lasted longer than an hour and was still going on when he arrived at our hospital. He had experienced a cerebral hemorrhage in his left putamen at the age of 58, and seizures similar to the seizure that brought him to our hospital had occurred 3 to 6 times a year since the age of 59. He had been prescribed 1500 mg of levetiracetam (LEV), 200 mg of LTG and 500 mg of CBZ per day, respectively, and had undergone vagus nerve stimulation (VNS) at the age of 63. His present seizure was stopped by intravenous administration of 1000 mg of phenobarbital sodium (PBNa) at the ER. His consciousness returned 6 h later, and his worsened aphasia and right hemiparesis gradually recovered to the same level as those observed before the seizure. It was clear that he had experienced a focal seizure as a sequela of his putamen hemorrhage. The modified VEP technique at flash repetition rates from 1.3 to 4.3 Hz was performed, and the results are shown in Fig. 5. They showed no P_{100} amplitude peaks.

Plotting of the P_{100} amplitude against the flash repetition rate revealed a maximum peak at a certain flash repetition rate for each of the generalized epilepsy patients, whereas there was no such peak for each of the controls or the focal epilepsy patients (Table 1, Fig. 5). The existence of this peak could be attributed to the series resonance phenomenon in the visual circuits.

5. Discussion

The idea that displacement current carries the electric current along the axon can help us understand why saltatory conduction is faster than continuous conduction. The hypothesis presented in this article is based on a model with an equivalent circuit in which the displacement current between two nodes of Ranvier is chained in a serial manner. The unit structure made up of one node and the next node forms a capacitor or an inductor depending on the geometry and the substance around the unit. The geometry and the substance around the nodes of Ranvier for the nearby axons are expected to be similar, as those axons will have grown in a similar way during the growth process. This means that the sets of Ls and Cs for the nearby axons are similar, and so is the resonance frequency. Therefore, the resonance frequency will be similar for all nearby regions of the brain. I propose that the brains of

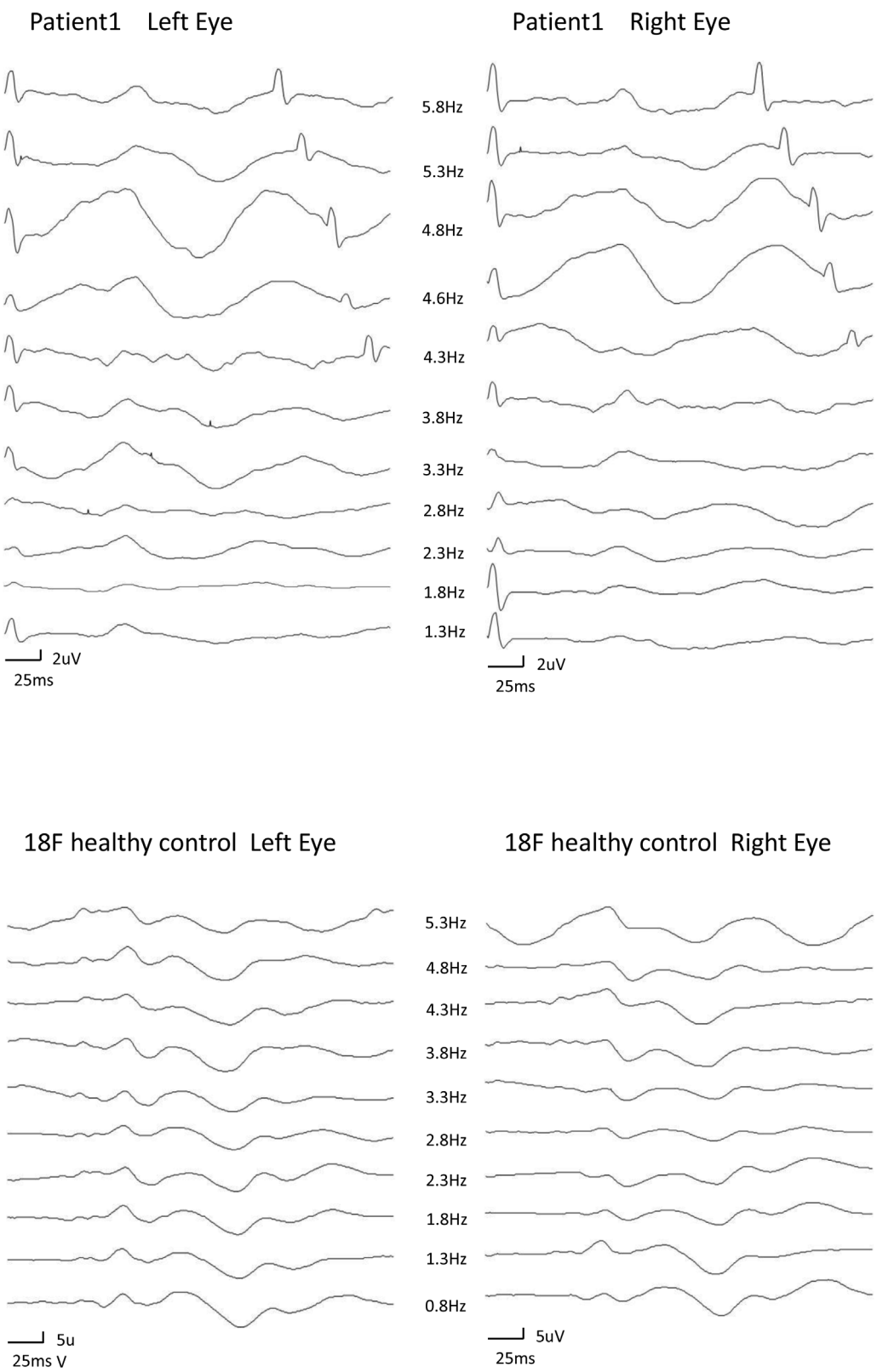

Fig. 4. Comparison of VEP waveforms between a generalized epilepsy patient and control. A set of waveforms in the modified VEP of Patient 1 observed at all of the flash repetition rates applied to her left eye (*left upper*) and her right eye (*right upper*), respectively. The set is compared with a corresponding set of waveforms from her age-matched healthy control (*lower*). The waveform of the patient exhibited drastic change with the change of the flash repetition rate, whereas no obvious change was observed for the control.

generalized epilepsy patients have a widespread homogeneous area with similar resonance frequencies in the range of around 2–5 Hz.

In constructing this hypothesis, I assume that the electric current conducting along an axon is a sine wave. This assumption seems consistent with the finding that the macroscopic appearance of several brain rhythms in the hippocampus resembled the sinusoid pattern of harmonic oscillators [23–25].

Marshall et al. [26] showed that the spike transmission in the

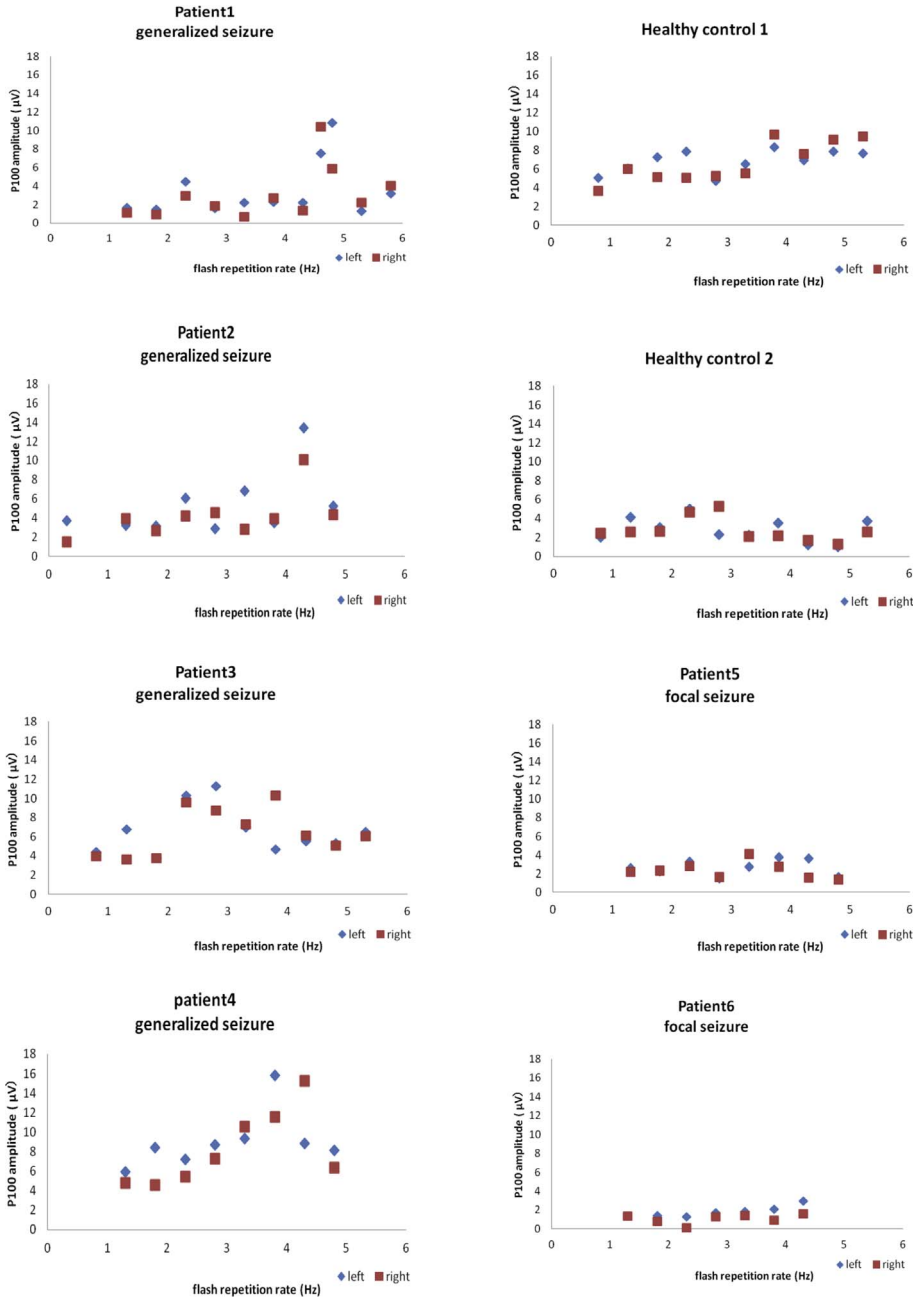

Fig. 5. The P_{100} amplitude dependency on the flash repetition rate. The graphs of P_{100} amplitude plotted against the flash repetition rate for the patients with generalized epilepsy (*left column*) and for the healthy controls or for the patients with focal epilepsy (*right column*). The maximum peak of P_{100} amplitude was observed for each of the patients with generalized epilepsy, whereas no prominent peak was observed for each of the controls or patients with focal epilepsy.

hippocampus is similar to band-pass filtering. Their finding is consistent with the series resonance hypothesis I proposed in this article, because the electric circuit consisting of capacitors and inductors chained in a serial manner is known to function as a band pass-filter [17]. Moreover, it has been shown that higher frequency oscillations are confined to a small neuronal space, whereas very large networks are recruited during slow oscillations [27,28]. These findings suggest that there is an inherent resonance frequency that corresponds with the size of a human brain. I infer that this inherent resonance frequency is around 2–5 Hz.

Wistar Albino Glaxo from Rijswijk (WAG/Rij) rats are a well-

Table 1
The existence of VEP peak and the seizure type. The maximum peak of P_{100} amplitude plotted against the flash repetition rate was observed only for each of the patients with generalized (spike-wave) seizures.

Patient	1	2	3	4	5	6
Age/Sex	16/F	18/M	32/F	32/M	36/M	65/M
seizure type	generalized	generalized	generalized	generalized	focal	focal
spike-wave frequency (Hz)	3–5	4	3	2–5	–	–
VEP peak frequency (Hz)	~4.5	4	3	4	–	–

established animal model of human generalized epilepsy [29]. Meeren et al. [2], who revealed the existence of a cortical focus initiating the spike-wave discharges in WAG/Rij rats, suggested that the generalized and synchronous character of the spike-wave discharges is caused by an "extremely fast" cortical spread of seizure activity. However, if, hypothetically, the resonance in the widespread white matter causes the large-amplitude discharges, it may not always be necessary to assume such an extremely fast spread in order to understand the synchronous character of the spike-wave discharges.

Here I used the VEP technique to test the validity of a hypothesis based on a series resonance model, since this technique may be the only way to evaluate brain circuits without including a contribution from the thalamus. Although the visual circuit contains the lateral geniculate body included in the thalamus, electrical mapping studies in WAG/Rij rats have shown that the thalamic lateral geniculate nucleus and the visual cortex are almost entirely spared during spike-wave seizures [30]. Therefore, if the series resonance phenomenon associated with spike-wave seizures is observable by the VEP technique, it may be due not to the lateral geniculate body or the occipital cortex, but rather to the white matter. Nersesyan et al. [31] also revealed that generalized seizures may not involve the whole brain homogenously; that is, they found that fMRI signals in focal regions including the perioral somatosensory cortex, which is known to be intensely involved during spike-wave seizures, were increased, whereas those signals in the occipital cortex were spared. These findings suggest that the difference between the spike-wave frequency on EEG and the resonance frequency for the P_{100} amplitude may have arisen because the visual pathway did not play an important role in the synchronous spike-wave discharges for the generalized epilepsy patients observed in this study.

Viravan et al. [32] pointed out the possibility of the occipital cortex initiating a generalized epilepsy network in Jeavons syndrome (JS), which is a form of idiopathic generalized epilepsy. However, even if the occipital cortex initiates the epilepsy, this would not necessarily be inconsistent with the idea that the large amplitude of spike-wave discharges is based on the resonance phenomenon of the electric circuits in the white matter. In fact, the EEGs in their report show that the maximum amplitude of spike-wave discharges was observed in the frontal area rather than the occipital area. In other words, onset focus does not need to exist in the area where the resonance in the white matter is dominantly observed.

Among the patients with generalized epilepsy in this investigation, the older patients (Patients 3 and 4) had smaller peaks of P_{100} amplitude than the younger patients (Patients 1 and 2), as shown in Fig. 5. This may be consistent with a previous report on VEP age-related changes in schoolchildren, in which VEP amplitude was shown to decrease steadily until adulthood [33].

Whether the unit structure of one node of Ranvier and the next node is regarded as an inductor or a capacitor depends not only on L and C but also on the current frequency ω itself (see *2.1*). This does not happen in the case of an ordinary electric circuit with fixed capacitors and inductors. If, for example, many of the unit structures regarded as capacitors for a certain frequency range are regarded as inductors for another frequency range, the resonance frequency f may have another value for the latter frequency range. This can lead to more than one resonance frequency, which means that we can observe more than one peak of the P_{100} amplitude in the modified VEP. The existence of another small P_{100} peak amplitude around 2.3 Hz of the flash repetition rate in Patients 1 and 2 (Fig. 5) may be explained by such a mechanism.

6. Conclusion

The present hypothesis that series resonance in the white matter can be modeled on the idea of axon conduction with displacement current can help us understand the mechanism of spike-wave seizures. I speculate that the brain of a generalized epilepsy patient has similar resonance frequencies over a widespread area.

7. Limitations

I made use of the VEP technique to test my series resonance hypothesis. Although this is a popular technique available at most general hospitals, it is difficult to confirm by only this method that the existence of the P_{100} peak is attributable to the resonance phenomenon. Thus the resonance phenomenon should be proved in a more direct way.

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Conflicts of interest

The author has no potential conflicts of interest to be disclosed.

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