Applied research papers

A Four-dimensional Virtual Brain Application for Visualization and Explanation of Abnormal Neural Activity and Medication Efficacy

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Abstract:
Purpose: The aim of this study was to develop and evaluate application software for physicians to explain medication efficacy to patients with epilepsy. Methods: We developed application software for visualization of the attenuation of epileptic seizures on a three-dimensional (3-D) brain-surface shape model using magnitude texture mapping of abnormal neural activity. The magnitude of the abnormal neural activity was mathematically simulated by the Kim–Robinson model. The efficacy of the developed application software was confirmed by neurosurgeons (n = 7) via questionnaire. Results: The developed software was useful in explaining brain anatomy and function, epileptic seizure and medication adherence. Conclusions: The virtual reality application software developed in this study can be used to support patient awareness of the pathophysiology of epileptic seizures.

Key words:
Epileptic seizures, medication adherence, virtual reality

1. Introduction

Approximately 50 million people worldwide suffer from epilepsy ¹. Epileptic seizures are classified into generalized and focal (partial) seizures. During generalized seizures, abnormal neural activity spreads rapidly throughout the entire brain; conversely, abnormal activity remains localized during focal (partial) seizures ². Antiepileptic drugs and surgical removal of the epileptic brain focus are the major treatments for patients with epilepsy. With drug therapy, patients must maintain consistent levels of the antiepileptic drug in their blood. Therefore, it is essential that these patients take their medication regularly. However, some patients discontinue their medication while they are asymptomatic without consulting a physician. Consequently, some of these patients have been involved in traffic accidents ³, perhaps believing that their epilepsy was cured and that medication was no longer necessary. These patients had likely been given some explanation of epilepsy, but may not have understand the pathophysiology and mechanisms of the disease due to its complex nature.

To mitigate these problems, physicians may need to explain not only the importance of medical adherence but also the pathophysiology of epilepsy at a level that patients can understand. Clinically, physicians commonly use two-dimensional (2D) images to explain epilepsy. However, epilepsy is a 4D phenomenon of neural activity in the brain, which makes it difficult to

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explain and describe to patients. Therefore, the aim of this study was to develop seizure-onset 4D-visualization application software to help physicians explain the importance of medication adherence to patients.

2. Methods

2.1 Requirement specifications
The application software was designed as a support tool to be used by physicians when giving medication instructions to patients. The requirement specifications were as follows:

i. The seizures were visualized on a 3D brain-surface shape model (BSM) in a virtual reality space to help patients intuitively understand anatomical information.

ii. The target epileptic seizures were focal seizures that occurred on the cerebral surface of the brain; temporal changes in the seizures were visualized on the BSM.

iii. Seizure suppression via antiepileptic drugs was visualized.

2.2 Equipment and materials

2.2.1 BSM generation
Manual segmentation of brain magnetic resonance (MR) images was performed by a physician using Avizo (FEI Co., Hillsboro, OR) and a BSM was generated (Fig. 1). Coordinate information in 2D, called the UV coordinate, was mapped at each vertex of the BSM, where the U axis was the horizontal axis and the V axis was the vertical axis. Spherical UV mapping was performed with Maya (Autodesk, Inc., San Rafael, CA). Fig. 2 shows the UV mapping results. The blue line is the BSM projected on the UV coordinate system. In this study, the scale of the UV coordinate was adjusted by a medical doctor.

2.2.2 Epileptic seizure simulation and visualization
Previous mathematical models of epilepsy include neural network model involving synaptic membrane structure and a cortical model representing seizures in the cortex\(^4,9\). In this study, we employed the Kim–Robinson model (KRM)\(^7,9\), which simulated seizures on a 2D finite plane by calculating and combining neuron potential (NP) values. This model works in real time because it uses several variables among dynamic models of complicated brain activity. NP is calculated in KRM using the following equation:

\[
\frac{1}{\gamma^2} \frac{\partial^2 \psi(r, t)}{\partial t^2} + \frac{2}{\gamma} \frac{\partial \psi(r, t)}{\partial t} = F(r, t) + C(r, t) + S(r, t)
\]

(1)

where \(\psi\) is NP activity, \(r\) is a coordinate, \(t\) is time, \(\gamma\) is the decay rate, \(F\) is a time term, \(C\) is spatial association,
and $S$ is an external stimulus. $F$, $C$, and $S$ are defined in the following equations:

$$F(r, t) = c_1(r, t)\psi(r, t) + c_2(r, t)\psi^2(r, t) + c_3(r, t)\psi^3(r, t) + c_0(r, t)\psi_0(r, t - t_0/2)$$  \hspace{1cm} (2)

$$C(r, t) = \gamma^2 \psi(r, t)$$  \hspace{1cm} (3)

$$S(r, t) = \psi_0\exp \left[ -\left( \frac{r}{\sigma} \right)^2 - \frac{(t - \tau)^2}{\sigma^2} \right]$$ \hspace{1cm} (4)

where, $c_1$, $c_2$, $c_3$, $c_0$, $\varepsilon_2$, $\varepsilon_3$, $t_0$, and $\psi_0$ are the parameter constants, $t_0$ is the loop delay, $\gamma$ is the length of the axon between the cortices, $t_1$ is the start time of the external stimulus, and $\psi_0$ is the initial potential of the external stimulus. Since $c_0(r, t)\psi_0(r, t - t_0/2)$ can be approximated by white noise\cite{9}, we used white gauss noise ($\sigma = 0.0003$). Table 1 shows the parameter values in this study. They were adjusted to represent actual epileptic seizures based on physicians’ advice. During visualization, a color was set for each NP value, and the linear interpolated color was used as an intermediate NP value. A 2D finite plane with NP values for each pixel was converted to a color (RGB) image (Fig. 3) and mapped to the BSM along the UV coordinate. In this study, red was used for the high absolute NP value, yellow represented the middle value, and green indicated a low value.

2. 2. 3 Visualization of seizure suppression via antiepileptic drugs

To promote intuitive understanding of drug effects and to explain the importance of medication adherence, suppression of seizures was visualized. In KRM, the oscillation of NP activity depends on the parameter $c_1$\cite{7,9}. So, we simulated suppression by changing $c_1$.

2. 2. 4 Implementation of the application software

The visualization software was developed for Windows 7 based on Unity3D (Unity Technologies, Inc., San Francisco, CA) and C#. Fig. 4 shows the graphical user interface (GUI) and BSM with simulated epileptic seizure colors. The focus was in the temporal lobe of the right cerebral hemisphere. The focal position was changed by right-clicking, and the eye direction could be

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$c_1$</td>
<td>-0.168</td>
</tr>
<tr>
<td>$c_2$</td>
<td>-0.50</td>
</tr>
<tr>
<td>$c_3$</td>
<td>0.00</td>
</tr>
<tr>
<td>$c_0$</td>
<td>-0.10</td>
</tr>
<tr>
<td>$\varepsilon_2$</td>
<td>0.20</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>100.00</td>
</tr>
<tr>
<td>$t_0$</td>
<td>0.08</td>
</tr>
<tr>
<td>$\psi_0$</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Table 1. Set parameters and their values

Figure 3. Kim–Robinson model (KRM) simulation results

Figure 4. The developed application software

1. Dose: adjusted seizure suppression via antiepileptic drugs
2. Pause/Restart: Stop during the current state/restart from a stopped state
3. Reset: Return to the initial state
rotated by left-clicking and dragging. The antiepileptic
drug dosage was controlled using a slider bar. The
pause, restart, and reset buttons were used to pause,
restart, or reset seizure simulation. The dose slider bar
in Fig. 4 controlled $c_1$ in (2) and suppressed the seizure
when the slider was raised.

2.3 Evaluation experiment

The subjects were 7 neurosurgeons. The sampling
method was opportunistic and an anonymous self-report
study was conducted. Two questionnaires (pre- and post-
survey) were administered. A visual analog scale was
employed for evaluation.

The pre-survey questionnaire included the following:
(1) “Are you an epileptic specialist?” (yes/no); (2)
“Have you ever treated patients with epileptic seizures
in an outpatient setting?” (yes/no); (3) “How do you
explain epilepsy to patients and their families?” (multiple
choice); (4) “Have you ever faced difficulty in properly
explaining the disease to patients and their families?”
(yes/no); (5) “What was difficult to explain?” (multiple
choice); and (6) a concrete example related to Question
5 (open-ended description).

The questionnaire for the post-survey was made based on
ISO/IEC 25000 international standards: Software Product
Quality Requirements and Evaluation (SQuaRE)\textsuperscript{10,11}.

The post-survey questionnaire was a functionality
assessment (FA) to measure whether the application
matched its purpose, and a usability evaluation (UE)
related to application operation. In this study, the FA
examined the advantages of using the 3D application
compared with conventional methods which were the
chooses in re-survey questionnaire.

The FA included the following possible answers: (1)
it will be easier to explain brain anatomy and function;
(2) it will be easier to explain the propagation of
epileptic seizures; (3) it will be easier to give medication
instructions; (4) it will help share visual information
between doctors and patients; (5) and it will reduce the
time spent in consultations. The UE consisted of the
following selections: (1) whether the application was
easy to use; and (2) whether the subject operated the
application smoothly.

The experiment was conducted with the approval of the
ethics committee of the Graduate School of Medicine
and the Faculty of Medicine at The University of Tokyo
[approval number: 2332-(2)].

3. Results

Tables 2-4 show the results of the pre-survey
questionnaire. Two out of seven participants were
epileptic specialists. All subjects had faced difficulty when
explaining epilepsy, and 6 subjects had given an oral
explanation only. It was especially difficult to explain brain
anatomy, brain function, and medication. Some subjects
reported that the reason for difficulty with “the things
related to medication” was that it is difficult to explain the
mechanism and necessity of antiepileptic drug treatment.

Table 5 shows the results of the post-survey FA
questionnaire. The answer “It will be easier to explain
brain anatomy and function” had the highest score:

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes (%)</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are you an epileptic specialist?</td>
<td>2/7 (28.6)</td>
<td>5/7 (71.4)</td>
</tr>
<tr>
<td>Have you ever treated patients with epileptic seizures in an outpatient setting?</td>
<td>7/7 (100)</td>
<td>7/7 (0)</td>
</tr>
<tr>
<td>Have you ever faced difficulty in properly explaining the disease to patients and their families?</td>
<td>7/7 (100)</td>
<td>7/7 (0)</td>
</tr>
</tbody>
</table>
Table 3. Results of the pre-survey questionnaire (multiple choice question) (n = 7)

<table>
<thead>
<tr>
<th>Selection</th>
<th>Ratio (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral explanation</td>
<td>7/7 (100)</td>
</tr>
<tr>
<td>Explanation using conventional images, etc.</td>
<td>1/7 (14.3)</td>
</tr>
<tr>
<td>Explanation describing an image</td>
<td>0/7 (0)</td>
</tr>
<tr>
<td>Explanation using videos</td>
<td>0/7 (0)</td>
</tr>
<tr>
<td>Other</td>
<td>0/7 (0)</td>
</tr>
</tbody>
</table>

Table 4. Results of the pre-survey questionnaire (multiple choice question) (n = 7)

<table>
<thead>
<tr>
<th>Selection</th>
<th>Ratio (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain anatomy and function</td>
<td>4/7 (57.1)</td>
</tr>
<tr>
<td>Medication</td>
<td>4/7 (57.1)</td>
</tr>
<tr>
<td>The relationship between seizures and physical symptoms</td>
<td>2/7 (28.6)</td>
</tr>
<tr>
<td>Brain surgery</td>
<td>1/7 (14.3)</td>
</tr>
<tr>
<td>Propagation of brain seizures</td>
<td>1/7 (14.3)</td>
</tr>
<tr>
<td>Other</td>
<td>1/7 (14.3)</td>
</tr>
</tbody>
</table>

Table 5. Post-survey questionnaire/functionality (visual analog scale [VAS]) (n = 7)

<table>
<thead>
<tr>
<th>Question</th>
<th>Mean</th>
<th>SD</th>
<th>95% CI (Lower, Upper)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advantages of using the three-dimensional (3D) application compared with conventional methods</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>It will be easier to explain brain anatomy and function</td>
<td>9.02</td>
<td>0.95</td>
<td>8.14, 9.90</td>
</tr>
<tr>
<td>It will help share visual information between doctors and patients</td>
<td>8.61</td>
<td>2.58</td>
<td>6.22, 11.00</td>
</tr>
<tr>
<td>It will be easier to give medication instructions</td>
<td>7.66</td>
<td>2.71</td>
<td>5.15, 10.17</td>
</tr>
<tr>
<td>It will be easier to explain the propagation of epileptic seizures</td>
<td>7.28</td>
<td>1.76</td>
<td>5.65, 8.91</td>
</tr>
<tr>
<td>It will reduce the time spent in consultations</td>
<td>5.96</td>
<td>2.51</td>
<td>3.64, 8.28</td>
</tr>
</tbody>
</table>

SD: Standard Deviation, CI: Confidence Interval

Table 6. Post-survey questionnaire/usability (VAS) (n = 7)

<table>
<thead>
<tr>
<th>Question</th>
<th>Mean</th>
<th>SD</th>
<th>95% CI (Lower, Upper)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was it easy to understand the operation of the application?</td>
<td>9.74</td>
<td>0.29</td>
<td>9.47, 10.01</td>
</tr>
<tr>
<td>Did you operate the application smoothly?</td>
<td>9.61</td>
<td>0.36</td>
<td>9.28, 9.94</td>
</tr>
</tbody>
</table>

SD: Standard Deviation, CI: Confidence Interval
9.02 out of 10 (standard deviation [SD] = 0.95, 95% confidence interval [CI] = 0.88). The answer “It will reduce the time spent in consultations” had the lowest score: 5.96 out of 10 (SD = 2.51, 95% CI = 2.32). Both UE scores were high, with little variation (Table 6).

4. Discussion

We developed application software to help patients intuitively understand the pathophysiology of epilepsy and to help physicians explain the importance of medication adherence to their patients. The main advantage of our system is that it allows 3D visualization of the brain and temporal abnormal neural activity at the onset of epileptic seizures. Further, it simulates the suppression of seizures when the antiepileptic drug dose is increased.

The lack of patient understanding of the disease and treatment regimen may affect compliance with drug treatment. In this study, the results of the pre-survey questionnaire showed that most physicians only gave oral explanations to patients with epilepsy, and that physicians felt it was difficult to explain the importance of medical adherence. In Japan, physicians did not have enough time to explain medical adherence but thought the patients understood their oral explanations. In fact, some physicians reported that most patients understood the content of their explanations to some extent.

In the FA questionnaire, the brain anatomy and function question score was high and the SD was small. The propagation of epileptic seizures and medication question scores were also high. This suggests that our software was useful in explaining brain anatomy and function, epileptic seizures, and medication adherence. The propagation of epileptic seizures and medication question scores were lower than the brain anatomy and function question score. The reason may be that the epileptic seizure simulation algorithm only applied to the brain surface. Therefore, physicians who wanted to use it for other seizure types (e.g., those due to hippocampal sclerosis) might have given the application a low score. Additionally, the seizure suppression simulation algorithm only allowed for visualization of the effect and did not describe the drug mechanism. Therefore, physicians who wanted to explain the drug mechanism during consultation might have given a lower score. We will attempt to refine these points in the next study.

The application received high UE scores for ease of understanding and operation. Reason for this result might be that it can be operated using a mouse only and that the GUI is easy to navigate.

A limitation of this study is that it was difficult to validate the seizure simulation using actual epileptic seizure phenomena. This is because scalp electroencephalograms (EEGs) are not always accurate and intracranial EEGs can only measure a limited area. Additionally, we did not evaluate the subjects’ perception of the software instructions.

5. Conclusion

We developed application software to help physician explain epileptic seizures to patients. It simulated and allowed visualization of epileptic seizures on the brain surface using the KRM and UV mapping. The results of the evaluation experiment indicated that it might be easier to explain brain anatomy and function using the application compared with using conventional explanations. We will evaluate the application from patient side in next study.

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Author Contributions

Planned experiments: MH, HK, TS, TK, HO
Performed experiments: MH, NS, TK, TS
Analyzed data: MH, HK, DI, TS
Contributed materials: NS, TK, NK, NS, HO
Wrote the paper: HK, MH, TS, HO

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References