

Review

Precision Epilepsy Surgery Using Digital Technologies

[Yosuke Sato](#)

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Director, Brain Function Analysis and Digital Medicine Research Institute, Showa Medical University;
Professor, Department of Neurosurgery, Showa Medical University Hospital, Tokyo, Japan.
E-mail: yosukens@med.showa-u.ac.jp

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Abstract

Seizure manifestations in epilepsy are heterogeneous, and lesions are often not clearly visualized even with multiple imaging modalities, which makes precise diagnosis challenging. Electrophysiological assessment using electroencephalography (EEG) is essential for localizing the epileptogenic focus; commonly used markers include preictal and ictal EEG changes and interictal spikes. However, these markers have limitations: they are not assessable when seizures do not occur, they may include normal brain activity, and some features can only be observed with invasive intracranial electrodes. Recent advances have digitized EEG data and enabled multifaceted interpretation through mathematical and computational approaches. We are implementing precision epilepsy surgery guided by rigorous focus evaluation that leverages digital technologies applied to EEG data. This article reviews our research to date on the development and application of these techniques.

Keywords: digital technology, EEG, epilepsy, gamma oscillation regularity, neurosurgery.

1. Excitation–Inhibition Balance in Epileptic EEG

Spike-and-wave complexes in focal epilepsy consist of a spike that often contains high-frequency oscillations (HFOs) followed by a post-spike slow wave (PSS). HFOs are associated with excitatory epileptic activity, whereas the PSS reflects inhibitory processes. Clarifying the spatiotemporal relationship between spike-associated HFOs and PSSs in patients with focal cortical dysplasia (FCD) type II may elucidate the excitation–inhibition balance in epileptic EEG. We analyzed intracranial EEG recordings from 10 patients with FCD type II. For each electrode site we computed the power of HFOs and PSSs and compared these measures across three regions: the seizure-onset zone (SOZ), resected cortex outside the SOZ, and non-resected cortex. Comparisons were performed for interictal period and the immediate preictal period using Spearman's rank correlation and simple linear regression to assess the relationship between HFO power and PSS power. A total of 1,614 HFO–PSS events

were analyzed. During interictal periods, HFO and PSS power showed significant positive correlations across all regions: SOZ $r=0.568$; resected non-SOZ $r=0.700$; non-resected cortex $r=0.320$. In the preictal period the correlation in the SOZ markedly decreased ($r=0.149$), whereas correlations in the resected non-SOZ ($r=0.704$) and non-resected cortex ($r=0.346$) were essentially unchanged. The regression slope (PSS power / HFO power) decreased in the SOZ from 0.349 to 0.051, while it increased in the resected non-SOZ from 0.534 to 0.734 and in non-resected cortex from 0.267 to 0.435 (Figure 1) [1]. Supplementary analyses showed that the change in regression slope became apparent approximately 1 minute before seizure onset [2] and those dynamic alterations of PSS occurred from the interictal to the preictal state [3]. These findings indicate a relative reduction of PSS power in the SOZ immediately before seizures, consistent with a transient loss of inhibitory control preceding seizure initiation. Conversely, during

interictal periods the SOZ may exhibit stronger inhibitory activity than surrounding normal cortex. This preserved interictal inhibition could serve as a marker for focal localization if it can be reliably detected. Motivated by these results, we proceeded to develop

methods to visualize interictal inhibitory strength to improve localization of the epileptogenic focus for precision surgical planning.

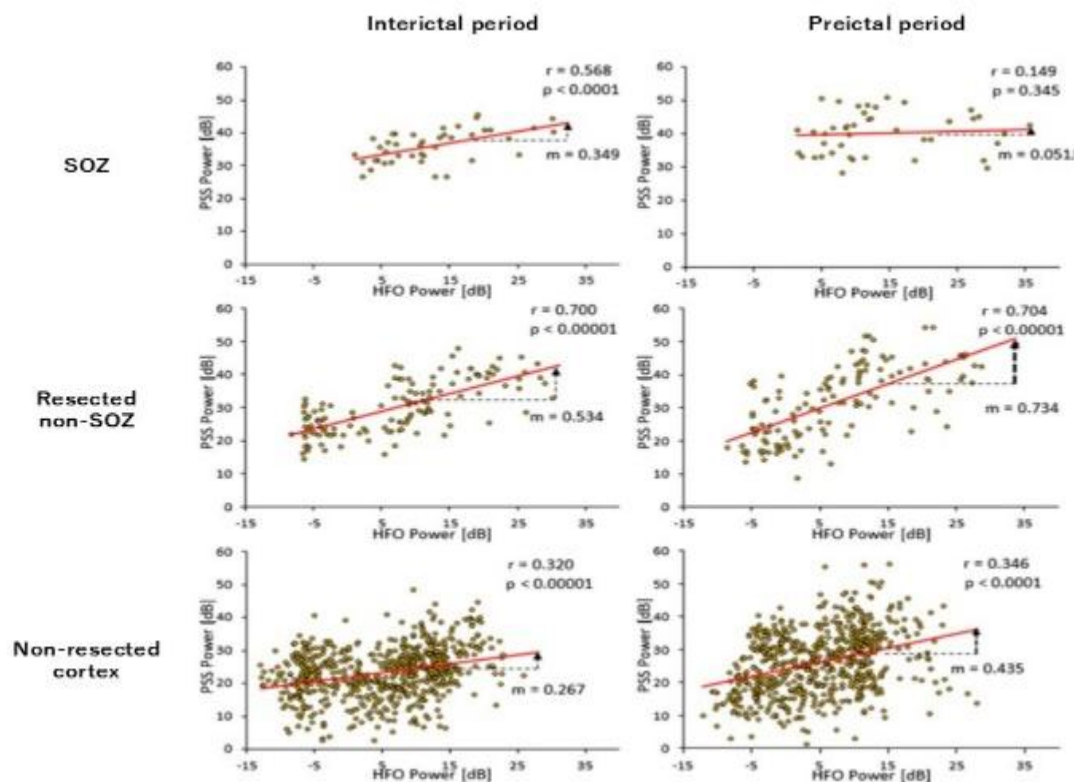


Figure 1 - Correlation analysis between HFO power and PSS power across regions during interictal and preictal periods.

In the interictal state, HFO and PSS power showed significant positive correlations in all regions, whereas the correlation in the seizure onset zone (SOZ) markedly diminished in the immediate preictal period. The simple linear regression slope (PSS power / HFO power) decreased only in the SOZ. Spearman's rank correlation coefficient (r) and regression slope (m) are indicated on the panels. Adapted from Reference 1

2. Gamma Oscillation Regularity (GOR) Analysis for Visualizing the Epileptogenic Focus

Gamma oscillations in focal epilepsy are linked to locally synchronized neuronal activity involved in inhibitory control, [4] and the rhythmicity of EEG oscillations that include gamma has been shown to correlate with local neuronal synchrony [5]. Based on these findings, we hypothesized that local neuronal synchrony—the principal component of interictal inhibitory strength—could be detected as changes in GOR. We applied multiscale entropy analysis, a method that quantifies signal regularity across arbitrary frequency bands, to intracranial EEG recorded from 13 patients with FCD type II. We quantified GOR at each electrode over interictal, preictal, and ictal epochs and examined characteristic spatiotemporal patterns. In an expanded cohort of 13 patients who achieved postoperative seizure freedom, we analyzed data from 1,164 intracranial electrodes to evaluate GOR quantitatively. Entropy values were used as the metric

of regularity (lower entropy indicates greater regularity). For each case, entropy values were converted to Z-scores for three regions: the seizure-onset zone (SOZ), resected cortex outside the SOZ, and non-resected cortex. Receiver operating characteristic analysis produced cutoff Z values, sensitivity, specificity, and area under the curve (AUC) for each region. We observed distinctive spatiotemporal changes in GOR. During interictal periods, GOR was significantly higher in the SOZ compared with surrounding regions. In the immediate preictal period, GOR in the SOZ decreased toward levels similar to adjacent cortex. During seizures, GOR increased broadly across both SOZ and non-SOZ regions (Figure 2) [6]. Quantitative analysis yielded the following diagnostic performance for detecting the SOZ during interictal periods: a cutoff $Z \leq -2.09$ produced 100% sensitivity and 97.1% specificity with $AUC = 0.992 \pm 0.002$. For detecting

resected non-SOZ cortex, a cutoff $Z \leq -0.12$ yielded sensitivity 54.2%, specificity 73.8%, $AUC = 0.673 \pm 0.019$. For non-resected cortex, a cutoff $Z \geq -0.11$ yielded sensitivity 73.8%, specificity 54.2%, $AUC = 0.673 \pm 0.019$. These results indicate that elevated GOR during interictal periods is a statistically robust marker of the epileptogenic focus [7]. For planning resections in cortical dysplasia type II, we implant subdural electrode grids that include sufficient adjacent normal cortex,

perform EEG acquisition, and compute gamma-band regularity. Regions with initial $Z \leq -1$ are considered candidates for resection. After an initial resection, we repeat EEG recording and gamma-regularity analysis on the resection margin and combine these findings with other electrophysiological data. Additional resection is considered for areas that continue to show $Z \leq -1$, enabling fine-tuning of the resection extent.

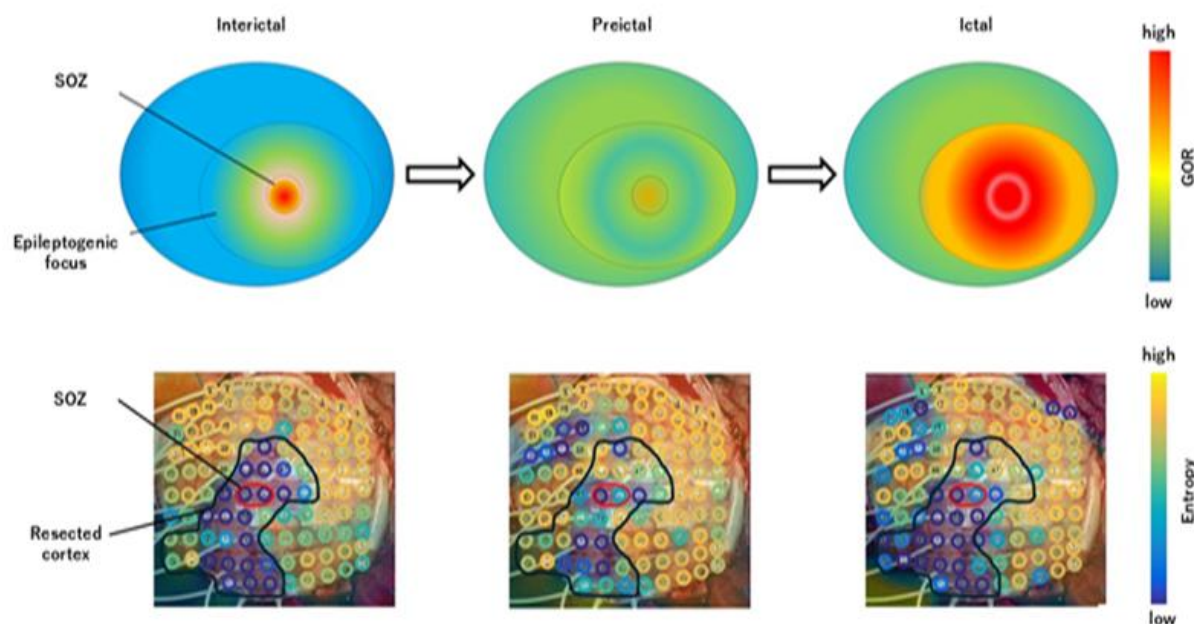


Figure 1 - Spatiotemporal changes of GOR from interictal to ictal epochs.

Upper panels: During the interictal period, GOR is significantly elevated around the seizure onset region; in the immediate preictal period the regularity in the SOZ declines to levels similar to surrounding cortex; during the ictal period gamma regularity increases widely, including outside the SOZ. Lower panels: Visualization of temporal and spatial changes in entropy values (reflecting GOR) derived from intracranial EEG in a patient with FCD type II. Lower entropy denotes higher GOR. Adapted from Reference 6

3. Application of GOR Analysis to Epilepsy Surgery

GOR was evaluated as a potential intraoperative marker for localizing epileptogenic tissue in patients with drug-resistant focal epilepsy related to cavernous malformations. Extended resection that includes the lesion, surrounding hemosiderin-stained cortex, and adjacent epileptogenic zones is known to improve postoperative seizure control, but clear intraoperative correlates of these pathological regions have been lacking. In six patients with cavernous malformations, we computed intraoperative EEG GOR from cortical recordings. GOR maps were inspected with respect to the lesion, adjacent hemosiderin-stained cortex, hippocampus when involved, and the surgical resection plan. High GOR co-localized with pathological hemosiderin deposition in four cases. In two

temporal-lobe cases, elevated GOR was observed in both the hippocampus and the lesion. Some cases showed no overt epileptiform waveforms on intraoperative electrocorticography, yet the regions of elevated GOR were resected in all six patients. Postoperatively, all patients achieved seizure freedom [8]. These findings suggest that intraoperative GOR can identify epileptogenic cortex associated with cavernous malformations and hemosiderin staining, including areas that lack clear conventional epileptiform discharges. Elevated intraoperative GOR thus has potential as a novel surgical marker to guide tailored resections and improve seizure outcomes.

4. Utility of GOR Analysis in MRI Negative Temporal Lobe Epilepsy

In temporal lobe epilepsy without any structural abnormality on MRI, traditional preoperative investigations often fail to predict seizure lateralization or precise localization. These patients typically require prolonged video EEG monitoring and invasive intracranial electrode evaluation to identify the epileptogenic focus. We applied preoperative high density scalp EEG to compute interictal GOR and assessed whether GOR could indicate seizure lateralization and focus localization without intracranial monitoring. Interictal GOR maps derived from high density EEG consistently matched intraoperative cortical GOR measurements and provided more detailed lateralization and localization

information (Figure 3) [9]. These results indicate that noninvasive high density EEG GOR analysis can contribute to lateralizing and localizing the epileptogenic focus in MRI negative temporal lobe epilepsy, potentially reducing the need for invasive monitoring and its associated complications. Traditional epilepsy surgery has steadily advanced through decades of research focused on accurately identifying foci in MRI negative cases. Precision epilepsy surgery, as advocated here, leverages digital signal methods such as GOR analysis to estimate focus localization with high accuracy in MRI negative patients and to define resection margins more precisely.

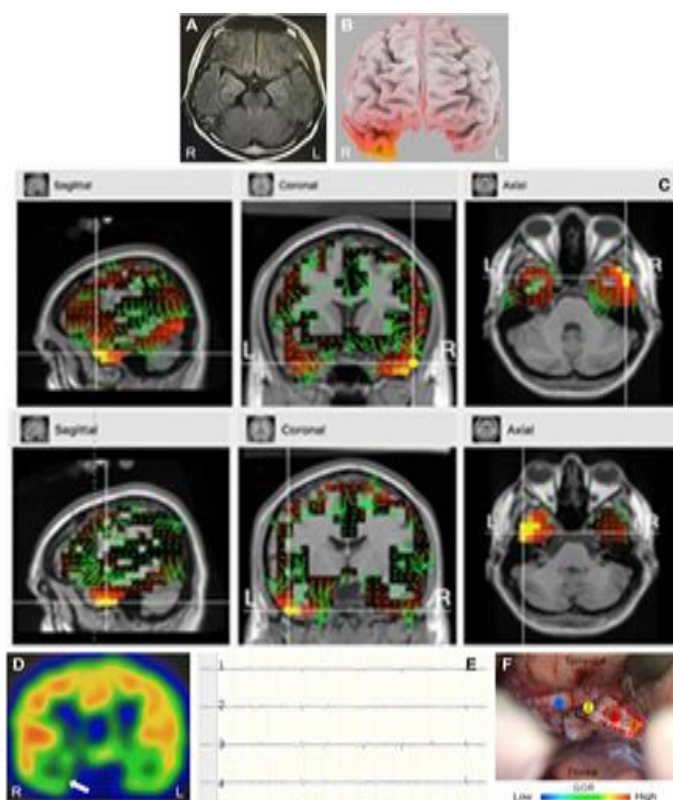


Figure 3 - Representative findings in an MRI negative temporal lobe epilepsy case.

(A) Preoperative MRI shows no overt structural abnormality.

(B) Interictal GOR map computed from 256 channel high density scalp EEG demonstrates a focal high GOR region in the right medial temporal area.

(C) Interictal magnetoencephalography localizes spike sources to bilateral medial temporal regions.

(D) Iomazenil SPECT shows reduced uptake in the right medial temporal region.

(E) Intraoperative EEG reveals spikes across all hippocampal contacts

(F) Intraoperative GOR analysis identifies significant high GOR in the posterior body and tail of the hippocampus (electrodes #3 and #4; red dashed circles), which were resected; the patient achieved postoperative seizure freedom. Adapted from Reference 9

5. Visualization of Ictal Networks by GOR Correlation Analysis

Accurate localization of the epileptogenic focus in focal epilepsy is challenging when seizures spread rapidly within cortex or when structural lesions are absent. Lesions near the motor cortex or within the

temporal lobe are especially difficult to evaluate using conventional imaging and semiology alone. We therefore examined whether correlation analysis of GOR from cortical EEG can reveal ictal network connections

that inform surgical planning. In a patient with a lateral temporal cavernous malformation but without hippocampal structural abnormality, intraoperative GOR correlation analysis identified elevated GOR in both the lateral temporal region and the hippocampus, and demonstrated functional linkage between them as an ictal network. After limited resection of the lateral temporal cortex and the cavernoma, elevated GOR persisted in the hippocampus; subsequent addition of hippocampal transection abolished the GOR abnormality and the patient achieved postoperative seizure freedom (Figure 4) [10]. In a focal motor epilepsy patient with a low-grade glioma adjacent to the primary motor cortex, ictal intracranial EEG GOR correlation analysis revealed elevated GOR in the supplementary

motor area and a network connection with the primary motor cortex. Resection of both the tumor and the high GOR supplementary motor region resulted in seizure freedom without neurological deficit [10]. GOR analysis not only localizes epileptogenic foci but, when combined with correlation mapping, visualizes ictal networks that may extend beyond the primary lesion. This capability is particularly valuable for complex pathologies that elude conventional diagnostics and enables real time intraoperative assessment. GOR based network mapping therefore represents a powerful tool to support precision epilepsy surgery by guiding targeted resections of functionally connected epileptogenic cortex.

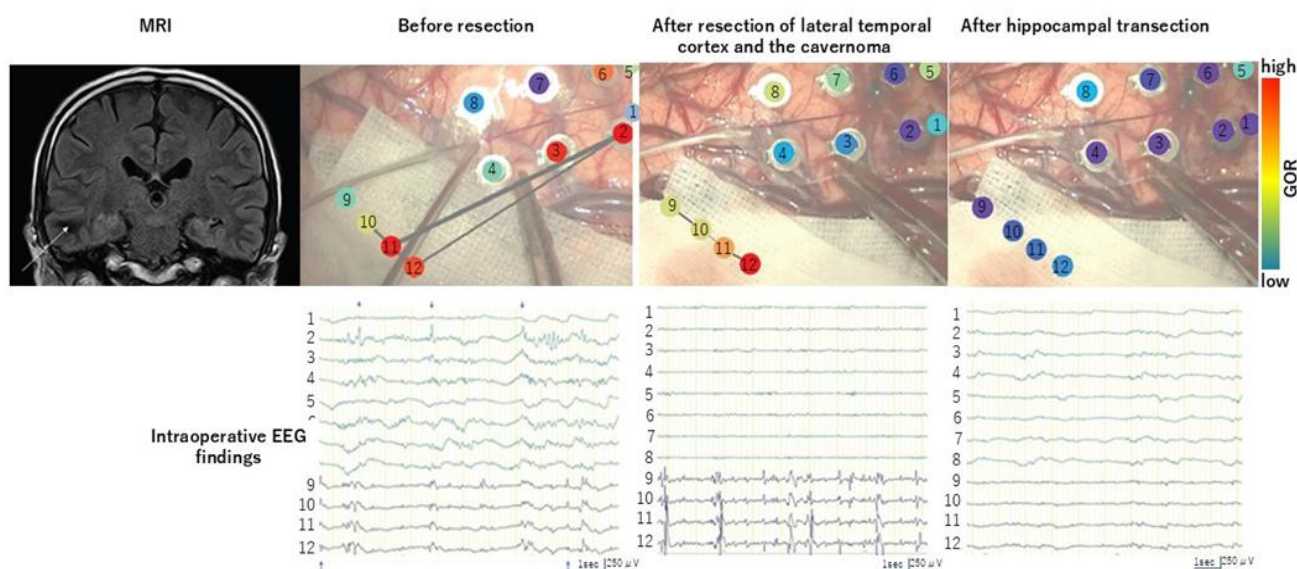


Figure 4 - Intraoperative application of GOR correlation analysis for visualization of ictal networks.

Upper panels: A patient with a lateral temporal cavernous malformation without hippocampal structural abnormality. Intraoperative GOR correlation mapping revealed elevated GOR in both the lateral temporal cortex and the hippocampus, demonstrating their linkage as an ictal network. After limited resection of the lateral temporal cortex and cavernoma, high GOR persisted in the hippocampus; subsequent hippocampal transection abolished the high-GOR signal and the patient became seizure free. Lower panels: Representative intraoperative electrocorticography. The top eight channels correspond to a 2×4 subdural grid over the lateral temporal cortex; the bottom four channels are a 1×4 subdural strip in the hippocampus. Prior to resection, synchronous spikes involving both lateral temporal cortex and hippocampus (downward arrows) and hippocampus-only spikes (upward arrows) are shown. After resection of the lateral temporal focus and cavernoma, lateral temporal spikes disappeared while hippocampal spikes persisted; these disappeared after additional hippocampal transection.

Adapted from Reference 10

7. Noninvasive GOR Analysis Using Scalp EEG

Accurate preoperative localization of the epileptogenic focus is essential to maximize the benefits of epilepsy surgery. We evaluated whether gamma band regularity (GOR) analysis can be applied noninvasively using high density scalp EEG to identify epileptogenic regions and to support presurgical decision making. We studied 21 patients with drug resistant focal epilepsy.

For each patient, GOR was computed from 20 second interictal epochs recorded with high density scalp EEG. GOR derived localization was compared with conventional presurgical localization methods and with postoperative seizure outcomes. In a separate analysis, five focal epilepsy patients were examined to assess GOR changes in scalp EEG before and after antiepileptic

drug (AED) administration. Finally, we applied scalp EEG GOR analysis to a case cohort originally diagnosed with alcohol related paroxysmal events to search for latent epileptogenic foci. High GOR regions were identified in all 21 patients and were included in the surgical resections; all 21 patients became seizure free after surgery. Concordance between high density scalp EEG GOR and spike source estimation was complete in 10 cases, partial in 8, and discordant in 3. Concordance with iomazenil SPECT was complete in 8 cases, partial in 11, and discordant in 2. In four MRI negative temporal lobe epilepsy cases, scalp GOR effectively identified focal lateralization and localization.¹¹⁾ In the AED response study (n = 5), focal high GOR regions that matched lesion location or clinical semiology were present before drug administration and disappeared in all patients after effective AED treatment, paralleling clinical improvement [12]. In cases initially labeled as alcohol related events, scalp GOR analysis revealed localized high GOR regions; subsequent introduction of AED therapy led to good seizure control [13]. GOR analysis applied to short epochs of high-density scalp

EEG reliably identifies candidate epileptogenic regions in a majority of cases and demonstrates strong agreement with established localization methods in many patients. The disappearance of high GOR regions after effective AED therapy suggests that scalp GOR can quantify pharmacologic response. Detection of latent high GOR foci in patients misclassified with alcohol related events indicates utility for uncovering occult epilepsy. Scalp EEG GOR analysis is a promising noninvasive, high throughput presurgical localization tool that can:

- Support lateralization and localization in MRI negative cases;
- Reduce the need for invasive intracranial monitoring in selected patients;
- Provide an objective measure of AED efficacy;
- Aid identification of occult epileptogenic foci in diagnostically ambiguous cases.

Incorporation of scalp GOR mapping into the presurgical workflow may improve patient selection, streamline evaluation, and contribute to Precision epilepsy surgery planning.

8. Conclusion

Advances in EEG analysis using GOR have enabled more precise localization of epileptogenic foci, laying an emerging foundation for precision epilepsy surgery driven by individualized care. As lesions become better visualized, surgical strategies must prioritize maximal preservation of surrounding normal cortex, which in turn demands higher levels of surgical skill and more advanced training programs for operators.

To convey lesion location and extent clearly to patients and multidisciplinary teams, intuitive three-dimensional visualization tools are required. To meet this need, we are developing a real time stereoscopic visualization pipeline that leverages artificial intelligence for monocular depth estimation and spatial reconstruction, enabling rich stereoscopic presentation from single view operative images (Figure 5) [14].

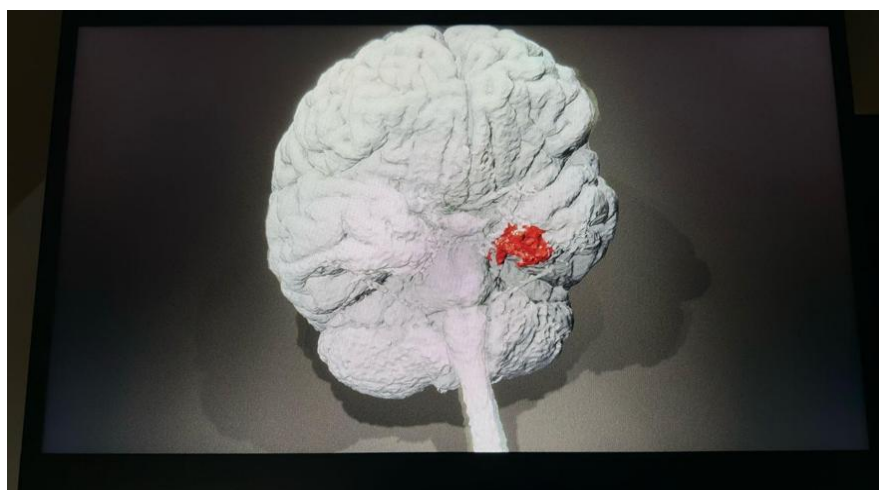


Figure 5 - AI assisted stereoscopic visualization technology.

A custom AI pipeline performs real time monocular depth estimation and spatial reconstruction to generate a stereoscopic view that conveys intuitive three-dimensional information of the cortical surface. The projected 3D brain surface shows the planned resection area in red

Broader clinical adoption will require algorithm generalization through multi center, multi case validation and a flexible analysis framework that accommodates diverse pathologies, age groups, and EEG recording conditions. Equally important is the design of adaptive, user centric interfaces that present information intuitively to surgeons, educators, and patients. Addressing these technical and operational challenges will involve closer collaboration with clinical teams and integrated hardware–software platform development. Through these efforts we aim to expand

clinical applicability and advance truly individualized precision epilepsy surgery.

Conflict of Interest. The author declares no conflicts of interest.

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Author contributions. Conceptualization – Y. S.; Methodology – Y. S.; Examination – Y. S.; Formal analysis – Y. S.; Writing (original draft preparation) – Y. S.; Writing (review and editing) – Y. S.

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Эпилепсияның сандық технологиялар қолданылған дәлдігі жоғары хирургиясы

[Yosuke Sato](#)

Ми қызметін талдау және сандық медицинаны зерттеу институтының директоры, Showa медициналық университеті; нейрохирургия бөлімшесінің профессоры, Showa медициналық университетінің ауруханасы, Токио, Жапония.

E-mail: yosukens@med.showa-u.ac.jp

Түйіндеме

Эпилепсияның ұстама кезіндегі көріністері гетерогенді, ал зақымдану ошақтары көп жағдайда әртүрлі бейнелеу әдістерімен де нашар көрінеді және дәл диагностикалауды қиындата түседі. Электроэнцефалографияны (ЭЭГ) қолдана отырып, электрофизиологиялық бағалау эпилептогендік ошақты анықтау үшін өте маңызды. Жиі қолданылатын маркерлерге преиктальды және иктальды ЭЭГ өзгерістері және интериктальды шыңдар жатады. Дегенмен, бұл маркерлердің шектеулері бар: оларды ұстамалар болмаған кезде бағалау мүмкін емес, олар қалыпты ми белсенділігін қамтуы мүмкін, ал кейбір ерекшеліктерді тек инвазивті бассүйекішілік электродтармен ғана байқауға болады. Соңғы жетістіктер ЭЭГ деректерін цифрландыруға мүмкіндік берді және математикалық және есептеу тәсілдерін қолдана отырып, көп қырлы түсіндіруді қамтамасыз етті. Біз ЭЭГ деректеріне қолданылатын сандық технологияларды қолдана отырып, зақымдануды мұқият бағалауға негізделген, эпилепсияның дәлділігі жоғары хирургиясын жүргізудің алғашқы бастамашысы болып табыламыз. Бұл мақалада аталмыш әдістерді әзірлеу және қолдану бойынша бүгінгі күнге дейінгі зерттеулер қарастырылады.

Түйін сөздер: сандық технология, ЭЭГ, эпилепсия, гамма-тербелістердің тұрақтылығы, нейрохирургия.

Высокоточная хирургия эпилепсии с использованием цифровых технологий

[Yosuke Sato](#)

Директор Института анализа функций головного мозга и исследований в области цифровой медицины, Медицинский университет Showa; профессор, отделение нейрохирургии, Больница Медицинского университета Showa, Токио, Япония.

E-mail: yosukens@med.showa-u.ac.jp

Резюме

Проявления эпилепсии при приступах гетерогенны, а очаги поражения часто плохо визуализируются даже при использовании различных методов визуализации, что затрудняет точную диагностику. Электрофизиологическая оценка с помощью электроэнцефалографии (ЭЭГ) необходима для локализации эпилептогенного очага. Обычно используемые маркеры включают преиктальные и иктальные изменения ЭЭГ и межиктальные спайки. Однако эти маркеры имеют ограничения: их невозможно оценить, когда приступы отсутствуют, они могут включать нормальную активность мозга, а некоторые особенности можно наблюдать только с помощью инвазивных внутричерепных электродов. Недавние достижения позволили оцифровать данные ЭЭГ и обеспечить многогранную интерпретацию с помощью математических и вычислительных подходов. Мы внедряем высокоточную хирургию эпилепсии, основанную на тщательной оценке очага, с использованием цифровых технологий, применяемых к данным ЭЭГ. В этой статье рассматриваются исследования на сегодняшний день по разработке и применению этих методов.

Ключевые слова: цифровые технологии, ЭЭГ, эпилепсия, регулярность гамма-колебаний, нейрохирургия.