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Magnetoencephalographic detection of synchronized epileptic activity between the hippocampus and insular cortex

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ABSTRACT

Most magnetoencephalographic signals are derived from synchronized activity in the brain surface cortex. By contrast, the contribution of synchronized activity in the deep brain to magnetoencephalography (MEG) has remained unclear. We compared stereotactic electroencephalography (sEEG) with simultaneous MEG findings in a patient with temporal lobe epilepsy to determine the conditions under which MEG could also detect sEEG findings. The synchrony and similarity of the waves were evaluated using visual inspection and wavelet coherence. A 45-year-old woman with intractable temporal lobe epilepsy underwent sEEG and MEG simultaneously to determine the laterality and precise location of the epileptic focus. When spike-and-waves were seen in the right hippocampal head alone, no distinct spike-and-waves were observed visually in the right temporal MEG. The seizure then spread to the right insula on sEEG with a rhythmic theta frequency while synchronous activity was observed in the right temporal MEG channels. When polyspikes appeared in the right hippocampus, the right temporal MEG showed electrical activity with relatively high similarity to that of the right hippocampal head and insular cortex but less similarity to that of the right lateral temporal lobe cortex. MEG might detect epileptic activity synchronized between the hippocampus and insular cortex.

1. Introduction

Magnetoencephalography (MEG) can detect whole-brain activity noninvasively with high sensitivity [1,2]. Subdural electrodes have revealed that most of the MEG signal is derived from synchronized activity in the brain surface cortex [3,4]. By contrast, researchers have continued to explore deep brain activity with MEG [5]. Several reports have detected magnetic activity generated in the deep brain with sophisticated signal processing [6–9]. Because these are indirect findings based on computational processing, direct sensing using depth electrodes under simultaneous MEG is warranted.

Stereotactic electroencephalography (sEEG) can potentially detect activity in the deep brain. Recent advancements in robotic technology have made sEEG less invasive and more accurate [10]. Furthermore, recent reports have shown a clinical correlation between sEEG and MEG [11,12]. Just as subdural electrodes have revealed that MEG detected synchronized activity in the surface cortex, sEEG may reveal that synchronized activity in the deep brain contributes to MEG.

In this case report, we compared sEEG with simultaneous MEG findings in a patient with temporal lobe epilepsy to determine the conditions under which MEG could also detect sEEG findings.

2. Methods

2.1. Patient

A 45-year-old woman with intractable epilepsy underwent sEEG and MEG simultaneously at the Hiroshima Epilepsy Center. At 39 years old, she started to experience visual hallucinations that were superimposed on her real vision. Her daily seizure was focal impaired awareness seizure, consisting of déjà vu, hallucinations, and brief confusion. She was medically refractory during the course of her seizures. EEG showed sharp waves in the bilateral anterior temporal regions. Bilateral mesial temporal lobes showed high intensity on fluid-attenuated inversion recovery magnetic resonance imaging (MRI). Her left and right hippocampi showed no difference in volume. MEG showed a bilateral

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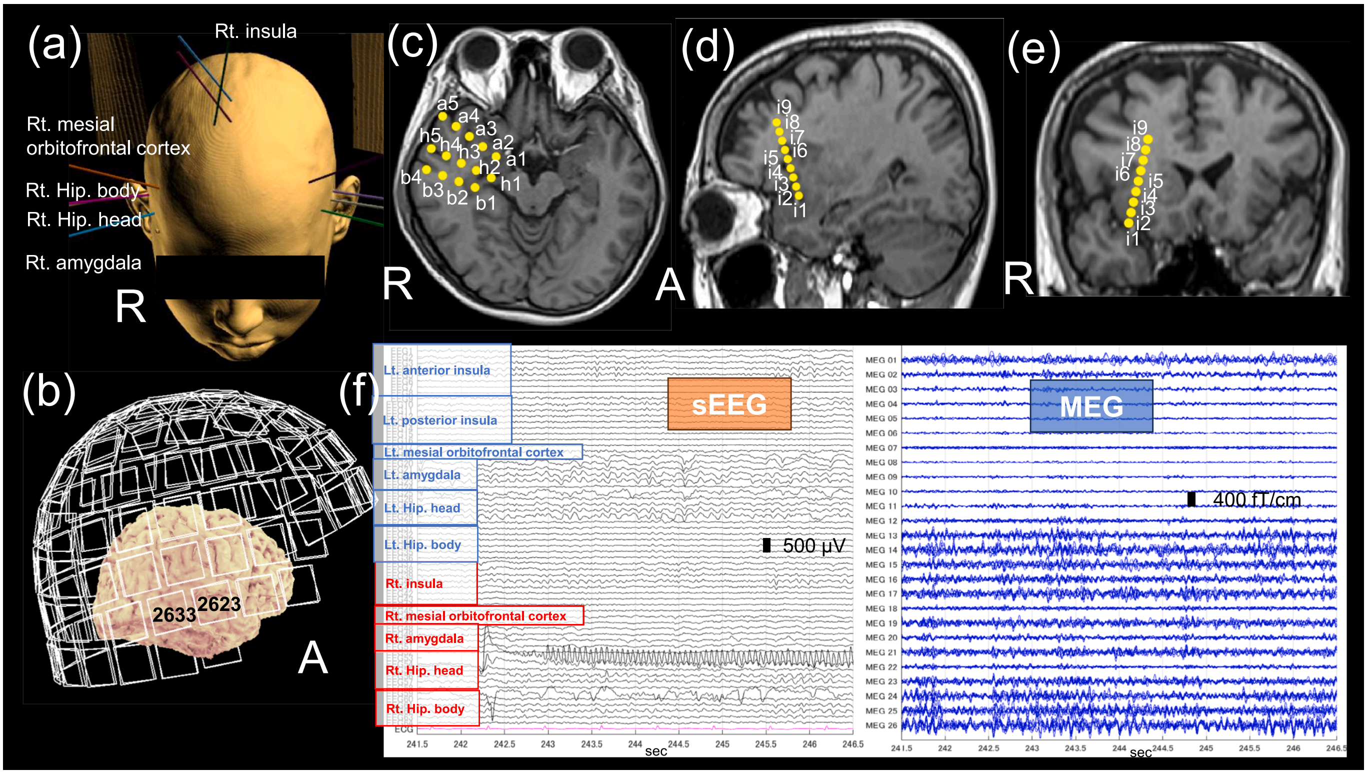

Fig. 1. Stereotactic electroencephalography (sEEG) electrodes and MEG sensors. (a) Left electrodes were placed in the anterior insula, posterior insula, mesial orbitofrontal cortex, amygdala, and hippocampal head and body. Right electrodes were placed in the insula, mesial orbitofrontal cortex, amygdala, and hippocampal head and body. (b) The positional relationship between the brain and the MEG sensor array. MEG2623 and MEG2633 sensors are just above the center of the right middle temporal gyrus. (c) The right amygdala, hippocampal head, and body electrodes are superimposed on an axial T1-weighted MRI. The sensing points are arranged in order from the tip as a1, a2, …, a5 for the amygdala; h1, h2, …, h5 for the hippocampal head; b1, b2, b3, b4 for the hippocampal body. The target points are a1, h1, and b1. The lateral temporal cortex points are a5, h5, and b4. (d, e) The right insular electrode is superimposed on sagittal and coronal T1-weighted MRI. The sensing points are arranged in order from the tip as i1, i2, …, i9. The right anterior insula includes i1 to i5. (f) Findings of all the channels of simultaneous MEG and sEEG around the onset of subclinical seizure (t = 241.5–246.5 s). Abbreviations: Hip., hippocampal; Lt., left; MEG, magnetoencephalography; MRI, magnetic resonance image; Rt., right; sEEG, stereotactic electroencephalography.

horizontal cluster in the anterior temporal lobes. Her neuropsychological test results were within normal limits. Bilateral mesial temporal lobes showed hypometabolism on positron emission tomography with fluorine-18 fluorodeoxyglucose and hypoperfusion on iodine-123 iomazenil single-photon emission computed tomography. Repeated scalp video-EEG captured seizures but failed to determine the seizure onset. Temporal lobe epilepsy was suspected, and she underwent sEEG to determine the laterality of the focal onset.

We performed sEEG using 11 depth electrodes (6 left-sided, 5 right-sided) comprising 96 channels under the support of a Rosa One Brain stereotactic robotic system (Zimmer Biomet). Left-sided electrodes were placed in the anterior insula, posterior insula, mesial orbitofrontal cortex, amygdala, and hippocampal head and body. Right-sided electrodes were placed in the insula, mesial orbitofrontal cortex, amygdala, and hippocampal head and body (Fig. 1). The insular electrodes were inserted vertically from the frontal region. She was admitted to our monitoring unit for a week after computed tomography (CT) to verify electrode placement. She maintained her daily medication of clonazepam and lacosamide during the study because epileptic discharges did not disappear. Seven electroclinical seizures, habitual for the patient, were captured, and all the ictal discharge originated from the right hippocampal head. On the last day, she underwent simultaneous sEEG and MEG. We excluded channels not related to the epileptic activity of the left anterior insula, posterior insula, and mesial orbitofrontal cortex, resulting in 64 sEEG channels. She underwent CT before electrode removal to check that the electrodes remained in the same position. She underwent CT again after electrode removal to check for bleeding. We discussed the comprehensive evaluation and concluded by consensus that right temporal lobectomy should be considered. She underwent a right anterior temporal lobectomy and currently has remained seizure free for 8 months.

2.2. Methods

We used a whole-head 306-channel MEG system, Triux Neo (Megin). The patient was instructed to rest on a bed with her eyes closed during measurement. Simultaneous MEG, sEEG, and electrocardiography were digitized at 1,000 Hz. The MEG system can record up to 64 sEEG channels simultaneously. We set a channel in the left frontal white matter as a reference channel. We obtained 3 sessions of 10 min recordings. To avoid motion noise derived from metallic connectors and sEEG electrodes, we fixed the connectors to the lateral edge of the sensor array. After MEG recordings, noise cancellation was performed with temporal signal–space separation on Maxfilter software (Megin). Recordings from magnetometer coils were not used for later analysis to avoid electrode-derived noise.

Recordings from planar gradiometers and sEEG electrodes were bandpass filtered at 0.5–50 Hz for visual inspection and single current dipole (ECD) estimation. The same digital filter was used to preserve and compare waveforms from sEEG and MEG. The brain was extracted from the head MRI and defined as a space where electric currents can exist to generate the magnetic field captured by the sensors. The positions of the electrodes were verified from the CT images and fusion with MRI. We used a MEG2623 sensor as the waveform control, just above the center of the right middle temporal gyrus (Fig. 1(b)). Then, we compared the control with the waveform of the right hippocampal head as a focus of

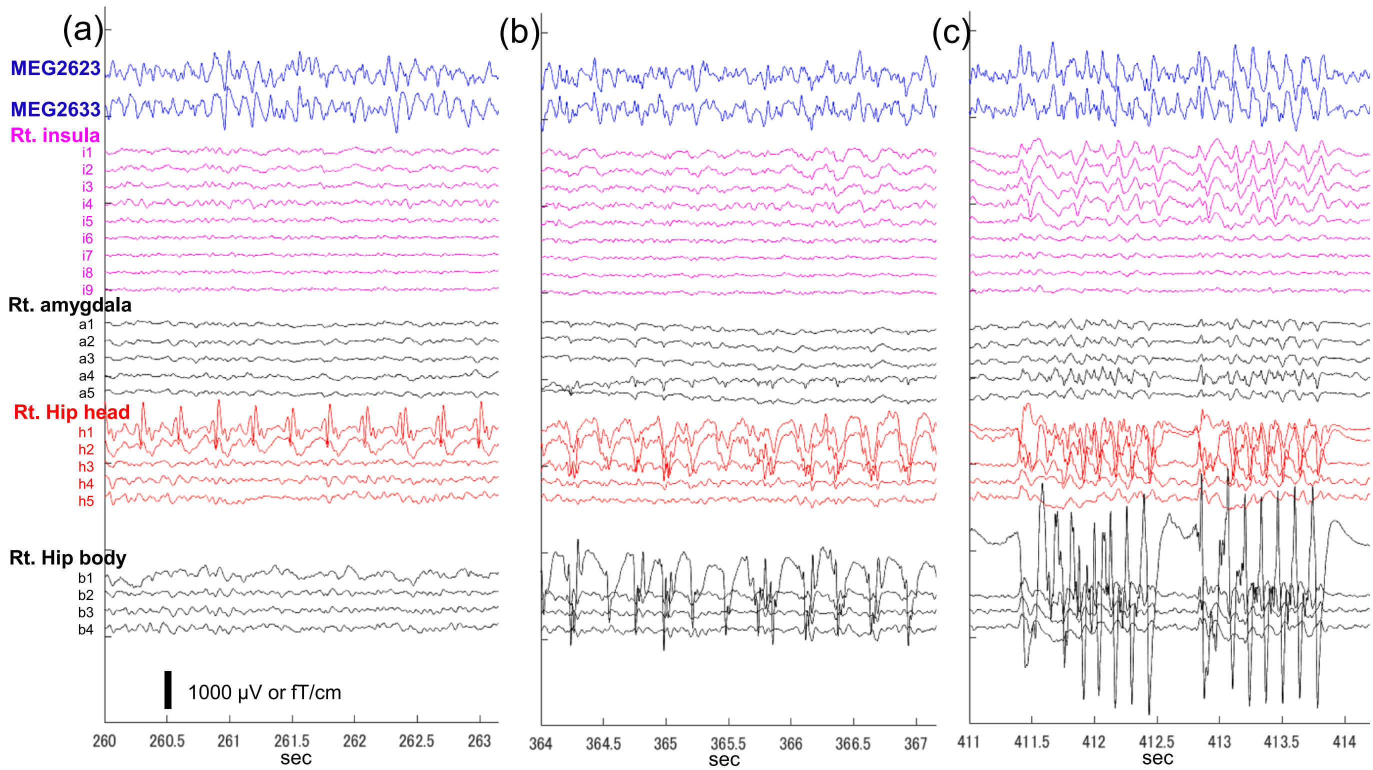

Fig. 2. Findings of simultaneous MEG and sEEG. See Fig. 1 for each sensing point. Recordings from planar gradiometers and sEEG electrodes digitized at 1,000 Hz were bandpass filtered at 0.5–50 Hz. (a) During the period when spike-and-waves continued in the hippocampal head alone (h1, t = 260–263 s). No distinct spike-and-waves were observed visually in the right insular cortex or other regions, including the lateral temporal lobe cortex on sEEG or the simultaneous temporal MEG. (b) During the period when spike-and-waves continued in the hippocampal head and body (h1 and b1, t = 364–367 s). The right insular cortex (i1–i5) gradually showed theta waves. (c) During the period when polyspikes appeared in the right hippocampus (h1 and b1, t = 411–414 s). The right insular cortex (i1–i5) and temporal MEG showed synchronized polyspikes visually, but the electrical waveforms in the right lateral temporal lobe cortex (a5, h5, and b4) and amygdala were somewhat unclear.

epileptic activity, lateral temporal cortex just below the MEG2623, and anterior insular cortex (Fig. 1(c)–(e)). Synchrony and similarity of the waves were evaluated subjectively by visual inspection and objectively by wavelet coherence, a measure of the correlation between the two signals. Magnitude-squared coherence was depicted as color maps, and the values > 0.8 were shown in yellow. We also calculated the mean and standard deviation of the magnitude-squared coherence of signals from 1.5 to 50 Hz. We estimated single current dipoles at the spike peak, which had a high signal-to-noise ratio, using all 204 planar gradiometers with MATLAB R2022b for signal and image processing and located the source using only the MEG data, adopting a single sphere model [13,14].

3. Results

During the simultaneous recording we observed a subclinical seizure originating from the right hippocampal head as did the habitual seizures. In the subclinical seizure, sEEG findings showed that after fast activity appeared in the right hippocampal head (Fig. 1(f)), continuous spike-and-waves were sustained in the right hippocampal head, and multiple spikes had spread to the right hippocampal body and right insular cortex (Fig. 2).

While spike-and-waves continued in the hippocampal head alone, no distinct spike-and-waves were observed visually in the right temporal MEG, insular cortex, or lateral temporal lobe cortex. The mean and standard deviation of the magnitude-squared coherence of signals from 1.5 to 50 Hz were 0.18 ± 0.15, 0.31 ± 0.23, and 0.20 ± 0.17 at i1, h5, and h1, respectively (Fig. 2(a), 3(a)). However, the right insular cortex gradually showed theta waves as ictal activity, and the right temporal MEG gradually showed high similarity to the electrical activity of the insular cortex, although the right lateral temporal lobe cortex did not show ictal activity. The mean and standard deviation of the magnitude-squared coherence of signals from 1.5 to 50 Hz were 0.39 ± 0.23, 0.19 ± 0.15, and 0.27 ± 0.19 at i1, h5, and h1, respectively (Fig. 2(b), 3(b)).

During the period when polyspikes appeared in the right hippocampal head and body, the right insular cortex and temporal MEG showed synchronized polyspikes visually, but the electrical waveforms in the right lateral temporal lobe cortex and amygdala were somewhat unclear. The electrical activity in the right temporal MEG showed relatively high similarity to that of the right hippocampus and insular cortex but less similarity to that of the right lateral temporal lobe cortex. The mean and standard deviation of the magnitude-squared coherence of signals from 1.5 to 50 Hz were 0.40 ± 0.25, 0.28 ± 0.21, and 0.42 ± 0.26 at i1, h5, and h1, respectively (Fig. 2(c) 3(c)). The 5 channels from the tip of the right insular electrodes showed synchronized waveforms. The equivalent current dipole was located in the insular cortex (Fig. 4).

4. Discussion

The possibility of detecting deep brain activity with MEG has long attracted the interest of investigators [5]. Although sEEG is not a whole-head examination, in our patient, it was reasonable to assume that the epileptic activity at onset was limited to the hippocampus due to the network of temporal lobe epilepsy. However, during periods of isolated right hippocampal epileptic activity, the right temporal MEG showed little similarity to the hippocampus. Synchronized activity over a sufficient area of the neocortex is required for simultaneous sEEG/MEG recordings [3,4,13,15–17]. Although the hippocampus and amygdala play pivotal roles in the epileptic network in temporal lobe epilepsy, microanatomical studies have shown that the hippocampus and amygdala have a closed field structure that does not easily generate a magnetic

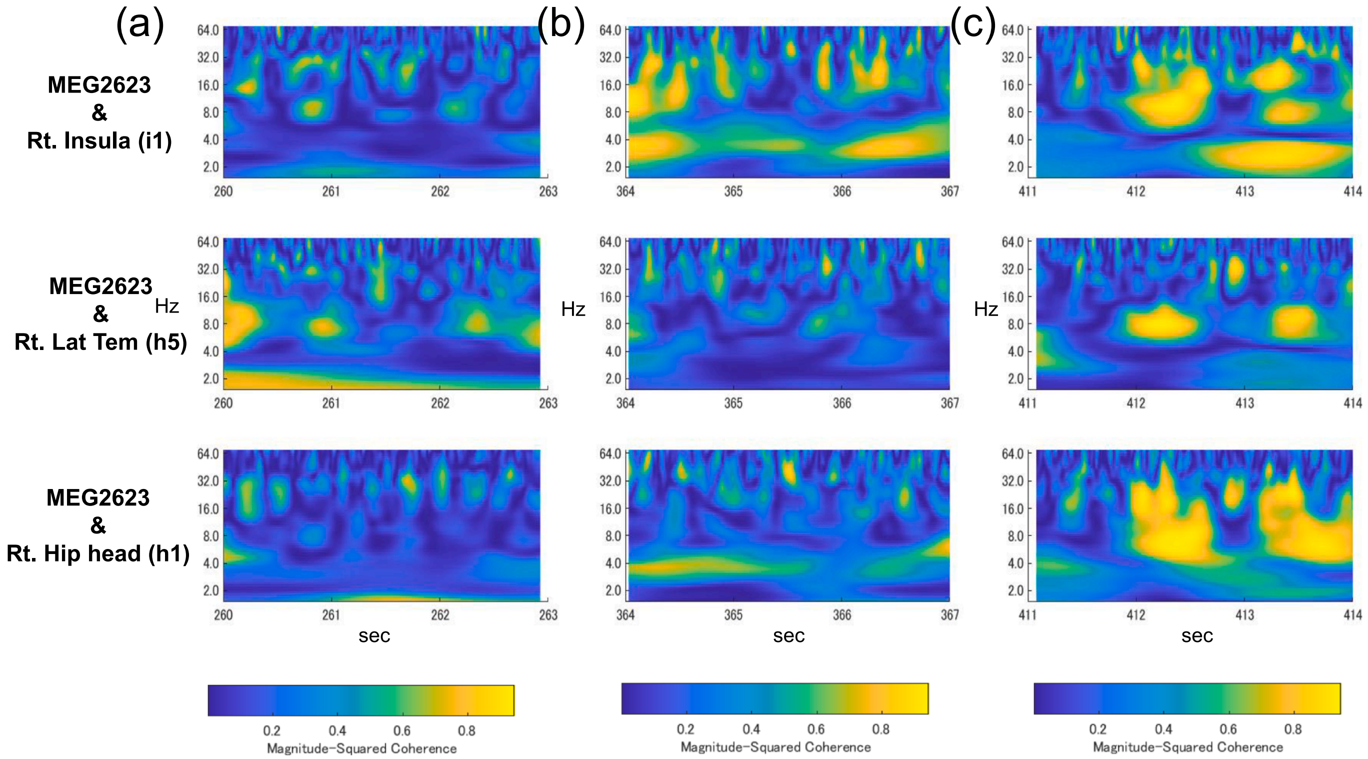

Fig. 3. Wavelet coherence between MEG2623 and sEEG (i1, h5, and h1) waveforms. See Fig. 1 for each sensing point. (a) During the period when spike-and-waves continued in the hippocampus head alone (t = 260–263 s). The right temporal MEG did not show clear similarity. (b) When spike-and-waves continued in the hippocampus and the right insular cortex, theta waves were gradually exhibited (t = 364–367 s). The right temporal MEG gradually showed high similarity to the electrical activity of the insular cortex. (c) When polyspikes appeared in the right hippocampus (t = 411–414 s), the right temporal MEG showed relatively high similarity to the electrical activity of the right hippocampal head and insular cortex but less similarity to the right lateral temporal cortex.

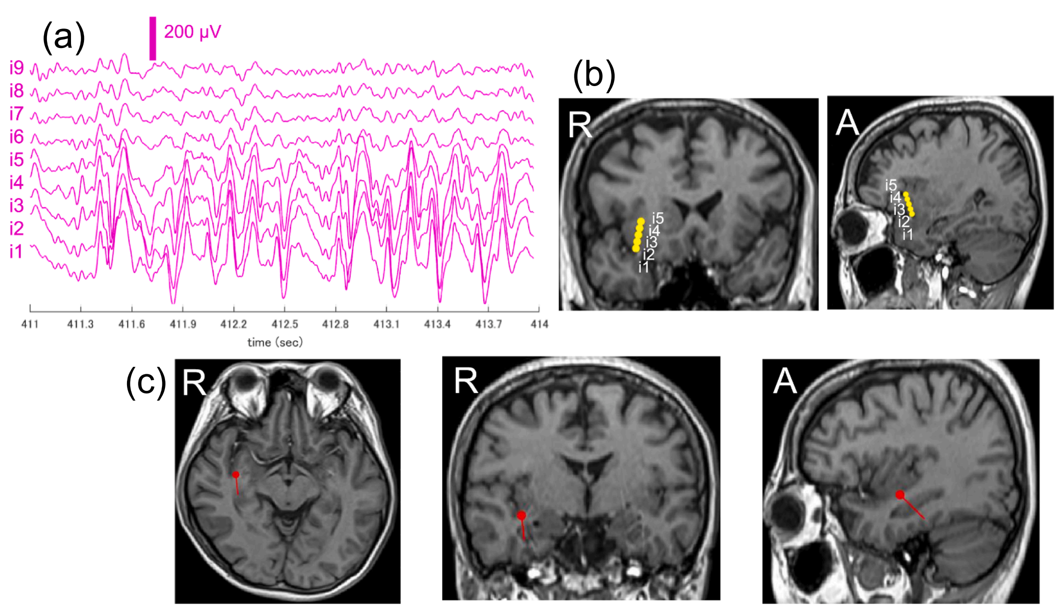

Fig. 4. The findings of the right insular electrodes and equivalent current dipole when polyspikes appeared in the right hippocampus (t = 411–414 s). (a) The 5 tips of the right insular electrodes showed synchronized waveforms. (b) The location of the 5 tips of the right insular electrodes. (c) The equivalent current dipole was located in the insular cortex (t = 413.234 s).

field [15–17]. Therefore, it is challenging to capture the activity of the hippocampus alone by MEG. Recent investigations tried to capture hippocampal activity with MEG using an independent component analysis, adaptive beamformer, and hippocampal sEEG-indexed averaging [6–9]. While such methodology has been reported, it remains unclear whether MEG can capture the activity of the hippocampus alone.

In the present patient, the right temporal MEG detected synchronous polyspikes in the hippocampus and insular cortex. Although the ECD model estimates in insular epilepsy have been reported as an insular pattern, few studies have determined insular epileptic activity by simultaneous MEG and sEEG [18]. Because the insular cortex exists deep in the brain, it needs to be activated widely and form an open field to be captured by MEG [13]. Channels from the tips of the insular electrode with intervals of 5 mm captured synchronous polyspikes and an ECD was located posterior to the electrode, suggesting widespread epileptic activity within the insular cortex. In addition, the insular cortex forms an open field due to the cortical structure that emits a detectable magnetic field [16,17]. Although a classical circuit does not include a direct pathway from the hippocampus to the insula, recent reports have described strong connectivity between the hippocampus and insular cortex [19,20]. MEG might detect epileptic activity synchronized between the hippocampus and insular cortex, which implied connectivity between the hippocampus and insular cortex in this case of temporal lobe epilepsy.

The present study includes a detailed review of simultaneous MEG and sEEG findings but has the limitation of being a case report. Although there are many analytical methods for MEG, this case report uses only a few of them and does not include high-frequency analysis. The positional accuracy of the electrodes depends on the computational performance of fusion because the positions were verified from the CT images and fusion with MRI. The accumulation of further cases is warranted.

CRediT authorship contribution statement

Akitake Okamura: Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Akira Hashizume:** Writing – review & editing, Validation, Supervision, Software, Methodology. **Kota Kagawa:** Writing – review & editing, Validation, Supervision, Investigation. **Go Seyama:** Writing – review & editing, Validation, Investigation, Data curation. **Atsuo Yoshino:** Writing – review & editing, Validation, Supervision, Investigation, Data curation. **Shigeto Yamawaki:** Writing – review & editing, Supervision, Project administration, Funding acquisition. **Nobutaka Horie:** Writing – review & editing, Validation, Supervision. **Koji Iida:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethics approval and consent to participate

The patient provided written consent for the procedures and publication of this research. This case study was approved by the Ethics Committee for Epidemiology of Hiroshima University, Japan (ethical approval E2020-1986-02).

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