The applications of time-frequency analyses to ictal magnetoencephalography in neocortical epilepsy

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Summary

Purpose: Ictal magenetoencephalographic (MEG) discharges convey significant information about ictal onset and propagation, but there is no established method for analyzing ictal MEG. This study sought to clarify the usefulness of time-frequency analyses using short-time Fourier transform (STFT) for ictal onset and propagation of ictal MEG activity in patients with neocortical epilepsy.

Methods: Four ictal MEG discharges in two patients with perirolandic epilepsy and one with frontal lobe epilepsy (FLE) were evaluated by time-frequency analyses using STFT. Prominent oscillation bands were collected manually and the magnitudes of those specific bands were superimposed on individual 3D-magnetic resonance images.

Results: STFT showed specific rhythmic activities from alpha to beta bands at the magnetological onset in all four ictal MEG records. Those activities were located at the vicinity of interictal spike sources, as estimated by the single dipole method (SDM), and two of the four ictal rhythmic activities promptly propagated to ipsilateral or bilateral cerebral cortices. The patients with FLE and perirolandic epilepsy underwent frontal lobectomy and resection of primary motor area respectively including the origin of

high-magnitude areas of a specific band indicated by STFT, and have been seizure free after the surgery.

Conclusions: STFT for ictal MEG discharges readily demonstrated the ictal onset and propagation. These data were important for decisions on surgical procedure and extent of resection. Ictal MEG analyses using STFT could provide a powerful tool for noninvasive evaluation of ictal onset zone.

1 Introduction

Precise localization of ictal onset and propagation in patients with symptomatic localization-related epilepsy (SLRE) is critical, especially in candidates for epilepsy surgery. Magnetoencephalography (MEG) is a new tool for assessing epileptic current that shows superior spatial and temporal resolution over the standard EEG (Hämäläinen et al., 1993). The single dipole method (SDM) is a useful way to monitor interictal MEG epileptiform activity (Stefen et al., 2003), although a method for analyzing MEG-measured ictal activity has not been established.

The ictal onset area was successfully demonstrated in cases with epilepsia partialis continua using a combination of jerk-locked back averaging and SDM with MEG (Shigeto et al., 1997; Oishi A et al., 2002). Tilz et al. also analyzed ictal MEG activities by SDM for epileptic patients that predominantly experienced mesial temporal lobe epilepsy (Tilz et al., 2002). This study determined the ictal onset area successfully in 6 out of 13 cases, while SDM was not available in the remaining patients. In another study of MEG analyses for ictal rhythmic activities in four cases with medial frontal lobe epilepsy (FLE), SDM was not applicable for two of these cases, while one case had no significant spike at

the onset zone in ictal MEG discharges, and the remaining patient showed no reliable spike sources by SDM (Shiraishi et al., 2001). The latter two cases were considered inapplicable for the SDM formula because the signals had already propagated broadly. Jongh et al. concluded that in patients with SLRE and brain tumor, interictal fast activities of 8-50 Hz did not localize to the tumor borders, and that SDM was not useful for analyzing fast waves in such cases (Jongh et al., 2003).

SDM is an established procedure for analyzing single or spatially and temporally limited activities such as interictal epileptiform activities; however, it has limitations for analyzing spatially propagated and temporally prolonged rhythmic magnetological activity including ictal data during the secondary generalization. Nevertheless, ictal activities contain valuable information (Tilz et al., 2002; Jongh et al., 2003), and a reliable confirmatory method for analyzing ictal MEG is needed.

Rhythmic ictal discharge of EEG in SLRE reflects the precise location of ictal onset (Westmoreland, 1998; Verma and Radtke, 2006). Furthermore, Guggisberg et al. recently reported that fast oscillations associated with interictal spikes in MEG detected by spike-locked frequency analysis successfully demonstrated the localized epileptogenic

zone (Guggisberg et al., 2008).

The present study analyzed the localization of ictal rhythmic activity onset and propagation using time-frequency analysis by short-time Fourier transform (STFT) in patients with neocortical epilepsy. The locations of specific-frequency bands were also correlated with conventional SDM results for interictal epileptiform spikes sources and with prognosis following surgical treatment.

2 Patients and Methods

2.1 Patients

Case 1: A 12-year-old girl with FLE. She had a past history of neonatal left-middle cerebral artery infarction. Seizures started at the age of 3 years presented as atonic seizure on the right side of her body, and postural seizure with right-limb extension. Her seizures occurred daily even with multiple antiepileptic drugs (AEDs). Brain MRI revealed an encephalomalacia at the left frontal and parietal lobes (Fig. 1A, left).

Case 2: A 14-year-old boy with perirolandic epilepsy. His seizures started at the age of 8 years, beginning with somatosensory auras (tingling in the right hand) and evolving into right hemiconvulsion with his face and eyes deviated to the right side. His seizures were precipitated by touch on the right side of his body and occurred daily even with multiple AEDs. Brain MRI demonstrated no abnormality. [18F]-fluorodeoxyglucose positron emission tomography (FDG-PET) showed glucose hypometabolism at the left postcentral gyrus (Fig. 2A).

Case 3: A 25-year-old woman with perirolandic epilepsy. Her seizures started at the age of 10 years, beginning with somatosensory auras in the left ear and evolving into complex partial seizures. The seizures were always precipitated by touch on the left side of her body and occurred daily in spite of multiple AEDs. She had no brain lesion on MRI or [18F]-FDG-PET.

In all cases, guardians gave written informed consent for this study.

2.2 MEG data analyses

MEG data were recorded using a 204-channel, helmet-shaped gradiometer (Vectorview system, Elekta-Neuromag Oy, Stockholm, Sweden) from patients in a supine position in a magnetically shielded room, and collected for about 40 minutes from each patient using a 600-Hz sampling rate. During the MEG recording, scalp EEGs were also recorded simultaneously using the international 10-20 system.

The segments containing ictal and interictal paroxysms were selected manually. The raw MEG data were filtered with band-pass filtering of 0.03-133 Hz for offline

analyses. We used SDM for localized interictal epileptiform activities and STFT for ictal rhythmic polyspike epileptiform discharges to determine the onset and propagation of the ictal discharges.

2.3 Single dipole method (SDM)

Dipole-fit software (Neuromag Oy, Helsinki, Finland) was used to calculate the equivalent current dipoles (ECDs). We defined acceptable ECDs by a goodness of fit (GOF) higher than 70%; this value measures how well the ECD model explains the measured signals. Acceptable ECDs were superimposed on the individual MRIs.

2.4 Short-time Fourier transform (STFT) analyses

STFT was used to show the distribution of MEG polyspikes (Oppenheim and Schafer, 1999) and the MATLAB (MathWorks, Natick, MA, USA) program was used to apply STFT to the MEG signals. Each signal was divided into defined sequential frames, and fast Fourier Transformation (FFT) was applied to each frame.

In the present study, STFT was implemented using a 256-point window. The time

of each window was 426.7 ms (i.e., 256 points × 1000 ms/600 Hz), and the window was shifted every four points, which corresponded to 6.7 ms (i.e., 1000 ms/600 Hz × 4 points). FFT applied to each window. This process was repeated for all selected signals. The time-frequency distributions are displayed graphically.

2.5 Selection of specific-frequency bands and projection to 3D-MRIs

The time-frequency distributions were analyzed up to 133 Hz and for 10 seconds until ictal motion artifact started. Specific-frequency bands that appeared continuously and were prominent from background activities were selected manually. Thus, the duration of graphs and selected bands varied.

The specific-frequency bands selected were then projected to individual 3D-MRIs. The power spectrum of these bands on 3D-MRI was located at the intersection of the line beneath the planer gradiometer coil and brain surface.

2.6 Electrocorticography (ECoG)

To define the epileptogenic focus, chronic subdural electrodes were implanted to

analyze the location of ictogenesis, according to the interictal and ictal scalp EEG and MEG results. Electrocorticography (ECoG) was conducted using Neurofax-1000 (Nihon-Kohden, Tokyo, Japan) amplifiers at a sampling rate of 1 kHz and time constant at 10 seconds with grid platinum/iridium electrodes (2.3-mm diameter, 10-mm inter-electrode spacing, Ad-Tech, Racine, WI). High frequent oscillation (HFO) was analyzed by ECoG, with 53 to 300 Hz band-pass filtering.

3 Results

Case 1

The interictal EEG showed left-frontal dominant polyspikes, polyspikes and wave complex. SDM analysis of the MEG showed clustered spike sources at the left frontal lobe in the vicinity of the encephalomalacia (Fig. 1B). Ictal EEG showed left-frontal slow waves followed by left-frontal dominant polyspikes (Fig. 1C, top).

Ictal MEG data with 4.0 seconds prior to ictal motion artifact analyzed by STFT (Fig. 1C, bottom) showed left-frontal dominant rhythmic magnetological activities of 7-12 Hz (Fig. 1D, 1E). These high-magnitude areas of activity were located at the left superior-frontal gyrus on 3D-MRI (Fig. 1F), which was consistent with the spike sources estimated by SDM (Fig. 1B). We also applied SDM to the ictal MEG data; however, ECDs were scattered broadly over the left frontal to occipital lobe regions and GOF was generally very low (< 50%). Based on the STFT results and other non-invasive examinations, we predicted the ictal onset zone location as anterior to the ischemic scar.

After noninvasive presurgical evaluation, the patient underwent long-term

intracranial EEG monitoring with subdural electrodes. Electrical stimulation in the vicinity of the left premotor area induced the patient's habitual seizure. The ictal ECoG were captured once and a low-amplitude HFO of 200-300 Hz was detected at the superior-frontal gyrus in pre-ictal period. She underwent frontal lobectomy including the high-magnitude areas of the ictal MEG (Fig. 1A, right). She has been seizure free for a year since surgery and has no mental or motor deficit.

Case 2

This patient showed left central and parietal spikes interictally by EEG. SDM analysis of the interictal MEG showed clustered spike sources at the left postcentral gyrus (Fig. 2B).

Ictal EEG demonstrated diffuse 10-Hz polyspikes bilaterally. Analysis of the ictal MEG data with 4.0 seconds duration prior to ictal motion artifact by STFT showed specific rhythmic activities of 10-15 Hz at the magnetological onset of the seizure. Those ictal activities originated from the left parietal and temporal lobes, and propagated to the bilateral parietal and temporal lobes (Fig. 2C). The ictal onset zone defined by ictal MEG

was in the vicinity of interictal spike sources estimated by SDM. This result was consistent also with the localization of glucose hypometabolism indicated by [18F]-FDG-PET (Fig. 2A). The SDM of this patient's ictal MEG located ECDs at the perirolandic area and deep white matter at the bilateral temporal and parietal lobes.

This patient underwent long-term intracranial EEG monitoring with subdural electrodes at the age of 15. Interictally, spikes were seen over the precentral and postcentral gyri, and ictal ECoG also revealed ictal onset zone at the precentral and postcentral gyri, corresponding to the ictal high-magnitude area of rhythmic activity assessed by STFT and spike sources estimated by SDM. His ictal ECoG was captured 10 times, showing a HFO of > 200 Hz intermittently at the supplementary motor area in the pre-ictal period that disappeared in the ictal period. The ECoG also detected the earliest activity in the primary motor area. We therefore proposed that the ictogenesis was located near the primary motor area, although ictal activity indicated bilateral propagation on MEG. Since the ictogenesis was supposed to be in the eloquent area in this case, the patient underwent only partial resection at the primary motor area. His seizures gradually decreased and disappeared completely within one year.

Case 3

Interictal EEG showed right central and parietal spikes. Interictal MEG showed clustered spike sources at the right postcentral gyrus by SDM (Fig. 3A). In the first seizure, the ictal EEG demonstrated bilateral frontal and central dominant 12-15-Hz polyspikes. In the second seizure, the ictal EEG showed right-frontal and temporal dominant 15-Hz polyspikes.

Ictal rhythmic activities were obtained from the first seizure of 4.0 seconds duration and the second one lasting 2.9 seconds, prior to the accumulation of ictal motion artifact. STFT showed specific rhythmic activities of 10-20 Hz at magnetological onset in the first seizure and 10-15 Hz in the second seizure. Rhythmic activities in the first seizure were generated from the right parietal and temporal lobes; they promptly propagated to the bilateral parietal and temporal lobes (Fig. 3B). Analysis of the same ictal data by SDM located ECDs in the deep white matter of the right parietal and occipital lobes, indicating no bilateral propagation. In the second seizure, rhythmic activity was also generated from right parietal and temporal lobes, however, propagation was limited to the ipsilateral

parietal and temporal lobes (Fig. 3C). Analyzed by SDM located these ECDs in the deep white matter of the right parietal and temporal lobes. Both in two ictal MEG, rhythmic activities originated in the vicinity of the interictal spike sources as estimated by SDM.

4 Discussion

4.1 Frequency analyses to ictal MEG

This study indicated that frequency analyses using STFT to ictal MEG provide information about ictogenesis (cases 1 and 2) and visualize dynamic changes in ictal activities (cases 2 and 3). Our method thus has practical applications for analyzing ictal rhythmic magnetological activity. Another advantage of the method was the lack of issue with the inverse problem, as different from SDM, meaning that rhythmic epileptiform activities could be evaluated directly without presupposition.

4.2 Limitations of SDM

Our study revealed two problems with SDM for analyzing ictal MEG. First, the ECDs had only low GOF value, with spike sources not generated from a localized area or the subjective spike having low signal to noise ratio. Second, most of the ECDs were estimated in the deep white matter, resulting in abnormal current being generated from a wide area simultaneously.

The localization of an ECD can be calculated only when a 3 cm^2 or wider area of

cerebral cortex is synchronously activated (Oishi M et al., 2002). The site of ECD could also be misleading if too wide an area is simultaneously activated, as in this study. Therefore, the activated areas of the cortex should be limited to obtain an acceptable ECD. SDM uses an inverse-problem formula based on the hypothesis that the spike is generated from a localized area; it is therefore not applicable for multiple spikes generated simultaneously or spikes originating from deep or very broad areas. Time-frequency analysis has the advantage of not needing to solve the inverse problem.

4.3 Rhythmic activities in MEG

Rhythmic activities indicate ictal onset zones on scalp EEG and electrocorticography (ECoG). However, scalp EEG has limited value in showing the precise location of ictal onset because the voltage declines via the cerebrospinal fluid and cranium. ECoG remains the gold standard for defining the location of seizure origin (Worrell et al., 2004), but it cannot be used for routine evaluation. In patients with focal cortical dysplasia, rhythmic epileptic discharges on EEG accorded well with the continuous epileptic discharges on ECoG (Gambardella, 1996). Dalal et al. also reported

good coherence of both beta band (12-30 Hz) and high gamma band (65-90 Hz) between MEG and ECoG by self-paced finger-movement tasks (Dalal et al., 2008). Their work indicated that MEG is equivalent to ECoG for evaluating epileptic rhythmic activities. The present study indicated that MEG analysis using STFT could provide valuable information on ictal onset zones. Using this method, the rhythmic activities successfully localized the origin of ictus and were colocalized with interictal discharges estimated by SDM. This finding emphasized the clinical value of routine interictal MEG analysis. In two patients (cases 1 and 2), the localization of rhythmic activities was concordant with the ECoG findings and surgical resection including the high-magnitude areas of the ictal MEG rendered the patient seizure free. This result may suggest the usefulness of STFT for deciding the area of surgical resection.

4.4 Visualization of ictal activity

Ictal STFT in two instances reported here (Case 2 and the first seizure of Case 3) showed that ictal rhythmic activities propagated promptly to contralateral homotopic areas, then went to and fro between the hemispheres, before finally spreading out broadly

throughout the brain. In other words, the propagation of ictal activities was well visualized by STFT analyses. Although ECoG analysis is regarded as the gold standard for precise evaluation of epileptic current, MEG analysis has an advantage over ECoG in analyzing changes in epileptic discharges over the entire cerebral cortices, noninvasively and repeatedly. Götz-Trabert et al. successfully evaluated the propagation of ictal activity in patients with mesial temporal lobe epilepsy and neocortical epilepsy using ECoG with success in depicting the propagation of ictal activity (Götz-Trabert et al., 2008). However, these authors also reported that intracranial EEG monitoring was limited in cerebral capacity and in investigating the invasion of contralateral hemispheres. The current results thus indicated another clinical value of MEG for ictal study.

4.5 High frequency oscillation (HFO)

In cases 1 and 2, although ictal ECoG showed over 200-Hz HFO, it was not feasible to detect over 30 Hz by SFT analyses of MEG in this study.

HFO were recently detected on ictal ECoG by Jirsch et al., with very good coincidence of a localized area of high-frequency band (250-500 Hz) in the ECoG and

ictal onset zone (Jirsch et al., 2006). This was an obvious limitation of MEG compared with ECoG, because spontaneous MEG recordings require synchronous activity among large assemblies of neurons and is therefore not able to detect very fine neurological activity (Pfurtscheller and Silva, 1999). However, improvements in distance between sensor and ictal activity onset zone or sensor density might reduce this limitation of MEG.

4.6 Conclusion

In conclusion, STFT is a new method for analyzing onset and propagation of ictal activities in whole brain. MEG is potentially as valuable as ECoG, and ictal MEG analyses using STFT could become a powerful tool for noninvasive evaluation of ictal onset zones, especially in candidates for surgical treatment of epilepsy.

Conflict of interest

The authors have no conflicts of interest.

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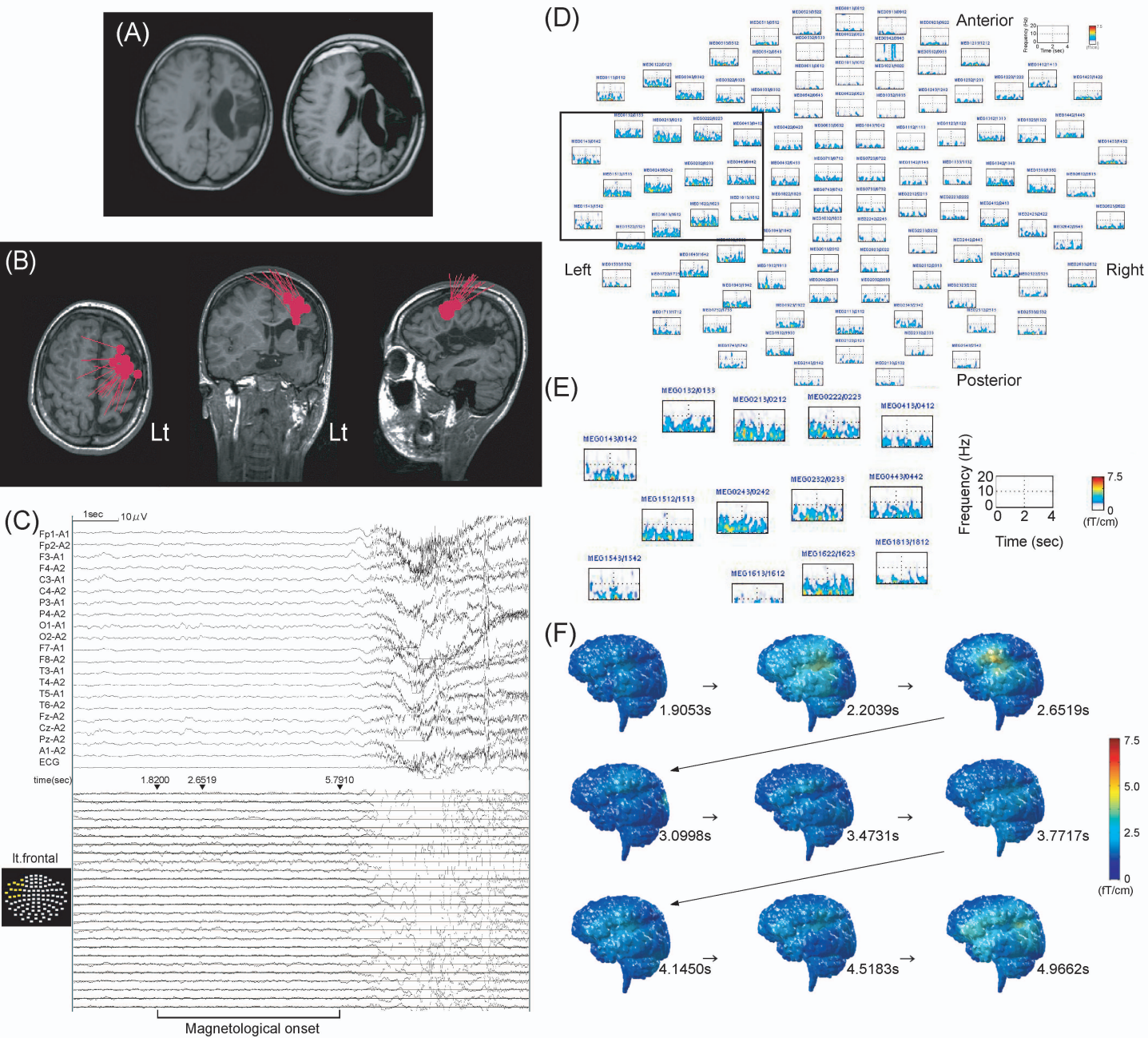
Figure Legends

Fig. 1. (A) Case 1 MRI: MRI before (left) and after (right) the operation showed encephalomalacia in the left hemisphere (left) and an operation scar in the left frontal lobe (right). **(B) Case 1 SDM:** Interictal spike sources were estimated to lie near the posterior lateral area of the left frontal lobe (red dot). **(C) Case 1 Ictal EEG and MEG:** representative ictal EEG (top) showing a left-frontal slow wave followed by left-frontal dominant polyspikes; MEG at the left frontal area (bottom) showing rhythmic discharges with a 7-20-Hz band oscillation (magnetological onset). **(D) Case 1 MEG/STFT:** Analysis of graph by STFT for magnetological onset duration of Fig. 1C (4.0 seconds), showing up to 12-Hz oscillations at the left frontal area. **(E) Case 1 MEG/STFT:** Representative STFT illustration of MEG channel at the left frontal area (corresponding to the boxed area of Fig. 1D) showing specific oscillations of up to 12 Hz (yellow and red areas). **(F) Case 1 3D-MRI overlay:** Sequential demonstration of specific-frequency band magnitudes projected on 3D-MRIs. Color bar indicates the magnitude of a specific-frequency band and numbers on the right lower part demonstrate the time scale corresponding to Fig. 1C.

Fig. 2. (A) Case 2 [18F]-FDG-PET: MRI (top) and [18F]-FDG-PET (bottom) showing hypometabolism of glucose consumption at the left post-central gyrus (arrow). **(B) Case 2 SDM:** Blue dot indicates somato-sensory-evoked field and red dots indicate spike sources estimated by SDM. Those spike sources were estimated in the left post-central gyrus. **(C) Case 2 3D-MRI overlay:** High-magnitude zone of 10-15 Hz oscillation was generated from the left parietal and temporal lobes and followed by propagation to the bilateral temporal and parietal lobes. Color mapping of 3D-MRI indicates the magnitudes of specific-frequency bands (10-15 Hz).

Fig. 3. (A) Case 3 SDM: Spike sources are clustered at the right post-central gyrus. **(B) Case 3 First seizure 3D-MRI overlay:** High-magnitude zone of 10-20 Hz oscillation projected to 3D-MRI. High-magnitude area starts at the right parietal and temporal lobes and promptly propagates to the bilateral temporal and parietal lobes. **(C) Case 3 Second seizure 3D-MRI overlay:** High-magnitude zone of 10-15 Hz oscillation generated from the right parietal and temporal lobes; these propagations were limited.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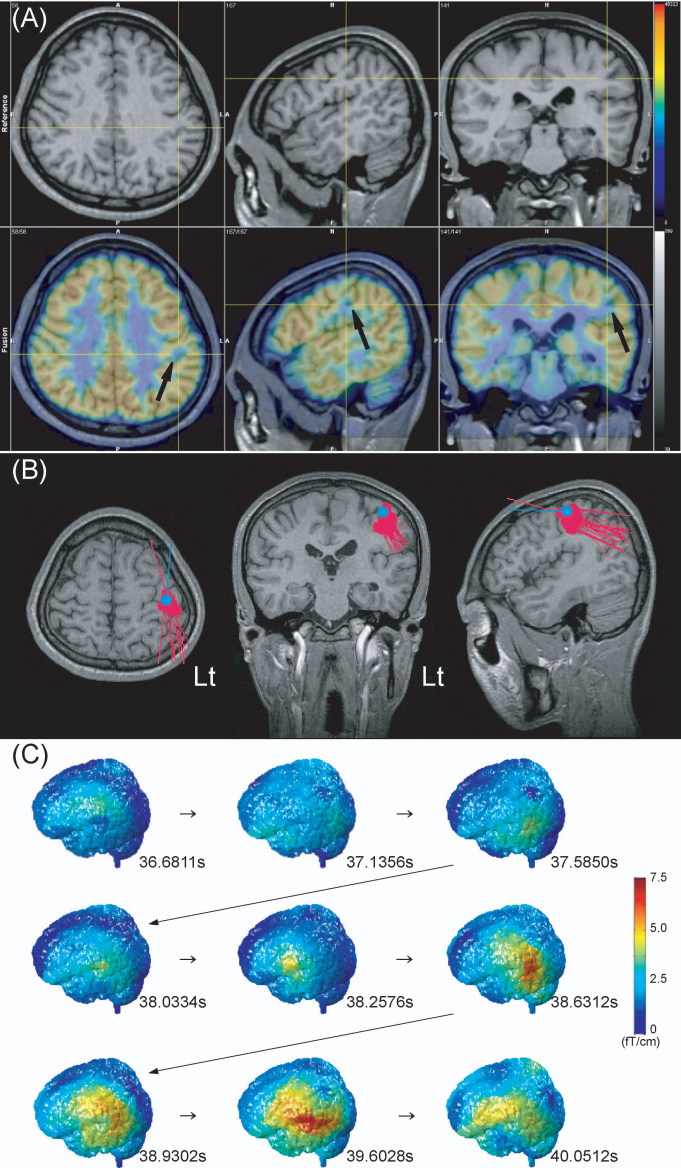
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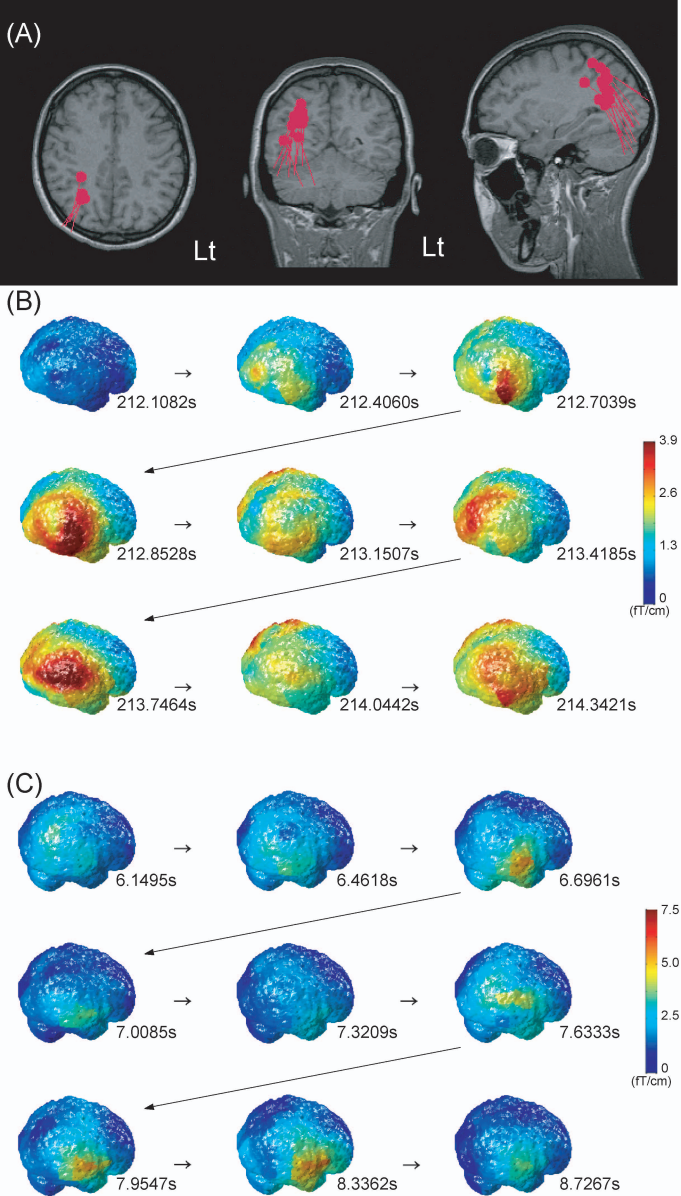
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