



# Localization of MEG pathologic gamma oscillations in adult epilepsy patients with focal cortical dysplasia<sup>☆</sup>



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## ABSTRACT

We aimed to evaluate the clinical value of gamma oscillations in MEG for intractable neocortical epilepsy patients with cortical dysplasia by comparing gamma and interictal spike events. A retrospective analysis of MEG recordings of 30 adult neocortical epilepsy patients was performed. Gamma (30–70 Hz) and interictal spike events were independently identified, their independent or concurrent presence determined, and their source localization rates compared. Of 30 patients, gamma activities were detected in 28 patients and interictal spikes in 24 patients. Gamma events alone appeared in 5 patients, interictal spikes alone in 1 patient, and no events in 1 patient. Gamma co-occurred with interictal spikes in  $20.1 \pm 22.1\%$  and interictal spikes co-occurred with gamma in  $15.0 \pm 19.2\%$ . Rates of event localization within the resection cavity were significantly different ( $p = 0.042$ ) between gamma ( $63.3 \pm 32.6\%$ ) and interictal spike ( $47.0 \pm 41.3\%$ ) events. In 4 of the 5 gamma-only patients the mean localization rate was 42.5%. Compared with the interictal spike localization rate, 4 of 9 seizure-free patients had higher gamma localization rates, 4 had the same rate, and 1 had a lower rate. Individual gamma events can be detected independently from interictal spike presence. Gamma can be localized to the resection cavity at least comparably to or more frequently than that from interictal spikes. Even when interictal spikes were undetected, gamma sources were localized to the resection cavity. Gamma oscillations may be a useful indicator of epileptogenic focus.

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## 1. Introduction

For over a decade, there has been interest in fast oscillations (>30 Hz) exhibited by the epileptic brain. Recent studies have suggested that fast oscillations may be a good indicator of the seizure onset zone (SOZ) and may be related to the outcome of epilepsy surgery (Andrade-Valencia et al., 2012; Blanco et al., 2011; Brazdil et al., 2010; Haegelen et al., 2013; Jacobs et al., 2008, 2009, 2010; Park et al., 2012; Urrestarazu et al., 2007; Worrell and Gotman, 2011; Zijlmans et al., 2009, 2012). For

clinical application, noninvasive recording modalities such as scalp-EEG and MEG are advantageous to invasive intracranial recording methods due to their relative safety and freedom from selection bias. Furthermore, MEG is more advantageous than scalp-EEG when used to localize sources because a much simpler forward model is acceptable. Moreover, gamma activity in MEG is less susceptible than EEG to contamination from muscle activity (Claus et al., 2012; Zimmermann and Scharein, 2004).

Since previous MEG studies employed interictal spike occurrence timing to detect fast oscillations, it has been difficult to evaluate the clinical value of fast oscillations as a diagnostic measure that can be used independently from the measurement of interictal spikes (Guggisberg et al., 2008; Mohamed et al., 2007). Although some previous studies have detected MEG gamma oscillations without the aid of interictal spike occurrence timing, one study used high gamma oscillations detected in intracranial EEG as a ‘trigger’ event for MEG (Rampp et al., 2010), while another study used sums of divided time segment spectrograms of 2 min MEG recordings (Xiang et al., 2009). Neither of those studies directly compared interictal spike and gamma oscillations.

Postoperative seizure outcome of neocortical epilepsy associated with focal cortical dysplasia (FCD) is poorer than that of epilepsy associated with hippocampal sclerosis or tumor (Chung et al., 2005; Jeong et al., 2012). To improve surgical outcome, epileptogenic focus localization

**Abbreviations:** FCD, focal cortical dysplasia; SOZ, seizure onset zone; ECD, equivalent current dipole; RSN, resting state network.

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that uses data on gamma oscillations in MEG may be feasible. This study evaluated the clinical value of gamma oscillations (30–70 Hz) in MEG for intractable neocortical epilepsy patients with cortical dysplasia by comparing independently detected and localized gamma and interictal spike events.

## 2. Material and methods

### 2.1. Subjects

Initially included in this retrospective study were 64 patients with intractable epilepsy and histologically proven FCD who underwent MEG examination and surgical resection between 2005 and 2011 at Seoul National University Hospital. Of that total, 16 patients with pathology CD type III (by definition associated with other pathologies), 7 patients aged <19 years at surgery, 3 patients without postoperative MRI, 4 patients who underwent more than two surgeries, and 1 patient with no follow-up history were excluded. Also excluded were three patients who had seizures during MEG. As a result, 30 adult neocortical epilepsy patients (mean age at surgery = 29.6 years; SD = 7.78; 15 females) were included in the study. The mean postoperative follow-up period was 4.6 years (SD = 1.8 years; range, 1.0–7.3 years). [Table 1](#) presents a summary of the patients' profiles. All patients provided informed consent. This study was approved by the institutional review board of Seoul National University Hospital (IRB No. H-0607-029-178).

### 2.2. Magnetic resonance imaging

All patients were examined before and after surgery by using either a GE 1.5 or 3 T MRI unit (GE Horizon Echospeed) or a Siemens 1.5 T scanner (Siemens Avanto System, Erlangen, Germany). The images were reconstructed offline and transferred to a UNIX workstation (HP C3750) for registration with MEG source images.

### 2.3. MEG recording

Magnetic and EEG activities were simultaneously recorded using a 306 channel, whole-head MEG system (VectorView™, Elekta Neuromag Oy, Helsinki, Finland). Spontaneous MEG/EEG signals were acquired in a magnetically shielded room for approximately 60 min while patients were supine and with eyes closed. The sampling rate was 600 Hz with an analog filter of 0.1–200 Hz. A bipolar electro-oculogram and an electrocardiogram were simultaneously recorded in order to monitor eye movement and cardiac artifacts. The procedure for co-registration of MRI and MEG data has been previously reported ([Jeong et al., 2012](#)). Ten minutes of artifact-free data for use in gamma and interictal spike analyses was selected from within 60 min of recorded data by visually inspecting simultaneously recorded MEG–EEG raw signals.

### 2.4. Interictal spike

MEG interictal spikes were visually inspected and localized by using the single equivalent current dipole (ECD) method in Neuromag software (Elekta Neuromag, Helsinki, Finland). The ECDs were estimated by performing a least-squares search in a spherical volume conductor model and by using subsets of 20–50 channels surrounding the maximum signals. Only ECD with a goodness-of-fit value >85% and a confidence volume <3 mm<sup>3</sup> were accepted. The accepted ECDs were superimposed on patients' individual postoperative MR images ([Fig. 1](#)).

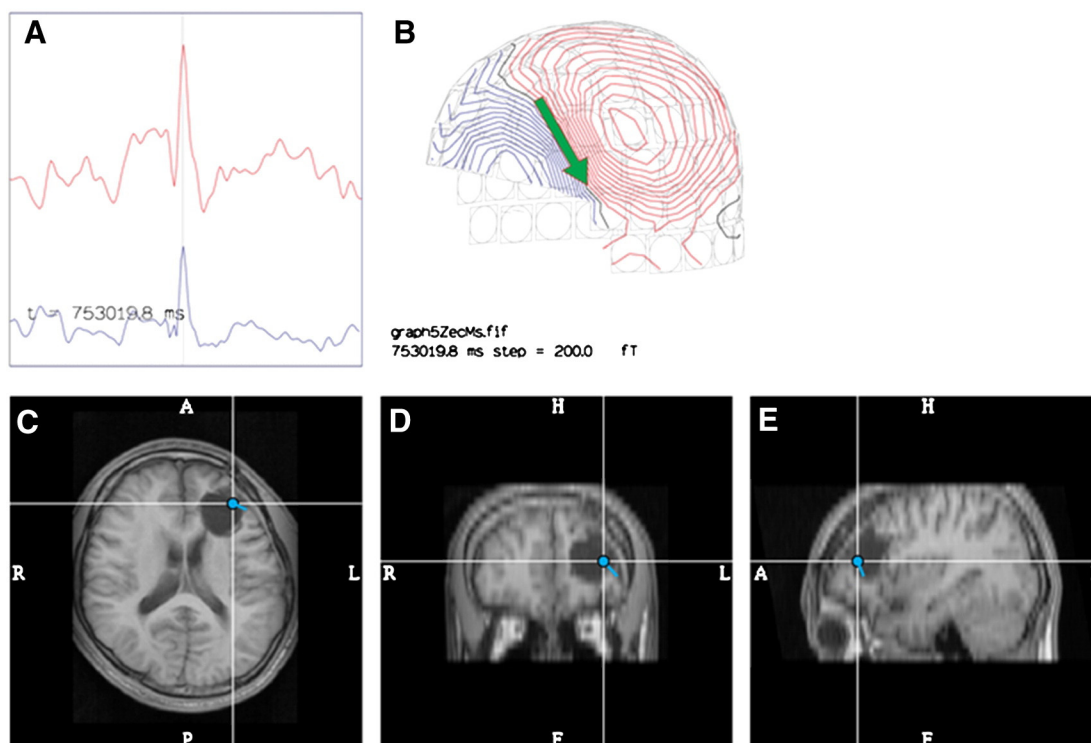
### 2.5. Gamma oscillation

Being to qualify as a gamma oscillations required a root-mean-square amplitude increase of more than five times the SD (compared to baseline activity) and the presence of more than six peaks that were greater than 3 SD above the mean baseline activity level ([Staba et al., 2002](#)). Ten minutes of data was used as the baseline activity level. A 30–70 Hz bandpass filter and a 60 Hz notch filter were applied before gamma detection and source localization. For comparison to

**Table 1**  
Patients' characteristics.

#	Age at surgery	Sex	Resection lobe	MRI findings	Pathology	ILAE outcome
1	19	F	Rt T	Rt hippocampus, atrophy with hyper SI	FCD IA	1
2	20	M	Lt F	Lt F lobe, focal cortical atrophy and cortical tissue loss	FCD IA	1
3	21	F	Rt T	Rt T lobe, cyst like lesion	FCD IA	1
4	26	F	Lt T	WNL	FCD IA	1
5	27	F	Rt T	WNL	FCD IA	1
6	36	M	Rt T	Rt T lobe, mild increased cortical thickness and hyper SI	FCD IA	1
7	26	F	Lt T	WNL	FCD IB	1
8	22	M	Rt T	Rt hippocampus, atrophy with hyper SI	FCD IIA	1
9	28	F	Lt F	Lt frontal cortex, focal cortical thickening	FCD IIB	1
10	30	F	Rt F	Rt F gyrus and white matter, focal hyper SI	FCD IIB	1
11	39	M	Rt T	WNL	FCD IA	2
12	22	M	Lt T	WNL	FCD IA	3
13	28	M	Lt T	WNL	FCD IA	3
14	43	F	Rt T	WNL	FCD IA	3
15	19	F	Rt T	WNL	FCD IIB	3
16	26	M	Lt F	Lt F gyrus, focal cortical thickening with subtle hyper SI	FCD IIB	3
17	24	F	Rt T	WNL	FCD IA	4
18	29	F	Lt T	Lt hippocampus, mild hyper SI	FCD IA	4
19	29	M	Rt F	WNL	FCD IA	4
20	30	F	Rt T	WNL	FCD IA	4
21	32	F	Rt F	WNL	FCD IA	4
22	33	M	Rt F	Rt F subcortical white matter and indistinct gray–white matter junction, focal subtle hyper SI	FCD IA	4
23	34	F	Lt F	WNL	FCD IA	4
24	39	M	Lt T	Lt hippocampus, atrophic change	FCD IA	4
25	41	M	Rt F	WNL	FCD IA	4
26	44	M	Rt O	WNL	FCD IA	4
27	47	M	Rt T	WNL	FCD IA	4
28	25	M	Lt F	Lt F lobe, focal decreased SI and	FCD IIB	4
29	22	M	Rt F	Rt parasylvian area, focal cortical thickening with subcortical hyper SI	FCD IA	5
30	26	F	Lt TP	WNL	FCD IA	6

Rt: right, Lt: left, F: frontal, T: temporal, P: parietal, O: occipital, WNL: within normal limit, SI: signal intensity, FCD: focal cortical dysplasia.



**Fig. 1.** Example of interictal spike source localization. (A) Time course of gradiometer signals (red) and power magnitude in 40 channels surrounding the maximum signals (blue). (B) Topographical map of the magnetic fields corresponding to (A). (C–E) ECDs (blue) superimposed on postoperative MR images, (C) axial view, (D) coronal view, and (E) sagittal view. R: right, L: left, H: head, F: foot, A: anterior, P: posterior. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

the baseline activity, the SD of the bandpass-filtered signal at each channel during the baseline period was computed. A 200 ms detecting window with a 50 ms overlap was sequentially moved along the MEG signals to detect gamma oscillations. If PGOs were consecutively detected, the segment showing the highest SD was selected from the consecutive segments. To image the detected gamma in a 200 ms time window at a bandpass of 30–70 Hz, a continuous wavelet transform was performed in all MEG channels (Morlet, 1983). A complex Morlet wavelet function with a wavelet width of 7 was used. The real and imaginary parts of the wavelet transform at the source space were computed separately by applying the sLORETA algorithm. Subsequently, the power spectrum was reconstructed in the source space by combining the real and imaginary parts in the source space. The mean power of the time window and the frequency band in the source space were also estimated. Details on the source–space power spectrum analysis have been previously reported (Kim and Chung, 2008). Finally, source images were overlain on individual postoperative MR images. To select only strong gamma in the brain, gamma activities over 80% maximum of source amplitudes in the whole brain were displayed.

## 2.6. Artifact rejection

After cessation of recording, a temporal signal space separation method was applied in order to reduce environmental and biological noise (Taulu and Hari, 2009); a preprocessing procedure was recommended for artifact removal for data recorded with the Elekta-MEG system (Hillebrand et al., 2013). To reduce the risk of confusing an artifact with a gamma, we adopted the artifact rejection procedure used in a previous scalp-EEG study (Andrade-Valenca et al., 2011). Oscillations with irregular morphology, very high amplitude compared to the background, or with great variation in amplitude and frequency during the oscillation period were considered artifacts. We also regarded oscillations involving more than 25 MEG channels simultaneously as artifacts.

Subsequently, the original MEG and simultaneously recorded EEG data were reviewed and artifacts were excluded from the record to be analyzed. We are confident that, by using this approach, the oscillations used in the analysis are of cerebral origin.

## 2.7. Surgery

Surgical procedures have been described in a previous report (Chung et al., 2005). We evaluated surgical outcome after a follow-up period of at least 1 year. Surgical outcome was classified according to the ILAE outcome classification (Wieser et al., 2001). Pathology was reviewed in all patients who underwent resection. All patients had FCD, which was classified according to Blumcke's criteria (Blumcke et al., 2011). Type of FCD, surgical outcome, and other clinical information are presented in Table 1.

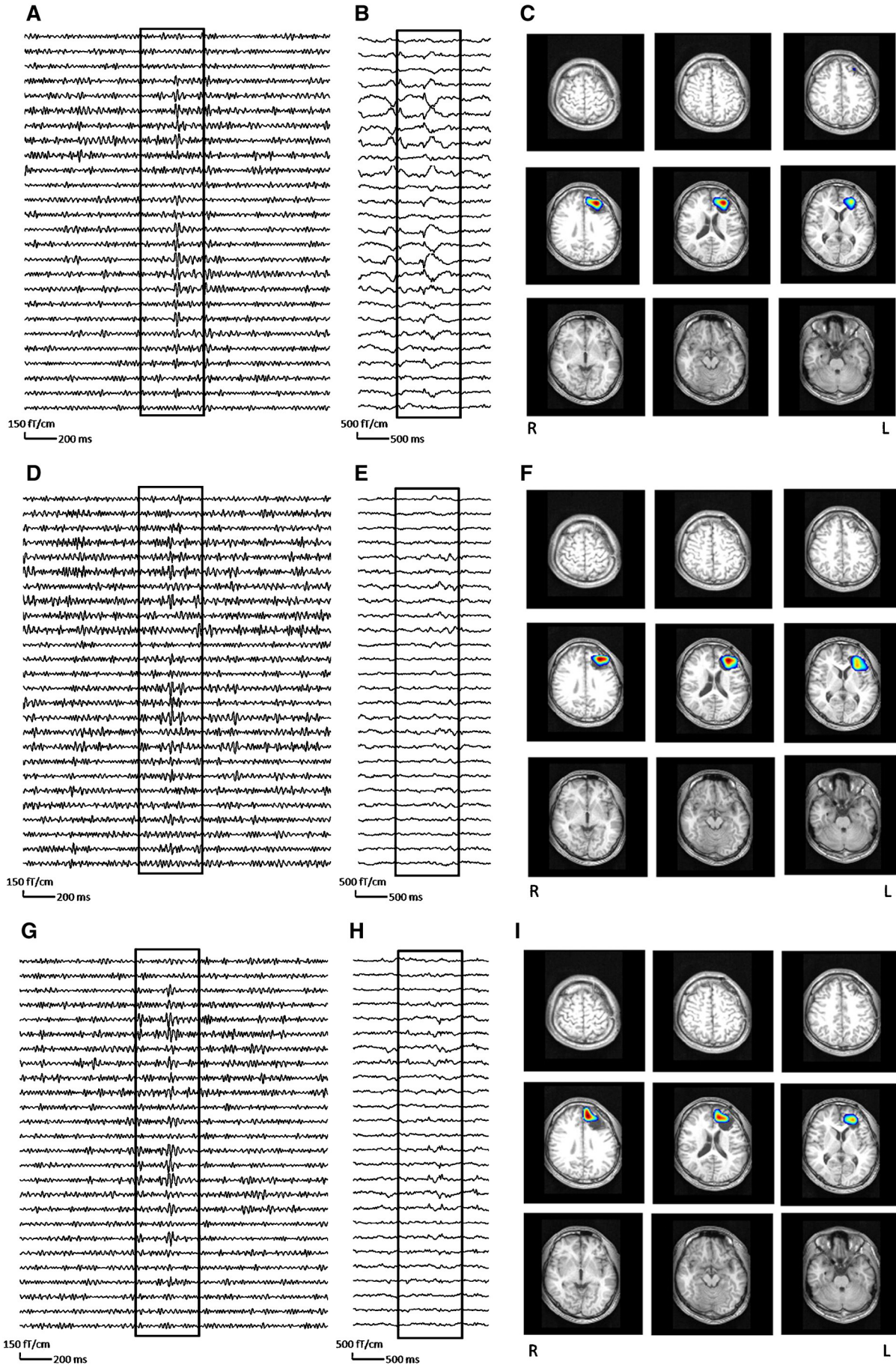
## 2.8. Statistical analysis

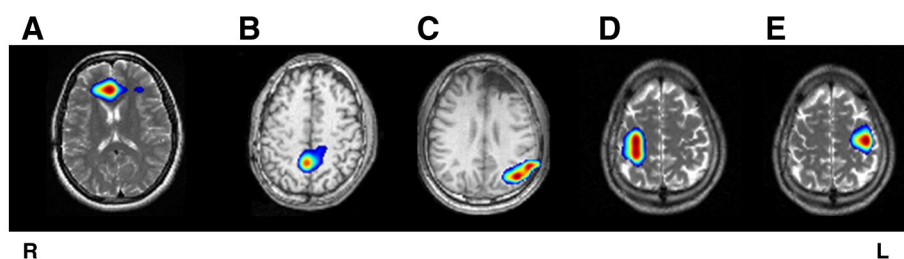
We analyzed gamma and interictal spike event rates, their co-occurrences, and their rates of localization within the resection cavity. All analyses were performed by using SPSS 19.0 software (IBM, Armonk, NY, USA). We applied the Shapiro–Wilk test to determine the type of distribution of the variables. Since the variables had a normal distribution, we used the parametric Student's paired *t*-test and the independent two-sample *t*-test. A value of  $p < 0.05$  was considered statistically significant. Data are presented as mean  $\pm$  SD.

## 3. Results

### 3.1. Frequency of gamma and interictal spikes

In 10 min recordings, the number of events per patient was  $21.9 \pm 29.7$  (range = 0–155) for gamma and  $16.9 \pm 27.7$  (range = 0–92) for interictal spikes ( $p = 0.352$ ). Of the 30 patients, gamma activities were





**Fig. 3.** Source localization of gamma in resting state network regions. (A) Medial prefrontal cortex; (B) posterior cingulate cortex; (C) superior parietal cortex, left; (D) sensory–motor cortex, right; and (E) sensory–motor cortex, left. R: right, L: left.

detected in 28 patients and interictal spikes were detected in 24 patients. Five patients had gamma-only, 1 patient had interictal spikes-only, and neither event type was detected in 1 patient. In the 23 patients exhibiting both gamma and interictal spikes, gamma co-occurred with interictal spikes in  $20.1 \pm 22.1\%$  and interictal spikes co-occurred with gamma in  $15.0 \pm 19.2\%$ . Fig. 2 shows representative examples of gamma oscillations co-occurring with spikes and independently of spikes, respectively.

### 3.2. Event localization within the resection cavity

The event localization rate within the resection cavity was expressed as a percentage [(events localized to the resection cavity / total events)  $\times$  100]. The gamma and interictal spike localization rates were  $41.2 \pm 30.7\%$  and  $43.7 \pm 41.7\%$ , respectively ( $p = 0.811$ ). Of the 629 gamma events, 235 were localized in resting state network (RSN) regions such as the medial prefrontal cortex, posterior cingulate cortex, cerebellum, sensory–motor cortex, and superior parietal areas (Fig. 3) (Raichle et al., 2001). Of the 508 interictal spike events, 57 were localized to RSN regions. The gamma and interictal spike localization rates to the RSN were  $36.8 \pm 25.9\%$  and  $9.4 \pm 19.3\%$ , respectively ( $p = 0.000$ ). The localization rate increased to  $58.1 \pm 32.8\%$  and  $45.1 \pm 41.5\%$  for the gamma and interictal spikes, respectively, when activities in the RSN areas were excluded. No statistically significant differences were found between gamma and interictal spikes ( $p = 0.213$ ). Differences in event localization rates were assessed among the 23 patients who exhibited both gamma and interictal spike events. In those 23 patients, gamma ( $63.3 \pm 32.6\%$ ) and interictal spike ( $47.0 \pm 41.3\%$ ) localization rates were significantly different ( $p = 0.042$ , paired-sample  $t$ -test). Furthermore, in 4 of the 5 patients who exhibited gamma-only, the localization rate, after exclusion of gamma activities in RSN regions, was 42.5%.

### 3.3. Surgical outcome

Surgical outcome was ILAE class 1 in 10 patients, class 2 in 1, class 3 in 5, class 4 in 12, class 5 in 1, and class 6 in 1 patient. Table 1 presents a summary of the patients' profiles. We compared the localization rates of gamma and interictal spikes in relation to surgical outcome. For the pathologic gamma oscillations, no statistically significant differences were detected between favorable ( $n = 15$ ; ILAE 1–3;  $57.3 \pm 34.0\%$ ) and unfavorable ( $n = 13$ ; ILAE 4–6;  $58.9 \pm 32.6\%$ ) surgical outcome groups ( $p = 0.899$ ). In addition, no statistically significant difference in interictal spike localization rates was detected between favorable ( $n = 15$ ,  $55.6 \pm 49.5\%$ ) and unfavorable ( $n = 13$ ,  $36.1 \pm 32.6\%$ ) surgical outcome groups ( $p = 0.258$ ).

Localization rates for gamma and interictal spike events were also compared in the 10 seizure-free patients. Neither gamma nor interictal spikes were detected in 1 patient whereas 3 patients only exhibited gamma events. The gamma source localization rates of those 3 patients were 50%, 20%, and 0%. Of the 6 patients who exhibited both event types, higher gamma localization than interictal spike localization rates were observed in 2 patients (50% vs. 0% and 59% vs. 22%). Three of those 6 patients had the same gamma and interictal spike localization rates (100%, 100%, and 0%), and 1 patient had a better interictal spike localization rate than gamma localization rate (100% vs. 73%). In short, among the 9 seizure-free patients who had either gamma or interictal spike events or exhibited both events, 4 had better event localization rate in gamma and 4 had the same event localization rate, and 1 showed better event localization rate in interictal spike.

## 4. Discussion

Recently, researchers have attempted to elucidate the role of gamma band oscillations in epilepsy by using noninvasive modalities. Early noninvasive studies used scalp-EEG to demonstrate the feasibility of gamma oscillation detection and its relation to SOZ (Andrade-Valencia et al., 2011; Willoughby et al., 2003; Wu et al., 2008; Yamazaki et al., 2009). Although those previous scalp-EEG studies demonstrated a relationship between gamma oscillation and SOZ, they only assessed the relationship at the channel level. In general, fast oscillation decreases according to the power law; thus, gamma activity may undergo subtle change. Both MEG and EEG signals are picked up outside the scalp, and each such sensor measures mixed signals coming from the entire brain. To clarify signal sources in such a mixture, source–space analysis may be advantageous, particularly when detecting subtle changes in gamma activities. Moreover, source–space analysis can identify the location of the gamma source, thus allowing comparison of gamma source and surgical resection area. In the study of the source localization, MEG has advantages over scalp-EEG since MEG has sufficient signal-to-noise ratio and requires a much simpler forward model than EEG.

A previous MEG-based study reported that sources of beta and gamma oscillations of interictal spikes were concordant with ECDs of interictal spikes and with SOZ delineated from intracranial EEG (Mohamed et al., 2007). Moreover, those sources were localized to the epileptogenic zone, which corresponded to the surgically resected areas in patients with good surgical outcomes (Guggisberg et al., 2008). Other previous MEG studies also showed that source localization of fast frequency components, including gamma band, was concordant with the epileptic focus (Rampp et al., 2010; Xiang et al., 2009). Those studies demonstrate that gamma oscillations detected in MEG recordings can be correlated to SOZ and surgical outcome. However, because none of the previous MEG studies on gamma oscillations compared interictal spikes

**Fig. 2.** Examples of gamma oscillations co-occurring with and without interictal spikes in MEG. Graph shows 26 channels near the left frontal area. (A, D, G) Gamma filtered from 30 to 70 Hz. (B) Interictal spike filtered from 0.1 to 40 Hz co-occurs with PGO. (C, F, I) Source maps of (A, D, G) signals, respectively. (E) No prominent interictal spike filtered from 0.1 to 40 Hz. (H) Spike-like activity filtered from 0.1 to 40 Hz co-occurs with gamma. R: right, L: left.

and gamma oscillations separately, and without the aid of another electrophysiological modality such as intracranial EEG, it has been difficult to evaluate the value of gamma oscillations in MEG as an independent diagnostic measure. In the present study, we detected gamma activity independently in MEG. In our study, by performing bandpass filtering of the raw data, gamma activities were detected in 28 of 30 patients without the aid of interictal spike timing and without the use of other assessment modalities.

In this study, we compared event rates and co-occurrence of gamma events with interictal spike events. The number of detected gamma events in 10 min ( $21.9 \pm 29.7$ ) was not significantly different from that of interictal spikes ( $16.9 \pm 27.7$ ). Andrade-Valenca et al. reported an interictal spike rate of  $1.93 \pm 2.08/\text{min}$  and a gamma event rate of  $0.65 \pm 1.03/\text{min}$  in scalp-EEG (Andrade-Valenca et al., 2011), a rate lower than that reported in this study. This difference might be due to fast oscillation sensitivity differences between MEG and scalp-EEG modalities.

With regard to temporal overlap of events, gamma events co-occurred with interictal spikes in 20% of interictal spikes and interictal spikes co-occurred with gamma oscillations in 15% of gamma events. Andrade-Valenca et al. reported that gamma co-occurred with spikes in 77.5% of their spike events, and spikes co-occurred with gamma in 14.5% of gamma events (Andrade-Valenca et al., 2011). Although the percentage of spikes that co-occurred with gamma events is similar to that in our study, Andrade-Valenca et al. reported a much higher percentage of spikes co-occurring with gamma events. Although gamma events frequently co-occurred with spike-like activity in the present study (Fig. 2), many of those spike-like activities had low amplitude, low goodness of fit, and high confidence volume, thus not meeting the conventional spike-detection criteria we used in this study. Hence, the present study did not include these activities as they were not deemed significant.

Most importantly among the results in this study, we observed that gamma oscillation in MEG does occur independently from interictal spike activity, thus suggesting that the use of gamma oscillation events as an independent diagnostic measure is feasible, even though its application would be limited to areas outside the RSN.

We also compared source locations of gamma events and interictal spikes with the location of the resection cavity. As far as we can determine, in MEG, detection and localization of interictal gamma activity independently from the observation of interictal spikes have not been reported previously. In our study, the mean gamma event ( $41.2 \pm 30.7\%$ ) and interictal spike ( $43.7 \pm 41.7\%$ ) localization rates to the resection cavity were not significantly different. Of 629 gamma events detected in this study, 235 were localized in previously well-known RSN regions including the sensory-motor network and the default mode network, which reflects a resting state brain function (Raichle et al., 2001). Although RSN regions have mostly been studied by using functional MRI, recent efforts have been made to reveal RSN characteristics by direct electrophysiological brain activity by using MEG (Brookes et al., 2011; de Pasquale et al., 2010, 2012). Since the inclusion of RSN in high-frequency domain studies is just emerging, more studies are required to determine RSN characteristics at frequencies  $>0.1$  Hz. The possibility of finding similar RSN topographies in functional MRI and MEG suggests the need for studies focusing on gamma band RSN.

It seemed prudent to determine whether gamma activities detected in the present study were pathological or physiological. Previous studies on epileptic fast oscillation activities consistently reported that pathological oscillations overlap with physiological oscillations (Zijlmans et al., 2012), and that reliance on spectral frequency alone is insufficient for separating normal from pathologic oscillations (Bragin et al., 2010). Although several characteristics, such as cellular mechanisms, specific regional and laminar distributions, as well as their shape, focal or scattered distribution, and other properties, may differ between physiological and epileptic gamma activities, and possibly may help to discriminate these two in experimental settings, at present it is not clinically

possible to differentiate physiological from pathological gamma activity (Bartos et al., 2007; Jacobs et al., 2012). Clinically there is only one circumstantial difference between these two activities; that is, fast oscillations are much more frequently observed inside the SOZ than outside of it (Jacobs et al., 2012).

In the present study, we observed that gamma sources were localized predominately in SOZ and RSN regions. We speculate that sources in the SOZ may reflect the pathological properties of gamma activity whereas sources in the RSN may reflect physiological properties of gamma activity. Supportive indirect evidence is that gamma activities co-occurred with interictal spikes, which may imply pathological properties of gamma events, and were localized to the SOZ 92% of the time in the present study. When it comes to physiological gamma oscillations, providing similarly obvious evidence is more difficult. As mentioned above, the role of RSN in gamma band activity has not been fully elucidated. Although not yet reported, because gamma activity is a result of a sequence of synchronous inhibitory and excitatory postsynaptic potentials (Bartos et al., 2007), there might be a relationship between RSN and gamma band.

When gamma events appearing in RSN-related areas, which we regarded as physiological gamma, were excluded, the gamma localization rate increased to  $58.1 \pm 32.8\%$  from  $41.2 \pm 30.7\%$ . To compare differences between gamma and interictal spike localization rates at the individual patient level, we analyzed data from 23 patients who exhibited both gamma and interictal spike events. A larger percentage of gamma ( $63.3 \pm 32.6\%$ ) than interictal spike ( $45.6 \pm 41.6\%$ ) events were localized within the resection cavity ( $p = 0.029$ ). Furthermore, in 4 of 5 patients who only exhibited gamma events (excluding gamma events localized to RSN areas), the mean localization rate was 42.5%. Therefore, even in the absence of interictal spikes, gamma sources were localized within the resection cavity.

With regard to surgical outcome, we found no difference in localization rates between gamma and interictal spike events. It is well known that surgical outcome of FCD patients is affected by various factors, such as the types of FCD, MRI visible abnormality, and lobar distribution (Kim et al., 2009; Rowland et al., 2012). The failure to detect differences in seizure outcome according to gamma or interictal spike source localizations in the present study may be due to our small sample size, which was too small to permit analysis of the various predictors of surgical outcome.

Among the 10 seizure-free patients, one did not exhibit gamma or interictal spike activity. Among the remainder, there was a better localization rate in the gamma event results than in those of interictal spikes: four of the nine patients had better localization through the use of gamma, four had the same localization rate from both event types, and one had a better localization rate in the interictal spike data. Interestingly, in one patient whose interictal spikes had a better localization rate than that of the gamma events, the gamma event localization rate was high (73%). Although further investigation is required, our results suggest that diagnostic usage of MEG gamma oscillation events in epilepsy surgery is feasible.

In this study, we only included neocortical epilepsy patients with FCD, which was pathologically verified. FCD is a common pathology in neocortical epilepsy patients whose surgical outcome is relatively unfavorable. There are few reports on fast oscillations ( $>30$  Hz) in epilepsy patients with FCD. An EEG study on an epilepsy patient group with FCD, mesial temporal atrophy, and nodular heterotopias reported that high-frequency oscillation (80–500 Hz) rates were associated with SOZ, regardless of the underlying pathology; however, only one FCD patient was included in that analysis (Jacobs et al., 2009). More recently, stereo EEG recordings of four epilepsy patients with FCD type IIA were analyzed, and their ripple (80–200 Hz) event rate was higher within the SOZ than outside of it (Brazdil et al., 2010). In our 30 FCD patients, gamma activities were detected and highly localized to the resection cavity. To the best of our knowledge, this is the first study of fast oscillations that included a reasonably large number of epilepsy patients with

FCD. In accord with previous studies, our results suggest that fast oscillation activity can be used to delineate the epileptogenic focus in FCD patients.

In this study, we showed that gamma oscillation detection and localization can be used as an independent diagnostic method to delineate the epileptogenic area of the brain. To provide additional support for this assertion, further studies are needed to assess whether the gamma-determined area is clinically significant in terms of surgical outcome. For example, there should be a difference in results of resections of gamma-determined areas between favorable and unfavorable surgical outcome groups. Such confirmatory studies would help elucidate the role of gamma events in epilepsy surgery. Since resection of the entire irritative zone is not necessary to achieve a seizure free outcome, it would also be interesting to investigate whether gamma oscillation represents the ictal onset zone or the irritative zone. This could be possibly achieved by assessing average distances from the locations of gamma sources to the resection cavity.

In addition, systematic characterization of gamma oscillations in normal human brain for comparison with those in the epileptic brain is not possible when using invasive recording methods. Future studies of normal human brain with MEG could contribute to elucidating the pathological and physiological aspects of gamma oscillations. This further investigation may be particularly helpful to epilepsy patients who have their epileptogenic focus in RSN regions.

Nevertheless, in this study we have demonstrated the feasibility of using gamma oscillations, recorded by using MEG modality, in neocortical epilepsy patient surgery. Individual gamma events in the 30–70 Hz range can be detected independently, without concomitant interictal spike activity, and can be localized to the resection cavity at a rate that is comparable to, or more frequent than, that of interictal spikes. In addition, in cases in which interictal spikes were not detected, gamma activities were correctly localized to the resection cavity. Therefore, we suggest that gamma oscillation events in MEG can be an important indicator of an epileptogenic focus.

### Conflict of interest

The authors declare no conflict of interest.

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