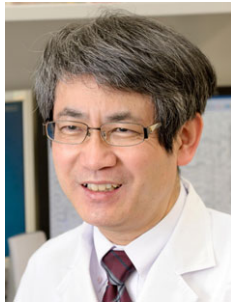


Complex observation of scalp fast (40–150 Hz) oscillations in West syndrome and related disorders with structural brain pathology

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SUMMARY

We investigated the relationship between the scalp distribution of fast (40–150 Hz) oscillations (FOs) and epileptogenic lesions in West syndrome (WS) and related disorders. Subjects were 9 pediatric patients with surgically confirmed structural epileptogenic pathology (age at initial electroencephalogram [EEG] recording: mean 7.1 months, range 1–22 months). The diagnosis was WS in 7 patients, Ohtahara syndrome in 1, and a transitional state from Ohtahara syndrome to WS in the other. In the scalp EEG data of these patients, we conservatively detected FOs, and then examined the distribution of FOs. In five patients, the scalp distribution of FOs was consistent and concordant with the lateralization of cerebral pathology. In another patient, FOs were consistently dominant over the healthy cerebral hemisphere, and the EEG was relatively low in amplitude over the pathological atrophic hemisphere. In the remaining 3 patients, the dominance of FOs was inconsistent and, in 2 of these patients, the epileptogenic hemisphere was reduced in volume, which may result from atrophy or hypoplasia. The correspondence between the scalp distribution of FOs and the epileptogenic lesion should be studied, taking the type of lesion into account. The factors affecting scalp FOs remain to be elucidated.

KEY WORDS: Fast oscillations, Infantile spasms, Cortical dysplasia, Hemimegalencephaly.

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We reported the stormy generation of fast oscillations (FOs) in the scalp electroencephalogram (EEG) data of West syndrome.^{1,2} West syndrome is a representative type of infantile epileptic encephalopathy that has a grave developmental prognosis, involving both interictal hypsarrhythmia and the ictal activity of epileptic spasms. It was previously reported that cortical high-frequency oscillations (HFOs) are observed in association with spasms corresponding to scalp FOs.^{3,4} HFOs include ripples (80–200/250 Hz) and fast ripples (200/250–500/600 Hz), and FOs include gamma (40–80 Hz) and ripple oscillations. Scalp FOs have been suggested to be a potential biomarker of epileptogenicity and the epileptogenic cortical region in several

studies.^{5–15} Hence, we initially hypothesized correspondence between the scalp distribution of FOs and epileptogenic lesions in West syndrome. The observation of FOs over the scalp may, however, be influenced by various factors, including the low skull conductance and probable blurring of electrical activity conducted from the cortex through the skull to the scalp, so it is not straightforward.

We attempted to preliminarily investigate whether our above hypothesis holds despite many possible confounding factors and to elucidate the factors that affect the observation of scalp FOs generated in association with structural brain pathology using clinical data from surgically treated patients with West syndrome and related epileptic disorders.

METHODS

Subjects

The subjects in this study were 9 infants with West syndrome and related disorders (5 boys, 4 girls; West syndrome in 7 [Patients 1–7], Ohtahara syndrome in 1 [Patient 8], and a transitional state from Ohtahara syndrome to West syndrome in 1 [Patient 9]), who were treated at Okayama University Hospital between January 2008 and August 2016 (Table 1). Age at initial EEG recording ranged from 1 to 22 months (mean 7.1 months). All patients with West syndrome or who were in a transition to West syndrome showed hypsarrhythmia in the interictal EEG, and the patient with Ohtahara syndrome showed a suppression-burst (SB) pattern. Epileptic spasms occurred in clusters in 3 patients, in both clusters and isolation in 5, and only in isolation in 1 in the transitional state. Their lesions are shown in Fig. S1. Patient 2 was previously reported on with respect to the ictal EEG data analyzed using a different type of averaged spectra (Patient 3 in Kobayashi et al.¹³), but analysis of this patient in terms of interictal hypsarrhythmia has not yet been reported. Outcome class¹⁶ is indicated for the last 1-year follow-up. The present study was approved by the Okayama University Ethics Committee.

In Patients 1–4, tetracosactide Zn (synthetic adrenocorticotropic hormone [ACTH]) was administered, but patients' initial EEGs and magnetic resonance imaging (MRI) were examined before the ACTH treatment. Vigabatrin was officially unavailable during the study period in Japan.

EEG recording

EEG was recorded for the analysis before the surgery using the international 10–20 electrode system (Neurofax; Nihon-Kohden, Tokyo, Japan). The sampling rate was 500 Hz. A low-cut frequency (LCF) filter at 0.016 Hz was used before digital sampling. We initially reviewed sleep EEG using a bipolar montage, including the derivations of Fp1-F7, Fp2-F8, F3-C3, F4-C4, T3-T5, T4-T6, P3-O1, and P4-O2 to select clean data.

EEG analysis

The investigation of FOs was performed conservatively according to our previous study on hypsarrhythmia² and is briefly summarized as follows. In each EEG record, we investigated the interictal non-rapid eye movement (NREM) sleep data with a duration of 60 s, including minimum artifacts in the bipolar derivations mentioned above. We used low-cut finite-impulse response (FIR) filters at 0.5, 40, and 80 Hz. Time-frequency analysis was performed based on the Gabor (short-time Fourier) transform with the frequency range of 20–150 Hz. Spectral data with the corresponding filtered EEG traces were shown in a sliding window with a width of 3 s. The Fourier transform was performed on 256 data points (512 ms; spectral resolution 1.9 Hz) at each 4-ms time point. We used the square-root power in microvolt units, which corresponded to EEG amplitude.

We identified an FO spectral peak with a power (1 μ V at minimum) greater than that at any other point in a given search area of the time-frequency spectrum with a temporal extent of 100 ms and a frequency extent of 20 Hz (spectral criterion). These criteria were systematically searched for over the entire time-frequency spectrum > 40 Hz to determine candidate peaks. Each candidate peak was then visually investigated to select one that corresponded to a clear FO with at least four consecutive oscillations in the combined filtered and unfiltered traces (waveform criterion). The waveform pattern of FO was systematically identified by searching a run of ≥ 4 oscillations with peak signals of identical polarity that had amplitudes higher than a predetermined threshold in the filtered EEG traces. The amplitude thresholds for gamma and ripple oscillations were arbitrarily assigned at 5 and 15 times, respectively, the root-mean-square (RMS) amplitude of 1-s background data, as in our previous study.² Automatically detected FOs were visually confirmed to have clear oscillations. The background was defined as a segment of EEG data from the same record as the analyzed data but containing minimal abnormalities and artifacts. The background was assumed to represent a segment of EEG with fewer abnormalities that occurred between groupings of discharges during sleep.

We recorded the ictal EEGs of epileptic spasms from 8 patients during the same period as the interictal EEGs and could analyze clean data in 7. Ten spasms in each patient were analyzed in a similar manner (3 s of data for each spasm) in the relatively unnoisy derivations of F3-C3, F4-C4, P3-O1, and P4-O2.

Frequencies of spectral peaks were categorized as gamma 1 (40–60 Hz), gamma 2 (60–80 Hz), and ripple bands (80–150 Hz). FO dominance over a given hemisphere was defined as the occurrence of two times or more FOs than the other hemisphere. Consistency was defined as that of FO dominance across all three frequency bands. Computation

Table 1. Patients

No./sex	Age at SZ onset/initial EEG	Epilepsy diagnosis/SZ type	Lesion and etiology (pathology)	Development and neurological findings at initial visit	Initial EEG findings ^a	Surgery (age)	Outcome (outcome classification/follow-up age)	FO dominance/its concordance to lesion
1/M	6 months/ 7 months	WS/ES with eye deviation to R, focal SZ	Tuberous sclerosis (a cortical tuber with calcification in the L occipital lobe ^b)	DQ = 74, R hemiparesis, head control at 4 months of age	L-dominant hypsarrhythmia	L occipital lobectomy (10 months)	SZ suppressed, R hemiparesis, able to walk and speak sentences (Class I/2 years, 10 months)	L/concordant
2/M	3 months/ 6 months	WS/ES, focal SZ occasionally combined with ES	Cortical dysplasia involving R frontal and parietal lobes	L hemiplegia, head control at 3 months of age	R-dominant hypsarrhythmia with periodicity	R hemispherotomy (12 months)	SZ transiently relapsed 3 years after surgery and medically suppressed thereafter, able to walk, no language, DQ < 20 (Class I/8 years, 11 months)	R/concordant
3/F	4 months/ 6 months	WS/ES combined with focal SZ	Cortical dysplasia involving L frontal and parietal lobes, ectopic gray matter (FCD IIa ^b)	DQ = 39, no head control at 6 months of age	Hypsarrhythmia with periodicity	L hemispherotomy (16 months)	SZ suppressed, R hemiplegia, able to sit, no language (Class I/2 years, 3 months)	Inconsistent
4/M	9 months/ 9 months	WS/ES with movements dominant in L upper extremity	R hemispheric atrophy (gliosis ^b)	L hemiplegia, DQ = 79, head control at 3 months of age	R-dominant hypsarrhythmia	R hemispherotomy (15 months)	SZ suppressed, L hemiparesis, able to run and speak sentences, DQ = 38 (Class I/5 years, 11 months)	Inconsistent
5/M	5 days/ 4 months	WS/ES, focal SZ	R hemimegalencephaly (compatible as hemimegalencephaly ^b)	L hemiplegia, DQ = 29, no head control at 4 months of age	R-dominant hypsarrhythmia	R hemispherotomy (4 months)	SZ suppressed, L hemiplegia, able to sit and speak words, DQ = 48 (Class I/2 years, 11 months)	R/concordant
6/F	4 months/ 22 months	WS/ES (mostly isolated), focal	L hemispheric cortical dysplasia with marked	R hemiparesis, DQ = 53, speaking words at 12 months and walking with	L-dominant hypsarrhythmia	L hemispherotomy (24 months)	SZ transiently relapsed 2 years after surgery and	Inconsistent

Continued

Table 1. Continued.

No./sex	Age at SZ onset/initial EEG	Epilepsy diagnosis/ SZ type	Lesion and etiology (pathology)	Development and neurological findings at initial visit	Initial EEG findings ^a	Surgery (age)	Outcome (outcome classification/ follow-up age)	FO dominance/ its concordance to lesion
		SZ combined with ES	ventricular dilatation (cortical dyslamination ^b)	assistance at 18 months of age			medically suppressed thereafter, R hemiparesis, able to sit and speak sentences, DQ = 37 (Class I/6 years, 2 months)	
7/F	1 month/ 7 months	WS/ES, focal SZ	Sturge-Weber syndrome (L hemispheric leptomeningeal angiomas with calcification ^b)	R hemiplegia, DQ = 66	R-dominant hypsarhythmia during sleep	L hemispherotomy (17 months)	SZ suppressed, R hemiplegia, able to walk with support and speak sentences, IQ = 35 (Class I/7 years, 11 months)	R/discordant
8/M	1 month/ 1 month	OS/ES combined with focal SZ	Cortical dysplasia involving R occipital and parietal lobes (microdysgenesis ^b)	Neurologically unremarkable, DQ = 58	R-dominant SB	R functional posterior quadrantectomy (2 months), R hemispherotomy due to relapse of focal SZ (14 months)	SZ suppressed, L hemiparesis, able to walk and speak words, DQ = 46 (Class I/4 years, 7 months)	R/concordant
9/F	2 days/ 2 months	Transition from OS to WS/focal SZ, ES occasionally combined with focal SZ	L hemimegalencephaly (nonspecific findings ^b)	Hypotonia, no visual following or head control	L-dominant hypsarhythmia during sleep	L hemispherotomy (3 months)	Focal SZ relapsed 2 months after surgery, R hemiplegia, able to sit, no language, DQ < 20 (Class 4/8 years, 11 months)	L/concordant

DQ, developmental quotient; EEG, electroencephalogram; ES, epileptic spasm; F, female; FCD, focal cortical dysplasia; FO, fast oscillation; L, left; IQ, intelligence quotient; M, male; OS, Ohtahara syndrome; R, right; SB, suppression-burst; SZ, seizure; WS, West syndrome.

^aFindings of EEG that was initially recorded at Okayama University Hospital.

^bOnly the biopsied tissue at the surgical margin could be investigated.

was performed using a program that was written in-house for Matlab (version 7.5.0; Mathworks Inc., Natick, MA, U.S.A.).

RESULTS

Five patients had left hemisphere–dominant epileptogenic pathology (Patients 1, 3, 6, 7, and 9), and the remaining 4 had right hemisphere–dominant epileptogenic pathology (Patients 2, 4, 5, and 8) (Table 1). Seizures were suppressed immediately after the surgery in 6 patients and transiently relapsed with subsequent medical control in 2 patients (Patients 2 and 6) (Class 1). In the remaining patient (Patient 9), seizures relapsed, but the seizure severity was far better after the surgery than before it (Class 4).

The scalp distribution of FOs was dominant over the left and right hemispheres in 2 (Patients 1 and 9) and 4 patients (Patients 2, 5, 7, and 8), respectively. FO lateralization was inconsistent in the remaining 3 patients (Patients 3, 4, and 6)

(Fig. 1). In 5 of the 6 patients with consistent scalp FO dominance, consistency was found in both the interictal data and the ictal data in 3 patients (Patients 1, 2, and 5), and only the interictal data in the other patients (Patients 8 and 9). In these patients, the distribution of scalp FOs was concordant with the lateralization of cerebral pathology along with the dominance of conventional EEG abnormalities, that is, hypsarrhythmia or the SB pattern (see Figs. S2 and S3 as representative data). The patient with Sturge-Weber syndrome (Patient 7), however, had a left hemispheric lesion and showed consistently right hemisphere–dominant scalp FOs and hypsarrhythmia. Her left hemispheric EEG was rather inactive and relatively low in amplitude (Figs. S4 and S5).

The characteristic common to 3 (Patients 4, 6, and 7) of the 4 patients with scalp FO distribution that was inconsistent or discordant with the epileptogenic hemisphere was that they had a unilateral volume reduction, which may be atrophy or hypoplasia in the pathological hemisphere.

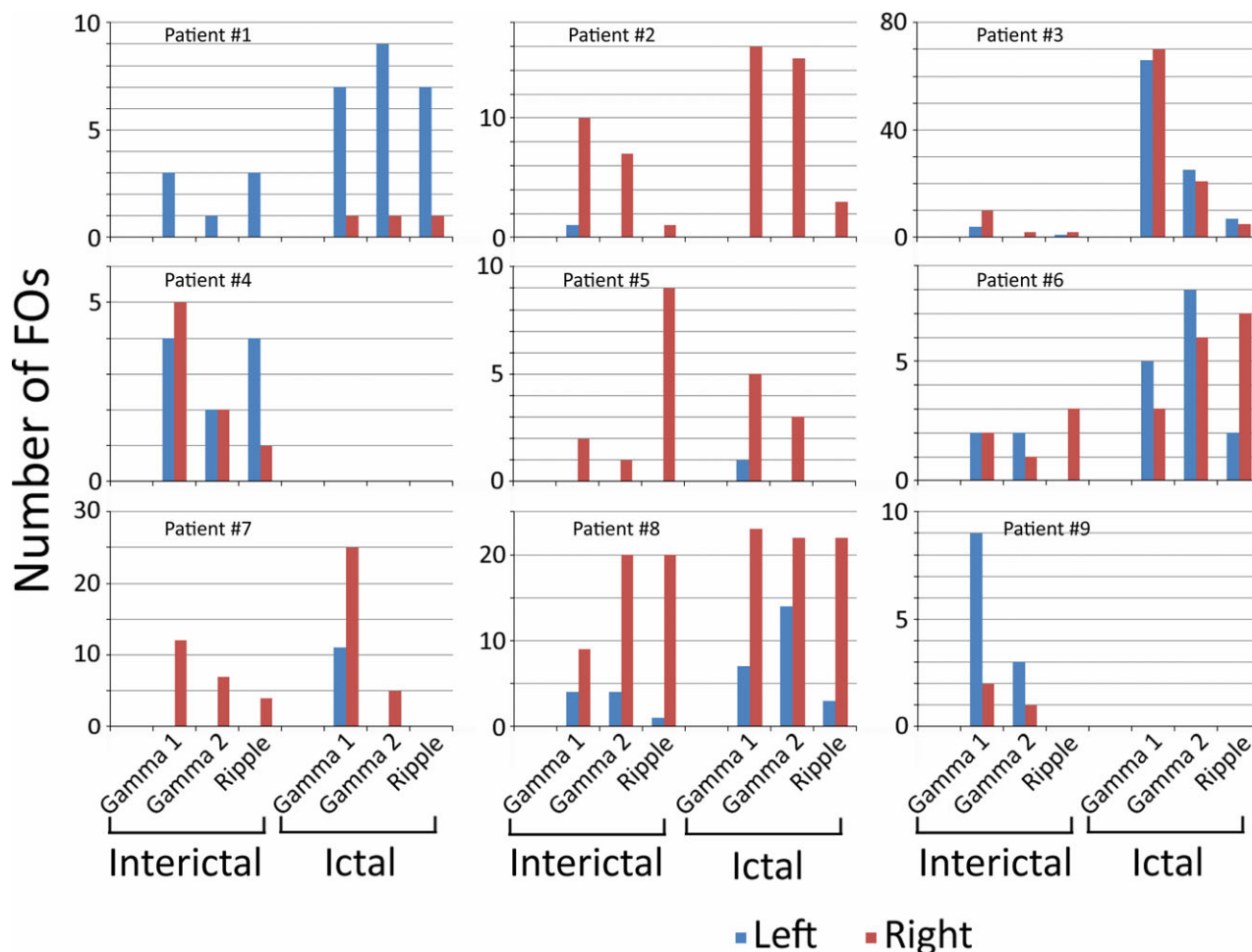


Figure 1.

Scalp distribution of fast oscillations (FOs). In each of Patients 1–9, data are arranged in order as interictal electroencephalogram (EEG) recorded before the surgery and the ictal data of epileptic spasms.

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DISCUSSION

Intracranial HFOs are suggested to indicate the epileptogenic cortical regions,^{17,18} and scalp FOs that probably occur as a result of volume conduction of cortical HFOs might also correspond to epileptogenicity.⁹ The scalp distribution of any EEG activity is, however, greatly influenced by many factors represented by the low electrical conductivity of the skull. FOs may be no exception. The correspondence between the cortical epileptogenic lesions and the scalp distribution of FOs should be studied, taking the type of lesion into account. This problem was shown to be complex in West syndrome and related disorders in the present study.

Five of the 9 (55.6%) patients exhibited scalp FOs that distributed concordantly with the surgically proven epileptogenic hemisphere. This concordance is in agreement with previous studies on the relationship between the localization of FOs and the epileptogenic regions or seizure-onset zones.^{5,9,19} We recognize, however, that this rate makes it an unsatisfactory tool to locate the epileptogenic regions, and the reason for the discordance or inconsistency in the remaining patients should be clarified.

One possible factor that would cause scalp FO distributions to be inconsistent or discordant with the epileptogenic hemisphere is the volume reduction of the affected hemisphere, which may be due to atrophy or hypoplasia. A space between the cortex and the skull, as in the case of Patient 7, may cause a substantial reduction in conducting electric current. Although HFOs have been reported to be linked with epileptogenicity independently of the underlying pathology in intracranial EEG,¹⁶ the types of pathology might influence the generation of FOs over the scalp, because scalp FOs should represent only a fraction of cortical HFOs/FOs, and scalp FOs may not be unbiased representations of cortical HFOs/FOs. Factors that may possibly influence the conduction of HFOs from the cortex to the scalp may include the cortical extent of HFOs, the degree of synchronicity of HFOs between cortical regions, and the dominant frequencies of cortical HFOs.

In conclusion, the presence of scalp epileptic FOs may indicate the occurrence of cortical HFOs/FOs and some sort of epileptogenicity, but care is needed when interpreting the meaning of the scalp distribution of FOs because there are many possible confounding factors. The present study is limited because it is preliminary, has only a small number of patients, and lacks statistical analysis. In future research we should investigate whether cortical dysplasia may generate corresponding lateralized scalp FOs during hypsarrhythmia while atrophic lesions may cause paradoxical false lateralization of scalp FOs that requires careful interpretation. Generally, the ictal EEG data are not always available, but they tend to show more intense FOs than the interictal data. As such, it remains to be determined which data

are better for the analysis. In the future, we hope to perform simultaneous recording using both scalp and intracranial electrodes to more precisely determine the relationship between scalp FOs and cortical HFOs/FOs in infants with West syndrome. The usage of dense array electrodes is also expected to provide valuable information regarding the detailed scalp distribution of FOs.

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DISCLOSURE

None of the authors have any conflicts of interest to disclose. We confirm that we have read the Journal's position on the issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. Neuroimaging, including magnetic resonance imaging (MRI) (T1-weighted image [T1WI], T2-weighted

image [T2WI], and fluid-attenuated inversion recovery [FLAIR]) and computed tomography (CT) with arrows indicating lesions.

Figure S2. Raw EEG traces of Patient 8 with Ohtahara syndrome associated with cortical dysplasia involving the right hemisphere showing a suppression-burst pattern (left-hand side) and the ictal EEG of an epileptic spasm (right-hand side, arrowhead).

Figure S3. Time-frequency spectra of the ictal EEG data of an epileptic spasm (corresponding EEG in Fig. S2 arrowhead) in Patient 8.

Figure S4. Raw EEG traces of Patient 7 with West syndrome associated with Sturge-Weber syndrome with left-hemispheric leptomeningeal angiomas showing right hemisphere-dominant hypsarrhythmia during sleep (left-hand side) and the ictal EEG of an epileptic spasm (right-hand side, arrowhead).

Figure S5. Time-frequency spectra of the ictal EEG data of an epileptic spasm (corresponding EEG in Fig. S4 arrowhead) in Patient 7.