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Review

Significance of High-frequency Electrical Brain Activity

Katsuhiro Kobayashi[a,c]*, Tomoyuki Akiyama[a,c], Takashi Agari[b,c], Tatsuya Sasaki[b,c], Takashi Shibata[a,c], Yoshiyuki Hanaoka[a,c], Mari Akiyama[a,c], Fumika Endoh[a,c], Makio Oka[a,c], and Isao Date[b,c]

Departments of [a]Child Neurology, and [b]Neurological Surgery,
Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences,
[c]Epilepsy Center, Okayama University Hospital, Okayama 700-8558, Japan

Electroencephalogram (EEG) data include broadband electrical brain activity ranging from infra-slow bands (< 0.1 Hz) to traditional frequency bands (e.g., the approx. 10 Hz alpha rhythm) to high-frequency bands of up to 500 Hz. High-frequency oscillations (HFOs) including ripple and fast ripple oscillations (80-200 Hz and > 200 / 250 Hz, respectively) are particularly of note due to their very close relationship to epileptogenicity, with the possibility that they could function as a surrogate biomarker of epileptogenicity. In contrast, physiological high-frequency activity plays an important role in higher brain functions, and the differentiation between pathological / epileptic and physiological HFOs is a critical issue, especially in epilepsy surgery. HFOs were initially recorded with intracranial electrodes in patients with intractable epilepsy as part of a long-term invasive seizure monitoring study. However, fast oscillations (FOs) in the ripple and gamma bands (40-80 Hz) are now noninvasively detected by scalp EEG and magnetoencephalography, and thus the scope of studies on HFOs / FOs is rapidly expanding.

Key words: high-frequency oscillations, fast oscillations, epilepsy, electroencephalogram, time-frequency analysis

The recording of electrical brain activity as an electroencephalogram (EEG) is a direct representation of the function of the central nervous system, particularly of the cerebral cortex. An EEG is recorded as the sum of extracellular potentials (field potentials) generated by currents emanating from each individual neuron. It is currently believed that the origin of EEG is excitatory or inhibitory post-synaptic potentials (PSPs), and that EEG signals are almost exclusively contributed to by excitatory (mostly pyramidal) neurons which have open dipolar fields, in contrast to inhibitory neurons with closed fields [1].

With the development of digital EEG recording and analysis techniques, the available EEG frequency bands have been greatly expanded from the traditional delta, theta, alpha, and beta bands (1-3, 4-7, 8-13, and 13-40 Hz, respectively) to include high frequencies (gamma, ripple, and fast ripple bands: 40-80 Hz, 80-200 Hz, and 200 / 250-500 / 600 Hz, respectively) as well as low frequencies (sub-delta and infra-slow bands: 0.1-1 Hz and < 0.1 Hz, respectively) [2]. The infra-slow activities are also called direct current (DC) shifts, and it has been suggested that glia cells might contribute to the generation of DC shifts [3].

Regarding the generation of high-frequency oscillations (HFOs) in the ripple and fast ripple bands, the contribution of bursts of action potentials (population

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*Corresponding author. Phone : +81-86-235-7372; Fax : +81-86-235-7377
E-mail : k_koba@md.okayama-u.ac.jp (K.Kobayashi)

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spikes) was demonstrated in animal studies as well as computerized simulation studies [4-8]. Very-HFOs (>1000 Hz) were reported in patients with neocortical epilepsy [9]. Although electroencephalography is a well-established technique, its neuroscientific significance has been greatly enhanced through the novel development of methodologies, and electroencephalography has thus emerged as a considerably expanded analytic technique in recent years.

We herein review the recent development of EEG studies of high-frequency activity, as this activity provides unprecedented information regarding brain function, particularly of epileptogenicity.

Epileptogenicity and High-Frequency EEG Activity

Initially, HFOs were recorded using only microelectrodes with a surface area less than 1/1,000 of that of an ordinary clinical intracranial macroelectrode. In 2006, however, the detection of HFOs using clinical intracranial macroelectrodes was reported [10], and clinical studies of HFOs have rapidly accelerated since that time [4, 11-14]. Most importantly, good outcomes of epilepsy surgery were significantly more closely related to the resection of HFO-generating cortical areas than to the removal of areas generating epileptic discharges (*i.e.*, spikes) or the removal of the seizure onset zone (SOZ) [15].

Further reports supported the possibility of a close relationship between HFOs and epileptogenicity in both adult and pediatric patients, and thus the presence of epileptic HFOs is suggested to be a surrogate biomarker of epileptogenicity [16-18]. A meta-analysis of 11 published studies that examined the relationship between the resection of HFO-generating areas to postsurgical outcomes (data on ripples and fast ripples in 10 and seven studies, respectively) [19] revealed that the resection ratio (*i.e.*, the ratio between the number of channels on which HFOs were detected and, among these channels, the number of channels that were inside the resected area) for both ripples and fast ripples is higher in postsurgically seizure-free patients than in non-seizure-free patients.

Techniques for detecting HFOs include various types of low-cut frequency filters that reduce EEG activity slower than a given cut-off frequency, and a time-frequency analysis that visualizes time-varying spectral patterns of EEG activity. We developed a sophisticated time-frequency analysis that detects statistically significant spectral changes related to spikes compared to the background activity (Figs. 1, 2) [20]. Using this technique, we observed a spike-associated increase and post-spike depression of high-frequency EEG activity in the SOZ, and these differences were more marked in mesial temporal discharges than in neocortical discharges [21]. However, when we compared the degree of the relationship to the SOZ between morphologically identified HFOs and spectrally detected high-frequency activity, the identification of distinct HFOs was shown to be more useful than spectral changes [22].

Epileptic HFOs have characteristics different from those of spikes, the traditional biomarker of epileptogenicity [23]. HFOs are thought to be specific to cortical areas of seizure generation and not to the substrate of pathological tissue in lesional epilepsy [14]. When antiepileptic medication is reduced, HFOs increase in number, reflecting the epileptogenic potential of the tissue, whereas spikes do not show such changes [24]. Although spikes increase in the SOZ after a recurrence of seizures, HFOs do not. However, a few seconds prior to a seizure, the rate of HFOs increases whereas that of spikes does not [25]. HFOs and spikes are probably not completely independent of each other as they often co-occur [26], and spikes with HFOs may be more strongly related to epileptogenicity compared to spikes without HFOs [23].

Regarding the relationship between HFOs and the types of pathology, patients with focal cortical dysplasia (FCD) type 2 were reported to have significantly more seizures and higher rates of HFOs compared to patients with FCD type 1, suggesting that the HFO rate may reflect the disease activity of a lesion [27]. HFOs rates have also been shown to vary depending on different pathologies, and are higher in FCD (particularly within the borders of MRI-visible dysplastic lesions), mesial temporal sclerosis, and nodular heterotopia than in atrophy, polymicrogyria, and tuberous sclerosis [28].

For the presurgical evaluation of patients with intractable epilepsy, interictal [18F] fluorodeoxyglucose-positron emission tomography (FDG-PET) is often used to detect the hypometabolic brain region as a candidate epileptogenic lesion. In an investigation of the relationship between such hypometabolism and intracranially recorded ictal HFOs, a significant correlation was found in cases of temporal lobe epilepsy, but low-

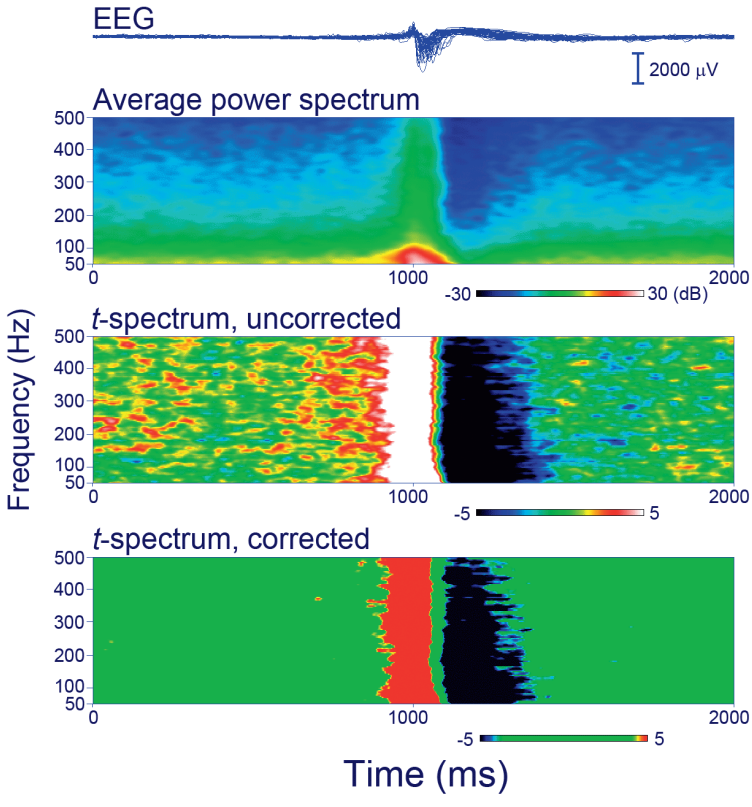

Fig. 1 Time-frequency power spectra and statistical spectra of spike-and-slow-wave complexes recorded from the seizure onset zone (SOZ) in the left hippocampus. Ordered from top to bottom: overlaid EEG traces including spikes, average power spectrum, *t*-spectrum without control, and *t*-spectrum controlled by the false discovery rate (FDR). The power of fast activity significantly increased in association with spikes and transiently decreased after the spikes. Cited with permission from ref. [20] (Clin Neurophysiol (2009) 120: 1070–1077).

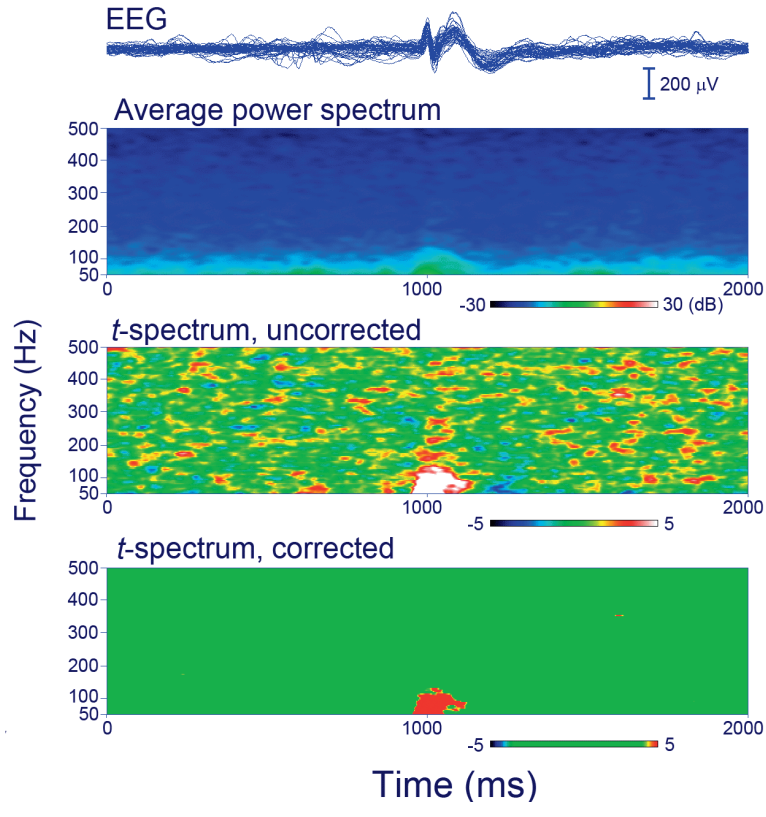

Fig. 2 Time-frequency power spectra and statistical spectra of spike-and-slow-wave complexes from a left temporal neocortical region that was outside of the SOZ. The arrangement is similar to that of Fig. 1. An increase in the power of fast activity is observed only up to approx. 100 Hz. Post-spike depression of fast activity was not observed. Cited with permission from ref. [20] (Clin Neurophysiol (2009) 120: 1070–1077).

er-frequency activity did not show a similar correlation [29].

The generation of HFOs varies depending on sleep stages. It was reported that HFOs are suppressed during rapid eye movement (REM) sleep compared to non-REM (NREM) sleep, and that HFOs near the epileptogenic zone are less suppressed during REM than are HFOs in the non-epileptogenic cortex [30]. In a comparison of epileptic discharges and HFOs between phasic REM sleep and tonic REM sleep, interictal epileptic discharges and HFOs were less frequent during phasic REM sleep; however, physiologic ripples were found to be more abundant during phasic REM sleep in contrast to epileptic ripples, suggesting a possible reflection of REM-related memory consolidation and dreaming [31].

It is still difficult to use the detection of HFOs as a clinical tool to determine the epileptogenic cortical area that should be surgically resected, because the identification of HFOs relies on the visual interpretation of EEG traces by experienced electroencephalographers, and the identification can thus be very time-consuming. The development of methodologies to automatically detect HFOs is progressing [32-35]. In the above-mentioned meta-analysis regarding the relationship of the resection of HFO-generating areas to postsurgical outcomes, the results of an automated detection of HFOs were found to be comparable to those of visual detection [19].

Case Report

We present the case of a representative female patient in order to illustrate the observation of HFOs. She was 19 years old at the time of surgery but had experienced intractable focal dyscognitive seizures (also known as complex partial seizures) that were characterized by 1-min episodes of a combination of an anxious feeling (aura) and subsequent motion arrest and unresponsiveness that had occurred since she was 7 years old. She had also experienced acute disseminated encephalomyelitis at the age of 2 years. MRI disclosed pathological findings in bilateral mesial temporal structures: sclerosis in the left hippocampus and a cystic lesion at the right hippocampus (Fig. 3A). Interictal EEG showed interictal epileptic discharges over the left temporal region.

Seizure monitoring was performed with intracranial electrodes including depth electrodes targeting the bilateral hippocampi. The ictal EEGs demonstrated seizure activity originating from the left hippocampus (bipolar EEGs from the left [LH1-2] and right [RH1-2] hippocampi in Fig. 3B). Temporally expanded and filtered EEG data showed HFOs in association with seizure discharges in LH1-2 but not in RH1-2 (Fig. 3C). Corresponding panels from the time-frequency analysis indicated a high-frequency spectral spot (blob) in the left hippocampal data but not in the right (Fig. 3D).

The detected HFOs were valuable for the identification of the epileptogenic focus, and a left selective amygdalohippocampectomy was performed. The patient is now 23 years old and has been seizure-free for 3 years.

Higher Brain Functions and Physiological High-frequency EEG Activity

Initially, fast ripples and ripples were considered epileptic / pathological and physiological, respectively, with clearly distinct clinical meanings [4]. However, the reality is not that simple. It is now known that physiological fast ripples are recorded from eloquent areas such as the visual cortex, and physiological HFOs are thought to be involved in higher brain functions such as memory, language, and calculation [36-38]. The differentiation between epileptic and physiological HFOs is critically important in epilepsy surgery because the brain regions generating epileptic HFOs can be resected whereas regions generating physiological HFOs should not be touched.

Pathological HFOs were described as having higher mean spectral amplitudes, longer mean durations, and lower mean frequencies compared to HFOs that were physiologically induced by visual or motor tasks [39]. Another study suggested that ripples co-occurring with sleep spindles should be considered models of physiological ripples and that such spindle-related ripples had lower amplitude features than epileptic ripples did [40]. Many more studies may be required to further clarify the differentiation between pathological / epileptic and physiological HFOs.

Inter-regional High-frequency Connectivity

Connectivity (or functional correlations) between brain regions have been investigated with respect to high-frequency intracranial EEG data, in the hope of

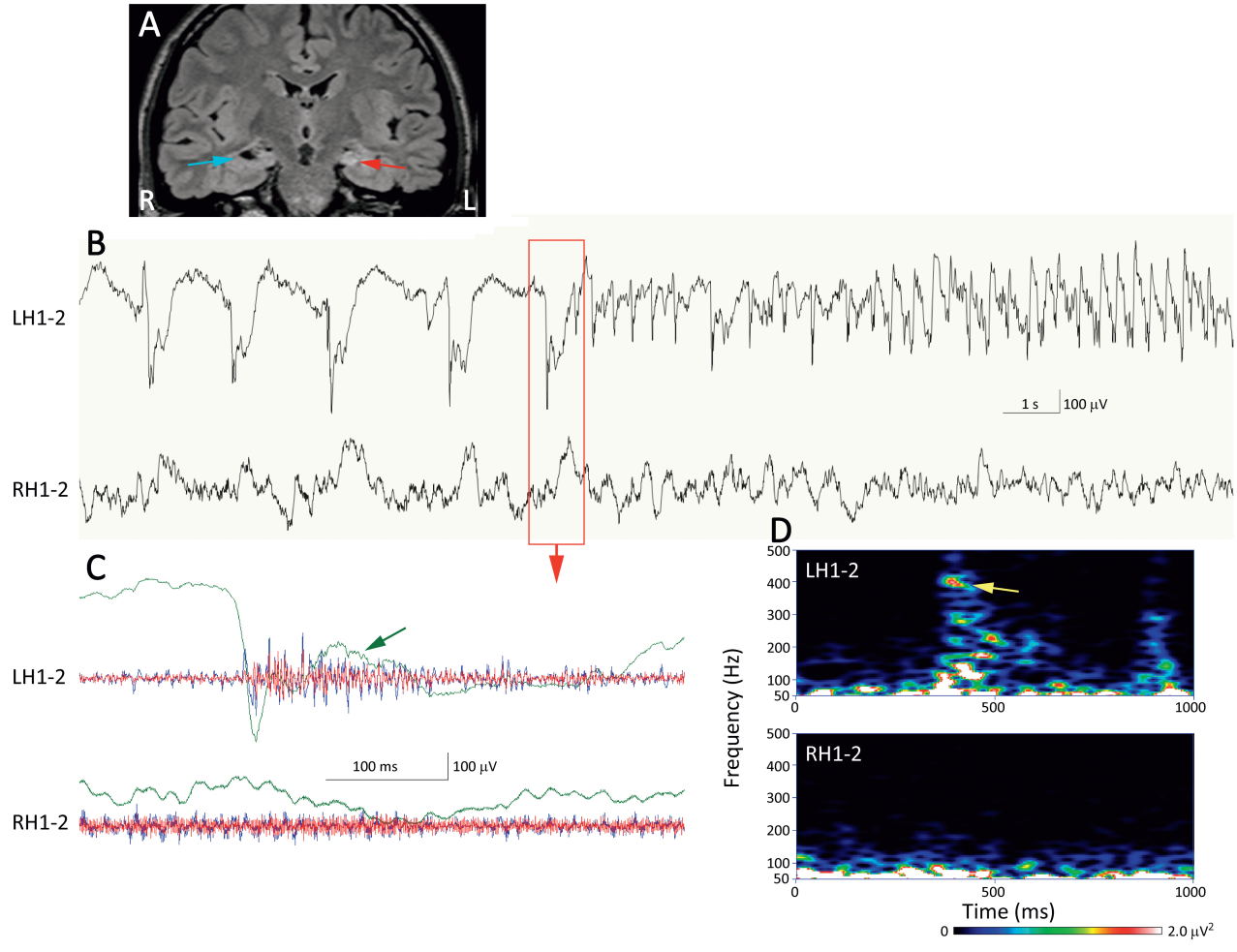

Fig. 3 MRI and the ictal invasive EEG data of a representative case, a 19-year-old woman. **A**, A coronal fluid-attenuated inversion recovery (FLAIR) MRI image showing a sclerosis in the left hippocampus (red arrow) and a cystic lesion in the right (blue arrow); **B**, The ictal depth EEG recorded from the left (LH1-2) and right (RH1-2) hippocampi. The part indicated by the red rectangle was temporally expanded and filtered to disclose HFOs in LH1-2 as shown in panel **C** (green arrow; low-cut frequency filters at 1.5, 80, and 200 Hz in the green, blue, and red traces, respectively). The results of the corresponding time-frequency analysis are shown in panel **D** with a high-frequency spectral spot at about 400 Hz in LH1-2 (yellow arrow).

detecting the node of the epileptic network that should be resected [41]. It was reported that prominent divergence and convergence of high-frequency activity propagation were identified at sites in the ictal onset zone [42]. In extra-temporal lobe epilepsy, strong HFO coherence indicating waveform similarity was observed in a consistent and spatially focused channel cluster during seizures, and cortical regions possessing strong ictal HFO coherence coincided with regions exhibiting high ictal HFO intensity, which indicated epileptogenicity [43].

In an investigation of the relationship between brain areas showing fast ripples and baseline functional connectivity within EEG networks — especially in the high-frequency bands — functional integration was observed in the fast ripple-band network of channels covering presumed epileptogenic tissue [44]. Based on these findings, it was suggested that the use of baseline high-frequency network parameters might contribute to the intra-operative recognition of epileptogenic tissue without the need to wait for the occurrence of epileptic events [44].

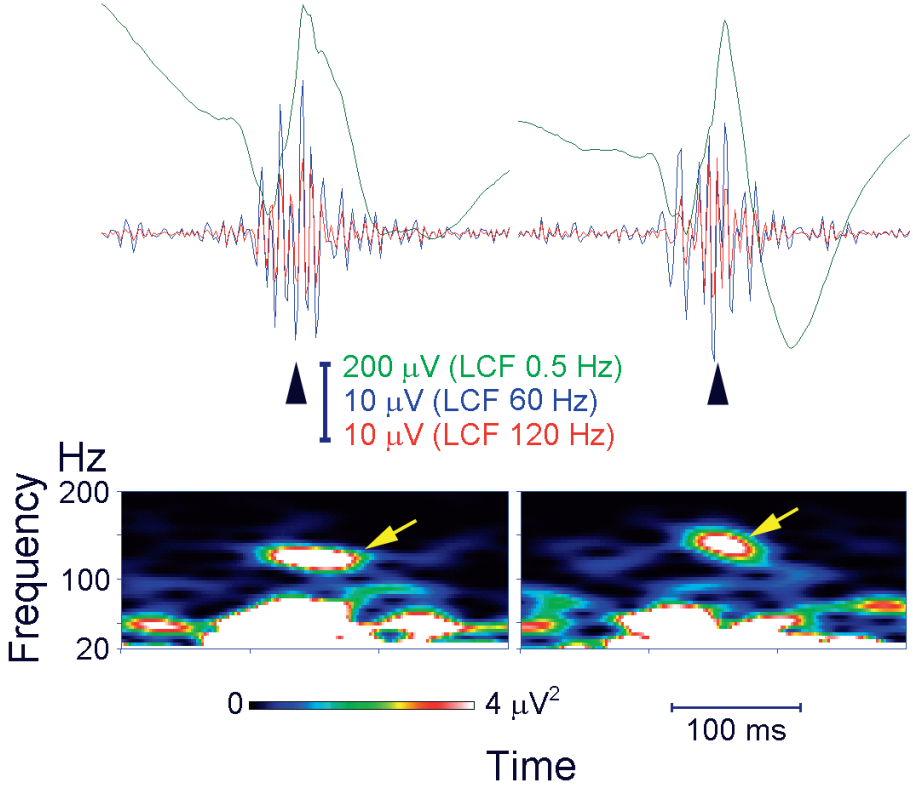

Fig. 4 Ripple oscillations in the scalp EEG recorded from a child with Landau-Kleffner syndrome. Representative spikes (arrowhead) are associated with ripple oscillation, which was largely invariant irrespective of the low-cut frequency (LCF) of either 60 or 120 Hz. (EEG traces filtered at 0.5, 60, and 120 Hz are shown in green, blue, and red, respectively.) The EEG was recorded during non-REM sleep and therefore did not include muscle activity or eye movements. EEG data are presented in a referential montage (top: O1 with reference to the average EEG of bilateral earlobes, indicated as O1-Aav). Note that spike-related ripples with at least four consecutive oscillations are clearly observed. Each panel of time-frequency spectra shows a corresponding discrete blob (arrow) with a frequency at around 130 Hz. Cited with permission from ref. [73] (Prog Neurobiol (2012) 98: 265–278).

Noninvasive Recording of High-frequency EEG Activity

The noninvasive detection of HFOs is a technical challenge, but such detections provide substantial benefits in the evaluation of epileptogenicity. We have demonstrated that ripple and gamma oscillations, collectively termed fast oscillations (FOs), are recordable over the scalp, particularly in pediatric patients [45-52] (Fig. 4); this has been confirmed by other researchers [53-57].

Compared to interictal epileptic discharges, FOs were found to be less sensitive but more specific and accurate for identifying the SOZ [54]. A functional MRI study revealed that scalp interictal epileptic discharges, when frequently accompanied by HFOs in the ripple but not in the gamma band, are associated with larger cortical metabolic responses and with thalamic involvement lateralized to the side of cortical ripples [55]. In patients with focal epilepsy with bilaterally synchronous discharges, the hemisphere of clinical lateralization and the ripple-dominant hemisphere were completely concordant [57].

Regarding the relationship between scalp FOs and cortical HFOs, simultaneous scalp and intracranial EEG recording demonstrated that scalp FOs directly correspond to cortical HFOs and that surprisingly small cortical areas generate FOs seen on the scalp [58]. A simulation study showed that FOs can be detected on the scalp with cortical generators of only 1cm^2 because the background activity is so small in fast-frequency bands [59]. It was suggested that even fast ripples may be detected over the scalp [60].

It was also reported that FOs with frequencies of 40-160 Hz are detectable by magnetoencephalography (MEG) with lower detection sensitivity but higher specificity than scalp EEG [61]. The MEG beamformer-based virtual sensor technique may be useful for identifying HFOs [62].

HFOs/FOs in Pediatric Epilepsies

Intracranial HFOs play an important role as the surrogate biomarker of epileptogenicity in the surgical treatment of intractable pediatric epilepsies, such as epileptic spasms or infantile spasms [63, 64] and epi-

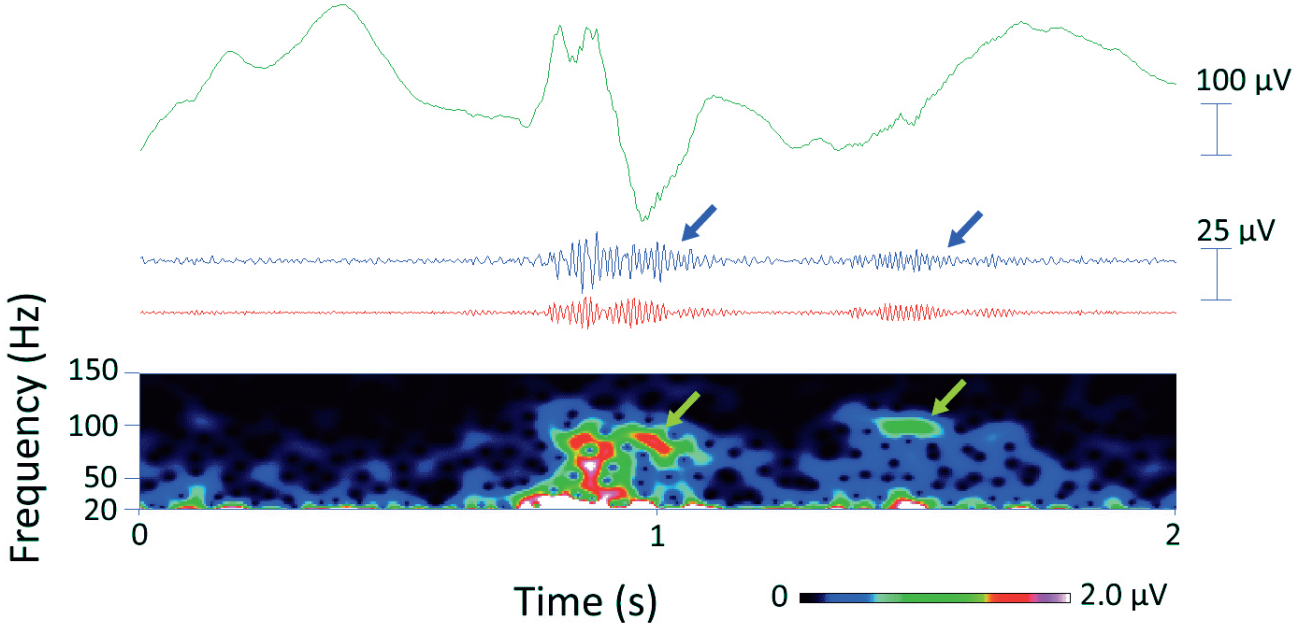

Fig. 5 Representative fast oscillations (FOs) during hypsarrhythmia recorded from an infant with West syndrome. EEG traces in a bipolar derivation (P4-O2) are low-cut filtered at 0.5 Hz (green traces), 40 Hz (blue), and 80 Hz (red). FOs are observed in association with spikes that were recorded before treatment with adrenocorticotropic hormone (ACTH). FOs are observed in filtered traces (blue arrows) and correspond to spectral blobs in the time-frequency analysis (yellow arrows). Cited with permission from ref. [51] (Ann Neurol (2015) 77: 58–67).

lepsy associated with tuberous sclerosis complex [65].

Scalp FOs are especially detectable in childhood. In West syndrome (a representative form of infantile epileptic encephalopathy), FOs are particularly abundant and stormy in interictal hypsarrhythmia and the ictal EEGs of epileptic spasms, at an amount approx. 100 times that in adult patients [51] (Fig. 5). It was reported that the ictal scalp FOs of spasms showed a strong association with neuroimaging abnormalities presumed to be the epileptogenic zone in infants with symptomatic West syndrome [66]. In an animal model of infantile spasms, high-frequency activity with frequencies up to 900 Hz was observed in the ictal cortical EEGs of spasm-like seizures, which reinforces the relationship between the cortical generation of HFOs and spasms [67].

In two children with surgically treated epilepsy, HFOs were noninvasively detected using both scalp EEG and MEG, and correspondence was reported between the HFO source estimated from these data and the results of invasive recordings [68].

With respect to idiopathic focal epilepsies in childhood, we reported that epileptogenicity is more closely related to FOs (particularly ripples) associated with functional spikes represented by rolandic spikes than with spikes themselves, a traditional biomarker of epileptogenicity [49]. The detection of scalp FOs in relation to rolandic spikes has been reconfirmed by other researchers [56], and a strong link between the sources of functional spikes and the presence or absence of associated FOs is indicated [52].

Idiopathic focal epilepsies in childhood occasionally worsen (*e.g.*, development into epileptic encephalopathy with continuous spike-and-wave during sleep [CSWS]), and we demonstrated an intense generation of scalp ripples associated with CSWS as the first-ever report on the observation of FOs over the scalp [48]. Ripples were also detected from the sleep EEG pattern of CSWS in patients with atypical benign partial epilepsy [69].

Relationship between Epileptic DC Shifts and HFOs in Broadband EEG

EEGs can now be recorded to cover a broad-frequency band that includes DC shifts as well as high-frequency activity. There is a close association between

HFOs and DC shifts, and both types of epileptic abnormalities have a restricted cortical area of generation in intracranial EEG data. Regarding their temporal relationship, ictal DC shifts were reported to precede HFOs in one study [3] and to be closely preceded or followed by HFOs in another study [70]. In a study of mesial temporal lobe epilepsy, it was noted that the onset and the spatial distribution of ictal conventional stereo-electroencephalography, ictal DC shifts, and ictal HFOs did not overlap, suggesting that they reflect different cellular or network dynamics [71].

The relationship between slow waves and FOs is also important in the scalp EEG data of pediatric epilepsy. In West syndrome, the ictal EEG pattern of epileptic spasms in traditional scalp EEG is a high-amplitude slow wave, and FOs are stormily generated in association with epileptic spasms, as mentioned above. An investigation of the temporal relationship between the two ictal EEG patterns was performed to demonstrate that FOs clustered at the positive peaks of the ictal slow waves, and the results indicated that active neuronal firing related to FOs underlies the generation of epileptic spasms and their ictal slow waves [72].

Conclusions and Future Development

Digital EEG data include much more information with respect to brain function than traditional analogue EEG data do, and should therefore be fully utilized as broadband EEG data extending from DC shifts to HFOs. Broadband EEG is an indispensable tool for the investigation of brain physiology and pathophysiology, particularly epilepsy.

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