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Epilepsy surgery and employment

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The aim of epilepsy surgery is to stop or at least reduce the seizures while preserving daily and professional functions. Most patients receiving surgery have had a long history of medically refractory disabling seizures, which impair their daily and social life directly or indirectly through chronic fear of seizure occurrence. They often have neuropsychological or neuropsychiatric comorbidities, which also contribute to the disabling condition. As a consequence, they have endured long periods of burden and handicap.

Once the surgery has been performed, there is usually a dramatic effect on seizures. The patients have to adapt to the abrupt change from a condition with seizures to one without seizures, although the comorbities usually do not or minimally change, which may pose psychological conflicts as a function of expectation for surgery of the patients and related persons. When the surgical effect on seizures is insufficient, the patients may remain the same as before, or become worse if there is any complication.

Employment is an important domain of social life. It contributes to economic life, personal identity and self-worth. The unemployment rate of people with epilepsy has been shown to be two to four times higher than that of the general population, and 40% of those employed are underemployed; the employment problems in epilepsy are the result of a set of adverse internal (personal) and external (social) factors interacting with each other in a complex manner [1].

As early as 1984, Augustine *et al.* [2] investigated occupational adjustment of 32 patients 1 to 10 years after surgery and found an increase of the employed, a decrease of the underemployed and little change of the unemployed. Poor occupational adjustment was often associated with fair or poor seizure control and also related to the presence of pre-operative psychiatric disorders, a history of past unemployment, and cognitive disturbances.

An appropriate intervention program before and after surgery may help facilitate the social integration of patients. There are some practices and practical proposals of the relevant interventions in various phases of the pre/post-surgery process [3].

This article reviews the effect of surgery on employment condition, adding our personal experience and discussions about the necessary interventions.

■ Epilepsy and employment

Employment rates vary widely according to the economic and social situations and between communities and countries. The rates among persons with epilepsy can also differ according to patient selection, definition of employment, and even treatment conditions. Moreover, the diagnosis of epilepsy was often hidden in the society. Surveys of members of Japan Epilepsy Association [4] found the employment rates of persons with epilepsy to be 51.6% in 1984, 40.2% in 2001 and 36.4% in 2007, although the members of the association changed and the socio-welfare system of Japan changed during these years. These figures suggest that employment rates reflect many factors in the society. Nevertheless, past studies clearly indicate that many people with epilepsy face difficulties in finding and maintaining employment.

Several factors have been suggested to contribute to lowered employment among persons with epilepsy [1]. Besides the actual risk of seizure-related injury and economic loss, many other factors are involved, such as stigma, perception of stigma, fear of seizure, low self-esteem, inappropriate work belief [5], anxiety and depression, as well as other psychopathologies. Some patients with epilepsy may have impaired sensorimotor or cognitive function due to organic, epilepsy-related or drug-related brain dysfunction. Growth with a chronic condition may hamper acquisition of interpersonal skills.

According to our study comparing the occupational performances and the results of work aptitude tests in 15 subsequently employed and 14 persistently unemployed patients, the unemployed showed significantly lower scores in volition and spontaneity for work habit, tendency of self-isolation in interpersonal relationship, and lower results in fine motor and motor coordination tasks, although the abilities to work and practice showed no differences. With regard to job maintenance, Fraser *et al.* [6] pointed that the best discriminators of keeping a job at 1 year post-employment are related to cognitive flexibility and motor speed. Furthermore, a literature review indicated that self-efficacy, self-directed activities, and active coping strategies are crucial in adapting to epilepsy and in finding and maintaining employment [1].

■ Surgery effect on employment

In so far as surgery is an option of treatment for seizures, the employment situation after surgery may not differ from that after medical treatment, as long as both treatments are equally effective in controlling seizures. However, there are some, mainly quantitative, differences. First, most patients who underwent surgery had experienced disabling seizures and drug effects for a long period of time, which profoundly impaired their daily and psychosocial lives. They grew up with this burden often from early childhood. Second, patients treated by surgery often had detectable brain lesions that cause, apart from the epileptic seizures, more serious brain dysfunction than patients without lesion and responsive to medical treatment. Third, the surgical patients and their environment have high expectation for surgery, which may sometimes be unrealistic. During the process of psychodynamic development after surgery, this unrealistic expectation may prevent them from adopting and adapting to new roles. Fourth, surgery may cause new neurological and neuropsychological complications not present before surgery, although surgery may also relieve some preexisting neuropsychological dysfunctions.

The issue of employment after surgery should be addressed taking all these differences into consideration. Numerous studies were devoted to identify the effects of surgery on employment *(Tables I and II)*. Generally, employment increased, and underemployment and unemployment decreased after surgery, although often not dramatically. Sperling *et al.* [7] suggested that the employment gains came slowly: unemployed patients took up to 6 years to obtain work after surgery. Wilson *et al.* [8] suggested that factors leading to employment gains evolve over the first 2 years alongside improvements in areas such as family dynamics, social functioning, and driving.

■ Factors relating to social improvement after surgery

Because surgery primarily aims at stopping or reducing seizures, all studies first investigated the relation between seizure outcome and employment outcome. Indeed, seizure relief is the essential factor for improved employment in most studies. Comparisons between surgery patients and medically treated patients made this difference more clear *(Table II)*. Surgery patients with residual seizures show closer figures to the medically intractable patients. Sperling *et al.* [7] suggested that complete seizure freedom and not just reduction in seizure frequency may be the most important issue in gaining employment.

However, besides seizure reduction, other factors have been shown to be important for employment outcome. Guldvog *et al.* [9] stressed that surgery resulted in significant improvements in the actual working situation only for those in regular education or work before treatment, concluding the superiority of surgical treatment to traditional therapy in assuring maintenance of full-time employment. Thorbecke *et al.* [3] also suggested that postoperative employment status was best predicted by pre-operative work status.

As factors for postoperative employment, Lendt *et al.* [10] indicated the importance of successful seizure control, pre-operative employment, young age, and postoperative improvements in the neuropsychological status. Students who underwent surgery are more likely to achieve employment after graduation than older patients [11].

Wilson *et al.* [12] regarded early anxiety as a marker for poor psychosocial outcome, and no vocational changes in the first 12 months as indicator for poor employment outcome. Dulay *et al.* [13] suggested that the frequency of unemployment was directly related to IQ, which might be related to onset of epileptic seizures at an earlier age, or more severe epilepsy.

Wilson *et al.* [14] reported on the difficulties associated with the cessation of seizures after surgery, *i.e.*, burden of normality. This burden may be felt by the majority of the patients, but could reach a pathological level in some, spanning a minimum of 2 years. They show inability to cope with a new situation that entails less social constraints but at the same time makes new demands. According to Thorbecke *et al.* [3], patients with few resources for adaptation, *i.e.*, those with a dearth of social skills and cognitive impairments before surgery, especially with IQ in the range of learning disability, are more susceptible to develop these maladaptive reactions.

■ Experience at Shizuoka Epilepsy Center

The data of two studies conducted at Shizuoka Epilepsy Center where epilepsy surgery has been performed since 1983 will be shown here.

Fifty-four patients who underwent resection surgery at ages older than 16 years and followed for more than 2 years postoperatively were randomly selected for pre- and post-surgical evaluations according to the criteria proposed by Dodrill *et al.* [15]. The epileptogenic foci

Table I. Employment outcome after surgery in the literature

Reference	Patients	Follow-up (mean)	Employment status and relevant findings
Taylor, 1968 [18]	100 TLE	2-12 years	Unemployment: pre 37%, post 21% (of which 81% unemployed before surgery)
Augustine, 1984 [2]	32 focal epilepsy	1-10 (3.9) years	Employed: pre 44%, post 72% Underemployed: pre 25%, post 0 Unemployed: pre 31%, post 28% Unemployment was related to seizure control, psychiatric disorder, past unemployment and cognitive disturbances
Bladin, 1992 [19]	107 TLE	1-10 (4) years	Full-time: pre 48%, post 59%
Sperling, 1995 [7]	86 TLE	3.5-8 years	Unemployed: pre 25%, post 11% Improvement in occupational status was related to the degree of postoperative seizure relief Employment gains came slowly Unemployed patients tended to be older than patients who became employed
Lendt, 1997 [10]	151 focal epilepsy	1-5 (3) years	Unemployed: pre 33%, post 16%. Improved 21%, unchanged 68%, deteriorated 11% Important factors were successful seizure control, pre-operative employment, younger age and improvements in the neuropsychological status
Reeves, 1997 [17]	134 TLE	4.2 years	Full- and part-time: pre 75%, post 74% Unemployed: pre 4%, post 7% Work outcome was influenced by presurgical work experience, successful postsurgical seizure control to allow driving, and obtaining further education after surgery
Eliashiv, 1997 [20]	49 TLE	1-30 (8.4) years	Employed/unemployed: pre 45%/47%, post 76%/16% A good seizure outcome was related to a good psychosocial outcome
Jarrar, 2002 [21]	32 TLE operated at age 7-18 years	4-27 (19) years	Employed 78%, part-time 3%, homemaker 9%, unemployed 3% Good seizure outcome was associated with good psychosocial outcome
Dupont, 2006 [22]	110 mesial TLE	1-17 (7) years	Professional status improved in 53% of seizure-free (> 1 year) patients and in 25% of patients with persisting seizures; worsened in 11% and 22%, respectively Employment status was not different for short- or long-term follow-up
Dulay, 2006 [13]	90 TLE	3-45 (11.3) months	Unemployment 46.7% before surgery and 35.6% after surgery A trend where employment was associated with good seizure outcome

Asztely, 2007 [23]	65 focal epilepsy	2 years, and 8.6-16.2 (12.4) years	Presurgery: 74% full or part-time employed 2 years: 76% of seizure-free and 44% with seizures were full- or part-time employed Long-term: 74% of seizure free and 30% with seizures were full- or part-time employed
Chin, 2007 [24]	299 focal epilepsy	2 years	Full-, part-time, disabled, unemployed: pre- 39.5%, 6.9%, 26.7%, 11.7%; 2 years 42.8%, 12.4%, 20.7%, 9.7% Net employment gains were modest 2 years after surgery and higher with better seizure outcomes
Benifla, 2008 [25]	42 TLE operated at 0-18 (12.5) years	10-20 (12) years	More seizure-free patients (86%) than residual seizure patients (57%) were employed or in school
Tanriverdi, 2008 [26]	63 TLE	6 months, 2 years and 12 years	Full- or part-time job: pre 37.5%, 6 months 62.5%, 2 years 74.5%, 12 years 67% Seizure free patients had higher employment rate than non-seizure free at short- and long-term follow-ups
Thorbecke, 2008 [3]	115 TLE	2 years	Unemployed: pre 20%, post 9%; improved in 22.5% Work-related problems: pre- 59%. post 25%. Postoperative employment status was best predicted by pre-operative work status General improvement after surgery except frequency of social contact

were in the temporal lobe in 49 patients, frontal lobe in 4, and temporo-occipital lobe in 1. The mean age at surgery was 30.9 years (16-55) and mean postoperative follow-up period was 3.2 (2-5) years. There were equal numbers of men and women. Resection side was the left in 18 and the right in 36. Seizure outcome was Engel class I (no seizure) in 47 patients, class II (rare disabling seizures) in 1, and class III (worthwhile improvement) in 6.

Vocational outcome is shown in *Table III*. One patient (Engel class I) in class 4 had a child so that she voluntarily reduced working hours, another patient (Engel class I) in class 4 was working part-time in a job that he wished to continue, hoping to become full-time in the near future. Two patients (Engel class I) in class 5 had psychiatric symptoms that continued or aggravated postoperatively (psychosis and severe anxiety-dissociative state). The remaining three patients (Engel class III in 1, and Engel class I in 2) in class 5 had mild aphasia, subjective memory decline or visual field defect.

Social outcome was evaluated for 6 domains (mobility, sports, leisure time activities, social contacts, living situation and financial situation) and the results are shown in *Table IV*. Two patients (Engel class I) in class 4 had memory disturbance or somatoform disorder, another patient (Engel class 1) became busy at work so that he had less time for leisure or sport activity. Two patients (Engel class I) in class 5 had psychosis or depression.

Table II. Comparison of employment outcomes between surgically treated and medically treated patients

Author	Subjects (surgery)	Control	Follow-up (mean)	Results
Guldvog, 1991 [9]	112 focal epilepsy	92 focal epilepsy medically treated	12-28 (17) years	Higher proportion of surgically (53.2%) than medically treated patients (24.2%) claimed that treatment had improved their "working ability", but this resulted in significant improvements in the actual working situation only for those in regular education or work before treatment
Vickrey, 1995 [27]	202 focal epilepsy	46 patients unfit for surgery	1-17 (5.8) years	Changed from unemployed to employed (surgery *vs.* non-surgery): 29.2% *vs.* 25.7%, unchanged: 66.1% *vs.* 65.7%, changed from employed to unemployed: 4,8% *vs.* 8.6% (no difference)
Kellete, 1997 [28]	94 focal epilepsy	36 patients unfit for surgery		80% of seizure-free and 53% of patients having less than 10 seizures per year in gainful employment postoperatively, compared with 28% and 27% of patients having greater than 10 seizures per year or those who were unsuitable for surgery
Wiebe, 2001 [29]	40 TLE	40 TLE medically treated	1 year	Employed/attending school: surgical group, 56.4%; non-surgical 38.5% (non-significant)
Jones, 2002 [30]	61 TLE	23 TLE unfit for surgery	2-9 (5.8) years	Full-time employment: surgery group (pre 56%, post 69%), medical group (pre- 48%, post 39%) Among surgery group with full-time employment, 69% were seizure-free

Table III. Experience at Shizuoka Epilepsy Center: vocational outcome after surgery (54 patients followed for > 2 years)

		N
Class 1	Marked improvement	8
Class 2	Some improvement	7
Class 3	No change	25 (incl. 7 students)
Class 4	Some deterioration	2
Class 5	Marked deterioration	5

In summary, for both vocational and social outcomes, no change was the most common outcome, followed by improvement and then deterioration. Patients with deterioration often had neurological, neuropsychological or neuropsychiatric complications that may explain their poor employment condition.

Table IV. Experience at Shizuoka Epilepsy Center: Social outcome after surgery (54 patients followed for > 2 years)

		N
Class 1	Marked improvement	7
Class 2	Some improvement	5
Class 3	No change	37
Class 4	Some deterioration	3
Class 5	Marked deterioration	2

We then looked at the long-term employment condition. Medical records of 170 patients who underwent resection surgery (temporal lobe in 142 and extratemporal lobe in 28) more than 15 years before were reviewed and their employment conditions were retrospectively investigated. The mean age at surgery was 25.5 years (4-55) and mean postoperative follow-up period was 18.6 (15-25) years. There were 102 males and 68 females. Resection side was the left in 79 and the right in 91. Seizure outcome was Engel class I in 129 patients (76%), class II in 16, class III in 8, and class IV in 16 (no worthwhile improvement) at the last follow-up. Seven patients died. Antiepileptic medication was discontinued in 78 patients, continued in 54, and unknown in 31. Most of the unknown cases were assumed not to be in a medically serious condition, otherwise they would have been under our care.

Employment outcome is shown in *Table V*. There is generally an increase of stable employment and a decrease of unemployment. Among 12 unemployed persons after long-term follow-up, only 6 were in Engel class I, 5 had neurologic complications (anomia, paresis, anopsia), and 9 had psychiatric symptoms. They were significantly younger at seizure onset, and were unemployed or unstably employed before surgery.

Table VI compares the employment status between patients who stopped medication and those who continued taking medication. Medication status of 31 patients was unknown. Reduction towards a cessation of medication was tailored to each patient with an extended period of tapering. A patient who has discontinued medication (also without seizure) is no longer regarded as a person with epilepsy. The number of unstable employment and unemployment was apparently higher in patients who continued to take medication.

■ Interventions and rehabilitation

Not all patients need intervention in the postoperative course. However, there are some who are more vulnerable in the ability to adapt to the postoperative situation and require support and interventions.

Horowitz *et al.* [16] described a five-phase model of psychosocial development after surgery, by which the patient detaches himself from his chronic disease: moratorium, reappraisal, great expectations, turbulent period within self, and gradual adaptation. The endpoint is an autonomic person or chronically ill person. This model can be applied to postoperative rehabilitation where appropriate interventions should be programmed according to

Table V. Experience at Shizuoka Epilepsy Center: Long-term (> 15 years) employment outcome of 163 patients

	Pre	Post (> 15 years)
Employed stable	41	67
Employed unstable	41	15
Sheltered	10	7
On welfare	1	7
Unemployed	27	12
Housekeeping	4	25
Student	39	0
Unknown	0	30

* Part-time was included in the unstable employment.

Table IV. Experience at Shizuoka Epilepsy Center: Employment situation of patients who discontinued and patients who continued to take medication after surgery

	AED discontinued (N = 78)	AED continued (N = 54)*
Employed stable	47	18
Employed unstable	4	9
Sheltered	3	4
On welfare	1	4
Unemployed	3	6
Housekeeping	11	12
Student	0	0
Unknown	9	1

* (Engel class I: 29, II: 10, III: 6, IV: 9); AED: antiepileptic drugs.

the phase of the patients. Thorbecke *et al.* [3] suggested that the first three phases are passed in the first 6-12 months after surgery and only in rare cases does it take longer, and it seems that the situation at 24 months after surgery can be taken as the outcome of surgery.

Smeets *et al.* [1] recommended specific training interventions that focus on increasing the self-efficacy and coping skills of people with epilepsy so that these individuals will be able to accept their disorder and make personal and health-related choices that help them achieving better employment positions in the society.

Reeves *et al.* [17] suggested the importance of further education after surgery in case of insufficient qualification before surgery.

Thorbecke *et al.* [3] indicated that postoperative improvements of the psychosocial situation depends strongly on pre-operative expectations or aims set in connection with the surgical intervention, and recommended rehabilitation to start before surgery in the form of working

out realistic expectations together with patient and family. Postoperatively, they proposed three occasions for considering rehabilitation support: 1) immediately after surgery if there is a high risk for psychosocial complications or complications have already occurred; 2) about 6 months after surgery when there are hints that the patient does not profit as much as would have been possible; and 3) when the seizure relapses after some time without seizures. Rehabilitation should be performed by a team composed of multidisciplinary professionals.

■ Conclusion

For patients with intractable epilepsy, surgery is more effective than medical treatment to achieve employment when there is complete control of seizures. Younger patients with pre-operative education or work experience have greater benefits, and employment integration needs time. Appropriate interventions and support as well as education help vulnerable patients integrate into employment life. Such interventions should be started before surgery and performed by a comprehensive team.

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Very high frequency oscillations (over 1000 Hz) in human epilepsy

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ABSTRACT

Objective: High frequency oscillations (HFO) of 100–500 Hz have been reported in epileptic human brain. However, the questions of how fast these oscillations can reach, and which frequency range is clinically important remain unanswered. We recorded interictal and ictal very high frequency oscillations (VHFO) of 1000–2500 Hz by subdural electrodes using 10 kHz sampling rate. We describe the characteristics of VHFO, and discuss their underlying mechanism and clinical significance.

Methods: Five patients with neocortical epilepsy were studied. All patients underwent intracranial EEG monitoring with subdural electrodes. EEG recording with sampling rate of 10 kHz was conducted. Histopathology revealed malformation of cortical development in all cases.

Results: In four of five patients, very high frequency activities of 1000–2500 Hz were detected in highly localized cortical regions (one to four electrodes in individual patient). We named these activities "very high frequency oscillations (VHFO)". Interictally, VHFO appeared intermittently, and were interrupted by spikes. Sustained VHFO without spikes appeared around the start of seizures.

Conclusions: Both interictal and ictal VHFO can be recorded by subdural electrodes. Compared to HFO previously reported, VHFO have much higher frequency, more restricted distribution, smaller amplitude, and different timing of onset.

Significance: Recording of VHFO may be useful for identifying the epileptogenic zone.

1. Introduction

Animal studies of strychnine discharges have already elucidated the association between high frequency oscillations (HFO) and ictal phenomena (Gastaut and Fischer-Williams, 1959). The occurrence of HFO having frequencies higher than the conventionally analyzed range in focal epilepsy has attracted attention. Most studies reported interictal HFO in the medial temporal lobe using microelectrodes (Bragin et al., 1999, 2002; Staba et al., 2002), or a combination of microelectrodes and macroelectrodes (Worrell et al., 2008). Recent reports have described ictal HFO during focal seizures recorded by macroelectrodes (Ochi et al., 2007; Jirsch et al., 2006; Khosravani et al., 2009; Yamaguchi et al., 2008; Nakamura et al., 2008). In these reports, the frequency range of ictal HFO was less than 500 Hz at sampling rate of 2–5 kHz. Because HFO were observed only at a limited number of electrodes within the epileptogenic zone, ictal HFO have been suggested to be clinically useful in epilepsy surgery. However, the questions of how fast these oscillations can reach, and which frequency range is clinically important remain unanswered.

In four of five patients with intractable neocortical epilepsy, we recorded interictal and ictal very high frequency oscillations (VHFO) of 1000–2500 Hz by routinely used subdural electrodes using a very high sampling rate of 10 kHz. Such high frequency EEG activities have never been reported previously. In this report, we describe the characteristics of VHFO, and discuss their possible underlying mechanism and clinical significance.

2. Methods

Five patients with intractable neocortical epilepsy (one with parietal lobe epilepsy, and four with frontal lobe epilepsy) were monitored with a sampling rate of 10 kHz. Histopathology revealed malformation of cortical development in all cases. The clinical characteristics of the patients are shown in Table 1. All patients underwent intracranial EEG monitoring as a part of presurgical evaluation. Subdural electrodes (Ad-tech Medical Instrument Corporation, Racine, WI, 2.3 mm contact, effective area 4.15 mm^2, 10 mm spacing, platinum/iridium alloy) were implanted over the cortical areas depending on the finding of the noninvasive presurgical evaluation (Fig. 1). Reference electrodes were placed on the

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Table 1
Clinical characteristics of the patients.

Patient	Diagnosis	Age at onset (yrs)	Age at surgery (yrs)	Seizure	Interictal scalp EEG	Ictal scalp EEG	MRI
1	PLE	4	14	Tonic posturing	Right parietal sharp waves	Right hemisphere	Right medial parietal
2	FLE	4	27	Gestural Automatism	Right F-T spikes	Right F-T	Right frontal operculum
3	FLE	3	19	Gestural Automatism	Normal	Right hemisphere	Right basal frontal
4	FLE	5	14	Tonic facial contraction	Left frontal sharp waves	Left frontal	Left frontal operculum
5	FLE	0	22	Tonic posturing	Left central spikes	Nonlateralizing	Left posterior frontal

PLE, parietal lobe epilepsy; FLE, frontal lobe epilepsy; F-T, fronto-temporal.

surface of the skull, with the contacts of the electrodes facing away from the skull to avoid the referential activation. The EEG signals were digitally recorded by EEG-1000 (Nihon-Kohden Corporation, Tokyo) at a sampling rate of 200 Hz and time constant of 10 s for clinical purposes. After completing the routine EEG recording at a sampling rate of 200 Hz, EEG recording using a higher sampling rate of 10 kHz was conducted. The time constant was set at 10 s. Due to the limitation of the EEG machine, only 16 channels could be monitored simultaneously. To visualize high frequency activities, the horizontal (time) and vertical (amplitude) axes of the EEG display were expanded, and EEG was digitally high-pass filtered at 160 Hz (a time constant of 0.001 s) and low-pass filtered at 3 kHz. Peaks of high frequency activities were visually identified on CRT screen, and the frequency, amplitude, and duration of these activities were measured by cursors with computer assistance (Fig. 2). In this study, high frequency activities faster than 200 Hz are defined as HFO, and those faster than 1000 Hz as VHFO.

Both ictal and interictal recordings were analyzed. Interictal sections of more than two hours were visually analyzed. They were distant from the seizures from 20 h to more than 40 h in each patient.

3. Results (Table 2)

Using 10 kHz sampling rate, two seizures were recorded in Patient 1, three seizures in Patient 2, four seizures in Patient 3, two seizures in Patient 4, and two seizure in Patient 5. In Patient 5, no high frequency activities faster than 200 Hz were detected both ictally and interictally. Fig. 1 shows the MRI lesion and the locations of subdural electrodes in Patient 2. In both interictal and preictal recordings, intermittent VHFO of very low amplitude were detected at two electrodes in Patient 1, one electrode in Patient 2, two electrodes in Patient 3, and four electrodes in Patient 4. VHFO were not detected at other electrodes (Figs. 3 and 4). The frequencies of intermittent VHFO ranged from 1000 to 2500 Hz. VHFO were interrupted by spikes. Interictal VHFO and preictal VHFO had identical characteristics in terms of frequency, amplitude, duration, temporal relationship with spikes, and distribution. The amplitudes of VHFO were 3.5–29.4 μV in Patient 1, 4.4–24.7 μV in Patient 2, 3.5–19.4 μV in Patient 3, and 5.3–15.0 μV in Patient 4. The VHFO durations were 4–45 ms in Patient 1, 2–75 ms in Patient 2, 20–226 ms in Patient 3, and 6–18 ms in Patient 4 (Fig. 5).

Sustained VHFO without interrupting spikes appeared at the start of seizures, superimposing on slower rhythmic activities (70–100 Hz) (Figs. 3 and 4). The VHFO lasted approximately 10 s in Patient 1, 12–13 s in Patient 2, 35–53 s in Patient 3, and 10–12 s in Patient 4. The frequencies of sustained VHFO were 1000–2000 Hz in Patient 1, 1000–2500 Hz in Patient 2, and 1000–1500 Hz in Patients 3 and 4. The amplitudes of sustained VHFO were 3.5–19.6 μV in Patient 1, 7.4–26.5 μV in Patient 2, 5.3–15.0 μV in Patient 3, and 6.2–10.6 μV in Patient 4. VHFO were detected in all seizures recorded with 10 kHz sampling rate. The characteristics of sustained VHFO were consistent among seizures in each patient.

On interictal recordings, HFO of 300–700 Hz were detected at ten electrodes including the three electrodes detecting VHFO in Patient 1 (Figs. 5A and 6A). HFO of 350–600 Hz were detected at nine electrodes including the one electrode detecting VHFO in Patient 2 (Figs. 5B and 6B). No HFO were detected in Patient 3 (Fig. 6C). HFO of 400–600 Hz were detected at six electrodes including the four electrodes detecting VHFO in Patient 4 (Fig. 6D). The amplitudes of interictal HFO were 11.8–279.4 μV in Patient 1, 8.8–150.0 μV in Patient 2, and 10.3–71.5 μV in Patient 4. The durations of interictal HFO were 7–33 ms in Patient 1, 8–35 ms in Patient 2, and 18–29 ms in Patient 4. Ictally, no HFO (over 200 Hz) were observed when sustained VHFO were recorded, while 70–100 Hz rhythmic activities were seen.

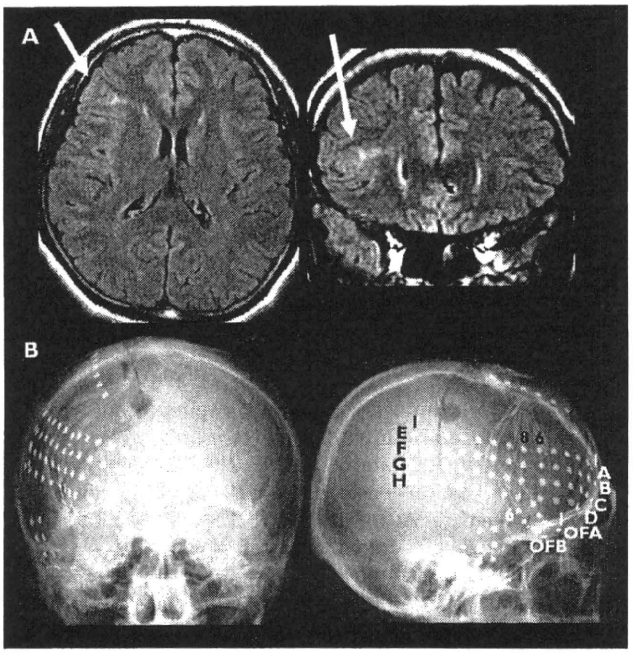

Fig. 1. MRI lesion and subdural electrodes (Patient 2). (A) Brain MRI with FLAIR sequences showing a high intensity area in the right frontal operculum (arrow). (B) X-ray photographs showing subdural electrodes. Subdural grid electrodes were implanted over the right fronto-temporal, and parietal areas.

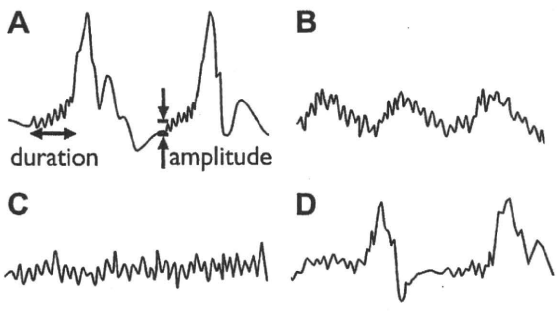

Fig. 2. Schematic illustrations of typical VHFO waveform. (A) Interictally and preictally, intermittent VHFO are followed by spikes. (B) VHFO become sustained at the start of the seizures. They are superimposed on slower rhythmic activities. (C) Then, slower rhythmic activities become less prominent, and disappear. (D) Thereafter, VHFO are intermixed with spikes.

Table 2
The characteristics of VHFO and HFO.

Patient	Number of seizures	Number of electrodes with VHFO	Amplitude (interictal) (μV)	Duration (ms)	Amplitude (ictal) (μV)	Number of electrodes with HFO	Amplitude (μV)	Duration (ms)
1	2	3	3.5–29.4	4–45	3.5–19.6	10	11.8–279.4	7–33
2	3	1	4.4–24.7	2–75	7.4–26.5	9	8.8–150.0	8–35
3	4	2	3.5–19.4	20–226	5.3–15.0	0	–	–
4	2	4	5.3–15.0	6–18	6.2–10.6	6	10.3–71.5	18–29

In four patients with VHFO, the electrodes recording VHFO were located above the MRI lesions, and surgical resection of the MRI lesion together with the sites where the electrodes recorded VHFO was performed. The locations of the electrodes with VHFO, those with HFO, and those with interictal spikes, seizure onset zone defined by conventional EEG, MRI lesion, and the extent of surgical

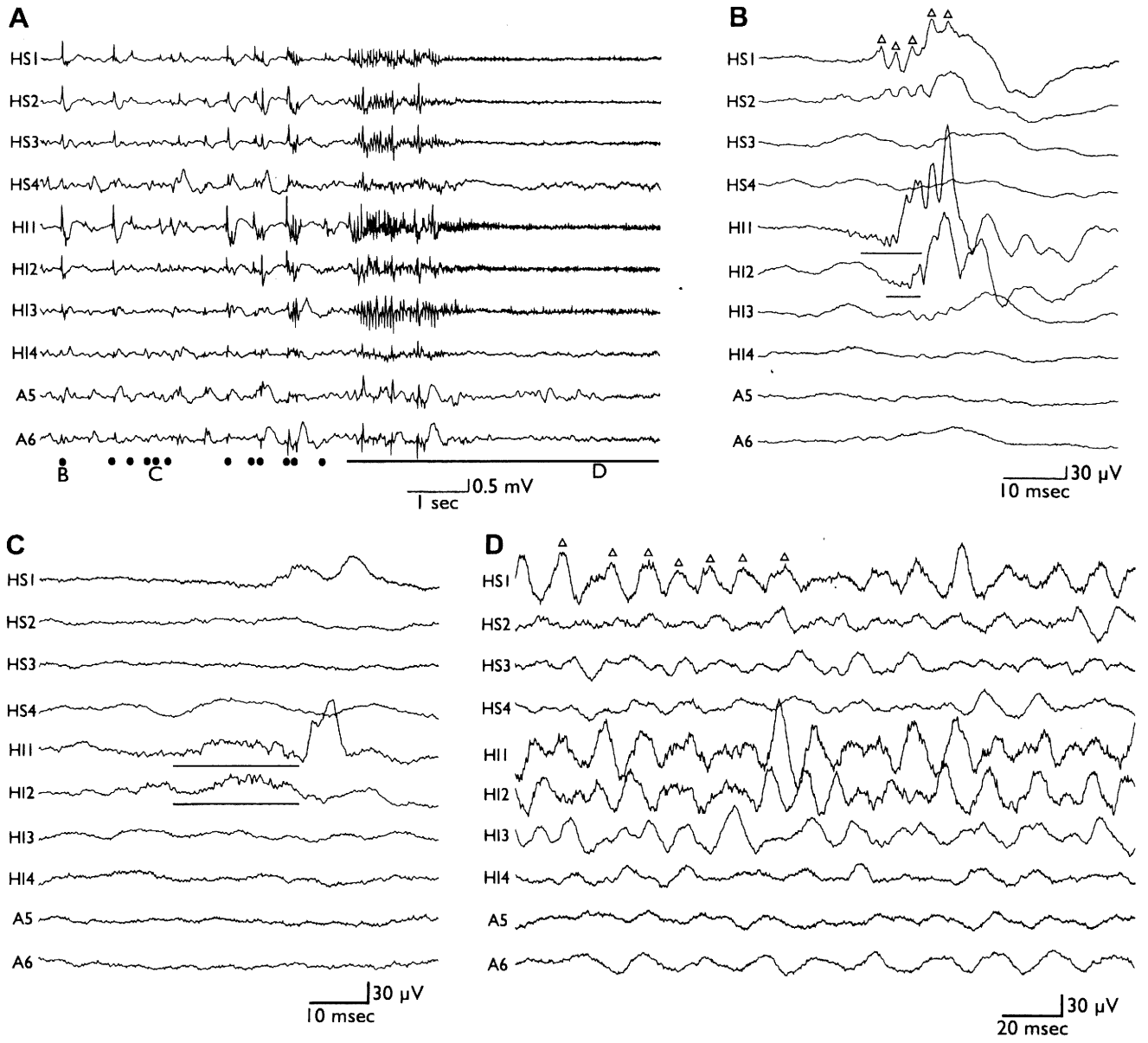

Fig. 3. Ictal EEG recorded at a sampling rate of 10 kHz (Patient 1). (A) Ictal EEG shown using conventional filter settings (low-pass filter 120 Hz, time constant 0.1 s). Only 10 channels are shown. Ictal EEG shows initial spike burst at HI1–4/HS1–4 and spike-and-waves at A5–6, followed by electrodecremental pattern and low amplitude fast activities at HI1–3/HS1. Filled circle and straight line indicate the presence of VHFO. The EEG at B, C, and D is shown using VHFO filter settings. (B and C) Preictal VHFO detected visually using low-pass filter of 3 kHz and time constant of 0.001 s. Preictal VHFO of 1000–2500 Hz are observed at HI1 and HI2 electrodes (underlined). They appear intermittently before the start of seizures, and are interrupted by spikes. The amplitudes are 3.5–22.1 μV (note the calibrations), and the durations were 12–27 ms. These activities are not observed at other electrodes. HFO of 350–550 Hz are seen at HS1–2 and HI1–2 electrodes, with durations of HFO of 10–14 ms and the amplitudes of 22.6–234.7 μV. Representative HFO peaks are marked by triangles (B). (D) VHFO recorded at HI1, HI2 (both electrodes also record preictal VHFO) and HS1 electrodes become sustained at the start of seizure. The frequencies of VHFO are 1000–2000 Hz and the amplitudes are around 8.8–14.1 μV. These activities superimpose on the slower rhythmic activities (70–90 Hz) (marked by triangles). Sustained VHFO lasted approximately 10 s. Again, these activities are not observed at other electrodes, although rhythmic activities are recorded.

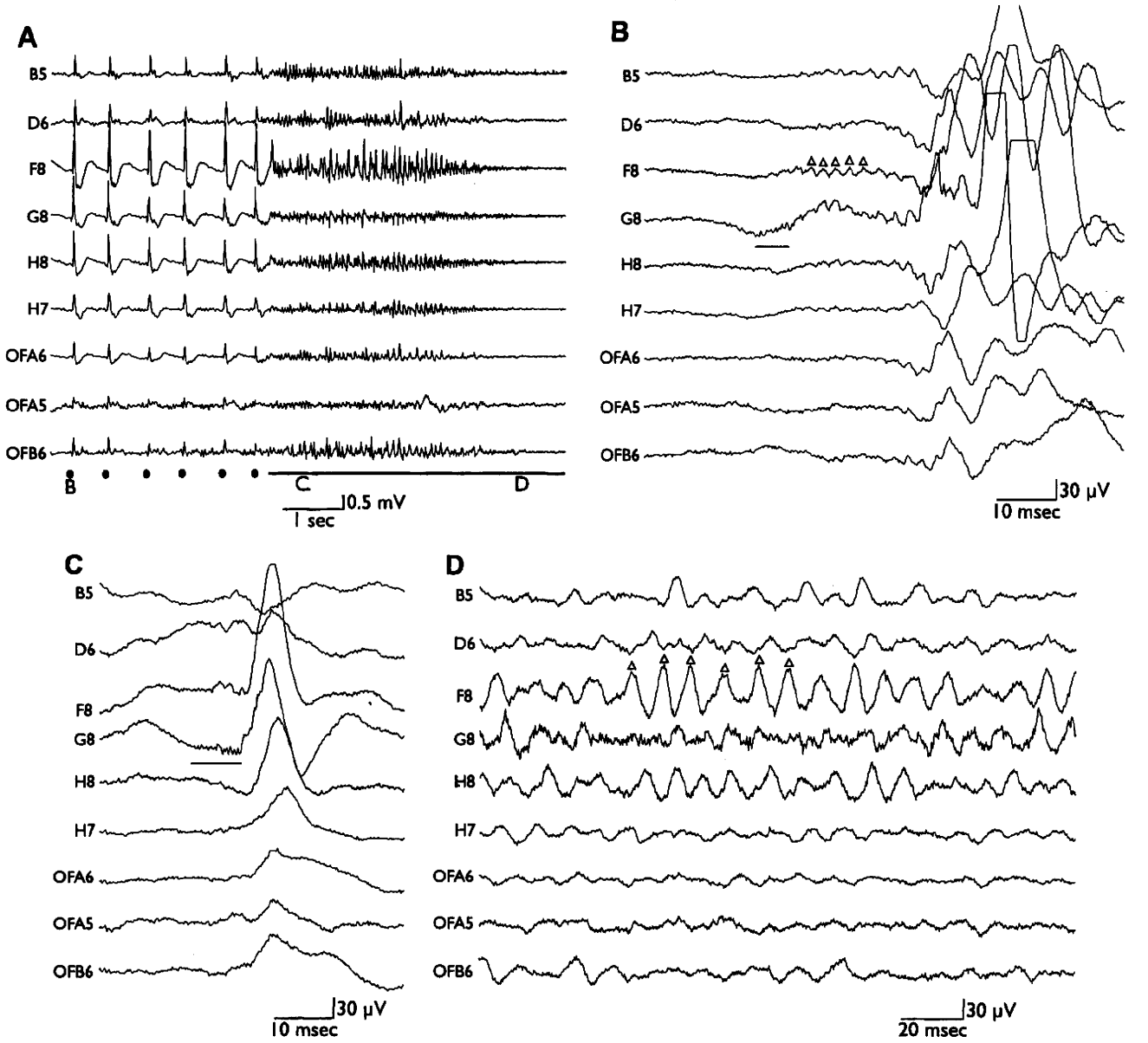

Fig. 4. Ictal EEG recorded at 10 kHz sampling rate (Patient 2). (A) Ictal EEG shown using conventional filter settings (low-pass filter 120 Hz, time constant 0.1 s). Only 9 channels are shown. Ictal EEG shows that repetitive spiking is replaced by spike bursts at ictal onset. Spike bursts are later followed by electrodecremental pattern. Filled circle and straight line indicate the presence of VHFO. The EEG at B, C, and D is shown using VHFO filter settings. (B) Preictal VHFO detected visually using low-pass filter of 3 kHz and time constant of 0.001 s. VHFO of 1000–2500 Hz are detected at G8 electrode. The duration of VHFO is 5 ms, and the amplitudes are 7.4–16.2 μV. HFO of 350–600 Hz are also observed at electrodes B5, D6, F8, G8, H8, and H7, with durations of 18–28 ms and amplitudes of 10.3–64.7 μV. Representative HFO peaks are marked by triangles. They are interrupted by spikes. (C) Intermittent VHFO of 1400–2000 Hz are recorded at G8 electrode around seizure onset. The duration is 7 ms, and the amplitudes are 8.8–17.6 μV. (D) VHFO of 1000–2500 Hz become sustained after the electrodecremental pattern appears using conventional EEG setting. The sustained VHFO superimpose on the slower rhythmic activity (80–100 Hz) (marked by triangles). The amplitudes are 8.8–20.6 μV.

resection in each patient are summarized in Fig. 6. The area with VHFO was always located within the seizure onset zone, the irritative zone, and area with HFO. In Patient 5, MRI lesion involved the left frontal lobe including the precentral gyrus, and the irritative zone and seizure onset zone defined by conventional EEG were located over the MRI lesion. Partial frontal resection sparing the precentral gyrus was performed. The postoperative follow-up period was nine months, seven months, ten months, two months, and four months, in Patients 1–5, respectively. Postoperatively, Patient 1 has only simple partial seizures characterized by lightheadedness and blurred vision for several seconds. The other three patients with VHFO (Patients 2–4) have been seizure free. Patient 5 had several motor seizures.

4. Discussion

Using routine subdural electrodes and 10 kHz sampling rate, we were able to identify visually low amplitude VHFO of 1000–2500 Hz both in the interictal and ictal states. Although we could record similar frequency "VHFO" in median nerve SEP (Sakura et al., 2009), such high frequency activities have never been reported before in association with spontaneous epileptic discharges in humans. Moreover, as described later, we suspect that the underlying pathophysiology of these activities is different from that of HFO. Therefore, we named these activities "very high frequency oscillations (VHFO)" to distinguish them from HFO.

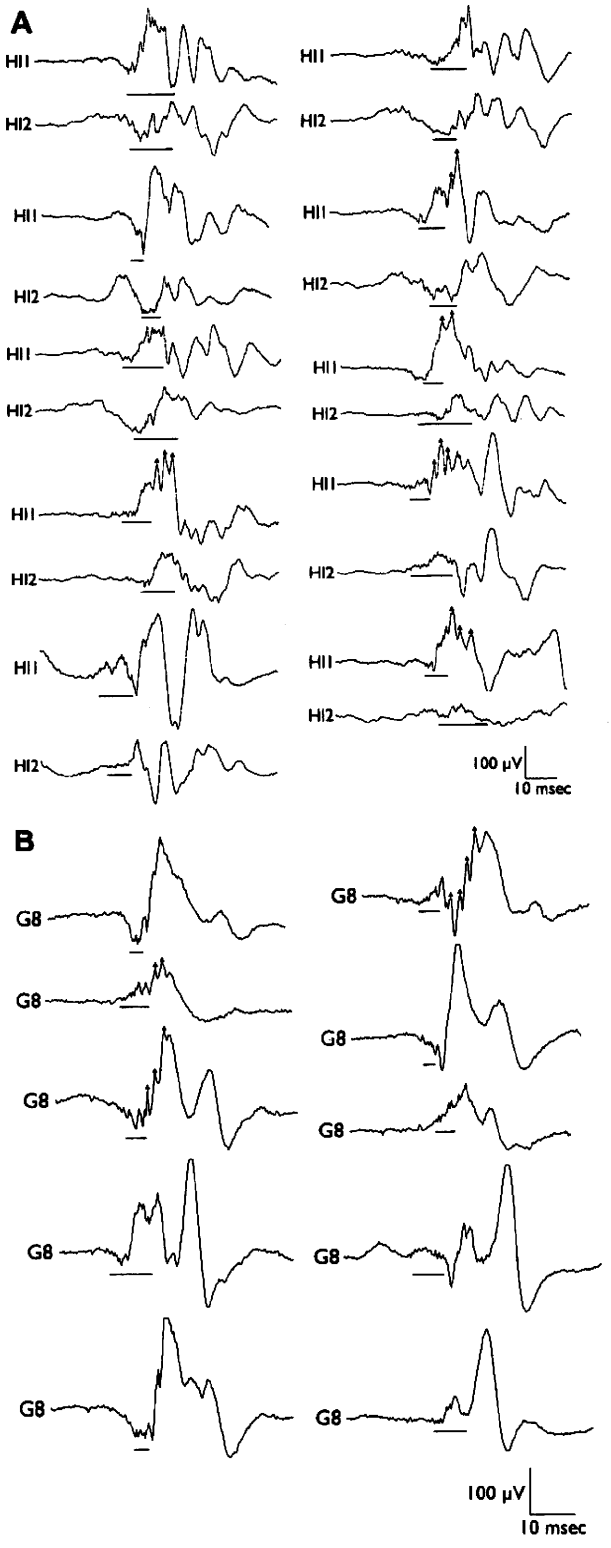

Fig. 5. Interictal EEG recorded at a sampling rate of 10 kHz (Patients 1 and 2). Interictal VHFO detected visually using low-pass filter of 3 kHz and time constant of 0.001 s. Only electrodes with VHFO are shown. Underlines indicate the presence of VHFO. Representative HFO peaks are marked by triangles. (A, Patient 1) Interictal VHFO of 1000–2500 Hz are observed at HI1 and HI2 electrodes. They are followed by spikes. Ten samples of VHFO for each electrode are shown. The amplitudes of interictal VHFO were 3.5–29.4 μV, and the durations were 4–45 ms. (B, Patient 2) Interictal VHFO of 1000–2500 Hz are observed at G8 electrode. Ten samples of VHFO are shown. The amplitudes of interictal VHFO were 4.4–24.7 μV, and the durations were 2–75 ms.

VHFO were highly localized and were recorded by one to four electrodes in each patient. Therefore, these activities were most likely not muscular or other artifacts although an extracranial reference electrode was used. VHFO were interrupted by spikes in the interictal state, while spikes were not seen when VHFO became sustained at the onset of seizures. Therefore, we speculate that the VHFO may be excitatory phenomena, and the spikes may have an inhibitory effect on VHFO, and probably inhibit seizure initiation. It has also been proposed that the after-inhibition produced by interictal spikes protects against the occurrence of ictal discharges by maintaining a low level of excitation in a general condition of hyperexcitability determined by the primary epileptogenic dysfunction (de Curtis and Avanzini, 2001).

Synchronously firing bursting neurons have been considered to be the mechanism of HFO generation (Bragin et al., 2002). Meanwhile, the amplitude of VHFO was very low, and the frequency was markedly higher than that of HFO. Considering that individual neuronal firing rates do not approach the VHFO range because of the presence of refractory period, we speculate that low amplitude VHFO recorded by macroelectrodes may represent summated activities from multiple subgroups of neurons with various, non-synchronous firing rates and phases. Synchronization of population activity may be important for the generation of HFO, whereas non-synchronized firing of many neuronal groups may be necessary for the generation of VHFO. The distribution of VHFO was more restricted than that of HFO. Considering that the distribution and the onset timing of VHFO are also different from those of HFO, VHFO and HFO may have different pathophysiological mechanisms.

The next question is why previous studies did not demonstrate VHFO. Khosravani et al. (2009) used 5 kHz sampling rate and recorded 100–500 Hz HFO in patients with temporal lobe epilepsy, but they did not detect VHFO faster than 1000 Hz. Worrell et al. (2008) also did not observe VHFO faster than 1000 Hz from the temporal lobe even though they used 32 kHz sampling. This difference in VHFO detection may be due to the location of the epileptogenic zone (temporal in previous studies versus extratemporal in this study) or pathology of epileptogenic lesions. Considering that histology revealed malformation of cortical development in our four cases, abnormal cellular profiles of malformation of cortical development may be important for the generation of VHFO. Further studies of epileptogenic lesions other than malformation of cortical development are necessary.

VHFO were recorded in highly localized cortical regions (only one to four electrodes in individual patient). The electrodes at which ictal VHFO were recorded were located within the seizure onset zone identified by conventional EEG recordings. The ictal discharges captured by conventional EEG usually spread from ictal onset zone to the other cortical areas, whereas the distribution of VHFO never spread during seizures in our four cases. Therefore, VHFO may be very specific for epileptogenic zone and/or ictal onset zone. The detection of VHFO may be clinically useful for identifying core of the epileptogenic zone although the whole epileptogenic zone cannot be delineated by VHFO. Although the reason why VHFO were not detected in one patient (Patient 5) is not clear, the core of the epileptogenic zone might not be covered by the electrodes considering that the patient has not been seizure free postoperatively.

In summary, VHFO were recorded by routinely used subdural electrodes with 10 kHz sampling rate. Compared to HFO previously reported, VHFO have much higher frequency, more restricted distribution, smaller amplitude, and different timing of onset. Therefore, VHFO generation may involve mechanisms different from those of HFO. It is likely that VHFO may directly reflect summation of activities arising from non-synchronized multiple neuronal subgroups, and will provide further insight into epilepto-

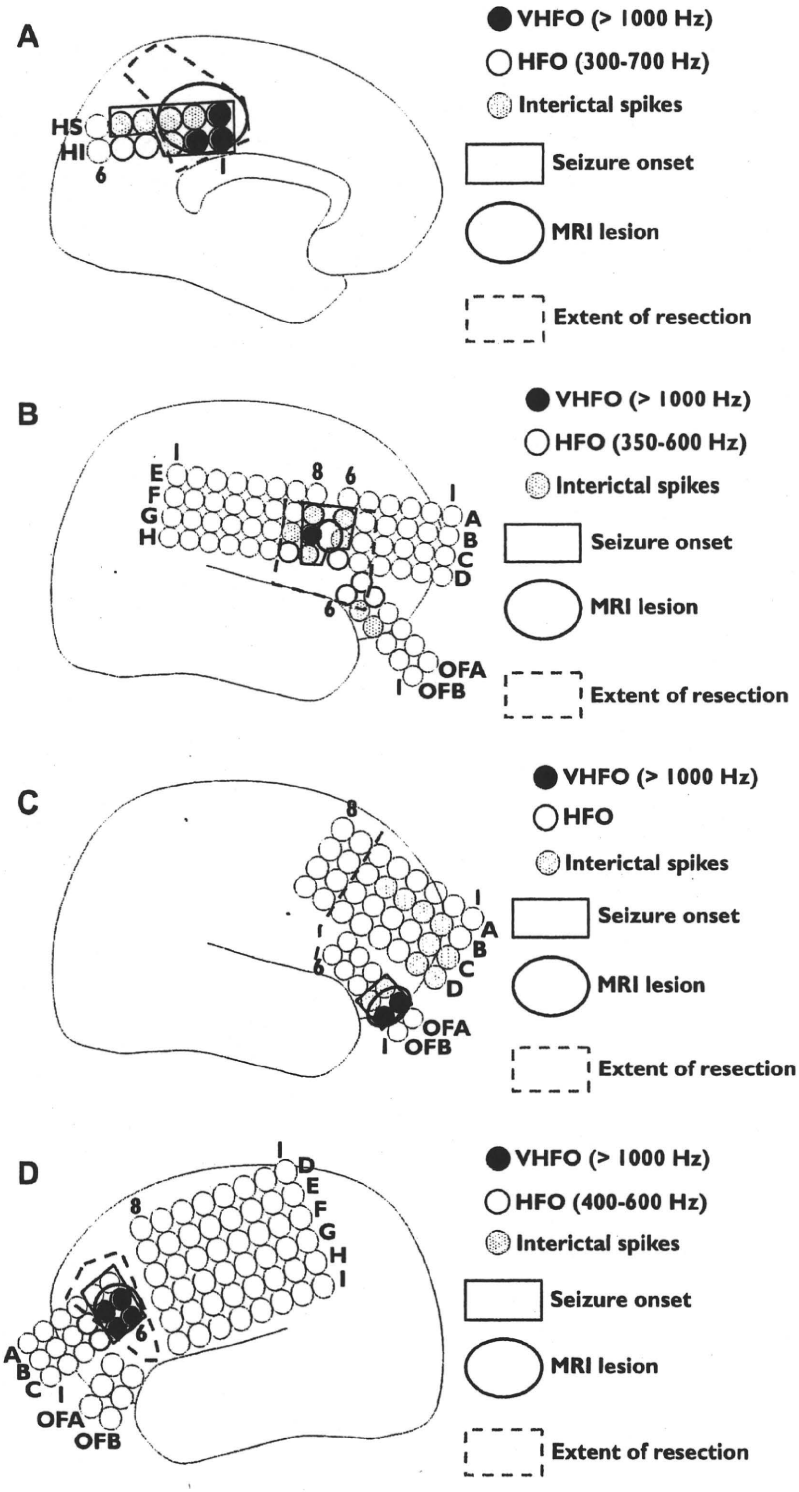

Fig. 6. The location of the electrodes with VHFO (red) and those with HFO (green circles), and those with interictal spikes (dotted circles), seizure onset zone defined by conventional EEG (solid line), MRI lesion (purple line), and the extent of surgical resection (orange broken line).

genesis and ictogenesis. The detection of VHFO may be very useful for identifying the epileptogenic zone. Further studies are necessary to clarify the clinical significance of VHFO.

Acknowledgement

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None of the authors has any conflict of interest to disclose.

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therefore, a diagnosis of exclusion because a disease morphological marker in the peripheral nerve is still lacking. However, a definite diagnosis of MN is possible.

The biopsy of the motor branch of the obturator nerve should be considered as a potential diagnostic tool for early differential diagnosis of selected cases of LMND and MN.

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Potential Conflict of Interest

Nothing to report.

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Ictal Very Low Frequency Oscillation in Human Epilepsy Patients

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Using intracranial electroencephalographic recordings, we identified a distinct brain activity in 3 patients with refractory epilepsy characterized by very early occurrence from 8 minutes 10 seconds to 22 minutes 40 seconds prior to clinical seizure onset, periodical appearance of slow negative baseline shift, long interpeak interval of 40 to 120 seconds, and disappearance after clinical seizure. We named this activity "very low frequency oscillation" (VLFO), which reflected a dynamic process during the preictal state.

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This observation may render new insight into epileptogenesis and provide additional information concerning the epileptogenic zone as well as prediction of epileptic seizures.

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Electroencephalography (EEG) is essential for assessing patients with epilepsy. Conventionally, EEG is usually analyzed at a narrow frequency band ranging from 0.5Hz to 70Hz. However, brain activities beyond the conventional frequency range, such as high-frequency oscillation (HFO) ranging from 100Hz to 500Hz,[1,2] very high frequency oscillation (VHFO)[3] (over 1,000Hz), infraslow brain activity,[4] and ictal direct current shift (IDS)[5] have also been observed. In recent years, these unconventional EEG findings have remained a topic of intensive investigation for their clinical significance.

We first report here a distinct ictal electrophysiological activity in the infraslow band, which was detected in 3 patients with refractory neocortical epilepsy by means of subdural electrodes. It was characterized by very early occurrence before the clinical seizure onsets, periodical appearance of slow negative baseline shifts, gradual evolution in amplitude, frequency, and distribution, and disappearance soon after the clinical seizures. Since it was distinguishable from any previously known ictal EEG patterns, we named it "ictal very low frequency oscillation" (VLFO) to highlight its unique neurophysiological features.

Patients and Methods

We investigated 26 patients with intractable neocortical epilepsy who underwent presurgical evaluation with subdural electrodes because noninvasive investigations could not delineate their epileptogenic zone (EZ), between July 2004 and June 2009 at the Shizuoka Institute of Epilepsy and Neurological Disorders. A low-frequency filter of 0.016Hz, which was in accordance with a time constant (TC) of 10 seconds was used during recording in these patients.

We used a digital EEG machine (Neurofax, Nihon-Koden Corp., Tokyo, Japan). The invasive electrodes were placed according to the clues indicated by noninvasive studies. Each subdural electrode was 2.3mm in diameter, linearly arrayed, made of platinum-iridium alloy, and with a center-to-center electrode distance of 10mm (Ad-Tech Medical Instrument Corp., Racine, WI). Recording sessions started 1 week after the implantation of electrodes, and lasted for 2 weeks.

The parameters for the conventional analysis of EEG are TC of 0.1 second, high frequency filter (HFF) of 70 Hz, and 10 seconds per epoch of EEG display. To pick up very slow periodic electrical potentials, we evaluated the EEG with TC of 10 seconds and a highly compacted EEG display with 5 minutes per epoch (30 times the routine EEG display). For each patient, a 2-hour EEG window with 1 hour before and 1 hour after the clinical seizures, and 5-hour continuous interictal EEG was evaluated.

Results

Among 26 patients, only 3 patients clearly demonstrated VLFO (Figs 1–3, Supporting Fig S1D, and Supporting Figs S2–S4). Patient 1 was an 18-year-old female, having drug-resistant seizures including simple partial seizures (SPS) manifesting focal motor symptoms and secondarily generalized tonic-clonic seizures (sGTC) since 2 years of age. Her brain magnetic resonance imaging (MRI) showed increased signal intensity on the right parietal cuneus in fluid attenuation inversion recovery (FLAIR) imaging. The scalp EEG demonstrated interictal low-amplitude spikes or sharp waves over the right parietal area. Ictal discharges started with low-amplitude slow waves over the right occipital and posterior temporal areas. Patient 2 was a 30-year-old female whose seizures occurred at the age of 16 years. Her seizures, including auras manifesting as complex auditory symptoms, complex partial seizures (CPS), and sometimes followed by sGTC, were refractory to antiepilepsy drugs (AEDs). Her brain computed tomography (CT) and MRI were normal. Scalp interictal EEG showed epileptiform discharges in the left anterior temporal area, and ictal discharges started with 6Hz, theta activities over the left anterior temporal area, evolving into the surrounding areas. Patient 3 was a 23-year-old male having seizures since 12 years of age. His refractory CPS started with the eyes and head turning to the left side, sometimes followed by sGTC. Surface interictal EEG showed intermittent spikes over the right frontal, temporal, and parietal lobes dependently, while diffuse ictal discharges were found widely over the right hemisphere. His brain MRI showed mild increased signal intensity in the right frontal inferior sulcus in FLAIR imaging (see Fig 3).

During intracranial EEG monitoring, 9 SPS and 7 sGTC in Patient 1; 2 SPS, 4 CPS, and 2 sGTC in Patient 2; and 4 CPS and 11 sGTC in Patient 3 were captured and analyzed in total.

With highly compacted EEG display and long TC of 10 seconds, very slow, irregular, low-amplitude baseline fluctuations were found during the interictal period. However, there was no regular, periodic, or evolving pattern (see Supporting Fig S1B). In contrast, VLFO were clearly identified only prior to CPS (8/8 seizures) and sGTC (20/20 seizures) but not SPS (0/11 seizures) in these 3 patients. The pattern of VLFO was homogenous, but with variation of time duration and amplitude