Brain Research 1652 (2016) 119–126

Contents lists available at ScienceDirect

Brain Research

journal homepage: www.elsevier.com/locate/brainres

Research report

Time-frequency analysis of intracranial EEG in patients with myoclonic seizures

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ARTICLE INFO

Keywords:
Myoclonic seizure
Time-frequency analysis
Electrocorticogram (ECoG)
Epileptogenic zone
Surgery

ABSTRACT

Myoclonic seizures are defined as generalized seizures according to the classification of seizure by the International League Against Epilepsy (ILAE). The pathogenesis of myoclonic seizures is not yet clear. There are very few studies on the focal surgical treatment of myoclonic seizures. The aim of this study is to investigate the characteristics of myoclonic seizure onset in different bands of the intracranial electroencephalogram (EEG) and their dynamic changes in temporal and spatial evolution. We studied four patients with myoclonic seizures who were under the focal resection of the epileptogenic zone. We retrospectively analyzed the semiology, electrocorticogram (ECoG) and imaging data of these patients, and conducted time-frequency analysis of broadband ECoG activity. We found that myoclonic seizures without clinical lateralizing signs could be improved by the resection of the epileptogenic zone. The ECoG power in different frequency bands increased to a peak at 0.5 s before the clinical seizure onset and decreased quickly afterwards. The power of alpha activity was highest during the preictal and ictal periods. The central zone had higher power than the epileptogenic zone in all frequency bands during the preictal period, but this difference was not statistically significant. Our results suggest that myoclonic seizures in some patients might have a focal origination, with a fast bilateral propagating network in all frequency bands, especially the alpha band.

1. Introduction

Myoclonus is defined as sudden, brief, shock-like movements caused by muscle contractions (positive myoclonus) or inhibitions (negative myoclonus). The major categories of myoclonus in the popular etiological classification scheme are: physiologic, essential, epileptic, and symptomatic (Marsden et al., 1982). Epileptic myoclonus can occur as one component of a seizure, the only manifestation (myoclonic seizure), or one of multiple seizure types within an epileptic syndrome. Myoclonic seizures are epileptic seizures in which the motor manifestation is myoclonus (Caviness, 1996). They are involuntary, sudden, brief, shock-like contractions that may be generalized or confined to the face, trunk or to one or more extremities or even to individual muscles or groups of muscles (Commission on Classification and Terminology of the International League Against Epilepsy, 1981).

Myoclonic seizures were defined as generalized seizures according to the classifications of seizure by the ILAE in 1981 and 2010 (Berg et al., 2010; Commission on Classification and Terminology of the ILAE, 1981). Their physiological mechanism is believed to involve interactions of cortical and subcortical centers (Caviness and Truong, 2011). The abnormal excessive reciprocal excitation of cortical and subcortical sites is much more diffuse and bilateral at the instant of myoclonus generation (Caviness, 2014). Despite the subcortical involvement, the cortical discharge precedes and drives the myoclonus event. Therefore, it is considered that myoclonic seizures are generalized without focal onset and are usually accompanied by generalized ictal epileptiform electroencephalogram (EEG) discharges (Caviness, 1996).

Abbreviations: ILAE, the International League Against Epilepsy; EEG, electroencephalogram; ECoG, electrocorticogram; MRI, magnetic resonance imaging; EZ, the epileptogenic zone; SEEG, stereoelectroencephalography; EMG, electromyography; MEG, magnetoencephalography; HFO, high-frequency oscillations; GTCS, generalized tonic-clonic seizures; SEM, standard error of the mean; STFT, Short-Time Fourier Transformation; ANOVA, analysis of variance.

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http://dx.doi.org/10.1016/j.brainres.2016.09.042
Received 1 May 2016; Received in revised form 18 August 2016; Accepted 27 September 2016
Available online 28 September 2016
0006-8993/

Table 1
Clinical characteristics of four patients.

Patient No.	Age/gender	History of epilepsy before surgery (years)	Seizure type (outcome)	Antiepileptic medications	Neuroimaging	Electrode placement	Surgery	Follow-up (months)	Pathology
1	22/female	17	myoclonic seizures (Eagle 1), tonic seizures (Eagle 1), GTCS (Eagle 1).	LEV	MRI: normal MEG: RF, RP, RT	RF, RT, RPCT	RF, RT	14	HS Ia , FCD IIIa
2	14/male	12	myoclonic seizures (Eagle 2), epileptic spasms (Eagle 2), GTCS (Eagle 3), complex partial seizures (Eagle 2).	VPA, CZM, GB	MRI: L hemispheric mild diffuse atrophy MEG: bilateral TP	LF, LT, LPTO, LMC, LP,	LF, LPTO, LPO	19	FCD IIId
3	8/male	4	myoclonic seizures (Eagle 2), GTCS (Eagle 2), complex partial seizures (Eagle 2).	VPA, OXC, LTG	MRI: RP, RPT and RO lesion, PET/CT: RP, RPT, RO	RPT, RCP, RPPO	RPTPO	39	GMH , FCD Ic
4	6/male	2.5	myoclonic seizures (Eagle 1), epileptic spasms (Eagle 1), GTCS (Eagle 1).	LEV, VPA, LTG	MRI: normal, MEG: L lateral fissure	LF, LP, LCPO	LF, LPTPO	24	GMH , FCD I

GTCS: generalized tonic-clonic seizures. LEV: levetiracetam, VPA: sodium Valproate, CZM: clonazepam, GB: gabapentin, OXC: oxcarbazepine, LTG: lamotrigine. MRI: magnetic resonance imaging, MEG: magnetoencephalogram, PET/CT: positron emission tomography/computed tomography. R: right, F: frontal, P: parietal, T: temporal, L: left, TP: temporal parietal, PT: posterior temporal, O: occipital, PCT: posterior centrotemporal, PTO: posterior temporal occipital, MC: medial central, CP: centroparietal, PPO: posterior parietal occipital, CPO: centroparietal occipital, PO: parietal occipital, PTPO: posterior temporal parietal occipital. HS: hippocampal sclerosis, FCD: focal cortical dysplasia, GMH: gray matter heterotopia.

The primary treatment for myoclonic seizures is antiepileptic drugs, but some seizures remain refractory to medication. Studies have shown that ketogenic diet therapy (Hartman, 2008), vagus nerve stimulation (Smith et al., 2000), and deep brain stimulation (Vesper et al., 2007) might be effective for some intractable myoclonic seizures. Surgery is a nonpharmacological alternative treatment. However, myoclonic seizures are often widespread at seizure onset and not easily localized, which makes epilepsy surgery difficult to perform, especially in the absence of associated focal brain lesions. Therefore, there are very few studies on the focal surgical treatment of myoclonic seizures. Akiyama et al. (2011) reported that one patient with myoclonic seizures and epileptic spasms underwent left frontal lobectomy, and remained seizure-free for 1 year. In a previous study in our epilepsy center, Yu et al. (2015) reported that six myoclonic seizure patients with brain lesions evident on magnetic resonance imaging (MRI) became seizure-free after focal resections of the epileptogenic zone (EZ). These results suggested that the myoclonic seizures might be induced by focal brain lesions.

Are myoclonic seizures generalized seizures, focal seizures, or generalized seizures with a focal component? EEG studies (Auvin et al., 2008) have shown that epileptiform discharges stimulating the motor cortex resulted in myoclonus jerk. In a given region of the primary motor cortex, a phasic discharge superimposed with a fast oscillation leads to a local myoclonic jerk (Chauvel et al., 1992). Studies in stereoelectroencephalography (SEEG) and electromyography (EMG) in central epilepsies showed that the motor cortex (MI) spike discharge is responsible for localized muscular activity, with a clear correlation between them in low frequencies (Chauvel and McGonigal, 2014). These studies suggested that myoclonic seizures might have focal origins and be related to the central zone.

EEG is one of the most important technologies used to locate the epileptogenic zone. Compared with scalp EEG, electrocorticogram (ECoG) can record electrical activity more accurately as it provides more detailed information especially in quantitative analysis. There is considerable interest in the analysis of intracranial EEG activity outside the conventional frequency bands (1–70 Hz), particularly with respect to determination of seizure onset (Rodin, 2009). Many studies have investigated the value of high-frequency oscillations (HFO) as a new biomarker for localizing seizure onset and determining epileptogenicity. In neocortical epilepsy, some studies have addressed the utility of HFOs in seizure onset localization (Modur and Scherg, 2009; Ochi et al., 2007). Previous studies have investigated the conventional frequency bands of EEG and HFOs independently; however, simultaneous research on broadband EEG activity (0.01–250 Hz range) in myoclonic seizures has not yet been done. One research study tried to explore the spatial distribution process of HFO in myoclonic seizures (Akiyama et al., 2011). Unfortunately, this research result was based on only one patient, and did not involve the dynamic changes in the temporal and spatial evolution of the broadband EEG.

We supposed that myoclonic seizures had some focal characteristics. In our study, we localized the EZ and performed surgery in each patient with myoclonic seizures. Because all patients had shown great improvement in myoclonic seizures after surgeries, we inferred that their EZ had been resected. We retrospectively analyzed the semiology, ECoG, and imaging data of these patients, and conducted a quantitative analysis of broadband ECoG activity. The main purpose of our study was to study the characteristics of myoclonic seizure onset in different band ECoG and their dynamic changes in temporal and spatial evolution. Moreover, we aim to study the relationship between the EZ of myoclonic seizures and the central zone. Through our study, we hope to deepen our knowledge of the pathogenesis of myoclonic seizures.

2. Results

2.1. Semiology and ECoG characteristics of myoclonic seizures

All patients had at least two types of generalized seizures including myoclonic seizures and generalized tonic-clonic seizures (GTCS) according to the semiology (Table 1). Two patients (patients 2 and 4) had epileptic spasms. One patient (patient 1) had tonic seizures. Two patients (patients 2 and 3) had complex partial seizures. Myoclonic seizure characteristics of four patients are shown in Table 2. Myoclonic seizures in all patients involved bilateral extremities without definite clinical lateralizing signs.

Epileptic ECoG discharges were found in all four patients just before the clinical seizure onset. Low-amplitude fast activities were observed in two patients and spike-and-wave was captured in the other two patients.

2.2. Surgical resection and postsurgical outcome

Focal EZ resections were performed in all patients. In all patients, the resected zone was not limited to a single lobe (Table 1). The resected zones involved the right frontal and temporal regions in patient 1, the left frontal lobe, the left posterior temporal-occipital conjunction, and the left parietal-occipital conjunction in patient 2, the right posterior temporal-parietal-occipital conjunction in patient 3, the left frontal region, and the left posterior temporal-parietal-occipital conjunction in patient 4.

The four patients had been postoperatively followed-up for 14–39 months. Two patients (patients 1 and 4) were seizure-free (Engel Class I) in myoclonic seizures and other seizures, one patient (patient 3) had greatly improved (Engel Class II) in myoclonic seizures and other seizures, and one patient (patient 2) had shown great improvement (Engel Class II) in myoclonic seizures and moderate improvement (Engel Class III) in GTCS. In summary, all patients had good postsurgical outcomes in myoclonic seizures.

2.3. Time-frequency analysis of ECoG in myoclonic seizures

After the entire video-ECoG of each patient was reviewed, a total of 11 ECoG segments with myoclonic seizures (Fig. 1A) and the same number of interictal ECoG segments met the inclusion criteria for analysis. Data in the following text and figures were expressed as mean ± standard error of the mean (SEM).

2.3.1. Dynamic changes of power

The power in the interictal period and in the peri-seizure-onset period, which means from 2 s prior to the clinical seizure onset until 3 s after the clinical seizure onset, showed approximately the same trend in every frequency band within the resected zone, the central zone, and other electrode covered areas (zone NON). The power was lowest during the interictal period, then increased 2 s prior to the clinical seizure onset. During the preictal period, power spiked and reached a peak 0.5 s before clinical seizure onset. At 1 s after clinical seizure onset, it slipped to its baseline level from 1 s prior to the clinical seizure onset (Fig. 2).

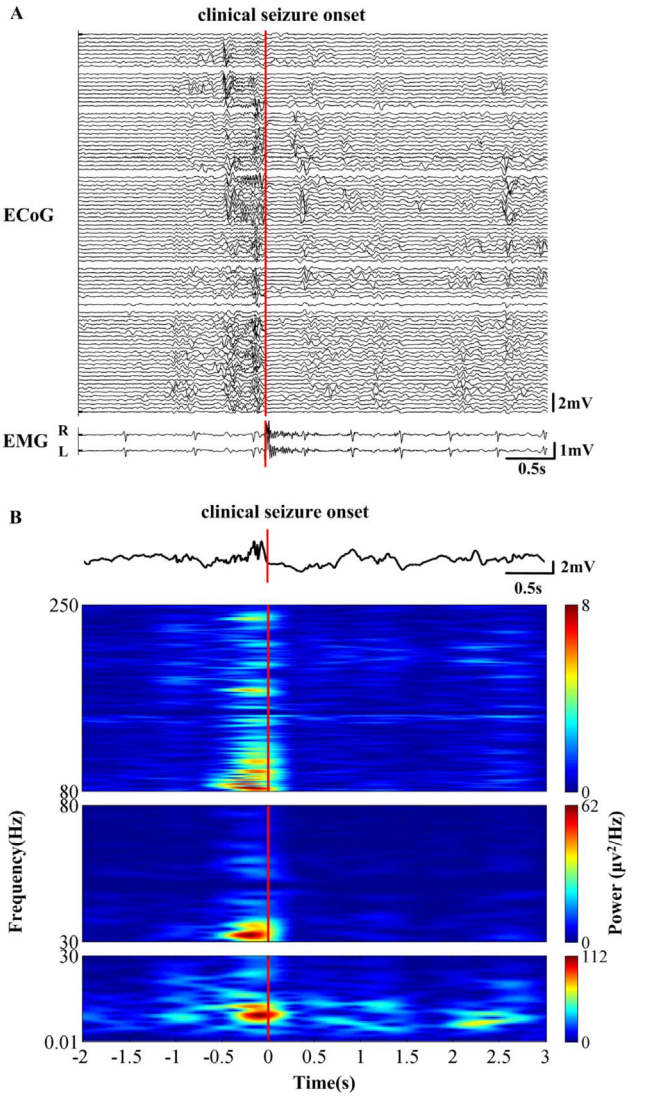

Fig. 1. (A) An example of a myoclonic seizure onset pattern: ECoG and EMG (patient 4). The ECoG recordings are shown above and EMG of bilateral deltoid muscles are shown below. R: right, F: left. The red vertical line indicates the clinical seizure onset. Paroxysmal epileptiform ECoG discharges appear before EMG discharges. (B) ECoG spectrograms for the seizure described in (A). The upper figure is the raw data recorded from the characteristic channel (channel 22 in patient 4 from (A)). The lower figure is the time-frequency power spectrum showing the dominant spectral activity in the alpha band at 0.5 s before clinical seizure onset. The red vertical line indicates the clinical seizure onset. The epileptiform discharges appear before the clinical seizure onset and power increases to a peak in the preictal period.

We selected ECoG data in representative segments (interictal period, preictal period and ictal period) to statistically compare the power in different periods. In each frequency band, we found that the power of the preictal period was highest, and became lower in the ictal period. The power of the interictal period was the lowest. The pairwise comparisons among the three periods are shown in Table 3.

Table 2
Myoclonic seizure characteristics of four patients.

Patient No.	First seizure type	Seizure frequency before surgery	Myoclonic seizure during ECoGs recording					
			No.	Sides	Regions	Ictal ECoG	EMG discharge duration (ms)	State
1	No	2–3/week	1	bilateral	upper extremities	Spike-and-wave	50	Sleep
2	No	10–12/day	6	bilateral	upper extremities	Fast activities	60	Sleep
3	No	5–15/day	2	bilateral	extremities	Spike-and-wave	55	Sleep
4	No	5–10/day	2	bilateral	upper extremities	Fast activities	50	Sleep

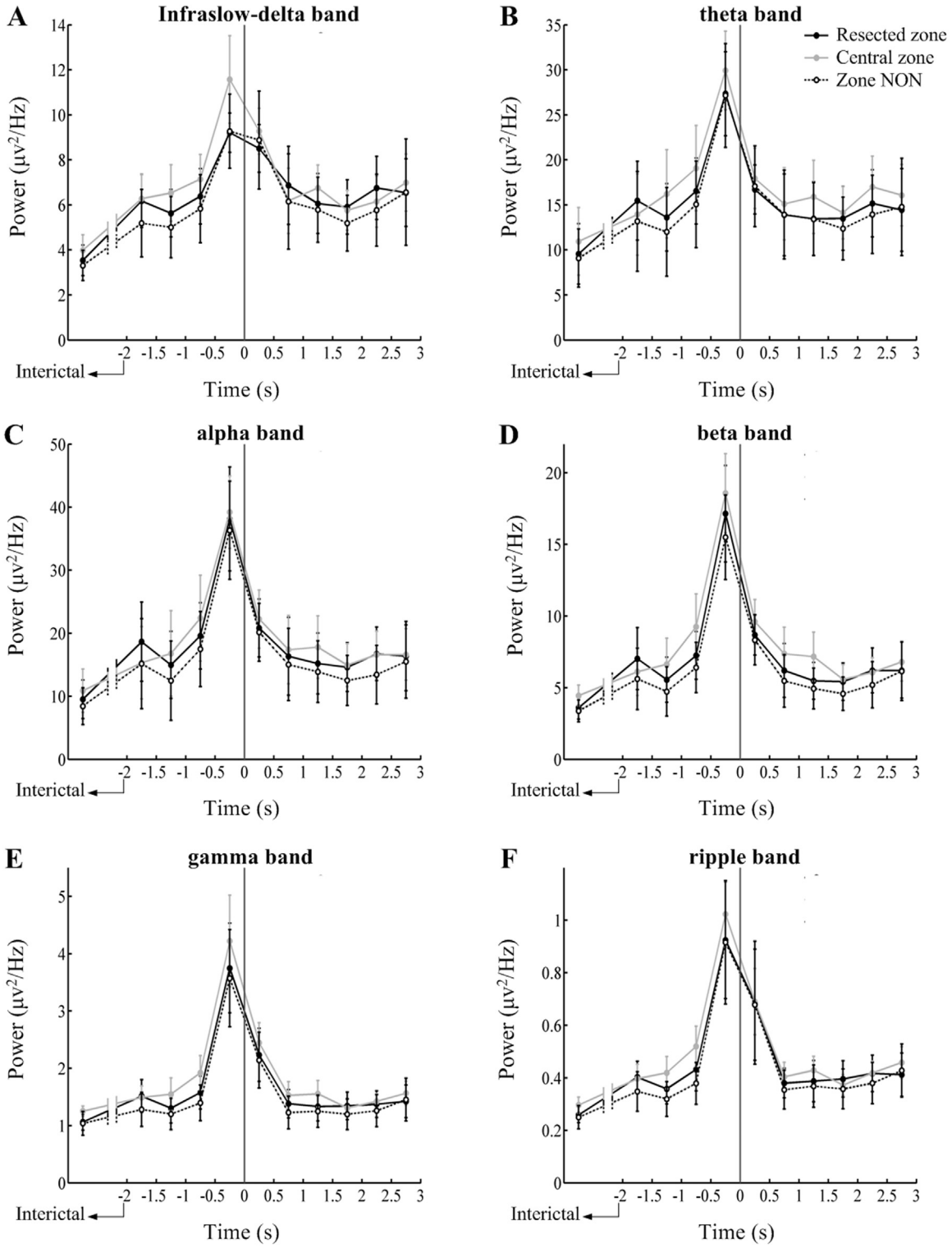

Fig. 2. Dynamic changes of the power in three regions in different frequency bands: (A) infraslow-delta band, (B) theta band, (C) alpha band, (D) beta band, (E) gamma band, and (F) ripple band. Error bars represent one standard error of the mean (SEM). The vertical line indicates the clinical seizure onset. The power of the ECoG in three regions tends to increase from the interictal period, reaches peak at 0.5 s before clinical seizure onset and then decreases.

Except for the resected zone and the zone NON for the ripple band, the power during the preictal period in each region and frequency band increased significantly compared with the power in the interictal period. In the ictal period, the power decreased significantly compared with the preictal period with several exceptions (in three regions for the infraslow-delta band, in the zone NON for the theta band, and in the resected zone for the beta band and ripple band). We found no interaction between period and region in either frequency band.

2.3.2. *Comparison between different frequency bands*

We found that the power in the alpha band was the highest among all frequency bands within all regions in the preictal and ictal periods. In all frequency bands, no interaction was found between period and region.

Table 3
The different frequency power in the regions and the periods.

Region		Resection Zone			Central Zone			Zone NON		
Period		Interictal	Preictal	Ictal	Interictal	Preictal	Ictal	Interictal	Preictal	Ictal
Frequency band	infraslow-delta	3.54 ± 0.68	9.21 ± 0.87**	8.51 ± 1.06**	3.99 ± 0.68	11.57 ± 1.95*	9.28 ± 1.02**	3.31 ± 0.67	9.28 ± 1.64*	8.88 ± 2.17*
	theta	9.56 ± 3.36	27.34 ± 4.67*	16.71 ± 2.72*,△	10.95 ± 3.76	29.92 ± 4.36**	17.94 ± 3.35*,△△	9.09 ± 3.24	27.15 ± 5.76*	17.07 ± 4.48
	alpha	9.52 ± 3.07	38.12 ± 8.24*	20.82 ± 4.58**,△	10.89 ± 3.45	39.20 ± 5.74**	22.24 ± 4.60**,△△	8.44 ± 2.93	36.33 ± 7.78*	20.15 ± 4.59*,△
	beta	3.60 ± 0.8	17.14 ± 3.36*	8.67 ± 1.39*	4.45 ± 0.72	18.57 ± 2.77*	9.60 ± 1.55*,△	3.39 ± 0.76	15.49 ± 2.95*	8.33 ± 1.75*,△
	gamma	1.06 ± 0.14	3.75 ± 0.78*	2.23 ± 0.46△	1.25 ± 0.09	4.22 ± 0.8*	2.45 ± 0.35*,△	1.04 ± 0.21	3.57 ± 0.85*	2.14 ± 0.49*,△
	ripple	0.26 ± 0.03	0.92 ± 0.22	0.69 ± 0.23	0.30 ± 0.03	1.02 ± 0.13**	0.69 ± 0.13△	0.25 ± 0.04	0.92 ± 0.23	0.68 ± 0.21△

All data represents as mean ± SEM.
* $P < 0.05$.
** $P < 0.01$ Comparing to interictal period in the same region of the same frequency band.
△ $P < 0.05$.
△△ $P < 0.01$ Comparing preictal period to ictal period in the same region of the same frequency band.

2.3.3. Spatial distribution of power

As described above, the highest power appeared in the preictal period. We further found that the power was higher in the central zone than that in the resected zone in all the frequency bands during the preictal period, but this was not statistically significant. Power spatial distributions for each patient for the preictal period in the alpha band are shown in Fig. 3.

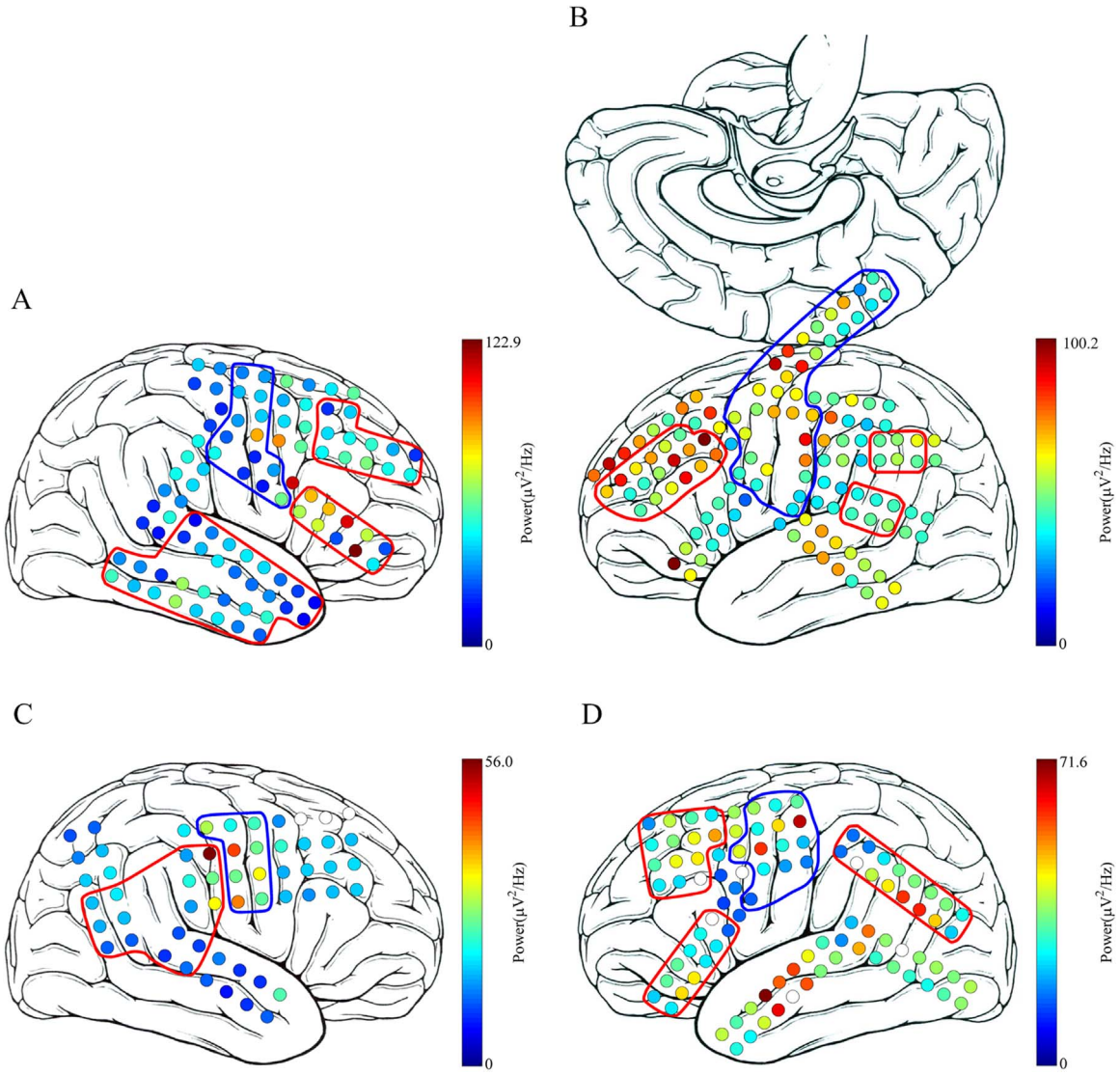

Fig. 3. Spatial power distribution in the alpha band during the preictal period in each patient. (A) Patient 1, (B) Patient 2, (C) Patient 3, and (D) Patient 4. The resected zone is circled in red, the central zone is circled in blue, and the zone NON is where other electrodes are located.

3. Discussion

We demonstrated that myoclonic seizures without clinical lateralizing signs could be improved by the focal resection of the EZ.

Myoclonic seizures were defined as generalized seizure according to the reports of the ILAE on the classification of seizures and epilepsies in 1981 (Commission on Classification and Terminology of the ILAE, 1981), in which the first clinical changes indicate initial involvement of both hemispheres, and motor manifestations are bilateral. Therefore, individual studies focused on the callosotomy. Cukiert et al. reported that one patient with myoclonic seizures was seizure-free after callosotomy because of the disruption of epileptic bilateral synchrony (Cukiert et al., 2009). However, other studies showed that myoclonic seizures do not seem to respond as well as other seizure types (e.g., drop attacks) to callosotomy and proposed that the corpus callosum circuit might not be necessary for seizures in idiopathic generalized epilepsy (IGE) because there are sub-cortical pathways (Cukiert et al., 2006; Jenssen et al., 2006).

The most recent ILAE definition published in 2010 states that "generalized epileptic seizures are conceptualized as originating at some point within, and rapidly engaging, bilaterally distributed networks. Such bilateral networks can include cortical and subcortical structures, but do not necessarily include the entire cortex" (Berg et al., 2010). However, focal EZ resection in patients with myoclonic seizures was rarely reported. Akiyama et al. (2011) reported one patient with asymmetric myoclonic seizures whose brain MRI showed local abnormalities and was seizure-free by focal resective surgery. In the study on symptomatic generalized seizures due to brain lesions, focal resection of the EZ was performed in 14 patients with myoclonic seizures, and six patients were seizure-free (Yu et al., 2015). These two studies suggested that unilateral dominant myoclonic seizures might have focal origins, and appropriate operations might be helpful. However, in our study, myoclonic seizures involving bilateral limbs without asymmetric features of behavior were observed in all patients, which means that their semiology showed generalized characteristics. As two patients' MRIs were normal, we lateralized and located the EZ using ECoG and MEG. Given the positive prognosis in each patient, we reasoned that the resected zone contained the EZ of myoclonic seizures. Based on those results, we concluded that myoclonic seizures with generalized symptom characteristics might have a focal origination. The discharges from the focal origination synchronized bilaterally in a fast way through the subcortical connection activating the entire epileptic network. Two hypotheses for the effective surgical treatment of myoclonic seizures were raised. One was that myoclonic seizures had potential focal origins, which were removed by the focal resection. The other was that myoclonic seizure, as a generalized seizure, had different origins and a complex transmission network, and that surgeries only effectively destroyed the key nodes of the epileptic network. To verify the hypothesis, our team will further explore the epileptic network in myoclonic seizures, hoping to find an answer.

Each patient involved in our study had different types of seizures. In one patient (patient 2), GTCS was barely improved, whereas other seizures including myoclonic seizures were significantly improved. We speculated that other epileptogenic foci unrelated to myoclonic seizures might not have been resected. That was the reason why a patient with different types of seizures could have a different surgical outcome. This indicated that there might be multiple epileptic networks in one patient and the ictal epileptic discharges propagated in different epileptic networks.

Although focal characteristics of myoclonic seizures can bring hope to patients with such disorders, the exact mechanism remains unclear. There is an opinion that myoclonic seizures could be caused by discharges originating from the focal cortex with rapid secondary generalization (Akiyama et al., 2011; Kobayashi et al., 2000). We are the first to study myoclonic seizures using broadband ECoG time-frequency analysis. We found that ECoG power in different frequency bands increased to a peak at 0.5 s before the clinical seizure onset and decreased quickly afterwards. Alpha activity was the highest in the preictal and ictal periods, and the power was higher in the central zone than that in the EZ in all frequency bands during the preictal period. However, there was no statistical significance in those findings.

The intracranial EEG time-frequency analysis, together with the semiology, can contribute to the study of the dynamic changes in the temporal and spatial evolution, and the identification of the source of epileptic seizure activity and its propagation within the brain (Blanco et al., 1997). To study the electrophysiological characteristics of myoclonic seizures, we conducted a broadband ECoG time-frequency analysis of myoclonic seizures in the patients. In the dynamic observation of the seizures, we found that in the EZ, the central zone, and the zone NON, the power in every frequency band (infraslow-delta, theta, alpha, beta, gamma, and ripple) started to rise 2 s before the clinical seizure onset, crested 0.5 s before the clinical seizure onset (there was no statistical significance in the EZ and the zone NON for the ripple band, which was probably owing to a small sample), and decreased subsequently. In the ictal period, there was a large drop in power compared with the preictal period with a few exceptions: in three regions of the infraslow-delta band, in the zone NON for the theta band, and in the resected zone for the beta band and ripple band, which was probably owing to the sample size. We reasoned that myoclonic seizures were induced by the sudden changes of power in every frequency band in the epileptic network. This might relate to the semiological characteristics in myoclonic seizures, which were sudden brief shock-like movements triggered by muscle contractions (the EMG discharge duration is usually less than 100 ms).

Based on the dynamic observation above, we found that the myoclonic seizures were related to activities in every frequency band. Oscillatory frequency of early discharge is one factor that determines the form of clinical semiology, such that, for example, tonic (high frequency) discharges in motor cortex will tend to cause tonic seizures and clonic (lower frequency) spike discharges will likewise give rise to clonic jerks (Chauvel and McGonigal, 2014). In our study, we found that the power in the alpha band (8–13 Hz) was the highest among all frequency bands in the preictal and ictal periods. Posterior dominant rhythm and mu rhythm are also in the alpha band. The posterior dominant rhythm, originally named the alpha (8–13 Hz) rhythm (Berger, 1929). They are recorded best under states of relaxed wakefulness with eyes closed over the posterior region. The EEG mu rhythm, oscillatory activity in the 8–12 Hz frequency range recorded from centrally located electrodes, is suppressed when an individual executes, or simply observes, goal directed actions (Bernier et al., 2014). In our study, all myoclonic seizures of each patients were captured during sleep. Moreover, fewer implanted recording electrodes were placed over occipital, but more over the frontal, temporal and parietal region in every patient. Other than that, the highest alpha band ECoG power was observed during the preictal and the ictal periods only. Finally, we reviewed the ECoGs of myoclonic seizures of each patient and no mu rhythm was found. Hence, we supposed that the possibility that posterior dominant rhythm and mu rhythm was involved in the alpha band activities is low. So we concluded that the alpha band was the dominant frequency band in myoclonic seizure generation.

Another factor that determines the form of clinical seizure semiology is the initial extent or spread of the ictal discharge. Chauvel et al. suggested that cortical myoclonus, of any type, results from an MI efferent volley, conversely, isolated spikes in MII and MIII never result in myoclonus (Chauvel and McGonigal, 2014). We studied the spatial distribution of ECoG activities, especially in the EZ and the central zone. The resection zone varied among patients, which indicated that the EZ of myoclonic seizures was not constant and the epileptic network might exist extensively. We found that most of the EZs in myoclonic seizures were located in the frontal region and posterior temporal-parietal-occipital region. This was consistent with previous

research: in symptomatic generalized seizures including epileptic spasms, myoclonic seizures, tonic seizures, atonic seizures, and atypical absence seizures, most of the EZs were located in the posterior frontal-central region and posterior temporal-parietal-occipital region (Yu et al., 2015). Another study showed that one patient with myoclonic seizures became seizure-free by the resection of the supplementary motor area, the left superior and middle frontal gyri (Akiyama et al., 2011). Although in our study the resected zone in each patient was different, the power was higher in the central zone than that in the resected zone in all frequency bands during the preictal period, even though this was not statistically significant, which was probably owing to a small sample. We supposed that the central zone might play an important role in the generation of myoclonic seizures, which might have a close relationship with the EZ. The functional connections of different cerebral regions might be helpful in the development of the special epileptic network. We will expand participants and further study the functional connections between the different cerebral regions in our future work.

In summary, the present study showed that the myoclonic seizure network might be widespread and bilaterally distributed. However, a myoclonic seizure might be initiated by abrupt focal activity in unilateral limited cortical areas. The various frequency activities can propagate in a brief time to the whole network. Furthermore, our findings indicated that even generalized clinical myoclonic seizures could be improved by focal resection of the EZ.

4. Experimental procedures

4.1. Patients

We enrolled four patients with diagnoses of myoclonic seizure according to the inclusion and exclusion criteria (3M/1F, ages 6–22 years; Table 1). The inclusion criteria consisted of (1) patients with refractory epilepsy undertaking surgical evaluation at the Comprehensive Epilepsy Center of Beijing in Xuanwu Hospital of Capital Medical University between 2012 and 2014; (2) electrodes implanted for presurgical long-term video-ECoG monitoring; (3) myoclonic seizure captured during ECoG recording, which was bilateral; and (4) good postsurgical outcome (Engel Class I and Engel Class II) with follow-up maintained at least 12 months after surgery. The exclusion criteria consisted of (1) the presence of massive brain malformations (such as large porencephaly, perisylvian polymicrogyria, or hemimegalencephaly), which are known to confound the anatomic landmarks of the central sulcus; (2) history of previous brain surgery; (3) family history of epilepsy; (4) accompanied by: myoclonic absence, myoclonic atonic seizures, or myoclonic tonic seizures; (5) diagnosis of electroclinical syndromes and other epilepsies (Berg et al., 2010); and (6) poor postsurgical outcome (Engel Class III and Engel Class IV) with follow-up maintained at least 12 months after surgery. The study has been approved by the Medical Research Ethics Committee at Xuanwu Hospital of Capital Medical University, and written informed consent was obtained from each patient or his/her guardians.

4.2. Intracranial electrodes

For subdural ECoG recording, grid macroelectrodes (contacts diameter: 10 mm, center-to-center distance: 10 mm; Ad-tech, Racine, WI, USA) were surgically implanted. The placement of subdural electrodes depended on semiology, EEG and neuroimaging by the epileptologists. Implanted electrodes were unilateral in all patients. The reference scalp electrode was placed at the vertex. Electrode positioning was confirmed by postoperative cranial x-rays and fine-cut computed tomography (3-mm cuts).

4.3. Extraoperative video-ECoG recording

ECoG monitoring was performed to further localize the EZ. Extraoperative video-ECoG recordings were obtained for 1–3 days. ECoG signals were sampled using a 256 channel amplifier system (16 bit, Beijing Yunshen Technology) at the rate of 2048 Hz with a band pass from 0.01 to 500 Hz. As part of our clinical routine practice, simultaneous EMG was also recorded. Surface EMG electrodes were placed on the bilateral deltoid muscles, biceps brachii muscles, extensor digitorum communis muscles, quadriceps femoris muscles, and anterior tibial muscles. Antiepileptic medications were reduced during ECoG monitoring until a sufficient number of habitual seizures were captured.

4.4. Myoclonic seizure

In the pre-surgical evaluation protocols, clinical seizure onset was identified and recorded by trained epileptologists. The time point of the earliest visible EMG discharges (duration < 100 ms) accompanied by ECoG discharges associated with a myoclonic seizure prior to EMG discharges was selected as the clinical seizure onset time.

4.5. Surgery and follow-up

All the electrode positions in each patient were allocated to three regions: the resected zone, the central zone, and the zone NON. The resected zone in each patient was identified during the preoperative evaluation by epileptologists. The location of the central zone (including the precentral and postcentral gyri) was identified by preoperative direct cortical stimulation.

Focal resection of the EZ was performed by neurosurgeons. A neuropathologist with extensive experience in surgical epilepsy interpreted all specimens. Postoperatively, patients were followed up by the epileptologists. Postsurgical outcomes were determined by structured telephone interviews. Long-term outcome classification was assessed using the Engel scale (Engel et al., 1993).

4.6. ECoG segment selection

For each patient, only the myoclonic seizures were selected for analysis. To eliminate interaction, we selected relatively independent myoclonic seizures, which means the interval between seizures was at least 30 min. Five seconds of ECoG data, from 2 s prior to the clinical seizure onset until 3 s after the clinical seizure onset, which was defined as a “peri-seizure-onset period”, was selected for analysis. Interictal periods were defined as periods in which there was no seizure within 1 h before or after the selected segment for each individual patient. 10 ECoG segments were selected and analyzed in the peri-seizure-onset period and in the interictal period respectively, and the length of each segment is 0.5 s. The power value used for statistical analysis was calculated in a 0.5 s window.

4.7. Data analysis

Following acquisition of the data, offline pre-processing was performed and included additional band-pass filtering (0.01–250 Hz) and automated artifact rejection. Signals were then filtered with a 50 Hz notching filter and baseline drifts were removed. Visual inspection was also performed and channels contaminated with artifact were excluded from the analysis.

The Short-Time Fourier Transformation (STFT) was applied to calculate the ECoG spectrogram in different frequency bands: infra-slow-delta (0.01–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), gamma (30–80 Hz) and ripple (80–250 Hz).

The STFT of the ECoG with a 1 s wide Hamming window was calculated as:

$$STFT(f, t) = \int_{-\infty}^{+\infty} [x(t)g(t-\tau]e^{-j2\pi f\tau}d\tau,$$

where $x(t)$ denotes the ECoG.

The time-frequency characteristics of ECoG with multi-tapers (1 s window, 0.025-s step, 0.5 Hz resolution) were examined separately for each patient, segment and channel (Fig. 1B). For statistical purposes, we defined the 0.5-s period prior to the clinical seizure onset time point as the preictal period, while the 0.5-s period following this time point was defined as the ictal period. The averaged 0.5-s period during the interictal time was defined as the interictal period. Then, the segment data were averaged separately for each patient, frequency and period.

The spatial distribution of power in different frequency bands was drafted according to the data in each channel and each frequency band (Fig. 3).

4.8. Statistical analysis

Repeated measures analysis of variance (ANOVA) and multivariate ANOVA under the general linear model in SPSS Statistics 17.0 software were performed using factors including: region (the resected zone, the central zone, and the zone NON), frequency band (infraslow-delta, theta, alpha, beta, gamma, and ripple), as well as measurement period (interictal, preictal, and ictal). The degrees of freedom were adjusted with a Greenhouse–Geisser correction whenever necessary. Meanwhile, some interactions among the studied factors were also evaluated, such as time and region, and frequency band and region. The repeated measures ANOVA was used to perform the pairwise comparisons for repeatedly measured data in different measurement periods for each region and each frequency band. Data in different regions of each measurement period were compared in a pairwise fashion using the means of the multivariate ANOVA. For *post hoc* analysis, LSD *t*-tests were used (Bonferroni *t*-tests were used in the case of lower bound value when epsilon < 0.7). *P*-values were considered statistically significant as follows: $^{*}P < 0.05$, $^{**}P < 0.01$, $^{\triangle}P < 0.05$, $^{\triangle\triangle}P < 0.01$.

Acknowledgments

This work was supported by National High-tech R & D Program (863 Program) (2015AA020514) and Beijing Municipal Science and Technology Project (Z121107001012007). We thank the Neural Engineering Laboratory Tianjin Medical University for the technical support and Dr. Fei Sun for providing statistical assistance.

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