Is high-frequency activity at seizure onset inhibitory? A stereoelectroencephalographic study of motor cortex seizures

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Abstract

Objective: In the era of stereoelectroencephalography (SEEG), many studies have been devoted to understanding the role of interictal high-frequency oscillations. High-frequency activity (HFA) at seizure onset has been identified as a marker of epileptogenic zone. We address the physiological significance of ictal HFAs and their relation to clinical semiology.

Methods: We retrospectively identified patients with pure focal primary motor epilepsy. We selected only patients in whom SEEG electrodes were optimally placed in the motor cortex as confirmed by electrical stimulation. Based on these narrow inclusion criteria, we extensively studied 5 patients (3 males and 2 females, mean age = 22.4 years) using time–frequency analysis and time correlation with motor signs onset.

Results: A total of 157 analyzable seizures were recorded in 5 subjects. The first 2 subjects had tonic or clonic semiology with rare secondary generalization. Subject 3 had atonic onset followed by clonic hand/arm flexion. Subject 4 had clusters of tonic and atonic facial movements. Subject 5 had upper extremity tonic movements. The median frequency of the fast activity extracted from the Epileptogenic Zone Fingerprint pipeline in the first 4 subjects was 76 Hz (interquartile range = 21.9Hz). Positive motor signs did not occur concomitantly with high gamma activity developing in the motor cortex. Motor signs began at the end of HFAs.

Interpretation: This study supports the hypothesis of an inhibitory effect of ictal HFAs. The frequency range in the gamma band was associated with the direction of the clinical output effect. Changes from inhibitory to excitatory effect occurred when discharge frequency dropped to low gamma or beta.

Introduction

High-frequency activity (HFA) in focal epilepsies has been a topic of interest for a decade.[1] Most studies have focused on interictal high-frequency oscillations with an emphasis on their correlation with the localization of the epileptogenic zone. However, few of these have recognized HFA as ictal patterns, and even fewer have analyzed their relation to clinical semiology.

One explanation for this omission is that HFAs are more easily detected by depth than by electrocorticographic electrodes. Until recent years, recordings from subdural grids were predominant in presurgical investigations, where the interpretation of seizure onset relied more on the time of change from background to ictal activity than on changes in frequency patterns. Since stereoelectroencephalographic (SEEG) utilization has expanded, HFAs have been considered the most specific marker of the epileptogenic zone,[2] either by themselves or in combination with other frequency characteristics.

Fast activities have been identified as ictal patterns since the early developments of SEEG.[3] They were also observed in seizures recorded from scalp electroencephalography (EEG) when they could be clearly differentiated from electromyographic (EMG) artifacts.[4] The concept of tonic seizures emerged as an electroclinical subclass along with clonic, tonic-clonic, and atonic seizures. The terms were coined by reference to their EEG features as they correlated well with the clinical motor sign types. A tonic seizure is characterized by a paroxysmal increase in muscle tone occurring either focally and unilaterally in a distal limb segment, in general as a prelude to a tonic–clonic propagation, or bilaterally in proximal limb segments and axial muscles with a symmetrical or asymmetrical posture, depending on the discharge localization and its cortical distribution. Clinically, tonic seizures are also electrically tonic in SEEG. An "electrodecremental" activity with HFAs recorded in the motor or premotor cortex is associated with a clinically tonic seizure in the corresponding peripheral territory.[5] A diffuse electrodecremental pattern has been related to tonic seizures of frontal origin.[6]

However, there are some exceptions to this association. Recent observations of ictal negative motor phenomena pointed to their correlation with simultaneous gamma band oscillations in the motor cortex. A mechanism of decoupling between primary motor and premotor activities resulting in a "disruption of the ongoing tonic motor activity" was postulated.[7]

A time-frequency (TF) pattern at the transition between interictal and ictal state has been identified as a fingerprint of the epileptogenic zone.[8] One of its features is a narrow-band gamma activity with a coincident suppression of delta to beta activities. By analogy with a model proposed by De Curtis and Avoli,[9] a pathophysiological hypothesis for the fingerprint includes a possible inhibitory role for its fast component.

The present study was designed to question whether fast activities reflect an inhibitory process in epileptogenic cortex. Its purpose is to study the relationship between narrow-band fast activity in the motor cortex and the corresponding motor signs. The choice of the primary motor cortex was made to assess the simplest objective clinical manifestations produced by a cortical area in the closest neural proximity to the periphery.

Materials and Methods

With Cleveland Clinic Institutional Review Board approval, we selected patients from the SEEG database between 2013 and 2020. In this study, we included patients (1) with spontaneous seizures with focal motor semiology, (2) with anatomically and physiologically checked electrodes in the primary motor cortex, and (3) whose ictal patterns in the primary motor cortex consisted of fast activity confirmed by TF analysis. We included only seizures where motor signs of interest were clearly observed from SEEG video monitoring. Based on these narrow inclusion criteria, we exclusively studied 5 patients (3 males and 2 females, mean age = 22.4 years) with a total of 157 analyzable seizures. Three independent epileptologists (P.C., H.S., and M.K.) reviewed all seizures and then agreed on electrical and clinical onset with proper semiology.

SEEG Recording and Stimulation

SEEG implantation was performed using multilead depth electrodes (AdTech: 400 W Oakview Pkwy, Oak Creek, WI 53154 (Wisonsion) Integra: 1100 Campus Road Princeton, NJ 08540 DIXI: 2a rte de Pouligney 25640 Marchaux-Chaudefontaine FRANCE or PMT: 1500 Park Road Chanhassen, MN USA 55317). The electrodes were implanted according to the Talairach

stereotactic method.[10] Anatomical locations of the electrode leads were checked by the digital fusion of a postimplantation thin-sliced computed tomographic 3-dimensional image with a preoperative T1-weighted volumetric magnetic resonance imaging (MRI). Images were aligned and verified using CURRY (5015 West WT Harris Blvd Suite E Charlotte, NC 28269, USA) 7 and 8 (Compumedics NeuroScan). SEEG investigation was performed according to the usual method.[11] The SEEG signals were recorded on Nihon Kohden (NK) (15353 Barranca Parkway, Irvine, CA 92618) EEG system with a sampling rate of 1,000 Hz. Functional mapping was performed at the end of the monitoring period. Bipolar stimulation was applied successively to adjacent electrode contacts. Stimulation pulses were delivered in biphasic mode, 5-second maximal duration trains, at a frequency of 50 Hz, with 0.3-millisecond pulse width and current intensity varying from 0.1 to 5 mA. This functional mapping confirmed the exact location of the electrodes in the primary motor cortex representation of the muscles involved in spontaneous seizures.

Video-SEEG

We used high-definition (HD) videos to analyze clinical semiology and determine the time of motor onset. The videos were recorded using HD Internet Protocol cameras with a resolution of 1,920x1,080 at a frame rate of 25 fps, then encoded with H.264 at a constant bit rate of 6,144kbps. As the latency between EEG frequency changes and clinical onset was based on EEG-video analysis, the time synchronization accuracy between the EEG recording and video recording needed to be investigated. The digital video system was initially calibrated for minimal latency at installation by changing the "synchronization offset" parameter in the NK Digital Video configuration. We further estimated the actual offset (post-calibration) by delivering 1 Hz single flashes every 7-10 seconds and measured the time difference between the EEG photic marks and the clipped videos at flashing. The averaged time offset between EEG and digital video was 5.6 milliseconds, which had minimal impact on the latency measures of motor onset (in the order of seconds).

Table 1. Clinical characteristics and patients.

	Age (Y)	Age at onset (Y)	Gender	Number of seizures	MRI brain lesion	Motor semiology of typical seizure	Target motor contacts	Cortical stimulation (Bipolar, 50 Hz)
Subject 1	26	7	Male	3	Cystic encephalomalacia in right dorsal frontal lobe and previous resection of this region.	Left arm tonic/clonic, +/- left face clonic -> GTC	D1-D2 (right precental gyrus - dorsal)	D1-2: Left arm tonic
Subject 2	12	5	Male	12	MRI negative (abnormality in right paracentral lesion on VBM)	Left leg tonic/clonic, +/- GTC	S3-4 (right paracentral lobule)	S2-3: induced typical seizure S4-5: left leg clonic
Subject 3	10	6 M	Female	25	Multifocal FCD II in left superior post central and left inferior frontal gyri.	(Somatosensory aura ->) +/- left arm atonic -> left arm clonic -> left side clonic (post ictally Todd's palasis in left side)	B3-4 (right precental gyrus - dorsal)	(monopolar) B3: left forearm/hand toinc B4: left forearm/hand tonic
Subject 4	35	3 M	Female	55	Polymicrogyria in left frontal lobe including left frontal/parietal operculum and left insular	Right face atonic and tonic (cluster)	Z'5-6 (left precentral sulcus - ventral)	Z'5-6: right face tonic
Subject 5	29	14	Male	62	Irregulality in the cortex of left superior frontal gyrus	Right arm tonic -> Left arm tonic	H'4-5 (left precentral gyrus - dorsal)	H'4-5: right arm tonic

Motor Semiology: Qualitative Analysis

In this study, we included only patients who had elementary motor semiology[12,13] with initial unilateral distal tonic or clonic movement in their typical seizure to evaluate the relationship between the primary motor cortex electrical activity and motor signs. We did not include patients with a more complex and bilateral motor semiology (e.g., asymmetric tonic-clonic or hyper-kinetic seizures), as those seizures are not initially generated in the primary motor cortex. The time of motor onset was determined from the HD videos. The electrode contacts in the primary motor cortex located in areas projecting to the muscles involved in individual ictal semiology were selected for analysis in each patient. The accuracy of localization of these contacts in the primary motor cortex was verified by the results of cortical stimulation mapping (Table).

Time–Frequency Analysis of SEEG Signal

Electrical activity recorded by the selected contacts was analyzed from the onset of fast activity. Following the method used in our previous work,[8,14] we performed a TF analysis on the extracted segments from channels of interest in the primary motor cortex using the Morlet wavelet transform (MWT). For this quantitative visual analysis, we used the MWT provided by Brainstorm[15] with a time resolution of 5 seconds for a central frequency of 1 Hz, which generated TF maps with 50 frequency bins in a logarithmic scale from 1 to 200 Hz. We identified the onset of the fast activity via visual analysis of the TF maps and measured the frequency of the fast activity. As the terminology for ictal fast activity varies among studies in the literature, we used the term HFA for brain activity that exceeds 40 Hz. Finally, we compared the time of onset and duration of fast activities with the time of onset of motor signs. This comparison led us to explore the relationship between the frequency range of fast activities and the motor onset time.

To test our hypothesis, we applied the feature extraction pipeline as described in our previous work[8,14] to the SEEG signals. For each seizure, we first extracted a 40-second window of ictal SEEG signal as well as another 40-second window of baseline signal at least 1 minute before the ictal onset, where no obvious ictal activity is present. Using our previously developed Epileptogenic Zone Fingerprint software,[14] we then (1) transformed SEEG time series into TF maps for both ictal and baseline segments using MWT with the default parameters, (2) removed possible artifact(s) in the TF maps based on complex independent components analysis and a manual identification of the artifact components, (3) normalized the ictal artifact-cleaned TF maps against the artifact-cleaned baseline TF maps, and (4) performed fast activity feature extraction as shown in our previous work.[8]

After the fast activity extraction procedure described above, a mask of the fast activity was obtained for each channel and each seizure. We then measured the duration of fast activity by computing the time lapse from the onset of the fast activity to the end of the fast activity. On the other hand, we converted the motor onset time obtained through visual analysis of the monitoring video for each seizure into a relative time with respect to the onset of fast activity, representing the latency of motor onset from the seizure onset. Finally, we visualized the relationship between the duration of fast activity and the latency of motor onset using a scatterplot across all seizures from Subjects 1-4 (Subject 5 was excluded from this analysis due to the lack of high gamma activity in his seizures as shown below in the Results section) and computed the Pearson correlation between the two measures.

A further special quantitative analysis was performed on Subject 4, because this subject had a bimodal semiology. This patient had multiple clusters of facial seizures with alternating tonic and atonic seizure types. We performed TF analysis on the extracted segments of each cluster for the contacts, which are located in the face motor area, the same as for other patients. The TF representation of each cluster showed a flip-flop phenomenon with ictal discharge frequencies alternating between two values corresponding to the tonic and the atonic states, respectively. Quantitatively, we measured the mean frequency of HFAs for each seizure and visualized them using boxplots across all seizures for tonic and atonic states separately.

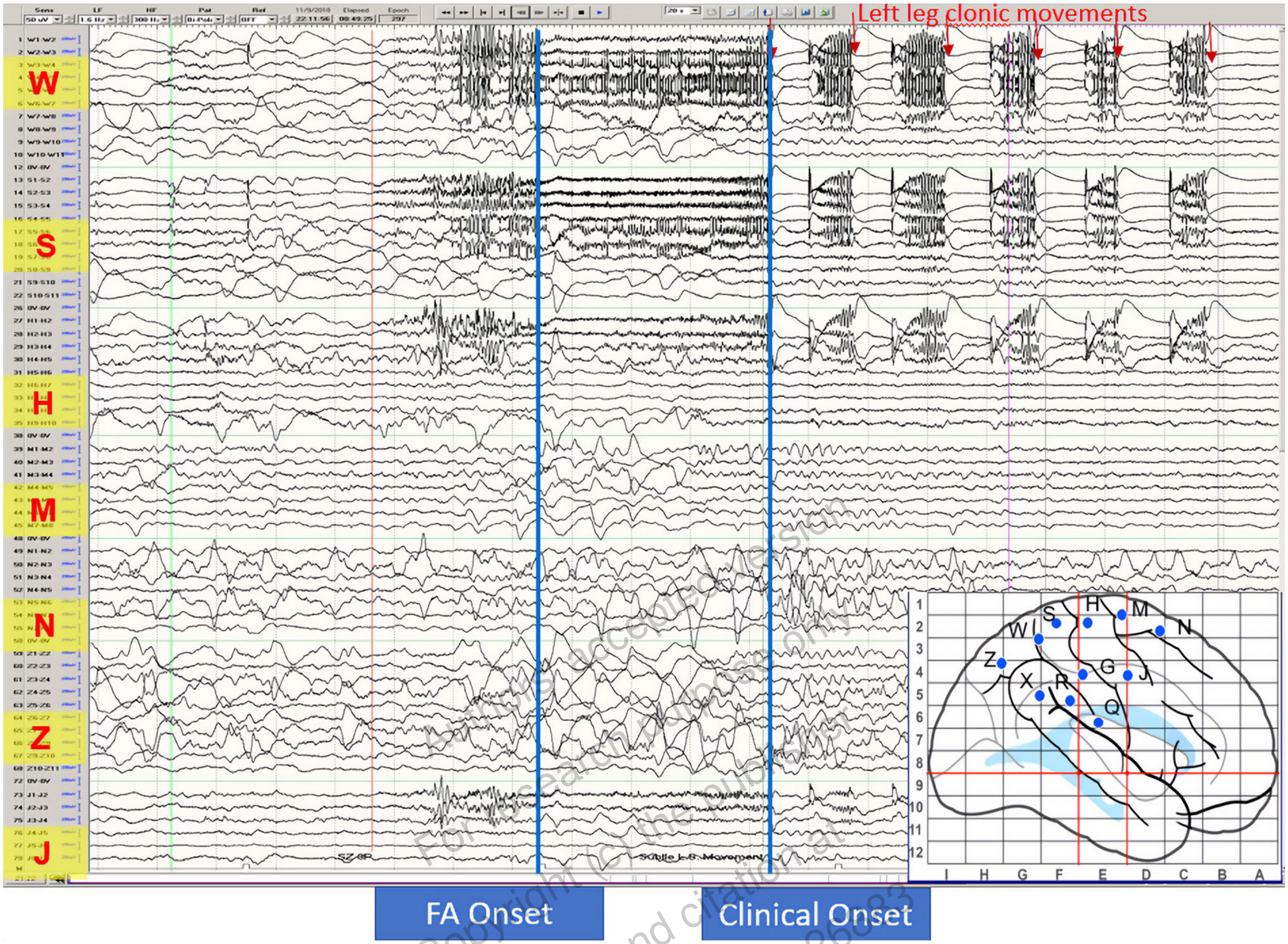

Fig. 1. Subject 2: 20-second typical stereoelectroencephalographic seizure on bipolar montage. Ictal high-frequency activity was seen in medial leads of orthogonal electrodes W, S, and H in the right paracentral lobule. On visual analysis, the fastest activity was recorded in S medial leads (1–4). A postimplantation map for the right hemisphere is seen in the right lower corner. Small vertical arrows point to the left leg clonic movements. Electrode numbering convention: increasing numbers after electrode letter name indicate medial to lateral direction.

Results

A total of 157 analyzable seizures were recorded in 5 subjects. Most seizures were tonic or clonic, then evolved to the ipsilateral and rarely contralateral limb and could secondarily generalize. Subject 3 had atonic onset followed by clonic hand/arm flexion. Subject 4 had clusters of tonic and atonic facial movements lasting 1 to 6 seconds each (see Table).

The main electroclinical observation was that the onset of ictal motor signs was typically delayed by a few seconds from the onset of fast activity in the motor cortex. It could even occur at the offset of fast activity (Fig 1).

TF Analysis: Relationship with Motor Semiology

Patient 1. This patient had a right posterior frontal cystic encephalomalacia that had been previously resected. The most medial contacts of electrode D (1, 2) were in the precentral gyrus; electrical stimulation delivered at D1-2 induced a left arm tonic movement (see Table). All the seizures were the same; they started with a left arm tonic movement followed by clonic

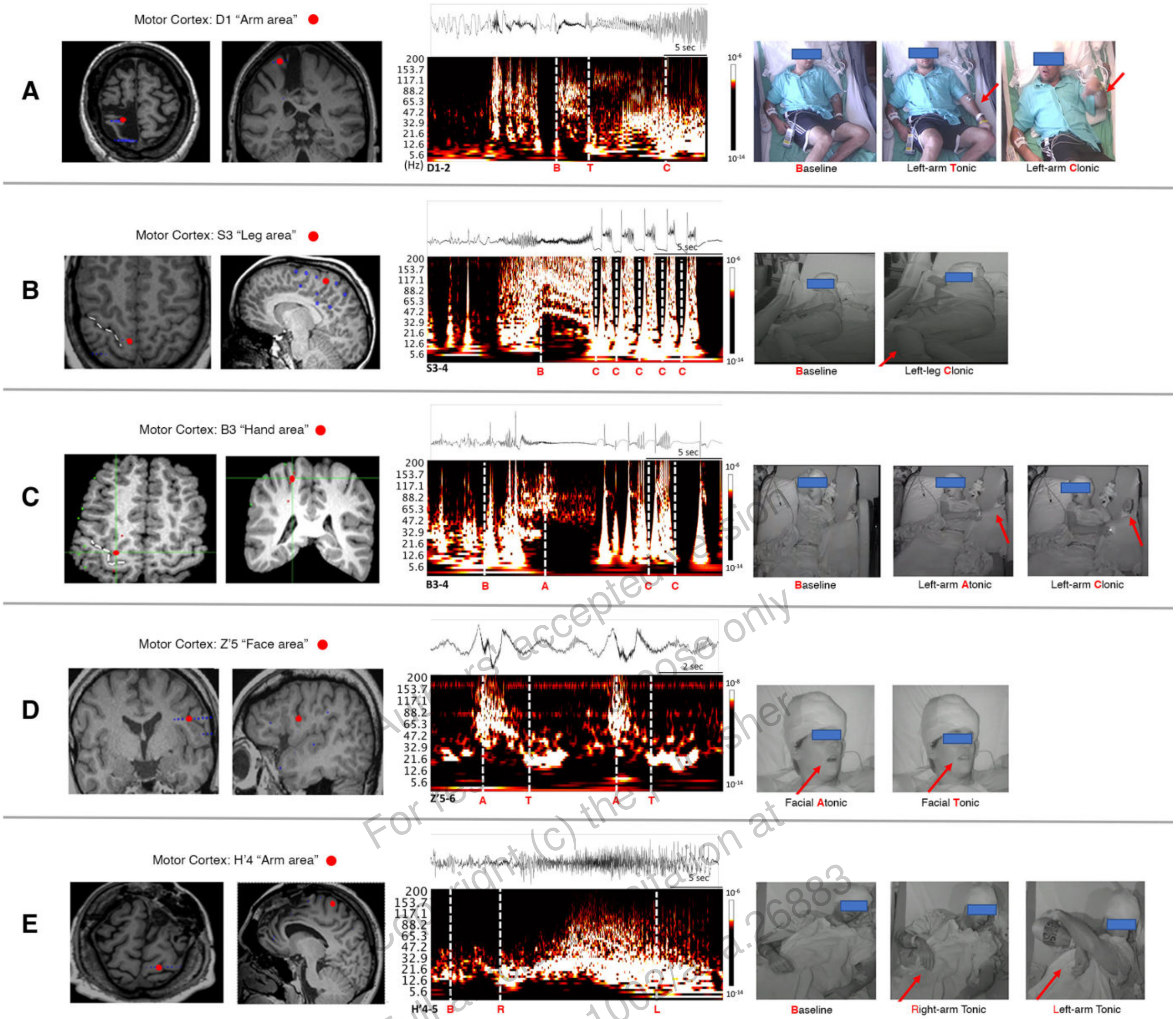

Fig. 2. (A) Subject 1: stereoelectroencephalographic (SEEG) trace and time–frequency (TF) plot from D1–2. "B" refers to clinical baseline. TF shows double narrow-band fast activity between "B" and "T" with absence of any motor semiology. Patient had a left arm tonic posture when the frequency significantly dropped down to lower frequency range. Left arm clonic corresponded to rhythmic broadband activity. (B) Subject 2: SEEG trace and TF plot from S3-4. "B" refers to clinical baseline. No motor sign occurred during ictal high-frequency activity (HFA) between time "B" and first "C". "C" indicates first left leg clonic movements when the frequency dropped down to lower frequency range. This pattern was rhythmical and coincident with the clonic jerks. White dotted line refers to central sulcus. (C) Subject 3: SEEG trace and TF plot from B3-4. "B" refers to clinical baseline. Between "B" and "A", the TF plot is made of 3 preictal spikes followed by the onset of the HFA. Immediately after HFA onset, there is a clear suppression of low frequencies. Then (approximately mid-time between "A" and "C"), a rebound of alpha–beta + gamma activity occurs: first, 3 isolated spikes, the first of them with a very short rapidly aborting narrow gamma discharge; from the third one, a narrow gamma discharge emerges followed by rebound of 3 fast spikes; the onset of the first visible clonic jerk follows this rebound. A similar sequence (between "C" and "C") precedes the second jerk: spike then short narrow gamma discharge and then a rebound made by a longer burst of fast spikes just before the onset of the second jerk. White dotted line refers to central sulcus. (D) Subject 4: SEEG trace and TF plot from Z'5-6. "A" indicates when the patient had atonic face at the onset of the high frequency; "T" indicates tonic facial contraction corresponding to alpha/beta frequency. Two clusters of similar seizures were seen in the TF plot. (E) Subject 5: SEEG trace and TF plot from H'4-5. "B" refers to clinical baseline, "R" right arm tonic, and "L" left arm tonic before the end of the seizure.

jerks in the same muscle groups, then the clonic manifestations spread to the left face before inconstant generalization (Fig 2A).

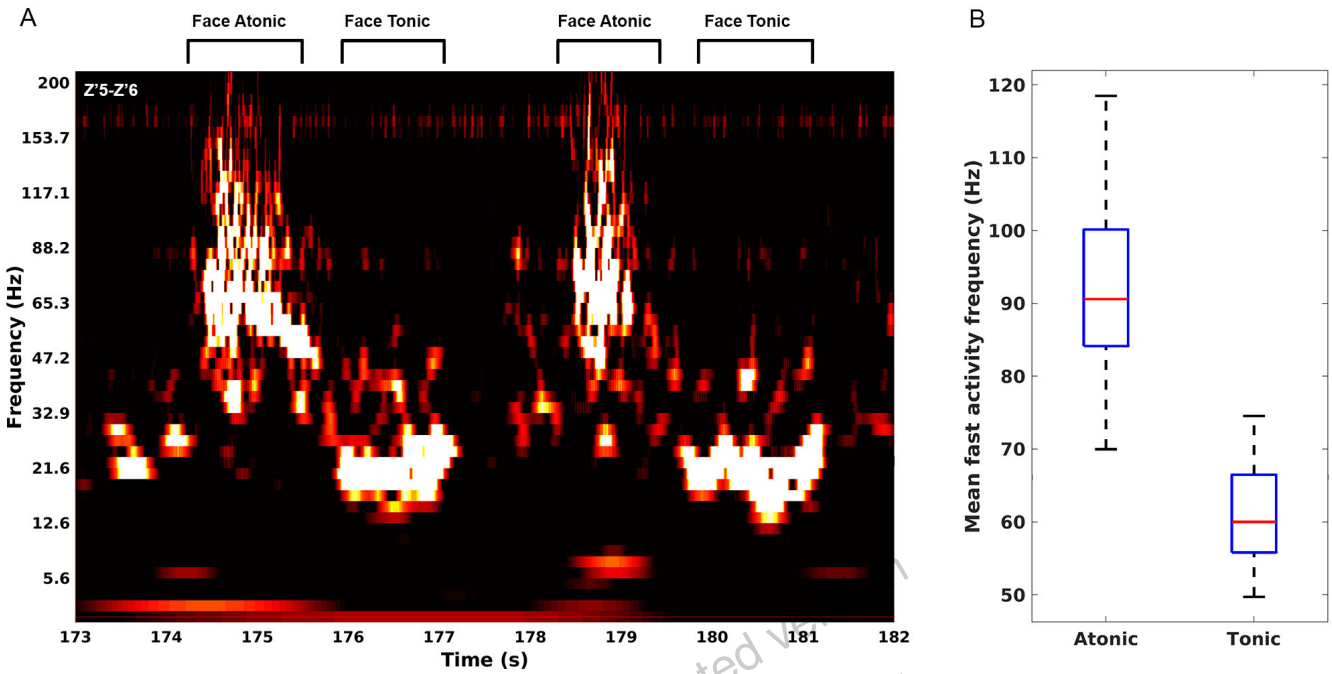

Fig. 3. An exemplary cluster of seizures in Subject 4, starting with atonic facial expression followed by tonic contraction. (A) Time-frequency for clusters of atonic and tonic facial seizures: Z'5-6 electrodes in the motor face area. Abscissa is time in seconds; ordinate is frequency in hertz. There is a clear separation in the frequency range, with higher frequency associated with atonic face, and lower frequency associated with tonic movement. (B) Mean frequency of fast activity in association with the motor expression. X-axis represents the motor facial expression, either atonic or tonic. Y-axis represents the frequency.

TF analysis of the corresponding electrical activity in D1-2 showed a burst of preictal spikes characterized by low and high frequencies scattered between 1 and 150 Hz, the last one followed by a double narrow-band HFA (60-90 Hz) simultaneous with a suppression of low-frequency activities (Fig 2A, between "B" and "T"). No concomitant clinical motor sign was detected as long as the frequency was in the HFA range (median = 80 Hz, interquartile range [IQR] = 3 Hz). The earliest motor sign, which was left arm tonic movement, corresponded to the onset of lower frequency activity with alpha then beta range in the TF plot (Fig 2A, "T"). When the subject started to have left arm clonic movement, the TF plot showed broadband theta to low gamma fast rhythmic activity (Fig 2A, "C"). The median latency of clinical motor onset from the onset of HFA was 9.24 seconds (IQR = 2.53 seconds).

Patient 2. This patient had no visible lesion on MRI. However, voxel-based morphometry showed an anomaly in the right paracentral lobule. Seizures consisted of left distal repetitive clonic jerks lasting up to 10 seconds. Electrode S3-4 was in the precentral leg area (see Fig 2B and Table).

TF analysis showed, after a few interictal sharp spikes, a burst of fast preictal spiking. Multiple narrow-band HFAs (median = 80 Hz, IQR = 20.6 Hz) arose simultaneously with suppression of lower frequency activity (Fig 2B, between "B" and "C"). No motor sign occurred during ictal HFA between time "B" and first "C". The earliest motor sign, a distal left leg clonic movement, occurred concomitantly with the reemergence of a pyramid-shaped broadband pattern with a low delta to beta frequency basis (Fig 2B, "C"). This pattern was rhythmical and coincident with the clonic jerks until the seizure ended (see Fig 1). The median latency of motor onset from HFA onset was 5.6 seconds (IQR = 1.39 seconds). The electrical-clinical correlation during the terminal clonic jerks phase had similar TF features, with the motor signs appearing at the time of the alpha/beta activity onset.

Patient 3. This child's MRI showed 2 focal cortical dysplasia lesions, one of them in the postcentral cortex. At seizure onset, she would cry as she felt an inability to move her left hand. Her left arm was atonic during 4 to 5 seconds, then clonic twitches appeared in her fingers and invaded her forearm and arm ipsilaterally. Electrode B3-4 was in the precentral hand area (see Table, Fig 2C).

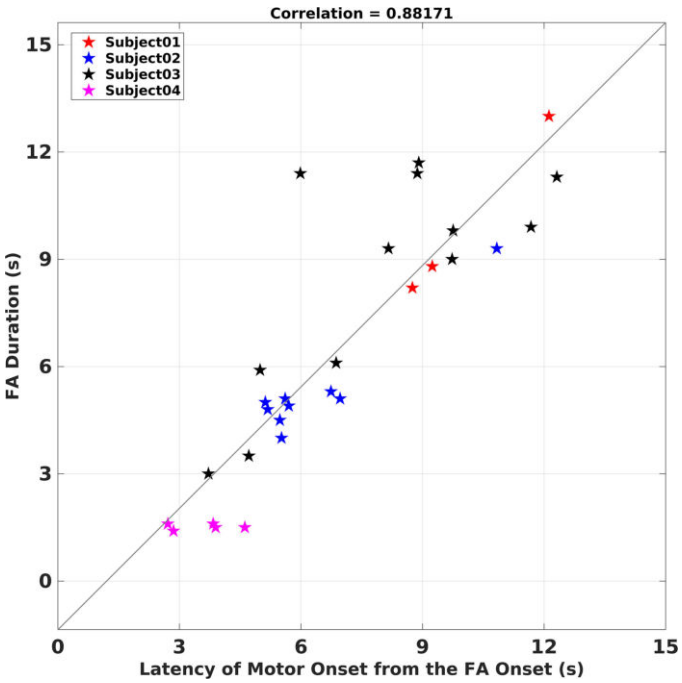

Fig. 4. Scatterplot showing the relationship between the latency of motor onset (in seconds) from the onset of fast activity (x-axis) and the duration (in seconds) of the fast activity (y-axis). Each color represents a distinct subject; subjects had variable number of seizures.

TF analysis of the electrical activity in electrodes B3-4 showed, after a few preictal spikes, the occurrence (Fig 2C, "A") of a double narrow-band HFA (median = 54.5 Hz, IQR = 16 Hz) concomitant with suppression of lower frequency activity. Her arm remained atonic as long as the motor cortex discharges stayed in the HFA range. The clonic movements in her left hand appeared when HFA vanished, and alpha/beta activity emerged (Fig 2C, "C"). The median latency of motor onset from the HFA onset was 8.52 seconds (IQR = 4.26 seconds).

Patient 4. This patient had polymicrogyria in the left anterior frontal lobe, frontal and parietal opercula, and left insula. Her seizures consisted of multiple clusters of brief right to left atonic-tonic facial movements. Electrode Z'5-6 was located in the left ventral precentral sulcus (motor face area; see Table, Fig 2D).

TF analysis of electrode Z'5-6 activity showed a flip-flop pattern with 2 distinct alternating frequency ranges (see Fig 2D and Fig 3). Visual analysis of the TF plot showed that the atonic facial states were associated with the presence of HFAs (median frequency = 90.6 Hz, IQR = 16 Hz; Fig 2D, "A"), whereas the tonic facial states were associated with relatively lower frequency activity in the beta range (median frequency = 22.9 Hz, IQR = 3.15 Hz; Fig 2D, "T"). A total of 66 brief seizure clusters were recorded. Paroxysmal ictal discharge frequencies corresponding respectively to the atonic and tonic states were significantly distinct (see Fig 3B).

Patient 5. This patient had had 2 previous left frontal surgical resections (see Fig 2E). His seizures consisted of a right proximal arm tonic flexion with his head turning to the left, followed by left arm tonic flexion and raising of both arms. Electrode H'4-5 was located in the left precentral gyrus (arm area; see Table and Fig 2E). TF analysis of electrode H'4–5 during the seizures showed a sustained beta frequency activity (median = 30 Hz, IQR = 3 Hz) with no HFA (see Fig 2E). The tonic flexion lasted as long as the beta discharge in the corresponding motor cortex persisted. This patient was excluded from the correlation study, below because his seizures involved the motor cortex with no evidence of HFA.

A first conclusion could be drawn from the electrophysiological analysis of the 5 patients: positive motor signs did not occur concomitantly with a high gamma activity developing in the motor cortex. Tonic or even clonic signs began at the end of HFA. This preliminary conclusion was further supported by our observation of Patient 5. In this case, a tonic arm seizure was correlated to beta and low gamma frequency activity.

Inhibitory Effect of HFAs

The inhibitory effect of motor cortex HFAs on the emergence of focal motor signs was evidenced in analyzing the relation between the duration of HFAs and the latency of clinical motor onset. The median frequency of the fast activity extracted from the Epileptogenic Zone Fingerprint pipeline in the first 4 subjects was 76 Hz (IQR = 21.9 Hz). Figure 4 shows the scatterplot between the latency of the motor onset (in seconds) with respect to the onset (x-axis) and the duration (in seconds) of the fast activity (y-axis). Each color represents a distinct subject; subjects had a variable number of seizures. For subjects who had many seizures, their electrical patterns and clinical semiology were very stereotypical with similar electrical-clinical correlations. Therefore, the corresponding measuring points in the scatterplot would overlap with each other across different seizures. So, the scattering pattern between the fast activity duration and the motor onset delay would not have any significant change when including all seizures. However, the correlation would be biased toward subjects who had more seizures simply due to the larger number of seizures. Hence, to get a valid statistical analysis, our strategy was to select representative seizures for each subject with a comparable number of seizures for a fair comparison and correlation

evaluation. A significant correlation ($r = 0.88$ with a p value of 2.7×10^{-10}) between the two measures was observed, indicating that the longer the HFA, the longer the delay in the occurrence of the motor signs.

Discussion

These findings support the hypothesis of an inhibitory effect of ictal HFAs. A correlation between the occurrence of a narrow-band fast activity at seizure onset and inhibition of motor cortex ictal efferent discharge was evidenced by (1) arrest of ongoing gesture or occurrence of brisk hypotonia during high fast activity and (2) linear correlation between the duration of fast activity and the latency of the focal motor clonic or tonic signs onset. The frequency range in the gamma band was related to the direction of the output effect. The switch from inhibition to excitation occurred when discharge frequency dropped from high to low gamma or beta. When a high gamma narrow-band discharge occurred, the TF pattern also included a simultaneous lower frequencies suppression.

Testing the hypothesis of an "inhibition"-related frequency pattern is challenging using SEEG macroelectrode recordings. Therefore, it is of critical importance to exclusively choose the primary motor cortex as the study target. The number of selectable cases was expected to be low. Due to the necessity of controlled physiological conditions in the clinical setting of presurgical video monitoring, confirmation of electrode placement in the very focal site from where the ictal discharge originated was a necessary and sufficient condition to ensure that the assessed peripheral effect was directly dependent on the cortical discharge we were observing.

A case report of a post-traumatic epilepsy described a similar phenomenon.[7] Physiological or pathological face contractions coincided with low-frequency motor cortex activations, whereas brief episodes of paroxysmal facial diplegia correlated with gamma discharges of approximately 60Hz. Referring to previous studies showing spatial decorrelation at fast ictal onset,[16] a decorrelation in the premotor-motor network leading to a disruption of functional connectivity was hypothesized. However, another possibility would be that cortical-motoneuronal coupling could be impaired in the case of cortical high gamma activity. The corticomuscular coherence reflects the corticomotoneuronal coupling.[17] With some variations depending on the contraction strength, the corticomuscular coherence is in the beta frequency range.[18]

This cortical oscillatory activity is generated in the primary motor cortex. When cortical frequency rises above the low gamma range, the corticomuscular coupling is likely to be disrupted with the arrest of movement as a consequence. In Patients 4 and 5, when the ictal frequency is steady at or drops to the beta range, a tonic muscle contraction is observed. In Patients 1, 2, and 3, the clonic phase starts only at the end of the HFA/suppression when the frequency pattern changes to broadband rhythmical spikes. Gamma activities during normal movement have also been described; low gamma seems to correspond to tonic isometric activity, and high gamma is broadband and not correlated with the timing of the movement itself.[19,20]

An alternate hypothesis is that high gamma narrow-band fast activity reflects a neuronal pool activity, which results in pyramidal cell inhibition. Synchronized fast spiking inhibitory interneurons (FSIIs) have been demonstrated to be the generators of gamma oscillations in the hippocampus and in the neocortex.[21] Inhibitory interneuron networks can generate coherent oscillations in the gamma range, whose frequency tuning depends on architectonic features in the network, including connection distances with conduction delays.[22] The neurobiological basis of an increase of FSII discharge has been demonstrated by Cossart et al[23] in hippocampal slices from experimental models (pilocarpine, kainate) of temporal epilepsy. The interaction between decreased dendritic and exacerbated perisomatic inhibition onto the principal cells at seizure onset was modeled by Wendling et al.[24] The result was the production of fast activity at the mesoscale level.

Therefore, the fast activity TF pattern identified in our study could be directly generated by such a population of FSIIs discharging synchronously or indirectly through their output onto the pyramidal postsynaptic membrane. The concomitant low-frequency suppression would correspond to the arrest of pyramidal cell discharge under FSII sustained discharge, causing hyperpolarization or shunting of the pyramidal cell membrane. At the end of this fast activity/suppression phase, a post-inhibitory rebound (PIR) would be responsible for triggering a broadband slower activity in the motor cortex concurrent with the onset of a clinical motor seizure.[25] Therefore, the delayed emergence of a motor seizure at the end of a steady narrow-band fast activity in the motor cortex at seizure onset is likely to be accounted for by an inhibitory mechanism.

Recent development of intracranial EEG has led to recognizing low-voltage fast activity as a reliable ictal feature in neocortical seizures.[2] A TF analysis of the transition from interictal to ictal activity revealed a specific pattern for an epileptogenic zone.[8,14] A consistent association of narrow-band fast with suppression of delta–alpha band activities was a feature of this fingerprint. The existence of an inhibitory mechanism corresponding to the fast/suppression pattern would add a pivotal element to the pathophysiology of ictal onset in focal seizures. It is not unreasonable to suggest that the same TF pattern when it occurs in other areas than the motor cortex results in an inhibitory output as well. Unfortunately, in clinical conditions where the ictal symptoms onset time is less objective to mark, direct evidence is difficult to provide.

A sustained inhibition correlated with the onset of a focal seizure was experimentally demonstrated by Gnatkovsky et al.[26] After bringing convincing experimental evidence, De Curtis and Avoli[9] developed an original hypothesis in favor of a "paradoxical involvement" of γ-aminobutyric acidergic (GABAergic) interneuronal activity at the "initiation of focal seizures characterized by low-voltage fast activity." This hypothesis was clearly confirmed by Elahian et al[27] with microelectrode recordings in patients undergoing presurgical intracranial investigations. Chang et al[25] confirmed the role of GABA-A receptor activation in this pathophysiological mechanism and showed the importance of a PIR in the transition to excitatory ictal events. The rebound of slower activities observed at the end of the suppression in the current study could well be a post-inhibitory rebound responsible for the generation of the initial muscular clonic jerks at the onset of a motor seizure. This opens new insights into the relationship between epileptogenic (electrical) and symptomatogenic (clinical) phenomena. Furthermore, activity-dependent elevated extracellular potassium and chloride concentration could represent an intermediate mechanism for the transition between increased FSII firing and excitatory bursting activity following the HFA (Gentiletti et al[28]). Depolarization block of these interneurons has been shown to initiate the rebound of pyramidal cell discharge (Calin et al[29]). Emphasis on the role of inhibition must be put back in the context of an interplay between excitation and inhibition at the onset of focal seizures. Preictal spiking is generated by increasing synchrony in pyramidal cells depolarization. This is the cause of inhibitory interneuron firing that gives rise to SEEG HFA. Then, gradual decline of perisomatic inhibitory barrage leads to post-inhibitory rebound of pyramidal paroxysmal activity. Narrow-band HFA with its chirping feature is best modeled by a subtle balance of positive and negative feedback between pyramidal cells and fast-inhibitory interneurons (Molaee-Ardekani et al[30]).

In an approach to understanding the mechanisms of epileptic negative myoclonus,[31] a few studies used EMG responses to single-pulse stimulation applied to the primary motor and premotor areas. A silent period following a brief motor evoked potential, or a direct initial inhibition of spontaneous muscular activity could be observed after stimulation of the primary motor as well as from the medial and lateral dorsal premotor cortex.[32,33] Hence, motor cortex inhibitory output can be triggered by a short (0.3 millisecond) pulse. This clinical situation had actually been modeled in experimental studies of the penicillin focus in rats. A phenomenon of "vertical inhibition" of deep (layer 5) pyramidal neurons generated by the upper layers while developing epileptic activity was meticulously demonstrated simultaneously and after the paroxysmal direct current (DC) shift corresponding to the EEG spike.[34] Consequently, a seizure onset zone located in the superficial layers of the cortex could initially induce a feedforward inhibition onto the deeper output cells. Such a translaminar inhibitory mechanism has recently been confirmed in physiological conditions.[35]

Ictal low-voltage fast activity has been observed on scalp EEG in focal or generalized seizures classified as tonic seizures. Tonic seizures or seizures with an electrodecremental pattern[4] have long been identified and included in seizure classifications.[36] Clinically presenting as generalized increased muscular tone throughout the body, they are electrically characterized by a "low voltage fast activity or a fast rhythm (10-25 Hz) decreasing in frequency and increasing in amplitude." Fast activity at seizure onset is bilateral and more or less symmetrical. Tonic axial seizures in Lennox-Gastaut syndrome are prototypical of tonic seizures with EEG fast activity.[37] There are few published observations with correlations between EEG HFAs and EMG tonic muscular activity. In most of the generalized syndromes, they have a nocturnal occurrence[38] and may be purely electrical, without motor semiology.[39] As they are associated with EEG attenuation or flattening and possibly contaminated by EMG artifacts, the presence of a fast activity on scalp EEG can be hard to ascertain. In the rare publications of tonic seizure polygraphic surface recording, the latency of EMG from EEG onset of fast activity was impossible to determine. In addition, EEG frequency was not estimated. Therefore, a possible universality of a frequency-dependent tonic/atonic mechanism like the one we are reporting cannot be further tested.

Interestingly, atonic seizures are also associated with low-voltage fast activity.[40] They were initially described in generalized epilepsies. With the development of video-EEG, focal atonic seizures have been identified.[36] A concept of "negative motor areas" emanated from subdural grid electrical stimulation studies.[41] Ictal atonic phenomena have been attributed to their activation.[42] These areas were broadly located in dorsal lateral, medial, and ventral premotor cortex.[43] A few case reports of focal seizures with subdural recordings also considered the primary motor cortex possibly responsible for atonic semiology. However, only a loose correlation of widespread rhythmic spikes partially recorded at the surface of the premotor and motor cortex with a weakness in the contralateral arm could be put forward.[32] However, the published cases of atonic seizures with EEG recording showed bilateral low-voltage fast activities in frontocentral areas.[44,45]

The present study has used the opportunity of direct primary motor cortex recording to figure out the neural mechanisms underlying HFA at seizure onset. During HFA, there is no motor sign. The end of HFA (and lower frequency suppression) is marked by a rebound of beta activity and coincides with clinical onset. Beta activity from the onset is the tonic seizure pattern. The inhibitory or excitatory drive of motor cortex output is frequency dependent. This phenomenon that was observed in motor cortex suggests that ictal onset mechanisms in seizures characterized by HFA could be built upon inhibition.

There may be some possible limitations in this study. First, the number of patients was small, due to the highly selective inclusion criteria. Indications for SEEG with implantation of electrodes in the pericentral region are rare. Among this population, a further selection was imposed by the necessity of ensuring strict electrical-clinical correlations within the primary motor cortex somatotopic organization. Second, measurement of the motor latency based on video-EEG recording is more imprecise than using EMG. The reason for relying on the former was the long-term monitoring clinical condition of the patients. The method could have proven to be inadequate if latencies between HFA onset in the motor cortex and movement onset had been within a tens of milliseconds timescale. Actually, the error due to video/EEG synchronization time could have been in the range of 5.6 milliseconds, whereas the minimal latency was 3 seconds. Finally, the pathophysiological hypothesis put forward to explain our findings could appear to be too speculative, as it is not possible to demonstrate an inhibitory mechanism without using intracellular recording. An alternative hypothesis could have been a depolarization-dependent inactivation. However, observation of Patient 4 showing alternance of atonic and tonic phases, in agreement with the Maillard et al case,[7] argues in favor of a peripheral inhibitory effect rather than a lack of excitation.

Author Contributions

H.S., J.L., R.M.L., and P.C. contributed to the conception and design of the study. H.S., J.L., M.K., O.G., J.B., and P.C. contributed to the acquisition and analysis of data. H.S., J.L., R.M.L., and P.C. contributed to writing the text and preparing the figures.

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