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Case Report

Non ictal onset zone: A window to ictal dynamics☆

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ABSTRACT

The focal and network concepts of epilepsy present different aspects of electroclinical phenomenon of seizures. Here, we present a 23-year-old man undergoing surgical evaluation with left fronto-temporal electrocorticography (ECoG) and microelectrode-array (MEA) in the middle temporal gyrus (MTG). We compare action-potential (AP) and local field potentials (LFP) recorded from MEA with ECoG. Seizure onset in the mesial-temporal lobe was characterized by changes in the pattern of AP-firing without clear changes in LFP or ECoG in MTG. This suggests simultaneous analysis of neuronal activity in differing spatial scales and frequency ranges provide complementary insights into how focal and network neurophysiological activity contribute to ictal activity.

1. Introduction

Epilepsy surgery can result in seizure freedom by successful resection of the epileptogenic zone (i.e. the area responsible for seizure generation). The ictal onset zone (IOZ) is considered one of the most accurate approximations to the epileptogenic zone and its delineation serves as the "gold standard" in surgical evaluation of focal onset epilepsies [1]. This focal concept [2] of ictogenesis is the basis of the clinical practice of epilepsy surgery.

The network concept [3] of ictogenesis suggests that widely distributed but interconnected networks of neurons and interneurons produce the electroclinical phenomenon of the seizure. This concept (supported by ictal and interictal intracranial EEG recordings of epileptic patients) is the basis for some models of seizure prediction [4,5] and serves as a mechanistic underpinning for the influence of central neuromodulation [6].

Although the above concepts influence treatments of focal onset epilepsies, there is not a unifying hypothesis that directly connects the two or explains which hypothesis is more "correct" for an individual patient [7]. Investigations into neuronal scale activity in human epilepsy may help to further clarify these concepts [8,9].

In this paper, we examined ictal dynamics of 3 seizures captured in one patient at the neuronal level, in an area outside the IOZ, and compare this with regional intracranial EEG changes.

2. Materials and methods

2.1. Patients and methods

Our patient is a 23-year-old right-handed male who underwent surgical evaluation for intractable focal onset epilepsy at the University of Utah Comprehensive Epilepsy Program. His first seizure occurred at 9 years of age. His seizure semiology had always been the same and consisted of an aura (feelings of heaviness, floatation, thought amplification and/or déjà vu) followed by focal onset impaired awareness seizure (consisting of loss of awareness, oral automatisms and bilateral, right earlier than left dystonic hand posturing and bilateral leg movements). Postictally he was confused and agitated. He had failed multiple medications including phenobarbital, sodium valproate, lamotrigine, and levetiracetam. He was poorly controlled on carbamazepine and phenytoin at the time of his referral. Pre-surgical evaluation included MRI, FDG-PET and phase I scalp video-EEG monitoring. His MRI was normal (classifying him as nonlesional focal onset epilepsy), and PET scan showed 20–25% decrease in FDG uptake in the left temporal lobe when compared to the right. Phase I scalp video-EEG monitoring captured two typical events as described above. Electrographically these events were similar with left fronto-temporal 2 Hz delta activity at the onset that evolved into 6 Hz rhythmic theta activity. Neuropsychological testing and Wada testing showed left-sided language

☆ The authors have no conflict of interest.

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dominance and bilateral memory. He was consulted and consented for surgical evaluation of epilepsy and placement of intracranial grid and strips. A separate informed consent was obtained for the Institutional Review Board approved MEA research protocol. He underwent a left fronto-temporal craniotomy for placement of intracranial electrodes and was admitted to the Neurological Intensive Care Unit at the University of Utah Hospital in Salt Lake City, UT.

3. Methods

3.1. ECoG electrodes

Recording electrodes consisted of an 8 × 8 grid of electrodes covering the left lateral fronto-temporal (LFT) areas and two sub-temporal 1 × 6 strips. Fig. 1 shows the location of the grid and two strips. For demonstration of grid and strip locations, the cortical surface was generated from a pre-operative MRI. Electrodes were co-registered with respect to the pre-operative MRI from the post-operative CT using the CTMR package [10].

3.2. Invasive intracranial video-EEG monitoring

Digital intracranial EEG was recorded with 128 channel XLTEK video-EEG monitoring (Natus incorporated, California, USA) with sampling rate of 250 Hz. Low frequency filter was set to 1 Hz and high frequency filter was set to 70 Hz. Video-EEG data were analyzed off-line and the display montage was adjusted as needed.

3.3. Microelectrode array (MEA)

A penetrating micro-electrode array (NeuroPort Array, Blackrock Microsystems) was implanted into the left MTG using a pneumatic insertion device [11]. Fig. 1 shows the location of the MEA in relation to the grid. The MEA consists of 100 microelectrodes (1.0 mm in length and 400 μm inter-electrode spacing) fabricated on a silicon waferbase (4 × 4 mm). Data were recorded with a sampling rate of 30 kHz. The low frequency filter was set to 0.3 Hz, and high frequency filter to 7.5 kHz. For analysis of individual APs, low frequency filter was set to 300 Hz and high frequency filter to 7.5 kHz. For analysis of local field potential (LFP) low frequency filter was set to 0.3 Hz and high frequency filter to 500 Hz. One representative electrode (electrode 35) was chosen for the LFP analysis. The analyses of AP firing rate were performed using the Chronux matlab toolbox [12].

4. Results

4.1. ECoG recordings and video-EEG monitoring

During 6 days of intracranial monitoring, five stereotypical focal onset impaired awareness seizures with no evolution to bilateral tonic-clonic seizures were captured (40–51 s in duration). All seizures started with 1.5–5 s of irregular spiking in the mesial contacts of the two ST-S followed by 7–10 s of focal ictal alpha activity (10–13 Hz). Thereafter the seizure spread to the lateral temporal neocortical areas with widespread spiking for 5–9 s at 2 Hz followed by 5 Hz before further spread. At seizure termination, ictal activity stopped in all ECoG electrodes except for LAT 1–3 and LPT 1–3 in which ictal activity stopped 3–6 s later.

4.2. Clinical and surgical outcome

A left anterior temporal lobectomy (including the area of MEA implantation) was performed with Engel Ia outcome at 34 months. Histopathology results showed no significant histopathology in the hippocampal tissue and subpial thickening consistent with Chaslin's Marginal sclerosis in the lateral temporal neocortical tissue.

4.3. Microelectrode array recordings

Successful recordings from the MEA were obtained for 4 of the 5 captured electroclinical seizures. The results were not used to make clinical decisions.

4.3.1. Field potential activity

The LFP signal recorded on the MEA was closely related to the signal recorded from the physically adjacent ECoG contact (LFT 43) in the MTG (Figs. 2 & 3).

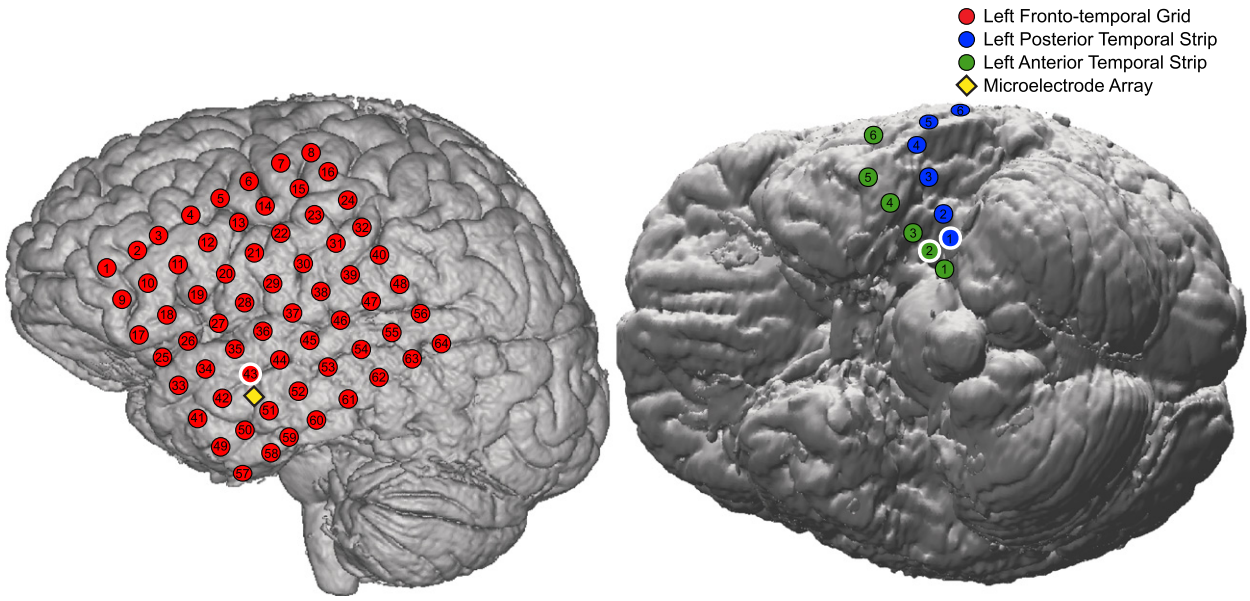

Fig. 1. Locations of the grid, strips and the MEA on the cortical surface. Each colored circle represents one ECoG electrode location. Red: left fronto-temporal grid (LFT), green: left anterior temporal strip (LAT); blue: left posterior temporal strip (LPT); yellow: research microelectrode array (MEA). The ECoG electrodes with recordings demonstrated in Figs. 2 and 3 are highlighted with a white rim. LPT 1 and LAT 2 were marked as the ictal onset zone (IOZ). LFT 43 and the MEA were in the MTG (middle temporal gyrus) region.

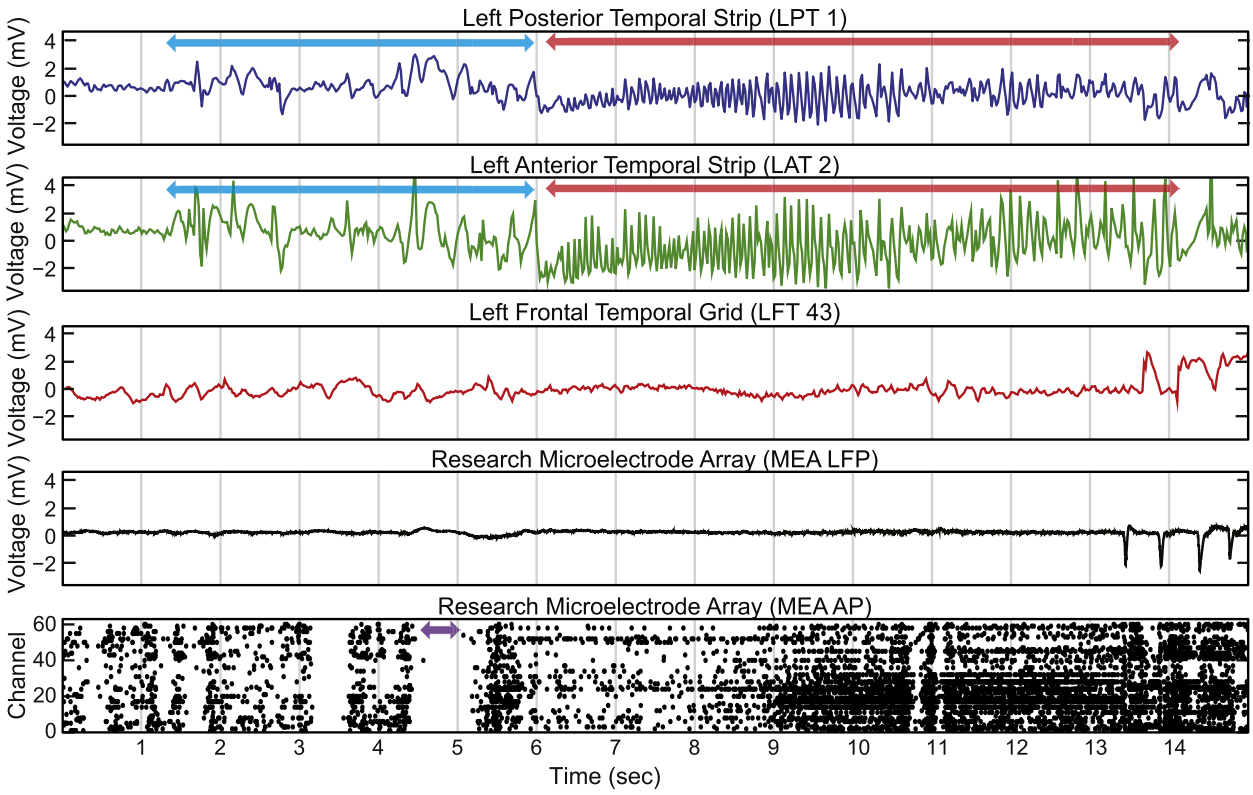

Fig. 2. The neurophysiological recordings from ECoG and MEA electrodes at seizure-1 onset. From top to bottom respectively: LPT1, LAT 2, LFT 43, LFP and AP. Recordings from LPT1 and LAT1 (top two rows) show 4.5 s of irregular spiking (blue arrow) followed by ictal alpha activity (red arrow). The MTG region ECoG recordings from adjacent LFT 43 electrode and LFP from the MEA showed no departure from physiological brain activity during the spike bursts. The AP recordings showed a brief silent period (cessation of firing) of 0.72 s (indicated by the purple arrow). The time from onset of irregular spiking at IOZ to onset of silent period at MTG was 2.9 s (left border of blue arrow to left border of purple arrow).

4.3.2. Action potential activity

Visual analysis of the AP firing pattern revealed it to be unexpectedly different from both the LFP signal and the ECoG signal recorded from the physically adjacent grid contact (LFT 43). The most notable difference was the period of cessation of AP firing at time of ictal onset and termination as described below. These differences are explained in relation to the changes in the ictal onset zone and during different periods of neural activity (periods of irregular spiking, ictal alpha build up, development of 2 Hz ictal activity, and ictal termination). Additionally, Table 1 summarizes the periods of cessation of AP firings at time of ictal onset and termination and their relative temporal relationship to irregular ictal spiking in IOZ.

4.3.3. Neural activity dynamics across both recording types

4.3.3.1. Period of irregular spiking. In two of the four seizures that had a longer period of irregular spiking (seizures 1 and 2, Table 1) in the mesial temporal contacts of ST-S, there was a brief cessation of AP firing in MTG (0.72 and 0.51 s in seizures 1 and 2 respectively). In two of the seizures with shorter periods of irregular spiking (seizures 3 and 4, Table 1), the cessation of AP firing was not observed in the MTG. It is important to note that no concomitant ictal change was detectable in the LFP recorded in MTG or ECoG recorded in the left fronto-temporal grid during the period of irregular spiking (Fig. 3, ~5 to 10 s)

4.3.3.2. Period of ictal alpha build-up. Across all seizures, during epochs of ictal alpha build up in the mesial temporal contacts of ST-S, the AP firing was noted initially in only a few units and then steadily increased, slowly building to most units firing at interictal epochs (Fig. 2, ~6 to 13 s).

4.3.3.3. Development of 2 Hz ictal rhythmic activity. Across all seizures, as the local ECoG and the local LFP signal developed into 2 Hz activity, the AP firing became progressively more synchronized to the 2 Hz activity and remained so during the seizure events.

4.3.3.4. Ictal termination. Across all seizures with a recorded ictal offset, at ictal offset the cessation of AP firing (2.04–2.5 s) was longer than the cessation of AP firing at ictal onset.

5. Discussion

Based on ECoG recordings from the five electroclinical seizures, our patient's IOZ was delineated in the left mesial temporal area with emergence of low-frequency, high-amplitude irregular spiking followed by ictal alpha activity. Based on the focal concept of epileptogenesis, our patient underwent a left anterior temporal lobectomy (i.e. removal of IOZ) with Engel Ia outcome at 34 months.

The network concept of ictogenesis would suggest that seizure onset in the IOZ be accompanied by measurable changes in neuronal activity outside of the IOZ. Four of five electroclinical seizures were captured with both MEA and ECoG allowing for precise comparison of temporal relationships of neural activity in the IOZ and in MTG (i.e. a site outside the IOZ). **Although seizure onset in the mesial temporal lobe was not accompanied by clear changes in LFP or ECoG activity in the MTG, it is possible that analysis of other aspects of these data, such as the high-frequency oscillatory component [13] could yield additional insights. In contrast,** clear changes in the action potential firing patterns in the temporal neocortex occurred in two of the seizures (with longer periods of irregular spiking). In these two seizures cessation of AP firing i.e. a "silent period" was noted at the onset of the seizure in IOZ and therefore is presumed to be the timing electrographic seizure

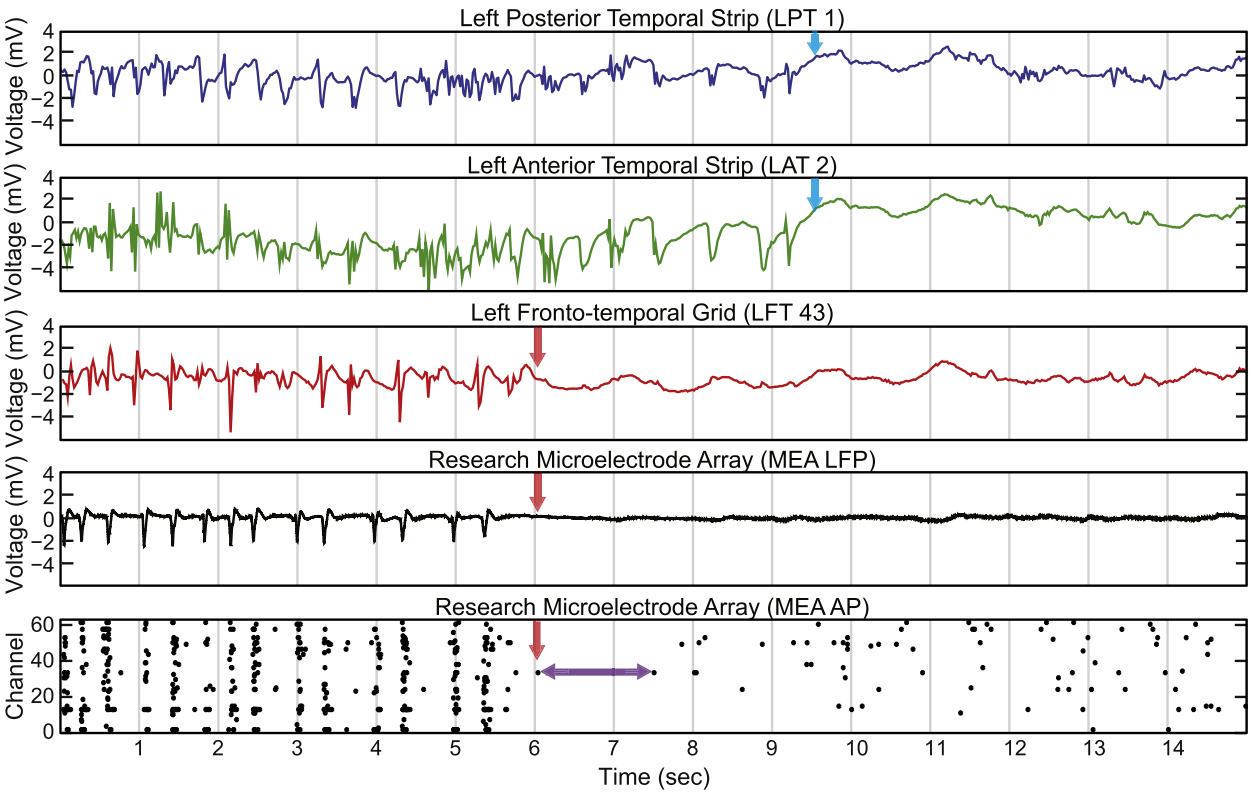

Fig. 3. The neurophysiological recordings from ECoG and MEA electrodes at seizure-2 termination. From top to bottom respectively: LPT1, LAT 2, LFT 43, LFP and AP. At seizure termination, there was an increase in synchronization (i.e. the timing of activity and inactivity of ECoG electrodes, LFP and AP become more coinciding). Synchronization climaxed at the end of the seizure with cessation of all activity in ECoG at IOZ (blue arrows), ECoG at MTG, LFP and AP electrodes (red arrows), including a longer "silent period" in the AP firing rates (indicated by purple arrow). The duration of the silent period at ictal termination in the MTG was 2.09 s.

onset. After the first "silent period", the neurophysiologic activity seemed desynchronized with fewer neurons firing and with a dramatically depressed firing rate. As the seizure progressed the AP firing rate increased and became more synchronized to the local LFP and local ECoG signal. The end of the seizure was heralded by a second "silent period" characterized by simultaneous cessation of all activity in AP, LFP and the left fronto-temporal grid (Fig. 3). It is important to note that ictal termination in mesiobasal contacts occurred 3–6 s later. Table 1 indicates the duration of irregular spiking as well as the silent periods.

The change at the onset of the seizure in the AP firing patterns in non-IOZ supports the network concept of ictogenesis [3]. Based on signal analysis of ECoG recordings during seizure, preictal synchronization is reported to be maximal before emergence of rapid discharges and to involve low frequencies [4,14]. Synchronization tends to decrease thereafter, then increases over the course of the seizure [4]. **Truccolo et al. examined spike heterogeneity at spatial scale of small cortical patches and based on intracranial MEA recordings. They reported highly heterogeneous neural spiking activity during seizure initiation and spread and decrease heterogeneity toward seizure termination. The seizure termination was reported to be a nearly homogenous phenomenon followed by an almost complete cessation of spiking across recorded neuronal ensembles** [15].

Our case is different from previous literature in that, somewhat unexpectedly, we observed cessation of AP firing at the time of ictal onset, in the non-ictal onset zone. This "silent periods" were similar to what we observed and has been described in ictal termination [15]. It is important to note that we also observed similar "silent periods" interictally but have chosen not to focus on interictal phenomenon for this report. It is the subject of future research to determine if these changes occur among other patients with mesial as well as neocortical epilepsies and if they can help to pinpoint the precise timing of ictal onset and narrow the temporal extent of the ictal-interictal continuum.

6. Conclusion

In this case of temporal lobe epilepsy (without mesial temporal sclerosis) successful surgery was performed based on the focal concept of ictogenesis as guided by ECoG. The network concept of ictogenesis would suggest that seizures are accompanied by measurable changes

Table 1
Summary of relative onset and duration of irregular ictal spiking captured by ECoG and periods of cessation of AP firing captured by MEA and their relative onset for the four seizures.

Neural activity (seconds)	Seizure 1	Seizure 2	Seizure 3	Seizure 4
Duration of ictal spiking in ECoG at IOZ	4.5	2.5	1	0.8
Duration of silent period at ictal onset at MTG	0.72	0.51	none	none
Time from onset of irregular spiking at IOZ to onset of silent period at MTG	2.9	0.66	n/a	n/a
Duration of silent period at ictal termination at MTG	*	2.09	2.04	2.5

ECoG electrocorticography; IOZ ictal onset zone; AP action potential; MTG middle temporal gyrus;
* The connector was hit briefly on the bed rail by the patient at the end of the seizures. This caused the amplifier to be temporarily saturated; therefore the duration of the silent period at ictal termination was not recorded.

in neuronal activity, even in the non-IOZ. Here, seizure onset in the mesial temporal lobe was not accompanied by clear changes in LFP or ECoG activity in the MTG in this patient. However, significant changes in the action potential firing pattern in the temporal neocortex reflected seizure onset in the mesial area. Thus, simultaneously recorded multiscale field potentials and action potential firing rates provided complementary insights into the nature of neurophysiologic activity at these different spatiotemporal scales during seizure, and with further analysis may lead to better understanding of how the network and focal concepts of ictogenesis reflect differing attributes of human epilepsy.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ebcr.2017.10.003.

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