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Understanding the physical mechanism of transition to epileptic seizures

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Abstract

The mechanisms of generating epileptic seizures are still unknown. To identify the mechanisms that underlie the transition to seizure a combination of features that include firing rate, power spectrum and complexity measures were simultaneously analyzed. Pre-ictal periods are characterized by large fluctuations of firing rate which reflect local dysfunctional regulation of neuronal activity. This local dysfunction in neuronal activity is translated in changes of endogenous electric field within clustered regions with high frequency oscillations (HFO) that act at fundamental level of charge dynamics and lead to chaotic dynamics followed by electrical resonances. Right before the onset of seizures the presence of chaotic behavior becomes persistent and leads all types of cells to fire simultaneously and generate the transition to ictal state. The alteration in neuronal regulation and the nature of physical phenomena involved in this transition supports some models of seizure generation and rules out others.

Keywords

Epilepsy; Seizure generation; KAM theory; Seizure prediction; Neuroelectrodynamics

1. Introduction

Epilepsy is a multifaceted neurological disorder where the occurrence of seizures leads to alterations in normal electric rhythms that can be recorded and analyzed. The hippocampus plays a central role in the generation and propagation of seizures (Parent et al., 1997; Buzsaïki, 2006) in both human and rodent models of temporal lobe epilepsy. Current models show that several factors which govern neuronal excitability and intrinsic neurochemistry (Farrant and Nusser, 2005) are involved in seizure generation, however little is yet known about how these factor operate and determine the seizure onset. Distinct electrophysiological phenomena originating from different epileptic brain regions precede the ictal discharge.

The presence of interictal spikes is associated with an increased risk for spontaneous seizure (Gotman, 1991; Staley et al., 2005). During interictal periods in epileptic focal regions quasi-localized clusters of high-frequency oscillations (HFO) have been previously revealed based on EEG analysis (Bragin et al., 1999; Buzsáki, 2002; Staba et al., 2002; Worrell et al., 2004; Bragin et al., 2010). These high frequency oscillations appear periodically in the epileptic brain and they manifest on a scale of centimeters generated by abnormal hyper-synchronization of large neuronal ensembles (Crépon et al., 2010). The formation of HFO clusters that become broader after the application of GABA_A receptor antagonist bicuculine was firstly reported in (Bragin et al., 2002). The presence of HFO in the seizure-generating

structures is highly related to temporal and spatial location of seizure onset (Crépon et al., 2010). On the other hand few analyses have highlighted the presence of focal low frequency oscillations that precede ictal discharge in EEG or MEG data (Adeli et al., 2003; Csercsa et al., 2010). While alterations at different levels can always facilitate abnormal neuronal activities, the occurrence of seizures is a rare event with a very low probability of occurrence.

From gene to gliogenesis (Bonni et al., 1997) and neurotransmitter release (Cartmell and Schoepp, 2000) to neurogenesis (Zhao et al., 2008) all mechanisms are highly regulated in the brain. This regulation further extends to synaptic activity (Newman, 2003) and firing activity of neurons in different brain regions. Therefore, changes in regulation at different levels can have broad consequences and influence rhythmic patterns of neuronal activity. The electric field generated by a population of neurons that fire was termed endogenous electric field by Jefferys (1995). Changes in endogenous electric field alter the dynamics of electric charges, the diffusion of ions as well as the neurotransmitter release (Fröhlich and McCormick, 2010). All these changes can significantly influence local neuronal activity. Therefore, we hypothesize that dysfunctional regulation of neuronal activity inside epileptogenic regions changes relevant characteristics of endogenous electric field and leads to seizure generation. To test this hypothesis recorded local field potentials from the dentate gyrus and unit data from putative granule cells in epileptic pilocarpine-treated rats were analyzed before and during spontaneous seizures. A combination of features that include firing rate, power spectrum and complexity measures were simultaneously analyzed.

2. Data collection materials and methods

All experiments were performed in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the Stanford University Institutional Animal Care and Use Committee. Tetrode implants, data acquisition and histological verification of the tetrodes position were previously performed by Bower and Buckmaster and the details of the protocol were published in Bower and Buckmaster (2008).

The seizure onset was identified electrographically from one of the tetrodes based on changes in the spectral power following the techniques presented in Bower and Buckmaster (2008). Recorded local field potentials from the dentate gyrus of four pilocarpine-treated, epileptic rats were analyzed using FFT power spectrum 1 h prior to spontaneous seizure onset. The power spectrum was computed for three different bandwidths: (high frequency oscillations HFO, $200 < f < 300$ Hz, main frequency oscillations (FO) $2-100$ Hz and low frequency oscillations (LFO) $0.1 < f < 2$ Hz). The harmonic components within these specific frequency bands were extracted and then averaged. Further the envelope is extracted from four different electrodes by using principal component analysis (PCA) and a zero phase-shift band pass digital filter is used to suppress the noise and improve the signal-to-noise ratio (Urbach and Pratt, 1986). The envelope of the first principal component of HFO, LFO or FO events is statistically analyzed using a windowed *t*-test or one-way ANOVA for all seizures with window size of 5 min. The windowed *t*-test is used to detect the existence of rare events in activity compared to a baseline period of the first 10 min. In each case the *t*-test indicates a rejection of the null hypothesis at the 5% significance level. For recorded local field potentials Kolmogorov complexity measure is estimated using techniques described in Small (2005). Tetrodes recording of unit data from putative granule cells during 12 spontaneous seizures were selected from HFO epileptogenic regions. An automated unsupervised classification of multidimensional data in the tetrode setup was used (KlustaKwik, Harris K.D. et al., Rutgers University) followed by manual selection of final clusters was performed (MClust-3.5, Redish A.D. et al., University of Minnesota).

3. Results

A selected example presents changes that occur during 60 min before the seizure (Fig. 1). Significant fluctuations of firing rate in an ensemble of neurons display wide uprising trend 20 min before the seizure onset (Fig. 1a and b). The high values of firing rate represented in top red color are generated by interneurons (mean firing rate > 5 Hz) while lower firing rates are generated by granule cells (Fig. 1a). Changes of high frequency oscillations (HFO, $200 < f < 300$ Hz), main frequency oscillations (FO, $2-100$ Hz) and low frequency oscillations (LFO, $0.01 < f < 2$ Hz) display a relevant trajectory in LFO, HFO, FO space during 60 min before seizure (Fig. 1b). Large amplitudes of HFO with local maxima (peaks) or minima (valleys) can be observed in HFO envelope determined by concomitant increase/decrease “kicks” in the firing rate of granule cell units that precede the seizure onset (Fig. 1a–c). Most of the time this trajectory in frequency domain remains bounded, only rarely is highly perturbed (see min 20 and min 6). The analysis of HFO data with a windowed t -test shows that a statistically significant change in HFO (in red) occurs 20 min before seizure followed by significant changes in LFO (in black) and main frequency (in blue color) band that correspond to strong firing rate fluctuations (Fig. 1d).

The presence of HFO was detected in 12 selected seizures recorded from four pilocarpine-treated rats. These data were statistically analyzed and one-way ANOVA test was performed during 60 min before seizure assuming independent estimates for groups of 5 min window. The estimated F -ratio and p -values summarize the result of statistical analysis. Statistically, significant changes in the amplitude of power spectrum harmonics precede the seizure onset. The ANOVA analysis shows a statistically significant change in HFO ($p = 3.78 \times 10^{-7}$, $F = 5.76$) and LFO ($p = 0.0091$, $F = 2.52$). A post hoc pairwise comparison is performed in order to reveal where in time these differences are significant. On average the significant change in HFO and LFO harmonics occurs between 5 and 10 min before the seizure onset (Fig. 2a and b). However, there is no significant trend in the main frequency bandwidth ($p = 0.821$, $F = 0.58$, Fig. 2c).

Indeed, averaging data from several seizures can show a certain trend of HFO characteristics and firing rate (Bower and Buckmaster, 2008) however this type of analysis hides significant details regarding nonlinear dynamics and transitory regimes that occur in every seizure (Fig. 1a and b).

A representative example of HFO propagation between granule cell layer (GCL), hilus and CA3 during 60 min before the seizure onset is shown in Fig. 3a. The statistically significant change in HFO occurs first in GCL layer then expands to CA3 region and hilus (Fig. 3b). The trajectory in frequency domain remains bounded and starts to be perturbed only during the preictal period.

The periods when chaotic dynamics become persistent show continuous high values of complexity that can be easily detected. The scaled measure of complexity, in red color and normalized changes of firing rate, in blue color, are both represented 1 h prior to seizure (Fig. 4a). Marked in yellow color are regions that correspond to low firing rate periods and exhibit persistent chaotic dynamics. The occurrence of persistent chaotic dynamics is followed by an increase of firing rate which correspond to peaks in HFO envelope (Fig. 1c). During inter-ictal period the duration of persistent chaotic dynamics is short. Right before the seizure an unusual longer period with abnormal persistent chaotic dynamics precedes the seizure (Fig. 4b). In (Fig. 4c) the presence of periods with persistent chaotic dynamics is displayed 1 h before the seizure.

The representation of regulatory system (Fig. 5a) schematically shows the relation between neuronal activity, electric field and dynamics of electric charges. The transitory regime

represents a general outcome after a perturbation. A comparison between a theoretical model of response to impulse perturbation and changes that occur in HFO envelope and average firing rate before, during and after spontaneous seizures are displayed in (Fig. 5). Globally, the impulse response of a regulatory system can be approximated with a sinc function and is represented in Fig. 5b. If the system is nonlinear this response and the resulting shape can become more complex. Remarkable, the shape of HFO envelope and average firing rate (Fig. 5c and d) follow this theoretical model where three main phases can be identified. The raising phase (preictal) shows an increasing trend in the average firing rate and HFO amplitude. The ictal phase is characterized by peak HFO and firing rate values and the postictal period is characterized by a decrease in HFO and firing rate fluctuations. The transitory regime that precedes seizure generation (preictal state) is characterized by brief periods when chaotic dynamics occur (Fig. 5c and d). These periods display increased values of signal complexity. The period after the seizure (postictal phase) shows a longer transition with prolonged chaotic diffusion regimes over 20 min when high values of complexity characterize the dynamics.

4. Discussion

The power spectrum analyses show that the regulatory mechanism is present in the frequency domain. Most of the time there are small fluctuations in frequency (Figs. 1c and 3a) which reflect a regulatory process that rarely is altered even in the epileptogenic regions. Dominant frequency oscillations of electric field (FO) are continuously maintained by neuronal activities. However, 10–20 min before the seizure in the focal epileptogenic region the broadband power spectrum occurs. Strong HFO and LFO harmonics reflect significant changes in the dynamics of endogenous electric field, the presence of electrical resonances and chaotic dynamics. Specifically, the increase in amplitude of LFO harmonics is related to chaos generation and reflects a universal behavior of nonlinear systems (Cvitanovic, 1995; Pritchard and Duke, 1992). Chaotic diffusion can develop and its presence becomes evident during the decrease, or absence of firing and corresponds to periods when high values of complexity are estimated (Fig. 4a). Abrupt changes in firing rate translate to significant changes in endogenous electric fields that generate alterations in the dynamics and interactions of electric charges. Chaotic dynamics correspond to periods of lower firing activity which are marked in yellow and magenta color. Large peaks of the HFO envelope or firing rate characterize electrical resonant regimes with low values of complexity (Figs. 4a–c and 5c, d).

The severe dysfunctional regulation of local neuronal activity represents the biological substrate of transition to seizure. Right before the seizure the decrease in firing rate, the absence of firing becomes unusual longer and is translated in a prolonged period of persistent chaotic diffusion (Fig. 4a–c). If chaotic dynamics lasts over 30 s the transition to ictal state is certain. Therefore, this prolonged persistent chaotic regime is a specific feature, characterizes dysfunctional regulation and marks the transition to seizure. Once the resonant regime occurs in the focal region it expands very fast in larger areas and generates the seizure. Since only a severe alteration of neuronal activity leads to seizure then the ictal state is a rare event.

The nature of regulation mechanisms and physical phenomena involved in this transition supports some models of seizure generation and rules out others. Before the seizure onset different types of neurons including granule cell units and interneurons display similar increasing fluctuations of firing rate (Fig. 1a). In the focal region 10–20 min in advance the process of recruitment of different types of neurons that perform similar dynamics is essential to generate the seizure. Therefore, independent of their type all neurons have similar active role in seizure generation. Under extensive, persistent chaotic diffusion

relevant differences between different types of neurons disappear and all types of cells start to fire together and generate the transition to ictal state.

Since different types of neurons do not seem to reveal distinct role in seizure generation, a more general model is required to explain the transition to seizure. Specifically, these analyses suggest that impaired regulation of local neuronal activity significantly changes the characteristics of endogenous electrical field in the focal region and is the fundamental source of seizure generation. Since dysfunctional regulation does not always occur, then indeed the ictal state is a rare event.

The increased fluctuations of firing rate during pre-ictal period is equivalent to a response to a ‘perturbation’ that changes local endogenous electric field and the dynamics of electric charges in the epileptogenic region. This approach offers a required framework to relate nonlinear dynamics of Kolmogorov Arnold Moser theory (KAM) (Kolmogorov, 1954; Arnold, 1963; Moser, 1967) and its extensions to explain essential changes in the characteristics of electric field and charge dynamics. In this case the KAM theory refers to Hamiltonian systems with many degrees of freedom that describe the motion of charged particles in electric field. The theoretical aspects involved in a transition to chaotic behavior were presented in Chirikov (1979), Reichl (2004). A perturbation with higher energy determines diffusion across the resonances lines (resonance interference) and a fast transition to chaotic dynamics. The interaction between resonances in perturbed and unperturbed orbits generates transitory regimes that lead to chaotic behavior (Luo, 2006). The prolonged period of chaotic diffusion (postictal phase) follows strong resonant regimes developed during the seizure and is maintained if neurons have low firing rates (Fig. 5c). Since in a nonlinear system, the resonance frequency depends on action, then changes in action (perturbations) are reflected in alterations of power spectrum harmonics. This phenomenon explains significant changes in the amplitude of power spectrum harmonics that precede the seizure onset (Fig. 2). In addition in systems with many degrees of freedom (e.g. charges in electric field) diffusion can occur *along the resonance lines* (Arnold diffusion) and determine a gradual transition to chaotic behavior.

Many factors that include changes in morphological and molecular basis can act together or separately and alter local regulation of neuronal activity. Genetic mutations of ion channels (Claes et al., 2001; Escayg and Goldin, 2010) failure of glutamate reuptake from the extracellular space (Moritani et al., 2005), aberrant synaptic connectivity (Jacobs et al., 1999), terminal sprouting (Tauck and Nadler, 1985), potassium lateral diffusion (Park and Durand, 2006) glial buffering on extracellular potassium are only few phenomena that can lead to impaired regulation of local neuronal activity.

This result strongly suggests that the regulation of neuronal activity (firing rate homeostasis) is required to avoid the persistent chaotic dynamics in the focal epileptogenic region. Therefore, maintaining a sustained neuronal activity in every brain region is required to control chaotic dynamics. However ‘excessive order’ needs also to be avoided. During the seizure (about 2 min, Fig. 5b) loss of consciousness can occur followed by confusion and lack of responsiveness (Fagan et al., 1990). Both phenomena suggests that information processing is altered either due to “excessive” order during the ictal state or due increased periods with abnormal low firing rate and persistent chaotic dynamics (disordered states) in the post-ictal phase. These results point to a relationship between altered conscious experience and intrinsic characteristics of endogenous electric field and reveal a general physical model of computation previously presented in neuroelectrodynamics (Aur and Jog, 2010).

5. Conclusion

The paper presents a combination of several methods applied together to analyze data recordings that brings a cross-disciplinary understanding of the mechanisms involved in seizure generation. Experimental data analysis and analytical models show that the process underlying seizure generation is a rare event, the effect of a severe dysfunctional regulation of neuronal activity inside epileptogenic region. This dysfunctional regulation of neuronal activity in the epileptogenic region is translated in significant changes in endogenous electric field that determines the occurrence of electrical resonances and chaotic dynamics that lead to seizure.

The result of this analysis rules out a precise long term seizure forecasting. However, it clarifies the possibility of accurate short time seizure prediction and effective close loop neuromodulation (Aur et al., 2010). The regularity of the motion and transitory regimes are specific characteristics of multi-dimensional physical systems. These results show that underlying physical principles are universal in nature, they can be observed and transferred between different fields and may reveal the secrets of disturbing neurological condition.

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Fig. 1.

Strong fluctuations of firing rate in the HFO region precede the seizure onset and determine significant changes in power spectrum. (a) The evolution of changes in firing rate in granule cell layer 1 h prior to seizure represented in different colors. The high values of firing rate represented in red color are generated by interneurons (mean firing rate >5 Hz) while lower firing rates are generated by granule cells. (b) The average of firing rate of neurons represented in (a). (c) The corresponding trajectory in LFO, HFO, FO space during 60 min before seizure. Most of the time the trajectory is bounded, rarely is highly perturbed (see min 20 and min 6). (d) The windowed t -test shows that statistically significant changes in HFO (in red) that occur 20 min before seizure followed by significant changes in LFO and in the main frequency band. The t -test outcome for LFO is represented in black and for FO in blue color. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Fig. 2.

One-way ANOVA analysis of changes in the amplitude of harmonics using a 5 min window. For each column the lines of the box display the lower quartile, median and upper quartile values. The red crosses mark data outliers with values not included between the whiskers. ANOVA displays statistically significant difference in case of (a), HFO ($F = 5.76$, $p = 3.78 \times 10^{-7}$) (b), LFO ($F = 2.52$; $p = 0.0091$) and does not provide statistical difference (c), for FO ($F = 0.58$, $p = 0.821$). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Fig. 3. Statistically significant changes in HFO envelope occur 20 min before seizure. (a) The propagation of HFO between (GCL), hilus and CA3 region. (b) Statistically significant changes in HFO occur first in GCL (black and red color for two different tips of tetrodes implanted in GCL) and they expand to CA3 region and hilus. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Fig. 4.

Specific transitory behavior precedes the seizure onset and reveals a severe dysfunction in local neuronal activity regulation. (a) The normalized change of firing rate is represented in blue color and the measure of complexity is scaled and represented in red color 1 h prior to seizure. The changes that occur in firing rate correlate with alterations in the dynamics of electric charges. High values of complexity correspond to increased chaotic dynamics (yellow marked regions). (b) The detail of chaos persistence represents the rectangle from (a). Right before the seizure onset high values of complexity in red color reveal an unusual longer period with abnormal persistent chaotic dynamics that marks the transition to seizure. (c) The presence of persistent chaotic dynamics represented 1 h before the seizure. Right before the seizure onset unusual persistent chaotic dynamics is detected. Each bar in blue color represents the duration of persistent chaotic. The horizontal dashed red line marks the critical time ($T_{cr} \approx 0.5$ min). The seizure is a rare event that occurs only if chaotic dynamic lasts longer than T_{cr} . (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Fig. 5.

A comparison between theoretical model of response to perturbation in a linear system and the transition to seizure represented by changes in HFO and average firing rate before, during and after spontaneous seizures. (a) Schematic representation of regulatory system where changes in neuronal activity, electric field and dynamics of electric charges are strongly related. (b) The response of regulatory linear system to impulse is the sinc function. (c) Fluctuations of average firing rate 1 h before the seizure represented in blue color show periods with lower neuronal activity characterized by increased chaotic dynamics revealed by high values of signal complexity plotted in red color. Chaotic dynamics develops during preictal periods (marked in yellow) and postictal periods (marked in magenta). (d) The changes in HFO envelope 1 h before the seizure represented in blue color includes brief periods when chaos develops and characterizes low HFO values. During postictal phase similar chaotic periods are developed (marked in magenta color). The peaks in HFO amplitude define elevated neuronal firing rates. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)