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Resolution revolution: epilepsy dynamics at the microscale

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Abstract

Our understanding of the neuronal mechanisms behind epilepsy dynamics has recently advanced due to the application of novel technologies, monitoring hundreds of neurons with single cell resolution. These developments have provided new theories on the relationship between physiological and pathological states, as well as common motifs for the propagation of paroxysmal activity. While traditional electroencephalogram (EEG) recordings continue to describe normal network oscillations and abnormal epileptic events within and outside of the seizure focus, analysis of epilepsy dynamics at the microscale has found variability in the composition of macroscopically repetitive epileptiform events. These novel results point to heterogeneity in the underlying dynamics of the disorder, highlighting both the need and potential for more specific and targeted therapies.

Introduction

Epilepsy involves the spontaneous generation, propagation, and termination of pathological network events, typically surrounded spatially and temporally by predominantly normal neural activity. The challenge in selectively treating the condition is determining what mechanisms cause this shift from the physiological to pathological state and what measures can be used to predict the time and location of seizures. The development of advanced multi-modal imaging and multi-electrode array technologies has dramatically increased the temporal and spatial resolution of recordings, leading to several novel insights into the underpinnings of the disorder. The spiral wave dynamic, in which propagating waves emanate from and rotate around a central rhythmic organizer [1], has been detected in the normal cortex in vivo using voltage-sensitive dye imaging [2], providing a powerful mechanism by which to entrain neuronal populations, while multi-electrode arrays have revealed that seizures may also exhibit spiral wave behavior [3]. Normal, interictal, and ictal (seizures) brain states are thought to coexist in the epileptic brain, but the transformation that allows a physiological mechanism such as the spiral waves to instead propagate recurrent pathological activity is unknown. From a dynamical systems theory perspective, a

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bifurcation barrier (separatrix) is thought to act between the normal and pathological brain states, and the onset of a seizure begins when the normal brain trajectory collides with this barrier [4•]. In addition to this theoretical barrier between brain states, a sharp demarcation can be present between the areas of the brain that become entrained and recruited into a seizure and other adjacent non-participating areas (“penumbra”) [5•,6], demonstrating a seizure core surrounded by an inhibitory restraint. Based on functional connectivity from multisite recordings in patients, seizures have been characterized as a consistent progression of brain states, in which the seizure onset zone is isolated at the seizure onset but gradually becomes more connected until seizure termination [7••]. Discovering the dynamics particular to the seizure focus thus becomes paramount to the localization and targeted treatment of the seizure disorder, and the levels of both physiological and pathological oscillations have recently been shown to be crucial for clinical intervention.

Spikes and oscillations at the seizure focus

After frontline anti-epileptic drugs fail to satisfactorily control seizures in patients, the clinical effectiveness of subsequent treatment is heavily influenced by the ability to localize the seizure-generating brain structures, as the removal of tissue associated with frequent seizure onset, not the surrounding infrequent onset areas, during surgical intervention predicts freedom from seizures [8]. As a result, the ability to localize the onset zone from current clinical measurements, such as EEG recordings, has obtained ever-increasing scrutiny. Interictal spikes (IISs) are generated by synchronized discharges of cell populations and precede the appearance of spontaneous seizures during epileptogenesis in experimental epilepsy models (reviewed in [9]; also [10,11]). The incidence of IISs is currently used as a diagnostic tool due to their high correlation with spontaneous seizures [12]. In contrast, gamma oscillations (defined as 30–100 Hz) have a more variable correlation with the seizure onset zone. While electrodes in the seizure onset zone have been shown to have higher mean gamma oscillation activity in some patients [13], secondary seizure areas or areas without seizures can have more frequent gamma oscillations than the seizure onset zone [14]. However, cross-frequency coupling between the high gamma oscillation (defined as 80–150 Hz) amplitude and the low frequency (1–25 Hz) ictal rhythm allows the core seizure territory to be distinguished from the penumbra [6]. In addition to these dynamics, physiological and pathological higher frequency oscillations have also been used to localize the seizure focus.

High frequency oscillations (HFOs) in the normal ripple (defined as 80–250 Hz) and pathological fast ripple (FR; 250–500 Hz) spectral domains have recently provided valuable additions to the clinical perspective, although the overwhelming variability in the epileptic condition often obfuscates universal changes. HFOs and IISs have been shown to occur both simultaneously as well as independently [15], but FRs have a particular potential in epilepsy diagnostics, as the FR frequency range typically reflects pathological activity in hippocampal and parahippocampal structures [16–20]. In patients with lesions, the presence of HFOs was found to be more tightly coupled to the seizure onset zone than to the location of the lesion, which does not necessarily coincide with the area where the seizure emerges [21]. This tight coupling of HFOs to the epilepsy onset zone proves to have a critical importance in surgical interventions, because the resecting of regions with HFO activity

correlated with a better seizure outcome after the surgery, with FRs serving as a more specific marker than ripples [15,22]. However, in neocortical epilepsy, ripple oscillations were found to be increased in the seizure onset zone more frequently than fast ripple oscillations [23]. In addition, a high degree of variability has been shown between patients with regard to the relative levels of ripples, fast ripples, and mixed events before, during, and after seizures [24], indicating the possible need for individualized seizure detection and treatment. While the oscillations present during interictal and ictal activity provide invaluable information for targeted surgical resection, determining the participating cells and networks in these pathological dynamics may lead to more mechanistic explanations for the transition to the epileptic state, which requires moving beyond broad EEG recordings. This avenue of study has been enabled by the development and application of methods aimed at the simultaneous recording of hundreds of neurons.

Synchrony during interictal events and seizures

Traditional EEG methods are not suitable to determine the participation of individual cells in the creation and propagation of pathological dynamics, which has led to the recent application of techniques that are able to monitor multiple cells simultaneously. For example, multibeam two-photon calcium imaging in hippocampal slices from chronically epileptic animals exhibiting spontaneous seizures revealed that epileptic networks are composed of multiple functional clusters of spatially localized neurons. Unexpectedly, these clusters co-activated in unpredictable combinations to give rise to interictal-like network events [25••] (Figure 1a). Although active neuronal clusters have been observed in both normal and epileptic hippocampal circuits, the epileptic tissue contains more functional clusters, and these clusters are more spatially localized [25••]. Similar heterogeneity has also been observed during interictal epileptiform activity in humans with intractable focal epilepsy [26]. This suggests that interictal network events do not simply represent a hypersynchronous entrainment of cells, but rather reflect a phenomenon that involves the interplay between spatially dispersed cell assemblies. A startling conclusion of these studies has been that, in fact, differing combinations of active neuronal clusters give rise to pathological interictal events that only appear self-repeating or recurrent when viewed at a macroscopic scale (e.g., using EEG or local field potential recordings).

Ictal events were similarly found to have a rather heterogeneous pattern of activity, instead of homogenous synchrony, when studied at the microscale, enabled by the application of multi-electrode single-unit recordings [27–30••]. In addition, the level of synchrony changed during the seizure, with a relatively asynchronous state in the seizure onset followed by a more synchronous state towards the termination phase [30••] (Figure 1b). These findings exemplify growing evidence for asynchrony before and during seizure generation followed by hypersynchrony facilitating seizure termination (reviewed in [31]). Accordingly, it has been suggested that a higher level of population activity can be maintained in a neuronal network if the cells are firing asynchronously [32–34]. Excessive synchronous firing may lead to communal refractoriness, in which the seizure terminates because the number of available excitable cells abruptly drops, though seizures can also terminate through depolarization block of principal cells [35]. Another explanation can be that during seizures, localized clusters of active cells are co-activated in an unpredictable order, similar to the

observations for interictal events [25••]. Indeed, the heterogeneity of cell spiking was much higher during seizures even if quite similar motifs of neuronal firing patterns were observed in consecutive focal seizures [30••]. Taken together, these findings suggest that epileptic seizures and interictal events are much more complicated network phenomena than previously thought.

Cell Type-Specific Microcircuit Interactions

Instead of simple runaway excitation, seizures reflect rather precise interactions between neuronal subgroups. The composition of these subgroups remains an open question, as previous studies have not addressed the various distinctions that exist between and within neuronal classes (e.g. [36,37]). Seemingly homogenous populations have been increasingly shown to instead be composed of heterogeneous subpopulations, forming functional dichotomies during network events. For example, in the case of the CA1 pyramidal cell population in the normal hippocampus, recent research has revealed that deep and superficial pyramidal cells form functionally distinct sublayers with regard to their participation in theta oscillations and in other aspects [38]. Consistent with this dichotomy, deep CA1 pyramidal neurons receive stronger inhibition from fast-spiking basket cells (a key interneuronal subtype implicated in a variety of normal and abnormal oscillatory phenomena [39]) than superficial pyramidal cells [40]. Subsequently, the participation of these basket cells in ripple oscillations has been shown to further segregate along specific anatomical features [41]. As predicted by theoretical studies [42], exceedingly rare but unusually well-connected hub-like cells may play crucial roles in epilepsy, and certain early born neurons during prenatal development have indeed been demonstrated to be able to serve as functional hub cells by exerting powerful effects on synchronous network events [43,44]. As a result, unmasking these primary generating and participating subpopulations in the epileptic condition has become an important goal for future research.

Concluding Remarks

While the recent shifts in focus to the microscale mechanisms enabled by high-resolution electrophysiological and optical imaging technologies have revealed unexpected levels of complexity, such new insights into microcircuit organization under healthy and pathophysiological conditions could also lead to a higher degree of specificity in targeting epilepsy, as well as to more individualized treatment. In particular, optogenetic techniques have provided significant recent progress toward higher specificity in controlling spontaneous seizures in models of experimental epilepsy, because they allow for targeting neurons in a time-, location, direction of modulation- (i.e. inhibition/excitation), and cell type-specific manner (reviewed in [45•]). The increased specificity of intervention offered by optogenetic approaches also highlighted the potential for efficient control of seizure activity from brain structures that are located outside of the area where the seizure focus resides [46–48]. As the microscale dynamics and mechanisms for each type of epilepsy and within each patient become increasingly elucidated due to these higher resolution technologies, treatment options of the future have the potential to become more and more focused as well, reducing the side effects associated with the currently available ‘macroscale’-targeting interventions.

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- Normal and pathological brain states have been proposed to coexist.
- Variability in the oscillatory dynamics within seizure foci has been shown.
- Recurrent epileptiform events involve heterogeneous cell populations.
- Increased resolution in epilepsy dynamics may lead to more focused therapy.

Figure 1.

Epileptiform activity has recently been shown to reflect heterogeneity rather than homogeneous synchrony when viewed at the microscale. **(A)** Interictal-like network events emerge due to the co-activation of functional clusters of spatially localized neurons in unpredictable combinations [25••]. The consecutive activation of different cell clusters brings about a seemingly recurrent pattern when observed on a local field potential recording. **(B)** Spontaneous seizures show heterogeneous activity patterns when viewed at the microscale. *Top:* Example seizure. *Middle:* Raster plot of cellular activity based on the findings of Truccolo and colleagues [30••]. At seizure onset, cells fire heterogeneously. At seizure termination, cellular activity becomes homogeneous, and the neurons enter a refractory state. *Bottom:* Possible arrangement of active cell clusters at the onset and offset

of the seizure. At onset, randomly activated cell clusters might give rise to seizure cycles, similar to interictal-like events. At offset, cells homogeneously fire and may act as one cluster.

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