REVIEW

Epilepsy as a dynamical disorder orchestrated by epileptogenic zone: a review

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Abstract Epilepsy is a group of chronic neurological disorders characterized with recurrent and hypersynchronous discharge. In the epileptic brain, epileptogenic zone (EZ) with abnormal firing patterns is considered as the culprit of hyperexcitable neuronal behaviors, increasingly manifested as alterations in dynamics. Meanwhile, the brain networks of epileptic patients show greater seizure susceptibility than those from healthy controls, referred as epileptogenic networks. There is a growing recognition of an intimate, but also complex, relationship between the self-organization of epileptogenic networks and abnormal dynamics of the EZ. In this review, we discussed the short- and long-term effects of recurrent epileptiform discharge on neural circuits, involving the regulation of connection weights and network topology. In addition, progressive abnormalities associated with secondary epileptogenesis imply that the excitability of regions connected with EZ may be enhanced, leading to frequent transitions from normal to epileptic states. From the perspective of network dynamics, EZ plays a dynamical pacemaker role in the evolution of epileptogenic networks as well as the activities generated by these networks. It may provide novel insights into the mechanism of epileptogenesis and inspire new therapeutic strategies.

Keywords Epileptogenic zone · Epileptogenic networks · Synaptic plasticity · Dynamical disorder

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1 Introduction

Epilepsy is a common chronic neurological disease characterized with intermittent functional disorder and progressive cognitive impairments. Since the early twentieth century, the idea of epileptic brain being susceptive to perturbations has guided pharmacological regulation and surgical treatment [1]. Substantial evidences suggested that epileptogenic zone (EZ) with abnormal firing patterns was responsible for seizure-prone peculiarity [2, 3]. Hyperexcitable neuronal behaviors, attributing to the imbalance between excitation and inhibition [4], were increasingly manifested

as dynamical transitions due to qualitative changes in physiological variables [5, 6]. However, the rather high rate of surgical failure in removing a restricted region highlighted the existence of network disorder [7, 8]. Hence, distinctive seizure-related connectivity patterns were revealed [9], and the difference between patients and healthy controls were also fully examined [10, 11]. Furthermore, computational models incorporated with data-inferred networks were used to understand the mechanism behind spontaneous transition and large-scale synchronization in the epileptic brain [12–14]. Particularly, the normal and epileptic states were represented by stable equilibrium point and limit cycle attractor, respectively. Increased seizure susceptibility of epileptogenic networks was associated with bifurcation behaviors in a bistable dynamical system [15, 16].

Epileptogenic networks are considered as indispensable support for the initiation and spread of epileptic activities, although the formation of pathological connectivity patterns remains unclear. Over the past years, great attention has been paid to self-organization of epileptogenic networks especially with the involvement of synaptic plasticity [17–19]. Through short- or long-term effects on neural circuits, partial regions even spatially distant from seizure focus can be recruited, contributing to widespread epileptic activities across the brain [20]. The fact that the ongoing epileptic activities led to temporary or even permanent functional changes in synapses was fully confirmed in animal experiments [21, 22]. Recurrent epileptiform discharge might drive the transition of synaptic strength from baseline to high level [23], resulting in attractor state of the network with sustained firing. To some extent, EZ promotes the adjustment of synaptic efficacy, acting like a pacemaker in the evolution of epileptogenic network. Furthermore, progressive structural abnormalities (e.g., reduction in subcortical volume and cortical thickness) could be found beyond clinically defined EZ [24, 25], and in most cases the severity was associated with the duration of epilepsy [26]. Part of these seizure-induced abnormal regions even showed dynamics similar to that in the EZ, and involved secondary epileptogenesis, referred as the extension of epileptogenicity [27].

Synaptic dynamics, the response properties of networks to perturbations and the patterns of activity generated by those networks are profoundly altered by the involvement of hyperexcitable neurons. The following sections will depict the possible dynamical processes orchestrated by EZ.

2 Spatiotemporal dynamics in the epileptic processes

2.1 Nontrivial dynamical characteristics of epileptogenic zone

The etiology of epilepsy varies in a wide range, such as tumors, brain injuries, parasites [28]. These pathophysiological alterations may induce spontaneous seizures and progressive cognitive deterioration. Moreover, nearly 40% of cases have an unknown etiology, and nonlesional areas involved in the onset of epileptic activities are found [29, 30]. Part of these imaging negative areas are even associated with pathological high-frequency oscillations (80–500 Hz) [31], increasingly recognized as a promising biomarker of epileptogenicity [32–34]. From functional mapping with cortical electrical stimulation, Leung et al. confirmed that ictal high-frequency oscillations were affiliated to cortical hyperexcitability [35]. There was also robust evidence for the existence of faster high-frequency oscillation (500–1000 Hz), which was primarily associated with seizure activities [36, 37]. A recent meta-analysis showed that residual high-frequency oscillations in the postoperative recordings had the potential to predict poor surgical outcomes [38]. Moreover, neurons in the EZ intermittently produces synchronized bursts embedded with traces of determinism [39]. Intrinsic hyperexcitability is increasingly considered as a manifestation of qualitative changes in dynamics. Therefore, EZ represents functional abnormality as well as dynamical disorder rather than simple structural lesion. It is significant to understand the mechanism of epileptogenesis by revealing the nontrivial dynamical characteristics of the EZ.

A general concept is to extract the characteristics of dynamical systems from the evolution of state variables. In the neurons, ionic current flows result in voltage fluctuations which can be captured by multiple extracranial electrodes [40], referred as Electroencephalograph (EEG) (Fig. 1a). For patients with epilepsy, it remains an essential clinical tool in the diagnostic workup [41, 42]. Repeated routine
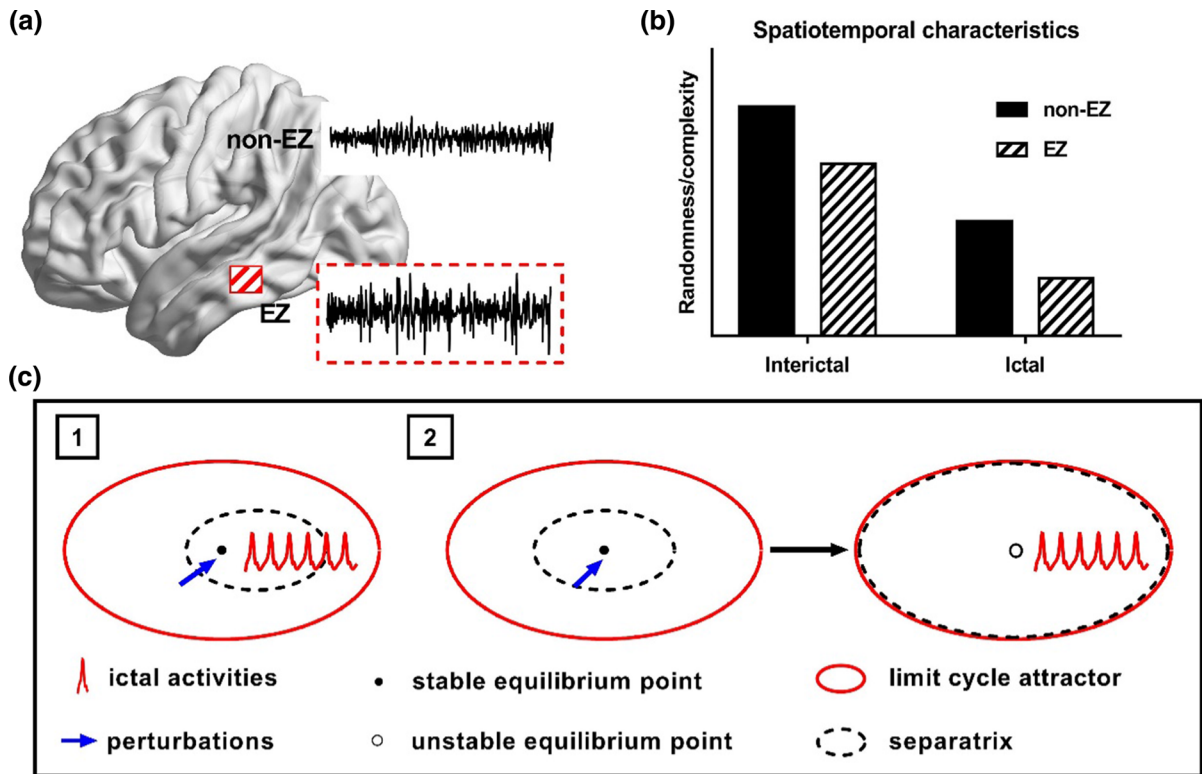
Fig. 1 Spatiotemporal dynamical characteristics inferred from recordings. Bistable dynamics was used to interpret the potential mechanism behind these significant dynamical differences. **a** EEG signals collected from patients with epilepsy. Particularly, EZ was characterized with abnormal epileptiform discharge. **b** A schematic diagram on significant spatiotemporal characteristics. Compared with non-EZ, recordings from the EZ showed lower complexity, higher determinism and more robust dependence. Meanwhile, signals in the ictal stage demonstrated deterministic and regular dynamical behaviors rather than randomness in the interictal stage. **c** Interictal and ictal states were represented by stable equilibrium point and limit cycle attractor, respectively. Two dynamical scenarios were assumed on the transition from norm to epileptic states. One was that ictal activities could be triggered for the existence of hyperexcitable oscillators sensitive to perturbations. The other was that perturbations were likely to cause the deformation of attractors. Seizures could emerge after a cascade of evolving electrophysiological events

recordings can assist in treatment choices and the evaluation of therapeutic outcomes [43]. Despite the fact that time-consuming visual inspections still prevail in clinical practice, different signal processing methods have been proposed to automatically identify the EZ, such as Granger causality [44, 45], Epileptogenicity Index [46]. Particularly, dynamical analysis always attracts much attention, and provides mechanistic insights into epileptogenesis. Correlation dimension analysis, a quantitative description of complexity, was applied to intracranially recordings of 20 patients with unilateral temporal lobe epilepsy [47]. The lowest dimension was found in the EZ during the ictal state. In other brain areas recruited by epileptiform discharge, the dimension also decreased.

Compared with physiological brain activities, epileptic events were accompanied with a loss of complexity. Furthermore, to investigate whether the complex behaviors in the epileptic processes originated from nonlinear deterministic or linear stochastic dynamics, a measure combining the methods of coarse-grained flow average and improved surrogates was applied to intracranial recordings in the interictal stage [48]. The recordings in the EZ showed unambiguous nonlinear determinism, while the behaviors in the normal region resembled linear stochastic dynamics. Andrzejak et al. also combined surrogates with a nonlinear prediction error to derive tests for randomness [49]. Compared with the normal regions, the signals from the EZ were less random (Fig. 1b). At the same time, the nonlinear

dependence tests further suggested that recordings within the EZ showed robust dependence. In phase space, their nearly synchronized trajectories also implied homogeneous dynamics with deterministic hyperexcitability [50, 51], which provided a conceivable explanation for their first outbreak in the ictal activities.

2.2 Dynamical changes during the epileptic transition

Suffczynski et al. [52] reported that the distributions of durations of interictal and ictal epochs were fitted with a gamma distribution. A vast mass of recordings from animal models of absence epilepsy, human epilepsies and in vitro models were analyzed. By estimating the fitted shape parameter of the distribution, they found that the dynamics of ictal epochs differed from those in the interictal states (Fig. 1b). Specifically, the transition from normal to paroxysmal state could be accounted for by a random walk, while deterministic time-dependent mechanism probably existed in the ictal state. Panahi et al. [53, 54] proposed a chaos-based mathematical model and interpreted abrupt seizures as the transition from chaotic to periodic state. This behavioral model provided additional insights into the development of state-dependent control strategy. Furthermore, maximum entropy ratio, a symbolic method for the detection of recurrence domains of dynamical systems, was used to investigate dynamical characteristics of epileptic phenomena [55]. Yan et al. found that the maximum entropy ratio was significantly lower in the ictal state than that in the interictal state. Similarly, Yang et al. [50] applied time-variant recurrence plot to demonstrate the evolution of the trajectories in the phase space. A large number of isolated dots were found in the recurrence plots during the interictal state, which represented lack of regular trajectory. In the ictal state, the recurrence plots consisted of diagonal structure, indicating relatively deterministic and regular behaviors. In addition, selected recurrence quantification parameters were extracted from these plots and applied to automatically classify the EEG signals [56, 57].

The differences of dynamical characteristics between interictal and ictal states have been widely investigated. However, whether there are specific dynamical warning minutes or seconds before seizures remains unanswered, despite of enhanced neuronal activities or characteristic EEG signals in advance of seizure onset [46]. Due to extensive individual difference, many electrophysiological phenomena are not universal or necessary in all epilepsies, which makes the prediction of epilepsy controversial [58, 59]. Nevertheless, great efforts have been paid to predict the time of seizure occurrence from the interictal recordings [60]. Meanwhile, either open-loop or close-loop (mainly based on automatic seizure detection) stimulation paradigms have been developed to prevent the predicted ictal state [61]. However, because of the intrinsic randomness of interictal activities as well as complex pathology and chronic development of the disease, stimulation therapy is still not popular in clinical practice, even as auxiliary means in most cases. It is significant to reveal more detailed temporal evolution of dynamical characteristics, especially those related to seizure onset, which may enlighten new prediction techniques as well as novel stimulation strategies [62].

2.3 Bistable dynamics and timescale separation

Seizures are characterized with paroxysmal hypersynchronous discharge in relatively large neuronal networks. They may be triggered by external stimulus or internal fluctuation [63]. In a normal brain, such changes would not cause more than a transient and uninjurious modification of brain activities, while an epileptic brain seems to be more vulnerable [64]. Based on the transition from normal to epileptic states, Lopes da Silva et al. considered epilepsy as a dynamical disease, and presented a theoretical framework on the potential dynamical mechanism [65]. In the epileptic brain, there are at least two states: the interictal state with seemingly normal and random activities and the ictal state with relatively deterministic synchronous oscillations. The former could be abstracted as vibrations near a stable equilibrium point in a stochastic environment, while the latter might be considered as oscillations around the limit cycle (Fig. 1c). In the phase space, the basins of the two attractors were separated by what is called a "separatrix".

From the dynamical perspective, the brain can be viewed as a network of interconnected oscillators [66]. The nontrivial dynamical behaviors of EZ means that at least the corresponding oscillators are significantly abnormal. Based on bistable theory, those changes in

dynamics might be related to the susceptibility of transition between attractors. Therefore, Lopes da Silva et al. proposed two possible dynamical routes to epileptic seizures [65]. First, the distance between attractors within the EZ is much smaller in contrast to that of normal brain tissue (Fig. 1c). In this case, external stimulus or internal fluctuation, which could be tolerable for healthy brain, might lead to the paroxysmal state in the epileptic brain [67]. Kalitzin et al. [68] used intermittent pulse stimulation in the frequency range 10–20 Hz to investigate the spatial distribution of excitability in patients with temporal lobe epilepsy. Relative phase clustering index was introduced to quantify the spectral phase demodulation of evoked intracranial signals. The findings supported that the EZ were more sensitive and more responsive than normal areas. Moreover, voltage clamp recordings from temporal lobe epilepsy rats revealed pro-excitatory shifts in sodium channel activity of subiculum neurons, which facilitated action potential bursts and spontaneous epileptiform discharge [69]. Second, the attractors can deform either progressively or abruptly under the influence of noisy perturbations (Fig. 1c). In this case, the two attractors started to approach each other and the separatrix tended to zero. Consequently, those perturbations, which were commonly not capable of triggering a seizure, might result in paroxysmal oscillations later. Highly localized subclinical seizure-like activities and prolonged bursts might be observed both inside and outside the EZ before observable clinical sign emerged [67, 70, 71]. Meanwhile, two types of interictal discharge with opposite roles, slow GABAergic discharge and fast activities, were found, and they were thought to promote or control the occurrence of ictal activities, respectively [72–74]. Truccolo et al. [70] believed that progressive dynamical modification might be required for the abrupt transition from normal to epileptic states.

These two dynamical scenarios seem to hold true, and are supported by corresponding physiological observations. Notably, the transitions are neither mundane nor uniform, but involve complex spatiotemporal diversity, especially the time-scale separation behavior [75]. Despite different pathologies or conditions, two major categories of activities are consistently recorded in experimental animal models and human epilepsy: fast oscillations and spikes with or without waves [76, 77]. Interestingly, such behaviors

could be well modelled by the fast and slow neural populations, which were coupled via signaling through a slow permittivity variable replicating extracellular effects [78, 79]. Permittivity coupling across brain regions were believed to perform a critical role in onset, recruitment and even termination in partial epilepsy [80]. Similarly, a common ultraslow variable interacting reciprocally with neural populations in the epileptogenic networks was introduced to interpret spontaneous seizures with complex patterns [81, 82]. In these slow-fast systems, the slow and fast timescales compete to determine the collective behaviors. Due to the complex etiology of epilepsy, the priority of the two effects are not necessarily the same. As a result, seizures may appear abruptly or begin with a cascade of evolving electrophysiological events.

3 Synaptic plasticity in the epileptogenic networks

3.1 Evolving epileptogenic networks

Epilepsy is increasingly considered as the result of network disorder. A number of well described alterations of anatomical or functional networks related with recurrent epileptic activities were reported [83]. Whelan et al. formed the ENIGMA-Epilepsy consortium to investigate structural abnormalities in the common epilepsies, pooling data from 24 research centers in 14 countries [84]. Compared to healthy controls, patients with epilepsy showed profound volume reduction in the ipsilateral subcortical structures and lower thickness in partial cortical regions. Typically, diffusion tensor imaging studies revealed that the absence of white matter connectivity associated with the EZ possibly resulted from recurrent epileptic activities [85]. Hutchings et al. applied a computational model to evaluate the seizure likelihood of individual anatomical network between patients and healthy controls [12]. As expected, patients tended to transit from normal to epileptic states more frequently in the model. van Mierlo et al. investigated the connectivity patterns during the first 20 s of ictal activities, and found that clinically defined EZ showed maximal out-degree [86]. Furthermore, EZ seemed to be the hub of epileptogenic networks not only during the ictal state, but also during interictal spike periods in some cases [87, 88].

In animal models, healthy rats begin to develop behavioral seizures 2–4 months after injecting kainic acid [89]. Progressive electrophysiological and anatomical abnormalities are found during the development of epileptogenesis. In human epilepsy, there is also a prolonged interval between an initial insult and the first emergence of spontaneous seizures, referred as silent period [25]. Moreover, seizures are often accompanied with developmental symptoms, it is reasonable to believe that epileptogenic networks are not innate but progressively shaped. There is a growing recognition of an intimate, but also complex, relationship between the evolution of epileptogenic networks and synaptic plasticity [90]. Wiemann et al. [91] found that epileptic neurons could induce augmenting synaptic depolarizations in non-epileptic neurons. Interactions between areas inferred from physiological recordings changed on various timescales [92]. Especially, connection strength between the EZ and parts of normal regions significantly increased with the occurrence of seizures [50]. Meanwhile, substantial model-based studies showed that synaptic plasticity was involved in spontaneous transition from desynchronous spikes to synchronous bursts [93]. Importantly, plasticity has been extended to account for structural self-organization of epileptogenic networks [18, 94]. Epileptogenic neurons are understood as the pacemaker of hypersynchronous behaviors in neuronal networks [95–97], and synaptic weights are regulated to facilitate the emergence of epileptic phenomena.

3.2 Bistable short-term plasticity

Experimental studies found that repetitive presynaptic firing could elicit either significant short-term decrease (depression) or increase (facilitation) in the amplitude of excitatory postsynaptic potential [98]. It was noticed that synapses might act like pass filters, and thus had preferred frequencies at which the efficacy of transmission was optimized [99]. Moreover, experimental evidence showed that the synaptic strength might be significantly enhanced after a high-frequency spike train [100]. Interestingly, the level of strength could maintain at least for a certain amount of time even for future low frequency spike trains [23]. González-Burgos et al. examined the effects of repetitive presynaptic stimulation on different types of neurons, including regular spiking pyramidal cells,

fast spiking interneurons and adapting non-pyramidal cells [101]. The cell class-specific differences in response to constant-frequency stimulation were observed, and the modification of firing patterns might lead to the differential activation of distinct neuronal populations. Therefore, epileptogenic neurons characterized with abnormal firing patterns probably recruited neurons with high-frequency preference, which might result in imbalance between excitability and inhibition and emergence of pathological oscillations, such as fast onset activity [102]. Theoretical studies also proposed that short-term changes in synaptic efficacy could drive the network into attractor state with sustained firing [103].

The transition of synaptic strength from baseline to high level could be viewed as a bifurcation in a bistable system [104]. Alamir et al. [90] proposed a systematic framework to reproduce the above behaviors. The synaptic strength was governed by:

$$\dot{\gamma} = (1 - \gamma)\big[a(\gamma - \gamma_{eq})(\gamma - \gamma_{th}) + bu_{in}\big] \quad (1)$$

where γ_{eq}, γ_{th} ($\gamma_{eq} < \gamma_{th} < 1$) represented the low efficacy attractor and threshold, respectively. u_{in} could be considered as presynaptic input or external stimulus. a, b were positive coefficients. In the absence of input ($u_{in} = 0$), the dynamics admitted two stable attractors, one at $\gamma = \gamma_{eq}$ and the other one at $\gamma = 1$ (representing high efficacy). Excitatory input would increase the low efficacy attractor to γ'_{eq}, and reduce the threshold to γ'_{th}. Furthermore, transition between attractors was fired under repetitive high-frequency spike trains but not low frequency input (Fig. 2a). In a neuronal population network with heterogeneous excitability, normal neural ensembles could be recruited by hyperexcitable epileptogenic population due to short-term enhancement of synaptic strength [104]. Such enhancement might push the brain network to a pathological state characterized by increased susceptibility to endogenous or exogenous perturbations [105], leading to the initiation and propagation of epileptiform discharge. Noteworthily, the recruitment process may contain complex excitatory and inhibitory regulation beyond these phenomena at the macrolevel. Both within-frequency and cross-frequency directional interactions between the EZ and surrounding regions suggested that the secondary generalization of focal seizures might be constrained by multiple oscillatory push–pull antagonisms [106].
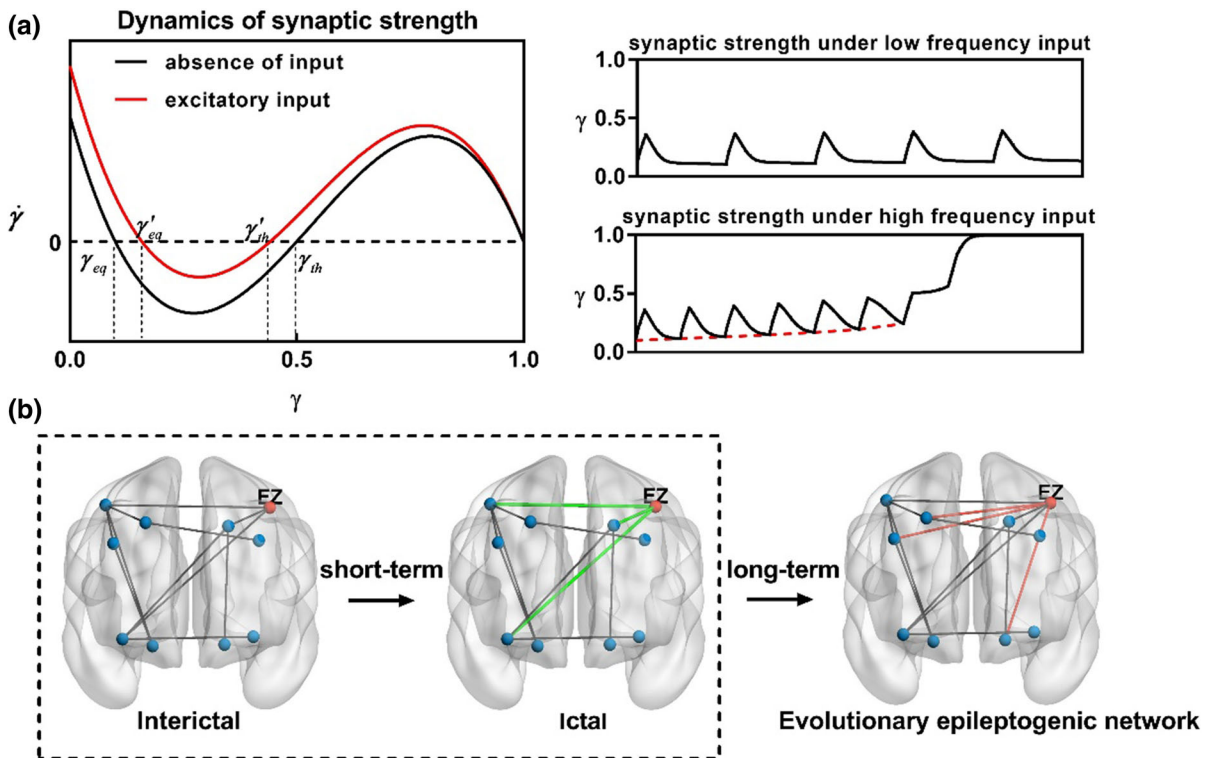
Fig. 2 Through short- and long-term synaptic plasticity, EZ with abnormal firing patterns had a profound effect on the structure of evolving epileptogenic networks as well as the activities generated by these networks. **a** Bistable short-term plasticity governed by Eq. (1). Excitatory input could shift the equilibrium points of synaptic system, resulting in increased synaptic efficacy and decreased threshold. Furthermore, synaptic strength could be transferred to high level beyond threshold after a high-frequency spike train. **b** Repetitive interictal spike activities might promote local enhancement of synaptic strength related with the EZ, contributing to the transition to ictal state. Meanwhile, recurrent seizures might cause irreversible alterations in neural circuits (e.g., the increase or disappearance of connections), pushing the formation of epileptogenic networks with the EZ as a hub

3.3 Long-term effects on neural circuits

Short-term changes of synaptic efficacy play a critical role in the transition between interictal and ictal states (Fig. 2b). Furthermore, structural and functional imaging from both clinical and experimental studies demonstrated that permanent changes in the brain networks existed and contributed to recurrent seizures [84, 86].

Wasling et al. [107] applied paired-pulse afferent stimulation to the hippocampal CA1 area in young (1–2 week) rats. Notable long-term depression was induced within ten such low frequency stimuli. Lippman-Bell et al. [108] further found that the expression of long-term depression was associated with calcium response. Higher response in brain slices from hypoxia-induced neonatal epileptic rats showed

that early-life seizures could alter synaptic calcium-permeable receptor function. Meanwhile, experimental evidence suggested that synaptic thresholds in the adult hippocampus were heterogeneous, which resulted in new timing rules for long-term potentiation [109]. The behavior of recurrent epileptic discharge causing large fluctuations of synaptic thresholds may disrupt circuit homeostasis [101, 110]. Under repeated actions, these alterations in neural circuits become irreversible (Fig. 2b), which may be involved in the formation of epileptogenic networks [111].

Recently, there has been a growing trend of epilepsy treatment and research strategies from the "molecular" level to the "circuit" level [112–114]. Technological advances, such as deep brain stimulation, optogenetics and chemogenetics, have also inspired novel strategies toward precise circuit therapy

[115–117]. Operational targets are not limited to epileptogenic focus, but also include the regions that have intensive connections with epileptogenic focus, such as piriform cortex and hippocampal CA3 [118, 119]. Furthermore, Neal et al. found that the magnitude of network disconnection after surgery was associated with postoperative outcomes [120]. It was shown that relatively improved neural circuits could disintegrate epileptogenic networks to reduce or even suppress the generation of recurrent seizures.

4 The extension of epileptogenicity

4.1 Abnormalities beyond epileptogenic zone

Epilepsy is a common acquired chronic neurological disorder. Although progressive cognitive decline and behavioral impairments in the epilepsies remains largely unexplained, the relationships between structural abnormalities and the duration of epilepsy have been widely studied. Bernasconi et al. collected volumetric MRI of the hippocampus, amygdale and entorhinal cortex from 86 consecutive patients with temporal lobe epilepsy and 44 age- and sex-matched healthy controls [24]. Linear regression analysis showed that duration of epilepsy was significantly related to the atrophy of these structures ipsilateral to seizure focus. Whelan et al. further claimed that progressive reduction in subcortical volume and cortical thickness could be widely observed in the all epilepsies [84]. Furthermore, similar structural abnormalities, remote from clinically defined epileptogenic zone [121, 122], were found. Interestingly, in the group of patients whose hippocampus was spatially distant from seizure focus, increased T_2 relaxation time indicated the occurrence of hippocampal sclerosis [123]. Experimental evidence from animal models showed that single or repetitive seizures might cause irreversible injury in brain structure (such as selective neuronal loss) and chronic changes in corresponding function [21, 124, 125].

In human epilepsy, these seizure-induced abnormalities were further found to be associated with secondary epileptogenesis [46]. Hypothalamic hamartoma was a developmental malformation often characterized by gelastic seizures [126]. Intracranial recordings suggested the hamartoma itself was intrinsically epileptogenic [127]. Unfortunately, the resection of hamartoma proved to be inefficient to achieve seizure free in up to 50% of cases despite partial improvements [128]. The poor operative outcomes might be explained by "hypothalamic plus" epileptogenicity. Scholly et al. reported two rare cases that the patients with gelastic seizures underwent two-step surgery: first a tailored resection of hamartoma, followed by temporal lobectomy [129]. Both patients became seizure free only after a complete two-step operation, which demonstrated that temporal lobe structures were likely to acquire epileptogenicity and even became secondary seizure focus. In addition, Goddard found that repeated electrical stimulation on hippocampus or subcortical nuclei could induce seizures artificially [130], referred as kindling effect. In the epileptic brain, partial normal regions might go through a similar process under continuous pacemaker-like action potential firing from primary EZ, and then become epileptogenic. Based on numerous electrophysiological findings, the concept of "the extension of epileptogenicity" was proposed [27], and the corresponding alterations in network dynamics were further explored. Theoretical results were used to provide novel insights into clinical findings, such as progressive behaviors, unsatisfactory long-term operative outcomes.

4.2 Seizure likelihood and synchronization patterns

Theoretically, Goodfellow et al. proposed a framework for discrete-time modelling of large-scale connected brain networks with distributed abnormalities, in which the spatial differences of intrinsic parameter were considered [131]. The differences in surrounding tissue excitability could offer a simple explanation for multiple onset patterns as well as previously conflicting clinical findings [132]. Moreover, Wang et al. found that independent patches of localized epileptiform activity would slowly invade the surrounding tissue and increase the excitability [133]. The extension of epileptogenicity is the manifestation of spatial heterogeneity progressively orchestrated by EZ. In order to investigate the possibility of transition in systems consisting of large number of interconnected heterogeneous neural populations (Fig. 3a), Kalitzin et al. proposed an analytical computational model which did not directly correspond to realistic neuronal processes (ion concentration regulation, synaptic
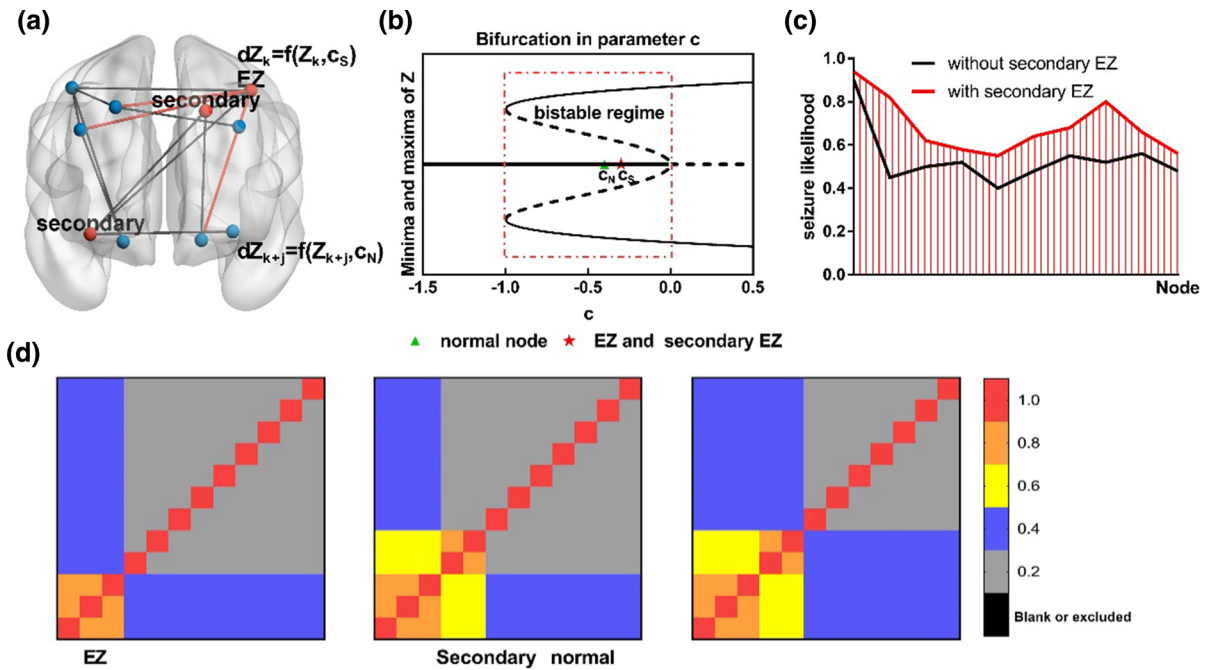
Fig. 3 Alterations of network dynamics with the extension of epileptogenicity. **a** A network with each node represented by a bistable computational model (Eq. (3)) was established. Heterogeneous excitability were incorporated to distinguish the EZ and normal nodes. Moreover, part of nodes connected with EZ had the same excitability as the EZ, indicating the emergence of secondary epileptogenicity. **b** In the absence of noise with $a = -1, b = 2$, bifurcation diagram in parameter c was shown. In the bistable regime, c_N, c_S represented the level of excitability of normal node and EZ, respectively. **c** The emergence of secondary EZ could significantly increase the overall seizure likelihood of network. **d** With the emergence of secondary epileptogenicity, connections between EZ and secondary EZ are significantly enhanced. Meanwhile, synchronization between secondary EZ and normal region may be progressively altered

interactions) [134, 135]. Despite numerous computational models even maintaining a certain degree of biological realism at the micro- or macroscales, such as Hodgkin–Huxley neuron model as well as simplified neuron models with less computational cost [136–138], kinds of neural mass model [139, 140], this analytical model could capture the general dynamics emerging in the epileptic process. The output of a realistic neuronal population consisting of excitatory and inhibitory subsets can be interpreted as the real and imaginary parts of a single complex variable Z. And seizure initiation can be well assumed to be a transition from stable fixed point to limit cycle attractor [52]. The dynamics of the complex variable Z was governed by:

$$dZ(t) = \left[\left(a|Z|^4 + b|Z|^2 + c + i\omega \right) Z \right] dt + \alpha U(t) \quad (2)$$

where ω determined the frequency of oscillation, (a, b) were real constant coefficients and c represented the balance between synaptic inhibition and excitation

inside the neural population. U denoted a complex Wiener process and α determined the noise level. In the absence of noise, for $-1 < c < 0$ and $a = -1$, $b = 2$, the fixed point and limit cycle attractor coexisted, separated by an unstable limit cycle (Fig. 3b). In the bistable regime, an increase in parameter c indicated the enhancement of local excitability. Therefore, heterogeneous parameters could be used to model different levels of excitability between epileptogenic and non-epileptogenic regions. To account for network-level epileptic phenomena, the dynamics of brain network was represented by:

$$dZ_k = \left[\left(a|Z_k|^4 + b|Z_k|^2 + c_k + i\omega \right) Z + \beta \sum_{j \neq k}^{N} G_{kj} \mathrm{Re}(Z_j) \right] dt + \alpha U_k$$

$$(3)$$

where N is the total number of nodes and G is the symmetric adjacency matrix, representing functional network. Escape time was introduced to quantify the likelihood of each node to develop into epileptic state [135]. Hutchings et al. validated the model by examining patient-control differences in seizure likelihood of brain networks [12]. Furthermore, the resection of those regions with higher seizure likelihood could contribute to satisfactory operative outcomes [13].

Contrary to the surgical procedure, the extension of epileptogenicity represents that part of normal areas even spatially distant from seizure focus may be "infected" with high seizure likelihood. Yang et al. established a small-world network with heterogeneous excitability, in which part of non-epileptogenic nodes connected with epileptogenic ones could be transformed into secondary epileptogenic nodes [27]. Simulations under different noise realizations suggested that the extension of epileptogenicity would significantly increase the overall seizure likelihood of network (Fig. 3c). Clinically, patients with multiple lesions often have higher seizure frequency. At the same time, it would require more surgical effort to achieve seizure free, and at the cost of greater physiological impairment. Model-based surgical resections, removing several nodes from initial networks, also demonstrated the necessity to wipe out those nodes with high seizure likelihood [12, 13].

Since epilepsy was understood as the result of network disorder, distinctive seizure-related connectivity patterns have been revealed. Wang et al. found that highly clustered with modular structures could suppress the emergence of explosive synchronization [141]. The alterations of cluster structure contributed to the onset and propagation of epileptic discharge. Meanwhile, self-initiation and self-termination of epileptic events were associated with the regulation of network topology for regularity and randomness [142]. Particularly, epileptogenic focus arises as the hub of functional networks, and synchronization between areas involved in the epileptic events are remarkable at all stages [9]. However, whether these pathological patterns are the basis or by-product of epileptic activities remains unanswered [27]. From the perspective of network dynamics, the occurrence of secondary epileptogenicity represents the alteration in the dynamics of individual nodes or oscillators. In simulated multiunit system, synchronization between

primary EZ and areas that were initially normal but later epileptogenic was greatly enhanced (Fig. 3d), indicating that the alterations in functional connectivity followed the extension of epileptogenicity. Intracranial recordings also demonstrated that those areas with frequent interictal epileptiform discharge showed robust dependence with each other [47, 50]. It probably meant that epileptogenic focus would drive the self-organization of epileptogenic networks through kindling-like effect, in addition to synaptic plasticity. As a result, epileptogenic networks are not just characterized with pathological topologies that are prone to synchronous behaviors, but also consist of epileptogenic nodes represented by abnormal oscillators, which are likely to play a pacemaker role in the epileptic process. The extension of epileptogenicity further increases the seizure susceptibility, which may provide additional understanding into progressive epileptic condition and cognitive impairment.

4.3 Possible prospect for localizing the EZ

Accurate localization of the EZ is the basis of successful resection operation, however postoperative recurrence in 30–50% of patients highlights that it is still an unsolved problem. We think that the extension of epileptogenicity may result in difficulty in determining the boundary and number of the EZ, accounting for the errors of localization. Based on clinical secondary epileptogenesis, seizures may be ignited by the pacemaker-like discharge from potential EZ (Fig. 4a). However, most of the existing methods tend to identify emerging EZ without uncovering potential effects [143]. Furthermore, when multiple EZs are calculated, it is ambiguous which should be chosen as surgical target (Fig. 4b). On the one hand, the extension of epileptogenicity can provide a reasonable explanation for the appearance of multiple epileptogenic tissues. On the other hand, it highlights the importance of revealing the dynamical characteristics of different nodes in the epileptogenic network. If the dynamical response of different regions can be accurately measured and mapped, tailored resection and excellent long-term operative outcomes may be realized.
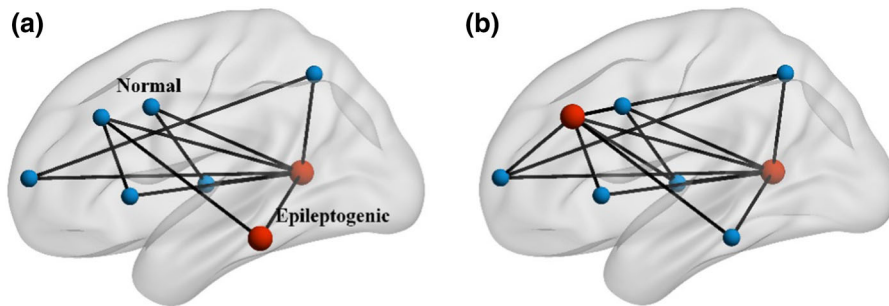
Fig. 4 Possible scenarios where localization errors often occur. **a** The extension of epileptogenicity may result in multiple EZs. One appears as the hub of epileptogenic network, while the others may act as potential pacemakers. **b** Multiple areas show epileptogenicity, but it is uncertain which should be surgical target

5 Conclusion

In this review, we summarized the current findings on the epileptic phenomena and corresponding dynamical explanations. There is no doubt that epilepsy especially focal epilepsy is characterized with locally initiated, network-supported hypersynchronous activities. In the epileptic brain, EZ shows relatively deterministic dynamical behaviors, which differs from the randomness in normal regions, and emerges as the hub of epileptogenic networks. But more than that, recurrent epileptic activities originating from EZ are likely to produce short- and long-term effects on neural circuits, involved in the self-organization of epileptogenic networks. Furthermore, spatially adjacent or distant regions from EZ may exhibit secondary epileptogenicity on account of kindling-like effect. From the perspective of network dynamics, epilepsy is a dynamical disorder orchestrated by EZ, which changes the topology of brain networks, the weights of connections and the excitability of partial normal regions. As a result, brain networks gradually evolves into epileptogenic networks labelled with great seizure susceptibility, which may be responsible for progressive impairments. These dynamical scenarios can help understand the mechanisms underlying epileptic processes, and aid the development of circuit therapy and tailored resection to reach satisfactory long-term outcomes.

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