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RESEARCH ARTICLE

Epileptic seizures in a heterogeneous excitatory network with short-term plasticity

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Abstract

Epilepsy involves a diverse group of abnormalities, including molecular and cellular disorders. These abnormalities prove to be associated with the changes in local excitability and synaptic dynamics. Correspondingly, the epileptic processes including onset, propagation and generalized seizure may be related with the alterations of excitability and synapse. In this paper, three regions, epileptogenic zone (EZ), propagation area and normal region, were defined and represented by neuronal population model with heterogeneous excitability, respectively. In order to describe the synaptic behavior that the strength was enhanced and maintained at a high level for a short term under a high frequency spike train, a novel activity-dependent short-term plasticity model was proposed. Bifurcation analysis showed that the presence of hyperexcitability could increase the seizure susceptibility of local area, leading to epileptic discharges first seen in the EZ. Meanwhile, recurrent epileptic activities might result in the transition of synaptic strength from weak state to high level, augmenting synaptic depolarizations in non-epileptic neurons as the experimental findings. Numerical simulation based on a full-connected weighted network could qualitatively demonstrate the epileptic process that the propagation area and normal region were successively recruited by the EZ. Furthermore, cross recurrence plot was used to explore the synchronization between neuronal populations, and the global synchronization index was introduced to measure the global synchronization. Results suggested that the synchronization between the EZ and other region was significantly enhanced with the occurrence of seizure. Interestingly, the desynchronization phenomenon was also observed during seizure initiation and propagation as reported before. Therefore, heterogeneous excitability and short-term plasticity are believed to play an important role in the epileptic process. This study may provide novel insights into the mechanism of epileptogenesis.

Keywords Heterogeneous excitability · Short-term plasticity · Epileptogenic zone · Synchronization

Introduction

Epilepsy encompasses a diverse group of seizure disorders (Badawy et al. 2009a), characterized by hypersynchronous electrical activity. For focal epilepsy, there exists clinically defined epileptogenic zone (EZ), where neurons with abnormal morphology or function are found to exhibit spontaneous and robust "pacemaker-like" action potential firing (Wu et al. 2005; Kerrigan et al. 2017). Increased excitability is the main electrical property, which has been confirmed by in vitro slice preparations of animal or human hippocampus (McCormick and Contreras 2001). However, heterogeneous excitability is rarely modeled in the complex epileptic processes including onset, propagation and generalized seizure. Furthermore, epileptogenesis increasingly refers to the alteration of networks (Badawy et al. 2009b), such as mossy fiber sprouting and local enhancement of functional connectivity (Maglóczky 2010; Burianová et al. 2017). Neuronal "reorganization", also called plasticity, appears to be the potential mechanism of the increased seizure susceptibility (Santos et al. 2011; Romcy-Pereira et al. 2009). Therefore, the role of heterogeneous

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excitability and synaptic plasticity in the epileptic process was investigated in this study.

The excitability of epileptogenic tissue has been paid particular attention. And various abnormalities, such as structural damage, channelopathy and neurotransmitter concentration fluctuations, are found to be associated with the alteration of excitability (Nigam et al. 2019; Leung et al. 2015). Regardless of extrinsic etiology, the imbalance between excitation and inhibition is considered as the underlying contributor of epileptogenesis (Botterill et al. 2019; Fan et al. 2019). Intracranial recordings in patients undergoing resective surgery show that a population of neurons in the EZ are related with the interictal epileptic events (Marchi et al. 2016; Varotto et al. 2012). When seizure occurs, epileptic discharges also tend to be seen first in the region (Bartolomei et al. 2008). Furthermore, the EZ is capable of producing complex stimulus responses such as after-discharges due to prolonged stimulation, and repetitive responses after single perturbations (Blume et al. 2004; Jacobs et al. 2010). Obviously, substantial evidences make the hyperexcitability of the EZ widely recognized. However, such hyperexcitable phenomena can be observed beyond the EZ (Jirsch 2006). For example, interictal epileptiform discharges also arise from the surrounding or even remote cortex of the EZ, part of which is involved in the propagation process (Varotto et al. 2012). Meanwhile, the propagation areas are prone to be recruited to produce a wider range of seizures. The fact that regular seizures have relatively fixed propagation path and symptoms may imply that the excitability of propagation areas is also enhanced, but second to that in the EZ. In this study, neuronal population model, first proposed by Jansen et al., was used to demonstrate local electrical activities at the population level (Jansen et al. 1993; Jansen and Rit 1995). Three regions (epileptogenic zone, propagation area and normal region) were given heterogeneous excitability through a lumped parameter relating to excitatory response, which was summarized from the relevant studies and clinical phenomena described above.

There is a growing recognition of an intimate, but also complex, relationship between neuropathology and synaptic plasticity (Alamir et al. 2011). A number of well-described alterations of anatomic network associated with recurrent epileptic activities are reported (Badawy et al. 2009b). Particularly, early life seizures were found to increase seizure susceptibility of various brain structures (Yue et al. 2018; Hernan et al. 2013). Functional connectivity between the EZ and other regions was also generally strengthened in the epileptic process (Yang et al. 2019). Recent model-based research showed that synaptic plasticity was involved in both synchronization and desynchronization during the seizures (Çetin 2020; Kim and Lim 2019; Wang et al. 2018). And epileptic neurons could induce augmenting synaptic depolarizations in non-epileptic neurons (Wiemann et al. 1997), suggesting that the synaptic dynamics might be altered due to abnormal discharges. Moreover, experimental studies showed that synaptic strength could be enhanced after a high frequency spike train, and maintained at a high level in the short term, regardless of future stimulus frequency (Thomson 1997). Such high frequency spike train might produce seizures as suggested by Hempel et al. (2000). However, the role of synaptic plasticity in epileptic seizures has rarely been studied in the framework of heterogeneous excitability. In this paper, a novel activity-dependent short-term plasticity model was proposed to investigate the varying coupling between the EZ and other regions.

In this paper, a full-connected weighted network was established with each node represented by neuronal population model. Three regions with heterogeneous excitability were defined. Moreover, a novel bistable model for short-term plasticity was proposed to describe the synaptic behaviors. Then the dynamics of single neuronal population and synapse were revealed. Numerical simulation based on the network was implemented to demonstrate the epileptic process, and the corresponding evolution of synaptic strength was also depicted. Finally, synchronization between different regions was quantitatively measured, and the results were compared with the known findings.

Methods

Neuronal population model

Cortical electrical activity can be measured from macroscopic electrodes when parallel-oriented neurons are quasi-synchronously activated. This principle allows us to investigate evoked response, functional connectivity and whole brain dynamics at the population level. In the classic form of the neuronal population model, a neuronal population contains two subsets, namely principal cells (e.g. pyramidal neurons) and inhibitory interneurons. Pyramidal neurons receive excitatory input from other pyramidal neurons or inhibitory input from interneurons. These latter neurons only receive excitatory input from pyramidal neurons. Each neuronal population, denoted by superscript i, is governed by:

$$\begin{cases} \dot{x}_1^i = x_4^i \\ \dot{x}_4^i = Aa\left[S\left(x_2^i - x_3^i\right)\right] - 2ax_4^i - a^2x_1^i \\ \dot{x}_2^i = x_5^i \\ \dot{x}_5^i = Aa\left[I + C_2S\left(C_1x_1^i\right) + g\sum_{j\neq i}^{K} W_{ij}(t)S\left(x_2^j - x_3^j\right)\right] - 2ax_5^i - a^2x_2^i \\ \dot{x}_3^i = x_6^i \\ \dot{x}_6^i = Bb\left[C_4S\left(C_3x_1^i\right)\right] - 2bx_6^i - b^2x_3^i \end{cases} \tag{1}$$

where g is a scaling factor, K is the size of functional network and W is a fully-connected weighted matrix,

representing the coupling between neuronal populations. $x_2^i - x_3^i$ is the model output, mainly used to interpret the recorded electrical signals. As detailed in Jansen et al. (1993), postsynaptic potential is transformed via the sigmoidal activation function S(v) into average density of action potential:

$$\mathrm{S(v)} = \frac{2e_0}{1 + e^{r(v - v_0)}} \tag{2}$$

The parameter interpretation and standard values are listed in Table 1.

For focal epilepsy, there exists clinically defined epileptogenic zone, where hyperexcitable neurons, responsible for the onset of seizures, were found. Furthermore, recurrent epileptic discharges could result in progressive alterations in neural circuits (Bertram 2007). And most patients have regular seizures, that is, the symptoms and the propagation path of abnormal discharge are relatively constant. It implies that the excitability of primary propagation zone may be enhanced, leading to the first recruitment by epileptic activities. Hence, three types of nodes are defined: normal node (A = 3.25 mV), propagation node (A = 3.40 mV) and epileptogenic node (A = 3.60 mV).

Bistable model for short-term plasticity

Experimental studies showed that the synaptic strength increased after a high frequency spike train. Interestingly, the level of strength could maintain at least for a certain amount of time even for future low frequency spike trains. Such phenomenon was thought to be related with short-term plasticity. Based on dynamical theory, low and high levels can be viewed as an attractor, respectively (Gastaldi et al. 2019). The transition is fired when the synaptic strength exceeds a certain threshold. Again, experimental evidence suggested that threshold was involved in the synapse dynamics (Wasling et al. 2002). In order to qualitatively interpret the experimentally observed behaviors, a novel bistable model for short-term plasticity is proposed:

$$\dot{W}_{ij} = (1 - W_{ij})\left[\alpha(W_{ij} - W_0)(W_{ij} - W_{th}) + \beta S(x_2^i - x_3^i) S(x_2^j - x_3^j)\right] \tag{3}$$

which is adapted from Alamir et al. (2011). Differently, presynaptic and postsynaptic action potential densities are considered instead of external stimuli. W_0 is related with the attractor corresponding to the low level, and W_{th} represents the threshold in the absence of synaptic activities. In this study, the parameter values are $\alpha = 0.8$, $\beta = 0.15$, $W_0 = 0.1$, $W_{th} = 0.5$. The magnitude W_{ij} is located in the range [0,1], and the value equal to 1 indicates saturated occupation of synaptic resources.

Synchronization measurements

In order to explore the synchronization in the simulated multiunit systems, cross recurrence plot (CRP), first proposed by Marwan and Kurths (2002), is used. It is a bivariate non-linear technique, visualizing the evolution of two phase space trajectories. For neuronal population i and j, a CRP in a given time window can be defined as:

$$CR^{ij}(p,q) = \Theta\left(\varepsilon - X^i(p) - X^j(q)\right), \mathrm{p,q} = 1, 2, \ldots, \mathrm{N} \tag{4}$$

where $\Theta(\cdot)$ is the Heaviside function, ε is the threshold distance, $\|\cdot\|$ is a norm (e.g., the Euclidean norm) and N is the length of the time window. $X^i(p)$ is a vector, representing the point in the phase space at time p. And simplistically, $X^i(p) = \left(x_2^i(p), x_3^i(p)\right)$ is adopted on the basis of Eq. 1. Then phase space trajectories are projected into a binary matrix, where the value was set to 1 whenever two points in the trajectory were close enough.

Table 1 Model parameters, interpretation and standard values

Parameter	Interpretation	Standard value
A	Excitatory synaptic gain	Varied
B	Inhibitory synaptic gain	22 mV
1/a	Time constant in the feedback excitatory loop	a = 100 s^{-1}
1/b	Time constant in the feedback inhibitory loop	b = 50 s^{-1}
C_1, C_2	Average number of synaptic contacts in the feedback excitatory loop	$C_1 = C, C_2 = 0.8C$ (with C = 140)
C_3, C_4	Average number of synaptic contacts in the feedback inhibitory loop	$C_3 = 0.25C$ $C_4 = 0.25C$
v_0, e_0, r	Parameters of the asymmetric sigmoid function S	$v_0 = 6, e_0 = 2.5,$ $r = 0.56$
I	Excitatory input to pyramidal neurons	Varied

Each CRP contains small scale structures, such as isolated dots, diagonal lines as well as horizontal/vertical lines. Generally, a horizontal (vertical) line marks a time length in which the state of one unit changes slightly or slowly. It seems that the unit is in the resting state for some time. Diagonal lines represent segments on both trajectories, which run parallel for some time. Therefore, maximum horizontal line length (MHL) is used to identify the transition between resting state and epileptic state. Similarly, maximum diagonal line length (MDL) is used to quantify the synchronization between different neuronal populations.

Furthermore, the level of global synchronization is also considered. As detailed in Muller et al. (2005), the matrix EC in the same time window is defined as:

$$EC_{ij} = \frac{1}{N}\sum_{p=1}^{N} \tilde{y}^i(p)\tilde{y}^j(p) \tag{5}$$

where $y^i(p) = x_2^i(p) - x_3^i(p)$ represents the postsynaptic potential of pyramidal neurons and $\tilde{y}^i$ is obtained after normalization:

$$\tilde{y}^i(\mathrm{p}) = \left(y^i(p) - \bar{y}^i\right)/\sigma^i \tag{6}$$

in which $\bar{y}^i$ and σ^i denote the mean value and the standard deviation in the time window.

Based on the matrix EC, the global synchronization index SI is introduced by:

$$\mathrm{SI} = \frac{K}{K-1}\left[\frac{\lambda_K}{\sum_{i=1}^{K}\lambda_i} - \frac{1}{K}\right] \tag{7}$$

where λ_i is the ith eigenvalue of the real symmetric matrix EC and λ_K is the maximum eigenvalue. And SI = 1 indicates perfectly synchronized for all neuronal populations.

Results

Bifurcation analysis on single neuronal population model

Seizure initiation can be described as a transition from resting state to epileptic state. It is well assumed to be a walk process between stable fixed point and limit cycle attractor, driven by stimulus or noise (Suffczynski et al. 2006). For single neuronal population model, bifurcation diagram for changing excitatory input I is shown in Fig. 1a. With I < 112.5 and A = 3.25, there is only one stable fixed point in the system, corresponding to the resting state. As the excitatory input increases, high amplitude oscillations occur, including spike-like and quasi-sinusoidal activity (Fig. 1b, c), both of which are observed in real intracranial epileptic recordings. In this study, we collectively classify these two types of oscillation as epileptic activity.

As a matter of fact, the minimum input required to produce epileptic activity is not constant, but dependent on system parameters. Excitatory (A) and inhibitory (B) synaptic gains determines the excitatory or inhibitory level of neuronal population, respectively. Consequently, a map for minimum input with respect to A and B is depicted (Fig. 1d). Obviously, increased excitability or decreased inhibition can reduce the need for input. Previous research indicated that neurons within the EZ showed high seizure susceptibility in response to external stimulus. Therefore, the parameter settings on normal, propagation and epileptogenic nodes give them heterogeneous seizure susceptibility, which is also consistent with the facts. In this study, the corresponding minimum inputs are 113, 102 and 89, respectively.

Synaptic dynamics in two coupled neuronal populations

Neuronal populations in the cortex are not independent, but interact with each other mainly through chemical synapses. And the synaptic strength is regulated by presynaptic and postsynaptic activities. To investigate the evolution pattern of synaptic strength, the coupling of homogeneous or heterogeneous neuronal populations is considered. Figure 2a shows postsynaptic potential of pyramidal neurons in the normal (N), propagation (P) and epileptogenic (E) zone with excitatory input I = 105. Since the input is greater than the minimum input for propagation and epileptogenic nodes, recurrent high amplitude oscillations are produced. They might regulate the synaptic strength just like high frequency spike train in the experiments. When homogeneous or heterogeneous neuronal populations are coupled, the evolution of synaptic strength is depicted in Fig. 2b. The synaptic strength between normal nodes remains weak because of the low level attractor, while epileptic activities can cause synaptic strength to exceed the threshold and approach the high level attractor. And the rate of transition between attractors depends on presynaptic and postsynaptic action potential density and synchronization. Obviously, the increase of synaptic strength within the EZ is ahead of other combinations. From the dynamical perspective, the high amplitude oscillations can dramatically change the fixed points in the synaptic system. Taking the coupling between the normal node and epileptogenic node as an example (Fig. 2c), epileptic activity can lower the threshold (blue) and raise the stable fixed point (black) corresponding to low level attractor. Previous research has also shown that epileptic neurons can induce augmenting synaptic depolarizations in non-epileptic neurons (Wiemann et al. 1997). Furthermore,

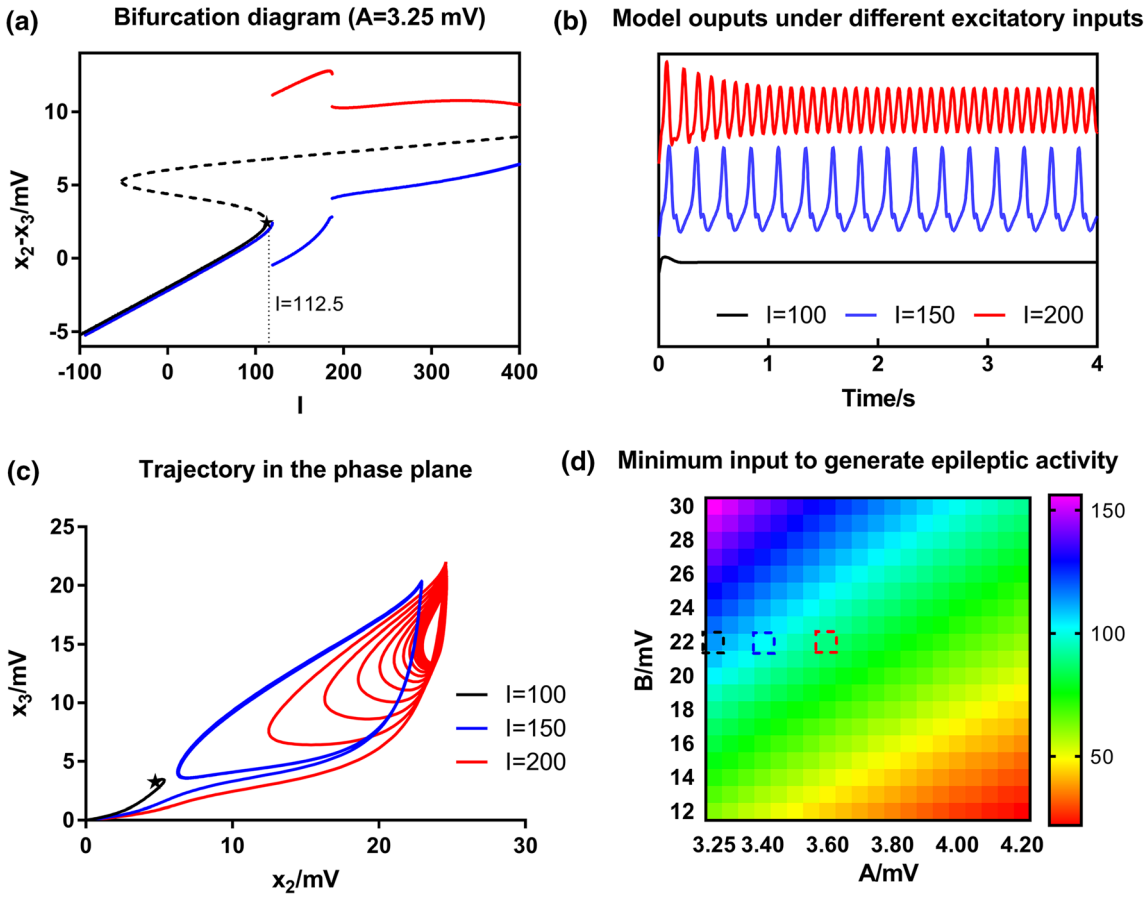

Fig. 1 Dynamics of single neuronal population model. **a** Bifurcation diagram for changing excitatory input I. The stable fixed points (black solid line) and the unstable fixed points (black dashed line) are depicted. The maxima and minima are represented by red and blue lines, respectively. **b** Postsynaptic potential of pyramidal neurons under different excitatory inputs. **c** Corresponding trajectories in the phase plane. **d** The map for minimum input to generate epileptic activity with respect to excitatory (A) and inhibitory (B) synaptic gains. The corresponding minimum inputs of the selected parameter settings are marked. (Color figure online)

the two fixed points may overlap and disappear, as shown in a partial enlarged view. In contrast, the fixed point $W_{ij} = 1$ always exists and keeps stable. Consequently, high synaptic strength can be maintained for a period of time.

Simulation based on the network

In order to investigate the dynamical behaviors of brain networks with short-term plasticity incorporated, 50 fully-connected neuronal populations are simulated under a uniform excitatory input I = 95 (Fig. 3a). Among them, 5 epileptogenic units (red) and 10 propagation units (blue) are included, others are normal units. Since the excitatory input is larger than the minimum input of epileptogenic units, epileptic discharges first appear in the EZ. Recurrent epileptic activities lead to a short-term enhancement of synaptic strength, and the propagation units and normal units are progressively recruited to produce generalized seizure. This qualitatively reflects the process of onset (0–4 s), propagation (5–9 s) and generalized seizure (10–15 s), which is consistent with the findings from intracranial electrophysiological recordings. The evolution of synaptic strength further indicates that the propagation path of epileptic activities is closely related with the level of excitability (Fig. 3b). Neuronal populations with higher excitability are preferred to be recruited. At the same time, the synapses connected with them are easier and faster to be strengthened. Therefore, bistable short-term plasticity may be the potential mechanism of regular seizures. Certainly, heterogeneous excitability is the basis, especially hyperexcitability.

Synchronization and desynchronization during the seizure

The phase space trajectories and corresponding CRPs of different combinations in a one second time window are depicted in Fig. 4a. Taking the interrelations between epileptogenic unit and propagation unit as an example, propagation unit progressively moves from resting state

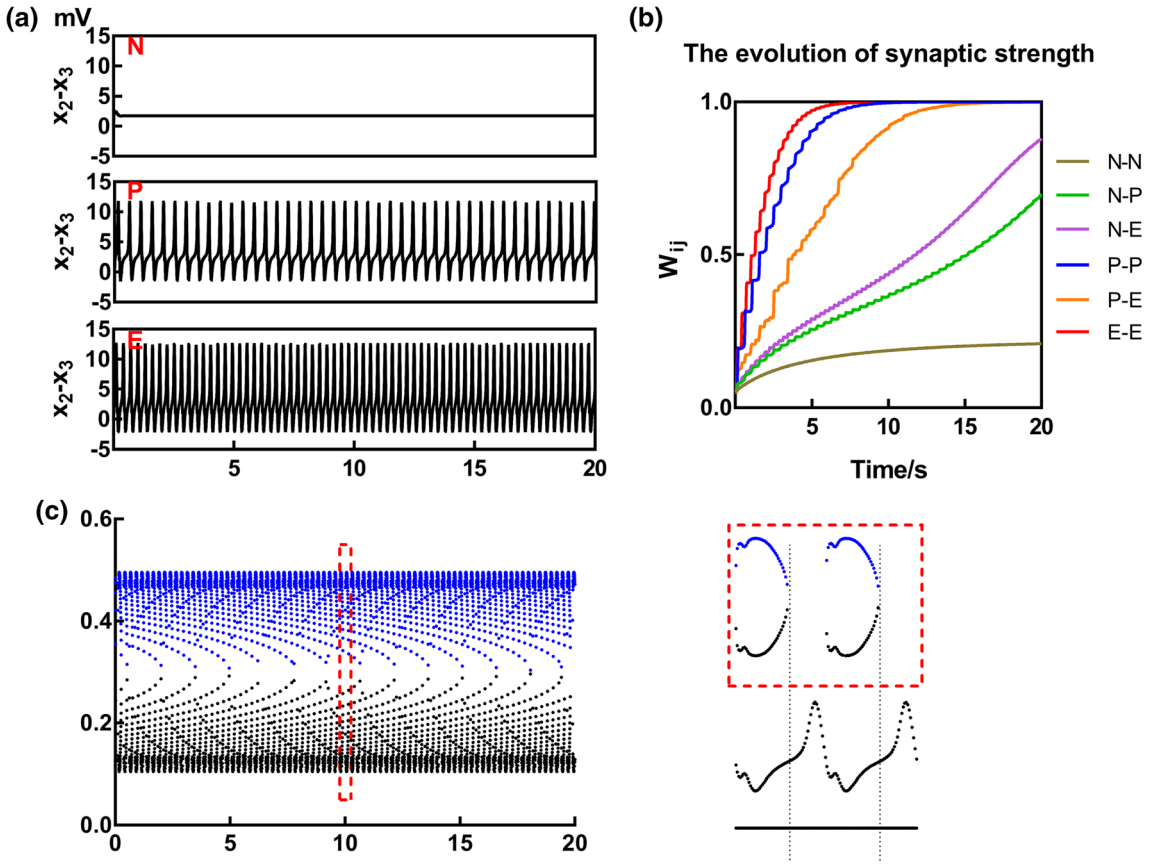

Fig. 2 Synaptic dynamics in two coupled neuronal populations. **a** Postsynaptic potential of pyramidal neurons in the normal (N), propagation (P) and epileptogenic (E) zone with excitatory input I = 105. **b** The evolution of synaptic strength under the coupling of different neuronal populations. The initial strength is set to 0.05. **c** When the normal node is coupled with epileptogenic node, the fixed points of the synaptic dynamical model changes with the presynaptic and postsynaptic activities. Among them, the fixed point $W_{ij} = 1$ always exists without shown in the figure. The right part is a partial enlarged view with corresponding presynaptic and postsynaptic activities

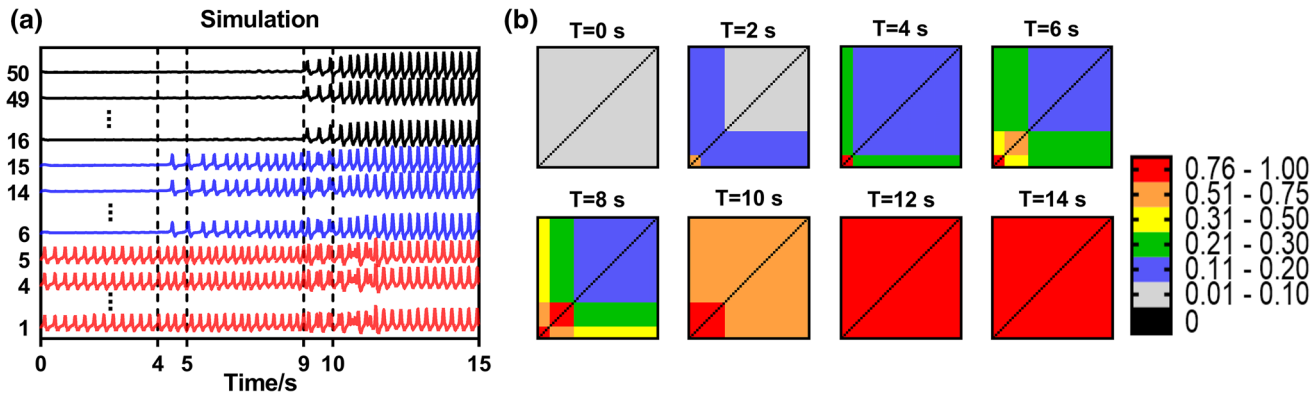

Fig. 3 **a** Simulation for 50 fully-connected neuronal populations, consisting of 5 epileptogenic units (red), 10 propagation units (blue) and normal units (black). 0–4 s, 5–9 s and 10–15 s correspond to the process of onset, propagation and generalized seizure, respectively. 4–5 s and 9–10 s are transient processes. **b** The evolution of synaptic strength. The initial strength is uniformly set to 0.05. (Color figure online)

(fixed point) to epileptic state (limit cycle), and due to the difference in excitability, its trajectory does not exactly coincide with that of epileptogenic unit. However, CRPs indicate that they finally maintain relatively high synchronization with each other. There are similar phenomena in other combinations. In order to quantitatively identify

these differences, MHL and MDL of each CRP are computed, and the values in same stage, including onset, propagation and generalized seizure, are averaged. T-tests with Welch's correction are performed and results are declared significant for p value < 0.01. A decrease in the MHL indicates that both units develop into epileptic state (Fig. 4b). Furthermore, with the recruitment of propagation units and normal units, the MDL of the combination P-E and N-E significantly increases, which means the enhancement of synchronization (Fig. 4c). Interestingly, the MDL of the combination N-P decreases sharply in the course of epileptic propagation. Similarly, the evolution of global synchronization index shows a desynchronization phenomenon when only propagation units are recruited (Fig. 4d). Previous studies on human single neuron recordings also suggested that neuronal spiking activity during seizure initiation and propagation was highly heterogeneous, not hypersynchronous (Truccolo et al. 2011). Based on the simulation results, the occurrence of desynchronization may be that the propagation units are far away from the normal unit which account for the majority and tend to the minority epileptogenic units. Therefore, heterogeneous excitability and short-term plasticity may be responsible for complex synchronization and desynchronization phenomena.

Conclusion

Based on previous studies and clinical phenomena, heterogeneous excitability and short-term plasticity are believed to play an important role in the process of onset, propagation and generalized seizure. In this study, three regions including epileptogenic zone, propagation area and normal region were represented by neuronal population model with heterogeneous excitability, respectively. The couplings between neuronal populations were governed by a bistable short-term plasticity model, which qualitatively described the synaptic dynamics at the population level. A simulation based on a full-connected weighted network showed that the incorporation of heterogeneous excitability and short-term plasticity could well demonstrate the process of epileptic seizures, and the synchronization and desynchronization phenomena presented were consistent with the findings of real electrophysiological data. The presence of hyperexcitability increased the seizure susceptibility of local area, providing the basis of seizure onset. And epileptic discharges might make the synaptic strength exceed threshold and maintain at a high level for a short term. Consequently, other regions might be recruited to form a wider range of hypersynchronous electrical activity. The second high excitability of the propagation

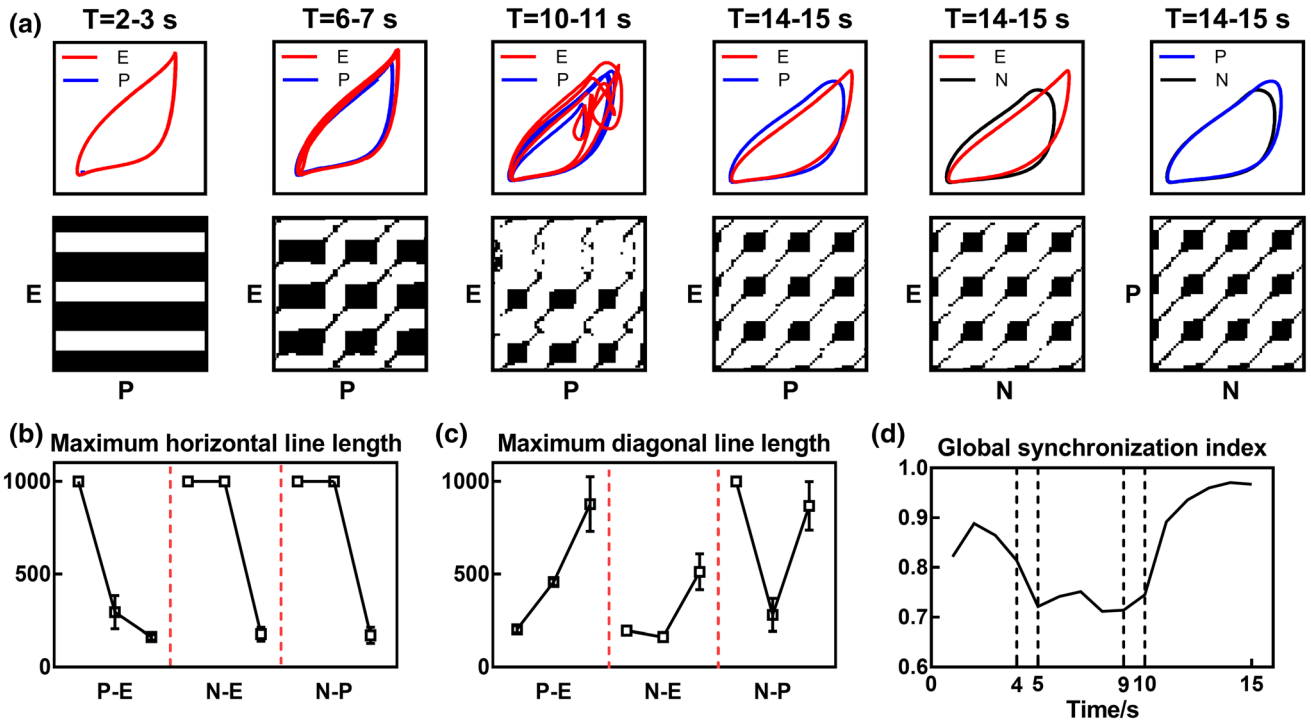

Fig. 4 **a** The upper is the trajectories of different neuronal populations in the phase plane $x_2 - x_3$. The bottom is the corresponding CRPs. These subgraphs visually show the synchronization between epileptogenic units and propagation units at different times and the final state of other combinations. **b** The mean value and the standard deviation of MHL for different combinations in the process of onset, propagation and generalized seizure. **c** The mean value and the standard deviation of MDL for different combinations in the process of onset, propagation and generalized seizure. **d** Global synchronization index at different times

area might be responsible for the first recruitment and relatively fixed propagation path. Therefore, heterogeneous excitability and short-term plasticity may be the underlying mechanism of epileptogenesis, and provide novel insights into epileptic processes and relevant phenomena.

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Author contributions CY, ZL, QW, GL and FZ designed and performed the research. CY and FZ drafted the manuscript and contributed equally to this work.

Compliance with ethical standards

Conflict of interest The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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