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Causality analysis in epileptic seizure genesis

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Abstract—Epileptic seizure is a paroxysmal and self-limited phenomenon characterized by abnormal hyper-synchrony of large population of neurons. No studies have investigated network dynamics of epileptic seizures in the hippocampus in vivo, because no good animal models have been available to study seizures in vivo with high reproducibility. We used optogenetic techniques to perturb normal hippocampal network to induce epileptic seizures. This enables us to induce epileptic seizures in the hippocampus with high reproducibility, and permit simultaneous neurophysiological monitoring. Using this model, we revealed state changes along the longitudinal hippocampus during seizure genesis and termination.

1. Introduction

Epileptic seizures are characterized by abnormal hyperexcitation and hypersynchrony of neurons which is usually initiated in the presence of pathological causes but sustained and propagated through normal neuronal networks [3]. Certain brain regions, such as hippocampus, are prone to epileptic seizures. However, it has not clearly known about the process on how epileptic seizures involve normal neuronal networks, because no good animal models have been available to study the initiation and propagation of epileptic seizures in normal brain with high reproducibility. We proposed a novel in vivo model of epileptic seizures using optogenetic techniques [5]. Repetitive pulse photo-stimulation applied to the hippocampus of Thy1.2-ChR2-Venus transgenic rat can induce epileptic seizures after the stimulation. Using this model, we here investigated the directional network dynamics during seizure genesis along longitudinal hippocampus.

Multi-site LFPs were recorded during hippocampal optical photo-stimulation in order to investigate the network dynamics of epileptic seizure genesis. The Granger causality analysis of the LFPs demonstrated discrete state changes in signal flows along longitudinal hippocampus: (1) resting state before and after the seizure, (2) initiation of seizure associated with dominant septo-temporal causality, (3) termination of seizure following dominant temporo-septal causality.

2. Methods

2.1. The Granger causality

Degree of information flow was evaluated by the Granger causality (GC) [4, 6]. In short, if knowing time series X_2 helps predict the future of the other time series X_1, X_2 "Granger causes" X_1.

Dominance of the information flow, from septal side to temporal side or its opposite direction, was evaluated by an index, we call it "Granger-index", defined by

$$\text{Granger-index} = \frac{G_{\text{s}\to\text{t}} - G_{\text{t}\to\text{s}}}{G_{\text{s}\to\text{t}} + G_{\text{t}\to\text{s}}},$$

where $G_{\text{s}\to\text{t}}$ and $G_{\text{t}\to\text{s}}$ denote the GC from septal to temporal sides and the GC from temporal to septal sides, respectively. The Granger-index, $\in [-1, 1]$, is positive if the $G_{\text{s}\to\text{t}} > G_{\text{t}\to\text{s}}$, otherwise it is negative.

2.2. Coherence

The coherence was introduced to evaluate the synchronization of signals in frequency domain. The coherence of $x_m(t)$ and $x_n(t)$ was calculated as follows,

$$\begin{aligned} \text{Coh}_{mn}(f) &= \sqrt{|\frac{S_{mn}(f)|^2}{S_{mm}(f)S_{nn}(f)}}, \\ S_{mn}(f) &= \frac{1}{2\pi}\int_{-\infty}^{\infty} C_{mn}(\tau)e^{-if\tau}d\tau, \\ C_{mn}(\tau) &= \overline{x_m(t)x_n(t-\tau)}, \end{aligned}$$

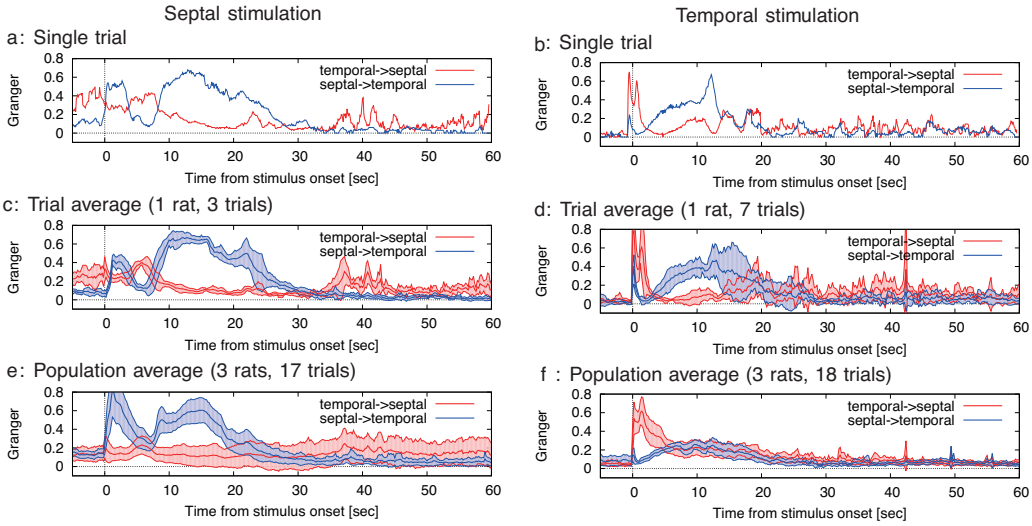

Figure 2: Granger causality analysis of LFPs in Septal-Temporal axis of hippocampus in macro-level neural network (2ch recording). **a,b**, Example traces of bidirectional GC scores from recorded LFP in the stimulation to septal (a) and temporal (b) side of hippocampus. **c,d**, Average traces, among three trials of one rat (c) and seven trials of one rat (d), of bidirectional GC scores on the stimulation to septal (c) and temporal (d) side of hippocampus. Colored regions indicate 95 % confidence interval. **e,f**, The same as the panels c and d, but the average traces were calculated using 17 trials of three rats (e) and 18 trials of three rats (f).

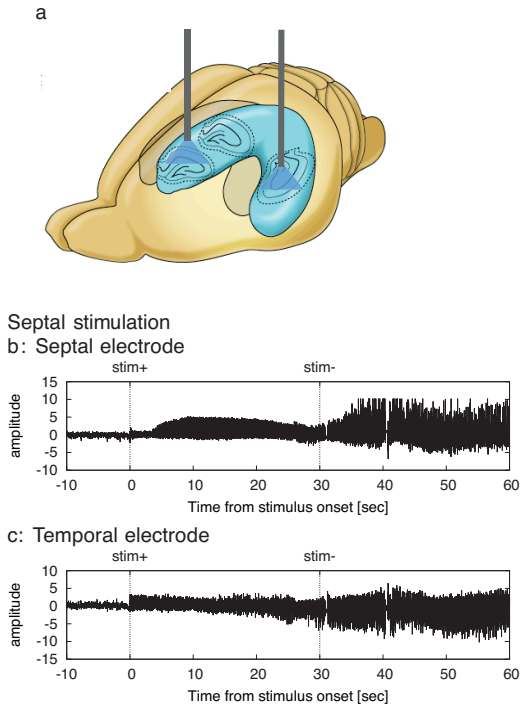

Figure 1: **a**, Schematic of experimental set-up used for hippocampal photostimulation in rat. Photostimulation was delivered in septal or temporal sides. **b,c**, Example trace of raw LFPs in septal (b) and temporal electrodes (c) in the case that the Photostimulation was applied in Septal side.

where overline $\bar{\cdot}$ represents a temporal averaging operation. $C_{mn}(\tau)$ and $S_{mn}(f)$ are the cross-correlation and cross-spectrum, respectively. The coherence is essentially the square of the correlation coefficient between corresponding frequency component $x_m(t)$ and $x_n(t)$.

Mean coherence, across pairs and frequencies, was defined as follows,

$$\overline{\mathrm{Coh}} = \frac{1}{(Q-1)!}\sum_{n=1}^{Q-1}\sum_{m=n+1}^{Q}\frac{1}{300-1}\int_{1[\mathrm{Hz}]}^{300[\mathrm{Hz}]}\mathrm{Coh}_{mn}(f)df,$$

where Q was the number of LFP pairs.

2.3. moving window

The GC and coherence was calculated with 1000 ms moving window. The window moved with 100 ms time step, so each window overlapped 900 ms. The center of the moving window moved from -10 second to 60 second (2ch recording) or 100 second (16ch recording) around stimulus onset,

3. Results

3.1. Macro-scale analysis (2ch recording)

To investigate the macro-scale information flow (flow between the site separated several mm), We recorded LFPs from septal and temporal side of the hippocampus (Fig.1 a).

Repetitive pulse photo stimuli were delivered to the septal (Fig.2 left) or temporal (Fig.2 right) hippocampus of anesthetized Thy1.2-ChR2V transgenic rat while LFP was simultaneously recorded by using hybrid optic fiber and electrode to observe the neuronal activities during and after the stimulation. Epileptic seizures were induced after repetitive photo stimulation of the hippocampus of Thy1.2-ChR2V transgenic rat. Fig.1 b and c depict examples of the induced epileptic seizure. Photo-stimuli were delivered from 0 to 30 sec.

Seizure activity observed in this study was characterized as follows. At the initial phase of stimulation, only evoked potentials followed each pulse photo-stimulus. High-amplitude spontaneous activities, which were not time-locked to stimuli, emerged in addition to the evoked potentials during stimulation, and gradually became rhythmic and dominant. This rhythmic activity was self-persisted after the end of stimulation and spontaneously ceased in 8.4-85.5 (39.8 1.9; n=115) seconds (Fig.1 b,c).

Information flow during and after the stimulation was inferred by the GC (Fig.2). At the beginning of the photo-stimulation, the GC from stimulus site to opposite site was larger than that of the opposite direction, regard less of trials and rats. After several second stimulation, the GC from septal to temporal side flow increases in both septal and temporal stimulation cases. The biased information flow settled down to the baseline after 30 sec from stimulus onset.

3.2. Micro-scale analysis (16ch recording)

To investigate the information flow in more small regions (micro-scale network), linear-array multicontact electrode (16 contacts with spacing of 150 μm, respectively) was inserted into dentate gyrus-to-hilus of temporal hippocampal formation parallel to the longitudinal axis (Fig.4 left panel). LFPs were recorded during and after pulse photo-stimulation of the septal hippocampus (30 seizures, n = 3). In order to see the causal relationship of the LFPs during seizure-genesis, the GC of LFPs was calculated between electrode pairs along the septo-temporal orientation of the hippocampus. To focus on the micro-scale network, only the electrode pairs whose distances were smaller than 450 μm were used. Induced seizures were characterized by increase in the causality along septo-temporal hippocampus, depicted in Fig.3 top panel. During the hippocampal stimulation, causality indices increased in both septo-temporal and temporo-septal directions, but were higher in the former. In course of self-sustained seizure after the end of stimulation, the septal-to-temporal causality gradually decreased to the same level to the temporal-to-septal one. Toward the final phase, the temporal-to-septal causality

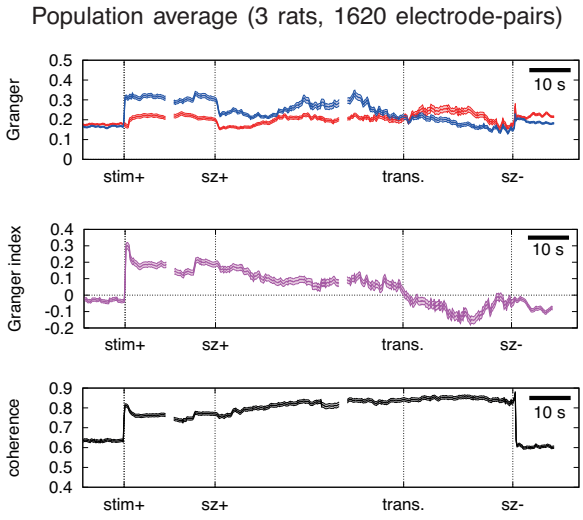

Figure 3: Granger causality and coherence analysis of LFPs in Septal-Temporal axis of hippocampus in micro-level neural network (16ch recording). Average traces of the Granger causality (top panel), Granger-index (middle panel), and coherence (bottom panel) from recorded LFPs in the stimulation to septal side of hippocampus. Average was calculated by 1620 electrode-pairs in three rats. "trans." indicates the time of the state-transition (Fig.4 center panel).

became higher than the septal-to-temporal one. Figure 3 middle panel show the dominance of the information flow using the Granger-index. Seizure activity was also characterized by increase in coherence. The coherence increased with the begging of the photo-stimulation and showed gradual increase toward the end of seizure (Fig.3 bottom panel).

State space plot between Granger-index and coherence disclosed the presence of at least three attractors. (Fig. 4 center and right panels): (1) resting state before and after the seizure; (2) initiation of seizure with dominant septo-temporal causality; (3) dominant temporo-septal causality toward termination of seizure. These changes were present across animals.

4. Discussion

On the hypothesis that the longitudinal network play dynamically in seizure activity and may influence its generation and termination, we studied the functional dynamics of neural activities in longitudinal axis of hippocampus by means of the GC and coherence. We demonstrated robust state transitions during the genesis, evolution and termination of epileptic seizures in dimensions of septo-temporal causality and synchrony (Figs. 3 and 4). These results suggest that attractors and transitions between each other for

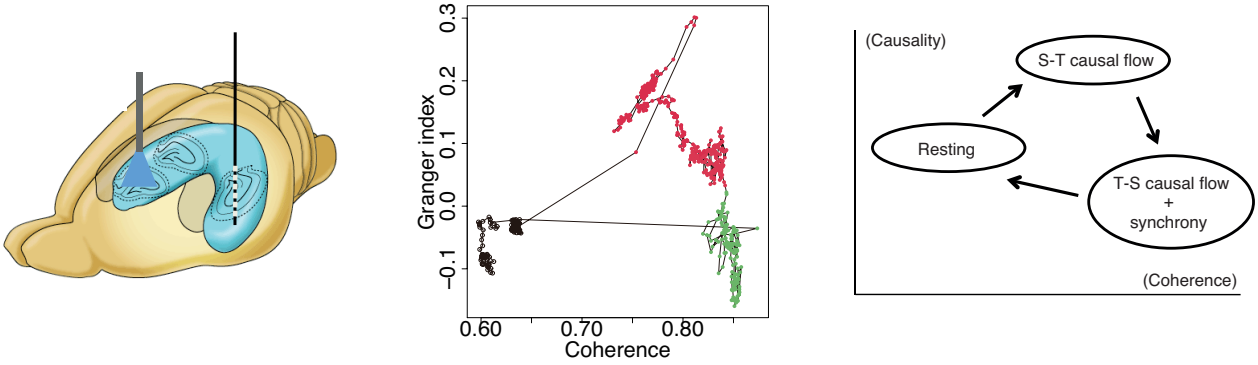

Figure 4: **left**, Schematic of experimental set-up used for hippocampal photostimulation in rat. **center**, Transients of (Granger index, coherence), clustered by the k-means methods, in population average (Fig.3). **right**, Schematic of the state-transients.

epileptic seizure is innate in normal hippocampus [2]. The possible substrates which cause such a dynamic changes of causality and coherences are both anatomical and functional mechanisms. As an anatomical mechanism, asymmetrical structures of hippocampal neurons in cell population or synaptic connections between sub-regions along longitudinal hippocampal axis may contribute the dynamic change observed in our study [1].

As a functional substrate, short-term synaptic plasticity is the most candidate. Short-term plasticity is discussed on the evidence for the several kinetic phases of synaptic enhancement and depression or contribution of glia, as well as the statistical changes in transmitter release, alterations in presynaptic Ca2+ influx or postsynaptic levels of intracellular Ca2+ for synaptic enhancement and depletion of pool of synaptic vesicles, inactivation of release site, feedback activation of presynaptic receptor. All of them are the candidate which causes state transition of this phenomenon.

As a complex system of neurons, repetitive small perturbations to hippocampal system can cause the collapse of normal activity and generate seizure. The theory of "critical transition" or "tipping point" will be able to explain this phenomenon. Although further evidence for cell-specific participation by unit-recording or patch-clamp method were to be studied, we demonstrated the causal association along the longitudinal axis during hippocampal seizures. The role of multiple recurrent networks consisting of CA3 recurrent circuit and dentate granule cell-mossy cell feedback. were studied not only in essential behaviors of memory and learning but also hypothesized facilitation factor in epileptic seizures as modifiable excitatory connections. In the GC and coherence analysis, our result revealed not only the bidirectionality of seizure propagation known in ex vivo study but also that it can change the direction of causal connectivity pattern even to reverse direction autonomously even in one seizure attack.

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