Characteristic neuronal firing interspike intervals in laterodorsal thalamic nuclei induced by tetanization of rat caudate putamen: possible relations to hippocampal electroencephalogram changes

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Abstract: The purpose of the present work was to study the effect of acute tetanization of the right caudate putamen nucleus (ATRC) on single neuronal interspike intervals (ISIs) in both laterodorsal thalamic nuclei (LDi), and electroencephalogram (EEG) wave interpeak intervals (IPIs) in both hippocampi (HPCi). Experiments were performed on 21 male Sprague-Dawley rats weighing 150~250 g. The seizures were induced by the ATRC (60 Hz, 2 s, 0.4~0.6 mA). Quadruple recordings were simultaneously carried out: two for single unit recordings from both LDi, and two for EEG recordings from both HPCi. The ATRC induced: (1) An interactive epileptic electrical network reconstructed in bilateral HPCi, which was driven by primary afterdischarges of single LD neuron. (2) A symmetric mirror-like ISI spot distribution of the LD neuronal firing before and after tetanus. (3) Gradually prolonged LD neuronal discharge intermitting. (4) Single LD neuronal spikes were phase- and time-locked to 20~25 Hz gamma oscillations in contralateral HPC. It suggests a particular temporal code patterning of single LD neuronal firing interspike intervals (ISIs) in both laterodorsal thalamic nuclei induced by tetanization of rat caudate putamen: possible relations to hippocampal EEG changes and its relationships to hippocampal EEG wave code in time series, the latter implies the LD neuronal encoding mechanisms of ATRC-induced epileptic electrical network in bilateral HPCi.

Key words: laterodorsal thalamic nucleus; hippocampus; caudate putamen; interspike intervals; interpeak intervals; tetanization; epilepsy

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In the last few decades, a great deal of experimental and clinical evidence proves that multiple abnormal neural networks can result from a unilateral active epileptic focus [1]. The hippocampus (HPC), thalamus, cerebral cortex and putamen are involved [2, 3]. Generally, the thalamocortical loop and the HPC are included in human or animal complex partial or temporal lobe epileptogenesis [1]. An argument is that direct stimulation of the caudate nucleus can control or generate seizures [4]. Furthermore, the relationship between single neuronal spike code patterning and remote neural network code patterning during epilepsy is still unclear. Recent experimental data demonstrate close relationship between single neuronal discharges and neural networks [5, 6].

Recently, scientists pay much attention to neural information encoding measured in real biological neural networks and at the cellular level. Actually, single neuronal encoding is tightly connected with network encoding, e.g. some hippocampal interneurons manifest specific firing patterns with particular interspike intervals (ISIs), which are closely coupled with hippocampal theta oscillations [7]. When linear analysis was used, the ISI signatures of pyloric neuron bursts depended on the synaptic connectivity of the network [8]. Using nonlinear prediction methods, synaptic transition could influence the nonlinear characteristics of chaotic spike trains [9]. In our previous works, tetanic stimulation-induced hippocampal neuronal bursts were coherent with evoked gamma frequency electrographic seizures, which expressed stratified ISI spot distribution [10].

It is important to understand how neuronal information encodes and decodes during epileptic seizures [11]. Physiologically, relative neuronal spike timing and ISI durations are thought to decode visual information in monkey primary visual cortex [11]. But it is difficult to understand the processes of highly complicated network encoding. Using nonlinear analysis of the first-return one-dimensional maps by fitting the scatter plots of interpeak intervals (IPIs) might predict seizures [12]. Little evidence exists showing epileptic network encoding processes in multiple regions distant from an epileptic focus, such as the HPC, laterodorsal thalamic nucleus (LD) when a focus is created in the caudate putamen nucleus (CPu). The present work was to focus on an epileptic electrical network of the hippocampal-thalamus reconstructed by overactivation of the CPu. Also, the specific LD neuronal spike ISIs and the hippocampal electroencephalogram (EEG) wave IPIs during this network reconstruction were observed. Importantly, not only can the hippocampal EEG wave IPIs reflect the temporal code patterning of the epileptogenic local network, but also can the LD neuronal spike ISIs, if the distant LD neuron is a member of the network.

1 MATERIALS AND METHODS

1.1 Animals and surgery

Experiments were performed on 21 male Sprague-Dawley rats, weighing 150–250 g. Under anesthesia with 10% urethane (i.p., 1 g/kg), the rat was endotracheally intubated and mounted on a stereotaxic apparatus (SN-3, Narishige, Japan). Cranial windows were opened. Two bipolar concentric stainless steel electrodes (tip resistance, 0.2–0.3 MΩ) were used for bilateral hippocampal EEG recordings. Another electrode was placed into the right CPu (RCPu) for stimulation. Two glass microelectrodes (tip resistance, 10–20 MΩ) were inserted into bilateral laterodorsal thalamic nuclei (LDi) for single unit recordings. The tip positions of the electrodes were as below, the HPC, P: –3.0 ~ –3.5 mm, R or L: 1.5~2.5 mm, H: 2.5~3.5 mm; the CPu, P: 1.2~1.6 mm, R: 2.0~2.3 mm, H: 3.7~4.2 mm and the LD, P: –3.0 ~ –3.5 mm, R or L: 1.5~2.5 mm, H: 3.5~5.0 mm. During the experiments, rats were artificially ventilated after intraperitoneal injection of pavulon (0.2 mg/kg, Netherlands Batch No.8039102), a muscle relaxant. The body temperature of the rats were maintained at (37 ± 0.5)°C.

1.2 Stimulation and recording

Tetanic trains (60 Hz, 2 s, 0.4–0.6 mA) were delivered into the RCPu through an electronic stimulator (SEN-7203 Nihon Kohden, Japan) via an isolator (SS102J, Nihon Kohden, Japan). To avoid the refractory period of the brain tissue following the tetanus, the tetanic trains were administered at intervals of 10 min. Bilateral hippocampal EEGs were recorded with two bioelectric amplifiers in an 8-channel polygraph system (RM-6008, Nihon Kohden, Japan).
Bilateral LD neuronal discharges were recorded by two microelectrode amplifiers (MEZ-7101 and MEZ-8201, Nihon Kohden, Japan), which were connected to two pre-amplifiers (FZG-81, Shanghai). They were monitored auditorily by two bioelectric amplifiers (SZF-1G, Shanghai). The four-channel bioelectric signals were simultaneously taped on videocassettes with two double-track cassette recorders (VR-HD 1000 PHILIPS).

1.3 Data analysis
Data on videocassettes were digitized off-line with a multiple-channel acquisition and analysis system (Neurolab, type I, Huazhong University of Science and Technology, 2000). Bioelectrical signals were treated with Clampfit 8.0 software (Axon Instruments). The spot distribution of LD neuronal firing ISIs and hippocampal EEG wave IPIs were exhibited in scatter diagrams by Sigmaplot software. Their ISI \((\text{IPI}_n)\) versus the ISI \((\text{IPI}_{n+1})\) scatter diagrams were also focused on. First, the ISI\(_{(n,n+1)}\) or the IPI\(_{(n,n+1)}\) spot distribution plotted automatically by Sigmaplot software. Second, a dense area was defined by drawing an oblique line across the same x and y axes value. All the spots were divided into two areas. One is the dense area without gap between spots. Another is the sparse area. Third, the convergent ratios were compared by calculating the percentage of the spots before and after tetanizations. Statistical differences were analyzed with the SPSS software. The characteristics and biological significance of epilepsy-related neuronal burst ISI spot distribution and primary unit afterdischarges are described elsewhere [10, 13].

1.4 Histological identification
At the end of the experiments, the tip positions of the glass microelectrodes were determined by deposition of Pontamine sky blue through DC current (20 mA, 20 min). The tip positions of the bipolar concentric stainless steel electrodes were marked with Prussian blue staining by small electrolytic lesion (0.5 mA, 25 s). Rats were intracardially perfused with 100 ml normal saline and 100 ml 10% formaldehyde solution (to which 1% potassium hexacyanoferrate was added). Brains were removed and stored in the last fixative at 4 °C for 7 d and then embedded in paraffin. Verification of stimulating and recording sites was done by examining the hematoxylin and eosin stained sections with a BX51 microscope and DP12 system (Olympus, Japan) (Fig. 1).

2 RESULTS
The electrophysiological data were obtained from 21 rats. From 4 of the 21 rats (19.0%) studied, four channel recordings from bilateral single LD neurons and hippocampal EEGs were obtained. In 13 out of the 21 rats (61.9%), hippocampal EEG wave enhancement coupled with inhibited LD neuronal firings was demonstrated. From 6 of the 21 rats (28.6%), partially synchronous discharges between bilateral LD neurons were observed.

The acute tetanization of the right caudate putamen nucleus (ATRC) induced results are described below.

2.1 An interactive hippocampal epileptic electrical network initiated by bilateral LD neuronal discharges
From 4 of the 21 rats (19.0%), correlation between primary unit afterdischarges in bilateral LD neurons and hippocampal EEG activities were induced by the ATRC. An example was shown in Fig. 2A. Initially primary unit afterdischarges were seen in the contralateral LD neuron (latency, 6.15 s), followed by primary unit afterdischarges in the ipsilateral LD neuron (latency, 6.94 s), and then primary afterdischarges were noted in the ipsilateral HPC (latency, 7.03 s), followed by desynchronized EEG activity in the contralateral HPC (latency, 7.12 s). It is noticeable that different EEG patterns were observed between the ipsilateral and contralateral hippocampi (HPCi), but similar firing pattern was detected in bilateral single LD neurons.

Figure 2(B1~4) illustrates the scatter diagrams of bilateral LD neuronal firing ISIs and hippocampal EEG wave IPIs within 15 s before and after tetanization. The ISI and IPI values decreased dramatically after the ATRC. The statistical difference was significant by using independent-samples t test as follows: contralateral LD neuronal ISIs, \(P<0.042\) (Fig. 2B1); ipsilateral hippocampal EEG wave IPIs, \(P<0.001\) (Fig. 2B3); contralateral hippocampal EEG wave IPIs, \(P<0.001\) (Fig. 2B4). In addition, the IPIs spot distribution was negatively correlated timely in ipsilateral and contralateral hippocampal EEGs (Fig. 2B3 and 2B4) \((r=–0.460, P<0.001, n=569\) dots and \(r=0.247, P=0.015, n=97\) dots).

Figure 2C illustrates the ISI\(_n\) (IPI\(_n\)) versus the ISI\(_{n+1}\) (IPI\(_{n+1}\)) scatter diagrams of bilateral LD neuronal firing or of bilateral hippocampal EEG waves. For the LD neuronal firing ISI\(_{(n,n+1)}\) plot, the convergent ratio increased ipsilaterally from 86.67% (65/75) up to 96.95% (127/131) and contralaterally from 84.26% (91/108) up to 92.97% (119/128). For the contralateral hippocampal EEG wave IPI\(_{(n,n+1)}\) plot, the convergent ratio increased ipsilaterally from 13.71% (27/197) up to 81.02% (380/469) and contralaterally from 70.48% (614/857) up to 96.17% (1756/1826) \((\chi^2\) test, \(P<0.05, P<0.005, P<0.005\) and \(P<0.005\)). It seems that
the ipsilateral LD neuronal firing ISI_{n,n+1} and the contralateral hippocampal EEG wave IPI_{n,n+1} manifested more obvious spot convergence into dense area after stimulation. On the other hand, it demonstrated that the number of ISI_{n,n+1} spots of LD neuronal firing and IPI_{n,n+1} spots of hippocampal EEG waves increased remarkably after the ATRC (Fig.2C b, d, f and h). The data indicated that ATRC promoted LD neuronal firing and hippocampal EEG waves into an evident temporal code patterning, which might reflect pathophysiological neural information flow between the LD and the HPC.

2.2 The electrophysiological properties of bilateral LD neuronal discharges
In 6 out of the 21 rats (28.6%), it was observed that related LD neuronal firing pattern induced by the ATRC. Some of them manifested special electrophysiological properties as described below.

A mirror-like ISI spot distribution of the LD neuronal firing was simultaneously noted in both the ipsilateral and contralateral recordings in 9.52% (2/21) rats. Fig.3A and B showed raw data of bilateral LD neurons manifesting similar firing patterns. Fig.3C, E and F displayed sharply resembled and reversed ISI spot distributions. The LD neuronal bursts followed unit discharges before stimulation, but after the ATRC, bursts preceded unit discharges. So the elevated ISI spots decreased gradually and back to the baseline. It created an incompletely symmetric ISI spot distribution along the artifact (Fig.3 B, C, E and F). The
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**Figure A**
- Contralateral LD unit discharges
- Ipsilateral LD unit discharges
- Ipsilateral hippocampal EEG
- Contralateral hippocampal EEG

**Figure B**
1. Contralateral LD neuron
2. Ipsilateral LD neuron
3. Ipsilateral hippocampal network
4. Contralateral hippocampal network

**Legend**
- 1 mV
- 50 μV
- Desynchronization 4 s
- 60 Hz, 2 s

Correlation values:
- $r = -0.480$, $P < 0.001$, $n = 589$
- $r = -0.247$, $P = 0.015$, $n = 97$
Fig. 2. Initiation of an interactive hippocampal epileptic electrical network by bilateral LD neuronal discharges. A: This figure showed four-channel raw data recorded from bilateral LD neurons and the HPCi. B: There was obvious time difference of evoked responses originating in sequence from primary unit afterdischarges of the contralateral LD neuron and the ipsilateral LD neuron, and primary afterdischarges in the ipsilateral hippocampal EEG and desynchronous EEG activities in the contralateral HPC. The bilateral LD neuronal ISI and hippocampal EEG wave IPI spots declined remarkably after the ATRC. The spot distributions were more closed to the baseline of time axis. C: Exhibited the plots of ISI\_n, n+1 and IPI\_n, n+1 spot distribution of four-channel biological electrical signals. Almost all the spots were more convergent and closed to the zero level of x and y axes.
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A
Ipallateral LD single unit recording
Contralateral LD single unit recording

Administration of the 9th ATRC

B
Ipsilateral

C
Contralateral

D
Ipallateral LD single unit recording
Contralateral LD single unit recording

Administration of the 14th ATRC

E
Ipsilateral

F
Contralateral

Time (s)
Fig. 3. Symmetric mirror-like ISI spot distributions of the LD neurons before and after stimulation in two hemispheres. The raw data and its ISI spot distribution (A, B, C, D, E, and F) of bilateral LD unit discharges appeared mirror-like reactions after the ATRC. This effect was strongly alike but mildly different between the ipsilateral (B and E) and the contralateral sides (C and F). This symmetric property of temporal code patterning occurred around the tetanic axis. The ISI of the ipsilateral LD unit firing were statistically different before and after tetani, but not of the contralateral LD unit firing. The ISI plots of ipsilateral LD neuronal firing showed a tendency to converge, while those of contralateral one were almost unchanged after the ATRC (G and H).
Fig. 4. Partially synchronized neuronal afterdischarges and their characteristic ISI spot distributions in bilateral LDi. Traces $A$, $C$, $E$, $G$ and $I$ show the raw data on the left side. Traces $B$, $D$, $F$, $H$ and $J$ exhibit their ISI scatter diagrams. The primary unit afterdischarges appeared at high firing rates so that they were characterized by ISI spots returning to the baseline. The initiation of bilateral primary unit afterdischarges and their characteristic ISI scatters were gradually delayed after a series of tetanic trains. The dashed lines in the ISI scatter diagrams demonstrate the initiation of the characteristic ISI spot distribution of the contralateral neuron. It seems that the contralateral LD neuron shows more plasticity to the ATRC.
ISI spot distribution symmetry enhanced after the 9th to the 14th tetanic train. In addition, contralateral LD neuronal unit afterdischarges appeared with shorter latency than ipsilateral afterdischarges after the 9th to the 14th train (raw data). This was also displayed in the ISI scatter diagrams.

The ISI\(_{\text{ISI}(n,n+1)}\) scatter of ipsilateral LD neuronal firing showed a tendency to converge after the ATRC (Fig.3 Ga, Gb, He, Hf). But the ISI\(_{\text{ISI}(n,n+1)}\) scatter of the contralateral LD neuronal firing was more symmetric (Fig.3 Gc, Gd, Hg, Hh). For the ipsilateral LD single unit firing, the concentrated parts of ISI\(_{\text{ISI}(n,n+1)}\) were statistically different by using independent-samples \(t\) test. However, for contralateral LD single unit firing, the concentrated parts of ISI\(_{\text{ISI}(n,n+1)}\) were nearly unchanged, especially after the 14th train.

This phenomenon reflected a higher contralateral LD susceptibility to the ATRC. It suggested an ATRC-induced information flow formation between bilateral LD neuronal networks.

The different plastic initiation between bilateral LD single unit afterdischarges following a series of trains was observed in 28.6\% (6/21) rats. As shown in Fig.4, on the left side, raw data exhibited ipsilateral or contralateral LD neuronal firing patterns respectively after all tetanic trains (Fig.4A, C, E, G and I). The neuronal firing patterns mainly included primary unit afterdischarges and long duration bursts. They were partially coupled with each other. The ipsilateral LD neuron initiated its primary unit afterdischarges first after the 1st train (Fig.4A up trace). The contralateral LD neuron started its primary unit afterdischarges first after the 3rd train (Fig.4E). Finally bilateral LD neurons began their primary unit afterdischarges almost at the same time after the 5th train (Fig.4I). Both neurons gradually prolonged the latency of their evoked responses to the repetitive ATRC.

On the right side, the ISI spot distribution of bilateral LD neuronal firings was exhibited. Primary unit afterdischarges

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Fig.5. Enhancement of hippocampal EEG wave amplitude and prolongation of LD neuronal burst intermittence on the contralateral side. C illustrates that prolonged burst intermittency is roughly correlated to hippocampal EEG wave enhancement after the 13th train. This effect was recruited by multiple tetanic trains.
appeared with high firing rates, such that the ISI spots distributed to the baseline. Neuronal bursts had both sparse and frequent spiking so that the ISI spots tended to stratify. Following a series of the ATRC, the higher density ISI spots concentrating on baseline were gradually delayed. Contralateral LD neuronal ISI scatters manifested more plasticity than the ipsilateral ISI’s. It might quantitatively verify the temporal code patterning of LD neuronal discharges shown in the raw data.

2.3 Inhibited LD neuronal firing coupled with enhanced hippocampal EEG waves on the contralateral side

In 13 of 21 (61.9%) rats, hippocampal EEG wave enhancement coupled with inhibited LD neuronal firing was demonstrated. Fig. 5 showed hippocampal EEG wave enhancement recruited by prolonged LD neuronal discharge intermittently on the contralateral side. Apparently, long duration LD unit afterdischarges were immediately followed by a couple of intermittent bursts after the 11th train (Fig. 5 A upper trace). It was shortened after the 12th tetanic train (Fig. 5 B upper trace). Note that those intermittent LD neuronal bursts with gradually prolonged durations took place between unit afterdischarges. It might be a cause of the shortened duration of primary unit afterdischarges. Fi-

![Fig. 6. Rhythmic spikes of the LD neuron coupled with 25 Hz hippocampal oscillatory waves on the contralateral side. A: Five single spikes are time- and phase-locked to the hippocampal oscillatory waves. B: Significant linear correlation between the five LD neuronal spikes and the hippocampal EEG waves over time. C: LD neuronal spikes and the hippocampal EEG waves are highly correlated to each other over time.](image-url)
nally those intermittent bursts were mixed into one trace with much longer duration (about 60 s) after the 13th train (Fig.5 C upper trace). It was coupled with the enhanced activities of hippocampal EEG waves (Fig.5 C down trace). There was significant statistical difference ($r= 12.231, P< 0.0001$) between the enhanced wave peak values $[(31.26±0.54 \mu V, n=946)]$ and the wave peak values before and after them $[(23.30±0.36 \mu V, n=1048)]$.

### 2.4 Characteristic single LD neuronal spikes phase- and time-locked with 25 Hz hippocampal EEG oscillations on the contralateral side

In 28.6% (6/21) rats, 20–25 Hz hippocampal EEG oscillations were closely related to single LD spiking on the contralateral side both in time and in phase. Fig.6A was an example. Moreover, each single spike mostly occurred during the ascending phase of the hippocampal oscillatory waves. The mean neuronal firing ISI value was $(40.75±4.169)$ ms ($n=5$). These oscillatory waves possessed mean IPI value of $(37.8±6.981)$ ms ($n=5$). The peaks of those LD neuronal spikes and the hippocampal EEG waves were linearly correlated over time (Fig.6B). From the six rats, 72 wave-spike trains exhibited linear correlation between hippocampal EEG oscillatory waves and single LD neuronal spikes ($r=0.990, P< 0.0001$) (Fig.6C). Each train was composed of $(4.9722 ± 0.1526)$ wave-spike ($n=72$). The mean LD neuronal ISI was $(47.5287 ± 0.8573)$ ms ($n=286$). There was a long pathway linkage from the LD neuron to hippocampal EEG initiated from the overactivated RCPu. This suggests that hippocampal EEG oscillations might be generated by the LD neuronal spiking.

### 3 DISCUSSION

The main findings of our present work demonstrate that repetitive ATRC can induce (1) an interactive epileptic electrical network reconstructed in bilateral HPCs, which was correlated to primary afterdischarges of single LD neurons; (2) a mirror-like ISI spot distribution of LD neuronal firing induced by the ATRC, and (3) single LD neuronal spikes were phase- and time-locked to 20–25 Hz hippocampal gamma oscillations.

The results imply an ATRC-reconstructed epileptic electrical network involved the LD and the HPC. In the process of pathological neural network reconstruction, there were interactions between the LD neuronal spikes and the hippocampal EEG waves. In some cases, hippocampal epileptiform activities correlated with epilepsy-related discharges of LD neurons on the contralateral side, suggesting a contralateral susceptibility to the ATRC.

#### 3.1 Hippocampal epileptic networks and their LD cellular electrophysiological mechanisms

Obvious neuroanatomical or functional projections from the thalamus to the CPu or to the HPC have been proved. Therefore single striatal neurons might receive convergent input from hippocampal formation and the thalamus. These connections might become the basis of an epileptic network reconstruction.

It has been still difficult to lateralize or to localize secondary epileptic foci inside or outside thalamus, the HPC and the CPu. But little attention has been paid to the role of the CPu in generating electrogenic hippocampal epilepsy though striatal neuronal bursting could be driven by cortical epileptiform activity in rats. The coherent bioelectrical activity existed from the cortex to the basal ganglia. The densities of hilar cells were positively correlated with the glucose metabolic rate in the thalamus, the putamen and the caudate nuclei in the temporal lobe epilepsy (TLE) patients. In TLE patients or animals, ipsilateral or contralateral HPC or thalamic abnormalities might be involved in epileptogenesis. In our previous work, following repetitive tetanization of the HPC, asymmetric T$_2$-MRI hyperintensities in the lateral ventricle area were seen especially contralaterally. Hippocampal and generalized epileptic seizures were bilaterally evoked by tetanization of the RCPu or of the right HPC in rats. But more severe behavioral seizures were observed in the CPu-stimulated rats. From our present experimental data, it has been proved that there might be a pathophysiological functional neural connections, established following activating the RCPu, from the contralateral LD to the ipsilateral LD and finally to bilateral HPCs. The evoked reactions of bilateral LD neurons were primary unit afterdischarges. But bilateral hippocampal EEGs reacted differently, i.e. primary afterdischarges in the ipsilateral hippocampal EEG and desynchronization in the contralateral HPC. Possibly, a thalamo-genic hippocampal neural circuit was reorganized. In the course of the seizure development, there might be transitions of neuronal firing patterns as well as local neural network activity from physiological to pathophysiological states.

The electrogenic epileptic electrical network reconstruction in bilateral HPCs was probably based on neural information coding of hippocampal neurons. For example, hippocampal neuronal ISIs and interbursting intervals were increased in hippocampal epileptogenesis along the temporal-septal axis. Furthermore, the spikes of LD neurons were phase- and time-locked to 20–25 Hz hippocampal EEG oscillations on the contralateral side. This shows a
cellular electrophysiological relations of the bilateral LDi to hippocampal epileptic network recruitment.

3.2 Characteristic LD neuronal firing ISI and its possible physiological significance

Important temporal and spatial information might be mainly interpreted by highly correlated temporal code and rate code of single hippocampal neuronal spikes[25]. The neuronal temporal code could be transformed into a rate code[26,27]. The neuronal firing pattern can be identified by the ISI, whose variability can be logarithmically quantified[28]. There exists an interaction between single neuronal spikes and complex spike bursts[29]. This neuronal bursting could be induced by electrogenic activation of intrinsic hippocampal networks, as we described previously[30,31].

In addition, Fig.2C exhibited a similar temporal code patterning both in LD neuronal spikes and in hippocampal EEG waves modulated by the repetitive ATRC. Most of the ISI\(_{(n,n+1)}\) and IPI\(_{(n,n+1)}\) values were reduced after the stimulation. It is noticeable that a dramatically convergent effect was only found in contralateral hippocampal EEG wave IPI\(_{(n,n+1)}\) spot distribution (Fig.2C g and h). The contralateral hippocampal EEG was more susceptible to the ATRC. On the other hand, ipsilateral LD neuronal firing ISI\(_{(n,n+1)}\) showed more convergent spot distributions after the ATRC (Fig.2C c and d). Fig.3G and H also demonstrated little variability and clear symmetry of ISI\(_{(n,n+1)}\) spot distributions on the contralateral side. Presumably, the ATRC might simultaneously modulate strongly the temporal code patterning of the ipsilateral LD neuronal firing and the contralateral hippocampal EEG waves. The main features of bilateral LD neuronal firing have physiological or pathophysiological significance. Possibly, a mirror-like ISI spot distribution of LD neuronal firing (Fig.3) reflects a reversible temporal coding modulated by extrinsic information input from the activated RCPu.

3.3 Relations between hippocampal EEG wave IPIs and LD neuronal firing ISIs on the contralateral side

Generally, neural information transmission in the central nervous system is based on communication between neurons and networks. However, single neuronal encoding and decoding underlie network behaviors for integrated recoding[11]. Because of the highly complicated network properties, it is hard to elucidate how networks encode, integrate neural information and execute some functions. Seizures could reflect some functional imbalance of synaptic transmission during epileptic network generation, e.g. excitation and inhibition, synchronization and desynchronization, or coupling, decoupling and recoupling[4,30,31].

In the past decades, some qualitative and quantitative analyses were used to disclose the characteristics of network information encoding. Nonlinear time series analyses of clinical and experimental data show that EEG wave IPI spot distributions bifurcate characteristically during seizures in epileptic patients and rats[32,33]. For epilepsy source localization and lateralization, all ictal events could be decomposed and reconstructed to increase the signal to noise ratio of the TLE patients’ EEG[34]. Nevertheless, it is difficult to define the characteristics and properties of network encoding or decoding in the pathophysiological situation of epilepsy.

We demonstrate that a recruitment of seizure-related activity is produced from the ATRC site to the hippocampal networks and to the LD neuronal networks. Presumably, there might be a tight link between LD neuronal temporal coding and hippocampal EEG temporal coding during the development of tetanic stimulation-induced seizure network recruitment. Because of the spatial distribution of the tip positions of the one stimulating and four recording electrodes we used, multiple spatial and temporal code patterning should be considered together as an integrative network information code process.

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