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High-Frequency Network Activity, Global Increase in Neuronal Activity, and Synchrony Expansion Precede Epileptic Seizures In Vitro

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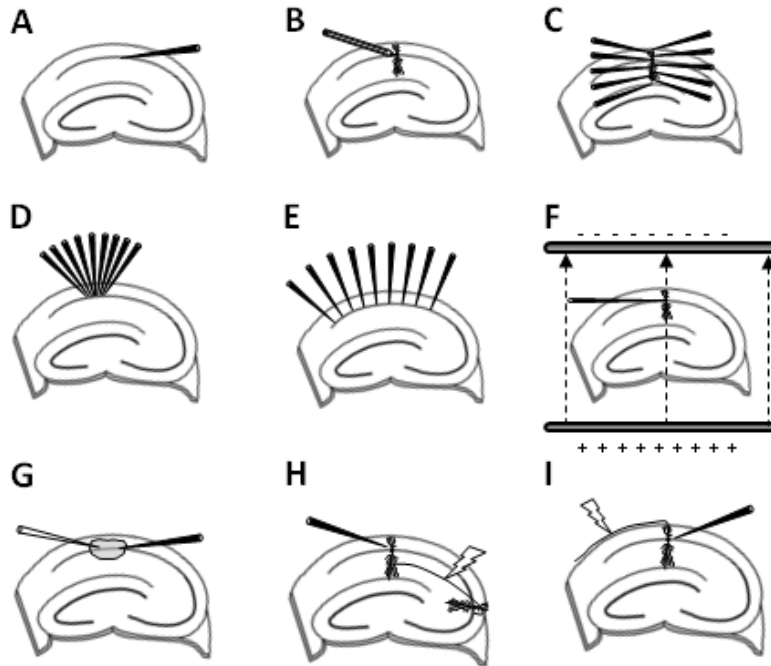
Supplementary figure 1 Schematics of experimental arrangements used in present study. *A*, Recording with glass electrodes. *B*, Recording with tetrodes. *C*, Current source density and laminar profile electrode arrangement. *D*, Multiple electrodes recording on a local scale. *E*, Multiple electrodes recording on a large (global) scale. *F*, Electric field application. *G*, Local glutamate application. *H*, Orthodromic response recording evoked by stimulating Schaffer collaterals. *I*, Antidromic stimulation of CA1 axons.
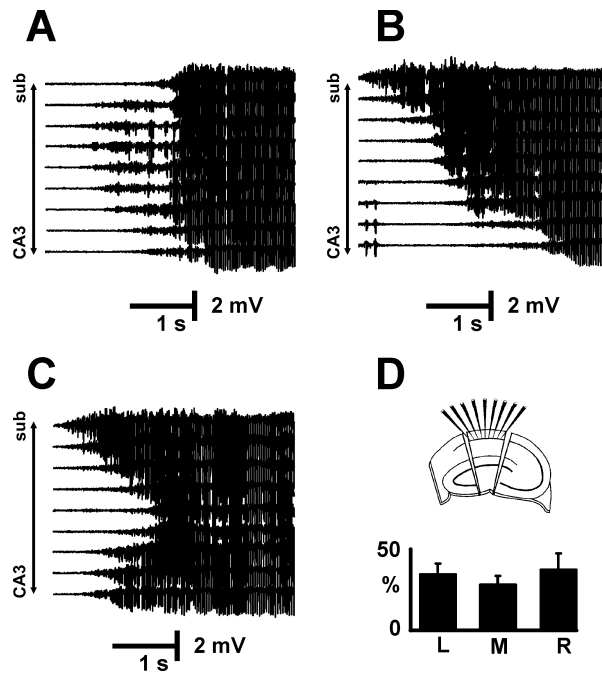
Supplementary figure 2 Multifocal seizure onset recorded with electrodes covering CA1 area. Seizure starting in: the middle of CA1 (*A*), the subicular end (*B*), and simultaneously at both subicular and CA3 ends of CA1 (*C*). *D*, In CA1 minislice multifocal onset is preserved with 35% seizures starting in left part of minislice, 28% in the middle and 37% in the right.

A

> 10 Hz

2 mV

10s

B

> 10 Hz

c

2 mV

10s

C

D

E

power

1 mV

0.5 s

0   150   300

D

E

0.2 mV

50 ms

0.5 mV

50 ms
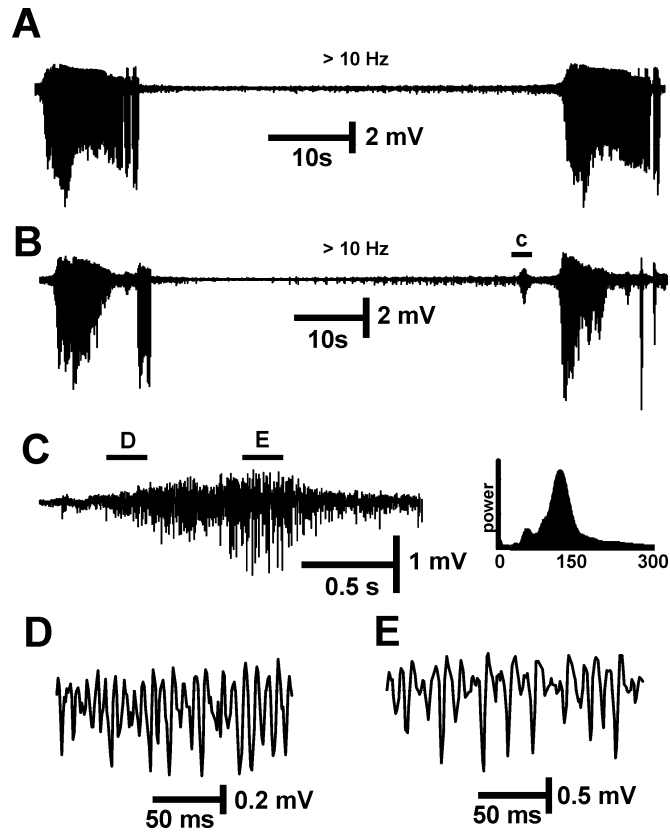
Supplementary figure 3 Seizures, interictal period and preburst. *A*, Two consecutive seizures and interictal period with HFA and multiunit activity, high-pass filtered at 10 Hz. *B*, Seizures and interictal period with preburst preceding second seizure. *C*, Example of preburst and associated wavelet power spectra. Prebursts have similar morphology to activity observed during the early stages of seizures. *D*, Detail of activity at an early stage of the preburst shown in *C* and during a more advanced stage (*E*).
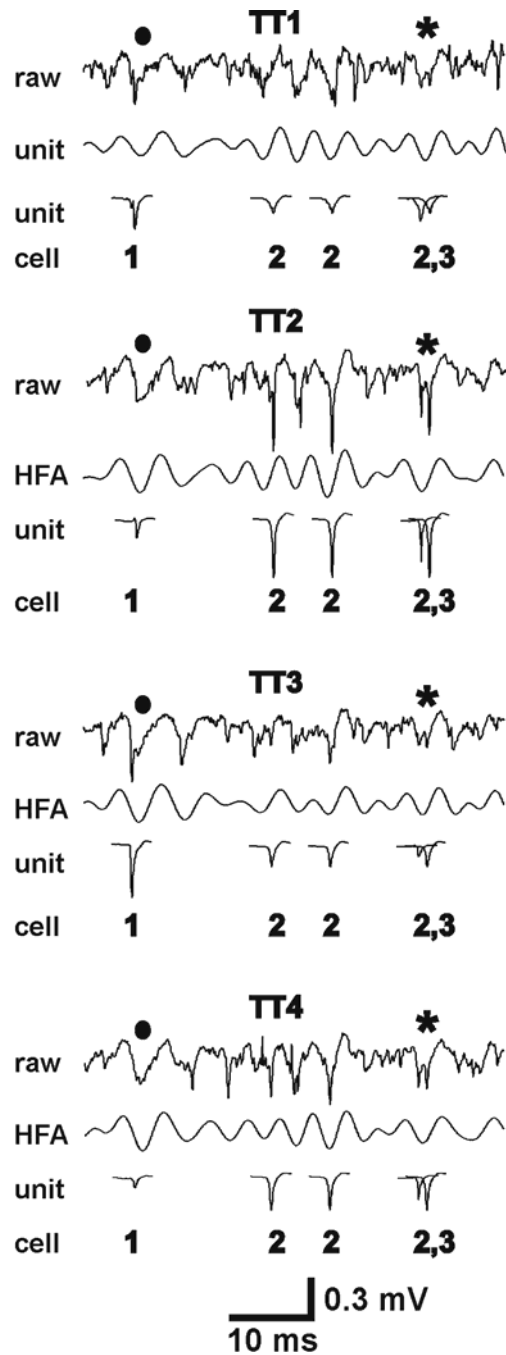
Supplementary figure 4 Detail of HFA from individual channels of a tetrode. Note that the relative sizes of units on the different channels: unit 1 is maximal on channel 3, and unit 2 on channel 2. Circle (●) shows comparison between extracellular action potentials and individual HFA activity oscillation. Asterisk shows two different neurons co-firing during the individual oscillation of HFA, which suggests that individual HFA cycles represent firing of action potentials of small neuronal populations.
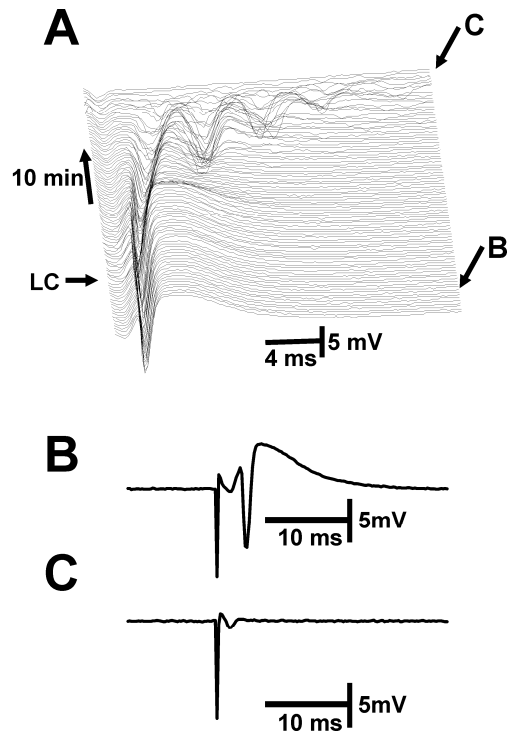
Supplementary figure 5 Block of synaptic transmission in the low-calcium model. *A*, Monitoring of orthodromic responses to Schaffer collateral stimulation before and after introduction of low-calcium aCSF. *B*, Normal synaptic response with superimposed population spike; response is preceded by a fibre volley. *C*, Disappearance of synaptic responses in low-calcium aCSF; only the fibre volley remains. Before the synaptic response disappears there is a transient period during which orthodromic stimulation evokes repetitive spikes (*A*: traces preceding *c*).

Characterizing signal complexity and local neuronal synchrony using entropy rates

Let us suppose that enhanced synchronization among neurons in some location will lead to increased level of regularity or rhythmicity; or, from another point of view, a decreased level of complexity of electrographic signal (field potentials) recorded from that location. In order to quantitatively characterize the regularity, or temporal complexity of the signal, we consider the field potential signal as an output of a complex, dynamic process evolving in time. A series of measurements done on such a system in consecutive instants of time $i = 1, 2, \ldots$ is called time series $\{x_i\}$. Consider further that the temporal evolution of the studied system is not completely random, i.e., that the state of the system in present time in some way depends on the states in which the system was in previous time instants. The strength of such a dependence per a unit time lag, or, inversely, a rate at which the system „forgets" information about its previous states, can be an important quantitative characterization of temporal complexity in the system's evolution.

The time series $\{x_i\}$, which is a recording of the system temporal evolution, can be considered as a realization of a stochastic process $\{X_i\}$, i.e., a sequence of stochastic variables, characterized by the joint probability distribution function $p(x_1, \ldots, x_n)$, $p(x_1, \ldots, x_n) = \Pr\{(X_1, \ldots, X_n) = (x_1, \ldots, x_n)\}$.

Uncertainty in a stochastic variable is measured by its entropy. The rate in which the stochastic process „produces" uncertainty is measured by its entropy rate. The entropy rate of a stochastic process $\{X_i\}$ is defined as (Cover & Thomas, 1991):

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$$h = \lim_{n \to \infty} \frac{1}{n} H\left(X_1, \ldots, X_n\right), \tag{1}$$

where $H\left(X_1, \ldots, X_n\right)$ is the entropy of the joint distribution $p\left(x_1, \ldots, x_n\right)$:

$$H\left(X_1, \ldots, X_n\right) = -\sum_{x_1} \ldots \sum_{x_n} p\left(x_1, \ldots, x_n\right) \log p\left(x_1, \ldots, x_n\right). \tag{2}$$

The concept of entropy rates is common to the theory of stochastic processes as well as to the information theory where the entropy rates are used to characterize information production by information sources (Cover & Thomas, 1991). Alternatively, the time series can be considered as a projection of a trajectory of a (chaotic) dynamical system, evolving in some measurable state space. A. N. Kolmogorov, who introduced the theoretical concept of classification of dynamical systems by information rates, was inspired by the information theory and generalized the notion of the entropy of an information source (Sinai, 1976). The Kolmogorov-Sinai entropy (Sinai, 1976), KSE thereafter, is a topological invariant, suitable for classification of dynamical systems or their states, and is related to the sum of the system's positive Lyapunov exponents (LE) according to the theorem of Pesin (Pesin, 1977). Thus, the concept of entropy rates is common to theories based on philosophically opposite assumptions (randomness vs. determinism) and is ideally applicable for characterization of complex biological processes, where possible deterministic rules are always accompanied by random influences. However, possibilities to compute the exact entropy rates from experimental data are limited to a few exceptional cases (Palus, 1996).

Let us consider that $\{X_i\}$ is a zero-mean stationary Gaussian process with spectral density function *f(ω)*. Then its entropy rate h_G, apart from constant term, can be expressed using $f(\omega)$ as [see (Palus, 1997) and references therein]:

$$h_G = \frac{1}{2\pi} \int_{-\pi}^{\pi} \log f(\omega) d\omega.$$ (3)

Dynamics of a stationary Gaussian process is fully described by its spectrum. Therefore the connection given by Eq. (3) between the entropy rate of such a process and its spectral density $f(\omega)$ is understandable. The estimation of the entropy rate of a Gaussian process (GPER) is reduced to the estimation of its spectrum.

If a studied time series was generated by a nonlinear, possibly chaotic, dynamical system, its description in terms of a spectral density is not sufficient. However, Palus (1997) have found that a relation between the KSE (or, equivalently, the sum of positive LE's) of a dynamical system and the entropy rate of a Gaussian process isospectral to time series generated by the dynamical system exists as a nonlinear one-to-one function when the KSE varies smoothly with variations of system's parameters, but is broken in critical states near bifurcation points. Thus Gaussian process entropy rate (GPER) can be used as a useful first approximation of level of complexity of studied signals.

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