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Control of phase synchronization of neuronal activity in the rat hippocampus

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Abstract

Analysis of the synchronization mechanisms of neural activity is crucial to the understanding of the generation, propagation and control of epileptiform activity. Recently, phase synchronization (PS) analysis was applied to quantify the partial synchrony that exists in complex chaotic or noisy systems. In a previous study, we have shown that neural activity between two remotely located sites can be synchronized through a complete cut of the tissue by endogenous non-synaptic signals. Therefore, it should be possible to apply signals to control PS. In this study, we test the hypothesis that stimulation amplitudes below excitation level (sub-threshold) can be used to control phase synchronization of two neural signals and we investigate the underlying mechanisms. PS of neuronal activity is first analysed in two coupled Rössler neuron models. Both synchronization and desynchronization could be generated with sub-threshold sinusoidal stimulation. Phase synchronization was then studied in *in vitro* brain slices. Neuronal activity between two sites was modulated by the application of small sinusoidal electric fields. PS between two remote sites could be achieved by the application of two identical waveforms while phase desynchronization of two close sites was generated by the application of a stimulus at a single site. These results show that sub-threshold stimuli are able to phase synchronize or desynchronize two networks and suggest that small signals could play an important role in normal neural activity and epilepsy.

1. Introduction

Synchronization is a phenomenon widely observed in neural systems (Eckhorn 2000, Glass 2001). It appears as functional oscillations such as the theta rhythm and pathological states such as epilepsy or tremor. For example, theta rhythm is one of the four dominant frequency patterns observed in brain activity and plays an important role in integrative and memory functions (Leung 1998). The mechanism by which separated regions of the brain synchronize in theta rhythm remains unclear (Steriade *et al* 1990, Sviderskaya and Korol'kova 1998). Synchronization of neural activity can also generate abnormal neural activity such as the debilitating symptoms of epilepsy resulting from excessive synchronized firing in a large population of neurons (Prince 1978).

Phase synchronization (PS) analysis is a recently developed mathematical tool useful for quantifying the general level of synchrony in dynamical systems such as neuronal populations (Pikovsky *et al* 2001). PS analysis has been used to study the correlation between several coupled systems such as cardiovascular and respiratory signals (Schäfer *et al* 1999) or brain activity and signals from the flexor muscles (Tass *et al* 1998). The chaotic sub-threshold oscillations of electrically coupled inferior olivary neurons have also been studied with PS methods (Makarenko and Llinas 1998). Controlling the level of synchronization is a crucial task for the nervous system since ensembles of neurons are recruited to fulfil information processing requirements, but excessive and abnormal synchrony must be prevented.

Although mathematical models have been used to analyse the control of PS (Parlitz *et al* 1996), little experimental data exist to show that the control of phase synchronization can be applied to abnormal neuronal signals as in epilepsy. Yet there has been a great deal of interest in determining how synchronization is induced by small amplitude external stimuli since function-related synchrony arising from different regions

of brain is always the response to a small input (Glass 2001). A previous study has shown that a small amplitude non-synaptic signal (potassium ion diffusion) propagating within the brain tissue can synchronize neural activity through a complete mechanical cut of the tissue (Lian *et al* 2001). The study of how these small amplitude signals cause synchrony in neural populations is important to the understanding of synchronization generation mechanisms and functional role of synchronization. Desynchronization of the chaotic periodic dynamic systems has also been observed by changing the coupling between the systems (Anishchenko *et al* 1998) or by applying various driving signals to coupled oscillator systems (Tass 2002).

Therefore, we tested the hypothesis that two neural networks can be synchronized or desynchronized by small sub-threshold sinusoidal waves similar to those known to be present within the brain. A Rössler model that mimics epileptiform activity was first used to analyse whether PS between two oscillators could be modulated by a small amplitude sinusoidal driving force. The relationship between coupling strength and driving force was studied. The hypothesis was also tested *in vitro* by modulating spontaneous neuronal activity in rat hippocampal brain slices with the application of sub-threshold sinusoidal fields. The possible PS mechanisms involved in the model and experiment are discussed.

2. Methods

2.1. Data analysis

The synchronization relationships between signals in both simulation and experiment were quantified by recently developed PS methods (Kurths and Abel 1998). Advantages of this method over normal cross-correlation analysis methods include insensitivity to noise, signal amplitude and the ability to compare signals having different frequency ratios (Fitzgerald 1999, Pikovsky *et al* 1997). The essential idea is to establish a valid phase definition for non-periodic oscillators (Pikovsky *et al* 1997). Briefly, an attractor is reconstructed from an original time series with an appropriate time delay in the phase space. The phase of the system can be calculated by

$$\varphi(t) = \arctan \frac{S_1(t) - S_{1c}}{S_2(t) - S_{2c}} \tag{1}$$

$$\psi(t) = \varphi(t) + 2\pi l(t) \tag{2}$$

where $S_1(t)$ and $S_2(t)$ are the original signals and (S_{1c}, S_{2c}) are the coordinates of the rotation centre of the trajectory. The phase in each cycle is represented by $\varphi(t)$and the accumulated phase is $\psi(t)$ with the corresponding cycle $l(t)$. An empty region in the centre of the attractor must be found to place the rotation centre and thus provide a usable definition of phase. The integer $l(t)$ increases or decreases by one depending on whether the next point in the phase space crosses the positive x-axis in a clockwise or anticlockwise direction, so that the phase value accumulates smoothly (Shuai and Durand 1999).

The generalized phase difference or relative phase between attractor 1 and 2 is defined as

$$\psi_{n,m} = n\psi_1(t) - m\psi_2(t) \tag{3}$$

where n and m are integers and $n{:}m$ is the mean frequency ratio of ψ_1 and ψ_2. The condition of PS is identified as $|\psi_{n,m}(t)| < K_{\mathrm{ps}}$, where K_{ps} is a constant ($\sim\pi$). An initial transient time of 5000 points for the model and 10 s for experimental data was excluded from the analysis.

The coefficient of variation (C.V.) of inter-event interval is the ratio of standard deviation to mean inter-event interval. The C.V. is an estimate of signal regularity. The Lyapunov or characteristic exponent (λ) measures the rate of exponential divergence (convergence) in phase space of two neighbouring trajectories of a dynamical system (Kantz and Schreiber 1997, Brown *et al* 1991).

The Lyapunov exponent was estimated with cspW (Contemporary Processor for Windows 95, Applied Nonlinear Sciences, LLC/Randle, Inc) according to the following algorithm. First, local neighbourhood-to-neighbourhood mappings are approximated by a third-order Taylor series. The linear term of the series is the Jacobian of this system. Following the reconstructed trajectory, the Jacobian matrices are multiplied together. The log of eigenvalues of this matrix gives the Lyapunov exponents λ_i. In this analysis, only the maximum exponent $\lambda_{\max}$ was used to characterize the intrinsic dynamic properties of oscillators or sub-network during the PS experiment.

2.2. Neural simulation model

The Rössler oscillator is a simple model that captures many important features of dynamic systems, such as periodicity, low dimension chaos and the ability of small networks to synchronize. This model simulates neuronal dynamics with three main variables—membrane potential $x(t)$, fast current $y(t)$ (associated with potassium and sodium ion channels) and slow current $z(t)$ (Makarenko and Llinas 1998). The coupling strength between two oscillators is directly proportional to the difference in membrane potentials. We modified the equations by adding a sinusoidal driving force to the oscillators:

$$\begin{aligned} \dot{x}_1 &= -w_1 y_1 - z_1 + e(x_2 - x_1) + A_1 \sin(2\pi f t) \\ \dot{y}_1 &= -w_1 x_1 + a y_1 \\ \dot{z}_1 &= b + x_1 z_1 - c z_1 \end{aligned} \tag{4}$$

where $a = 0.15$, $b = 0.2$, $c = 10$, $e = 0.035$, $f = 1$. w is the mean rotation frequency around the centre of the attractor. A is the stimulation amplitude. Similar equations were used for a second oscillator and the coefficient e determined the coupling strength. The forward-Euler method was used to integrate the equations with time step $t = 0.02$.

2.3. In vitro experimental model

Several methods have been developed to induce epileptiform activity in hippocampal slices (Durand 1993). We used the low calcium model of epilepsy that produces low frequency oscillations in the absence of synaptic activity (Jefferys and Haas 1982, Jones and Heinemann 1987, Taylor and Dudek 1982). The brain was rapidly removed and one hemisphere glued to the stage of a Vibroslicer (Vibroslice, Campden) in cold (3–4 °C) oxygenated sucrose-based artificial

cerebrospinal fluid (ACSF) consisting of (in mM): sucrose 220, KCl 3, NaH_2PO_4 1.25, $MgSO_4$ 2, $NaHCO_3$ 26, $CaCl_2$ 2 and dextrose 10. 350 μm thick slices were cut and immediately transferred to a holding chamber containing 'normal' ACSF consisting of (in mM): NaCl 124, KCl 3.75, KH_2PO_4 1.25, $CaCl_2$ 2, $MgSO_4$ 2, $NaHCO_3$ 26 and dextrose 10, held at room temperature and bubbled with 95% O_2–5% CO_2. After about an hour, a slice was transferred to a standard interface recording chamber with 'normal' ACSF at 35 $\pm$ 0.5°C, and a warmed, humidified 95% O_2–5% CO_2 vapour maintained over the exposed surface of the slice. After 10 min, slices were perfused with 'low calcium' ACSF (low Ca^{2+}) consisting of (in mM): NaCl 124, KCl 5.25, KH_2PO_4 1.25, $CaCl_2$ 0.2, $MgSO_4$ 1.5, $NaHCO_3$ 26 and dextrose 10.

Neural signals were recorded extracellularly from two sites within the CA1 pyramidal cell layer separated by about 700 μm. Identical low amplitude 50 Hz sinusoidal currents were delivered to the two regions adjacent to the corresponding recording locations (figure 1). The extracellular voltage signal was low-pass filtered at 10 Hz to eliminate the stimulus artefacts generated by the sinusoidal stimuli.

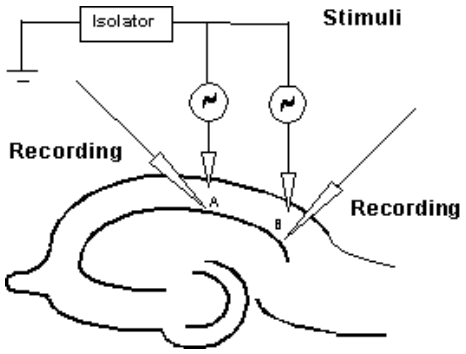

Figure 1. Stimulation diagram for phase synchronization experiments. The recording electrodes (glass electrode filled with 150 mM NaCl) were placed in the somatic layer of the CA1 region. Stimulation electrodes (Tungsten, A.M. Systems, Inc.) were positioned within 5 μm of the recording electrode. 50 Hz sinusoidal signal was generated by a waveform generator (Wavetek, Inc), converted into current by an isolator (Grass Instrument Co) and applied to the slice. The recorded signals were low-pass filtered at 10 Hz and stored to the tape.

3. Results

3.1. Phase synchronization of Rössler oscillators

3.1.1. Phase synchronization in Rössler network. PS was first studied using a computational analysis of two slightly different coupled Rössler oscillators defined as oscillators I and II ($w_1 = 1.025, w_2 = 0.975$). The coupling coefficient (e) was fixed at 0.035 and driving force amplitude (A) varied from 0 to 60 to analyse the control of PS by a sinusoidal driving force. Large amplitudes were not tested because the trajectories became too noisy and a rotation centre could not be accurately determined. Figures 2(A)–(C) show the variable (x) as a function of time, the attractor constructed in the x–y plane and the phase of oscillator I in the absence of a driving force ($A_1 = A_2 = 0$) respectively. The burst waveform of a Rössler oscillator (x) is similar to the epileptiform activity of hippocampal neurons in the low calcium medium (see figure 6(A)). Similar data (figures 2(D)–(F)) are shown for the oscillator under the influence of sinusoidal stimuli ($A_1 = A_2 = 19$). The variable x became noisy with superimposed fast spikes coming from the relatively faster external driving force (figure 2(D)). The attractor (figure 2(E)) still had a clear centre of rotation so that the calculation of phase from equation (2) was possible (figure 2(F)). The phase of both oscillators looked similar. The phase difference between I and II without any driving force and driven by sinusoidal stimuli is shown in figure 3. The phase difference in the absence of a driving force increased almost linearly with time. However, when stimulation was added ($A_1 = A_2 = 19$), the phase difference was restricted within the values 0 to π (figure 3). Simultaneous stimulation in both oscillators is required to achieve the PS state. A single stimulus was ineffective at synchronizing the two oscillators. Similar PS results were obtained when the coupling coefficient was gradually changed from 0.035 to 0.050.

3.1.2. Relationship between coupling and driving force. The role of coupling and threshold of driving force in the PS of two individual oscillators was studied for the case of $w_1 = 1.025$ and $w_2 = 0.975$ (figure 4). The minimum driving force A required to synchronize two attractors within a phase difference less than π was calculated as the coupling (e) was varied from 0.030 to 0.050. The driving force displayed a threshold effect. For a value of A larger than a specific value ($A_1 = A_2 = 15$, when $e = 0.035$), a synchronization state was always obtained as long as the phase could be measured. For a small value of the coupling coefficient such as 0.030, a large driving force was needed to achieve PS. For coupling values between 0.0325 and 0.045, the minimum amplitude remained nearly constant. For values of (e) greater than 0.0475, the minimum amplitude decreased to zero. A similar relationship was found for oscillators with other values of w ($w = 1 \pm 0.030$).

3.1.3. Desynchronization of two synchronized oscillators. To determine the feasibility of desynchronizing the two oscillators, the parameters of the model were set to maintain phase differences less than 1.25 between two oscillators ($w_1 = w_2 = 1.025, e = 0.05$). Only a small phase difference ($<$1.5) between them from time 0 to 15 000 can be observed (figure 5). Desynchronization could then be induced when sinusoidal stimulation ($A_1 = 0, A_2 = 20$) was applied to only one of the two oscillators as indicated in figure 5. Similar results were obtained for $e = 0.01$.

3.2. Phase synchronization of in vitro neural activity

PS was also studied in hippocampal slices with activity induced by perfusion in a low calcium solution. Two recording electrodes were separated by a distance of 700 μm in the pyramidal cell layer. Signals were obtained from 17 slices and examples are shown in figure 6. In all slices, no PS could be observed without stimulation as the phase difference

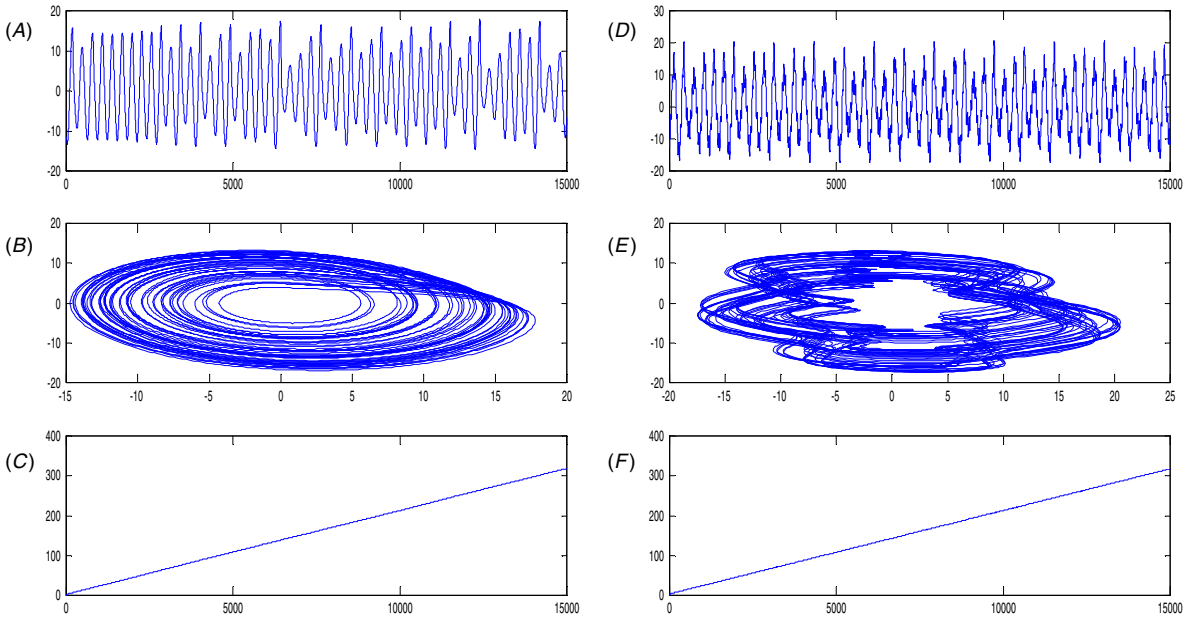

Figure 2. Burst waveform, reconstructed attractor and phase of the Rössler oscillator I. (*A*)–(*C*), no driving force ($A_1 = A_2 = 0$); (*D*)–(*F*), 50 Hz sinusoidal driving force ($A_1 = A_2 = 19$).

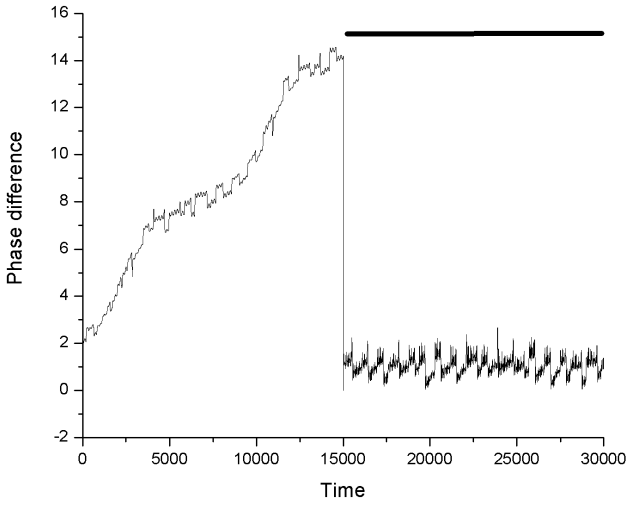

Figure 3. Phase difference of coupled Rössler oscillators I and II. With no applied stimulation ($A_1 = A_2 = 0$), the phase difference between the two slightly different oscillators ($w_1 = 1.025$, $w_2 = 0.975$) is plotted from time 0 to 15 000 and increased linearly with time; with a stimulus applied to the two oscillators ($A_1 = A_2 = 19$), the phase difference between them plotted from time 15 000 to 30 000 was restricted within 0 to π. In this and the following figures, the solid bar indicates the application of electric field at both sites and the dashed bar indicates the application of electric field at only one site.

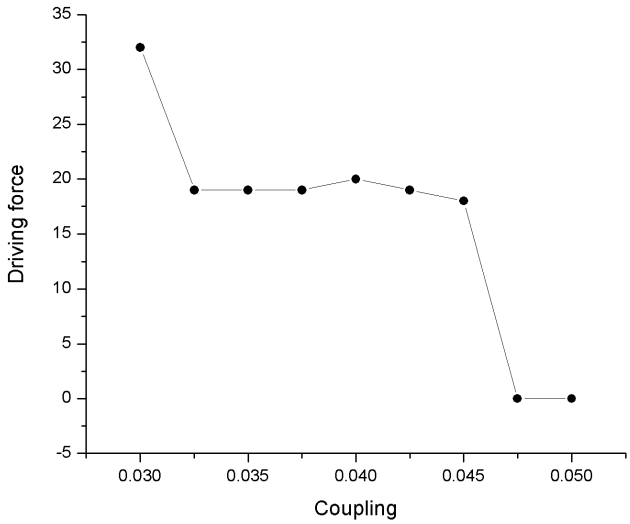

Figure 4. Relationship between minimum driving force and coupling coefficient for the PS of two Rössler oscillators. When the coupling coefficient was less than 0.030, the required driving force was larger than 60; for any coupling coefficient larger than 0.0475, no driving force was needed for synchronization.

increased monotonically with time in all cases. However, when sub-threshold stimulation was applied simultaneously to both sites, PS was achieved in 15 out of 17 slices tested with the application of sinusoidal 50 Hz current (21.1 $\pm$ 5.3 μA, $n = 15$). The minimum amplitude of the stimuli to evoke the neuronal activity was referred to as the threshold amplitude and the currents used to achieve PS are all sub-threshold. These successful cases can be divided into two groups, (1) PS of two signals with the same frequency ratio and (2) PS of two signals with different frequency ratios.

3.2.1. Phase synchronization of two signals with the same frequency ratio. Spontaneous seizure-like activity

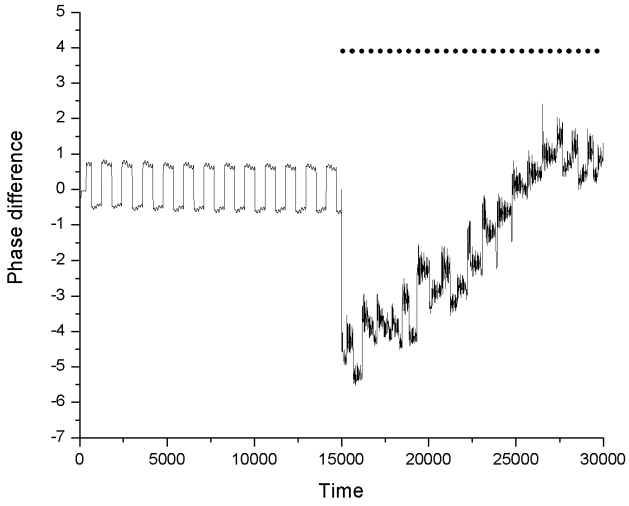

Figure 5. Desynchronization of two coupled Rössler oscillators. With no stimulus ($A_1 = A_2 = 0$), the phase difference between two identical oscillators ($w_1 = w_2 = 1.025$) was in a small range; when stimulus was applied to one oscillator only ($A_1 = 0$, $A_2 = 20$), PS between two oscillators plotted from time 15 000 to 30 000 was destroyed.

recorded at site A is shown in figure 6(*A*). The reconstructed attractor with rotation centre (0, 0) is shown in figure 6(*B*). Equations (1) and (2) were used to compute the phase of the signal (figure 6(*C*)). The phase increased by 2π for each complete burst cycle. Similarly, the attractor for site B was reconstructed and its phase calculated. The phase difference between A and B was calculated from equation (3) and plotted (figure 7(*A*), $0 < t < 150$ s). No consistent delay between the two signals was observed, with A either leading or lagging behind B. The phase difference curve between A and B varied in a large range (∼40), indicating strong desynchronization. Neural activity, attractor and phase at site A are shown in figure 6(*D*)–(*F*) during the application of sinusoidal electric fields at the two sites ($I = 15$ μA). Similarly, the phase was calculated for site B. The phase difference decreased to less than π as soon as the control was applied (figure 7(*A*), $150 < t < 300$ s). The small and relatively stable phase difference shown in figure 7(*A*) indicates that A could burst a little earlier or later than B, but the phase difference between them was never more than one half of a burst period. Similar results were found in all other slices. Two signals with phase difference as large as 28.7 ± 6.3 are all controlled to be in the PS state with a maximum phase difference of 2.6 ± 0.5 ($n = 5$).

3.2.2. Phase synchronization of two signals with different frequency ratios. Synchronization control experiments were also done for oscillations with different frequency ratios. Following the application of sinusoidal fields ($I = 15$ μA), two desynchronized oscillators with a 6:5 frequency

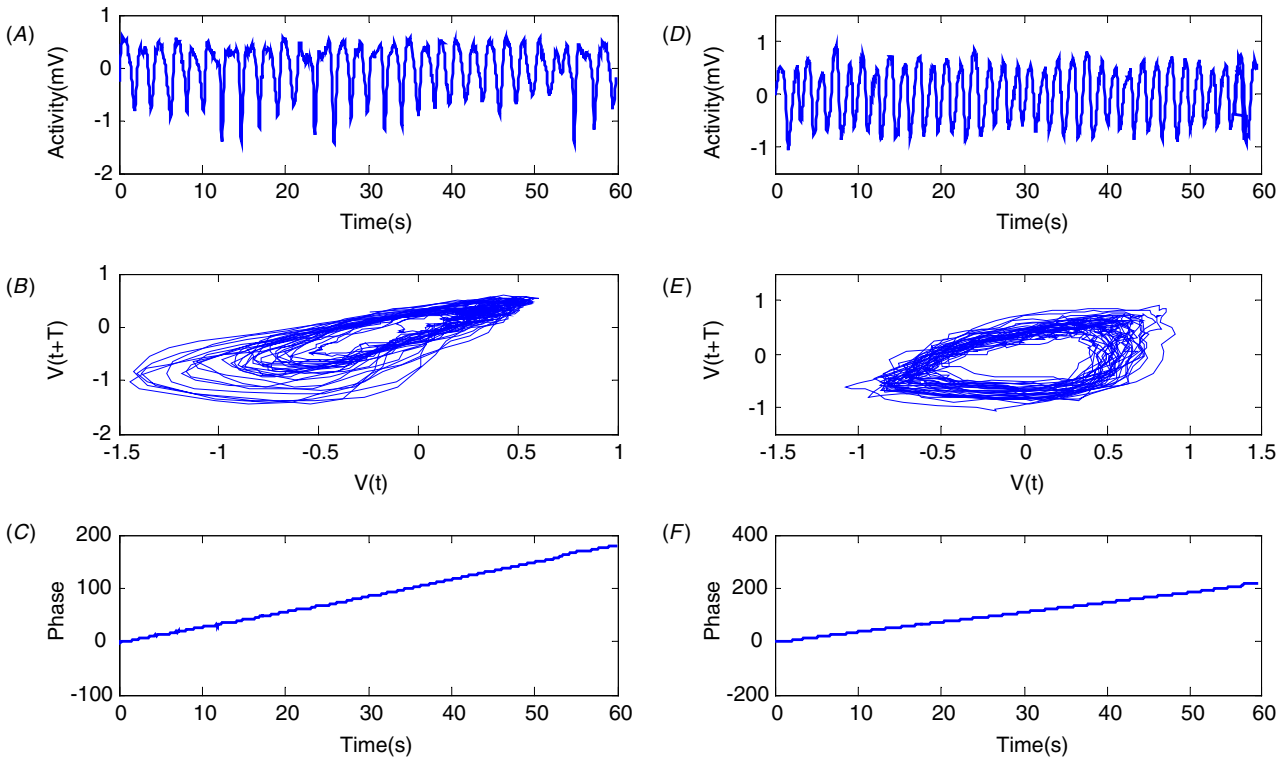

Figure 6. Phase of the seizure-like activity. (*A*) Spontaneous epileptiform activity induced by low calcium solution; (*B*) experimental data are represented by an attractor with time delay ($T = 4$) in the phase space. (*C*) Phase of the neuronal activity was calculated using equation (3) from attractor. (*D*)–(*F*) show the neural activity, attractor and phase respectively in the presence of sinusoidal stimulation applied at two sites.

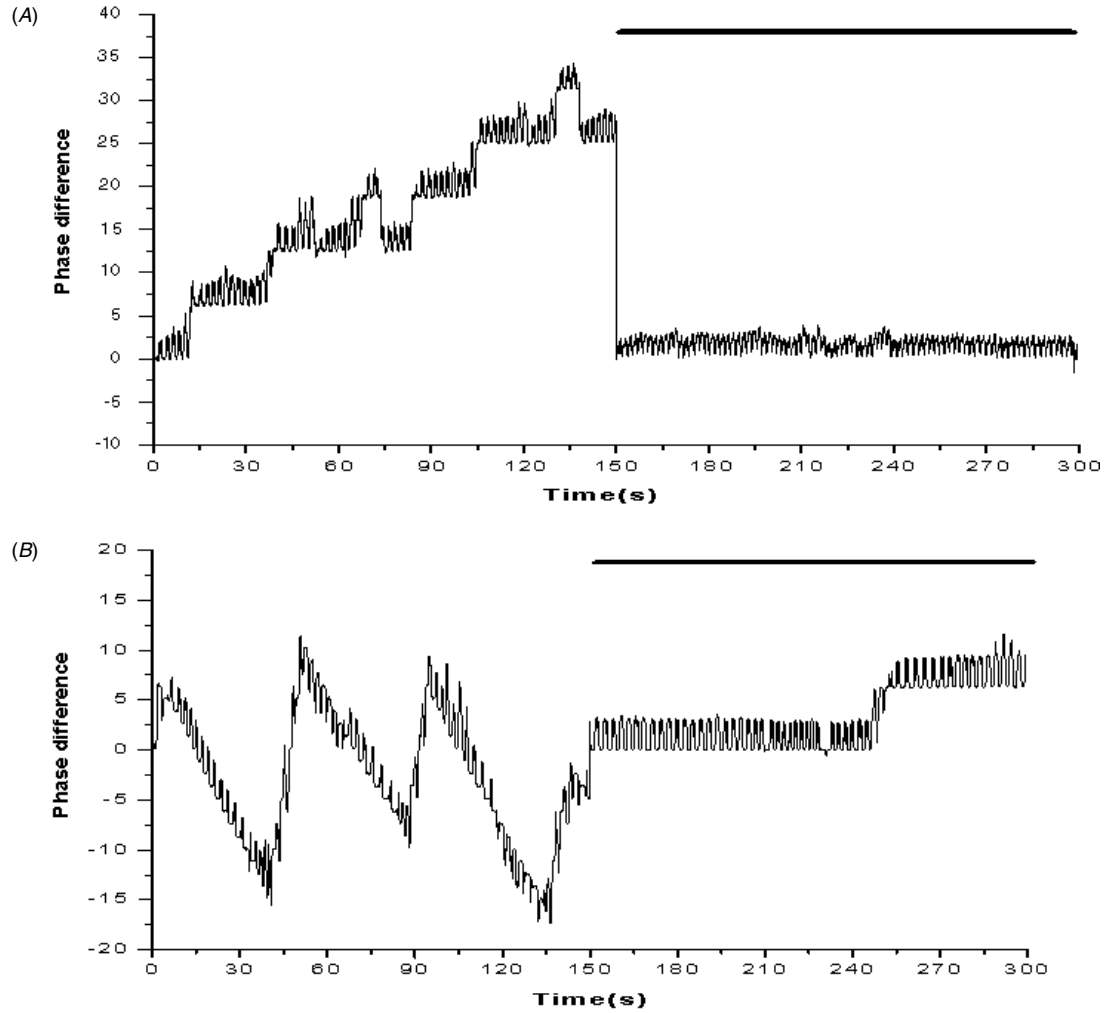

Figure 7. Phase synchronization of epileptiform activity. (*A*) From 1:1 to 1:1 frequency ratio. The phase difference between site A and B without stimulation increased with time (time 0 to 150 s), and phase difference decreased within the range of 0 to π when stimulation current was applied. (*B*) From 6:5 to 1:1 frequency ratio. The phase difference between sites A and B with applied stimulation (time 150 to 300 s) can occasionally display a 2π phase jump which is in contrast to the large oscillations of phase difference observed in the absence of stimulation (time 0 to 150 s).

ratio were controlled and phase synchronized to be 1:1 frequency ratio (figure 7(*B*)). The phase difference remains in a small range less than π with only an occasional instantaneous 2π phase slip. Similar results were found for activities with other frequency ratios such as 5:4 and 3:2 ($n = 10$). The phase difference decreased from 30.5 ± 6.5 to 2.4 ± 0.6 with the control stimulation applied.

3.2.3. Dynamical analyses of the signal. Dynamical analysis methods were used to characterize the properties of the oscillator. The C.V. of inter-event interval, ratios of standard deviation to mean inter-event interval, decreased significantly ($p < 0.001$; Student's *t*-test) from 13.6 ± 0.42 before the stimulation to 5.5 ± 0.008 under the influence of sinusoidal stimulation ($n = 15$). The maximum Lyapunov exponent also decreased from 0.51 ± 0.08 to 0.34 ± 0.05 ($n = 4$) but not significantly. These results show that the activity became more regular and predictable, suggesting that the individual dynamic properties of each sub-network are modulated by the external driving force.

3.2.4. Experiments in lesioned slices. In order to understand the role of interaction between neurons on PS, we studied the effect of stimulation on the lesioned slices. As reported above for intact slices, two stimuli were required to phase synchronize activities as stimulation electrode with single stimulus was found to be ineffective for achieving synchrony. A lesion was made through the entire thickness and across the entire width of the hippocampal slice between the two electrode recording sites. Consistent with our previous finding that epileptiform activity can propagate across the lesion (Lian *et al* 2001), we found that PS could also be achieved in lesioned but unseparated slices ($n = 3$). However, PS could not be achieved in separated halves either from the same slice or from different slices (1 mm distance separation; $n = 5$). These results support the idea that sub-threshold electrical

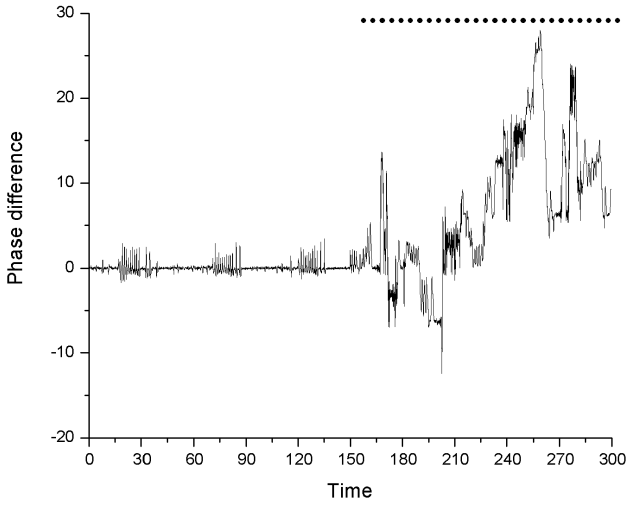

Figure 8. Desynchronization of epileptiform activity in the *in vitro* model. Low calcium neural signals from two sites (separated by 400 μm) were found synchronized (time 0 to 150 s). The application of 50 Hz stimulation (20 μA) at one of the two sites was found to generate desynchronization (time 150 to 300 s).

stimulation generates a non-synaptic signal responsible for the synchronization process capable of crossing a mechanical cut in the tissue.

3.2.5. Desynchronization by monopolar electrode stimulation. Consistent with the simulation results, desynchronization could also been generated *in vitro*. Two extracellular recording electrodes were positioned at around 400 μm and strong synchrony was observed (figure 8, $0 < t < 150$ s). Stimulation ($I = 20$ μA) applied from 150 s to 300 s at A was found to destroy synchrony between the two sites, as shown by a significantly increased phase difference (figure 8, $n = 3$). Further increase of stimulation intensity could cause local annihilation of activity as previously observed (Lian *et al* 2003). Similar results were obtained in all other slices tested and phase difference increased significantly from 3.1 ± 0.6 to 27.5 ± 7.1 ($n = 3$) ($p < 0.005$; Student's t-test).

4. Discussion

4.1. Mechanism of phase synchronization in computer model

Although the Rössler model is a simple system that ignores many physiological details such as ion flux in the extracellular space between neurons, its waveform and response to periodic stimuli mimic *in vitro* epileptiform activity. The attractor generated by each cell has a clear centre of rotation that can be used to calculate the phase. The two terms in equation (2), sinusoidal driving force ($A \sin(2\pi f t)$) and direct coupling ($e(x_2 - x_1)$) can be summed and thought of as a general coupling force between two oscillators. Increasing driving force intensity increases this general coupling and therefore helps to phase synchronize the two oscillators. Each oscillator will be more synchronized with its respective stimulus as the driving force A is increased (Pikovsky *et al* 1997). Since the two periodic driving forces are identical, the oscillators must become more synchronized with each other. The model also predicts that a single stimulus applied to one of the two oscillators can cause desynchronization of the two previously coupled and synchronized oscillators. This prediction on desynchronization, as well as the synchronization of two oscillators by the low-threshold simulation were successfully tested and reproduced in an *in vitro* slice preparation.

4.2. Mechanism of phase synchronization in in vitro experiment

The physiological mechanism for the *in vitro* PS results is much more complex than that in the Rössler oscillator system. Our results suggest that the PS in low calcium activity driven by sinusoidal electrical fields depends on both the intrinsic sub-network properties and the coupling forces between separated regions. Several observations support this hypothesis: (1) stimulation results in a decrease of the coefficient of variation of the inter-event interval and a small decrease in the Lyapunov exponents implying that individual activity becomes more regular. Therefore, the dynamic properties of each oscillator were probably altered by the external periodic driving force; (2) the *in vitro* neuronal activity used in this study was induced by a low calcium solution that blocks synaptic transmission. Therefore, synaptic transmission between neurons is not required for the synchronization of low calcium activity; (3) PS was observed in lesioned but not separated slices. This result shows that similar inputs applied to separate regions of the neural tissue can synchronize neuronal activity through a complete cut of the neural tissue. Therefore, the synchronization mechanism in this low-calcium model does not require synaptic transmission or gap junctions. Previous experiments in the same preparations have eliminated ephaptic interactions as a possible mechanism and shown that the synchronization signal going through the cut is a small propagating increase in extracellular potassium concentration (Lian *et al* 2003). Moreover, the results suggest that this non-synaptic synchronization signal can be induced by sub-threshold electrical stimulation applied across a distance as large as 700 μm. The synchronization effects produced by both intrinsic neuronal properties and changes in the coupling between the two regions could be related. Computer simulations have shown that the Lyapunov coefficients decrease when a system of coupled neurons is synchronized by increased coupling coefficients (Dhamala *et al* 2004).

Although sustained phase synchronization could be induced by applying 50 Hz sub-threshold stimulation, phase desynchronization could also be generated and could be used to control abnormal neural activity. Desynchronization of the activity generated at two sites previously synchronized was achieved both in computer simulations and in *in vitro* experiments by sub-threshold stimulation at only one of the two recording sites. The desynchronization effect requires a small signal amplitude since strong stimulation at this frequency would produce neural suppression (Lian *et al* 2003) but large enough to disrupt the synchronizing signals between the two sites. The mechanism of this desynchronization is

not clear. Desynchronization of neural activity was previously achieved in penicillin induced epileptiform activity (Durand and Warman 1994). The mechanism of this desynchronization required a single well-timed pulse with a latency that could be described by phase resetting analysis. More recently, Tass (2002) has shown that a phase stochastic approach can be used to desynchronize the activity of a large cluster of phase coupled oscillators with composite signals including high frequency sinusoidal waveforms. It is unlikely that this soft phase resetting mechanism plays a role in the desynchronization of the epileptiform activity reported above since it requires both a sinusoidal stimulation (synchronization) followed by a single pulse (desynchronization). However, the sinusoidal stimulation applied to one site could modify the properties of the oscillator in a region around the electrode thereby producing desynchronization with respect to the other site.

4.3. Role of synchrony in the brain

A major focus of understanding neural processing is synchronization between groups of neurons, ranging from individual pairs to much larger networks both within one area of the brain and between different regions of the brain (Bawin *et al* 1973, Bressler *et al* 1993, Elson *et al* 1998). Rhythmic activity in the brain has proven to have a tremendous capacity to influence the processing and transfer of information (Fitzgerald 1999). It is unclear whether synchronous rhythms require specific intrinsic properties of individual neurons or if such rhythmic activity emerges chiefly from interactions in large neuronal networks (Durand 1993).

It has been suggested that all useful computations in the brain are performed in states of partial synchrony: unrelated signals from individual neurons are useless for information processing (Fitzgerald 1999). PS analysis is currently one of the best quantitative methods for identifying states of partial synchrony (Hu and Zhou 2000, Shuai and Durand 1999). Small rhythmic electrical activities are measured in the brain by an electroencephalogram (EEG) and are well established to be related to specific states such as waking or sleep (Kandel *et al* 2000). We have demonstrated for the first time that sub-threshold sinusoidal fields can generate PS of neural populations *in vitro*. Our results suggest that different areas of the brain can respond to sub-threshold stimuli and the signal does not have to depend on axon propagation, gap junctions or synaptic transmission.

Excessive synchronization can lead to pathological conditions such as epilepsy (Fitzgerald 1999, Schiff 1998) which is characterized by a sudden, synchronized and disproportionate discharge in a population of neurons. The desynchronization of this abnormal neural activity is of special interest for the treatment of epilepsy (Durand 1986, Durand and Warman 1994). Modulation of neuronal dynamics, such as phase resetting (Hahn and Durand 2001), chaos control (Schiff *et al* 1994), and desynchronization of neural populations (Durand and Warman 1994) have been proposed as methods to annihilate seizure-like activity (Durand and Bikson 2001). We have demonstrated that it is possible to desynchronize the activities in two sites with a localized stimulus that could modulate local activity and possibly alter the strength of couplings between groups of neurons by raising the extracellular potassium concentration (Bikson *et al* 2001, Lian *et al* 2003). The results show that a single, low amplitude stimulus in one region of neural tissue can effectively desynchronize the activity of that region from another region. This effect could generate a functional disruption of the abnormal neural messages and explain some of the effect of deep brain stimulation electrodes (Benabid 2003).

In conclusion, both computer simulation using coupled Rössler oscillators and brain slice experiments have shown that it is possible to control the phase synchronization between the activity of two neural sites with small amplitude sub-threshold sinusoidal signals in the gamma frequency range. The applied stimulation generates small amplitude non-synaptic signals that can synchronize neural activity over large distances and across a complete mechanical cut of the tissue. Desynchronization can also be produced and this effect could have important consequences for the control of epilepsy.

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