Invited Review

Neural oscillations and information flow associated with synaptic plasticity

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Abstract: As a rhythmic neural activity, neural oscillation exists all over the nervous system, in structures as diverse as the cerebral cortex, hippocampus, subcortical nuclei and sense organs. This review firstly presents some evidence that synchronous neural oscillations in theta and gamma bands reveal much about the origin and nature of cognitive processes such as learning and memory. And then it introduces the novel analyzing algorithms of neural oscillations, which is a directionality index of neural information flow (NIF) as a measure of synaptic plasticity. An example of application used such an analyzing algorithms of neural oscillations has been provided.

Key words: synaptic plasticity; neural oscillation; neural information flow; cognitive functions; weak coupling

与突触可塑性相关的神经振荡和信息流研究

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摘 要：作为一种有节律的神经活动，神经振荡现象发生在所有的神经系统中，例如大脑皮层、海马、皮层下神经核团以及感觉器官。本综述首先给出了已有的研究结果，即基于theta和gamma频段的同步神经振荡揭示了认知过程的起源与本质，如学习与记忆。然后介绍了关于神经振荡分析的新技术和算法，如表征神经元突触可塑性的神经信息流方向指数，并例举了神经振荡分析的一个新方法以及其应用实例。

关键词：突触可塑性；神经振荡；神经信息流；认知功能；弱耦合
中图分类号：Q42；R338

Neural oscillation is rhythmic or repetitive neural activity and appears throughout the nervous system, in structures as diverse as the cerebral cortex, hippocampus, subcortical nuclei and sense organs[1]. They are present in the intracellular voltages, individual spike trains and/or in local field potentials generated by populations of synchronized cells. Neural tissue can produce oscillatory activity in many ways, driven either by mechanisms localized within individual neurons or by feedback interactions among populations of neurons. In individual neurons, oscillations can appear either as subthreshold rhythms of membrane potential rise and fall, or as rhythmic increases and decreases in action potential activity, which then produce rhythmic activation of synapses in target neurons. At the level of neural population, synchronized oscillations of large numbers of neurons can give rise to macroscopic oscillatory electric fields, which can be observed in the electroencephalogram (EEG).

It is alpha rhythm, ranged from 8 to 12 Hz, which was described as the first human EEG pattern. From scalp recordings, researchers identified various other oscillatory patterns that were particularly obvious during rest and sleep[2]. Previous investigation reported

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that even single neurons were endowed with complex dynamics, including their intrinsic abilities to resonate and oscillate at multiple frequencies, which suggested that precise timing of their activity within neuronal networks could present information[3]. The synchronous activity of oscillating neural networks has been considered to be the critical "middle ground" linking single-neuron activity to behavior[4–6]. The research area related to neuronal oscillations has created an interdisciplinary

platform that cuts across several disciplines, such as psychophysics, cognitive psychology, neuroscience, biophysics, computational modeling, physics, mathematics, and philosophy[7].

1　Neural oscillations

It shows that neuronal networks in the mammalian forebrain demonstrate several oscillatory bands cover-
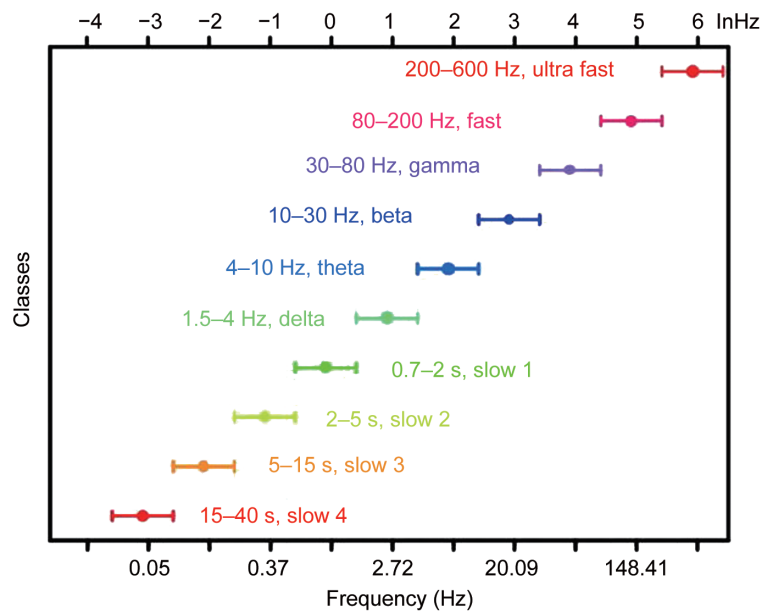

Fig. 1. Oscillatory class in the rat cortex. Note the linear progression of the frequency classes on the scale of natural logarithm. For each band, the range of frequencies is shown, together with its commonly used term. Adopted with permission from Buzsaki *et al*. [2].

ing frequencies from approximately 0.025 Hz to 600 Hz (Fig. 1). The mean frequencies of oscillator categories form a linear progression on a natural logarithmic scale with constant ratio between neighboring frequencies, leading to the separation of frequency bands[8]. Neighboring frequency bands within the same neuronal network are typically associated with different brain states and compete with each other. On the other hand, several rhythms can temporally coexist in the same or different structures and interact with each other[2, 9]. Figure 2 shows that the power spectrum of EEG or local field potential (LFP) is inversely proportional to frequency (f) in the mammalian cortex[2]. The $1/f$ power relationship means that perturbations occurring at slow frequencies can bring out a cascade of energy dissipation at higher frequencies. Furthermore, it implies that widespread slow oscillations modulate faster local events[10]. The properties of neural oscillators are the
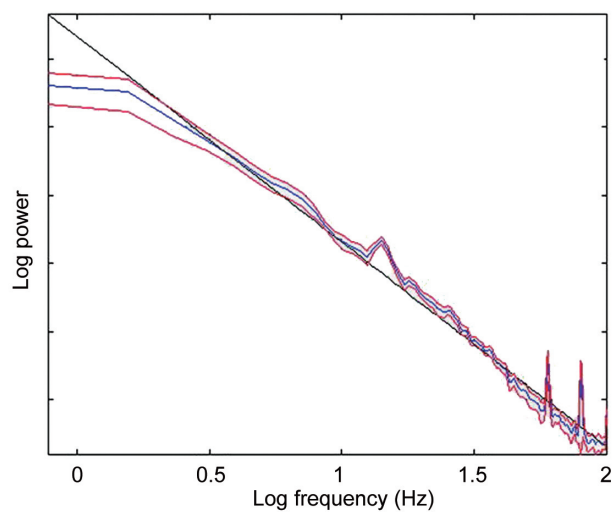

Fig. 2. Power spectrum of EEG from the right temporal lobe in a sleeping subject. Note the near-linear decrease of log power with increasing log frequency from 0.5 to 100 Hz. Adopted with permission from Buzsaki *et al*. [2].

results of the physical architectures of neural networks and the restricted speed of neural communication because of axon conduction and synaptic delay[2]. The period of oscillation is constrained by the size of the neural pool engaged in a given cycle since most neural connections are local. Large networks are recruited during slow oscillations, while higher frequency oscillations are restricted to a small neuronal space[9]. These relations between anatomical architecture oscillatory patterns let brain operations to be performed simultaneously at multiple temporal and spatial scales[2].

2　Theta and gamma oscillations govern cognitive processes of learning and memory

As oscillatory responses to a cognitive event, evoked or event-related oscillations are usually classified according to the 'natural frequencies' of the brain (delta 0.5–3 Hz, theta 3–8 Hz, alpha 8–13 Hz and gamma 30–80 Hz). As will become clear below, this approach is well suited for comparative analysis of findings at the level of single neurons, field potentials, EEG or magnetoencephalogram (MEG)[11].

It is important to note that the most general dynamics in the brain are governed by the brain's natural oscillations. The neural oscillations provide basic links to brain functions, especially for communication and associated functions. Because learning and memory processes are most closely related to theta and gamma rhythms, recently, many neuroscientists have been associating the theta and gamma bands with the expression 'oscillations' and these two frequencies bands are treated extensively. It is argued that selectively distributed theta and gamma oscillatory systems act as resonant communication networks through large populations of neurons. Thus, oscillatory processes might play a major role in functional communication in the brain in relation to learning and memory[11].

2.1　Theta oscillations

Theta power tends to increase in memory tasks, especially during encoding. These complementary efforts were considered to display different cognitive operations. Although theta oscillations have been found in lower animals such as rats, they are seldom directly in EEG recordings from humans and it has been difficult to understand what the classically-observed increases in theta power meant[12]. However, intracranial EEG (iEEG) recordings obtained from epileptic patients have recently uncovered significant theta oscilla-

tions from many areas of the human brain[13, 14]. In the experiments, periods with apparent theta oscillations were more frequent when patients were navigating through a virtual maze by memory alone, relative to when they were guided through the maze by arrow cues. The theta periods were longer the longer the maze. Theta did not covary, however, with the time taken to make decisions at choice points; instead gamma oscillations were more prevalent the longer the decision time. Thus, theta oscillations are more closely linked to encoding and retrieval in memory than they are to other cognitive processes[15].

The theta rhythm is a LFP oscillation in the 4–10 Hz frequency range that has long been recognized as the defining electrophysiological signature of hippocampal activity[16]. It is well known that theta oscillations are able to modulate neural activity not only within the hippocampus, but also in subcortical, limbic, and cortical structures. Therefore, theta oscillations play a ubiquitous property of neural networks, and phase locking to theta oscillations appears to be an important organizing principle of neural activity during awake behavior and rapid eye movement (REM) sleep[17].

Theta oscillations represent the "on-line" state of the hippocampus. The rhythm is believed to be critical for temporal coding/decoding of active neuronal ensembles and the modification of synaptic weights[16]. Theta oscillation is the most regular in frequency and largest amplitude in the stratum lacunosum-moleculare of the hippocampal CA1 region. Both the amplitude and phase of theta waves change as a function of depth, whereas in the same layers they are robustly similar along the long axis of the hippocampus. In addition to the hippocampus, theta oscillations and phase-locked discharge of neurons to theta waves have been observed in several other structures, which are thus the main current generators of the extracellularly recorded theta field. However, none of these cortical structures are capable of generating theta activity on their own. Several subcortical nuclei have been postulated to be critically involved in the rhythm generation of theta. Afferents from these nuclei may release neurotransmitters that may allow for the emergence of network oscillations in the hippocampus and associated structures or may provide a coherent, theta frequency output[16]. Because lesion or inactivation of medial septum-diagonal band of Broca (MS-DBB) neurons abolishes theta waves in all cortical targets, it has been regarded as the ultimate rhythm generator of theta[18]. The minimum
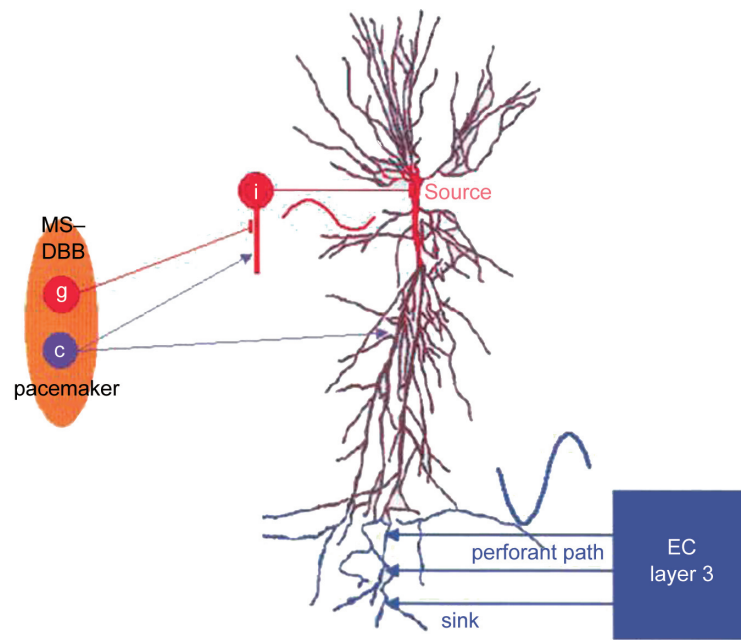
Fig. 3. "Classic" model of extracellular theta current generation. Adopted with permission from Buzsaki (2002) [16].

conditions necessary for the generation of oscillating extracellular currents in the theta frequency band are the proper connections between the hippocampus and the MS-DBB.

The MS-DBB has been assumed to be the rhythm generator which supplies phasic modulation to the hippocampus in the first theta model. Figure 3 shows subsequent theta models with new components. It is assumed that the extracellular field is generated by the summed activity of IPSPs and EPSPs on the somata and dendrites of principle cells, respectively. These models used a single canonical CA1 pyramidal cell with passive membrane properties. It has been supposed that all pyramidal neurons obtain coherent excitatory (from perforant path) and inhibitory (from septum to feed-forward inhibitory neuron) inputs. The interaction between these two current generators (dipoles) is assumed to be responsible for the unique amplitude/phase *versus* depth profiles of hippocampal theta oscillation.

It is an important issue about hippocampal plasticity during theta oscillations. Several observations imply that theta oscillations may be involved in synaptic plasticity. Many studies either *in vitro* or *in vivo* have reported that induction of long-term potentiation (LTP) is optimal when the time interval between stimuli is approximately 200 ms[19]. Rhythmic stimulation at theta frequency is not needed though and two high-frequency bursts are sufficient. Why is potentiation so efficient during theta? Various factors that act in concert during the theta cycle may be responsible. When theta-like oscillation is induced in the slice by carbachol, part of the effect may be explained by the drug's blocking effect of $GABA_A$ receptor. Thus, theta oscillation may provide a mechanism for bringing together in time afferent-induced depolarization of pyramidal cell dendrites and dendritic invasion of fast spikes, the key elements for the induction of synaptic plasticity. During theta oscillation, for example, repeated pairing of distal dendritic depolarization by the entorhinal input and the trisynaptically activated CA3 recurrent/Schaffer collaterals to CA3 and CA1 pyramidal cells can result in synaptic modification of the intra-hippocampal associational pathways. As a result, these modified pathways will give rise to endogenous population patterns in the absence of the entorhinal inputs during non-theta activity. Reactivation of the same synapses can further strengthen their efficacy. The synaptic modification, brought about by the two-step process, in turn, will allow memory retrieval. The significance of theta oscillations is that they reliably correlate with a variety of behaviors. The theta *versus* non-theta dichotomy objectively groups behaviors into preparatory *versus* consummatory classes.

2.2 Gamma oscillations

Synchronous gamma activity has been observed in numerous structures. *In vivo*, in the hippocampus, this oscillation appears to be controlled by the dentate gyrus

and to project CA3 and CA1[20]. Gamma oscillations are considered to momentarily connect distributed neuron assemblies that are processing related information[21, 22], a function that is almost certainly essential for network processes such as memory[23]. This 'binding' mechanism requires that spatially distributed neurons fire together with millisecond range precision[6]. Evoked or spontaneous gamma-band activity of LFPs is involved in information processing in many brain regions, including the hippocampus and cortex[24].

Neural oscillations in the gamma band play an important role in learning and memory processing. Intracranial EEG recordings, obtained from epileptic patients memorizing words, reveal that during successful memory formation the rhinal cortex is first coupled to the hippocampus via 40 Hz gamma oscillations and then decoupled from it[25]. Gamma oscillations have been implied to be a common mechanism for accomplishing such transient coupling of functional brain areas based on evidence of gamma band coherence across the brain during associative learning[15]. Furthermore, during successful recollection, as opposed to merely experiencing a feeling of familiarity, there is greater gamma-band functional connectivity between frontal and parietal cortex along with more spectral power in both theta and gamma bands[26]. The phenomenon that gamma-band activity was observed to be modulated at the theta rate suggested that interactions of gamma and theta activity might be involved in memory function[15].

Among the models of memory processes it was suggested linking neural oscillations to memory processes. Memories were stored in groups of pyramidal neurons firing in synchrony in the model. The synchronous firing leans to dissipate with time and requires being refreshed periodically. The individual memories were refreshed at the gamma frequency and the overall refresh cycle was replicated at the theta frequency[15]. The model needs that gamma oscillation, which were collected from human cortex, modulated at the theta frequency band in the human brain.

Several studies indicated that there was a relationship between cognitive function and the gamma-band power of the LFP[27]. In the previous investigation, the effects of synaptic plasticity on the gamma-band power of the LFP were determined [28–30]. Furthermore, gamma-band power elevation was observed in LTP but not in long-term depression in posterior dorsal hippocampus CA1 (pdCA1)-prefrontal cortex (PFC)[27]. The sustained elevation of gamma-band activity appears to be related to

the working memory functions because memory representation is required to sustain neural activity patterns in the PFC. Gamma-band frequencies in the LFPs of many regions of the brain are involved in highly integrated functions, including information binding, attention and working memory. It has been suggested that different sets of neurons in a network (neuron assemblies), which correspond to diverse information from each group, fire in different gamma cycles or at different gamma frequencies[31]. The strength of synaptic connectivity may have some correlation with the spontaneous gamma-band powers[27]. Synaptic plasticity such as LTP, which is believed to be a neural basis for memory functions, appears to enable neuron assemblies to be dynamic. Taken together, the synaptic plasticity may be reflected in gamma-band frequencies.

3 Detecting and measuring neural oscillations

Neural oscillators belong to limited-cycle and weakly chaotic oscillators and share features of both harmonic and relaxation oscillators[32]. The macroscopic appearance of several brain rhythms, such as the theta and gamma oscillations, resembles the sinusoid pattern of harmonic oscillators. A major advantage of harmonic oscillators is that their long-term behavior can be predicted from short-term observations of their phase angle[32]. Nevertheless, groups of harmonic oscillators poorly synchronize their phases. On the other hand, the macroscopic oscillations are generated by neurons, whose spiking patterns share characteristic with relaxation oscillators. Relaxation oscillators synchronize robustly and with great stability[33].

The strength of neural oscillations can be assessed in both time and frequency domains. In the time domain, oscillations in spike trains are measured by means of periodic peaks in the autocorrelogram; in the frequency domain, power spectral analysis is applied to characterize their frequency features. However, the autocorrelograms are subject to confounds caused by the refractory period and spectral peaks often fail to reveal weak rhythms[1]. Another approach, named oscillation score, reduces these problems[34]. It combines analyses in the time and frequency domains to show the strength of oscillations as one dimensionless number. Also, oscillations shared by local groups of cells can be detected in population responses, such as the LFP or in patterns of synaptic input.

Furthermore, traditional cross-correlation techniques

only provide symmetric estimates of the strength of interaction. Importantly, they lack significant information about causal relationships in interactions, that is, directionality and asymmetry of coupling. Such information is crucial in unraveling the structure of a system from observation of signals from its several components. Recently, several algorithms were proposed to deal with the issue of causality. Approaches based on the concept of generalized chaos synchronization were developed[35] and were applied to experimental neurophysiologic data. These methods are based on mutual nonlinear predictabilities or mutual nearest neighbors in the reconstructed phase space of the system. They are similar to the concept of Granger causality[36] where statistical tests are used to inquire whether the predictability of one time series can be improved by the knowledge of a second signal.

In many cases, particularly in neuroscience, interacting physiological subsystems can be represented by weakly coupled nonlinear oscillators, so that information about the instantaneous phases of oscillators is sufficient to describe their dynamics [37]. To determine directionality of weak coupling between two neural subsystems, two approaches, which quantify the direction of coupling between the phases of two oscillatory (sub-) systems, are introduced in this review. One of them, named evolution map approach (EMA), was proposed by Rosenblum and Pikovsky[38], and then improved by Smirnov and Andrzejak[39]. Another algorithm, which was developed in knowledge of information-theoretic measures, is called conditional mutual information (IM).

It is well known that the phase dynamics technique is a particularly useful approach to investigating physiological oscillations, because it can deal with their time-variable nature, and lets us to study their amplitudes and phases separately. It can reveal the underlying rules that contribute to the deterministic part of the variability, thus yielding evidence about its physiological origins. It also illuminates the question of whether causal relationships exist between the oscillations, and whether some or all of the time variability results from a uni-directional interaction[40].

4 EMA

The directionality index[38] is a measure for directional influences based on hypothesis of weak coupling in self-sustained systems. Main features of EMA are ro-

bustness against noise and small influence of frequency mismatch[38, 41]. This technique has been successfully applied not only to model systems[42], but also to EEG data from epileptic patients[39, 43] and Alzheimer's patients[44], MEG motor control experiment[45], experimental time series data from electroreceptors of paddlefish[37], and intracranial EEG between human neocortex and hippocampus[46].

The most important idea of this approach is to model the phase dynamics of two systems

$$\dot{\phi}_{1,2} = \omega_{1,2} + q_{1,2}(\phi_{1,2}) + \varepsilon_{1,2} f_{1,2}(\phi_{1,2}, \phi_{2,1}) + \xi_{1,2}(t),$$

and fit the parameters in $f_{1,2}$ using aligned Fourier series

$$F_{1,2} = \sum_{m,l} A_{m,l} e^{im\phi_1 + il\phi_2}.$$

The mutual influence of the systems was quantified by the coefficients

$$c_{1,2}^2 = \int_0^{2\pi}\int_0^{2\pi} \left(\frac{\partial F_{1,2}}{\partial \phi_{2,1}}\right)^2 d\phi_1 d\phi_2.$$

Then we can calculate their coupling direction and denote the direction index as

$$d^{(1,2)} = \frac{c_2 - c_1}{c_2 + c_1},$$

where coefficients c_2 and c_1 describe cross-dependence in $X_1 \rightarrow X_2$ and $X_2 \rightarrow X_1$ respectively, obtained by fitting it in the least mean square sense. As a result, $d^{(1,2)}$ is normalized to the range between [−1, 1], which means system 1 predominantly drives system 2 in the case of a positive directionality index and vice versa[46]. In addition, coefficients c_2 and c_1 can be used to analyze unidirectional information transfer, which describe cross-dependence in $X_1 \rightarrow X_2$ and $X_2 \rightarrow X_1$ respectively, obtained by fitting it in the least mean square sense. We normalized $c_{1,2}$ with $c_{1,2}^0 = \dfrac{c_{1,2}}{c_1 + c_2}$ to limit it in [0, 1]. To extract instantaneous phase, Hilbert transform is applied, which obtains the phase approximately from the original broadband signals in a frequency adaptive manner.

5 IM - A directionality index based on conditional mutual information

It is proposed and applied to the instantaneous phases of weakly coupled oscillators[47, 48], with which the coupling direction between oscillators can be identified. Main features of IM are suitability of aperiodicity exhibited in EEG signals and robustness against noise and its advantage is that it can reveal and quantify the pos-

sible asymmetry in the couplings. This technique has been successfully applied not only to model systems[48–50], but also to EEG data from epileptic patients[51] and rats in different levels of anaesthesia[40], as well as to the amplitude and frequency of cardiac oscillations[52]. However, the IM estimator is quite sensitive to the length of data sequence, while the bias and variance of IM reduces with the increasing length of data sequence. The simulation results exhibit that the IM can reliably detect the coupling direction between two chaotic oscillators if the length of data sequence is larger than 10^4.

Generally, the mutual information $I(X;Y)$ of two random variables X and Y is given by

$$I(X;Y) = H(X) + H(Y) - H(X,Y).$$

Given the variable Z, the conditional mutual information is defined as

$$I(X;Y|Z) = H(X|Z) + H(Y|Z) - H(X,Y|Z). \quad (1)$$

Supposing two processes $\{X_1\}$ and $\{X_2\}$, their instantaneous phases $\phi_1(t)$ and $\phi_2(t)$ [38, 41] can be estimated by application of the discrete Hilbert transform[53], which obtains the phase approximately from the original broadband signals in a frequency adaptive manner. Next, we can estimate the "net" information about the $\tau - \text{future}$ of the process $\{X_1\}$ contained in process $\{X_2\}$ (or the $\tau - \text{future}$ of the process $\{X_2\}$ contained in process $\{X_1\}$) using $I(\phi_2;\phi_{1\tau}|\phi_1)$ (or $I(\phi_1;\phi_{2\tau}|\phi_2)$), to infer the coupling directionality [48]. To establish possible causality relations, we consider phase increments

$$\Delta_\tau \phi_{1,2} = \phi_{1,2}(t+\tau) - \phi_{1,2}(t).$$

Then the conditional mutual information is $I(\phi_{1,2}(t); \Delta_\tau \phi_{2,1}|\phi_{2,1}(t))$. Now, the directionality index is calculated by

$$D(1,2) = \frac{i(1 \to 2) - i(2 \to 1)}{i(1 \to 2) + i(2 \to 1)} \quad (2)$$

where the measure $i(1 \to 2)$ and $i(2 \to 1)$ are defined using the conditional mutual information $I(\phi_1(t); \Delta_\tau \phi_2|\phi_2(t))$ and $I(\phi_2(t); \Delta_\tau \phi_1|\phi_1(t))$. $D(1,2)$ should be positive if system 1 drives system 2, and negative for the opposite case. $D(1,2) = 0$ means that the interactions between the two systems are symmetrical.

6 Directionality index of neural information flow (NIF) in delta and theta bands as a measure of synaptic plasticity

Synaptic plasticity is well understood to comprise the cellular basis for memory formation and cognition. Growing attention has recently been focused on LTP of PFC, because of its close relationship with cognitive function, which can be found altered in depression[54]. A recent study demonstrated that synaptic plasticity of laterodorsal thalamic nucleus (LD) to PFC pathway was impaired in an animal model of psychiatric diseases[55]. It is well known that NIF is constrained by the synaptic linkage. Obviously, it is not enough to reveal how transmit information passed through nerve pathway by handling structural changes alone. Recently, transmissions of neural signals have been measured by various algorithms[56], by which the directionality of NIF can be determined[57–59]. Because interacting neural subsystems can be represented by weakly coupled nonlinear oscillators, information about the instantaneous phases of oscillators is sufficient to describe their dynamics[37]. To determine directionality of weak coupling between two neural subsystems, a method named EMA was proposed by Rosenblum and Pikovsky[38] and then improved by Smirnov and Andrzejak[39]. Recently, Zheng *et al*. introduced EMA to measure the direction of information flow between the medial prefrontal cortex (mPFC) and thalamus and tried to address an issue as to whether the directionality of NIF can be used to index the measurement of synaptic plasticity in the chronic unpredictable stress (CUS) animal model[60]. This was done by inducing LTP of the thalamocortical pathway after recording LFP at the same two locations in Wistar rats of both CUS and control groups.

The LFP were filtered by FIR filter into delta and theta bands. The phase series by means of Hilbert transform was extracted and the directional index d and the unidirectional influence c_2^0 between two filtered time series were calculated. EMA analysis of thalamus-PFC pathway in rats between both states was showed (Fig. 4*A*). There was significant difference of the directional index d between the normal and CUS rats (Fig. 4*A1*). Furthermore, the group values of the unidirectional influence c_2^0, indicating the unidirectional coupling thalamus-PFC were presented in Fig. 4*A2*, and it was found that the unidirectional influence of NIF in normal Wistar rats was significantly higher than that in stressed rats[60]. Data representing the time course of fEPSP (field excitatory postsynaptic plasticity) slopes normalized to the 30 min baseline period was exhibited in Fig.
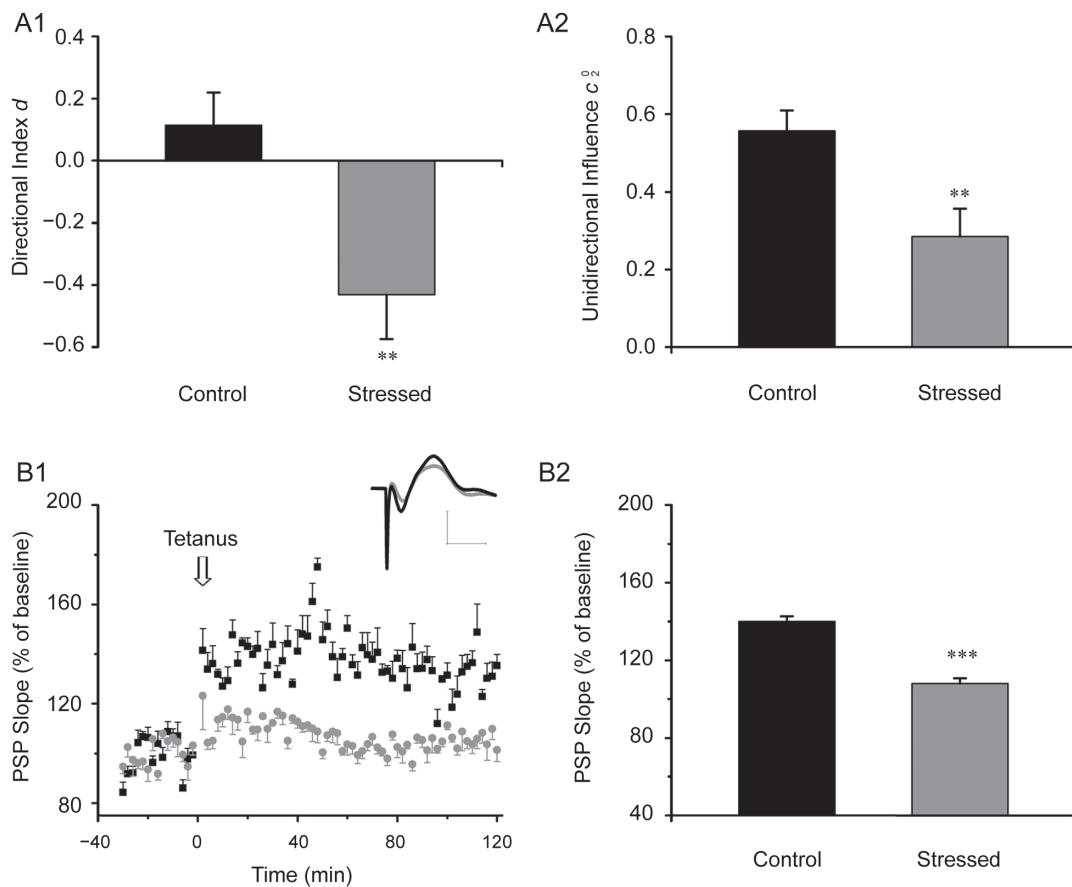
Fig. 4. The effects of chronic stress on directional coupling analysis of thalamus and cortex and fEPSP slopes of LTP. *A1*: Coupling direction index *d* between thalamus and cortex in both control and stressed groups. *A2*: Normalized unidirectional influence index c_2^0, indicating thalamus to cortex in both control and stressed groups. *B1*: Time coursing changes in PSP slopes. *B2*: Mean fEPSP slopes of 6 time points in two groups. ** $P < 0.01$ and *** $P < 0.001$ *vs* control group. Adopted from Zheng *et al*. (2011)[60].

4*B1*. The fEPSP slopes increased immediately after the high-frequency stimulation and stabilized to a level above the baseline period. For further statistical analysis, Student's *t*-test of mean fEPSP slope of the 6 time points was applied in the two groups, which presented that the mean fEPSP slope was statistically smaller in CUS animals compared with that in normal Wistar rats (Fig. 4*B2*).

7 Neural oscillations and synaptic plasticity

Although indirect, several observations suggest the possible involvement of theta oscillations in synaptic plasticity. A number of *in vitro* and *in vivo* studies have reported that induction of LTP is optimal when the time interval between stimuli is approximately 200 ms. Studies suggest a relationship between neural oscillatory bands, such as theta and gamma, and behavioral states. However, few studies have examined the synap-

tic plasticity and neural activity of LFPs in various frequency bands. An issue has been raised as to whether the directionality index of NIF, based on different oscillatory bands, could be used to index the measurement of synaptic plasticity. EMA analysis showed that the coupling direction index was significantly diverted in pathological condition compared to that in normal state[60], suggested that the pattern of information flow in delta and theta bands was drastically affected in CUS animal model. Moreover, the nonnegative index *c2* showed that the strength of thalamus driving frontal cortex was considerably decreased in the rats of CUS model[60], suggested that the cognitive dysfunction could be in part caused by the reduction of information transfer along the thalamocortical pathway. Meanwhile, the LTP experiments showed that chronic stress decreased mPFC synaptic plasticity, which was undoubtedly in accordance with the LFP findings. Together these results showed that using EMA method, direc-

tionality index of NIF may be as a measure of synaptic plasticity. However, phase-based approaches are still at an early stage of development. It remains an open question if phase-based directionality methods are best fitted to identify the neuronal mechanisms underlying functional interactions between brain areas.

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