Two generalized algorithms measuring phase–amplitude cross-frequency coupling in neuronal oscillations network

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Abstract An increasing number of studies pays attention to cross-frequency coupling in neuronal oscillations network, as it is considered to play an important role in exchanging and integrating of information. In this study, two generalized algorithms, phase–amplitude coupling-evolution map approach and phase–amplitude coupling-conditional mutual information which have been developed and applied originally in an identical rhythm, are generalized to measure cross-frequency coupling. The effectiveness of quantitatively distinguishing the changes of coupling strength from the measurement of phase–amplitude coupling (PAC) is demonstrated based on simulation data. The data suggest that the generalized algorithms are able to effectively evaluate the strength of PAC, which are consistent with those traditional approaches, such as PAC-PLV and PAC-MI. Experimental data, which are local field potentials obtained from anaesthetized SD rats, have also been analyzed by these two generalized approaches. The data show that the theta–low gamma PAC in the hippocampal CA3–CA1 network is significantly decreased in

the glioma group compared to that in the control group. The results, obtained from either simulation data or real experimental signals, are consistent with that of those traditional approaches PAC-MI and PAC-PLV. It may be considered as a proper indicator for the cross frequency coupling in sub-network, such as the hippocampal CA3 and CA1.

Keywords Neuronal oscillations · Phase–amplitude coupling (PAC) · Phase–amplitude coupling-evolution map approach (PAC-EMA) · Phase–amplitude coupling-conditional mutual information (PAC-CMI) · Local field potentials (LFPs)

Abbreviations

CFC	Cross-frequency coupling
PAC	Phase–amplitude coupling
LFPs	Local field potentials
PAC-CMI	Phase–amplitude coupling-conditional mutual information
PAC-EMA	Phase–amplitude coupling-evolution map approach
PAC-MI	Phase–amplitude coupling-modulation index
PAC-PLV	Phase–amplitude coupling-phase locking value
LG	Low gamma
HG	High gamma

Introduction

Since cross-frequency coupling (CFC) plays an essential role to integrate functional systems across multiple spatiotemporal scales in neuronal computation, communication

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and learning, it has recently attracted considerable interest from theoreticians as well as experimentalists (Canolty and Knight 2010; Nikolai et al. 2010; Palva et al. 2005). At present, three types of CFC phenomena have been experimentally observed and reported, which are nested oscillation (phase–amplitude coupling, PAC) (Cohen et al. 2009b; Tort et al. 2010; Wang et al. 2014; Xu et al. 2013b), phase synchronization (phase–phase coupling, PPC) (Belluscio et al. 2012; Fell and Axmacher 2011), and cross-frequency amplitude envelope correlation (amplitude–amplitude coupling, AAC) (Friston 1997; Shirvalkar et al. 2010; Siegel et al. 2009). In particular, PAC, which occurs when the amplitude of a higher frequency is coupled to the phase of a lower frequency, is well studied in recent years (Buzsaki 2006; Cohen 2008; Jensen and Colgin 2007), and has been proposed as a mechanism for supporting information exchange and integration of learning and memory across different temporal and spatial scales (Nikolai et al. 2010). There are abundant evidences for PAC in animal as well as human data. For example, theta–gamma PAC is related with phase advance in hippocampal place cells, which could improve the accuracy of place coding (O’Keefe and Recce 1993; Skaggs et al. 1996). Other previous studies suggest that the theta–gamma PAC, mostly between hippocampus and cortex (Adhikari et al. 2010; Onslow et al. 2011) or within hippocampus (Scheffer-Teixeira et al. 2011; Tort et al. 2009) of rodents, and also in human neocortex (Canolty et al. 2006; Foster and Parvizi 2012; Osipova et al. 2008), is a mechanism for both multi-item working memory maintenance and long-term memory retrieval. Moreover, it was found that there was PAC phenomenon between alpha and gamma rhythms in different brain areas when performing other tasks (Cohen et al. 2009a; Osipova et al. 2008).

A number of approaches have recently been developed and proposed for the study of PAC between low- and high-rhythms (Bruns and Eckhorn 2004; Canolty et al. 2006; Li et al. 2013; Osipova et al. 2008), some of which have been applied in various neural oscillatory coupling of different brain regions under behavioral states, such as modulation index (PAC-MI) (Canolty et al. 2006; Xu et al. 2013a, b; Zheng and Zhang 2015), phase locking value (PAC-PLV) (Penny et al. 2008; Qun et al. 2015; Xu et al. 2015), modulation index by Tort (PAC-MIT) (Tort et al. 2008), wavelet bicoherence method (Li et al. 2013). Each algorithm has its own characteristics and advantages to evaluate different aspects of PAC. For example, the two phases of interest in the PAC-PLV algorithm are the phase of slow rhythm oscillation, and the phase of high frequency amplitude, which is obtained with a second Hilbert transform (Penny et al. 2008).

In the present study, two generalized approaches, termed as phase amplitude coupling–evolution map approach (PAC-EMA) and phase amplitude coupling–conditional mutual information (PAC-CMI), are proposed and developed based on either phase dynamics or information theory, respectively. It is well known that the classical EMA (Rosenblum and Pikovsky 2001) and CMI (Palus and Stefanovska 2003) are initially proposed to assess the weak coupling between two phase signals of similar rhythms. Accordingly, the intrinsic properties of both EMA and CMI algorithms were preserved, and the improvements of them were carefully made in order to be successfully applied in measuring PAC. In contrast to PAC-MI, one of traditional PAC measurements which transiently combines the amplitude of high frequency with the phase of low frequency into an analytic signal, the approaches of both PAC-EMA and PAC-CMI focus on the relationship between the phase of high frequency amplitude and the phase of low frequency in the range of weak coupling. Accordingly, the effectiveness of quantitatively distinguishing the alterations of coupling strength from PAC measurement by the two generalized approaches was verified and the real experimental data analysis was further performed.

Materials and methods

Generation of simulation data

In the study, general coupling frequencies at theta (3–4 Hz) and gamma (40 Hz) were used for measuring PAC coupling. The following model is established to generate simulation data:

$$RAW = low + b * (a * low * high + high1) \quad (1)$$

where *low* represents a sine function with variable phase from 3 to 4 Hz as the low frequency. *high* is generated from a sine function (40 Hz) as the high frequency, which is modulated by the *low*. *high1* denotes a disturbance variable nearby *high* (42 Hz), and its form is a sine function as well. $b = 0.2$ controls the amplitude size of entire high frequency. a is an important variable, which represents the coupling strength. The bigger the a , the greater the strength of the coupling. During the numerical experiments, the strength of coupling will be limited within the range of weak level. Accordingly, in order to satisfy the above requirements, the parameter a is set from 0 to 1 with a step of 0.1. Clearly, there is no PAC at all if $a = 0$. On the contrary, there is a weakly PAC oscillation rather than strong coupling if $a = 1$ (Fig. 1). Here, the total number of data was 200,000.

Fig. 1 Examples of simulation data for PAC measurement. From left to right, each curve represents a different coupling strength, respectively. The data length is 1000 sample points

Phase amplitude coupling-evolution map approach (PAC-EMA)

The algorithm of PAC-EMA is deduced and developed based on that of evolution map approach, which is a measurement for direction of information flow generated by phase dynamics (Rosenblum et al. 2002; Rosenblum and Pikovsky 2001), and the main idea of which is to model the phase dynamics of two processes $\{X_1\}$ and $\{X_2\}$:

$$\dot{\varphi}_{1,2} = \omega_{1,2} + q_{1,2}(\varphi_{1,2}) + \varepsilon_{1,2}f_{1,2}(\varphi_{1,2}, \varphi_{2,1}) + \xi_{1,2} \quad (2)$$

And fits the parameters in $f_{1,2}$ using aligned Fourier series

$$\Delta\varphi_{1,2}(t) = \sum_{m,l} A_{m,l} e^{im\varphi_1 + il\varphi_2} \quad (3)$$

Here $\varphi_{1,2}$ are phase variables, so that the functions $q_{1,2}, f_{1,2}$ are 2π -periodic in all arguments. Parameters $\varepsilon_{1,2}$ characterize the strength of the coupling and $\xi_{1,2}$ are random terms. The bidirectional influence of the systems is quantified by the coefficients $c_{1,2}$ respectively, denoted as:

$$c_{1,2}^2 = \int_0^{2\pi} \int_0^{2\pi} \left(\frac{\partial \Delta\varphi_{1,2}}{\partial \varphi_{2,1}} \right)^2 d\varphi_1 d\varphi_2 \quad (4)$$

In the present study, the PAC-EMA, used to measure the neuronal oscillatory coupling between the low frequency phase φ_{low} and the phase of high frequency amplitude envelope $\varphi_{highamp}$, was defined as:

$$\text{PAC-EMA}_{ph-phamp} = \int_0^{2\pi} \int_0^{2\pi} \left(\frac{\partial \Delta\varphi_{highamp}}{\partial \varphi_{low}} \right)^2 d\varphi_{low} d\varphi_{highamp} \quad (5)$$

Phase amplitude coupling-conditional mutual information (PAC-CMI)

With the purpose of measuring the information transmission between two phase signals across different frequencies, the algorithm of PAC-CMI has been developed based on the conditional mutual information theory. Generally,

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

$$I(X; Y) = H(X) + H(Y) - H(X, Y) \quad (6)$$

And then the conditional mutual information is defined as

$$I(X; Y|Z) = H(X|Z) + H(Y|Z) - H(X, Y|Z) \quad (7)$$

Here Z is another random variable correlated with X and Y , and $H(\cdot)$ refers to the information entropy, which needs to be estimated by mean of the probability distribution of the variables. Extracting the instantaneous phase from two processes $\{X_1\}$ and $\{X_2\}$, we can assess the “net” information about the τ -future of the process $\{X_2\}$ contained in process $\{X_1\}$ by $I(\varphi_1; \varphi_{2\tau}|\varphi_2)$ to infer the unidirectional coupling (Palus and Stefanovska 2003; Zheng et al. 2012).

Here, the algorithm of PAC-CMI, which can be used to evaluate the coupling between the low frequency phase and the phase of high frequency amplitude envelope, is defined as

$$\text{PAC-CMI}_{ph-phamp} = I(\varphi_{low}(t); \Delta\varphi_{highamp,\tau}(t) | \varphi_{highamp}(t)) \quad (8)$$

With phase increments computed for each time point,

$$\Delta\varphi_{highamp,\tau}(t) = \varphi_{highamp}(t + \tau) - \varphi_{highamp}(t) \quad (9)$$

where φ_{low} is the phase of low frequency, and $\varphi_{highamp}$ is the phase of high frequency amplitude envelope.

Moreover, in order to compare those traditional algorithms with the above two generalized ones, two frequently-used algorithms, PAC-PLV (Penny et al. 2008) and PAC-MI (Canolty et al. 2006; Onslow et al. 2011), are employed as control approaches to validate the generalized measures in both simulation data and LFPs data.

Surrogate data

Since the individual difference of real signals themselves, there might be great fluctuations of raw values computed from the algorithms, and some of them were obtained perhaps by chance. In this case, all the results of real signals should be compared to that of surrogate data (Theiler et al. 1991). Moreover, all the indexes are normalized using surrogate data to Z score value, which can be used to

determine the probability that such a result would have been due to chance.

The Z score is defined as

$$\hat{Z} = \frac{Z\text{-mean}(Z_{\text{surrogate}})}{\text{std}(Z_{\text{surrogate}})} \quad (10)$$

Here Z refers to the raw values of the indexes, and surrogate data are generated either by shuffling the high frequency amplitude series for PAC-MI, or by shuffling the low frequency phase series for PAC-EMA, PAC-CMI and PAC-PLV. Therefore, all these modified (normalized) indexes are applied in the final results of LFPs data (surrogate number: $n = 100$).

Generation of experimental data (local field potentials, LFPs)

All the animal surgery and experimental protocol were approved by the Ethical Commission at Nankai University, China. Experiments were carried out on 24 male Sprague–Dawley (SD) rats purchased from the Laboratory Animal Center of Academy of Military Medical Science of People's Liberation Army, P. R. China. They were weighed from 180 to 220 g. The rats were randomly divided into two groups, namely control group (CTRL, $n = 12$) and C6 glioma group (GLIO, $n = 12$). Animals were anaesthetized with 10 % chloral hydrate (3.5 ml/kg, intra-peritoneal) and afterward placed on a stereotaxic frame (Narishige, Japan) for surgery. After drilled a small hole (1 mm in diameter) at the coordinates of 3–3.5 mm right to the midline and 0.5 mm posterior to bregma, rats in GLIO group were injected with tumor cells in striatum, with 1.0×10^6 cells in 10 μ l Dulbecco's modified Eagle's medium (DMEM; Gibco BRL, USA), at a rate of 1 μ l/min. The rats of CTRL group received a single intracerebral injection of the equivalent volume of DMEM. Following the surgical procedure, the animals were placed back into the cage with free access to water and food and cared in a 12 h light: 12 h darkness cycle and a thermo regulated environment. The more details can be found in our previous report (Wang et al. 2011).

The electrophysiological recordings were performed on the left hippocampus of brain, contralateral to tumor, at the 17th day after C6 cells or DMEM implantation in the animals. Following 30 % urethane anesthesia (3–3.5 ml/kg, intra-peritoneal), A rat was placed in a stereotaxic frame again. Two small holes were drilled in the skull at the site of the recording electrodes. One recording electrode was slowly implanted into the Schaffer collateral/commissural pathway in CA3 area (4.2 mm posterior to bregma, 3.5 mm left to midline), and the other into the stratum radiatum area of CA1 (3.5 mm posterior to bregma, 2.5 mm left to

midline). The ground and reference electrodes were placed over the two hemispheres of the cerebellum symmetrically. The local field potentials of CA3 and CA1 areas were recorded simultaneously at a sampling rate of 1 kHz, by means of a dual-channels bioelectric amplifier and PowerLab/8SP acquisition (Powerlab, AD Instruments).

Data pretreatment and statistical analysis

To extract instantaneous phase, Hilbert transform was used to obtain the phase of neural signals approximately from the narrow band signals in a frequency rhythm. All data processing was performed off-line using custom routines in MATLAB 2011 (MathWorks).

All the data were expressed as Mean $\pm$ SEM. For comparisons of PAC indexes between two groups in experimental data, the Student's *t* test was used. All the statistical analyses were performed using SPSS 22.0 software and the significant level was set at 0.05.

Results

Simulation data

In order to assess the number of data points required for a reliable estimation of the PAC index by these two generalized algorithms, i.e. PAC-EMA, PAC-CMI, a numerical test was performed by increasing the length of a moving-window from 1000 to 20,000 in steps of 1000, and a was set to 1. From the measurements of these two methods, it was found that there was a linear segment in which the slope converges to a constant value as the number of data points increase (8000 for PAC-EMA and 5000 for PAC-CMI, respectively; data not presented). Such a result is consistent with our previous works (Zhang et al. 2011) and other published papers (Yokota 2004).

Accordingly, a numerical experiment was done to assess how the index values vary with the increased coupling strength a from 0 to 1 in steps of 0.1 for each measurement. Here, a sliding window was 40,000 with an overlap of 50 % by all these four algorithms. It can be seen that the PAC indexes of all these four algorithms visibly increase with the augmentation of coupling strength a (Fig. 2). It suggests that both generalized PAC algorithms, namely PAC-EMA and PAC-CMI, may effectively distinguish the alteration of coupling strength from changing parameter a in range of weak coupling. Furthermore, the curves of both PAC-EMA and PAC-PLV show that there is comparatively linear relation between the PAC measures and coupling strength a (Fig. 2a, c). It is well known that the PAC-PLV is a linear approach, while the PAC-EMA is a

Fig. 2 The indexes of PAC measurements based on the simulation data, which include four approaches PAC-EMA, PAC-CMI, PAC-PLV and PAC-MI, respectively. The parameter a denotes the

coupling strength of PAC ranged from 0 to 1 in steps of 0.1. All the data points are expressed as Mean $\pm$ SEM. Error bars indicate SEM

nonlinear method. Under the condition of weak coupling, the measurements of these two algorithms represent similar linear distribution, suggesting that there is a positive correlation between them. On the other hand, the PAC indexes of PAC-CMI appears nonlinear increment with a progressive strength (Fig. 2b), which is in line with the PAC-MI measurement. However, it was found that there was poor performance of PAC-MI at the small values of parameter a , when it increases from 0 to 0.5 (Fig. 2d).

Experimental data: LFPs

In the present study, the measurements of theta–gamma PAC between the hippocampal CA3 and CA1 regions were performed. The low frequency bands were focused on theta rhythm, which ranged from 4 to 8 Hz. On the other hand, the high frequency bands were concentrated on gamma rhythm (30–100 Hz), and it was divided into low gamma (LG, 30–60 Hz) and high gamma (HG, 60–100 Hz), respectively. All of the results were presented based on both surrogate data and Z score values.

The representative examples of PAC strength measured by these four approaches in the CTRL group are presented respectively in Fig. 3a. The measurements of the four

approaches were performed in integral theta band (4–8 Hz) and gamma narrow frequency bands (bandwidth = 1 Hz). It can be seen that the theta–LG phase–amplitude modulation regularly appears at about 40 Hz from CA3 to CA1 regions in the CTRL group. However, there is much weak coupling strength for theta–HG coupling measurements for all these algorithms (Fig. 3a).

From the statistical analyses, it can be seen that the values of theta–LG PAC in CA3–CA1 network are significantly decreased in the GLIO group compared to that in the CTRL group ($t_{(22)} = 3.640$, $p = 0.001$ for PAC-EMA and $t_{(22)} = 3.375$, $p = 0.003$ for PAC-CMI). In addition, the same analyses were performed for theta–HG PAC. The data show that there is no statistical difference of the theta–HG PAC between two groups by either PAC-EMA ($t_{(22)} = 0.192$, $p = 0.850$) or PAC-CMI ($t_{(22)} = 1.958$, $p = 0.063$) measures (Fig. 3b).

On the other hand, measured by both PAC-PLV and PAC-MI approaches, the coupling strength of theta–LG PAC is visibly decreased in the GLIO group. There are significant differences between the CTRL group and the GLIO group in CA3–CA1 network ($t_{(17)} = 4.649$, $p < 0.001$ for PAC-PLV data and $t_{(17)} = 4.187$, $p < 0.001$ for PAC-MI data). However, there are no statistical

Fig. 3 The indexes (Z score value) of PAC measurements based on the rat's experimental signals and the analysis has been performed by these four approaches, including two generalized algorithms and two traditional ones. **a** Four representative examples of theta–gamma PAC detection (Z score value) measured by both generalized and traditional approaches from CA3 to CA1 region in CTRL group, respectively. **b** The group data representations. There were a strong coupling of theta–LG PAC and a weak coupling of theta–HG PAC.

The strength of theta–LG PAC was significantly reduced in the GLIO group ($n = 12$) compared to that in the CTRL group ($n = 12$) by PAC-EMA, and PAC-CMI. There were no significant differences of theta–HG PAC measurements between these two groups. The similar results were obtained from the traditional approaches, PAC-PLV and PAC-MI, in both the GLIO group ($n = 10$) and the CTRL group ($n = 9$). ** $p < 0.01$ and *** $p < 0.001$ for comparisons of theta–gamma PAC between the CTRL and GLIO groups

differences of the theta–HG PAC between the CTRL group and the GLIO group, analyzed by either PAC-PLV or PAC-MI (Fig. 3b).

Discussion

In this study, we introduced two generalized algorithms, namely PAC-EMA and PAC-CMI, which were used to evaluate the strength of cross-frequency coupling. Based on simulation data, the numerical test shows that these two generalized algorithms are able to effectively measure the strength of PAC, which are consistent with those traditional approaches, such as PAC-PLV and PAC-MI. Based on experimental data, the measurement indicated that the brain glioma significantly impaired the theta–LG PAC between CA3 and CA1 regions. It further suggests the practicability of two generalized methods in cross-frequency of neuronal oscillations network.

Current algorithms for PAC detection, mostly focused on assessing phase–amplitude and phase–phase of amplitude envelope interaction (Tort et al. 2010), seldom evaluate the direction of functional coupling. Recently, a study reported a method based on the phase-slope index to estimate the directionality between different frequencies (Jiang et al. 2015). It reminds us that whether PAC-EMA and PAC-CMI are able to assess the directionality of PAC. After all, classical EMA and CMI are initially proposed to simultaneously assess directional coupling between two phase signals of an identical rhythm. However, it remains unknown what the meaning of the other directional index by calculation of generalized algorithms in physiology. In particular, it is still unclear whether the reverse indicator represents that the phase of high frequency envelope drives the phase of low frequency.

A numeric test was performed based on the simulation data. The aim is to ensure that the generalized algorithms take effect under the circumstance of weak coupling

oscillations. Our previous experimental studies in vivo animal models suggested that there was a weak coupling if the value of PLV was smaller than 0.5, else a relatively strong coupling when PLV index was bigger than 0.5 (Xu et al. 2012, 2013a, b, 2015; Zheng et al. 2012; Zheng and Zhang 2013). An issue is how to properly generate simulation data, by which not only the weak PAC coupling can be obtained but also the two generalized approaches are validated in a way. The data shows that all of the PAC-PLV values (the parameter α increases from 0 to 1) are under 0.2 (Fig. 2), verifying that there is the weaker strength of PAC coupling. Moreover, an important justification is that the generalized algorithms do not change intrinsic qualities of the methods themselves. For example, a previous investigation recommended that the number of data points required for a reliable estimation is about 8000 for the EMA performance and approximately 5000 for the CMI, respectively (Zhang et al. 2011). Since the two generalized algorithms, PAC-EMA and PAC-CMI, originate from the EMA and CMI, it is certainly believed that the main part of the algorithm feature are consistent with both the EMA and CMI algorithms, such as the sensitive to the signal-to-noise ratio, the coefficient of variance analysis and computationally efficient. In addition, it is well known that the surrogate data and Z score values are usually employed when dealing with real experimental data, but they are not used for simulation data. The only reason is that the simulation system, from which simulation data are generated, is controllable and observable. On the other hand, the data obtained from real system are much complex and fluctuant that may lead to sham results generated by the algorithms. Consequently, it is necessary to use the surrogate data and Z score value to rule out such influences by chance.

Several previous investigations showed that the phenomenon of PAC between low and high frequency bands emerged in the hippocampus and prefrontal cortex of rodents during rapid eye movement (REM), awake state (Claudia et al. 2011; Scheffer-Teixeira et al. 2011) and various behaving tasks (Sirota et al. 2008; Tort et al. 2009, 2010), and also in human neocortex, e.g. during the tasks of visual recognition (Voytek et al. 2010) or item memory (Axmacher et al. 2010; Mormann et al. 2005). In rodent hippocampus, theta oscillations are prominent LFPs (Young 2011), and the periodic events in the 30–100 Hz band are defined as gamma oscillations, which can be divided into low band (LG, 30–60 Hz) and high band (HG, 60–100 Hz) (Buzsaki and Wang 2012; Freeman 2007). An interesting observation is that, the LG and HG rhythms in the CA1 area synchronize respectively with LG in CA3 and HG in the medial entorhinal cortex layer III, and they typically occur during different theta phases (Colgin et al. 2009). Consequently, it is supposed that whether or not the

coupling between theta phase and gamma (LG/HG) amplitude in the hippocampal CA3–CA1 network can reveal the synchronization of neuronal oscillations involved in the cognitive function, which could be further altered depending on the different behavioral states and dysfunction by pathology impairments. In the present study, the two generalized algorithms have been employed to analyze real experimental data. In order to show the effectiveness of the algorithms, the theta–gamma PAC between CA3 and CA1 was also measured by the modulation index (PAC-MI), a conventional approach proposed for the PAC analysis of neocortex ECoG (Canolty et al. 2006), because of its reliable character when surveying noisy data for unknown frequency bands of coupling (Onslow et al. 2011). Based on the results obtained from both PAC-EMA and PAC-CMI measurements, it was found that the theta phase in the CA3 area modulated the LG amplitude rather than the HG rhythm in the CA1 (Fig. 3). Since the synaptic plasticity is usually believed to comprise the cellular basis for memory formation and cognition in neuroscience (Davis et al. 2002), we wondered whether the theta–gamma PAC between the CA3 and CA1 areas would be altered under the condition of cognitive deficits. Accordingly, the glioma rat's model was established. One of our previous studies showed that the karyopyknosis and neuronal loss could be observed by HE examination in the hippocampal region of contralateral side to the tumor in the glioma-bearing rats (Wang et al. 2011). According to the PAC-EMA and PAC-CMI analysis, it was found that the coupling strength of theta–LG PAC between CA3 and CA1 region was significantly decreased in the GLIO group compared to that in the CTRL group ($p < 0.01$, Fig. 3b-upper panel), which was in line with the measurements of PAC-PLV and PAC-MI (Fig. 3b-lower panel).

Overall, the two generalized algorithms, PAC-EMA and PAC-CMI, have been tested their effectiveness for evaluating phase–amplitude coupling based on the simulation data. Furthermore, the PAC between theta and gamma rhythms in the hippocampal CA3–CA1 network is also measured in both normal and glioma-bearing rats. The results, obtained from either simulation data or real experimental signals, are consistent with that of those traditional approaches, such as PAC-MI and PAC-PLV. Accordingly, the indexes obtained from the PAC-CMI and PAC-EMA measurements could be considered as a proper indicator for the cross frequency coupling in sub-network, such as the hippocampal CA3 and CA1 areas precisely. However, the limitations, conditions and applicability of PAC-CMI and PAV-EMA need to be further investigated.

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Compliance with ethical standards

Conflict of interest There is not a conflict of interest for all authors.

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