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Time-resolved phase-amplitude coupling in neural oscillations

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ABSTRACT

Cross-frequency coupling between neural oscillations is a phenomenon observed across spatial scales in a wide range of preparations, including human non-invasive electrophysiology. Although the functional role and mechanisms involved are not entirely understood, the concept of interdependent neural oscillations drives an active field of research to comprehend the ubiquitous polyrhythmic activity of the brain, beyond empirical observations. Phase-amplitude coupling, a particular form of cross-frequency coupling between bursts of high-frequency oscillations and the phase of lower frequency rhythms, has recently received considerable attention. However, the measurement methods have relatively poor sensitivity and require long segments of experimental data. This obliterates the resolution of fast changes in coupling related to behavior, and more generally, to the non-stationary dynamics of brain electrophysiology.

We propose a new measure of phase-amplitude coupling that can resolve up to one, optimally two, cycles of the underlying slow frequency component. The method also provides a measure of the coupling strength, for augmented insight into the mechanisms involved. We demonstrate the technique with synthesized data and compare its performances with existing methods. We also show that the method reveals rapid changes in coupling parameters in data from the entorhinal cortex of a free-behaving rat. The time-resolved changes revealed are compatible with behavior and complement observed modulations of oscillatory power.

We anticipate that this new measure of dynamic phase-amplitude coupling will contribute to accelerate research into the dynamics of inter-dependent oscillatory components related to brain functions and dysfunctions.

1. Introduction

Classical studies of the role of neural oscillations in brain functions and behavior have reported on oscillatory rhythms within distinct, band-limited frequency ranges (Goldman et al., 2002; Klimesch, 1998; Tallon-Baudry and Bertrand, 1999) (see (Cohen, 2008) for a review). The oscillations that compose brain rhythms are known to be interdependent across frequency bands (Buzsáki and Draguhn, 2004). This form of interaction known as *cross-frequency coupling* is a phenomenon readily observed in electrophysiology at multiple scales and with a range of experimental techniques (Buzsaki, 2006). Phase-amplitude coupling (PAC) is one of the best-studied subtypes of cross-frequency coupling (Canolty and Knight, 2010), accounting for the more frequent occurrence of higher-frequency bursts at preferred phases of underlying low-frequency cycles. PAC has received tremendous attention recently, with several studies revealing modulations of such coupling depending on task and resting-state conditions in health and disease (Tort et al., 2008, 2009; Axmacher et al., 2010; Fell and Axmacher, 2011; Schutter and Knyazev, 2012; Florin and Baillet, 2015; De Hemptinne et al., 2015). The physiological relevance for PAC is in the assumption that slow oscillations mark the cycles of relative net excitability of neural ensembles (Von Stein and Sarnthein, 2000; Fries, 2005; Haider et al., 2006; Lisman and Buzsáki, 2008), which in turn pace the occurrence of neural spiking and that of faster post-synaptic activity, marked by high-frequency and often broadband bursts (Canolty and Knight, 2010).

One can further hypothesize that such coupling is transient by nature, reflecting the elusive dynamics of polyrhythmic brain activity. Some early task-related evidence of this assumption was demonstrated in humans by Tort et al. (2008). Ideally, measures of PAC need to provide the best possible frequency estimates of the oscillatory components related in phase and amplitude through this form of coupling. We would also need to assess the strength (intensity) of such coupling, to evaluate how it might be affected by behavior or physiopathological mechanisms. Finally and ideally, these measures would need to be accessible at the best possible temporal resolution, to detect and track such PAC changes at the natural "speed" of brain activity. This latter aspect has proven to be methodologically challenging, essentially because of the relatively poor signal-to-noise ratio affecting the higher-frequency portion of

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electrophysiological brain signals – in particular with non-invasive measures such as electro (EEG) and magnetoencephalography (MEG).

Event-related phase-amplitude coupling (ERPAC) was recently introduced in an attempt to bridge that methodological gap (Voytek et al., 2013). The method indeed provides a PAC measure with high temporal resolution, however under the constraint that expected PAC changes are time-locked to a stimulus or event of interest across repeated trials. This aspect restricts the sensitivity and the range of applications of ERPAC to event-related experimental designs and analyses.

More recently, Dvorak and Fenton (2014) proposed to estimate PAC over two complementary *global* and *local* time scales. The global time scale – defined over 10 s or more, typically – is to identify the frequencies of the most coupled pair of oscillatory components: a slower oscillation (frequency for phase, f_P), which phase modulates the amplitude of faster bursts expressed at frequency f_A (frequency for amplitude). In turn, a local time scale – defined over the f_A cycles – is for detecting time variations in coupling strength. One identified issue with the approach though is that it assumes stationarity in coupled frequency pairs (a.k.a. modes) (f_A, f_P) over possibly long periods of observations: this is an unlikely eventuality in neurophysiology.

The strength of PAC is another measure of interest to obtain dynamically (Tort et al., 2008, 2009). However, existing methods to assess PAC strength are also challenged by poor temporal resolution (see (Tort et al., 2010) for a review).

We propose a new approach and practical method to address these issues in the widest range of experimental settings (task-related and spontaneous, ongoing electrophysiological data).

2. Material and methods

2.1. Principles

Formally, let us define PAC as the modulation of the amplitude A_{f_A} of an oscillatory component of frequency f_A by the phase ϕ_{f_P} of a slower rhythm of frequency f_P, with $f_P < f_A$. Our approach to derive a time-resolved measure of PAC (tPAC) was inspired by Cohen (2008) and Canolty et al. (2006), which methods we combined and optimized to achieve the best possible temporal resolution and sensitivity to coupling strength. The methodological steps are detailed below and summarized in Fig. 1.

The principle of the tPAC procedure is that it searches for the f_P oscillation with strongest PAC coupling with f_A bursts, over time windows that slide along the electrophysiological data signal $x(t)$. The user is first required to define a spectral range of interest for f_P and f_A – for instance, $[f_{P_{min}}, f_{P_{max}}]$ (e.g., [2, 12] Hz) for the f_P range. The range for f_A is then subdivided into twenty centre frequencies either linearly or logarithmically, determined by the user. The other parameter that should be defined by the user is the length of sliding time window. This window should be long enough to cover at least one full cycle of $f_{P_{min}}$.

For each f_A centre frequency tested, $x(t)$ is bandpass filtered around f_A with a zero-phase-shift, even-order, non-causal finite impulse response (FIR) filter. The bandwidth of each filter around each f_A centre frequency is defined as the maximum between i) the difference between consecutive f_A centre frequencies, and ii) the highest tested frequency for f_P. Thus, the filter bandwidth spans the interval between consecutive f_A frequency candidates and is inclusive of the range of interest for possible f_P oscillations. Note that to minimize the filter edge effects and increase frequency resolution, bandpass filtering needs to be performed on the full-length signal before extracting its components in the sliding time window.

The amplitude envelope $A_{f_A}(t)$ of the bandpass filtered signal around the f_A centre frequency, $x_{f_A}(t)$ is then extracted using the Hilbert transform before a sliding time window is applied to assess dynamic changes in PAC.

If in the current time-window, the amplitude of f_A oscillations is coupled to the phase of a slower rhythm oscillating at frequency f_P, then the power spectrum density (PSD) P_A of the windowed $A_{f_A}(t)$ is expected to feature a peak at f_P. Further, to avoid registering spurious manifestations of PAC, a peak around f_P shall also be expected in P_x, the PSD of the original data signal $x(t)$ limited to the same time window, as recommended by Aru et al. (2015). P_x and P_A are estimated using the Discrete Fourier Transform (DFT) magnitude coefficients. The best candidate for the frequency for phase (f_P^*) corresponds to the frequency of the highest peak of P_A coinciding with a peak of P_x. A tolerance threshold for the correspondence between peaks of P_A and P_x is set to the maximum between 1.5 the power spectrum's resolution (i.e. the inverse of the time window length) and 1.5 Hz. If no actual peak or peak coincidence is found, the coupling intensity is set to zero and an arbitrary value – outside the range of interest – is assigned to f_P. For robustness purposes, the peaks in P_x with an amplitude below 10% of that of the highest peak

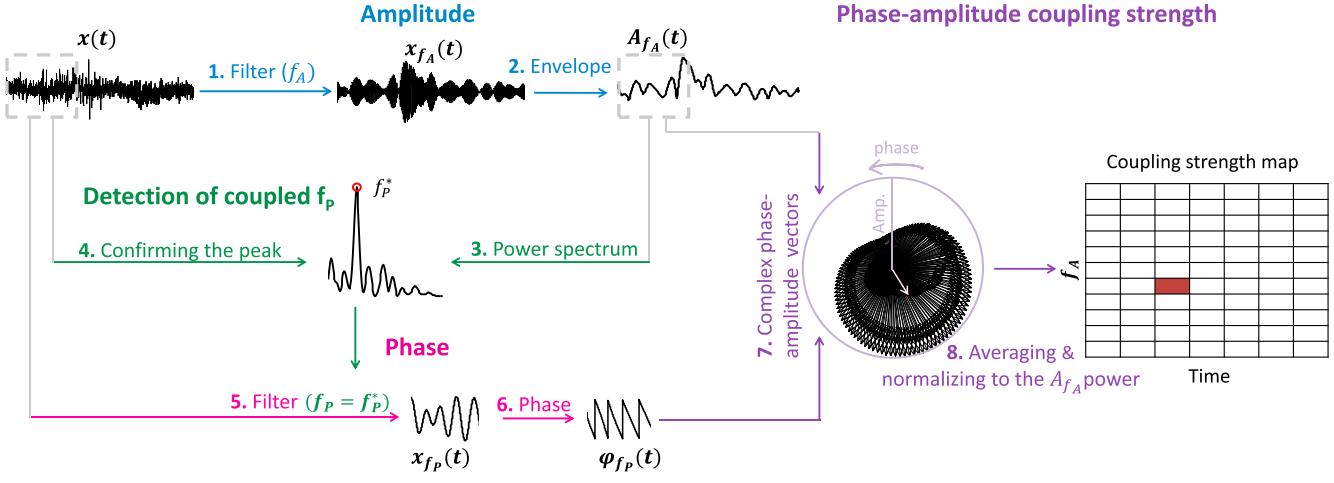

Fig. 1. tPAC procedure: (1) The electrophysiological signal $x(t)$ is bandpass filtered around f_A, the tested frequency for amplitude modulations; (2) the envelope of the resulting bandpass filtered signal is extracted using standard Hilbert transform; A short temporal window slides on the resulting envelope: (3) the power spectrum of the windowed envelope (P_A) is estimated and its peaks are extracted; (4) the power spectrum of the original signal in the same time window is estimated, and is used for finding the highest peak in P_A that co-occurs with a peak in P_x. This determines the dominant frequency for phase f_P^*; (5) windowed $x(t)$ (with a signal buffer on both sides) bandpass filtered around the selected frequency for phase f_P^*, (6) and its analytic phase is obtained via Hilbert transform; (7) for each time point, the amplitude of the fast-oscillation envelope and the instantaneous phase of the slow oscillation are reported using a polar vector; (8) the Euclidean norm of the summed vectors averaged over an integer multiply of f_P cycles is a measure of coupling strength within these time and frequency intervals. This value is further normalized with respect to the magnitude of $x_{f_A}(t)$, to minimize the influence of signal magnitude in the measurement of coupling strength. These steps are repeated for all predefined f_A frequency bins, and for all sliding time windows.