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A global coupling index of multivariate neural series with application to the evaluation of mild cognitive impairment

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HIGHLIGHTS

- The GCI method proposed in this paper could be applied to indicate genuine and stochastic synchronization in multivariate EEG series at different frequency bands.
- The GCI method proposed in this paper was less influenced by the frequency bands than the GSI and *S*-estimator methods, indicating that the GCI method was more robust. And the GCI method had a better performance on the coupling coefficient relative to GSI and *S*-estimator.
- The GCI method proposed in this paper was more sensitive than GSI and *S*-estimator methods in differing synchronization strength of EEG between MCI and NC, and could be considered as a potential indicator diagnosing MCI.

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ABSTRACT

Recently, the synchronization between neural signals has been widely used as a key indicator of brain function. To understand comprehensively the effect of synchronization on the brain function, accurate computation of the synchronization strength among multivariate neural series from the whole brain is necessary. In this study, we proposed a method named global coupling index (GCI) to estimate the synchronization strength of multiple neural signals. First of all, performance of the GCI method was evaluated by analyzing simulated EEG signals from a multi-channel neural mass model, including the effects of the frequency band, the coupling coefficient, and the signal noise ratio. Then, the GCI method was applied to analyze the EEG signals from 12 mild cognitive impairment (MCI) subjects and 12 normal controls (NC). The results showed that GCI method had two major advantages over the global synchronization index (GSI) or *S*-estimator. Firstly, simulation data showed that the GCI method provided both a more robust result on the frequency band and a better performance on the coupling coefficients. Secondly, the actual EEG data demonstrated that GCI method was more sensitive in differentiating the MCI from control subjects, in terms of the global synchronization strength of neural series of specific alpha, beta1 and beta2 frequency bands. Hence, it is suggested that GCI is a better method over GSI and *S*-estimator to estimate the synchronization strength of multivariate neural series for predicting the MCI from the whole brain EEG recordings.

1. Introduction

The synchronization occurs between the neurons, and between different regions of brain (Pikovsky, Rosenblum, & Kurths, 2001). Generally, the synchronization may be realized by integrating the function of various regions of brain and interacting continuously between various regions (Fell et al., 2001; Varela, Lachaux, Rodriguez, & Martinerie, 2001; Womelsdorf et al., 2007). To be specific, the neuronal groups from various regions regulate their

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own dynamical features, and lock the activity of brain within the scope of a certain time and frequency band (Pikovsky, 1984; Pikovsky et al., 2001; Rosenblum, Pikovsky, & Kurths, 1996; Rulkov, Sushchik, Tsimring, & Abarbanel, 1995). Therefore, the analysis of synchronization has been a focus in understanding the mechanisms on brain signals (Courtemanche, Robinson, & Aponte, 2013; Ivancevic, Jain, Pattison, & Hariz, 2009; Knyazeva et al., 2012; Park et al., 2008; Pikovsky et al., 2001; Rosenblum, Cimponeriu, Bezerianos, Patzak, & Mrowka, 2002). The synchronization strength of neural signals, which describe the synchronization activity, may reveal the information processing in a normal or abnormal brain (Buzsáki & Draguhn, 2004; Fell et al., 2001; Varela et al., 2001). Multi-channel EEG is often used in the estimation of the synchronization strength of neural signals. The global synchronization strength of multi-channel EEG signals is a signature of brain function and a bio-marker for the early diagnosis of brain diseases such as mild cognitive impairment and Alzheimer's diseases (Aarabi, Wallois, & Grebe, 2008; Carmeli, Knyazeva, Innocenti, & De Feo, 2005; Darvas, Ojemann, & Sorensen, 2009; Knyazeva et al., 2012, 2010; Rudrauf et al., 2006; Stam, Jones, Nolte, Breakspear, & Scheltens, 2007). However an effective estimation method for the global synchronization strength of multi-channel EEG signals is critical.

Many methods have been applied to estimate the synchronization strength between two neural signals, including phase synchronization analysis (Allefeld & Kurths, 2004), cluster analysis (Stuart, Walter, & Borisyuk, 2005), frequency flows and time–frequency dynamics analysis (Rudrauf et al., 2006), mixture-of-Gaussians analysis (Matsumoto, Okada, Sugase-Miyamoto, Yamane, & Kawano, 2005), and graph theoretic analysis (Stam et al., 2007). However, none of the above methods can be used to calculate the global synchronization strength among multivariate neural series. Lately, the S-estimator method had been proposed to estimate the global synchronization strength of multi-channel EEG signals (Carmeli et al., 2005). Nevertheless, the S-estimator did not consider the effect of the random and/or artifact components, and the bias was due to the finite length of the signal. Global field synchronization (GFS) was another method to measure functional synchronization in frequency-domain EEG data, which could estimate the functional connectivity between brain areas in different EEG frequency bands (Koenig et al., 2005). However, the GFS method did not give the strength of the synchronized cluster and a threshold was needed to be set in advance. Recently, an improved S-estimator was proposed to obtain a global synchronous index (GSI) of multiple neural series (Cui, Liu, Wan, & Li, 2010). The correlation coefficient between neural series was calculated by an equal-time correlation method, which was a simple way to measure a linear correlation between two series. However, this method cannot reveal the nonlinear interaction between two series, nor depressed the effect of the noise. Therefore, it is necessary to explore a new method for obtaining an accurate synchronization index among neural series and the reliable global synchronization strength among multivariate neural series.

Permutation mutual information (PMI) (Ouyang, 2009) was a new method to estimate the interdependency of two time series, which had the advantages of the mutual information (Baruchi, Volman, Raichman, Shein, & Ben-Jacob, 2008; Chen et al., 2008) and the permutation analysis (Bandt & Pompe, 2002). Namely, mutual information considered the nonlinear and linear relationship between two EEG series, and permutation analysis could detect the hidden patterns of time series accurately and was excellent in overcoming the effect of noise (Ouyang, 2009). PMI method was preferable to calculate the synchronization strength between neural series than other methods, such as equal-time correlation and mutual information (Ouyang, 2009). Therefore, in this study, we integrated the PMI into the GSI method, and proposed a new method called global coupling index (GCI) for estimating the global synchronization strength in multivariate neural signals. To test the performance of the method, the simulated EEG time series from multi-channel neural mass model was analyzed. The effects of different frequency bands, coupling coefficient, and signal noise ratio (SNR) on the GCI, GSI, and S-estimator methods were investigated for comparisons. The proposed GCI was then applied for the analysis of the multivariate EEG recordings from subjects with mild cognitive impairment (MCI) and normal controls (NC), and the correlation between the GCI values and scores of Mini-mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) in all subjects were also analyzed.

2. Methods

2.1. Multi-channel neural mass model for simulation analysis

A neural mass model (NMM) is often used to generate simulated EEG data that are very similar to real EEG signals (David, Cosmelli, & Friston, 2004; Ursino, Zavaglia, Astolfi, & Babiloni, 2007; Zavaglia, Astolfi, Babiloni,& Ursino, 2008). And a modified multi-channel neural mass model (MMNMM) simulated successfully multi-channel EEG signals (Cui, Li, Ji, & Liu, 2011; Cui et al., 2010). By using the neural series from the MMNMM, the global synchronization index and random synchronization index have been demonstrated to track the amount of genuine synchronization and stochastic synchronization in multivariate neural series (Cui et al., 2011). Therefore, in this study MMNMM was used to test whether the GCI was able to track the synchronization as well. This study used many parameters, which are the same as those used in the references (Cui et al., 2011, 2010), including the channel number ($M = 10$), parallel subpopulations number ($N = 3$), weight parameters ($W = [w_j^1, w_j^2, w_j^3], j = 1, \dots, M$), coupling coefficients ($q_{jk} = q(j, k = 1, \dots, M, j \neq k)$), extrinsic inputs ($p_j(t)$) and their mean value ($\langle p_j \rangle = 220$) and standard deviation ($\sigma_{p_j} = 22$), propagation time delay ($\tau_0 = 10$ ms), the sampling frequency (500 Hz), and other specified parameters in the model. In Sections 3.1.2 and 3.1.3, 10-channel neural series was generated by the MMNMM with the weight coefficients ($W = [0.5, 0.3, 0.2]$) to demonstrate the performance of proposed method.

2.2. S-estimator and global synchronization index

The S-estimator (Carmeli et al., 2005) quantized the global synchronization of multivariate time series recorded synchronously from multiple sites. The global synchronization index (GSI) (Cui et al., 2010) improved the S-estimator method. To calculate the S-estimator and GSI value, a matrix with synchronizing information between all possible pairs of time series needed to be evaluated. Firstly, an equal-time correlation method was used to calculate a correlation matrix C, and $\lambda_1 \leq \lambda_2 \leq \cdots \leq \lambda_M$ were the eigenvalues of C, where M was the row and column number of C. And then amplitude-adjusted Fourier transform (Schreiber & Schmitz, 1996) was applied to generate surrogate data. Based on the surrogate data, the equal-time surrogate correlation matrix R was calculated, and the eigenvalues of R denoted $\lambda_1^s \leq \lambda_2^s \leq \cdots \leq \lambda_M^s$. Then, the eigenvalues of matrix C were normalized:

$$\lambda_i^{(1)} = \frac{\lambda_i}{\sum_{i=1}^{M} \lambda_i}, \quad i = 1, \dots, M. \tag{1}$$

To reduce the effects of the random components in the total synchronization, the eigenvalues were divided by the averaged surrogate eigenvalues:

$$\lambda_i^{(2)} = \frac{\lambda_i / \bar{\lambda}_i^s}{\sum_{i=1}^{M} \lambda_i / \bar{\lambda}_i^s}, \quad i = 1, \dots, M, \tag{2}$$