DECOMPOSING DYNAMIC FUNCTIONAL CONNECTIVITY ONTO PHASE-DEPENDENT EIGENCONNECTIVITIES USING THE HILBERT TRANSFORM

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ABSTRACT

Dynamic functional connectivity (dFC) based on resting-state functional magnetic resonance imaging (fMRI) is a new avenue to explore brain network dynamics. Considering the time-varying evolution of the connectivity between spatially-defined regions increases drastically the dimensionality of the data with respect to static FC. Two of the more common approaches explored so far to analyze the large amount of data and to identify connectivity states are k-means clustering of the connections’ timecourses, revealing the average patterns of connections mainly recurring, and multivariate statistical methods like principal component analysis (PCA), identifying consistent connectivity patterns across time and population, so-called eigenconnectivities. In this work, we propose for the first time to explore the frequency content of dFC timecourses, with two objectives: 1) to decrease the computational load of the analysis by reducing the temporal redundancy intrinsically present in the data due to the sliding-window estimation; 2) to gain additional information about eigenconnectivities by using the Hilbert transform to explore phase information, that has been ignored until now. Results for resting-state fMRI data of 20 healthy subjects showed perfect consistency between the reduced and the original data, proving that we can safely ignore frequencies above the fundamental frequency of the window (i.e., fundamental frequency of the window length)

1. INTRODUCTION

Resting-state functional magnetic resonance imaging (fMRI) is a powerful imaging technique that allows exploring functional connectivity (FC) at the macroscopic scale. Most of the approaches explored in the past decade estimate FC between anatomically-defined regions in terms of temporal correlation of the fMRI signals over the complete acquisition (typically 5-10 minutes), relying on the implicit assumption that the connectivity is stationary over time. Recent evidence has highlighted, however, the dynamic nature of FC [1] and increasing attention has been consequently drawn to methods describing the time-varying features of functional resting-state networks (see [2] for a review). One of the most common approach to estimate dynamic FC (dFC) consists in observing the changes of the correlation between spatially-defined regions using a sliding-window technique [3-7]. The application of multivariate methods to dFC then emerged to extract the major patterns of reoccurring couplings between brain regions [4-5]. In particular, previous work by Leonardi et al. showed the application of principal component analysis (PCA) [4] and dictionary learning [8] to the dFC timecourses, leading to the identification of the so-called eigenconnectivities; i.e., patterns of connections mainly recurring across time and subjects. More efforts are needed to interpret the dFC mechanisms and exploit all possible information about network dynamic behavior, which appears promising for the characterization of neurological diseases as well; e.g., recent findings related dFC already to multiple sclerosis [4], schizophrenia [9] and post-traumatic stress disorder [10]. The main idea of this study is to analyze in more detail the frequency content of dFC timecourses, both to reduce the large amount of temporal redundancy present in the data, and to gain potentially useful information about network dynamics by the observation of their phase. One characteristic and often critical aspect of whole-brain dFC is indeed the large dimensionality of the data to be dealt with. The analysis, in fact, usually concerns thousands of connections whose strengths vary in time, and tens/hundreds of subjects. One way of reducing the data dimensionality without loss of content is removing redundant frequencies. We know, in fact, that the meaningful frequency content of the dFC is intrinsically limited by the use of the sliding-window technique, which constrains the temporal resolution of the observed events by the size of the window [11]. We can therefore reasonably expect that the removal of frequencies above the fundamental frequency of the window (i.e., 1/window length) would decrease the redundancy of the data without affecting the results. A first goal of this work is to validate this point and obtain an approach with significant reduction of computational load. Then, by means of an equivalent Hilbert transform, we want to exploit and analyze the phase information of the eigenconnectivities, which is not revealed by standard eigenconnectivity analysis. In particular, we will transform the dFC timecourses into the Fourier domain and consider a one-sided spectrum. The SVD decomposition of this data representation then renders eigenconnectivities that carry both amplitude and phase, thus providing quadrature relationships between large-scale brain networks that were ignored before.
2. METHODS

2.1. Subjects and acquisition scheme

In total, Ns = 20 healthy subjects underwent MRI using a 3T Siemens TIM Trio MR scanner with the following acquisitions: 1) 3D T1-weighted image, voxel size 1mm³ isotropic, 256x256x176 matrix, TE=2.27 ms, TR=3000 ms, 180 repetitions for 9 minutes duration during which a carbon dioxide (CO₂) challenge was administered via a nasal canula in a concentration of 7% mixed in synthetic air, following a block-based paradigm of 1 min OFF, 2 min ON, 2 min OFF, 2 min ON, 2 min OFF. Subjects were asked to breathe normally through the nose and to lie still keeping their eyes closed without thinking at something particular, following the standard resting-state acquisition practice. The effect of the CO₂ challenge was removed in the data preprocessing (see below).

2.2. MRI preprocessing

Functional images were first spatially realigned to the mean image and then spatially smoothed by convolution with a Gaussian kernel (8mm FWHM), using SPM8 (FIL, UCL, UK). The high-resolution T1 image was linearly registered to the mean functional volume and individual tissue maps were segmented (white matter, gray matter, cerebrospinal fluid). The anatomical AAL atlas [12] (Nc = 90 regions without the cerebellum) was mapped onto the subjects’ functional space using the IBASPM toolbox [13]. The first 10 volumes (given M=[tag2(Ts)]) were normalized by removing the global mean and dividing by the time courses of all connections. The dFC matrices of all subjects were concatenated into the functional atlas, yielding Ns regional time series, and band-pass filtered ([0.01 – 0.15Hz]).

2.3. Identification of eigenconnectivities

First of all, the previously published pipeline [4] was applied to estimate the dFC. For every subject i, dFC was assessed by computing the sliding-window correlation between every pair of timecourses, with window length Δt = 20 TR (60s) and a step size s = 3 TR (9s). This yielded a Nc × Ts (where Nc = (Ns² – Ns) / 2 and Ts=n number of windows) dFC matrix Ci, containing in its rows the time courses of all connections. The dFC matrices of all subjects were normalized by removing the global mean and dividing by the standard deviation. Further, the time courses were centered by row-wise demeaning in order to focus on deviations from the baseline. The obtained dFC matrices were then concatenated together in the matrix \( X = [ C_1, C_2, \ldots, C_{N_s} ] \) of size Nc × NsTs and PCA was applied by means of singular value decomposition (SVD) of X (Eq. 1):

\[
X = U \Lambda V^T.
\]

The columns of U contain the eigenconnectivities that represent patterns of connections capturing most of the dFC variance across time and subjects. We typically limit the dimensionality to N = 10 components.

2.4. Reducing temporal redundancy

Knowing that the correlations between regional time courses were computed with a sliding-window, we can expect the meaningful fluctuations in the connection dynamics to be essentially limited to a maximum frequency of 1/Δt [11]. Hence, we can reduce the data redundancy by removing the higher-frequency content without loss of information. For every subject \( i = 1, \ldots, N_s \), we transformed the time course \( c_{ij} \) of every connection \( j = 1, \ldots, N_c \) to the frequency domain with the discrete Fourier transform (DFT) and then applied a low-pass filter \( H_1 \) with cutoff frequency \( 1/\Delta t \) (Eq. 2), corresponding to frequency bin \( K' = \lfloor (s2^{39}/TR/\Delta t) \rfloor \) (given \( M=[tag2(Ts)] \)):

\[
\hat{c}_{f,ij} = H_1 F c_{ij},
\]

with \( H_1 \) being a diagonal matrix containing the filter response on its diagonal. This yielded the \( N_c \times 2^{39} \) matrices \( C_i \) and \( C_{f,i} \), containing in their rows the Fourier transform of all connections’ timecourses (full and filtered, respectively). After filtering, the size of \( C_{f,i} \) can be safely reduced to \( N_c \times 2K' \), where only the lowest frequencies (positive and negative) are kept. This means an effective reduction in size by a factor of the number of volumes included in the sliding-window, i.e. \( \Delta t/8TR = 7 \) in our case. To verify that the filtering does not negatively affect the results, we concatenated the matrices \( C_{f,i} \) of all subjects into \( \hat{X}_f = [ C_{f,1}, C_{f,2}, \ldots, C_{f,N_s} ] \) and applied SVD: \( \hat{X}_f = U_f A_f \hat{V}_f^T \). The first \( N \) eigenconnectivities (columns of \( U_f \)) are real-valued (since we kept positive and negative frequencies) and were selected and compared with the original ones (columns of \( U \)).

2.5. Exploiting the phase dependency of eigenconnectivities

We proceeded by selecting only the positive frequency bins of the filtered data \( C_{f,i} \) of each subject \( i \). By discarding the negative frequencies, we obtained the equivalent of the Hilbert transform of the filtered data (Eq. 3):

\[
\hat{c}_{\text{H},ij} = H_2 \hat{c}_{ij},
\]

where \( H_2 \) only keeps the positive frequencies up to the cutoff frequency bin \( K' \). Performing this for each connection \( j \) yields the \( N_c \times K' \) matrix \( \hat{C}_{\text{H},i} \) for each subject \( i \), containing in its rows the filtered and Hilbert transformed series. We then concatenated the matrices of all subjects into \( \hat{X}_H = [ \hat{C}_{\text{H},1}, \hat{C}_{\text{H},2}, \ldots, \hat{C}_{\text{H},N_s} ] \) and applied again SVD: \( \hat{X}_H = U_H A_H \hat{V}_H^T \). The obtained complex eigenconnectivities contained in the columns of \( U_H \) can now be explored in terms of modulus and phase. We selected the connections whose module proved to be stable across decompositions on different samples. In a split-half cross-validation framework with \( K = 40 \) repetitions, we obtained 2K different PCA decompositions yielding 2K left singular matrices \( U^{(k)}_{\text{H}} \) (\( k = 1, \ldots, 2K \)), whose first \( N \) columns \( U^{(k)}_{\text{H},i} \) were selected and matched among the different decompositions with the Hungarian algorithm [15], using the module of their inner product as similarity measure (Eq. 4):
Fig. 1. Illustration of the first five eigenconnectivities (in rows) for A) original method, (B) filtering approach, (C, D) Hilbert approach with in-phase and quadrature components, respectively.

\[
\left| \langle \mathbf{u}^{(k1)}_{\mathcal{H},n1}, \mathbf{u}^{(k2)}_{\mathcal{H},n2} \rangle \right| = (4)
\]

with \( n_1, n_2 = 1, \ldots, N \) and \( k_1, k_2 = 1, \ldots, 2K \), where the inner product \( \langle \mathbf{u}, \mathbf{v} \rangle \) between two complex vectors \( \mathbf{u} \) and \( \mathbf{v} \) is defined as (Eq. 5):

\[
\langle \mathbf{u}, \mathbf{v} \rangle = \sum_k u_k^* v_k. \quad (5)
\]

To obtain matching components with the same sign, the phase of the inner product \( \psi = \angle \langle \mathbf{u}^{(k1)}_{\mathcal{H},n1}, \mathbf{u}^{(k2)}_{\mathcal{H},n2} \rangle \) was used and the pairs of components for which \( |\text{mod}(\psi, 2\pi) - \pi| < \pi/2 \) were flipped in sign. For every eigenconnectivity \( n = 1, \ldots, N \), the variance of connections across decompositions was tested with a non-parametric test using 999 surrogates obtained by permutation of the component order within every decomposition, and testing the null hypothesis of equal variance in case of randomly matched components. Connections with \( p < 0.05 \) were selected and split into two groups, according to their phase \( \phi_n = \angle \mathbf{u}_{\mathcal{H},n} \): a) in phase connections, with: \( |\text{mod}(\phi_n, \pi) - \pi/2| \geq \pi/4 \); b) quadrature connections, with: \( |\text{mod}(\phi_n, \pi) - \pi/2| < \pi/4 \).

### 3. RESULTS

The eigenconnectivities obtained from the decomposition of the original \( \mathbf{X} \) and the filtered \( \mathbf{X}_f \) dataset were identical (Fig. 1, A, B). The variance explained by the first \( N \) components was 43% for the conventional eigenconnectivities and 48% for the new eigenconnectivities in Hilbert space. The proportion of stable connections \( (p < 0.05) \) across different decompositions was high \((> 75\%)\) for the first three eigenconnectivities (explaining the largest variance in the data) and decreased gradually for further components (Fig. 1, C, D). The analysis of the phase of eigenconnectivities highlighted a subset of quadrature connections (Fig. 1, D) that instead increased in number compared to the in-phase connections, for higher order (e.g., components 4, 5, in Fig. 1, C, D). In line with previous literature \[4\], eigenconnectivity 1 identifies global FC excursions around the mean and, as expected, is characterized by almost all in-phase connections. Eigenconnectivity 2 showed to be very stable and the in-phase map contrasted connections of the anterior default mode network (DMN, blue) with posterior DMN and sensori-motor areas (red). The identified quadrature phase subnetwork included inferior frontal regions, hippocampus, parahippocampus (red), frontal and paracentral areas (blue) (Fig. 2, A, B). These connections (Fig. 1, D) are not strong in the original eigenconnectivity (Fig.1, A). Eigenconnectivity 3 contrasted occipito-pairential areas (blue) with fronto-temporal connections (red). Quadrature connections included instead fronto-occipital and paracentral-temporal connections, also not present in the original eigenconnectivity. The last two eigenconnectivities are mainly characterized by the quadrature connections, involving precentral, DMN, frontal (red) occipital and temporal (blue) areas for component 4 (Fig. 2, C, D), and sensory motor cortex for component 5.

### 4. DISCUSSION AND CONCLUSION

We proposed to explore the frequency content and phase dependency of recurring dFC patterns with the aim of both reducing data redundancy and revealing additional information. Results on 20 healthy subjects were promising and encourage further extensive applications, especially to clinical studies of neurological diseases. Our method presents several novel aspects. Firstly, by low-pass filtering the data we considerably decreased the computational load without loss of information, as proved by the matching between the results of the full and filtered datasets (Fig. 1, A, B). Secondly, by testing the dFC variance across repetitions, we supplied a way to threshold the eigenconnectivities, keeping connections that are stable across decompositions. The identification of the more meaningful connections and the consequent thresholding of eigenconnectivities is indeed one current issue of the dFC approach. Further, the computation of Hilbert-pair eigenconnectivities, which permit the exploration of the phase information, allowed to highlight quadrature components that indicate meaningful subnetworks, satisfying particular phase relationships (Fig. 1, D). The exploitation of these subnetworks offers a more complete picture of the dynamic connectivity patterns recurring during resting-state and, therefore, might contribute to a deeper understanding of mechanisms of network dynamics. In our future research, the temporal evolution of the Hilbert-paired eigenconnectivities will be investigated, which may help in providing a clearer interpretation of the phase/quadrature components. The additional information provided by the phase could identify more subtle interactions of networks (e.g., in terms of segregation/integration) that can be altered for instance due to neurological disease. The use of tapered windows or the wavelet transform could also further refine the analysis, at the expense of additional frequency bins or subbands.
Fig. 2. Brain graphs of Hilbert-paired (A, B) eigenconnectivity 2 and (C, D) eigenconnectivity 4 for in-phase and quadrature connections, respectively (left: axial and right: sagittal views).

5. REFERENCES


