Individual Topological Analysis of Synchronization-Based Brain Connectivity

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Functional connectivity analysis aims at assessing the strength of functional coupling between the signal responses in distinct brain areas. Usually, functional magnetic resonance imaging (fMRI) time series connections are estimated through zero-lag correlation metrics that quantify the statistical similarity between pairs of regions or spectral measures that assess synchronization at a frequency band of interest. Here, we explored the application of a new metric to assess the functional synchronization in phase space between fMRI time series in a resting state. We applied a complete topological analysis to the resulting connectivity matrix to uncover both the macro-scale organization of the brain and detect the most important nodes. The synchronization metric is also compared with Pearson’s correlation coefficient and spectral coherence to highlight similarities and differences between the topologies of the three functional networks. We found that the individual topological organization of the resulting synchronization-based connectivity networks shows a finer modular organization than that identified with the other two metrics and a low overlap with the modular partitions of the other two networks suggesting that the derived topological information is not redundant and could be potentially integrated to provide a multi-scale description of functional connectivity.

Introduction and background

A wide range of biological phenomena are characterized by synchronization of systems whose complex cooperation and integration explain the emergence of vital functions [1]. Several synchronization metrics have been introduced to quantify the coupling behavior of interacting dynamic systems [2, 3]. In particular, there has been a growing body of literature addressing the application of complex network analysis for the characterization of dynamical systems based on time series. These combined approaches have clarified fundamental issues about the organization of nonlinear dynamics in different fields. As an example, the complex and nonlinear nature of brain dynamics is widely discussed in the literature [4, 5, 6]. The human brain is modeled as a complex network composed of anatomical and functional sub-systems whose interactions allow the performance of both high- and low-level cognitive functions. Such interactions have been extensively modeled through the mathematical framework of the complex networks, which allows the treating of each subsystem as a node of a network and to identify specific topological properties of nodes and links in the network [7, 8]. Topological data analysis have been largely applied to investigate the architecture of brain networks and connectivity differences between individuals at several levels of the data hierarchy [9, 10, 11]. These techniques can be applied both to functional data, which describe the dynamic brain activity through functional magnetic resonance imaging (fMRI) or electrophysiological acquisitions [12, 13]. In particular, over the past decade, there has been an increasing interest in inferring connectivity properties from fMRI data [14, 15]. Functional connectivity (FC) analysis aims at assessing the strength of functional coupling between the signal responses in distinct brain areas [16]. According to the complex network framework, the anatomical regions of interest are modeled as the nodes of the network, linked by edges resulting from the selected synchronization metric. Pairwise Blood oxygenation level dependent (BOLD) time series connections can be estimated through different metrics including cross-correlation, cross-coherence and causal modeling [17]. Each FC metric quantifies different forms of dependency between the BOLD signals: zero-lag correlation metrics quantify the statistical similarity between pairs of region, other metrics assess synchronization at frequency band of interest [18, 19], others capture direct coupling between time series [20, 21].

Recently, new metrics to assess the coupling behavior of BOLD time series have been introduced to capture both linear and nonlinear interactions in human brain. In particular, a generalized synchronization index (SYNC) has been proposed to assess the functional connectivity with fMRI data [22, 23]. Such metric has been proven effective in detecting active sub-networks during a high-level cognitive process, describing age-related functional patterns [24] and identifying and quantifying pathological states [25]. The analyses of functional brain connectivity in the state of rest have revealed different modular configurations of the brain activity, which reflect specific functions and varied spatial topologies [26]. Moreover, the role of specific regions acting as network hubs for the efficient functioning of the human brain has been extensively documented [27, 28]. Brain hubs facilitate the integration of functionally specialized neural systems by supporting long-range connections [29, 30] and by routing a large amount of neural information [31]. The dysfunction of some brain hubs has been also related to pathological conditions and psychiatric disorders [32, 33].

In this work, we performed a comparison of the synchronization connectivity pattern derived from the SYNC metric, statistical Pearson correlation and spectral coherence functional connectivity. In particular, we exploited the resting state fMRI data of a single subject to construct three functional connectivity networks and explore the topological organization of their macro-scale architectures by means of a modularity analysis. We investigated the topological properties of the most important nodes of the networks to detect stable hubs. Here, the SYNC hub nodes represent regions with a high level of synchronization over the entire time interval with different functional sub-systems. Such nodes differ from the hubs of correlation and coherence networks as statistical correlation is related to the average synchronization level over the observation period, while spectral coherence can identify the frequencies that drive the linear association between the two time courses. One of the principal objectives of this work is to verify whether an overlap of these nodes exists with respect to those identified in the Pearson and coherence networks in order to better elucidate the synchronization index method in functional connectivity analysis. Recent precision functional mapping has shown that individual brain organization is qualitatively different from group average estimates and that individuals can exhibit distinct brain network topologies [34, 35]. For this reason, we have chosen a single subject-based analysis. Indeed, the individual analysis address a targeted comparison of the regions included in each module and the hub roles between the three functional networks obtained respectively with SYNC metric, Pearson statistical correlation and spectral coherence. We also tested the reliability of the results by analyzing ten
scans of the same subjects.

**Materials and Methods**

We included ten resting-state baseline fMRI sessions of two subjects (first subject 0025427, sex: male, age: 23 years; second subject 0025432, sex: male, age: 21 years) from the Hangzhou Normal University (HNU) cohort of the Consortium for Reliability and Reproducibility (CoRR) [36]. More details about recruitment, inclusion criteria and assessment protocols are available on the project website (http://fcon_1000.projects.nitrc.org/indi/CoRR/html/hnu_1.html).

The data sessions were preprocessed using the configurable pipeline for the analysis of connectomes (CPAC).

Functional synchronization connectivity between all pairwise combinations of ROI time series was assessed by estimating their cross-recurrence plots (CRP) and then by calculating the SYNC index resulting in a weighted connectivity matrix for each fMRI session.

A system could be represented in the phase space, i.e., a topological representation of its behavior under different initial conditions. This method assumes that each signal represents a projection of a higher-dimensional dynamical system evolving in time, whose trajectories are embedded into a manifold, i.e., a region of its phase space.

The phase space of a system could be reconstructed by means of the Takens’s Theorem [38].

A CRP exhibits characteristic patterns that show local time relationships of the segments of the trajectories of the two interacting systems.

As an example, diagonal lines occur when the evolution of the states is similar at different times and their lengths are related to the periods during which the two systems move in similar ways remaining close to each other [42]. The main diagonal of a CRP represents a line of synchronization (LOS), since it implies the identity of the states of the two systems in the same time intervals.

The LOS structure can be analyzed to extract information about the synchronization of the two time series [43]. In particular, the presence of LOS suggests that the two time series are fully synchronized, while discontinuities appear when the two signals are not fully synchronized.

We defined the synchronization time metric (SYNC) to quantify the mean period during which the two systems are synchronized in order to reflect the dynamical synchronization behavior of the series throughout the observation period [22,25].

The coupling behavior in phase space can be illustrated by referring to a pair of simple sine waves. We compare the SYNC approach to Pearson correlation coefficient and spectral coherence.

In Figure 1, the CRPs and the extracted LOS are represented for three different cases:
- a sine wave synchronized with itself throughout the observation period 0-T;
- a sine wave and a second sine wave fully synchronized during half of the observation period 0-T/2;
- a sine wave and a second intermittently synchronized sine wave during a first observation interval 0-T/4 and a second observation interval T/2-3T/4.

For the first case, $R=1$, $C_{xy}=1$ and $SYNC=1$, since the LOS is complete. For the second case $R=0.7$, $C_{xy}=0.16$ and $SYNC=0.5$, while for the third case $R=0.7$, $C_{xy}=0.15$ and $SYNC=0.25$. The Person correlation measures the overall statistical similarity between the two time series, the coherence metric measures their linear relationship in the frequency domain while the SYNC metric takes into account also the intermittency.
We performed a connectivity analysis of fMRI based on Synchronization metric. In particular:
- a modularity analysis to determine the most representative community structure of each functional network across sections based on Louvain algorithm
- identification of hub nodes

These graph metrics are often used to capture the centrality of nodes in brain networks and to map regions that act as hubs. Here, we used a cartographic system mapping each node in a plane through the ordered pair of values $(PC_i,z_i)$ to identify the connective hubs, i.e., those nodes with higher connection strength and high centrality values. This cartographic system allows identification through a statistical threshold level, different roles of the nodes in a network. Hub nodes are central nodes, so they are characterized by high $z$ values. In addition, hubs can be divided into three different categories: provincial hubs, i.e., hub nodes with the vast majority of links within their module (lower values of $PC_i$); connector hubs with many links to most of the other modules and kinless hubs with links homogeneously distributed among all modules (highest $PC$ values). We used the 25th and 75th percentile of both metrics to divide the plane $(PC,z)$ into nine regions to identify the hubs of the networks.

To compare the topologies of the three functional networks across all the sections of the subject, we included into the final three sets only the hubs that appear with a specific role in at least six sessions of each functional connectivity network.

**Results and Discussions**

The three functional connectivity networks are shown in Figure 2 with the empirical probability distributions of the weights in semi-logarithmic scale. The three matrices are very different form each other: the SYNC network is sparser, with only a small number of entries with high synchronization values. This aspect is also emphasized by the probability distribution which shows a right long-tailed trend, with few outliers between 0.2 and 1.

This finding highlights a first important difference between the connectivity matrices, i.e., most regions exhibit a very intermittent synchronization behavior, although on average the pairs of ROIs are moderately statistically correlated in time and frequency (median value of Pearson matrix $\sim 0.3$ and median value of coherence matrix $\sim 0.25$).
Figure 2. Pearson correlation matrix (a), SYNC matrix (b) and coherence matrix (c) with the empirical probability distributions of the links of the three matrices in semi-logarithmic scale (d).

Figure 3 shows the most representative network partition across the fMRI session of the subject. Seven modules were detected in the SYNC matrix; the first module comprises areas almost becoming from the cingulate cortex, e.g., cingulate gyrus, anterior and mid cingulate. Several specialized control areas of frontal regions such as medial orbital superior frontal gyrus are included in the second module. The third module resembles both peripheral and central visual networks as it includes all the occipital lobe, the calcarine fissure and surrounding cortex. The fourth module resulted the largest as it includes all the other regions from the frontoparietal network. The fifth module overlaps with most regions of the cerebellar network; the sixth module includes: superior frontal gyrus, middle temporal gyrus, inferior temporal gyrus and cerebellar crus areas. These modules are equally distributed across the default and control networks previously described in the resting-state literature. The seventh is mainly composed by areas from the limbic system such as amygdala and para-hippocampal gyrus.

In contrast, the Pearson and coherence network are composed by only four and three modules, respectively.

The three network configurations resemble different functional organization of the brain during the resting state. The SYNC network shows very specialized co-synchronized patterns, also including very small modules clearly related to salient control functions of the brain; on the other hand, both~Pearson and coherence connectivity capture functional organization at macro-scale highlighting patterns of different degree of average statistical correlation between regions. These findings suggest that the modular organization of the three functional connectivity could be integrated to describe the hierarchical behavior of the multi-scale synchronization between the interacting regions during different cognitive states or conditions.
Figure 3. The functional modules detected in SYNC networks (top panel), Pearson correlation network (middle panel) and coherence network (bottom panel). All the ROIs within the same module are indicated with spheres of the same color.

The three networks showed significant differences among them. First, the modularity analysis showed higher values of modularity index $Q$ in SYNC networks than the other two networks thus indicating a clearer division into communities. Second, the analysis of NMI values highlighted that the three networks showed modular partitions with a low overlap between them (below 50%). The different topological configurations in the three networks were confirmed by the analysis of the hubs, which outlined the presence of different central roles of functional areas. The results suggest that statistical correlation and coherence networks show more evenly distributed synchronization patterns of comparable size in the brain, while SYNC networks exhibit more granular partitions, highlighting more varied synchronization patterns.

**Conclusion**

In this work, we analyzed the topological organization of SYNC-based, Pearson correlation and spectral coherence networks of a single subject. We showed that even if the metrics are mutually linked, the SYNC metric emphasizes the intermittent behavior of the interacting systems showing a greater matrix sparsity. The resulting network topologies were examined to identify the macro-scale modular organization of the nodes and compared to each other. Our analysis revealed some interesting aspects of the structure of SYNC network during resting rest such as the presence of multi-domains highly synchronized brain regions.

In addition, the hub nodes of the networks were detected showing only a partial overlap across the three networks. It is important to note that the three measures provide different descriptions of the interaction behaviors between BOLD signals. Indeed the results suggest that the topological information derived from each matrix is not redundant and could be integrated into a multi-view logic to retrieve different information on the interaction and integration of functional sub-systems by using a multilayer connectivity matrix.

**Keywords**

functional connectivity; synchronization; cross-recurrence plots; resting state fMRI
