Synchrony and Complexity in State-Related EEG Networks: An Application of Spectral Graph Theory

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The brain may be considered as a synchronized dynamic network with several coherent dynamical units. However, concerns remain whether synchronizability is a stable state in the brain networks. If so, which index can best reveal the synchronizability in brain networks? To answer these questions, we tested the application of the spectral graph theory and the Shannon entropy as alternative approaches in neuroimaging. We specifically tested the alpha rhythm in the resting-state eye closed (rsEC) and the resting-state eye open (rsEO) conditions, a well-studied classical example of synchrony in neuroimaging EEG. Since the synchronizability of alpha rhythm is more stable during the rsEC than the rsEO, we hypothesized that our suggested spectral graph theory indices (as reliable measures to interpret the synchronizability of brain signals) should exhibit higher values in the rsEC than the rsEO condition. We performed two separate analyses of two different datasets (as elementary and confirmatory studies). Based on the results of both studies and in agreement with...
our hypothesis, the spectral graph indices revealed higher stability of synchronizability in the rsEC condition. The k-mean analysis indicated that the spectral graph indices can distinguish the rsEC and rsEO conditions by considering the synchronizability of brain networks. We also computed correlations among the spectral indices, the Shannon entropy, and the topological indices of brain networks, as well as random networks. Correlation analysis indicated that although the spectral and the topological properties of random networks are completely independent, these features are significantly correlated with each other in brain networks. Furthermore, we found that complexity in the investigated brain networks is inversely related to the stability of synchronizability. In conclusion, we revealed that the spectral graph theory approach can be reliably applied to study the stability of synchronizability of state-related brain networks.

1 Introduction

At the macroscopic scale, the healthy brain may be considered as a synchronized complex network that is constructed by several coherent dynamical neural units (Fries, 2005, 2015; Kitzbichler, Smith, Christensen, and Bullmore, 2009; Klimesch, 1996; Rodriguez et al., 1999). However, concerns remain about synchronizability as a stable state in brain networks (Papo & Buldú, 2018) and about its measurement at the macroscopic scale when several brain regions or recording electrodes are involved. One of the matters of confusion about this general question is which types of brain networks should be analyzed when synchronizability is an important consideration. Previous studies have investigated different kinds of neuroimaging data, including diffusion tensor imaging (DTI), magnetic resonance imaging (MRI), electroencephalography (EEG), and magnetoencephalography (MEG), to reveal the synchronizability of various brain networks (Bialonski & Lehnertz, 2013; de Haan et al., 2012; Niso et al., 2015; Phillips, McGlaughlin, Ruth, Jager, & Soldan, 2015; Schindler, Bialonski, Horstmann, Elger, & Lehnertz, 2008; Stam & Reijneveld, 2007; Tang et al., 2017; Ton, Deco, & Daffertshofer, 2014; van Wijk, Stam, & Daffertshofer, 2010; Zhu et al., 2019).

The use of appropriate mathematical methods to investigate the synchronizability of brain networks is another important issue that should be considered. In most of the previous studies, the master stability function (MSF), with examination of the eigenvalue spectrum of the Laplacian matrix, has been used to investigate the stability of network synchronizability. In this term, the lower dispersion of eigenvalue spectrum (lower eigenratio) is interpreted as a higher stability of synchronizability in the brain network (Tang et al., 2017; Zhu et al., 2019).

Contrary to the above notion, a recent study (Papo & Buldú, 2018) has shown that the dispersion of eigenvalues cannot specify the
synchronizability for a partly synchronized system (which stays synchronized in a specific condition and in the range of defined thresholds) such as the brain. More strictly, they suggested that this type of analysis for finding the synchronizability should not be used in neuroscience (Papo & Buldú, 2018) while reasoning that the MSF was originally introduced to find synchronizability of diffusively coupled identical dynamical systems (Pecora & Carroll, 1998). Thus, within this framework, the MSF is applicable only to report the stability of synchronizability of a specific mode with complete synchronization (i.e., when all the units exhibit the same amplitude and frequency in their dynamical fluctuation). Certainly the brain is not such a system. This argument can raise serious debates about the application of eigenratio as a reliable measure to find the stability of neural network dynamics. Therefore, in cases with an obvious synchronized condition in the brain, we require a reliable measure to further investigate and clearly interpret the synchronizability of brain networks.

To this aim, we applied three proposed indices from spectral graph theory (see Figure 1): the energy of the graph, the largest eigenvalue, and the second smallest eigenvalue (Daianu et al., 2015; Wang et al., 2015). In general, the energy is not considered in relation to the MSF and is proposed as an applicable index to evaluate the stability of synchronizability in the chemical and physical systems (Gutman, 2013; Gutman & Zhou, 2006; Li, Shi, & Gutman, 2012). Therefore, this measure (energy) may disclose and clarify the stability of synchrony in a network that is constructed by functional connectivity among different EEG electrodes. The largest eigenvalue and the second smallest eigenvalue are also suggested to predict the dynamical range of weighted networks (Larremore, Shew, & Restrepo, 2011). Since the brain synchrony and complexity are frequently reported to be related (Ahmadlou & Adeli, 2017; Dimitriadis, 2018; Huang, Ho, Lu, & Kurths, 2015), we investigated the complexity of networks through the novel application of the Shannon entropy (see Figure 1).

To test the reliability of these measures, we used a well-studied classical example of synchrony in the neuroimaging literature—differences of the alpha activity synchronization between the resting-state eye close (rsEC) and the resting-state eye open (rsEO) conditions. Since the 1920s, when the alpha rhythm was first observed on an electroencephalogram by Hans Berger (1929), several studies have demonstrated that the alpha rhythm is more synchronized during the rsEC than the rsEO condition (Ben-Simon et al., 2013; Brodoehl, Klingner, & Witte, 2015; Chapman, Shelburne, & Bragdon, 1970; Kirkup, Searle, Craig, McIsaac, & Larsen, 1998; Liu et al., 2012). This synchronization is supposed to be associated with the dominant activation of the thalamocortical pathways in the rsEC condition (Hughes & Crunelli, 2005; Liu et al., 2012). Then, if our suggested measures reliably reveal the synchronizability of the brain network, it should exhibit higher values in the rsEC than the rsEO condition.
Figure 1: EEG networks can be constructed by functional connectivity measures like coherence. Functional connections between EEG electrodes construct a complex network that can be characterized by an adjacency matrix. An eigenvector equation determines the spectrum of eigenvalues, and measures related to the spectral graph theory are obtained based on this spectrum. These measures indicate synchronizability of graph. The Shannon entropy may be calculated for adjacency matrix. We suppose this measure can indicate complexity of network.

Furthermore, we tested methodological problems such as weight-conserving (Rubinov & Sporns, 2011) and dependence on randomness of graphs for the measures that we employed. After that, to separate the two state-related EEG networks (rsEC and rsEO), we compared the efficiency of the suggested spectral graph theory indices (energy, largest eigenvalue, and second smallest eigenvalue) with the topological indices derived by statistical graph theory approaches: conventional graph theory (Bullmore & Sporns, 2009; Rubinov & Sporns, 2010) and minimum spanning tree (Jalili, 2016; Tewarie, van Dellen, Hillebrand, & Stam, 2015). Moreover, we also computed the possible correlations of the indices for brain-generated and random networks. Consistent with our hypothesis, we showed that the spectral graph theory indices are reliable in finding the stability of synchronizability in EEG networks. Furthermore, we found an inverse relation between network complexity and synchrony. To our knowledge, this is the first time the relationship of spectral graph theory indices, Shannon entropy, and topological graph indices has been investigated.

2 Method

2.1 Studies, Participants, and Ethical Considerations. We reanalyzed two open access datasets (https://figshare.com/articles/Over_zip/5970886) in the rsEC and the rsEO conditions. The ethical processes and
the EEG acquisition and data were similar to our previously published paper (Ghaderi, Moradkhani et al., 2018b). Originally, the first dataset contains the EEG data from 47 participants, and the second dataset contains 17 participants. These datasets were acquired in two separate studies (see Ghaderi, Moradkhani et al., 2018b, for more details), and we selected these datasets here for performing an elementary study with 47 participants and a confirmatory study with 17 participants. The confirmatory study was accomplished to further test the reliability of new results from the elementary study.

Three participants (two participants from the first dataset and one participant from the second dataset) were rejected because of too many artifacts in their EEG in the eye-closed condition. We were left with 45 participants for the elementary study and 16 participants for the confirmatory one.

### 2.2 EEG Acquisition and Preanalysis of EEG Data

In each condition (rsEO and rsEC), the EEG activity was recorded for five minutes using a Discovery 24 amplifier (Brainmaster) with a sampling rate of 256 Hz and digitalized at 24-bit resolution. A Butterworth bandpass filter (0.1–40 Hz) was applied to the signals, which were recorded by an appropriate size Electrocap (based on the head size) via 19 EEG channels in the 10/20 system. Two differential channels were also connected to the left and right ears (A1 and A2) as references. Then the EEG signal acquisition and analyses were performed in linked-ear montage as used in several clinical and cognitive studies (Ghaderi, Andevari, & Sowman, 2018a; Ghaderi, Nazari, Shahrokhi, & Darooneh, 2017; Jouzizadeh, Khanbabaie, & Ghaderi, 2020; Khayyer, Ngaosuvan, Sikström, & Ghaderi, 2018; Thatcher, North, & Biver, 2005, 2008).

The EEGs were divided into segments with a length of 3 seconds. Segments were checked visually and by a z-score-based algorithm (NeuroGuide software, Applied Neuroscience) for artifacts. In each condition, 30 to 35 artifact-free signal segments with a length of 3 seconds were selected for fast Fourier transform (FFT) analysis. The FFT analysis was performed separately for each segment with a 25% sliding window (Kaiser & Sterman, 2005). Because alpha rhythm is more affected by eye conditions (Barry, Clarke, Johnstone, Magee, & Rushby, 2007; Miraglia, Vecchio, Bramanti, & Rossini, 2016), we applied a bandwidth filter (8 to 12 Hz, i.e., alpha rhythm) on the original signal and then used the alpha band for further analysis.

### 2.3 EEG Connectivity and Adjacency Matrix

Although high-density EEG studies with more than 64 recording channels can display a high spatial resolution of the brain function and the number of electrodes or nodes can improve the graph theory analysis, several recent studies with limited recording channels have indicated that reliable results can also be obtained
using the standard 10/20 system with 19 EEG channels (Ghaderi, Andevari, et al., 2018a; Ghaderi, Nazari, & Darooneh, 2019; Ghaderi et al., 2017; Tóth et al., 2017; Utianski et al., 2016; Vecchio et al., 2017).

In order to construct functional brain networks and calculate the graph theory indices, we used coherence as a simple and well-studied EEG connectivity measure (Bassett & Bullmore, 2006; Bowyer, 2016; Finger et al., 2016; Ghaderi, Moradkhani et al., 2018b, 2017; Jalili, 2016; Thatcher et al., 1986). Although several criticisms (the most important is the effect of volume conduction) have been raised against coherence (Nunez et al., 1997), it is still a useful and meaningful measure when revealing coupling and synchronizing between neural units is important (Bowyer, 2016; Buzsáki & Schomburg, 2015; Fries, 2015; Niso et al., 2015). Furthermore, when the topological properties of brain networks were investigated, a recent study suggested that coherence might be a better measure than the phase-order parameter and the synchronization likelihood to expose more significant differences between groups or conditions (Jalili, 2016). But the effect of volume conduction is more important when the EEG electrodes are located very close together (high-density EEG). Notably, in the 19-channel system used in this study, the reliability of $1 \times N$ connectivity derived by coherence is greater than phase synchrony estimates (Miskovic & Keil, 2015).

We used the function `mscohere` in Matlab to find magnitude-squared coherence in the alpha band (8–12 Hz). Mathematically, this function calculates (Gómez-Gonzalez, Rodríguez, Sagartzazu, Schuhmacher, & Isasa, 2010)

$$\text{Coh}(f) = \left( \frac{G_{xy}(f)}{G_{xx}(f)G_{yy}(f)} \right)^2,$$

where $G_{xy}(f)$ is a cross-spectrum between signals $x$ and $y$ and $G_{xx}(f)$, $G_{yy}(f)$ are autospectra for $x$ and $y$, respectively. In this equation, coherence is related to the phase difference between signals $x$ and $y$. When the phase changes randomly between signals, then coherence is close to zero, whereas it is equal to one when the phase is constant between signals (Thatcher et al., 2008).

Furthermore, in the confirmatory study, we also used weighted phase lag (Hardmeier et al., 2014) in addition to coherence to find how the spectral indices are influenced by another connectivity measure. More details about the weighted phase lag have been presented in the online supplementary materials (see section 1).

In both studies, connectivity measures (coherence and weighted phase lag) were calculated between 171 pairs ($\frac{19 \times 18}{2}$) of channels, which were then used to generate the adjacency matrix. In the adjacency matrix, each row/column represents a channel, and their intersection in the matrix corresponds to the value of connectivity between channels. This weighted
adjacency matrix was subsequently used for further analysis (as described in the following sections).

2.4 Topological Indices.

2.4.1 Clustering Coefficient and Characteristic Shortest Path of Weighted Graphs. We used two well-studied measures, the clustering coefficient \( C \) and the characteristic shortest path \( L \), to investigate the topology of weighted graphs (Bassett & Sporns, 2017; Bullmore & Sporns, 2009; Rubinov & Sporns, 2010). These measures are briefly described in Table 1. The clustering coefficient allows identifying features related to the level of segregation in the network (Rubinov & Sporns, 2010). The \( C \) of the node \( i \) in an undirected weighted network, such as that in our study, is defined as (Wang, Ghumare, Vandenberghe, & Dupont, 2017)

\[
C(i) = \frac{1}{k_i(k_i - 1)} \sum_{j,h} a_{ij}a_{ih}a_{jh},
\]

where \( k_i \) is the degree of the node \( i \) and \( a_{ij} \) defines the connectivity weight between the nodes \( i \) and \( j \).

The characteristic shortest path (Rubinov & Sporns, 2010) of a functional brain network uncovers information about the brain integration. In an undirected weighted graph, the shortest path between two nodes \( i \) and \( j \) is measured by the minimum summation of weights between those two nodes, where the characteristic shortest path is the average of all the shortest paths between all possible pairs of nodes (Rubinov & Sporns, 2010),

\[
L^w = \frac{1}{n} \sum_{i \in N} \sum_{j \neq i} \frac{d_{ij}^w}{n - 1},
\]

where \( N \) is the neutral number set, \( d_{ij}^w \) is the distance between two nodes \( i \) and \( j \), and \( n \) is number of the paths in the graph.

To calculate these measures, we used the matrices obtained in the previous section that contain coherence values for each combination of the 19 pairs of electrodes. These matrices were calculated for both the rsEO and rsEC conditions—two matrices (rsEO, rsEC) for each participant—as well as random matrices with normal and exponential distributions. We used the brain connectivity toolbox (Rubinov & Sporns, 2010) to calculate the clustering coefficient and the characteristic shortest path of weighed graphs.

2.4.2 Minimum Spanning Tree (MST) Analysis. Typically the MST finds a backbone (tree) for a weighted graph (Stam et al., 2014). In weighted networks, nodes can be connected through multiple paths to each other, and
Table 1: Graph Theory Indices Are Used in This Study.

| Approach                          | Index                        | Abbreviation | Description                                                                                                                                                                                                                                                                                                                                 | Equation                                                                                     |
|-----------------------------------|------------------------------|--------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| Topological indices (weighted graphs) | Clustering coefficient       | C            | In a weighted graph, C measures the triangles around a node in a graph. If all the neighborhoods of a given node connect with maximum weight (one) to each other, the C for this node is 1, and if all the neighborhoods are disconnected from each other, then C will be 0. The average of C over all nodes is associated with segregation in the graph. | $C(i) = \frac{1}{k_i (k_i - 1)} \sum_{j,h} a_{ij} a_{jh} a_{jh}$ $k_i$: The degree of the node i $a_{ij}$: The connectivity weight between the nodes I and j |
|                                   | Characteristic shortest path | L            | In a weighted graph, the shortest path is the one that has minimum summation of edge’s weights between two given nodes. The L is the average of the shortest paths across all nodes. In a graph, the L is inversely associated with the level of integration (e.g., higher L is associated with lower integration in the graph). | $L_w = \frac{1}{n} \sum_{i \in N, j \neq i} d_{ij}^w$ $N$: Neutral number set $d_{ij}^w$: The distance between two nodes I and j $n$: Number of the paths in the graph |
| Topological indices (minimum spanning tree) | Maximum betweenness centrality | $BC_{max}$  | In a tree (a graph without any loop), the $BC$ of a given node is the summation of the shortest paths (between other pairs of nodes) that are crossing the node. The $BC_{max}$ is the largest value of $BC$s among all nodes. A high value of $BC$ for a node indicates that the given node plays the role of a hub in the graph. The higher value of $BC_{max}$ in a graph shows the network is more centralized. | $BC(k) = \sum_{i \neq j \neq k} L_{ij}(k)$ $L_{ij}$: Shortest path between nodes i and j $k$: The index of a given node (the maximum of BC is the largest value among all nodes) |
Table 1: Continued.

| Approach                | Index  | Abbreviation | Description                                                                                                                                                                                                 | Equation |
|-------------------------|--------|--------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|
| Leaf fraction           | LF     | LF           | In a tree, the LF represents the number of nodes with just one connection (nodes that are located at the end of chain). In a spanning tree, the minimum LF is equal to 2, which is associated with a straight chain of nodes. A higher value of the LF in a graph shows that the graph is more centralized. | $LF = \sum_i N_i(K = 1)$ |
|                         |        |              | $N_i(K = 1)$: Nodes with degree $= 1$.                                                                                                                                                                       |          |
| Diameter                | D      | D            | In a tree, the D is the largest distance between any pair of nodes. A lower value of D indicates the tree is more centralized.                                                                               | $D = \max d_{ij}$ |
|                         |        |              | $d_{ij}$: Number of the edges between nodes $I$ and $j$                                                                                                                                                      |          |
| Eccentricity            | E      | E            | In a tree, the E of a given node is the largest distance between that node and any other node. A lower value of E indicates the tree is highly centralized.                                                     | $E(k) = \max d_{ik}$ |
|                         |        |              | $d_{ik}$: Number of the edges between the given node $k$ and any other node $i$                                                                                                                               |          |
| Spectral indices (weighted graph) | Energy | H            | In an undirected (symmetric) weighted graph, the summation of absolute values of associated eigenvalues (eigenvalues of adjacency matrix) is $H$. The $H$ is dependent on synchronizability in the graph. | $H = \sum_{i=1}^n |\lambda_i|$ |
|                         |        |              | $\lambda_i$: Eigenvalues of graph $n$: Number of nodes                                                                                                                                                      |          |
| Largest eigenvalue      | EigL   | EigL         | In an undirected (symmetric) weighted graph, the $\text{Eig}_L$ is the largest value among associated eigenvalues (eigenvalues of adjacency matrix). Higher values of $\text{Eig}_L$ show higher synchronizability in the graph. | $\text{Eig}_L = \max \lambda_i$ |
|                         |        |              | $\lambda_i$: Eigenvalues of graph                                                                                                                                                                         |          |
Table 1: Continued.

| Approach                  | Index                  | Abbreviation | Description                                                                                                                                                                                                 | Equation                                                                                   |
|---------------------------|------------------------|--------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| Second smallest eigenvalue| $Eig_{SS}$             |              | In an undirected (symmetric) weighted graph, the $Eig_{SS}$ is the second-smallest value among associated eigenvalues (eigenvalues of adjacency matrix). The $Eig_{SS}$ is used to find how connected a graph is. The $Eig_{SS}$ is higher than zero if and only if the graph is connected. $Eig_{SS}$ is also associated with robustness and synchronizability in the graph. | $\lambda_1 < \lambda_2 < \cdots < \lambda_n \quad Eig_{SS} = \lambda_2$ where $\lambda_i$: Eigenvalues of adjacency matrix                                      |
| Complexity index          | Shannon entropy        | $S$          | In a weighted graph, the $S$ is associated with probability of occurrence of values (weights) in the associated adjacency matrix. If all the weights in the adjacency matrix are same, then $S = 0$. The higher value of $S$ is achieved when the weights (array in adjacency matrix) are nonrepetitive. | $S = -\sum_i p_i \log_2 p_i$ where $p_i$: The probability of occurrence of $i$             |
several loops may be generated via a graph. These loops and multiple paths lead to graph measure dependency on factors such as the average of connection power and the distribution of weights (Tewarie et al., 2015; van Diessen et al., 2015). To investigate changes of the MST measures according to the weight distribution and randomness of weights and to evaluate correlations between the MST and the spectral graph theory measures, we performed the MST analyses for two experimental conditions, rsEO and rsEC, versus two randomly generated datasets with different weight distributions.

To compare these matrices, four MST indices were calculated: (1) the betweenness centrality, (2) the leaf fraction, (3) the diameter, and (4) the eccentricity. The betweenness centrality of a node is defined as the number of paths (specifically shortest paths) that emerge from a specific node. In the MST approach, all the paths between nodes are the shortest path (because no loops are possible), which allows us to define the betweenness centrality simply as a function of all the paths that cross a node. This allows us to report the betweenness centrality measure for all the nodes in a network; however, we can also average this measure across all nodes for a condition and report a single value only. The more integrated the graph is, the higher is betweenness centrality the nodes will exhibit (Rubinov & Sporns, 2010).

In the MST approach, the second index is the leaf fraction, which is associated with the number of nodes at the end of the chain. Here, a chain is known as a specific set of connections of nodes in a network from the beginning to the end. Within the chain, a leaf is defined as a node that has a degree equal to a value of one. Mathematically, the leaf fraction is equal to the number of nodes with a degree of value equal to one \( \left( \frac{N_{(k=1)}}{N-1} \right) \) divided by \( N-1 \), where \( N \) represents the total number of nodes in a tree (van Diessen et al., 2015). When the tree has a central node connected to all other nodes, the value of the leaf fraction is maximal, whereas the leaf fraction is at a minimum for a tree with a line shape where one node is connected uniquely to another node in the network (Ghaderi, Moradkhan, et al., 2018b). In terms of the integration of a network, trees with a network in the shape of a line that have low leaf fraction value are deemed to be less integrated than graphs with a flower shape and high leaf fraction value (Stam et al., 2014).

The maximum path length in a tree defines the third MST index, the diameter. This is the same as the shortest path measure in a weighted graph. The diameter is inversely proportional to the level of integration in a network, such that a longer path is associated with less integration and a shorter path is reflective of greater integration (van Diessen et al., 2015).

The final MST index is the eccentricity, which is defined as the longest distance of a node to any other node in either direction of a chain. Each node can be assigned an eccentricity, but we can also calculate average eccentricity for the entire tree. In a tree, the eccentricity is negatively related to integration, whereby graphs with a higher average eccentricity have highly isolated nodes and show less integration, and vice versa.
All of the MST indices are briefly described in Table 1. First, we used the biograph toolbox in Matlab (version R2019a) to compute the MST tree of weighted graphs, and then the results were subsequently fed into the brain connectivity toolbox (Rubinov & Sporns, 2010) to obtain the final four MST indices.

2.5 Dynamical Indices.

2.5.1 Spectral Graph Theory. Mathematically, each oscillatory system with different units of oscillators can be presented by a symmetric connectivity matrix \( A \) of oscillations between units (e.g., an EEG channel), and each symmetric connectivity matrix can be decomposed into a set of eigenvalues and eigenvectors (see Figure 1) that follow

\[
(A - \lambda I)x = 0,
\]

where \( I \) is a single unit matrix, \( x \) is eigenvector of \( A \), and \( \lambda \) is the eigenvalue matrix, if and only if the determinant of \( |A - \lambda I| = 0 \).

In the spectral graph theory in particular, the energy, the largest eigenvalue, and the second smallest eigenvalue are important indices related to the stability of the network (without considering the MSF) (Gutman, 2013; Gutman & Zhou, 2006; Kim & Mesbahi, 2006; Larremore et al., 2011; Li et al., 2012; Morone & Makse, 2015). Since our EEG networks are constructed by measures of synchrony (coherence or phase lag index) between electrodes, one can assume that these spectral measures describe the stability of synchronizability in an EEG network. The energy of a graph is defined as the sum of the absolute values of eigenvalues (Gutman, 2013). This energy is directly related to the number of nodes and the value of edges (Gutman, 2013). Therefore, it is expected that in a dynamical system with constant nodes (e.g., 19 in this study for each of the 19 electrodes), higher energy would be achieved when the stability of synchronizability is increased in the graph (Gutman, 2013). Energy is defined by

\[
H = \sum_{i=1}^{n} |\lambda_i|,
\]

where \( \lambda_i \) is the eigenvalue spectrum and \( n \) is the number of nodes. Since the adjacency matrices of undirected brain networks are symmetric and positive, the spectral graph theory approach can be easily applied to them. As a result, the eigenvalues of these networks are always computable and nonnegative.

The spectral graph theory indices are briefly explained in Table 1. We took our adjacency matrices for these conditions and then applied the eig function in Matlab (version R2019a) to these matrices in order to calculate eigenvalues.
2.5.2 The Shannon Entropy of EEG Network. Entropy measures have been employed to investigate the functional brain connectivity. The transfer entropy (Wollstadt, Martínez-Zarzuela, Vicente, Díaz-Pernas, & Wibral, 2014) and the mutual information (Jeong, Gore, & Peterson, 2001) are appropriate measures to evaluate the level of disorder between two signals. However, although these measures can demonstrate the complexity of synchronization and desynchronization between two neural regions or electrodes, they cannot evaluate the complexity of global brain networks. To study the global complexity of a network, the entropy of graph degrees (Albert & Barabási, 2002) and the graph spectrum (Takahashi, Sato, Ferreira, & Fujita, 2012) have been proposed as two valid measures. It is important to note that the network entropies that focus on the complexity of the overall network require a relatively large number of nodes (e.g., \( N \approx 100 \)). However, the limited number of electrodes in many EEG setups (same as our setup) precludes the use of such measures. Thus, in order to investigate the complexity of a brain network, given this limitation, we used the Shannon or information entropy that can be calculated for a limited number of units (electrodes) (Shannon & Weaver, 1949). Mathematically, the Shannon entropy is defined by

\[
S = -\sum_i p_i \log_2 p_i, \tag{2.6}
\]

where \( p \) is the probability of \( i \) (the possible values within an array in the adjacency matrix). According to this equation, a system with maximum Shannon entropy (with fully random behavior) has nonrepetitive values in the array, while the Shannon entropy is equal to zero in a deterministic system (e.g., matrix of ones). The number of possible values of array cells (i.e., histogram count) is directly related to the Shannon entropy (Blanchet & Charbit, 2013).

In this study, we considered the Shannon entropy for a 19 \( \times \) 19 adjacency matrix. We introduced the application of the Shannon entropy of an adjacency matrix to provide the information entropy of brain network. This measure is suggested for the use of evaluating the complexity of global brain connectivity. We calculated this measure for a weighted adjacency matrix derived from short-term signals (duration on the order of seconds). We used the entropy function in the image processing toolbox of Matlab (version 2019a) that works based on the Imhist function.

2.6 Statistical Analysis.

2.6.1 Probability Distribution of an Adjacency Matrix. The probability distributions of the adjacency matrix were considered in the rsEO and rsEC conditions (see Figure 2). To this end, we constructed 45 adjacency
Figure 2: (a) The probability distribution of weights in adjacency matrices. We generated two sets of random networks (45 networks with random exponential distribution and 45 networks with random normal distribution of weights) using the mean and the SD of the brain-generated networks (rsEC and rsEO conditions). The rsEC and rsEO networks show semiexponential distribution while the normal distribution is completely different from the brain-generated distributions. (b) Average of adjacency matrices (over 45 matrices for each subject). In the rsEC and the rsEO matrices, each row/column represents an EEG channel (not applicable for random distribution matrices). Lighter colors are associated with higher coherence between channels, while, darker colors correspond to lower coherence.

matrices with a normal distribution and 45 adjacency matrices with a random exponential distribution. We used the mean and the standard deviation of brain-generated adjacency matrices to construct the random values. The probability distribution was presented through histograms. We used 200 bins for each histogram between 0 and 100 (the values of coherence are between zero and one, and we multiplied all the coherence values by 100 for the ease of visualization and analysis). This number of bins results in an appropriate representation of the data. Then the $R$-squared errors between the distributions were calculated and ultimately used to determine the distances between probability distributions. We used this probability distribution analysis to find the effects of probability distribution on dynamical or statistical graph indices.
2.6.2 Permutation Test. A nonparametric permutation test (Maris & Oostenveld, 2007) with 10,000 random shuffles was used to compare graph indices between two conditions. To avoid a type 1 error, a false discovery rate (FDR) analysis (Hochberg, 1995) was performed, and then corrected \( p \)-values (\( q \)-values) were obtained. We performed the FDR separately for the weighted graph measures (the clustering coefficient, the characteristic shortest path), the MST indices (the betweenness centrality, the leaf fraction, the eccentricity, and the diameter), and the dynamical measures (the largest eigenvalue, the energy, and the Shannon entropy). The permutation test was carried out using a previously created Matlab function (Ghaderi, Andevari et al., 2018a; Ghaderi, Moradkhani et al., 2018b). After that, an individual comparison was performed to identify significant measures between the two conditions. We also used the FDR analysis to correct multiple comparisons between conditions (e.g., rsEC, rsEO, random exponential, random normal).

2.6.3 Correlation Analysis and K-Means. Correlation analysis was performed between all indices using the Matlab function corr, and then the \( p \)-values were obtained. To avoid the effect of multiple comparisons, Bonferroni correction was performed.

Based on the results of the FDR analysis on the data from the two conditions, we used the spectral and the topological indices that had significant differences between them—the clustering coefficient, the characteristic shortest path, the energy, the largest eigenvalue, and the Shannon entropy (see section 3)—as inputs for the linear k-means approach. The input patterns were all possible combinations of two-dimensional topological-spectral patterns (see Table 2), a two-dimensional pattern that is made by topological indices, a three-dimensional pattern that is constructed by spectral indices, and a five-dimensional pattern that contains both the spectral and the topological indices. All of these combinations of inputs were tested, and sensitivity (Genders et al., 2012), specificity (Genders et al., 2012), accuracy (Genders et al., 2012), and the Caliński-Harabasz index (Caliński & Harabasz, 1974) were calculated to find the performance of k-means with different input patterns (see the supplementary materials for definitions of sensitivity, specificity, accuracy, and the Caliński-Harabasz index). All statistical analyses were performed in Matlab (version R2019a), and the ttest function (for within subject t-test analysis) was used specifically to compare the means of the conditions.

3 Results and Discussion

3.1 Differences between rsEC and rsEO. In this section, various topological and dynamical measures are compared between two eyes conditions. We briefly explain each index and then discuss the similarities and differences of two networks.
Synchrony and Complexity in State-Related EEG Networks

Table 2: Performances of k-Mean Clustering Approach Using Different Inputs.

| Inputs          | Sensitivity | Specificity | Accuracy | Caliński-Harabasz Index |
|-----------------|-------------|-------------|----------|-------------------------|
| C, H (topological-spectral) | EO: 0.8     | EO: 0.53    | 0.67     | 239.6                   |
| C, EigL (topological-spectral) | EC: 0.53    | EC: 0.8     | 0.48     | 120.9                   |
| C, S (topological-spectral) | EO: 0.8     | EO: 0.47    | 0.63     | 171.2                   |
| L, H (topological-spectral) | EC: 0.53    | EC: 0.8     | 0.67     | **239.8**               |
| L, EigL (topological-spectral) | EC: 0.53    | EC: 0.8     | 0.49     | 121.1                   |
| L, S (topological-spectral) | EO: 0.97    | EO: 0.31    | 0.64     | 173.0                   |
| C, L (topological) | EC: 0.84    | EC: 0.4     | 0.62     | 131.5                   |
| H, EigL, S (spectral) | EO: 0.8     | EO: 0.53    | **0.67** | 183.5                   |
| C, L, H, EigL, S (topological-spectral) | EC: 0.53    | EC: 0.8     | **0.67** | 182.9                   |

Note: The highest values are in bold.

3.1.1 Topological Measures of the Weighted Graph. The results of the false discovery rate (FDR) analysis showed that there were significant differences between the two eye conditions in the clustering coefficient (C) ($F = 6.647$, $p$-value $< 0.0001, df = 44$) and the characteristic shortest path (L) ($F = 3.749$, $p$-value $< 0.0001, df = 44$). Higher values of C and L were found in the rsEC condition (see Figure 3). Investigation of individual participant activity indicated that 40/45 (89%) participants exhibited the same pattern for the C, whereas 37/45 (82%) participants showed a similar pattern for L (rsEC > rsEO) (see Figure 3).

The C is closely associated with brain segregation, while brain integration is inversely related to the L (Bullmore & Sporns, 2009; Rubinov & Sporns, 2010). Based on our findings, the alpha network that we explored here exhibited higher segregation and lower integration in the rsEC condition compared with the rsEO condition. This result confirms the recent results of an EEG study that showed increased path length and the clustering coefficient during the rsEC condition in comparison with the rsEO condition (Miraglia et al., 2016). Therefore, it can be proposed that the alpha network tends to engage in more local processing when the eyes are closed versus open. Previous findings also indicated that a particular thalamocortical circuit is involved in the alpha band oscillation generation (Bollimunta, Mo, Schroeder, & Ding, 2011). In particular, this oscillation band
Figure 3: Top: Weighted graph measures. The rsEC network exhibits higher value of the $C$ while the random exponential network shows the lowest value. The $C$ is sensitive to distribution but not to randomness. The random normal network shows the highest $L$, while the rsEO and random exponential networks have lower values of the $L$. The $L$ is sensitive to the distribution of weights. Middle: MST measures. The Max BC, the $LF$, the diameter and the eccentricity are sensitive to randomness but not to distribution. These measures cannot distinguish the rsEC and rsEO networks. Bottom: Dynamical measures. The highest values of the energy and the largest eigenvalue are related to the rsEC network, whereas the rsEO network shows the highest value of the Shannon entropy. The energy is sensitive to distribution. The largest eigenvalue is sensitive to randomness but not to distribution. The second smallest eigenvalue exhibits same values for the rsEC and rsEO networks, but it can distinguish the brain-generated and the random networks. Significant differences are indicated with stars.

can be attributed to more posterior cortical regions (Klimesch, Sauseng, & Hanslmayr, 2007). Thus, it is no surprise that more segregation occurs in the rsEC condition than in the rsEO condition. However, noticing less integration in the rsEC condition is an emergent finding derived by the graph theory approaches described here.

3.1.2 MST Measures. After applying the FDR correction to the results of a within-subject permutation $t$-test, we found no significant differences in the betweenness centrality ($F = 0.0567$, $p$-value = 0.521, $df = 44$), the leaf fraction ($F = -0.2633$, $p$-value = 0.354, $df = 44$), the eccentricity ($F = 0.333$, $p$-value = 0.355, $df = 44$), and the diameter ($F = 0.4997$, $p$-value = 0.308, $df = 44$) between the rsEO and rsEC conditions. Individual results indicated that
participants did not share the same pattern of results for these measures (see Figure 3).

This result could be related to a lack of weak weights and loops as they are removed in the MST approach. In some studies, the weak connections are considered in relation to noise (van Diessen et al., 2015). However, based on the nature of the coherence, global noise (which can affect all the electrodes) can induce high coherence between electrodes. But local noise (which can affect a fewer numbers of electrodes) may lead to weak connections between noisy and other electrodes. In this study, we performed a high-level control on selected signals that were artifact free. Moreover, two conditions (rsEC and rsEO) were recorded at successive sessions; then the possible local noise should affect both conditions. Thus, weak weights (which possibly cause significant differences between two conditions) cannot be considered in relation to noisy signals, thereby playing a significant role in distinguishing the rsEC and rsEO conditions (at least when the connectivity measure is coherence).

3.1.3 Dynamical Measures (Synchrony and Complexity). In the elementary study, after the FDR analysis, significant differences between the two eye conditions (rsEO and rsEC) across the tested dynamical indices were observed. Significantly higher values of the energy ($F = -10.852$, $p$-value < 0.001, $df = 44$), and the largest eigenvalue ($F = -7.045$, $p$-value < 0.001, $df = 44$) were observed in the rsEC condition in comparison with the rsEO condition, while higher values of the Shannon entropy were observed in the rsEO condition in comparison with the rsEC condition ($F = -6.828$, $p$-value < 0.001, $df = 44$). However, there was no significant difference between the rsEC and rsEO conditions in the second-smallest eigenvalue (Figure 3).

In the confirmatory study, the FDR analysis indicated that the spectral and complexity indices of adjacency matrices, derived by coherence, were significantly different in various conditions (see supplementary Figure 1a). Significantly higher values of energy were observed in the rsEC condition in comparison with the rsEO condition ($F = 5.17$, $p$-value < 0.001, $df = 15$). The largest eigenvalue was significantly higher in the rsEC condition than the rsEO condition ($F = 4.43$, $p$-value < 0.001, $df = 15$). However, the second-smallest eigenvalue was significantly lower in the rsEC condition than the rsEO condition ($F = -4.22$, $p$-value = 0.002, $df = 15$). Further, significantly lower entropy was also observed in the rsEC condition in comparison with the rsEO condition ($F = -3.26$, $p$-value = 0.005, $df = 15$). Box plots and scatter plots of these measures are presented in supplementary Figure 1a. These results are similar to the results of the elementary study.

To find the effect of connectivity measures on the reliability of the spectral graph theory measures and the Shannon entropy, a confirmatory analysis was also performed on the adjacency matrices that were generated by calculating the weighted phase lag index between the EEG electrodes (more details about weighted phase lag index have been presented in section 1 of
the supplementary materials). The FDR analysis indicated that the spectral indices of these adjacency matrices in the rsEC condition exhibited significant differences in comparison with the rsEO condition (see supplementary Figure 1b). Significantly higher values of the energy were observed in the rsEC condition in comparison with the rsEO condition ($F = 3.05$, $p$-value = 0.008, $df = 15$). The largest eigenvalue was significantly higher in the rsEC in comparison with the rsEO condition ($F = 2.6$, $p$-value = 0.020, $df = 15$). The second smallest eigenvalue showed a significant decrease in the rsEO in comparison with the rsEC condition ($F = -2.68$, $p$-value = 0.018, $df = 15$). These results are matching with the results that have been obtained by coherence. However, despite the coherence results, the Shannon entropy of adjacency matrices that were constructed by phase lag index was not significantly changed in the rsEC compared with the rsEO condition ($F = -1.08$, $p$-value = 0.29, $df = 15$).

Overall, these results showed that by using the spectral graph theory and the Shannon entropy, we were able to distinguish between the two eye conditions in the brain network. Specifically, our results indicated that the rsEC condition exhibited higher energy than the rsEO condition, and it was confirmed by an alternative connectivity measure (i.e., weighted phase lag) in the confirmatory study. This result is completely consistent with our hypothesis that the energy can determine the stability of synchronizability in complex brain networks, since rsEC is more synchronized in the alpha band (Ben-Simon et al., 2013; Brodoehl et al., 2015; Chapman et al., 1970; Kirkup et al., 1998; Liu et al., 2012). Therefore, we can introduce the energy as a reliable measure to find the stability of synchronizability in the functional brain networks.

Consistent with the spectral graph theory literature (Arenas, Díaz-Guilera, & Pérez-Vicente, 2006; Atay, Biyikoglu, & Jost, 2006; Spielman, 2007), we found that another spectral graph theory index, the largest eigenvalue, can also be used to explore the stability of synchronizability in functional brain networks that are constructed by either coherence or weighted phase lag. We suggest that this dynamical measure can be used in a reliable manner to ascertain the presence of differences in dynamical synchronization and desynchronization in resting-state brain networks. Another spectral graph theory measure that we considered in this study was the second-smallest eigenvalue, which was not significantly different between the two conditions in the first study with larger data set. However, in a confirmatory study, it was significantly changed in the rsEC compared to the rsEO condition revealed through either coherence or weighted phase lag. The second-smallest eigenvalue of graph is supposed to be associated with the robustness of the network dynamic system (Kim & Mesbahi, 2006). It also demonstrates whether networks are connected (de Abreu, 2007). There is not enough literature in network neuroscience to find the dynamical robustness and stability in functional brain networks during different cognitive states (e.g., eyes closed or eyes open). Only a recent study has shown
that Alzheimer’s disease decreases dynamic robustness in the functional brain network (Daianu et al., 2014). Methodologically, since the results of the second-smallest eigenvalue are not convergent in both studies, we can assume that the synchronizability of brain network is more related to the larger eigenvalues than the smaller eigenvalues.

Furthermore, the Shannon entropy was also significantly different between the two conditions when the coherence was used to construct the brain networks. Specifically, higher entropy was observed in the rsEO condition compared with the rsEC condition. To frame this in terms of what is already known about entropy and network analysis, the Shannon entropy describes the level of complexity and unpredictable information in a system (on a more general level) (Shannon & Weaver, 1949). When entropy is measured in a network, higher entropy is attributed to a random and unpredictable network, whereas a network that has repeating or similar units is associated with the lowest entropy (i.e., an entropy of zero). A recent study (Demertzzi et al., 2019) showed that the entropy of brain networks (ones that were constructed from the anatomical connections between brain regions) is lower for patients in a vegetative state or an unresponsive wakefulness syndrome than healthy control participants. This result suggests that complex patterns of consciousness in the brain can increase the entropy of brain networks (Demertzzi et al., 2019).

In terms of our results, the network units (or the coherence between the electrodes in this case) in the rsEC condition are more predictable and simpler than for the rsEO condition. This suggests that there may be a decreased global synchronization of the alpha band coherence in the rsEO condition compared with the rsEC condition. Systems with more stability of synchronizability (such as that associated with brain activity in the rsEC condition) exhibit similar correlations between coherence values. The Shannon entropy may thus be another excellent tool to evaluate the synchrony (as well as complexity) in the EEG brain networks. However, we should consider that this measure was not changed between conditions when we used weighted phase lag as the connectivity measure. It suggests that the Shannon entropy of network is hardly dependent on the type of connectivity measure that constructed the network. More investigations with other connectivity measures (e.g., synchronization likelihood, phase locking) may clarify more details on this issue.

3.2 Effects of Weight Distributions and Randomness on the Graph Theory Indices. In evaluating the reliability and applicability of graph theoretical measures, the effects of weight distributions and randomness of networks on these measures are important issues. A good measure should be invariant to the distribution changes but sensitive to the randomness of network. Here, since the brain-generated networks exhibited semi-exponential distribution of weights (see Figure 2a), we constructed two random sets of adjacency matrices: one with exponential weight
distribution (approximately the same distribution with brain-generated networks) and another with normal weight distribution (a different distribution from brain-generated networks). The average weights and weight distributions of these networks have been presented in Figure 2. To find the strength of similarity and differences between all networks (rsEC, rsEO, normal, and exponential), we computed the $R^2$-squared values between distributions. The $R^2$-squared value between histograms of weight distributions indicated that considerable correlations were obtained for (1) rsEO and rsEC conditions (0.883), (2) rsEC and random exponential (0.877), and (3) rsEO and random exponential (0.899). In contrast, the $R^2$-squared values between normal and exponential distributions (0.398), normal and EC distributions (0.474), and normal and EO distributions (0.412) exhibited a weak correlation.

Then we evaluated the dependence of various graph measures (see Table 1) to distributions and randomness. The FDR analysis indicated that the $C$ and the $L$ were significantly different for two random sets of graphs. The $C$ was significantly different between the exponential random graphs and the two brain-generated data sets (rsEC and rsEO). However, the $C$ of the normal random graphs was not significantly different from the rsEC condition. For the $L$, although significant differences were observed between random graphs with exponential distribution and the two brain-generated graph sets (rsEC and rsEO), the random graph with normal distribution exhibited significant difference only with the rsEO condition. Furthermore, we found that both random data sets showed significant differences from brain-generated graphs (in all the MST measures). However, there were no significant differences between the two randomly generated graphs. The differences between the random graphs were significant for the energy, the Shannon entropy, and the second-smallest eigenvalue, but the two random graph sets exhibited statistically no significant deference in the largest eigenvalues. Significant differences were observed between brain-generated and random-generated graphs in the largest eigenvalue, the second-smallest eigenvalue, and the energy. However, there was no significant difference between the brain-generated and the randomly generated graphs in entropy (all the differences between brain-generated and randomly generated networks are shown in Figure 3).

Based on the results derived by calculating the $L$, the $C$, and the Shannon entropy over brain-generated networks versus random networks, we did not observe a specific pattern to distinguish these two types of networks. While the $L$, the $C$, and the Shannon entropy in random exponential networks are in the order of brain-generated networks, the normal random network exhibited higher values for both the $L$ and the $C$ and a lower value for the Shannon entropy. It suggests that topological measures of a weighted graph and the Shannon entropy are more sensitive to the distribution of weights and less sensitive to the randomness of weight values. This is consistent with the previous findings (Tewarie et al., 2015) that suggested that
these measures are strongly related to the distribution of weights and possible differences between networks may be affected by this bias (Tewarie et al., 2015). Despite the measures of the weighted graph, the results indicate that the MST measures are not dependent on the distribution of weights, but they are sensitive to the randomness of weights. This result confirms a previous study that suggested the MST as a weight-conserving approach (Tewarie et al., 2015). Like the MST indices, the spectral graph theory indices can clarify differences between the brain-generated networks and the random graphs. Both measures, the energy and the largest eigenvalue, showed lower values for the random networks. This suggests that the brain-generated networks exhibit more stability of synchronizability than the random networks with the same mean and standard deviation of weights. Overall, these results suggest that topological properties of weighted networks are invariant to the randomness of weights, but synchrony of networks differs from weight randomness.

3.3 Correlation Analysis, Linking Shannon Entropy, Topological, and Spectral Indices. One of the goals for this study was to ask whether the topological and the spectral measures are linked. To this aim, we performed the linear correlation analysis between measures that are derived from two kinds of networks: functional brain networks and random networks. Figure 4 indicates that several significant positive and negative correlations exist between the graph indices that we tested (all correlational measures as well as p-values—after Bonferroni correction—are presented in Figure 4).

According to the correlation analysis, in both random networks, generally three main clusters were observed that exhibited high correlation: a cluster between the dynamical indices (the energy, the largest eigenvalue, and the second smallest eigenvalue), one between the weighted graph indices (the $C$ and the $L$), and one of the MST indices (the $BC$, the $LF$, the diameter, and the eccentricity). For these analyses, we did not find any significant correlation across these three clusters. However, for the brain-generated graphs (rsEC and rsEO), we found several significant correlations across dynamical, weighted, and MST indices.

For both brain-generated networks, significant positive correlations were observed between the spectral indices (the energy and the largest eigenvalue) and the weighted graph measures (the $C$ and the $L$). These correlations suggest that in the EEG networks, higher synchrony is associated with higher segregation (higher values for the $C$) and lower integration (higher values for the $L$). Therefore, one can conclude that local processing in EEG networks causes higher stability of global synchronizability, while global integration reduces the level of stability of synchronizability in the EEG networks. Mathematically, it can be justified by the argument that synchrony (energy and largest eigenvalue) is directly related to the magnitude of weights, but integration is reduced by higher values of weights (because the $L$ is directly associated with value of weights). This type of correlation
Figure 4: Top: Heat map of correlations between measures. Light blue is associated with negative high correlation between measures, and red indicates a positive high correlation between measures. Dark blue, dark red, and black indicate a low correlation between measures. Bottom: The $p$-value of correlations after Bonferroni correction. Black cells indicate significant correlation between measures ($p < 0.05$), while red indicates nonsignificant correlations ($p > 0.05$). Different groups of correlations are observed for random networks with exponential and normal distribution of weights. In the correlation heatmap of these networks, we can distinguish at least three groups for three types of measures: spectral, topological for weighted graph, and the MST. These groups are completely separated for random networks with no correlation across them. However, several correlations are observed across these groups for EEG networks.

has not been distinguished for the random graph. Then it can imply that this type of correlation between the spectral and the topological graph measures is observed for specific types of complex networks, such as EEG networks.

In both conditions, the Shannon entropy exhibited a significant negative correlation with the spectral indices (the energy and the largest eigenvalue) and the weighed graph measures (the $C$ and the $L$). The negative correlation between entropy and spectral measures suggests that EEG networks with high stability of synchronizability have less complexity. Correlations between the Shannon entropy and the weighted graph measures can be considered in relation to the segregation and integration in the EEG networks. The negative correlation between the Shannon entropy and the characteristic shortest path suggests that the EEG network complexity is associated with integration within the graph. The negative correlation between the Shannon entropy and the clustering coefficient reveals that complexity is inversely related to segregation in EEG networks. Mathematically, a regular graph (with the same connectivity weights between nodes) presents minimum Shannon entropy, while it exhibits maximum values for the $C$ and the $L$ (Watts & Strogatz, 1998); thus, it is not surprising to see the negative
correlation between these measures. However, as our results show, the negative association between the Shannon entropy and the $C$ and the $L$ has not been observed in randomly generated graphs. Thus, our results suggest that this correlation is specifically distinguished in brain-generated networks (as a complex network).

There was no significant correlation (in the rsEO condition) between the second-smallest eigenvalue (related to the stability of dynamical networks) and other measures—especially the energy and the largest eigenvalue (associated with synchrony at dynamical networks). This result may suggest that in a low-level synchronized EEG network (rsEO), smaller eigenvalues cannot relay information about the synchronizability of networks, but in the high-synchronized EEG network (rsEC), the smaller eigenvalues are informative about synchronizability.

In the rsEC condition, there was a significant correlation between the largest eigenvalue and the MST indices (positive correlation with the LF and negative correlation with the diameter and eccentricity). Significant correlations between the weighted graph measures and the MST indices were also observed in both conditions. This result was consistent with a previous study that suggests the same correlation (Tewarie et al., 2015). As Tewarie et al. (2015) recommended, the correlations suggest that both the MST and the weighted graph measures show the same properties in the topological brain networks (e.g., segregation and integration).

### 3.4 Clustering Analysis

We also analyzed whether we could separate the two eye conditions by the dynamical or the topological properties of EEG networks that were constructed by local connectivity (i.e., coherence) among EEG electrodes. We approached this problem using a k-means method (Ghaderi, Moradkhani et al., 2018b) where the graph theory indices were selected as inputs and the output of model (k-mean approach) was eye condition. To find which indices can best distinguish between conditions, we computed the sensitivity, the specificity, the accuracy, and the Caliński-Harabasz index of k-mean approach with different patterns of inputs (see Table 2). The best performances were achieved when both the spectral and the topological indices were selected as inputs. Samples of clustering results with two and five dimensions of inputs have been presented in Figure 5.

### 3.5 Finding the Best Measure to Characterize Synchronizability in EEG Networks

While revealing the EEG networks related to the variable that is being tested (in our case, the cognitive state related to whether the eyes are open or closed), it is important to consider which measures are capable of distinguishing these different states. However, it is more intricate than that. A good measure has to meet four important criteria: (1) it must be able to distinguish between variable-related and randomly generated data; (2) it must be independent of the distribution of weights (see Tewarie...
Figure 5: The scatter plot of clustering results by k-means approach. Circles show individual values of graphs in the EC (blue circles) and the EO (red diamonds) condition. Dots show clusters that are assigned to each circle (individual data). If the color is matched between circle and dot (red-red or blue-blue), the clustering assignment is correct. (a) Results of two-dimensional clustering based on the weighted graph measures (left) and dynamical measures (right) are shown in the scatter plot. (b) Results of five-dimensional clustering based on both topological weighted measures (the clustering coefficient and the characteristic shortest path) and dynamical measures (the energy, the Shannon entropy, and the largest eigenvalue). Both charts show the same clustering results but in different views (e.g., weighted dimensions on the left side and dynamical dimensions on the right).
et al., 2015, for more details); (3) it must be able to differentiate between the levels of the variable being tested (i.e., between the rsEO and rsEC condition networks here); and (4) it should be applicable and effective with different types of connectivity indices (e.g., coherence, phase lag).

From our results, we were able to determine the measures that have met these criteria. Importantly, only one measure met three criteria: the largest eigenvalue. Previously, weighted graph measures were used to distinguish variable-related states (Bullmore & Sporns, 2009; Rubinov & Sporns, 2010). Furthermore, it has also been proposed that the MST measures could be used to accomplish this goal (Stam et al., 2014; Tewarie et al., 2015). Here, we showed that weighted graph measures met the third criterion only, whereas most MST measures met the first two criteria. Taken together, we suggest that when it is important to distinguish between dynamical networks (such as the EEG network) while satisfying all of these criteria, the largest eigenvalue could be used; otherwise, the weighted graph and the MST measures should be applied based on the nature of the variable being tested.

We also proposed spectral indices (the energy, the largest eigenvalue, and the Shannon entropy) as possible measures that could distinguish between the rsEO and the rsEC condition-related networks. However, from these three measures, the energy met three of the four criteria, whereas the Shannon entropy met only one criterion. The energy was able to distinguish between variable-related and random data and differentiate between rsEO and rsEC condition networks with both connectivity measures (coherence and phase lag), but it was sensitive to the weight distribution. The Shannon entropy was sensitive only to rsEO versus rsEC condition networks (when coherence was employed to generate network), which is a similarity between the Shannon entropy and other weighted graph measures.

Overall, these considerations suggest that it is important to consider the nature of the independent variable being tested, as well as which criteria need to be met. Certain analyses may require that only some criteria need to be met, and thus the appropriate measure(s) should be chosen, be it the weighted graph, the MST, or those proposed here, based on the requirements of the network.

4 Conclusion

In this study, our aim was to investigate the applicability of the spectral graph theory indices to find the stability of synchronizability in the functional brain networks. We performed two studies (one as an elementary study and another as a confirmatory study) to clarify these issues. Also, we considered the overall link between different approaches to functional network connectivity analysis. To this aim, we investigated the topological and the spectral features of brain networks in two eye conditions (eyes open vs. eyes closed), as well as two randomly generated networks. Moreover, we calculated the Shannon entropy, which we propose to be a plausible index.
for evaluating the brain’s functional complexity. This would allow us to determine if there are any links between the topology, the synchrony, and the complexity of brain networks versus random networks. Our results indicated that (1) the stability of synchronizability in the brain networks can be best relayed by the energy and the largest eigenvalue, (2) the topological indices that we tested are effective in determining a state-dependent difference in brain connectivity, and (3) there was no link between the topology, the synchrony, and the complexity in random networks. However, in the case of brain networks, we found several interactions between these measures.

The results of this study provide direct evidence that the largest eigenvalue and the energy can very well specify the stability of synchronizability in EEG networks. Also, we showed that the topological and the spectral measures exhibited different properties of networks. These two types of measures were completely independent in the case of random-generated networks; however, we found several significant correlations between the topology and the dynamic of EEG network (brain-generated networks). In terms of complexity, the Shannon entropy showed that the complexity of the rsEO state is higher than for the rsEC state. The Shannon entropy may thus be used to investigate the level of complexity in an EEG network. In conclusion, the methodology proposed in this study helps to provide information about the synchronicity and the complexity of brain networks. However, it is especially important to consider which measures are best suited to distinguish between such state-related networks (i.e., sensitivity to random networks, distribution, connectivity measure, and the ability to separate between cognitive-related states). Of all the measures that we investigated, we found that the largest eigenvalue and the energy are great candidates for this goal because they met almost all the criteria. Overall, continuing investigations of spectral measures in brain network analysis are required, as these findings may have major implications for many cognitive and clinical studies.

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