

Dynamic small-world behavior in functional brain networks unveiled by an event-related networks approach

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There is growing interest in studying the role of connectivity patterns in brain functions. In recent years, functional brain networks were found to exhibit small-world properties during different brain states. In previous studies, time-independent networks were recovered from long time periods of brain activity. In this paper, we propose an approach, the *event-related networks*, that allows one to characterize the dynamical evolution of functional brain networks in time-frequency space. We illustrate this approach by characterizing connectivity patterns in magnetoencephalographic signals recorded during a visual stimulus paradigm. When compared with equivalent random and regular networks, the results reveal that functional connectivity varies with time and frequency during the processing of the stimulus, while maintaining a small-world structure. This approach may provide insights into the connectivity of other complex and spatially extended nonstationary systems.

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Empirical studies have led to the hypothesis that transient synchronization between distant and specific neural populations underlies the integration of neural activities as unified and coherent brain functions [1]. Thus, specialized brain regions would be largely distributed and linked to form a dynamical weblike structure of the brain [2]. An important question is whether this transient connectivity has a functional role in brain processes, such as the ongoing awareness of sensory stimuli or perception.

In recent years, complex networks have provided an increasingly challenging framework for the study of collective behaviors based on the interplay between complexity in the wiring architecture and dynamical properties of the coupled units [3]. For brain networks, anatomical connectivity was found to exhibit small-world features that can neither be captured by regular connectivity models as lattices, nor by random configurations [4–6]. Small-world (SW) networks are characterized by a small average distance between any two nodes while keeping a relatively highly clustered structure [4]. Thus, SW architecture is an attractive model for brain connectivity because it leads distributed neural assemblies to be integrated into a coherent process with an optimized wiring cost [7].

Recent studies have attempted to characterize functional connectivity (patterns of statistical dependencies) observed between brain activities recorded by electroencephalography (EEG), magnetoencephalography (MEG), or functional magnetic resonance imaging (fMRI) techniques [8,9]. Surprisingly, functional connectivity patterns obtained from MEG and EEG signals during different pathological and cognitive neurodynamical states were found to display SW attributes [9]; whereas functional patterns of fMRI often display a structure formed by highly connected hubs, which yield an exponentially truncated power law in the degree distribution [8].

In functional networks, two different nodes (electrodes and voxels or source regions) are supposed to be linked if some defined statistical relation exceeds a threshold. Regard-

less of the modality of recording activity (EEG, MEG, or fMRI), topological features of functional brain networks are currently defined over long periods of time, neglecting possible instantaneous time-varying properties of the topologies. Nevertheless, evidence suggests that the emergence of a unified neural process is mediated by the continuous formation and destruction of functional links over multiple time scales [1,2,10].

In this paper, we propose a method, the *event-related networks* (ERNs), that allows characterizing the dynamic evolution of functional brain networks in the time-frequency space. We illustrate this approach by characterizing connectivity patterns extracted from MEG data recorded from epileptic patients during a visual stimulus paradigm. The results reveal that brain connectivity patterns vary with time and frequency, *while maintaining* a small-world structure.

The scheme depicted in Fig. 1 illustrates the basic steps of our approach: (a) the relations between different brain regions are first defined in the time-frequency space, (b) a statistical criterion is then used to define a functional connectivity matrix for each time-frequency point, and (c) topological attributes are extracted from connectivity patterns to obtain a time-frequency characterization of brain networks. To assess the SW behavior of brain connectivity, functional networks are compared with equivalent regular and random networks.

Here, we discuss functional connectivity patterns associated with dynamic brain processes elicited by the repetitive application (trials) of an external visual stimulus [11]. In this paper, we define the functional links in brain signals by means of the phase-locking value (PLV) computed between all pairs of sensors [13]. By means of a complex wavelet transform an instantaneous phase $\phi_i^{\text{trial}}(t, f)$ is obtained for each frequency component of signals $i = 1, \dots, M$ at each trial [14]. The PLV between any pair of signals (i, k) is inversely related to the variability of phase differences across trials:

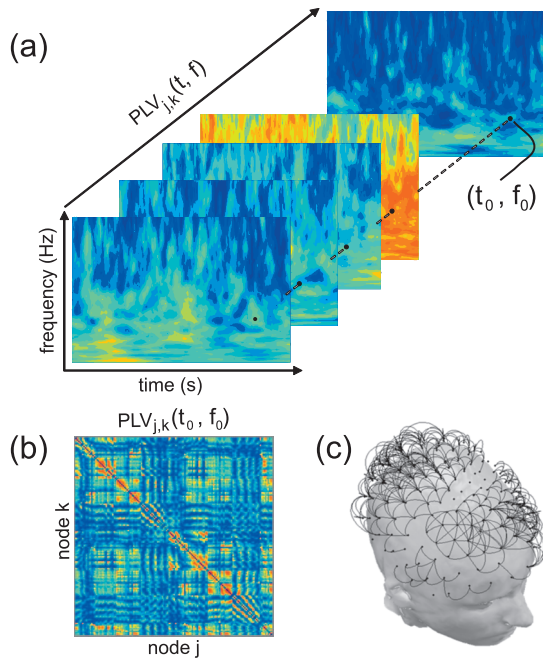


FIG. 1. (Color) Extraction of the event related brain networks: (a) from time-frequency relations between all pairs of signals (b) functional connectivity matrices are extracted at each point of the time-frequency plane, defining (c) the functional brain networks. See details in the text.

$$\text{PLV}_{i,k}(t,f) = \frac{1}{N_{\text{trials}}} \left| \sum_{\text{trial}=1}^{N_{\text{trials}}} \exp^{j(\phi_i^{\text{trial}}(t,f) - \phi_k^{\text{trial}}(t,f))} \right|, \quad (1)$$

where N_{trials} is the total number of trials. If the phase difference varies little across trials, its distribution is concentrated around a preferred value and $\text{PLV} \sim 1$. In contrast, under the null hypothesis of a uniformity of phase distribution, PLV values are close to zero.

Finally, to assess whether two different sensors are *functionally* connected, we calculated the significance probability of the PLV values by a Rayleigh test of uniformity of phase. According to this test, the significance of a PLV value determined from N_{trials} can be calculated as $p = \exp(-N_{\text{trials}} \text{PLV}^2)$ [15]. To correct for multiple testing, the false discovery rate (FDR) method was applied to each matrix of PLV values [16]. With this approach, the threshold of significance was set such that the expected fraction of false positives is restricted to $q \leq 0.05$.

Once the functional networks are determined, their topology is studied. To characterize the topological properties of a network, a number of parameters have been described [3]. Here we use three key parameters: mean degree $\langle K \rangle$, clustering index C , and global efficiency E . Briefly, the degree k_i of node i denotes the number of functional links incident with the node and the mean degree is obtained by averaging k_i across all nodes of the network. The clustering index quantifies the local density of connections in a node's neighborhood. The clustering coefficient c_i of a node i is calculated as the number of links between the node's neighbors divided by all of their possible connections and C is defined as the av-

erage of c_i taken over all nodes of the network [4]. The global efficiency E provides a measure of the network's capability for information transfer between nodes and is defined as the inverse of the harmonic mean of the shortest path length L_{ij} between each pair of nodes [6]. The local efficiency E_i of the i th node is likewise defined as the inverse of the harmonic mean of the minimum path length between node i and all other nodes in the network.

To assess the small-world behavior of functional networks, we perform a benchmark comparison of the functional connectivity patterns [4]. For this, the clustering and efficiency coefficients of functional networks are compared with those obtained from equivalent random and regular configurations. Regular networks were obtained by rewiring the links of each node to its nearest (in the sensor's space) neighbors, which yielded a nearest-neighbor connectivity with the same degree distribution as the original network. To create an ensemble of equivalent random networks we use the algorithm described in [4]. According to this procedure, each edge of the original network is randomly rewired avoiding self- and duplicate connections. The obtained randomized networks thus preserve the same mean degree as the original network, whereas the rest of the wiring structure is random.

To illustrate our approach, we consider the brain responses recorded during the visual presentation of unfamiliar pictures. Although our approach is applicable to any of the functional methods available (EEG, fMRI, and MEG), here we use the magnetoencephalography. This modality of acquisition has the major feature that collective neural behaviors, as synchronization of large and sparsely distributed cortical assemblies, are reflected as interactions between MEG signals [12]. In this experiment, a collection of 48 simple structural images and scrambled images were randomly shown to patients during 150 ms with an interstimulus interval of 2 s. Patients were required to respond by pressing a button each time an image was perceived. The event-related brain responses were recorded (from two patients who gave informed consent) with a whole-head MEG system (151 sensors; VSM MedTech, Coquitlam, BC, Canada) digitized at 1.25 kHz with a bandpass of 0–200 Hz.

Figure 2 shows the topological attributes of functional networks elicited by the unexpected images. Pictures show the values of the mean degree, clustering index, and efficiency of networks, calculated at each point in the time-frequency space, between 600 ms before and 1 s after the onset of the stimulus. In the construction of all networks, a functional connection between two sensors was assumed as an undirected and unweighted edge. Topological features can also be straightforwardly generalized to weighted networks [17]. Nevertheless, qualitative similar results (not reported here) were obtained for weighted networks with a functional distance between nodes given by $1 - \text{PLV}$.

The first crucial observation is that functional connectivity patterns are not time invariant, but instead they exhibit a rich time-frequency structure during neural processing. All topological features (especially $\langle K \rangle$ and C) exhibit high values in a frequency band close to 10 Hz, which is a spectral component mostly involved in the processing of visual information [11]. Whereas the functional networks in the frequency range of 10–30 Hz display large patterns of

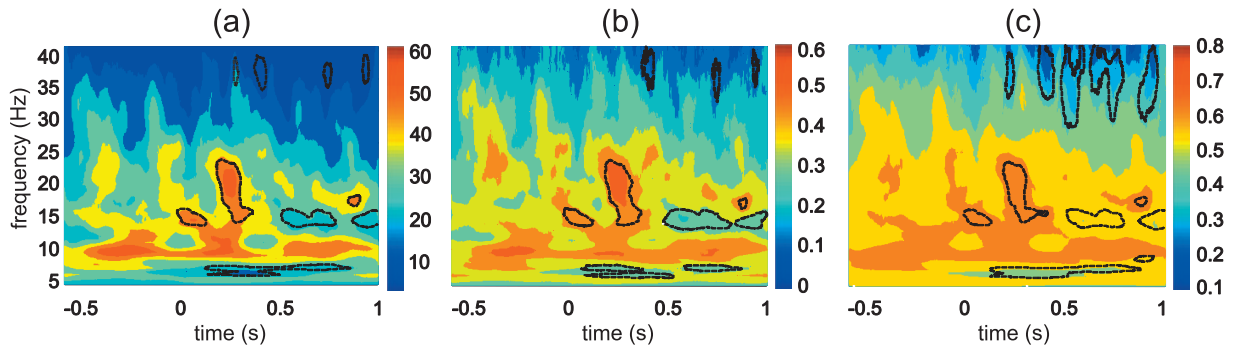


FIG. 2. (Color) Time-frequency maps of topological features extracted from brain networks associated with a visual stimulus presentation (arriving at $t=0$). (a) Mean degree $\langle K \rangle$, (b) clustering index C , and (c) efficiency E . The reported values refer to the average over two subjects. Dotted lines outline the regions revealing a significant change from the prestimulus region.

synchronization/desynchronization before the stimuli, a highly connected pattern is induced by the stimulus at about 250 ms and between 15 and 25 Hz, which suggests a connectivity induced by the unexpected sensory stimuli. This is followed by weak connected structures at frequency bands close to 7 and 15 Hz arising during the poststimulus activities and marking the transition between the moment of perception and the motor response of the subject. The topological features of these connectivity patterns were detected as statistically different from the prestimulus epoch by a Z-test corrected by a FDR at $q \leq 0.05$. Brain activities above 30 Hz are characterized by poor global connectivity.

The evolution of functional brain networks is further illustrated in Fig. 3. Local parameters— k_i , c_i and E_i —for each sensor of the network are shown at three different time instants for a frequency of 20 Hz. During the processing of the stimulus, a time-space variability of connectivity is observed. Before the onset of the stimulus, the networks are characterized by very sparse connectivity. Then, a clear clustered structure triggered by the stimulus appears at $t=250$ ms, which defines two main regions (frontal and occipital) with a high density of connections. After the stimulus, the functional wiring again displays a sparse structure.

The comparison of the brain networks against random and regular configurations is shown Fig. 4. Typically, small-world networks exhibit a E_{SW} greater than regular lattices,

but less than random wirings $E_{lat} < E_{SW} < E_{rnd}$; while for the mean cluster index, $C_{rnd} < C_{SW} < C_{lat}$ is expected [4]. The results reveal that, despite the variability observed, functional networks display a topology different from regular and random networks. Namely, $\langle \frac{C}{C_{rnd}} \rangle > 1$ and $\langle \frac{C}{C_{lat}} \rangle < 1$, which indicates a SW structure ($\langle \dots \rangle$ stays for an average over the ensembles of equivalent networks). Further, $\langle \frac{E_{lat}}{E} \rangle < 1$ and $\langle \frac{E_{rnd}}{E} \rangle > 1$ support the hypothesis of SW connectivity.

It is important to emphasize that, in contrast with previous studies which have focused on time-invariant networks [8,9], our results reveal *dynamical* small-world connectivity at multiple time scales [18]. This is a remarkable result, insofar as it suggests that the processing of a stimulus involves optimized (in a SW sense) functional integration of distant brain regions by *dynamic* reconfiguration of links.

In conclusion, we address a fundamental problem in complex networks research: whether the ongoing dynamics of a complex system is correlated with changes in its connectivity patterns. We propose a methodology to study the time-frequency dependencies of functional brain networks, offering an *instantaneous* description of the brain architecture. Applied over a visual stimulus paradigm, the exposed framework reveals that functional brain connectivity evolves with a small-world structure during different episodes of the neural processing.

The conclusions of our study provide meaningful insights

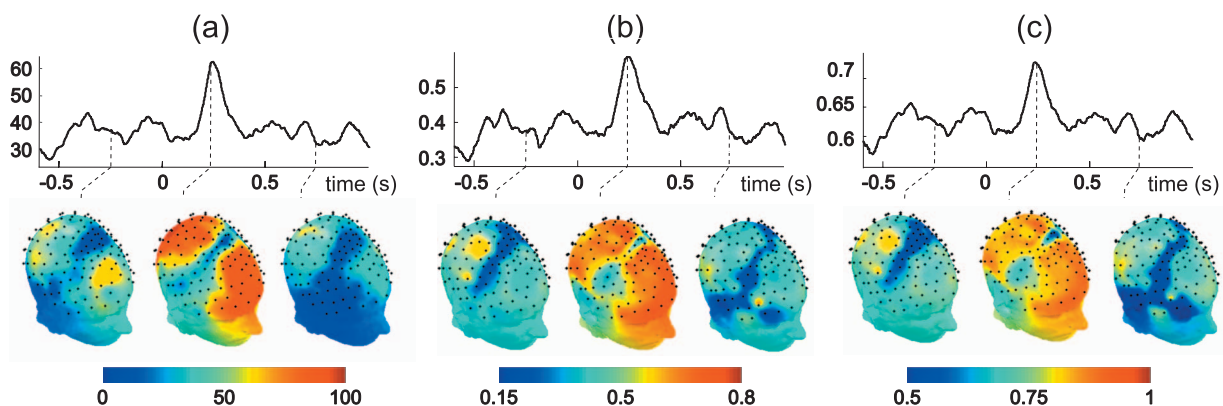


FIG. 3. (Color) Upper row: time evolution of the (a) mean degree $\langle K \rangle$, (b) clustering index C , and (c) efficiency E parameters for a frequency $f=20$ Hz. Lower row: topographic distribution of the local parameters for the same frequency at three different time instants (indicated by the vertical dashed lines).

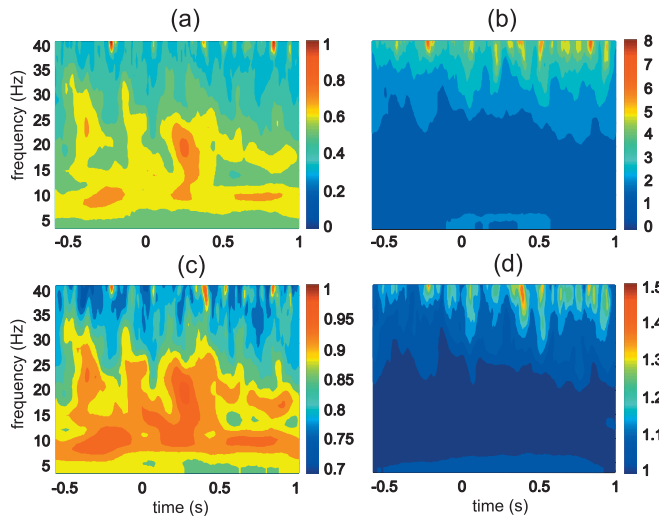


FIG. 4. (Color) Comparison of functional networks with random and regular configurations: time-frequency maps of (a) $C/\langle C_{lat} \rangle$, (b) $C/\langle C_{rnd} \rangle$, (c) $\langle E_{lat} \rangle / E$, and (d) $\langle E_{rnd} \rangle / E$. Results of equivalent random and regular networks refer to the average of 20 realizations.

into how brain networks can efficiently manage local processing and global integration for the transfer of information and are capable of adapting to satisfy changing neural demands. Although the neurophysiological mechanisms involved in the functional integration of distant brain regions are still largely unknown, a dynamic SW organization is a plausible solution to the apparently opposing needs of local

specificity of activity versus the constraints imposed by the coordination of distributed brain areas. The evidence of a time-varying SW connectivity might thus provide some hints for the modeling of neural dynamics with dynamical networks.

The present work was performed on MEG data in sensor space, which contains some inherent spurious correlations between magnetic fields on the surface of the brain. Although this caveat does not affect the characterization of the global network topology, future work will include a source reconstruction of the activity in the cortex, which will allow accurate inferences about anatomical locations. In this study, we have reduced the influence of spurious correlations by simply excluding the nearest sensors from the computation of PLV values.

Applied to other multivariate data, our approach could provide insights into the structure of the time-varying connectivity at a certain time. In this study, functional links have been defined by means of the phase-locking value. We notice, however, that other time-frequency methods (e.g., wavelet cross-spectra) can also be used to detect and characterize a time-varying connectivity of spatially extended non-stationary systems (e.g., financial or epidemiological networks).

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