



Review article

Connectome: Graph theory application in functional brain network architecture

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ABSTRACT

Network science and graph theory applications have recently spread widely to help in understanding how human cognitive functions are linked to neuronal network structure, thus providing a conceptual frame that can help in reducing the analytical brain complexity and underlining how network topology can be used to characterize and model vulnerability and resilience to brain disease and dysfunction. The present review focuses on few pivotal recent studies of our research team regarding graph theory application in functional dynamic connectivity investigated by electroencephalographic (EEG) analysis. The article is divided into two parts. The first describes the methodological approach to EEG functional connectivity data analysis. In the second part, network studies of physiological aging and neurological disorders are explored, with a particular focus on epilepsy and neurodegenerative dementias, such as Alzheimer's disease.

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1. Introduction

Network science and graph theory methods can significantly contribute to understand age-related brain function and dysfunction

(Bullmore and Sporns, 2009; Griffa et al., 2013) and, in particular, to map brain from structure to function, to explore how cognitive processes emerge from their morphological substrates, and to better evaluate the linkage between structural changes and functional derangement (Sporns et al., 2005); in the near future, this approach might even help to develop new individualized therapeutic/rehabilitative strategies.

Several research groups (Sporns and Zwi, 2004; Stam and Reijneveld, 2007; De Vico et al., 2007; He et al., 2007; de Haan

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et al., 2009; Rubinov and Sporns, 2010; Vecchio et al., 2014a, 2015b; Miraglia et al., 2017) have recently engaged themselves with brain functional dataset analysis by graph theory applications. These applications are made with different methodological approaches and on different kinds of datasets.

The present review focuses on few pivotal recent studies of our research team regarding graph theory application in functional dynamic connectivity investigated by electroencephalographic (EEG) analysis. Much of the text has been adapted from a series of articles from our Unit, particularly Miraglia et al. (2015, 2016, 2017) and Vecchio et al. (2015a, 2016a,b,c) as listed in the References. The article is divided into two parts. The first one describes the methodological approach to EEG functional connectivity data analysis. The second one explores network studies of physiology and neurological disorders, particularly neurodegenerative diseases, such as Alzheimer's disease (AD) and epilepsy.

2. Graph theory approach

The human brain is probably the most complex container of interconnected networks in nature, and the “network science of the brain,” or network neuroscience, remains a very recent venture in its starting exploring phase. It defines the connection matrix of the human brain as the human “Connectome.”

Network-based algorithms provide parameters that define the global organization of the brain and its alterations at different levels of investigation (Griffa et al., 2013). Previous studies have applied graph theory to EEG data for the investigation of brain network organization during aging and, in particular, along the continuous line that connects normal aging (Nold), mild cognitive impairment (MCI), and dementia (Vecchio et al., 2014a,b). Thus, it was observed that both measures of global integration (path length as an index of information transfer efficiency) and local segregation

(clustering as an index of local interconnectedness and network segregation) can discriminate cortical network features, which represent the boundaries separating physiological from pathological neurodegenerative brain aging. On the basis of how both specialized and integrated information processing in the brain are supported by the small-world model (Sporns et al., 2004; Bassett and Bullmore, 2006), this new approach allows the evaluation of functional connectivity patterns and aims to specify whether an optimal balance can be found between local independence and global integration as a favorable condition for information processing (Gaal et al., 2010).

Fig. 1 shows a picture from Tijms et al. (2013) to help the readers in the comprehension of the graph theory concepts.

A brain graph theory network is a mathematical representation of the real brain architecture that consists of a set of nodes (vertices) and links (edges) interposed between them. Nodes usually represent brain regions, while links represent anatomical, functional, or effective connections (Friston, 1994; Rubinov and Sporns, 2010), depending on the problem under investigation. In general, the number of nodes is important, but it is not clear whether a minimum number is required.

Mathematically speaking, a network is a matrix, where each row represents a node and each column represents the relationship between the current node and every other node in the network. Links between nodes can be weighted or unweighted. Weighted links can represent the size, density, or coherence of anatomical tracts in anatomical networks, whereas these links can represent the strength of correlation or causal interactions in functional networks. Unweighted (binary) networks are often used by applying a threshold to a weighted network, with links indicating the presence or absence of connection. Although in literature most studies use unweighted networks, interest in weighted network analysis is increasing because of the more specific information they can provide (Telesford et al., 2011).

In this review, network analyses on resting-state EEG data, which are considered undirected and weighted or unweighted networks, are reported, focusing on their applications to physiological aging and neurological diseases such as AD and epilepsy. Analysis from EEG in a resting-state condition was chosen because it provides a measure of connectivity based on the level of co-activation between the functional time series of brain regions (Biswal et al., 1995).

Finally, although MRI technique is not discussed in the present review, the potential usefulness of combining EEG and MRI technologies should be critically considered, particularly MRI, which provides much higher spatial resolution and detailed structural information. The use of functional MRI techniques, including activation and resting-state studies, has reduced the use of EEG in clinical research also, but the reasons for using EEG for connectome analysis instead of MRI could be as follows: the low cost and large diffusion of EEG in clinical centers. Furthermore, the physiological meaning of connectivity within different frequency bands should be obtained just in EEG data and could be more correlated with behavioral pathologies.

2.1. Data recording and analysis

In general, few minutes of resting EEG with subjects' eyes closed and eyes open are recorded with subjects seated relaxed in a sound attenuated and dimly lit room. EEG signals are usually recorded at least from 19 scalp electrodes (Fp1, Fp2, F7, F8, F3, F4, T3, T4, C3, C4, T5, T6, P3, P4, O1, O2, Fz, Cz, and Pz) positioned according to the International 10–20 system. The sampling rate frequency was set at 256 or 512 Hz. Eye movements were monitored by two different channels: vertical and horizontal EOGs; skin/electrode impedances were kept below 5 k Ω .

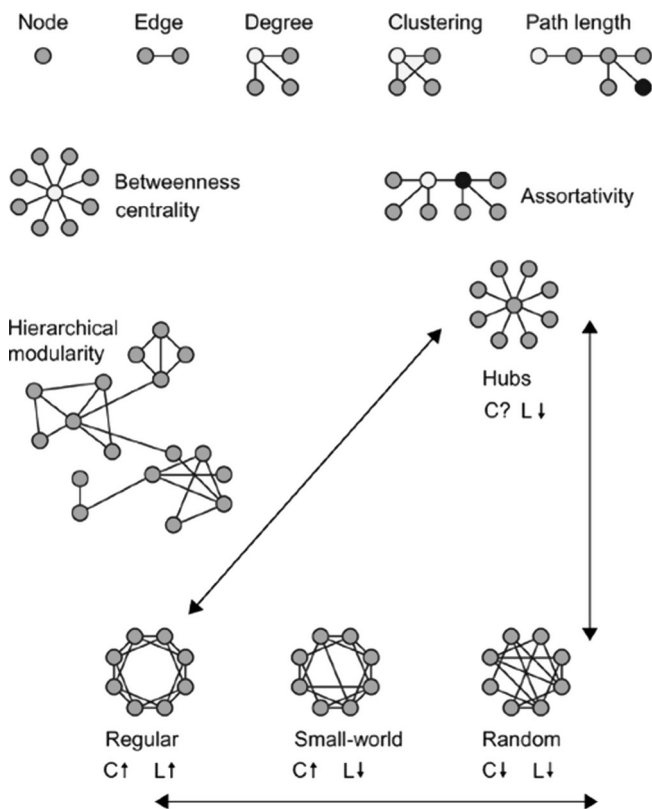


Fig. 1. Adapted image from Tijms et al. (2013) showing the main graph theory concepts. Reproduced with permission.

2.2. Preprocessing of EEG data

EEG signals were band-pass filtered from 0.1 to 47 Hz using a finite impulse response filter. Imported EEG data were segmented in 2-s epochs after identifying and extracting visible artifacts (i.e., eye movements, cardiac activity, and scalp muscle contraction) and after using an independent component analysis (ICA) procedure for artifact rejection. Data were analyzed with Matlab R2011b software (MathWorks, Natick, MA) and using scripts based on EEGLAB 11.0.5.4b toolbox (Swartz Center for Computational Neurosciences <http://www.sccn.ucsd.edu/eeGLAB>). ICA was performed using the Infomax ICA algorithm (Bell and Sejnowski, 1995) as implemented in EEGLAB.

2.3. Functional connectivity analysis

EEG connectivity analysis was performed using the exact low-resolution electromagnetic tomography eLORETA (Pascual-Marqui et al., 2011). The eLORETA algorithm is a linear inverse solution for EEG signals that has no localization error to point sources under ideal (noise-free) conditions (Pascual-Marqui, 2002). The connectivity values were obtained by lagged linear coherence (LagR) algorithm as a measure of functional physiological connectivity (Pascual-Marqui, 2007a; Pascual-Marqui, 2007b). On the basis of the scalp-recorded electric potential distribution, eLORETA was used to compute the cortical three-dimensional distribution of current density. The description of the method, together with the proof of its exact zero-error localization property, is provided by Pascual-Marqui (2007b, 2009).

Several recent studies from independent groups (Canuet et al., 2011; Barry et al., 2014; Vecchio et al., 2014a,b, 2015, 2016b; Aoki et al., 2015; Ikeda et al., 2015; Ramyeed et al., 2015) have supported the idea of a correct source localization using eLORETA, also by the 10–20 EEG montage.

By performing an individual analysis, brain connectivity was computed by eLORETA software in the regions of interest (ROIs) defined according to the available Brodmann areas for left and right hemispheres (Talairach and Tournoux, 1988). Intracortical LagR, extracted by “all nearest voxels” or those in a sphere of 19 mm radius method, selected on the basis of the number of considered nodes (Pascual-Marqui, 2007a; Pascual-Marqui et al., 2011), was individually computed between all possible pairs of ROIs for each EEG frequency band (Kubicki et al., 1979; Niedermeyer and da Silva, 2005): delta (2–4 Hz), theta (4–8 Hz), alpha 1 (8–10.5 Hz), alpha 2 (10.5–13 Hz), beta 1 (13–20 Hz), beta 2 (20–30 Hz), and gamma (30–45 Hz). We used the eLORETA current density time series of each Brodmann area (BA) to estimate the functional connectivity; LagR algorithm was implemented in eLORETA as a measure of functional physiological connectivity that is not affected by volume conduction and low spatial resolution (Pascual-Marqui, 2007a). For each EEG frequency, we computed the mean connectivity matrix between all frequency bins for each subject.

2.4. Parameters derived by graph theory

The core measures of graph theory were computed using the toolkit available at <http://www.brain-connectivity-toolbox.net> and adapted by Matlab scripts (Vecchio et al., 2014b; Miraglia et al., 2015, 2016). In such scripts, *segregation* refers to the degree to which network elements form separate clusters and correspond to clustering coefficient (C) (Rubinov and Sporns, 2010), while *integration* refers to the capacity of network to become interconnected and exchange information (Sporns, 2013), and it is defined by the characteristic path length (L) coefficient (Rubinov and Sporns, 2010).

The mean clustering coefficient is computed for all the nodes of the graph and then averaged (Onnela et al., 2005; Rubinov and Sporns, 2010). It is a measure of the tendency of network elements to form local clusters (de Haan et al., 2009). Starting by the definition of L (Onnela et al., 2005; Rubinov and Sporns, 2010), the weighted characteristic path length L^w (Onnela et al., 2005; Rubinov and Sporns, 2010) represents the shortest weighted path length between two nodes.

Small-world (SW) parameter is defined as the ratio between normalized C and $L - C^w$ and $L^w -$ with respect to the frequency bands. For example, to obtain individual normalized measures, in our studies, we divided the values of the characteristic path length and the clustering coefficient by the mean obtained from the average values of each parameter in all the EEG frequency bands of each subject. Of note, it should be emphasized that the normalization of the data with respect to surrogate networks could not be done because of the weighted values of the considered networks.

The SW coefficient describes the balance between local connectivity and global integration of a network. Small-world organization is intermediate between that of random networks, the short overall path length which is associated with a low level of local clustering, and that of regular networks or lattices and the high level of clustering which is accompanied by a long path length (Vecchio et al., 2014b). This implies that nodes are linked through relatively few intermediate steps, and most nodes maintain few direct connections.

3. Graph theory applications to EEG data

Considering the above methodological remarks, in the following sections, network studies of physiological aging and neurological disorders, such as AD and epilepsy, are explored.

3.1. EEG for the study of physiological aging

This first section reviews studies aimed at understanding whether graph theory application can reveal how normal aging affects the network structure.

Boersma and colleagues recorded resting-state eye-closed EEG of young children (5–7 years). The graphs were weighted using synchronization likelihood (SL); the results showed an increase in average clustering and path length, suggesting that a shift from random to more organized small-world functional networks characterizes normal brain maturation (Boersma et al., 2011).

Micheloyannis and colleagues studied SL in the EEG of children (8–12 years) and young students (21–26 years). They found that beta and gamma values of C in children were higher than those in students. They also found that in beta band SW was significantly higher in children than in students. They concluded that the higher synchronization of fast frequencies observed in children reflects brain maturational processes (Micheloyannis et al., 2009).

Smit and colleagues found that connectivity was more random in adolescence and old age but was more “structured” in middle age. Decrease in SW was also observed in older adults (Gaal et al., 2010; Smit et al., 2010).

When we analyzed (Vecchio et al., 2014a) EEG data in a sample of 113 healthy human volunteers divided into three groups depending on their ages (young, adult, and elderly), we found that in physiological aging, the normalized characteristic path length showed the pattern Young > Adult > Elderly in the higher alpha band. Furthermore, elderly subjects showed an increase in delta and theta bands unlike young subjects (Fig. 2).

This alpha result extends those of previous clinical EEG studies (Delbeck et al., 2003; de Haan et al., 2009), in which a reduction in the characteristic path length in the alpha band was observed in

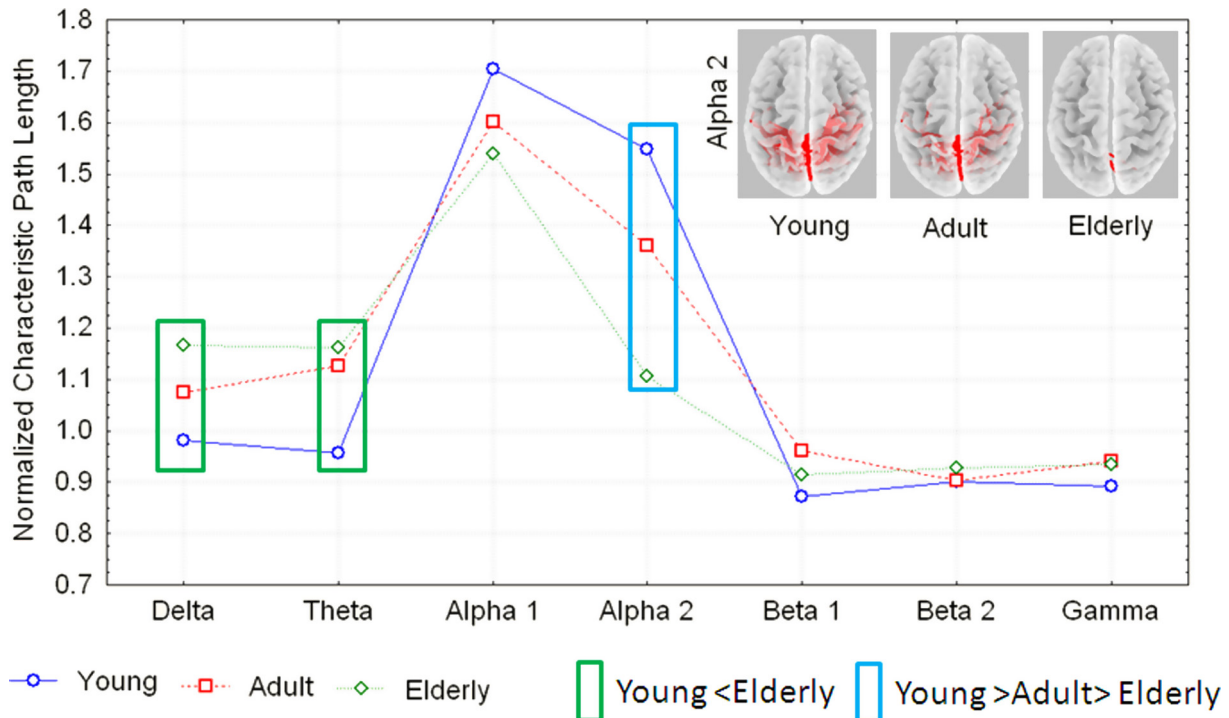


Fig. 2. ANOVA interaction of the normalized characteristic path length (λ) among the factors group (young, adult, and elderly) and band (delta, theta, alpha 1, alpha 2, beta 1, beta 2, and gamma). The lower panel of the figure shows the concomitant cerebral connectivity, mapped by eLORETA, for the alpha 2 band in the three groups, in which the red tract representation belongs to ROIs well connected over the cut-off threshold.

patients with AD, compared with that in normal elderly subjects. The increase in normalized alpha path length characterizing AD (Vecchio et al., 2014b) was also interpreted as a loss of efficiency of communication between distant brain regions. An increase in delta connectivity might therefore reflect a progressive disconnection process of the aging brain as a loss of efficiency of communication between distant brain regions. The loss of structure, as partially expressed by the lower path length in the higher alpha frequency bands, supports, together with the well-known slowing of EEG brain activity and the loss of functional connectivity, the idea that brain aging is –at least in part– a process of progressive disconnection.

Of note, a shorter path length related to physiological aging seems counter-intuitive. However, at least in theory, a shorter path length is not necessarily an advantage in a complex network affected by age because it might increase the processing time and the background “noise” and because the overall structure must maintain an effective balance between local specialization and global integration. In this context, the modulation of the global but not of the local network parameters during the aging process could be considered a loss in the balancing of the most efficacious type of brain connectivity of the young–adult group. A possible interpretation of the present results is that aging processes provoke progressive disconnection among brain areas. This effect has been revealed in older subjects by an increase in slow and a decrease in fast EEG characteristic path length values, which measure the average shortest path length of a network. This indicates a progressive loss of efficiency in a global index of transfer of information from one part of the network to another.

3.2. EEG for the study of pathological aging

Searching for signs of pathological aging, several studies tested whether it was possible to find a trend linking different conditions such as normal elderly subjects (Nold) and demented (AD) patients

passing through MCI, by applying graph theory methodology in cortical sources of EEG data.

AD is considered a disease that initially affects synaptic transmission with an overall disconnection, which could be investigated using a network approach because the structural elements of the brain form an intricate network at different spatial scales (ranging from neurons to anatomical regions) from which functional dynamics emerge. In this way, graph theory approach could provide a general language that enables to understand the association of the various pathological processes interacting with each other in AD, such as spatial patterns of cortical atrophy and functional disruptions, and why the disease propagates along specific routes. (Tijms et al., 2013).

Stam and colleagues applied graph theory to functional connectivity EEG data in beta band of patients with AD and control subjects. Results showed that a loss of small-world network features typifies AD. In fact, in patients with AD, the cluster coefficient C did not significantly change, whereas the characteristic path length L increased. These data suggest a loss of complexity and a less optimal organization (Stam et al., 2007).

Furthermore, by applying graph theory on EEG data of patients with AD and healthy controls, de Haan and colleagues demonstrated in the first group a reduction in both the clustering coefficient, especially in the lower alpha and beta bands, and the characteristic path length, especially in the lower alpha and gamma bands. Because of the decrease in both local and global connectivity parameters, the functional brain network organization in AD deviates from the optimal small-world network structure toward a more random type. This is associated with less efficient information exchange between brain areas, supporting the disconnection hypothesis of AD (de Haan et al., 2009).

We analyzed (Vecchio et al., 2014b) a dataset of 378 EEGs (174 AD, 154 MCI, and 50 Nold). Significant differences between normal cognition and dementia were identified in cortical sources' connectivity. Normalized characteristic path length significantly

increased for AD patients compared with those for MCI and Nold subjects in the theta band alone. Instead, normalized clustering coefficient significantly increased in the theta band of AD patients compared with those of MCI and Nold groups and in the alpha 1 band of AD patients and MCI subjects compared with those of Nold group. The slow EEG frequency increase in both global (clustering coefficient) and local (characteristic path length) parameters could be seen as the disease's effect on network's edges and as a sign of functional disconnection (Vecchio et al., 2014a).

With regard to the outcome observed at low alpha rhythm (8–10.5 Hz) – which is supposed to reflect the regulation of global cortical arousal (Klimesch, 1999; Pfurtscheller and Lopes da Silva, 1999) – there is a general consensus that the high-frequency alpha rhythms reflect the functional modes of thalamo-cortical and cortico-cortical loops that facilitate/inhibit the impulse transmission and the retrieval of sensorimotor information processing (Steriade and Llinas, 1988; Brunia, 1999; Klimesch, 1999; Pfurtscheller and Lopes da Silva, 1999).

Because a decrease in path length implies a shift toward network randomness (Bartolomei et al., 2006), it can be argued that an increase in high-frequency normalized clustering coefficient for both AD and MCI subjects could reflect compensatory neuroplastic mechanisms. The fact that AD patients are more impaired than MCI subjects in theta but not in alpha band is in line with the hypothesis of an intermediate status of MCI between normal condition and overt dementia, in which the alpha bands are the first to be affected by neurodegenerative mechanisms.

3.3. Comparison between physiological and pathological brain aging

On assessing both physiological and pathological brain aging, it was observed (Miraglia et al., 2016) that eye opening causes variations in the processes of cerebral integration and segregation and that small-world values had different patterns in pathological aging in open/closed eye EEG reactivity, with different trends in the various frequency bands.

Gaal and colleagues analyzed EEG resting-state data of a group of young (18–35 years) and elderly (60–75 years) people. Comparing elderly to young, they found that C decreased after eye opening in almost all frequency bands; L decreased following eye opening in theta, alpha 1, alpha 2, and beta 1 bands; and SW parameter decreased following eye opening in beta 1 and beta 2 frequency bands. Eye opening causing a decrease in both the path length and the clustering coefficient in most frequency bands may indicate a more random topology of

functional brain networks, which is to be expected during desynchronization, especially for path length. A decrease in SW index was found as a result of eye opening in beta 1 and beta 2 bands corresponding to a shift toward a random-like topological condition in these frequency bands (Gaal et al., 2010). Zou and colleagues indicated that the alpha rhythm had the largest amplitude in relaxed EC or a waken state (Zou et al., 2009). These results are in line with those of other studies that the activity of the alpha would be restrained because of extrinsic visual stimulus and information processing in EO state.

Tan and colleagues (Tan et al., 2013) found that the small-world characteristics decreased in the theta band but slightly increased in the alpha band from EC to EO states. The reduction in small-world characteristics in the theta band may be due to the external visual input, which induces a decrease in resting-state networks' activity. Moreover, the increase in small-world features in the alpha band may be due to the alpha desynchronization after opening the eyes, which facilitates effective information communication.

Knyazev and colleagues found that age-related differences in eye opening resulted in a decrease in C and an increase in L (Knyazev et al., 2015).

In a recent study (Miraglia et al., 2016) of ours, in order to address differences in functional brain networks between eyes-closed (EC) and eyes-open (EO) conditions in Nold people, amnesic MCI (Petersen et al., 2001), and AD patients, the small-world parameter, which is sensitive to the progression of aMCI or conversion into AD (Toth et al., 2014) in the eye opening, has been investigated. Ninety subjects were analyzed: 30 AD, 30 aMCI, and 30 Nold. An intermediate trend of the aMCI group was found: in EC condition, aMCI displayed more small-world compared with AD and nearer to Nold's network topology in line with other evidence, whereas in the EO, aMCI showed less small-world with a pattern superimposable to that of AD (Fig. 3).

The cognitive impairment of aMCI subjects probably reflects the small-world architecture alteration, and the effect seen on the EO reactivity could lead to the absence of the subject ability to react as rapidly and efficiently as in normal conditions when the brain is visually connected to the external environment. In fact, because of the decrease in local and global connectivity parameters, the functional brain network organization deviates from the small-world network structure typical of the healthy toward a less small-world organization, associated with less efficient information exchange between brain areas, supporting the disconnection hypothesis of AD. This trend also supports the idea that the disease processes induce a functional impairment of cortical neural

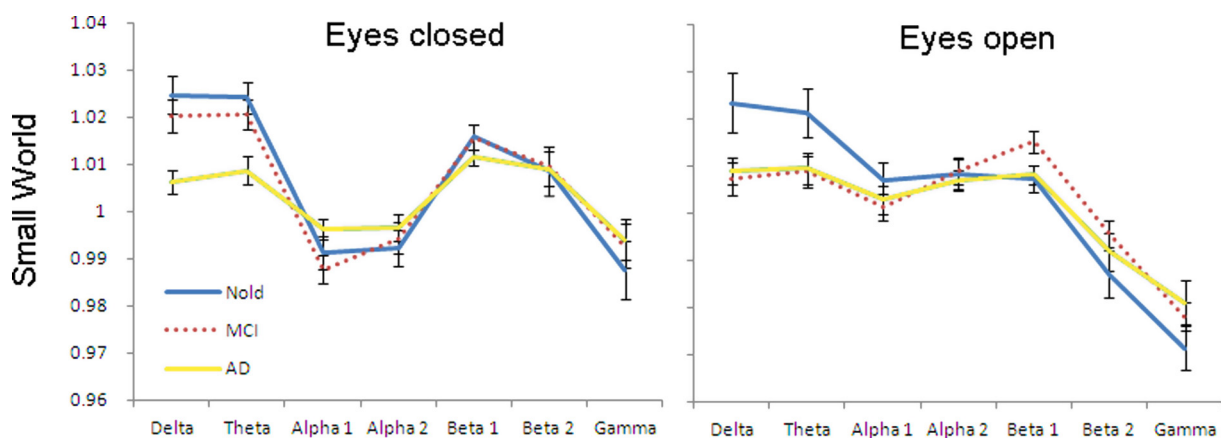


Fig. 3. Left panel: Mean values and standard errors of ANOVA interaction of the small-world parameter among the factors band (delta, theta, alpha 1, alpha 2, beta 1, beta 2, and gamma) and group (Nold, aMCI, and AD) in eyes-closed condition. Right panel: Mean values and standard errors of ANOVA interaction of the small-world parameter among the same factors in eyes-open condition.

synchronization and the hypothesis of a progressive impairment of cortical reactivity across aMCI and AD subjects.

Furthermore, correlation analysis between structural damage of callosal fractional anisotropy (FA), measured by MRI-DTI, and functional abnormalities of brain integration, measured by the characteristic path length (L) detected in resting-state EEG source activity, was carried out in order to find possible correlations between structural damage and functional abnormalities of brain integration. It was verified that the callosal FA reduction could be associated with a decrease in brain interconnection as reflected by an increase in delta and a reduction in alpha path length. The low-frequency increase in path length, which represents a measure of global integration, could be interpreted as the consequence of the decrease in connectivity, defined by the shortest length of links in the network edges, which is a sign of functional disconnection. The correlation observed at low-frequency alpha rhythm (8–10.5 Hz), which is supposed to reflect the regulation of global cortical arousal (Klimesch, 1999; Pfurtscheller and Lopes da Silva, 1999), suggests a progressive (probably cholinergic) impairment of the attentional systems rather than inter-hemispherical coordination of the synchronization pattern.

Considering the decline of memory through physiological brain aging and how memory deficits are considered as a primary symptom of AD (Petersen et al., 2001), a further set of studies aimed to determine whether small-world characteristics of the resting-state brain networks, as reflected in the EEG rhythms, correlate with memory measures in subjects with AD and those in a prodromic stage of dementia as MCI. A significant correlation was found between the small-world properties and short-term memory performance. In particular, higher gamma band small-world characteristic during resting state correlates with better performance to short-term memory tasks as evaluated by the digit span tests. These results are reflected on the EEG by the observation that a more small-world brain network in gamma band is associated with better memory performance.

Finally, remaining in this vein of dementia characterization, a recent correlation analysis (Vecchio et al., 2016c) between hippocampal volume measured by volumetric MRI and small-world parameter, detected in resting-state EEG source activity, showed that alpha band SW was negatively correlated, while slow- (delta) and fast-frequency (beta, gamma) bands positively correlated with hippocampal volume. In particular, larger hippocampal volume was associated with lower alpha and higher delta, beta, and gamma small-world characteristics of connectivity. Of note, it is

possible to speculate that the small-world connectivity pattern could represent a functional counterpart of structural hippocampal atrophy and related-network disconnection.

3.4. EEG for the study of epilepsy

Brain networks constantly change their dynamic state, switching between movement and rest, behavioral and cognitive tasks, and wakefulness and sleep. The epileptic brain represents a further network's feature with the transient occurrence of paroxysmal firing within neuronal assemblies, which end up with a seizure as time progresses.

Characterization of neural networks in epilepsy has gained relevance through time because localized forms of epilepsy are related to an abnormal functioning of specific brain networks without structural damage. Seizures and EEG spiking are considered the result of an imbalance between inhibitory and excitatory signals, thus leading to a hyperexcitable state in which the abnormal rhythms of neural firing cannot be sufficiently controlled by the physiological inhibition mechanism, generating a paroxysmal depolarization shift (Stafstrom and Carmant, 2015).

In a recent study (Vecchio et al., 2016a), we focused on the exploration of the interictal network properties of EEG signals from temporal lobe structures in the context of fronto-temporal lobe epilepsy. Therefore, the graph characteristics of the EEG data of 17 patients suffering from focal epilepsy of the fronto-temporal type, recorded during interictal periods, were examined and compared in terms of affected versus unaffected hemispheres. In this study, EEG connectivity analysis was performed using eLORETA software in 15 fronto-temporal regions (Brodmann Areas BAs 8, 9, 10, 11, 20, 21, 22, 37, 38, 41, 42, 44, 45, 46, and 47) on both affected and unaffected hemispheres.

Evaluation of the graph analysis parameters, such as characteristic path length and clustering coefficient—indices of global and local connectivity, respectively—showed a statistically significant interaction among side (affected and unaffected hemispheres) and band (delta, theta, alpha, beta, and gamma). Statistical testing showed that local and global graph theory parameters increased in the alpha band in the affected hemisphere. This could result from the combination of overlapping mechanisms, including reactive neuroplastic changes, seeking to maintain constant integration and segregation properties and trying to contrast the progressive loss of the natural complexity of EEG signals.

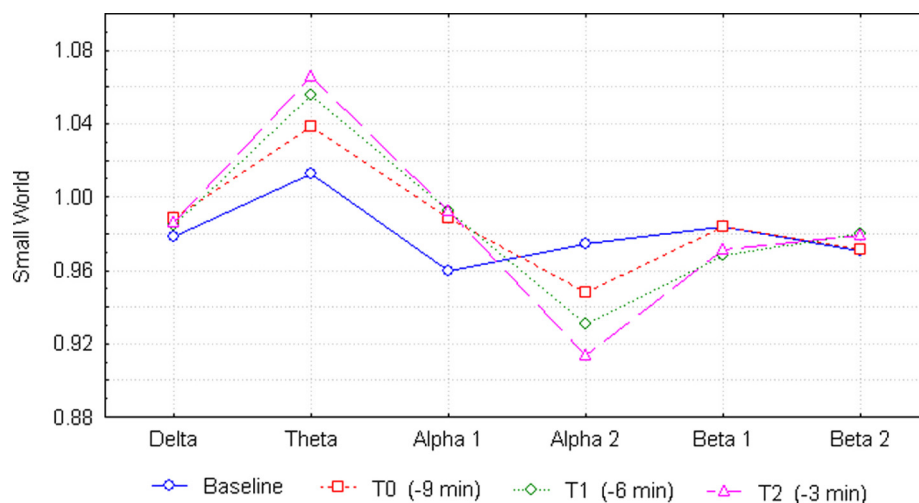


Fig. 4. Small-world parameter among the factors time (Baseline, T0, T1, and T2) and band (delta, theta, alpha 1, alpha 2, beta 1, and beta 2).

Furthermore, epilepsy is characterized by unpredictable and sudden paroxysmal neuronal firing and/or synchronization occurrences eventually evolving into a seizure. To predict the seizure event, small-world characteristics of a 9-min time epoch immediately preceding individual seizures, each epoch fragmented in three 3-min periods (T0, T1, and T2), were investigated on stereotaxic EEG of drug-resistant epileptic patients explored with depth electrodes before surgery (Vecchio et al., 2016a). In Vecchio et al.'s (2016a) work, the importance of using a large number of nodes was evidenced; in this case, the number of contacts was about 100.

Seizures are caused by a progressive hypersynchronization of the firing of a critical mass of neuronal assemblies. This implies that a single neuron cannot cause a seizure; instead, a population of cells or – better – a network of neuronal assemblies is needed (Engel et al., 2013).

Effective connectivity and optimal network structure are believed essential for proper information processing in the brain. Indeed, an association exists between functional abnormalities of the brain and pathological changes in connectivity and network structures. Intracerebral recordings were obtained for 10 patients with drug-resistant focal epilepsy examined by stereotactically implanted electrodes; analysis was performed in a seizure-free period of low spiking (Baseline) and during two seizures. Networks' architecture is undirected and weighted. Electrodes' contacts close to epileptic focus are the vertices, and edges are weighted by *mscohere* (=magnitude squared coherence).

Differences were observed (Fig. 4) between Baseline and T1 and between Baseline and T2 in theta band; and between Baseline and T1, between Baseline and T2, and near-significant difference between T0 and T2 in alpha 2 band. Moreover, an intra-band index was computed for small world as difference between theta and alpha 2. An increasing trend of index was observed from Baseline to T2. The more seizure onset was approaching, the less SW characteristics were evident, with an overall progressive loss of complexity of neural network architecture sustaining the EEG signals.

According to the results of this study, cortical network features significantly modify their configuration up to about 10 min before seizure onset. Additionally, a proof-of-concept attempt suggests that this type of analysis could predict the incoming epileptic seizure with good performance, thus representing an interesting marker of epileptic risk factor.

4. Conclusions

Evidence from this review confirms the utility of an innovative mathematical approach to investigate relevant neurological features in real complex brain networks through EEG data. We chose EEG in all our studies because it is a widely used, noninvasive, and low-cost procedure and is an ideal candidate to functional connectivity analysis with a time frame appropriate for brain function (from seconds to tens of milliseconds). Network analysis in neuroscience could help understand how human cognitive functions are linked to neuronal network structure and how they deal with time-varying networks' dynamics, thus providing a window for an online view on brain complexity and dynamics. As human brains vary largely in size and surface shape, network analysis is appropriate for assessing this variability and can characterize brain network organization. The characterization of brain networks using connectivity matrices and graphs has the advantage of obtaining a rich structural description that allows an efficient computation and comparison of different connection topologies within a common theoretical framework (Bullmore and Sporns, 2009).

A complex topology of brain networks has been demonstrated in structural and functional networks. The presence of a direct

anatomical connection between two brain areas is associated with stronger functional interactions between these two areas. However, functional interactions have also been detected between brain areas without direct anatomical connections. It can be speculated that functional analyses could follow in a better way the dynamics of the cerebral modulations in physiological conditions, including learning and training, and clinical conditions when the brain networks are suddenly or progressively modified like in stroke, AD, or epilepsy.

In this line, the importance of using connectome analysis on an individual basis for classification for diagnostic and prognostic purposes, at least for AD and seizure prediction in epilepsy, should be considered at sensitivity and specificity levels. Few studies, for example, used graph theory at individual level for the discrimination of MCI subjects who will rapidly progress to AD subjects. The most promising result (Hojjati et al., 2017) presented until now is that using graph theory and a learning machine, it is possible to obtain accuracy, sensitivity, specificity, and the area under the receiver operating characteristic (ROC) curve of 91.4%, 83.24%, 90.1%, and 0.95, respectively. These results are very promising for individual diagnosis.

In summary, graph analysis applications described in this review represent an interesting probe to analyze the distinctive features of real life by focusing on functional connectivity networks. The application of this technique to patient data might provide more insight into the pathophysiological processes underlying brain disconnection and might aid in monitoring the impact of eventual pharmacological and rehabilitative treatments.

Conflict of interest

All authors report no conflict of interest.

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