Behavioural Brain Research 317 (2017) 292–300

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Review

Searching for signs of aging and dementia in EEG through network analysis

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HIGHLIGHTS

- Alzheimer's disease is associated with pathological changes in connectivity and network structures.
- Review of recent graph theory application to EEG data.
- Aging and cognitive decline were evaluated.

ARTICLE INFO

Article history:
Received 5 August 2016
Received in revised form
23 September 2016
Accepted 24 September 2016
Available online 28 September 2016

Keywords:
Connectome
Resting state networks
Graph theory
EEG
Functional connectivity

ABSTRACT

Graph theory applications had spread widely in understanding how human cognitive functions are linked to dynamics of neuronal network structure, providing a conceptual frame that can reduce the analytical brain complexity. This review summarizes methodological advances in this field. Electroencephalographic functional network studies in pathophysiological aging will be presented, focusing on neurodegenerative disease –such Alzheimer's disease-aiming to discuss whether network science is changing the traditional concept of brain disease and how network topology knowledge could help in modeling resilience and vulnerability of diseases. Aim of this work is to open discussion on how network model could better describe brain architecture.

Contents

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http://dx.doi.org/10.1016/j.bbr.2016.09.057
0166-4328/

1. Introduction

Understanding brain functioning in aging and brain disease is of preeminent importance to develop new therapeutic and rehabilitative approaches; in particular, *network science* and *graph theory* methods can significantly contribute to the identification of quantitative and specific biomarkers [9,21], to map brain mechanisms from structure, to understand cognitive processes development from their morphological substrates, in order to know the linkage between structural and functional changes and brain dysfunction [50].

Several research groups [12,13,22,47,52,62] moved towards graph theoretical applications, with different methodological approaches and datasets.

This review is a collection of recent studies regarding graph theory application on functional dynamic neuronal connectivity investigated via electroencephalographic (EEG) data. Aim of this work is to look globally at this innovative methodological approach in order to implement the neuroscientific community discussion on which network model could better describe brain architecture and its relationship in behavior and cognition.

The present review is divided into two parts: in the first section it will be described the methodological approach to EEG functional connectivity data analysis and the role of node and edge definitions in brain networks' architecture.

Then, network studies of physiological aging and neurological disorders will be explored, focusing on neurodegenerative disease –such as Alzheimer's disease-, aiming to appraise how brain network science is changing the traditional views on disease mechanisms and how network topology knowledge could help in modeling resilience and vulnerability of diseases and dysfunctions.

2. Graph theory approach

The brain is an interconnected network –probably the most complex one in nature- and the network science of the brain, or network neuroscience, is still a very recent endeavor in its rapidly developing stage. It is called the human "Connectome" and it represents the connection matrix of the human brain.

Using network analysis in neuroimaging research could help understanding how human cognitive functions are linked to neuronal network structure and –most important- how they deal with time-varying networks' dynamics providing an innovative conceptual view helping in reducing complexity of brain mechanisms investigation. For instance, human brains show a large variability in size and surface shape; network analysis hides this variability [57] and can support the characterization of brain networks organization. Furthermore, inter- and intra-individual (i.e. follow-up in time) comparisons between subjects' brain networks are allowed by the use of the same frame of reference [47].

If brain architecture is equalized to a system of elements and relationships among them, networks' based algorithms provide measures that characterize white matter organization and alterations [21]. The application of the modern technique of graph theory to EEG data was investigated for both physiological and pathological brain network in recent studies. Analyzing the basic principles of brain organization –such as integration with the characteristic path length index and segregation with the clustering coefficient – it was found a recurrent continuous trend from normal elderly (Nold) subjects passing through mild cognitive impairment till to demented patients [59,62]. Both global (path length index of efficiency in the information transferring) and local (clustering coefficient as an index of local interconnectedness) measures can discriminate cortical network features in healthy brain and neurodegenerative brain aging [32]. The small-world model summarizes both specialized and integrated information processing of the brain [4,49]. If a network have small world characteristic, there is a balance between local and global processes and the system have favorable conditions for information transfer [19].

2.1. Nodes and edges identifications

A brain network is a mathematical representation of brain architecture composed by nodes and edges between pairs of nodes. The nature of networks' elements are determined by brain mapping methods, schemes of anatomical parcellation, and with connectivity's measures [24]. Brain regions are usually represented by nodes, while edges are represented by functional or effective connections [18,47].

Mathematically speaking, a network is a matrix, where rows are nodes and columns are the relationship between the i-th node and *n*-th node for all network's nodes.

Edges could be weighted or unweighted. Edges's weight could be related to size, density, coherence of anatomical tracts or causal interactions in anatomical or functional networks, respectively. Unweighted networks are obtain applying a threshold and binarizing a weighted network and links indicate only the presence or not of a connection. Many studies analyzed unweighted networks, but in the last years weighted network approach is being of greater interest because it provides more complete information in the relationship between node pairs [54].

Weighted graph analysis attemps to preserve information that in binary scale could be lost, as connectivity values between conditions and avoids the selection of an arbitrary threshold [30]. For this reasons, methodological approach in several research groups is based on weighted networks because it seems to be more close to the real brain organization.

Anyhow, the correct identification of the brain network –with the definition of nodes and edges- is fundamental for the validity of any graph-based model because it should represent a true subsystem with its interactions [15]. In node definition, different strategies could be use in connectome: anatomical, functional, random, and voxel-based, as described in Table 1 [15].

In edges' definition, it should be decided methods and type of connectivity measures. Structural connectivity concerns to anatomical connections describing the physical (axonal and dendritic) brain wiring. Functional connectivity is based on the statistical dependencies between spatially distinct areas and could be evaluated in directed or undirected graphs. The causal influence employed in the neural systems is denoted by effective connectivity.

In this review, they will be reported network analyses on resting state electroencephalographic (EEG) data, where cortical networks are designed as undirected and both weighted or unweighted. EEG was chosen because it is a widely available, non-invasive 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).

2.2. Why resting state condition?

Resting-state analysis provides a method to measure connectivity by examining the level of co-activation between the functional time-series of brain regions during waking rest [6]. These patterns of resting-state correlations are hypothesized to reflect the stable and intrinsic functional architecture of the brain.

This intrinsic architecture is defined as the spontaneous fluctuations between elements of the neural system in the absence of an explicit task, which can be assessed through the acquisition of functional data such as in resting-state. This architecture may provide

Table 1
Summary of different approaches to node definition in imaging connectomics.

	Description	Strenghts	Limitation
Anatomical	Node definitions based on a priori anatomical information, such as sulcal and gyral landmarks	Rapid and intuitive parcellation; low computational burden; high reliability	Low resolution; likely low validity; large variations in node size
Random	Randomly parcellates brain into discrete nodes of similar size, and at varying resolutions	Minimizes node size variations; multi-resolution	Unclear validity/reliability
Functional	Node definitions based on a priori functional information, such as coordinates of peak activations or meta-analytic results	Strong validity, given research hypotheses; good reliability; equal node sizes	Definitions are data-specific; difficult to apply to diffusion data; may miss some regions; definitions based on activation criteria may be unrelated to connectivity
Voxel-based	Each image voxel represents a distinct node	Data-driven; good reliability; high resolution	Unclear validity; computationally intensive; risk of spurious short-range connectivity due to partial volume/smoothing effects

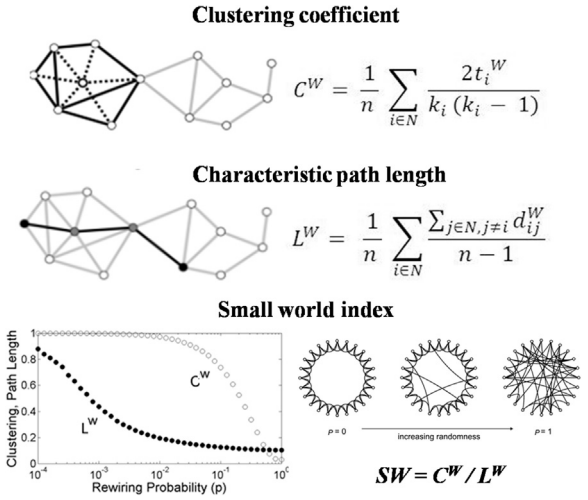


Fig. 1. Graph theory parameters: clustering coefficient, characteristic path length and small world index. Small world index description panels: in left panel graph illustrating the fact that when p is only slightly higher than 0 (which represents a completely regular network with p = 0, high C, high L) and thus a few edges are randomly rewired, the path length L drops sharply, while C hardly changes. At the other end of the graph a completely random graph (p = 1, low C, low L) is represented [45]. The right panel shows different types of networks. Regular network in which all cells are only coupled to their nearest neighbors (left). Small-world network in which small numbers of connections are broken and rewired in order to make long-distance connections at random locations (middle). Random network with more long-distance connections (right), the network loses the property that most connections are local [45].

a framework for the moment-to-moment responses or the brain interaction with the "internal" and "external" worlds [17].

2.3. Data recordings

In general, few minutes of resting EEG with subjects' eyes closed and eyes open are recorded with subjects seated and relaxed in a silent and shield room. EEG signals have been 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) in a position in accord to the International 10–20 system. Sampling rate frequency was fixed from 256 to 512 Hz. Eyes movements were monitored with two EOGs channels, vertical and horizontal; impedances between skin and electrode were lowered of 5 KΩ. Specific EEG data analysis procedure only related to the present researchers' group studies was reported in Appendix A.

2.4. Graph theory parameters

Core measures of graph theory (Fig. 1 and Fig. 2) can be computed with http://www.brain-connectivity-toolbox.net and adapted by Matlab scripts [34,35,62]. Segregation represents network elements' tendency to form separate clusters and is obtain by clustering coefficient (C) [47]. Integration is network's ability to exchange information, and it is computed by characteristic path length (*L*) coefficient [47] (Fig. 1).

C around a vertex i is quantified by the number of triangles in which the i-th vertex participates normalized by the maximum possible number of such triangles.

C is defined as [38,47]:

$$C = \frac{1}{n}\sum_{i\subset N} C_i = \frac{1}{n}\sum_{i\subset N}\frac{2t_i}{k_i(k_i-1)}$$

with Ci the clustering coefficient of node i (Ci = 0 for ki < 2), ki the node's degree, ti the number of triangles around the i-th node. C is normalized between 0 and 1 and characterizes the tendency of the nearest neighbors of the i-th node to be inter-connected.

The weighted clustering coefficient C^w is obtain replacing the number of triangles ti with the sum of triangle intensities as [38,47]

$$C^W = \frac{1}{n}\sum_{i\in N}\frac{2t_i{}^W}{k_i(k_i-1)}$$

where $t_i{}^w$

$$t_i^w = \frac{1}{2}\sum_{j,h\in N}\left(w_{ij}w_{ih}w_{jh}\right)^{1/3}$$

represents triangles' geometric mean. w_{ij} are connection weights related to edges (i,j). Weights are normalized, such that w_{ij} is between 0 and 1 for all i and j [38,47]. For all nodes, the mean clustering coefficient is computed and then averaged. [12].

The characteristic path length of the network is defined as [38,47]

$$L = \frac{1}{n}\sum_{i\subset N} L_i = \frac{1}{n}\sum_{i\subset N}\frac{\sum_{j\subset N, j\neq i} d_{ij}}{n-1}$$

where Li is the average of distances d_{ij} between node i and all other nodes.

Weighted characteristic path length L^w is defined as [38,47]

$$L^W = \frac{1}{n}\sum_{i\in N}\frac{\sum_{j\in N, j\neq i} d_{ij}^W}{n-1}$$

with

$$d_{ij}^w = \sum a_{uv} \in g_{i\leftrightarrow j}^w f(w_{uv})$$

the shortest weighted path length between the i-th and j-th node. f is a map (e.g., an inverse) from weight to length and $gi^w\leftrightarrow j$ the shortest weighted path between i and j.

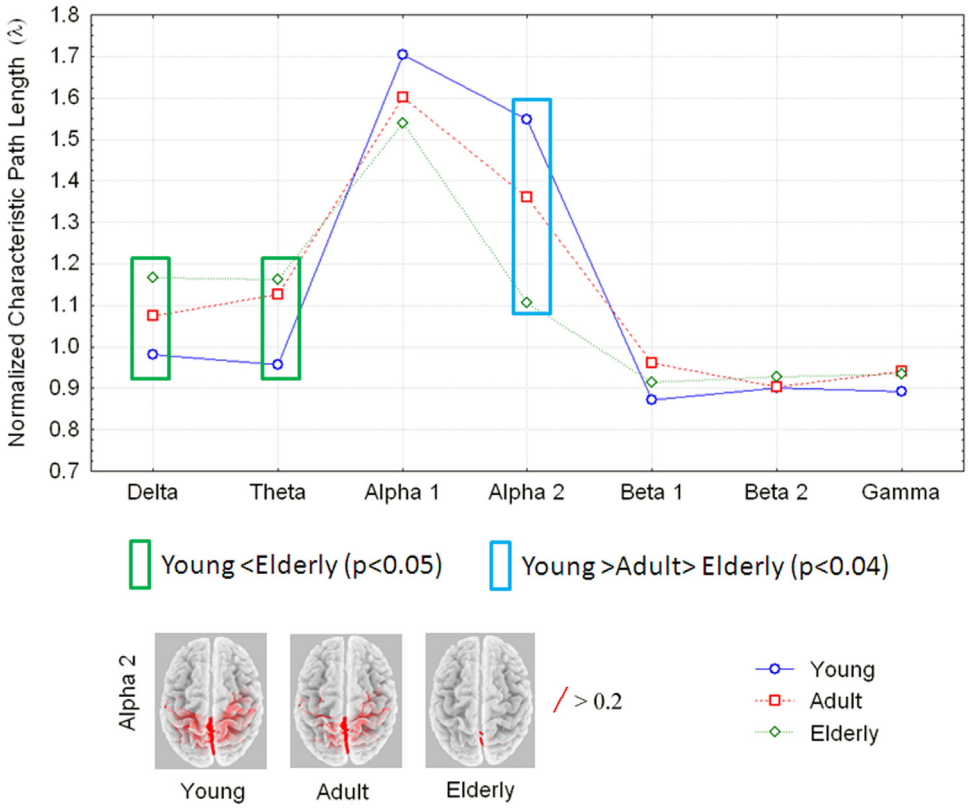


Fig. 2. ANOVA interaction of the normalized characteristic path length (λ) among the factors Group (Young, Adult, and Elderly) and Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2, gamma). The down panel of the figure shows the concomitant cerebral connectivity, mapped by eLORETA, for the alpha 2 band in the three groups, in which the red tract representation belongs to ROIs well connected over the cut-off threshold. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Small-worldness (SW) coefficient is obtain as the ratio between C^w and L^w, in each frequency bands. The SW index represents the balance between local and global connectedness of a network. When SW is larger than 1, a network is a small-world network. Small-world is an intermediate organization between that of random networks, where to a short path length is associated a low level of local clustering, and that of regular networks, where a high level of clustering is accompanied by a long path length [62](Fig. 1).

3. EEGs studies

Keeping in mind the above methodological remarks, in the following sections network studies of brain physiological aging and neurological disorders will be explored, with a particular focus on neurodegenerative disease —such as Alzheimer's disease.

3.1. Physiological aging

Aim of this first group of studies was to observe whether normal ageing influences network structure.

Boersma and colleagues recorded resting-state eyes-closed EEG from young children at 5 and 7 years of age. They calculated a Synchronization likelihood (SL) weighted graphs and found increases in average clustering and path length indicating that normal brain maturation is characterized by a shift from random to more organized small-world functional networks [7].

Micheloyannis and colleagues studied synchronization likelihood of EEG resting state networks in children (8–12 years) and students (21–26 years). They found that beta and gamma values of C in children at rest were higher in relation to those of students and that in beta band the values of *SW* at rest was significant higher in children respect to students. They concluded the higher synchronization of fast frequencies observed in children compared to adults reflects maturational processes [33].

Smit and colleagues found that connectivity was more random in adolescence and in old age, but was more "structured" in middle age. Decrease of small-world properties in older adults was also shown for connectivity patterns [19,48].

In a recent study [59], eyes closed resting EEG data in 113 healthy human volunteers divided in three groups with respect to their ages (young, adult and elderly) were analyzed. It was found that in the physiological aging, the normalized characteristic path length showed the pattern Young > Adult > Elderly in the higher alpha band. Furthermore, elderly subjects showed also an increase in delta and theta band unlike young subjects (Fig. 2).

This results extends previous clinical EEG studies [12,14] where it was found an alpha band decreasing of characteristic path length in Alzheimer's disease patients respect to normal elderly subjects [62] and was interpreted as a loss of communication efficiency between distant brain regions. Delta connectivity increasing might reflect a process of progressive disconnection of the aging brain that could appears as a loss communication efficiency in the brain too. The loss of structure, as partially expressed by the shorter path length in the higher alpha frequency bands, supports, together with the well-known slowing of 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 not necessarily is an advantage in an aging network, since it might increase the processing time and the background "noise", and because the overall structure must maintain an effective balance in global integration and local specialization and. In this context, the modulation of the global but not of the local network param-

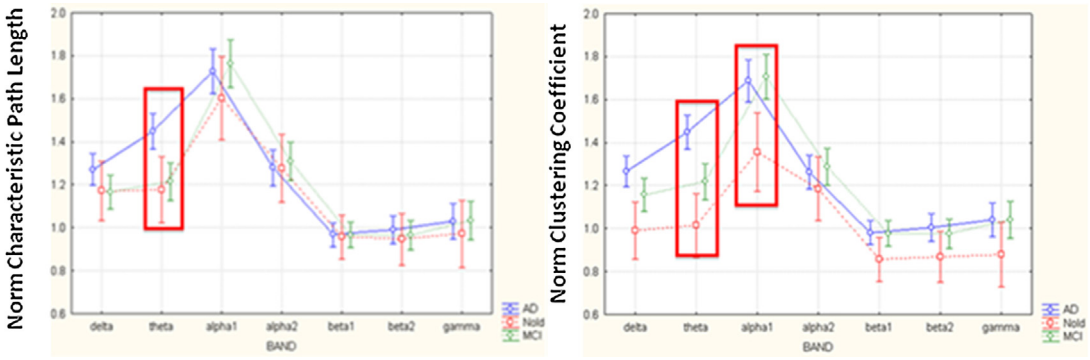


Fig. 3. ANOVA interaction of the normalized Characteristic Path Length (Left Panel) and of the normalized Clustering Coefficient (Right Panel) among the factors Group (AD, MCI, and Nold) and Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2, gamma).

eters 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. From this results, it could be speculated that aging processes provoke progressive disconnection among brain areas. This effect has been revealed in older subjects by increase of low and decrease of high EEG frequency 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. Pathological aging

Searching for signs of pathological aging, several studies tested whether by applying graph theory methodology on cortical sources of EEG data it was possible to find a trend linking different conditions, namely normal elderly subjects (Nold) and demented (Alzheimer Disease AD) patients passing through mild cognitive impairment (MCI, a condition prodromal to AD in a high percentage of MCI subjects)[46].

AD is considered a disconnection disease that could be studied with a network approach. Graph theoretical analysis could provide a general language that enables to disentangle the pathological processes in AD, such as cortical atrophy and functional disruptions, and could support to understand how this processes are associated with each other to origin the disease propagation along specific routes [55].

Stam and colleagues applied graph theory application to beta band filtered EEG data of Alzheimer patients and control subjects. They found that AD showed a loss of small-world network characteristics. In fact, the resulting synchronization matrices converted to graphs showed that the characteristic path length L was higher in the Alzheimer patients, whereas the cluster coefficient C showed no significant changes. Higher path length with a relatively preserved clustering coefficient indicates less complexity and organization [51].

Using EEG and graph theory, de Haan and colleagues found a decreased in the lower alpha and beta bands in AD clustering coefficient and a decreased in the lower alpha and gamma bands AD characteristic path length, respect to controls. This reflect a deviation from the optimal small-world network structure towards a more random type, with decreasing of local and global connectivity parameters in AD, associating a less efficient information exchange between brain areas and supporting the disconnection hypothesis of AD [12].

Vecchio and colleagues analyzed [62] a dataset of 378 EEGs (174 AD, 154 MCI and 50 Nold) in eyes closed resting state condition. In this contest, connectivity of cortical sources showed significant differences between normal cognition and dementia. Normalized characteristic path length showed a significant increase in AD patients respect to MCI and Nold subjects only in theta band. Instead, normalized clustering coefficient showed a significant increment in theta band AD patients respect to MCI and Nold group and in alpha 1 band in AD patients and MCI subjects respect to Nold group (Fig. 3). The low frequency increase of both global (clustering coefficient) and local (characteristic path length) parameters could be seen as disease's effect on network's edges and as a sign of functional disconnection [59].

Regarding the outcome observed at low alpha rhythm (8–10.5 Hz) –that reflect the regulation of cortical arousal [28,43]- there is general consensus that the alpha rhythms reflect the functional modes of thalamo-cortical and corticocortical loops, facilitating/inhibiting transmission and retrieval of sensorimotor information processes [8,28,43].

Since a decrease in path length means a shift toward network randomness [3], it can be argued that an increase in high frequency normalized clustering coefficient in both AD and MCI 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 that MCI is an intermediate status between normal condition and dementia in which the alpha bands are the first to be affected by neurodegenerative mechanisms.

3.3. Physiological and pathological aging

Looking at both physiological and pathological aging, it was observed [34] that in eyes open reactivity, the cerebral processes of integration and segregation, represented by Small-World (SW) index, had different trends in the various frequency bands.

Gaala and colleagues analyzed EEG resting state data in a group of young (18–35 years) and elderly (60–75 years). Comparing elderly to young, they found C decreased after eyes opening in almost all frequency bands, L decreased following eyes opening in theta, alpha 1, alpha 2, beta 1 and SW parameter decreased following eyes opening for the beta 1 and beta 2 frequency bands. The reduction of both path length and clustering coefficient in most frequency bands in eyes opening may indicate a less small worldnessy topology, which is to be expected during EEG desynchronization especially for path length. [19]. Zou and colleagues found a largest amplitude of alpha rhythm in relaxed EC [66]. In line with other studies, these results indicated that the alpha lowering is linked to the occurrence of extrinsic visual stimulus and to the intrinsic information processing in the eyes opening.

Tan and colleagues [53] demonstrated that small-world features reduced in theta band but slightly increased in alpha one from EC to EO states. Small world decreasing in theta band may be due to external visual inputs which provoke a reduction of resting state networks' activity. The increase of small-world features in alpha band may be interpreted as process of alpha desynchroniza-

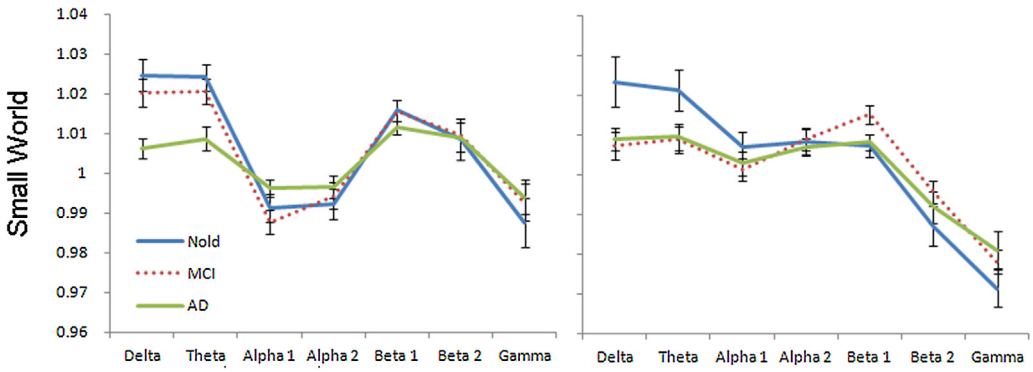


Fig. 4. Left panel: Mean values and standard errors of ANOVA interaction of the small-world parameter among the factors Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2, gamma) and Group (Nold, aMCI, AD) in eyes-closed condition. Right panel: Mean values and standard errors of ANOVA interaction of the small-world parameter among the same factors in eyes-open condition. Nold group is represented by a continuous blue line, aMCI group with a dashed red line, AD group with a continuous green line. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

tion after opening the eyes, which facilitates effective information communication.

Knyazev and colleagues found age-related differences in eyes opening resulted in a decrease of C and an increase of L [29].

In a recent study[34], the small-worldness parameter –which is sensitive to the conversion of aMCI into AD [56] in the eyes opening- has been investigated, in order to find differences in the reactivity of eyes opening in a group of Nold people, amnestic Mild Cognitive Impairment (aMCI) [42], and AD patients. Ninety subjects were analyzed: 30 AD, 30 aMCI, 30 Nold. Results suggested that in EC condition, aMCI were more small-worldnessy respect to AD and nearer to Nold's network topology [60,64], while in the EO, aMCI were less small-worldnessy respect to Nold people, with a pattern superimposable to the AD (Fig. 4).

The cognitive impairment of aMCI subjects probably provoke small-world architecture alteration, and the effect observed in the reactivity of eyes opening could reflect the redoubts subjects' ability to rapidly and efficiently react when is visually connected to the external environment. In fact, with the decrease of local and global parameters, the network topology deviates toward a less small-worldnessy organization. This networks' modulation could be associated to a redoubts information exchanging between brain areas, supporting the idea of a progressive impairment of cortical reactivity across aMCI and AD subjects and of a functional impairment of cortical neural synchronization during the disease process. Furthermore, correlation analysis [60,64] between structural damage of callosal fractional anisotropy (FA) –obtain with MRI-DTI- and characteristic path length (L) computed in resting state EEG source analysis, was made in order to find possible correlations between structural damage and functional abnormalities of brain integration. It resulted that FA reduction could be related to a reduction of brain interconnection as reflected by an increase of delta and decrease of alpha path length. The increasing characteristic path length in low frequency could be seen as the disease effect on the process of cerebral integration, 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 [28,43] – suggests a progressive (probably cholinergic) impairment of the attentional systems rather than inter-hemispherical coordination of the synchronization pattern.

Keeping in mind that memory deficits are both related to physiological aging and to the initial symptom of AD [42], a further set of studies [60,64] aimed to evaluate whether EEG small-world characteristics could correlate with memory measures in AD patients and in a prodromic stage of dementia as MCI. It was shown a significant correlation between small-worldnessy and short term memory performance evaluated by the digit span tests. In particular, higher the gamma band small-worldnessy, better the short term memory tasks. It means that a more small-worldnessy gamma band architecure is associated to better memory performance.

Finally, remaining in this vein of dementia characterization, a recent correlation analysis [63] between hippocampal volume and Small World parameter, detected in resting state EEG source activity, showed that the SW negatively correlated with hippocampal volume in alpha, while in slow (delta) and fast-frequency (beta, gamma) bands positively correlated. Namely, larger the hippocampal volume, lower the alpha and higher delta, beta, and gamma small worldnessy. Of note, it is possible to speculate that small world index could be used as a functional counterpart to structural hippocampal atrophying and network-related disconnection.

4. Conclusions

Brain networks' characterization by graph theory provides a significant advantage in structural description allowing efficient computation and comparison of brain topologies within a common theoretical context [9].

Evidences from this review confirm the utility to adopt a mathematical approach in the study of relevant neurological features in brain networks.

The graph analysis applications described in this review represent an interesting probe to analyze the distinctive features of physiological and pathological aging through a focus on functional connectivity networks. This technique, applied to patient data, could add information to the pathophysiological processes of brain disconnection and might aid in monitoring the impact of eventual pharmacological and rehabilitative treatments. The methodological choice of EEG data was nicely integrating information from MRI investigation for a large scale recruitment and disease progression analysis due to the fact that EEG is a low cost, largely diffuse and non invasive technique allowing a cost-effective large population screening. Using network analysis in neuroimaging research could help understanding how human cognitive functions are linked to neuronal network structure and –most important- how they deal with time-varying networks dynamics providing an abstraction that can reduce the analytical complexity. Aim of this review has been to look globally at this innovative methodological approach in order to discuss whether network science might change the traditional views of brain disease mechanism and in which way networks' topology knowledge can be adopted to model and characterize vulnerability of diseases and dysfunctions.

Concluding, the connectome grants a model to formulate and test hypotheses of disease mechanisms. The related findings linked

to the concept of cerebral integration and segregation properties are surely informative, but probably not sufficient by itself.

It remains extremely important to use caution in interpreting complex neuroimaging data sets and the indirect inferences related to brain connectivity because of a variety of methodological biases [20]. As, for example, the presence of physiological and instrument noise or the low resolution with several distortions due to high background noise and field dishomogeneity (MRI) and other limitations in using only one technique that does not explicitly capture the rich variety of neuronal morphologies, the diversity of physiological and biochemical neural subtypes, glial cells, or brain vascularization [11]. Recent growing evidences in connectomic projects showed progresses in each of the macroscopic, mesoscopic and microscopic levels both in methodological advancement than in understanding of connectivity maps in different organisms, which revealed challenging complexity of brain circuitry [37] but these methods are still imperfect. Further advancement is essential in each modality of imaging methods, but combinations of the different modalities could revolutionalize our understanding about both structural and functional connectome [16,37]. A complete investigation would require an integrated framework that links brain connectivity with brain dynamics, as well as the biological details that relates this connectivity more directly to function for studying the so-called brain's "dynome" and its relationship to cognition in order to studying dynamic changes in brain networks also in task-related connectivity [31].

Acknowledgements

Dr. Francesca Miraglia participated to this study in the framework of her Ph.D. program at the Doctoral School in Neuroscience, Department of Neuroscience, Catholic University of Rome, Italy. All authors do not declare any conflict of interest.

Appendix A.

EEG data pre-processing

EEG recordings were band-pass filtered from 0.1 to 47 Hz using a finite impulse response (FIR) filter. Imported EEG data were fragmented in 2 s duration epochs, identifying and extracting visible artifacts (i.e., eye movements, cardiac activity, and scalp muscle contraction) using an independent component analysis (ICA) procedure. ICA is a blind source decomposition algorithm that enables the separation of statistically independent sources from multichannel data. It has been proposed as an effective method for separating frequent artifact sources –i.e. ocular movement and blinking- from EEG data [23,26,27].

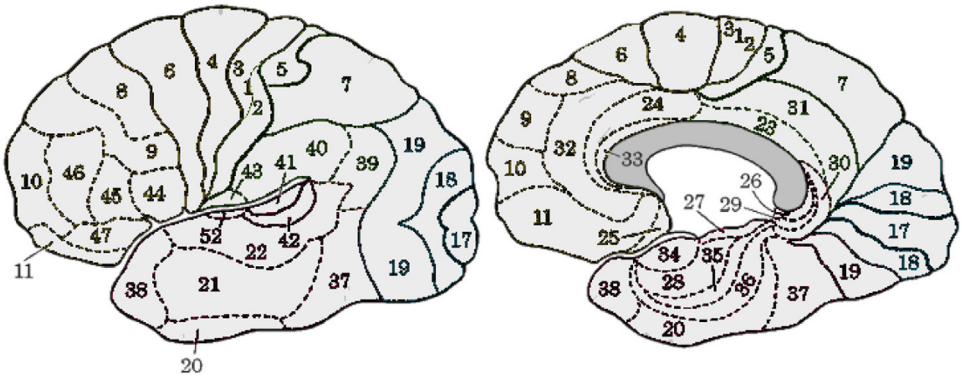
Data were analyzed with Matlab R2011b software (MathWorks, Natick, MA) and using scripts based on EEGLAB 11.0.5.4b toolbox (Swartz Center for Computational Neurosciences, La Jolla, CA; http://www.sccn.ucsd.edu/eeglab). ICA was performed using the Infomax ICA algorithm [5] as implemented in EEGLAB.

Functional connectivity analysis

EEG connectivity analysis has been performed using the exact low resolution electromagnetic tomography eLORETA [41]. The eLORETA algorithm is a linear inverse solution for EEG signals that has no localization error to point sources under ideal (noise-free) conditions. The connectivity values were obtained by Lagged Linear Coherence algorithm implemented in eLORETA as a measure of functional physiological connectivity not affected by volume conduction and low spatial resolution [39]. Based on the scalp-recorded electric potential distribution, the exact low resolution brain electromagnetic tomography (eLORETA) software (publicly available free academic software at http://www.uzh.ch/keyinst/loreta.htm) 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, are described in Pascual-Marqui 2007 and 2009 [39,40].

Several recent studies from independent groups [1,2,10,25,44,58,59,64,62,65] supported the idea of a correct source localization using eLORETA, also by the 10–20 EEG montage.

Via 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. Intracortical Lagged Linear Coherence, extracted by "all nearest voxels" or those in a sphere of 19 mm radius method, chosen with respect to the number of considered nodes [39], was individually computed between all possible pairs of ROIs for each of EEG frequency bands [36]: 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).



Brodmann areas external and internal view

We used the eLORETA current density time series of each BAs to estimate the functional connectivity within each hemisphere (left and right); Lagged Linear Coherence (LagR) algorithm has been implemented in eLORETA as a measure of functional physiological connectivity not affected by volume conduction and low spatial resolution [39].

Starting by the definition of the complex valued coherence between time series x and y in the frequency band ω, which is based on the cross-spectrum given by the covariance and variances of the signals, the lagged linear coherence in the frequency band ω is reported on the following equation [41]:

$$LagR^2_{xyw} = \frac{[ImCov(x,y)]^2}{Var(x) * Var(y) - [ReCov(x,y)]^2}$$

where x and y are the time series of two BAs, Im and Re are the imaginary and real part, Var and Cov are variances and covariance of the signals [39,41].

The connectivity matrices are composed by nXn elements, where n is the number of nodes (BAs of each network) and the nij element is the connectivity value between the i-th and the j-th node.

For each EEG frequency we computed the mean connectivity matrix between all frequency bins for each subject.

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