



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.

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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.

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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 sum-

marizes 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 attempts 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

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