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A Mathematical Proposal to Evaluate Functional Connectivity Strongness in Complex Brain Networks

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Abstract

The brain is a really complex organization of connectivity whose principal elements are neurons, synapses and brain regions. To date this connectivity is not fully understood. Graph Theory represents a powerful tool in the study of brain networks.

Though the complex organization of connectivity in human and animal brain has found a great impulse by the use of Graph Theory, some points result to be not very clear and need to be clarified, the weakness lies in the mismatching between the mathematical and neuroscientific approach. In this paper we focus, in particular, on two points: the concept of distance and a mathematical approach in treating functional and structural connectivity by means of the introduction of the parameter time.

It is known that neural connectivity is classify into three categories: structural (or anatomical) connectivity, functional connectivity and effective connectivity. Structural connectivity can be visualized as the anatomical neural network in particular range of the life of human beings (and animals). It represents the synaptic connections, or directed anatomical pathways derived from neural tract tracing. It can be retained static only in absence of injuries or cerebral illnesses, or far from the childhood and old age. The functional connectivity, i.e. the temporal correlations between remote neurophysiological events as reaction to well specific external stimuli (e.g. social paradigms, social cognitive functions or other specific tasks), interests cerebral areas not necessarily close each other (in the sense of Euclidean distance). Aside we emphasize that the functional connectivity is very distinctive from effective connectivity, i.e. the influence a neural system exerts over another one [27]. The point is that these categories demand different kinds of graphs, except the case of resting state. In this paper we formalize in a mathematical way

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the concept of distance and we introduce a function $W(i,j,t)$ whose peculiarity is to give the weight of the edges composing the graph representing the functional connectivity.
This function $W(i,j,t)$ depends on the position of nodes i, j and on the time t at which a specific task is submitted to an health volunteer (and in in relation to the future to subjects affected by neurological diseases). Interestingly this function, in particular cases, comes down to the probability of edge formation. Basically these particular cases are the resting state and when a particular task do not affect the cerebral region the nodes belong to. This second case is rare since when performing a task the region of interest, ROI, are well known.

Keywords: Brain networks, connectivity, distance, Graph Theory, time, edge weights

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1. Introduction

The brain is a very complex structure, more precisely it has a complicated structural and functional connectivity between its basic constituents, i.e. neurons, synapses and brain regions.
It is remarkable how substantially different systems share key characteristics identified by specific parameters such as: connectivity, centrality, clustering, hub, module (just to mention a few).
If we restrict our attention to the brain connectivity, we should introduce other very important concepts in Neuromathematics:
The *connectome*, defined as the network map of the anatomical connections in the brain (regardless it is human or animal).
The *parcellation* which is the subdivision of the brain into areas or regions.
The *structural connectivity*, that may be viewed as the anatomical description of all connections between the different areas or neurons; when we talk about projections we mean both the anatomical projections and directed anatomical pathways and synaptic connections between different neurons.
The *functional connectivity*, which is strictly related with the activation of different cerebral areas not necessarily close to one another. It is the statistical dependence between the time series of two network nodes (e.g. brain regions or neurons) [68]. Importantly, there is a particular cerebral state where the functional and structural networks seems to coincide: the resting state. The resting state network is the set of brain regions showing coherent

functional connectivity during *task free* spontaneous activity.
As concerns the brain architecture, we cite the *small world organization.* The small world organization is a network that has well defined characteristics: high level of clustering, or better, higher than that proper of regular networks, and an average shortest path length equal to the one observed in random networks. Basically the small world organization shares characteristics typical of both regular network and random network. It is important to clarify a point regarding the small world organization: the length of a path. Above we have mentioned the "average shortest length path", but concerning the longest paths, we tacitly assume a small number of long-distance shortcuts among locally connected nodes. A first approach states that these shortcuts are randomly placed within the network's architecture but there are other conjectures, in hub modeling, that suggest that these shortcuts aggregate hub nodes [67].
We organize the paper as follows: section 2 has the purpose to show how concepts proper of Graph Theory could be applied to shed more light on unaddressed questions in Neuroscience. In section 3 the definitions of Euclidean distance and of Discrete distance are shown, the goal is to emphasize that these two distances cannot be employed together in the same analysis. In section 4 we propose a function whose scope is to assign a weight to an edge between two arbitrary nodes. Its most interesting characteristics is the time-dependence. Finally, Section 5 is devoted to the discussion of conclusions.

2. Graph Theory applied to Neuroscience: basics

In this section we are going to give some useful notions proper of Graph Theory and largely employed in Neuroscience: edge, node, graph, path length, efficiency, cost, hub, modularity, small world.

2.1. Edge, node, graph

A graph is a mathematical tool useful to describe a network. It is defined as a collection of nodes (also known as vertices) and of connection between edges, called edges.

2.2. Path length, mean path length, efficiency

Given two nodes i and j, the path length, $l_{i,j}$, is defined as the number of edges that must be traversed in a sequence of connections starting from i

and arriving to j.
The *shortest path length* is the minimum number of edges needed to link one node to another. If we consider the whole-brain network architecture, than it is useful to define another topological concept: the mean shortest path length, $\bar{l}$ (generally the reference scalar), is defined as the average of the shortest path lengths between any pair of nodes in the network. It measures the distance (i.e., the number of edges) between any pair of nodes in a network or the extent of overall communication efficiency of a network. The mean path length can be short, for example in the case of random and/or complex networks, or long in the matter of regular lattices[1]. The mean path length is a measure of the global connectivity of the network and it is strictly related to the *global efficiency*, its inverse. This means that random and complex networks have high global efficiency of parallel information transfer. On the contrary, for regular lattices, the global efficiency is low.
Nonetheless the beauty of the intuitive definition of mean path length, there is an important problem to face with: what about if the network has nodal pairs that have no connecting path? It is clear that the shortest path length for such disconnected node pairs is infinite. It is possible to bypass this problem by mean of the "harmonic mean", that is calculating the reciprocal of the average of the reciprocals [42].
A shorter distance means higher routing efficiency, because information is exchanged via fewer steps.

2.3. Cost

In this paper we shall not deal with the concept of *cost of a graph*. For the moment it is enough to know that the simplest estimator of the physical cost of a network is the *connection density*, which is the proportion of the number of edges in the observed graph with respect to the number of edges of the complete graph on the same number of vertices. The cost is threshold-dependent [1], [38], the threshold plays a fundamental role in determining the adjacency matrix which resumes the vertex-adjacencies in the given graph. Thus, it is possible to represent various measures of network organization within each group as a function of the cost and to compare

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[1] A regular lattice is a graph where each node has the same degree, i.e. each vertex has the same number of neighbors.

topological and anatomical properties of the graphs between groups under the constraint that the number of edges is the same for each group over the range of the considered thresholds [15].

2.4. Hub, clustering

Clustering is the tendency of a small groups of nodes to form connected triangles (which are particular motifs[2]) or in other words the clustering coefficient (the measure of clustering) is an index of local structure, and has been interpreted as a measure of resilience to random error (if vertex i is lost, do its neighbors remain still connected?). Moreover clustering is related to the *local efficiency*, i.e. can be regarded as a measure of information transfer in the immediate neighborhood of each node. It follows that clustering is a measure of the local connectivity of a regional node. The clustering coefficient is defined by the following ratio:

$$C = \frac{1}{N_{G_i}(N_{G_i}-1)} \sum_{j,k \in G_i} \frac{1}{l_{j,k}}, \tag{1}$$

Where G_i is the subgraph connected to the node i and $l_{j,k}$ is the (shortest) path length connecting the nodes j and k in the subgraph G_i.
The clustering coefficient can be averaged across an entire network.

The basic question underpinning the concept of clustering is to determine the likelihood of a vertex to have a degree k, i.e. the bayesian distribution $P(V, E|k)$. Its advantage is that it is a global measure of a graph. While for a random graph the corresponding degree distribution is a Gaussian one, many complex networks show non-Gaussian degree distributions. When a given vertex shows a high-degree centrality, it is called *hub* [54].

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[2] A motif is a small subset of network nodes and edges, forming a subgraph. Basically motifs are visually represented by building blocks (in analogy to driving elements that are elaborated in a musical theme or composition) of different forms, and they are very common in contexts such as Genetics, Neuroscience, and other biological and artificial networks. Motifs occur in distinct classes, that can be distinguished according to the size of the motif, equal to the number of nodes (vertices), and the number and pattern of interconnections. For a more formal definition of motifs and related concepts we refer the reader to [53]

The hub is a node that occupies a central position inside the network. A central hub can be a connector hub, i.e. an hub that is mainly connected to vertices in other modules, or a provincial hub, which is a high-degree node that is primarily connected to node in the same module. Provincial and connector hubs may play different functional roles within a network. It is interesting to note that a connector hub mediate a high proportion of intermodular, and often *long-distance*, connections.

There are several criteria/measures of a graph to identify centrality, but none of them is unquestionable to select an hub. A few of them are described below:

2.5. Node degree

Node degree is the number of edge attached to a single node. Highly connected nodes have large node degree. The node degree distribution represents the probability of a given node degree over all node degrees in the network.

2.6. Closeness centrality

Closeness is based on the length of the average shortest path between a node and all nodes in the graph. It can be identified as the inverse of the sum of all length paths joining two arbitrary nodes:

$$C_c(i) = \frac{1}{\sum_{j=1}^{n} l_{i,j}}. \tag{2}$$

Someone refers to Normalized Closeness Centrality, it is the ratio between the closeness centrality and the total number of nodes minus one:

$$C_c^{'}(i) = \frac{C_c(i)}{N-1}. \tag{3}$$

2.7. Betweenness centrality

The basic intuition on which betweenness centrality (B_C) rests, is that a node is central if it is between many pairs of other nodes [9].
More formally, betweenness centrality counts the fraction of shortest paths going through a given node with respect to the total number of shortest paths

from the starting node to the ending one [17]. In a mathematical way, for an arbitrary node i belonging to a graph G, the betweenness centrality of the node i is given by:

$$B_C(i) = \sum_{j \neq k \neq i \in G} \frac{\sigma_{j,k}(i)}{\sigma_{j,k}}, \tag{4}$$

where $\sigma_{j,k}(i)$ is the number of geodesic[3] paths connecting node j and k with the constraint to pass through node i and $\sigma_{j,k}$ is the number of geodesic path between the node j and k.

Since this paper is concerned with Neuroscience, as domain of application of Graph Theory, it is helpful to remark that when we mention the word "node", experimentally speaking, it can be associated to a cerebral region, identified for example by a point of the scalp where an electrode is placed during an EEG experiment.

We would like to remark that betweenness centrality, as well as the other criteria mentioned above and in the following, is not an unquestionable criterium to select an hub. In fact, it can be shown that there may exist distinct vertices of a tree[4] endowed with the same set of "paths-through", i.e. $\sigma_{j,k}(i)$, for each $i, j \in V(G)$[5]. This implies that the selection of a hub based only on the evaluation of its "paths-from" can be misleading, since two vertices can have very different numbers of paths-from but the same number of paths-through, in other words if the node $i^{'}$ is adjacent to the node i then it can happen that $\sigma_{j,k}(i) = \sigma_{j,k}(i^{'})$ [23].

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[3] For any two vertices j and k in a graph G, the geodesic is the distance between j and k defined to be the length of the shortest path between j and k, often denoted with $d(j,k)$.

[4] A tree is a specialized case of a graph. A tree is a connected graph with no circuits and no self loops. As already mentioned graph consists of three sets: vertices, edges and a set representing relations between vertices and edges. A circuit is an alternating sequence of edges and vertices wherein edges are not repeated and starting and ending vertices are the same; this forms a loop. A self loop is a vertex looping on to itself and in the middle, no vertex is traveled twice. As a tree does not contain any loops and is connected, it is also called a minimally connected graph on the same number of nodes, i.e. there is just one path between any two vertices.

[5] $V(G)$ is the set of the nodes of a graph G.

2.8. Eigenvector centrality

In this case the intuition is that a node is central, if it has many central neighbors. Bonacich [16] suggested that the eigenvector of the largest eigenvalues of an adjacency matrix could make a good network centrality measure. So the eigenvector centrality of the node i is the i-th component of the eigenvector of the adjacency matrix A associated with the largest eigenvalue.
Unlike degree, which equally weights every contact, the eigenvector weights ties with others according to their centralities. Eigenvector centrality can also be seen as a weighted sum of not only direct connections but indirect connections of every length. Thus it takes into account the whole pattern in the network.

2.9. Graph Theory and the study of neuropathologies

We do emphasize the importance to detect a central hub since they play a crucial role in explaining cerebral damages or pathologies. Hubs play a very important role in brain dysfunctions.
Van den Heuvel and Sporns in their lovely paper [68] listed a series of interesting studies on this topic, we shall cite the most relevant in the following sections.
Basically Graph Theory could help to answer questions on neuropathologies such as autism, schizophrenia and Alzheimer. We base on the paper of Van den Heuvel and Sporns to give a brief overview on the relations between the above neuropathologies and Graph Theory. Some studies speculate that functional connectivity as well as an abnormal anatomical connectivity of hub regions are related to behavioral and cognitive impairment in several neurological and psychiatric brain disorders [12], [18], [20], [48]. For example, it has been shown a reduced frontal hub connectivity [5], [25], [36], [41], [66], [73] and disturbed rich club[6] formation in patients [69], [72] as well as their offspring [49], which provides empirical evidence for the long-standing disconnectivity hypothesis of the disease [25]. Developmental studies have reported altered intra-modular and inter-modular connectivity[7] of densely

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[6] Rich club nodes are highly interconnected, high degree hub nodes.

[7] Intra-modular connectivity is the connectivity of nodes to other nodes within the same module. The inter-modular connectivity gives a measure about how different modules are connected one each other. The participation coefficient, P_C measures the inter-modular connectivity of node i and, for each cortical region, may be mathematically expressed, in

connected limbic, temporal, and frontal regions in children with autism [50]. Furthermore, childhood-onset schizophrenia, COS, has been associated with a disrupted modular architecture [3], together with disturbed connectivity of network connector hubs in multimodal association cortex [4]. In late aging, network analyses applied to neurodegenerative conditions such as Alzheimer's disease [22], [29], [57], [59] and frontotemporal dementia (FTD) [2] have indicated the involvement of, respectively, medial parietal and frontal regions in the etiology of these disorders, regions that have high spatial overlap with network hubs. Computational network studies have further suggested an important role for the brain's highly connected nodes in the spread of neurodegenerative disease effects within and between functional network [46], [48], [62], [64], [63].

2.10. Module and modularity

Many complex networks consist of a number of modules. Modules are subgraphs or group of nodes that consist of sets of vertices that are more strongly connected to each other than to the rest of the network. This allows to maintain a large number of mutual connections and a small number of connections to nodes outside their module. Modules often correspond to different functional aspects of the networks. Modules may also be important for the way normal and abnormal activity can spread through the network. It is also possible to define sub-modules within modules. It is evident how the identification of modules and sub-modules within complex networks is important.

Networks with such a structure are said to have a hierarchical modularity. The concept of a module is a statistical one.

There are various algorithms that estimate the modularity of a network, many of them based on hierarchical clustering. Each module contains several densely interconnected nodes, and there are relatively few connections between nodes in different modules. Hubs can therefore be described in terms

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terms of their inter-modular connection density, by means of the following equation:

$$P_C(i) = 1 - \sum_{s=1}^{N_M} \left(\frac{\omega_{is}}{\omega_i} \right)^2 , \qquad (5)$$

where N_M is the number of modules and ω_{is} is inter-modular connectional weight between the node i and module s and ω_i is the total weight of node i in the network. The P_C of node i will be close to 0 if all weights are within its module.

of their roles in this community structure. Provincial hubs are connected mainly to nodes in their own modules, differently from connector hubs, that are connected to nodes in other modules [19].

Given the modular nature of neuronal networks, the modularity M of a graph describes the degree to which a given network can be broken up into clusters of highly connected nodes, also called modules or communities, with only sparse inter-cluster connections. There are different definitions of modularity, and the most common one is the modularity function defined by Newman [43], which expresses the ratio of the number of existing edges in a cluster relatively to the number of all possible edges in the community. Equivalently up to a multiplicative constant, it is the number of edges falling within groups minus their expected number in an equivalent random network. Inside modules, hubs are called provincial, while hubs connecting different modules are called connector hubs. They serve to measure hierarchical structures in complex networks in as much as a hierarchical network exhibits many provincial and only few connector hubs [37], [47].

Taking about the human cerebral cortex, modularity is a sort of synonym of specialization (of particular tasks). The cerebral cortex combines attributes that promote modularity with attributes that ensure efficient communication, or in other words integration.

2.11. Small world

The small-world [71] is an important model for characterizing the organization principles that govern a remarkable variety of complex networks, such as social, economic, and biological networks. In details, the small-world is a network with specific characteristics: high local clustering (high clustering coefficient C compared to the clustering of a comparable random graph C_R), and low minimum path length between any pair of nodes (low characteristic path length $\bar{l}$, i.e. comparable with the one of a random network $\bar{l}_R$).

If we introduce a scalar σ, defined as $\sigma = \frac{\frac{C}{C_R}}{\frac{\bar{l}}{\bar{l}_R}}$, then the small world is characterized by having $\sigma > 1$ [31] .

In short, small world is a topological organization mostly structured with a few random connections.

Basically, there are different types of small world networks. We cite three of them and we emphasize their characteristics:

2.11.1. Scale free organization

We talk about scale free organization when a network has a proper degree node distribution whose mathematical expression is a power-law function, for example $k^{-\gamma}$ where γ is a coefficient that represents the hierarchy of the network; generally γ ranges from 2 to 3 [21], [44].

One important features of this network is the dependance of the clustering coefficient upon a voxel's degree. It was found that in many cases $C(k)$ scales in the following way:

$$C \sim k^{-\gamma}, \tag{6}$$

that is an indication of hierarchical organization [32], [47]. Bassett et al. [11] estimated a parameter β by fitting a linear regression line to the plot of $\log C$ versus $\log k$ for the network at a given cost. A large positive value of β means that the hubs of the network have high degrees. The network is totally connected, but low clustering, so this suggests that a local connection is favored. These two facts show that, for large positive values of β, hubs are connected predominantly to other nodes not otherwise connected.

Notably, a scale-free network always has small-world property [6], but the converse is not necessarily true. This observation holds for both broad- and single-scale organizations.

2.11.2. Broad-scale organization

This kind of network is characterized by a degree that has a power law regime followed by a sharp cutoff, like an exponential or Gaussian decay of the tail [6].

2.11.3. Single-scale organization

This class of small-world network is characterized by a connectivity distribution with a fast decaying tail, such as exponential or Gaussian. Some examples are shown in [6].

2.12. Matrices of importance in Graph Theory

In order to study structural and functional brain networks, it is fundamental to handle important matrices and follow a sequence of steps to create them. First, it needs to define the network nodes. Second, generate an association matrix (also known as connection matrix), i.e. a matrix to establish the interrelationships between nodes to determine how all pairwise associate between them. Third, to fix strategies for thresholding association matrices. Generally the threshold is represented by a cost to get a graph. Four, to produce an adjacency matrix, namely a matrix A representing which vertices (or nodes) of a graph are adjacent[8] to which other vertices. Generally A is a binary matrix, that is its entries $a_{ij} = 1$ if two distinct nodes i and j are adjacent, and $a_{ij} = 0$ otherwise. For undirected graph adjacency matrix is symmetrical.

3. Distance

A metric on a set X is a function (called the distance function or simply distance) $d : X \times X \to \mathbb{R}$ (where $\mathbb{R}$ is the set of real numbers) such that for all x, y, z belonging to X, it is required to satisfy the following conditions:

1. $d(x, y) \geq 0$ (non-negativity, or separation axiom)
2. $d(x, y) = 0$ if and only if $x = y$ (identity of indiscernibles, or coincidence axiom)
3. $d(x, y) = d(y, x)$ (symmetry)
4. $d(x, z) \leq d(x, y) + d(y, z)$ (subadditivity/ triangle inequality).

Basically, as far as the Complex Brain Networks analysis is concerned, two kinds of distance are of great interest: one is derived by the Graph Theory and it is a discrete metric, the other is a metric directly linked to a continuous space (e.g. the Euclidean metric, which is associated to the Euclidean space).

3.1. Discrete metric

The discrete metric on a set S is the metric satisfying:

$$d(x, y) = \begin{cases} 0 & \text{if } x = y, \\ 1 & \text{if } x \neq y. \end{cases} \tag{7}$$

The resulting metric space $M = (S, d)$ is the discrete metric space on S.

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[8] Two vertices are said to be adjacent if they are the end vertices of an edge.

The discrete metric plays a fundamental role anytime we are interested in studying connections rather than physical distances, like anatomical distances. In detail, when we use the discrete metric we deal with the number of edges that join a node with another, in a network modeling the brain, and importantly, it does not matter if the anatomical distance between the two nodes is small or large when compared with the average largest distance in the brain. In fact, just to give an example let us consider two cases:

Case a If a node represents the Dorso Lateral Prefrontal Cortex ($DLPF$) and the other the Primary Visual Cortex ($V1$) and these two areas are connected through another node, set in Brodmann Area 7 ($BA7$) then the distance between $DLPF$ and $V1$ is 2, since we have the path consisting of the edge connecting the nodes $DLPF$ and $BA7$ *plus* the edge linking the nodes $BA7$ and $V1$.

Case b Now let us consider the connection of two other different nodes such as the Frontal Eye Fields (FEF) and Superior Colliculus (SC) via Lateral Intraparietal Area (LIP).

So the discrete distance in *Case a* and *Case b* is the same, but of course the anatomical distances in these two cases are different.

3.2. Euclidean Metric

On way to define the Euclidean metric is by means of the inner product on $\mathbb{R}^3$ whose origin is $\mathbf{0} = (0,0,0)$. Let us define two vectors belonging to $\mathbb{R}^3$, namely $\mathbf{x} = (x_1, x_2, x_3)$ and $\mathbf{y} = (y_1, y_2, y_3)$, then the Euclidean inner product is:

$$< \mathbf{x}, \mathbf{y} >= \mathbf{x} \cdot \mathbf{y} = x_1\, y_1 + x_2\, y_2 + x_3\, y_3.$$

This inner product, denoted by $\cdot$, “induces” a norm and consequently a length (and in turn a metric):

$$d(\mathbf{x}, \mathbf{0}) = ||\mathbf{x}|| = \sqrt{< \mathbf{x}, \mathbf{x} >}. \tag{8}$$

and an angle:

$$\theta = cos^{-1}\left(\frac{< \mathbf{x}, \mathbf{y} >}{||\mathbf{x}||\, ||\mathbf{y}||}\right). \tag{9}$$

Generalizing, if we consider the Euclidean space $(\mathbb{R}^n, d)$, where n is a natural finite number, then the metric d on such a space assumes the well known expression:

$$d(\mathbf{x}, \mathbf{y}) = ||\mathbf{x} - \mathbf{y}|| = \sqrt{< \mathbf{x} - \mathbf{y}, \mathbf{x} - \mathbf{y} >} = \sqrt{\sum_{i=1}^{n} (x_i - y_i)^2}. \qquad (10)$$

This is called the Euclidean metric in its more general form.

The Euclidean metric plays an important role whenever the physical distance should be taken into account, for example when talking about wiring and physical distance between cerebral areas.

The focal point is that these two metrics, the discrete and the Euclidean, cannot be mixed since they are associated to different spaces. A big corp of literature seems to show that different metrics are employed together when studying the neural network. In these cases we must be careful to avoid confusion between the two different metrics. It becomes immediately evident that the difference in using the discrete or the Euclidean distance when talking about the costs.
It is not correct to mix two different metrics, but it is possible to note that despite cerebral areas may be far away each others from an Euclidean point of view, they can be activated simultaneously and so connected from a point of view of Graph Theory.

4. Quantitative proposal for functional connectivity: the analysis

4.1. Précis

Graph Theory is of great help in studying the functional organization of the brain. It plays a fundamental role in specific and critical cases such as the evaluation of fetal brain functional organization, where *a priori* knowledge is limited.

We begin our analysis by specifying two working assumptions:

1. We consider, for the moment, healthy subjects.
2. We consider an homogeneous synaptic activity growth (namely in the whole brain as well as in single regions). This hypothesis may be

dropped if the function describing the synaptic activity growth in single brain areas is known.

A number of papers start their analysis by assuming that the probability of connection, $P(i, j)$, between two arbitrary nodes, that can represent, for example, a pair of brain regions, is a function of the Euclidean distance $d(i, j)$. More precisely the probabilistic law is assumed to be:

$$P(i, j) = \beta \, \exp\left[-\eta \, d(i, j)\right], \tag{11}$$

$d(i, j)$ represents the anatomical distance between the arbitrary regions i and j, β is a parameter in the range $(0, 1]$, while η is a non-negative parameter regulating the dependence of edge formation on the distance of two existing nodes [4], [35].

4.2. Theoretical tenets

We intend to introduce the parameter time since, in our opinion, several neural phenomena such as the onset of neurological disorders or the structural and functional development could be accounted for, at least partially, by this approach. Moreover we propose a function whose role is to give the weight of the edges of a functional graph.

So we suggest that a law underpinning the functional connection between two nodes, i and j, is not only function of the distance but also of time. Consequently we proposed to modify:

$$W(i, j, t) = \beta \left(i, j, x(t_{fix})\right) \, \exp - \left[\eta(t) \, d(i, j) - \alpha(i, j, t)\right]. \tag{12}$$

Here $x(t_{fix})$ is the relative density of the synaptic activity[9] at time t_{fix}, which is the (fixed) time denoting the starting time of a specific task, in order to inquire the functional connectivity, so $\beta(i, j, x(t_{fix}))$ is time dependent but in a discrete fashion. On the contrary, the weight $W(i, j, t)$ depends continuously on time due to the exponent in the power law.
This choice is motivated by the following observations:

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[9] With relative density of synaptic activity we denote the ratio between the synaptic activity of an arbitrary region of brain containing the nodes i and j and the overall synaptic activity, these synaptic activities are both evaluated at a specific time t_{fix}.

- In Neuroscience functional and structural connectivities are very important concepts, both of them involve distinct neural regions but with a main difference: the structural connectivity exists regardless the execution of a cognitive task performed by a subject.

- The connection strength is quantified by assigning a weight to the edge of the graph representing that particular connection. This operation is made by means of different methods, most of them are of empirical nature [13], [39].

- The weights associated to the edges of the structural network should be viewed as a borderline/extreme case of the ones associated to the functional network. Typical is the case of the resting state, and this is the case represented by $\alpha = 0$. Notably there is another case where $\alpha = 0$, when a task do not involve the activity of the cerebral areas (or area) to which the nodes i and j belong, in fact in these case the correlation between the activities of the interested areas vanish.

- There is the need to explain in which way the functional connectivity varies across the human lifespan. Note that the parameter t inside α is related to this spanning.

In the next steps we show how to evaluate $\beta(i, j, x(t_{fix}))$ and $\alpha(i, j, t)$.

Evaluation of the function $\beta(i, j, x(t_{fix}))$

Let us suppose to consider the brain as a continuum. For each point i we can consider an open ball $\mathscr{U}(i, \epsilon)$ of center i and radius ϵ, where ϵ can be arbitrarily small. In addition we consider the relative density of the synaptic activity, x, in the open ball, where $0 < x < 1$. For the sake of simplicity, from now on we shall write just x by understanding $x(t_{fix})$.

The following data are known:

a. N, the number of nodes.

b. The reciprocal position of such nodes.

c. The Euclidean distance between any pair of nodes.

In order to model the brain connectivity, we suggest the introduction of a *synaptic field* so defined:

$$B_i(x) = \iint\limits_{\mathscr{D}_j \subset \mathbb{R}^2} x^{d_e(i,j)} \, d\mathscr{D}_j, \tag{13}$$

where $\mathscr{D}_j$ is the closed subset of $\mathbb{R}^2$. It represents a part of the cranial surface containing the node j, $d_e(i,j)$ stands for the Euclidean distance between two nodes i and j, and $d\mathscr{D}_j$ is the differential surface (or area) element on a surface $\mathscr{D}_j$. If $\mathscr{D}$ is the cranial surface, the following relation holds: $\mathscr{D}_j \subset \mathscr{D}$.

For application purposes we should discretize the equation (13), so obtaining:

$$B_i(x) = \sum_{j \in V} x^{d_e(i,j)}. \tag{14}$$

where V is the set of nodes on the surface $\mathscr{D}$.

We need to introduce a combinatorial evaluation of all synaptic interactions between two arbitrary nodes i and j. To that end let us introduce the following polynomial function $\beta(i,j,x)$:

$$\beta\,(i,j,x) = B_i(x)\,B_j(x) = \sum_{k \in V} x^{d_e(i,k)} \sum_{k' \in V} x^{d_e(j,k')} \tag{15}$$

Now we can study the neural network as a graph $G = (V;E)$, which is an ordered pair $(V;E)$ comprising a set V of vertices or nodes together with a set E of edges. It is worth remarking that once a graph has been introduced in the analysis, then the distance must no longer be regarded as Euclidean $(d_e(i,j))$ *but* only as discrete $(d(i,j))$. Consequently, in the following, we must approximate $d_e(i,j)$ with $d(i,j)$.

$$d_e(i,j) \sim d(i,j) = min\,\bar{l}(i,j) = min|N(i,j)| - 1, \tag{16}$$

where $\bar{l}(i,j)$ is the characteristic path length between two nodes i and j, $min\,\bar{l}(i,j)$ is the shortest path length and $min|N(i,j)|$ is the total number of nodes[10] on the shortest path length joining two nodes i and j.

By plugging (16) into (15) we get:

$$\begin{aligned}\beta(i,j,x) = \sum_{k\in V} x^{d(i,k)} \sum_{k'\in V} x^{d(j,k')} = &\left(1 + x\,(deg(i)) + x^2\,N_{2i} + o(x^2)\right) \\ &\left(1 + x\,(deg(j)) + x^2\,N_{2j} + o(x^2)\right),\end{aligned} \tag{17}$$

where $deg(i)$ is the degree of the node i (similarly for node j), N_{2i} is the number of nodes set at distance 2 from the node i, $o(x^2)$ represent the terms that could be neglected due to the fact that they are infinitesimal of higher order[11].

If no self-loops are considered in the analysis then an additional constraint is demanded: $i \neq j$, i.e. a node can not interact with itself.
In this case equation (17) takes the simplest form:

$$\begin{aligned}\beta(i,j,x) = &\left(x\,(deg(i)) + x^2\,N_{2i} + o(x^2)\right)\ \left(x\,(deg(j)) + x^2\,N_{2j} + o(x^2)\right) \\ &\sim (deg(i))(deg(j))x^2 + o(x^2)\end{aligned} \tag{18}$$

The expression (18) is very similar to the probability of connection of a new vertex with any other vertex in the network found by Barabási and Réka [7]. It is also quite close to the expression of the coefficient appearing in probability of connection of the *economical preferential attachment model*, suggested by Vértes, Alexander-Bloch, Gogtay, Giedd, Rapoport and Bullmore [70]. In [7] the exponent γ in the linear case equals to 1, while in the non-linear case ranges from 1.2 to 4; in [70], γ, the parameter of preferential attachment, in principle goes from 0 to 6. In particular the authors showed an interesting phase diagram of the economical clustering model, where it appears that most values of two parameters η and γ yield small-world networks, whereas only high values of γ yield networks with heavy-tailed (skew > 1) degree distribution. The study was done on both healthy volunteers

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[10] The number of nodes (vertices of the graph), which represents the cardinality of V, is called the order of the graph and denoted by $\mid V \mid$.

[11] It is often used the "little-oh" notation in this way: $f(x) = g(x) + o(h(x))$. This intuitively means that the error in using $g(x)$ to approximate $f(x)$ is negligible in comparison to $h(x)$. The little-oh notation was first used by E. Landau in 1909.

and participants with childhood onset schizophrenia (COS).

We emphasize that during the discretization of the synaptic field, the interaction of a node with itself was neglected. This is not a trivial remark since a node can represent a single neuron as well as cerebral region.
So theoretically speaking we could interested in considering also a special case: the interaction of a node with itself. In this case it is worth giving some details: first, we do not have to set any constraint on vertices so $d(i,i) = 0$. Second, if i is fixed then $d(i,j) = 1$ for any j adjacent to i. Third, $deg(i)$ is the number of nodes, adjacent to i and connected with it.
Starting from equation (17) and after a bit of algebraic work, it comes out that:

$$\begin{aligned} \beta(i,j,x) = &\big(1 + x\,(deg(i)) + x^2\,N_{2i} + o(x^2)\big) \\ &\big(1 + x\,(deg(j)) + x^2\,N_{2j} + o(x^2)\big) \\ &= 1 + (deg(i) + deg(j))\,x + (deg(i)\,deg(j) + N_{2i} + N_{2j})\,x^2 + o(x^2) \end{aligned} \tag{19}$$

It is interesting to note how the expressions (18) and (19) differ. So introducing or not self-looping has great impact on the analysis. It is also worth pointing out that generally Neuromathematics disallow self-loops, in fact connectivity (and similarly adjacency) matrices are matrices with the main diagonal elements equal to zero and all other elements either positive numbers or zero.

The evaluation of the function $\alpha(i,j,t)$

The function $\alpha(i,j,t)$ depends on the specific test submitted to the healthy volunteer and on age (different stages of life implies different cognitive performances).
We propose that $\alpha(i,j,t)$ could be represented by the product of two functions $f(i,j)$ and $g(t)$:

$$\alpha(i,j,t) = f(i,j)\,g(t), \tag{20}$$

where $f(i,j)$ is strictly related to the task, while $g(t)$ is connected to stage of life in which the healthy volunteer fall when performing the cognitive task. It is responsible for the changing of the weights associated to the functional edges. We further suggest that $f(i,j)$ is strictly dependent on the correlation, derived from the particular task, between the two nodes i and j.

From the available neuroscientific literature there are interesting evidences about the evolution of the neural architecture. The following information will be of great help for our (neuro)mathematical analysis.

In the period going from the fetal stage to birth it is not possible to state that both anatomical and functional connections in the brain can be assumed to exhibit small-world topology [10], [52][12].
By studying fetuses of different gestational ages, Thomason et al. [61] by means of fMRI analysis revealed that human fetal brain has modular structure, wherein connections are much stronger within, than between, modules, and modules overlap functional systems observed postnatally. This is in agreement with observations in adults, and suggests modularity is an early emergent characteristic of the developing brain.
In particular, Thomason et al. showed that the brain modularity decreases, and more negative intermodular functional connectivity of the posterior cingulate cortex (PCC) occurs with the advancing gestational age [61]. By mimicking functional principles observed postnatally, these results support early emerging capacity for information processing in the human fetal brain. It should be noted that a reduced intermodular connection strength, and high modularity in younger fetuses, suggests that in early fetal life functional systems are independent, and only with time they begin to collaborate more fully as members of a whole brain system. Prior observations in late childhood, adolescence, and adulthood, have provided mixed evidence about age-related independence of brain modules. Early research demonstrated that brain modules become increasingly independent and separable with advancing age [24], [58].
Notably, from birth to 2 years, the human brain undergoes several extraordinary changes, including rapid brain volume increases reaching $80-90\%$ of adult volume by age 2 [45], rapid elaboration of new synapses [30], very rapid gray matter volume increasing [28], rapid development of a wide range of cognitive and motor functions [33]. In addition, modular organization and

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[12] A small-world organization can support and justify several phenomena and processes proper of brain dynamics, e.g. the segregation and integration of information. In addition this kind of network represents a trade off between wiring cost minimization and high dynamic complexity. In this sense small-world are “economical” networks.

small-world attributes are evident at birth with several important topological metrics increasing monotonically during development. Most significant increases of regional nodes occur in the posterior cingulate cortex, which plays a pivotal role in the functional default mode network[13] [30].

Fransson et al. in their paper [26] provided the possibility to assess whether the topographical functional network structure of the infant brain possesses small-world characteristics, a network property that has previously been detected in the adult human brain [65], as well as in children aged from 7 years and upward [24], [60].

In the childhood the human brain still develops. In this period several microstructural and macrostructural changes take place in order to reshape the brain's anatomical networks. Moreover, the relation between these cerebral anatomical networks and the functional networks still evolves, that will lead to the cognitive functions and human behaviors.

In the adulthood, it is believed that the brain could develop up to 21-25 years. A study, conducted by Sarah-Jayne Blakemore of University College London, [14], with brain scans showed that the prefrontal cortex is modified until the age of 30-40 years, and in fact she stated that the prefrontal cortex begins to develop in the first childhood. Later development continues in late adolescence and up to 30-40 years, even if the wiring growth is slower than in childhood. Culture, job career, social relations and environment may play a causal role in the "extra" frontal lobe wiring in adult age. We recall that the prefrontal cortex is a part of the brain associated with higher cognitive functions, including decision-making, planning and social behavior.

Finally it is well known that with aging cerebral performances decrease. For example Liu et al. [40] demonstrated age-related changes in the topological organization of large-scale functional brain networks.

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[13] The term "default mode" was first used by Dr. Marcus Raichle in 2001 to describe resting brain function. During the resting state the brain uses hardly less energy than a brain engaged in a task, for example a decision making process. The default mode network involves low frequency oscillations (about one Hertz). This kind of network is most active when the brain is at rest, while is deactivated when the brain is focused towards a task. The default mode network includes areas associated with some aspect of internal thought, such as the medial temporal lobe, the medial prefrontal cortex, and the posterior cingulate cortex, as well as the ventral precuneus and parts of the parietal cortex. It is interesting to note that there may be more than one default mode network, so what is known as default mode network actually should be thought of as a collection of smaller networks, each dedicated to something which is a bit different than the other.

In order to give a quantitative form of the above discussion we suggest a division of the human life into six different characteristic periods. This splitting roughly reflects the evolution of the brain architecture. More precisely:

Period 0: $t = 0$**. The "Neural Big Bang."**
This is the onset of brain evolution in human beings. In analogy with Astrophysics, we can name this period the "Neural Big-Bang". At this time, we remark that $\alpha(i, j, t = 0) = 0$, since, of course, no task is involved. As a consequence, equation (12) assumes the form:

$$W(i, j, 0) = \beta(i, j, x) \cdot \exp\left[-\eta(t = 0)\, d(i, j)\right] \tag{21}$$

Again, since we are in the Neural Big Bang ($t = 0$), this equality, must be identically null. Immediately we get the constraint on β: $\beta(i, j, x) = 0$.

We showed that β is proportional to the product of the degrees of i and j. The constraint $\beta(i, j, x) = 0$ means that even if neurons are present in the brain, or better in the gray matter, at $t = 0$ no connections are established between nodes.

Period 1: $0 \leq t \leq \bar{t}$**.**
In this interval of time, represented by the time interval going from 0 to a time $\bar{t}$, it was believed that the small world, had not begun to take a shape yet, but studies [60] pointed out that at age 7 the brain already shows small world characteristics. Consequently we can set $\bar{t}$ equal to 7 years, in order to consider that the brain shows, at least partially, this kind of architecture. So in (12) the contribution of α to $W(i, j, t)$ is a monotonically growing function:

$$W(i, j, t) \propto \exp h_0 t, \tag{22}$$

being h_0 a constant depending on the stage of life.

Period 2. $\bar{t} \leq t \leq \tilde{t}$
A third period follows. It spans a time interval from $\bar{t}$ to $\tilde{t}$, where $\tilde{t}$ may be fixed in age 20-25, typically the adulthood. So this case ranges from childhood to adulthood. Generally, in this period, we have a great increasing in cognitive performances also due to the monotonic increasing of cerebral

connectivities (structural, functional and effective). From a mathematical point of view, the function $W(i,j,t)$ is proportional to:

$$W(i,j,t) \propto \exp h_1 \left(t^2\right), \tag{23}$$

being h_1 a constant depending on the stage of life.

Period 3. $\tilde{t} \leq t \leq t^*$.
Here we consider the possibility of an extra cerebral wiring. Of course we expect that the growing is pretty slow in comparison with the previous cases. We can realistically assume that $W(i,j,t)$ is proportional to a power law:

$$W(i,j,t) \propto t^{h_2}, \tag{24}$$

being h_2 a constant depending on the stage of life. Just to give an estimation we could set $\tilde{t}$ equal to 25 years.

Period 4. $t^* \leq t \leq t^{**}$.
This span of time is characterized by a steady situation, there is neither an increase nor a decrease in edge formations, and the functional connectivity, on average, does not show any change during a task performing. As a consequence we get:

$$W(i,j,t) \propto W(i,j,t^*) \qquad \forall t \in \left[t^*, t^{**}\right]. \tag{25}$$

We estimate t^* as 50 years and t^{**} as 60 years.

Period 5. $t^{**} \leq t \leq t_{end}$.
Finally, there is a fifth period where the small world architecture and connectivities, as well as other topological properties of the brain, decrease with aging. So we need to assume an inverse power law for $W(i,j,t)$:

$$W(i,j,t) \propto \exp\left(h_4 \frac{1}{t}\right) \tag{26}$$

being h_3 a constant depending on the stage of life.

Remark. We observe that the temporal evolution of the functional connectivity highlights alternating periods of higher and lower growth with respect to the previous period. In detail, in period 2 the temporal evolution of the functional connectivity grows faster than in period 1, in period 3 it grows more slowly than in period 2. In period 5 grows more slowly than in period 4.

Since $W(i,j,t)$ is strictly connected with the changing in the weight of the edges of a functional graph, and from the above observations, it comes natural to propose a form of $g(t)$ (cf. equation (20)), which depends of course on the reference period of life.

As a first step we identify five functions $g_0(t)$, $g_1(t)$, $g_{-1}(t)$, $g_{\widetilde{k}}(t)$, $g_{-2}(t)$[14], so defined:

$$g_0(t) \sim h_0 t, \tag{27}$$

$$g_1(t) \sim h_1 t^2, \tag{28}$$

$$g_{-1}(t) \sim h_2 \ln t, \tag{29}$$

$$g_{\widetilde{k}}(t) \sim h_3 = constant. \tag{30}$$

For example a remarkable choice is $constant = g_{-1}(t^*)$.

$$g_{-2}(t) \sim h_4 \frac{1}{t}. \tag{31}$$

We emphasize that h_0, h_1, h_2, h_3, h_4 are constants and that the functions g's come from a neuroscientific analysis about the cerebral activity in different periods of life. In addition it should be taken into account that the brain evolves in a continuous fashion, so it would be desirable to consider the functions as special cases of a general law. To this we can summarize the above results in an elegant form that describes well all the mathematical comments written for Periods $0, 1, 2, 3, 4$, namely:

$$g_k(t) = c_k \int t^k \, dt, \tag{32}$$

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[14] The particular choice of the subscripts will soon be clear to the readership.

where k is a non-negative real number, and c_k is a constant depending on the period of time.

Specifically it is possible to distinguish five basic cases:

$k = 0$, then (32) takes the form: $g(t) = c_0 t + \widetilde{c_0}$, clearly a monotonically growing function. Where c_0 and $\widetilde{c_0}$ are two constants to be determined. In particular $c_0 = h_0$ (cf. (27)) while $\widetilde{c_0}$ may be found by imposing that at $t = 0$ holds $g_0(0) = 0$, i.e. the continuity of function $g_k(t)$ with the "Neural Big Bang". This leads to set $\widetilde{c_0} = 0$.

$k = 1$, in this case (32) takes the form: $g(t) = \frac{c_1}{2} t^2 + \widetilde{c_1}$, where $c_1 = 2\,h_1$ (cf. (28)). In $t = \bar{t}$, it must hold $g_1(\bar{t}) = g_0(\bar{t})$. This means that $h_1 \bar{t}^2 + \widetilde{c_1} = h_0 \bar{t}$, then $\widetilde{c_1} = h_0 \bar{t} - h_1 \bar{t}^2$.
It is a monotonically growing function and its growth is faster than that in the case $k = 0$.

$k = -1$, then (32) takes the form: $g(t) = c_{-1} \ln t + \widetilde{c}_{-1}$, being as usual c_{-1} and $\widetilde{c}_{-1}$ two constants to be determined. It is a monotonically growing function, and it is immediate to observe that it grows slower than the one for $k = 1$. By (29) it follows $c_{-1} = h_2$. In $t = \widetilde{t}$ must hold $g_{-1}(\widetilde{t}) = g_1(\widetilde{t})$, so $h_2 \ln \widetilde{t} + \widetilde{c_{-1}} = h_1 \widetilde{t}^2 + h_0 \bar{t} - h_1 \bar{t}^2$, then $\widetilde{c_{-1}} = h_1 \widetilde{t}^2 + h_0 \bar{t} - h_1 \bar{t}^2 - h_2 \ln \widetilde{t}$.

Remark. Immediately one notes its monotonic increasing, even if it increases in a slow fashion.

Interestingly this case demands some clarifications: as we wrote before there could be an extra wiring also in age 30-40, and this additional wiring is strictly dependent on some social factors, such as the environment, the kind of job, social relations and culture. So it could be possible to take into account all these factors to improve the function $g(t)$, by introducing a weight ξ in (32), so that the equation becomes:

$$g_{-1}(t) = c_{-1}\,\xi \int t^{-1}\,ds \tag{33}$$

For example, similarly to an empirical technique used in Behavioral Economics (see for example [34]) one could associate to ξ the weight equal to 1 in case of "best scenario", i.e. high quality job, stimulating

environment, good social relations and high education level. Differently, if one of these factors is not top ranked then the weight could be $\xi = 0.9$. If two of the four factors are not top ranked then the weight could be $\xi = 0.6$. Finally if three or more factors are not top ranked then $\xi = 0.3$.
The final result is an increasing trend, varying with the four socio-psychological selected factors.

$k = \widetilde{k}$, where $\widetilde{k}$ is any value of k. In this case (32) takes the form: $c_{\widetilde{k}} \frac{t^{\widetilde{k}+1}}{\widetilde{k}+1} + \widetilde{c}_{\widetilde{k}}$. A comparison with (30) leads to set $c_{\widetilde{k}} = 0$. In $t = t^*$ the functions $g_{\widetilde{k}}(t)$ and $g_{-1}(t)$ must get the same value, i.e. $g_{\widetilde{k}}(t^*) = g_{-1}(t^*)$. It is easy to find that: $\widetilde{c}_{\widetilde{k}} = h_3 = h_2 \ln t^* + \widetilde{c}_{-1}$.
We assumed $g_{\widetilde{k}}(t)$ constant over the interval of time going from t^* to t^{**}, nevertheless it could be possible to refine the analysis by introducing a function either slightly increasing or slightly decreasing, depending on the subject.

$k = -2$, here (32) takes the form: $-c_{-2}\left(\frac{1}{t}\right) + \widetilde{c}_{-2}$. Immediately, by (31) we note that $c_{-2} = -h_4$. Similarly to the other cases we must impose the condition of continuity of the functions: $g_{-2}(t^{**}) = g_{-1}(t^{**}) = \widetilde{c}_{\widetilde{k}}$. It follows that $\frac{h_4}{t^{**}} + \widetilde{c}_{-2} = h_2 \ln t^* + \widetilde{c}_{-1}$, so $\widetilde{c}_{-2} = h_2 \ln t^* + \widetilde{c}_{-1} - \frac{h_4}{t^{**}}$.
Additionally, also in this case the decreasing depends upon the subject, so similarly to case $k = -1$ one could enrich the study by introducing, once again, a weight in order to modulate the decreasing with the change in the four socio-psychological factors.

5. Conclusions

In this paper we dealt with Graph Theory and Neuroscience. After surveying the state of the art we proposed a quantitative approach for the evaluation of the weights of the edges of a graph representing the functional connectivity of the neural network. We introduced the parameter time in the usual approach of Neuroscience. This allows a unified vision of different periods of life where changing in cognitive processes and behavior may happen. Moreover this paper suggests a refinement of the probability of the edge formation that is usually involved in the present literature [4], [35].
Notably, we remark that (12) in resting state becomes the probability of connection between any pair of nodes, representing for example cerebral regions

[35], [70], despite the fact that in general $W(i, j, t)$ is not a distribution of probability. If we are not in the resting state, $W(i, j, t)$ changes the functional connectivity depending on the specific task submitted to the volunteer.

Interestingly, in this approach there is not any experimental constraint so it may be applied to different brain survey techniques, e.g. fMRI, MEG, EEG, etc.

The function $W(i, j, t)$ could contribute to shed more light on understanding how, in different periods of life, the functional graph and its topological characteristics change.

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