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A Mathematical Model for Evaluating the Functional Connectivity Strongness in Healthy People

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Abstract

The human brain is a really complex organization of connectivity whose principal elements are neurons, synapses and brain regions. Up to now this connectivity is not fully understood, and recent impulse in investigating its structure has been given by Graph Theory. However, some points remain unclear, mainly due to possible mismatching between the Mathematical and the Neuroscientific approach. It is known that neural connectivity is classified into three categories: structural (or anatomical) connectivity, functional connectivity and effective connectivity. The point is that these categories demand different kinds of graphs, except in the case of the resting state, and sometimes topological and metrical parameters are involved simultaneously, without a specific distinction of their roles.

In this paper we propose a mathematical model for treating the functional connectivity, based on directed graphs with weighted edges. The function $W(i, j, t)$, representing the weight of the edge connecting nodes i, j at time t, is obtained by splitting the model in two parts, where different parameters have been introduced step by step and rigorously motivated. In particular, there is a double role played by the notion of distance, which, according to the different parts of the model, assumes a discrete or an Euclidean meaning. Analogously, the time t appears both from a local and from a global perspective. The local aspect relates to a specific task submitted to an health volunteer (in view of possible future applications also to subjects affected by neurological diseases), while the global one concerns the different periods in the human life that characterize the main changes in the neural brain network. In the particular case of the resting state, we have shown that W reduces to the usually employed probabilistic growth laws for the edge formation. We tested the correctness of our model by means of synthetic data, where the selection of all involved parameters has been motivated according to what is known from the available literature. It turns out that simulated outputs fit well with the expected results, which encourages further analysis on real data, and possible future applications to neurological pathologies.

Keywords: Brain networks, connectivity, distance, time, weighted graph

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1. Introduction

The human brain is a very complex structure, due to an intricate linking involving the structural and functional connectivity of the basic constituents, i.e. neurons, synapses and brain regions. It is remarkable how substantially different systems share key characteristics, which can be identified by specific parameters such as: connectivity, centrality, clustering, hub, module (just to mention a few of them). If we restrict our attention to the brain connectivity, other Neuromathematics concepts are worth to be considered. The *connectome*, which is the network map of the anatomical connections in the brain (regardless it is human or animal). The connectome plays a fundamental role in the neurobiological research (see for example [26]). The *parcellation* which is the subdivision of the brain into areas or regions. The *structural connectivity* represents the anatomical description of the synaptic connections, namely of all connections among different areas or neurons, forming the 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* is the statistical dependence between the time series of two network nodes (e.g. brain regions or neurons) [37], and can be represented by means of temporal correlations among remote neurophysiological events as reaction to well specified external stimuli (e.g. social paradigms, social cognitive functions or other specific tasks). It interests cerebral areas, not necessarily close each other (in the sense of Euclidean distance), and it is different from effective connectivity, which is the influence that a neural system exerts over another one [13]. Interestingly Van den Heuvel et al. [35] showed the relationship between efficiency of functional brain networks and intellectual performances. Note that there is a particular cerebral state where the functional and the structural networks seems to coincide. It is the *resting state*, namely, the network of brain regions showing coherent functional connectivity during *task free* spontaneous activity.

A special feature of the brain architecture is the *small-world organization* [41]. This relates to a network whose level of clustering is higher than in a *regular network*, and whose "average shortest path length" behaves like in random networks. Basically, the small-world organization shares characteristics which are typical of both regular network and random network. It is tacitly assumed 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, even if different conjectures suggest their aggregation in hub nodes [36].

Structural (or anatomical), functional, and effective connectivity can be profitably explored by means of Graph Theory [8], [28], and several papers are available where interesting neurological results have been presented and commented with this approach. The point is that these three categories of connectivity demand different kinds of graphs, where topological and metrical parameters are sometimes involved simultaneously without a specific distinction of their roles. It would be desirable that different models could be obtained one from the others, and also that all agree in the case of the resting state.

Starting from these remarks, we propose a mathematical model for treating the functional connectivity, based on directed graphs with weighted edges. In Section 2 we detail how a general weight function $W(i, j, t)$ can be obtained for the edge connecting two arbitrarily selected nodes i, j at the time t. In particular, we emphasize a double role played by the notions of distance and of time in our model. Distance assumes both a discrete and an Euclidean meaning, according as it occurs in the evaluation of topological or metrical parameters, respectively. Analogously, the time t appears both from a local and from a global perspective. The local aspect relates to a specific task submitted to an health volunteer, while the global view concerns the different periods in the human life that characterize the main changes in the neural brain network. Also, we have shown that, in the case of the resting state, W reduces to the usually employed probabilistic growth laws for the edge formation. This occurs even when a particular task does not affect the cerebral region the nodes belong to, even if it is not so frequent, since when performing a task the regions of interest (ROI) are usually well known. In Section 3 we test the correctness of our model by means of synthetic data, where all the involved parameters have been selected and motivated according to what is known from the available literature. It turns out that simulated outputs fit well with the expected results, which encourages further analysis on real data, and possible future applications to neurological pathologies. Sections 4 and 5 are devoted to the discussion of results and conclusions, respectively.

2. Proposal of a mathematical model for functional connectivity

2.1. Précis

Graph Theory is of great help in studying the organization of the brain, both from the anatomical, or structural connectivity, and from the functional connectivity point of view. 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.

In this paper we consider the brain as a neural network, namely, as a graph $G = (V; E)$, being V the set of vertices, or nodes, representing neural regions of interest, and E the set of edges, or synaptic connections between pairs of nodes.

From the available literature we have noted that, in dealing with the various aspects of neural connectivity, different kinds of graphs are employed. Concerning the structural connectivity, a few growth models have been adopted for evaluating the probability of connection $P(i, j)$ between two arbitrary nodes i, j representing a pair of brain regions. A number of papers (see for instance [1], or [18]) base on the spatial growth of real-world networks model, which assumes that $P(i, j)$ is the following function

$$P(i, j) \propto \exp\left[-\eta\, d_e(i, j)\right], \tag{1}$$

where η is a non-negative parameter which tunes the dependence of edge formation on the Euclidean distance $d_e(i, j)$ between the centroids of two existing nodes. A different approach exploits a $P(i, j)$ depending on the product between a power law of some topological parameter $\beta(i, j)$, and a decreasing function of $d_e(i, j)$. This idea comes from growth models employed in other real-life complex systems, such as genetic networks or the world wide web. For instance, in the *Economical Preferential Attachment* model ([2], [42]), it results

$$P(i, j) \propto \beta(i, j)^{\gamma} d_e(i, j)^{-\eta}, \tag{2}$$

where $\beta(i, j) = deg(i)deg(j)$, being deg the degree of a vertex (number of adjacent nodes), and γ is a suitably selected parameter. In the *Economical Clustering Model* considered in [40], the same formula has been proposed, but with the topological parameter $\beta(i, j)$ computed as the number of nearest neighbors shared by i and j. In particular the authors showed an interesting phase diagram of the economical clustering model, where it appears that most values of the 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 and participants with childhood onset schizophrenia (COS).

In any case, since the employed parameters have a topological meaning, their evaluation in terms of Graph Theory has nothing to do with the Euclidean metric, and connections in the underlying graph have just a binary code, where 1 denotes the presence of a synapsis, and 0 means no connection. In a sense, two kinds of distances are simultaneously considered for weighting the edges of a same graph $G(V, E)$. The Euclidean distance $d_e(i, j)$ explicitly appears in equation (1), while the discrete distance $d(i, j) = N(i, j) - 1$ works when focusing on $\beta(i, j)$, being $N(i, j)$ the total number of nodes on the shortest path joining i and j.

On the contrary, as far as we know, up to now no specific procedure has been proposed concerning a specific methodology for the assignment of weights to the functional connections. In fact, functional connectivity is usually estimated by fixing, empirically, a threshold on the connectivity matrix resulting from the correlation between each pair of neural regions. This involves the use of metrical parameters, and consequently the distance is intended from an Euclidean point of view. Further, it is reasonable to assume that functional connectivity changes with age, so that correlations and thresholds related to a given task should also change accordingly. In order to sketch a possible general approach, we wish to propose a mathematical model for the weights of the edges of the graph representing the functional connectivity, depending on parameters usually appearing in neuroscience, and, in addition, also including the role of time in the steering law for the edge formation.

2.2. Theoretical tenets

We assume, for the moment, to work with healthy subjects, and 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. Before the explicit presentation, we wish to resume the main cornerstones underlying our proposal.

- In Neuroscience, both the functional and the structural connectivity are basic concepts involving 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 edges of the graph representing the functional network. This operation is made by means of different methods, most of them are of empirical nature [6], [20].

- The weights associated to the edges of the structural network should be viewed as borderline/extreme values of the weights associated to the functional network. Typical is the case of the resting state.

- In fixing the weights, one should consider also the role of time, mainly from two different perspectives. From one side, there is the need to explain in which way the functional connectivity varies across the human lifespan. On the other side, a temporal diversification is required between the long-time evolutionary aspect and the one related to the execution of a particular cognitive test.

As a consequence, we are proposing the following law underpinning the functional connection between two nodes, i and j,

$$W(i,j,t) = \beta\left(i,j,t_{fix}\right) \exp\left(-\left(\eta(t)\, d_e(i,j) - \alpha(i,j,t)\right)\right), \tag{3}$$

where t_{fix} is an instant arbitrarily fixed in the interval of time related to some specific task designed to inquire the functional connectivity. On the contrary, the time t in $\alpha(i,j,t)$ ranges on the whole life of the investigated neural network. Therefore, the function $\beta(i,j,t_{fix})$ is time dependent from a local point of view, while $\alpha(i,j,t)$ is time dependent in a global way. Consequently, in our model, the weight is time dependent both from a local and from a global perspective.

In the next subsections we give all details supporting our choice. In particular, we show how $\beta(i,j,x(t_{fix}))$ and $\alpha(i,j,t)$ should be evaluated, pointing out the neurological meaning of the mathematical steps. In addition, we enlighten a possible link between the functional and the structural connectivity in the case of the resting state.

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

For evaluating the function $\beta(i,j,t_{fix})$ we assume that connections in $G(V,E)$ are binary weighted, so that, for $i,j \in V$, $d(i,j)$ is the number of steps of the shortest path from i to j.

When the brain is stimulated, we can associate to each vertex i a random variable X_i, corresponding to the functional stimulus produced by i on the other nodes in the brain, due to the performed task. Note that X_i depends only on i, so that, for different vertices i,j, X_i, X_j are independent random variables. Let M_i be the maximal distance from i to any other vertex in the graph $G(V,E)$. Then, the possible values that can be assumed by X_i result in a sequence of positive real numbers $\{\gamma_{in}\}_{n=0}^{M_i}$, where γ_{in} denotes the correlation induced by the node i on each nodes at distance n from i as a consequence of the considered solicitation. According to the growing consensus [29] that brain networks are approximately scale-free[1], with a preponderance of highly connected hub areas that, together, constitute a rich club, it is quite reasonable to assume

$$\gamma_{in} \propto N_{in}^{\gamma}, \tag{4}$$

where $N_{in} \subset V$ is the set of nodes having distance n from i, and γ is a parameter depending on the topological growth of the neural network. Now, let $B_i(t)$ be the *generating function* associated to X_i, namely

$$B_i(t) = \sum_{n=0}^{\infty} \gamma_{in} t^n.$$

Of course, since the brain is modeled by means of a finite number $N = |V|$ of neural regions, then n can assume only a finite number of values, corresponding to all the possible distances between i and the other nodes in V. Therefore, $B_i(t)$ must be assumed to be the *truncated generating function*, namely

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[1] A scale-free organization is a network characterized by a degree distribution that follows a power law. More precisely, there is a general opinion that brain networks besides showing a small-world organization also have broad degree distributions that often follow a power law, i.e. a scale free organization.

$$B_i(t) = \sum_{n=0}^{M_i} \gamma_{in} t^n. \tag{5}$$

Let us consider now a pair i, j of two different points. Since X_i and X_j are independent random variables, a good representation of the functional stimulus resulting in the brain by the mutual activity of i and j can be assumed to be

$$\beta(i, j, t) = B_i(t) B_j(t) = \sum_{n=0}^{M_i} \gamma_{in} t^n \sum_{n=0}^{M_j} \gamma_{jn} t^n. \tag{6}$$

Since $\beta(i, j, t)$ is computed as a consequence of the brain stimulation related to a particular task, the involved interval of time is very small if we normalize with respect to the medium span of the human life, so that, without loss of generality, we can assume t close to 0. This means that, in the expansion of (6), the preponderant terms have lower exponent. Therefore, we can write

$$\beta(i, j, t) = \left(1 + t\,\gamma_{i1} + t^2\,\gamma_{i2} + o(t^2)\right)\left(1 + t\,\gamma_{j1} + t^2\,\gamma_{j2} + o(t^2)\right), \tag{7}$$

where $o(t^2)$ represents the terms that could be neglected, being infinitesimal of higher order[2]. In general we are not interested in self-loops, i.e. a node can not interact with itself, which implies that the additional constraint $n > 0$ must be added. In this case equation (7) takes the simplest form:

$$\beta(i, j, t) = \left(t\,\gamma_{i1} + t^2\,\gamma_{i2} + o(t^2)\right)\left(t\,\gamma_{j1} + t^2\,\gamma_{j2} + o(t^2)\right) \sim \gamma_{i1}\gamma_{j1} t^2 + o(t^2). \tag{8}$$

By (4) we get

$$\beta(i, j, t) \sim (deg(i)deg(j))^{\gamma} t^2 + o(t^2), \tag{9}$$

where $deg(i)$ (resp. $deg(j)$) is the degree of the node i (resp. j). Note that, up to infinitesimal of higher order, we have

$$\beta(i, j, t_{fix}) \sim (deg(i)deg(j))^{\gamma} t_{fix}^2 \propto (deg(i)deg(j))^{\gamma}, \tag{10}$$

so that the resulting approximation equals the topological factor appearing in the growth models (2) proposed in [2], [42]. In particular, in [2] the exponent γ can be 1 (linear case) or ranges from 1.2 to 4.

2.4. Self-loops

In the discretization of the synaptic field, the interaction of a node with itself was neglected. This agrees with the usual approach in Neuroscience where zero valued entries on the main diagonal of connectivity (and similarly adjacency) matrices are assumed. However, a node can represent a single neuron as well as a whole cerebral region, and consequently, in principle, we could allow also self-loops in our model. In this case (7) provides

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

$$
\begin{aligned}
\beta(i,j,t) &= \left(1 + t\,(deg(i)) + t^2\,\gamma_{i2} + o(t^2)\right) \\
&\quad \left(1 + t\,(deg(j)) + t^2\,\gamma_{j2} + o(t^2)\right) \\
&= 1 + (deg(i) + deg(j))\,t + (deg(i)deg(j) + \gamma_{i2} + \gamma_{j2})t^2 + o(t^2).
\end{aligned} \tag{11}
$$

Since self-looping results in increasing values of $\beta(i,j,t)$, it is not surprising that the second order approximations of $\beta(i,j,t)$ provided by (8) and (11) are different, even if a precise quantification of the change is not achievable. However, note that, in the case of self-looping allowed, the best approximation of $\beta(i,j,t)$ is a first order approximation, and we can assume

$$\beta(i,j,t_{fix}) \sim 1 + (deg(i) + deg(j))\,t_{fix} \sim (deg(i) + deg(j))\,t_{fix} \propto deg(i) + deg(j). \tag{12}$$

Remark 1. *Denoting by* $N_1(i,j)$ *the number of nearest neighbors shared by i and j, we can observe that in the case of the* Economical Clustering Model *suggested by Vértes, Alexander-Bloch, Gogtay, Giedd, Rapoport and Bullmore in [40], it is reasonable to assume* $deg(i) + deg(j) \sim N_1(i,j)^{\gamma}$*, for some suitable exponent* γ*. Therefore* (12) *provides the coefficient appearing in the probability of connection of the* economical preferential attachment model*, suggested by Vértes, Alexander-Bloch, Gogtay, Giedd, Rapoport and Bullmore [40], where* γ*, in principle, ranges from* 0 *to* 6*.*

Remark 2. *As a consequence of all previous considerations, we can speculate that the proposed* $\beta(i,j,t)$ *provides a rigorous mathematical justification of the usual topological parameters of the growth models employed in studying the structural connection. These represent a good first order approximation when modeling the edge formation in a real neural network, which usually can be quite acceptable. However, for possible deeper investigations, our approach suggests how a finer choice could be done.*

2.5. Aging evolution of neural architecture

Before commenting on the evaluation of the function $\alpha(i,j,t)$ we wish to motivate our choices with a (neuro)mathematical analysis based on the available neuroscientific information (to the best of our knowledge) concerning the evolution of the neural architecture.

First of all, in the period ranging from the fetal stage to the birth, it is not possible to assume that both anatomical and functional connections in the brain exhibit small-world topology [5], [25][3].

By studying fetuses of different gestational ages by means of fMRI analysis, Thomason et al. [33] revealed that human fetal brain has modular structure, wherein connections are much stronger within, than between, modules, and that modules overlap functional systems observed postnatally. This is in agreement with observations in adults, and suggests that 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

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[3] A small-world organization can support and justify several phenomena and processes proper of brain dynamics, e.g. the segregation and integration of information. It is worthy to note that, talking about networks, an important notion is the *efficiency* in exchanging information. For example, Latora and Marchiori [19] found that real systems such as neural networks and man-made communication and transportation systems have a small-world architecture of high efficiency. 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.

with the advancing gestational age [33]. 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 [11], [31].

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 [24], rapid elaboration of new synapses [15], very rapid gray matter volume increasing [14], rapid development of a wide range of cognitive and motor functions [16]. In addition, modular organization and small-world attributes are evident at birth, with several important topological metrics increasing monotonically during development. Most significant increasing of regional nodes occurs in the posterior cingulate cortex, which plays a pivotal role in the functional default mode network[4] [15].

Fransson et al. [12] 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 [34], as well as in children aged from 7 years and upward [11], [32].

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, which 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 with brain scans (URL: `http://www.ted.com/talks/sarah_jayne_blakemore_the_mysterious_workings_of_the_adolescent_brain#`) 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. 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 the 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. [21] demonstrated age-related changes in the topological organization of large-scale functional brain networks.

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[4] 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 one dedicated to something which is a bit different than the other.

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

The function $\alpha(i,j,t)$ depends on the specific test submitted to a volunteer, and on age (different stages of life implies different cognitive performances). Therefore, we propose that $\alpha(i,j,t)$ is represented as the product of two functions $f(i,j)$ and $g(t)$:

$$\alpha(i,j,t) = f(i,j)\, g(t), \tag{13}$$

where $f(i,j)$ is strictly related to the task, while $g(t)$ is connected to stage of life in which the volunteer falls 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 discussion presented in Subsection 2.5 we can derive a quantitative form for $g(t)$. To this, we propose a splitting of the human life into six different characteristic periods, which 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 (3) assumes the form:

$$W(i,j,0) = \beta(i,j,x)\, \exp\left[-\eta(t=0)\, d_e(i,j)\right]. \tag{14}$$

Since we are in the Neural Big Bang ($t = 0$), this equality must be identically zero, which implies $\beta(i,j,x) = 0$.

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 range of time, represented by the interval going from 0 to a time $\bar{t}$, we assume that small-world has not begun to take a shape yet. Some studies [32] point out that at age of 7 the brain already has a few 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 (3) the contribution of α to $W(i,j,t)$ is a monotonically growing function:

$$W(i,j,t) \propto \exp\left(h_0 t\right), \tag{15}$$

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 identified with 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:

$$W(i,j,t) \propto \exp\left(h_1 t^2\right), \tag{16}$$

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. Realistically, we can assume that $W(i,j,t)$ is proportional to a power law:

$$W(i,j,t) \propto t^{h_2}, \tag{17}$$

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:

$$W(i,j,t) \propto W(i,j,t^*) \qquad \forall t \in [t^*, t^{**}] \,. \tag{18}$$

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

Period 5. $t^{**} \leq t \leq t_{end}$. Finally, during a sixth period, 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 $W(i,j,t)$:

$$W(i,j,t) \propto \exp\left(h_4 \frac{1}{t}\right) \tag{19}$$

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, where it remains constant.

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 (13)), which depends of course on the reference period of life.

Excluding the Neural Big Bang, which is characterized by $g(t) = 0$, we can identify five functions $g_0(t)$, $g_1(t)$, $g_{-1}(t)$, $g_{\tilde{k}}(t)$, $g_{-2}(t)$[5], so defined:

$$g_0(t) \sim h_0 t, \tag{20}$$

$$g_1(t) \sim h_1 t^2, \tag{21}$$

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

$$g_{-1}(t) \sim h_2 \ln t, \tag{22}$$

$$g_{\widetilde{k}}(t) \sim h_3 = constant. \tag{23}$$

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

$$g_{-2}(t) \sim h_4 \frac{1}{t}. \tag{24}$$

2.7. A unifying law

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:

$$g_k(t) = c_k \int t^k \, dt, \tag{25}$$

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 (25) 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. (20)) while $\widetilde{c_0}$ may be found by imposing that, at time $t = 0$, $g_0(0) = 0$ holds. This means a continuous connection of $g_0(t)$ with the "Neural Big Bang", leading to assume $\widetilde{c_0} = 0$.

$k = 1$, in this case (25) takes the form: $g(t) = \frac{c_1}{2} t^2 + \widetilde{c_1}$, where $c_1 = 2\, h_1$ (cf. (21)). 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 (25) 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 (22) 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 $\widetilde{c_{-1}} = h_1 \widetilde{t}^2 + h_0 \bar{t} - h_1 \bar{t}^2 - h_2 \ln \widetilde{t}$.

Note that it is monotonically increasing, even if it increases slowly than in the previous period.

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. It could be possible to take into account all these factors to improve the function $g(t)$, by introducing a weight ξ in (25), so that the equation becomes:

$$g_{-1}(t) = c_{-1}\, \xi \int t^{-1} \, ds \tag{26}$$

For example, similarly to an empirical technique used in Behavioral Economics (see for example [17]), 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 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 (25) takes the form: $c_{\widetilde{k}} \frac{t^{\widetilde{k}+1}}{\widetilde{k}+1} + \widetilde{c}_{\widetilde{k}}$. A comparison with (23) 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 (25) takes the form: $-c_{-2}\left(\frac{1}{t}\right) + \widetilde{c}_{-2}$. Immediately, by (24) 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 $\widetilde{c}_{-2} = h_2 \ln t^* + \widetilde{c}_{-1} - \frac{h_4}{t^{**}}$.
Also in this case decreasing depends upon the subject, so similarly to the case $k = -1$ one could enrich the study by introducing a weight, in order to modulate the decreasing with the change in the four socio-psychological factors.

2.8. The resting state

When a task performed at a time t does not involve the activity of the cerebral areas (or area) which the nodes i and j belong to, then $\alpha(i, j, t) = 0$, since the correlation between the activities of the interested areas vanishes. In this case our model provides

$$W(i, j, t) = \beta(i, j, t_{fix}) \exp(-\eta(t) d_e(i, j)) \propto \exp(-\eta(t) d_e(i, j)).$$

Comparing with 1 this shows that the functional connectivity between nodes i, j reduces to the probabilistic weight related to the structural connectivity. Moreover, in the typical situation of the resting state we have, independently of t, $\alpha(i, j, t) = 0$ for each $i, j \in V$. In this case due to (10), (12) and to Remark 2, our model provides the typical growth laws for the structural connectivity employed in the literature.

3. Model validation through simulation with synthetic data

In order to give an idea on the potential usefulness of our model, we implemented a simulation about the change in time of the edge weights of the cerebral networks. We made use of softwares *Matlab*®, *Excel*® and *Gephi*™ to generate our analysis.
We focused on one healthy subject taking part to a particular cognitive test (e.g. a saccade test[6]) and we computationally evaluated both his/her cerebral network and the most significative topological and

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[6] Saccade tests are often involved in decision making processes.

physical metrics in different periods of his/her life.
We considered the six periods introduced in the previous sections, then we identified, for any of this "macro" period two or more most representative times. We emphasize that we fixed particular times in subject's life by following neurological observations in literature. For example, we chose $t = 7$ years in $Period1$ since it has been detected in children aged from 7 years, and upward [11], [32], that the brain reveals a presence of a small-world modular organization. The final step was devoted to compute the average of some network metrics. We wish to remark that this is just a choice, since, of course, many other kinds of statistical approaches could be considered.

3.1. Expected results

The reader will note we basically work with random matrices[7], so we expect the application of our model on healthy subjects gives the values of the most significative topological and physical metrics reflecting their general mean values. In other words, for example, we expect that the Average Clustering Coefficient is close to 0.5 since it ranges from 0 to 1. Similarly, in consideration that the Average Degree, in a graph of N nodes, assumes a value between 0 and $N-1$, it is expected its value is nearly 8.5, since in our study we worked with graphs on 18 nodes.

Finally we expect to get information on the graph order as well as the density of connection by means of the values of the Average Path Length and Graph Density. We recall that the Average Path Length is a value between 1 and the graph diameter[8], while Graph Density measures how close the network is to a complete graph. A complete graph has all possible edges and density equal to 1, so we expect that its value is 0.5 or so. Correctness of expected results reflects in validate the hypothesis of working with healthy subjects, i.e. not affected by neuropathologies that could change the values proper of the topological metrics by deviating them from their mean values.

3.2. Procedure

We started by fixing the number of nodes representing different cerebral areas, assumed to be 18, and the value of threshold to select the entries of the matrices. We generated in a random way the matrix of wiring anatomical Euclidean distances of nodes, whose entries are positive numbers ranging from 0 to 10. This choice comes from the simple consideration that the anatomical evolution between birth and adult age undergoes dramatic changes. In a neuroscientific analysis it should be taken into account the fact that the cerebral anatomical distances vary with time. Anyway, this makes sense with real/experimental data, so lies a bit outside of our aim, i.e. supplying the reader with a possible useful procedure to evaluate functional connectivity strongness in healthy subjects. So, we considered the connectivity matrix as constant throughout the life, this matrix should be thought of as a "lifelong average matrix". We decided to generate its entries from 0 to 10 basing on the paper by Supekar, Musen and Menon [32], where they analyzed the functional connectivity versus wiring distance analysis

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[7] In particular we generated the matrix of the anatomical distances as a matrix with random elements uniformly distributed on the interval $(0, 10)$, while the functional matrix as a matrix with normally distributed pseudo-random elements having zero mean and variance one. This is because its entries reflect the indices of correlations, that may be positive or negative ranging from -1 to 1.

[8] Connected nodes have graph distance 1. The diameter is the longest graph distance between any two nodes in the network, i.e. how far apart are the two most distant nodes. Two measures derive from the distance: Betweenness Centrality [4] and Closeness Centrality [27].

using Euclidean distance instead of DTI-based wiring distance. Their results showed that functional connectivity between more proximal anatomical regions in Euclidean space was significantly higher in children, whereas functional connectivity between more distal anatomical regions in Euclidean space was significantly higher in young-adults ($p < 0.0001$, where p is the the p-value). In particular they found that the mean wiring distance of the connections that showed higher correlation values in young-adults, compared to children, was $63.09\,mm$, while the mean wiring distance of the connections that showed higher correlation values in children, compared to young-adults, was $54.12\,mm$. They considered *the connections that showed higher correlation values*, so since we are interested also in areas both with lower correlation values, and not necessarily anatomically close each other, we fixed the interval going from 0 to 10.

Concerning the matrix of functional connections, we operated in a different way. This time the entries where both positive and negative to represent positive and negative correlations between nodes (cerebral areas) activities.

Since the matrix of functional connections depends on a particular cognitive test, only specific areas are always activated. Then, in order to reproduce a task, we made the assumption that three nodes were always active throughout the life, whenever the subject performed the experiment. With the purpose of reckoning that the activation is supposed to decrease with age, we calculated the magnitude of the activations as a function of the age; for example areas such as FEF (Frontal Eye Field), SC (Superior Colliculus) and LIP (Lateral Intraparietal area) are involved in the signal transformations from cerebral cortex to superior colliculus for the generation of saccades during a decision making process.

The matrices of anatomical distances and functional connections, for any selected time, have the principal diagonal equal to zero since a node is not allowed to interact with itself.

It is then possible to calculate the exponent of equation (3) and apply a threshold that, according to the choices usually done in the available literature, we fixed equal to 0.3. It was crucial to set the values of η and $g(t)$, where t is a reference time belonging to a particular period of time. We decided to choose $\eta = 8$, a typical value for macaques [18], since, as far as we know, it does not exist a value of η for human beings. In order to evaluate the g's in different times we need, as a first step, to calculate the constants h_0, h_1, h_2, h_3, h_4. We did that by imposing the continuity condition between the functions $W(i,j,t)$ characterizing the pairwise consecutive periods. Once the constants h_0, h_1, h_2, h_3, h_4 are known, it is immediate to compute the expressions of g_0, g_1, g_{-1}, $g_{\tilde{k}}$ and g_{-2}.
For a fixed t the function $g(t)$ corresponds respectively to $g_0(t)$, $g_1(t)$, $g_{-1}(t)$, $g_{\tilde{k}}(t)$ and $g_{-2}(t)$, according to the period where t falls.
We chose one, two or more most representative values belonging to a selected range of time inside Periods $0, 1, 2, 3, 4$.
In order to nail the evaluation of $W(i,j,t)$ we need to know $\beta(i,j,t_{fix})$, which we showed to have a first order approximation equals to the product $degi\, degj$ of the degrees of nodes i and j, respectively.
For any considered time (corresponding to a particular age) we gave the graph representation of the cerebral functional network for a healthy subject, the most representative topological properties of the network, and their averages. In detail, we identified five network statistics of particular neurobiological interest: the average degree, the graph density, the modularity, the average clustering coefficient and the average path length. For their meaning we invite the readership to refer to the box below.

Most significative topological and physical metrics in this study.

The *average degree* of a graph $G = (V; E)$ is the measure of how many edges are in E compared to the number of vertices in V. Because each edge is incident to two vertices, and counts in the degree of both vertices, the average degree of an undirected graph is $2\,\frac{|E|}{|V|}$, where $|E|$ and $|V|$ are the cardinality of the set of edges and nodes respectively. The average degree is a way to classify nodes and may influence graph measures (see for example [39]).

The *density of a graph G* computes how many edges are in E compared to the maximum possible number of edges between vertices in V. The graph density calculation changes according as the graph is undirected or direct:

- An undirected graph can have at most $|V|\,\frac{(|V|-1)}{2}$ edges, so its the density is $2\,\frac{|E|}{|V|\,(|V|-1)}$.
- A directed graph can have at most $|V|\,(|V|-1)$ edges, so its the density is $\frac{|E|}{|V|\,(|V|-1)}$.

It is crucial to remark that graph density is a function of the threshold used to generate the matrix $\eta(t)\,d_e(i,j) - \alpha(i,j,t)$. In fact, as shown in [9], different thresholds generate graphs (or subgraphs) of different sparsity or connection density. It is evident how graph density plays a fundamental role in Neuromathematics since network properties are often explored over a range of plausible thresholds.

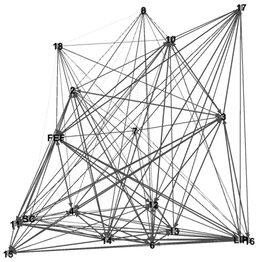
Modularity is the characteristic of a system whose components can be separated, or integrated, without a change in their own properties or those of the rest of the system. A system lacks modularity when a tweak to one of its components affects the functioning of others. In other words modularity describes how the network is compartmentalized into sub-networks. A high modularity score indicates a sophisticated internal structure. Basically modularity is a quality measure for graph clusterings. In order to understand the neurobiological meaning of modularity the reader can refer to [10], [22], [23], [28] where it is evident how modularity, as well as clustering coefficient, are related topological properties that are linked to specialized or segregated information processing in brain networks.

Average clustering coefficient. In undirected networks, the clustering coefficient C_n of a node n is defined as $C_n = 2\,\frac{e_n}{k_n(k_n-1)}$, where k_n is the number of neighbors of n, and e_n is the number of connected pairs between all neighbors of n [3]. In directed networks, the definition is slightly different: $C_n = \frac{e_n}{k_n(k_n-1)}$. In both cases, the clustering coefficient is the ratio $\frac{N_n}{M_n}$, where N_n is the number of edges between the neighbors of n, and M_n is the maximum number of edges that could possibly exist between the neighbors of n. The clustering coefficient of a node is always a number between 0 and 1. The average clustering coefficient (also known as network clustering coefficient) is the average of the clustering coefficients for all nodes in the network. Here, nodes with less than two neighbors are assumed to have a clustering coefficient of 0. The clustering coefficient is considered to be a measure of the local connectivity or “cliqueness” of a graph [7]. High clustering is associated with robustness of a network, that represents the resilience against (random) network damage.

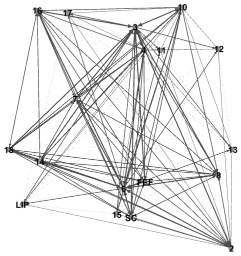
Average path length is defined as the average number of steps along the shortest paths for all possible pairs of network nodes. It is a measure of the efficiency of information and of the order of the network.

4. Discussion

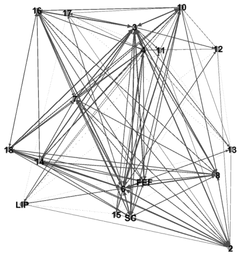
Let us now consider the six periods of reference and select in any of them two or more times (of course with the exception of the Neural Big Bang), then we perform the analysis.
In the following a global view about the change in time of the functional brain network is shown.



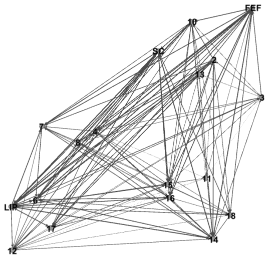
(a) Period 0. Network for t=0y



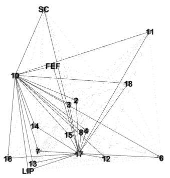
(b) Period 1. Network for t=3y



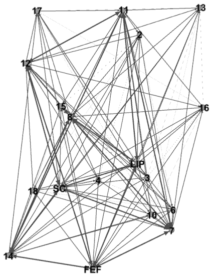
(c) Period 1. Network for g=7y



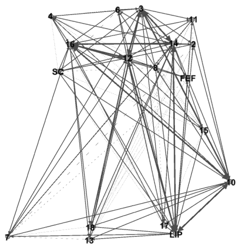
(d) Period 2. Network for t=10y



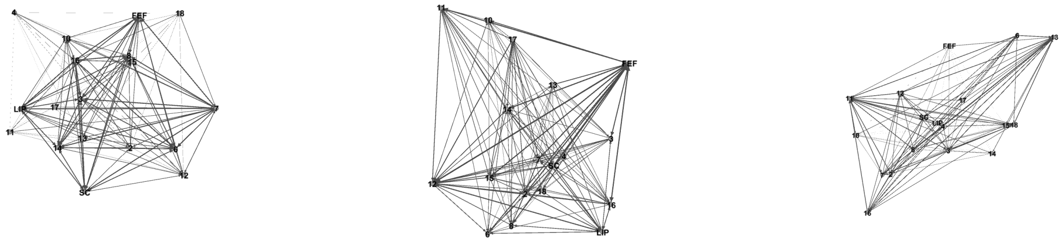
(e) Period 2. Network for t=16y



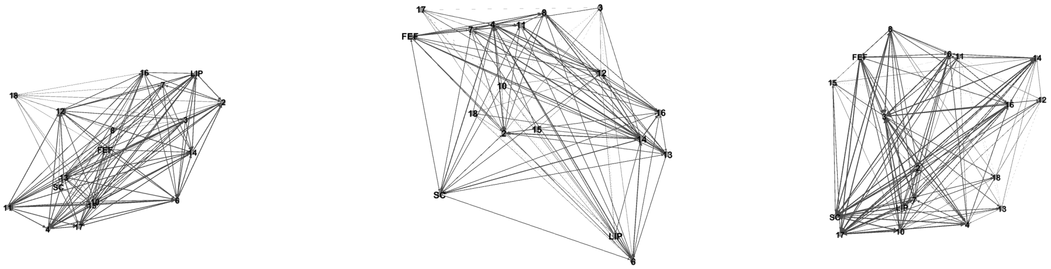
(f) Period 2. Network for t=20y



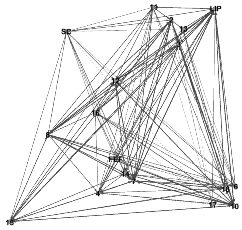
(g) Period 2. Network for t=25y



(h) Period 3. Network for g=35y (i) Period 3. Network for g=42y (j) Period 3. Network for g=50y



(k) Period 3. Network for g=60y (l) Period 4. Network for g=70y (m) Period 4. Network for g=80y



(n) Period 4. Network for g=85y

Figure 1: Global view about the change in lifetime of the functional neural networks.

The following table summarizes the most important topological properties characterizing the functional brain networks for any selected period.

	Networks Statistics						
Time (years)	N. of nodes	N. of edges	Avg. Degree	Graph Density	Modularity	Avg. Clustering Coefficient	Avg. Path Length
0	18	153	8.5	0.5	0.056	0.495	1.5
3	18	155	8.611	0.507	0.066	0.549	1.493
7	18	149	8.278	0.487	0.147	0.595	1.593
10	18	154	8.556	0.503	0.083	0.513	1.516
16	18	148	8.222	0.484	0.127	0.553	1.516
20	18	152	8.444	0.497	0.077	0.515	1.503
25	18	150	8.333	0.49	0.086	0.565	1.51
35	18	151	8.389	0.493	0.071	0.531	1.507
42	18	161	8.944	0.526	0.015	0.498	1.474
50	18	149	8.278	0.487	0.147	0.595	1.513
60	18	157	8.722	0.531	0.037	0.51	1.487
70	18	149	8.278	0.487	0.147	0.595	1.513
80	18	151	8.389	0.493	0.092	0.537	1.507
85	18	150	8.333	0.49	0.086	0.504	1.529
Avg.	18	152	8.448	0.499	0.091	0.540	1.512

Table 1: Overview about the neural networks statistics.

Table 1 shows a global view about the statistics concerning the considered topological and physical metrics. As already mentioned in the previous section we generated connectivity (and consequently adjacency) and functional matrices either with random entrances uniformly distributed on the interval $(0, 10)$, or with normally distributed pseudo-random entries having zero mean and variance one, respectively. So we expect some metrics, whose values range from 0 to 1, could get a value close to 0.5. By casting a glance over the Table 1, it is immediate to note that this is the case for Graph Density and Average Clustering Coefficient. Interestingly we observe that the values of Modularity show fluctuations. This could be unexpected but we recall that we used synthetic data and that we worked with 18 nodes, so it is reasonable to think that the smaller the number of nodes the greater is the fluctuation of modularity values. The average path length is 1.5, a small value compared to 17, that is not a surprise since randomness is reflected in short part length. In addition this small value is close to 1, the value proper of complete graphs. We could lead to speculate that a number of cerebral areas in a healthy subject undergoing a specific task (for example a saccade test), on average, are well connected.
Looking at figures, it is apparent that at age 16 there are several edges between the same nodes with the same weight. This could means that, at that time, there is not a net effective connectivity, i.e. the causal influence of one neuronal system over another. This could be a possible neurobiological explanation of some irrational behaviors in adolescence (for example in risk taking, as show for instance in [30]). Another interesting information regards the average degree. We found that average degree is 8.448. The degree spans a range of value going from 0 to $N - 1$, where N is the number of nodes, in our case $N = 18$, so the average is 8.5 which is very close to the value we found.

Furthermore, it is worth making a comparison between the average degree, and the degree of the three nodes we decided to keep active over the lifespan when the subject performs a particular test (in our case we supposed to consider a saccade test where FEF, LIP, SC are active areas).

	Total Degree		
Time (years)	FEF	LIP	SC
0	19	17	15
3	19	13	19
7	17	15	17
10	19	19	19
16	16	16	16
20	18	18	18
25	16	18	16
35	19	19	19
42	23	20	18
50	15	15	17
60	17	19	13
70	17	15	17
80	17	17	19
85	14	19	15
Avg.	17.571	17.143	17

Table 2: Degree of FEF (Frontal Eye Field), LIP (Lateral Parietal Area) and SC (Superior Colliculus) in different times of life. Degree is the sum of In-Degree and Out-Degree.

Table 2 exhibits a clear result: the areas always activated during a saccade test (FEF, LIP and SC), shows a degree higher than the average degree, which is equal to 8.448 (cf. Table 1). This is a further validation of the correctness of our model since we expected that these three areas are more connected than the others, due to higher amount of information they must elaborate.

This kind of analysis could be helpful in view of applications to “real” data, i.e. coming from experiments, since a comparison would offer the opportunity to inquire on the brain’s architecture. For example interesting information on small-world organization could be obtained, in fact our approach gives information on the random organized networks.

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 edge weights of a graph representing the functional connectivity of the neural network. In our model the weight function $W(i, j, t)$ depends explicitly on the time, which allows a unified vision of different periods of life, where changing in cognitive processes and behavior may happen. Moreover, we suggest a refinement of the probability of the edge formation that is usually involved in the present literature [1], [18]. It provides a rigorous mathematical justification of the usual growth models employed in studying the structural connection, and proposes how finer choices could be done in possible deeper investigations. In particular, we emphasized a double role played by the notions of distance, which can assume an Euclidean or a discrete meaning. Analogously, the time t appears both from a local and a global perspective.

Notably, we remark that equation (3), in the resting state, leads to the probability of connection between pair of nodes, representing for example cerebral regions, as in [18], or [40], despite the fact that, in general, $W(i, j, t)$ is not a distribution of probability. When the brain is not in the resting state, then $W(i, j, t)$ changes the functional connectivity depending on the specific task submitted to the volunteer. Further, in our 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 in understanding how, in different periods of life, the functional graph and its topological characteristics change.

Finally in order to check the correctness of our model a computational analysis was performed. Its aim was to simulate the change in time of the functional neural networks throughout the life. We assumed to perform the analysis on healthy people and what we found, by means of synthetic data, is a validation of the consistency of the model we have proposed. Of course there are several different statistics that could be performed. For example the threshold could be changed, or a sample of healthy (or with neural pathologies) subjects, rather than only one single subject, could be consider too. We hope this could help the analysis of experimental data. Next faithful step will be apply our model to the study of functional connectivity in people affected by neuropathologies, so to point out anomalies in topological and physical metrics, and to highlight deviation from neural architecture like small-world (with respect of healthy subjects). We feel that the proposed model could be of help in the field of cerebral brain network analysis.

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