Networking Brains: Modeling Spatial Relationships of the Cerebral Cortex

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Abstract

Brain mapping has always been a priority in neurobiology and evolutionary neuroanatomy. In the last century, methodological issues and technical advances have generated a vivid debate on the parcellation and functions of the cortical territories. Brain structure is generally analyzed by considering the network of connections associated with neural pathways. Nonetheless, there is still a major debate on the recognition of the spatial and geometrical components of the cerebral cortex. The maps produced by Korbinian Brodmann in the early twentieth century on the basis of histological patterns represented a pioneering and decisive step in this sense, being a reference until the present day. Network models allow a numerical analysis of the spatial relationships among anatomical elements, supplying a quantitative tool to evaluate their reciprocal geometrical organization. This approach is able to analyze the spatial parameters associated with an anatomical system, characterized by the relationships of its elements. The network analysis of the spatial contiguity of Brodmann's areas approximately describes the major cerebral lobes. A frontal cluster includes only the prefrontal areas. There is a large parieto-occipital block including also the precentral and paracentral cortex. The cortical areas identified by the model match different areas of craniocerebral relationships, namely, the anterior fossa influenced by the upper face (prefrontal cortex), the middle fossa influenced by cranial base and mandibular integration (temporal cortex), and the vault which is characterized by more linear brain-bone dynamics (parieto-occipital cortex). The maps of Brodmann, after one century of contributions, are now replaced by finer parcellations obtained with new technical approaches based on histology, biochemistry, and metabolism, enhanced by advances in brain imaging and digital biology. Besides issues associated with cognitive processing, structural factors can influence geometrical and mechanical properties of the cerebral morphology. Network theory, applied to alternative parcellation schemes or to specific brain districts, can provide essential information on evolutionary factors channeling or constraining the evolution of the brain spatial organization.

Keywords

Brain maps • Network modeling • Brodmann's areas • Brain lobes • Evolutionary neuroanatomy

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13.1 Mapping the Brain Cortex

Since the earliest modern studies in neuroanatomy, researchers have tried to understand a possible association between cortical areas and functions, probably reflecting an expectation which is rooted in far more ancient popular beliefs. According to this view, specific brain areas may be responsible of specific behavior or cognitive processes. The main evidence came from observations of altered behaviors in impaired and injured individuals, with historical case studies ranging from the language areas (Broca's and Wernicke's areas) to the famous case of Phineas Gage (Goldenberg 2004). Such view of the brain as a compartmentalized computer formed by interacting but specialized areas found an extreme expression in the positivistic approach of phrenologists, trying to associate every mental attitude or capacity with a specific and determined cerebral area. This is somehow similar to some current approaches to genes and molecules, aimed at associating specific biological traits with specific physiological or behavioral conditions. A large debate, still in vogue, was then developed contrasting the localized view against holistic perspectives aimed at highlighting the importance of the entire brain system over its specific parts.

In craniology, bones refer to units which have a clear structural, embryological, and generally homologous roles, and that can be defined according to clear borders and landmarks. In contrast, in neuroanatomy, lobes and sulci are terms without such firm biological characterization and whose boundaries are not strictly defined. Thus, traditional neuroanatomical terminology refers to elements – lobes, sulci, and gyri – which do not represent real biological units but conventional areas which have been named to supply a shared and convenient language. Generally, lobes have been defined according to generalized functional associations or to raw and imprecise anatomical borders. This is why, very early in the story of the field, neuroanatomists have tried to find units based on objective biological features, beyond the general and irregular appearance of the sulcal schemes.

Many different methods and techniques were used in the last century to supply alternative maps of the brain cortex, but without any doubt, the most popular and distinguished are the ones proposed by Korbinian Brodmann (see Zilles and Amunts 2010). Brodmann (1868–1918), a German histologist, was influenced by Oskar and Cécile Vogt, dedicating his life to analyze the distribution of different cell types on the cortical surface of the brain in many different mammal species (Pearce 2005; Annese 2009). By using the stain procedure developed by Franz Nissl, he identified 52 brain areas (Fig. 13.1), publishing a seminal book in 1909 (Šimić and Hof 2015). All along his career, he further revised his maps and areas, introducing questions and issues which are still open (Judaš et al. 2012).

Brodmann did not conclude his work; he had many personal and professional difficulties during his life, dying prematurely, apparently because of an infection contracted during an autopsy. An important part left out of his work was the recompilation of a visual atlas, necessary to display the cytoarchitectural features and criteria he used to put forward his parcellation of the brain cortex.

There are at least three main issues with brain maps: *variability*, *correspondence*, and *homology*. Anatomical and morphological differences associated with individual variations can be notable, and mapping requires a statistical approach to distributions and sample variability (Eickhoff et al. 2005; Van Essen and Dierker 2007). Correspondence between anatomical and architectural elements is also very variable, and gross anatomy (sulcal pattern) is hardly associated with strict histological or functional areas (Amunts et al. 1999; Amunts and Zilles 2012). Homology among mammals or among primates is often scarcely known at functional, histological, and anatomical levels. For example, Brodmann recognized in humans only 43 areas of the 52 described in other species (Zilles and Amunts 2010).

Brain mapping can deal with functional and structural aspects of the cerebral anatomical networks (Raichle 2010; Alexander-Bloch et al. 2013; Craddock et al. 2013). In terms of *function*, it can represent the system of elements involved in the underlying cerebral processes and associated with physiological and cognitive mechanisms. In this case, the network formed by these elements influences and is influenced by the functional result associated with the system (e.g., cognition, metabolism, etc.). Generally, functional networks are based on co-activation during specific processes. In terms of *structure*, mapping is aimed at representing the system of elements involved in the spatial organization of cerebral anatomy. From a structural perspective, we can identify two different targets. In neuroanatomy, structural relationships generally refer to axonal connections between neural areas. In this case structural networks are defined in terms of shared neural pathways. In morphology, structural relationships generally refer to shared morphogenetic and biomechanical influences, due to spatial requirements and geometric properties associated with growth, development, allometric rules, and physical constraints. These contexts, the functional and the structural, are associated with different factors, involved in different activities, and often analyzed through different methods. Nonetheless, in terms of biology and evolution, they are the two sides of the same coin; they must be integrated, and such integration is the actual combination of traits and processes evaluated by natural selection.

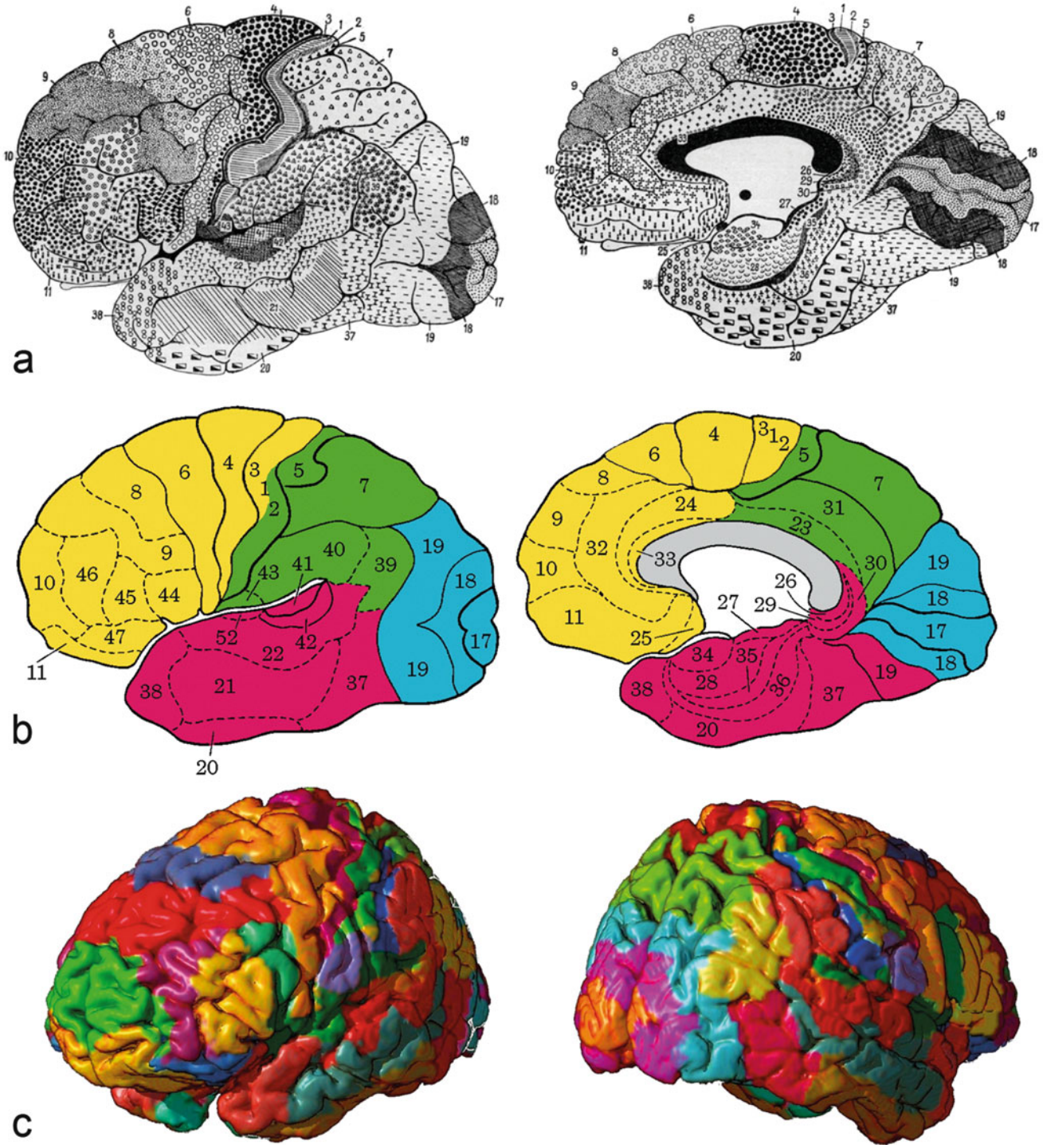

Fig. 13.1 Brodmann's areas: (**a**) original drawings by Brodmann; (**b**) a traditional schematic map of Brodmann's areas, as used in this study to compute network modeling based on spatial contiguity, with colors referring to frontal (*yellow*), parietal (*green*), occipital (*blue*), and temporal (*red*) lobes; (**c**) 3D view of Brodmann's areas (After Mark Dow, University of Oregon; Wikimedia Commons Public Domain)

13.2 Anatomical Network Analysis

Numerical modeling can be used to quantify and analyze different anatomical aspects, including metric covariance among morphological components, functional processes associated with morphological variation, or evolutionary and phylogenetic factors. In biology, network modeling concerns the relationships among the components of a biological system, and it is aimed at evaluating possible underlying rules which generate the actual organization of the system (in an organism, its phenotype). In neurobiology,

network approaches have been widely used to investigate neural connectivity (e.g., Sporns et al. 2004; Meunier et al. 2010). The functioning of the brain strictly depends on its patterns of neural connections, so these schemes are a crucial issue to investigate the organization or the cerebral system. Furthermore, current advances in digital imaging have provided essential tools in this sense, supplying reliable morphological reconstruction of the neural fibers (Rilling 2008).

Nonetheless, network models can be also used to investigate the spatial arrangement of the anatomical elements. Such spatial organization is the final result of a morphogenetic process that is influenced by both intrinsic and extrinsic factors, in which a genetic program is executed within a specific physical environment, constrained by a system of forces (pressures and tensions) due to neighboring anatomical elements. Hence, in this case, we consider not the neural connectivity of the brain areas but the physical spatial connectivity, that is, the set of relationships associated with the direct spatial contiguity among cortical districts.

To generate a spatial model, we use anatomical network analysis (AnNA), a framework for the analysis of connectivity relations in a morphological system. Conceptually, it relies on an old anatomical adagio, the "Principe des connexions," which identifies physical connections among anatomical elements (i.e., bones, muscles, cartilages) as carriers of important biological information, often more so than their size and shape. Indeed, this assumption is at the foundation of comparative anatomy itself; it was championed by the French anatomist Etienne Geoffroy St. Hilaire in the XIX century, and it has been the focus of attention for comparative anatomy ever since. Geoffroy recognized that the shape and size of the same anatomical elements in different organisms vary greatly; so much that, in order to correctly identify them, it was more useful to analyze how they were connected to their anatomical surroundings. The study of connections, although intuitively sound, lacked until very recently a suitable mathematical framework to codify, manipulate, and analyze the patterns underlying these physical relationships in a meaningful way. AnNA has been developed in the past decade to fill this gap, applying and conceptualizing mathematical tools from graph theory and network analysis in a morphological context (for a review on AnNA, see Rasskin-Gutman and Esteve-Altava 2014 and references therein).

To begin a study with AnNA, one must first understand the biological meaning of the connectivity patterns it is about to analyze. This is a first, paramount step that determines the results and the usefulness of the conclusions drawn. But, why focusing on connections? Besides its classical appeal mentioned above, it is worth noting that any anatomical system can be teased apart on different levels of morphological organization. Such a division could encompass four related but semi-independent levels: (1) proportions, (2) connections, (3) orientations, and (4) articulations (Rasskin-Gutman and Buscalioni 2001). Of these four levels, the level of proportions (level 1) is the most studied one because it is related to size and shape and can be analyzed comparatively by using traditional morphometric tools with size and shape measurements or landmark-based geometric morphometrics using Cartesian coordinates. Other levels need different types of formalisms. AnNA is useful at the connection level (level 2), where the formalism is a codification of the physical connection among elements; this codification results on an adjacency matrix, filled by 1 s (representing connections) or 0 s representing the absence of connections. The other two levels can be formalized with a set of angles (orientation, level 3) and tables of motion range, to account for articulation (level 4).

The assumptions that we make about how morphological data represents function, development, or evolution determine the kind of conclusions we finally are able to draw. Connections describe the topological relations between anatomical parts, that is, their arrangement in a morphological system. Connections might also capture the presence of functional and developmental relationships (codependences) among parts. For example, connections among skull bones not only represent the topological boundaries among bones but also primary sites of bone growth and remodeling and sites of stress diffusion (Esteve-Altava et al. 2013).

Network theory supplies all the mathematical tools for the analysis of network models. A network is the combination of two sets: a set of nodes and a set of links; each link has two endpoints, that is, it represents a connection between two nodes. In this mathematical abstraction, the nodes stand for anatomical elements, and the links stand for interactions among elements. The most common representation of a network is a drawing of dots joined by lines: a line connecting two nodes indicates the presence of a mutual relation. Direct links indicate nonreciprocal relations, while weighted links indicate the strength of the interaction. Notice that all network representations are equivalent as long as the same links between nodes are kept. For simplicity we will describe only undirected (reciprocal) and unweighted networks.

The *adjacency matrix* ($A_{i,j}$) codifies the connections among the nodes of the network, that is, the number and the particular distribution of links between nodes. For undirected, unweighted networks, this is a symmetric binary matrix of size *N*x*N*, where 1 indicates the presence and 0 indicates the absence of connection. Thus, the adjacency matrix defines the neighborhood, the connectivity context of each node as all the nodes to which it connects. An adjacency matrix is the main source of data in many programs used to analyze networks, but it is not the only one. For example, a

list of edges is also a very common source: a list in which each row indicates the origin and the destination of a link.

Some important descriptors and parameters for individual nodes and the whole matrix are listed below. While node descriptors are very useful to study the properties of individual elements in relation to others, system descriptions are useful to compare whole networks.

Node Degree sum of links a specific node has to other nodes in the network:

$$k_i = \sum\nolimits_j A_{i,j}$$

Clustering Coefficient ratio between the total number of links connecting its nearest neighbors and the total number of all possible links between all these nearest neighbors:

$$C_i = \frac{\sum t_i}{k_i(k_i - 1)}$$

where t_i is the number of links between the neighbors of node i.

Shortest Path Length between two nodes: their shortest distance measured as number of links to go from one node to the other:

$$l_{i,j} = d\left(n_i, n_j\right)$$

where $d(n_i,n_j)$ is the minimum distance in number of links to connect nodes i and j. Note that more than one path might have the shortest length.

Density total number of existing links (K) divided by the maximum number of possible links for a given number of nodes (N):

$$D = \frac{2K}{N(N-1)}$$

Average Clustering Coefficient arithmetic mean of the clustering coefficient of all nodes in the network:

$$C = \frac{1}{N}\sum C_i$$

Average Shortest Path Length arithmetic mean of the shortest path length between all pairs of nodes:

$$L = \frac{1}{N-1}\sum l_{i,j}$$

Degree Distribution frequency of occurrence of nodes with a given number of links:

$$P(k) = \frac{N_k}{N}$$

Clustering Coefficient Distribution clustering coefficient mean of all nodes with k links:

$$C(k) = \frac{\sum C_{i,k}}{N}$$

In addition, the organization of the network can be informative about its properties for a given function. For example, networks are often seen as scale-free, hierarchical, and/or small world, depending on the values of some of the parameters we just listed above. The presence of a community structure, or modules inside the network, is also very important in AnNA.

A network with a hierarchical organization shows a stratification of connections in various nested layers. The P(k) and the C(k) help assess the presence of a hierarchical organization in a network. The functional form of these distributions (e.g., uniform, Poisson, or power law) characterizes the organization of connections among the nodes. In general, a power-law distribution in both parameters indicates that the neighborhoods of low-degree nodes are highly clustered, forming blocks, while those of high-degree nodes are sparsely connected, which suggest that high-degree nodes are acting as connectors between blocks. The hierarchical organization of a network is defined as opposed to a random or a scale-free organization. In the former, the P(k) fits a Poisson function; in the latter, it fits a power-law function; in both the C(k) fits a discrete uniform function. A hierarchical organization is commonly observed in anatomical networks with a community structure.

A network with a small-world organization has a higher C and a lower or similar L to that of a random network, as a consequence of the presence of shortcut nodes. These nodes connect other nodes that would otherwise be far apart (i.e., high shortest path length). The presence of a small world is assessed by measuring the values of C and L and then comparing them to those of random equivalent networks (i.e., networks with the same number of nodes and links but randomly rewired). A common problem in anatomical networks is the small number of nodes ($N < 100$), which can hamper statistical comparisons to random models like this. A method to circumvent this problem has been proposed by Humphries and Gurney: a network is small world if $[(C/C_{\text{rand}})/(L/L_{\text{rand}})] \geq 0.012 \times N^{1.11}$. A small-world organization is common in anatomical networks and is related to the identification of a community structure.

Small-World Networks have a special kind of organization between regularity and randomness; their low shortest path

length (L) gives them special dynamic relationships among nodes, and their high clustering coefficient (C) provides them with distinctive structural features. Having a low L means that the communication of any kind of properties among nodes (e.g., stress forces among bones) is more efficient, thanks to shortcut links; having a high C means that there are many clusters or associations between nodes, which can be putative modules.

Hierarchical Networks take their name from a very specific idea about hierarchy: nodes are organized as clusters within clusters; thus, C is also high in these types of networks, where the organization somehow depends on the existence of these clusters that become necessarily modular. Hierarchical networks are also scale-free, which means that its structure is preserved at any scale of observation; in addition, these networks always host highly connected nodes or hubs.

What does this mean in terms of the structural architecture of the brain? Hierarchical and small-world organizations are characteristic of biological systems that are integrated and, at the same time, able to maintain groupings of nodes tightly connected. Networks that are either hierarchical or small world can be said, thus, to hold structures that can be, at the same time, modular and integrated.

A network with a community structure is divided into groups of nodes that are more densely connected within the group than to nodes outside the group. A community, or connectivity module, is then a group of nodes with more links among them than to other nodes outside the module. Due to the enormous number of ways to divide networks into modules, there are many different methods and algorithms to find communities in networks, as well as to estimate the quality of different community structures in order to decide between the many possible. Fortunato (2010) has recently compiled the many methods available in the specialized literature in a systematic way.

The parameters associated with a specific network represent the way we can quantify the properties of the network, with three main scopes: to compare groups, to compare hypotheses, and to correlate functions. *Comparing groups* means testing differences between different networks. *Comparing hypotheses* requires a priori (hypothetical) models based on theoretical assumptions, which can be contrasted against the observed (real) networks. *Correlating functions* means to investigate the covariation between parameters and whatever biological or ecological variable. In all cases, the anatomical systems are described and compared by virtue of the structure and organization of the relationships among their elements.

13.3 Brodmann's Network

Cortical morphology is the results of a complex morphogenetic process, in which biomechanical factors are crucial in shaping the final cerebral form, at local and global level (e.g., Van Essen 1997; Hilgetag and Barbas 2005; Toro and Burnod 2005; Bayly et al. 2014; Tallinen et al. 2016). Therefore, the spatial organization of the cerebral areas supplies an interesting case study to apply AnNA and to investigate possible rules and constraints associated with brain parcellation in terms of spatial proximity and topology. In this example, we rely on the most basic and comprehensive criterion, modeling the spatial relationships between Brodmann's areas with a network based on the physical contiguity between areas, namely, considering whether or not two parts are in direct physical contact (Fig. 13.2). This criterion is simplistic, but it provides a preliminary survey on the issue and a direct example of application of network modeling to cortical spatial arrangement. The criterion is, thus, based on the assumption of structural interaction due to direct physical contact. Each node represents one individual area, and its connections represent their topological contiguity according to Brodmann's graphic scheme. We calculated its degree distribution, density, mean clustering coefficient, and mean shortest path length. We tested the fit of the degree distribution to four distribution functions: Poisson, log normal, exponential, and power law. Parameters were estimated by maximum likelihood and different functions compared using the negative log likelihood (nLLV), the Akaike information criterion (AIC), and the weighted Akaike information criterion (wAIC). The presence of a small-world effect in the network organization has been assessed by comparing the mean clustering coefficient and mean shortest path length of the network to that of 1000 random equivalent networks, which were generated by randomly rewiring the network connections among nodes keeping the original degree distribution. We calculated the small-world-ness (sw) of the network as the ratio between its clustering and path length and that of random equivalent networks $\left(\frac{C}{C_{\text{rand}}}/\frac{L}{L_{\text{rand}}}\right)$. A network is small world if sw $\geq 0.012n^{1.11}$ (Humphries and Gurney 2008).

We used a community detection algorithm to find hierarchical, overlapping modules in Brodmann's network. This algorithm was created by Shen et al. (2009) and implemented in *R* by Esteve-Altava (2015). It comprises the following steps:

1. Find all maximal cliques. A maximal clique is a subset of nodes in a network that is completely connected and is not a subset of another clique. Every maximal clique and subordinate node (i.e., a node that does not belong to any maximal clique) form the initial modules. We consider

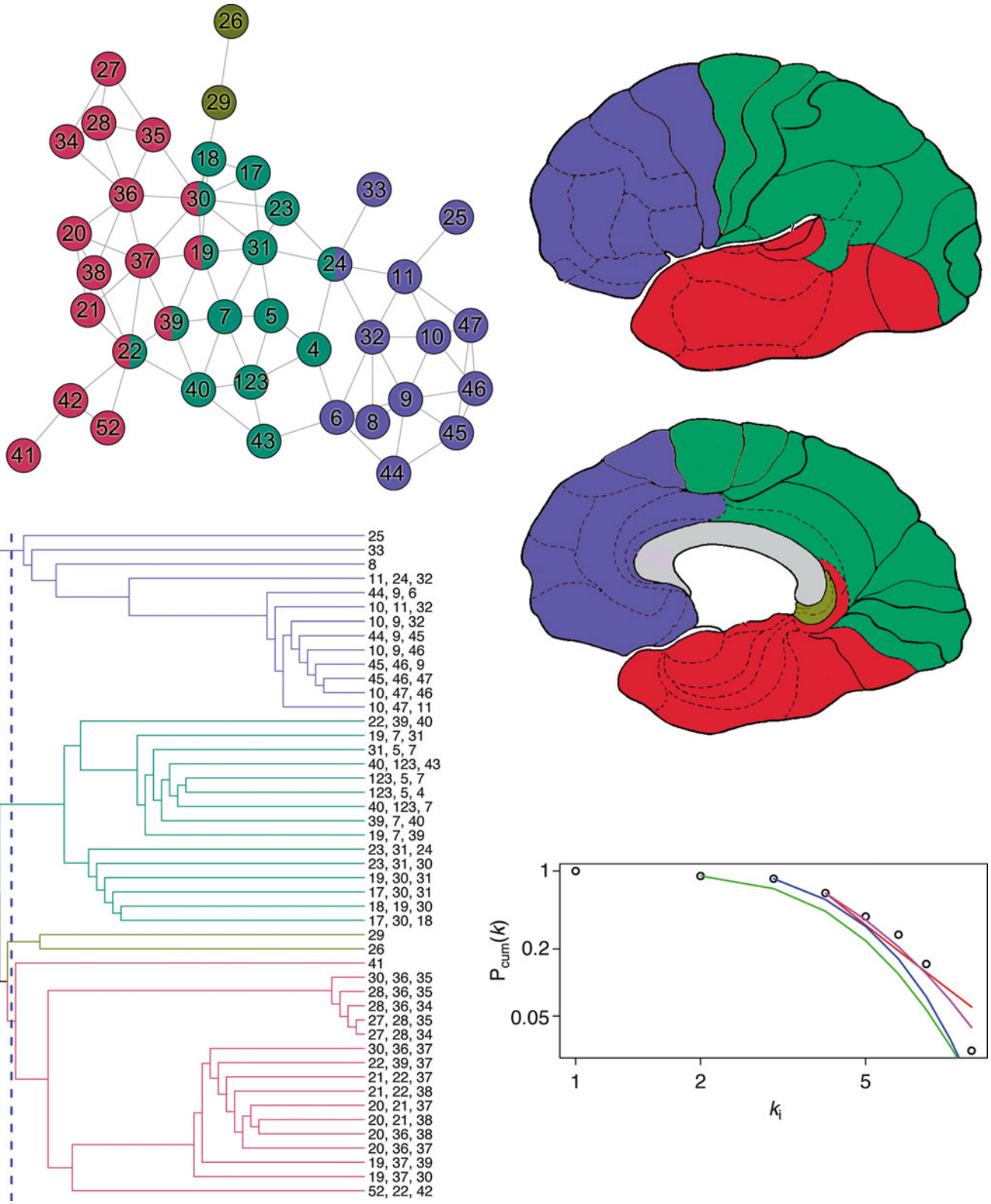

Fig. 13.2 Network used in this study, with nodes colored according to the module they belong following the results of the analysis. Numbers refer to Brodmann's areas (areas 1, 2, and 3 are considered as a single node, as in the original figure). Nodes belonging to more than one module (i.e., overlapping) are indicated with two colors. The colors of the clusters are used to evidence the groups onto Brodmann's maps. The dendrogram shows clusters composed by maximal cliques equal or larger than three nodes. Colors indicate modules identified according to the maximal extended modularity value calculated for the optimal partition (*dashed line*). The plot shows the cumulative degree distribution of Brodmann's network, showing the fit to log-normal (*green*), Poisson (*blue*), exponential (*purple*), and power-law (*red*) distributions

maximal cliques of length equal or greater than three nodes.

2. Calculate similarity between modules. The higher the number of connections between modules, the higher the similarity:

$$S = \frac{1}{2m} \sum_{v \in C_i,\, w \in C_j,\, v \neq w} \left(A_{vw} - \frac{k_v k_w}{2m} \right)$$

where A_{vw} is the element v,w of the adjacency matrix (1 if nodes connect and 0 if they do not), m is the total number of connections of the network, and k_v and k_w are the degree of nodes v and w, respectively.

3. Find and merge modules with maximal similarity. Select the pair of initial modules with the highest similarity and merge them into a new module. Repeat this step until there is only one module: the resulting grouping can be visualized as a dendrogram (Fig. 13.2).
4. Calculate the quality of each potential partition. For each branching event of the resulting dendrogram, we calculate its extended modularity:

$$QE = \frac{1}{2m} \sum_{i} \sum_{v \in C_i,\, w \in C_i} \frac{1}{O_v O_w} \left(A_{vw} - \frac{k_v k_w}{2m} \right)$$

where O_v and O_w are the number of modules to which node v and node w belong, respectively. The higher the QE, the better the partition of nodes in highly connected modules.

The resulting network of Brodmann's areas has 41 nodes and 87 connections ($D = 0.106$). This is a highly clustered, efficient network ($C = 0.472$; $L = 3.483$) that shows a small-world organization ($sw = 4.106$). The degree distribution of the network fits better to a log-normal decay (Table 13.1; Fig. 13.2).

According to the spatial contiguity criterion and to the threshold of extended modularity, we can identify four groups (Fig. 13.2). One group includes all the areas of the prefrontal cortex. A second group includes the parietal cortex, the occipital cortex, and the precentral gyrus/paracentral lobule. A third cluster includes the temporal cortex. A small fourth group includes the retrosplenial cortex, isolating area 26 and area 29 because of a scarce triangulation with the other areas.

This simple application of network modeling to the contiguity scheme of Brodmann's areas may suggest that the brain lobes, although representing conventional regions, are nonetheless spatially arranged in a way that generates a modular structure grouping the areas into larger units. If these four modules are real spatial units, we must consider the possibility that their spatial arrangements influenced the functional organization of the cortical areas. Of course we must also evaluate the opposite hypothesis that functional associations may have oriented their spatial arrangements due to intrinsic or extrinsic structural factors (like wiring or cranial constraints) or functional reasons (neural efficiency). In both cases, such arrangement was partially recognized by our anatomical terminology.

The frontal cluster only includes the prefrontal cortex. Despite the many studies on the topic, there is still a general debate on whether or not humans display, beyond a larger absolute size, specific frontal features when compared with other hominids (Bruner and Holloway 2010) or with living apes (Rilling 2006; Sherwood and Smaers 2013; see Chap. 14). There is no doubt that frontal areas changed their spatial relationships during human evolution: in Neanderthals and modern humans, they are positioned onto the orbital roof, introducing some constraints associated with the relationships between the brain and the upper facial block (Bruner et al. 2014). The precentral gyrus is rather grouped with the parieto-occipital cluster, instead than with the frontal areas. Actually, also in terms of functions, the motor areas are necessarily integrated with the sensorial and visuospatial cortex, namely, with the postcentral cortex and with the superior parietal lobules (Ackerley and Kavounoudias 2015). The parietal and occipital areas are clustered in a single large block. A morphological association between parietal and occipital cortex has been long recognized, also in terms of histological organization (Eidelberg and Galaburda 1984). Because of their noticeable contiguity, the parietal and occipital volumes are often analyzed together (e.g., Semendeferi and Damasio 2000). Also in terms of evolutionary variation of the braincase, these two districts are strongly integrated, suggesting shared morphogenetic patterns (Gunz and Harvati 2007). There is apparently an inverse relationship at an evolutionary level: modern humans are supposed to display larger parietal areas and smaller occipital areas (Bruner et al. 2003; De Sousa et al. 2010; see Chapt. 15). Nonetheless, when considering the volumetric variations in adult humans, there is no correlation between the parietal and occipital lobes, being the former inversely correlated to the

Table 13.1 Degree distribution fits to four functional functions

	Estimated parameters	nLLV[1]	AIC[2]	wAIC[3]
Poisson	$\lambda = 3.96$, for $k \geq 3$	−60.520	−58.52	4.40e-02
Log normal	$\mu = 1.46$, $\sigma = 0.354$, for $k \geq 2$	−68.768	−64.768	1.00e + 00
Exponential	$\lambda = 0.555$, for $k \geq 4$	−41.616	−39.616	3.45e-06
Power law	$\alpha = 3.682$, for $k \geq 4$	−41.616	−41.729	9.93e-06

frontal and temporal volumes (Allen et al. 2002). The temporal lobes are relatively larger in humans when compared with living apes' allometric patterns (Rilling and Seligman 2002). When compared with extinct human species, in modern humans, a more anterior tip of the temporal pole was hypothesized to be due to a specific increase of the temporal lobe volume (Bastir et al. 2008). According to the network clusters, the isolation of the retrosplenial cortex is also interesting, being these areas in contact with subcortical regions not included in this study. These areas are also associated with an allometric stretching influencing the morphology of the midsagittal brain and of the corpus callosum, tentatively interpreted as a mechanical effect of the tension exerted by the tentorium cerebelli (Bruner et al. 2010, 2012).

13.4 Networks and Evolution

13.4.1 Brains and Geometry

The pioneering work by Brodmann integrated histology and phylogeny, opening an essential methodological perspective in neurobiology and evolutionary neuroanatomy. The technical advances in the last decades have allowed an outstanding development of tools and approaches in digital and physical neuroscience (Preuss 2011; Rilling 2014). Cytoarchitectural studies are getting more and more specific with neural mapping, multiplying the number of areas, and adding different principles and criteria (e.g., Toga et al. 2006). Brain mapping is today also developed using information on biochemical elements (neurotransmitters and receptors) and on connectivity among areas. Modules and submodules of the brain are probably arranged with nodes and hubs as to integrate spatial and functional issues, with local nodes coordinating specific areas and global nodes coordinating together different areas (Meunier et al. 2010). Such schemes linking different elements are the results of genetic, physiological, and anatomical factors, and the resulting patterns of association are essential in normal ontogenetic processes as well as for pathological conditions (Alexander-Bloch et al. 2013). These same schemes are also the prime matter for any evolutionary change. Brain anatomy is probably organized on small-scale factors, modular organization, and local spatial interactions, which can facilitate evolutionary changes because of the degree of independence among areas (Gómez-Robles et al. 2014). Structural and functional networks share some important topological features (Hagmann et al. 2008), and in this sense, some crucial areas of integration between the two systems, like the precuneus, belong to districts which have undergone important morphological changes in our species (Bruner et al. 2014; Bruner et al. 2017). Interestingly the frontoparietal network, which is hypothesized to represent a relevant cognitive system, shows many similarities between humans and nonhuman primates (Caminiti et al. 2015) suggesting that evolutionary changes may be subtle, or associated with a matter of degree and reuse of plesiomorphic processes and structures, more than of brand-new elements.

Network modeling can be a useful tool to integrate multiple evidences from brain and cranial morphology, combining information from geometry and brain mapping (Fig. 13.3). These methods can be applied to cranial, endocranial, and brain elements, separating the brain and braincase or else describing their reciprocal relationships. Results can be used to describe and quantify the relationships within these anatomical systems or to match data from other kinds of brain mapping principles. This approach can reveal underlying patterns of structural organization, as well as phylogenetic differences. Most analyses on brain network modeling concern the organization of the neural connections (e.g., Sporns et al. 2004; Meunier et al. 2010). These studies are opening an exciting brand-new perspective in neuroscience, where functions are investigated by numerical models associated with spatial properties of the fiber arrangements. Brain functions are strongly based on wiring schemes, so connections are clearly a main issue. Nonetheless, from the pioneering works by D'Arcy Thompson on spatial functions and evolution (1942) to the seminal book by Stephen Jay Gould on ontogeny and phylogeny (1977), until the last advances in shape analysis and computed morphometrics (e.g., Mitteroecker and Bookstein 2008; Mitteroecker and Gunz 2009), we are further aware that spatial organization is also essential to channel the variation of the anatomical systems. Allometric rules, spatial constraints, and mechanical relationships are sensitive to geometrical factors underlying the phenotypic plasticity and the selective processes associated with its evolutionary success or failure. Therefore, beyond the scheme of neural connections, network analysis can be useful to investigate the spatial properties of the anatomical elements in terms of geometrical relationships among their parts. Such quantitative analyses can reveal underlying schemes and phenotypic patterns constraining evolutionary and functional processes.

The structure of the brain organization is supposed to be the consequence of selective forces optimizing costs and efficiency of the neural networks (Bullmore and Sporns 2012). An evolutionary pressure in this sense is likely, most of all when considering the ecological and metabolic costs of brain management. Nonetheless, we must always bear in mind that selection works only on characters influencing the reproductive rates and that many characters are integrated by polygenic and pleiotropic effects. For most features, optimization is therefore relative and secondary to

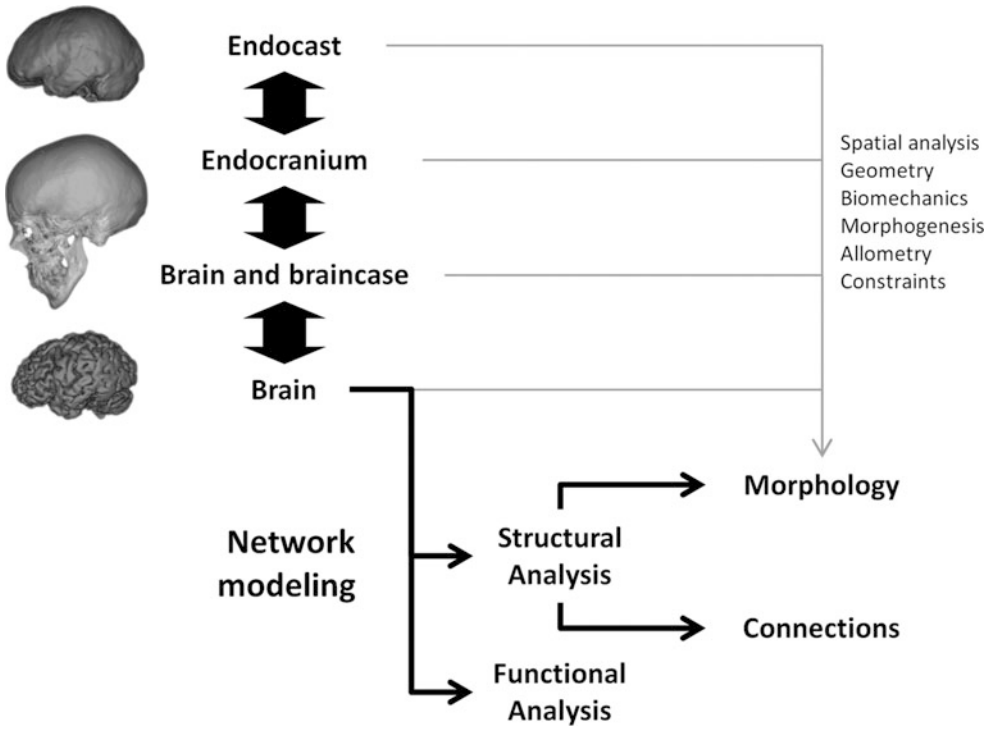

Fig. 13.3 Network modeling can be used to investigate functional and structural brain organization. Structural analyses concern the neural connections as well as the spatial and geometrical properties of the brain, which must take into account different levels of the brain-braincase system

a set of limits and constraints intrinsic to the biology of a species, channeled by rules and a given degree of phenotypic plasticity.

Spatial and functional parameters are necessarily related, but they are also influenced and constrained by distinct factors. In particular, many behavioral and cognitive aspects are currently interpreted in terms of functional imaging. The old popular view of a compartmentalized brain has permeated functional imaging, giving sometimes a modern appearance to past phrenological perspectives. It is necessary, hence, to take into considerations that brain functional imaging is based on biochemical and metabolic markers, whose relationships with the underlying cognitive processes are, to date, largely unknown (Raichle 2003). Therefore, apart from any possible shared mechanism associating spatial and functional data, mapping is generally the result of a biological distribution, while cognitive issues require an interpretation based on processes which are, at present, largely ignored.

13.4.2 Sulcal Patterns and Brain Structure

The limited correspondence between sulcal elements and cytoarchitecture and the complex relationships between cortical areas and cognitive functions further advise against using sulcal patterns for phylogenetic or cognitive inferences, at least as traditional evolutionary characters. Nonetheless, brain gross morphology still represents a major source of neuroanatomical information in those fields in which soft tissues are not available (like in paleoneurology) or in which histological studies are not feasible for physical, economic, or logistic reasons (as in living human samples and other medical contexts). Sulcal patterns can supply at least three kinds of information (Fig. 13.4): it can reveal changes in relative volumes and proportions, it can provide geometrical references to analyze spatial variations, and it can disclose underlying genetic programs and morphogenetic mechanisms.

Changes in relative volumes of different cortical areas can be evidenced analyzing the position and proportions of the cortical elements (gyri and sulci). Although with a lower resolution when compared with histological studies, the sulcal pattern can provide a direct quantitative evidence of relative volumetric differences between species or individuals. Dealing with fossil species, such information is the only direct evidence available in this sense (Bruner 2015).

Concerning brain form, the sulcal pattern can supply information on the spatial reciprocal organization of the brain elements, about the spatial relationships between brain and braincase, and about any functional factor statistically correlated with geometry. Beyond a strict shape comparison, the geometrical relationships among brain elements are relevant for all those functional issues associated with

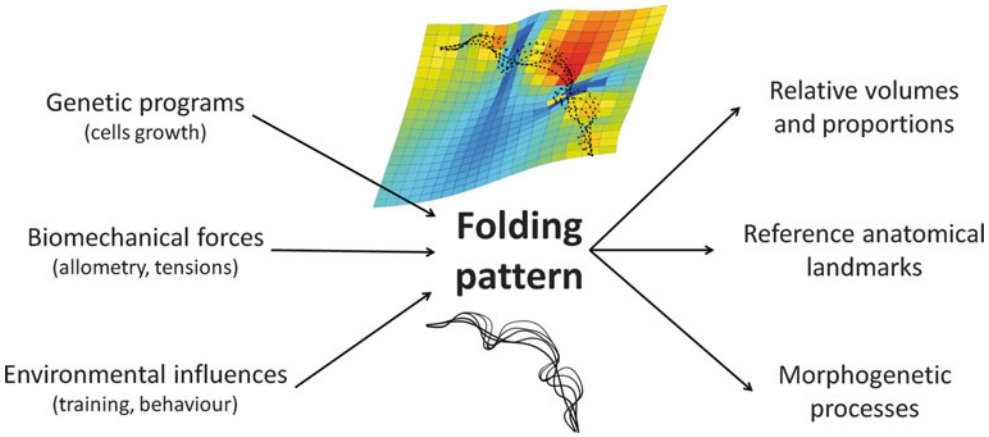

Fig. 13.4 Folding pattern is the result of genetic programs, biomechanical strains, and environmental effects. The analysis of its organization and geometry can therefore supply information on the cortical proportions, on the spatial variations, and on the underlying morphogenetic processes

spatial organization, such as connectivity. As a matter of fact, using information on spatial contiguity of the cortical element in fossil species can extend network analysis into a paleoneurological perspective, especially when dealing with higher taxonomic ranks (i.e., comparative analyses among genera, families, and orders). Among functional factors that can be investigated indirectly through their correlation with geometry, it is important to mention also thermoregulation and metabolism. Although brain thermoregulation mostly depends upon vascular physiology, heat dissipation patterns are also influenced by size and shape (Bruner et al. 2011). Human species displayed notable brain form differences, and these variations influenced the distribution of cortical heat. These patterns can be numerically simulated, linking spatial and functional information (Bruner et al. 2012). Furthermore, the spatial relationship between the brain and braincase is a relevant issue in neurosurgery and medicine (Ribas et al. 2006; Richtsmeier et al. 2006; Bruner et al. 2015).

Finally, sulcal morphology can also reveal underlying growth and developmental patterns associated with genetic pathways and morphogenetic constraints. Actually, there is a consistent relationship between genetic expression and cortical blocks (Chen et al. 2012). There is also a direct association between genes and the development of large cortical regions (Rakic 2004), and a correlation between sulcal morphology and genetic ancestry has been also recently described (Fan et al. 2015). Nonetheless, the genetic programs are probably aimed only at regulating the time and rate of cell growth, while the sulcal morphology is likely to be the result of intrinsic and automatic mechanical folding processes based on allometric responses, strain distributions, and surface adjustments (Tallinen et al. 2016). The spatial organization of the brain cortex is the result of differential growth of its areas, influenced by geometrical rules and energetic constraints (Hofman 2012). Beyond direct genetic programs influencing cell proliferation and diversification, macro- and microanatomical elements are linked through shared morphogenetic mechanisms (Van Essen 1997; Hilgetag and Barbas 2005 2006). Neurons can act themselves as biomechanical tensors redistributing growth forces and contributing to the final sulcal morphology. In this case, the final phenotype will depend also upon mechanical properties of the neurons as cortical mechanical units (Toro and Burnod 2005; Bayly et al. 2014) and upon their influence along growth trajectories (Toro 2012). Therefore, beyond the spatial and geometric information, it is possible to use sulcal patterns to evaluate indirectly changes and parameters of the underlying morphogenetic processes. Evolutionary changes in the sulcal pattern can reveal changes in relative proportions of the cortical areas or changes in the general morphogenetic sequence leading to that specific folding scheme. In this sense, the sulcal variation and arrangement are not relevant per se but as witness of an underlying structural difference (relative volumes, tissue mechanical properties, developmental forces, folding sequences).

According to the results of this introductory example on Brodmann's maps, it is interesting that the contiguity among areas is able to reveal three blocks that approximately correspond to the frontal, temporal, and parieto-occipital districts. If this is not by chance, it means that our conventional "lobes" may represent actual spatial and structural units. Modularity is often a matter of degree and hierarchical inclusive blocks, more than of absolute isolation between morphological regions. Nonetheless, it may reveal consistent groups of anatomical elements influenced by reciprocal or shared factors. In this case, it is worth noting that the three blocks described in this survey correspond also to different cranial districts and different kinds of relationships with the

cranial morphogenetic system (Bruner 2015). The prefrontal cortex is housed in the anterior cranial fossa, which is structurally constrained by the upper facial block (Bruner et al. 2014). The temporal lobes are housed in the middle cranial fossa, constrained by the midface, the endocranial base, and the mandibular biomechanics (Lieberman et al. 2000; Bastir et al. 2004; Bastir and Rosas 2005, 2006). The parieto-occipital block is the largest component of the cranial vault, free from cranial constraints except for the spatial relationships between bones and suture. The three mentioned endocranial areas are quite independent in terms of morphological variation, probably because they are influenced by independent factors (Bruner and Ripani 2008). Actually, within the human genus, different morphological changes have been described for the prefrontal (Bruner and Holloway 2010), parieto-occipital (Bruner 2004; Gunz and Harvati 2007), and temporal (Bastir et al. 2008) areas. If these three cortical blocks based on contiguity of Brodmann's areas are real structural units, it remains therefore to be evaluated whether their internal cohesion is a cause or a consequence of the different relationships with the corresponding cranial districts. It is likely that a joint analysis on the cerebral and cranial elements can further add to these structural models, taking into consideration their reciprocal spatial relationships and consequent mechanical influences (Ribas et al. 2006; Bruner et al. 2015; Goriely et al. 2015).

13.4.3 Extending Networks

A final note concerns the relationships between brain morphology and environmental influences. Many current cognitive theories are giving more importance to nonneural components, like the whole body and the environment (Clark 2007, 2008). According to hypotheses on extended cognition and embodiment, the body and the environment are active parts of the cognitive experience (Malafouris 2010, 2013). The interaction between body and tools strongly influences the organization of the neural circuits, inducing micro- and macroanatomical changes in the brain (Iriki and Sakura 2008; Quallo et al. 2009; Iriki and Taoka 2012). Visuospatial integration is a clear example of cognitive functions in which biological and cultural factors can interact to generate feedbacks and integrative dynamics between the brain, body, and environment (Bruner and Iriki 2016). In this sense, selection can operate on specific traits or on the sensitivity of those traits to undergo biological responses after environmental influences. Phenotypic plasticity and evolvability can be targeted by selective forces, promoting or demoting the capacity of a biological component to respond to changes or training (Crispo 2007). It is therefore critical to investigate further to what extent cortical morphology is due to genetic, epigenetic, and environmental influences. A recent study suggests that modern humans show an apparent heritability for brain size and dimensions but, contrary to apes, less genetic constraints on the sulcal patterns (Gómez-Robles et al. 2015). Such phenotypic plasticity can be the result of a selective process increasing the environmental sensitivity of the brain structure. In all cases, a proper knowledge of the "brain geography," accounting for its neural groups and clusters, is a mandatory step, necessary to reveal the distribution of the spatial factors involved in the neural responses.

13.5 More Networks

In this study, we have shown how network modeling can be applied to brain spatial mapping taking into consideration contiguity among different areas, being the physical contact a factor relevant to structural analysis in ontogeny and phylogeny and a crucial aspect when dealing with morphological integration and local effects. Network approaches are often used to evaluate brain connectivity, but, in this case, we used network modeling to evaluate possible associations and constraints due to spatial proximity between adjacent areas. In this example, we used Brodmann's areas, a parcellation scheme which has been long applied in the last century. The results suggest that spatial contiguity generates a network which approximately separates the main lobe and matches different areas of brain-braincase relationships. Nonetheless, brain mapping is currently a proficient field of investigation, and different methods and criteria are at present providing different schemes and perspectives (Glasser et al. 2016). The same approach used here can be used with different kind of parcellations or considering different kind of spatial elements. Working with endocasts, spatial contiguity can be investigated as to evidence whether major evolutionary changes have influenced the underlying organization of brain morphology. Among human species, gross anatomical differences are more subtle, but among primates or mammals, variations in the position or composition of the brain elements have been more apparent. Also, in this introductory analysis, we consider only contiguity in terms of the presence or absence of physical contact. Future studies should weight such contact in terms of absolute and relative extension of the physical interfaces. Furthermore, such networks should be extended including the relationships between cortical and subcortical areas and between the brain (soft tissues) and braincase (hard tissues). Allometric and spatial constraints, as well as vascular and metabolic components, will be probably essential to provide consistent models able to evidence modular and/or integrated levels of organization associated with the brain spatial arrangement.

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