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ORIGINAL ARTICLE

A network approach to brain form, cortical topology and human evolution

Emiliano Bruner[1] · **Borja Esteve-Altava**[2] · **Diego Rasskin-Gutman**[3]

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Abstract

Network analysis provides a quantitative tool to investigate the topological properties of a system. In anatomy, it can be employed to investigate the spatial organization of body parts according to their contiguity and patterns of physical contact. In this study, we build a model representing the spatial adjacency of the major regions of the human brain often considered in evolutionary neuroanatomy, to analyse its topological features. Results suggest that the frontal lobe is topologically independent of the posterior regions of the brain, which in turn are more integrated and influenced by reciprocal constraints. The precentral gyrus represents a hinge between the anterior and posterior blocks. The lateral temporal cortex is particularly influenced by the neighbouring regions, while the parietal cortex is minimally constrained by the overall brain organization. Beyond the reciprocal spatial influences among cortical areas, brain form is further constrained by spatial and mechanical influence of the braincase, including bone and connective elements. The anterior fossa and the parietal bones are the elements more sensitive to the brain–braincase spatial organization. These topological properties must be properly considered when making inferences on evolutionary variations and macroscopic differences of the human brain morphology.

Keywords Anatomical network analysis · Brain morphology · Paleoneurology · Functional craniology

Introduction

In adult humans, brain form is the result of multiple factors: genetic programs (Chen et al. 2012), plasticity and functional responses to environmental factors (Sherwood and Gómez-Robles 2017), and structural intrinsic constraints (Hofman 2012). This latter factor has been less investigated and, to date, we still ignore many crucial mechanisms involved in brain folding and topological arrangements (Bayly et al. 2014; Garcia et al. 2019). Mechanical forces at neuronal levels are supposed to have a major role in shaping the cortical surface (Hilgetag and Barbas 2005, 2006) and in orienting brain morphogenesis (Van Essen 1997; Toro and Burnod 2005; Van Essen et al. 2018) (Fig. 1). Actually, surface to volume growth constraints are sufficient to explain a consistent part of the human folding pattern (Tallinen et al. 2016). Brain geometry is further influenced by structural and functional relationships with the braincase at ontogenetic (Moss and Young 1960; Richtsmeier et al. 2006) and phylogenetic levels (Bruner et al. 2014; Bruner 2015). In primates, the cranial base and the facial block represent extremely complex structural systems (Lieberman et al. 2000; Bastir et al. 2006); thus, they are expected to exert important physical constraints on the brain spatial organization. For example, in modern humans, the frontal lobes lie onto the orbits (Pereira-Pedro et al. 2017) and the temporal lobes onto the mandibular ramus (Bastir and Rosas 2005), suggesting reciprocal influences between soft and hard tissues. Physical interactions between brain and braincase are relevant when dealing with brain evolution, but also in health and disease (Ribas et al. 2006; Richtsmeier and Flaherty 2013; Goriely et al. 2015). Brain topological constraints are particularly

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✉ Emiliano Bruner
emiliano.bruner@cenieh.es

[1] Centro Nacional de Investigación sobre la Evolución Humana, Paseo Sierra de Atapuerca 3, 09002 Burgos, Spain

[2] Department of Experimental and Health Sciences, Institute of Evolutionary Biology (UPF-CSIC), University Pompeu Fabra, Barcelona, Spain

[3] Theoretical Biology Research Group, Cavanilles Institute of Biodiversity and Evolutionary Biology, University of Valencia, Valencia, Spain

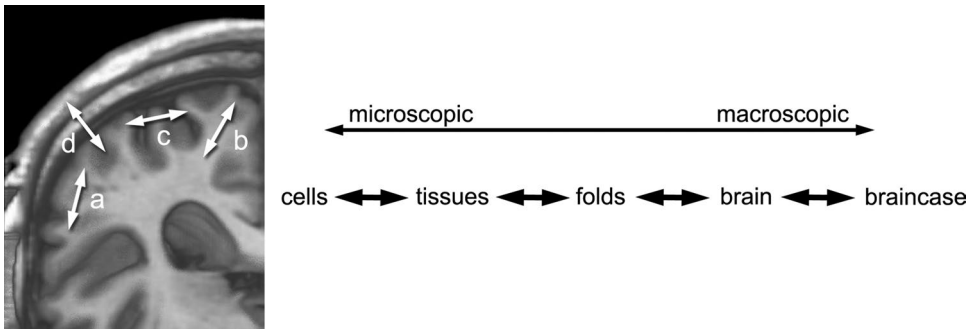

Fig. 1 Morphogenetic processes are associated with mechanical strains and tensile forces due to cell and tissue growth and development that generate reciprocal influences between anatomical elements at different scales. Through the cortex, physical interactions are expected between cells of the same type (**a**), between white and grey matter (**b**), between folds (**c**), and between cerebral, meningeal, and cranial components (**d**). Such biomechanical environment is crucial for the formation of the final phenotype

relevant in paleoneurology, when brain form and endocranial casts are used to make inferences on brain evolution in fossil species, interpreting cortical volumes and sulcal schemes to extrapolate anatomical changes and regional proportions of cortical elements (Holloway et al. 2004; Bruner 2017a, 2019) (Fig. 2a). Apart from the uncertainties due to the recognition of cortical features on the endocranial surface, the task is further complicated by the difficulties in separating primary brain changes due to genetic adaptations or functional plasticity, from secondary effects due to extrinsic factors, like spatial and mechanical constraints due to the braincase or to adjacent brain regions.

In the last decade, network analysis has been applied to evaluate the structural organization and the topological properties of macroscopic anatomical systems (Esteve-Altava et al. 2011; Rasskin-Gutman and Esteve-Altava 2014; Dos Santos et al. 2017; Esteve-Altava and Rasskin-Gutman 2018; Murphy et al. 2018; Kerkman et al. 2018). According to this perspective, the traditional network approach (e.g. Proulx et al. 2005; Butts 2009) is used to model the spatial contiguity and connection among anatomical elements to quantify, test, and compare the topological properties associated with their position and spatial contacts. When applied to the human skull bones, network analysis revealed two modular blocks formed by the face and the braincase, structured onto the ethmoid and sphenoid hubs, respectively, and connected through the frontal and zygomatic elements (Esteve-Altava et al. 2013; Esteve-Altava 2017a). In neuroscience, network analysis is generally used to deal with neural connectivity (e.g. Sporns et al. 2004; Hagmann et al. 2008; Meunier et al. 2010). Nonetheless, applications to the brain's macroanatomical level are generally lacking. A first preliminary survey was used to describe the topological properties of the human brain according to the general Brodmann's

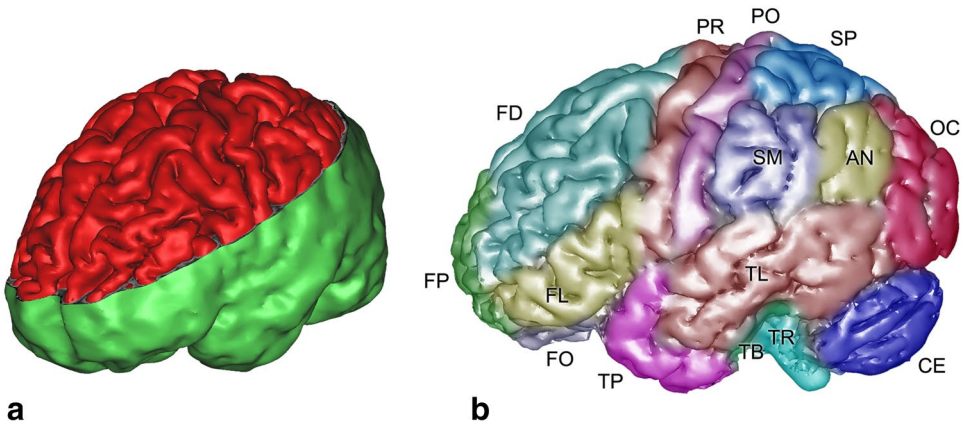

Fig. 2 **a** Endocasts (green) can provide only general information on the macroscopic anatomy of a brain (red). **b** In this study, we have considered the topological relationships between gross morphological districts commonly used when describing macroanatomical brain regions. Labels: *AN* angular gyrus, *CE* cerebellar hemisphere, *FD* fronto-dorsal cortex, *FL* fronto-lateral cortex, *FO* fronto-orbital cortex, *FP* frontal pole, *OC* occipital lobe, *PO* postcentral gyrus, *PR* precentral gyrus, *SM* supramarginal gyrus, *SP* superior parietal cortex, *TB* temporal base, *TL* temporo-lateral cortex, *TP* temporal pole, *TR* trunk

parcellation scheme (Bruner et al. 2018). This analysis identified a prefrontal cluster, a second modular block formed by parietal lobe, paracentral lobule, and occipital lobe, and a third module formed by the temporal region. These modules roughly match the endocranial main districts, namely the anterior fossa, the middle fossa, and the vault, suggesting a topological correspondence between the main sulcal and cranial regions.

In this study, we apply anatomical network analysis to those cortical regions of the human brain that are generally used in macroanatomical surveys to determine and describe brain morphological features and variations. In particular, we consider those regions frequently involved in human paleoneurology and evolutionary neuroanatomy. We aim to investigate the topological properties of these main brain districts, looking for factors or constraints that can influence the variation and variability of their macroscopic anatomical traits, under the null hypothesis of no differences in the topological properties of the distinct elements.

Materials and methods

Brain and endocranial topology

In this study, we considered only the external macroscopic morphology of the brain. In paleoneurology and other fields that employ macroanatomical surveys, the main brain regions are generally defined according to the sulcal elements, or to the bosses and grooves they leave on the endocranial wall (Holloway et al. 2004; Bruner 2017a). In this case, we used 15 regions (Fig. 2b) and modelled a bilateral network of 29 nodes and 65 links (Fig. 3a, b). The fronto-lateral region (FL) corresponds to the inferior frontal gyrus, and the fronto-dorsal region (FD) corresponds to the middle and superior frontal gyrus. These regions are often considered in terms of sulcal pattern or proportions because of their association with language and executive functions in early hominid, modern humans, and Neanderthals (Bruner 2017b). Precentral (PR) and postcentral (PO) sulci mark the boundary between the frontal and parietal lobes. The superior parietal lobules (SP) include the external dorsal cortex, although in anatomical terms it also includes the precuneus and the intraparietal sulcus (see Bruner et al. 2017a). The inferior parietal lobule is separated into the supramarginal (SM) and angular (AN) gyri. All these parietal areas have been hypothesized to be derived in Neanderthals and modern humans (Bruner 2018a). The fronto-orbital region (FO) is the part in contact with the orbital roof, the temporo-lateral region (TL) includes the superior, middle and inferior temporal gyri, and the temporal base (TB) includes the temporo-occipital, inferior temporal and parahippocampal gyri. These regions were supposed to be derived in modern humans (Bastir et al. 2011). In most paleoneurological surveys, these regions are recognized by mean of bosses and furrows left by the cortical impressions that, although with a large uncertainty, allows estimating the cortical proportions in fossil species (Bruner 2018b). The occipital lobe (OC) and the cerebellum (CE) occupy the posterior fossa, above and below the trace of the transverse sinus. The former has been hypothesized to be larger in Neanderthals (Pearce et al. 2013), while the latter can have expanded in modern humans (Gunz et al. 2019). The frontal (FP) and temporal (TP) poles represent the tips of the two lobes, housed in their respective bony socket. We have also included the cerebral trunk (TR), although it has apparently no influence in the analysis. In

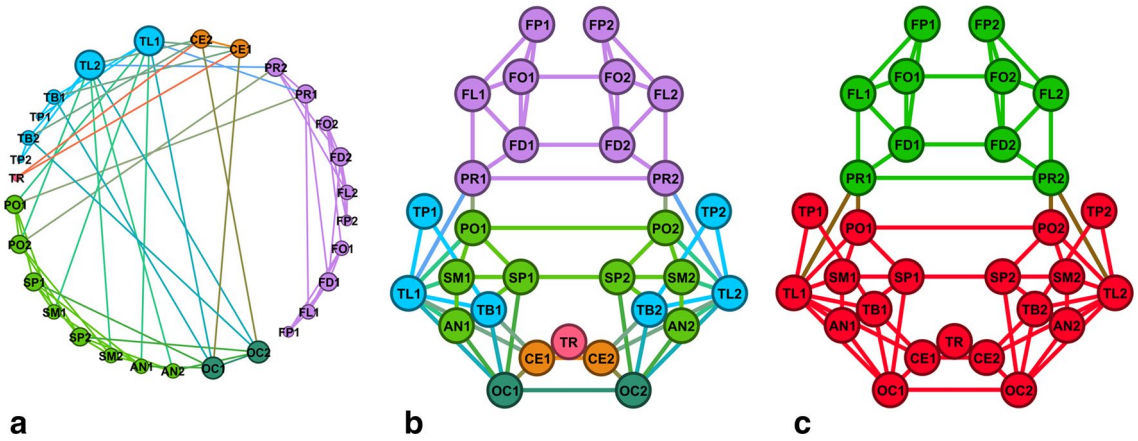

Fig. 3 Circular layout of the network (**a**) with node size proportional to the number of connections) and anatomical layout (**b**) with nodes approaching the anatomical topology of the brain in dorsal view (frontal lobe: violet; parietal lobe: light green; temporal lobe: light blue; occipital lobe: dark green; cerebellum: orange; trunk: pink). Network topology suggests two modules (**c**), one anterior (green; frontal lobe) and one posterior (red; the rest of the network)

this study, both hemispheres have been considered to supply a more balanced representation of the brain. Nonetheless, preliminary analyses using only one hemisphere gave similar results.

The human folding pattern is extremely variable, and many mechanisms behind such variations are still not clear (Van Essen and Dierker 2007). Different cortical regions display different degree of variability, and individual plasticity is even more pronounced in humans when compared with the other primates (Gómez-Robles et al. 2015; Croxson et al. 2018). Furthermore, in humans, grey matter and white matter undergo growth and development until the age of 20 years, with distinct rates and timing in different regions (Giedd et al. 1999), which suggests the possibility of late ontogenetic changes in folding morphology. Therefore, we must consider that the scheme of proximity and contiguity between areas can suffer changes according to individual or ontogenetic diversity. Nonetheless, the regions used for our model are sufficiently large to provide a rather consistent topology, at least when taking into account the cortical morphology observed in the human genus.

We also built a second network model (40 nodes, 129 links) that included some endocranial bone elements to provide preliminary considerations on the effect of the spatial contiguity with the endocranial bones. In particular, we have taken into account the spatial effect of the anterior fossa, frontal squama, middle fossa, temporal squama, posterior fossa, occipital squama, parietal bones and clivus. Anterior and posterior fossae have been considered as single elements and not separated in their right and left side. Although this cranial model is very general, it includes nonetheless the major braincase regions and helps to evaluate the broad spatial frame of the brain–skull organization.

Anatomical network analysis

In its basic form, anatomical network analysis takes into consideration the presence or absence of contact between pairs of anatomical elements (see Rasskin-Gutman and Esteve-Altava 2014; Esteve-Altava and Rasskin-Gutman 2018 for a methodological review). Such physical contiguity is expected to have an influence during morphogenesis (Esteve-Altava et al. 2013), being at once the final phenotypic result of growth and development and a main factor channelling phenotypic topological organization. The analysis of the network on the basis of the spatial contiguity of its elements can hence provide information on the structure and organization of the anatomical system, properties that are associated with developmental constraints, modularity, and morphological integration (Esteve-Altava and Rasskin-Gutman 2014; Esteve-Altava 2017a, b). An adjacency matrix is coded by assigning every pair of element a value of 0 if the elements are not in contact, and a value of 1 if they are in physical contiguity. In this study, we have not discriminated contiguity based on tissue continuity or physical contact; thus, taking into account only the adjacency of the regions as the main source of mutual spatial influence. Contiguity among regions was checked through anatomical educational casts and according to Damasio (2005), White and Folkens (2000) and Rohen et al. (2006). The extension of the bones onto the brain regions have been further defined according to Ribas et al. (2006) and Bruner et al. (2015). The adjacency matrices are available as Supplementary Information. The properties of the elements (nodes) within the network are then calculated with parameters based on the number of connections and on the distance between the elements (see Watts and Strogatz 1998; Newman 2005; Landherr et al. 2010; Rasskin-Gutman and Esteve-Altava 2018). Different centrality metrics are used as topological measures of the importance and influence of a node within the network organization (Bullmore and Sporns 2009). Here, we used six centrality measures. Node degree refers to the number of connections of a node, which is proportional to its importance as a hub of the system. Betweenness is the proportion of minimum paths between nodes that pass through a specific node, showing the function of that node as a bridge between different regions of the system. Closeness is computed as the average distance between a node and all the other nodes and refers to the topological (in anatomical networks, spatial) proximity of a node from the rest of the nodes. Clustering coefficient refers to the degree of interconnectivity among the neighbour nodes of a node, which is proportional to the level of integration of that region; it is the percentage of neighbours that are connected with all the other neighbours of a node, forming a complete network (cliques). Eigenvector centrality considers the degree of connections of the neighbours, being higher for nodes connected to highly connected nodes. K-neighbour centrality measures the average degree of the neighbours. All these centrality parameters quantify different topological aspects of the nodes within the system and have different anatomical interpretations (see "Discussion"). All parameters have been normalized. For each parameter, a similar value in distinct nodes indicates a similar importance or sensitivity to the effects of global and local morphological changes. A principal component analysis (PCA) was computed on all the parameters to provide a comprehensive synthesis of the similarities and differences between different brain regions. Network analysis was computed in R (R Core Team 2013) using functions from the package igraph (Csardi and Nepusz 2006). Layout and visualization were displayed with Gephi 0.9.2 (Bastian et al. 2009).

We also considered the potential modular organization of the current brain's anatomical network model. Modularity in anatomy is not generally a matter of completely independent units, but instead of a given degree of independence from

the rest of the system (Newman and Girvan 2004; Esteve-Altava 2017a, b). In network analysis, this means localizing groups of highly interconnected nodes that can be nonetheless organized in a hierarchical structure or representing connector elements between modules (Meunier et al. 2010). Accordingly, modularity analyses are aimed at localizing clusters of elements that share strong patterns of variation, connections, or functional relationships (modularity patterns), more than to identify isolated sub-systems (modules). That is, anatomical networks are generally expected to be nearly decomposable systems, in which the interactions among different blocks are weak, but probably not negligible (Simon 1962). In this survey, we used an order statistics local optimization method (OSLOM) (Lancichinetti et al. 2011; source code available from http://www.oslom.org; Esteve-Altava 2017a, b). We ran 100,000 iterations for values of statistical tolerance (a priori p values) between 0.05 and 0.1 (default OSLOM tolerance) at 0.001 intervals. Significant modules are found with a given p value (below the tolerance threshold), which should be interpreted as an estimation of the probability of finding a module like this one in a random network with the same degree distribution. OSLOM's coverage parameter threshold for merging communities was set at the default value, because the algorithm's outcome did not vary for different values (we ran 100 iterations for merging significant modules). Since OSLOM is a stochastic algorithm, we set the random seed number to 73 for reproducibility. We only found non-overlapping modules, which allowed us to compute the Newman and Girvan (2004) modularity value Q for every partition using the function modularity in igraph. As a reference, we also used a traditional method to delimit modules based on a linear optimization of the modularity value Q as implemented in the function cluster_optimal in igraph.

Results

The network model of the brain presented here has an average degree value of 4.48 and a density value of 0.16. That is, modelled brain regions have on average of four to five connections each, and there are only 16% of all the possible connections. Table 1 shows the centrality metrics for each node, and the average values for the frontal, parietal and temporal lobes. Figure 4 shows the model with node colour and size proportional to the value of each centrality measure. Degree is higher in the lateral temporal cortex, followed by the occipital lobes. The lowest values are associated with the frontal and temporal poles, which are isolated within their respective bony sockets. Betweenness is higher for the precentral gyrus, followed by the lateral temporal region. The other regions display low values, especially the frontal and temporal poles and the inferior parietal lobule (angular and supramarginal gyrus). Closeness is high in the precentral gyrus, lateral temporal region, and postcentral gyrus, although the other regions display high proximity, except

Table 1 Centrality parameters (highest values in bold)

	Degree	Betweenness	Closeness	Clustering	Eigenvector	K-neighbour
Frontal lobe						
FP	0.107	0.000	0.280	**1.000**	0.124	4.333
FL	0.143	0.050	0.354	0.667	0.214	4.250
FD	0.179	0.095	0.368	0.400	0.257	4.200
FO	0.143	0.020	0.289	0.500	0.148	4.000
PR	0.179	**0.275**	**0.459**	0.200	0.546	5.400
Mean	*0.150*	*0.088*	*0.350*	*0.553*	*0.258*	*4.437*
Parietal lobe						
PO	0.179	0.088	**0.431**	0.300	0.718	5.400
SM	0.143	0.004	0.354	0.667	0.615	5.500
AN	0.143	0.004	0.359	0.667	0.646	**5.750**
SP	0.179	0.036	0.373	0.300	0.719	4.800
Mean	*0.161*	*0.033*	*0.379*	*0.483*	*0.674*	*5.363*
Temporal lobe						
TP	0.071	0.000	0.315	**1.000**	0.315	**6.000**
TL	**0.286**	**0.222**	**0.444**	0.286	**1.000**	4.375
TB	0.143	0.012	0.359	0.667	0.580	5.250
Mean	*0.167*	*0.078*	*0.373*	*0.651*	*0.632*	*5.208*
OC	**0.214**	0.079	0.400	0.333	**0.905**	5.333
CE	0.179	0.067	0.384	0.400	0.688	5.000
TR	0.071	0.000	0.326	**1.000**	0.274	5.000

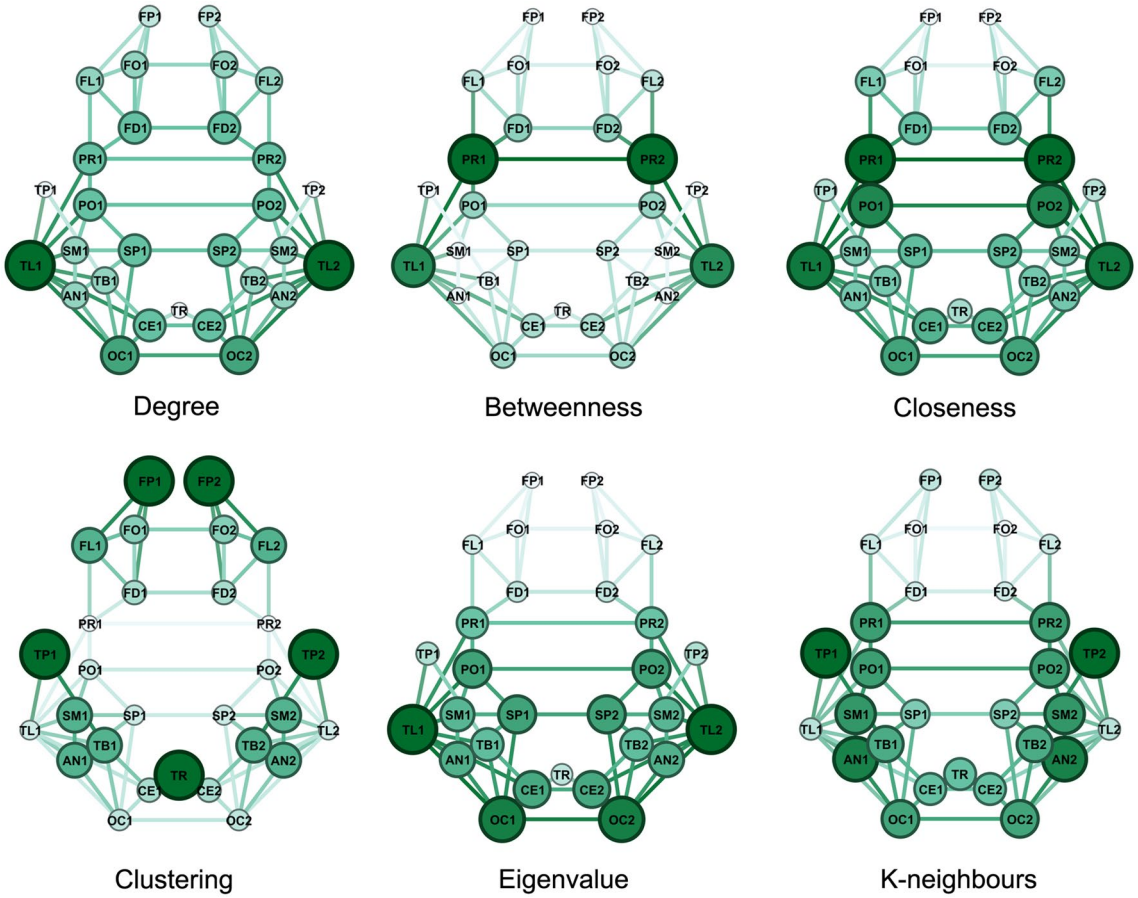

Fig. 4 Centrality measures showed onto the anatomical layout. Node size and colour density are both proportional to the node value

the most frontal ones. Clustering coefficient is high for the frontal and temporal poles and for the trunk, because they are terminal extremes of the networks, integrated with their respective larger regions. A cluster is also formed by the angular gyrus, the supramarginal gyrus, and the temporal base. Eigenvector centrality is high in the lateral temporal regions and occipital lobes, but has general higher values for the whole posterior brain district. Also k-neighbour centrality is high for the whole posterior region, although showing a large value for the temporal pole and a low value for the lateral temporal region. Most centrality measures (degree, closeness, eigenvector and k-neighbours) have higher values in the posterior district (parietal, occipital, and temporal lobes), while the frontal lobes look generally less topologically connected within the network.

These parameters show a modest to moderate reciprocal correlation ($R^2 = 0.53 \pm 0.25$; Table 2). Degree and betweenness display a non-linear correlation (Fig. 5), which can be particularly interesting because of their direct relationship with local and global connectivity, localizing local hubs and bridging elements, respectively. According to their correlation, the lateral temporal region has high betweenness because of a high degree of centrality. By contrast, the precentral gyrus is associated with a level of betweenness

Table 2 Correlation between parameters

R/p	Degree	Betweenness	Closeness	Clustering	Eigenvector	K-neighbour
Degree		0.003	0.001	0.000	0.001	0.376
Betweenness	0.70		0.000	0.003	0.113	0.715
Closeness	0.76	0.83		0.000	0.001	0.420
Clustering	− 0.85	− 0.71	− 0.80		0.013	0.642
Eigenvector	0.74	0.43	0.76	− 0.62		0.167
K-neighbours	− 0.25	− 0.10	0.23	0.13	0.38	

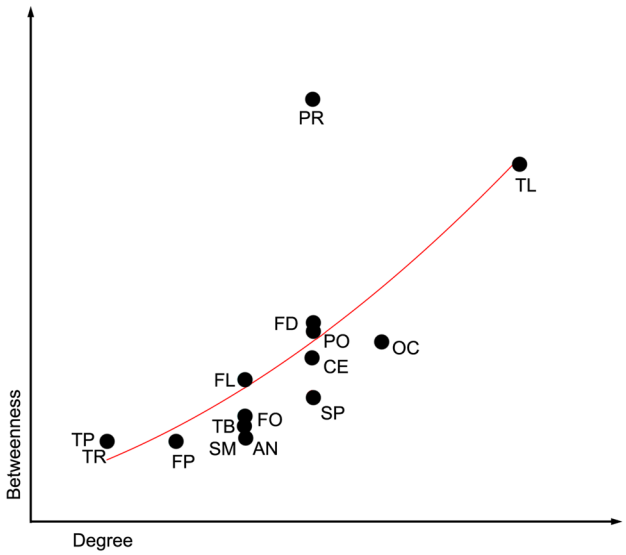

Fig. 5 Correlation between degree and betweenness centrality (labels as in Fig. 1)

centrality which is not due to its degree of connections, but instead to its topological position within the brain.

A PCA computed on all the centrality measures (Fig. 6) reveals a first component explaining 65% of the variation. A second component is slightly below a threshold of random variation, explaining 22% of the variance. PC1 is associated with an increase in eigenvector, closeness, betweenness and degree, and a decrease of clustering coefficient. Temporal poles, frontal poles, and the trunk display the lowest figures, namely high clustering coefficient, and low degree and betweenness. The opposite extreme is represented by the temporal lateral cortex and precentral gyrus. PC2 is mainly associated with an increase of k-neighbours and separates the prefrontal cortex from the rest of the elements because of its low values.

Adding the bony elements of the endocranial cavity, we have a model with an average degree of 6.45 and density of 0.16 (Fig. 7). The degree is higher at the parietal bones, frontal squama, anterior fossa, and lateral temporal cortex. Betweenness evidences a main bridging role of the parietal bones and of the anterior fossa.

The modules identified for the network model of the brain vary depending on tolerance values (Table 3). For tolerance between 0.05 and 0.053, we found two modules: one anterior ($p=0.040$) and one posterior ($p=0.009$), with an overall quality of the partition of $Q=0.376\pm0.048$. The anterior module groups the frontal and precentral regions together, whereas the posterior module groups all other elements posterior to the precentral region. For tolerance between 0.054 and 0.056, we found three modules: the previously anterior module and two posterior modules, one grouping the left posterior elements plus the cephalic trunk ($p=0.032$) and one grouping the right posterior elements ($p=0.032$), with an overall quality of the partition of $Q=0.528\pm0.043$. Finally, for tolerance between 0.057 and 0.1, we found the same three modules, but now the cephalic trunk was not assigned to any of the posterior modules (it is left as an unassigned singleton) because it does not contribute significantly to the modular organization of the brain. This is the best partition found with an overall quality of $Q=0.540\pm0.043$. For reference, we also computed the modularity of the network following a traditional optimization method (see Table 3), which yields a separation in the left and right parts also for

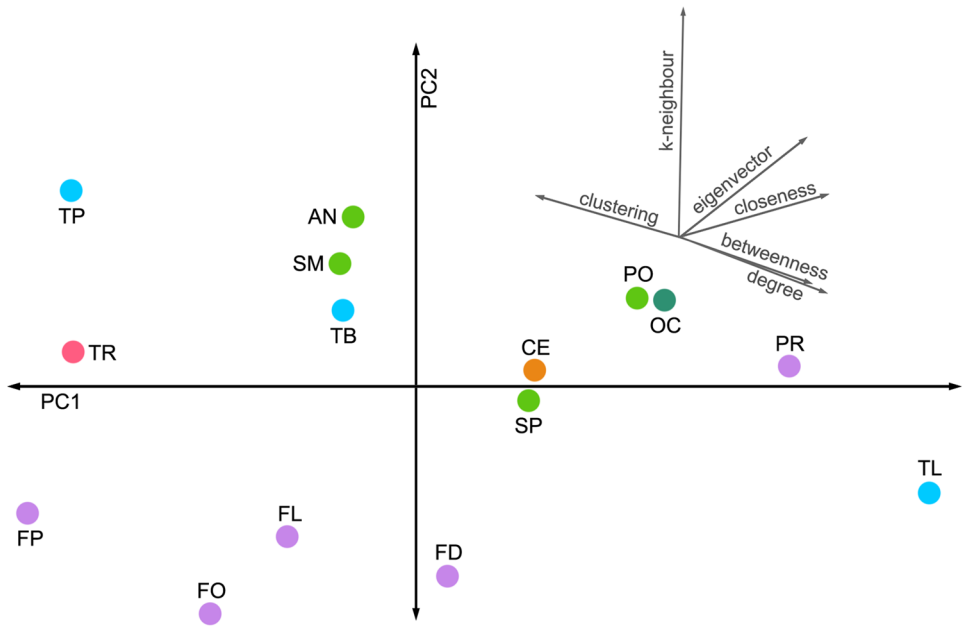

Fig. 6 Principal component analysis based on the six centrality measures (colours and labels as in Fig. 2b)

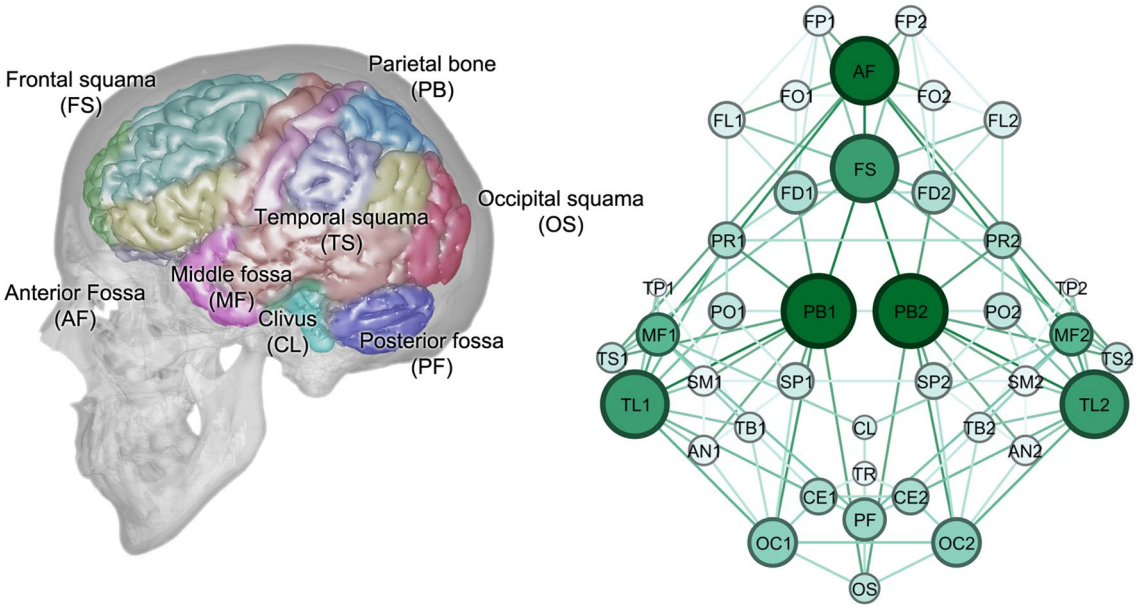

Fig. 7 Network including eight endocranial bone regions, with the size of the node proportional to the degree, and the colour density proportional to the betweenness centrality

the anterior module ($Q = 0.534 \pm 0.051$). The best modular separation splits the frontal lobes from the rest of the brain, identifying an anterior and a posterior module (Fig. 3c). Interestingly, despite the comparable position and topology of the precentral and postcentral gyri, they are assigned to different blocks, marking the central sulcus as a topological frontier between the two modules.

Discussion

Brain form and topology

Network analysis offers mathematical tools to investigate relationships between elements and can be used to disentangle the structure of biological, economical, or social systems (Proulx et al. 2005; Knight and Pinney 2009; Newman 2018). Elements can be objects, persons, concepts, or species, and relationships can deal with social bonds, energy flow, mechanical effects, biochemical reactions, or information. In neuroscience, network analysis is a powerful method to investigate connectivity and neural pathways (Sporns et al. 2004). Nonetheless, it can be also applied to the spatial and topological relationships between anatomical components which interact in terms of structure and morphogenesis (Esteve-Altava et al. 2013; Esteve-Altava and Rasskin-Gutman 2014, 2018). The spatial and biomechanical environments associated with the topology of the anatomical elements channel phenotypic changes and constrains morphogenesis and evolution. Hence, the spatial interactions among cerebral elements are relevant to understand the mechanical and geometric aspects of cortical folding, linking topology to developmental mechanisms (Toro 2012; Garcia et al. 2019; Tallinen et al. 2016). Macroanatomical partitions are also related to the neural connectivity patterns, by virtue of the effects of tensile forces due to tissue growth and expansion (Bullmore and Sporns 2012) and because of spatial commonalities between structure and function (Meunier et al. 2009, 2010). However, the brain is formed of multiple neural areas and many non-neural components and, when dealing with its morphology, it can be difficult to distinguish intrinsic anatomical changes (e.g. cell multiplication within a region) from extrinsic influences of neighbouring elements (e.g. spatial conflicts or biomechanical strains). This task is even more complicated when considering that brain evolution and development must be integrated with the bones of the skull, in functional, developmental, and structural terms (Moss and Young 1960; Lieberman et al. 2000; Bastir et al. 2006; Richtsmeier and Flaherty 2013; Bruner 2015). The spatial constraints within the brain organization, and between brain and braincase, are particularly relevant in paleoneurology, namely when the form and traces of the endocranial cavity are used to make inferences on brain evolution in fossil species (Bruner 2017a). In fact, if we observe a macroanatomical change in the cortical geometry, we have to exclude possible extrinsic influences before claiming that the change is due to a specific neural variation (hypothetically associated with some cognitive or behavioural aspect).

The network model used in this analysis suggests that in the overall cerebral topology, we can identify at least two

Table 3 Modularity results of the OSLOM algorithm and optimal modularity

Brain regions	Tolerance			Optimal modularity algorithm
	0.050–0.053	0.054–0.056	0.057–0.10	
FP1	Anterior	Anterior	Anterior	Anterior left
FP2	Anterior	Anterior	Anterior	Anterior right
FL1	Anterior	Anterior	Anterior	Anterior left
FL2	Anterior	Anterior	Anterior	Anterior right
FD1	Anterior	Anterior	Anterior	Anterior left
FD2	Anterior	Anterior	Anterior	Anterior right
FO1	Anterior	Anterior	Anterior	Anterior left
FO2	Anterior	Anterior	Anterior	Anterior right
PR1	Anterior	Anterior	Anterior	Anterior left
PR2	Anterior	Anterior	Anterior	Anterior right
PO1	Posterior	Posterior left	Posterior left	Posterior left
PO2	Posterior	Posterior right	Posterior right	Posterior right
SP1	Posterior	Posterior left	Posterior left	Posterior left
SP2	Posterior	Posterior right	Posterior right	Posterior right
SM1	Posterior	Posterior left	Posterior left	Posterior left
SM2	Posterior	Posterior right	Posterior right	Posterior right
AN1	Posterior	Posterior left	Posterior left	Posterior left
AN2	Posterior	Posterior right	Posterior right	Posterior right
TL1	Posterior	Posterior left	Posterior left	Posterior left
TL2	Posterior	Posterior right	Posterior right	Posterior right
TB1	Posterior	Posterior left	Posterior left	Posterior left
TB2	Posterior	Posterior right	Posterior right	Posterior right
TP1	Posterior	Posterior left	Posterior left	Posterior left
TP2	Posterior	Posterior right	Posterior right	Posterior right
OC1	Posterior	Posterior left	Posterior left	Posterior left
OC2	Posterior	Posterior right	Posterior right	Posterior right
CE1	Posterior	Posterior left	Posterior left	Posterior left
CE2	Posterior	Posterior right	Posterior right	Posterior right
TR	Posterior	Posterior left	Unassigned	Posterior left
Modularity Q	0.376	0.528	0.540	0.534
Q error	0.048	0.044	0.043	0.051

main blocks: an anterior one including the frontal lobe, and a posterior one including all the other districts. A similar network analysis based on the Brodmann's parcellation scheme suggested that, because of their physical contact, the parietal and occipital lobes are further spatially integrated (Bruner et al. 2018), a result also observed for the resting state functional connectivity (Meunier et al. 2009) and for the parietal and occipital bones (Gunz and Harvati 2007). Interestingly, this spatial influence is not apparent in terms of cortical dimensions, because the parietal and occipital lobes do not display a volumetric correlation, at least when dealing with human intra-specific variation (Allen et al. 2002). That is, the posterior region is probably more integrated in terms of topology and functions than it is for size. However, intra-specific variation does not always follow the same rules as inter-specific differences and, actually, Neanderthals have been also hypothesized to display smaller parietal lobes and larger occipital lobes when compared with modern humans (Pearce et al. 2013). Also, among hominoids the parieto-occipital volume is pretty constant (Semendeferi and Damasio 2000). So, if we assume that parietal and association cortex underwent an expansion in humans, occipital lobes must have necessarily underwent a relative reduction. Because of the many structural and functional relationships in the human parieto-occipital block, morphogenetic constraints may be expected and can even explain epigenetic hypostotic features associated with the Neanderthal's braincase development (Bruner 2014).

Our model also suggests that the central sulcus is actually a frontier between the two blocks and that, in terms of cortical spatial factors, the frontal lobes are supposed to be less influenced by the geometrical changes of the rest of

the brain. The role of the paracentral lobule as an interposing element between the two blocks is, in this analysis, due to the coronal and parallel orientation of the precentral and postcentral gyri, generating a coronal barrier between the anterior and posterior regions. This spatial organization is established very early during ontogeny (Tallinen et al. 2016) and shared by all anthropoids (Radinsky 1974). Accordingly, this structural role as spatial hinge of the central sulcus can be probably generalized to all monkeys and apes, as part of the broad Bauplan of the taxon. The paracentral lobule represents the largest primary cortical region of the brain, separating association areas which underwent major expansion during the human encephalization process (Ardesch et al. 2019). Several authors point at crossing gradients between primary cortical regions as possible interpretation of the mosaic appearance of the cortical areas (Huntenburg et al. 2017). It should be hence considered that the paracentral lobule is not only a topological barrier, but also a main source of cortical differentiation between the anterior and the posterior blocks.

Because of the interposing pericentral gyri, the frontal cortex is topologically isolated from the rest of the brain in terms of contiguity. This suggests that, if we only consider the cerebral system, gross morphological changes of the prefrontal cortex are more sensitive to intrinsic factors than to secondary influences of the rest of the brain. The prefrontal region has probably undergone evolutionary changes in both humans and apes (Smaers et al. 2017), and such variations could be therefore recognized when analysing the gross brain form. However, at the same time the prefrontal cortex is housed in the anterior fossa, and consequently strongly constrained by the cranial architecture and in particular by the upper face (Pereira-Pedro et al. 2017). The facial block has been demonstrated to be a distinct module within the cranial network organization, connected by the structural hinge of the sphenoid bone (Esteve-Altava et al. 2013), and the anterior fossa is a crucial bridge between the brain and skull topology (this study). Taking into account both cranial and cerebral information, we can conclude that the frontal cortex, in terms of spatial influences, is probably more constrained by the face than by other cortical regions. Namely, the effects due to spatial variation of the rest of the brain are probably negligible, but those due to facial spatial conflicts are probably not. The fronto-lateral region includes the Broca's area, which is largely investigated in evolutionary anthropology (see Bruner 2017b). This region is relatively wider in modern humans and Neanderthals, but the network perspective confirms that in this case it can be difficult to differentiate changes due to cortical evolution from those due to cranial constraints (Bruner and Holloway 2010).

Brain regions and centrality

The other topological information on the macroanatomical organization comes from the centrality metrics. These parameters inform about some topological properties of the anatomical elements (e.g. the sensitivity to spatial constraints), and the comparison of their values and distribution in the network supply information on similarities and differences among distinct elements of the same anatomical system. This information is useful when providing structural hypotheses on morphological variation and dealing with issues such as integration or evolvability (Wagner and Altenberg 1996; Hansen et al. 2019). Taking into account all the parameters used in this study, the regions (nodes) are principally separated along an axis ranging from more clustered and local ones to those with higher degree and betweenness centrality. Accordingly, our first principal component (see Fig. 6) scores the regions used in this model from those with more local influences (lower values) to those with more global influences (higher values). The lateral temporal region is the one with higher degree of connections (probably because of its longitudinal extension), and it ought to be considered a hub in terms of cortical topology. The correlation between degree and betweenness is expected, but nonetheless it is quantitatively important to assess to what extent the number of connections of an element can also determine its central position. Even more interestingly, the analysis of this association is relevant to localize departures from the relationship, like in the case of the precentral gyrus, which has a central role by virtue of its position and not of its number of connections. Since the precentral gyrus is a major bridge between distinct regions, it ought to be considered a crucial spatial hinge between the anterior and posterior cerebral blocks. Hubs can integrate local units (local hubs, with high degree connectivity and low betweenness centrality) or distinct blocks (connectors, with low degree connectivity and high betweenness centrality), and the study of the correlation between parameters is able to identify these roles.

Anatomical elements with many topological contacts are assumed to be more influenced by structural constraints and, at the same time, they can exert more effects on the global organization of the anatomical system. Namely, they have a higher biological and evolutionary burden (Rasskin-Gutman and Esteve-Altava 2018). In this case, a PCA based on the set of parameters is able to highlight topological similarities between distinct elements and to reveal combinations of topological properties underlying the variability (i.e. the susceptibility to vary) of the anatomical system. Actually, the axes of our PCA can be hence interpreted as a quantitative proxy for burden: while the first principal component directly quantifies the general topological burden for each element, the second component is associated with the

burden of the neighbouring elements, separating the prefrontal regions (non-influential neighbourhood) from the rest of the brain (influential neighbourhood). Because of their many connections, any change in highly connected elements would have effects on many neighbouring components, and their variation will be therefore restricted by such a conservative frame. At the same time, these elements will be influenced by any change of their many neighbours. We must hence conclude that, at least in terms of topology, the morphology of the precentral region and of the temporo-lateral region can be easily influenced by extrinsic changes and global effects. There is no patent paleoneurological evidence on the evolutionary changes of the precentral gyrus, probably because its boundaries are not easy to identify on endocasts. In contrast, temporal lobe length has been assumed to be proportional to temporal lobe size and, accordingly, its extension has been used to suggest a volumetric increase of the temporal cortex in *Homo sapiens* (Bastir et al. 2008). Further spatial conflicts at the temporal lobe can be associated with its proximity with the orbits, with the mandible, and with the ethmomaxillary block (McCarthy 2001; Bastir et al. 2004; Pereira-Pedro et al. 2017). Preliminary morphometric analyses suggest a good correspondence between middle cranial fossa size and temporal lobe dimension (Pearson and Bruner 2018). Nonetheless, the fact that the lateral temporal cortex is in contact with so many structural elements must be taken into account when dealing with its gross anatomical changes. The endocranial temporal surface is very fragile and is hence a poorly represented region in the fossil record. However, because of the many morphogenetic spatial conflicts, sulcal imprints are clear and apparent when the bone is preserved (Rosas et al. 2014). It remains to be evaluated to what extent such patterns are expression of cortical programmes or else structural constraints and extrinsic influences.

It is important to remark that these parameters describe the degree of connections according to the principle of spatial proximity or anatomical adjacency, and not of cortical connectivity. In general, two neighbouring regions have a higher probability to be also more neuronally connected and functionally integrated, for example, by way of local fibre tracts. However, the complex system of long-range connections makes such correlation between spatial proximity and neural connectivity not always certain. For example, the frontal and parietal cortex are topologically separated in terms of spatial modules, but strongly connected in terms of function, forming a very integrated fronto-parietal system (Caminiti et al. 2015). Probably future research should consider the correlation between proximity and connectivity, and particularly in those situations in which a marked departure from a linear relationship points at specific evolutionary changes. Spatial proximity and neural connectivity are supposed to share some structural and morphogenetic factors, and an effort should be made to consider their reciprocal influences. It is worth noting that neural elements with high degree connectivity and topological centrality, beyond structural or functional importance, are also assumed to have higher metabolic levels and energy consumption (Bullmore and Sporns 2012). Because of their biological burden, these central elements are also more sensitive to functional damages (e.g. Buckner et al. 2008; van den Heuvel et al. 2010). We wonder whether, in the case of structural elements, their topological centrality makes them also more sensitive to structural or developmental damages: on other words, whether a topological centrality makes the element more sensitive to morphogenetic failures.

The paracentral and temporo-lateral regions are also, on average, the closest to the other cortical districts, and closeness is a crucial parameter in the connectivity and speed of the neural signals. Because of the huge number of processing units and information exchange, even minor changes can seriously enhance or demote computational speed (Hofman 2012). However, the whole posterior cerebral block is generally characterized by close spatial relationships, because of the globular organization of the human brain, and this factor is probably more relevant when comparing different species with very different brain form.

The centrality measures based on the pattern of connections of the neighbouring nodes stress further that the whole posterior block is more densely integrated, in terms of topology and spatial contiguity. Interestingly, in primates, gyrification and folding increase from the anterior to the posterior regions (Zilles et al. 1988, 1989), and the same posterior regions also display a stronger modularity and more hub areas (Meunier et al. 2009). Accordingly, we must assume that increasing surface complexity is associated with increasing topological complexity, confirming a possible bridge between cortical organization and folding mechanisms.

The cluster coefficient, which is generally useful to localize local integrated units in larger system, in this case can supply only minor information. Actually, in this model high clustering is found only in the frontal and temporal poles which, by definition, are secluded in their bony socket and hence necessarily integrated only with their respective lobes. As terminal ends of the frontal and temporal cortex, these districts are sensitive to most morphological changes associated with the respective lobes. Nonetheless, as previously mentioned, both poles are strictly in contact with cranial elements (orbits, ethmoid, and mandible) and hence constrained by spatial conflicts and morphogenetic extrinsic limitations of the skull. The proximity between face and temporal poles, more pronounced in modern humans than in any other hominids, can be actually the reason of the twist displayed by their distal surface in our species (Bruner et al. 2017b).

A further point concerns the parietal lobes. The model used here suggests that the parietal cortex is not formed by

crucial nodes in terms of spatial contiguity. Accordingly, its elements have less spatial constraints, and morphological changes are more likely to be the result of local variations. The lower lobule is somehow more influenced by the temporal cortex, but the dorsal regions are, topologically, peripheral elements. These regions are supposed to be wider in Neanderthals and definitely more expanded in modern humans, when compared with extinct hominids or living apes (Bruner 2018a). The modest centrality displayed by these regions stresses further that any form variation is more likely to be due to actual intrinsic cortical changes, and not particularly to neighbouring influences. It remains to be tested whether non-neural components (like the meninges and the connective tensors of the brain) can exert some global effect constraining these medial districts of the endocranial space (Bruner 2004). Of course, the superior parietal lobule includes deep cortical areas which have, in turn, a relevant topological, connective, and metabolic burden (Cavanna and Trimble 2006; Hagmann et al. 2008; Meunier et al. 2009; Sotero and Iturria-Medina 2011). Hub connection properties in the medial parietal cortex were found to be correlated with psychometric tests of intelligence (Langer et al. 2012).

Like the parietal cortex, the cerebellar hemispheres also have a modest centrality within the system. However, this result is expected, because of the external and peripheral position of the cerebellum relative to the cerebral system. Also in this case, cranial constraints are expected to be stronger than cortical constraints, taking into account that the cerebellum is completely housed onto the endocranial base.

When including endocranial bone regions in the model, the parietal bones and the anterior cranial fossa outstand for their centrality, which suggests that these elements are associated with many distinct influences during morphogenesis and evolution. It can be hypothesized that the parietal bones are passively moulded by many cortical factors (Moss and Young 1960; Bruner et al. 2015, 2017b), while the anterior cranial fossa represents a region of spatial conflict between soft and hard tissues (Lieberman et al. 2000; McCarthy 2001; Bastir et al. 2004; Pereira-Pedro et al. 2017). The fact that in this region the sulcal pattern is particularly imprinted onto the endocranial table further confirms the presence of stress forces due to the fine spatial packing of brain, bone, and orbits. Pronounced sulcal imprints are also observed in the middle cranial fossa, suggesting a similar situation for the temporal lobes.

Limitations and future steps

Network analyses are based on the topological and statistical study of a specific model based on a set of assumptions and criteria (Butts 2009). Accordingly, results specifically refer to the model employed (Rasskin-Gutman and Esteve-Altava 2014). Change of the model can be associated to changes in the general topological parameters, most of all in small networks like the ones used in generalized macroscopic studies. In this study, we only considered the spatial proximity between cortical region, under the rationale of a direct relationship between adjacency and spatial influence. Accordingly, our parameters only describe this aspect of the brain organization. The topological metrics is also sensitive to operational choices and, although basic parameters generally converge on similar conclusions, there are several debates on their specific meanings and applications (e.g. Freeman 1977; Bonacich 1987; Bonacich and Lloyd 2001; Landherr et al. 2010; Ghosh and Lerman 2011, 2014). Therefore, as in any method based on quantitative analyses or numerical modelling, the final results will depend on the sample and variables used in the analysis. In network studies, results strictly deal with the choice of the elements (nodes) and of the criterion of relationship (links) and must be interpreted accordingly (Butts 2009). In our case, however, the anatomical regions are large and topologically consistent, and the criterion is straightforward (spatial contact), so the results are probably general but meaningful. In particular, more connections evidence more spatial constraints and anatomical burden. The morphology of regions with less constraints will be more influenced by intrinsic changes, while the morphology of regions with more constraints will be also influenced by extrinsic spatial factors. This information must be taken into account when discussing the morphological evolution or development of those cortical surfaces. That said, our model does not discriminate between continuity (that is, a proper tissue connection) and contiguity (that is, a physical spatial contact) between anatomical components. Also, for the sake of simplicity, we did not take into account the extension of the contact. An ongoing study is taking into consideration these two additional factors. A second project is extending the analysis to a finer anatomical detail. We have currently restricted this study to the macroscopic regions used to describe evolutionary changes in neuroanatomy, but a finer parcellation will be able to reveal subtler relationships. In particular, internal cerebral components will be crucial to understand the global spatial system. The external (visible) cortical surface is only 1/3 of the total brain surface (Toro 2012), so we must assume that the deeper elements hidden in the folds (2/3) have a major role in constraining and channelling the patterns of growth and development and, accordingly, in the balance of the general brain topology. Finally, in future analyses will be also mandatory to include the rest of the skull as well as non-neural elements of the endocranial cavity (e.g. using interconnected multilayer networks), like the meninges, which may exert a biomechanical tension within the endocranial cavity (Moss and Young 1960).

Conclusion

Brain topology can provide information on the morphogenetic patterns and constraints, bridging microscopic and macroscopic anatomical scales during ontogeny and evolution. Cortical folds, areas, and connections are embedded into a spatial and physical environment that has a major role in the morphogenetic processes of the brain. Too often, evolutionary changes are still interpreted according to the variation of single features, neglecting possible influence of extrinsic factors moulding the geometry and appearance of the anatomical traits. In brain evolution, comparative neuroanatomy, and paleoneurology, strict conclusions in this sense can be misleading, when the general changes in the whole anatomical system are not taken into account. Anatomical network analysis is a useful tool to evaluate possible influences and constraints due to neighbouring and adjacent regions. In this case, our pilot study suggests that in the adult human brain, the frontal lobe morphology is less influenced from topological changes of the posterior brain districts which, in turn, are more reciprocally integrated. This posterior block corresponds to regions which show higher gyrification and, in terms of functional connections, higher hierarchical modularity and more hub areas. The precentral gyrus bridges the anterior and posterior blocks, and the lateral temporal cortex is particularly constrained by the general brain form because of its longitudinal contacts. The parietal cortex has a lower structural burden because of its peripheral position. The model presented here is a general one, which considers only those large cortical and visible districts commonly described in human evolutionary studies. Accordingly, results only refer to the possible spatial interactions between superficial cortical regions, without taking into account internal elements or detailed cranial influences. The topological perspective on brain form outlined here is a first step towards a more integrated view of brain macroscopic organization and evolution, and towards a more comprehensive interpretation of the endocranial evolutionary architecture.

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