Imaging-based parcellations of the human brain

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Abstract | A defining aspect of brain organization is its spatial heterogeneity, which gives rise to multiple topographies at different scales. Brain parcellation — defining distinct partitions in the brain, be they areas or networks that comprise multiple discontinuous but closely interacting regions — is thus fundamental for understanding brain organization and function. The past decade has seen an explosion of in vivo MRI-based approaches to identify and parcellate the brain on the basis of a wealth of different features, ranging from local properties of brain tissue to long-range connectivity patterns, in addition to structural and functional markers. Given the high diversity of these various approaches, assessing the convergence and divergence among these ensuing maps is a challenge. Inter-individual variability adds to this challenge but also provides new opportunities when coupled with cross-species and developmental parcellation studies.

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The organization of the human brain is governed by two fundamental principles: functional integration into large-scale networks, which is realized through long-range connections, and functional segregation into distinct regions, which is realized through local differentiation[1]. Importantly, these two principles are not mutually exclusive but rather jointly form the neurobiological basis of all higher brain functions that arise from interactions between specialized regions. The spatial arrangement of cortical areas and subcortical nuclei presents a highly heterogeneous landscape, and ample evidence suggests that this complex topography is crucial for mental processes[2] and inter-individual differences thereof[3–5]. Accordingly, brain parcellation — that is, delineation of spatial partitions of the brain — is fundamental for decoding the human brain.

The study of brain organization is complicated by evidence of multiple axes of organization according to different neurobiological properties and their measures. For example, microstructure evidences different hippocampal subregions along the medio–lateral axis[6], whereas patterns of long-range interactions vary along the hippocampal anterior–posterior axis[7]. Similarly, the premotor cortex can be distinguished from the adjacent prefrontal and primary motor cortex on the basis of microstructural characteristics[8] and can also be subdivided into ventral and dorsal regions by connectivity and function[9]. Thus, from both a methodological and a conceptual standpoint, understanding human brain organization requires a dual perspective, considering both local properties and connectivity fingerprints[10].

Brain cartography has a long history[11] (BOX 1), over which different properties of brain tissues have been progressively integrated towards the now commonly accepted conceptualization of brain areas[12] as entities that show distinct connectivity, microarchitecture, topography and function[13]. The concept of brain areas is closely related to the perspective of a so-called universal map that has driven the brain cartography field for more than a century[14–16]. However, the goal of creating a universal map is challenged by the complexity of brain organization at several levels and across several axes, as well as the divergence of patterns across different neurobiological properties. Furthermore, substantial inter-individual variability in brain network and areal topography has been documented[17–19] but is still poorly understood, thus challenging the very existence of a universal brain atlas. Hence, the axiom of a universal map that grounds the field of brain cartography remains a matter of conjecture.

Not only can brain parcellations provide fundamental insights into the organizational principles of the human brain, but they are also of great practical relevance as biologically informed strategies of data reduction, enabling information from hundreds of thousands of voxels or vertices to be compressed into manageable sets of nodes reflecting distinct entities. Such reduction is important for some emerging big-data approaches that aim to predict behavioural or clinical phenotypes from brain imaging data[20–23]. Likewise, the study of brain connectivity with tools from graph theory requires a limited set of nodes[24]. Importantly, however, for such aggregation to provide a valid compression, the parcels should reflect a biologically meaningful patterning. This reasoning renders macrostructural characteristics (for example, sulci and gyri; see macroanatomy

Box 1 | **Early brain cartography and histological approaches to brain parcellation**

The very first endeavours to map the human brain in the 19th and early 20th centuries were based on ex vivo investigation of brain microstructure and macrostructure. Flattened out, the cortex is organized vertically, into columns and dendritic bundles, and horizontally, in layers parallel to the pial surface. From the earliest studies, these neurobiological features were observed to vary across the brain. More specifically, properties of these features regularly reveal zones of homogeneity and abrupt changes between zones. Accordingly, the point at which the pattern of a marker — for example, the thickness of cortical layers, the size of pyramidal cells or the extent of myelination — changes represents a border between distinct areas[13,118]. A pioneering cartography work illustrating this approach is the map created by Korbinian Brodmann, widely known as Brodmann areas[14]. Other researchers of this period, such as Cécile and Oscar Vogt, capitalized on different local properties, in particular myeloarchitecture, to define brain areas[119]. In addition, the first localization of brain macrostructure in a stereotactic coordinate system was proposed by Talairach and Tournoux[120].

According to the means of their time, all these cartographers transcribed their observations by manually drawing 2D maps of brain regions on paper. Importantly, these first maps were highly observer-dependent and based on subjective classification criteria and therefore suffer from reproducibility issues[121]. This motivated the subsequent development of observer-independent techniques based on computerized image analysis[122] using a border detection approach[47,77]. Combined with 3D reconstruction and spatial registration of multiple postmortem brains into a standard reference space, this development allowed rigorous investigations of microstructure, providing evidence for more than 200 histologically distinct brain areas[13,123].

Over time, other histological approaches complemented cytoarchitecture and myeloarchitecture, such as immunochemistry or receptoarchitectonic studies (for a review, see REF.[13]). In receptoarchitectonic studies, examining the local density of various transmitter receptors allows the definition of specific 'receptor fingerprints' that differ between cortical areas and also reflect functional relationships[77]. Interestingly, although not all cortical area borders are reflected by changes in all receptor types, those borders that are evident colocalize very well with each other and also with cytoarchitectonic and myeloarchitectonic differences[77]. As histological mapping is performed on directly observable — rather than modelled or inferred — markers, it provides important reference points for mapping the human brain. Conversely, the main drawback of histological brain mapping is the reliance on the use of postmortem specimens, thus precluding any comparison with functional data within the same individual. Moreover, given the labour-intensive preparation of tissue, sample sizes are inevitably and severely limited. However, developments of high-resolution MRI will offer an alternative approach by allowing whole-brain microstructural investigations without sample size restriction.

Large-scale networks
Constellations of brain areas that are strongly connected to each other, presumably subserving specific functions.

Connectivity fingerprints
Patterns of the interactions of brain regions with other brain regions.

Brain cartography
The study of brain organization with the particular objective of representing the organization of the brain as a map of distinct areas.

Brain areas
Brain regions showing specific structure, function and connectivity.

Universal map
A unique division of the brain into individual areas, each having specific structure, connectivity and function, which can be found in all humans.

Graph theory
The use of graphs to study and model relationships between objects with elements such as nodes and edges.

Cytoarchitecture
Tissue composition with regard to cell characteristics.

Myeloarchitecture
The pattern of myelinated fibres.

atlas examples in TABLE 1) notoriously unsuited for such tasks, as they do not converge with the heterogeneity of functional, structural or connectional markers[13,25]. Thus, brain parcellation contributes to a better understanding of brain function and dysfunction not only at the conceptual level but also by providing critical priors for connectomics and large-scale analyses of brain–behaviour relationships.

In spite of the technical and conceptual heterogeneity in the burgeoning field of brain parcellation, for more than a century its fundamental idea has remained to identify components (either topographically distinct regions or distributed networks) that are internally homogeneous with respect to a particular neurobiological measure but that are different from each other. This goal can be achieved by two conceptually distinct approaches: boundary mapping and clustering or factorization. In the boundary mapping approach, a border is detected by localizing the most abrupt spatial changes in the assessed feature using a local border detection (or edge detection) technique. In clustering and factorization approaches, spatial elements (voxels or vertices) are grouped on the basis of their similarity and dissimilarity according to a given marker. Hence, boundary mapping and clustering (or factorization) approaches can be referred to as local partitioning and global partitioning approaches, respectively. Note that here we consider only 'hard partitions' in which each location is assigned to one and only one spatial component of the brain, as opposed to 'soft' partitions[26] (BOX 2).

Almost any parcellation approach can be applied to almost any neurobiological property (TABLE 1). Hence, we can further divide brain parcellation approaches according to the type of marker by distinguishing markers that describe underlying tissue properties (that is, capitalizing on local structural or functional properties) from markers that reflect integration into larger networks (that is, capitalizing on long-range connections). In other words, a further conceptual distinction can be proposed based on whether the parcellation builds on local architecture or function (local properties) or on connectivity fingerprints (global or connectivity properties). In this Review, we discuss the history of brain parcellation and its current state along this taxonomy of two independent dimensions — that is, the marker approach and the partitioning approach (FIG. 1) — and examine conceptual questions regarding the relationships among parcellations derived from different markers.

Parcellation based on local properties

Early efforts to parcellate the brain on the basis of local properties have mostly been histological, using, for example, cytoarchitecture and myeloarchitecture, neurochemical markers or (more recently) receptor expression (BOX 1). However, these approaches usually require postmortem tissue, hence preventing parallel studies of function and leading to the highly laborious examination of only small samples. By contrast, neuroimaging techniques such as MRI allow the acquisition of whole-brain images in vivo, in large samples of individuals.

Table 1 | **Whole-brain or cortical parcellations available for download or visualization**

Name (group or institution)	Brain coverage	Granularity (number of parcels/networks)[a]	Original format (and other formats)	Links	Refs
Macroanatomy					
AAL Atlas	Whole brain	82 parcels	Volume	http://www.gin.cnrs.fr/en/tools/aal-aal2/	102
Harvard–Oxford Atlas	Cerebrum	69 parcels	Volume	Included in the installation package of FSL (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases) and MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron) and can be found here: http://neuro.debian.net/pkgs/fsl-harvard-oxford-atlases.html	138–141
Desikan–Killiany Atlas	Cerebral cortex	70 parcels	Surface	Included in the installation package of FreeSurfer: https://surfer.nmr.mgh.harvard.edu/fswiki/CorticalParcellation	140
Destrieux Atlas	Cerebral cortex	148 parcels	Surface	Included in the installation package of FreeSurfer: https://surfer.nmr.mgh.harvard.edu/fswiki/CorticalParcellation	142
MarsAtlas	Cerebrum	89 parcels	Surface and volume	http://meca-brain.org/software/marsatlas-colin27/	143
Rs-fMRI					
Bellec et al. (2010)	Whole brain	7, 12, 20, 36, 64, 122, 197, 325 and 444 parcels	Volume	https://figshare.com/articles/Group_multiscale_functional_template_generated_with_BASC_on_the_Cambridge_sample/1285615	61
Power et al. (2011)	Cerebrum	14 networks	Volume	https://www.jonathanpower.net/2011-neuron-bigbrain.html	144
Yeo et al. (2011), Buckner et al. (2011) and Choi et al. (2012)	Cerebral cortex, cerebellum and striatum	7 and 17 networks	Surface of cerebral cortex and volume of cerebellum and striatum	Included in the installation package of FreeSurfer: https://surfer.nmr.mgh.harvard.edu/fswiki/CorticalParcellation_Yeo2011, http://surfer.nmr.mgh.harvard.edu/fswiki/CerebellumParcellation_Buckner2011 and https://surfer.nmr.mgh.harvard.edu/fswiki/StriatumParcellation_Choi2012 The 7 and 17 spatially distributed cortical networks have also been converted into 51 and 114 spatially connected parcels, respectively: https://github.com/ThomasYeoLab/CBIG/tree/master/stable_projects/brain_parcellation/Yeo2011_fcMRI_clustering	70,145,146
Craddock et al. (2012)	Whole brain	10 to 1,000 parcels	Volume	http://ccraddock.github.io/cluster_roi/atlases.html	83
Shen et al. (2013)	Whole brain	93, 184 and 278 parcels	Volume	www.nitrc.org/frs/?group_id=51	147
Gordon et al. (2016)	Cerebral cortex	333 parcels	Surface (and volume)	www.nil.wustl.edu/labs/petersen/Resources.html	59
Atlas of Intrinsic Connectivity of Homotopic Areas	Cerebrum	384 parcels	Volume	In the installation package of AAL toolbox (http://www.gin.cnrs.fr/en/tools/aal-aal2/) and MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron) and can be found here: https://omictools.com/atlas-of-intrinsic-connectivity-of-homotopic-areas-tool	148
Wang et al. (2015)	Cerebral cortex	18 networks	Surface	Pre-compiled code for individual-specific network parcellations: http://nmr.mgh.harvard.edu/bid/DownLoad.html	18
Gordon et al. (2017)	Cerebral cortex	Subject dependent	Surface	Individual-specific network and areal-level parcellations for the Midnight Scan Club subjects: https://www.openfmri.org/dataset/ds000224/	97
Schaefer et al. (2018)	Cerebral cortex	100, 200, 400, 600, 800 and 1,000 parcels	Surface (and volume)	https://github.com/ThomasYeoLab/CBIG/tree/master/stable_projects/brain_parcellation/Schaefer2018_LocalGlobal	54

Table 1 (cont.) | **Whole-brain or cortical parcellations available for download or visualization**

Name (group or institution)	Brain coverage	Granularity (number of parcels/networks)[a]	Original format (and other formats)	Links	Refs
Rs-fMRI (cont.)					
Kong et al. (2018)	Cerebral cortex	17 networks	Surface	Code for individual-specific network parcellations: https://github.com/ThomasYeoLab/CBIG/tree/master/stable_projects/brain_parcellation/Kong2019_MSHBM	5
Other					
PrAGMATiC, based on task fMRI	Cerebral cortex	320 parcels	Volume (and surface)	For visualization only: http://gallantlab.org/huth2016/	33,149
Brainnetome, based on PDT	Cerebral cortex and subcortical structures	246 parcels	Volume	http://atlas.brainnetome.org/download.html	103
Varikuti et al. (2018), based on sMRI (SC)	Whole brain	2 to 500 parcels	Volume	http://anima.fz-juelich.de/studies/Varikuti_NMFBrainAge_2018	23
HCP Multimodal Parcellation, Glasser et al. (2016)	Cerebral cortex	360 parcels	Surface	https://balsa.wustl.edu/WN56	16

AAL, automated anatomical labelling; fMRI, functional MRI; FSL, FMRIB Software Library; HCP, Human Connectome Project; PDT, probabilistic diffusion tractography; rs-fMRI, resting-state functional MRI; SC, structural covariance; sMRI, structural MRI. [a]Granularity refers to the number of parcels, clusters/components or networks. Only parcellations or segmentations based on MRI data are reported in this table. Manual segmentation and atlases based on other techniques (for example, Brodmann atlas) are not included here. The atlases are organized by modality and by publication date within each modality.

Different types of parcellation based on local properties. The MRI approach that is most similar to histological methods is the mapping of myelin[27]. One popular estimate of myelin content that is used to create myelin density maps is yielded by the T1-weighted:T2-weighted ratio[28]. Myelin markers can be used to disentangle primary areas from associative areas. For example, V1 and V2 delineated using functional imaging and histological measures are much more heavily myelinated than higher visual cortical areas[28] (FIG. 2). However, MRI-based (and histology-based) myelin mapping for cartography purposes has been mostly limited to auditory[29], visual[30] and sensorimotor[28] regions. Owing to a lack of distinctiveness in myelination densities across the association cortex, the application of myelin mapping for cartography beyond the sensorimotor cortex often requires the incorporation of additional information, such as cortical thickness or cytoarchitecture[28].

Other local markers that can be used for parcellation are functional signals in response to specific external stimulation or mental tasks. Following the modelling of local responses across time or across different contexts, distinct areas can be disentangled based on their response patterns. The most widespread application of such approaches is visuotopic mapping[31] (FIG. 2). Importantly, visual areas defined based on functional MRI (fMRI) visuotopic mapping correspond well with the areas defined by cytoarchitecture, supporting the validity of using fMRI signals for brain parcellation (FIG. 2).

Visuotopic mapping
The identification of visual areas based on differential cortical responses to different visual stimuli. An example of a mapping stimulus would be a rotating sector of a flashing checkerboard.

However, beyond visuotopic mapping, parcellation based on local functional signal has been surprisingly rarely explored. Although parcellation on the basis of local functional responses presumably represents a powerful approach to understand brain organization in terms of areas and networks, recording the complete repertoire of functional responses remains a major challenge. Accordingly, parcellations based on functional response have thus far been limited to a particular set of tasks or a comparably confined brain region. For example, one study parcellated the brain into functional networks by clustering task-evoked responses during finger tapping[32]. Another recent study proposed a parcellation based on response to semantic content during several hours of story listening by seven individuals[33] (TABLE 1). Nevertheless, the richness of these recordings probably did not come close to reflecting the entirety of the brain's functional repertoire. Together with the small sample sizes used, this point raises the question of the universality of the resulting parcellation.

To tackle these limitations directly, meta-analytic approaches have been used to define subregions within, for example, the insular cortex[34] on the basis of the convergence of activation during tasks involving different cognitive domains, such as motor tasks and cognitive or affective processing. This approach was recently automated in a clustering procedure, thus highlighting the potential to parcellate cortical and subcortical regions by local activation data[35] (FIG. 1). Importantly, the extension of such approaches to other brain regions (such as the hippocampus) would require an extensive repertoire of functional responses, complicating developments. Recent progress in the aggregation of activation data[36–38] may help to overcome these challenges. Whole-brain maps of local response patterns to various task conditions and stimuli may thus be computed from large sets of activation data. Such an approach would enable the delineation of brain areas based on their pattern of activations across many dimensions of behavioural tasks (depending on the task, stimulus, response and so on). However, this approach might be biased towards tasks that can readily be applied in the scanner and by the fact that activations are

Box 2 | **Defining brain components with clustering and factorization**

Neuroimaging data typically consist of values for thousands of voxels or vertices. Different approaches can be used to identify latent patterns of spatial organization in the data. These approaches are frequently referred to as unsupervised learning because the spatial pattern is unknown a priori, in contrast to supervised learning approaches, in which the true assignment of each data point is known a priori. In the framework of brain parcellation, two main unsupervised learning approaches can be distinguished: clustering and factorization. Clustering is used to group similar voxels or vertices together and apart from other, different voxels or vertices, whereas factorization organizes the data sets into dimensions and components that best represent variations in the data. Please note that this distinction is only for didactic purposes, as from a mathematical point of view, some clustering algorithms (such as k-means) can be seen as matrix factorization problems, and some factorization approaches (such as non-negative matrix factorization (NMF)) are frequently used within a clustering perspective. Accordingly, some variants of k-means and NMF are mathematically equivalent[124].

As mentioned above, from a more conceptual point of view, clustering approaches are typically used to group a set of objects into different groups in such a way that objects from the same group are more similar to each other than are objects from different groups. The clustering is based on the mathematical distance (that is, the dissimilarity) between the elements (in this context, voxels or vertices), computed usually based on their connectivity fingerprints. Elements are grouped into clusters such that two elements that have similar connectivity fingerprints are assigned to the same cluster and, conversely, elements that have highly dissimilar connectivity profile are assigned to different clusters. The most widely used clustering algorithms in the connectivity-based parcellation (CBP) field are k-means clustering, spectral clustering and hierarchical clustering (see REF.[53] for a comparative study).

Factorization approaches, by contrast, extract latent dimensions from data or find a low-dimensional representation of the elements' profiles. The classical matrix factorization is principal component analysis (PCA), which identifies the main dimensions along which different data points vary.

By contrast, NMF[19] approaches constrain the decomposed components to be strictly non-negative. Together with additional constraints (for example, that components should be mostly zero, except in a small number of locations), NMF often yields a part-based decomposition of the data. For example, when applied to face photographs, NMF will yield components that represent distinct facial parts (such as nose, eyes and mouth). Accordingly, NMF has an inherent clustering property, which allows the parcellation of the brain into localized components that mirror brain regions and has thus been successfully used for whole-brain partitions[23,125].

Importantly, all methods have distinct advantages and disadvantages, and thus the choice of approach should depend on the data at hand, as well as the objective of the parcellation. For example, NMF can model many different data distributions owing to the flexibility of matrix factorization, whereas k-means attempts to capture spherical clusters (in feature space). However, standard k-means yields a hard clustering, whereby each element (voxel or vertex) is uniquely assigned to either one cluster or another, whereas factorization approaches (such as fuzzy or soft clustering[71]) do not yield a clear, deterministic assignment. In soft partitioning, any given element (voxel or vertex) can be assigned to several groups by obtaining, for example, the probability of assignment to each group. However, a final spatial hard partition can be obtained when the scores from fuzzy clustering or factorization are integrated in a 'winner-takes-all' approach[126]. Currently, there are no clear guidelines for the use of these techniques in brain parcellation, owing to a lack of comprehensive empirical and theoretical studies that evaluate the advantages and limitations of each approach and variants thereof for different data sets and parcellation purposes.

Non-negative matrix factorization
A multivariate statistical approach to factorize data into components promoting a part-based representation of the data.

more frequently reported in certain brain regions (for example, the insula) than in others[39]. Furthermore, a fundamental limitation of meta-analysis is the spatial blurring that is inherent to combining participants from studies across different laboratories and coordinate systems. Therefore, extensive recordings of activation paradigms in a small number of participants[40] and extensive aggregation of activation studies are highly complementary.

Future challenges for parcellations based on local properties. Although MRI-based measurements of the brain's local properties, such as myelination or functional responses, are less time-intensive and labour-intensive than ex vivo microstructural examination, their clear drawback is that the respective properties are not directly observable but must be inferred from the measured data, rendering the ensuing brain maps contingent on the model for measuring these properties. Nevertheless, as illustrated in FIG. 2, the delineation of cortical areas based on MRI-measured local properties converge with those from histology-based architectonic approaches, clearly supporting the biological validity of the former[41]. Furthermore, the ongoing development of high-field scanners should provide the possibility of MRI-based architectonic parcellation[41,42]. That is, in the future, parcellations could capitalize on imaging properties that are closer to the microstructure of the brain, such as the laminar patterns in the human medial temporal cortex that were observed through ex vivo MRI[43]. Such advances could provide an important bridge to histological investigations in the same specimen[44–46]. Thus, brain parcellation based on local properties not only has a storied tradition (BOX 1; FIG. 1) but also should see substantial future progress[42].

Parcellation based on connectivity

Local differentiation and network integration are complementary characteristics of brain organization[47], as each brain area is characterized by its regional makeup and its specific interactions with other regions[48]. Thus, a connectivity profile distinct from neighbouring tissue has been a longstanding criterion for defining a cortical area. Accordingly, information on functional interaction and anatomical connectivity, which reflect functional integration, can be used for mapping the regional segregation of a brain area[48].

We note that connectivity is itself a heterogeneous concept, referring to, for example, functional dependencies (functional connectivity) or a physical connection (structural connectivity). To provide an overview on the key lines of research, we focus on the three approaches that have been used most frequently in brain parcellation to date (BOX 3): the estimation of anatomical connectivity by tractography on diffusion-weighted images[49]; task-free functional connectivity assessed through resting-state echo planar imaging time series correlations[50]; and co-activations during task performance revealed through meta-analytic connectivity modelling[51,52]. These approaches all allow the inference of voxel-wise or vertex-wise structural or functional connectivity with other brain locations, which in turn allows the computation of a connectivity fingerprint[15]. Brain areas can be delineated directly from their functional connectivity or from their whole-brain connectivity fingerprint using either boundary mapping or clustering approaches. Of note, the parcellation technique can, in theory, be applied to any connectivity measure, such as structural covariance, although the latter has been less commonly used (BOX 3). Thus, the most frequently used connectivity-based parcellations are based on

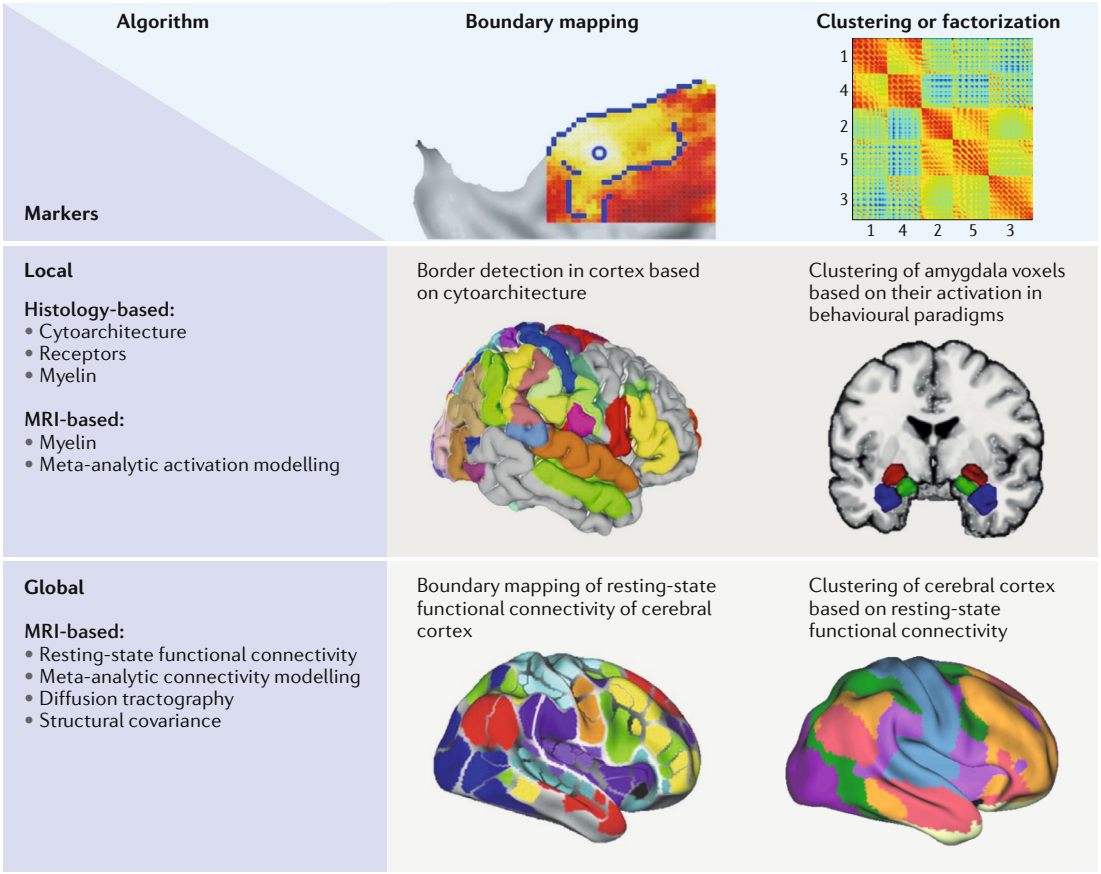

Fig. 1 | **A 2D taxonomy of brain parcellation approaches.** Parcellation approaches can be classified along two dimensions. The marker dimension ranges from markers that capitalize on local properties of brain tissues, such as cell body density or functional MRI (fMRI) signal time course, to markers that capitalize on connectivity fingerprint[48] across the brain. The other dimension categorizes parcellation approaches according to the algorithm used for defining parcels, distinguishing local boundary mapping techniques[55] from global clustering (or factorization) approaches. At the top of the table are two examples of such approaches: on the left (under 'Boundary mapping'), cortical regions were partitioned according to their resting-state functional connectivity[55] and, on the right (under 'Clustering or factorization'), a matrix reveals five distinct clusters of voxels in area 44 that show similar patterns of whole-brain co-activation, measured using fMRI/PET during different tasks[72]. In theory, any type of parcellation approach can be used for regional or whole-brain parcellation. Accordingly, each cell illustrates an example application of a local (left column) or global (right column) parcellation technique to markers of local (top row) or global (bottom row) properties. Top left cell: regions of the JuBrain atlas identified by border detection according to architectonic properties. Top right cell: parcellation of the amygdala into subregions with a clustering approach applied to behavioural meta-analytic data[35] (activation studies across a wide range of paradigms probing cognitive, motor and socio-affective functions from the BrainMap database[36]). Bottom left cell: parcellation of the cerebral cortex based on boundary mapping applied to resting-state functional connectivity[59]. Bottom right cell: parcellation of the cerebral cortex into functional networks based on clustering applied to the resting-state functional connectivity[70]. "Boundary mapping" heading image adapted with permission from REF.[55], Elsevier. "Clustering or factorization" heading image adapted with permission from REF.[72], Elsevier. Left-hand cell images adapted with permission from REF.[11], Elsevier. Top-right cell image adapted with permission from REF.[35], Elsevier. Bottom-right cell image adapted with permission from *J. Neurophysiol.*, Yeo, B. T. et al., **106**, 2011, 1125–1165 (REF.[70]).

Spectral clustering
A clustering approach based on the eigenvectors of the matrix of similarity (such as connectivity) between brain locations (voxels or vertices). The term 'spectral' refers to the spectrum (eigenvalues) of the similarity matrix.

Hierarchical clustering
A clustering approach that disentangles clusters in a hierarchical fashion, in such a way that relationships between clusters can be visualized as a tree structure.

Principal component analysis
A multivariate statistical approach to factorize data into orthogonal components that best represent variance in the data.

Fuzzy or soft clustering
A clustering approach in which points are not assigned to one single group but have a fractional value that represents their relative membership in each group.

structural connectivity inferred from diffusion MRI, resting-state functional connectivity and task-based functional connectivity.

Boundary mapping versus clustering. In contrast to histological brain mapping, which has largely relied on border detection, connectivity-based parcellation (CBP) has mainly used clustering approaches to group voxels, such that connectivity fingerprints are as similar as possible within a group of voxels and as different as possible between groups of voxels. The resulting clusters represent different brain areas or networks. All methods have their inherent assumptions, strengths and limitations, and the choice of algorithm imposes those assumptions on the resulting parcellation. Accordingly, different algorithms can yield different parcellations on the same data[25,53,54]. To date, relatively few studies have applied boundary mapping techniques to resting-state functional connectivity markers[55–59] (FIG. 1) or clustering to markers of local properties[32,35]. There are, however, no technical or conceptual reasons for the dominant partnering of local properties and border detection on the one hand and the pairing of connectivity markers and clustering approaches on the other. Rather, either

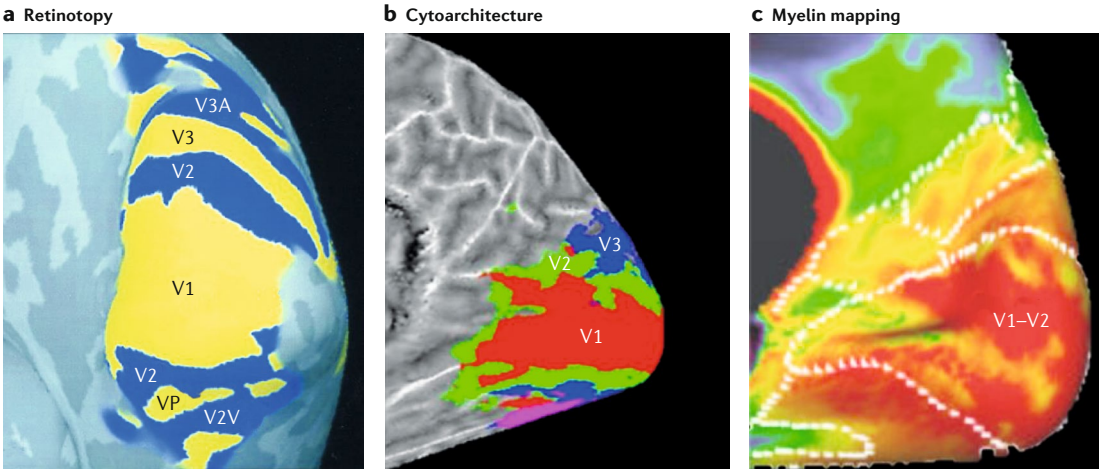

Fig. 2 | **Mapping of visual areas with local markers.** Different parcellation approaches converge towards similar delineations of visual areas. Visuotopic mapping (based on functional MRI (fMRI)) and cytoarchitecture mapping (based on ex vivo brain tissues) show consistency in the delineation of V1 from V2. Furthermore, myelin mapping (based here on MRI) distinguishes V1 and V2 from higher visual areas in a similar way to visuotopic and cytoarchitecture mapping. **a** | Delineation of V1 and V2 based on fMRI visuotopic mapping[136]. **b** | Mapping of visual areas based on cytoarchitecture[137]. **c** | Myelin mapping, based on MRI T1-weighted:T2-weighted ratio[28], differentiates V1 and V2, which are heavily myelinated (red), from higher visual areas (such as V3), which show lower myelin ratios (yellow and green). Part **a** is adapted with permission from REF.[136], National Academy of Sciences. Part **b** is adapted with permission from REF.[31], Elsevier. Part **c** is republished with permission of Society for Neuroscience, from Mapping human cortical areas in vivo based on myelin content as revealed by T1- and T2-weighted MRI. Glasser, M. F. & Van Essen, D. C. **31**, (2011)[28]; permission conveyed through Copyright Clearance Center, Inc.

type of neurobiological property may be assessed using either approach; the current predilection seems historically driven.

Indeed, boundary mapping and clustering can be considered complementary for capturing different aspects of brain organization and as such were very recently integrated into a single hybrid model[54]. This was done by using an objective function that promoted the assignment of vertices with similar connectivity profiles to the same region (that is, clustering) but at the same time encouraged the assignment of spatially adjacent vertices with different profiles to different regions (that is, boundary mapping). As illustrated in Supplementary Figure 1, the resulting brain parcellation outperformed local and global approaches in terms of the homogeneity of the functional signal within the derived regions and also captured topographic organization in sensorimotor and visual areas. Thus, combining local border detection with clustering may be a promising direction for future brain parcellations.

Examples of connectivity-based parcellations. CBP was first performed on structural connectivity markers estimated from diffusion MRI. Behrens et al.[49] and Johansen-Berg et al.[60] computed probabilistic tractography for each seed voxel in the thalamus and medial frontal cortex, respectively, and then grouped these voxels according to their connectivity profiles. The resulting thalamic subregions corresponded to nuclei identified by histological studies, and spatial clusters in the medial frontal cortex matched the supplementary and pre-supplementary motor areas defined by task activation, providing important face validity. In another study, CBP applied to resting-state functional connectivity markers[55] demonstrated the existence of sharp local transitions in functional connectivity patterns across the cortex. Following these pioneering studies, CBP based on resting-state functional connectivity markers or on probabilistic tractography has been widely applied. Resting-state functional connectivity has proved particularly popular and accessible for estimating connectivity and has already been widely used for parcellation not only at the areal level but also at the network level, while still representing the focus of technical developments[61,62].

Soon after, CBPs based on meta-analytic connectivity modelling[63–65] and on structural covariance[64,66] data were also introduced. As a proof of concept, meta-analytic connectivity modelling was first used to delineate the pre-supplementary motor area and the supplementary motor area[65], and both approaches (CBP based on meta-analytic connectivity modelling and CBP based on structural covariance) were then used to parcellate the insula[63,64]. Meta-analytic connectivity modelling has since been extensively used to parcellate cortical regions and subcortical structures, whereas structural covariance has been only sparingly used. The relatively limited use of the latter approach may relate to its complicated interpretation; it is based on structural data but used as a proxy for functional interactions. Importantly, CBPs based on different markers seem to converge towards a similar pattern of brain organization[64,67], suggesting that they capture robust aspects of brain topography. Nevertheless, we should note that often such convergence was explicitly searched for or requested as a proof of concept, and some evidence suggests that at higher granularity, partitions based on different connectivity

Echo planar imaging
An MRI sequence used for functional and diffusion imaging.

Meta-analytic connectivity modelling
A method that aims to model functional connectivity in the brain based on a co-activation pattern across various activation studies.

Probabilistic tractography
An approach to estimate white-matter tract pathways in the brain from diffusion MRI images.

Structural covariance
The pattern of covariations in measures of morphometry (such as grey-matter volume) across brain regions.

Box 3 | **Main connectivity measures used for parcellation**

Traditionally, the term 'connectivity' refers to physical connections via white-matter tracts, which can be demonstrated using invasive tracing techniques in experimental animals or ex vivo fibre-dissection methods. Moreover, structural connectivity can also be estimated using tractography based on diffusion-weighted images[127] (although see REF.[128]). By contrast, functional relationships between different parts of the brain may be revealed by correlating the time series of signals from different voxels or vertices during task performance or, more commonly, in the absence of a behavioural task — that is, in the resting state[129]. Notably, anatomical connectivity and functional connectivity represent very broad concepts with many different measurement and computation approaches, each carrying its own advantages and challenges, as well as potentially unique contributions, to multimodal brain-mapping endeavours. The four approaches assessing connectivity most frequently used in brain parcellation are resting-state functional connectivity, meta-analytic connectivity modelling, diffusion tractography and structural covariance (see the table).

Meta-analytic connectivity modelling reflects task-based functional organization estimated from the co-activation patterns of voxels across many studies, whereas structural covariance reflects functional coupling that is suggested by concurrent morphological variations across a group of subjects. Both approaches rely on covariation across a population sample (structural covariance) or multiple group studies (meta-analytic connectivity modelling), in contrast to probabilistic diffusion tractography and resting-state functional connectivity, in which measures are inferred independently for each subject. Within the structural versus functional taxonomy, structural covariance is in an ambiguous position, as it is a proxy for functional connectivity but inferred from statistical covariance in the brain structure.

Connectivity-based parcellation (CBP) was initially developed for connectivity computed at the individual subject level but was quickly extended to connectivity inferred from statistical dependencies across a data set. Each type of connectivity measure has its own strengths and limitations and is prone to particular artefacts. For example, diffusion tractography might yield spurious results[128] owing to several factors. Crossing fibres might cause the tractography model to 'jump' between tracts, leading to false positives. Furthermore, diffusion tractography shows a gyral bias: more connections may be detected, hitting the crown of a gyrus rather than its wall, owing to the intrinsic geometry of cortical folds[130,131]. Conversely, tractography may also fail to infer the connectivity of grey-matter voxels or vertices near pial surfaces that are particularly spatially distant from white matter[68]. In addition, the limited spatial resolution of current tractography methods can potentially result in false negatives (missed connections), particularly with regard to small white fibres[132].

Functional connectivity approaches are less affected by geometric factors, but signal loss and distortion are nevertheless common with functional MRI (fMRI) near air–tissue interfaces. Furthermore, functional connectivity approaches are based on statistical dependencies between regions (either at the subject level in resting-state functional connectivity or at the group level in meta-analytic connectivity modelling and structural covariance) and are therefore sensitive to confounding factors. For example, fMRI, particularly resting-state fMRI (rs-fMRI), is sensitive to various systemic influences, such as motion, respiratory and cardiovascular noise[133,134]. Task-based fMRI might be less influenced than rs-fMRI by physiological noise but is usually more limited than the latter in terms of sample size (for example, the mean sample size across experiments in the BrainMap database[36] is 12 subjects). Although aggregation of studies (that is, in meta-analyses) can overcome the size limitation of individual studies, averaging across subjects and studies with different stereotaxic spaces limits spatial precision. Given that several known and unknown factors might potentially result in artefactual patterns, one approach for increasing the likelihood of a parcellation representing some true biological property is to retain only patterns that are consistent across markers and methods.

Type	Data measured	Main method	Variant methods	Parameters	Refs
fMRI and PET imaging (functional)					
Task-based fMRI and PET	Activation during task	Meta-analytic connectivity modelling	Within-fMRI study functional connectivity	• Task domains • Map or peak data	65
Resting-state fMRI	Signal fluctuations at rest	Cross-time correlation in signal fluctuations		• Signal denoising • Target voxels or ROI	55
Imaging of co-plasticity (structural)					
Anatomical MRI	Structural variation in morphology in anatomical scan	Cross-subject correlation in grey-matter volume (structural covariance)	Cortical thickness[135]	• Segment modulation • Smoothing • Target voxels or ROI	64,66
Structural or anatomical					
Diffusion MRI	Estimation of fibre direction	Probabilistic diffusion tractography	Deterministic tractography	• Seed WM masking • Target voxels or ROI	49

fMRI, functional MRI; PET, positron emission tomography; ROI, region of interest, WM, white matter.

Crossing fibres
Individual white-matter fibres whose spatial direction result in points where they meet or cross each other, complicating the estimation of their respective paths.

k-means
A clustering algorithm that divides a set of data points into k clusters by iteratively optimizing the definition of each cluster centroid and data points assigned to the clusters.

measures tend to diverge[64,68]. Below, we briefly discuss challenges associated with CBP and new technical developments before returning to the issue of divergence and convergence between partition schemes based on different markers.

Challenges associated with connectivity-based parcellations. Parallel with the increase in the range of markers, CBP has undergone rapid development, which has produced divergent methods, leading to a rather heterogeneous literature. In fact, there are hardly any examples of CBP papers using the same approach. These technical developments and the ensuing challenges are reviewed elsewhere[69] but, here, we wish to highlight one critical aspect: the issue of selecting the number of clusters or parcels. First, we note that this may represent an ill-posed problem, as the brain has a multilevel organization, and therefore, there may be no right number of parcels[61,70]. Instead, different granularities may reflect different levels of brain organization. Second, it must be remembered that clustering algorithms such as k-means can partition any data set into any number of clusters[71]. In combination with a lack of biological ground truth, the question of how many clusters or parcels to select has necessitated the development of evaluation procedures. Many studies have used internal information; that

is, information within the data. For example, considering that a good clustering should maximize variance between clusters and minimize variance within clusters, the ratio of these variances can be used to characterize cluster separation and to select the optimal number of clusters. Such internal information criteria mainly target the quality of the yielded clustering when considered purely from a technical point of view — that is, within the framework of an unsupervised learning problem. Although these criteria have been frequently used in CBP studies[72–74], a good clustering from a data representation perspective might not necessarily represent a good partition with regards to the neurobiology that the approach aims to reveal — particularly in the presence of, for example, structured noise or outliers.

Consequently, there is increasing interest in evaluation criteria for assessing parcellations that go beyond characterizing the quality of data representation. For example, assuming that partitions driven by biological truth should be more stable across different samples, reproducibility may indicate biological validity. Many studies have hence investigated stability across re-sampling and reproducibility across independent samples to propose optimal partitions[70,75]. Along the same lines, some recent studies have capitalized on the richness of technical variants (that is, the use of different data preprocessing and/or clustering algorithms) to examine the robustness of the parcellation scheme across different analyses[22,31]. The underlying idea here is that a partition scheme that is constant across different techniques is likely to be driven by the underlying neurobiology rather than methodological effects. Nevertheless, because such resampling methods do not rule out the influence of consistent artefacts within the same measurement technique, evidence of convergence across different markers has also more recently been used for so-called cross-modal validation[67,68,70,76]. Thus, in the absence of apparent ground truth, current parcellation work capitalizes on replication, robustness and convergence as proxies for biological validity.

Divergence between properties

The idea that different neurobiological properties should show similar patterns of organization was already noted in 1925 by von Economo and Koskinas and has remained a fundamental axiom of brain mapping. As written by Zilles and colleagues[77] in 2002, "all these architectonic and functional imaging studies support the hypothesis of a correlated structural and functional subdivision of the cortex." Such convergence across properties is indeed frequently observed (FIG. 2). Accordingly, especially with the emergence of CBP, convergence with previous brain maps (particularly from cytoarchitecture) has been used to argue for the validity of newly developed methods. We stress, however, that no property, be it resting-state connectivity, cytoarchitecture, diffusion tractography or task-based activation patterns, should be considered conceptually superior to any other modality, as each represents its own specific window into the topographic organization of the human brain. The prevailing notion that there is a gold-standard parcellation method thus seems misleading. Rather, the critical question is how to examine and interpret the convergence and divergence across parcellation results.

Although consistency across neurobiological properties certainly instils confidence in the robustness of a parcellation, we note a confusing development. There seems to have been a gradual shift from providing arguments that a newly conceived method may identify meaningful patterns towards the notion that parcellations must necessarily converge if they are to be considered biologically relevant[41,78]. This notion is in stark contrast to the fundamental idea that different properties reflect different aspects of brain organization[79]. In fact, divergences in the topographical maps evidenced by different markers can actually be found quite frequently in the literature, although they are rarely highlighted[80]. For example, histological features mainly show an organization of the hippocampus along the medial–lateral axis[6], whereas connectivity markers will primarily reveal an organization along the anterior–posterior axis[81,82]. Notably, such differences are largely irrelevant from a data compression perspective, as the best representation of the data is specific to the data in hand and to the purpose of the representation[11,83]. For example, a CBP derived from resting-state functional connectivity provides a good condensed representation of voxel-wise data for subsequent analyses of fMRI signals, with resulting parcels being more homogeneous in terms of resting-state signal than, for example, cytoarchitectonic areas[83].

From a conceptual view, however, such differences between topographical maps that have been derived using different markers arguably deserve more attention than they have received up to now. The fact that each neurobiological property represents a unique window into brain organization suggests that several different, equally valid maps can be derived from the analysis of different markers, such as cytoarchitecture, connectivity or function. Furthermore, this conceptualization implies that parcellation based on any given characteristic (such as cytoarchitecture) cannot be used as a completely faithful surrogate for parcellation based on another characteristic (such as anatomical connectivity)[44,84], although it can be expected to have some predictive value (see below).

Nevertheless, inferences on brain organization that are based on any one specific marker in isolation might also be difficult because all methods are susceptible to artefacts. In particular, MRI-based markers indirectly represent biological features (BOX 3), whereas analyses of histological sections are susceptible to geometric distortions resulting from tangential sectioning. Hence, one approach for increasing the likelihood that a parcellation represents a biological property of the brain is to retain only those patterns that are consistent across parcellations based on different markers and methods, even though this approach comes at the cost of potentially missing important aspects of brain organization not revealed by all markers and methods.

Multimodal approaches

Although the idea of integrating different approaches towards a universal whole-brain (or cortical) map has been around for many years[12], the perspective has been only recently concretized in humans[16,85]. Although we

refer to these approaches as 'multimodal', this term should not be taken as referring to different MRI modalities but more generically to studies investigating different markers for parcellation, be they MRI-based (such as resting-state functional connectivity) or not (for example, based on a receptor fingerprint).

First endeavours of multimodal approaches. Several studies have derived multimodal parcels by retaining the spatial overlap between clusters from unimodal parcellations. For example, resting-state functional connectivity, meta-analytic connectivity modelling and probabilistic tractography parcellation schemes were superimposed to derive robust parcels in the superior parietal lobule[86], in the dorsal premotor cortex[68] and even in a small subcortical structure, the nucleus accumbens[87]. Thus, the cluster conjunction approach has provided encouraging results for brain cartography in terms of representing robust, fundamental units[11].

However, such conjunction allows unequivocal mapping only when all unimodal parcellations reveal a similar pattern, whereas the procedure for dealing with substantial discrepancies between unimodal parcellations remains an open challenge. Most previous studies chose to exclude ambiguous voxels, but doing this can lead to a fragmented and incomplete map. Furthermore, we anticipate that when a convergence between partition schemes based on different markers can be observed, it will be restricted to subdivisions at certain spatial scales[64,68], thus enforcing the conjunction at a level of partitions that might not be optimal (for example, less stable) for each unimodal partition when considered in isolation. Thus, there is no guarantee that this approach could be successfully applied to the whole brain and yield a biologically valid map.

One strategy to avoid such a situation lies in multimodal integration before partitioning. Using a semi-automated border identification approach, an innovative integration of MRI-derived local and connectivity measures into a unique parcellation was recently performed[16]. As a fully automated detection of borders is prone to false positives (because abrupt changes in marker distribution can be driven by artefacts), a trained (human) observer supervised the procedure and ultimately accepted or rejected each automatically detected border. This approach has the advantage of being able to integrate decades of prior knowledge on brain organization but conversely comes with the drawback that a priori knowledge and expectations of brain organization may bias the ensuing parcellation.

Challenges in integrating properties. An important but underappreciated aspect of multimodal brain parcellation is the fact that different properties should be expected to provide complementary information about regional brain organization[80]. Arguably, only a combination of different measures may allow a true understanding of topographic organization in the human brain. However, three sub-goals may potentially conflict here. First, a multimodal approach should retain information relating to each property. Second, a multimodal approach should neutralize artefacts or spurious patterns that occur in only one measure. Third, the approach should be data-driven to minimize potential biases from a priori and subjective expectations. These are potentially contradictory requirements because a pattern observed in only one modality could reflect a biological aspect that is uniquely captured by that modality or an artefact of the technique. In turn, artefacts can be detected by human inspection, but such intervention is ultimately observer-dependent and may hinder the discovery of new patterns that are not expected from previous literature. Considering these issues, we discuss below two potential strategies to maximize the information retained and to minimize manual intervention.

Maximizing the number of modalities. One basic axiom is that different modalities reflect the many dimensions along which the brain is organized. For example, the frontal lobe is organized along rostro–caudal, ventro–dorsal and medial–lateral axes[88]. Let us accordingly consider three dimensions A, B and C. Suppose a given marker predominantly reflects dimension A; to a lesser extent, dimension B; and to an even more minor extent, dimension C. By contrast, another marker might mostly reflect dimension B; to a lesser extent, dimension A; and to even lesser extent, dimension C. Integrating both modalities would maximize the likelihood of capturing brain organization along both dimensions A and B. Such integration would also offer greater insights into dimension C than either of the modalities considered in isolation. However, the integration of modalities might still not optimally represent brain organization along dimension C. An additional modality sensitive to dimension C would be necessary to fully capture this last dimension.

In other words, we expect that the higher the number of different modalities is, the higher the chance to fully capture each dimension or organizational aspect. This strategy would not only promote an optimal coverage of the multiple organizational dimensions of the brain but also contribute to disentangling true neurobiological aspects from artefacts with minimal human intervention. We therefore argue that a multimodal approach should maximize the number and the diversity of modalities. This pertains particularly to the integration of structural, functional and connectional measures across both MRI and, importantly, histological measures. To the best of our knowledge, such integration has not yet been achieved. Thus far, the few published multimodal studies have focused exclusively on MRI-based features[16,68,86,87,89], and integration of histological features with MRI-based features has been performed in only one specimen[85]. For example, the integration of histological myelin maps with MRI-derived proxies thereof has been unexplored to date, but such integration would provide at least some protection against method-specific artefacts or biases.

Towards a multimodal map with predictive value. The integration of different markers poses technical challenges, and how divergent parcellations should be conceptualized also remains an open topic. That is, if different properties, such as microstructure and

long-range connectivity, indeed reflect different organizational dimensions, how should a multimodal map of cortical areas be defined? Although certainly a premature idea at the current stage, we suggest that an optimal representation of multiple divergent parcellations is defined by an 'or' combination of unimodal borders. Concretely, wherever the local information-processing infrastructure or the pattern of interactions changes, a new region should be defined. Such an approach might potentially contribute to disentangling small regions, called domains, that have been observed in invasive studies in non-human primates and that are hypothesized to exist in humans. The primary example of domains are separable entities in the posterior parietal cortex, primary motor and premotor cortex that seem to be related to different kinds of movements (for example, defence of the head) and could support close functions in humans, such as protective behaviour of peripersonal space[90,91]. An 'or' combination across a multimodal map might help to disclose those small entities but could also include spurious borders owing to modality-specific artefacts.

One avenue to empirically evaluate different methods for combining multiple maps is through supervision on a meta-level by testing which approach holds the highest predictive value for brain function and dysfunction. In other words, an optimal multimodal map should provide the best prediction of task-related activations, behavioural phenotype and/or clinical symptoms. For example, a map that divides the hippocampus along both the anterior–posterior axis (based on connectivity) and the medial–lateral axis (based on histology) might better predict clinical phenotype (in Alzheimer disease or major depressive disorder) with supervised machine learning than either connectivity-based or histological maps alone.

We note that this view is in line with a long tradition in brain cartography, as even early brain-mapping books sought to relate partitioning to behavioural (dys-) function. For example, intracranial stimulation in two distinct areas in non-human primates induced different patterns of interference with animal behaviour[92]. In humans, invasive cortical stimulation mapping in surgical patients mirrors such functional validation[18]. The neuropsychological lesion–deficit approach can also contribute to the distinction of different brain areas, despite several limitations[93]. Alternatively, the validity of functional maps can be tested in surgical patients based on their ability to predict post-surgical deficits. Hence, being more controlled than the post hoc lesion approach, investigation in surgical patients can be seen as a gold standard for functional mapping. This deficit-based view should then be complemented by a detailed, again multimodal characterization of the physiological properties of the delineated areas in order to build a functionally comprehensive atlas upon the spatial parcellation scheme.

Multimodal and unimodal maps. Importantly, testing the validity of a multimodal map based on its predictive value remains relatively unexplored. Given that each type of neurobiological property is differentially informative[80], the concept of such map may itself be open to debate. For example, Glasser et al.'s[16] multimodal parcellation gives an excellent separation between motor and somatosensory areas but does not provide somatotopic or visuotopic information. Accordingly, the interpretability and relevance of such a map can be debated, although the latter may be proxied by its predictive value. We initially proposed that a multimodal map would have more predictive value than any unimodal map. We nevertheless should raise the point that, conceptually, individual maps may outperform multimodal maps with respect to the prediction of some phenotypes. For example, a map yielded by tractography mapping could have a higher predictive value in multiple sclerosis atrophy and symptoms than would a map derived from resting-state functional connectivity, whereas the latter may have better predictive value for schizophrenia diagnosis and subtyping. Accordingly, a collection of unimodal maps may have its own place in understanding brain–behaviour relationships and may complement multimodal maps.

Future questions and challenges

Inter-individual variability. An important consideration for building a general representation of brain organization pertains to inter-subject variability, which is encountered at all spatial levels and in all neurobiological properties, from histology[6,17,94] to large-scale networks[95,96]. Group-based parcellation schemes generally capture the main aspects of organization evident across individuals, whereas the size, shape and position of areas and networks can vary substantially between individuals[5,18,19,76,97] (FIG. 3). Furthermore, divergent patterns of brain organization from the most common pattern (that is, changes in the spatial arrangement of cortical regions) can be observed in approximately 5–10% of the healthy population[16,19], and care should therefore be taken to avoid the undue influence of such outliers. Notwithstanding their non-conformation to a theoretically universal map of the brain, such topological outliers, if they do not result from artefacts, can also be considered to be interesting cases of inter-individual variability to understand brain–phenotype relationships[98]. Indeed, recent studies have suggested that the topography (location and size) of individual-specific brain parcellations is predictive of individual differences in demographics, cognition, emotion and personality[3,5,99]. In this context, we would argue that the quest to understand robust patterns of brain topography across different markers and the investigation of inter-individual differences are closely intertwined challenges. Only by understanding the generic characteristic of topographic organization can we start to appreciate idiosyncrasies and their relationships to socio-demographic, cognitive or affective profiles.

Further complicating the understanding of inter-individual differences, regions that show high inter-individual variability often also show substantial changes across ontogenesis and phylogenesis and even exhibit inter-hemispheric asymmetry[35,95,100,101]. This coexistence of different, albeit related, issues has caused many debates on the true structure and function of these 'hot

Domains
Spatial units in the brain that are smaller than usual brain regions and show specific functions.

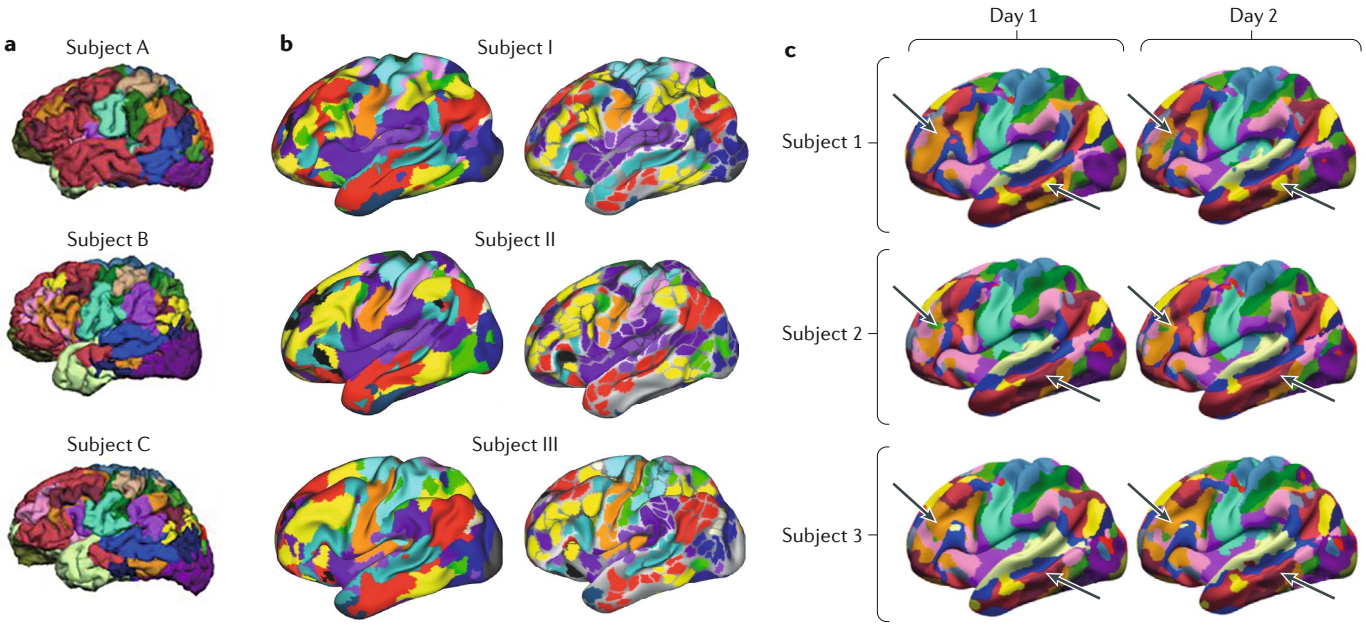

Fig. 3 | **Inter-individual variability in functional parcellation.** Organization of individual-specific cortical parcellations echoes that of group-level parcellations but also exhibits substantial inter-individual variability. **a** | Network-level parcellations of Human Connectome Project (HCP) individuals using a half hour of resting-state functional MRI (rs-fMRI) data per participant[18]. **b** | By exploiting a large quantity of data (5 hours per participant) from the Midnight Scan Club, highly detailed network-level (left) and area-level (right) parcellations of individual participants were generated[97]. **c** | Recent algorithmic advances allow the delineation of highly detailed network-level parcellations using a half hour of data per HCP participant[5]. Consistent with multiple studies, individual-specific networks exhibit unique topological features that are highly replicable across two different days (black arrows). Part **a** is adapted from REF.[18], Springer Nature Limited. Part **b** is adapted with permission from REF.[97], Elsevier. Part **c** is adapted from Kong, R. et al. Spatial topography of individual-specific cortical networks predicts human cognition, personality and emotion, *Cereb. Cortex*, 2018, https://doi.org/10.1093/cercor/bhy123 (REF.[5]), by permission of Oxford University Press.

regions', which include, for example, the inferior portion of the posterior middle frontal gyrus. Although this region had long been somewhat neglected, the recent multimodal parcellation by Glasser et al.[16] found striking local and connectivity marker changes in that region relative to adjacent regions, as well as activation during language tasks, leading to the hypothesis of the existence of a new 'area 55b' devoted to language functions. However, the authors also pointed out that this area showed high inter-individual variability. Furthermore, meta-analytic investigation revealed an engagement of this region in language functions only in the left hemisphere[68]. Generally, as many brain structures seem to be symmetric at the macrostructural and microstructural levels[102], hemispheric symmetry is implicitly assumed and often prioritized in parcellation studies[16,103]. Nevertheless, studies that do not pose such constraints have revealed different patterns of organization across hemispheres (that is, asymmetry) in neocortical[70] but also evolutionarily older brain structures[81,104]. In sum, the extent to which the brain is symmetrically organized can be considered an open question. Asymmetries in brain structure can be observed early in human development[105], but functional asymmetries are probably further shaped across ontogenesis to varying extents in different individuals. In other words, functional (a)symmetry is highly variable across individuals, making it difficult to draw conclusive evidence for a strict symmetry or asymmetry in some regions. Following these assumptions, future studies should test whether individual patterns of brain functional asymmetry are associated with or predict individual phenotypes.

Studies of ontogeny and phylogeny. The question of symmetry and the influence of ontogeny will become particularly interesting when considering, for example, the prefrontal cortex — a highly variable, evolutionarily new brain region that matures relatively late compared with other brain regions and shows evidence for strong hemispheric specialization[106,107]. Both developmental and phylogenetic aspects, however, are still rarely considered in the context of studies of brain parcellation, though we expect this may change rapidly. Although multimodal MRI captures only a limited repertoire of neurobiological properties, it has the advantage of being readily performed not only at different stages across the human lifespan but also in non-human primates or rodents. Comparisons with non-human primates have often highlighted similarities in brain organization to humans[8,108–113], but there is also evidence of differences[114]. For example, a recent study has suggested the existence of an area called FPl (referring to its lateral frontal pole location) in humans that lacks correspondence with any region in the macaque prefrontal cortex[115]. Similarly, the first studies of brain organization in non-human primates with approaches mirroring those used in humans have been only recently performed[44,84,116,117]. In turn, and quite surprisingly, systematic comparisons of

parcellations across the human lifespan are still completely absent, even though there is no doubt that brain structure, function and connectivity dynamically change throughout the entire human lifespan.

Conclusions

In contrast to histological brain mapping, which has a long history and is a relatively mature field, imaging-based parcellation is a recent approach that has evolved across different dimensions, including various different methods, markers and evaluation approaches. The recent combination of local and global mapping techniques has raised the opportunity for parcellations that capture both areal and network organization. This double optimization might reconcile the objective of optimal whole-brain representation for data compression and accurate representation of well-defined brain areas for neuroscientific inferences. Recent progress in high-field scanners will provide support for mapping of imaging properties that are closer to the microstructure, such as whole-brain patterns of lamination. We can expect that, in the future, the application of hybrid algorithms to high-resolution MRI data should open new vistas in which brain areas are delineated in vivo based on a combination of information related to their microstructure and their integration into larger networks.

From a cartography perspective, the many markers offered by MRI should support robust mapping of brain areas by crossing partition schemes that are revealed by different modalities. Nevertheless, considered separately, the different organizational topographies revealed by markers reflecting different neurobiological properties are also likely to have a crucial role in our understanding of the organizational dimensions of the brain. Given that these dimensions underlie the architecture of the human mind, characterizing the relationship between these topographies and behavioural functions should bring new insight into the understanding of the human mind, behaviour and dysfunction[93]. In addition to the richness of MRI markers, large MRI data sets have been acquired around the world and across different periods of the human lifespan. The availability of these data opens up new possibilities towards the characterization and understanding of inter-individual variability, brain asymmetry and the dynamics of inter-individual variability and brain asymmetry across lifespan development. Along the same lines, although parcellation in non-human primates is still in its infancy, it should bring complementary insights into brain phylogeny. Thus, imaging-based brain parcellation, following extensive developments and applications in the recent decade, still holds great promise for revolutionizing our understanding of human brain organization and its relation to human behaviour.

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