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 based on 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.

Introduction

The organization of the human brain is governed by two fundamental principles: functional integration into **large-scale networks** [G], 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 adjacent prefrontal and primary motor cortex based on 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, as well as **connectivity fingerprints** [G] [10].

Brain cartography [G] 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] [G] 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 [G] 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 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 100,000s 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** [G] 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 atlas examples in Table 1) notoriously unsuited for such task, 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 remains to identify components (either topographically distinct regions or distributed networks) that are internally homogeneous with respect to a particular neurobiological measure yet 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 could be referred to as local partitioning and global partitioning approaches, respectively. Note that here we only consider 'hard partitions' in which each location is assigned to one and only one brain's spatial component, as opposed to 'soft' partitions[26] (see 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, marker approach and 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 [G] and myeloarchitecture [G], neurochemical markers or (more recently) receptor expression (Box 1). However, these approaches usually require post-mortem 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.

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-to-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 compared with higher visual cortical areas (Fig. 2)[28]. However, MRI-based (and histology-based) myelin mapping for cartography purposes has been mostly limited to auditory[29], visual[30] and sensorimotor regions[28]. Owing to a lack of distinctiveness in myelination densities across association cortex, the application of myelin mapping for cartography beyond 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** [G] (Fig. 2)[31]. Importantly, visual areas defined based on fMRI visuotopic mapping correspond well with the areas defined by cytoarchitecture, supporting the validity of using fMRI signals for brain parcellation (Fig. 2).

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 neither 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.

Directly tackling these limitations, 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, 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 (Fig. 1)[35]. 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 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 task, stimuli, responses, 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 more frequently reported in certain brain regions (e.g., insula) compared with others[39]. Furthermore, a fundamental limitation of meta-analysis is the spatial blurring that is inherent to combining participants from studies across different labs and coordinate systems. Therefore, extensive recordings of activation recording (that is, deep phenotyping) 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 brain 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 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[44,45,46]. 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 neighboring 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 to physical connection (structural connectivity). For the sake of providing an overview on the key lines of research, therefore, we will 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 [G]** time-series correlations[50]; and co-activations during task performance revealed through **meta-analytic connectivity modelling [G]**[51,52]. All of these approaches 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 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 frequent connectivity-based parcellations are based on 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 an 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[55,56,57-59] (Fig. 1) or clustering to markers of local properties[32,35]. There is, however, no technical or conceptual requirement 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 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 S1, the resulting brain parcellation outperformed either local or global approach 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 [G]** 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 have been widely applied. Resting-state functional connectivity

has proven 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, and still represents the focus of technical developments[61,62].

Soon after, CBP based on meta-analytic connectivity modelling[63-65] and structural covariance **[G]**[64,66] data were also introduced. As a proof of concept, meta-analytic connectivity modeling 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 modeling and CBP based on structural covariance) were then used to parcellate the insula[63,64]. Meta-analytic connectivity modeling has since been extensively used to parcellate cortical regions, as well as subcortical structures, whereas structural covariance has only been sparingly used. The relatively low use of the latter approach may relate to its complicated interpretation; it is based on structural data but used as a proxy of functional interactions. Importantly, CBPs based on different markers seem to converge towards a similar pattern of brain organization[64,67], suggesting that they may 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 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 and divergence of 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** **[G]** 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 an 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 pattern 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 than 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 instills 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 the purpose of 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 signal, 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 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 only been recently concretized in humans[16,85]. Although we will 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], 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 only allows unequivocal mapping 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 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 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, therefore, 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 two potential strategies below 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's 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, the higher the chance to fully capture each dimension or organizational aspect. This strategy not only would promote an optimal coverage of the multiple organizational dimensions of the brain but also would contribute to disentangling true neurobiological aspects from artefacts with minimal human intervention. We therefore argue that a multimodal approach should maximize the number, but also diversity, of modalities. This pertains particularly to the integration of structural, functional and connectional measures across both MRI and also, importantly, histological measures. To the best of our knowledge, such integration has not yet been achieved. So far, the few published multimodal studies have focused exclusively on MRI-based features[16,68,86,87,89], and integration of histological with MRI-based features has only been performed in 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 might be 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 **[G]**, that have been observed in invasive studies in non-human primates and 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, defense of the head) and could support close functions in humans, such as protective behavior 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, compared with 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 mirror such functional validation[18]. The neuropsychological lesion–deficit approach can also contributes 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 multi-modal 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 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 relationship[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 interindividual variability often also show substantial changes across ontogenesis and phylogenesis, and even exhibit inter-hemispheric asymmetry[35,95,100,101]. This co-existence of different, albeit related, issues has caused many debates on the true structure and function of these 'hot 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 as 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, evolutionary 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 only captures 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 macaque prefrontal cortex[115]. Similarly, the first studies of brain organization in non-human primates with approaches mirroring those used in humans have only been 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 progresses 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 in 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, as well as the dynamics of inter-individual variability and brain asymmetry across the 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.

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 a 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 post-mortem 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 co-localize very well with each other but 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 post-mortem 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.

Box 2 | Defining brain components with clustering and factorization

Neuroimaging data typically consists 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 **[G]** (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 CBP field are k-means clustering, spectral clustering **[G]** and hierarchical clustering **[G]** (see[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** **[G]** (PCA), which identifies the main dimensions along which different data points vary.

642 By contrast, non-negative matrix factorization[19] approaches constrain the decomposed
643 components to be strictly non-negative. Together with additional constraints (e.g., components
644 are encouraged to be mostly zero, except in small numbers of locations), non-negative matrix
645 factorization often yields a "part-based" decomposition of the data. For example, when applied
646 to face photographs, NMF will yield components representing distinct face "parts" (e.g., nose,
647 eyes, mouth). Accordingly, NMF has an inherent clustering property, which allows the
648 parcellation of the brain into localized components that mirror brain regions and has thus been
649 successfully used for whole-brain partitions[23,125].
650
651 Importantly, all methods have distinct advantages and disadvantages, and so the choice of the
652 approach should depend on the data at hand, as well as the objective of the parcellation. For
653 example, NMF can model many different data distributions owing to the flexibility of matrix
654 factorization, whereas k-means attempts to capture spherical clusters (in feature space).
655 However, standard k-means yields a hard clustering, whereby each element (voxel or vertex) is
656 uniquely assigned to either one cluster or another, whereas factorization approaches (such as
657 **fuzzy or soft clustering** **[G]**[71]) do not yield a clear, deterministic assignment. In soft
658 partitioning, any given element (voxel or vertex) can be assigned to several groups, by
659 obtaining, for example, the probability of assignment to each group. However, a final spatial
660 'hard partition' can be obtained when the scores from fuzzy clustering or factorization are
661 integrated in a 'winner-takes-all' approach[126]. Nevertheless, comprehensive empirical and
662 theoretical studies evaluating the advantages and limitations of each approach and variants
663 thereof for different data sets and parcellation purposes are lacking for clear guidelines of their
664 use in brain parcellation.
665
666 **Box 3 | Main connectivity measures used for parcellation**

667 Traditionally, the term 'connectivity' refers to physical connections via white-matter tracts,
668 which can be demonstrated using invasive tracing techniques in experimental animals or ex
669 vivo fibre-dissection methods. Moreover, structural connectivity can also be estimated using
670 tractography based on diffusion-weighted images[127] (although see[128]). By contrast, functional
671 relationships between different parts of the brain may be revealed by correlating the time series
672 of signals from different voxels or vertices during task performance or, more commonly, in the
673 absence of a behavioural task — that is, in the 'resting state'[129]. Notably, anatomical and
674 functional connectivity represent very broad concepts with many different measurement and
675 computation approaches, each carrying its own advantages and challenges as well as their

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 brain structure.

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 are prone to particular artefacts. For example, diffusion tractography might yield spurious results[128] due to several factors. Crossing fibres **[G]** 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 than its wall, owing to intrinsic geometry of cortical folds[130,131]. Conversely, tractography may also fail to infer the connectivity of grey matter voxels or vertices near the pial surface particularly spatially distant from white matter[68]. In addition, the limited spatial resolution of current tractography methods can potentially result in false negative (missed connections), in particular with regards to small white fibres[132].

Functional connectivity approaches are less affected by geometric factors, but signal loss and distortion are nevertheless common with 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 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	Ref
fMRI and PET imaging (functional)					
Task-based fMRI and PET	Activation during task	Meta-analytic connectivity modeling	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.

Fig. 1 | A two-dimensional taxonomy of brain parcellation approaches. Parcellation approaches could 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 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

729 factorization) approaches. In theory, any type of parcellation approach can be used for regional
730 or whole-brain parcellation. Accordingly, each cell illustrates an example application of a local
731 (left column) or global (right column) parcellation technique to markers of local (top row) or
732 global (bottom row) properties. Top left cell: Regions of the JuBrain atlas identified by border
733 detection according to architectonic properties (illustration from ref. [11]). Top right cell:
734 Parcellation of the amygdala into subregions with a clustering approach applied to behavioural
735 meta-analytic data[35] (activation studies across a wide range of paradigms probing cognitive,
736 motor and socio-affective functions from the BrainMap database[36]). Bottom left cell:
737 Parcellation of the cerebral cortex based on boundary mapping applied to resting-state
738 functional connectivity[59] (illustration from ref. [11]). Bottom right cell: Parcellation of the cerebral
739 cortex into functional networks based on clustering applied to the resting-state functional
740 connectivity[70].

741 **Fig. 2 | Mapping of visual areas with local markers.** Different parcellations approaches
742 converge towards similar delineations of visual areas. Visuotopic mapping (based on fMRI)
743 and cytoarchitecture mapping (based on ex-vivo brain tissues) show consistency in the
744 delineation of V1 from V2. Furthermore, myelin mapping (based here on MRI) distinguishes
745 V1 and V2 from higher visual areas in a similar way than visuotopic and cytoarchitecture
746 mapping do. **a** | Delineation of V1 and V2 based on fMRI visuotopic mapping[136]. **b** | Mapping
747 of visual areas based on cytoarchitecture[137] (illustration from[31]). **c** | Myelin mapping, based on
748 MRI T1-weighted-to-T2-weighted ratio[41], differentiates V1 and V2, which are heavily
749 myelinated (red), from higher visual areas (such as V3), which show lower myelin ratios
750 (yellow, green).

751 **Fig. 3 | Interindividual variability in functional parcellation.** Organization of individual-
752 specific cortical parcellations echoes that of group-level parcellations, but also exhibits
753 substantial inter-individual variability. **a |** Network-level parcellations of Human Connectome
754 Project (HCP) individuals using half hour of resting-state fMRI data per participant[18]. **b** | By
755 exploiting a large quantity of data (5 hours per participant) from the Midnight Scan Club, highly
756 detailed network-level (left) and area-level (right) parcellations of individual participants were
757 generated[97]. **c** | Recent algorithmic advances allow the delineation of highly detailed network-
758 level parcellations using half hour of data per HCP participant[5]. Consistent with multiple
759 studies, individual-specific networks exhibit unique topological features that are highly
760 replicable across two different days (black arrows).

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

Name (group or institution)	Brain coverage	Granularity (number of parcel/networks)[a]	Original format (and other format)	Link	Refs
Macroanatomy					
Automated Anatomical Labeling (AAL) Atlas	Whole brain	82 parcels	Volume	http://www.gin.cnrs.fr/en/tools/aal-aal2/	138
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	139,140, 141,142
Desikan–Killiany Atlas	Cerebral cortex	70 parcels	Surface	Included in the installation package of Freesurfer: https://surfer.nmr.mgh.harvard.edu/fswiki/CorticalParcellation	141
Destrieux Atlas	Cerebral cortex	148 parcels	Surface	Included in the installation package of Freesurfer: https://surfer.nmr.mgh.harvard.edu/fswiki/CorticalParcellation	143
MarsAtlas	Cerebrum	89 parcels	Surface and volume	http://meca-brain.org/software/marsatlas-colin27/	144
Rs-fMRI					
Bellec et al. (2010)	Whole brain	7, 12, 20, 36, 64, 122, 197, 325, 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	145
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 striatu	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	70;146; 147

			m	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	
Craddock et al. (2012)	Whole brain	10 to 1000 parcels	Volume	http://ccraddock.github.io/cluster_roi/atlases.html	83
Shen et al. (2013)	Whole brain	93, 184, 278 parcels	Volume	www.nitrc.org/frs/?group_id=51	148
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	149
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, 1000 parcels	Surface (and volume)	https://github.com/ThomasYeoLab/CBIG/tree/master/stable_projects/brain_parcellation/Schaefer2018_LocalGlobal	54
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/	33,150
Brainnetome, based on PDT	Cerebral cortex and	246 parcel	Volume	http://atlas.brainnetome.org/download.html	103

	subcortical structures	s			
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

[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 atlas based on other techniques (for example, Brodmann atlas) have not been included here. The atlases are organized by modality and by publication date within each modality. AAL, automated anatomical labeling; HCP, Human Connectome Project; FSL, FMRIB Software Library; PDT, probabilistic diffuction tractography.

Large-scale networks

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

Connectivity fingerprint

The pattern of interactions between a brain region and 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 area

A brain region showing specific structure, function and connectivity.

Universal map

A unique division of the brain into individual areas, each having specific structure, connectivity and function, and 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 regards to cell characteristics.

Myeloarchitecture

The pattern of myelinated fibres.

Visuotopic mapping

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.

Echo planar imaging

An MRI sequence used for functional and diffusion imaging.

Meta-analytic connectivity modelling

Method that aims to model functional connectivity in the brain based on 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

Pattern of co-variations in measures of morphometry (such as grey matter volume) across brain regions.

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.

Domains

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

Non-negative matrix factorization

A multivariate statistical approach to factorize data into components promoting part-based representation of the data.

Spectral clustering

A clustering approach based on the eigenvectors of the matrix of similarity (e.g., connectivity) between brain locations (voxels/vertices). The terms "spectral" refers to the spectrum (eigenvalues) of the similarity matrix.

Hierarchical clustering

A clustering approach that disentangle clusters in a hierarchical fashion, in such a way that clusters' relationships 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 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.

Crossing fibres

Individual white matter fibers whose spatial direction result in point where they meet or cross each other complicating the estimation of their respective path.

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Author contributions

S.B.E., B.T.T.Y. and S.G. researched data for the article. S.B.E., B.T.T.Y. and S.G. made substantial contributions to discussion of content, wrote the manuscript and reviewed or edited the manuscript before submission.

Competing interests

The authors declare no competing interests.

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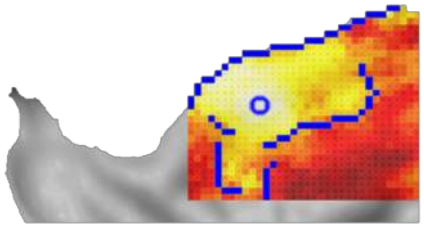
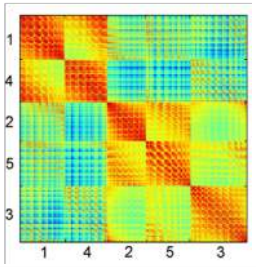
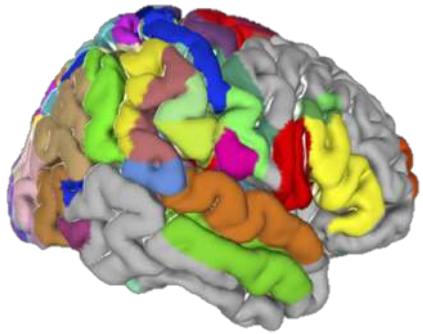
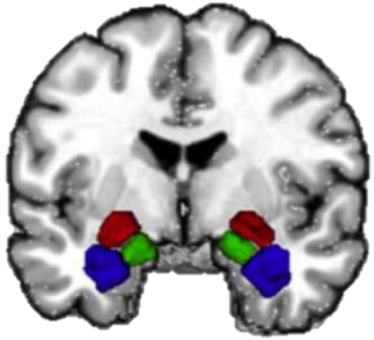
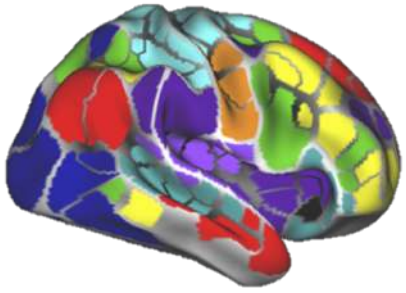
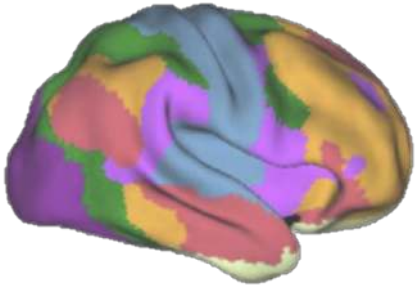
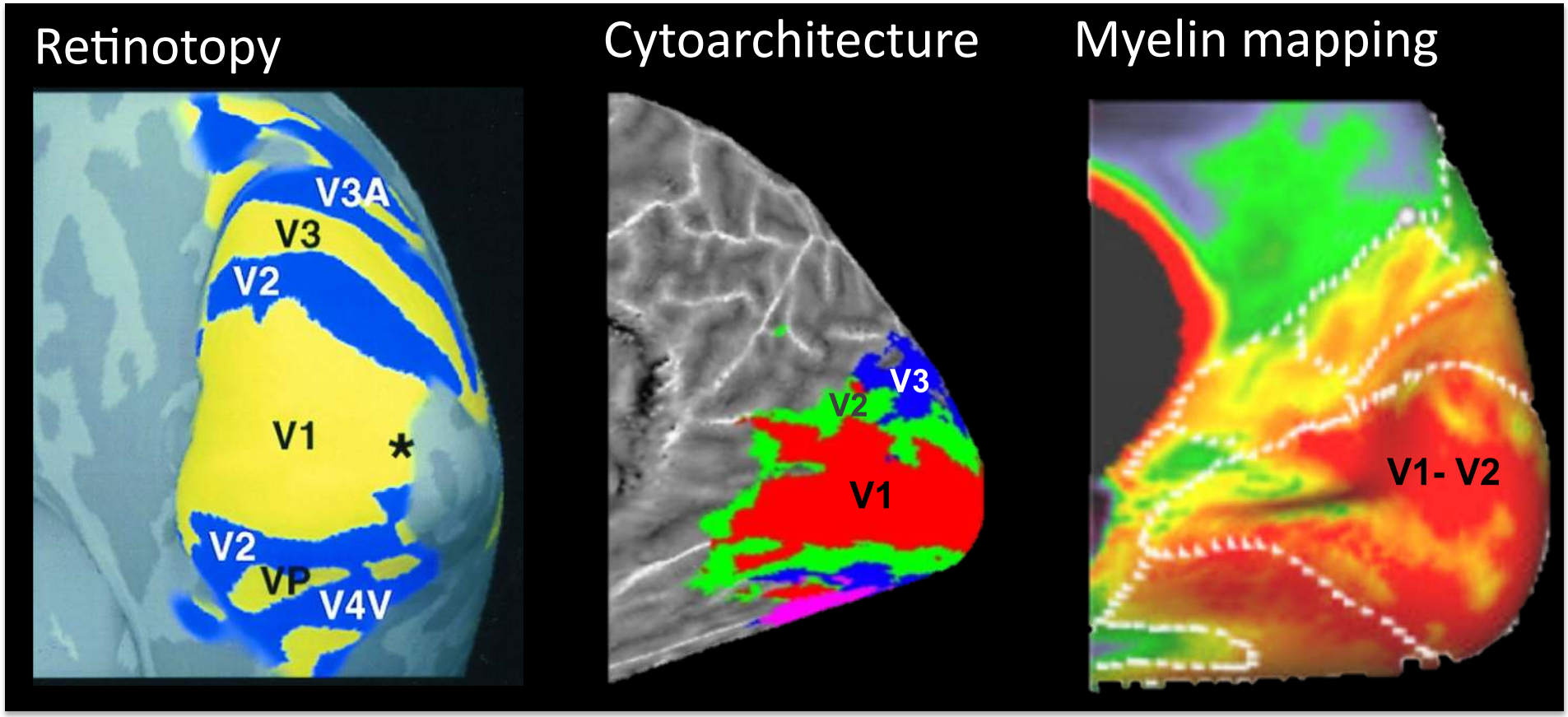
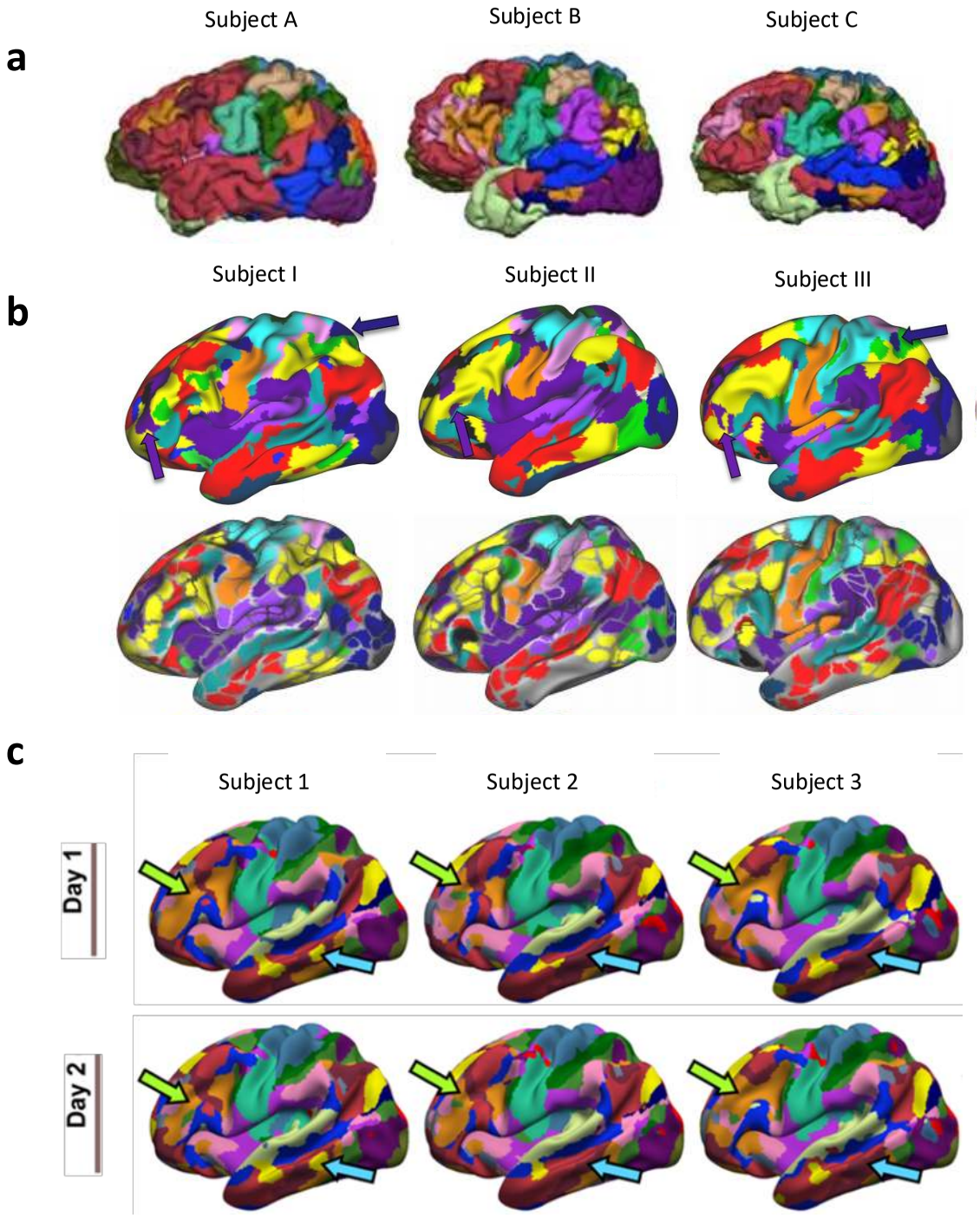
Markers \ Technical procedure	Boundary-mapping	Clustering/Factorization
		
Local ***Histology-based:*** Cytoarchitecture mapping Receptors mapping Myelin mapping ***MRI-based:*** Myelin mapping Meta-analytic activation modeling	*Border detection in cortex based on architectonics* 	*Clustering of amygdala voxels based on their activations in behavioural paradigms* 
Global ***MRI-based:*** Resting-state functional connectivity Meta-analytic connectivity modeling Probabilistic diffusion tractography Structural covariance	*Boundary mapping of resting-state functional connectivity of cerebral cortex* 	*Clustering of cerebral cortex based on resting-state functional connectivity* 


Retinotopy
V3A
V3
V2
V1
*
V2
VP
V4V
Cytoarchitecture
V3
V2
V1
Myelin mapping
V1- V2


a
Subject A
Subject B
Subject C
b
Subject I
Subject II
Subject III
c
Subject 1
Subject 2
Subject 3
Day 1
Day 2