Imaging-based parcellations of the human brain

Simon B. Eickhoff[1,2,*], *B.T. Thomas Yeo*[3,4,5,6] *and Sarah Genon*[1,2]

[1]Institute of Neuroscience and Medicine, Brain and Behavior (INM-7), Research Centre Jülich, Germany.

[2]Institute of Systems Neuroscience, Medical Faculty, Heinrich-Heine-University Düsseldorf, Germany.

[3]Department of Electrical and Computer Engineering, ASTAR-NUS Clinical Imaging Research Centre, Singapore Institute for Neurotechnology and Memory Networks Program, National University of Singapore, Singapore.

[4]NUS Graduate School for Integrative Sciences and Engineering, National University of Singapore, Singapore

[5]Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Harvard Medical School, Charlestown, USA.

[6]Centre for Cognitive Neuroscience, Duke-NUS Graduate Medical School, Singapore.

*simon.eickhoff@med.uni-duesseldorf.de

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

69   aggregation to provide a valid compression, the parcels should reflect a biologically meaningful

70   patterning. This reasoning renders macrostructural characteristics (for example, sulci and gyri;

71   see macroanatomy atlas examples in Table 1) notoriously unsuited for such task, as they do not

72   converge with the heterogeneity of functional, structural or connectional markers[13,25]. Thus, brain

73   parcellation contributes to a better understanding of brain function and dysfunction not only at

74   the conceptual level, but also by providing critical priors for connectomics and large-scale

75   analyses of brain-behaviour relationships.

76   In spite of the technical and conceptual heterogeneity in the burgeoning field of brain

77   parcellation, for more than a century its fundamental idea remains to identify components

78   (either topographically distinct regions or distributed networks) that are internally

79   homogeneous with respect to a particular neurobiological measure yet that are different from

80   each other. This goal can be achieved by two conceptually distinct approaches: boundary

81   mapping and clustering or factorization. In the boundary-mapping approach, a border is

82   detected by localizing the most abrupt spatial changes in the assessed feature, using a 'local'

83   border-detection (or edge-detection) technique. In clustering and factorization approaches,

84   spatial elements (voxels or vertices) are grouped on the basis of their similarity and dissimilarity

85   according to a given marker. Hence, boundary mapping and clustering (or factorization)

86   approaches could be referred to as local partitioning and global partitioning approaches,

87   respectively. Note that here we only consider 'hard partitions' in which each location is

88   assigned to one and only one brain's spatial component, as opposed to 'soft' partitions[26] (see

89   Box 2).

90   Almost any parcellation approach can be applied to almost any neurobiological property (Table

91   1). Hence, we can further divide brain parcellation approaches according to the type of marker,

92   by distinguishing markers that describe underlying tissue properties (that is, capitalizing on

93   local structural or functional properties) from markers that reflect integration into larger

94   networks (that is, capitalizing on long-range connections). In other words, a further conceptual

95   distinction can be proposed based on whether the parcellation builds on local architecture or

96   function ('local' properties) or on connectivity fingerprints ('global' or 'connectivity'

97   properties). In this Review, we discuss the history of brain parcellation and its current state

98   along this taxonomy of two independent dimensions — that is, marker approach and

99   partitioning approach (Fig. 1) — and examine conceptual questions regarding the relationships

100   among parcellations derived from different markers.

101

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

4

135 parcellated the brain into functional networks by clustering task-evoked responses during

136 finger-tapping[32]. Another recent study proposed a parcellation based on response to semantic

137 content during several hours of story listening by seven individuals[33] (Table 1). Nevertheless,

138 the richness of neither of these recordings probably did not come close to reflecting the entirety

139 of the brain's functional repertoire. Together with the small sample sizes used, this point raises

140 the question of the 'universality' of the resulting parcellation.

141 Directly tackling these limitations, meta-analytic approaches have been used to define

142 subregions within, for example, the insular cortex[34] on the basis of the convergence of activation

143 during tasks involving different cognitive domains, such as motor tasks, cognitive or affective

144 processing. This approach was recently automated in a clustering procedure, thus highlighting

145 the potential to parcellate cortical and subcortical regions by local activation data (Fig. 1)[35].

146 Importantly, the extension of such approaches to other brain regions (such as the hippocampus)

147 would require an extensive repertoire of functional responses, complicating developments.

148 Recent progress in the aggregation of activation data[36-38] may help overcome these challenges.

149 Whole-brain maps of local response patterns to various task conditions and stimuli may thus be

150 computed from large sets of activation data. Such an approach would enable the delineation of

151 brain areas based on their pattern of activations across many dimensions of behavioural tasks

152 (depending on task, stimuli, responses, and so on). However, this approach might be biased

153 towards tasks that can readily be applied in the scanner and by the fact that activations are more

154 frequently reported in certain brain regions (e.g., insula) compared with others[39]. Furthermore,

155 a fundamental limitation of meta-analysis is the spatial blurring that is inherent to combining

156 participants from studies across different labs and coordinate systems. Therefore, extensive

157 recordings of activation recording (that is, deep phenotyping) in a small number of participants[40]

158 and extensive aggregation of activation studies are highly complementary.

159

160 ***Future challenges for parcellations based on local properties.*** Although MRI-based

161 measurements of brain local properties such as myelination or functional responses are less

162 time-intensive and labour-intensive than ex vivo microstructural examination, their clear

163 drawback is that the respective properties are not directly observable but must be inferred from

164 the measured data, rendering the ensuing brain maps contingent on the model for measuring

165 these properties. Nevertheless, as illustrated in Fig. 2, the delineation of cortical areas based on

166 MRI-measured local properties converge with those from histology-based architectonic

167 approaches, clearly supporting the biological validity of the former[41]. Furthermore, the ongoing

168 development of high-field scanners should provide the possibility of MRI-based architectonic

169 parcellation[41,42]. That is, in the future, parcellations could capitalize on imaging properties that
170 are closer to the microstructure of the brain, such as laminar patterns in the human medial
171 temporal cortex that were observed through ex vivo MRI[43]. Such advances could provide an
172 important bridge to histological investigations in the same specimen[44,45,46]. Thus, brain
173 parcellation based on local properties not only has a storied tradition (Box 1; Fig. 1), but also
174 should see substantial future progress[42].

175

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

183

184 We note that 'connectivity' is itself a heterogeneous concept, referring to, for example,
185 functional dependencies (functional connectivity) or to physical connection (structural
186 connectivity). For the sake of providing an overview on the key lines of research, therefore, we
187 will focus on the three approaches that have been used most frequently in brain parcellation to
188 date (Box 3): the estimation of anatomical connectivity by tractography on diffusion-weighted
189 images[49]; task-free functional connectivity assessed through resting-state **echo planar imaging**
190 **[G]** time-series correlations[50]; and co-activations during task performance revealed through
191 **meta-analytic connectivity modelling [G]**[51,52]. All of these approaches allow the inference of
192 voxel-wise or vertex-wise structural or functional connectivity with other brain locations, which
193 in turn allows the computation of a connectivity fingerprint[15]. Brain areas can be delineated
194 directly from their functional connectivity or from whole brain connectivity fingerprint using
195 either boundary mapping or clustering approaches. Of note, the parcellation technique can in
196 theory be applied to any connectivity measure, such as structural covariance, although the latter
197 has been less commonly used (Box 3). Thus, the most frequent connectivity-based parcellations
198 are based on structural connectivity inferred from diffusion MRI, resting-state functional
199 connectivity and task-based functional connectivity.

200

201 *Boundary mapping versus clustering.* In contrast to histological brain mapping, which has
202 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

271 minimize variance within clusters, the ratio of these variances can be used to characterize

272 cluster separation and to select the 'optimal' number of clusters. Such 'internal information'

273 criteria mainly target the quality of the yielded clustering when considered purely from a

274 technical point of view, that is, within the framework of an unsupervised learning problem.

275 Although these criteria have been frequently used in CBP studies[72-74], a 'good' clustering from a

276 data representation perspective might not necessarily represent a 'good' partition with regards

277 to the neurobiology that the approach aims to reveal — particularly in the presence of, for

278 example, structured noise or outliers.

279

280 Consequently, there is an increasing interest in evaluation criteria for assessing parcellations

281 that go beyond characterizing the quality of data representation. For example, assuming that

282 partitions driven by biological truth should be more stable across different samples,

283 reproducibility may indicate biological validity. Many studies have hence investigated stability

284 across re-sampling, and reproducibility across independent samples, to propose optimal

285 partitions[70,75]. Along the same lines, some recent studies have capitalized on the richness of

286 technical variants (that is, the use of different data preprocessing and/or clustering algorithms)

287 to examine the robustness of the parcellation scheme across different analyses[22,31]. The

288 underlying idea here is that a partition scheme that is constant across different techniques is

289 likely to be driven by the underlying neurobiology rather than methodological effects.

290 Nevertheless, because such resampling methods do not rule out the influence of consistent

291 artefacts within the same measurement technique, evidence of convergence across different

292 markers has also more recently been used for so-called cross-modal validation[67,68,70,76]. Thus, in the

293 absence of apparent ground truth, current parcellation work capitalizes on replication,

294 robustness and convergence as proxies for biological validity.

295

296 **Divergence between properties**

297 The idea that different neurobiological properties should show similar pattern of organization

298 was already noted in 1925 by von Economo and Koskinas and has remained a fundamental

299 axiom of brain mapping. As written by Zilles and colleagues[77] in 2002, *"All these architectonic*

300 *and functional imaging studies support the hypothesis of a correlated structural and functional*

301 *subdivision of the cortex"*. Such convergence across properties is indeed frequently observed

302 (Fig. 2). Accordingly, especially with the emergence of CBP, convergence with previous brain

303 maps (particularly from cytoarchitecture) has been used to argue for the validity of newly

304 developed methods. We stress, however, that no property, be it resting-state connectivity,

305 cytoarchitecture, diffusion tractography or task-based activation patterns, should be considered
306 conceptually superior than any other modality, as each represents its own specific window into
307 the topographic organization of the human brain. The prevailing notion that there is a gold-
308 standard parcellation method thus seems misleading. Rather, the critical question is how to
309 examine and interpret the convergence and divergence across parcellation results.

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

326 From a conceptual view, however, such differences between topographical maps that have been
327 derived using different markers arguably deserve more attention than they have received up to
328 now. The fact that each neurobiological property represents a unique window into brain
329 organization suggests that several different, equally valid, maps can be derived from the
330 analysis of different markers, such as cytoarchitecture, connectivity or function. Furthermore,
331 this conceptualization implies that parcellation based on any given characteristic (such as
332 cytoarchitecture) cannot be used as a completely faithful surrogate for parcellation based on
333 another characteristic (such as anatomical connectivity)[44,84], although it can be expected to have
334 some predictive value (see below).
335 Nevertheless, inferences on brain organization that are based on any one specific marker in
336 isolation might also be difficult, because all methods are susceptible to artefacts. In particular,
337 MRI-based markers indirectly represent biological features (Box 3), whereas analyses of

338 histological sections are susceptible to geometric distortions resulting from tangential
339 sectioning. Hence, one approach for increasing the likelihood that a parcellation represents a
340 biological property of the brain is to retain only patterns that are consistent across parcellations
341 based on different markers and methods, even though this approach comes at the cost of
342 potentially missing important aspects of brain organization not revealed by all markers and
343 methods.

344

345 **Multimodal approaches**
346 Although the idea of integrating different approaches towards a universal whole-brain (or
347 cortical) map has been around for many years[12], the perspective has only been recently
348 concretized in humans[16,85]. Although we will refer to these approaches as 'multimodal', this term
349 should not be taken as referring to different MRI modalities, but more generically to studies
350 investigating different markers for parcellation, be they MRI-based (such as resting-state
351 functional connectivity) or not (for example, based on a receptor fingerprint).

352

353 *First endeavours of multimodal approaches.* Several studies have derived 'multimodal
354 parcels' by retaining the spatial overlap between clusters from unimodal parcellations. For
355 example, resting-state functional connectivity, meta-analytic connectivity modelling and
356 probabilistic tractography parcellation schemes were superimposed to derive robust parcels in
357 the superior parietal lobule[86], dorsal premotor cortex[68] and even in a small subcortical structure,
358 the nucleus accumbens[87]. Thus, the 'cluster conjunction' approach has provided encouraging
359 results for brain cartography in terms of representing robust, 'fundamental' units [11].
360 However, such conjunction only allows unequivocal mapping when all unimodal parcellations
361 reveal a similar pattern whereas the procedure for dealing with substantial discrepancies
362 between unimodal parcellations remains an open challenge. Most previous studies chose to
363 exclude ambiguous voxels, but doing this can lead to a fragmented and incomplete map.
364 Furthermore, we anticipate that, when a convergence between partition schemes based on
365 different markers can be observed, it will be restricted to subdivisions at certain spatial scales[64,68],
366 thus enforcing the conjunction at a level of partitions that might not be optimal (for example,
367 less stable) for each unimodal partition when considered in isolation. Thus, there is no guarantee
368 that this approach could be successfully applied to the whole brain and yield a biologically valid
369 map.

370

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

380

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

396

397   ***Maximizing the number of modalities.*** One basic axiom is that different modalities reflect the
398   many dimensions along which the brain is organized. For example, the frontal lobe is organized
399   along rostro-caudal, ventro-dorsal and medial-lateral axes[88]. Let's accordingly consider three
400   dimensions A, B and C. Suppose a given marker predominantly reflects dimension A, to a lesser
401   extent, dimension B, and to an even more minor extent, dimension C. By contrast, another
402   marker might mostly reflect dimension B, to a lesser extent, dimension A, and to even lesser
403   extent, dimension C. Integrating both modalities would maximize the likelihood of capturing
404   brain organization along both dimensions A and B. Such integration would also offer greater

405 insights into dimension C than either of the modalities considered in isolation. However, the

406 integration of modalities might still not optimally represent brain organization along dimension

407 C. An additional modality sensitive to dimension C would be necessary to fully capture this last

408 dimension.

409 In other words, we expect that the higher the number of different modalities, the higher the

410 chance to fully capture each dimension or organizational aspect. This strategy not only would

411 promote an optimal coverage of the multiple organizational dimensions of the brain but also

412 would contribute to disentangling true neurobiological aspects from artefacts with minimal

413 human intervention. We therefore argue that a multimodal approach should maximize the

414 number, but also diversity, of modalities. This pertains particularly to the integration of

415 structural, functional and connectional measures across both MRI and also, importantly,

416 histological measures. To the best of our knowledge, such integration has not yet been achieved.

417 So far, the few published multimodal studies have focused exclusively on MRI-based

418 features[16,68,86,87,89], and integration of histological with MRI-based features has only been performed

419 in one specimen[85]. For example, the integration of histological myelin-maps with MRI-derived

420 proxies thereof has been unexplored to date, but such integration would provide at least some

421 protection against method-specific artefacts or biases.

422

423 ***Towards a multimodal map with predictive value.*** The integration of different markers poses

424 technical challenges, and how divergent parcellations should be conceptualized also remains

425 an open topic. That is, if different properties, such as microstructure and long-range

426 connectivity, indeed reflect different organizational dimensions, how should a multimodal map

427 of cortical areas be defined? Although certainly a premature idea at the current stage, we suggest

428 that an optimal representation of multiple divergent parcellations might be defined by an 'or'

429 combination of unimodal borders. Concretely, wherever the local information-processing

430 infrastructure or the pattern of interactions changes, a new region should be defined. Such an

431 approach might potentially contribute to disentangling small regions, called domains **[G]**, that

432 have been observed in invasive studies in non-human primates and are hypothesized to exist in

433 humans. The primary example of domains are separable entities in the posterior parietal cortex,

434 primary motor and premotor cortex that seem to be related to different kinds of movements (for

435 example, defense of the head) and could support close functions in humans, such as protective

436 behavior of peripersonal space[90,91]. An 'or' combination across a multimodal map might help to

437 disclose those small entities but could also include spurious borders owing to modality-specific

438 artefacts.

13

439   One avenue to empirically evaluate different methods for combining multiple maps is through

440   supervision on a meta-level, by testing which approach holds the highest predictive value for

441   brain function and dysfunction. In other words, an optimal multimodal map should provide the

442   best prediction of task-related activations, behavioural phenotype and/or clinical symptoms.

443   For example, a map that divides the hippocampus along both the anterior-posterior axis (based

444   on connectivity) and the medial-lateral axis (based on histology) might better predict clinical

445   phenotype (in Alzheimer disease or major depressive disorder) with supervised machine

446   learning, compared with either connectivity-based or histological maps alone.

447   We note that this view is in line with a long tradition in brain cartography, as even early brain

448   mapping books sought to relate partitioning to behavioural (dys-) function. For example,

449   intracranial stimulation in two distinct areas in non-human primates induced different patterns

450   of interference with animal behaviour[92]. In humans, invasive cortical stimulation mapping in

451   surgical patients mirror such functional validation[18]. The neuropsychological lesion–deficit

452   approach can also contributes to the distinction of different brain areas, despite several

453   limitations[93]. Alternatively, the validity of functional maps can be tested in surgical patients

454   based on their ability to predict post-surgical deficits. Hence, being more controlled than the

455   post-hoc lesion approach, investigation in surgical patients can be seen as a 'gold standard' for

456   functional mapping. This deficit-based view should then be complemented by a detailed, again

457   multi-modal characterization of the physiological properties of the delineated areas, in order to

458   build a functionally comprehensive atlas upon the spatial parcellation scheme.

459

460   ***Multimodal and unimodal maps.*** Importantly, testing the validity of a multimodal map based

461   on its predictive value remains relatively unexplored. Given that each type of neurobiological

462   property is differentially informative[80], the concept of such map may itself be open to debate.

463   For example, Glasser et al.'s[16] multimodal parcellation gives an excellent separation between

464   motor and somatosensory areas but does not provide somatotopic or visuotopic information.

465   Accordingly, the interpretability and relevance of such a map can be debated, although the latter

466   may be proxied by its predictive value. We initially proposed that a multimodal map would

467   have more predictive value than any unimodal map. We nevertheless should raise the point that,

468   conceptually, individual maps may outperform multimodal maps with respect to the prediction

469   of some phenotypes. For example, a map yielded by tractography mapping could have a higher

470   predictive value in multiple sclerosis atrophy and symptoms than would a map derived from

471   resting-state functional connectivity, whereas the latter may have better predictive value for

472   schizophrenia diagnosis and subtyping. Accordingly, a collection of unimodal maps may have

473 its own place in understanding brain-behaviour relationships, and complement multimodal
474 maps.

475

476 **Future questions and challenges**

477 *Inter-individual variability.* An important consideration for building a general representation
478 of brain organization pertains to inter-subject variability, which is encountered at all spatial
479 levels and in all neurobiological properties, from histology[6,17,94] to large scale-networks[95,96]. Group-
480 based parcellation schemes generally capture the main aspects of organization evident across
481 individuals, whereas the size, shape and position of areas and networks can vary substantially
482 between individuals[5,18,19,76,97] (Fig. 3). Furthermore, divergent patterns of brain organization from
483 the most common pattern (that is, changes in the spatial arrangement of cortical regions) can
484 be observed in approximately 5–10% of the healthy population[16,19], and care should therefore be
485 taken to avoid the undue influence of such outliers. Notwithstanding their non-conformation to
486 a theoretically 'universal' map of the brain, such topological outliers, if they do not result from
487 artefacts, can also be considered to be interesting cases of inter-individual variability to
488 understand brain–phenotype relationship[98]. Indeed, recent studies have suggested that the
489 topography (location and size) of individual-specific brain parcellations is predictive of
490 individual differences in demographics, cognition, emotion and personality[35,99]. In this context,
491 we would argue that the quest to understand robust patterns of brain topography across different
492 markers and the investigation of inter-individual differences are closely intertwined challenges.
493 Only by understanding the generic characteristic of topographic organization can we start to
494 appreciate idiosyncrasies and their relationships to socio-demographic, cognitive or affective
495 profiles.

496

497 Further complicating the understanding of inter-individual differences, regions that show high
498 interindividual variability often also show substantial changes across ontogenesis and
499 phylogenesis, and even exhibit inter-hemispheric asymmetry[35,95,100,101]. This co-existence of
500 different, albeit related, issues has caused many debates on the true structure and function of
501 these 'hot regions', which include, for example, the inferior portion of the posterior middle
502 frontal gyrus. Although this region had long been somewhat neglected, the recent multimodal
503 parcellation by Glasser et al.[16] found striking local and connectivity marker changes in that
504 region relative to adjacent regions, as well as activation during language tasks leading to the
505 hypothesis of the existence of a new 'area 55b' devoted to language functions. However, the
506 authors also pointed out that this area showed high inter-individual variability. Furthermore,

15

507   meta-analytic investigation revealed an engagement of this region in language functions only

508   in the left hemisphere[68]. Generally, as many brain structures seem to be symmetric at the

509   macrostructural and microstructural levels[102], hemispheric symmetry is implicitly assumed and

510   often prioritized in parcellation studies[16,103]. Nevertheless, studies that do not pose such

511   constraints have revealed different patterns of organization across hemispheres (that is,

512   asymmetry) in neocortical[70] but also evolutionarily older brain structures[81,104]. In sum, the extent

513   to which the brain is symmetrically organized can be considered as an open question.

514   Asymmetries in brain structure can be observed early in human development[105], but functional

515   asymmetries are probably further shaped across ontogenesis to varying extents in different

516   individuals. In other words, functional (a)symmetry is highly variable across individuals,

517   making it difficult to draw conclusive evidence for a strict symmetry or asymmetry in some

518   regions. Following these assumptions, future studies should test whether individual patterns of

519   brain functional asymmetry are associated with or predict individual phenotypes.

520

521   ***Studies of ontogeny and phylogeny.*** The question of symmetry and the influence of ontogeny

522   will become particularly interesting when considering, for example, the prefrontal cortex — a

523   highly variable, evolutionary new brain region that matures relatively late compared with other

524   brain regions and shows evidence for strong hemispheric specialization[106,107]. Both developmental

525   and phylogenetic aspects, however, are still rarely considered in the context of studies of brain

526   parcellation, though we expect this may change rapidly. Although multimodal MRI only

527   captures a limited repertoire of neurobiological properties, it has the advantage of being readily

528   performed not only at different stages across the human lifespan, but also in non-human

529   primates or rodents. Comparisons with non-human primates have often highlighted similarities

530   in brain organization to humans[8,108-113], but there is also evidence of differences[114]. For example, a

531   recent study has suggested the existence of an area called 'FPl' (referring to its lateral frontal

532   pole location) in humans that lacks correspondence with any region in macaque prefrontal

533   cortex[115]. Similarly, the first studies of brain organization in non-human primates with

534   approaches mirroring those used in humans have only been recently performed[44,84,116,117]. In turn,

535   and quite surprisingly, systematic comparisons of parcellations across the human lifespan are

536   still completely absent, even though there is no doubt that brain structure, function and

537   connectivity dynamically change throughout the entire human lifespan.

538

539

540

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

608 approach by allowing whole brain microstructural investigations without sample size
609 restriction.

610

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

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

625

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

636

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

641

By contrast, non-negative matrix factorization[19] approaches constrain the decomposed components to be strictly non-negative. Together with additional constraints (e.g., components are encouraged to be mostly zero, except in small numbers of locations), non-negative matrix factorization often yields a "part-based" decomposition of the data. For example, when applied to face photographs, NMF will yield components representing distinct face "parts" (e.g., nose, eyes, 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 so the choice of the 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 [G]**[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]. Nevertheless, comprehensive empirical and theoretical studies evaluating the advantages and limitations of each approach and variants thereof for different data sets and parcellation purposes are lacking for clear guidelines of their use in brain parcellation.

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[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 and functional connectivity represent very broad concepts with many different measurement and computation approaches, each carrying its own advantages and challenges as well as their

676 potentially unique contributions to multimodal brain-mapping endeavours. The four approaches

677 assessing connectivity most frequently used in brain parcellation are resting-state functional

678 connectivity, meta-analytic connectivity modelling, diffusion tractography and structural

679 covariance (see the table).

680

681 Meta-analytic connectivity modelling reflects task-based functional organization estimated

682 from the co-activation patterns of voxels across many studies, whereas structural covariance

683 reflects functional coupling that is suggested by concurrent morphological variations across a

684 group of subjects. Both approaches rely on covariation across a population sample (structural

685 covariance) or multiple group studies (meta-analytic connectivity modelling), in contrast to

686 probabilistic diffusion tractography and resting-state functional connectivity, in which

687 measures are inferred independently for each subject. Within the structural versus functional

688 taxonomy, structural covariance is in an ambiguous position, as it is a proxy for functional

689 connectivity but inferred from statistical covariance in brain structure.

690

691 CBP was initially developed for connectivity computed at the individual subject level, but was

692 quickly extended to connectivity inferred from statistical dependencies across a data set. Each

693 type of connectivity measure has its own strengths and limitations and are prone to particular

694 artefacts. For example, diffusion tractography might yield spurious results[128] due to several

695 factors. Crossing fibres **[G]** might cause the tractography model to 'jump' between tracts,

696 leading to false positives. Furthermore, diffusion tractography shows a gyral bias: more

697 connections may be detected hitting the crown of a gyrus than its wall, owing to intrinsic

698 geometry of cortical folds[130,131]. Conversely, tractography may also fail to infer the connectivity

699 of grey matter voxels or vertices near the pial surface particularly spatially distant from white

700 matter[68]. In addition, the limited spatial resolution of current tractography methods can

701 potentially result in false negative (missed connections), in particular with regards to small

702 white fibres[132].

703 Functional connectivity approaches are less affected by geometric factors, but signal loss and

704 distortion are nevertheless common with fMRI near air–tissue interfaces. Furthermore,

705 functional connectivity approaches are based on statistical dependencies between regions

706 (either at the subject level in resting-state functional connectivity, or at the group level in meta-

707 analytic connectivity modelling and structural covariance), and are therefore sensitive to

708 confounding factors. For example, fMRI, particularly rs-fMRI, is sensitive to various systemic

709 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]

		s			
	subcortical structures				
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.

793 **Cytoarchitecture**

794 Tissue composition with regards to cell characteristics.

795

796 **Myeloarchitecture**

797 The pattern of myelinated fibres.

798

799 **Visuotopic mapping**

800 Identification of visual areas based on differential cortical responses to different visual stimuli.

801 An example of a mapping stimulus would be a rotating sector of a flashing checkerboard.

802

803 **Echo planar imaging**

804 An MRI sequence used for functional and diffusion imaging.

805

806 **Meta-analytic connectivity modelling**

807 Method that aims to model functional connectivity in the brain based on co-activation pattern

808 across various activation studies.

809

810 **Probabilistic tractography**

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

812

813 **<u>Structural covariance</u>**

814 **<u>Pattern of co-variations in measures of morphometry (such as grey matter volume) across</u>**

815 **<u>brain regions.</u>**

816

817 **k-means**

818 A clustering algorithm that divides a set of data points into k clusters by iteratively optimizing

819 the definition of each cluster centroid and data points assigned to the clusters.

820

821 **<u>Domains</u>**

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

823

824 **Non-negative matrix factorization**

825 A multivariate statistical approach to factorize data into components promoting part-based

826 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.

861

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.

866

867

Competing interests

The authors declare no competing interests.

870

871

<u>References</u>

873

1   Tononi, G., Sporns, O. & Edelman, G. M. A measure for brain complexity: relating functional segregation and integration in the nervous system. *Proceedings of the National Academy of Sciences* **91**, 5033-5037 (1994).

2   Fox, P. T. & Friston, K. J. Distributed processing; distributed functions? *NeuroImage* **61**, 407-426 (2012).

3   Bijsterbosch, J. D. *et al.* The relationship between spatial configuration and functional connectivity of brain regions. *eLife* **7**, e32992 (2018).

4   Cachia, A. *et al.* How interindividual differences in brain anatomy shape reading accuracy. *Brain Structure and Function* **223**, 701-712 (2018).

5   Kong, R. *et al.* Spatial Topography of Individual-Specific Cortical Networks Predicts Human Cognition, Personality and Emotion. *Cereb Cortex* (2018).

6   Amunts, K. *et al.* Cytoarchitectonic mapping of the human amygdala, hippocampal region and entorhinal cortex: intersubject variability and probability maps. *Anatomy and embryology* **210**, 343-352 (2005).

7   Strange, B. A., Witter, M. P., Lein, E. S. & Moser, E. I. Functional organization of the hippocampal longitudinal axis. *Nature reviews. Neuroscience* **15**, 655-669, doi:10.1038/nrn3785 (2014).

8   Geyer, S. & Zilles, K. in *Higher-Order Motor Disorders: From Neuroanatomy and Neurobiology to Clinical Neurology*   3-22 (Oxford University Press, 2005).

9   Schubotz, R. I., Anwander, A., Knösche, T. R., von Cramon, D. Y. & Tittgemeyer, M. Anatomical and functional parcellation of the human lateral premotor cortex. *NeuroImage* **50**, 396-408 (2010).

896   10   Churchland, P. S. & Sejnowski, T. J. Perspectives on cognitive neuroscience. *Science*
897   **242**, 741 (1988).

898   11   Eickhoff, S. B., Constable, R. T. & Yeo, B. T. Topographic organization of the
899   cerebral cortex and brain cartography. *NeuroImage*,
900   doi:10.1016/j.neuroimage.2017.02.018 (2017).

901   12   Felleman, D. J. & Van Essen, D. C. Distributed hierarchical processing in the primate
902   cerebral cortex. *Cerebral cortex (New York, NY: 1991)* **1**, 1-47 (1991).

903   13   Amunts, K. & Zilles, K. Architectonic Mapping of the Human Brain beyond
904   Brodmann. *Neuron* **88**, 1086-1107, doi:10.1016/j.neuron.2015.12.001 (2015).

905   14   Brodmann, K. *Vergleichende Lokalisationslehre der Grosshirnrinde in ihren*
906   *Prinzipien dargestellt auf Grund des Zellenbaues.* (Johann Ambrosius Barth, 1909).

907   15   Preuss, T. M. & Goldman-Rakic, P. S. Architectonics of the parietal and temporal
908   association cortex in the strepsirhine primate Galago compared to the anthropoid
909   primate Macaca. *Journal of Comparative Neurology* **310**, 475-506 (1991).

910   16   Glasser, M. *et al*. A Multi-modal parcellation of human cerebral cortex. *Nature*
911   (2016).

912   17   Amunts, K. *et al*. Broca's region revisited: cytoarchitecture and intersubject
913   variability. *Journal of Comparative Neurology* **412**, 319-341 (1999).

914   18   Wang, D. *et al*. Parcellating cortical functional networks in individuals. *Nature*
915   *neuroscience* **18**, 1853-1860, doi:10.1038/nn.4164 (2015).

916   19   Gordon, E. M., Laumann, T. O., Adeyemo, B. & Petersen, S. E. Individual variability
917   of the system-level organization of the human brain. *Cerebral Cortex* **27**, 386-399
918   (2017).

919   20   Finn, E. S. *et al*. Functional connectome fingerprinting: identifying individuals using
920   patterns of brain connectivity. *Nature neuroscience* **18**, 1664-1671,
921   doi:10.1038/nn.4135 (2015).

922   21   Davatzikos, C. Computational neuroanatomy using brain deformations: From brain
923   parcellation to multivariate pattern analysis and machine learning. *Medical image*
924   *analysis* **33**, 149-154, doi:10.1016/j.media.2016.06.026 (2016).

925   22   Miller, K. L. *et al*. Multimodal population brain imaging in the UK Biobank
926   prospective epidemiological study. *Nature neuroscience* **19**, 1523-1536,
927   doi:10.1038/nn.4393 (2016).

928 23 Varikuti, D. P. *et al*. Evaluation of non-negative matrix factorization of grey matter in
929 age prediction. *NeuroImage* **173**, 394-410, doi:10.1016/j.neuroimage.2018.03.007
930 (2018).

931 24 Bullmore, E. & Sporns, O. Complex brain networks: graph theoretical analysis of
932 structural and functional systems. *Nature Reviews Neuroscience* **10**, 186-198 (2009).

933 25 Arslan, S. *et al*. Human brain mapping: A systematic comparison of parcellation
934 methods for the human cerebral cortex. *NeuroImage*,
935 doi:10.1016/j.neuroimage.2017.04.014 (2017).

936 26 Smith, S. M. *et al*. Correspondence of the brain's functional architecture during
937 activation and rest. *Proceedings of the National Academy of Sciences* **106**, 13040-
938 13045 (2009).

939 27 Lutti, A., Dick, F., Sereno, M. I. & Weiskopf, N. Using high-resolution quantitative
940 mapping of R1 as an index of cortical myelination. *NeuroImage* **93**, 176-188 (2014).

941 28 Glasser, M. F. & Van Essen, D. C. Mapping human cortical areas in vivo based on
942 myelin content as revealed by T1-and T2-weighted MRI. *Journal of Neuroscience* **31**,
943 11597-11616 (2011).

944 29 De Martino, F. *et al*. High-Resolution Mapping of Myeloarchitecture In Vivo:
945 Localization of Auditory Areas in the Human Brain. *Cereb Cortex* **25**, 3394-3405,
946 doi:10.1093/cercor/bhu150 (2015).

947 30 Sereno, M. I., Lutti, A., Weiskopf, N. & Dick, F. Mapping the human cortical surface
948 by combining quantitative T 1 with retinotopy. *Cerebral cortex* **23**, 2261-2268 (2012).

949 31 Wilms, M. *et al*. Comparison of functional and cytoarchitectonic maps of human
950 visual areas V1, V2, V3d, V3v, and V4 (v). *NeuroImage* **49**, 1171-1179 (2010).

951 32 Orban, P. *et al*. The Richness of Task-Evoked Hemodynamic Responses Defines a
952 Pseudohierarchy of Functionally Meaningful Brain Networks. *Cereb Cortex* **25**, 2658-
953 2669, doi:10.1093/cercor/bhu064 (2015).

954 33 Huth, A. G., de Heer, W. A., Griffiths, T. L., Theunissen, F. E. & Gallant, J. L.
955 Natural speech reveals the semantic maps that tile human cerebral cortex. *Nature* **532**,
956 453-458, doi:10.1038/nature17637 (2016).

957 34 Kurth, F., Zilles, K., Fox, P. T., Laird, A. R. & Eickhoff, S. B. A link between the
958 systems: functional differentiation and integration within the human insula revealed by
959 meta-analysis. *Brain structure & function* **214**, 519-534, doi:10.1007/s00429-010-
960 0255-z (2010).

961   35   Yang, Y. *et al.* Identifying functional subdivisions in the human brain using meta-
962   analytic activation modeling-based parcellation. *NeuroImage* **124**, 300-309,
963   doi:10.1016/j.neuroimage.2015.08.027 (2016).

964   36   Laird, A. R., Lancaster, J. L. & Fox, P. T. BrainMap: the social evolution of a human
965   brain mapping database. *Neuroinformatics* **3**, 65-78 (2005).

966   37   Yarkoni, T., Poldrack, R. A., Nichols, T. E., Van Essen, D. C. & Wager, T. D. Large-
967   scale automated synthesis of human functional neuroimaging data. *Nature methods* **8**,
968   665-670 (2011).

969   38   Gorgolewski, K. J. *et al.* NeuroVault. org: A repository for sharing unthresholded
970   statistical maps, parcellations, and atlases of the human brain. *NeuroImage* **124**, 1242-
971   1244 (2016).

972   39   Langner, R., Rottschy, C., Laird, A. R., Fox, P. T. & Eickhoff, S. B. Meta-analytic
973   connectivity modeling revisited: controlling for activation base rates. *NeuroImage* **99**,
974   559-570 (2014).

975   40   Pinho, A. L. *et al.* Individual Brain Charting, a high-resolution fMRI dataset for
976   cognitive mapping. *Scientific data* **5**, 180105, doi:10.1038/sdata.2018.105 (2018).

977   41   Glasser, M. F., Goyal, M. S., Preuss, T. M., Raichle, M. E. & Van Essen, D. C. Trends
978   and properties of human cerebral cortex: correlations with cortical myelin content.
979   *NeuroImage* **93 Pt 2**, 165-175, doi:10.1016/j.neuroimage.2013.03.060 (2014).

980   42   Fischl, B. & Sereno, M. I. Microstructural parcellation of the human brain.
981   *NeuroImage* (2018).

982   43   Augustinack, J. C. *et al.* MRI parcellation of ex vivo medial temporal lobe.
983   *NeuroImage* **93 Pt 2**, 252-259, doi:10.1016/j.neuroimage.2013.05.053 (2014).

984   44   Gao, Y. *et al.* Tests of cortical parcellation based on white matter connectivity using
985   diffusion tensor imaging. *NeuroImage*, doi:10.1016/j.neuroimage.2017.02.048 (2017).

986   45   Eickhoff, S. *et al.* High-resolution MRI reflects myeloarchitecture and
987   cytoarchitecture of human cerebral cortex. *Human brain mapping* **24**, 206-215,
988   doi:10.1002/hbm.20082 (2005).

989   46   Walters, N. B. *et al.* Observer-independent analysis of high-resolution MR images of
990   the human cerebral cortex: in vivo delineation of cortical areas. *Human brain mapping*
991   **28**, 1-8, doi:10.1002/hbm.20267 (2007).

992   47   Toga, A. W., Thompson, P. M., Mori, S., Amunts, K. & Zilles, K. Towards
993   multimodal atlases of the human brain. *Nature reviews. Neuroscience* **7**, 952-966,
994   doi:10.1038/nrn2012 (2006).

995	48	Passingham, R. E., Stephan, K. E. & Kotter, R. The anatomical basis of functional
996		localization in the cortex. *Nature reviews. Neuroscience* **3**, 606-616,
997		doi:10.1038/nrn893 (2002).
998	49	Behrens, T. E. J. *et al.* Non-invasive mapping of connections between human
999		thalamus and cortex using diffusion imaging. *Nature neuroscience* **6**, 750-757 (2003).
1000	50	Raichle, M. E. The restless brain: how intrinsic activity organizes brain function.
1001		*Philosophical transactions of the Royal Society of London. Series B, Biological*
1002		*sciences* **370**, doi:10.1098/rstb.2014.0172 (2015).
1003	51	Gilbert, S. J., Gonen-Yaacovi, G., Benoit, R. G., Volle, E. & Burgess, P. W. Distinct
1004		functional connectivity associated with lateral versus medial rostral prefrontal cortex:
1005		a meta-analysis. *NeuroImage* **53**, 1359-1367, doi:10.1016/j.neuroimage.2010.07.032
1006		(2010).
1007	52	de la Vega, A., Chang, L. J., Banich, M. T., Wager, T. D. & Yarkoni, T. Large-scale
1008		meta-analysis of human medial frontal cortex reveals tripartite functional organization.
1009		*Journal of Neuroscience* **36**, 6553-6562 (2016).
1010	53	Cha, J., Jo, H. J., Gibson, W. S. & Lee, J. M. Functional organization of the human
1011		posterior cingulate cortex, revealed by multiple connectivity-based parcellation
1012		methods. *Human brain mapping* **38**, 2808-2818, doi:10.1002/hbm.23570 (2017).
1013	54	Schaefer, A. *et al.* Local-Global Parcellation of the Human Cerebral Cortex from
1014		Intrinsic Functional Connectivity MRI. *Cereb Cortex*, 1-20,
1015		doi:10.1093/cercor/bhx179 (2017).
1016	55	Cohen, A. L. *et al.* Defining functional areas in individual human brains using resting
1017		functional connectivity MRI. *NeuroImage* **41**, 45-57 (2008).
1018	56	Barnes, K. A. *et al.* Identifying basal ganglia divisions in individuals using resting-
1019		state functional connectivity MRI. *Frontiers in systems neuroscience* **4** (2010).
1020	57	Nelson, S. M. *et al.* Role of the anterior insula in task-level control and focal attention.
1021		*Brain structure and function* **214**, 669-680 (2010).
1022	58	Nelson, S. M. *et al.* A parcellation scheme for human left lateral parietal cortex.
1023		*Neuron* **67**, 156-170 (2010).
1024	59	Gordon, E. M. *et al.* Generation and Evaluation of a Cortical Area Parcellation from
1025		Resting-State Correlations. *Cereb Cortex* **26**, 288-303, doi:10.1093/cercor/bhu239
1026		(2016).

1027	60	Johansen-Berg, H. *et al*. Changes in connectivity profiles define functionally distinct
1028		regions in human medial frontal cortex. *Proceedings of the National Academy of*
1029		*Sciences of the United States of America* **101**, 13335-13340 (2004).
1030	61	Bellec, P., Rosa-Neto, P., Lyttelton, O. C., Benali, H. & Evans, A. C. Multi-level
1031		bootstrap analysis of stable clusters in resting-state fMRI. *NeuroImage* **51**, 1126-1139,
1032		doi:10.1016/j.neuroimage.2010.02.082 (2010).
1033	62	Ryali, S., Chen, T., Padmanabhan, A., Cai, W. & Menon, V. Development and
1034		validation of consensus clustering-based framework for brain segmentation using
1035		resting fMRI. *Journal of neuroscience methods* **240**, 128-140,
1036		doi:10.1016/j.jneumeth.2014.11.014 (2015).
1037	63	Cauda, F. *et al*. Meta-analytic clustering of the insular cortex: characterizing the meta-
1038		analytic connectivity of the insula when involved in active tasks. *NeuroImage* **62**, 343-
1039		355 (2012).
1040	64	Kelly, C. *et al*. A convergent functional architecture of the insula emerges across
1041		imaging modalities. *NeuroImage* **61**, 1129-1142 (2012).
1042	65	Eickhoff, S. B. *et al*. Co-activation patterns distinguish cortical modules, their
1043		connectivity and functional differentiation. *NeuroImage* **57**, 938-949,
1044		doi:10.1016/j.neuroimage.2011.05.021 (2011).
1045	66	Cohen, M. X., Lombardo, M. V. & Blumenfeld, R. S. Covariance-based subdivision
1046		of the human striatum using T1-weighted MRI. *European Journal of Neuroscience* **27**,
1047		1534-1546 (2008).
1048	67	Genon, S. *et al*. The Right Dorsal Premotor Mosaic: Organization, Functions, and
1049		Connectivity. *Cereb Cortex* **27**, 2095-2110, doi:10.1093/cercor/bhw065 (2017).
1050	68	Genon, S. *et al*. The heterogeneity of the left dorsal premotor cortex evidenced by
1051		multimodal connectivity-based parcellation and functional characterization.
1052		*NeuroImage* **170**, 400-411, doi:10.1016/j.neuroimage.2017.02.034 (2018).
1053	69	Eickhoff, S. B., Thirion, B., Varoquaux, G. & Bzdok, D. Connectivity-based
1054		parcellation: Critique and implications. *Human brain mapping* **36**, 4771-4792,
1055		doi:10.1002/hbm.22933 (2015).
1056	70	Yeo, B. T. *et al*. The organization of the human cerebral cortex estimated by intrinsic
1057		functional connectivity. *J Neurophysiol* **106**, 1125-1165, doi:10.1152/jn.00338.2011
1058		(2011).
1059	71	Jain, A. K. Data clustering: 50 years beyond K-means. *Pattern recognition letters* **31**,
1060		651-666 (2010).

1061 72 Clos, M., Amunts, K., Laird, A. R., Fox, P. T. & Eickhoff, S. B. Tackling the
1062   multifunctional nature of Broca's region meta-analytically: co-activation-based
1063   parcellation of area 44. *NeuroImage* **83**, 174-188,
1064   doi:10.1016/j.neuroimage.2013.06.041 (2013).
1065 73 Kahnt, T., Chang, L. J., Park, S. Q., Heinzle, J. & Haynes, J.-D. Connectivity-based
1066   parcellation of the human orbitofrontal cortex. *The Journal of Neuroscience* **32**, 6240-
1067   6250 (2012).
1068 74 Kelly, C. *et al*. Broca's region: linking human brain functional connectivity data and
1069   non-human primate tracing anatomy studies. *European Journal of Neuroscience* **32**,
1070   383-398, doi:10.1111/j.1460-9568.2010.07279.x (2010).
1071 75 van Oort, E. S. B. *et al*. Functional parcellation using time courses of instantaneous
1072   connectivity. *NeuroImage*, doi:10.1016/j.neuroimage.2017.07.027 (2017).
1073 76 Laumann, T. O. *et al*. Functional System and Areal Organization of a Highly Sampled
1074   Individual Human Brain. *Neuron* **87**, 657-670, doi:10.1016/j.neuron.2015.06.037
1075   (2015).
1076 77 Zilles, K. *et al*. Architectonics of the human cerebral cortex and transmitter receptor
1077   fingerprints: reconciling functional neuroanatomy and neurochemistry. *European*
1078   *neuropsychopharmacology* **12**, 587-599 (2002).
1079 78 van den Heuvel, M. P., Scholtens, L. H., Feldman Barrett, L., Hilgetag, C. C. & de
1080   Reus, M. A. Bridging Cytoarchitectonics and Connectomics in Human Cerebral
1081   Cortex. *The Journal of neuroscience : the official journal of the Society for*
1082   *Neuroscience* **35**, 13943-13948, doi:10.1523/jneurosci.2630-15.2015 (2015).
1083 79 Sporns, O. Cerebral cartography and connectomics. *Philosophical transactions of the*
1084   *Royal Society of London. Series B, Biological sciences* **370**,
1085   doi:10.1098/rstb.2014.0173 (2015).
1086 80 Cloutman, L. L. & Ralph, M. A. L. Connectivity-based structural and functional
1087   parcellation of the human cortex using diffusion imaging and tractography. *Frontiers*
1088   *in neuroanatomy* **6** (2012).
1089 81 Chase, H. W. *et al*. Evidence for an anterior–posterior differentiation in the human
1090   hippocampal formation revealed by meta-analytic parcellation of fMRI coordinate
1091   maps: Focus on the subiculum. *NeuroImage* **113**, 44-60 (2015).
1092 82 Adnan, A. *et al*. Distinct hippocampal functional networks revealed by tractography-
1093   based parcellation. *Brain structure & function* **221**, 2999-3012, doi:10.1007/s00429-
1094   015-1084-x (2016).

1095 83 Craddock, R. C., James, G. A., Holtzheimer, P. E., Hu, X. P. & Mayberg, H. S. A
1096   whole brain fMRI atlas generated via spatially constrained spectral clustering. *Human*
1097   *brain mapping* **33**, 1914-1928 (2012).

1098 84 Cerliani, L., D'Arceuil, H. & Thiebaut de Schotten, M. Connectivity-based
1099   parcellation of the macaque frontal cortex, and its relation with the cytoarchitectonic
1100   distribution described in current atlases. *Brain structure & function* **222**, 1331-1349,
1101   doi:10.1007/s00429-016-1280-3 (2017).

1102 85 Ding, S. L. *et al*. Comprehensive cellular-resolution atlas of the adult human brain.
1103   *Journal of Comparative Neurology* **524**, 3127-3481 (2016).

1104 86 Wang, J. *et al*. Convergent functional architecture of the superior parietal lobule
1105   unraveled with multimodal neuroimaging approaches. *Human brain mapping* **36**, 238-
1106   257 (2015).

1107 87 Xia, X. *et al*. Multimodal connectivity-based parcellation reveals a shell-core
1108   dichotomy of the human nucleus accumbens. *Human brain mapping* (2017).

1109 88 Nachev, P., Kennard, C. & Husain, M. The functional anatomy of the frontal lobes.
1110   *Nature Reviews Neuroscience* **10**, 829, doi:10.1038/nrn2667-c1 (2009).

1111 89 Wang, C., Yoldemir, B. & Abugharbieh, R. in *International Conference on Medical*
1112   *Image Computing and Computer-Assisted Intervention*. 21-28 (Springer).

1113 90 Kaas, J. H. Evolution of columns, modules, and domains in the neocortex of primates.
1114   *Proceedings of the National Academy of Sciences* **109**, 10655-10660 (2012).

1115 91 Kaas, J. H. & Stepniewska, I. Evolution of posterior parietal cortex and parietal-
1116   frontal networks for specific actions in primates. *The Journal of comparative*
1117   *neurology* **524**, 595-608, doi:10.1002/cne.23838 (2016).

1118 92 Vogt, C. & Vogt, O. Die vergleichend-architektonische und die vergleichend-
1119   reizphysiologische Felderung der Großhirnrinde unter besonderer Berücksichtigung
1120   der menschlichen. *Naturwissenschaften* **14**, 1190-1194 (1926).

1121 93 Genon, S., Reid, A., Langner, R., Amunts, K. & Eickhoff, S. B. How to Characterize
1122   the Function of a Brain Region. *Trends in cognitive sciences*,
1123   doi:10.1016/j.tics.2018.01.010 (2018).

1124 94 Fischl, B. *et al*. Cortical folding patterns and predicting cytoarchitecture. *Cerebral*
1125   *cortex* **18**, 1973-1980 (2007).

1126 95 Mueller, S. *et al*. Individual variability in functional connectivity architecture of the
1127   human brain. *Neuron* **77**, 586-595 (2013).

1128 96 Braga, R. M. & Buckner, R. L. Parallel interdigitated distributed networks within the
1129   individual estimated by intrinsic functional connectivity. *Neuron* **95**, 457-471. e455
1130   (2017).

1131 97 Gordon, E. M. *et al*. Precision functional mapping of individual human brains. *Neuron*
1132   **95**, 791-807. e797 (2017).

1133 98 Zilles, K. & Amunts, K. Individual variability is not noise. *Trends in cognitive*
1134   *sciences* **17**, 153-155 (2013).

1135 99 Salehi, M., Karbasi, A., Shen, X., Scheinost, D. & Constable, R. T. An exemplar-
1136   based approach to individualized parcellation reveals the need for sex specific
1137   functional networks. *NeuroImage* (2017).

1138 100 Power, J. D., Schlaggar, B. L., Lessov-Schlaggar, C. N. & Petersen, S. E. Evidence for
1139   hubs in human functional brain networks. *Neuron* **79**, 798-813 (2013).

1140 101 Sepulcre, J. *et al*. The organization of local and distant functional connectivity in the
1141   human brain. *PLoS computational biology* **6**, e1000808,
1142   doi:10.1371/journal.pcbi.1000808 (2010).

1143 102 Tzourios-Mazoyer, N. *et al*. Automated anatomical labeling of activations in SPM
1144   using a macroscopic anatomical parcellation of the MNI MRI single-subject brain.
1145   *NeuroImage* **15**, 273-289 (2002).

1146 103 Fan, L. *et al*. The human brainnetome atlas: a new brain atlas based on connectional
1147   architecture. *Cerebral Cortex*, bhw157 (2016).

1148 104 Robinson, J. L. *et al*. Neurofunctional topography of the human hippocampus. *Human*
1149   *brain mapping* **36**, 5018-5037, doi:10.1002/hbm.22987 (2015).

1150 105 Chi, J. G., Dooling, E. C. & Gilles, F. H. Gyral development of the human brain.
1151   *Annals of neurology* **1**, 86-93 (1977).

1152 106 Semendeferi, K., Lu, A., Schenker, N. & Damásio, H. Humans and great apes share a
1153   large frontal cortex. *Nature neuroscience* **5**, 272-276 (2002).

1154 107 Wood, J. N. & Grafman, J. Human prefrontal cortex: processing and representational
1155   perspectives. *Nature Reviews Neuroscience* **4**, 139-147 (2003).

1156 108 Geyer, S., Matelli, M., Luppino, G. & Zilles, K. Functional neuroanatomy of the
1157   primate isocortical motor system. *Anatomy and embryology* **202**, 443-474 (2000).

1158 109 Rizzolatti, G., Luppino, G. & Matelli, M. The organization of the cortical motor
1159   system: new concepts. *Electroencephalography and clinical neurophysiology* **106**,
1160   283-296 (1998).

1161 110 Rizzolatti, G. & Luppino, G. The Cortical Motor System. *Neuron* **31**, 889-901,
1162   doi:http://dx.doi.org/10.1016/S0896-6273(01)00423-8 (2001).
1163 111 Petrides, M. & Pandya, D. Dorsolateral prefrontal cortex: comparative
1164   cytoarchitectonic analysis in the human and the macaque brain and corticocortical
1165   connection patterns. *European Journal of Neuroscience* **11**, 1011-1036 (1999).
1166 112 Petrides, M. & Pandya, D. Comparative cytoarchitectonic analysis of the human and
1167   the macaque ventrolateral prefrontal cortex and corticocortical connection patterns in
1168   the monkey. *European Journal of Neuroscience* **16**, 291-310 (2002).
1169 113 Vincent, J. L. *et al*. Intrinsic functional architecture in the anaesthetized monkey brain.
1170   *Nature* **447**, 83-86 (2007).
1171 114 Orban, G. A., Van Essen, D. & Vanduffel, W. Comparative mapping of higher visual
1172   areas in monkeys and humans. *Trends in cognitive sciences* **8**, 315-324 (2004).
1173 115 Neubert, F.-X., Mars, R. B., Thomas, A. G., Sallet, J. & Rushworth, M. F.
1174   Comparison of human ventral frontal cortex areas for cognitive control and language
1175   with areas in monkey frontal cortex. *Neuron* **81**, 700-713 (2014).
1176 116 Xu, T. *et al*. Delineating the Macroscale Areal Organization of the Macaque Cortex
1177   In Vivo. *Cell Reports* **23**, 429-441,
1178   doi:10.1016/j.celrep.2018.03.049 (2018).
1179 117 Croxson, P. L., Forkel, S. J., Cerliani, L. & Thiebaut de Schotten, M. Structural
1180   Variability Across the Primate Brain: A Cross-Species Comparison. *Cerebral Cortex*,
1181   1-13 (2017).
1182 118 Zilles, K. & Amunts, K. Centenary of Brodmann's map--conception and fate. *Nature*
1183   *reviews. Neuroscience* **11**, 139-145, doi:10.1038/nrn2776 (2010).
1184 119 Klatzo, I. *Cécile and Oskar Vogt: the visionaries of modern neuroscience*. Vol. 80
1185   (Springer Science & Business Media, 2002).
1186 120 Talairach, J. & Tournoux, P.   (Thieme, New York, 1987).
1187 121 Frackowiak, R. & Markram, H. The future of human cerebral cartography: a novel
1188   approach. *Phil. Trans. R. Soc. B* **370**, 20140171 (2015).
1189 122 Schleicher, A., Amunts, K., Geyer, S., Morosan, P. & Zilles, K. Observer-independent
1190   method for microstructural parcellation of cerebral cortex: a quantitative approach to
1191   cytoarchitectonics. *NeuroImage* **9**, 165-177 (1999).
1192 123 Eickhoff, S. B. *et al*. A new SPM toolbox for combining probabilistic
1193   cytoarchitectonic maps and functional imaging data. *NeuroImage* **25**, 1325-1335
1194   (2005).

1195   124   Ding, C., He, X. & Simon, H. D. On the equivalence of nonnegative matrix

1196   factorization and spectral clustering. *Proceedings of the 2005 SIAM International*

1197   *Conference on Data Mining*, 606-610 (2005).

1198   125   Sotiras, A., Resnick, S. M. & Davatzikos, C. Finding imaging patterns of structural

1199   covariance via non-negative matrix factorization. *NeuroImage* **108**, 1-16 (2015).

1200   126   Yeo, B. T., Krienen, F. M., Chee, M. W. & Buckner, R. L. Estimates of segregation

1201   and overlap of functional connectivity networks in the human cerebral cortex.

1202   *NeuroImage* **88**, 212-227 (2014).

1203   127   Catani, M. The functional anatomy of white matter: from postmortem dissections to in

1204   vivo virtual tractography. *Diffusion MRI: Theory, Methods, and Applications. Oxford*

1205   *University Press, Oxford, UK*, 5-18 (2010).

1206   128   Maier-Hein, K. H. *et al.* The challenge of mapping the human connectome based on

1207   diffusion tractography. *Nature communications* **8**, 1349 (2017).

1208   129   Biswal, B., Zerrin Yetkin, F., Haughton, V. M. & Hyde, J. S. Functional connectivity

1209   in the motor cortex of resting human brain using echo-planar mri. *Magnetic resonance*

1210   *in medicine* **34**, 537-541 (1995).

1211   130   Van Essen, D. C. *et al.* Mapping connections in humans and nonhuman primates:

1212   aspirations and challenges for diffusion imaging. *Diffusion MRI, 2nd edition (eds.*

1213   *Johansen-Berg, H. & Behrens, TEJ)*, 337-358 (2013).

1214   131   Jbabdi, S. & Johansen-Berg, H. Tractography: where do we go from here? *Brain*

1215   *connectivity* **1**, 169-183 (2011).

1216   132   Catani, M. *et al.* Short frontal lobe connections of the human brain. *Cortex; a journal*

1217   *devoted to the study of the nervous system and behavior* **48**, 273-291 (2012).

1218   133   Birn, R. M. The role of physiological noise in resting-state functional connectivity.

1219   *NeuroImage* **62**, 864-870, doi:10.1016/j.neuroimage.2012.01.016 (2012).
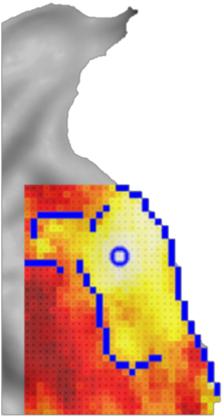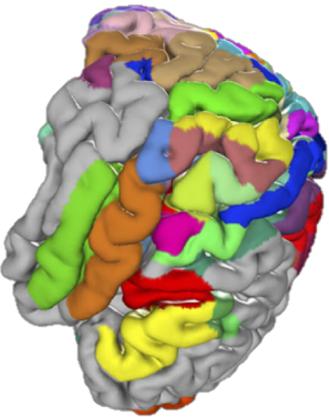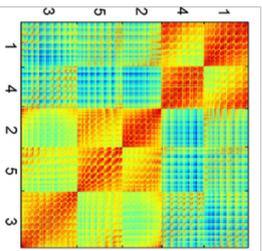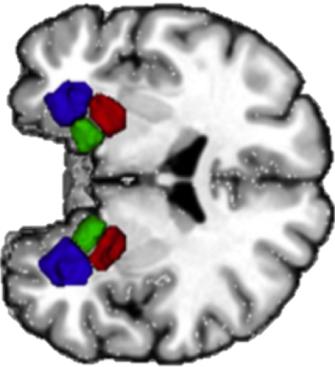
1220   134   Power, J. D., Barnes, K. A., Snyder, A. Z., Schlaggar, B. L. & Petersen, S. E. Spurious

1221   but systematic correlations in functional connectivity MRI networks arise from subject

1222   motion. *NeuroImage* **59**, 2142-2154 (2012).

1223   135   He, Y., Chen, Z. J. & Evans, A. C. Small-world anatomical networks in the human

1224   brain revealed by cortical thickness from MRI. *Cerebral cortex* **17**, 2407-2419 (2007).
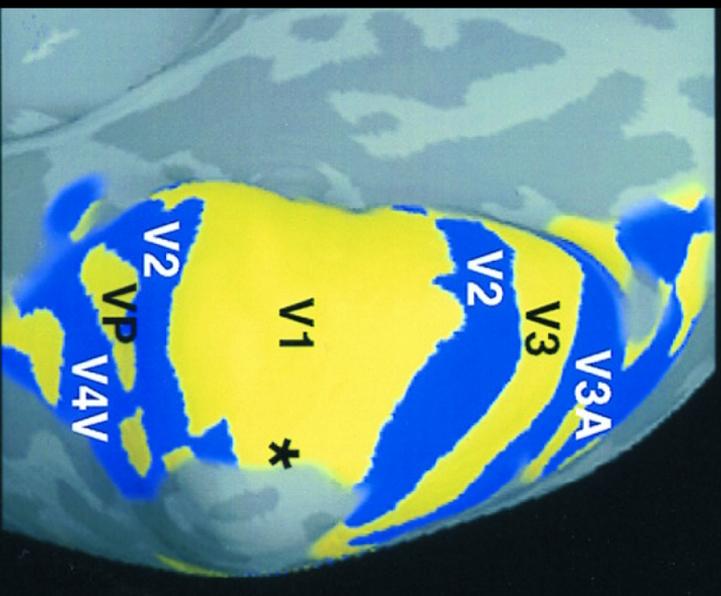
1225   136   Tootell, R. B. H. *et al.* Functional analysis of primary visual cortex (V1) in humans.

1226   *Proceedings of the National Academy of Sciences* **95**, 811 (1998).

1227 137 Amunts, K., Malikovic, A., Mohlberg, H., Schormann, T. & Zilles, K. Brodmann's
1228 areas 17 and 18 brought into stereotaxic space-where and how variable? *NeuroImage*
1229 **11**, 66-84, doi:10.1006/nimg.1999.0516 (2000).

1230 138 Tzourio-Mazoyer, N. *et al*. Automated anatomical labeling of activations in SPM
1231 using a macroscopic anatomical parcellation of the MNI MRI single-subject brain.
1232 *NeuroImage* **15**, 273-289, doi:10.1006/nimg.2001.0978 (2002).

1233 139 Frazier, J. A. *et al*. Structural brain magnetic resonance imaging of limbic and
1234 thalamic volumes in pediatric bipolar disorder. *American Journal of Psychiatry* **162**,
1235 1256-1265 (2005).

1236 140 Makris, N. *et al*. Decreased volume of left and total anterior insular lobule in
1237 schizophrenia. *Schizophrenia research* **83**, 155-171 (2006).

1238 141 Desikan, R. S. *et al*. An automated labeling system for subdividing the human cerebral
1239 cortex on MRI scans into gyral based regions of interest. *NeuroImage* **31**, 968-980
1240 (2006).

1241 142 Goldstein, J. M. *et al*. Hypothalamic abnormalities in schizophrenia: sex effects and
1242 genetic vulnerability. *Biological psychiatry* **61**, 935-945 (2007).

1243 143 Destrieux, C., Fischl, B., Dale, A. & Halgren, E. Automatic parcellation of human
1244 cortical gyri and sulci using standard anatomical nomenclature. *NeuroImage* **53**, 1-15
1245 (2010).

1246 144 Auzias, G., Coulon, O. & Brovelli, A. MarsAtlas: A cortical parcellation atlas for
1247 functional mapping. *Human brain mapping* **37**, 1573-1592 (2016).

1248 145 Power, J. D. *et al*. Functional network organization of the human brain. *Neuron* **72**,
1249 665-678 (2011).

1250 146 Buckner, R. L., Krienen, F. M., Castellanos, A., Diaz, J. C. & Yeo, B. T. The
1251 organization of the human cerebellum estimated by intrinsic functional connectivity. *J*
1252 *Neurophysiol* **106**, 2322-2345, doi:10.1152/jn.00339.2011 (2011).

1253 147 Choi, E. Y., Yeo, B. T. & Buckner, R. L. The organization of the human striatum
1254 estimated by intrinsic functional connectivity. *J Neurophysiol* **108**, 2242-2263,
1255 doi:10.1152/jn.00270.2012 (2012).

1256 148 Shen, X., Tokoglu, F., Papademetris, X. & Constable, R. T. Groupwise whole-brain
1257 parcellation from resting-state fMRI data for network node identification. *NeuroImage*
1258 **82**, 403-415 (2013).

1259 149 Joliot, M. *et al*. AICHA: An atlas of intrinsic connectivity of homotopic areas. *Journal*
1260 *of neuroscience methods* **254**, 46-59, doi:10.1016/j.jneumeth.2015.07.013 (2015).
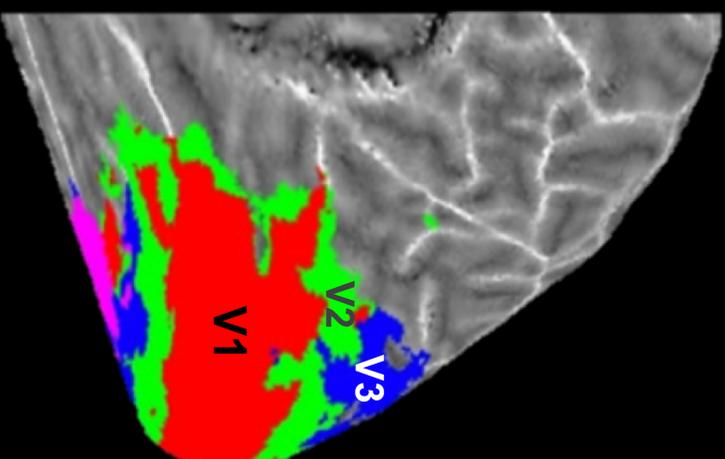
1261   150   Huth, A. G., Griffiths, T. L., Theunissen, F. E. & Gallant, J. L. PrAGMATiC: A

1262   probabilistic and generative model of areas tiling the cortex. *arXiv preprint*

1263   *arXiv:1504.03622* (2015).

1264

	Boundary-mapping	**Clustering/Factorization**
Markers / **Technical procedure**		
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

Cytoarchitecture

Myelin mapping

a

Subject A   Subject B   Subject C

b

Subject I   Subject II   Subject III

c

Day 2   Day 1

Subject 1   Subject 2   Subject 3