

Review article



Towards a biologically annotated brain connectome

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Abstract

The brain is a network of interleaved neural circuits. In modern connectomics, brain connectivity is typically encoded as a network of nodes and edges, abstracting away the rich biological detail of local neuronal populations. Yet biological annotations for network nodes – such as gene expression, cytoarchitecture, neurotransmitter receptors or intrinsic dynamics – can be readily measured and overlaid on network models. Here we review how connectomes can be represented and analysed as annotated networks. Annotated connectomes allow us to reconceptualize architectural features of networks and to relate the connection patterns of brain regions to their underlying biology. Emerging work demonstrates that annotated connectomes help to make more veridical models of brain network formation, neural dynamics and disease propagation. Finally, annotations can be used to infer entirely new inter-regional relationships and to construct new types of network that complement existing connectome representations. In summary, **biologically annotated connectomes** offer a compelling way to study neural wiring in concert with local biological features.

Sections

Introduction

Embracing regional heterogeneity

Annotations and neural wiring

Annotations and network architecture

Annotation-enhanced models of the brain

Geometry, topology and annotations

Annotation similarity networks

Concluding remarks

Introduction

Advances in imaging and tracing technology are yielding increasingly detailed wiring diagrams of neural systems¹. These wiring diagrams, termed connectomes, encode connection patterns among neural elements². Over the past 15 years, the dominant paradigm has been to represent connectomes as graphs, in which nodes represent single neurons or neuronal populations and edges represent anatomical projections or functional interactions³.

The graph model has become the lingua franca of network neuroscience, helping to quantify architectural features of brain networks^{4,5}. These include regionally specific connection profiles^{6–8}, a tendency for functionally similar areas to form spatially contiguous communities⁹ and a small set of disproportionately well-connected hub nodes that promote signal integration^{10–13}. These features have been observed across multiple spatial scales and reconstruction techniques and in multiple model organisms^{14,15}, including invertebrate^{16–19}, avian²⁰, rodent^{21–23}, feline^{24–26} and primate species^{27–29}. The ubiquity of these

architectural features suggests conserved and universal wiring principles of brain connectomes.

However, connectomes are typically represented and analysed as graphs with identical nodes³, abstracting away important micro-architectural features (including cytoarchitecture, neurotransmitter receptor profiles and laminar differentiation) that may drive macroscale structure–function coupling^{30–32}. How does macroscale wiring between neuronal populations relate to their microscale features? Concomitant advances in imaging technology and data science allow us to generate and access high-resolution maps of the brain across multiple modalities^{33–35}. By superimposing these maps of biological annotations onto connectomes, we can generate a new type of data object in neuroscience: annotated connectomes.

Here we review the nascent field of annotated connectomics. We argue that connectome representations enriched with biological features open fundamentally new avenues for quantifying and articulating brain network organization. We review new findings, as well as classical and emerging theories, of how local annotations relate to neural wiring. We then explore methodological and conceptual advances, including adapting network theoretic measures for annotated networks, incorporating annotations in dynamic models of network formation, network function and disease propagation, and disentangling the relationships between annotations, brain network topology and geometry. Finally, we outline how entirely new classes of connectivity modes can be reconstructed using biological annotations. Throughout, we focus on a singular theme: what new questions about brain organization can be addressed by jointly considering connectome architecture and biological annotations?

Box 1

Annotating network edges

Throughout this Review, we focus primarily on annotating the nodes of the network. However, brain connectomes can also have annotated edges. Edges capture pairwise relationships between brain regions and are usually weighted by the strength of the relationship between the two brain regions. For structural connectomes, edges are generally weighted by the number or density of streamlines between brain regions.

Similar to how nodes can be annotated by local biological or micro-architectural properties, edges too can be annotated with features besides connection strength^{215,216}. For example, it is possible to annotate edges based on neurite density²¹⁷, axon diameter distribution^{218,219}, myelin content²²⁰ or the g-ratio (ratio of inner and outer diameters of myelinated axons)^{221,222}. These techniques theoretically reflect the velocity and fidelity with which electrical impulses propagate via anatomical projections, although validation efforts are ongoing²²³. In some instances, physical projection lengths may also serve as edge annotations, such as when modelling the speed of diffusion of pathogenic molecules in neurodegenerative diseases¹⁷⁸. In model organisms, tools such as radioactive tracers, genetic labelling and electron microscopy can be used to comprehensively reconstruct finer properties of individual axonal projections and synaptic contacts²²⁴. Finally, edges can be annotated with directionality, such that each edge represents a direction of information flow. Directionality, sometimes referred to as ‘effective connectivity’, can be inferred using model-based techniques²²⁵, empirical estimation of temporal precedence^{226,227} and asymmetry of network-theoretic statistics²²⁸.

The concepts outlined in the present Review can be readily extended to annotated edges. Edge annotations — whether biological, physical or directional — can enrich network reconstructions, leading to more biologically refined estimates of network features such as hubs and modules (Fig. 2). Connectomes with annotated edges can also be seamlessly integrated into models of communication and disease propagation (Fig. 3).

Embracing regional heterogeneity

The conventional workflow in connectomics is to parcellate the brain into a set of discrete regions and to focus on their connection patterns. Multiple subfields have emerged in loose-knit tandem, focusing on quantifying architectural features using network theoretic methods³⁶, identifying individuals using connection patterns^{37–39}, relating connection patterns to cognition and behaviour^{40,41}, isolating connectivity markers of disease⁴² and mapping connection patterns across phylogeny and ontogeny^{8,43}. Implicit in all those approaches is the idea that brain regions are identical, insofar as none of these methods explicitly takes differences in node biology into account.

Yet, high-resolution maps of the brain can be readily generated using standard protocols in a wide array of histological, imaging and recording technologies, such as microarray and single-cell sequencing, microscopy, autoradiography, magnetic resonance imaging (MRI), electroencephalography (EEG) and magnetoencephalography (MEG), and positron-emission tomography (PET). These maps chart the spatial distribution of multiple structural and functional attributes, including gene transcription^{44,45}, neurotransmitter receptors and transporters^{46–51}, cell density⁵², cell types^{53,54} and morphology⁵⁵, laminar differentiation^{56,57}, myelination^{58–61}, grey matter morphometry^{62,63}, evolutionary and developmental expansion^{64–67}, metabolism^{68,69}, and intrinsic electromagnetic dynamics and haemodynamics^{70–75}. Network nodes can also be annotated using meta-analytic features, such as propensity to activate during particular tasks^{76–78} or disease vulnerability^{79–81}. In network neuroscience, nodes are also traditionally annotated according to their affiliations with larger discrete classes (for example, intrinsic networks⁸² or cortical types^{83–85}). Finally, we note that network edges can analogously be annotated with biological metadata (Box 1). Such maps are increasingly shared via open-access

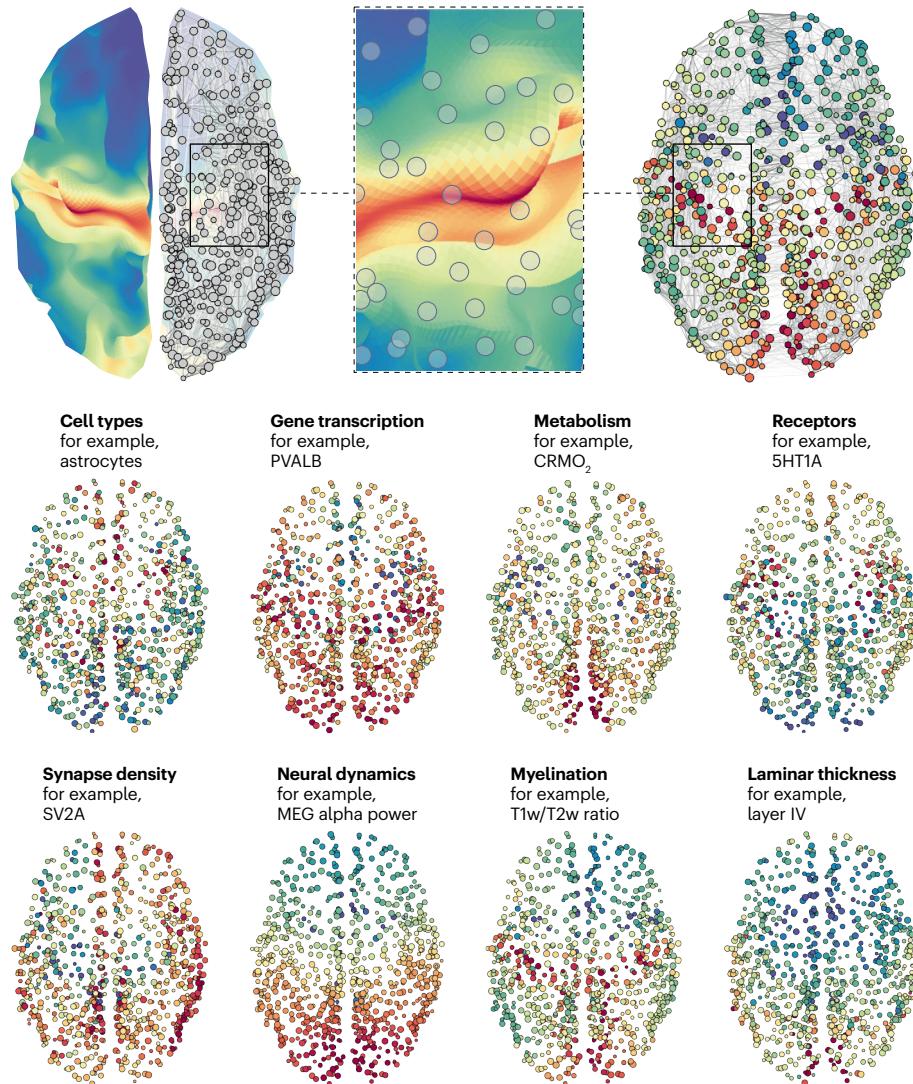


Fig. 1 | Constructing an annotated connectome. Top row: annotated connectomes are built by integrating a brain map representing some biological feature ('annotation', depicted by the surface map), and a brain network representing brain regions and their connection patterns (depicted by the grey nodes and edges; top left panel). Vertex or voxel values in the biological map are parcellated according to the same atlas used to define the nodes of the connectome. Annotation values for each region are estimated by calculating a summary measure (for example, mean, median or first principal component; top centre panel). The resulting object is a connectome in which nodes are enriched with weights that reflect a specific biological phenomenon – the annotated connectome (top right panel). Centre and bottom rows: brain networks can be annotated with a wide range of biological metadata capturing, for instance, regional variations in cell types (for example, astrocyte-specific gene expression⁵⁴), gene transcription (for example, PVALB, a proxy for parvalbumin-expressing interneurons), metabolism

(for example, PET-derived cerebral metabolic rate for oxygen (CMRO_2)⁶⁸), neurotransmitter receptors (for example, PET-derived 5HT1A receptor density⁴⁷), synapse density (for example, PET-derived synaptic vesicle glycoprotein 2A density (SV2A)²¹²), neural dynamics (for example, magnetoencephalography (MEG)-derived 8–12 Hz alpha band power spectral density), myelination (for example, MRI-derived T1w/T2w ratio) and laminar thickness (for example, layer IV thickness, derived by segmenting cortical layers in the Merker-stained BigBrain histological atlas^{52,56}). Supplementary Table 1 lists resources for accessing annotations. The figure was generated using open neuroimaging data in the neuromaps toolbox and open gene expression data from the Allen Human Brain Atlas^{35,44}. Data from neuromaps were downloaded, parcellated to 800 cortical regions according to the Schaefer atlas²¹³ and then plotted. Gene expression data from the Allen Human Brain Atlas were processed using default parameters in the abagen toolbox⁸⁸, parcellated to the same 800 cortical regions and plotted.

repositories and toolboxes, with a concerted effort to standardize coordinate systems^{35,86,87} and workflows^{88–91}.

How do we use these datasets to build an annotated connectome? Once you have a biological map, annotating a connectome is straightforward. Vertex or voxel values in the biological map are

subdivided into parcels according to the same atlas that was used to reconstruct the connectome (Fig. 1). The most common approach is to take the mean value, but alternative methods, such as the median or the first principal component, are also possible. If annotations are not densely sampled across the surface, such as in the case of

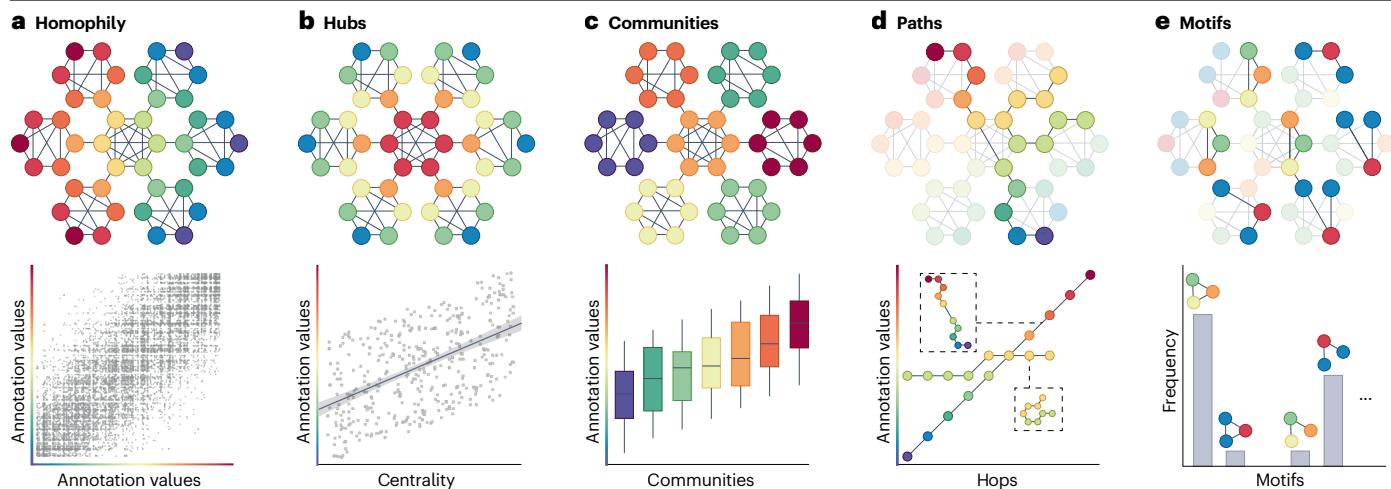


Fig. 2 | Architectural features of annotated connectomes. Biological features add further depth to conventional graph theoretic measures. In all panels, nodes represent brain regions, edges represent connections between regions and colours represent the value of a biological annotation for each node. **a**, Top: the network displays homophily, whereby nodes with similar annotations (colours) have a higher tendency to be connected. Bottom: homophilic attachment can be estimated using assortativity – the correlation between annotation values of connected nodes. **b**, Top: relating node centrality (how connected or influential a node is) with biological features provides insight into the neural circuit attributes that support information integration. Bottom: node centrality is correlated with annotation values, suggesting that well-connected hub nodes have different biological features compared with non-hub nodes. **c**, Top: the network has prominent communities with distinct biological annotations (colours). Bottom: boxplots show the distributions of annotation

values for the nodes in each community, and are coloured according to the mean annotation value in each community. **d**, Top: annotating communication pathways in brain networks sheds light on how signals traverse diverse neuronal populations and how they are transformed en route from source to target. The figure highlights two paths in the network and the annotations (colours) of the nodes in each path. Bottom: variations in annotation values are displayed as a function of hops (steps) along each path. Insets show the isolated paths from the network that correspond to each line. **e**, Top: annotated networks can be used to investigate how network motifs (for example, closed triangles versus open triangles, highlighted in the figure) are supported by different types of biological annotations (colours). Bottom: frequency of occurrence (count) of different motifs stratified by the annotation values of their constituent nodes. Scatter plots were generated using synthetic data. All other plots are conceptual illustrations.

microarray probes for gene transcription⁴⁴ or intracranial electrodes in electrocorticography⁷³, it is necessary to ensure that discrete samples are matched to the appropriate parcel^{88,92}. Ideally, the parcel boundaries should be aligned with spatial variation in annotations to optimize within-parcel homogeneity and between-parcel differentiation. By ‘colouring’ network nodes with biological annotations, we now have an enriched representation of the brain that opens fundamentally new opportunities for discovery^{93,94}.

Annotations and neural wiring

Once a biological feature map has been parcellated and used to annotate a brain network, it is natural to ask how the annotations of two brain regions are related to the connectivity between them. Numerous studies have explored whether brain regions exhibit homophilic mixing: areas that are connected being more similar than areas that are not connected. This simple wiring principle appears to be ubiquitous across a wide range of attributes including gene expression^{95–97}, cytoarchitecture (for example, laminar differentiation, neuron density and morphology, intracortical myelin)^{57,61,98–100}, morphometry in healthy and clinical populations^{101–103}, neurotransmitter receptors^{49,104} and local neural dynamics^{71,74,105}. Collectively, these results may reflect the influence of molecular and genomic gradients that guide axon formation during development, resulting in connectivity among neural populations with similar attributes^{32,106,107}. In practice, homophilic mixing can be readily quantified using the network-theoretic statistic of assortativity: the correlation between the annotation values across pairs of connected

nodes¹⁰⁸ (Fig. 2a). Although assortativity has been primarily used to assess the tendency for hub nodes to be connected with each other (degree assortativity)¹⁰⁹, the concept is more general and can be used to quantify the homophily of any biological annotation¹¹⁰.

The relationship between annotations and connectivity is conventionally conceptualized as homophilic mixing. An underexplored direction is to consider heterophilic mixing, that is, whether regions with different classes or types of annotations tend to be connected¹¹⁰. For example, do populations enriched in a particular cell type have a higher tendency to be connected to neural populations enriched in a different cell type, or could populations that express a particular neurotransmitter receptor connect to populations that express a different neurotransmitter receptor? Indeed, connectivity is highly structured across cortical layers, with heterogeneous patterns of connectivity between brain regions with specific laminar and cytoarchitectonic features^{111–114}. Similarly, interactions between slow-acting and fast-acting neurotransmitter systems coordinate functions across timescales, from arousal to goal-directed behaviour¹¹⁵. However, connectivity-mediated mixing among receptor types is not fully understood. Quantitative investigation of heterophilic mixing between biological annotations is an exciting new frontier for understanding complex interactions between cytoarchitecture, chemoarchitecture and cortico-cortical connectivity¹¹⁰.

One salient example of how neural wiring can demonstrate both homophilic and heterophilic mixing comes from neuroanatomical tract-tracing studies in non-human primates. These studies have

examined the cellular architecture of source and target cortical regions of neural projections to develop a theory of neural wiring called the Structural Model^{32,112,116}. Interestingly, they observed heterophilic mixing whereby feedback connections from poorly differentiated to highly differentiated regions originate in deep layers (layers V and VI) and terminate in primarily upper layers (layer I). Likewise, feedforward connections from highly differentiated regions to poorly differentiated regions originate in upper layer III and terminate in middle layers (deep layer III to upper layer V)³². These studies have also observed homophilic mixing whereby regions with similar laminar differentiation were connected by neural projections that originate and terminate in all layers of the cortex¹¹⁷. In other words, neural projection patterns depend on whether the connection is homophilic or heterophilic (from the perspective of laminar architecture). Biologically annotated connectomes make it possible to extend these theories to the whole human brain, as well as to features other than lamination.

Annotations and network architecture

Moving beyond statistical associations between wiring and annotations, we next turn our attention to network features that have been extensively studied in connectomics^{3,4,36}. Hallmark features, such as the tendency for nodes to form specialized modules or communities, the existence of highly interconnected hubs, and the communication pathways that support integration, can be recast from the perspective of biological annotations. Here we consider how concepts from graph theory can be enriched by incorporating information about biological attributes.

Traditionally, hubs are defined as brain regions that are disproportionately well connected with the rest of the brain¹⁰ (Fig. 2b). They are considered to be functionally important and have occupied the attention of the field for more than a decade¹². Hubs display characteristic activity patterns, dominated by slow fluctuation and high autocorrelation^{105,118,119}, consistent with the notion that regions with many inputs integrate information over longer timescales and across sensory modalities^{70–72}. What are the biological hallmarks of these neural populations that make them suited for integrating and disseminating signals? At the microscale, hub regions are composed of neurons with larger dendritic trees and more dendritic spines, presumably to enhance integrative capacity^{55,99,120}. This is reflected in their transcriptomic profile: hub regions show greater transcription for genes related to dendrite and synapse development¹²¹. Hubs also exhibit more differentiated laminar organization and larger layer III neurons, which are thought to support long-range cortico-cortical communication¹²². The energetic cost of this complex architecture is well documented: hubs tend to be more metabolically active, with greater transcription of metabolic-related genes⁹⁶, greater cerebral blood flow^{123–125}, greater glucose metabolism^{55,69} and greater aerobic glycolysis^{126–128}. Perhaps as a consequence, hub nodes also appear to be more vulnerable to particular neurological disorders, displaying greater cortical abnormalities^{129,130}, greater accumulation of misfolded proteins¹³¹ and greater expression of disease-specific risk genes¹³².

Another well-studied feature of the connectome is community structure: the tendency for regions to form strongly interconnected communities (or ‘modules’) that support specialized processing^{82,133–136} (Fig. 2c). Modules are conventionally defined on the basis of connectivity, but they can be readily re-imagined from the perspective of brain annotations. One way is to use established modules (for example, intrinsic resting-state networks) and superimpose maps of annotations to ask whether specific modules (for example, the visual network) are

enriched for micro-architectural features. The goal of these analyses is to identify micro-architectural features that support the functional characteristics of each module. For instance, intrinsic networks tend to have distinct transcriptional¹³⁷ and metabolic¹²⁸ signatures. These differences manifest in the cytoarchitecture; for example, unimodal networks have greater intracortical myelin than transmodal networks^{139–141}, perhaps providing the capacity to transmit signals with greater speed and fidelity. An alternative approach is to directly use biological annotations in conjunction with connectivity patterns to guide the detection of communities. The conventional community detection methods can be extended to identify groups of nodes that not only share dense connectivity but also have similar biological make-up. To our knowledge, this direction has been less explored in network neuroscience, but principled methods already exist in network science and statistical physics, including annotated stochastic block models^{93,142} and multilayer community detection¹⁴³.

We close this section by considering additional biologically meaningful architectural features of connectomes that could be enriched with biological annotations, including communication pathways, motifs, cliques and cavities. Measures of network communication are frequently studied to infer node centrality, inter-regional relationships and the global capacity of brain networks to process information. These methods typically involve tracing out sequences of connected nodes along which signals propagate. How do signals traverse neural circuits and what types of neuronal populations do they encounter along the way (Fig. 2d)? By annotating the sequence of nodes in a communication path using biological attributes, it is possible to infer how diverse neuronal populations exchange signals¹⁴⁴. In a similar way, network motifs – small 2-node, 3-node or n -node subgraphs that constitute the building blocks of a network¹⁴⁵ – can potentially be annotated to understand whether specific circuit configurations align with specific micro-architectural features (Fig. 2e). For instance, numerous studies have reported that chains of reciprocally connected nodes are over-represented in brain networks across multiple species, scales and reconstruction techniques^{29,146,147}, potentially acting as a substrate for functional integration and recurrent processing. High-order structures, such as cliques and cavities, are also thought to reflect the capacity for neural circuits to engage in parallel versus serial information processing^{29,148,149}. A salient question for future research is whether the formation and arrangement of these higher-order network features is guided by their underlying microscale architecture.

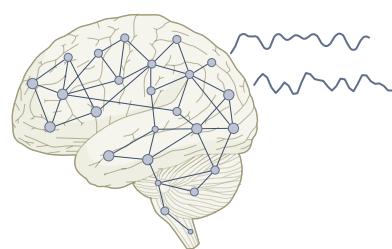
Annotation-enhanced models of the brain

So far, we have focused on the static annotation of brain networks and on comparing network organization with annotations. But annotations can also be used to inform more dynamic models of brain network formation, communication and disease propagation. As we outline below, a consistent thread in these studies is that imparting biological heterogeneity on regional nodes yields more veridical models of brain structure and function.

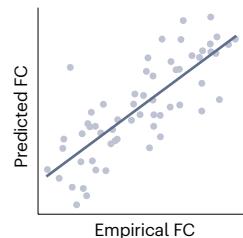
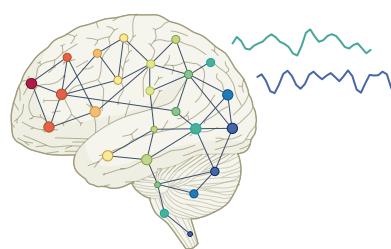
A key question in systems neuroscience is how structural connectivity (white matter projections between neuronal populations) is related to functional connectivity (co-fluctuations in neural activity)³⁰. Early studies focused on statistical and dynamical models to relate the two, but they typically assumed that structure–function coupling was uniform across the brain. Yet recent reports consistently find that structure–function coupling is regionally heterogeneous, with stronger coupling in unimodal cortex and weaker coupling in transmodal cortex^{150–154}. In a similar vein, biophysical models in which

a Biophysical models

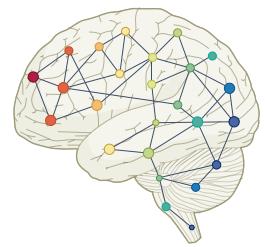
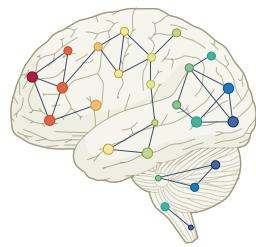
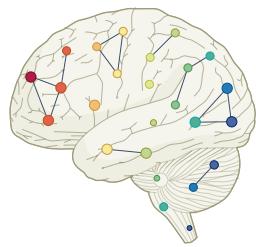
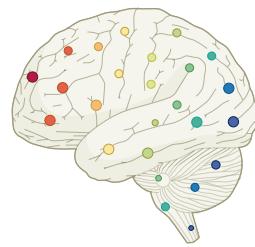
Homogeneous model



Heterogeneous model



b Generative models



Annotation-guided progressive placement of edges

c Disease models

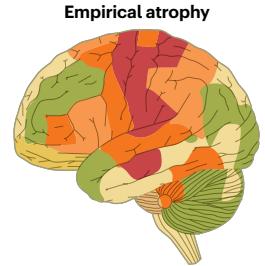
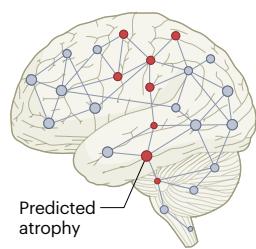
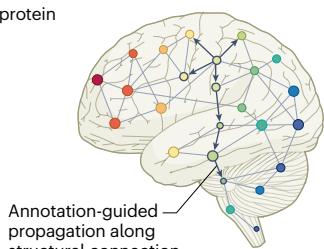
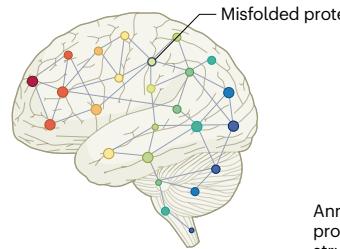


Fig. 3 | Annotation-enhanced models of the brain. Adding biological heterogeneity to brain regions improves structural and functional models of the brain. **a**, Biophysical models of the brain fit local microcircuit parameters at every brain region to predict regional functional dynamics. Models are often evaluated according to how well they can generate patterns of co-activation (predicted functional connectivity (FC)) that resemble experimentally measured patterns of co-activation (empirical FC). Circuit models that tune local parameters according to heterogeneous biological annotations (indicated by the different coloured nodes, right) predict functional connectivity between all pairs of brain regions better than models that retain default homogeneous local parameters (left)^{141,155}. **b**, Generative models seek to identify the principles that govern

network formation. Annotations can be used to guide the progressive placement of structural edges according to biological similarity between brain regions (indicated by nodes of a similar colour)¹⁷⁴. **c**, Annotated networks can be used to model the spread of disease. Misfolded proteins are initially located in one or more brain regions. Misfolded proteins then diffuse via structural connections, but their propagation is guided by biological annotations (indicated by node colour). For example, misfolded proteins may spread preferentially to regions with high expression of a specific gene¹⁷⁸. The aggregation of misfolded proteins causes cell death and atrophy. Model fit is evaluated by comparing predicted atrophy patterns with empirically measured atrophy patterns. No data were used to generate this figure.

regional dynamics are allowed to vary across cortex show an identical unimodal-transmodal gradient of dynamical parameters, representing regional differences in excitation–inhibition ratio and subcortical input¹⁵⁵. Collectively, these results open the possibility that taking into account regional heterogeneity can help us to build better models of brain function.

Indeed, several recent studies have shown that models that combine structural connectivity and local biological annotations generate more accurate predictions about functional dynamics¹⁵⁶, including models enriched with intracortical myelin^{141,157}, neurotransmitter receptors^{49,158–162} and gene expression¹⁶³ (Fig. 3a). As a practical

example, Demirtaş and colleagues enriched a biophysical neural field model using a map of intracortical myelin^{141,164,165}. They fitted two classes of model: a homogeneous model in which all node parameters are identical and a heterogeneous model in which different nodes may take on different local microcircuit characteristic (excitatory-to-inhibitory strength and recurrent excitatory strength) that were scaled according to the intracortical myelin map. The authors found that the heterogeneous model better predicted resting-state blood oxygen level-dependent (BOLD) functional connectivity and MEG-estimated power spectral density, demonstrating the utility of annotation-informed dynamical models.

A parallel literature has emerged in which biological annotations are used to guide generative models of network formation (Fig. 3b). In these models, the goal is to recapitulate the architecture and development of the connectome by placing nodes and/or edges according to simple rules¹⁶⁶, such as cost minimization (placing connections between spatially proximal regions) or the optimization of some topological feature, such as clustering or the degree distribution^{167–169}. These models can be used to study sequences of anatomical changes over phylogeny or ontogeny, allowing one to test theories about how network formation and arealization interact over time^{166,170}. Earlier empirical work has shown that the existence of connections can be predicted from correlated gene expression or cellular type^{26,99,171–173}. A natural next step is to build formal generative models in which edge placement is governed by biological rules in addition to spatial (cost-minimizing) and topological rules. For instance, a recent report explored an ensemble of generative models in which the placement of connections is also governed by similarity of gene expression, intracortical myelin or laminar differentiation¹⁷⁴. However, there still exist many annotations, such as metabolism, chemoarchitecture or cell types, whose roles in network formation have not been directly studied. Furthermore, generative models typically embody homophilic mixing rules, in which edge placement is more probable between brain regions with similar annotations. The same methodology can also be readily implemented to test the contribution of heterophilic mixing rules.

Just as biological features shape the formation of networks and the emergence of functional dynamics, they also impart local vulnerability to pathology. As a result, annotation-enriched connectomes have seen substantial use in disease modelling. Accumulating evidence has demonstrated that multiple syndromes, particularly neurodegenerative diseases, are caused by trans-synaptic propagation and aggregation of misfolded proteins^{42,175}. Although the specific proteins differ between syndromes (tau in Alzheimer disease, α -synuclein in Parkinson disease and TDP-43 in fronto-temporal dementia), the spreading principle is the same. The propagation of pathology is, therefore, typically modelled as a guided diffusion process on white matter connectomes (Fig. 3c). A common strategy has been to use regional differences in the transcription of genes associated with disease-specific proteins to scale the synthesis and clearance of proteins *in silico*^{176,177}. For example, models of Parkinson's disease or other synucleinopathies in which α -synuclein synthesis and clearance are scaled by the expression of disease-related genes (*SNC1* and *GBA*) better predict atrophy patterns compared with a homogeneous model in which synthesis and clearance are uniform across the brain^{178–180}. Taking this approach further, separate dynamic models of disease propagation can be built on connectomes annotated with expression of risk genes associated with specific subgroups of a particular syndrome, such as in genetic variants of fronto-temporal dementia¹⁰³. More generally, biological annotations may help to model local vulnerability and explain the spatial patterning of many other brain diseases or disorders that do not necessarily involve misfolded proteins but may involve a different network-mediated mechanism, such as spreading excitotoxicity or the propagation of aberrant signals or trophic factors^{80,181,182}.

Geometry, topology and annotations

How do we test whether a biological annotation is correlated with a network feature? The principal challenge is to disambiguate relationships between annotations and connectivity from the background effect of spatial proximity¹⁸³. Guided by genomic gradients, the gradual process of axonal growth and synapse formation results in a series of

overlapping neural circuits^{184,185}. Therefore, areas that are physically close together have a higher tendency to be connected with each other, and the strength of these connections is probably greater^{186,187}. At the same time, areas that are close together also have a higher tendency to share similar biological features, such as gene transcription, cell types and intrinsic electrophysiological rhythms. In other words, spatial proximity influences both annotations and connectivity. As a result, inferential procedures that take spatial autocorrelation into account are necessary to disentangle relationships between connectivity, annotations and geometry.

Fortunately, this has been an active topic of research, and multiple methods have been developed that randomize either the spatial layout of annotations or wiring topology while controlling for spatial autocorrelation^{139,188}. For almost any type of analysis, such as correlating biological annotations and network features, spatial null models allow us to build a distribution of statistical parameters (for example, correlation coefficients between randomized annotations and network features) that embody the null hypothesis that any observed relationship between annotations and connectivity is because of the passive influence of spatial autocorrelation. A popular set of methods for randomizing annotation maps are non-parametric 'spin tests' that project annotations to a sphere, apply random angular rotations and bring annotation values back onto the cortical surface¹⁸⁹. An alternative family of methods are parameterized models that estimate specific statistical features of

Glossary

Annotations

Any measurements or features that can be attached to the nodes of a network, either as a unidimensional scalar or multidimensional vector.

Arealization

The developmental process by which cortical cell types and circuits come to support unique specialized functions.

Cliques and cavities

Cliques are groups of all-to-all connected nodes, and cavities are groups of mutually unconnected nodes that participate in cliques.

Community

A group of nodes densely connected with each other but sparsely connected with the rest of the network.

Connection profiles

Vectors describing the connectivity of a brain region, detailing all of its pairwise connections with other brain regions.

Hub

A region that has many connections.

Multilayer community detection

Techniques for identifying communities that simultaneously take into account multiple types of connectivity or other interactions between nodes, such as annotation similarity.

Stochastic block models

Statistical models of network organization that formally take into account both connection patterns and local node annotations.

Transmodal networks

Networks that respond to multiple sensory modalities and specialize for higher-order cognitive function, such as the salience and default networks.

Unimodal networks

Networks that specialize for one primary sensory or motor function, such as the visual and somatomotor networks.

Vertex or voxel values

The main units of brain images, representing a spatial location in the brain, defined either for a brain volume (voxel) or on the surface (vertex).

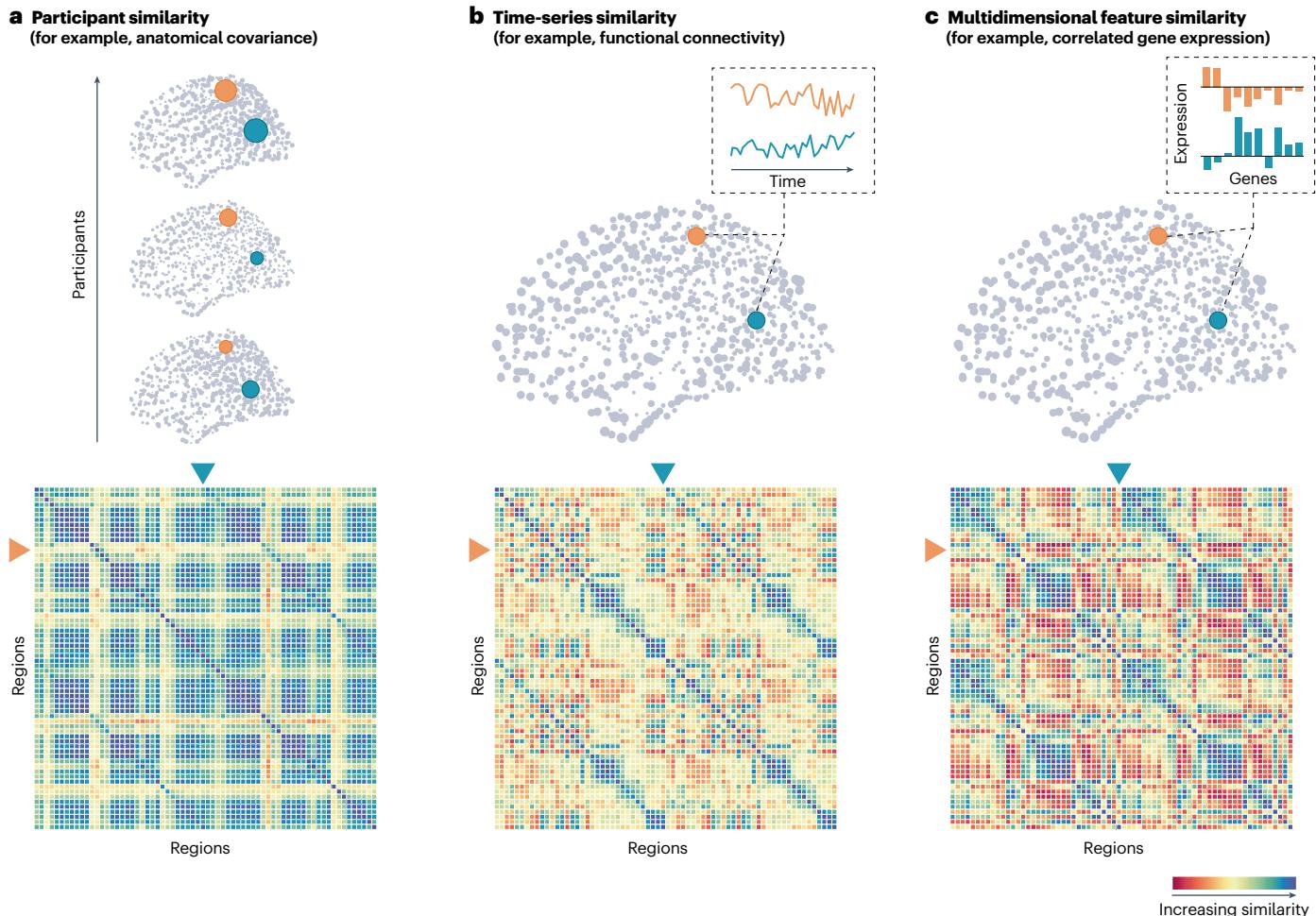


Fig. 4 | Annotation similarity networks. New networks of the brain can be derived by quantifying annotation similarity between pairs of brain regions. Blue and orange nodes indicate an example pair of brain regions; all other regions are shown as grey dots. Orange and blue arrowheads in the similarity matrix mark the row and column that correspond to the orange and blue nodes, respectively. The matrix entry at their intersection represents the correlation, or annotation similarity, between the measurements made at the orange and blue nodes. **a**, Top: a single annotation (for example, cortical thickness) is measured and correlated across multiple individuals. Bottom: the resulting annotation similarity network represents how pairs of brain regions are correlated across participants (for example, anatomical covariance network¹⁹⁶). **b**, Top: a single annotation (for example, blood oxygenation from functional MRI²¹⁴) is measured

and correlated across multiple time points. Bottom: the resulting annotation similarity network represents inter-regional synchronization between the two nodes (for example, functional connectivity). **c**, Top: multidimensional annotations (for example, gene expression measurements for many genes) are measured and correlated. Bottom: the resulting annotation similarity network represents multidimensional feature similarity between pairs of nodes (for example, correlated gene expression²⁰⁰). Panel **a** was generated using open MRI-derived cortical thickness fSLR-32k maps for 48 random participants in the Human Connectome Project S1200 data release²¹¹. Images were downloaded, parcellated to 800 cortical regions according to the Schaefer atlas²¹³ and correlated (Pearson's r) to generate the region \times region correlation matrix. Heat maps in panels **b** and **c** were generated by plotting networks published in ref. ²⁰⁴.

annotation maps, such as the variogram, and generate random annotation maps that approximately match those features^{59,190,191}. Although spin-based nulls can be applied only to cortical surfaces, parameterized nulls are more versatile and can be applied to cortical volumes, as well as extracortical structures, such as the subcortex or cerebellum. Conversely, methods that randomize connectivity typically build on conventional edge randomization algorithms, such that edges are randomly swapped if and only if the resulting swaps approximately preserve the edge length distribution¹⁹². Collectively, spatial null models test whether an observed relationship between biological annotations and network features exists above and beyond the effects of spatial proximity.

We close this section by emphasizing that the effect of spatial proximity should not be treated as a confound but as a natural and fundamental feature of this spatially embedded system. Indeed, many analytic procedures in network neuroscience explicitly take into account geometry. For example, state-of-the-art generative models of brain network formation include a geometric term that promotes the placement of connections among spatially proximal populations^{167,168,170}. Similarly, in dynamic models of communication or disease propagation, spreading agents (signals or misfolded proteins) are endowed with velocities defined by the lengths of anatomical connections^{178,193,194}. Alternatively, analyses that do not explicitly take into account geometry can be

readily reformulated to do so. For instance, homophilic and heterophilic attachment can be assessed with respect to permuted annotation maps to benchmark the extent to which these principles extend above and beyond the effect of spatial proximity¹¹⁰.

Annotation similarity networks

Although the connectome is considered the full set of network elements and connections in the brain², there is an alternative perspective of brain connectivity in which the definition is not based on structural connectivity: annotation similarity. In this case, a network edge is not physical but rather represents statistical associations between brain regions with respect to some annotation (for example, cortical thickness, BOLD signal and gene transcription) across some independent variable (for example, participants, time and genes). In other words, instead of annotating brain regions using micro-architectural or molecular features, local annotations are used to construct an entirely new type of network (Fig. 4). Annotation similarity is generally represented as a brain region \times brain region matrix in which elements are the chosen statistical measure of similarity.

Every version of annotation similarity provides a new perspective on the relationships between brain regions, while preserving a set of ubiquitous organizational principles. Perhaps the earliest representation of an annotation similarity network is metabolic connectivity, derived by correlating regional glucose metabolism across participants¹⁹⁵. This type of annotation similarity – that is, a network that tells us how brain regions are coupled across individuals with respect to a specific phenotype – has also been applied to cortical thickness (anatomical covariance¹⁹⁶) and can be extended to any

measurement that is measured across individuals (Fig. 4a). A second, and probably the most common, conceptualization of annotation similarity is ‘functional connectivity’, that is, how annotations of neural activity are synchronized over time. This definition is most often applied to the BOLD signal from functional MRI (fMRI) but can also be applied to other time courses such as glucose metabolism from fluorodeoxyglucose-PET (FDG-PET)^{197,198} and electromagnetic neural activity from EEG and MEG¹⁹⁹ (Fig. 4b). Finally, a third form of annotation similarity has emerged, whereby multiple measurements of an annotation are collected at each brain region, and these regional fingerprints are correlated (Fig. 4c). These annotation similarity networks have been constructed for phenotypes such as genes (correlated gene expression²⁰⁰), receptors (neurotransmitter receptor similarity⁴⁹) and cell types (laminar similarity^{57,100,201}), and tell us how regions share similar biological building blocks. Interestingly, regardless of the annotation or data type, annotation similarity consistently decreases with distance, is larger for structurally connected regions and is symmetric across hemispheres, suggesting common organizational principles in the brain^{71,114,200,202}.

With annotation similarity networks, we can ask new questions about how brain circuitry emerges from a confluence of local properties. For example, the rich club of the brain – densely interconnected brain regions that are thought to support signal integration – was originally viewed only from the perspective of the structural connectome²⁰³. Recent studies have found that structural rich club links exist between brain regions with similar gene expression and receptor density profiles^{96,200,204}. By defining edges on the basis of information about local biological similarities, annotation similarity

Box 2

From population to individual annotated connectomes

Current work in annotated connectomics typically uses datasets sampled from different populations. Sometimes, this is because of the cost associated with acquiring data. At other times, it is because of the ethical considerations and/or invasiveness of the imaging or tracing technique. For instance, PET imaging involves injecting radioactive tracers, precluding comprehensive sampling in the same individuals, whereas gene expression, cell staining and autoradiography are measured post-mortem. Annotation-enriched connectomic analyses, therefore, involve comparing annotations from groups that are not necessarily matched with respect to sample size, chronological age, biological sex or disease status. This induces statistical challenges and limits possible inferences and the extent to which findings can be extrapolated to other populations. For example, disease phenotypes in clinical populations (for example, cortical thinning) are often referenced against connectomes and annotations generated from healthy populations (for example, connectomes from the Human Connectome Project and gene transcription from the Allen Human Brain Atlas). Furthermore, annotations are frequently shared and analysed as group averages, blurring individual differences. Thus, the diversity of a population should be explicitly taken into account when building annotated connectomes.

An added challenge is how to align individual-specific annotations with group-level parcellations. The choice of parcellation – how

the brain is divided into brain regions – can influence connectome reconstruction^{229,230}, may not appropriately represent individual-specific biological annotations and can have downstream effects on analyses, including modelling cognition²³¹ and disease²³². For example, if parcel boundaries are defined functionally, these parcels may be misaligned with histological boundaries, resulting in parcels with non-homogeneous annotation measurements²³³. Therefore, it is necessary to define nodes to reflect both the individual and the annotation.

Going forward, the acquisition of highly sampled and multimodal datasets combining a wide range of imaging modalities in individual participants is highly desirable. Such deep phenotyping datasets would capture not only the connectivity profiles of individual brain regions but also their local genetic and cellular make-up, and are in line with recent work aimed at better capturing individual variability^{234–236}. Furthermore, precision imaging and deep phenotyping can guide the development of personalized multimodal parcellations that take into account multiple levels of description of brain anatomy^{233–238}. With the emergence of annotated connectomes that represent both individuals and multiple brain phenotypes, we can ask new questions about how annotations and neural wiring interact throughout development, during ageing and in disease.

networks shed light on the biological mechanisms of macroscale architectural features. Likewise, using the graph theoretic approaches presented above (see ‘Annotations and network architecture’), we can ask whether annotation similarity networks present novel architectural features not found in the more standard structural or fMRI-derived functional connectomes. Indeed, FDG-PET-derived functional connectivity has revealed hubs of neural synchronization in frontoparietal regions: regions not traditionally considered hubs from the perspective of the classical structural and fMRI-derived functional connectomes^{12,197}. Additionally, network architecture of morphometric similarity, an annotation similarity network in which the annotations are MRI-derived white-matter and grey-matter measurements, has been shown to vary with individual differences in cognitive performance¹⁰¹.

Ultimately, each annotation similarity network is only a single perspective of inter-regional relationships. The integrated, multiscale nature of the brain is reflected by these annotation similarity networks, from shared molecular mechanisms to dynamics to function. How these annotation similarity networks interact with one another and with the structural backbone of the brain remains an exciting direction for future research. Indeed, with the emergence of new datasets, diverse annotation similarity networks are rapidly being introduced^{57,71,80,205,206}. This sets the stage for generating new integrative networks derived either by combining multiple annotation similarity networks into a single fused network²⁰⁴ or by concatenating multiscale annotations to create a single comprehensive annotation fingerprint at each node^{104,207}. Thus, we envision that the future of annotated connectomics involves a holistic, multiscale perspective of inter-regional relationships.

Concluding remarks

The present Review summarizes a single, consistent and altogether unsurprising principle: that including information about the underlying biology can help us to build more realistic connectome representations. Annotations add depth and meaning to the roles of hallmark architectural features, such as hubs and modules. Annotations boost virtually all models of brain network formation, neural dynamics and disease propagation. Finally, annotations can be used to recover new inter-regional relationships that complement existing structural and functional networks.

It is with surpassing wonder that we consider how modern advances in imaging and tracing technology will shape next-generation connectomics. Going forward, we envision the incorporation of other biologically meaningful annotations that can be reliably measured but have seen little uptake in connectomics. These include data on the vascular system (particularly measures of neurovascular coupling), spatially comprehensive gene transcription and cell type deconvolution estimated using single-cell RNA sequencing (as opposed to microarray), receptor density estimated using autoradiography, synapse types, enzymes and more specific markers of pathology (for example, tau imaging) or inflammation (for example, microglial activation). To complement annotation-enriched connectomic analyses in humans, experiments in animal models – for which we have access to additional techniques and a wider variety of measurements – will generate a more complete set of annotations, such as synaptomes²⁰⁸, metabolomes²⁰⁹ and direct assays of pathology²¹⁰. More broadly, whereas numerous studies have looked at single annotations, the time is right for more comprehensive studies that simultaneously look at entire classes or even multiple classes of annotations in a single analytic framework^{110,204}. Finally, modern precision

imaging and deep phenotyping efforts will enhance our capacity to build individualized annotated connectomes (Box 2).

In summary, biological annotations add a new dimension to brain connectomes. The resulting mathematical object – the annotated connectome – unlocks an entirely new way of thinking about the interdigitation of global connectivity and local features. The datasets, analytics and theory are all in place to start an exciting new chapter in network neuroscience.

Data availability

Data used to generate Fig. 1 are available in the neuromaps toolbox (<https://netneurolab.github.io/neuromaps/> (ref. 35)) and the Allen Human Brain Atlas^{35,44}. Synthetic data were used to generate Fig. 2. Figure 3 is a conceptual illustration and is not based on real data. Data used to generate Fig. 4 can be found at https://github.com/netneurolab/hansen_many_networks and the Human Connectome Project^{204,211}.

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Author contributions

V.B. and J.Y.H. researched data for the article. All authors made substantial contributions to the discussion of content and wrote, reviewed and edited the manuscript before submission.

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The authors declare no competing interests.

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