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Review

Closing the mechanistic gap: the value of microarchitecture in understanding cognitive networks

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Cognitive neuroscience aims to provide biologically relevant accounts of cognition. Contemporary research linking spatial patterns of neural activity to psychological constructs describes 'where' hypothesised functions occur, but not 'how' these regions contribute to cognition. Technological, empirical, and conceptual advances allow this mechanistic gap to be closed by embedding patterns of functional activity in macro- and microscale descriptions of brain organisation. Recent work on the default mode network (DMN) and the multiple demand network (MDN), for example, highlights a microarchitectural landscape that may explain how activity in these networks integrates varied information, thus providing an anatomical foundation that will help to explain how these networks contribute to many different cognitive states. This perspective highlights emerging insights into how microarchitecture can constrain network accounts of human cognition.

Highlights

Characterising the mechanisms of human cognition can benefit from integrating local microstructural properties with the macroscale organisation of the brain.

Digitised datasets of the human brain, including histology, brain maps, transcriptomics, and high-resolution imaging, provide unprecedented opportunities to link microarchitectural features to functional networks that contribute to complex thought.

Microarchitectural heterogeneity of higher cognitive networks [e.g., the default mode network (DMN) and multiple demand network (MDN)] underpins their broad involvements in cognition.

The positioning of the DMN and the MDN with respect to hierarchical and parallel processing streams supports and sheds light onto their functional differences.

Complex functional dynamics and the inter-relationship between functional networks may be better understood by taking a multidimensional perspective informed by changes in local microarchitecture.

Bridging the gap between neuroanatomy and higher-order cognition

Classic neuroscientific experiments revealed a complex pattern of functional specialisation across the brain [1]. Despite evidence of functional localisation, more than 100 years later, core questions remain about how this modular architecture gives rise to flexible behaviour (Box 1). Recent work has established that the activity of brain areas often varies in concert, giving rise to the notion of functional brain networks [2], as well as to the associated hypothesis that the relationship between brain activity and complex behaviours is best operationalised by the interaction of distributed nodes that constitute these networks [3,4]. Methods for the analysis of complex systems, such as graph theory [5], describe how brain regions interact but do not specifically address the underlying regional variability in the make-up of the human cortex [6]. In this review we consider how investigating the **microarchitecture** (see Glossary) of functional networks can help to refine possible mechanistic accounts of how the observed patterns of brain activity contribute to higher-order cognition.

This approach rests on the long-standing assumption that neuroanatomy can deepen our understanding of the mechanisms of cognition, for example, by narrowing the search space of conceivable solutions and by constraining theories [7]. Converging evidence from experimental studies in non-human animals and electroclinical observations in neurological patients have demonstrated relationships between the structure and core functions of the human brain [1,8]. Defining specific functions is relatively straightforward in the context of sensory and motor processes, where associations with structure can be circumscribed; however, the anatomical basis of higher-order cognition has proved to be more difficult to isolate. One reason for the difficulties is that forms of higher-order cognition, such as 'task focus' and 'imagination', are probably neither independent nor circumscribed in the brain [9], and rely on overlapping component processes [10]. This motivates a shift in focus from

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Box 1. Motivations for multiscale models of cortical architecture and function

As stimulation and lesion studies revealed functional localisation in the brain [99], cyto- and myeloarchitectural studies showed that the cortex can be subdivided into areas with relatively homogeneous architectures [33,100]. Together, these insights gave rise to the notion of area-based modularity – that the cortex may be understood by the coordinated interaction of functionally and structurally distinct areas ([101] for critical review). This perspective provided the foundation to discern functional specialisation at a larger scale and to develop theories on how networks support higher-order cognition [2]. Nevertheless, recent work on the dynamics of brain function suggests the need to move beyond simplistic area-based modularity.

Two key findings from functional neuroimaging that challenge area-based modularity are (i) functional boundaries shift depending on cognitive task [102] and (ii) areas seem to contain overlapping modes of function [103]. For example, within the primary visual area, eccentricity (distance from the centre of the visual field) is represented along the calcarine sulcus, whereas the angle (relative to the centre of the visual field) is represented in the perpendicular direction [104]. These properties suggest that microcircuits within areas must vary to enable different types of physiological sensitivity. Indeed, contemporary microscale evidence shows that, although areas are distinct from their neighbours, variations exist within areas [105]. Insight into local variations of microcircuits may therefore shed light on dynamic functional patterns observed in the cortex.

Another challenge to area-based modularity is the complexity of the relationship between structure and function in biological systems, especially in association cortex. One-to-one mapping of structure and function fails to account for degeneracy and pluripotency. Degeneracy is a common property of complex biological systems [106], indicating that two cortical areas with different structures may fulfil the same function. By contrast, pluripotency means that one brain area can produce many different functions [103]. Both degeneracy and pluripotency are broadly consistent with a many-to-many mapping between structure and function, and this in turn motivates the examination of distributed networks rather than independent areas.

Although area-based accounts continue to provide a useful level of description, especially for *in vivo* imaging, several properties crucial to explaining the dynamic patterns of neural activity deviate from the classic perspective of a pure area-based modularity. This motivates multiscale investigations of the relationship between structure and function [105] whereby local variations, the intrinsic properties of areas, and macroscale patterns can be taken together to model brain function.

identifying the neural substrates of concepts associated with higher-order cognition towards explaining the neural processes enacted within functionally defined networks.

From 'where' to 'how': using functional networks to understand cognition

Intersecting perspectives on the MDN and DMN

Recent advances in neuroimaging, notably in fMRI, have allowed distributed patterns of neural activity to be described while subjects perform tasks. The resultant descriptions of the landscape of human brain activity are an important starting point for understanding the mechanisms behind patterns of 'complex thought' or 'complex cognition' – widely used but underspecified terms encompassing a broad range of mental activities that involve a combination of more elementary processes [11,12]. The application of fMRI during behavioural paradigms (also known as task-based fMRI) has helped to distinguish functional networks associated with different forms of complex cognition [11,13], but the difficulty of defining their elementary processes adds impetus to investigating networks from a brain-based perspective. Furthermore, some features of complex thought in humans may not be amenable to studies using animal models, since these combinatorial processes may be absent from other species (e.g., [14]).

Using fMRI in humans, two macroscale systems have been specifically related to complex forms of cognition. One system, the MDN, is defined by the tendency of particular brain regions to increase activity when task difficulty increases [15] (and overlaps with the 'frontoparietal' or 'central executive' networks [16–19]). Another system, the DMN, shows the opposite pattern, declining in activity when external difficulty drives task performance, but the regions increase in activity when tasks rely more on memory [20,21] (Figure 1A–C). Despite this apparently antagonistic relationship, converging evidence highlights broad similarities in how these networks contribute to cognition. For example, contemporary views of both the MDN and DMN assume that they provide top-down control at a relatively abstract level, and this may be why they

are involved in such a wide range of different situations [15,22]. Task-based studies are complemented by a large body of work establishing that the regions in these systems have temporally coordinated activity during wakeful rest [16–18]. The MDN and DMN are especially distinguished by data-driven approaches that resolve the principal **axes** of resting-state functional connectivity (Figure 1D) [23]. The replicable identification of the DMN and MDN across domains [24] prompts their consideration as 'scientific objects' [25], phenomenological entities that attract scientists precisely because they outline what is not yet known [26,27].

The impetus for microarchitecturally informed mechanistic accounts of functional networks

Studies examining the MDN and DMN have shaped our understanding of the brain basis of complex thought in important ways. First, they establish candidate cortical areas involved in such forms of cognition, highlighting 'where' in the brain activity is most likely to be linked to processes underlying complex thought. Second, the distributed nature of network subregions suggests that core features of human cognition depend on the communication of many brain areas. Third, the specific topography of these regions can constrain theoretical accounts on their type of contribution to cognition. For example, the distribution of MDN and DMN regions across cortical lobes is thought to enable interactions between a range of cortical zones and sensory modalities [15,28]. In addition, the distance of both networks to primary sensory areas, in particular the DMN, highlights the possibility that the role of this system in cognition emerges because its location allows the integration of multiple perceptual processing streams [23]. Drawing all these ideas together has led to the hypothesis that these systems contribute to cognition through their interactions with other neural systems, including those oriented towards external or internal sources of information [28,29].

Although the aforementioned studies outline the cortical landscape of complex thought, they leave open important questions about the computational processes that allow these regions to contribute to higher-order cognition. Closing this mechanistic gap is critical in forming a mature scientific account of the brain mechanisms behind human thought, and for enabling next-generation models of the orchestrated functioning of network subcomponents. In the context of contemporary neuroscience, this is equivalent to understanding the specific operations of cortical and subcortical areas, and how they function together to support particular aspects of human cognition. We aim to demonstrate that this mechanistic gap can be closed by understanding how the 'hardware' [30] (e.g., the microarchitecture of cortical regions) relates to the patterns of observed brain activity in particular contexts.

To illustrate why it is important to go beyond the observed characteristics of brain activity during tasks, consider the roles that the MDN and DMN play in cognition. Both large-scale networks are implicated in a wide range of cognitive and behavioural states. These networks sometimes appear to be acting in opposition, for example, during 'resting' (i.e., task-free) contexts [31]. In other states, these networks seem to work in tandem, as demonstrated during semantic feature-matching tasks [32]. Although the diversity of the states that these systems are involved in underscores their probable broad contribution to human cognition, it also presents a challenge in forming a consensus view of the functions that these systems perform [28]. Understanding what allows the MDN and DMN to take on the functions that they do is an important next step in developing a more mechanistic account of human cognition as it would help us to understand 'how' neural activity in these regions contributes to thoughts and actions.

One possibility is that understanding the contribution of the DMN and MDN to human cognition will be improved by detailing the underlying differences in their microstructure. Historically, an integrated view of microstructure and function was limited because details of neuroanatomy

Glossary

Agranular: areas of the isocortex that lack the inner granular layer (layer IV), in contrast to the granular six-layered cortex.
Allocortex: cortex that exhibits a distinctive cytoarchitecture and development relative to the isocortex. Comprises archicortex (e.g., the hippocampus) and palaeocortex (e.g., the piriform cortex).
Archicortical: relating to the archicortex, which is the part of the allocortex that includes the hippocampal formation. Distinguished by phylogeny from neo- and palaeocortex.
Axis: a reference line which in this context orders cortical points according to the prominence of a particular feature. Typically derived by dimensionality reduction.
Dual trends: division of the cortex into two large-scale cortical gradients, known as the allocortical and palaeocortical trends.
Gradient: a spatially graded change in the expression of a particular neurobiological feature that occurs across the brain. Can be more abrupt (nonlinear) or smooth.
Granular: six-layered isocortex.
Heteromodal: involving input from more than one sensory modality.
Hierarchical: ranked organisation of brain areas that dictates sequences of information processing.
Interdigitation: spatial variation in neurobiological properties that resembles the pattern of interlocking fingers.
Koniocortex: meaning 'powder cortex', pertains to cortex highly enriched with granule cells and a broad layer IV (also known as the internal granule layer). Includes the primary visual, somatosensory, and auditory areas.
Laminar: refers to layered microstructure of the cortex; the pattern is referred to as lamination.
Microarchitecture: microscale structural features, including cyto- and myeloarchitecture, as well as projections mapped at the cellular level.
Microcircuit: the organisation of nerve cells into a specific pattern to carry out a specific operation within a region.
Palaeocortical: relating to the palaeocortex – the part of the allocortex that includes the piriform cortex. Distinguished by phylogeny from neo- and archicortex.
Sensory-fugal: a functional characterisation of the cortical gradient that runs from externally focused primary

were largely gleaned from post-mortem studies which provided exquisite descriptions and quantitative data of cortical architecture but no direct accounts of function in the same individuals [6,33]. Recent progress in cytoarchitectonic mapping, large-scale neuroinformatics initiatives, and high-field neuroimaging has resulted in the generation and sharing of digitised datasets of the human brain, thus allowing more flexible approaches to charting cortical microarchitecture and novel experiments that systematically cross-reference brain microstructure with function (Box 2). These resources make it possible to form integrated models of brain organisation, meaning that now is the right time for our community to recognise the potential of microarchitecture in constraining our accounts of brain function and higher-order cognition.

sensory areas to limbic areas that are relatively decoupled from environmental inputs.

General principles linking microarchitecture and function

The core of our argument is that mechanistic accounts of cognition can be constrained by a better understanding of what microarchitectural features of the cortex enable neural activity to contribute to particular functions. Foundational research has shown that microarchitecture and function covary across regions. From this work, two key principles may be derived which surmise the most prominent regional differences across the cortex that occur in both microarchitecture and function: (i) a **hierarchical sensory-fugal** axis and (ii) parallel streams within **dual trends**. Together, these organisational axes provide a window into how particular functions emerge from the interactions of distinctive forms of microarchitecture.

The sensory-fugal axis indexes differences in regional **microcircuits** and their patterns of connection with other areas, which can together distinguish regions based on their preference to respond specifically to a single modality. The architecture of cortical microcircuits determines the computation of a neuronal assembly (Figure 2A). For example, cortical areas with clearly differentiated layers can better separate incoming neural signals [34], and this probably influences the degree of integration and segregation possible within a neuronal assembly. Based on non-

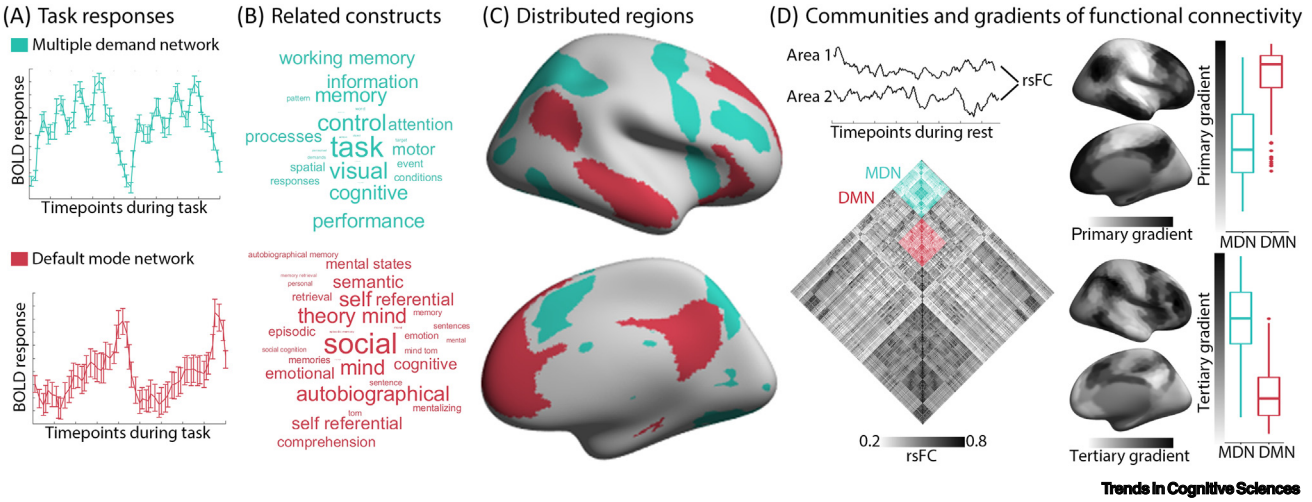

Figure 1. Defining the multiple demand network (MDN) and the default mode network (DMN). (A) Blood oxygenation-level dependent (BOLD) response during a multistep task [93] shows the phasic response of the MDN throughout task episodes, whereas the DMN deactivates at episode onset then tonically increases across task episodes. The plots were produced with data from [93]. (B) Meta-analytic decoding [94,95] highlights the varied cognitive terms associated with each network. (C) Distributed regions of the cortex are defined as the MDN by task-related activation [96] or as the DMN based on resting-state functional connectivity (rsFC) [17]. (D) rsFC across the whole cortex, shown in the matrix, contains communities [97] indicating higher intra- versus inter-network connectivity. Another increasingly prominent strategy to deconstruct whole-cortex resting-state connectivity is focused on the principal axes of functional differentiation, or gradients [23]. The DMN occupies the apex of the primary gradient, which explains the most variance in the rsFC matrix and differentiates the DMN from visual and somatomotor networks, whereas the MDN is distinguished by the third gradient, as shown in the boxplots. The plots were produced with data from [98].

Box 2. Modern microarchitectural approaches with open resources

Mapping microstructure to function is becoming increasingly possible using a new generation of detailed atlases of cytoarchitecture. A key resource is 'BigBrain', a 3D reconstructed model of the human brain based on serial cell-body staining [56]. BigBrain was coregistered to standard neuroimaging reference spaces, notably the MNI152 stereotaxic space, which makes it possible to study the relationship between cytoarchitecture and *in vivo* function. BigBrain has fostered innovations in large-scale cellular data processing [56], cortical segmentation [107,108], and imaging-histology registration [62,109–111]. Collaboration around the BigBrain has resulted in the HIBALL project (https://bigbrainproject.org/hiball.html), an international initiative aimed at processing, integrating, and disseminating the next generation of human brain models. These include new 3D histological reconstructions that take BigBrain to the scale of single neurons, paving the way for cytoarchitectural studies with enhanced precision and specificity. Other deliverables will expand the repertoire of post-mortem modalities, including neurotransmitter architecture via 3D receptor autoradiography [112] and ultra-high-resolution measures of tissue composition, fibre orientation, and inter-regional wiring via 3D polarised light imaging [113,114] (https://kg.ebrains.eu/). Despite the unprecedented insight that these resources offer into microarchitectural anatomy of human brain networks, the effort and costs required for data generation and curation remain a key limitation, resulting in data being restricted to relatively few subjects. In the future, it will be necessary to broaden the diversity of these datasets to better capture the variability seen in the general population, for example, with respect to sex, ethnicity, age, or potential disease status.

A viable complement to histological approaches is to study the human brain with high-field MRI. Higher magnetic field strengths produce greater signal [115], which can be used to increase spatial resolution. Scanning at 7 Tesla now approaches the mesoscopic scale of 0.1–0.5 mm voxels [116]. For instance, the Digital Brain Bank [117] provides open access to post-mortem MRI of both healthy and pathological cases (https://open.win.ox.ac.uk/DigitalBrainBank/). Moreover, gains in spatial resolution are increasingly allowing *in vivo* modelling of cortical microstructure [118], structural connectivity [119], and neural signals across cortical layers and columns [120]. Perhaps the most important advantage of high-field MRI is that linking microstructure and function in the same living individual is possible, making the platform a core part of the development and evaluation of mechanistic models of structure–function coupling [121], where resources are increasingly being made available (https://portal.conp.ca/dataset?id=projects/mica-mics; https://www.humanconnectome.org/) [98,122].

human primate studies, both microarchitecture and functional specialisation have been suggested to vary along a cortex-wide sensory-fugal axis [8]. The sensory-fugal axis, that captures graded changes in neurobiological properties across the cortical surface, is anchored at one end by primary sensory areas and at the other by the **allocortex** (Figure 2B). Microstructurally, the degree of **laminar** differentiation decreases along the isocortical components of this axis, from six or more clearly defined layers (**koniocortex**) to five or less poorly differentiated layers (**agranular**) [35]. Studies have shown that the timescale of neuronal oscillations also varies along this axis [36] (Figure 2C), reflecting the ability of neuronal assemblies further from sensory systems to maintain information for longer periods of time [37]. Consequently, moving away from sensory cortex along this axis relates to decreases in the coupling of neural activity to immediate environmental inputs, allowing neural activity to take on more abstract features. In addition, in sensory systems the vast majority of connections are between regions of the same or neighbouring levels of the axis [38], and cortex-wide connectivity is more likely between areas of similar types [39]. Such an architecture is typically described as hierarchical because it shows projections that are organised across multiple levels within a broader system ([40] for critical review). Combined architectonic/functional studies suggest that hierarchical connection schemes provide the basis for processes such as multimodal integration of different aspects of the same input or the maintenance of abstract similarities across different situations [41–43] (Figure 2D). Thus, the sequential transformation of neural signals along the sensory-fugal axis is argued to allow integration of information from several sources, and this may explain why neural activity further along the sensory-fugal axis is correlated with more abstract features of thought or perception. Importantly, the sensory-fugal axis is expanded in humans, relative to other animals, thus providing further support for its role in features of higher-order cognition such as social cognition and language [8,44].

Finally, although hierarchies emphasise serial processing streams, influential computational theories posit that complex behaviours in mammals, and especially humans, are enabled by parallel processing [45]. It has been argued that parallel processing enables simultaneous

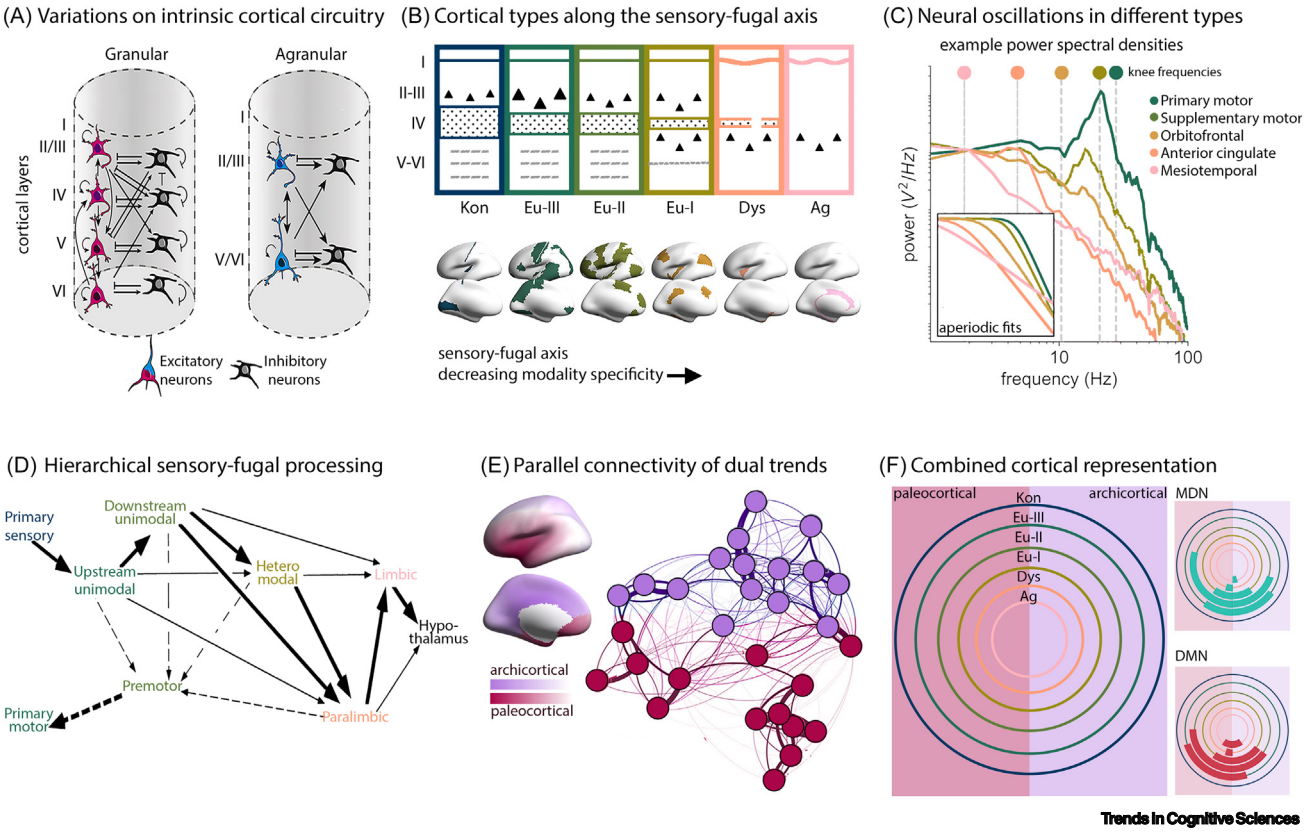

Figure 2. Cortex-wide models of the relationship between microstructure and function. (A) Different cortical layering patterns (e.g., granular vs. agranular) reflect distinct intrinsic circuitries of neuronal assemblies (modified, with permission, from [57,123]). (B) Stepwise differences in cortical layering along the sensory-fugal axis concord with functional changes such as modality specificity. The schema highlights the multivariate changes in cytoarchitecture across types of isocortex, pyramidal neurons (triangles), thickness of layer IV, sublayers (grey broken lines), and regularity of the layer I/II boundary (straightness of line). Cytoarchitecture and locations of types are based on [124]. (C) Covariation of cytoarchitectural types with electrophysiological differences is exemplified by neuronal timescale which increases along the sensory-fugal axis (and is inverse to the knee frequency, where a bend in the power spectrum occurs) [36]. Power spectral density plots evaluated from intracranial electrode recordings have distinct aperiodic components that reflect different knee frequencies and thus different neuronal timescales. Areas are coloured according to approximate cortical types. (D) Sensory-driven hierarchical processing in the cortex involves stepwise transformation across distinct cortical types of the sensory-fugal axis (modified, with permission, from [8]). (E) Approximate division of the human cortex into dual trends based on mapping geodesic distance from piriform cortex (palaeocortex) and the posterior hippocampus/retrosplenial cortex (archicortex) (adapted from [125]). Darkness indicates proximity to an origin, and the hue represents assignment to palaeo- or archicortex trend based on closer proximity. Connectivity is stronger within the dual trends than between the trends [48,126], producing two parallel systems (shown by the network plot; modified, with permission, from [48]), with each system related to distinct functional roles. (F) Cortical organisation may be represented by cortical types and the dual trends whereby each point on the cortex can be attributed to a semicircle of the schema. Embedding neuronal assemblies and connections into this schema informs on the type of information processing, such as hierarchical (between rings) or parallel (within coloured rectangle). Circular bar plots approximate the number of areas within each network that can be assigned to the respective cortical type (ring) or trend (left vs. right) based on comparison of the multiple demand network (MDN) and the default mode network (DMN) (Figure 1C) with atlases in (B) and (E). The more of the semicircle covered by a bar, the more areas within that network that can be attributed to that type and that dual origin. Abbreviations: Ag, agranular; Dys, dysgranular; Eu, eulaminate; Kon, koniocortical.

consideration of information from different sources and generalisation of intelligence [46]. Furthermore, it has been proposed that the brain can be seen as a complex, self-organised system with nonlinear dynamics in which principles of distributed, parallel processing coexist with serial operations within highly interconnected networks [47]. One way in which serial and parallel processing are combined in the mammalian brain is by the branches of the sensory-fugal axis [38,48]. For example, visual processing is divided into a dorsal stream that is important for spatial features and a ventral stream that is important for object recognition ([49] for consideration of dorsal and ventral streams across various domains). These dual streams may reflect a deeper developmental and cytoarchitectural division of the cortex into the **archicortical** and **palaeocortical** trends

(Figure 2E) [48]. In characterising the origins and microarchitectures of these dual trends, neuroanatomists have identified functional commonalities across systems. Regions in the archicortical (dorsal) trend are consistently associated with explorative behaviours such as searching or foraging, whereas regions in the palaeocortical (ventral) trend are associated with more exploitative behaviours that take advantage of the goals offered by the local environment [50,51]. Parallel systems, such as the archicortical and palaeocortical trends, in combination with the sensory-fugal axis, therefore provide a powerful perspective on how functional differentiation emerges across the brain.

Moving forward, the general principles become a useful framework within which to understand the common and unique anatomical features of brain networks that are relevant to their distinct functional characteristics. These neuroanatomical perspectives illustrate how knowledge of microarchitecture provides an important set of constraints, rooted in the evolution and development of the cortex, that help to close the mechanistic gap between the brain and complex forms of cognition and behaviour [50]. We suggest that insights that emerge from integrating local microstructural properties with larger-scale organisation and connectivity (Figure 2F) will be an important next step in building a mechanistic account of cognitive processes in the human association cortex.

Mechanistic insights into the DMN and MDN

Recent advances in histology, *in vivo* imaging, and computational modelling are facilitating a better understanding of the microarchitecture of the human association cortex [52–55]. Several studies capitalising on these developments provide an outline of the microarchitectural composition of the DMN and MDN and highlight neuroanatomical features that may underlie their unique roles in human cognition.

Unpacking the cytoarchitectural heterogeneity of the DMN and MDN

The broad involvement of the DMN and MDN in many states is difficult to reconcile with a single cognitive process. Likewise, their cytoarchitectural composition is poorly defined by a single anatomical feature. In one recent study [52], we used BigBrain [56] (Box 2) to discern the cytoarchitectural diversity of the MDN and DMN towards understanding how these systems contribute to such a wide range of cognitive functions. To do so we generated a simple metric of cytoarchitectural similarity between each region of the cortex and identified the principal axis of cytoarchitectural variation using nonlinear dimensionality reduction (Figure 3Ai). This nonlinear approach derives lower-dimensional axes that summarise broad features of the higher-dimensional space (based on similarity between brain regions) while preserving the local geometry of the original dataset. Such nonlinear approaches allow clusters to be embedded in larger-scale axes that align with the known arealisation of the cortex [57]. The principal axis, that explains the most variance in cytoarchitectural variation, primarily captures laminar differentiation, namely, the prominence of distinct cortical layers (Figure 3Aii), and the spatial pattern was correlated with the sensory-fugal axis [52]. This data-driven cytoarchitectural axis provides a human-specific representation of the sensory-fugal axis with higher **granularity** than the atlases approximated from non-human primate studies [58]. In addition, the data-driven axis can be registered to standard MRI spaces for direct comparisons with functional networks. We found that both the MDN and the DMN are widely spread across this principal axis (Figure 3Aiii), indicating that these networks are relatively heterogeneous in their microstructural features. Emerging nonparametric frameworks such as spin tests [59], variogram matching [60], and Moran's spectral randomisation [61] further allow the quantification of the similarity between whole-brain patterns of different features (e.g., microstructure and function) and provide statistical support that the heterogeneity of these networks goes beyond the heterogeneity derived from null models.

This study highlights one of the challenges in determining the uniqueness of each functional network: both the MDN and DMN overlap along the sensory-fugal axis. Machine-learning approaches have also failed so far to distinguish the networks based on cytoarchitectural features alone [62]. Similarly, transcriptomic analyses demonstrate gene expression similarities between these two association networks [63,64]. The expression of only a few genes distinguishes the DMN or resting-state subnetworks of the MDN (frontoparietal and dorsal attention networks) from other functional networks, whereas the visual and limbic networks each exhibit >1000 distinctive genes [64]. A similar conclusion can be made by assessing cortical microarchitecture: both networks span eulaminate to agranular cortex and include archicortical and palaeocortical trends (Figure 2F). These data indicate that both the DMN and the MDN combine microstructural features of multiple levels of the sensory-fugal axis and dual trends, which may help to explain their broader similarities in their contribution to cognition. The DMN, however, occupies positions that are further from the sensory areas than the MDN [23] and has a more balanced distribution of unimodal, **heteromodal**, and agranular cortex (Figure 2F). By contrast, the MDN occupies positions between the DMN and sensory areas, and is more skewed towards heteromodal eulaminate cortex. These differences may explain why the DMN is more involved in perceptually decoupled states than the MDN [21,65]. More generally, these data illustrate how, by considering similarities in the network-level microarchitectural make-up of these networks, we can learn how their common anatomical features engender broad involvements in cognition, whereas the proportions of each network associated with each level of the sensory-fugal axis can account for key functional differences.

Targeted investigation of microstructure within a subregion can also help to define how cortical organisation enables complex forms of cognition. The mesiotemporal lobe, for example, contains manifold changes in cytoarchitecture from the isocortical inferior temporal cortex to the allocortical hippocampus [54,66] (Figure 3Bi). This axis involves complex variations in cortical layers [66–70], as well as changes in the content of the neural code, for example, from dynamic representations of the world in entorhinal cortex to more stable, unique encoding in the hippocampus [71,72]. The iso-to-allocortical axis of the mesiotemporal lobe is distinct from the anterior–posterior axis, and this can account for some aspects of connectivity into the hippocampus [73]. We recently modelled these intersecting axes using BigBrain [54] and found that they disambiguate functional connectivity to the DMN and MDN (Figure 3Bii,iii). The overlapping structural axes of the mesiotemporal lobe can therefore support the coexistence of multiple motifs of neural activity with intersecting axes of structural organisation, thereby helping to account for the complex relationship between the DMN and MDN. Taking a multidimensional perspective, especially in the mesiotemporal lobe [74], will probably be crucial for understanding how the functions of these networks dynamically change across cognitive states [75]. Such fine-grained approaches are also warranted across subregions of the DMN and MDN. The prefrontal cortex, for instance, harbours a different form of microarchitectural pattern: **interdigitation**. First discovered in foundational tract-tracing studies [76], interdigitated connectivity patterns in the prefrontal cortex (alongside interdigitated fractionation of networks in the parietal and lateral temporal cortex) have been more recently revealed by precision functional mapping that prioritises extended scanning per individual [77]. Interdigitation is thought to enable cross-domain integration by virtue of the close proximity of microcircuits that receive inputs from different regions [76]. Broad comparison of these regions with the DMN and MDN suggests that the networks contain distinctive combinations of microarchitectural patterns, and these probably contribute to their capacity to engage in different forms of information integration. Fine-grained cytoarchitectural mapping is essential to address these questions and their relation to neural dynamics (Box 3).

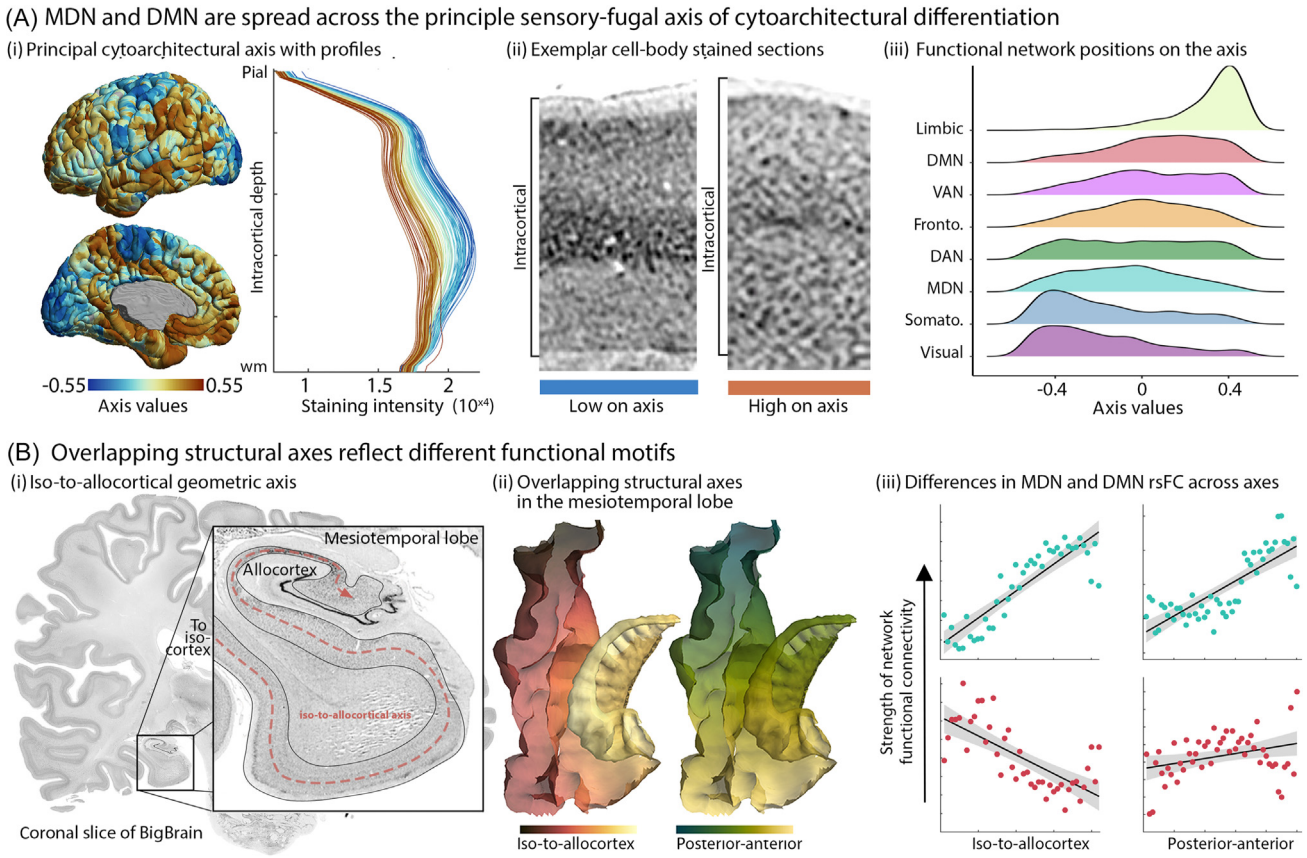

Figure 3. Microarchitectural investigations into the multiple demand network (MDN) and the default mode network (DMN). (A) (i) The principal cytoarchitectural axis (blue–red) reflects regional differences in the underlying staining intensity profiles. (ii) The profiles capture depth-wise variations in cellular density and soma size, as shown in the 2D sections (from https://bigbrainproject.org/hiball.html). Areas low on the axis (blue) exhibit stronger laminar differentiation (i.e., a bumpier profile) than areas high on the axis (red) which have less distinguishable layers. (iii) Comparison of functional networks (Figure 1C and [17]) with the principal axis (Ai) indicates a broad distribution of axis values in the DMN and MDN. Plots were produced with data from [52,62]. (B) (i) The geometric iso-to-allocortical axis [66], shown on a coronal BigBrain slice, runs in a lateral–medial direction and then follows the curvature of the hippocampus. (ii) The iso-to-allocortical and posterior–anterior are intersecting organisational axes of the mesiotemporal lobe. (iii) Average resting-state functional connectivity (rsFC) of the MDN (top) and DMN (bottom) to the mesiotemporal lobe varies as a function of the axes and is distinguished by the iso-to-allocortical axis, showing the utility of multidimensional, microarchitecture-informed approaches to disambiguate

(Figure legend continued at the bottom of the next page.)

Box 3. Practical challenges of working in MDN and DMN

Characterising the function of the association cortex is complicated by variation at both individual and population levels. The MDN and DMN (alongside the ventral attention network [17], also known as cingulo-opercular [18]) exhibit the highest levels of interindividual variation in their functional connectivity [127]. Relatedly, the topography of these networks differs the most between individuals [128]. Even within an individual, the MDN and DMN comprise many nodes that flexibly reconfigure their connectivity across states, unlike, for example, the visual network [129,130]. Therefore, it can be difficult to reliably define areas of the MDN and DMN and their connectivity profiles. Pronounced intra- and interindividual variation adds impetus to precision functional mapping of these networks, whereby many hours of fMRI are scanned per subject (resulting in several notable open datasets; e.g., the Midnight Scan Club [131] and Individual Brain Charting [132]). Recent work suggests that the MDN and DMN may be divided at the individual level into several closely juxtaposed subnetworks [77,133]. Although the MDN and DMN are not considered to be perfectly unified systems in the present review, their functional subdivisions have not been deeply interrogated from the microarchitectural perspective because it remains infeasible to acquire many hours of functional imaging and perform post-mortem cytoarchitectural mapping on the same individual. As precision functional mapping helps to address the challenges of intra- and interindividual variation in these networks, parallel advances in personalised cytoarchitectural mapping will be necessary to understand their relationship.

Cytoarchitectural areas are defined by their relative internal homogeneity, as well as by the appearance of an abrupt change in cellular distribution at their boundary [105]. Early neuroanatomists already noted, however, that the cytoarchitectural changes were less abrupt in association cortex, especially in the frontal lobe, than between areas in sensory cortex [33]. Although atlases show a clear consensus on the positioning of sensory areas, they reveal greater variation in association cortex [134]. One factor contributing to these discrepancies is interindividual variation [101]. To overcome this challenge, more recent cytoarchitectural mapping has been carried out on multiple brain specimens and has been made openly available [135]. The Julich Brain Atlas has shown that, although the general topography of areas is conserved across individuals, the precise location of the borders differs to a larger degree. As probabilistic cytoarchitectural maps of MDN and DMN areas are made available [135], more in-depth investigations of how interindividual variability impacts on the cytoarchitectural make-up of the networks will be possible.

Importance of multiscale anatomy for capturing functional organisation

The internal organisation of the DMN and MDN may therefore be posed as a two-sided puzzle encompassing microarchitecture and connectivity. Many studies have attempted to predict functional connectivity from diffusion-based tractography, but accuracy is consistently lower for DMN and MDN than for sensory networks [78]. Although methodological challenges of *in vivo* tract tracing may partially account for lower accuracy (e.g., due to the presence of crossing and kissing fibres), one-to-one correlations between structural and functional connectivity are probably not suited to the dense and dynamic connectivity of the DMN and MDN [79]. Sensory-driven networks are dominated by serial information flow through the sensory-fugal axis, which can be predicted based on the hierarchical organisation of tracts [38]. By contrast, association networks exhibit dense connectivity between widely distributed areas at varied levels of the sensory-fugal axis [80]. Indeed, communication models suggest that simulation of polysynaptic transmission is especially important to approximate functional connectivity in the DMN and MDN [81,82]. In addressing these difficulties, we recently used multimodal MRI to measure the microstructural similarity, distance, and structural connectivity across the cortex (Figure 3Ci) [53]. We found that multimodal features provide better predictions of functional connectivity than did models that did not incorporate microstructure (Figure 3Cii). In line with this evidence, biophysical models of functional connectivity that allow regional heterogeneity of circuit properties

functional organisation. Plots were produced with data from [54]. (C) (i) Cortical structure can be modelled with a combination of geodesic distance, microstructural similarity, and diffusion-based tractography. (ii) Prediction of rsFC from various structural features shows the advantage of integrating markers of microarchitecture and connectivity. Lower mean squared error (*x*-axis) indicates higher accuracy of the prediction. The ridgeplots show the lowest mean squared errors for the MDN (blue) and DMN (red) using the multimodal model, compared with a distance- or tractography-based model. Plots were produced with data from [53]. (iii) A biophysical model involving local microcircuit parameters (w^{EI}: excitatory to inhibitory strength, w^{EE}: recurrent excitatory strength) and a global network parameter (g, long-range scaling factor) can be used to predict functional connectivity from structural connectivity. In the homogeneous (Hom.) model, local microcircuit parameters are identical across nodes. In the heterogeneous (Het.) model, local microcircuit parameters are scaled according to a microstructural feature. Notably, the heterogeneous model significantly outperforms the homogeneous model, showing the advantage of adding microarchitecture in simulations of human brain function. Adapted, with permission, from [55]. Abbreviations: DAN, dorsal attention network; Fronto., frontoparietal; Somato., somatosensory; VAN, ventral attention network; wm, white matter.

outperform models where regions differ only by connectivity [83]. Similarly, scaling regional circuit parameters according to microstructure improves biophysical model performance [55] (Figure 3Ciii). These studies highlight the value of incorporating microarchitectural information into a multidimensional conceptualisation of the relationship between structure and function in the DMN and MDN.

In sum, recent investigations into the microarchitecture of the DMN and MDN provide several insights that can shape mechanistic accounts of their roles. Data-driven (Figure 3A) and atlas-based (Figure 2F) assessments of MDN and DMN cytoarchitecture indicate that they encompass heterogeneous subcomponents. The MDN is dominated by a type of microcircuit that is typically associated with heteromodal processing, thereby lending itself to balancing input from multiple sensory systems. The DMN contains a more balanced composition of microcircuits that span the sensory-fugal axis, and therefore may be poised to transform and integrate information from internal and external sources. Evaluating and further specifying these hypotheses is dependent upon deeper microarchitectural investigation of the networks. In particular, our review highlights the need to consider regional microarchitectural heterogeneity in models of network function (Figure 3C) and emphasises that fine-grained microarchitectural variations within a subregion can help to describe the complex way that processes within specific brain regions interact with other regions across the cortex (Figure 3B).

Concluding remarks and future perspectives

We suggest that a brain-based interpretation of human cognition can be enriched and guided by studying the microarchitecture of large-scale functional networks, notably the DMN and MDN. This perspective is predicated on the replicable identification of large-scale functional networks in the human brain [17,24,84], as well as on the up- and downregulation of activity in the DMN and MDN across a wide variety of tasks, including those that involve reasoning, decision-making, and hierarchically structured thought [11,15,21,65,85]. Although these observations are important, we demonstrate that candidate hypotheses describing 'how' regions of association cortex contribute to cognition can be generated from their underlying microarchitecture, a process that is possible given modern brain imaging tools and analytic methods. In particular, our review highlights how microarchitectural heterogeneity impacts on brain function across scales: (i) local cytoarchitectural variations within subregions echo motifs of functional organisation across the brain [54], (ii) microarchitecture provides complementary information to structural connectivity in predicting functional connectivity [53,55,83], and (iii) the DMN and MDN are variably spread across large-scale axes of microarchitecture and function [8,48,52].

A major impetus for discussing these issues now is the recent surge in microarchitectural datasets of the human brain and modern analytic strategies that facilitate exploration of high-dimensional data and multimodal imaging. Microarchitectural information can be incorporated into models to better approximate healthy brain function, and can be used to define cognitive mechanisms enacted by brain networks [86,87] (see Outstanding questions). Moreover, emerging work highlights the value of this approach in understanding deficits in common neurological and psychiatric conditions [88–91]. For example, common conditions such as epilepsy and autism are increasingly recognised to have microstructural perturbations coupled to imbalances in brain connectivity and function [92]. In the future, integrated multiscale approaches may prove valuable for generating viable, system-level understanding of the biological risk factors that underpin many of the diseases that affect our species.

Outstanding questions

How do local microarchitectural patterns constrain transformations of neural codes? For instance, in regions encompassing a cytoarchitectural **gradient** compared with regions exhibiting interdigitation.

How does information processing differ between heteromodal association networks and more sensory-driven hierarchies? Such work will probably help to further disentangle the implementation of serial and parallel processing, and shed light on the interaction of top-down and bottom-up signalling.

How do individual differences in microarchitecture account for functional idiosyncrasies, which are specifically pronounced in higher networks such as the DMN and MDN?

How does the dynamic reconfiguration of functional connectivity play out on the microarchitectural scaffold? In this context, ongoing developments in the formulation and validation of computational models of brain activity can help to mechanistically test how heterogeneous microcircuits contribute to macroscale dynamics and ultimately cognition.

How do developmental as well as learning- and disease-related changes in microarchitecture contribute to changes in functional network organisation and cognition?

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Declaration of interests

The authors declare no conflicts of interest.

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