

The brain's default network: updated anatomy, physiology and evolving insights

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Abstract | Discoveries over the past two decades demonstrate that regions distributed throughout the association cortex, often called the default network, are suppressed during tasks that demand external attention and are active during remembering, envisioning the future and making social inferences. This Review describes progress in understanding the organization and function of networks embedded within these association regions. Detailed high-resolution analyses of single individuals suggest that the default network is not a single network, as historically described, but instead comprises multiple interwoven networks. The multiple networks share a common organizational motif (also evident in marmoset and macaque anatomical circuits) that might support a general class of processing function dependent on internally constructed rather than externally constrained representations, with each separate interwoven network specialized for a distinct processing domain. Direct neuronal recordings in humans and monkeys reveal evidence for competitive relationships between the internally and externally oriented networks. Findings from rodent studies suggest that the thalamus might be essential to controlling which networks are engaged through specialized thalamic reticular neurons, including antagonistic subpopulations. These association networks (and presumably thalamocortical circuits) are expanded in humans and might be particularly vulnerable to dysregulation implicated in mental illness.

A serendipitous discovery was made by researchers in cognitive neuroscience who first began to use neuroimaging to study human brain function: that large distributed regions of the association cortex show reduced activity when participants perform active attention-demanding tasks, relative to their activity levels during passive conditions^{1,2} (FIG. 1). This set of regions, which comprises extensive portions of the frontal and posterior midline and inferior parietal lobule, came to be known as the brain's default network (or default mode network)^{3–5}. Regions of the default network fall within territories of the association cortex that are late to develop and have expanded greatly during hominid evolution^{6,7}. Human neuroimaging studies, by way of an unexpected form of activity attenuation, had stumbled onto some of the most interesting and least understood zones of the cerebral cortex.

Following its accidental discovery, a series of findings emerged about the default network. The activity reductions, originally discovered using positron emission tomography (PET) and generalized across numerous functional MRI (fMRI) studies⁸, could be robustly

detected within individuals⁹, and parallels were found in monkeys and rodents^{10–12}. Moreover, spontaneous activity fluctuations across the distributed regions comprising the default network were correlated with one another, which suggested that they formed an interacting network^{13,14}. Furthermore, tasks that rely on internally constructed representations (including remembering, envisioning the future and making social inferences) increased activity in default network regions beyond the level observed during passive conditions. These functional observations raised the possibility that the default network is active during especially advanced forms of human thought^{15–22}.

Despite these reproducible observations, many findings about the default network have been challenging to integrate. One difficulty arises because empirical observations made about the default network might not reflect a unitary phenomenon or even the behaviour of a single network. In our own past reviews and those of others, commonalities and unified explanatory theories were emphasized. However, a key emerging insight is that, rather than being a single monolithic network as originally envisaged, the default network is likely to consist of

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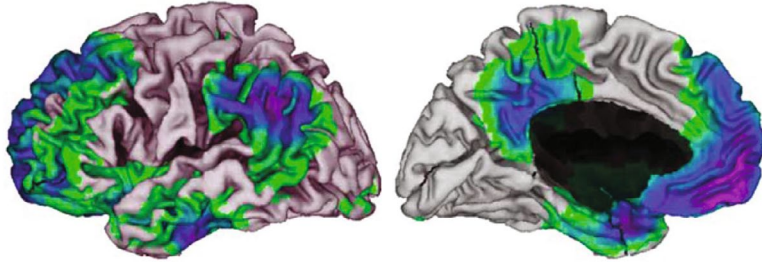
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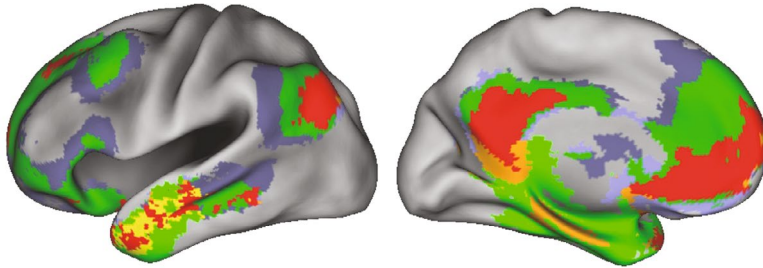
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a Group-averaged task-induced suppression



b Group-averaged functional connectivity



c Group-averaged task activation

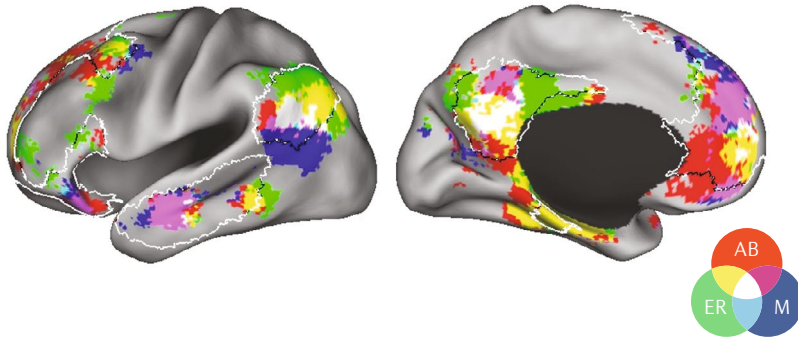


Fig. 1 | The brain's default network as defined in averaged groups of individuals. The default network was initially defined in neuroimaging studies of averaged groups of individuals, which revealed modulation and correlation among extensive regions of the association cortex. **a** | Distributed regions across the human brain show task suppression of default network activity when externally directed tasks are contrasted with passive task states. **b** | Resting-state functional connectivity studies reveal a correlated set of regions (which could be a network) that spatially resembles the pattern of regions suppressed by externally directed tasks. **c** | Tasks that demand multiple forms of internal mentation activate regions that overlap the group-averaged default network, including autobiographical remembering (AB), episodic retrieval (ER) and mentation associated with theory of mind (M) — that is, inferences about another's thoughts and beliefs. Part **a** is adapted with permission from REF.³, Proceedings of the National Academy of Sciences, and utilizes data published in REF.¹. Part **b** is adapted with permission from REF.¹⁸, Wiley-VCH. Part **c** is adapted with permission from REF.⁶⁸, Elsevier.

Task suppression

As used here, the reduced default network activity observed during an active task relative to its activity level during a passive (control) task.

Intrinsic functional connectivity

Correlations between spatially separate brain regions in their spontaneous functional MRI activity signal that can be used to generate hypotheses about network organization.

multiple, juxtaposed, individual networks. Another challenge relates to an over-reliance on correlational findings from human neuroimaging studies, which are inherently ambiguous. The observations that initially drew attention to the presence of the default network were compelling. Yet, unlike in other domains of systems neuroscience — in which such correlational observations are interpreted within the context of data from neuropsychological studies in patients with lesions and insights gleaned from animal models — relatively little work on the default network has been drawn from different levels of analysis.

In this Review, we present evidence suggesting the existence of multiple networks within the default

network and explore the implications of these new observations. We focus on phenomena observed in neuroimaging studies and converging findings from human neurophysiological recordings and explorations in monkey and rodent models. We also refer the interested reader to complementary reviews discussing the processing contributions of the default network to spontaneous forms of cognition and directed tasks, which are not the focus of the present Review^{22–26}.

Origins of the default network

Before exploring new perspectives on the brain's default network, we first survey four categories of historical findings, each of which is based on distinct empirical observations made at different times in the evolution of the concept of the default network: task suppression, intrinsic functional connectivity, anticorrelations and positive task modulation. We highlight the experimental approaches used to make each set of observations and stress ambiguities in their interpretation. We also address how these different groups of observations relate to one another and how their origins can be clarified by interpreting them in the context of anatomical and neurophysiological findings.

Task suppression. The brain regions now called the default network were first identified in isolated PET studies^{15,27} and were later highlighted in two reviews of PET data showing that these regions are consistently and robustly 'deactivated' during active external tasks (such as word judgements or visual object classification) relative to levels of activity in control conditions (such as passively viewing objects or fixing the gaze on a cross hair)^{1,2} (FIG. 1a).

Two classes of hypotheses were offered to explain these effects: either ongoing processes during the passive conditions could be activating these regions^{15,16}, or brain engagement in the active task could be inhibiting these regions through direct suppression¹. As PET measures of brain activity are relative (because they compare blood perfusion patterns in one task state with those in another), their findings are necessarily ambiguous as to whether neural firing or synaptic activity (that is, excitatory or inhibitory) contributes to the observed effects. Thus, it is not possible to determine from the initial observations of a relative difference whether the effect is symmetrical (meaning that the regions 'deactivated' are those involved in tasks driven mostly by the processes engaged by the passive reference task) or whether the active task is causing broad suppression of large-scale networks through an active mechanism. Alternative explanations, including redistribution of blood supply (blood stealing), are unlikely because they are not consistent with the known properties of vascular reserve¹ and also because the network can be identified by imaging approaches that rely on measures of glucose metabolism rather than blood perfusion (as discussed further elsewhere¹⁸).

Explorations of the processes that might be engaged during passive tasks provided an insight that guided a great deal of future work in this field: subjects' minds wandered in stereotyped ways during the passive tasks administered in neuroimaging studies^{8,15,28}. In an early

Anticorrelations

Negative correlations in the spontaneous functional MRI signal that are present between separate networks of regions positively correlated among themselves.

study that specifically addressed understanding the role of the default network in spontaneous thought, momentary behavioural measurements of task-unrelated thoughts correlated with default network activity levels²⁹, an observation that was confirmed in other studies^{30,31}. By focusing on the observation that the default network could be identified in relation to passive (or resting) conditions, an orientation emerged that emphasized the network's activity during spontaneous cognitive events. As will be illustrated later, such events are just one of the several classes of processing that are correlated with activity in default network regions. Directed remembering, envisioning the future and certain forms of social inference also activate regions that overlap with the default network. These observations clearly show that the domain of default network involvement is broader than that of undirected cognition.

Intrinsic functional connectivity. Spontaneous brain activity is strongly and selectively correlated across all of the distributed regions of the default network^{13,14} (FIG. 1b). As activity levels (measured indirectly by fMRI) increase in one region within the default network, activity levels in the other regions also increase. Although activity is often measured during passive rest, these spontaneous correlations are pervasive across all task states, including those that demand external attention^{32,33}. This observation suggests that the mechanism underpinning these correlations is distinct from that initially used to discover the default network through task suppression (discussed in detail elsewhere⁵).

The observations afforded by analyses of task suppression and functional connectivity converge on similar anatomical patterns in group-averaged data (FIG. 1). When directly contrasted in an aligned atlas space, these patterns overlap throughout the association cortex¹⁸. The discovery that the multiple distributed regions of the default network are strongly correlated suggests that this set of regions might be a network or brain system much like other distributed systems with anatomical connectivity and shared functional dependencies.

Anticorrelations. A third major observation about the default network is derived from studies of its functional connectivity. In addition to regions within the network showing strong positive correlations with one another, they also show anticorrelations (that is, negative correlations) with regions involved in external attention^{34,35}. The two studies that initially revealed this discovery both used the same general method: the time course of signal fluctuations from a region in the posterior midline was extracted from the resting fMRI signal. The regions distributed across the brain that were positively correlated with the selected region recapitulated the default network. Plotting the regions negatively correlated with the same posterior midline region revealed an entirely different pattern, which included regions along the intraparietal sulcus, the frontal cortex near to the estimate of the frontal eye field and the visual extrastriate cortex near the middle temporal area. When these 'anticorrelated' regions were themselves examined, they also formed a network of strongly positively correlated

regions. This separate network, often called the dorsal attention system, is functionally engaged during externally oriented, attention-demanding tasks³⁶.

These findings suggest that the default network, which is hypothesized to be involved in internal forms of mentation and spontaneous cognition, is antagonistic to another major network that is engaged by active attention to the external sensory environment. Importantly, this antagonism can be revealed through analysis of intrinsic activity fluctuations that are independent of any changes in external task demands, which raises the possibility that stable mechanisms might exist that support competitive relationships between networks (alternative suggestions are discussed elsewhere³⁷).

However, a challenge lies in inferring an antagonistic mechanism from the human functional connectivity data. In both the initial studies and the many that followed, correlation was estimated after the normalization of local fMRI signal time courses, which involved regression of global signal fluctuations. This processing step forces the distribution of correlations across all regions of the brain to centre around zero, meaning that half of such correlations will be assigned as positive and half as negative. Without such normalization, a low-level positive correlation exists across the brain that is believed to represent a combination of neuronal and non-neuronal noise sources that affect fMRI measurements^{38–40}. An extended debate about the interpretation of anticorrelations ensued, followed by proposals for new normalization methods and new concerns^{41–43}.

Two lessons can be taken from the discovery of anticorrelations and the debate that followed. First, the observed between-network differences are robust. Regardless of whether the anticorrelations are interpreted mechanistically, it is still true that the network linked to external attention is less correlated with the default network than with any other network in the brain. Second, ambiguity is inherent in the interpretation of relative correlation values. Although the presence of robust anticorrelations raises the important possibility that an antagonistic relationship between the networks exists, data sources other than functional connectivity studies are needed to confirm these relationships and provide insight into their mechanisms.

Positive task activation. Despite the name, default network regions do increase in activity during specific forms of directed tasks. The tasks that suppress default network activity tend to be externally oriented; that is, they require participants to selectively focus on and respond to stimuli in their environment. By contrast, tasks that increase default network activity tend to rely on internally constructed information; that is, mental representations that are flexibly built from memory and schema well beyond the immediate sensory environment. Two prominent examples of such tasks emerged in early studies, namely, autobiographical memory and tasks that require certain forms of social or self-referential inference (FIG. 1c).

Autobiographical memory tasks require individuals to recollect details of past episodes. When analysed in group-averaged data, autobiographical memory

Internal mentation

Cognitive operations arising from internally constructed representations minimally dependent on stimuli in the immediate environment.

tasks activate distributed regions that closely resemble the default network^{44–46}. Several interesting features of autobiographical memory tasks provide insight into the function of this network. First, they rely on declarative (that is, medial temporal lobe-dependent) memory^{47–49}. Second, from a task-demand standpoint, they fall at the extreme internal end of the external–internal continuum of orientation. Although an external cue often provides guidance during task instruction, the participant quickly moves into a mode of internal mentation, in which remembering progresses with minimal input from the external world⁵⁰. Interesting extensions of this work noted that similar regions of the default network are also engaged when individuals imagine hypothetical future scenarios^{19,51} and generally invoked “whenever attention is directed away from the current external situation and instead focused inwards towards a rich internal representation of an event, real or imagined” (REF.²¹). In 2018, component regions of the default network were shown to be engaged when information from recent past trials is used to constrain the response to an upcoming trial, in contrast to equivalent stimulus-directed responses^{52,53}. These findings suggest that specific component processes could be the building blocks of more-elaborate faculties tapped into by autobiographical memory and related tasks.

Tasks involving social inference also increase activity in regions of the default network. Social inference tasks take many forms and are unlikely to involve a single mental construct. One well-studied class of such tasks probes humans’ ability to represent the mental states of others⁵⁴, which is commonly termed theory of mind⁵⁵. Theory-of-mind tasks recruit a largely consistent network of brain regions^{56–58} that overlap with the default network^{19,59}. These tasks require understanding an agent’s beliefs, rather than a reality provided by cues in the immediate environment^{60,61}. Participants must suspend their own perspective (also termed decoupling^{57,62}) to consider the unobservable thoughts, beliefs or feelings of another person. Tasks involving other aspects of social cognition and self-knowledge also reveal anatomy that overlaps regions of the default network^{16,63}. Knowing about one’s own mind or knowing about another’s mind are similar cognitive tasks, in that they both require a point of view to be flexibly adopted that is different from the currently experienced world⁶⁴.

These collective observations raise the possibility that the default network participates broadly in advanced forms of thought and inference that depend on internal mentation. An open question is to what degree such diverse internal mentation tasks rely on truly shared (versus related or even separable) processes^{65,66}. The next section surveys observations from the past decade that find distinctions in the specific anatomical regions active between task forms, which raise questions about their functional specialization.

Functional heterogeneity

Studies of tasks that activate the default network initially emphasized commonalities in their findings^{17,19}. These explorations used group-averaged data and coarse comparisons between studies to demonstrate that a wide

range of internal mentation tasks (including remembering, envisioning the future and making inferences about other people’s beliefs) activate a similar set of distributed regions (FIG. 1c). This germinal observation focused on broad cortical resources that share properties and functions, and operate in ways that are distinct from the canonical sensorimotor networks. However, these coarse descriptions did not probe in detail the architecture of the embedded patches, areas and networks.

Different classes of task are now known to activate distinct juxtaposed regions when the form of internal mentation task is manipulated within the same experiment^{67–75}. Although the findings of these studies are still limited by the spatial blurring resulting from group averaging, a particularly telling difference emerges when tasks involving remembering are contrasted with tasks requiring inferences about other people’s thoughts and beliefs (theory of mind). Tasks that tap into autobiographical memory preferentially engage the parahippocampal cortex and the ventral portion of the posterior midline, near to the retrosplenial cortex^{70,72}. Within the inferior parietal lobule, tasks involving remembering also engage more-posterior (that is, caudal) regions, whereas theory-of-mind tasks preferentially engage more-anterior (that is, rostral) regions extending into the temporoparietal junction^{68,70,72}.

Two studies that manipulated the content of recalled material have revealed clear examples of functional dissociation within subregions of the canonical (that is, group-defined) default network. In both studies, judgements were made about people versus places, and the most compelling evidence for specialization occurred through analysis of spatial details within individual participants. In the first of these studies (published in 2015), individuals scanned using high-field strength (7T), high-resolution fMRI were asked to decide which of two known locations (nearby cities) were closer to them in space or which of two known people were personally closer to them⁷¹. Although the two tasks both activated regions broadly within the canonical default network, they were notably spatially separated, including around the posterior midline. The person-oriented judgements activated a central region of the posterior cingulate, whereas the spatially oriented judgements preferentially activated multiple surrounding regions in the ventral posterior cingulate and the retrosplenial cortex as well as dorsal regions. The interdigitation of these responses provides evidence for differential specialization across closely juxtaposed regions of the default network. Similarly, in another study, individuals underwent fMRI while recalling famous and personally known people (Tom Hanks, their friends) versus well-known and personally familiar locations (Times Square, their workplace)⁷⁵. Multiple regions of the canonical default network were active when participants recalled information from both domains, yet there was again clear separation within the posterior midline between tasks involving people and places, replicating the functional specialization across adjacent regions found in the 2015 study⁷¹.

Collectively, these observations suggest that distinct forms of internal mentation tasks activate adjacent

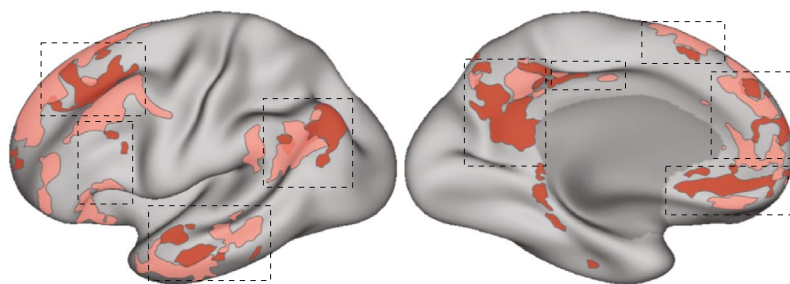
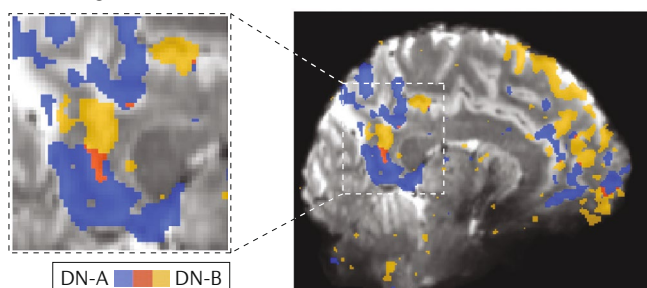
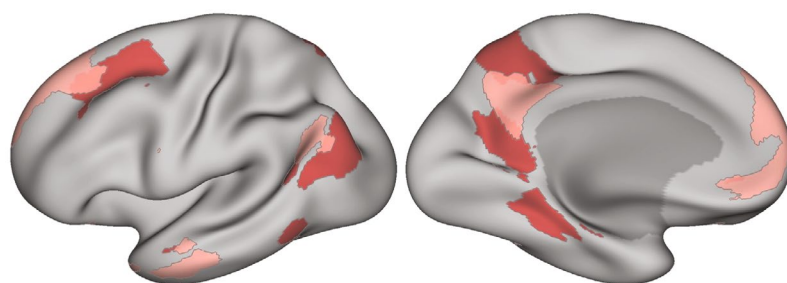
a Within-individual functional connectivity**b Within-individual high resolution****c Candidate networks in UK Biobank**

Fig. 2 | Single-individual analyses reveal that the default network comprises multiple distinct but interwoven networks. Within-individual functional connectivity analyses reveal that the canonical default network as defined in group-averaged data comprises multiple distinct interwoven networks that can be distinguished in individuals. **a** | Each network is displayed in a separate colour; the highlighted brain regions show that these networks are juxtaposed throughout the brain. The boxes delineate spatially close regions that dissociate the two networks. **b** | This finding of separation between the two networks has been replicated and extended in high-resolution (7 T) neuroimaging studies. Right image, a sagittal section showing complex interdigitation of the two principal networks (termed default network (DN)-A and DN-B) along the posterior and anterior midline of the brain. Left image, a zoomed view of the posterior midline that illustrates juxtaposition of the two networks along the cortical sulci. DN-A and DN-B are shown in blue and yellow, respectively, with overlap shown in red. **c** | Group-averaged functional connectivity analyses reveal some, but not all, features of the two distinct networks. The two networks can be detected particularly within the parietal cortex and posterior midline, but certain features of the networks (such as those in the medial prefrontal and the temporal association cortex) are lost, presumably owing to the spatial blurring inherent in group-averaged data¹⁶⁴. Part **a** is adapted from REF.⁷⁶, CC-BY-4.0. Part **b** is adapted from REF.⁷⁷, CC-BY-4.0. Part **c** is based on data from REF.¹⁶⁵ included in the UK Biobank ($n = 4,181$) analysis of resting-state networks using K-means classification.

regions within the broader cortical territories originally ascribed to a singular default network. More-detailed anatomical separations are likely to emerge as more tasks are contrasted and analysed in individuals (that is, without group averaging). The shifts in the positions of group-averaged regional responses across the

default network and the few within-individual analyses reported to date suggest the presence of fully (or largely) dissociated networks. Distinct networks can indeed be separated when high-resolution individualized approaches are employed to explore the details of network organization, as is illustrated in the next section.

Updated anatomy***Multiple distributed association networks are present.***

The default network, although originally envisaged to be a single network, is most probably composed of multiple distinct networks that are near to one another (FIG. 2). The detailed organization of these networks is revealed when intrinsic functional connectivity is studied fully within an individual, which enables fine spatial details to be appreciated without the blurring associated with group averaging^{76–79}. Evidence emerging from such studies suggests that the default network comprises at least two separate networks with clear spatial distinctions along the posterior and anterior midline, which have often been described as hubs of convergence.

These multiple distributed networks possess organizational features that provide insights into their function and developmental origins. The first salient feature is that the component networks include distributed, parallel nodes. Each network comprises many spatially separate regions that fall throughout the association cortex. With a few exceptions, the nodes of one network lie side by side with those of another. One possibility is that this distributed and parallel organization might arise as a result of fractionation and specialization occurring at an early developmental stage; thus, a single, less-differentiated proto-organization becomes specialized during development by activity-dependent processes (BOX 1).

A second critical feature is that, although the two networks are juxtaposed across many association zones, they show separation in relation to their coupling to the posterior parahippocampal cortex within the medial temporal lobe^{76,77}. A prevailing theme in the literature is that the default network is engaged across a broad set of tasks, including remembering and making inferences about other people's thoughts and beliefs, which led to ideas about the core processes that might be shared by these tasks^{17,19}. The functional heterogeneity described in the preceding section, combined with the presence of distinct networks (with only one of the networks coupled prominently to the posterior parahippocampal and retrosplenial cortices) raises the possibility that specialized networks have been lumped together. The broad similarities between the two networks indicate that they might have a common functional mode, but the fact that they are spatially separated suggests specialization.

The specialization of the extrastriate visual cortex is again informative to understand specialization of the multiple juxtaposed association networks (BOX 1). Although the processing modes of distinct extrastriate visual areas are shared and all areas contain parallel feedforward anatomical projections beginning in the retina, separate specialized areas respond to distinct classes of stimuli, including faces and scenery^{80,81}. The multiple networks that fractionate the default network

Box 1 | How hierarchical development might drive cortical organization

Development of the primate visual cortex provides insight into how cortical specialization arises. In adult humans and monkeys, multiple extrastriate regions (termed patches in monkeys) are preferentially responsive to face stimuli^{157–159}. Face-responsive regions are spatially distinct from those that respond to other visual categories, including scenery^{80,160}, and localize to zones of the cortex that preferentially map the central rather than the peripheral visual world^{81,161}. Retinotopic organization and face selectivity both emerge hierarchically during development. Just after birth, the extrastriate cortex does not possess face specialization but does feature retinotopic organization, in which the central to peripheral portions of the retina are mapped repeatedly¹⁶². This retinotopic organization is likely to be sculpted before birth by waves of spontaneous activity in the retina that cascade to the developing cortex¹⁶³. On exposure to the typical visual environment after birth, this proto-organization fractionates and specializes. Ultimately, certain regions in the temporal cortex near to the representation of central vision become specialized for faces¹⁶². Thus, the retinotopic organization formed by the innate anatomical arrangement of the retina and its connectivity to the cortex provides the scaffolding for specialization that emerges later, through experience.

Similar processes might organize the protracted development of association networks. An important question then arises as to what factors serve as the early foundation for specialization. A clue to the origins of specialization in the two principal networks linked to the default network (termed default network (DN)-A and DN-B) is that DN-A is strongly coupled to posterior parahippocampal memory structures, whereas DN-B is not⁷⁶. Otherwise, the organizations of the two networks are broadly similar and demonstrate repeating adjacencies throughout the brain (FIG. 2).

One possibility is that a less specialized, large, distributed proto-organization exists early in development. Within that proto-organization, the strength of parahippocampal projections might show a gradient, with stronger projections to specific portions of the association cortex. This difference might bias the proto-organization to fractionate during development into two distinct, specialized networks, such that one network preferentially processes information from the medial temporal lobe. The emergent adult networks might develop functional properties consistent with these early developmental biases, resulting in one network participating in mnemonic processes to a much greater extent than the other.

might similarly have a common processing mode that is dependent on internally constructed rather than externally constrained representations, and include separate juxtaposed networks that are specialized for distinct processing domains.

The fine spatial details apparent in individuals (FIG. 2) have also necessitated the re-evaluation of organizational hypotheses about the default network. In this section, although our critique focuses on descriptions arising from our own laboratory's past work^{67,82}, the need for re-evaluation similarly applies across the literature. Specifically, certain regions of the default network have been estimated to be 'hubs' — that is, nodes that are central to information flow between multiple subnetworks of the default network^{82–84}. The newly appreciated fine-scale organization of the default network suggests that the modelling approaches used to identify such regions of strong centrality will need to be revisited because blurring from population averaging across multiple networks might have distorted centrality estimates. Related points are discussed elsewhere⁸⁵. Along similar lines, a prominent hypothesis is that the default network comprises subnetworks linked by a set of hubs positioned along the midline^{67,86}. The possibility that such hubs interact with specialized subnetworks needs to be revised, given that the putative convergence zones, including those within the medial prefrontal cortex, have now been shown to participate in multiple distinct, spatially juxtaposed networks^{71,75–77}.

Distributed association networks are supported by anatomical connectivity. The human default network comprises multiple association networks that each possess a similar, distributed motif. The present section focuses on what is known about the anatomical basis of these networks. In terms of position, the regions in the adjacent networks preferentially occupy the higher-order association cortex that matures late in development, as estimated by its white-matter (myelin) maturation and expansion⁶⁷. The networks populate zones that are spatially distant from primary sensory and motor cortices^{7,87} and display high spatial variability from one person to the next⁸⁸. Beyond these broad observations, insights have been gained by examining human neuroimaging network patterns in relation to anatomical details^{18,20,87,89,90}.

A first point to make is that no simple relationship seems to exist between specific, traditionally defined, architectonic areas and estimates of the default network. We start with this point because an often-held assumption is that functionally specialized networks will have definable and informative relationships with architectonically defined brain areas.

Comparative studies of the human and monkey myeloarchitecture and cytoarchitecture suggest that the default network is composed of multiple widely distributed clusters of areas, including areas that extend from the frontal pole (areas 9, 10 and, possibly, 11) through the anterior cingulate (areas 24 and 32), the posterior midline extending from the retrosplenial cortex through to the precuneus just ventral to area 7m, a region of the posterior parietal cortex near Opt, extensive regions of the temporal association cortex and additional areas within the dorsolateral prefrontal cortex¹⁸. The extent of the network across multiple adjacent areas, which often overlap the boundaries of architectonic areas, suggests that correspondence is unlikely between the networks and underlying architectonic areas as they have been defined to date. One possibility is that alignments between architectonics, function and topography present in early sensory areas become less prominent as one examines the higher-order association zones that mature late in development (discussed elsewhere^{77,91–93}). Models that seek to link architectonic area transitions to network organization should be mindful of the possibility that strict alignments might not exist.

Anatomical connectivity provides a different view. Clear homologies between human neuroimaging estimates of the broad default network pattern and monkey anatomy have emerged from studies of projection patterns derived from tracer injections. FIGURE 3a illustrates one composite estimate of the rhesus macaque homologue of the human default network. Several features of these anatomical projections parallel the canonical human default network. First, the projection zones spatially echo the multiple distributed regions that define the human default network (FIG. 1) and overlap with estimates in the macaque derived from functional neuroimaging studies^{11,89,94,95}. Second, the projection patterns are recapitulated by tract tracing studies using injection sites in multiple regions distributed across the brain. For example, a parahippocampal injection identified the majority

Tract tracing

An anatomical method by which brain regions are injected to map the neurons receiving (anterograde) or sending (retrograde) projections from or to the region.

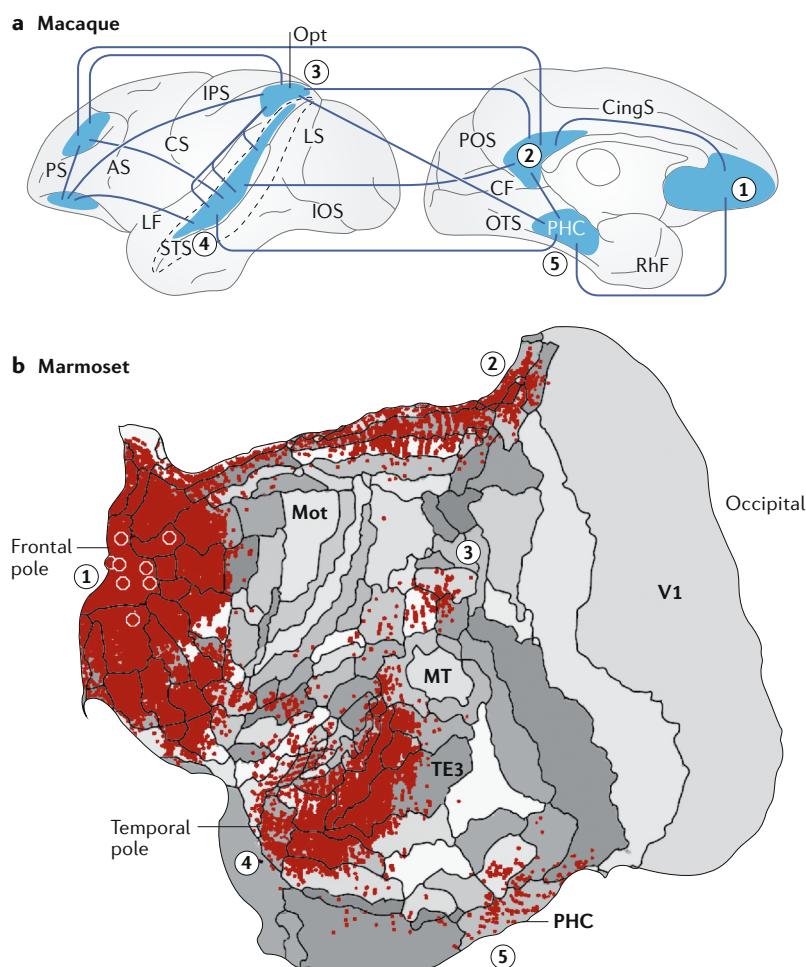


Fig. 3 | Tract tracing studies in non-human primates suggest that the default network is supported by direct anatomical connectivity. **a** | An estimate of the default network based on macaque anatomical tracer injections. Blue zones mark major regions of the default network, some of which are labelled with encircled numerals 1–5. Blue lines indicate known anatomical projections. Abbreviations denote prominent structures (AS, arcuate sulcus; CF, calcarine fissure; CingS, cingulate sulcus; CS, central sulcus; IOS, inferior occipital sulcus; IPS, intraparietal sulcus; LF, lateral (Sylvian) fissure; LS, lunate sulcus; OTS, occipitotemporal sulcus; PHC, parahippocampal cortex; POS, parietooccipital sulcus; PS, principal sulcus; RhF, rhinal fissure; STS, superior temporal sulcus). **b** | An estimate of the default network based on marmoset anatomical tracer injections to the frontopolar cortex areas 9, 10 and 11. White circles represent the eight injection sites. Red shading marks the summed retrograde label for these injections across the full cortical surface of the marmoset, projected here as a flat map. Black outlines demarcate architectonically defined areas, among which the occipital visual cortex (V1), middle temporal (MT) area, temporal association cortex (TE3), primary motor cortex A4ab (Mot) and PHC have been labelled for reference. Encircled numerals 1–5 indicate major zones of the default network that correspond to the similarly labelled locations in the macaque. Part **a** is adapted from Binder, J. R. et al. Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. *Cereb. Cortex* **19**, 2767–2796 (2009), by permission of Oxford University Press (REF.²⁰). Part **b** is adapted from REF.⁹⁰, CC-BY-4.0.

of the distributed network⁹⁶, an observation replicated in subsequent studies^{96,97}, as did a posterior cingulate injection included in a different study⁹⁸, also replicated elsewhere^{99,100}. Frontopolar injections also recapitulate many regions across the network¹⁰¹. Finally, the projection zones within a region (most notably the parietal association cortex) can be anatomically specific. The zone of the

parietal association cortex that receives⁹⁷ and sends^{96,102} projections to the parahippocampal cortex is Opt, which is a specific focal posterior portion of the inferior parietal lobule. Injections within the parietal cortex near to Opt sometimes give the impression of a connection to a broader region, especially considering that local projections are almost always found near to the injection site. By contrast, the focal and convergent zones identified by injections in the parahippocampal cortex^{96,97} and the posterior cingulate^{98–100} triangulate, with improved specificity, a region that is probably central to the default network.

A candidate anatomical homologue of the default network has been described in the common marmoset (*Callithrix jacchus*)^{90,95,103}. This small New World monkey has a brain 180th of the size of the human brain; the marmoset cortex is particularly smooth (lissencephalic) for a primate brain, which makes many areas accessible for detailed anatomical and physiological analysis. Another major advantage of marmoset studies is the existence of an open-access neuroinformatics database¹⁰⁴ that includes the results of large numbers of tracer injections, characterized using a common coordinate system, which provides the opportunity to pool injection data and to contrast distinct connectivity patterns.

Striking observations have emerged from this approach. The marmoset possesses an anatomically connected network that includes all of the distributed zones found in the human default network^{90,103}. For example, retrograde tracer injections into frontopolar cortex area 10 and the immediately adjacent frontopolar cortex areas 9 and 11 reveal projections from areas of the parahippocampal cortex, the anterior cingulate, the ventral posterior cingulate, a parietal association zone at or near Opt and extensive anterior temporal association cortex extending into the temporal pole (FIG. 3b). These projections are selective and spare regions that participate in the marmoset homologue of the dorsal attention system (for example, the middle temporal area).

Humans' most recent common ancestor with New World monkeys, including the marmoset, lived about 45 million years ago^{105,106}. This fact raises the intriguing possibility that the basic anatomical motif that supports the human default network might have been already well represented in a primate ancestor many tens of millions of years ago. A key feature of this network is its connectivity to the anterior apex of the prefrontal cortex, which is supported by convergent anatomical data from three separate New World and Old World species of monkey^{101,107,108}.

One important topic that remains unresolved is whether animal models provide anatomical bases for the multiple, closely juxtaposed networks found in humans (FIG. 2). Interpretation of monkey anatomical studies presents challenges, much like the interpretation of group-averaged human neuroimaging studies. Although the projection patterns of individual monkeys can be resolved with high precision, the injections themselves are often large and not precisely aligned between individual monkeys¹⁰⁴. The consensus networks illustrated in FIG. 3 might, therefore, be a blurred combination of multiple adjacent networks.

A critical test of the ideas in this Review will emerge when next-generation anatomical techniques¹⁰⁹ are

Bowtie organization

As used here, refers to a core–periphery anatomical organization that resembles a bowtie with wings.

harnessed to resolve the comprehensive projection patterns of distributed association regions within individual primate brains. We hypothesize that the interwoven parallel networks identified in humans reflect an underlying organization of anatomical connectivity that is shared by multiple primate species. Alternative hypotheses based on aggregate properties of the primate connectivity matrix have been put forward, including the possibility of a bowtie organization that includes association areas in the core and preferentially includes sensory areas in the periphery¹¹⁰. We hypothesize that there are parallel networks interwoven throughout the association cortex that might have been missed in aggregate analyses of anatomical data to date, much as human neuroimaging analyses can miss details when findings are averaged across individuals.

We further expect that, even if a default-network-like architecture is broadly confirmed to exist in monkeys, it might be less differentiated in all or some primate species than it is in humans. Comparisons of frontopolar cortex area 10 across primate species provide insight into this point. This area is more homogeneous in the marmoset than in the macaque, which in turn is more homogeneous than in humans^{111,112}. Differences between humans and apes have also been noted¹¹³, as well as differences between small and large New World monkeys¹⁰⁸. The available data suggest that monkeys do have a homologue of the human default network, but its level of differentiation remains unresolved. If the evolution of distributed association networks parallels the expansion and differentiation of frontopolar cortex area 10 in living primate species, then it becomes possible to imagine how the same ancient anatomical motif could take on specialized forms in the large-brained primates. The multiple networks that comprise the human default network are therefore intriguing from an evolutionary standpoint, given their relative expansion and differentiation. As discussed in the next section, these networks are also positioned as the apex transmodal networks situated far from the sensorimotor hierarchies. These features — expansion, differentiation and freedom from the strong constraints of sensory hierarchies — might have been critical evolutionary gateways accounting for their functional roles in humans^{7,114}.

A repeating network motif is embedded within a macro-scale organization. A striking feature of the multiple interwoven networks that populate the human association cortex is how similar they are to each other in terms of broad network organization^{76,115,116}. This organizational motif applies not only to the two principal networks that fractionate the default network (depicted in FIG. 2) but also to several other adjacent distributed association networks, including those that support external sensory attention and aspects of cognitive control¹¹⁵. Although exceptions exist, each distributed association network tends to have a component in each of the major association zones across the cortex. Furthermore, when all of the networks are examined together, they reveal an orderly spatial progression on the cortical surface^{76,87}. The same motif and spatial relationships between multiple association networks are also observed in marmoset anatomical

connectivity studies⁹⁰ (FIG. 4), as well as in functional network studies in marmosets and macaques⁹⁵. These two properties — an organizational motif that is conserved across networks and an orderly spatial progression of different networks — raise the possibility that a macro-scale organization might emerge from evolutionary and developmental constraints^{7,87,114,117}.

The multiple distributed association zones are each spatially distant from the sensory areas⁸⁷ (FIG. 4). These association zones — which should perhaps be considered to fill the gaps between well-specified sensory systems — contain multiple association networks, including those that define the default network. The association networks linked to external sensory attention lie closest to the primary sensory areas and are succeeded by the multiple higher-order networks, one after the other. In terms of spatial progression outward from the primary sensory cortex, the default network is the most distant⁸⁷ (FIG. 4). Smallwood and colleagues nicely summarize the potential functional implications of this organization as follows: “neural systems can be understood along a spectrum, from unimodal systems more directly involved in acting in the here and now to transmodal association cortex, which supports neural operations less tethered to input” (REF. 118). Thus, on the basis of its relative position on the cortical mantle, the default network is considered the apex transmodal association network.

Interestingly, the orderly spatial arrangement of cortical network representations in the human cerebellum also converges on this same sequence: the anterior lobe of the cerebellum contains the primary somatomotor map, after which subsequent areas of the cerebellum represent the same association networks as are reflected in the cortical sequence¹¹⁹. At the boundary of Crus I and Crus II, where the horizontal fissure is prominent, the cerebellar map inverts and progresses a second time in reverse order through the full hierarchy of networks, ending in the secondary somatomotor map. The order of networks present in the cerebral association cortex is mirrored twice in the cerebellum. Within the cerebellar sequences, the default network is again nominated as the apex association network furthest from the sensory cortex¹¹⁹.

The observation that the default network (or, more specifically, the multiple juxtaposed networks that together comprise the canonical default network) is positioned at the apex of transmodal networks has intriguing implications. First, this observation provides a context to understand the myriad empirical findings that emerged in the early years of neuroimaging, which predominantly targeted perceptual tasks and stimulus-controlled decisions. Studies that focused on tasks demanding external attention collectively emphasized the contributions of networks that process information about the immediate environment. Only passive task states serendipitously relaxed the demands on external attention enough to reveal activity in the apex transmodal networks, probably because these networks are specialized for distinct internally oriented processing modes. Second, the notion that multiple parallel networks are sequentially situated next to one another along a macroscale gradient raises important questions. For example, the existence of multiple separate networks

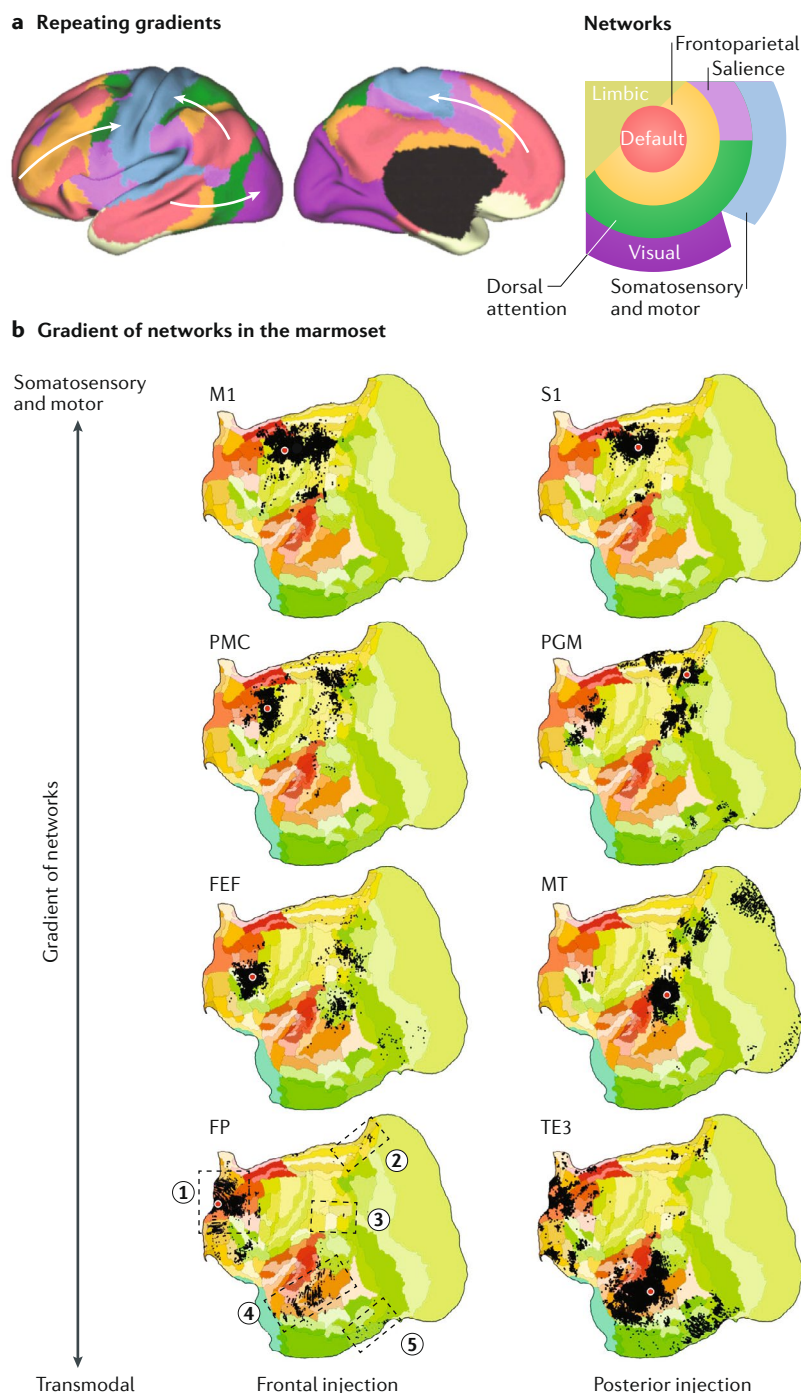


Fig. 4 | The default network is situated within a macroscale gradient. **a** | The gross spatial ordering of networks is repeated across multiple zones of the association cortex, which suggests that the same organizing forces are invoked multiple times to form the tapestry of networks observed in adults that includes the default network at its apex. Different colours represent distinct large-scale networks. The white arrows indicate zones of the cortex that repeat transmodal to primary-modality sequences of networks. **b** | Tracer injection studies in marmosets illustrate the ordering of four of the many networks that radiate outwards from the primary motor cortex (M1). Each network is shown on one row, with an anterior injection defining the network on the left and a posterior injection on the right. As one progresses from M1 through the premotor cortex (PMC), frontal eye field (FEF) and frontopolar cortex (FP), the injections identify progressively more rostral, distributed networks culminating in the final apex transmodal network that is a candidate homologue of the human default network. One hypothesis is that homologous sequential anatomical networks are the basis of the macroscale organization observed in the human brain. Red circles represent injection sites. Black dots represent retrograde label sites. Encircled numbers 1–5 represent major regions of the default network. MT, middle temporal area; PGM, an area within the posterior parietal association cortex; S1, primary somatosensory cortex; TE3, an area within the temporal association cortex. Part **a** is adapted with permission from REF.⁸⁷, Proceedings of the National Academy of Sciences. Part **b** is adapted from REF.⁹⁰, CC-BY-4.0.

Neurophysiology

Human intracranial recordings reveal evidence of suppression of the default network during active externally directed tasks^{120–126} (reviewed elsewhere¹²⁷). In a study of high-frequency broadband (HFB) signals, which reflect population-spiking activity from many thousands of neurons, electrodes placed in both the posterior cingulate and the medial prefrontal cortex detected substantially decreased signals when individuals were engaged in active tasks¹²⁰ (FIG. 5a; see also FIG. 5b). These responses are anatomically selective, and electrodes placed in the supplementary motor area and the primary visual cortex detect opposite effects. Broad spatial surveys of task-induced suppression of HFB signals find these effects across the multiple distributed nodes of the default network^{123,124}. Moreover, both the magnitude and the duration of HFB task suppression are positively correlated with task difficulty¹²³, which converges with another feature of the human neuroimaging findings⁸. These findings demonstrate that the original defining feature of the default network — the modulation of its activity levels by externally oriented and passive task states — is robustly present in directly recorded neuronal activity.

In the monkey, both single-unit and multi-unit activity correlates of task suppression are found in the posterior cingulate¹⁰. Relative to the pre-stimulus baseline, neuronal activity is robustly suppressed when monkeys shift their gaze towards transiently present visual targets, a task that demands external attention. On receipt of a cue that the active task will be delayed, single-unit activity increased in the posterior cingulate of these animals, similarly to the cued-rest increases in default network activity

offers the possibility of exploring competition between networks. Of particular note, intrinsic functional connectivity studies revealed negative correlations (anti-correlations) between transmodal apex networks and early networks close to sensory cortices. In addition to suggesting a functional specialization of these networks, these observations might also reflect stable mechanisms that influence competition between broad groups of networks at a global level. We consider this possibility further in a later section of this Review. In the next section, however, we discuss neurophysiological observations that offer additional evidence of antagonistic relationships between networks.

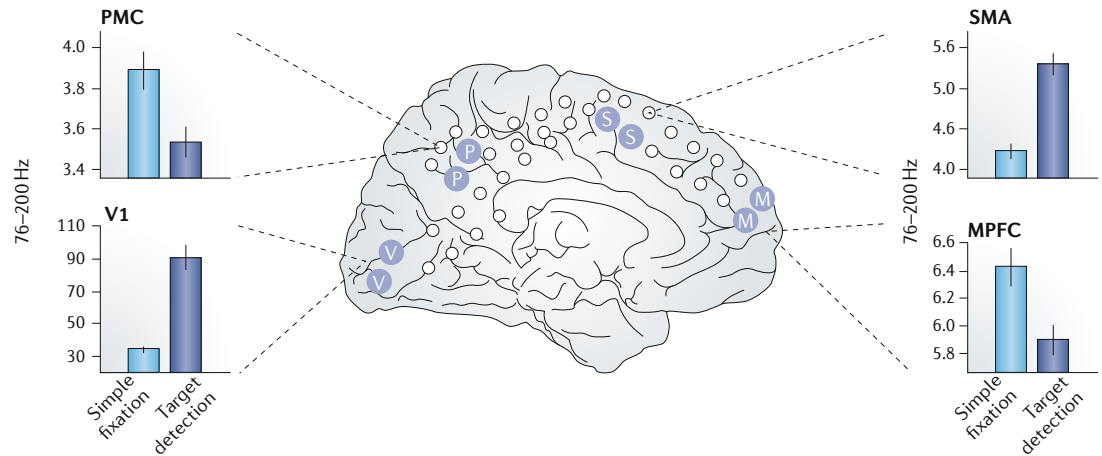
High-frequency broadband (HFB). High-frequency (>50 Hz) non-oscillatory activity recorded in the local field potential that reflects population-spiking activity.

observed in human intracranial recordings¹²² (FIG. 5c). The suppression effect is anatomically selective in monkeys as well as in humans; the lateral intraparietal area, an area linked to external sensory attention, shows

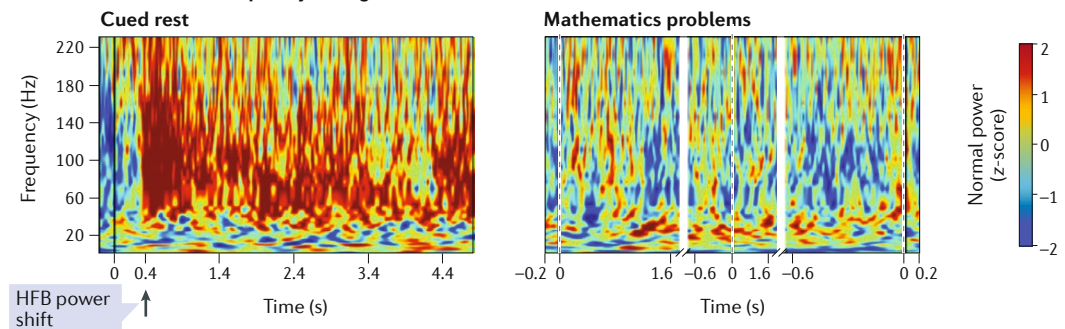
enhanced rather than suppressed activity under similar conditions.

Emerging techniques that enable chronic recording from widespread cortical regions in the monkey¹²⁸ offer

a Human intracranial recordings



b Human time versus frequency histograms



c Macaque electrophysiology

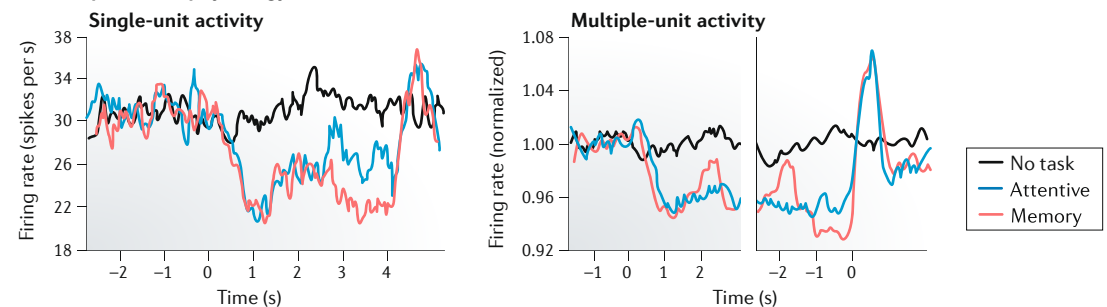


Fig. 5 | Electrophysiology studies in humans and monkeys reveal rapid, anatomically selective task suppression of the default network. **a** | Human intracranial recordings from multiple sites across the brain show robust decreases in high-frequency broadband (HFB) signals during engagement in an active externally oriented task (namely, visual target detection). The task-suppression effect is present in regions of the default network, including the posterior medial cortex (PMC; recorded by an electrode pair in the brain, marked 'P') and the medial prefrontal cortex (MPFC; recorded by a separate electrode pair, marked 'M'). Areas of active task engagement, such as the occipital visual cortex (V1; recorded by the 'V' electrode pair) and the supplementary motor area (SMA; recorded by the 'S' electrode pair), demonstrate the opposite effect. **b** | Time versus frequency histograms from an electrode within the PMC demonstrate that rapid shifts in HFB power occur within 400 ms when individuals enter epochs of cued rest. By contrast, individuals engaging in an active mathematics task do not show such an HFB power change. A region near to the estimated lateral intraparietal cortex showed the opposite pattern: increased activity during mathematics problems and attenuated activity during cued rest (not shown). **c** | Electrophysiology studies reveal rapid reductions in both single-unit activity and multiple-unit activity in awake, trained monkeys engaging in an externally oriented task involving active working memory. Part **a** is adapted with permission from REF.¹²⁰, Proceedings of the National Academy of Sciences. Part **b** is adapted with permission from REF.¹²², Proceedings of the National Academy of Sciences. Part **c** is adapted with permission from REF.¹⁰, Proceedings of the National Academy of Sciences.

an approach to explore in depth the electrophysiological correlates of task suppression. These powerful methods, which survey neuronal response properties simultaneously in many distinct networks, have revealed that task-associated enhancement and suppression effects are extensive throughout the brain. For example, during a demanding external task, suppression is evident near to putative monkey homologues of the default network, such as the parietal association cortex at or near Opt¹²⁹. These intriguing approaches are poised to shed light on several questions about the physiology of default network task suppression, and to do so in a way that can be related to the human observations.

Direct neuronal recordings in humans (which provide insights that cannot be obtained by slow haemodynamic measures) indicate that HFB signal suppression begins soon after initiation of an externally oriented task (within ~250–600 ms)^{121,123} and that HFB activity increases rapidly once cued rest begins (within ~400 ms)¹²². In monkeys, suppression of posterior cingulate activity also occurs rapidly (~300–400 ms), and is sustained in a tonic manner during attentive epochs (see also REF.¹²⁵). The tonic characteristic of this suppression contrasts with the transient responses to various other task-relevant events, including target presentation and reward delivery, and might be a clue to its mechanistic origin¹⁰.

Direct neuronal recordings in humans have also revealed examples of increases in HFB signals to levels that are often above the passive baseline during classes of tasks broadly thought to rely on forms of internal mentation^{125,130}. In a detailed study of task-related increases in HFB signals, intracranial electrodes placed at or near the posterior cingulate exhibit HFB suppression during attention-engaging mathematics tasks and show increased HFB signals when individuals confirm autobiographical memory questions (such as ‘I ate at a restaurant this week’)¹³⁰. This hierarchy of response (HFB suppression is highest during active external tasks, intermediate during rest and lowest during tasks that demand focused internal mentation) parallels results in the neuroimaging literature³.

However, the task-modulated increases in activity do not yet reveal a simple organizational pattern. Heterogeneity is evident in multiple dimensions, including differences in response magnitude between nearby sites, variability in response latency along anatomical gradients^{125,130} and variability in responses to separate tasks within the domain of internal mentation¹³⁰. A perplexing observation is that electrode positions in the posterior midline show more overlap between those demonstrating autobiographical memory and suppression effects than between autobiographical memory and cued-rest increases in activity¹²⁵. We suspect that these complex patterns reflect a combination of poorly understood fine-scale organization as well as technical sources of noise and normalization^{127,131,132}. An important avenue for future investigation is to combine emerging knowledge about the detailed organization of brain networks within individuals (FIG. 2) with targeted explorations in patients who have widely implanted intracranial recording electrodes.

Control of the default network

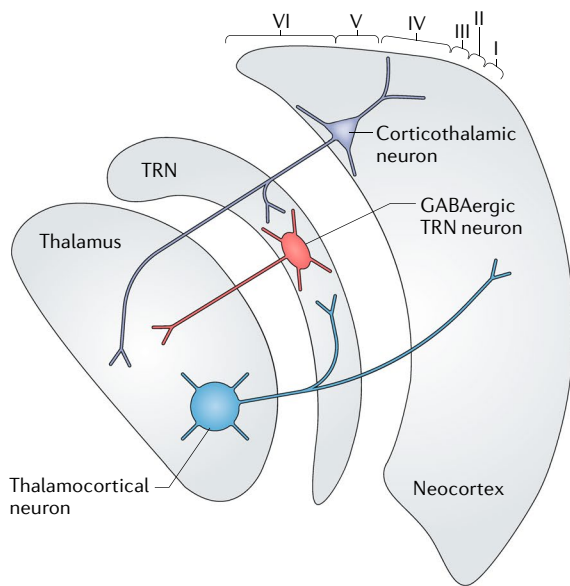
The task suppression stumbled on in the earliest studies of the default network^{1,2} and the subsequently discovered anticorrelation^{34,35} phenomena might reflect stable antagonistic suppression between broad sets of networks. One possibility is that external and internal processing modes employ incompatible (and perhaps even opposing) functions. Critically, each of the networks and regions that support external and internal processing modes are not themselves monolithic. For example, the visual cortex possesses an array of specialized processing areas and patches embedded within parallel pathways; these pathways interact with the broader distributed networks that serve to extract and process information from the external world^{80,133}. As discussed throughout this Review, we now know that the originally described monolithic default network also possesses multiple specialized regions and networks (FIG. 2) that provide for diversity of function in relation to internal mentation. However, the mechanisms through which these antagonistic and interacting networks are controlled remain to be fully defined.

Candidate thalamocortical and basal forebrain mechanisms. Thalamocortical circuits are candidates for the control of information flow both within and between distributed cortical networks^{134–136}. Certain thalamic nuclei in primates project to distributed association regions of the cortex, with the medial pulvinar (and potentially also portions of the medial dorsal nucleus) having broad connectivity to anterior and posterior cortical regions^{137,138} (FIG. 6). These regions might be homologues of the association networks comprising the default network in humans. These thalamic association nuclei are directly gated by the surrounding thalamic reticular nucleus (TRN). The TRN must exert this gating through GABAergic inhibition of thalamic projection neurons, as the TRN has no direct projections to the cortex¹³⁸. Because thalamic projection neurons innervate the TRN, this structure has been implicated in lateral inhibition¹³⁹ and can also be involved in feed-forward inhibition by implementing the effect of prefrontal inputs onto the thalamus¹⁴⁰. Thalamocortical circuits, therefore, are anatomically well situated to exert broad influence within and between cortical networks and to act as modulatory hubs¹⁴¹.

Circuit-based manipulations in rodents illustrate opposing effects in distinct subpopulations of TRN neurons that suggest possible mechanisms of network control. In mice, recordings from chronically implanted electrodes placed near TRN neurons during epochs of sleep and awake exploratory behaviour show that distinct populations of TRN neurons were correlated (either positively or negatively) with the two arousal states¹². Probing this difference using optogenetic circuit-tracing strategies revealed segregation of distinct sensory-projecting and limbic-projecting TRN neurons, along with segregation of their physiological properties. The TRN neurons that correlated positively with quiescence were preferentially sensory-projecting, whereas those that correlated negatively were limbic-projecting. The distinct patterns of behaviour observed in association with these two subpopulations of TRN neurons

Thalamic reticular nucleus (TRN). A modulatory nucleus surrounding the thalamus composed of GABAergic inhibitory neurons projecting to the thalamus.

a Circuitry of the TRN



b Candidate antagonistic circuits in the marmoset

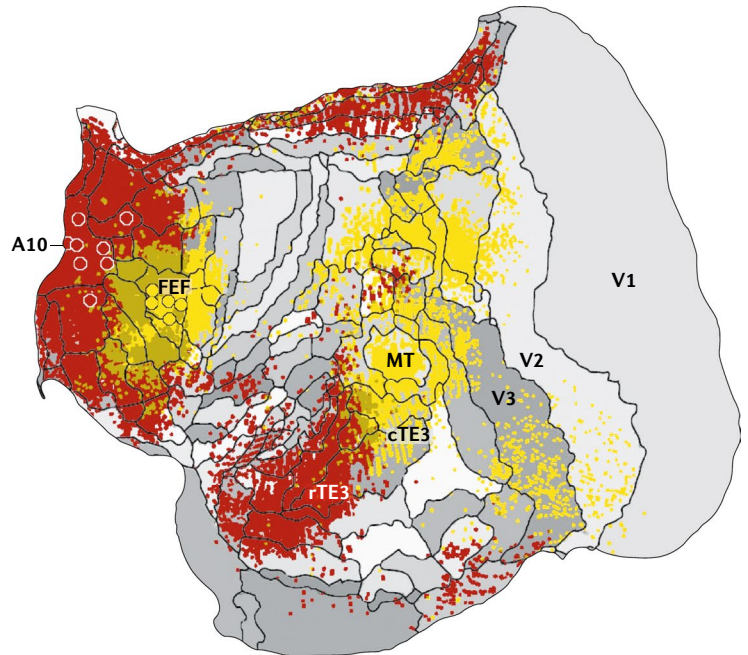


Fig. 6 | Thalamocortical circuits are candidates for controlling the activity of the default network, including task-suppression effects. a | The thalamic reticular nucleus (TRN) sits between the thalamus and the cerebral cortex. Excitatory neurons that project from the thalamus to the cortex also project to inhibitory TRN neurons, which project back to the thalamus and provide inhibitory feedback as well as gating state-dependent thalamocortical activity patterns. Individual TRN neurons can possess bifurcating projections that innervate multiple thalamic zones, and TRN neurons with overlapping dendritic arbors can innervate separate thalamic zones (not illustrated). Thalamocortical projections display marked diversity and can similarly target multiple areas and cortical layers, particularly in association regions (also not illustrated). These anatomical properties are consistent with a broad modulatory influence of thalamocortical circuits on the activity levels of brain networks, including the default network, via enhancement and competition between networks (reviewed elsewhere¹⁴¹). Dysregulation of thalamocortical circuits might also increase the risk of certain forms of mental illness, including schizophrenia. **b** | An estimate of the anatomical projections that support the default network in the marmoset (dark red label) juxtaposed with a distinct sensorimotor network (yellow label) involving one candidate frontal eye field (FEF) area, where the tracer injections (yellow circles) were located, and its distributed regions including the middle temporal (MT) area and the lateral intraparietal cortex. The presence of distinct distributed networks that parallel the human default network and canonical sensorimotor networks positions the marmoset as an excellent primate model to explore the mechanisms of interaction between the networks, including hypothesized antagonistic mechanisms. A10, frontopolar cortex area 10; TE3, an area within the temporal association cortex with rostral (rTE3) and caudal (cTE3) subdivisions that differentiate the two networks; V1–V3, areas of the occipital visual cortex. Part **a** is adapted with permission from REF.¹⁴¹, Elsevier. Part **b** is adapted from REF.⁹⁰, CC-BY-4.0.

extended beyond sleep–wake state differences to more subtle differences in arousal during an attention-demanding visual task. Although no evidence links the modulatory effects observed in rodents to effects observed in humans, it is notable that distinct sensory-associated and limbic-associated TRN neurons can exhibit opposing effects reminiscent of the large-scale network changes observed in the human phenomena of task suppression and anticorrelation.

Other candidate circuits might also contribute to modulation of the default network. For example, studies in rats suggest that gamma power in the basal forebrain, which provides the major cholinergic efferents to the cortex, is decreased when rats are transported from their home cage to a novel arena that encourages intensive exploration¹⁴². Basal forebrain gamma power is relatively increased during periods of grooming and quiet wakefulness compared with levels in active exploration, including in the novel environment, where infrequent

periods of grooming are associated with transient increases in gamma power¹⁴². These modulatory effects in the basal forebrain parallel features of default network task suppression and, therefore, provide an additional target for exploratory studies aimed at improving our understanding of modulation of the default network¹⁴³.

In discussing control of the default network, it is important to relate our emphasis on local circuit properties to the broader literature on prefrontal cortical networks, which have been a common focus of studies in humans and monkeys^{36,144–147}. Considerable evidence indicates that prefrontal regions participate in top-down control and modulate information-processing networks across the brain. However, limited attention (with a few exceptions^{148,149}) has been given to the specific mechanisms by which this control is exerted. In focusing on thalamocortical and basal forebrain circuits that modulate firing properties in distinct task states, we emphasize local circuit properties that might support

the mechanisms by which cortical networks exert control over other networks. Interestingly, many features of circuit properties are conserved between rodents and primates¹³⁶. This conservation provides an opportunity to study mechanisms of control using modern molecular genetic tools in non-human primates and humanized models of dysfunction. Additionally, such conservation implies that ancient features of this circuitry could be the building blocks of the competitive network interactions observed in human neuroimaging studies.

Hierarchical network control. One aspect of default network control that we have little insight into is whether only one or multiple mechanisms operate at distinct scales of organization. The first scale of control concerns the broad task suppression that emerges when individuals perform externally focused tasks. A second scale of control relates to the selective enhancement of local networks during different forms of internal mentation, such as remembering versus making social inferences. One possibility is that a common mechanism is at work: the activity of specific networks driven by the task context might be enhanced over other possible networks, such that the appearance of broad task suppression is merely a byproduct of the extreme contrast between states of directed attention to internal versus external information channels. Local modulation might emerge when the contrasted tasks differ in more-subtle ways.

An interesting alternative is that multiple mechanisms might exist to hierarchically control network selection at distinct scales, with a broad antagonistic mechanism that suppresses large zones of the cortex between the default network and other networks important to external attention. But within those broad zones of the cortex, distinct mechanisms might also support the selection of narrow cortical regions and networks as required by the task at hand. That is, multiple networks might be jointly suppressed when attention is directed to the external world, but enhanced selectively when required for active information processing in specific task contexts.

Mechanisms of network control might provide insight into mental illness. The default network and associated large-scale networks involved in cognitive control are dysregulated in individuals with schizophrenia and bipolar I disorder with psychotic features^{150–153}. Schizophrenia and bipolar disorder are also among the most heritable forms of mental illness. We might consider, therefore, whether molecular genetic variations could lead to dysregulation of the default network and hence increase the risk of mental illness. Studies of schizophrenia, in particular, provide intriguing clues about how dysfunction might arise.

Well-powered studies of genetic variation in individuals with schizophrenia have identified a candidate risk locus linked to the T-type calcium channel, which is prominently expressed in the TRN^{154,155}. These observations provide a possible link between mental health and dysregulation of cognitive networks, although we recognize that this represents only one potential contributing mechanism in a landscape of many. Given that the irregularities of oscillatory activity patterns (including sleep spindles)

observed in patients with schizophrenia are dependent on TRN circuitry¹⁵⁶, one possibility is that disrupted thalamocortical circuitry might cause default network dysregulation. Genetic variants that alter thalamocortical circuit function could, in turn, lead to clinically relevant perturbations of network selection and interactions.

Conclusions

Large distributed zones of the association cortex are populated by multiple networks that are active during varied forms of internal mentation. These networks, often collectively referred to as the brain's default network, are suppressed when attention is focused on the external world. The serendipitous discovery of the default network accordingly provides a window into the fundamental specialization of brain processing networks — those involved in extracting information from the external world versus those that construct representations that are partially or fully detached from the immediate external environment. The most recently appreciated understanding is that the 'default network' is not a monolithic entity, but rather comprises multiple parallel interdigitated networks that show specialization across juxtaposed regions, similar to those found in the well-studied sensory systems (BOX 1).

Suppression and engagement of the multiple networks that make up the default network are robust phenomena that can be measured by direct neuronal recordings in humans¹²⁷ and in non-human primates¹⁰, and have parallels in the network modulation observed in rodents^{12,142}. A critical topic for future study, therefore, is how the networks that comprise the default network are controlled, including the mechanisms that support broad suppression of the default network during external attention. Such studies reveal that major competition exists between broad modes of information processing supported by distinct groups of segregated networks. Understanding how these networks are modulated to control information flow could provide insight into the general mechanisms of cognitive control as well as their disturbance in mental illness. Work on the default network to date suggests the involvement of intriguing phenomena that could provide insight into other networks that are important to advanced human thought.

A further lesson from the past few decades is that human neuroimaging observations are difficult to interpret in isolation. Reproducible findings, by themselves, cannot overcome the ambiguity inherent in the correlational methods used to obtain them. Constraints from convergent approaches (including neurophysiology studies and animal models amenable to circuit dissection) are becoming increasingly available to help interpret the human findings. For example, strong candidate anatomical homologues of the default network are present in macaques and marmosets. Deep understanding of the brain's default network will require combining insights from these accessible primate models, findings emerging from electrophysiological and circuit-modulation studies in human clinical populations and neuroimaging approaches that provide the foundational observations.

Published online: 06 September 2019

Sleep spindles

Abrupt bursts of oscillatory activity (12–14 Hz) generated by circuit interactions between the thalamic reticular nucleus and the thalamus during stage 2 sleep.

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Competing interests

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