Review

Special Issue: The Connectome – Feature Review

The evolution of distributed association networks in the human brain

Randy L. Buckner[1,2,3] and Fenna M. Krienen[1,2]

[1] Harvard University Department of Psychology, Center for Brain Science, Cambridge, MA, USA
[2] Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital, Charlestown, MA, USA
[3] Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA

The human cerebral cortex is vastly expanded relative to other primates and disproportionately occupied by distributed association regions. Here we offer a hypothesis about how association networks evolved their prominence and came to possess circuit properties vital to human cognition. The rapid expansion of the cortical mantle may have untethered large portions of the cortex from strong constraints of molecular gradients and early activity cascades that lead to sensory hierarchies. What fill the gaps between these hierarchies are densely interconnected networks that widely span the cortex and mature late into development. Limitations of the tethering hypothesis are discussed as well as its broad implications for understanding critical features of the human brain as a byproduct of size scaling.

A speculative hypothesis

Our ancestors advanced tool use, evolved language, and achieved complex social order during the past 3 million years. From one perspective, that is a lot of time for drift and selection to mold a new species. Changes in gene frequencies and adaptive mutations can arise rapidly in isolated populations. From another perspective, it is unexpected given the trajectories of closely related primate species. To anchor this point, consider the divergent evolution of the common chimpanzee and the bonobo over the past 1–2 million years. These two great apes became genetically isolated from one another when the Congo River formed allowing distinct phenotypes to evolve over a short time period [1]. Bonobos display a matriarchal social order that differs from the aggressive alpha male-dominated society of the chimpanzee [2,3]. Chimpanzees use primitive tools to extract food in the wild, whereas

Corresponding author: Buckner, R.L. (randy_buckner@harvard.edu).
Keywords: cortical circuits; prefrontal cortex; social cognition; default network; prospection; cerebellum.

1364-6613/$ – see front matter
 http://dx.doi.org/10.1016/j.tics.2013.09.017

Glossary

Allometric evolution (within the context of brain evolution): evolutionary changes in one brain component that are predicted by changes in whole-brain size or by changes in another brain component. The relationship can deviate from isometric scaling, meaning that one component differs to a greater degree than the other, but the two components must show a predictable relationship.
Association cortex: portions of the cerebral cortex that do not fall within primary sensory or motor projection areas. The term was popularized by Flechsig (1896) to identify regions of cortex that function as integration or association centers for more complex or elaborated mental processes.
Australopiths: an early, extinct hominin genus discovered in Africa that walked upright but possessed brains only slightly larger than those of apes.
Canonical circuit (canonical macrocircuit): a network of brain areas characterized by dense local connectivity between areas and a serial, hierarchical flow of information across areas. Such networks link incoming sensory information to the development of a motor response or action.
Default network: a set of brain regions more active when people rest passively compared with when they focus on features of the external environment. The network is also active when people remember, think about the future, or engage in other forms of internal mentation, leading to the hypothesis that the network is important to advanced forms of cognition including the ability to mentally imagine oneself in alternative scenarios.
Encephalization: brain size that exceeds the size predicted by body mass. Across species, most variation in brain size is predicted by body mass. The ratio of actual brain size versus the predicted brain size from body mass is known as the encephalization quotient. Humans have the highest encephalization quotient among mammals.
Hierarchical organization: organization by which connections between areas facilitate ascending (forward) information flow and are often paired with reciprocal (descending) feedback connections. Information is successively transformed and elaborated at each step in the hierarchical sequence. Note that the term hierarchical as used here to describe anatomical connection patterns differs from other (but related) forms of hierarchical control that refer to how certain networks control other networks (e.g., [59]).
Hominin: humans and extinct human ancestors that are more closely associated with the human line of evolution than with chimpanzees and other apes.
Hominids: humans, the great apes (chimpanzees, gorillas, orangutans), and their extinct ancestors.
Mosaic evolution (within the context of brain evolution): evolutionary changes in one brain component without simultaneous changes in another brain component. Also called modular evolution.
Noncanonical circuit: network organization in which widely distributed regions possess connections that do not conform to a sequential sequence of feedforward and feedback relationships; rather, they tend to be reciprocally connected with multiple violations for simple feedforward/feedback connectivity and share common targets and inputs that are distributed across the brain.
Spandrel (in evolutionary biology): a characteristic or feature that was not the product of direct adaptive selection, but rather emerged as a side effect of direct pressure on some other feature.

bonobos do not [3]. Differences in brain structures exist between the two species that may be important to social behaviors [4], but these differences pale in comparison with the expansion of the life cycle, social organization, and cognitive abilities that emerge in hominins over a slightly longer time frame [5].

Given the quick pace of change observed in the hominin lineage, we are left with a puzzle: how did brain networks that underlie extraordinary human capabilities evolve so rapidly? A large part of the explanation must lie in the brain expansion that separates us from our ape cousins (Box 1). The human brain is more than triple the size of the chimpanzee brain [6]. Fossil evidence suggests that this increase occurred over roughly the time period when our ancestors advanced their extraordinary abilities [7], but not necessarily in lock step with the exact timing of behavioral and cultural achievements (Box 2). Key genetic events also occurred that may interact with or cause brain expansion in hominins (e.g., [8–15]; see [16] for discussion).

How might a large brain enable complex cognitive functions? One possibility is that the human brain possesses more computational capacity because it has a large number of neurons – estimated at 86 billion neurons using modern cell-counting techniques [17]. Other large-brained mammals, such as whales and elephants, radiate from ancestors that had reduced neuronal densities. The

Box 1. The evolutionary road to the human brain's expanded cerebral cortex

The hominin brain grew rapidly over the past 3 million years in a primate lineage that had already experienced multiple events that increased brain size (Figure I depicts hominin brain evolution estimated from fossil endocasts, with labels for representative individuals from major species). The most significant determinant of our large brain size is that we are large animals: absolute brain size scales allometrically with body size [148]. After factoring out body weight, which accounts for as much as 85% of the total variance in brain size across mammalian species, the human brain is about five times larger than one would expect for a typical mammal [149,150]. Primates generally have disproportionately larger brains for their body size than other mammals (quantified as the encephalization quotient). This relative size difference is present at early embryonic stages, suggesting an ancient evolutionary event that shifted a greater proportion of the embryonic precursor cells to commit to a neuronal lineage ([151], data interpreted in [152]; see also [153]). Differences across primate suborders hint at other major evolutionary events including a step increase in brain size in monkeys (e.g., macaque and squirrel monkey) relative to prosimians (e.g., lemur). The acceleration over the past several million years probably derives from a distinct mechanism. Chimpanzees and humans have roughly the same body size and share a common ancestor about 5–7 million years ago. The early phases of brain development for chimpanzees and humans are conserved, with a similar proportion of the total body size devoted to the brain. At late phases, the brain continues to grow relative to the body in humans but stops earlier in chimpanzees, leading to a relative brain size expansion [152] (see also [154,155]). An interesting feature of brain scaling is that brain enlargement disproportionately expands some brain structures more than others. The cerebral cortex in mammals has the most privileged position in brain growth. A key contributor to disproportionate cortical expansion is constraints from embryonic development [135]. Cerebral cortex progenitor cells are the last to be born among different neuronal pools. Because embryonic development is temporally stretched in large-brained mammals, the cerebral progenitor pool continues to divide for the longest period and forms the largest cell pool. This 'late equals large' developmental feature causes the cerebrum to have the greatest relative size increase. The cerebral surface area is ~120 cm^2 in the macaque and a remarkable ~960 cm^2 in the highly gyrified human brain [25] (see also [156]).

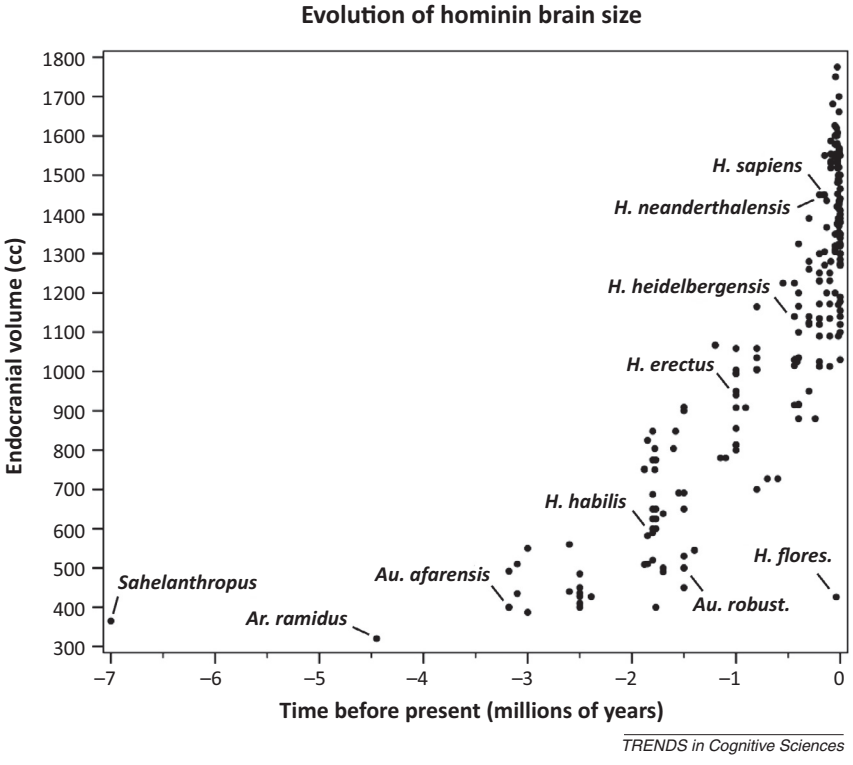

Figure I. Hominin brain evolution estimated from fossil endocasts.

Box 2. Scaling exceptions and the paradox of *Homo floresiensis*

The central point of this review is that brain size scaling may have essential, underexplored implications for large-scale circuit organization. However, it is also important to note observations that make clear how brain scaling is not the only factor at work in the evolution of hominin capabilities. For example, a marked increase in brain size was not the initial gateway to stone tool use. The oldest documented stone tools are 2.6 million years old [157] and were made by hominins with moderate encephalization, possibly australopiths. Stone-cut marks are claimed by some to have been made as early as 3.4 million years ago [158]. Living 2.0 million years ago, *Australopithecus sediba* possessed hand features suggesting stone tool use [159], but had a brain size small even for australopiths [160]. *Au. sediba*'s virtual endocast hints toward reorganization of the frontal lobe (see also [7]). As another example, *Homo neanderthalensis* (Neanderthals) had a brain slightly larger than contemporary humans but similar in size to early modern humans [154,161]. Neanderthals mastered sophisticated technologies, but whatever neurological differences there were between Neanderthals and modern humans, absolute brain size was not likely to have been a significant contributor. Furthermore, modern brain size evolved long before the Upper Paleolithic and many traces of modern, symbolic behavior such as cave paintings, figurines, and personal ornamentation [162]. Hominin brain capacity may have achieved its full functional advantage only with the amplifying effects of accumulated knowledge – sometimes referred to as the 'cultural ratchet' [121,122]. Mosaic evolutionary events that reorganized the brain and cultural innovations probably played important roles in hominin advancement.

The recently extinct hominin species *H. floresiensis* provides a striking counterexample to a simplistic model that brain size alone determines capabilities [163,164]. Living within the past 100,000 years, *H. floresiensis* stood 3 feet tall with a cranial capacity similar to that of a chimpanzee [165]. Although debate persists regarding *H. floresiensis*'s origins, it seems likely that the species experienced some degree of brain size reduction through insular dwarfism from a larger-brained ancestor that was *Homo erectus* (or possibly *Homo habilis*) [166]. Certain archeological discoveries suggest that *H. floresiensis* may have used sophisticated stone tools requiring multistage construction and hunted juvenile dwarfed elephants [164]. The exact level of stone tool technology mastered by *H. floresiensis* is a matter of ongoing debate. A reasonable hypothesis is that brain size reduction did come with a cognitive cost, but evidence that *H. floresiensis* was able to construct and use sophisticated tool technologies with a brain size comparable to a small *Australopithecus* emphasizes that the other stuff acquired during hominin evolution beyond brain size scaling is functionally significant.

The focus of this review on critical implications of brain scaling should not be taken to imply brain scaling alone accounts for hominin evolution.

sparser neuronal matrix of a whale brain is expected to have fewer neurons than that of a chimpanzee although it is more than double the size of a human brain [17]. Neuronal number and the connectional properties that go along with differences in neuronal density [18] are likely to explain much about human cognitive capabilities.

However, what has captured our interest is a peculiar feature of brain scaling that might prove critical. The feature concerns how brain scaling shifts the predominant circuit organization from one primarily linked to sensory–motor hierarchies to a noncanonical form vital to human thought. The emergent circuit organization may be a side effect, perhaps even to be considered a spandrel [19], of developmental rules and an organization inherited from our simpler mammalian ancestors but now expressed in a massively scaled cerebral cortex. The rapid expansion of the cortical mantle may have untethered large portions of the cortex from strong constraints of molecular gradients and early activity cascades that lead to local sensory hierarchies. What fill the gaps between these hierarchies are distributed, interconnected association networks that widely span the cortex, develop late, and are preferentially more dependent on protracted activity-dependent influences.

Distributed zones of association cortex show disproportionate expansion

A striking feature of the human cerebral cortex is that it follows an ancient mammalian prototype but also displays relative enlargement of regions distributed throughout association cortex (Figure 1). The proportion of cortical surface occupied by sensory and motor areas decreases as the overall size of the cortex expands [20]. This observation can be made in several ways. Certain cortical areas (Box 3) are conserved across mammals, suggesting that they were present in an ancient mammalian ancestor (e.g., primary visual cortex [V1] [21]). A phylogenic tree of the relationships between major lineages can be constructed by comparing homologous areas across species and the 'prototype' mammalian and primate ancestors can be estimated [22–24] (Figure 1). What emerges from such an analysis is that the general spatial relationships among primary sensory areas are consistent across mammalian species, but also that the cortical mantle of the primate is mostly occupied by zones that fall between the primary and secondary sensory areas.

Divergence in cortical organization from our last common ancestor approximately 25 million years ago can be inferred by comparing the human with the macaque. Using a novel approach to comparative analysis, Van Essen and colleagues identified putative homologous areas on the cortical surface and estimated expansion by finding the surface deformation that would bring the human areas into spatial alignment with their macaque homologues [25,26]. The results reveal a distributed pattern of disproportionate cortical expansion that includes multiple association zones in the temporal, parietal, and frontal lobes (Figure 2). Insight into more recent evolution is provided by analysis of the chimpanzee brain [6,27]. Although only a handful of areas have been studied in small numbers of individuals, chimpanzee anatomy uniquely informs us of how the cortex has changed since the human clade emerged approximately 5–7 million years ago. The human cerebral cortex is over three times the size of the chimpanzee's. Relative expansion estimates reveal disproportionate growth of association cortex including both anterior and posterior regions (Figure 2). By contrast, the absolute sizes of primary sensory cortices are almost equivalent between humans and chimpanzees.

The idea that the human cortex has multiple, distributed zones of association cortex that are expanded (or even de novo) has a lengthy history. In his treatise on the principles of cerebral localization, Korbinian Brodmann noted that cytoarchitectonic subdivisions of prefrontal cortex (his areas 44, 45, 46 and 47) (Figure 3) and parietal cortex

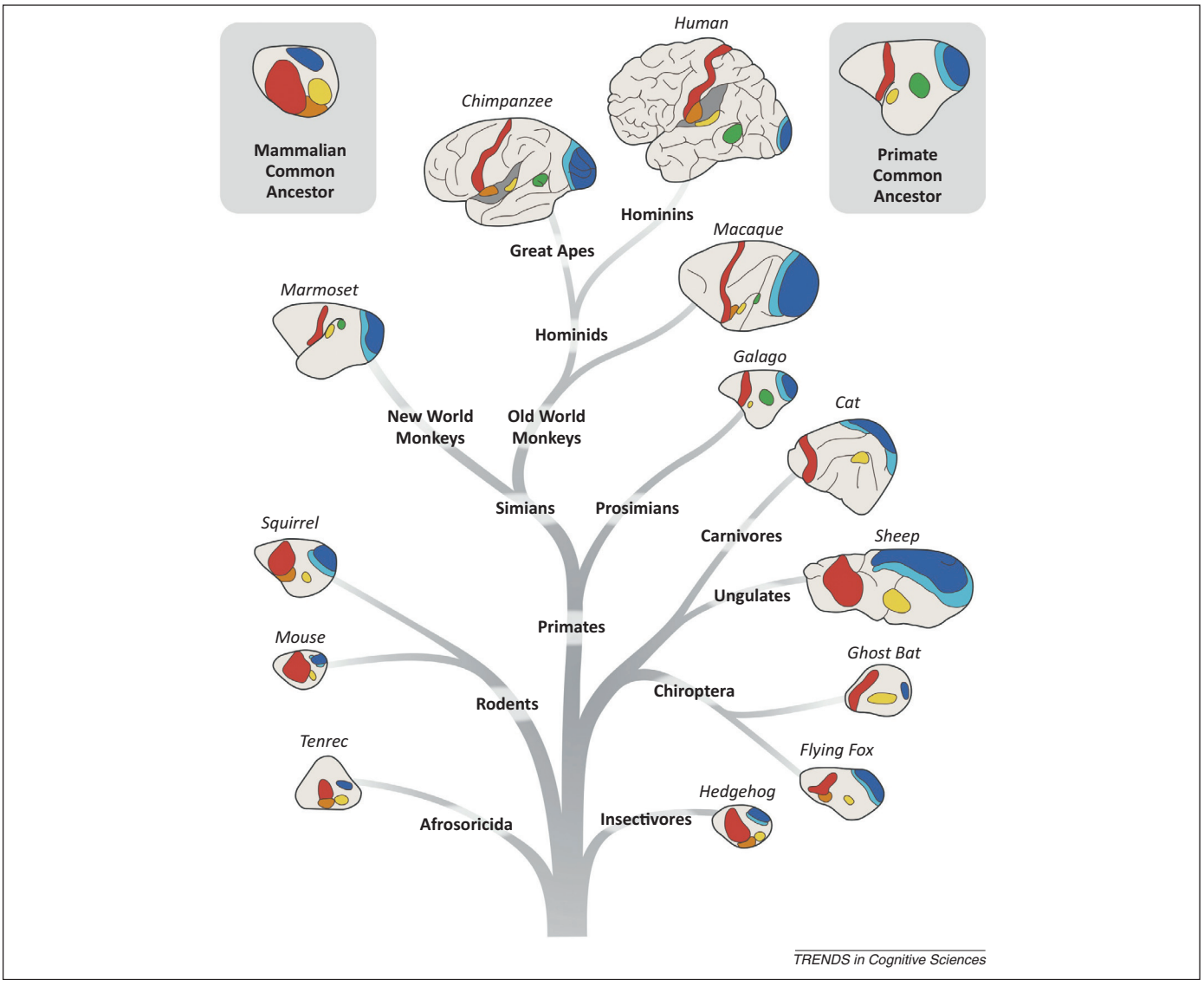

Figure 1. Phylogeny of the cortical mantle. Schematic depictions of the cortex of placental mammals are shown with the size and positions of several conserved areas. Two organizational features are apparent in the phylogenic tree. Across all species, the relative positions of the areas are preserved, suggesting they arise from an ancient developmental template, or *Bauplan*, that is conserved. Second, as the brain is enlarged in primates a greater percentage of the cortical mantle falls between the primary and secondary sensory systems. The insets at the top represent hypothetical estimates of the mammalian common ancestor and the primate common ancestor. Dark blue, primary visual area (V1); light blue, secondary visual area (V2); green, middle temporal (MT) visual area; yellow, primary auditory area (A1); red, primary somatosensory area (S1); orange, secondary somatosensory area (S2). Adapted, with permission, from [22–24].

near the angular gyrus (areas 39 and 40) reflect a 'series of new areas, which cannot even be demonstrated in monkeys' [28]. Extending from Brodmann's ideas, Norman Geschwind proposed that the expansion of association cortex near the angular gyrus was central to the evolution of language [29], leading to a period in the 1970s when this region of the cerebral cortex was referred to as Geshwind's territory [30]. Brodmann's position is probably too strong. Candidate homologs have been identified in many of the association zones in the macaque (e.g., areas 44 and 45 in prefrontal cortex [31], area Opt in parietal association cortex; see [32] for discussion), but the broader point is critical: human association cortex has markedly diverged from that of other primates.

Understanding human cognitive abilities depends on unraveling the mechanisms that give rise to expanded association cortex. Several questions present themselves. First, did the connectivity patterns of association cortex maintain the properties of more ancient sensory–motor circuits or did new circuit properties arise? The answer to this first question speaks directly to whether human cognitive abilities came about from the scaled computational power of a large brain or from new circuit properties that became prominent with increased brain size. Second, how did the gross area of association cortex expand disproportionately relative to sensory and motor cortices? Much as scaling principles contribute to size differences across brain structures (cortex versus midbrain, Box 1), it seems likely that constraints of embryonic development play a role in the nonuniform changes within the cortex. It is not that sensory cortices are unexpectedly small in large brains – they are predictably small [33,34]. Lastly, how did distant association regions distributed throughout the cortical lobes expand in a coordinated manner? This final question brings up a common misconception that prefrontal cortex is the epicenter of cortical expansion in primate

Box 3. The concept of a cortical area

The cerebral cortex possesses a mosaic of distinct zones, often called areas, that are central to its information-processing capabilities. The zones were initially distinguished by architectonic patterns (differences in cellular structure, laminar organization, and myelination). The transitions between some zones are abrupt, such as between the dense layer-IV neurons of primary visual cortex (the stria of Gennari) and the less prominent layer IV of V2 and between the large layer-V pyramidal neurons of the primary motor cortex (Betz cells) and its surroundings. Other transitions are graded. The appearance of distinct zones led the early anatomists Alfred Walter Campbell (1905) and Korbinian Brodmann (1909) to parcellate the cortex into anatomically separate areas [28,167]. Border zones with intermediate properties were recognized. For example, von Bonin and Bailey's 1947 map of the macaque cortical mantle [168], printed on the inset of their monograph and displayed in Figure I, used a folio of watercolor to illustrate gradual architectonic transitions. Ambiguity in architectonic criteria challenged the strong view that distinct areas could be delineated on histological criteria alone [169].

What emerged next was the concept that discrete areas could be defined based on multiple criteria that include functional response properties, architectonics, connectivity to other areas, and topography [21]. Areas within sensory hierarchies such as V1 and the MT area can be delineated by all four criteria. Based on the presence of areas with clear boundaries, Kaas (1987) argued that all of the cortex is occupied by sharply delineated areas. However, many areas, particularly those within association cortex, display ambiguities even when modern histological techniques are applied [90]. To better understand these complexities, study of the development and evolution of cortical organization has become essential (e.g., [170,171]). An open question is the degree to which association cortex possesses a set of sharply divided areas [21] or core fields that are filled in by messy developmental sculpting [90]. An intriguing recent observation is that supra-areal groups of topographic maps, such as the retinotopic maps of V1, V2, and V3, form map clusters [91,92] that may reflect developmental constraints [89] (see Figure 7 in main text).

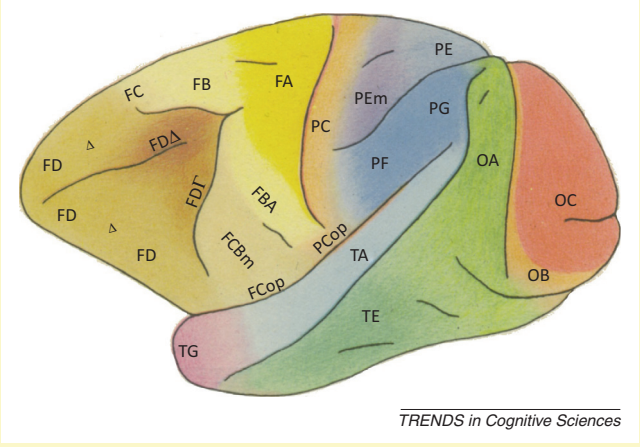

Figure I. von Bonin and Bailey's (1947) map of the cerebral cortex of the macaque.

and specifically hominin evolution (see [35–38] for discussion). Although prefrontal cortex is markedly expanded, so too are the temporal and parietal association regions, suggesting a coordinated increase in distributed cortical territories. Theories of cortical evolution should look for a parsimonious explanation for how multiple, distributed regions of association cortex might concurrently expand disproportionately relative to sensory regions.

Association cortex possesses noncanonical circuit properties

The mosaic of brain areas that populate the cerebral cortex are interconnected in complex networks [39–42]. Each area has a distinct pattern of connectivity to other areas – a connectivity 'fingerprint' [43]. One way to gain insight into network organization is to examine laminar projection patterns between areas [39,44]. For some connections the laminar pattern suggests ascending (forward) information flow from lower to higher areas. These connections are often paired with reciprocal descending connections that have patterns suggesting feedback from higher to lower areas [45]. Laminar patterns for other connections suggest lateral arrangements between areas that fall at the same level within a hierarchy.

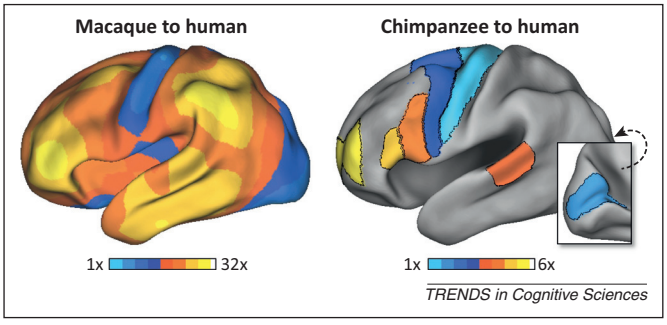

Figure 2. Distributed association zones are disproportionately expanded in humans. Estimated cortical expansion is illustrated for macaque to human (left; data from [26]) and for chimpanzee to human (right; data from [6]). Colors represent the scaling value required to achieve the size in the human brain. The data are projected onto the left hemisphere cortical surface of the population-average, landmark- and surface-based atlas [172]. For the macaque, a continuous surface estimate of expansion is computed from 23 distributed landmarks. For the chimpanzee expansion plot, area estimates for a limited set of discrete areas are presented from Table 2 in [6]. The primary visual area (V1) is displayed in the inset.

Many cortical circuits are organized as serial, hierarchical pathways. A canonical example of such a pathway has been studied extensively in the macaque during behaviors that link motion cues to eye movements [46]. The pathway involves early retinotopic visual areas that are hierarchically organized and project to specialized extrastriate fields representing direction and speed, including the middle temporal (MT) area. Information flow then progresses to the lateral intraparietal (LIP) area and finally to the frontal eye field (FEF), which guides eye movements (Figure 4). In a trained monkey, a 200–400 ms cascade of activity through this circuit is sufficient to extract relevant perceptual information from a moderately noisy background and select a specific eye movement [47]. We refer to this pathway as canonical because the areas form a step-wise progressive circuit by which raw sensory information is transformed to guide an immediate action. Forward and feedback anatomical connections between areas are consistent with the direction of information flow. Areas of association cortex that are positioned at mid-levels, such as the LIP, serve the intermediary role of accumulating and prioritizing information in the service of the upcoming action [47,48]. The question at hand is what kinds of network occupy the expanded portions of association cortex in humans?

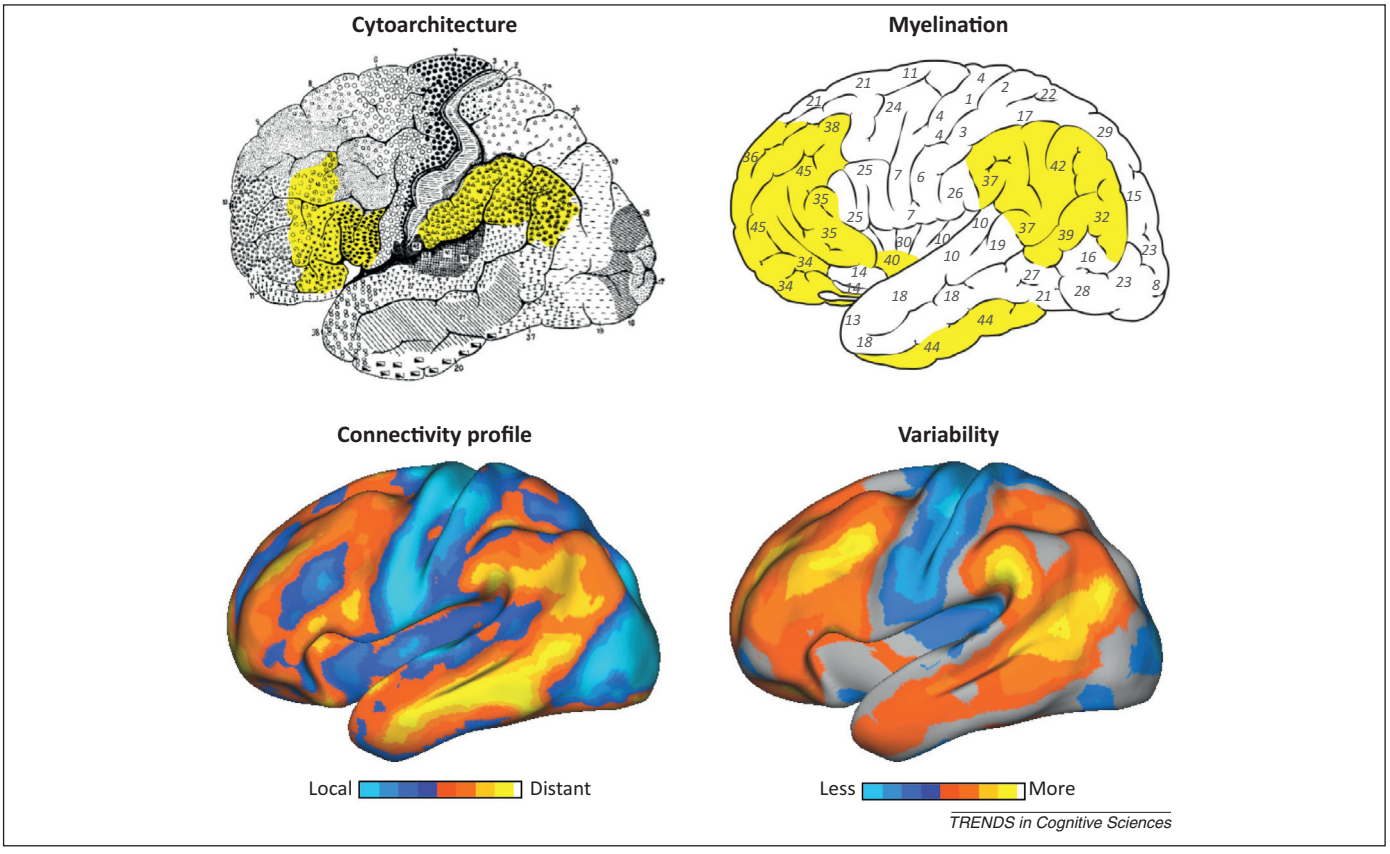

Figure 3. Association cortex matures late and possesses functional properties that are different from sensory regions. Top: Brodmann's (1909) cytoarchitectonic map and Fleschig's (1920) developmental myelination estimates are displayed [28,79]. Numbers for cytoarchitecture arbitrarily label the distinct zones of cortex and have come to be known as Brodmann areas. Regions shaded in yellow are frontal and parietal areas that Brodmann (1909) proposed had no monkey homologs. Myelination numbers designate the relative ordering of developmental myelination, with higher numbers indicating late development. The regions shaded in yellow mature late. Bottom: Functional MRI estimates of organizational properties. Distant connectivity quantifies the relative percentage of strong functional correlations that are distant from the region (e.g., across lobes) versus local correlations. Warmer colors reflect regions that have preferentially long-range functional connectivity. Variability displays regions with the greatest between-subject variation in functional organization estimated by functional connectivity. Data from [72,99].

One possibility, which can be considered an elaboration of the canonical circuit, is that intermediate areas in sensory–motor hierarchies are expanded, allowing diverse forms of information to be integrated and more complex motor actions to be generated [49]. In their seminal work on association cortex in the macaque, Jones and Powell [50] observed that specific temporal and prefrontal association regions receive convergent projections from multiple information modalities. They commented 'it would appear that a region of convergence such as that demonstrated in the present study could furnish a necessary substratum out of which in the course of further cerebral evolution, a region devoted to "language and symbolic thought" (Critchley) could arise.' Noting the proximity of 'Broca's area' to the face representation of motor cortex, Krubitzer [23] highlights that certain human language areas might reflect an expansion of orofacial motor representations that have become specialized for speech (see also [51]). The arcuate fasciculus in humans, but less so in chimpanzees, strongly connects Broca's area to anterior portions of the middle temporal gyrus, presumably an adaptation for language [27,52].

A second possibility is that preferential expansion might involve areas participating in control functions that are separate from sensory–motor hierarchies [53]. That is, the expanded regions of association cortex may contain brain networks that control other brain networks. 'Top-down' control allows context-dependent goals to regulate processing when perceptual information cannot be automatically mapped to a familiar behavioral response [54]. In a recent analysis of candidate control systems, Petersen and Posner [55] highlighted a frontoparietal network that is centered within the expanded regions of the human cerebral cortex but distinct from canonical sensory–motor hierarchies (see also [56,57] for description). Direct comparative analysis of functional network organization has so far failed to detect an equivalent of the human frontoparietal network in the macaque [58], suggesting that the human brain possesses unique features or, more likely, that the network is sufficiently expanded to allow it to be detected more easily. Badre and D'Esposito [59] have suggested that the most rostral prefrontal regions, which are components of the frontoparietal network, control networks linked to more caudal prefrontal regions, consistent with a functional hierarchy of cognitive control.

A third possibility is that the expanded association cortex contains networks operating in parallel with the canonical sensory–motor hierarchies in the service of information processing that is detached from sensory perception and motor actions – what one might term 'internal mentation'. This is an intriguing possibility because it brings to the forefront the kinds of information processing that humans do so well such as remembering, imagining the future, social judgments, and other cognitive acts that

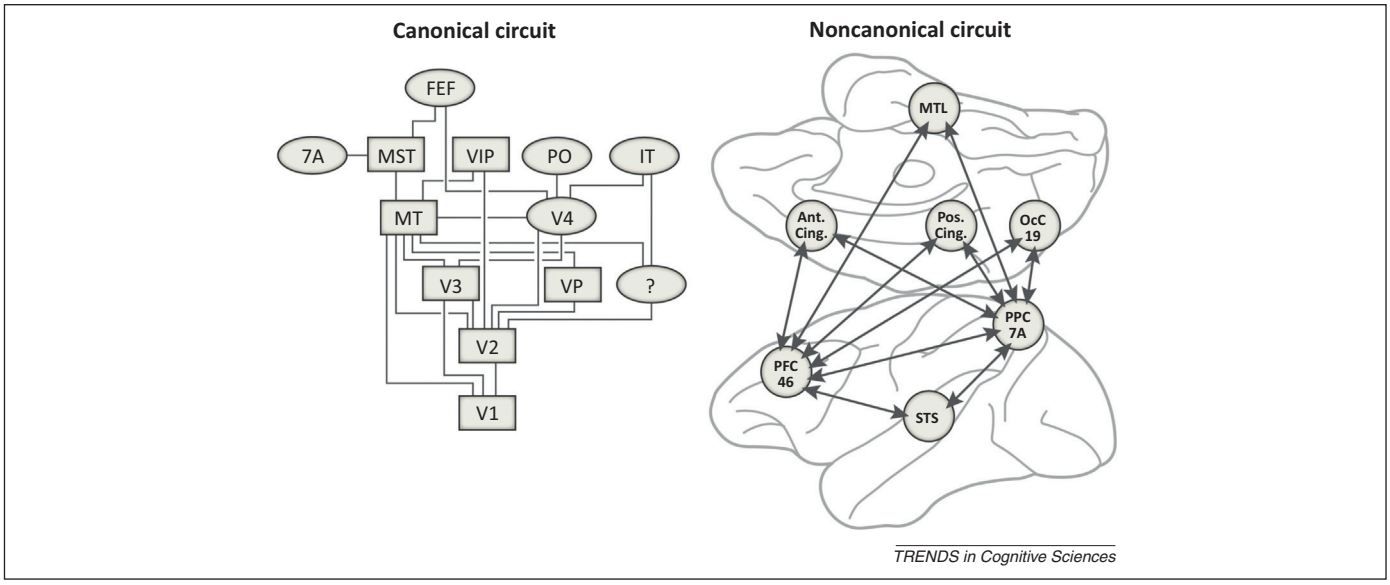

Figure 4. Association cortex displays noncanonical circuit properties. Connectivity fingerprints and laminar projection patterns can be used to estimate the organization of cortical circuits. Left: The canonical circuit organization that has been well-studied in systems neuroscience involves a serial, hierarchical pattern of connectivity by which sensory areas project in a feedforward/feedback fashion to progressively higher-order areas that then project to motor areas. Connected areas are preferentially near to one another on the cortical surface. Convergence and divergence exist but mid-level areas are generally considered intermediate processing stages in a sequential pathway. Boxes represent areas and lines represent connections. Areas receiving feedforward patterns of connections are displayed higher in the diagram. Adapted with permission from [39]. Right: An alternative noncanonical circuit organization, proposed by Goldman-Rakic and Selemon [63,64], is illustrated. They noted that association areas distributed widely across cortex have a propensity to project to highly similar sets of areas and display laminar projection patterns that do not have a rigid feedforward/feedback structure. Adapted with permission from [63].

manipulate information in working memory. Functional imaging studies of remembering and imagining the future have consistently demonstrated extensive involvement of the expanded regions of association cortex, in particular a large-scale network that has come to be known as the 'default network' [60–62]. This third possibility forces consideration of circuit forms that might underlie internal mental events. Here is where we come to a critical insight: the kind of network structure that has been most extensively studied in systems neuroscience, that of the canonical sensory–motor hierarchy described above, may not be the most abundant circuit structure in the human cerebral cortex. But what is the alternative?

A noncanonical circuit structure that may be central to the expanded association zones was proposed by Goldman-Rakic and Selemon [63,64] (see also [41] and Figure 4). Enabled by the advance of double-labeled tracer injections, they asked two questions. First, if two areas of association cortex are connected to one another, do they also share connections to other areas? Second, when pairs of areas do show convergent connections, what are their columnar and laminar patterns? What they discovered is that association networks in the macaque display noncanonical circuit properties. Prefrontal and parietal areas that are connected to one another are interconnected with as many as 15 other cortical areas widely distributed throughout association cortex (including paralimbic zones of association cortex). Although certain projections follow the canonical form, including feedforward and feedback laminar termination patterns (e.g., parietoprefrontal projections), the interconnected circuit also possesses connections that lack consistent hierarchical organization. For example, prefrontal and parietal areas project to complimentary layers in the parietal operculum and alternating columns in the anterior cingulate. Finally, the large-scale association networks that display cortical interconnectivity are unified by common thalamic input from the medial pulvinar nucleus, a nucleus that is particularly prominent in primates [65].

The upshot of these findings is that association cortex, unlike canonical sensory–motor hierarchies, possesses densely interconnected networks of widely separated areas that can be recruited from common thalamic inputs. There are limitations to the data Goldman-Rakic and Selemon based their ideas on, including that the key anatomical cases involved rather large tracer injections [42]. Nonetheless, the findings lead toward a different emphasis than the canonical circuit – 'one that focuses on the distributed functions' and further 'that of a highly integrated but distributed machinery whose resources are allocated to several parallel functional systems that bridge all major subdivisions of the cerebrum' [63]. Mesulam came to a similar conclusion: 'Neural pathways arising from sensory receptors and leading toward motor nuclei display hierarchical polarity. In contrast, the flow of information used for intermediary processing displays patterns consistent with parallel and re-entrant processing' [41]. This form of circuit, which may be expanded in hominin evolution, is suited to functions related to top-down control and internal mentation.

Observations from human neuroimaging studies also point toward the expanded zones of association cortex being occupied by large-scale distributed networks that possess noncanonical properties. Figure 5 illustrates this point using data from functional connectivity MRI (fcMRI). Functional connectivity measures spontaneous low-frequency fluctuations that correlate between brain regions within a functionally coupled network. The measure is not a direct proxy for anatomical connectivity but is sufficiently constrained by anatomical connectivity to

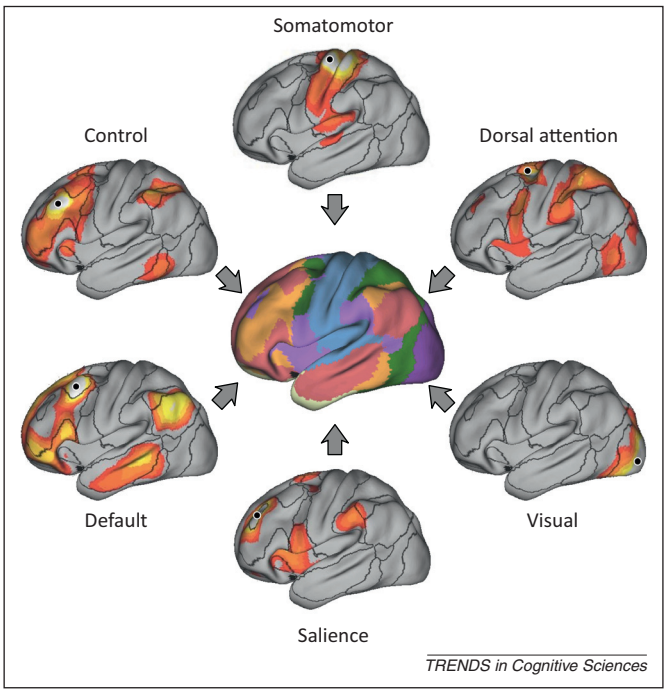

Figure 5. Human association cortex is organized as a series of interdigitated large-scale networks. Human functional connectivity maps illustrate major networks. Each outer map shows the functional connectivity of a small seed region marked by a dark circle. The data were acquired while subjects rested passively. The red–yellow color scale shows the regions functionally coupled to the seed region. Labels indicate the common reference name for the network in the neuroimaging literature, but the names should be considered heuristics. Networks obtained from seed regions placed in primary sensory and motor areas display largely local connectivity (somatomotor and visual networks). The canonical hierarchical network described in Figure 4 can be observed by placing a seed region in the frontal eye field (FEF). This network is displayed as the dorsal attention network. The remaining networks, which comprise a major portion of the human cortical mantle, may be of the noncanonical form. Three are illustrated as the default network, the control network, and the salience network. Each network is coupled to distributed regions of association cortex and each network lacks strong coupling to sensory or motor areas. Moreover, the association networks are juxtaposed to one another in each broad region of cortex. The center map represents a composite image showing the juxtaposition of multiple distributed association networks. Adapted from [66].

estimate broad properties of cortical organization (see [66–68] for discussion of caveats and limitations). For example, functional coupling among putative human homologs of the macaque V1, MT and LIP areas, and FEF reveals the network structure of the canonical sensory–motor hierarchy [32].

A consistent observation across studies using fcMRI is that the expanded regions of human association cortex contain multiple, large-scale distributed networks. When the full cortical mantle is analyzed using approaches that emphasize connectional similarities [32,69], most of association cortex is found to contain a series of interwoven networks that each span all of the major portions of association cortex (e.g., prefrontal, temporal, parietal association cortices and the cingulate). These association networks largely lack functional coupling to sensory and motor regions and are active during tasks that demand high-level cognitive processes. Aggregate analyses of task-based coactivation patterns reveal similar distributed networks across multiple association regions (e.g., prefrontal and parietal association zones) rather than in one region selectively, such as prefrontal cortex (see supplementary materials in [70]). These networks are likely to possess complex relationships with each other, including certain networks controlling the function of other networks in hierarchical [59] or interacting [71] configurations.

Analyses of fcMRI connectivity profiles also note a broad tendency for association regions to show preferentially distant compared with local functional connectivity. To make this assessment, Sepulcre *et al.* [72] calculated for each point along the cortical surface the number of coupled cortical partners that were more than 14 mm away versus those within 14 mm. This distance threshold roughly separates connectivity between lobes from connectivity targeting nearby areas. Plotting the preferential coupling mode (primarily local versus distant) produces a map that divides sensorimotor from association cortices (Figure 3). Distributed regions of association cortex show preferentially long-distance connectivity profiles.

A further interesting property of association cortex is that certain features develop late relative to sensory and motor regions. Measurements of gray matter maturation through either MRI estimates of gray matter density [73] or local surface expansion [26] suggest that cortical association regions undergo protracted development. In connecting their findings to the prior literature (e.g., [74]), Hill *et al.* noted that certain association regions undergoing rapid cortical surface expansion at birth are far from their peak synaptic densities and show low cerebral metabolic rates consistent with protracted postnatal development. Recent comparisons of humans, chimpanzees, and the macaque suggest that synaptic proliferation in the human and chimpanzee is protracted relative to the macaque, with pyramidal neurons in prefrontal cortex delayed relative to sensory and motor areas [75]. Myelination patterns provide convergent evidence. Myelination of the cerebrum is delayed relative to other brain structures [76,77] and in humans is globally protracted compared with other primates, including chimpanzees [78]. By charting local patterns of myelination in *post mortem* histological sections, Flechsig [79] observed that distributed regions of association cortex are the last to fully myelinate (Figure 3) (see also [76]).

Taken together, these collective observations suggest that the expanded cortical mantle of the human brain comprises networks that widely span the cortex without consistent feedforward/feedback connectivity and, further, that these circuits mature late into development. In the next sections we describe one hypothesis about how a noncanonical network structure might arise during development and why it becomes disproportionately represented in the human. We begin with a brief overview of cortical development.

Intrinsic signaling gradients and extrinsic activity shape cortical areas

Cortical formation begins when proliferating cells in the ventricular zone (VZ) of the telencephalon undergo a series of symmetrical divisions that create a large, thin sheet of cellular columns. Increasing the number of cell divisions or survival rate within the VZ will cause enlargement of the cortical mantle [80]. As development progresses the cells within these columns and the associated subventricular zone (SVZ) undergo asymmetric divisions

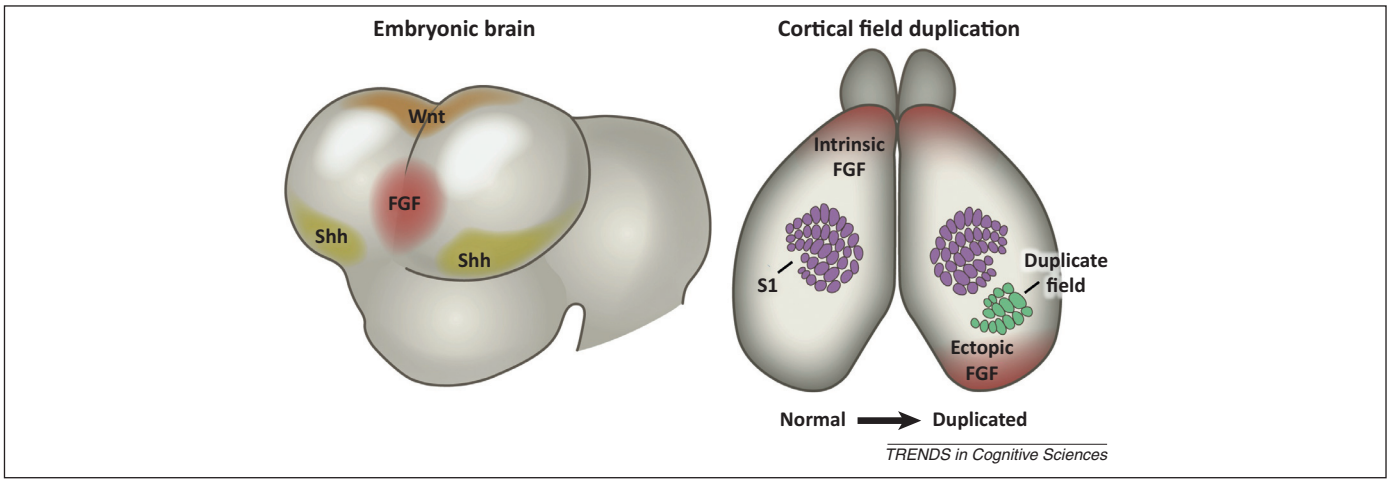

Figure 6. Signaling gradients in the developing embryo initiate formation of cortical areas. Left: The developing telencephalon of the mouse embryo illustrates major patterning centers. Signaling gradients including Wnt (orange), fibroblast growth factor (FGF) (red), and sonic hedgehog (Shh) (yellow) are transiently expressed at specific locations in the telencephalon and influence the fate of neurons emerging in the neuronal proliferation zones. The neurons migrate to the cortical plate, maintaining the identities they acquired in the protomap formed by the signaling gradients. Right: Manipulation of signaling molecules can shrink or enlarge cortical fields. A dramatic example is illustrated from [82]. In this experiment, FGF8 was expressed in an ectopic posterior location of the telencephalon. The normal somatosensory field (illustrated as purple whisker barrels in the left hemisphere) was duplicated (green duplicated whisker barrels in the right hemisphere).

that form neurons through the process of neurogenesis. The committed neurons then migrate along radial glial cells to the cortical plate, preserving much of the topographic pattern established in the VZ. The result is that the spatial relations of cellular columns in the proliferative zones are transferred to the adult cerebral cortex.

Signaling molecules secreted at specific positions in the proliferative zones, called patterning centers, determine the identities of neurons before they migrate to the cortical plate or form any synaptic connections [80,81] (Figure 6). Once the neurons reach their position in the cortical plate, the neuron's identity guides appropriate area-specific targeting of thalamocortical axons. Evolutionary events that expand or decrease cell proliferation, alter patterning centers, or modify cellular mechanisms that determine cell fate are viable paths for reshaping cortical areas. As an illustration of how signaling molecules control area formation, Fukuchi-Shimogori and Grove [82] demonstrated that varying the amount of a single signaling molecule, FGF8, in its normally occurring anterior location of the telencephalon could expand and contract the somatosensory map of the adult mouse cerebral cortex. In their final study, they formed a duplicate somatosensory map of mouse barrel cortex by unnaturally expressing FGF8 in a second posterior location (Figure 6).

The other determinant of area formation is external input to the developing cortical plate from thalamocortical axons [83]. Waves of spontaneous neural activity in retinal ganglion cells are present long before eye opening and even before maturation of photoreceptors [84]. In a recent experiment illustrating the importance of external signals, O'Leary and colleagues used a genetic manipulation to selectively ablate thalamocortical inputs to the developing visual cortex [85]. What emerged was an ill-defined visual zone that diffusely displayed molecular markers across all of the visual cortex in the region that would normally differentiate V1 from its neighboring extrastriate areas. A related series of studies on somatosensory map formation further suggests that thalamocortical axons possess a topographic ordering before they reach the cortical plate that they impart on the developing cortical map following their arrival [86].

These results suggest that intrinsic signaling molecules are sufficient to guide a cortical region to its sensory domain. Certain zones are preprogrammed to become visual and others fated to become distinct modalities. However, the results also reveal that activity-dependent input is required to organize the multiple primary and higher-order areas that define the canonical sensory hierarchies. Without appropriate thalamocortical inputs, second-order areas do not fully differentiate from primary areas and topography within primary areas is absent. The topic addressed in the next section is how these arealization processes might play out in the expanded human brain, where large territories of the cortical plate are distant from influences of the primary patterning centers and input from thalamic sensory nuclei.

The tethering hypothesis

Signaling gradients set up the basic areal plan, or protomap, of the cortex, which is refined by thalamocortical input. However, it is unclear how organization arises within the scaled association zones. Two frameworks that tackle visual area formation in the monkey offer insight. These frameworks are discussed first and then an extension is proposed, the tethering hypothesis, which focuses on association cortex.

The first framework proposes that specific evolutionary events might cause duplications of discrete areas [49,87] (see [88] for discussion). Primary visual cortex, V1, possesses a complete topographical map – neighboring points in the visual hemifield are represented by neighboring columns in the cortical map. The architectonic boundary of V1 can be readily recognized by an abrupt change in laminar organization, including the stria of Gennari. The extrastriate MT area also possesses a complete first-order topographical map of the visual world with its borders sharply defined by an architectonic field (87).

The characterization of the MT area and its similarities to V1 led Allman and Kaas to point out 'that a common mechanism of evolution is the replication of body parts due to a genetic mutation in a single generation which is then followed in subsequent generations by the gradual divergence of structure and functions of the duplicated parts.' They were partly motivated by the segmental duplications in body parts that occur throughout evolution in crustaceans, arthropods, and other species. Similar evolutionary mechanisms of duplication, budding, and subdivision might be one path to sprout new cortical areas.

However, duplication or related mechanisms that form new areas do not straightforwardly explain other organizational features of extrastriate cortex. For example, V2 is not an intact topographic representation but rather is split, forming a second-order representation; the foveal portions of V1 and V2 abut each other but the remainder of the V2 visual hemifield is divided at the upper and lower quadrants. A second framework to explain discontinuities has been proposed by Rosa [89] that incorporates a key role for self-organization during development (see also [90]). Rosa's model is motivated by the presence of a supra-areal visuotopic organization that can be appreciated by displaying the early visual areas on a flat map colored by their representation of visual eccentricity (Figure 7, left). Displayed in this manner, a macro-level organization is apparent by which groups of columns with similar response properties are near to one another and radiate outward from V1 in smoothly changing eccentricity bands. A similar radiation originates from the MT area into the surrounding MT crescent (MTc). Human studies of retinotopy also reveal this supra-areal organization (e.g., [91–93]).

Based on the observation of supra-areal organization and the complexity of gradients that would be required to specify a series of second-order maps, Rosa proposed that arealization may emerge from a small number of key 'hard-wired' maps controlled by molecular signaling molecules (e.g., the patterning centers discussed above). These core maps serve as anchors that form the remainder of areal topography through activity-dependent self-organizing rules. Both V1 and the MT area may be anchors, with the MT area possibly formed as an ancient duplication of

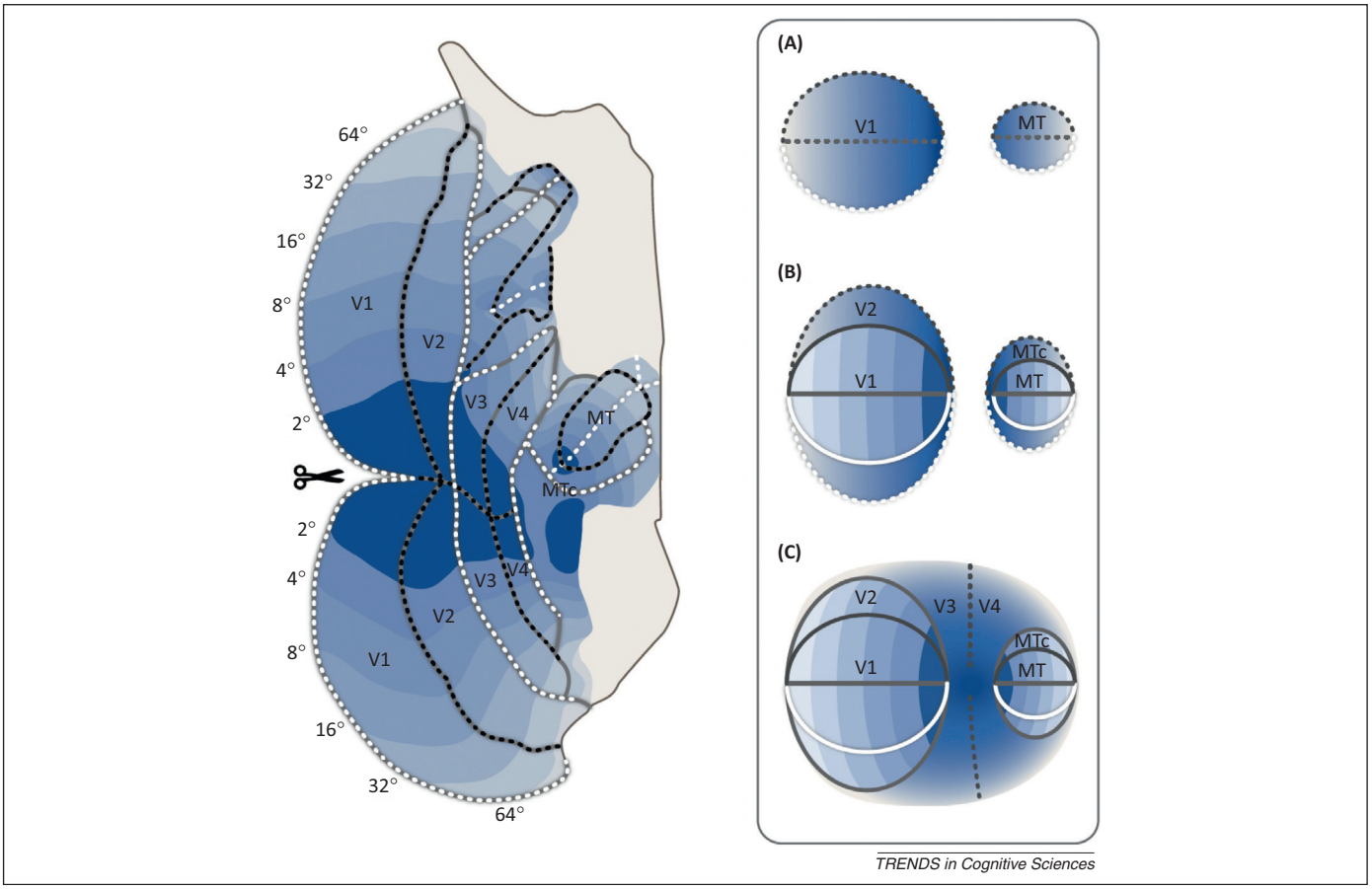

Figure 7. Competitive activity-dependent processes refine the detailed topography of cortical areas. Left: Monkey visual areas are displayed on a flattened cortical surface to illustrate a supra-areal organization. The flattened cortex represents a portion of the occipital and temporal lobes of the marmoset monkey that includes the early retinotopic visual areas through the middle temporal (MT) area. The primary visual area (V1), which possesses a complete and continuous visual hemifield map, is drawn at the left edge. V1 is cut and flattened along the horizontal meridian. The lines demarcate the borders of individual areas. The shaded blue color illustrates the organization of eccentricity, with the darkest blue representing the fovea and lighter shades of blue progressively representing more peripheral eccentricities (degree of eccentricity noted by labels). The foveal representations of V1, V2, and V3 are aligned with eccentricity bands radiating outwards from V1 through the multiple visual areas forming a map cluster. The MT area also possesses a complete and continuous visual hemifield map, with the MT crescent (MTc) displaying radiation outward of the MT eccentricity map. Right: A model of how eccentricity bands might develop. (**A**) In the earliest stage, core visual field maps form in V1 and the MT area, gaining their constrained topography from thalamocortical inputs. (**B**) As development progresses, activity-dependent processes sculpt the cortical territory between the V1 and MT area representations such that columns with similar response properties cluster near one another. (**C**) The fully formed maps that emerge contain multiple representations of the visual field but also possess a supra-areal organization that reflects their emergence from the V1 and MT area anchors. Adapted, with permission, from [89].

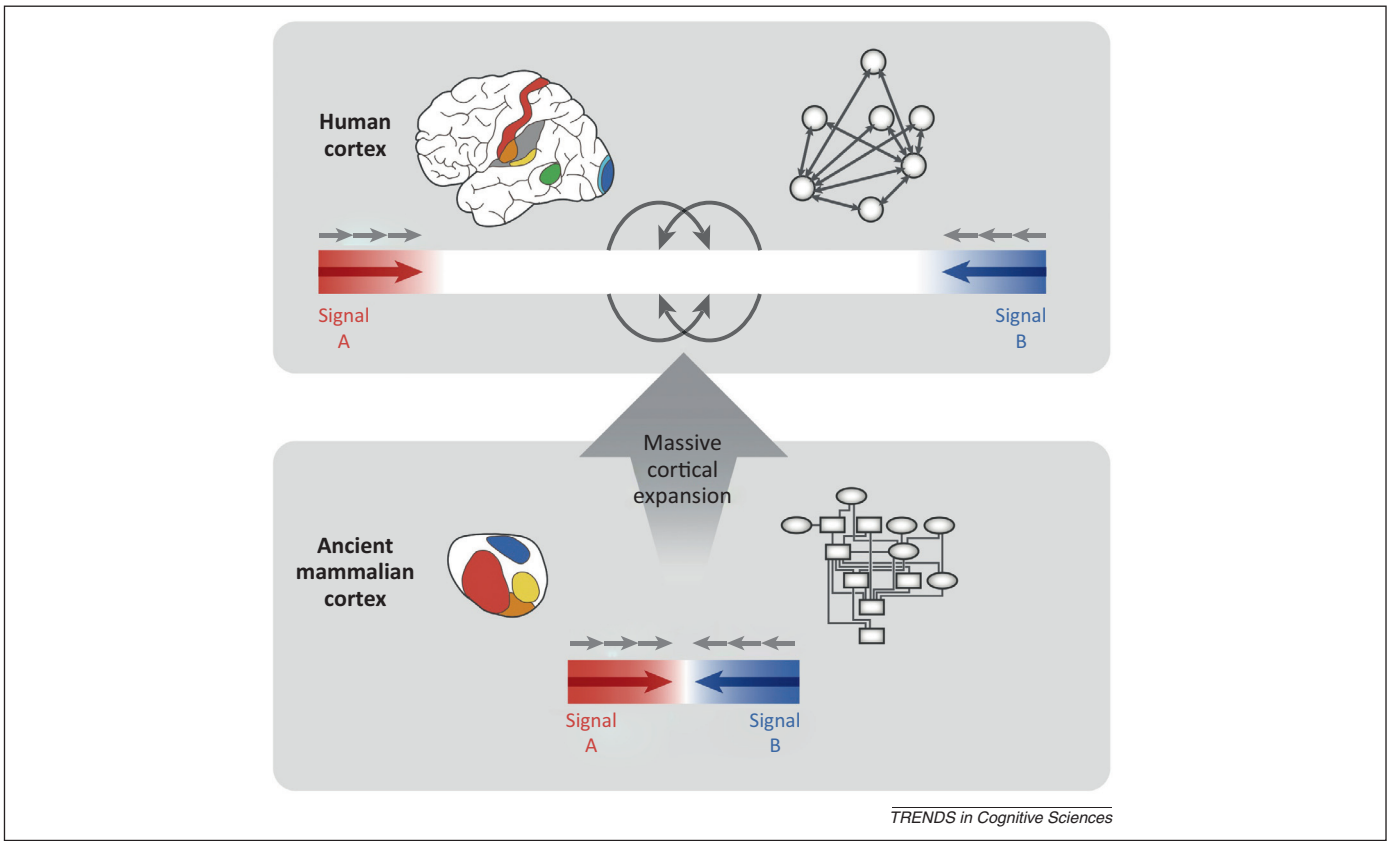

Figure 8. The tethering hypothesis. Bottom: The developing cortical mantle of the estimated mammalian common ancestor is schematically displayed as a thick line with two representative signaling gradients, labeled Signal A (red) and Signal B (blue). These gradients are heuristic presentations of the signal gradients present in the embryonic telencephalon (Figure 6). In the ancestral mammal, the signaling gradients and extrinsic activity from the sensory systems placed strong constraints on most of the developing cortex. Intermediate zones existed, colored in white, but represented a small portion of the cortical mantle. The resulting cortical organization included multiple sensory–motor hierarchies that occupied most of the mantle and formed canonical networks. Top: Following massive evolutionary expansion of the cortical mantle, in the presence of the same core signaling gradients, most of the cortical mantle emerges that is distant from the combined constraints of signaling gradients and extrinsic sensory activity. This emergent zone is illustrated as the large white area in the expanded cortical mantle. Untethered from sensory hierarchies, these distributed in-between zones are hypothesized to wire to one another and emerge as association cortex. The tethering hypothesis, which at this point should be considered a speculation, offers one framework to explain how association networks evolved their prominence and came to possess circuit properties vital to human cognition. The tethering hypothesis awaits further support or falsification.

V1. These two key anchors tether the remaining organization of early retinotopic cortex (Figure 7, right). Consistent with this idea, the MT area matures early in development, concurrent with the primary sensory areas (A1, S1, and V1) as assessed by neurofilament staining [94].

The idea of some form of radiation outward from core organizing centers is appealing because the hominin cerebral cortex vastly expanded in a short time. It seems implausible that molecular gradients could emerge fast enough to specify new cortical areas, although developmental expression patterns have clearly been modified [95]. Building from Rosa and colleagues' ideas about visual cortex organization, we propose a more general tethering hypothesis to explain how new features of cortical organization might have emerged during the rapid evolutionary expansion of the cerebral mantle (Figure 8). The word 'tether' is used to emphasize that the expanding cortical plate is tethered to gradients that initially evolved in a cortex with a far smaller surface area. Much as taffy, being pulled apart, thins until it breaks in the middle, the expanding cortical zones far from the strong constraints of developmental gradients and sensory input may become untethered from the canonical sensory–motor hierarchies.

The tethering hypothesis has two assumptions. First, the developing cerebral cortex forms from a modest number of core organizing maps that act as anchors. Candidate organizing fields include V1, the MT area, S1, and A1, which presumably emerge early in development from constraints of molecular gradients and typical thalamocortical inputs. These anchors covered much of the ancestral mammalian cortex but now occupy little of the modern human cerebral mantle. Other anchors are likely to exist but are more difficult to specify with certainty (Box 4). Detailed analysis of visual eccentricity maps in humans suggests five distinct map clusters (see Figure 9 in [92]). A possibility worth exploring further is that these clusters provide insight into additional developmental anchors. Generally, emergence of a new organizing anchor is expected to be a rare evolutionary event. The major determinant of disproportionate expansion of association cortex is speculated to arise from scaling, not new patterning centers. One caveat to this assumption is that recent studies have shown tremendous complexity in the spatial patterning that is possible in the developing human forebrain, including expression pattern asymmetries [96] and local expression of gene-regulatory sequences (e.g., [97]). An assumption of the tethering hypothesis is that conserved patterning centers are major determinants of cortical organization.

Second, self-organizing activity-dependent interactions are a dominant constraint in the formation of zones that

Box 4. Outstanding questions and future directions

- Does association cortex possess cortical areas with sharply delineated borders or is it better described as having organizational gradients radiating from core patterning centers?
- Cortical areas conserved across species provide evidence for core patterning centers that anchor arealization. But are there other anchors and are there specific anchors that emerge recently in evolution? Approaches to surveying cortical functional organization in humans (e.g., [173,174]) and its variability across individuals may provide insight into candidate anchors.
- The circuit organization proposed by Goldman-Rakic and Selemon [63,64] has remained largely unexplored using modern tracer techniques. It will be important to revisit the possibility that primates possess widely distributed, densely interconnected association circuits that lack rigid hierarchical relationships. Such circuits may be the key basis for internal mentation.
- Recent focus on connectional and functional anatomy has summarized broad organizational properties of brain networks using quantitative graph-theory metrics [175,176]. How do the properties of association networks contribute to global measures of network topology? And can graph theory metrics shed insight into how size scaling of association networks influences network topology across diverse species?
- An assumption of the tethering hypothesis is that in-between zones emerge in the cortex of large-brained mammals that are less constrained by bottom-up (sensory) activity cascades. Neurodevelopmental sequences are complex [177]. An open question is whether true gaps form during early stages of embryonic development within the protomap, whether the absence of activity from thalamic sensory nuclei at later stages is the more important feature or whether alterative mechanisms that we do not understand are responsible.
- The tethering hypothesis assumes that self-organizing rules are central to arealization. But what are these rules? And why do distributed association regions wire to one another? Research programs able to model candidate rules (e.g., [89,110,111] that explain known properties of cortical arealization and then test their viability in perturbed systems will provide critical insight. Perturbations might include genetic alterations to progenitor cell pool size or signaling gradients. Human cortical organization might be examined in naturally occurring disorders that affect cortical plate formation [178]. Measurement of the development of anatomical connectivity will be critical.
- Although association regions show more architectonic and functional variability between subjects than do sensory regions, the global organization of association networks is fairly consistent across people, including spatial relationships among multiple prefrontal areas. What are the constraints that govern regional organization in association cortices?
- The protracted development of association networks may make them preferentially vulnerable to deficient mechanisms central to activity-dependent sculpting as well as environmental influences. An open question is whether disorders emerging in early postnatal development such as Rett syndrome and autism, or late-emerging illnesses such as schizophrenia, are partially explained by vulnerability of association networks. For example, loss of one copy of MECP2 in Rett syndrome [179] may not bottleneck early phases of prenatal nervous system development, but may present a severe rate-limiting step in development when the broad association networks accelerate their maturation.

are far from the sensory patterning centers. These zones are distributed throughout cortex in the regions between the ancient gradients and come to form prefrontal, temporal, and parietal association cortices in the adult brain. Within this hypothesis, the reason why coordinated expansion of association zones is observed in comparative analyses between primate species (Figure 2) is because there are multiple gaps between the primary patterning centers. Although the broad organizational properties are consistent across individuals, these in-between zones show the greatest between-subject variation [98,99] (Figure 3). For incompletely understood reasons, without the strong constraints of primary signaling gradients and input from sensory systems, these zones wire to each other.

Figure 8 illustrates the key features of the tethering hypothesis. As the cortical proliferative zones expand their surface area in the presence of stable patterning centers, an increasingly large portion of the cortex emerges between the gradients that define sensory systems. Spontaneous activity and evoked activity from the sensory systems are expected to have minimal influence on the intermediate zones of the large developing cortical plate. Untethered border zones emerge. As the brain scales through the hominin line, the border zones become the majority of the cortical mantle.

Gaps

The tethering hypothesis draws attention to certain features of brain scaling that may be critical to the evolution of distributed association networks. However, in drawing attention to these features it also highlights major gaps in our understanding. The most notable gap concerns the unresolved question of why the in-between regions wire to each other. The widely separated regions of association cortex densely interconnect, as highlighted by the work of Goldman-Rakic and Selemon [63,64] as well as Mesulam [41]. Other sources of anatomical evidence argue for distinct connectivity patterns in association cortex in contrast to areas embedded within sensory hierarchies. For example, Felleman and Van Essen [42] noted more violations of clear hierarchical laminar projection patterns in areas late in otherwise hierarchical pathways, an observation that could represent a key insight or simply uncertainties in the available data. Close examination of individual tracer injections also reveals anatomical patterns consistent with the notion of densely interconnected, distributed circuits. For example, tracer injections across multiple distributed regions of macaque association cortex produce a pattern that closely resembles the distributed default network studied extensively in humans (see the combined projection patterns from Cases 1, 2, and 3 in [100], Cases 2 and 4 in [101,102], Cases 5 and 15 in [103], Cases 1 and 2 in [104], Case M-2-90 in [105], Cases 1 and 5 in [106], the posterior cingulate case in [107], Case 5 in [108], and Cases 1 and 2 in [109]).

It is unclear why regions distant from strong developmental anchors come to possess substantial long-range connectivity in contrast to the preferentially local connectivity patterns characteristic of sensory pathways. One speculative possibility is that the self-organizing rules in place in ancient mammals in some way found an optimal organization that connects regions that are not otherwise entrained by sensory-guided activity events. Spontaneous activity waves arising from sensory systems during development cascade with a strong bottom-up directionality [84]. In this sense, the sensory organs act as powerful anchors during development. The untethered border regions of association cortex may primarily have each other to constrain their wiring. Self-organizing rules such as the

principle 'like attracts like' [110,111] have been thoughtfully considered in the context of how contiguous sensory and motor maps organize. Similar principles might resolve to distributed solutions in the absence of bottom-up sensory-guided activity events.

A further possibility is raised by the recent discovery that low-weight, long-distance connections are more common across the cortex than previously estimated, even for sensory systems [112,113]. These long-distance connections are often highly specific, differentiating neighboring target areas. A possibility is that noncanonical distributed circuits form in regions where the absence of sensory activity cascades shifts the balance between local and distant connectivity patterns. Still another possibility is that thalamocortical projections from association nuclei provide a synchronized signal of some form across the distributed association zones (see [114] for an interesting discussion). More work is clearly needed to understand this key organizational property of association cortex.

The tethering hypothesis is also incomplete in that it does not provide insight into the adaptive value of a large brain. The large human brain comes at a tremendous cost both in terms of its metabolic demands [115,116] and because human birth is a precarious event due to the infant head being larger than the pelvic space, often described as the 'obstetric dilemma' [117]. Many theories have been put forward about the driving forces behind brain enlargement, including ideas about its adaptive value to social cognition and cooperation (e.g., [118,119]), and the critical changes in diet, cooperative breeding, and stabilization of food supply that provided the necessary evolutionary context to support brain expansion [115,116,120].

Although the tethering hypothesis does not speak to adaptive value, it does raise questions about the target of selection. Absolute brain size itself may be the target of selection, but it need not be. Selection may have rewarded expansion of the association networks. That is, as the adaptive benefits of association networks emerged, selection may have driven overall brain enlargement as a spandrel of direct selection for association network function. As another possibility, brain size may be secondary to other adaptive features of the scaled brain. For example, the prolonged postnatal sculpting of the cortex may have conveyed an advantage as hominins became dependent on the acquisition of learned skills and cultural innovations [121,122]. Selection may have been for labile cortical networks, not directly brain size. These alternatives remind us that it is difficult to infer evolutionary processes, especially when features that are spandrels at one stage of evolution become selected features at another stage.

Cerebellar spandrels

To what extent can features of subcortical structures and their connectivity with cerebral association cortex be explained by emergent properties of brain scaling? The cerebellum presents a particularly interesting case. Until recently the cerebellum was primarily considered a motor structure [123,124]. The cerebellum sits atop the spinal cord and is organized in an ipsilateral fashion with spinal projections, leading Charles Sherrington to refer to it as the 'head ganglion of the proprioceptive system' [125]. Cerebellum size increases with the general expansion of the cerebrum, inspiring debates about why the cerebellum is so large. Holmes [126] argued that the expansion of the lateral lobes in primates and humans, regions sometimes referred to as the neocerebellum, occurred in parallel with the evolution of 'delicate purposive movements'. Glickstein [127] articulates a similar perspective, further noting that monkeys and apes are partially bipedal, and humans entirely so, causing a gradation between species in the freedom to use the hands independent of locomotion. On the other side of the debate, Leiner, Leiner, and Dow [128] compiled multiple lines of evidence to support the possibility that the human cerebellum contains extensive regions linked to cerebral association areas. Their proposal, which initially met resistance [129], was based on the observation that the dentate nucleus – one of the deep cerebellar nuclei that carry cerebellar output – is expanded in apes and humans relative to other species. The expansion is accounted for by preferential enlargement of the newer ventrolateral portion of the dentate nucleus and occurred in parallel with expansion of cerebral association cortex (see also [130]).

The debate about whether the expanded zones of the cerebellum are solely elaborate motor circuits has been resolved through anatomical studies in the macaque [123,124] and findings from human functional connectivity [131–133]. The polysynaptic circuits that connect the cerebellum to the cerebrum repeat over and over throughout the extent of the cerebellum, with extensive zones projecting densely to association cortex. The cerebellar association zones are disproportionately expanded in humans [134], but the functional origins and importance of cerebellar expansion remain unresolved. Adaptionist ideas, like the few mentioned above, seek explanations for cerebellar enlargement as a specific, selected feature of evolution. There is an alternative: the growth of cerebellar projections to association cortex may be a spandrel or byproduct of coordinated evolution.

Several observations motivate leaning toward a spandrel hypothesis or coordinated evolution as opposed to a selective pressure on the cerebellum. The first observation is that, across numerous mammalian species, the absolute size of the cerebellum scales predictably in relation to overall brain size and disproportionately to other brain structures, second only to the cerebrum [135]. The relation is not of perfect allometry but is sufficiently close that a large cerebellum is the expected outcome of brain scaling whatever the pressure causing the brain enlargement (e.g., see [136] for an interesting discussion). Second, neuronal counting studies reveal that the numbers of neurons in the cerebral cortex versus the cerebellum remain constant across species, with an approximately 4:1 ratio favoring the cerebellum [17]. Thus, across diverse niches, developmental constraints fix a relation between the two structures. Finally, maps of the topography of the human cerebrum [32] and cerebellum [137,138] suggest that, with a few exceptions, the portion of the cerebellum dedicated to a cerebral network is proportionate to the size of its corresponding zone within the cerebral cortex. To a first approximation, the gross topography of much of the cerebellum mirrors the cerebrum.

Given leeway for minor deviations, the human cerebellum has the expected size, cell number, and topography of a typical primate. An ancient ancestor whose cortex was largely devoted to sensory–motor hierarchies probably possessed a circuit organization that pervasively connected the cerebral cortex to the cerebellum. That general circuit organization may simply have carried forward as brain scaling enlarged the cerebellum. This does not mean that the expanded cerebellum is without function or that important grade shifts are absent [136,139], but selective pressures are not required to account for the general observation that the human cerebellum is large and disproportionately represents association networks.

Specializations of the human brain beyond its large size

Beyond differences in brain size, many specializations are observed in the human brain at the cellular level, including novel types of neurons, expanded neuronal diversity, and differences in developmental steps and migratory paths [6,16,80,140–142]. Surveying some of these differences provides critical insight into how brain circuits have evolved in concert with brain scaling.

Gene expression differences are the signature of neuronal differentiation and may be an important driver of evolution. Recent study of laminar expression patterns in human *post mortem* brain tissue suggests expanded support for corticocortical projections [16,143]. In a major undertaking as part of the Allen Brain Institute, expression patterns for 995 genes were visualized at cellular resolution in *post mortem* mouse and human brains [143]. Although most genes were expressed similarly between mouse and human, 21% differed. For genes with species-specific expression patterns, there was an asymmetric shift between cortical layers. Mouse brain showed a preponderance of markers in layer V, where neurons predominantly project to subcortical structures. Half of the layer-V mouse markers showed no or diminished expression in humans. Of most interest, a subset of these genes shifted to expression in layer III in humans, where many corticocortical projection neurons reside. One possibility is that these genes support a newly evolved set of layer-III pyramidal neurons with long-range intracortical projections that arose after the last common rodent/primate ancestor [143].

Morphological analysis of pyramidal neurons between areas provides further insight. Pyramidal neurons in prefrontal cortex show more dendritic complexity, with as many as 23 times more dendritic spines than primary visual cortex [144]. Dendritic complexity increases as one goes from new world monkeys to old world monkeys to humans [144]. Recent comparison of the human and chimpanzee demonstrates that humans generally show more elaborate dendritic branching than chimpanzees, but also that a similar amplification of neuronal integration in prefrontal cortex is present in chimpanzees [145]. Pyramidal neurons are the central excitatory neuron type within cortical circuits and it is thus intriguing that their morphology differs in association cortex in a way that allows broader integration of inputs.

Of further importance, dendritic spine densities in prefrontal association areas mature late during development [74,146], suggesting that activity-dependent influences may continue to sculpt the broad connectivity of association networks far into adolescent development. Bianchi *et al.* [75] recently discovered that protracted development of prefrontal pyramidal neurons is present in chimpanzees, indicating that the enhanced window of postnatal development is likely to have evolved in an ape ancestor.

The human brain also possesses a new class of migratory neurons that provide a glimpse into how adaptations overcome disproportionate scaling of certain structures (cerebral cortex) over others (thalamus). Cortical neurons send and receive projections from a large number of subcortical structures that themselves possess subnuclei and orderly topography. As noted earlier, a key feature of the noncanonical circuit described by Goldman-Rakic and Selemon [63,64] is that distributed cortical association areas receive projections from a common thalamic nucleus – the medial pulvinar. How is critical thalamocortical circuitry maintained if cerebral cortex size is scaling at a faster rate than thalamus size?

Rakic and colleagues discovered a novel migratory pathway by which neurons from the telencephalic ganglionic eminence migrate to become interneurons in the thalamic association nuclei including the medial dorsal and pulvinar nuclei [80,147]. This pathway is absent in the rodent and monkey species studied to date; neurons from the ganglionic eminence do not migrate to the thalamus. Although no evolutionary mechanism has been identified, it is interesting to consider that a specialized event, such as loss of a chemorepellent influence steering interneurons away from the thalamus, could adaptively change the context into which the large human brain develops. A novel migratory pathway may have evolved a new source of thalamic neurons during development to accommodate the exhaustion of the more ancient neuronal pool source.

These collective observations illustrate several points. First, the consequences of increased brain size are certainly only part of the explanation for human cognitive capabilities. They are the focus of the present review to highlight how scaling effects can form a critical foundation for understanding the human brain, but the emphasis should not be taken to imply that scaling alone accounts for the human brain's evolution. Second, many of the cellular differences may be enablers or responses to brain scaling. Expansion of association cortex has evolved in the context of critical cellular adaptations. It is unclear which, if any, of the cellular adaptations mentioned above arose specifically during hominin evolution. Where they have been studied in great apes, such as the analysis of pyramidal neurons, humans and apes show many similarities. Evolved cellular specializations are likely to be a hodgepodge that occurred at many points in our evolutionary past. Critical to function, the human brain has accumulated cell types that suggest mechanisms to integrate information over large territories of cortical input – adaptations that may have allowed our ancestors to benefit from the expansion of distributed association zones.

Concluding remarks

The inherited constraints of development and the general plan, or *Bauplan*, of the brain are powerful limiters on how

neural circuits can evolve across generations. Here we raise the possibility that critical features of association cortex, linked to size scaling, may contribute to the human brain's extraordinary capabilities. The central idea is that a distributed form of circuit may have become increasingly prominent when ancient rules of development were expressed in an expanding cortical mantle. The possibility that simple mechanisms play a major role in recent brain evolution is comforting because it demystifies the gap between our brain's capabilities and those of our ancestors. Of course, the ideas presented here say nothing about the selective pressures or mechanisms that sculpted the circuits into forms that drive a child to communicate, attend to a social interaction, and ultimately become self-aware. They also say little about the history of innovation that has depended on the transmission and expansion of knowledge across generations [121,122]. What the framework emphasizes is a peculiar feature of cortical expansion that might underpin the evolutionary opportunity for such extraordinary feats.

Acknowledgments

The authors thank Felix Warneken, Dan Lieberman, Chet Sherwood, Jim Rilling, and two anonymous reviewers for comments, discussion, and pointers to relevant literature, Dan Lieberman for providing the data plotted in Box 1, and Anna Rieckmann for translating Flechsig's work. Haderer & Müller Biomedical Art provided illustrations.

References

1 Prüfer, K. *et al.* (2012) The bonobo genome compared with the chimpanzee and human genomes. *Nature* 486, 527–531
2 Boesch, C. *et al.* (2002) *Behavioural Diversity in Chimpanzees and Bonobos*, Cambridge University Press
3 Hare, B. (2011) From hominoid to hominid mind: what changed and why? *Annu. Rev. Anthropol.* 40, 293–309
4 Rilling, J.K. *et al.* (2012) Differences between chimpanzees and bonobos in neural systems supporting social cognition. *Soc. Cogn. Affect. Neurosci.* 7, 369–379
5 Sherwood, C.C. *et al.* (2008) A natural history of the human mind: tracing evolutionary changes in brain and cognition. *J. Anat.* 212, 426–454
6 Sherwood, C.C. *et al.* (2012) Human brain evolution writ large and small. *Prog. Brain Res.* 195, 237–254
7 Holloway, R.L. *et al.* (2004) *The Human Fossil Record, Brain Endocasts: The Paleoneurological Evidence*, John Wiley & Sons
8 Enard, W. *et al.* (2002) Molecular evolution of FOXP2, a gene involved in speech and language. *Nature* 418, 869–872
9 Ferland, R.J. *et al.* (2004) Abnormal cerebellar development and axonal decussation due to mutations in AHI1 in Joubert syndrome. *Nat. Genet.* 36, 1008–1013
10 Mikkelsen, T.S. *et al.* (2005) Initial sequence of the chimpanzee genome and comparison with the human genome. *Nature* 437, 69–87
11 Bailey, J.A. and Eichler, E.E. (2006) Primate segmental duplications: crucibles of evolution, diversity and disease. *Nat. Rev. Genet.* 7, 552–564
12 Vallender, E.J. *et al.* (2008) Genetic basis of human brain evolution. *Trends Neurosci.* 31, 637–644
13 Dennis, M.Y. *et al.* (2012) Evolution of human-specific neural SRGAP2 genes by incomplete segmental duplication. *Cell* 149, 912–922
14 McLean, C.Y. *et al.* (2011) Human-specific loss of regulatory DNA and the evolution of human-specific traits. *Nature* 471, 216–219
15 Konopka, G. *et al.* (2012) Human-specific transcriptional networks in the brain. *Neuron* 75, 601–617
16 Somel, M. *et al.* (2013) Human brain evolution: transcripts, metabolites and their regulators. *Nat. Rev. Neurosci.* 14, 112–127
17 Herculano-Houzel, S. (2012) The remarkable, yet not extraordinary, human brain as a scaled-up primate brain and its associated cost. *Proc. Natl. Acad. Sci. U.S.A.* 109, 10661–10668
18 Changizi, M.A. (2007) Scaling the brain and its connections. In *Evolution of Nervous Systems* (Kaas, J., ed.), pp. 167–180, Elsevier
19 Gould, S.J. and Lewontin, R.C. (1979) The spandrels of San Marco and the Panglossian paradigm: a critique of the adaptationist programme. *Proc. R. Soc. B: Biol. Sci.* 205, 581–598
20 Diamond, I.T. and Hall, W.C. (1969) Evolution of neocortex. *Science* 164, 251–262
21 Kaas, J.H. (1987) The organization of neocortex in mammals: implications for theories of brain function. *Annu. Rev. Psychol.* 38, 129–151
22 Krubitzer, L. and Kahn, D.M. (2003) Nature versus nurture revisited: an old idea with a new twist. *Prog. Neurobiol.* 70, 33–52
23 Krubitzer, L. (2007) The magnificent compromise: cortical field evolution in mammals. *Neuron* 56, 201–208
24 Krubitzer, L. (2009) In search of a unifying theory of complex brain evolution. *Ann. N. Y. Acad. Sci.* 1156, 44–67
25 Van Essen, D.C. and Dierker, D.L. (2007) Surface-based and probabilistic atlases of primate cerebral cortex. *Neuron* 56, 209–225
26 Hill, J. *et al.* (2010) Similar patterns of cortical expansion during human development and evolution. *Proc. Natl. Acad. Sci. U.S.A.* 107, 13135–13140
27 Preuss, T.M. (2011) The human brain: rewired and running hot. *Ann. N. Y. Acad. Sci.* 1225, E182–E191
28 Brodmann, K. (1909/1994) *Brodmann's Localization in the Cerebral Cortex* (Garvey, L.J., transl.) Springer
29 Geschwind, N. (2010) Disconnexion syndromes in animals and man: part I. 1965. *Neuropsychol. Rev.* 20, 128–157
30 Catani, M. and ffytche, D.H. (2005) The rises and falls of disconnection syndromes. *Brain* 128, 2224–2239
31 Petrides, M. *et al.* (2012) The prefrontal cortex: comparative architectonic organization in the human and the macaque monkey brains. *Cortex* 48, 46–57
32 Yeo, B.T.T. *et al.* (2011) The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *J. Neurophysiol.* 106, 1125–1165
33 Frahm, H.D. *et al.* (1984) Comparison of brain structure volumes in insectivora and primates. V. Area striata (AS). *J. Hirnforsch.* 25, 537–557
34 Kaskan, P.M. *et al.* (2005) Peripheral variability and central constancy in mammalian visual system evolution. *Proc. Biol. Sci.* 272, 91–100
35 Semendeferi, K. *et al.* (2002) Humans and great apes share a large frontal cortex. *Nat. Neurosci.* 5, 272–276
36 Bush, E.C. and Allman, J.M. (2004) The scaling of frontal cortex in primates and carnivores. *Proc. Natl. Acad. Sci. U.S.A.* 101, 3962–3966
37 Barton, R.A. and Venditti, C. (2013) Human frontal lobes are not relatively large. *Proc. Natl. Acad. Sci. U.S.A.* 110, 9001–9006
38 Sherwood, C.C. and Smaers, J.B. (2013) What's the fuss over human frontal lobe evolution? *Trends Cogn. Sci.* 17, 432–433
39 Maunsell, J.H. and Van Essen, D.C. (1983) The connections of the middle temporal visual area (MT) and their relationship to a cortical hierarchy in the macaque monkey. *J. Neurosci.* 3, 2563–2586
40 Ungerleider, L.G. and Desimone, R. (1986) Cortical connections of visual area MT in the macaque. *J. Comp. Neurol.* 248, 190–222
41 Mesulam, M-M. (1990) Large-scale neurocognitive networks and distributed processing for attention, language, and memory. *Ann. Neurol.* 28, 597–613
42 Felleman, D.J. and Van Essen, D.C. (1991) Distributed hierarchical processing in the primate cerebral cortex. *Cereb. Cortex* 1, 1–47
43 Passingham, R.E. *et al.* (2002) The anatomical basis of functional localization in the cortex. *Nat. Rev. Neurosci.* 3, 606–616
44 Friedman, D.P. (1983) Laminar patterns of termination of cortico-cortical afferents in the somatosensory system. *Brain Res.* 273, 147–151
45 Van Essen, D.C. *et al.* (1992) Information processing in the primate visual system: an integrated systems perspective. *Science* 255, 419–423
46 Shadlen, M.N. and Newsome, W.T. (2001) Neural basis of a perceptual decision in the parietal cortex (area LIP) of the rhesus monkey. *J. Neurophysiol.* 86, 1916–1936
47 Gold, J.I. and Shadlen, M.N. (2007) The neural basis of decision making. *Annu. Rev. Neurosci.* 30, 535–574
48 Bisley, J.W. and Goldberg, M.E. (2010) Attention, intention, and priority in the parietal lobe. *Annu. Rev. Neurosci.* 33, 1–21

49 Kaas, J.H. (1989) The evolution of complex sensory systems in mammals. *J. Exp. Biol.* 146, 165–176
50 Jones, E.G. and Powell, T.P. (1970) An anatomical study of converging sensory pathways within the cerebral cortex of the monkey. *Brain* 93, 793–820
51 Petrides, M. *et al.* (2005) Orofacial somatomotor responses in the macaque monkey homologue of Broca's area. *Nature* 435, 1235–1238
52 Rilling, J.K. *et al.* (2008) The evolution of the arcuate fasciculus revealed with comparative DTI. *Nat. Neurosci.* 11, 426–428
53 Posner, M.I. and Petersen, S.E. (1990) The attention system of the human brain. *Annu. Rev. Neurosci.* 13, 25–42
54 Miller, E.K. and Cohen, J.D. (2001) An integrative theory of prefrontal cortex function. *Annu. Rev. Neurosci.* 24, 167–202
55 Petersen, S.E. and Posner, M.I. (2012) The attention system of the human brain: 20 years after. *Annu. Rev. Neurosci.* 35, 73–89
56 Dosenbach, N.U.F. *et al.* (2007) Distinct brain networks for adaptive and stable task control in humans. *Proc. Natl. Acad. Sci. U.S.A.* 104, 11073–11078
57 Vincent, J.L. *et al.* (2008) Evidence for a frontoparietal control system revealed by intrinsic functional connectivity. *J. Neurophysiol.* 100, 3328–3342
58 Mantini, D. *et al.* (2013) Evolutionarily novel functional networks in the human brain? *J. Neurosci.* 33, 3259–3275
59 Badre, D. and D'Esposito, M. (2009) Is the rostro–caudal axis of the frontal lobe hierarchical? *Nat. Rev. Neurosci.* 10, 659–669
60 Buckner, R.L. *et al.* (2008) The brain's default network: anatomy, function, and relevance to disease. *Ann. N. Y. Acad. Sci.* 1124, 1–38
61 Spreng, R.N. *et al.* (2009) The common neural basis of autobiographical memory, prospection, navigation, theory of mind, and the default mode: a quantitative meta-analysis. *J. Cogn. Neurosci.* 21, 489–510
62 Andrews-Hanna, J.R. (2012) The brain's default network and its adaptive role in internal mentation. *Neuroscientist* 18, 251–270
63 Goldman-Rakic, P.S. (1988) Topography of cognition: parallel distributed networks in primate association cortex. *Annu. Rev. Neurosci.* 11, 137–156
64 Selemon, L.D. and Goldman-Rakic, P.S. (1988) Common cortical and subcortical targets of the dorsolateral prefrontal and posterior parietal cortices in the rhesus monkey: evidence for a distributed neural network subserving spatially guided behavior. *J. Neurosci.* 8, 4049–4068
65 Armstrong, E. (1981) A quantitative comparison of the hominoid thalamus. IV. Posterior association nuclei – the pulvinar and lateral posterior nucleus. *Am. J. Phys. Anthropol.* 55, 369–383
66 Buckner, R.L. *et al.* (2013) Opportunities and limitations of intrinsic functional connectivity MRI. *Nat. Neurosci.* 16, 832–837
67 Craddock, R.C. *et al.* (2013) Imaging human connectomes at the macroscale. *Nat. Methods* 10, 524–539
68 Murphy, K. *et al.* (2013) Resting-state fMRI confounds and cleanup. *Neuroimage* 80, 349–359
69 Power, J.D. *et al.* (2011) Functional network organization of the human brain. *Neuron* 72, 665–678
70 Yarkoni, T. *et al.* (2011) Large-scale automated synthesis of human functional neuroimaging data. *Nat. Methods* 8, 665–670
71 Spreng, R.N. *et al.* (2013) Intrinsic architecture underlying the relations among default, dorsal attention, and frontoparietal control networks of the human brain. *J. Cogn. Neurosci.* 25, 74–86
72 Sepulcre, J. *et al.* (2010) The organization of local and distant functional connectivity in the human brain. *PLoS Comput. Biol.* 6, e1000808
73 Gogtay, N. *et al.* (2004) Dynamic mapping of human cortical development during childhood through early adulthood. *Proc. Natl. Acad. Sci. U.S.A.* 101, 8174–8179
74 Elston, G.N. *et al.* (2009) Spinogenesis and pruning scales across functional hierarchies. *J. Neurosci.* 29, 3271–3275
75 Bianchi, S. *et al.* (2013) Synaptogenesis and development of pyramidal neuron dendritic morphology in the chimpanzee neocortex resembles humans. *Proc. Natl. Acad. Sci. U.S.A.* 110, 10395–10401
76 Yakovlev, P.A. and Lecours, I.R. (1967) The myelogenetic cycles of regional maturation of the brain. In *Regional Development of the Brain in Early Life* (Minkowsky, A., ed.), pp. 3–70, Blackwell
77 Brody, B.A. *et al.* (1987) Sequence of central nervous system myelination in human infancy. I. An autopsy study of myelination. *J. Neuropathol. Exp. Neurol.* 46, 283–301
78 Miller, D.J. *et al.* (2012) Prolonged myelination in human neocortical evolution. *Proc. Natl. Acad. Sci. U.S.A.* 109, 16480–16485
79 Flechsig, P.E. (1920) *Anatomie des menschlichen Gehirns und Rückenmarks auf myelogenetischer Grundlage*, G. Thieme (in German)
80 Rakic, P. (2009) Evolution of the neocortex: a perspective from developmental biology. *Nat. Rev. Neurosci.* 10, 724–735
81 Rakic, P. (1988) Specification of cerebral cortical areas. *Science* 241, 170–176
82 Fukuchi-Shimogori, T. and Grove, E.A. (2001) Neocortex patterning by the secreted signaling molecule FGF8. *Science* 294, 1071–1074
83 O'Leary, D.D. and Sahara, S. (2008) Genetic regulation of arealization of the neocortex. *Curr. Opin. Neurobiol.* 18, 90–100
84 Katz, L.C. and Shatz, C.J. (1996) Synaptic activity and the construction of cortical circuits. *Science* 274, 1133–1138
85 Chou, S.J. *et al.* (2013) Geniculocortical input drives genetic distinctions between primary and higher-order visual areas. *Science* 340, 1239–1242
86 Lokmane, L. *et al.* (2013) Sensory map transfer to the neocortex relies on pretarget ordering of thalamic axons. *Curr. Biol.* 23, 810–816
87 Allman, J.M. and Kaas, J.H. (1971) A representation of the visual field in the caudal third of the middle temporal gyrus of the owl monkey (*Aotus trivirgatus*). *Brain Res.* 31, 85–105
88 Krubitzer, L. (1995) The organization of neocortex in mammals: are species differences really so different? *Trends Neurosci.* 18, 408–417
89 Rosa, M.G.P. (2002) Visual maps in the adult primate cerebral cortex: some implications for brain development and evolution. *Braz. J. Med. Biol. Res.* 35, 1485–1498
90 Rosa, M.G.P. and Tweedale, R. (2005) Brain maps, great and small: lessons from comparative studies of primate visual cortical organization. *Philos. Trans. R. Soc. B: Biol. Sci.* 360, 665–691
91 Wandell, B.A. *et al.* (2005) Visual field map clusters in human cortex. *Philos. Trans. R. Soc. B: Biol. Sci.* 360, 693–707
92 Wandell, B.A. *et al.* (2007) Visual field maps in human cortex. *Neuron* 56, 366–383
93 Schira, M.M. *et al.* (2009) The foveal confluence in human visual cortex. *J. Neurosci.* 29, 9050–9058
94 Bourne, J.A. and Rosa, M.G.P. (2006) Hierarchical development of the primate visual cortex, as revealed by neurofilament immunoreactivity: early maturation of the middle temporal area (MT). *Cereb. Cortex* 16, 405–414
95 Ip, B.K. *et al.* (2010) Investigating gradients of gene expression involved in early human cortical development. *J. Anat.* 217, 300–311
96 Sun, T. and Walsh, C.A. (2006) Molecular approaches to brain asymmetry and handedness. *Nat. Rev. Neurosci.* 7, 655–662
97 Visel, A. *et al.* (2013) A high-resolution enhancer atlas of the developing telencephalon. *Cell* 152, 895–908
98 Hill, J. *et al.* (2010) A surface-based atlas of hemispheric asymmetries and folding of cerebral cortex in term-born human infants. *J. Neurosci.* 30, 2268–2276
99 Mueller, S. *et al.* (2013) Individual variability in functional connectivity architecture of the human brain. *Neuron* 77, 586–595
100 Mesulam, M-M. *et al.* (1977) Limbic and sensory connections of the inferior parietal lobule (area PG) in the rhesus monkey: a study with a new method for horseradish peroxidase histochemistry. *Brain Res.* 136, 393–414
101 Cavada, C. and Goldman-Rakic, P.S. (1989) Posterior parietal cortex in rhesus monkey: I. Parcellation of areas based on distinctive limbic and sensory corticocortical connections. *J. Comp. Neurol.* 287, 393–421
102 Cavada, C. and Goldman-Rakic, P.S. (1989) Posterior parietal cortex in rhesus monkey: II. Evidence of segregated corticocortical networks linking sensory and limbic areas with the frontal lobe. *J. Comp. Neurol.* 287, 422–445
103 Andersen, R.A. *et al.* (1990) Corticocortical connections of anatomically and physiologically defined subdivisions of within the inferior parietal lobule. *J. Comp. Neurol.* 296, 65–113
104 Barnes, C.L. and Pandya, D.N. (1992) Efferent cortical connections of multimodal cortex of the superior temporal sulcus in the rhesus monkey. *J. Comp. Neurol.* 318, 222–244
105 Lavenex, P. *et al.* (2002) Perirhinal and parahippocampal cortices of the macaque monkey: projections to the neocortex. *J. Comp. Neurol.* 447, 394–420

106 Blatt, G.J. *et al.* (2003) Parcellation of cortical afferents to three distinct sectors in the parahippocampal gyrus of the rhesus monkey: an anatomical and neurophysiological study. *J. Comp. Neurol.* 466, 161–179
107 Vogt, B.A. *et al.* (1979) Thalamic and cortical afferents differentiate anterior from posterior cingulate. *Science* 204, 205–207
108 Pandya, D.N. *et al.* (1981) Efferent connections of the cingulate gyrus in the rhesus monkey. *Exp. Brain Res.* 42, 319–330
109 Morecraft, R.J. *et al.* (2004) Cytoarchitecture and cortical connections of the posterior cingulate and adjacent somatosensory fields of the rhesus monkey. *J. Comp. Neurol.* 469, 37–69
110 Graziano, M.S.A. and Aflalo, T.N. (2007) Rethinking cortical organization: moving away from discrete areas arranged in hierarchies. *Neuroscientist* 13, 138–147
111 Aflalo, T.N. and Graziano, M.S.A. (2010) Organization of the macaque extrastriate visual cortex re-examined using the principle of spatial continuity of function. *J. Neurophysiol.* 105, 305–320
112 Markov, N.T. *et al.* (2012) A weighted and directed interareal connectivity matrix for macaque cerebral cortex. *Cereb. Cortex* http://dx.doi.org/10.1093/cercor/bhs270
113 Markov, N.T. *et al.* (2013) The role of long-range connections on the specificity of the macaque interareal cortical network. *Proc. Natl. Acad. Sci. U.S.A.* 110, 5187–5192
114 Shipp, S. (2003) The functional logic of cortico-pulvinar connections. *Philos. Trans. R. Soc. B: Biol. Sci.* 358, 1605–1624
115 Leonard, W.R. *et al.* (2007) Effects of brain evolution on human nutrition and metabolism. *Annu. Rev. Nutr.* 27, 311–327
116 Navarette, A. *et al.* (2011) Energetics and the evolution of human brain size. *Nature* 480, 91–94
117 Whitman, A.B. and Wall, L.L. (2007) The evolutionary origins of obstructed labor: bipedalism, encephalization, and the human obstetric dilemma. *Obstet. Gynecol. Surv.* 62, 739–748
118 Dunbar, R.I.M. (1998) The social brain hypothesis. *Evol. Anthropol.* 6, 178–190
119 Tomasello, M. *et al.* (2005) Understanding and sharing intentions: the origins of cultural cognition. *Behav. Brain Sci.* 28, 675–691
120 Aiello, L.C. and Wheeler, P. (1995) The expensive-tissue hypothesis: the brain and the digestive system in human and primate evolution. *Curr. Anthropol.* 36, 199–221
121 Tennie, C. *et al.* (2009) Ratcheting up the ratchet: on the evolution of cumulative culture. *Philos. Trans. R. Soc. B: Biol. Sci.* 364, 2405–2415
122 Boyd, R. *et al.* (2011) The cultural niche: why social learning is essential for human adaptation. *Proc. Natl. Acad. Sci. U.S.A.* 108 (Suppl. 2), 10918–10925
123 Strick, P.L. *et al.* (2009) Cerebellum and nonmotor function. *Annu. Rev. Neurosci.* 32, 413–434
124 Schmahmann, J.D. (2010) The role of the cerebellum in cognition and emotion: personal reflections since 1982 on the dysmetria of thought hypothesis, and its historical evolution from theory to therapy. *Neuropsychol. Rev.* 20, 236–260
125 Sherrington, C.S. (1906) *The Integrative Action of the Nervous System*, Yale University Press
126 Holmes, G. (1939) The cerebellum of man. *Brain* 62, 1–30
127 Glickstein, M. (2007) What does the cerebellum really do? *Curr. Biol.* 17, R824–R827
128 Leiner, H.C. *et al.* (1986) Does the cerebellum contribute to mental skills? *Behav. Neurosci.* 100, 443–454
129 Leiner, H.C. (2010) Solving the mystery of the human cerebellum. *Neuropsychol. Rev.* 20, 229–235
130 Matano, S. (2001) Proportions of the ventral half of the cerebellar dentate nucleus in humans and great apes. *Am. J. Phys. Anthropol.* 114, 163–165
131 Krienen, F.M. and Buckner, R.L. (2009) Segregated fronto-cerebellar circuits revealed by intrinsic functional connectivity. *Cereb. Cortex* 19, 2485–2497
132 Habas, C. *et al.* (2009) Distinct cerebellar contributions to intrinsic connectivity networks. *J. Neurosci.* 29, 8586–8594
133 O'Reilly, J.X. *et al.* (2010) Distinct and overlapping functional zones in the cerebellum defined by resting state functional connectivity. *Cereb. Cortex* 20, 953–965
134 Balsters, J.H. *et al.* (2010) Evolution of the cerebellar cortex: the selective expansion of prefrontal-projecting cerebellar lobules. *Neuroimage* 49, 2045–2052
135 Finlay, B.L. and Darlington, R.B. (1995) Linked regularities in the development and evolution of mammalian brains. *Science* 268, 1578–1584
136 Rilling, J.K. (2001) Allometric departures for the human brain provide insights into hominid brain evolution. *Behav. Brain Sci.* 24, 292–293
137 Buckner, R.L. *et al.* (2011) The organization of the human cerebellum estimated by intrinsic functional connectivity. *J. Neurophysiol.* 106, 2322–2345
138 Wang, D. *et al.* (2013) Cerebellar asymmetry and its relation to cerebral asymmetry estimated by intrinsic functional connectivity. *J. Neurophysiol.* 109, 46–57
139 Smaers, J.B. *et al.* (2013) Laterality and the evolution of the prefronto-cerebellar system in anthropoids. *Ann. N. Y. Acad. Sci.* 1288, 59–69
140 Clowry, G. *et al.* (2010) Renewed focus on the developing human neocortex. *J. Anat.* 217, 276–288
141 DeFelipe, J. (2011) The evolution of the brain, the human nature of cortical circuits, and intellectual creativity. *Front. Neuroanat.* 5, 29
142 Preuss, T.M. (2012) Human brain evolution: from gene discovery to phenotype discovery. *Proc. Natl. Acad. Sci. U.S.A.* 109 (Suppl. 1), 10709–10716
143 Zeng, H. *et al.* (2012) Large-scale cellular-resolution gene profiling in human neocortex reveals species-specific molecular signatures. *Cell* 149, 483–496
144 Elston, G.N. (2003) Cortex, cognition, and the cell: new insights into the pyramidal neuron and prefrontal function. *Cereb. Cortex* 13, 1124–1138
145 Bianchi, S. *et al.* (2012) Dendritic morphometry of pyramidal neurons in the chimpanzee neocortex: regional specialization and comparison to humans. *Cereb. Cortex* http://dx.doi.org/10.1093/cercor/bhs239
146 Petanjek, Z. *et al.* (2011) Extraordinary neoteny of synaptic spines in the human prefrontal cortex. *Proc. Natl. Acad. Sci. U.S.A.* 108, 13281–13286
147 Letinic, K. and Rakic, P. (2001) Telencephalic origin of human thalamic GABAergic neurons. *Nat. Neurosci.* 4, 931–936
148 Jerison, H.J. (1955) Brain to body ratios and the evolution of intelligence. *Science* 121, 447–449
149 Jerison, H.J. (1975) Evolution of the brain and intelligence. *Curr. Anthropol.* 16, 403–426
150 Marino, L. (1998) A comparison of encephalization between odontocete cetaceans and anthropoid primates. *Brain Behav. Evol.* 51, 230–238
151 Count, E.W. (1947) Brain and body weight in man: their antecedents in growth and evolution: a study in dynamic somatometry. *Ann. N. Y. Acad. Sci.* 46, 993–1122
152 Striedter, G.F. (2005) *Principles of Brain Evolution*, Sinauer Associates
153 Charvet, C.J. and Finlay, B.L. (2012) Embracing covariation in brain evolution: large brains, extended development, and flexible primate social systems. *Prog. Brain Res.* 195, 71–87
154 Lieberman, D.E. (2011) *The Evolution of the Human Head*, Harvard University Press
155 Sakai, T. *et al.* (2012) Fetal brain development in chimpanzees versus humans. *Curr. Biol.* 22, R791–R792
156 Rilling, J.K. and Insel, T.R. (1999) The primate neocortex in comparative perspective using magnetic resonance imaging. *J. Hum. Evol.* 37, 191–223
157 Semaw, S. *et al.* (2003) 2.6-Million-year-old stone tools and associated bones from OGS-6 and OGS-7, Gona, Afar, Ethiopia. *J. Hum. Evol.* 45, 169–177
158 McPherron, S.P. *et al.* (2010) Evidence for stone-tool-assisted consumption of animal tissues before 3.39 million years ago at Dikika, Ethiopia. *Nature* 466, 857–860
159 Kivell, T.L. *et al.* (2011) *Australopithecus sediba* hand demonstrates mosaic evolution of locomotor and manipulative abilities. *Science* 333, 1411–1417
160 Carlson, K.J. *et al.* (2011) The endocast of MH1, *Australopithecus sediba*. *Science* 333, 1402–1407
161 Ruff, C.B. *et al.* (1997) Body mass and encephalization in Pleistocene *Homo*. *Nature* 387, 173–176
162 Klein, R.G. (2000) Archeology and the evolution of human behavior. *Evol. Anthropol.* 9, 17–36

163 Brown, P. *et al.* (2004) A new small-bodied hominin from the Late Pleistocene of Flores, Indonesia. *Nature* 431, 1055–1061
164 Morwood, M.J. *et al.* (2004) Archaeology and age of a new hominin from Flores in eastern Indonesia. *Nature* 431, 1087–1091
165 Kubo, D. *et al.* (2013) Brain size of *Homo floresiensis* and its evolutionary implications. *Proc. Biol. Sci.* http://dx.doi.org/10.1098/rspb.2013.0338
166 Lieberman, D.E. (2009) Palaeoanthropology: *Homo floresiensis* from head to toe. *Nature* 459, 41–42
167 Campbell, A.W. (1905) *Histological Studies on the Localisation of Cerebral Function*, Cambridge University Press
168 Von Bonin, G. and Bailey, P. (1947) *The Neocortex of* Macaca mulatta, University of Illinois Press
169 Lashley, K.S. and Clark, G. (1946) The cytoarchitecture of the cerebral cortex of *Ateles*: a critical examination of architectonic studies. *J. Comp. Neurol.* 85, 223–305
170 Kaas, J.H. and Catania, K.C. (2002) How do features of sensory representations develop? *Bioassays* 24, 334–343
171 Krubitzer, L.A. and Seelke, A.M.H. (2012) Cortical evolution in mammals: the bane and beauty of phenotypic variability. *Proc. Natl. Acad. Sci. U.S.A.* 109, 10647–10654
172 Van Essen, D.C. (2005) A population-average, landmark- and surface-based (PALS) atlas of human cerebral cortex. *Neuroimage* 28, 635–662
173 Huth, A.G. *et al.* (2012) A continuous semantic space describes the representation of thousands of object and action categories across the human brain. *Neuron* 76, 1210–1224
174 Konkle, T. and Caramazza, A. (2013) Tripartite organization of the ventral stream by animacy and object size. *J Neurosci.* 33, 10235–10242
175 Bullmore, E. and Sporns, O. (2009) Complex brain networks: graph theoretical analysis of structural and functional systems. *Nat. Rev. Neurosci.* 10, 186–198
176 Bullmore, E. and Sporns, O. (2012) The economy of brain network organization. *Nat. Rev. Neurosci.* 13, 336–349
177 Workman, A.D. *et al.* (2013) Modeling transformation of neurodevelopmental sequences across mammalian species. *J. Neurosci.* 33, 7368–7383
178 Manzini, M.C. and Walsh, C.A. (2011) What disorders of cortical development tell us about the cortex: one plus one does not always make two. *Curr. Opin. Genet. Dev.* 21, 333–339
179 Chahrour, M. and Zoghbi, H.Y. (2007) The story of Rett syndrome: from clinic to neurobiology. *Neuron* 56, 422–437