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REVIEW ARTICLE

Evolution of prefrontal cortex

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Subdivisions of the prefrontal cortex (PFC) evolved at different times. Agranular parts of the PFC emerged in early mammals, and rodents, primates, and other modern mammals share them by inheritance. These are limbic areas and include the agranular orbital cortex and agranular medial frontal cortex (areas 24, 32, and 25). Rodent research provides valuable insights into the structure, functions, and development of these shared areas, but it contributes less to parts of the PFC that are specific to primates, namely, the granular, isocortical PFC that dominates the frontal lobe in humans. The first granular PFC areas evolved either in early primates or in the last common ancestor of primates and tree shrews. Additional granular PFC areas emerged in the primate stem lineage, as represented by modern strepsirrhines. Other granular PFC areas evolved in simians, the group that includes apes, humans, and monkeys. In general, PFC accreted new areas along a roughly posterior to anterior trajectory during primate evolution. A major expansion of the granular PFC occurred in humans in concert with other association areas, with modifications of corticocortical connectivity and gene expression, although current evidence does not support the addition of a large number of new, human-specific PFC areas.

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INTRODUCTION

Many neuroscientists assume that cortical organization is highly conserved among mammals—the cortex might differ in size or number of neurons, but its basic elements and pattern of organization are shared by all. The current concentration of research on a few "model" species reinforces this view. In addition to the cerebral cortex of humans, neuroscience devotes the vast majority of its effort to study the favored four: rats, mice, and rhesus monkeys, with common marmosets recently augmenting this limited roster. Because translational neuroscience depends on features of organization shared among species, presumably including humans, there is a tendency to neglect the diversity of mammalian cortex (for discussions, see [1–6]).

If one adopts a broader, comparative perspective, however, it becomes difficult to sustain this view. Of course, some features of the mammalian cortex are widely shared among species by virtue of common ancestry. Nevertheless, the cortex also exhibits the same high level of diversity characteristic of other aspects of mammalian biology [7], different lineages having evolved a wide variety of cortical specializations, just as they evolved numerous specializations of behavior, skeletal anatomy, physiology, macromolecules, and genome.

The same principles apply to the topic of this special issue: the prefrontal cortex (PFC). In this paper, we discuss features of PFC organization that appear to be widely shared among mammals, along with evidence that primates possess a set of PFC areas that most or all other mammals lack: namely, the granular PFC, the part of the PFC that dominates the human frontal lobe.

SOME EVOLUTIONARY FUNDAMENTALS

In order to reconstruct the evolution of the PFC, we need an accurate picture of who is related to whom among mammals. In addition, we need a terminology for designating shared features of brain organization that reflects those relationships.

Who's related to whom?

Prior to the development of efficient DNA sequencing techniques in the 1990s [8], accounts of the relationships of mammals came mainly from anatomy and have been fraught with uncertainties. For example, at one time bats and certain insectivores were thought to be closely related to primates [9], a view no longer supported [10]. Those inadequacies not only obscured our understanding of which mammals are most closely related to primates but also how primate brains differ from those of our closest relatives. With the newfound ability to sequence large blocks of DNA, the relationship of primates to other mammals have largely been resolved (Fig. 1). Now, we can be confident that the closest relatives of primates are tree shrews and colugos (flying lemurs), although which of those two groups is most closely related to primates remains uncertain, and they could be equally closely related [11, 12]. Together with primates, these animals constitute a group called Euarchonta. Molecular phylogenies also show that rodents are closely related to rabbits (settling another long-running debate), and together this group, called Glires, is the lineage most closely related to Euarchonta. Euarchonta and Glires constitute an even higher-order group, the Euarchontoglires (Fig. 1). And so it goes, with increasingly distantly related branches coalescing in deeper and deeper nodes of the evolutionary tree.

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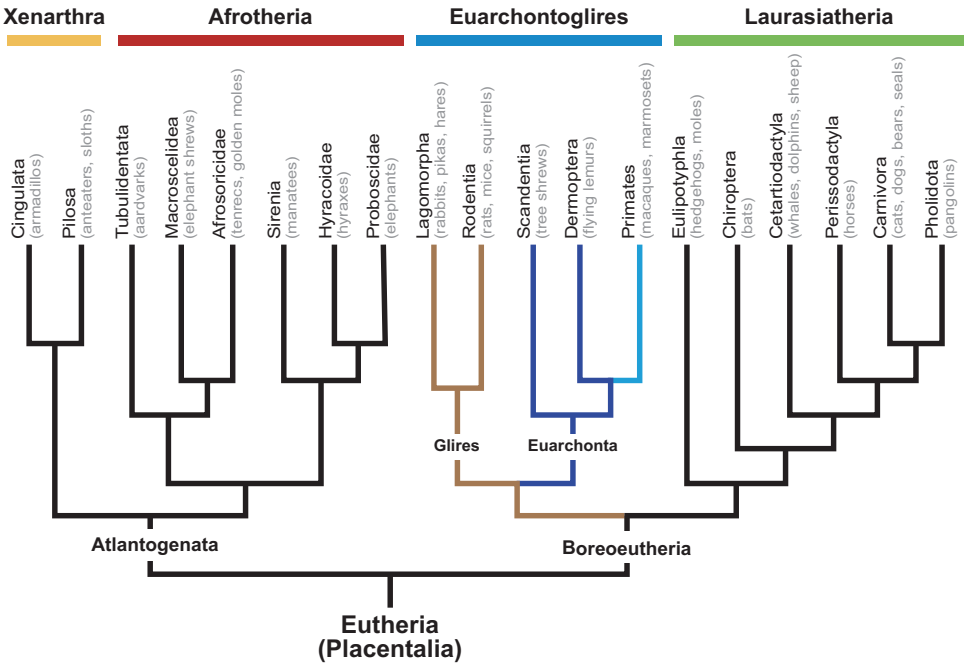

Fig. 1 A phylogenetic tree of placental mammals, based on molecular phylogenomics. The best-established supraordinal clades are labeled at the top. Adapted from Murphy et al. [12, 327].

Homology and analogy

Among the most important concepts in biology are homology and analogy, which provide the framework for understanding similarities and differences among organisms [13, 14]. The concept of homology refers to the "same" feature of an organism present in different species, where sameness implies descent from a common ancestor. A feature can be anything a lineage reproduces across generations. While homology suggests that a feature present in two species shares some attributes, it does not require that they be identical in all respects or even that they have a high degree of similarity. Analogy, in common English, refers to similarity, but in biology it indicates a particular kind of similarity, one that results from independent evolution (also known as convergent or parallel evolution), the feature in question having not been present in the common ancestor of the taxa involved. Because homology and analogy are defined in terms of their relationship to ancestry, they are mutually exclusive. Neuroscientists have sometimes been reluctant to use the term "homology" when comparing the cortex of different species, even when it is clear from the context that they are making a claim of homology, as that concept is currently understood. Even worse, they may imply homology by applying the same term to regions that are similar in some respects, although the balance of evidence indicates they are likely not homologous. For example, we believe the evidence adduced in this review indicates that rodents possess homologs of the agranular medial frontal (MF) and agranular orbital areas of primates but lack homologs of the granular cortex that makes up the largest part of PFC in most primate species. To label the rodent agranular areas as "PFC" and to generalize results in rodents to primates (including humans) without reference to both rodent–primate homologs and primate specializations can only create confusion.

Recognizing homologs and analogs is thus every bit as important in neuroscience as in other branches of biology, and there are some compelling examples. We have good reasons to conclude that all mammals possess homologs of the primary visual (V1), auditory (A1), and somatosensory (S1) areas [15, 16]. For one, in all mammals studied, they occur in the same relative locations within the cerebral cortex: V1 at the posterior end of the cortex; A1 laterally; and S1 anteriorly. For another, in all mammals studied, V1 receives inputs from the retina via the thalamus; A1 gets inputs from the cochlea via a different thalamic nucleus; and S1 has thalamic inputs that relay signals from cutaneous mechanoreceptors. While the location of an area within the cortical mantle and its connections with the thalamus are commonly employed as indicators of homology for cortical areas, any feature is grist for the mill: other features of connectivity, topographic organization (especially for the sensorimotor areas), architectonics (cyto-, myelo-, and chemoarchitecture), neurophysiological properties, behavioral functions, and so forth. In comparative anatomy, the location of a structure within the body plan has long been considered a critical clue to homology, on the assumption that bodypart locations tend to be stable in evolution. Functions, by contrast, can be quite changeable: for example, homologs of Broca's and Wernicke's areas exist in nonhuman primates [17], but only humans have language.

Comparative cortical neuroscience is not all about homology. Convergent evolution is also important. For example, primates and carnivores both possess a large number of extrastriate visual areas [18], and in cats and at least some other carnivores, area V1 includes prominent "blobs" in their upper layers, similar in their enrichment with cytochrome oxidase and certain features of connectivity to those of primates [19]. Because mammals more closely related to primates than carnivores, specifically rodents and tree shrews (Fig. 1), lack these features, we can be confident they evolved convergently, and are thus analogous [19, 20].

Identifying homologous cortical areas or regions in different mammalian groups is complicated by the fact that the number of areas differs across mammals [15, 21]. Moreover, areas that are located in close proximity to each other often share many features, especially of connectivity and function, such as the multiple extrastriate visual areas of primates. It is not enough, then, to simply identify a set of similarities between areas to declare them homologous. Rather, we need to identify sets of diagnostic features that distinguish areas from each other.

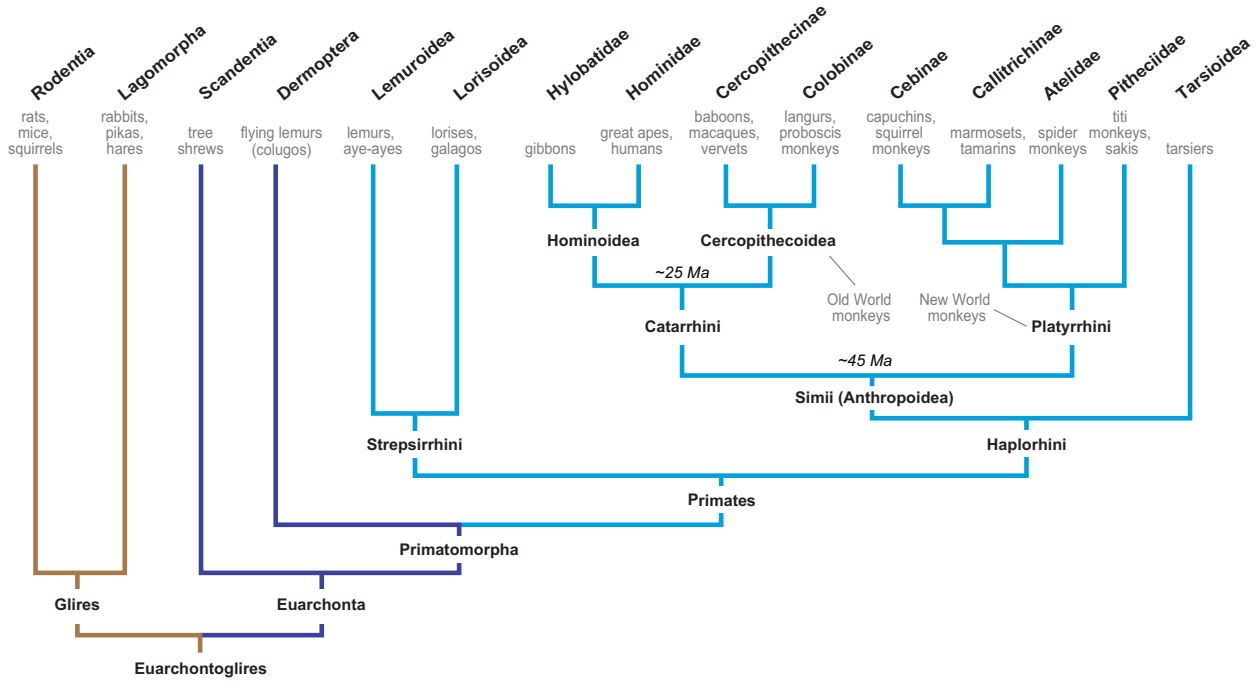

Fig. 2 Relationships among Euarchontoglires [12, 28]. Estimated times for the catarrhine–platyrrhine and the hominoid–cercopithecoid divergences appear in italics. Ma million years ago.

Scale thinking versus tree thinking

Today, the accepted metaphor for evolution is, for most purposes, a branching tree, not a phylogenetic scale [13, 14, 22–24]. While one sometimes still hears neuroscientists speak of primates as "higher mammals" and rodents as "lower mammals," you are unlikely to hear that from an evolutionary biologist. To reject the older metaphor of the phylogenetic scale is not to deny that primates evolved distinctive specializations, but rather to acknowledge that primates, rodents, and other mammalian orders each evolved distinctive features since their divergence in the Mesozoic Era (Fig. 1) [12]. The turn to tree thinking also applies to the Order Primates. In the past, primate evolution was commonly seen as an ascending scale, with tree shrews (which are no longer considered primates) at the bottom, then progressing through a ranked series of lemurs, tarsiers, monkeys, and apes, culminating in the highest rank: humans [25, 26]. Modern views of primate evolution emphasize diversification rather than ascent, with hundreds of species organized in multiple, nested lineages [27, 28]. Figure 2 presents an evolutionary tree of primates in the context of other Euarchontoglires.

What, if anything, is a monkey?

This change in perspective has important consequences for how neuroscientists should think about primates. For example, one thing that is clear from Fig. 2 is that there is no such thing as "the monkey" from an evolutionary viewpoint. A "thing" from that perspective is a monophyletic group, also known as a natural group or a clade. A monophyletic group comprises the complete set of species that descended from a common ancestor and only those species [13, 22].

New World and Old World monkeys are not a natural group, but rather two distinct lineages that are not even each others' closest relatives. The closest relatives of the Old World monkeys (the Cercopithecoidea) are members of the ape–human clade (the Hominoidea). Collectively, these two groups compose the Catarrhini. The closest relatives, collectively, of the Catarrhini are the New World monkeys (the Platyrrhini). Thus, references to "the monkey" are problematic; it is important to specify which monkeys are under consideration. Similarly, the term "prosimian"—consisting of lemurs, bushbabies, and tarsiers—does not refer to a natural group because the descendants of their last common ancestor include the simians (the catarrhines and platyrrhines), which are not prosimians. Because tarsiers are more closely related to simians than to the lemur–loris–bushbaby group, primates are now usually considered to be comprised of two main clades, the Strepsirrhini (lemurs, lorises, and bushbabies) and the Haplorhini (tarsiers plus simians) (Fig. 2).

If "the monkey" is problematic, references to "the primate" are even more so, unless it is clear from the context exactly which of the myriad primate species are under discussion (Figs. 1 and 2). Brain organization varies among primates, so it is dangerous to assume that what is true of one primate species is true of all. Similar considerations apply to "the mammal" and "the rodent." However, given that most rodent studies are carried out in rats and mice, we will use "rodent" as convenient shorthand for those taxa. A somewhat wider array of primates has been studied, so we will usually specify from which primate data were obtained.

Although it is desirable to obtain data from a broad range of species when reconstructing evolutionary change, the general paucity of species studied by neuroscientists means that analyses of brain structures usually depend on a regrettably small number of species (e.g., [1, 2, 6, 19, 29–32]). Even in primates, almost all our information about the frontal cortex of strepsirrhines comes from studies of bushbabies (also known as galagos), and then from just two species of the genus *Otolemur*. (These two species were formerly classified as members of the genus *Galago* but are now recognized as a separate genus in the galagid family, all of which are termed "galagos.") Similarly, almost all our knowledge of Old World monkeys comes from studies of rhesus macaques (*Macaca mulatta*) and a few other macaque species.

CORTICAL ORGANIZATION

Having established the evolutionary rules of the road, we now turn to the organization and evolution of cerebral cortex, with emphasis on the frontal cortex. As has long been understood, the

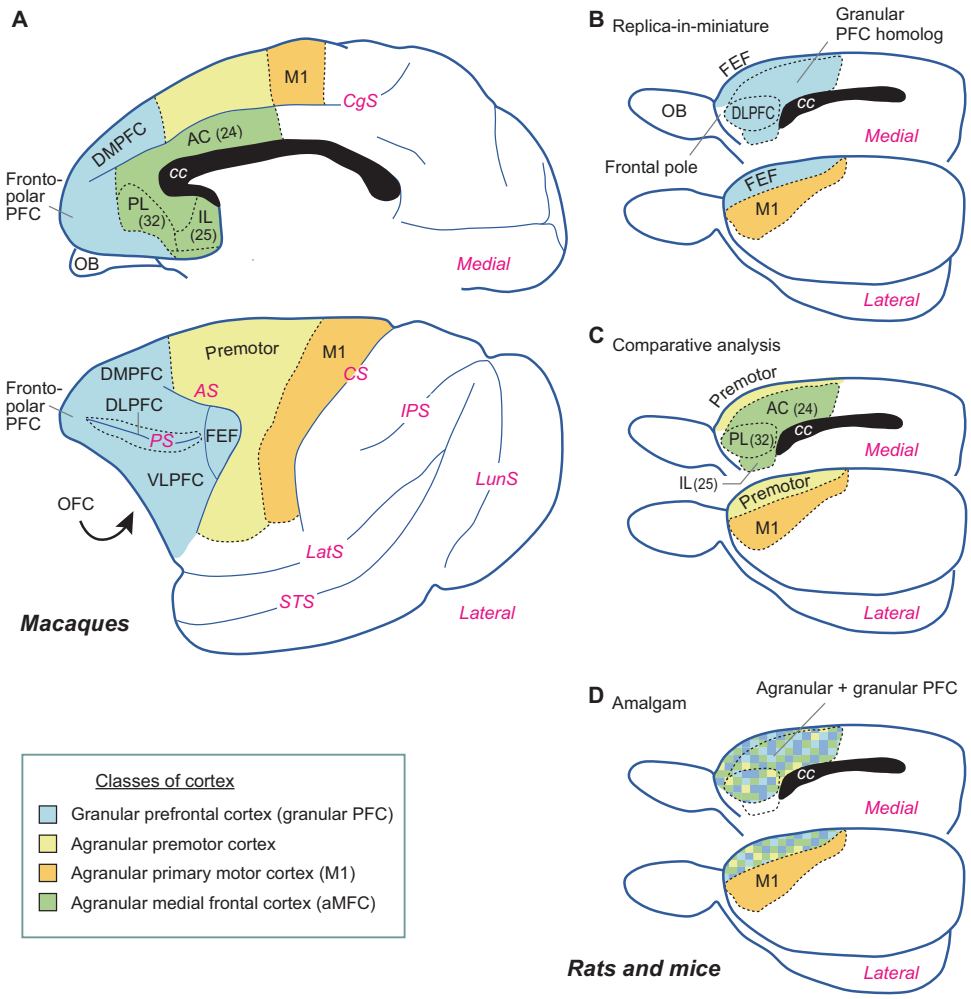

Fig. 3 Proposed homologies among frontal areas in primates and rodents. Areas shaded with the same color have been advanced as homologs. **A** Macaque brains serve as representative simians for comparison with rodents. The curved arrow indicates the location of OFC on the hidden, ventral surface of the macaque frontal lobe. **B** An example of the idea that rodents have some or all of the granular PFC areas observed in simians, albeit in miniature form. **C** The view advocated here, which is based on comparative neuroanatomy. **D** The amalgam theory, in which alternating colored voxels indicate the intermixing of areas. AC anterior cingulate cortex (area 24 in primates), aMFC agranular medial frontal cortex, AS arcuate sulcus, cc corpus callosum, CgS cingulate sulcus, CS central sulcus, DLPFC dorsolateral PFC (also known as the periprincipal PFC), DMPFC dorsomedial PFC, FEF frontal eye field, IL infralimbic cortex (area 25 in primates), IPS intraparietal sulcus, LatS lateral sulcus, LunS lunate sulcus, M1 primary motor cortex, OB olfactory bulb, PFC prefrontal cortex, OFC orbitofrontal cortex, VLPFC ventrolateral PFC, PL prelimbic cortex (area 32 in primates), PS principal sulcus, STS superior temporal sulcus. Adapted from Preuss and Robert [6].

gray matter of the cortex is a mantle or sheet of tissue, however much it might be folded in large-brained mammals. The central region (or core) of the sheet is occupied by isocortex, which contains most of the sensorimotor and association areas. The isocortex is surrounded by three rings of cortex [33–36]. The outermost ring, which forms the rim of the cortical mantle, is the three-layered cortex called allocortex. This consists of the hippocampus and the primary olfactory (piriform) cortex, along with some smaller olfactory structures. It develops in a different way than the isocortex and the other rings, all of which emerge in an "inside-out" manner, meaning that neurons born earlier take positions in the deeper layers.

Two additional rings of cortical tissue lie between the core isocortex and the allocortex: the periallocortex and proisocortex (sometimes collectively referred to as "mesocortex"). The periallocortex, which borders the allocortex, includes the entorhinal cortex, subiculum, para- and presubiculum, part of the insular cortex, and, in the frontal lobe, the posterior-most orbital cortex, contiguous with the insular cortex. The frontal proisocortex, which is sandwiched between the core isocortex and the periallocortex, is comprised of the agranular MF cortex (aMFC), consisting of area 24 (the anterior cingulate area, AC), area 32 (the prelimbic area, PL), and area 25 (the infralimbic area, IL), as well as parts of the orbital and insular cortex adjacent to isocortex. The aMFC corresponds to the anterior part of Brodmann's cingulate region. Primates, but not rodents, have subdivisions of area 32 that are dysgranular as well as agranular [37], but it is convenient to refer to this cingulate region collectively as aMFC. Similarly, primate orbitofrontal cortex (OFC) is a component of the PFC that includes posterior agranular and dysgranular components, as well as anterior, granular divisions, whereas rodent OFC is exclusively agranular. Posterior proisocortex includes the retrosplenial and parahippocampal cortex. Histologically, many of the proisocortical areas resemble isocortex, but may lack one or more layers characteristic of it.

The three rings surrounding the isocortex—proisocortex, periallocortex, and allocortex—have long been considered parts of the limbic system, owing not only to their location along the margin (limbus) of the cortical mantle but also to their close functional relationship with the autonomic nervous system [38–46]. The

distinction between isocortex and proisocortex, in particular, is significant for understanding homologies relevant to PFC evolution, because agranular parts of the orbital and MF cortex, much of which is proisocortex, are usually (but not always) classified as part of the PFC. This inconsistency raises a deceptively simple question: What is the PFC?

WHAT IS THE PFC?

Historical perspective

For the past 60–70 years, neuroscientists have commonly defined the PFC as the cortical territory targeted by projections from the mediodorsal nucleus (MD) of the thalamus [47, 48]. Brodmann [49] recognized a large *Regio frontalis* in multiple primate species, including areas occupying the anterior-most lateral, dorsal, medial, and orbital surfaces of the hemisphere. This region became known as the "PFC," "granular frontal cortex," "frontal association cortex," or some variant of those terms. We will call it the granular PFC. Brodmann indicated it consists of isocortex with a "compact inner granular layer" (layer 4). In fact, this is not true for the entirety of his frontal region, because layer 4 granule cells progressively diminish from anterior to posterior in the OFC, which thus consists of granular, dysgranular, and agranular territories [50–55], and only the granular areas are definitely isocortical. Brodmann also concluded that carnivores and ungulates have a single, small region of granular PFC, whereas rodents and rabbits have none.

Brodmann's conclusions have been controversial because they imply that the granular PFC, and presumably the higher-level cognitive functions it supports, is absent in the most widely used neuroscience models: rodents. By the middle of the 20th century, however, it seemed difficult to reconcile Brodmann's views with evidence about thalamocortical connectivity. Based on studies of retrograde degeneration in the thalamus following cortical lesions, anatomists generated a parcellation of the cortex based on its thalamic afferents (e.g., [56–58]), illustrations of which can still be seen in modern neuroanatomy textbooks. According to this schema, MD projects to the granular PFC, whereas other parts of the frontal lobe receive projections from other nuclei—the cingulate gyrus (including the aMFC) from the anterior thalamic nuclei, and the primary and nonprimary motor areas from the ventral tier nuclei.

On the assumption that MD projections are diagnostic of the granular PFC in primates, and the fact that MD is a readily identifiable in all the commonly studied mammalian brains, a solution to Brodmann's dilemma presented itself: to identify the granular PFC homolog in nonprimate mammals, even if it is not granular, one need but find the MD-projection cortex. Rose and Woolsey pursued this approach in their lesion-degeneration studies of sheep (cetartiodactyls) and cats (carnivores) [59], and in both, the MD-projection cortex was localized to anterior parts of the frontal lobe. They concluded: "… a cortical field equivalent to the frontal granular cortex of primates is present in all the animals studied." Subsequently, Akert [60] went further, proposing homologs in cats of the primate OFC, dorsolateral PFC (DLPFC), and the frontal eye field (FEF; granular area 8), based on the medial-to-lateral distribution of degeneration in MD after cortical lesions, which matches the topography of connections between MD and the granular PFC in nonhuman primates.

One vexing problem remained: where is the MD-projection cortex in rodents? Definitive resolution of this issue awaited the development of improved axonal fiber-tracing techniques—first, stains to identify anterogradely degenerating fibers, then injectable tracers. In 1969, in studies of rats, Leonard reported tracing fibers to the orbital cortex along the anterior end of the rhinal sulcus after lesions of the medial-most MD, to the medial wall of the hemisphere superior and anterior to the genu of the corpus callosum after lesions more laterally in MD, and dorsomedially, along the "shoulder" of the hemisphere (where the medial and lateral surfaces meet) after lesions of the lateral-most MD ([61–63], see also [64, 65]). Subsequent studies using injectable tracers in rats confirmed the existence of reciprocal connections between MD and the sulcal cortex (i.e., the agranular orbito-insular cortex) and the aMFC, as well as the "shoulder" cortex, although it is significant for claims about homology that they also revealed reciprocal connections with the anterior thalamic nuclei, as well as the ventral, intralaminar, and midline thalamic nuclei [66–81]. Research in other rodents [82–84] and in rabbits [68, 85] yielded similar results.

Leonard's [61] initial interpretation of homologies was similar to that of Akert [60], as illustrated in Fig. 3B. On that view, rat orbital cortex corresponds to the most posterior parts of primate OFC and the shoulder cortex to the primate FEF. As for the cortex of the medial wall (the aMFC), Leonard argued, "tentatively and largely by exclusion," for homology with the granular PFC in primates. Interestingly, Leonard explicitly acknowledged that while the granular PFC in primates is isocortical, rat aMFC is a "primitive, relatively undifferentiated type of cortex"—that is, *not* isocortex [61]. Although they did not address the histological classification of the aMFC, Krettek and Price [86] reached a similar conclusion, stating: "… the functional significance of the cortical areas rostral to the level of the genu of the corpus callosum in the rat should be considered in terms of their relationship with the MD nucleus and their possible correspondence to PFC of primates rather than on their traditional association with the cingulate gyrus, which was based largely on topographical considerations."

Collectively, these studies were instrumental in establishing the idea that rodents possess cortical fields corresponding to those that comprise primate PFC including, significantly, the granular PFC [87–90]. Typically, the proposed homolog or counterpart of the primate granular PFC is localized mainly to the rat's aMFC (areas 24, 32, and 25). That raises a serious problem, however: if the aMFC of rodents is homologous to primate granular PFC, then where is the rodent homolog of primate aMFC?

Comparing the PFC in primates and rodents

At the same time that new fiber-tracing techniques were being employed in rodents, they were also being applied in primates. The results threw a monkey wrench, as it were, into the revised interpretation of rodent frontal cortex (reviewed by Preuss [48]; see also [91–93]).

These studies in Old World macaques, New World owl monkeys and marmosets, and strepsirrhine galagos confirmed some of the results of the older lesion-degeneration studies in macaques and humans, specifically that nucleus MD projects to the dorsal, lateral, and medial granular PFC and to the OFC. Significantly, however, they also demonstrated that MD connections reach a much greater expanse of cortex than Brodmann's *Regio frontalis*, including the aMFC (areas 24, 32, and 25), the agranular insula, and the temporal pole [55, 94–102]. MD also projects to primary and premotor areas (e.g., [96, 97, 103–106]), although these are not as numerous as the projections from the ventral nuclei. There are also weak connections with parahippocampal cortex and temporal and parietal isocortex, and possibly the posterior insular cortex, although these may be mainly corticothalamic projections only [107–114]. Moreover, primate PFC, including granular PFC, agranular MFC, and agranular OFC, is connected not only with MD but also with additional thalamic nuclei including the anterior, ventral, midline, intralaminar, and medial pulvinar nuclei (see the citations earlier in this paragraph, plus [115–118]), although not every part of PFC is connected with all these nuclei.

These findings show that MD projects to areas outside the PFC, and they highlight two problems. First, to sustain a practical definition of the primate PFC in terms of MD projections, one would have to restrict the PFC to those regions that receive a majority or plurality of their thalamic inputs from MD, which would likely yield something corresponding closely to

Brodmann's *Regio frontalis*, with the addition of agranular insular cortex. But quantification of axons or terminals in the requisite way remains more aspirational than practical. An alternative, simpler approach would be to define PFC as all the frontal cortex exclusive of motor and premotor cortex [91]. Other definitions have been suggested, such as the cortical territory with MD projections plus certain additional attributes (e.g., [119–121]). A recent data-driven approach in mice based on thalamic and cortical connectivity yielded a PFC "module" consisting of the agranular OFC and aMFC [122, 123]. Second, if primate PFC includes both the granular PFC and the aMFC, then the idea that the rodent aMFC is homologous to the former rather than the latter, as illustrated in Fig. 3B, is severely challenged.

There is additional evidence undermining claims of homology of the rodent aMFC with the primate granular PFC but supporting its homology with the primate aMFC. For one thing, primate aMFC and rodent aMFC share the same location in the cortical mantle: on the medial wall superior, anterior, and ventral to the genu of the corpus callosum. Both consist of agranular proisocortex. Both receive projections from nucleus MD, and detailed analysis of the topography of MD projections to aMFC cortex in rats and macaques highlights their similarity [124, 125]. Significantly, both have connections with the anterior thalamic nuclei—classically regarded as the hallmark of the aMFC. Moreover, both have efferent projections to nucleus accumbens, hypothalamus, and periaqueductal gray, reciprocal connections with the amygdala, and inputs from the hippocampus [43, 45, 94, 102, 126–135], indicating that they are elements of the limbic system. The homology of these rodent and primate regions is now commonly acknowledged (e.g., [37, 43, 44, 47, 91, 131, 132, 136–140]).

If the rodent aMFC is homologous to the primate aMFC (Fig. 3C), and the rodent sulcal cortex to the caudal-most, agranular parts of the primate OFC (the latter not being disputed), then there simply is no good candidate for a granular PFC homolog in rodents. Evidence for such a homolog would require the identification of features that are: (1) characteristic of both the granular PFC of primates and its proposed homolog in rodents and (2) absent from the aMFC or agranular OFC of primates. MD projections are not diagnostic of granular PFC because they fail this test and because, as explained above, they also target areas outside of the PFC by any definition. Other similarities between granular PFC and rodent aMFC have been cited, notably the existence of strong projections from dopaminergic neurons [71], and involvement in spatial-delay tasks, such as the delayed alternation task (e.g., [87, 88, 141, 142]), the latter being typified by a delay period prior to a choice between two spatial locations. Neither of these is diagnostic of the primate granular PFC, either. The aMFC and OFC of primates receive dense dopaminergic innervation, as do some (but not all) of the granular PFC areas [143–151]. However, the primary motor and premotor areas are also strongly innervated by dopaminergic neurons in macaques and humans, but not in rats [152]. Likewise, although lesions of the periprincipal region of granular PFC (the cortex within and surrounding the principal sulcus) produce impairments on spatial-delay tasks in macaques, modest impairments also follow lesions of the aMFC in macaques [153, 154]. There is also evidence of delay-period single-neuron activity [155, 156] and functional-imaging activations [157] in the macaque aMFC during performance of these tasks. In humans, a distributed network of areas that includes the aMFC and the DLPFC is involved in spatial-delay tasks [158]. Thus, spatial-delay-period activity and lesion effects are not diagnostic of the periprincipal PFC. What is more, if the analysis of area homologies presented below is correct, homologs of periprincipal cortex are not even present in all primates, being a specialization of simians.

Studies of corticostriatal projections provide additional support for the conclusion that rodents and primates share homologs of the agranular OFC and MFC areas, and that rodents lack a homolog of the granular PFC. Using conventional tract-tracing techniques to compare rats and macaques, Heilbronner et al. [137] found that projections from the aMFC and OFC of rats and macaques occupy topographically corresponding domains within the striatum. Using resting-state functional magnetic resonance imaging (MRI) signals in mice, macaques, and humans, Balsters et al. [159] examined signal covariance that depended on corticostriatal projections. They then analyzed the total pattern of corticostriatal projections from each voxel of the imaged brains, creating a "connectional fingerprint" for different areas. Balsters et al. concluded that anterior parts of the granular PFC in macaques and humans have no counterparts in mouse brains.

There is also the matter of rodent shoulder cortex and the proposal that it is homologous to the primate FEF, as depicted in Fig. 3B. Support for this idea came from reports that eye movements can be evoked from this area with intracortical microstimulation [160–162]. More recent results, however, suggest that this region represents movements of the vibrissae [161, 163–168] and may be part of M1 [166, 168]. In addition, there is evidence that in rodents, eye movements are represented in the aMFC rather than in the shoulder cortex [163]. Notably, there is evidence for an oculomotor representation in the macaque aMFC [169] as well as in multiple premotor areas of macaques and other simians, in addition to the arcuate FEF [169–173]. Thus, an oculomotor representation is not diagnostic of the FEF or any other part of granular PFC.

Figure 3D illustrates another idea about homologies, which is that the rodent aMFC, and perhaps the "shoulder" cortex, contain an amalgam of the aMFC and granular PFC areas of primates [62, 174]. This idea attempts to resolve the problem of the missing aMFC in rodents by positing that the granular PFC and aMFC are undifferentiated, and the region in question mixes their features. The proposal has little to recommend it, as rodent aMFC does not appear to have properties of the primate granular PFC that are not also properties of primate aMFC, such as afferents from the anterior thalamic nucleus and involvement in spatial-delay tasks. If the granular PFC is a primate specialization, moreover, we should expect it to have properties that rodents and other mammals lack. There are indeed such properties, both structural and functional.

Perhaps the most important primate specialization from a comparative perspective is the system of connections of the granular PFC. This is best understood in the broader context of primate cortical organization. All primates that have been examined possess regions that correspond to the classical higher-order association territories: the granular PFC, the posterior parietal cortex, and large portions of the temporal cortex. Each of these regions includes multiple areas, and those areas are linked in multiple transcortical networks, which are themselves linked with limbic cortical areas (e.g., [102, 175–182]). No other mammal studied to date has a comparable system of transcortical networks. Moreover, in macaques and marmosets, in which the connections have been studied adequately, these association and limbic areas receive inputs from the medial pulvinar [101, 112, 115, 117, 183–188], a thalamic nucleus present in all primates studied that has no apparent homolog in nonprimate mammals ([189, 190], and see [191]). Thus, the granular PFC is part of a larger system of association areas with features unique to primates among mammals that have been studied.

The granular PFC also has functional properties that the aMFC lacks. Although involvement in spatial-delay tasks per se is not diagnostic of the periprincipal granular PFC, aMFC lesions in rats do result in mild and temporary impairments on such tasks. However, these effects contrast with the severe and permanent effects seen after lesions of the periprincipal cortex in macaques (reviewed in [48, 92]). In addition, macaque granular PFC neurons encode associations between acoustic stimuli and abstract behavior-guiding rules [192] and between color–shape stimuli and abstract problem-solving strategies [193], some of which

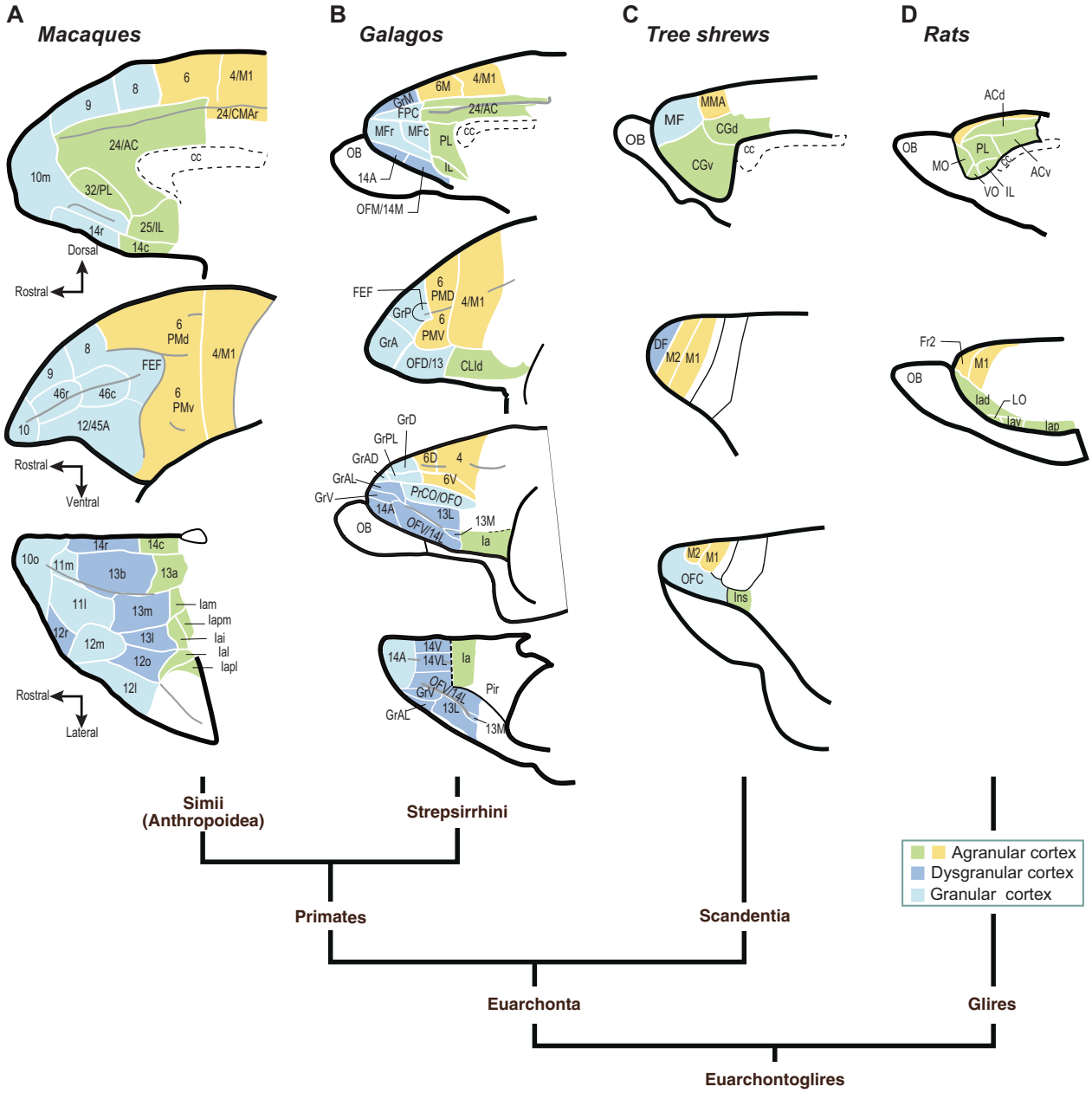

Fig. 4 Types of cortical areas in the frontal cortex of Euarchontoglires. A Macaques (*Macaca*) as representative simians. Adapted from Carmichael and Price [328]. **B** Galagos (*Otolemur*) as representative strepsirrhines. This is an amalgamation of the interpretations of Preuss and Goldman-Rakic [203] and Wong and Kaas [205]. **C** Tree shrews (*Tupaia*) as representative non-primate Euarchontans. Adapted from Wong and Kaas [198]. **D** Rats (*Rattus*) as representative Glires. Adapted from Palomero-Gallagher and Zilles [329]. Labeling has been retained from the originals to the extent possible. a or A anterior or a subdivision of an area (versus b or B), AC anterior cingulate cortex, c caudal, cc corpus callosum, CG cingulate-gyrus cortex, CLI claustral isocortex, CMA cingulate motor area, d or D dorsal, DF dorsal frontal area, FPC frontopolar cortex, Fr2 second frontal area, also known as the medial agranular area, Gr granular, i inferior, Ia agranular insular cortex, IL infralimbic cortex, Ins insular cortex, l or L lateral, LO lateral orbitofrontal cortex, m or M medial, M1 primary motor cortex, M2, in this case, another part of M1 or a premotor area (not homologous with M2 in simians or rodents, which, in turn, are not homologous with each other), MF medial frontal area, MMA medial motor area, MO medial orbitofrontal cortex, o or O orbital, OB olfactory bulb, OF orbitofrontal cortex, OFO opercular orbitofrontal cortex, p posterior, Pir piriform cortex, PL prelimbic cortex, PM premotor cortex, PrCO opercular proisocortex, r rostral, v or V ventral, VO ventral orbitofrontal cortex.

correlate with correct or incorrect task performance [194]. No evidence for such properties has been reported for the aMFC of rodents. Furthermore, lesions of specific parts of the granular PFC in macaques cause profound impairments in rapid learning of arbitrary associations between color–shape stimuli and behavioral goals [195], whereas lesions of the aMFC cause no impairment in rats performing a similar task [196], and even facilitate early stages of learning these associations [197].

Recall that the original intention of the Rose–Woolsey–Akert project was to identify homologs of the primate granular PFC in nonprimate mammals [48]. While studies in rodents initially seemed to indicate that their aMFC (Fig. 3B) filled that role, the balance of evidence indicates that this part of the rodent cortex is homologous to the aMFC of primates (Fig. 3A, C), and that those animals lack a homolog of the primate granular PFC (Figs. 3C and 4). Indeed, the effect of defining the PFC as MD-projection cortex

has not been so much to find the rodent PFC [63], as was the original intent, as to rebrand the aMFC as part of the PFC [6]. We see nothing inherently wrong with including the rodent aMFC and the agranular OFC or orbito-insular cortex in the PFC, as long as the correct homologies among PFC regions are recognized [6, 48, 91]. In our view, however, attempts to interpret data from rodent aMFC or agranular OFC based on homology or similarity to the granular PFC of humans or nonhuman primates are unwarranted.

Comparing the PFC of primates and tree shrews

Although it now seems likely that the granular PFC is absent in rodents, rodents are not the mammals most closely related to primates, and it is possible that some or all the areas and attributes found in the primate granular PFC are present in mammals that are more closely related to primates, specifically, in colugos ("flying lemurs") and/or tree shrews (Fig. 2). Colugos have rarely been studied. In tree shrews, however, there is a small area, labeled DF (dorsal frontal cortex) in Fig. 4C, that is perhaps best described as dysgranular based on Wong and Kaas [198]. However, they describe both an anterior part of the OFC and a medial frontal area (MF) as having a "well-developed layer 4." It is unknown whether either MF or DF is homologous with parts of the granular PFC in primates. More likely is the possibility that the granular OFC of tree shrews is homologous with small parts of the granular OFC in galagos and macaques. These proposed homologies, however, lack support from data about connectivity and other attributes. The connections of tree shew areas DF and MF are also largely unknown, but we know something about connections they do not have. In contrast to the parietal visual areas of galagos, macaques, and humans, which have extensive interconnections with dorsolateral and dorsomedial PFC (DLPFC and DMPFC in Fig. 3A), the visual areas of tree shrews confine their projections to motor areas [199]. This suggests that the network connecting posterior parietal and granular prefrontal areas, which is such a prominent feature of primate cortical organization, is absent in tree shrews.

Changes in shared mammalian areas

In focusing on the frontal cortex at the level of its broad regional organization, we have perhaps created the impression that the evolution of primate PFC simply involves the addition of the granular PFC to the aMFC and agranular OFC of rodents and other mammals. Evolution is not that boring: within the aMFC, macaques and humans appear to have more subdivisions of area 24 than do rodents, and there are differences in the connectivity, functions, and receptor distribution of rodents and primates in the areas they share (e.g., [37, 43, 140, 152]). There are also differences in the aMFC among rodent species (e.g., [37, 200]) and among primates, as discussed below.

PFC IN PRIMATE EVOLUTION

Primates are a diverse group of mammals and understanding how the PFC evolved requires acknowledging that diversity. Comparative neuroanatomy indicates that much of the action in primate PFC evolution involved the granular PFC.

Shared primate areas

All modern primates share certain granular PFC areas, while additional areas evolved later, during simian evolution. Comparing galago (strepsirrhines) and New World and Old World simians indicates that these animals share at least two parts of the granular PFC: a region located posteriorly, adjacent to the premotor cortex along the anterior bank of the arcuate sulcus in macaques, that includes the FEF (part of area 8 of macaques), and a region that includes the granular, and possibly dysgranular, components of the OFC.

The evidence for homologous FEFs in strepsirrhine and simian primates is very strong (for strepsirrhines (galagos), see, e.g., [97, 180, 181, 201–206]; for platyrrhines: [173, 207–217]; for catarrhine monkeys: [209, 212, 218–225]; and for apes and humans, see [226]). The area in question is located on the lateral surface immediately anterior to the junction of the dorsal and ventral premotor areas, and it is a strongly myelinated isocortical field, has major connections with the most lateral part of nucleus MD and with visual areas of both the dorsal and ventral streams, and projects to the superficial and intermediate layers of the superior colliculus. Intracortical microstimulation of this region with very low currents elicits eye movements, although as mentioned earlier, eye movements are represented in the premotor cortex and aMFC, as well.

What of the possibility that the FEF evolved prior to the divergence of primates and their euarchontan relatives? Two comprehensive mapping studies of the frontal cortex in tree shrews failed to find any evidence for an FEF [227, 228]. It is possible that FEF was present in an ancestral lineage but lost secondarily in tree shrews, although this seems unlikely because these animals have a very well-developed visual system [229].

The OFC has been well-studied only in simians, but the architectonics and corticocortical connections of this region in galagos closely resemble those of simians [180, 181, 203, 205, 230]. In platyrrhines and catarrhines, the OFC has direct connections with the agranular insular cortex, which represents conjunctions of olfactory, gustatory, somatosensory, and visceral inputs. In addition, the OFC is interconnected with the aMFC and lateral granular PFC, with the temporopolar cortex, and with components of the ventral visual stream, including both inferior temporal cortex and the perirhinal cortex [52, 231–238]. The OFC also projects to the nucleus accumbens, ventral striatum, and hypothalamus, and has reciprocal connections with the amygdala [102, 126, 127, 239–248].

Simian-specific areas

Comparison of galago and simian brains (Fig. 4A, B) reveals that the granular PFC of the latter possesses a number of additional areas, located mainly anterior to the FEF. Some of these areas are less heavily myelinated than are the granular PFC areas shared by galagos and simians, such as the FEF [203, 208, 236, 249]. Figure 4A, B depicts cytoarchitectonics by different shading, as indicated by the key. Based on these observations, and features of corticocortical connectivity, Preuss and Goldman-Rakic [48, 180, 203] concluded that most, if not all, of these more anterior granular PFC areas evolved in haplorhines or simians after their divergence from strepsirrhines. Unfortunately, there is little information about tarsiers, although their frontal lobes are tiny and appear to have little cortex anterior to the precentral region [250, 251], which suggests that the additional areas evolved in simians. The presumably simian-specific areas correspond to the DLPFC (Fig. 3A; also known as the periprincipal cortex and as areas 46 and 9/46 in macaques), ventrolateral PFC (areas 12 and 45, along with area 47 in some species), DMPFC (area 9), and (with somewhat less confidence) frontopolar PFC (area 10).

To summarize the comparative evidence, the FEF appears to be an evolutionary innovation of primates, while most of the anterior, lateral, and medial components of the granular PFC—including the periprincipal cortex—are innovations of simian primates. Most of the granular, and probably dysgranular, OFC is also a primate specialization, although a small part might predate the divergence of tree shrews and primates.

Diversity among simians

Comparative studies of differences in relative brain size (or encephalization—i.e., brain volume scaled for body mass) reveal that simians almost always have larger brains than strepsirrhines [252–255]. What is more, studies of fossil brain casts reveal that

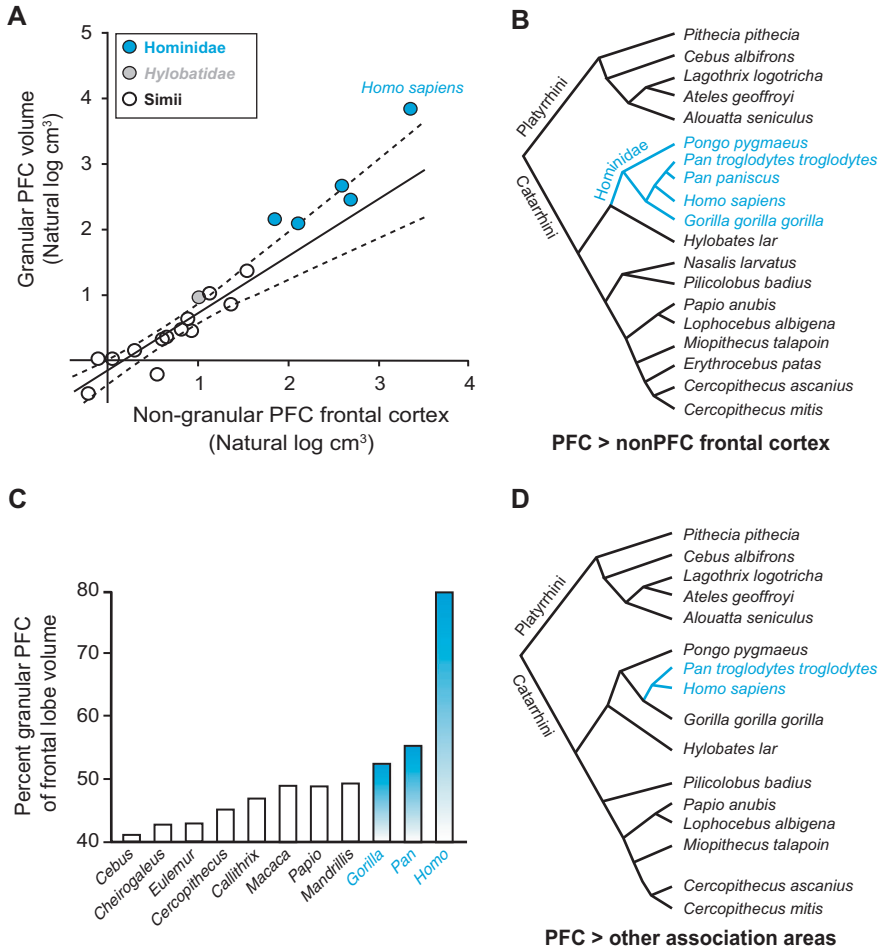

Fig. 5 Enlargement of the granular PFC in human evolution. A Granular PFC size relative to the remainder of the frontal lobe. Solid line: regression; dashed lines: confidence limits. **B** Phylogenetic statistical tests reveal that the increase in hominids (blue) is significant. **C** Percentage of granular PFC within the frontal lobe. **D** Phylogenetic statistics show that the clade including chimpanzees and humans underwent a significantly greater increase in relative granular PFC volume contrasted with other homotypical association areas, namely those in the parietal and temporal lobes. **A**, **B**, **D** Reproduced, with permission (RightsLink license 5035380571023, license date March 24, 2021) from Smaers et al. [282]. **C** Plotted from data in Elston et al. [330]. PFC prefrontal cortex.

relative brain size increased independently in many primate lineages, with early members of the strepsirrhine, platyrrhine, and catarrhine lineages usually having smaller brains (and smaller frontal lobes) than most of their extant counterparts [256–260]. Given these differences, we might expect that those lineages have different complements of granular PFC areas. Alternatively, all the simian-specific parts of the granular PFC could had evolved in the last common ancestor of simians, and subsequently expanded independently in platyrrhines and catarrhines. Unfortunately, we do not have contemporary, high-quality frontal-lobe maps for many of the numerous platyrrhine species to compare to the well-studied macaque frontal lobe, apart from capuchins (*Cebus*) and marmosets (*Callithrix*). The results are interesting, nonetheless, as the large-brained *Cebus* is reported to have a very similar complement of prefrontal areas as macaques [236], which it closely resembles in its convergently acquired sulcal morphology. By contrast, the small-brained marmosets evidently have a somewhat simplified areal organization, especially in the mid-frontal granular PFC (DLPFC), with a relatively small area 46 and possibly fewer subdivisions than *Cebus* or *Macaca* [208, 233].

The New World callitrichid monkeys (marmosets and tamarins) are especially interesting from the standpoint of size. They are the smallest of the platyrrhines, similar in size to the small strepsirrhines, probably as a result of evolutionary dwarfism [261–263]. It is unclear whether callitrichids underwent a corresponding reduction in relative brain size in evolution, but their brains are among the smallest in absolute size of all simians [264]. This is potentially functionally significant, given the evidence that absolute brain size is a better predictor of cognitive ability than relative brain size across primate species [265, 266].

PFC in human evolution

Recent years have seen a surge of new research on human brain evolution (see, e.g., [267–271]). The evolutionary specializations of the human PFC and especially of the granular PFC have received particular attention.

Size. Since at least the time of Brodmann [49, 272], it has commonly been accepted that association cortex, including the granular PFC, underwent enormous expansion in human evolution, both absolutely and relative to the amount of primary sensorimotor cortex. This view has been challenged, however. Based on scaling studies, Barton and colleagues [273, 274] have argued that even though PFC is absolutely much larger in humans than in other primates, humans have the expected amount of PFC for a primate of our brain size. Semendeferi and colleagues [275, 276] have made a similar claim, arguing that the frontal lobe occupies about the same proportion of the cortex in humans as it does in the great apes. So,

those authors would argue that human PFC is not exceptionally large. Other authors, however, have maintained that the data support the traditional view [249, 277–282].

We also support the traditional view, based in part on recent phylogenetic regression analyses (Fig. 5) and studies of cranial endocasts in fossil humans [267]. But one can look at the issue a bit differently [268]. One would never expect a great ape to have a brain as large as ours. In body size, humans overlap the chimpanzees and other African great apes (our closest relatives), but our brains, at about 1450 cc on average, are 3–4 times larger than theirs. One would expect humans to have a brain size similar to that of a chimpanzee (~400 cc). What is the difference? Most human primary sensorimotor areas are only marginally larger than those of chimpanzees, but certain parts of the association cortex—including the dorsolateral, frontopolar, and anterior orbital parts of the granular PFC—are enormously larger [283]. Figure 5A–C shows, for example, that great apes and humans have significantly more granular PFC relative to other components of the frontal lobe. Thus, the increased size of the human brain reflects the nonuniform enlargement of specific cortical areas, especially in the higher-order association cortex. This is the real crux of the matter: humans have far more neural machinery in our granular PFC and in certain other association regions than do great apes or other primates, presumably because natural selection favored enhancement of their functional capacities. Figure 5D indicates that, in humans and chimpanzees, the granular PFC expanded marginally but significantly more than the other association areas.

Areas. If granular PFC areas evolved in the earliest primates from ancestral brains that lacked them, and if additional granular PFC areas evolved in simians, it is reasonable to suppose that the complement of granular PFC areas differs between humans and other simians, given the enormous expansion of this region in human evolution, and the view that the addition of cortical areas is an important correlate or cause of brain-size enlargement and the acquisition of new functions (e.g., [20, 49]). While measuring brain size or cortical extent is seemingly straightforward, comparing complements of cortical areas across species is fraught with difficulties, as meaningful comparisons require the application of a common set of reliable techniques across species. Historically, the most widely used technique has been cytoarchitectonics, which involves microscopic inspection of Nissl-stained sections is now considered inadequate by itself. Today, it is widely accepted that parcellations are better when based on multiple techniques, including architectonics (especially observer-independent, quantitative architectonics), connectivity, physiological mapping, and roles in behavior [284, 285].

Naturally, we would especially like to know more about our own species, *Homo sapiens*. There have been a number of modern area-mapping studies comparing humans and macaques, and these suggest that both species share a similar complement of granular PFC areas (e.g., [286–289]). Sallet et al. [289] and Neubert et al. [288] have, however, highlighted some possible differences based on their structural-connectivity MRI parcellation of frontal areas. For example, they found that the cortex on the lateral aspect of the frontal pole in humans has no clear counterpart in macaques, an intriguing result given the involvement of that region in higher cognitive function, such as generalized relational reasoning (e.g., [290, 291]). The study of Balsters et al. [159], based on corticostriatal "fingerprints," led to a similar conclusion. In their comparison of human and macaque brains, they found that the major difference involved the lateral frontopolar cortex and the territories to which it projects in the anterior caudate nucleus. In addition, there appear to be important differences in the aMFC of macaques and humans, with humans possessing additional dysgranular subdivisions of area 32 [37].

While findings of human–macaque differences such as these certainly bear on what we can learn about human PFC functions from studying macaques, we cannot assume that areas humans possess but macaques lack are necessarily human specializations. For one thing, we have no comparable information about apes, so we do not know whether these are hominoid (i.e., ape–human) specializations or human specializations (for an example of the difference this makes, see [292]). Second, it is possible, if seemingly unlikely, that these features of PFC were present in the ancestors of macaques, but subsequently lost. Addressing this possibility requires studying additional species, with platyrrhines being especially useful for reconstructing the ancestral state of the catarrhine lineage. Nevertheless, the currently available—albeit limited—evidence suggests that the complement of granular PFC areas in macaques and humans is quite similar, which, given that human frontal lobes are much larger than those of macaques (and apes), implies that at least some of the areas shared by these primates are much larger in humans than in the other species.

Histology, connectivity, and genomics. Even though we currently lack the kinds of maps required to compare the complement of areas that make up the granular PFC in apes and humans, we do have tools that enable us to compare other features of PFC organization of humans to chimpanzees, our closest relatives, and to macaques. There are new comparative histological studies, employing Nissl and Golgi staining, and immunohistochemistry (e.g., [148, 293–298]). There are also MRI studies in all three species, providing information, for example, about myeloarchitecture [249] and hemispheric asymmetries [299]. In addition, diffusion-weighted MRI studies have demonstrated human specializations of connectivity, including modified connections of the arcuate fasciculus and other systems that interconnect temporal, parietal, and frontal association cortex [300–305].

There are now also abundant resources, and data, for comparing genes and gene expression in humans, chimpanzees, and other nonhuman primates. Space limitations preclude a review of this active area of research. Significantly, however, much of the gene-expression research has focused on the granular PFC (typically area 46 in the DLPFC), and numerous human specializations involving (if not necessarily limited to) this region have been identified (e.g., [283, 306–312]). These gene-expression changes are likely to have modified the cellular organization and physiology of human cortex, although we currently lack direct evidence of such modifications.

PFC EVOLUTION IN MAMMALS OTHER THAN THE EUARCHONTOGLIRES

The account above has focused on the PFC in the Euarchontoglires, especially primates. There have been few studies of other mammalian groups, apart from carnivores, a group of placental mammals that, as indicated in Fig. 1, is quite distantly related to primates. Many different mammalian groups underwent enlargement of their frontal cortex during their evolution, including carnivores [14, 254, 313]. The predominant cortical connections of carnivore PFC are with limbic regions [314, 315], suggesting it underwent elaboration of the agranular OFC and/or aMFC. It is reasonable to assume that the PFC expanded independently in other mammalian lineages as well.

FUTURE RESEARCH DIRECTIONS

There remain several outstanding issues regarding PFC evolution:

(1) The status of dysgranular areas, especially those in the OFC, requires further attention: Are these separate cortical fields or are they transition zones? Some evidence from macaques points to the former [316], but more data are needed. Also unknown is whether there are homologs of the dysgranular OFC in rodents or other nonprimates.

(2) Are there homologs of the granular PFC areas in the nonprimate members of the Euarchonta (i.e., tree shrews and flying lemurs)? We know that tree shrews have small granular PFC areas but not whether they are homologs of primate areas. We should be cautious about assessing "granularity" across species based on qualitative descriptions, however, as these accounts are often in poor agreement even among closely related species (see, for example, the contrasting descriptions of layer 4 in carnivore proreal cortex [49, 60, 317–319]). Such disparities emphasize the need to adopt multimethod parcellations, including observer-independent architectonics [320–322].
(3) Given that platyrrhines and catarrhines underwent independent enlargement of the brain, did they also undergo independent addition of new granular PFC areas? If so, could it be that some of the areas assigned the same numbers and names in platyrrhines and catarrhines evolved independently?

CONCLUSIONS

The PFC is evolutionarily dynamic and diverse, with new areas and new systems of connections evolving in primates. Despite deficiencies in the data, we can state with reasonable confidence that the rodent PFC consists of homologs of the primate aMFC (areas 24, 32, and 25) and primate posterior, agranular OFC. We can also state with reasonable confidence that the granular PFC is a specialization of primates or possibly of primates and their close euarchontan relatives. From comparisons among primates, we infer that early primates possessed a small set of granular PFC areas, while additional areas, including the DLPFC, evolved later in the simian branch of the primate tree. Our understanding of the evolution of the limbic, agranular PFC is comparatively poor, but given its involvement in social behavior (e.g., [174, 323, 324]) and given the diversity of social behavior among mammals, its organization was likely modified in many primate groups.

We are aware that our view regarding the uniqueness of the primate granular PFC has been unpopular among some neuroscientists who study rodents and other nonprimate species, although we note that in the 30 years since it was first articulated no data have been advanced that convincingly contradict it. We believe, moreover, that many of the ambiguities about the behavioral role of the PFC in rodents as compared to primates are resolved by the interpretation of homologies offered here. What is more, our view by no means negates the importance of rodents as biomedical models. For one thing, the parts of the PFC that rodents and primates do share—namely, the limbic parts—are unquestionably of functional importance, and in some respects of even greater clinical importance than the granular PFC. That is not to say that we should study the limbic PFC only in rodents—any nonhuman primate is more closely related to humans that any rodent and their behavioral phenotypes are more readily compared to those of humans [325]—but rather that our evolutionary analysis does not exclude an important role for rodent research. We note, too, that the caution that we have expressed about uncritically extrapolating findings from model animals to humans applies to catarrhine primates as well as to rodents and platyrrhines, although the much closer relationship of human to other catarrhines mitigates this problem to a considerable extent [326].

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Both authors wrote the manuscript.

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The authors declare no competing interests.

ADDITIONAL INFORMATION

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