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Not all cortical expansions are the same: The coevolution of the neocortex and the dorsal thalamus in mammals

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Abstract

A central question in comparative neurobiology concerns how evolution has produced brains with expanded neocortices, composed of more areas with unique connectivity and functional properties. Some mammalian lineages, such as primates, exhibit exceptionally large cortices relative to the size of sensory inputs from the dorsal thalamus, and this expansion is associated with a larger number of distinct cortical areas, composing a larger proportion of the cortical sheet. We propose a link between the organization of the neocortex and its expansion relative to the size of the dorsal thalamus, based on a combination of work in comparative neuroanatomy and experimental research.

Introduction

One of the defining features of the human brain is the exceptional size of the neocortex and the large number of cortical areas that compose it. Beyond the primary sensory and motor areas that we share with other mammals, humans and other primates exhibit additional functionally, anatomically, and architectonically distinct cortical areas involved in higher-order sensory processing and the generation of complex movements [1,2]. These changes in the human neocortex are, in part, responsible for many of our unique behavioral specializations such as precise manual control, cognitive flexibility, and language comprehension and production. Because of the important role that the neocortex plays in generating these behaviors, there has been a concerted effort to understand how the neocortex increases in size and why and how it fissures and folds [3,4,5].

A plethora of studies on cortical neurogenesis stemming from decades of elegant molecular experiments have detailed how progenitor cell pools have been modified to generate expansions in the cortical sheet, both in primates generally [6,7] and humans specifically [8,9]. Without question, these studies have increased our understanding of the evolution of the developmental mechanisms that generate an increase in the size of the cortical sheet over

Conflicts of Interest

We declare no conflicts of interest.

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the course of mammalian evolution [10]. Nevertheless, how novel cortical areas emerge in evolution and become integrated with existing cortical networks remains one of the most puzzling and fundamental questions in neuroscience. Furthermore, developmental studies often overlook the important observation that cortical sheet expansion in mammals occurs in at least two different ways.

First, if we consider a particular mammalian lineage with a wide range of brain sizes – e.g. anthropoid primates, or carnivores – the neocortex tends to become disproportionately large as the whole brain, including non-cortical structures, also increases in size. These size-associated patterns of variation (i.e. allometric effects) are commonly called *concerted brain evolution* [11], and are thought to reflect systematic changes to neurodevelopmental schedules [12,13; but see 14]. Second, when comparing brains across mammalian lineages, it becomes apparent that some groups exhibit a disproportionate increase in the size of the neocortex relative to subcortical structures. These evolutionary features are observed irrespective of brain size, and are called *mosaic brain evolution* within particular lineages relative to others. Below we examine two ways in which the neocortex has expanded relative to the size of the structure that serves as the primary source of its sensory input: the dorsal thalamus. We also explore how these two types of expansion relate to alterations in cortical field number and cortical field size. We then review data that demonstrates that sensory input plays a prominent role in determining the functional organization of the cortical sheet, and postulate that this is particularly true for mammals that have a disproportionately large neocortex, like primates.

Concerted evolution of the neocortex and the dorsal thalamus

Mammalian brains vary in absolute size by five orders of magnitude, and the relative proportion of different brain components, such as the neocortex, dorsal thalamus and brain stem, have long been known to follow regular “concerted” patterns associated with total brain size [15]. Concerted effects have been linked to regular changes in the onset of neurogenesis from progenitor cell populations across species [12], and are associated with prenatal brain growth patterns [16] as well as differences in adult brains, such as gross structure size [12,13], neuron densities across the neocortex [17], rod/cone ratios in the retina [18], and even variation in brain structure size within a species, such as humans [19]. In many mammalian lineages studied, such as carnivores [20], dermoptera [21], primates, and insectivorous Afrotherian and Laurasiatherian mammals [15], concerted evolution accounts for how the neocortex composes a larger proportion of the brain in larger-brained species. The same relationship seems to apply to thalamus:cortex scaling – larger brains have exceptionally large neocortices relative to the size of the dorsal thalamus.

Figure 1 shows the scaling of the thalamus relative to the neocortex in 39 species (Figure 1A), with trend lines applied to diverse mammalian groups (Figure 1B). Cladistic levels were chosen to aid comparisons of major primate lineages against a number of shrews, tenrecs, and other species (Afrotheria and Laurasiatheria, previously “Insectivora”) for which data is available [15]. Every lineage exhibits a slope greater than 1 (apes: 1.45; Old World monkeys: 1.21; New World monkeys: 1.20; lemurs: 1.01; lorises and galagos: 1.07; Afrotheria: 1.17; Eulipotyphla: 1.09), indicating positive allometry. Simply put, as the dorsal

thalamus gets larger, the neocortex outpaces it in size. For example, within New World monkeys, the small-brained pygmy marmoset (brain weight: 4.5g) exhibits a thalamus-to-neocortex volume proportion of 1:13, while the larger-brained spider monkey (brain weight: 108g) has nearly twice as much neocortex, proportionally speaking – 1:24 (Figure 1)[15]. Even after we account for evolutionary relationships (phylogenetic generalized least squares [PGLS] regression using a mammalian supertree from [22] and the {ape}, {gieger} and {caper} libraries for R), we see a robust and positive allometry between the thalamus and neocortex (slope=1.25, $p<0.001$, $R^2=0.98$).

While concerted evolution describes the expansion of the neocortex associated with total brain size – the cortex getting larger “faster” than the medulla, for example – a second form of cortical expansion can be observed *between* mammalian lineages, even when subcortical structures, like the dorsal thalamus, are similar in size. Here, important differences emerge when we compare mammalian lineages to one another.

Mosaic evolution of the neocortex and dorsal thalamus

Comparing the trend lines of diverse mammalian lineages, it becomes apparent that some lineages have larger neocortices even when thalamus is similar in size (Figure 1A). This kind of disproportionate expansion beyond concerted effects is frequently called *mosaic brain evolution*, and plays a major role in the evolution of brain structure size in both birds [23,24] and fish [25,26,27]. In mammals, the evolution of different brain structures appears to be more constrained (i.e. concerted) than in non-mammalian vertebrates, except in certain structures such as the olfactory bulbs [15; but see 28,29]. Nevertheless, one of clearest cases of mosaic evolution in mammals is the disproportionate expansion of the neocortex or “neocorticalization.” Several mammalian clades, such as carnivores [20] and primates [15,30], exhibit larger neocortices than other mammalian lineages, after we control for subcortical brain structure size. For example, the mouse lemur, which has the smallest primate brain, has a higher neocortex:thalamus proportion than even the largest rodent, the capybara (Figure 1C). This is despite the fact that larger brains *usually* have proportionally larger neocortices (concerted expansion), and the capybara’s brain (~50g [31]) is 30 times larger than that of the mouse lemur (1.8g [15]).

Of course, not all of the dorsal thalamus is composed of first-order sensory relay nuclei, and not all of the neocortex is composed of “primary” areas receiving these inputs (Figure 2). First-order sensory relay nuclei of the thalamus (e.g. ventral posterior nucleus (VP), dorsal lateral geniculate nucleus (dLGN), ventral medial geniculate nucleus (vMGN)) compose a smaller fraction of the dorsal thalamus in larger primate brains [15, 32]. A similar effect is observed as the neocortex increases in size: larger primate neocortices have relatively less space dedicated to primary sensory fields (with the exception of V1)[33,34]. Instead, a larger proportion of the neocortex is devoted to higher-order areas, such as posterior parietal (PPC) and inferotemporal (ITC) cortex, which are associated with multi-sensory integration, reaching and grasping, object recognition and other complex behaviors [35,36]. However, these effects have largely been observed among primate species, and it has yet to be determined whether these same principles of expansion are found in non-primate lineages.

Both concerted and mosaic evolution shape thalamocortical relationships and cortical organization.

Both concerted and mosaic forms of neocortical expansion result in a similar effect, with relatively smaller first-order thalamic nuclei sending projections to a relatively larger cortical sheet (Figure 1A). However, the two forms differ in important ways that are obscured by the general term “cortical expansion.” Recognizing these differences can inform research on the developmental mechanisms responsible for different types of neocortical expansion and allow us to appreciate the consequences of cortical sheet expansion on cortical organization.

First, whether cortical expansion is concerted or mosaic changes our perspective on the developmental mechanisms responsible for how the cortex has increased in size in different species. In concerted evolution, the cortex increases in size alongside other brain structures, suggesting that there are changes to *global neurodevelopmental mechanisms* that affect cortical development (i.e. the entire schedule of brain development [12, 37] rather than changes to cortex-specific mechanisms). By contrast, mosaic effects are likely to be the result of neurodevelopmental programs that are *specific to the neocortex*, and which do not alter subcortical structure size. Unfortunately, many of the species that serve as animal models represent mammalian lineages that reflect both types of evolution. For example, early comparative work on cortical neurogenesis in mouse vs. macaque demonstrated an expansion of the macaque embryonic subventricular zone (SVZ) and its differentiation into inner and outer subdivisions [38]. Is this transient embryonic phenotype in primates a signature of larger and more highly folded cortices in general (concerted evolution), or is it specific to primate “neocorticalization” (mosaic evolution)? While SVZ compartmentalization into outer (OSVZ) and inner (ISVZ) regions was originally thought to be primate-specific [38], subsequent work has shown that these developmental features are shared by various carnivores, rodents, and artiodactyls [6,39,40] and are linked to neocortex size rather than phylogeny. Interestingly, Garcia-Moreno and colleagues [41] compared the larger-brained (20.3g [15]) gyrencephalic rodent agouti (*Dasyprocta*) with the smaller-brained (7.9g [15]) lissencephalic marmoset (*Callithrix*) and found similar SVZ compartmentalization at mid-gestation in both species, although the size and the proportions of specific cell types in the OSVZ were different. This suggests that the presence of an OSVZ and some of its characteristics are more closely related to absolute neocortex size than they are to phylogeny or gyrification, and may reflect concerted evolutionary effects rather than mosaic neocorticalization. The approach of minimizing brain size differences in comparative developmental research (e.g. comparing larger-brained rodents with smaller-brained primates) allows us to untangle the mixed concerted and mosaic evolutionary processes at work.

Second, the mosaic evolution of the primate neocortex relative to its thalamic inputs may be especially important for understanding the exceptional increase in the number of cortical areas observed in even the smallest primate brains. Both the rat and the prosimian mouse lemur share a similar brain size, but mouse lemurs have larger neocortices that are composed of more cortical areas and expanded parietal and temporal regions (Figures 2, 3). In fact, a larger number of neocortical areas is a characteristic of primates in general [1], particularly

in parietal, temporal, and frontal regions that are proportionally larger in primates (Figure 2) [35,36,42], Deacon [43] proposed that changes in the relative *size* of brain structures – a consequence of either concerted or mosaic evolution – might necessarily result in alterations in their connections. Since axons compete for targets during development, an exceptionally large axonal source might out-compete other axons for the same target, thereby “displacing” ancestral connections. Alternatively, an expanded innervation target (e.g. an expanded cortex relative to its thalamic inputs) might relax the process of competition, allowing for novel combinations of connections to form on an expanded target. How much of the increased complexity in primate neocortical organization might be a consequence of a disproportionate expansion of the cortical sheet relative to the structure which provides its main source of sensory inputs, the dorsal thalamus (Figure 2)? Could an expansion of the target of thalamocortical axons be sufficient to generate novel combinations of inputs and thus a new cortical field?

While it is true that neocortical expansion relative to the dorsal thalamus is *associated* with a larger number of cortical fields (at least in mammals for which both allometric and functional data are available, e.g. euarchontoglires), other mechanisms are involved in the emergence of new cortical fields over the course of evolution. These include alterations in the expression of genes associated with axon guidance, as well as alterations in the types and relative ratio of incoming sensory inputs. As discussed above, the capybara brain exhibits similar proportions of thalamus to neocortex as does the mouse lemur brain (~1:9), but the brain of the capybara appears to have a simpler cortical organization and a smaller number of higher-order cortical fields. In fact, capybara neocortical organization looks like a scaled-up version of the guinea pig [31], despite the fact that the capybara has a thalamus:neocortex proportion within the range of prosimian primates (Figure 1A). Exceptional cases such as the capybara – which has a large neocortex but relatively simple organization – allow us to appreciate that cortical field evolution does not involve only simple scaling rules, but is more complicated and can only be fully understood using a comparative approach.

The role of sensory input in determining the functional organization of the neocortex.

Primary sensory fields (V1, S1, A1) and several other sensory areas (V2, S2, PV, R) are ubiquitous across every investigated mammal [44]. Each of these fields has retained specific patterns of thalamocortical and corticocortical projections from the common mammalian ancestor, and each has a number of readily identified architectonic features, including a dense layer IV in primary areas. For example, all mammals possess a primary visual area with dense projections from the dorsal lateral geniculate nucleus of the thalamus, even when the animal is eyeless (enucleated or anophthalmic mice [45,46]) or does not engage in visually mediated behavior (blind mole rat [47])(Figure 4). V1 in these animals is reduced in size and the subcortical connections of the lost or reduced sensory system have been altered, such that the dLGN receives input from other sensory systems. Despite the absence of a functional visual system, basic aspects of the connection network are maintained, as are features of cytoarchitecture, even as “V1” becomes functionally dedicated to auditory processing [48].

Experimental studies in which visual input to the developing brain is removed via bilateral enucleation very early in development also supports the important role of sensory driven activity for anatomical and functional specification of primary sensory areas. In opossums in which the eyes are removed prior to the onset of spontaneous activity (and well before the onset of sensory driven activity) a greatly reduced primary visual area, defined architectonically, is still present as are aspects of thalamocortical and corticocortical connections. However, neurons in V1 are activated by both auditory and somatosensory stimulation, and the reorganized V1 receives new input from somatosensory and auditory structures of the cortex and the dorsal thalamus [49,50]. The annexation of visual cortex by the spared sensory systems has also been demonstrated in congenitally blind humans. Visual cortex in these individuals is activated when performing a variety of non-visual tasks such as Braille reading [51], sound localization [52,53], and language processing [54, see 55 for review]. While primary cortical areas are generally defined by a combination of criteria including their architectonic appearance, connectivity, and functional organization, the available evidence suggests that these features can be decoupled when sensory input is altered, either in evolution or in experimental studies, emphasizing the central role that sensory input plays in generating “normal” cortical fields.

The persistence of these primary fields – even when their input is reduced or removed – is likely due to the contingent nature in which genes are expressed during the development of the neocortex. A wide range of genetic cascades involved in cell proliferation, adhesion, axon fasciculation and guidance have been well described for the development of primary and secondary cortical fields [56]. Alterations in the expression of these genes can alter the size and relative location of these cortical areas, but never result in their total absence [56,57]. This temporal and contingent deployment of genes early in development acts to constrain cortical evolution and explains the ubiquity of these fields in all mammals. However, our knowledge of how higher-order cortical areas develop and how new cortical fields are added to this evolutionarily old, genetically specified network is not well understood.

We propose that the addition of non-primary cortical fields in primates may reflect the disproportionate expansion of the cortical sheet relative to its primary inputs from the dorsal thalamus, rather than the type of genetic specification that has been described for primary fields. There are several lines of evidence that indicate that the portions of the neocortex that have greatly expanded within the primate order include temporal cortex, posterior parietal cortex (PPC) and prefrontal cortex [35,36,42]. Certain features of non-primary sensory cortical fields – e.g. the mirror reversals of visual field representation across visual fields, or topographic representation across somatosensory areas – suggest a role for self-organization in generating network structure during development [58]. This indicates that the functional role played by cortical areas in the expanded posterior parietal and temporal cortex are, to a large extent, contingent on their functional inputs during development. Much of the evidence for this comes from studies in humans. For example, the fusiform face area in the temporal lobe of humans, which normally is activated by faces, is instead activated by particular voices in congenitally blind individuals [59], suggesting that this area is only loosely specified for person perception and is built by the available inputs that signal a given individual's identity. Another example comes from studies of individuals born without

hands, and who develop remarkable dexterity with their feet which serve as their major effectors [60]. As we might expect, the regions of primary somatosensory and motor cortex that would normally represent the missing hand instead represent adjacent body parts. However, posterior parietal cortex, a region normally associated with reaching and grasping and generating coordinated hand/eye movements, is activated by the foot in these individuals, rather than by the forelimb as it is in individuals with hands. Thus, these expanded, higher-order regions of cortex are, in a sense, mimicking what happens via traditional evolutionary mechanisms, with their functional role emerging from pervasive exposure to unique combinations of sensory input that are dependent on context and use. In short, the functional organization of these areas is built during development.

Conclusions

The available comparative data suggests that there is a relationship between the proliferation of cortical areas and the disproportionate expansion of the neocortex relative to its sensory inputs from the thalamus, especially in “neocorticalized” lineages such as primates. The functional plasticity of the neocortex during development is supported by experimental studies and studies in naturally blind animals in which sensory inputs are completely lost or reduced, in which the neocortex that normally subserves the lost input is functionally re-specified. Nevertheless, the question of how cortical areas are added or functionally altered in evolution and development remains a central question in neurobiology. One clue to this puzzle may lie in distinguishing between the two forms of neocortical expansion – concerted vs. mosaic – relative to the size of the dorsal thalamus, or to the size of other structures that provide inputs to the cortex. Primates of every brain size have unusually large neocortices relative to the size of the dorsal thalamus, and this expansion is associated with a larger number of non-primary cortical fields involved in higher-order processing such as multisensory integration, the generation of body-centered coordinates for manipulating objects with the forelimbs, and face recognition (e.g. PPC and ITC).

Undoubtedly genes intrinsic to the early developing neocortex play a central role in the process of cortical arealization. In fact, the genetic regulation of ephrins, which guide axons from thalamic nuclei to their cortical targets, plays an essential role in organizing thalamocortical networks. However, the emergence of cortical areas that are not strictly specified by genes intrinsic to the developing cortex – and that are not tightly specified by peripheral input from the primary sensory nuclei of the dorsal thalamus – may be more plastic in their functional role and, to a large extent, may be built within the lifetime of an individual. This increased functional plasticity for areas of cortex that are differentially expanded in primates (e.g. PPC, ITC) may be one of the driving forces in the behavioral flexibility that is characteristic of humans, and the primate lineage to which we belong.

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Highlights

- Mammals differ in the size of the neocortex and number of areas that compose it
- Neocortical expansion occurs in different ways relative to inputs from the thalamus
- Species with expanded cortices relative to thalamic inputs have more cortical areas

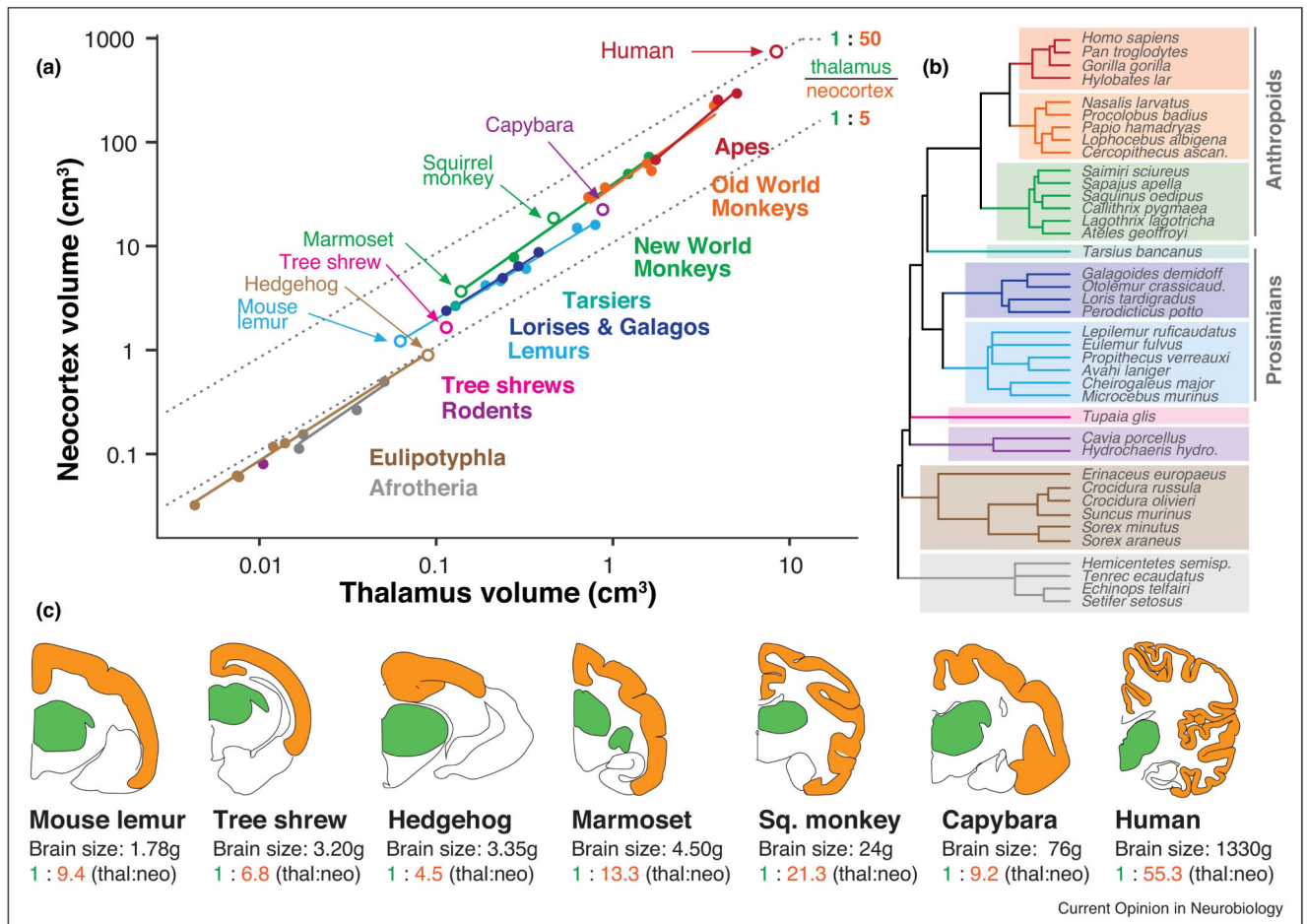


Figure 1. Primate “neocorticalization” relative to the dorsal thalamus.

Across a wide range of brain sizes, primates exhibit larger neocortices relative to the size of the dorsal thalamus than many mammalian groups. **(A)** Neocortex volume is plotted against dorsal thalamus volume in log-log coordinates, demonstrating effects of both concerted and mosaic evolution. Concerted evolution is demonstrated by each group having a slope greater than 1 (i.e. more than isometric scaling, or constant proportions across size variation). Mosaic evolution is exemplified by intercept shifts between mammalian lineages. Open circles indicate species shown in coronal section below. **(B)** A phylogenetic tree of included species, with colors corresponding to mammalian clades in **(A)**. Even after correcting for phylogenetic relatedness, the neocortex always gets larger “faster” than the thalamus does (see text). **(C)** Coronal sections of selected brains in the dataset above, taken from a similar rostrocaudal level (ventral posterior [VP] nucleus of the thalamus), with associated brain sizes and thalamus:neocortex proportions. Primates, and particularly anthropoids (monkeys and apes) have an unusually large neocortex volume that dwarfs size-associated concerted effects. This mosaic evolution of the primate neocortex is so extreme (over & above size-related concerted effects) that only the largest rodent brain (capybara) has similar thalamus-to-neocortex proportions as the smallest primate brain (mouse lemur). Data from [15,22]. Coronal section outlines (dorsal thalamus in green, neocortex in orange) are from the Comparative Mammalian Brain Collection from the University of Wisconsin, and are not to

scale. Thal = dorsal thalamus; neo = neocortex. Marmoset (*Callithrix jacchus*) thalamus size was estimated from the dataset in [15].

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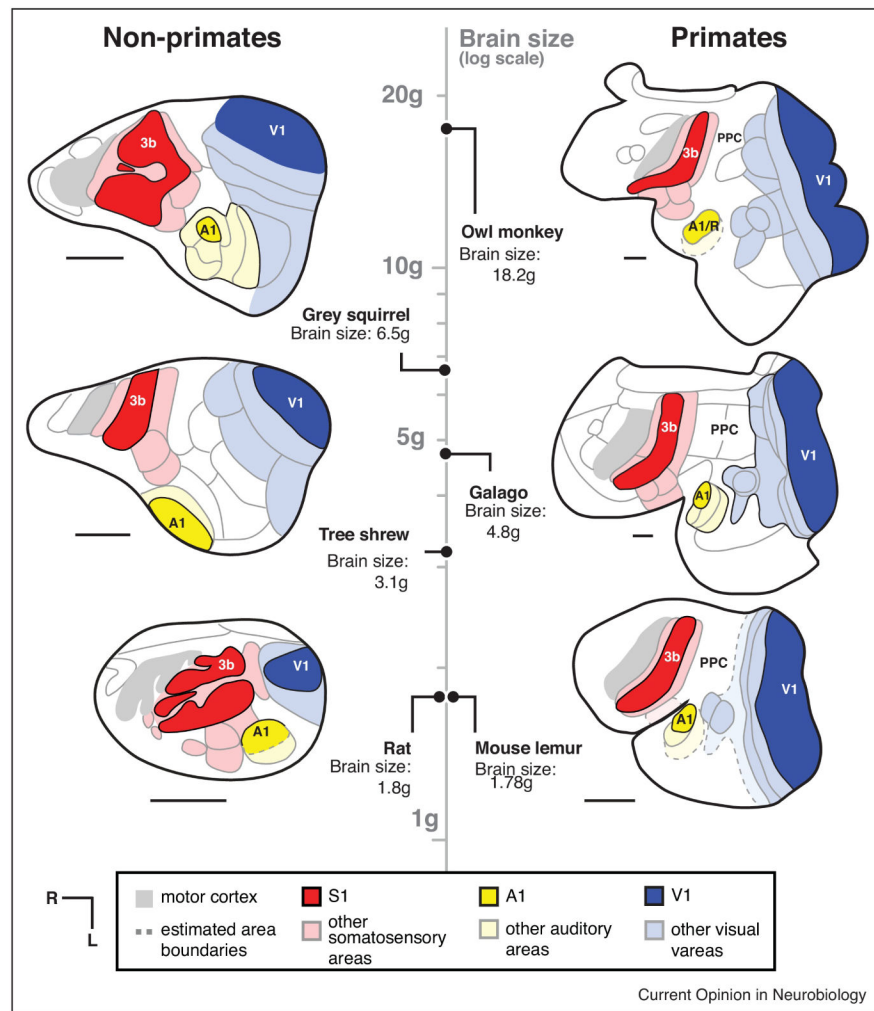


Figure 2. Neocortical organization in primates and non-primate mammals with varying brain size.

Maps of cortical organization from flattened sections are drawn from architectonic and functional studies, and are aligned according to log-transformed brain size (vertical axis) with primates to the right, and closely-related euarchontoglires species to the left. Compared with mammals of similar brain size, primates have larger neocortices (parietal, temporal and frontal regions), as well as more non-primary sensory areas. While thalamus size is not available for every species included, larger brains have larger neocortex:thalamus proportions (concerted evolution), and primates have a larger neocortex:thalamus proportions across every brain size than do closely related species (mosaic evolution). All scale bars = 4mm. Maps are redrawn from [61,62,63,64].

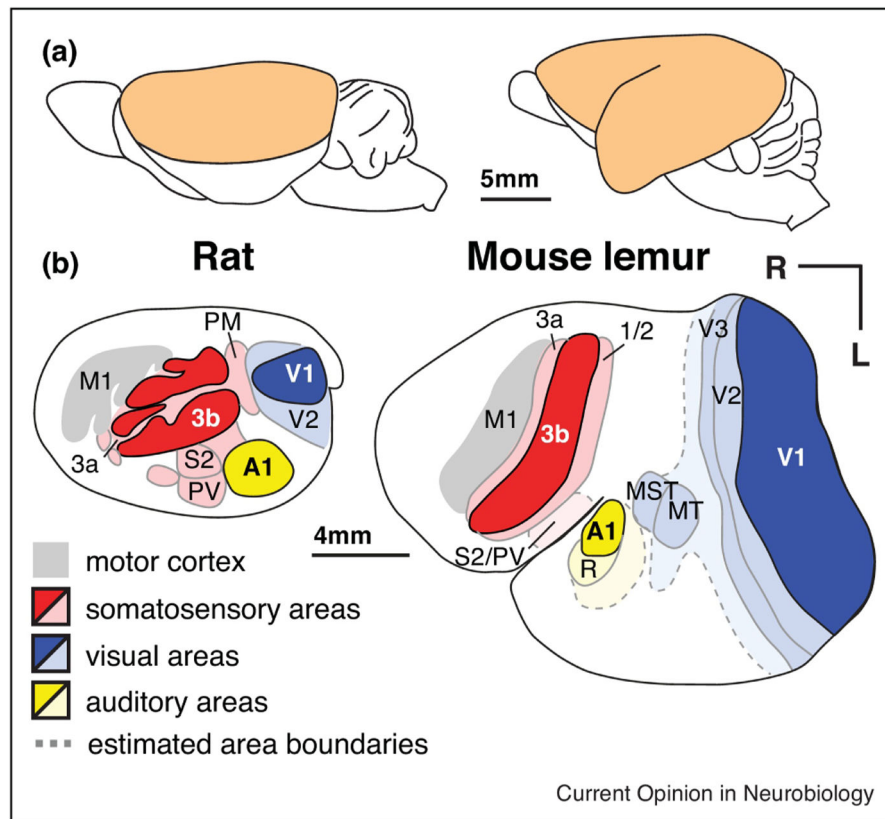


Figure 3. Neocortex of a rat and mouse lemur drawn to scale.

Although rats and mouse lemurs have a similar size brain (~1.8g), the neocortex of the mouse lemur has a surface area ~3 times that of the rat. The mouse lemur also has a larger number of distinct cortical fields in the expanded area of cortex between S1, V1 and A1. The white region in mouse lemur between area 1/2 and other visual areas (light blue) is likely composed of multiple parietal subdivisions (as in the galago; see Fig 2) that have not been fully characterized. Temporal and frontal cortex have also expanded in mouse lemurs. Modified from [61,62] (rat) and [63] (mouse lemur).

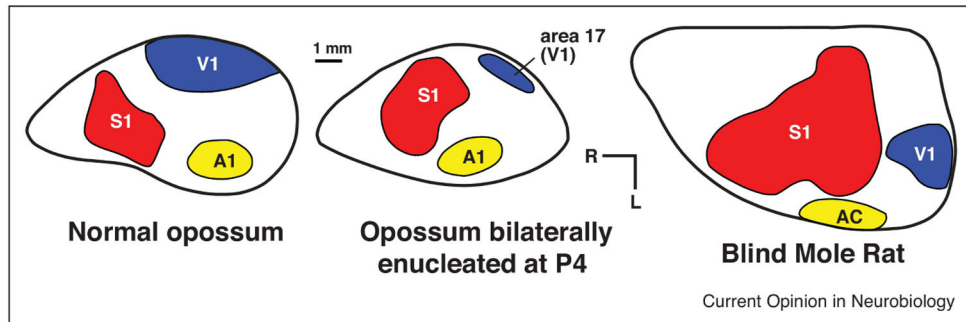


Figure 4. Neocortex in normal and bilaterally enucleated opossums and blind mole rats. Although the neocortex in bilaterally enucleated opossums never receives either spontaneous or sensory driven input from the eyes, an architectonically defined primary visual area (V1 or area 17) is still present. Likewise, the blind mole rat has anophthalmic eyes with skin grown over them, yet they still possess an architectonically defined V1. In blind opossums, what would have been visual cortex is co-opted by the somatosensory and auditory system, and in blind mole rats V1 is activated by auditory inputs. Figures redrawn from [47,49].