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Phenotypic Alterations in Cortical Organization and Connectivity across Different Time Scales

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Evolution · Development · Cortex

Abstract
In the following review, we describe the types of phenotypic changes to the neocortex that occur over the longer time scale of evolution, and over the shorter time scale of an individual lifetime. To understand how phenotypic variability emerges in the neocortex, it is important to consider the cortex as part of an integrated system of the brain, the body, the environment in which the brain and body develops and evolves, and the affordances available within a particular environmental context; changes in any part of this brain/body/environment network impact the neocortex. We provide data from comparative studies on a wide variety of mammals that demonstrate that body morphology, the sensory epithelium, and the use of a particular morphological structure have a profound impact on neocortical organization and connections. We then discuss the genetic and epigenetic factors that contribute to the development of the neocortex, as well as the role of spontaneous and sensory driven activity in constructing a nervous system. Although the evolution of the neocortex cannot be studied directly, studies in which developmental processes are experimentally manipulated provide important insights into how phenotypic transformations could occur over the course of evolution and demonstrate that relatively small alterations to the body and/or the environment in which an individual develops can manifest as large changes to the neocortex. Finally, we discuss how these phenotypic alterations to the neocortex impact an important target of selection – behavior.

Introduction

How does the neocortex evolve from a simple form with few cortical fields, present in our early ancestors, to a complex form with multiple, interconnected cortical fields as evidenced in a number of extant mammals? While it is tempting to answer this question from a purely evolutionary perspective, it is important to keep in mind that there are many timescales over which phenotypic change can emerge. One is the long evolutionary time scale in which alterations in the phenotype occur over thousands to millions of years. Another is over much shorter time scales such as generations, years, days, and even seconds; the shortest occurring at the synaptic level with potentia-

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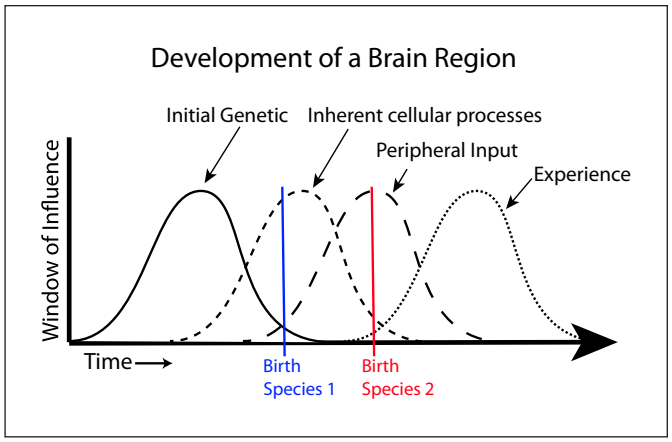

Fig. 1. The developmental cascade. Example of the development of a single hypothetical brain region illustrating how different developmental processes cascade in time (*x*-axis), beginning with initial genetic processes such as cell type specification and proliferation. Each process has a window of influence (*y*-axis) where intrinsic (genetic) or extrinsic (environmental/epigenetic) factors can impact brain development. For example, an alteration in genes which regulate cell cycle kinetics during neurogenesis could result in larger progenitor pools and affect the overall size of a brain region, such as the neocortex. Moreover, differences in the developmental stage at which a species is born (blue and red vertical lines) would determine the extent to which the environment and sensory driven activity impacts development.

tion and protein synthesis. Indeed, we have previously argued that phenotypic changes occurring over shorter timescales can masquerade as evolutionary transformations if the context in which an animal develops is static for long periods of time [Krubitzer and Stolzenberg, 2014]. While evolutionary transformations are due to changes in DNA sequence or patterns of stable epigenetic marks, resulting in altered brain or body morphology and function, phenotypic modifications occurring over shorter time scales are due to multiple factors inexorably tied to the context in which the brain and body develop, and ultimately live. Both the evolutionary and developmental timescales heavily influence the number, size and connectivity of cortical fields, while very short timescales have less of an impact on large-scale features of cortical organization. During development, the in utero environment and the stage at which an animal is born determines the extent to which sensory input can impact the cortical phenotype (Fig. 1). In addition, the overall environmental context including temperature, toxins present, sensory stimuli and available affordances also impact the brain and the body. Therefore, to understand how phenotypic change occurs in any part of the brain we must consider the brain and body as parts of a single interacting entity, *the organism,* behaving in and being influenced by the environment in which it resides and develops.

The Body and the Environment Alter the Brain over Long and Short Timescales

To appreciate how the body and the environment impact the cortical phenotype over longer timescales, we can examine a variety of species with different sensory, morphological, and neocortical specializations that live and behave in unique environmental contexts with different affordances. Some of the best examples are found in species with extreme specializations, occupying different niches (e.g., aquatic, arboreal, burrowing), such as the duck-billed platypus [Krubitzer et al., 1995], the star nosed mole [Catania and Kaas, 1996], and the blind mole rat [Necker et al., 1992). For instance, the platypus has a unique bill lined with rows of mechanosensory and electrosensory receptors [Pettigrew, 1999]. When engaging in important, ethologically relevant behaviors such as feeding, navigating and mating, it closes its eyes, ears, and nose; receiving all information about the world almost exclusively through the receptors on its bill [Manger and Pettigrew, 1995]. When somatosensory cortex is examined using electrophysiological recording techniques, it is found to be dominated by the representation of the bill. In fact, almost 90% of primary somatosensory cortex (S1) is devoted to processing inputs from the bill, and about 60% of the entire cortical sheet is dominated by the representation of the bill. Similar types of cortical magnification are observed in other mammals. For example, in S1, there is an enlarged representation of nose rays in the star-nosed mole, who forages for small invertebrates using its exquisitely sensitive tactile "nose" [Catania and Kaas, 1995]. An enlarged representation of the incisors characterizes the representation of S1 in naked mole rats who live in underground highways and use their incisors to dig extensive tunnel networks, carry objects and young, chew, and investigate their surroundings by tapping their incisors against objects of interest [Catania and Remple, 2002]. These types of changes, where the structure and function of the neocortex mirror the body, behavior, and niche of the organism, have been observed to a greater or lesser extent in every mammal examined for all sensory systems [Krubitzer, 2007], and in part, are the product of evolutionary changes to peripheral morphology and sensory epithelia (e.g., evolving from a snout to a bill with electroreceptors).

The magnification associated with peripheral morphological specializations is not limited to the cortex but is also observed in the dorsal thalamus. For example, in the platypus, the dorsal thalamus is dominated by the ventral posterior nucleus [Ashwell, 2012; Mikula et al., 2008]; so much so that it is difficult to identify other major relay nuclei (lateral geniculate nucleus [LGN], medial geniculate nucleus). Similarly, in the blind mole rat, the LGN is extremely small and undifferentiated [Rehkämper et al., 1994], while the ventral posterior nucleus is enlarged. Conversely, in species that rely heavily on vision, like the arboreal grey squirrel, the LGN and pulvinar occupy a large portion of the dorsal thalamus, an uncommon feature of the thalamus compared to commonly studied terrestrial, whisking rodent models [Baldwin et al., 2011; Robson and Hall, 1977; Wong and Kaas, 2008]. Interestingly, the relative magnification of the pulvinar complex has independently evolved in other mammals that rely heavily on vision such as primates and carnivores, which both exhibit a relatively larger pulvinar complex volume-to-brain-weight ratio compared to rodents [Chalfin et al., 2007]. Clearly, an animal's ability to navigate in and explore its environment is a driving force of selection. Thus, evolution has tinkered with both the body plan that allows mammals to interact and move in the environment, and with sensory receptor array type and structure, which determines the type and magnitude of sensory stimuli that is captured and transduced; in turn, both factors impact brain organization.

These evolutionary changes to the brain and body have resulted in species adaptations suited for environments that persist over long timescales (i.e., the more stable aspects of an organism's environment, such as the platypus hunting in muddy water, or a star nosed mole catching small prey in a subterranean environment). Over shorter timescales (one or a few generations), similar, but less dramatic, changes to the brain can occur. For example, alterations in cortical field size, magnification of behaviorally relevant sensory surfaces, or alterations in representations of muscle synergies in motor cortex can emerge in dynamic physical and social environments with no structural changes to the body. In humans, for example, rapid migration of populations, changes in food sources, or alterations in manual behaviors such as using keyboards and texting can rapidly influence features of the cortex noted above. These changes are observed across sensory and motor systems and across species. For example, rats who spent the first month of life in an enriched environment show an earlier expansion of the forelimb representation in motor cortex compared to rats reared in standard laboratory conditions [Young et al., 2012]. In humans born without arms and who use their feet in a dexterous fashion, motor, somatosensory, and posterior parietal cortex re-organizes to reflect the use of their major effector (the feet) [Liu et al., 2020]. In auditory cortex, Pantev et al. [1998] found that in skilled musicians (regardless of the instrument they play), there were enlarged representations for piano tones, but not pure tones, compared to individuals who had never played an instrument, [Pantev et al., 1998]. Numerous examples of this type of plasticity have been demonstrated in the visual system in different species. For example, wild-caught rats have a greater density of neurons in area 17 compared to laboratory rats of the same strain - although whether this effect is confined to a given cortical layer or spans all layers is unknown [Campi et al., 2011]. In opossums reared in vertically striped cages, neurons in V1 are preferentially tuned to striped stimuli [Dooley et al., 2017]. These examples demonstrate that activity-driven plasticity allows the neocortex to alter the function of sensory and motor areas to match short time-scale environments (see below). The social environment, which is a complex extension of the sensory environment, also has a strong influence on the rate and outcome of developmental processes throughout the nervous system, but a full discussion of this is beyond the scope of this review [see Bales et al., 2018 for review on "social" touch during development]. Lastly, since plasticity itself is a trait that is selected for (e.g., meta-plasticity), we should note that species may have varying levels of cortical plasticity due to species-specific intracellular mechanisms and synaptic transmission/modulation (e.g., species-specific developmental trajectories of NMDAR subunit NR2A/NR2B ratios) [Cho et al., 2009, Erzurumlu and Gaspar, 2012].

Functional changes that emerge over short time scales are often, if not always, accompanied by alterations in anatomical connections. Thus, despite the constraints imposed on evolving and developing brains and bodies [Krubitzer and Prescott, 2018], aspects of cortical organization and connectivity can change very rapidly over the course of a lifetime. While extraordinary diversity in brain organization and behavior can occur over shorter timescales, it is important to note that there are limits to this plasticity; the presence and relative location of a number of cortical fields is maintained as are patterns of cortical and subcortical connections. Furthermore, while some aspects of body morphology can be influenced by environmental factors (e.g., gravitational stress on bone density and diet on orofacial morphology), to a large extent the body plan of a particular mammal and the limits

imposed by joint configuration highly constrain the types of cortical changes that can occur over shorter timescales (see below).

What Factors Contribute to Phenotypic Transformations over Different Time Scales?

Of course, over the longer evolutionary timescale, changes to DNA sequence and species-specific epigenetic markers are the main drivers of phenotypic change. Changes to gene sequences occur via point or chromosomal mutations along with variation in copy number. On the other hand, long-timescale epigenetics changes alter gene expression without changing DNA sequence through distinct histone acetylation or DNA methylation patterns (e.g., some genes are methylated in some species but not in others; Shulha et al. [2012]. Thus, both epigenetic and genetic changes alter the quantity and/or function of gene product over evolutionary time. These genetic differences, which can alter cell cycle kinetics during proliferative periods, are responsible for the orders of magnitudes of difference in brain and body size between species [Cárdenas et al., 2018; Liu et al., 2017; Smaers et al., 2021; Suzuki et al., 2018; Tomasello et al., 2021]. Furthermore, changes to genetic sequence and epigenetic markers can alter the graded expression of transcription factors during cortical development (e.g., Emx2, Pax6, Coup-TF1,Sp8), which in turn alters the number and gross organization of cortical fields, and connections [Cholfin and Rubenstein, 2008; Fukuchi-Shimogori and Grove, 2001; Sur and Rubenstein, 2005]. This is also true for genes that are involved in the construction of the body. Homeobox genes (*Hox*) are a large family of highly conserved genes involved in the development of the body and limbs [Petit et al., 2017]. As with transcription factors in the neocortex, changing the spatial and temporal patterning of *Hox* genes can alter forelimb development profoundly, as revealed in comparative studies of limb development in bats versus mice [Cretekos et al., 2008; Petit et al., 2017]. Changes in limb morphology, in turn, alter the types of movements animals are capable of and the way in which sensory receptor arrays interface with the environment, which then manifest as differences in cortical magnification (i.e., the size of the forelimb representation in S1 of a bat vs. a mouse), in cortical and subcortical connections, and functional changes in neural circuits.

Importantly, genetic changes that have a direct broad scale effect on the size of the brain, particularly the neocortex, also can impact the organization and connectivity of cortical fields. For instance, Florio et al. [2015] discovered that the human-specific ARHGAP11B gene, the result of a duplication followed by a point mutation occurring near the time of the human-chimpanzee split, contributed to the expansion of the cortical sheet by increasing the number of basal progenitors . Recently, Heide et al. [2020] used a lentiviral vector to express the human ARHGAP11B variant in marmoset monkeys. Extending Florio's findings, this recent study found that expressing the human ARHGAP11B gene in marmoset fetus brains resulted in an increase in the number of outer subventricular zone (oSVZ) progenitors, an increased number of upper layer neurons, and an expanded cortical sheet. Together, these studies show how a long timescale event, in this case a duplication and point mutation, causes a cascade of events across neurodevelopment (increasing progenitors in the oSVZ increases layer 2/3 neurons and affects subsequent developmental events) (Fig. 1).

While the specific changes to connections and cortical field organization caused by expressing the human ARHGAP11B variant in the laboratory have yet to be studied, comparative studies indicate that increasing the relative size of the cortical sheet impacts aspects of cortical organization. For example, while the absolute size of V1 scales with brain size and the size of the retina across mammals, the relative size of V1 to association areas has decreased in humans [Arai and Pierani, 2014; Kaskan et al., 2005]. Further, the differential expansion of frontal, posterior parietal, and inferotemporal cortex in humans compared to other primates, suggests that as the neocortex increases in size, there is not a simple scaling up of existing cortical fields [Finlay and Uchiyama, 2015; Hill et al., 2010; Van Essen, 2018; Van Essen and Dierker, 2007]. Rather, there appears to be widespread alterations in the organization, number and size of cortical fields, and likely connections as well [for review, see Halley and Krubitzer, 2019]. Given these examples, it is easy to imagine how early and specific changes to DNA sequence, such as with ARHGAP11B, initiates developmental cascades that lead to global alterations to the neocortex. Yet direct changes to the genome are not the only mechanism by which the neocortex can be significantly altered. Epigenetic changes including histone modifications, chromatin remodeling, and posttranslational modifications can also strongly influence cortical neurogenesis [for review, see Adam and Harwell, 2020], which could, in turn, orchestrate a similar cascade of events as that described above.

In addition to genetic and epigenetic alterations to the brain and the body, spontaneous and sensory-driven ac-

tivity has a broad impact on subcortical and cortical organization and connectivity. For example, Gezelius et al. [2017] found differential expression of genes that appear to specify the location and identity of distinct thalamic nuclei around embryonic day 14 in mice. Cells in these putative thalamic sensory nuclei later exhibit gap junction-mediated spontaneous calcium waves that propagate among nuclei, altering the patterns of other nuclei's calcium waves and triggering changes in thalamic gene expression, which in turn alters the size of cortical fields [Moreno-Juan et al., 2017]. Further, these calcium transients also play an important role in establishing the internal organization of cortical fields via thalamocortical-corticothalamic interactions, since the elimination of the calcium transients disrupts the initial columnar organization of barrel cortex in mice and causes a delay in the maturation of corticothalamic axons [Antón-Bolaños et al., 2019; Moreno-Juan et al., 2020]. Perhaps the most important feature of spontaneous calcium waves is that they are modulated by peripheral input. While this has only been shown for the retina, it is probable that early spontaneous activity from somatosensory and auditory afferents from the skin and cochlea affect thalamic calcium waves in the same way. Regardless, the existence of peripheral control over thalamic and cortical patterning shows that while early morphogens and transcription factors play an initial role in cortical patterning, evolutionary tinkering with the ratio of sensory inputs and associated afferents alone is enough to drastically change subcortical and cortical structure and function. In summary, altering the way genes are expressed in the brain and body during development alters cell type, number, and location. Cells then undergo specific processes in specific locations (such as transient calcium waves in the thalamus), which then affect the development of brain regions (such as patterning of the cortex) (Fig. 1). Although epigenetic mechanisms also play a critical role in cortical development by enhancing or repressing the expression of different genes involved in brain and body development, altering where and when genes are expressed and the magnitude of their expression [Albert and Huttner, 2018; Elsen et al., 2018; Kawaguchi, 2019], a full discussion of this is beyond the scope of this review.

As described briefly at the beginning of this review, environmental context during development (sensory driven activity/affordances) also impacts cortical organization, connectivity, and functionality via activity-dependent mechanisms and changes to epigenetic markers. That is, neocortical structure and function are thought to be altered in a way that reflects the sensory receptor array and how it is used. For instance, decades of research in rats and mice have shown that the timing and type of visual experience onset controls the maturation and function of visual cortex via epigenetic activity-dependent mechanisms [Duffy and Mitchell, 2013; Ishikawa et al., 2014; Nott et al., 2015; Tropea et al., 2006]. To give one example, visual experience stimulates histone modifications near the transcription site of micro-RNA 132 (miR-132) in visual cortical neurons, resulting in the upregulation of the miR's expression [Tognini et al., 2011]. Importantly, the level of miR-132 expression regulates a number of developmental processes in primary visual cortex including the maturation of dendritic spines and synaptic transmission, both of which impact the receptive fields of neurons in V1 [Mazziotti et al., 2017]. Thus, the miR-132 pathway provides one mechanism by which sensory activity alters neocortical function. Sensory driven activity also generates systems-level changes by altering inhibitory parvalbumin (PV) networks, which play a key role in refining neocortical sensory and motor maps [Lunghi et al., 2015; Reh et al., 2020]. Dark rearing, monocular deprivation, whisker trimming, and environmental enrichment (i.e., changes in sensory driven activity within the lifetime of an individual) have all been shown to alter the maturation and function of PV-expressing inhibitory networks. One mechanism by which this may occur involves experience-dependent transsynaptic transfer of gene products from sensory afferents to cortical areas. Discovered by the Hensch lab, visual experience was found to facilitate anterograde cell-to-cell transfer of retina-derived *OTX2* homeoprotein through the LGN to visual cortex (V1) [Sugiyama et al., 2008]. Once aggregated in visual cortex, *OTX2* is taken up by PV cells, where it regulates the visual critical period by affecting extracellular matrix maturation [Rebsam and Mason, 2008; Beurdeley et al., 2012]. Thus, either a change in visual experience, a change in the presence, absence, or number of retinal afferents, or an epigenetic or genetic change to the transcription rate of *OTX2*, all effect the accumulation of the protein in visual cortex, thereby changing the duration of the visual critical period and ultimately the extent to which visual cortex function is shaped by the environment.

On a network level, numerous studies which blocked or weakened inhibitory neuron function, by using local infusion of bicuculine into specific cortical areas, have shown that altering levels of inhibition within cortical fields in turn alters the size of functional representations within those fields [Jacobs and Donoghue, 1991]. For instance, Brown et al. [2020] recently showed that infusing

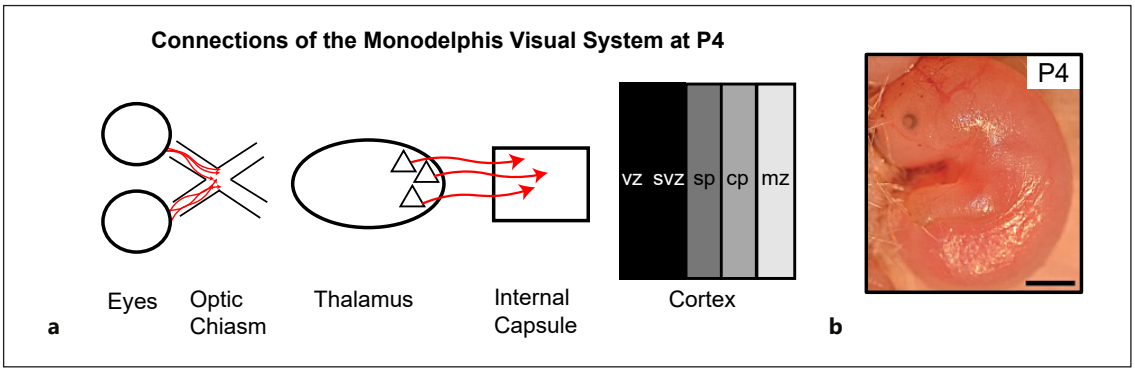

Fig. 2. Altering the ratio of sensory inputs in short-tailed opossums via bilateral enucleation. **a** Diagram showing the state of the nervous system at the time of enucleation. Red arrows indicate axonal projections and their location at postnatal day 4 (P4). **b** Image of P4 opossum. Scale bar is 1 mm. VZ, ventricular zone ; SVZ, subventricular zone; SP, subplate ; CP, cortical plate.

bicuculine into the motor cortex of rats during critical periods of development expanded the forelimb area of the motor map and altered the types of movements represented in motor cortex. While we limited our discussion to a few key ways in which sensory experience alters cortical area structure and function during short timescales, there are numerous ways in which sensory-driven activity modulates cortical development. These activity-based mechanisms (along with competition and self-organizing principles not discussed here) appear to be conserved across mammals, although species-specific differences in the cortical epigenome during development are not well studied [Kaschube et al., 2010]. At any rate, these changes occur over shorter timescales but can persist for generations if the sensory context is static, or if they are incorporated into the genome or epigenome. For this incorporation to occur, the differences in the DNA sequence or epigenetic marks that support these activity-dependent alterations must first become stable in a population. However, the transgenerational stability of allele frequencies and epigenetic markers is not well-studied in the context of the neocortex due to experimental constraints (only mammals have a neocortex), long generation times (even in mice), and the fact that genetics and epigenetics are constrained by absolute time (e.g., mutation rates). As the field of epigenetics continues to grow, we will gain the knowledge required to determine the transgenerational effects of experience on cortical development, organization, and function. For example, comparative analysis of area-specific (thalamus, cortex) single-cell sequencing experiments in developing, closely related species will solve many of the experimental difficulties posed by transgenerational studies. The experiments described in the following section outline some of the changes to the brain that can occur over short time scales compared with similar alterations to the brain that occur over longer, evolutionary timescales.

Mirroring Evolutionary Transformations with Developmental Manipulations

Comparative studies provide important insights into what happens when changes to developmental processes occur over long timescales and elucidate the types of systems level changes that evolution has produced. To study what these specific changes to developmental processes may be, and where in the nervous system they occur, we can "tweak" the nervous system in developing animals and determine if we can produce a phenotype that is consistent with what evolution has produced. Specifically, we experimentally induced a complete loss of input from the eyes to understand what happens to the neocortex when the ratio of incoming sensory inputs is dramatically altered, as is the case with extreme morphological specializations like the platypus and star-nosed mole. To accomplish this, our laboratory has worked on a highly altricial, slowly developing mammal, the short-tailed opossum (*Monodelphis domestica*). These animals have a well-developed visual system with a relatively large V1 compared to mammals with similar sized brains (e.g., mice, voles). We bilaterally enucleated opossums at early stages of development (P4; Fig. 2), prior to the onset of spontaneous activity in the retina, and well before ganglion cell axons

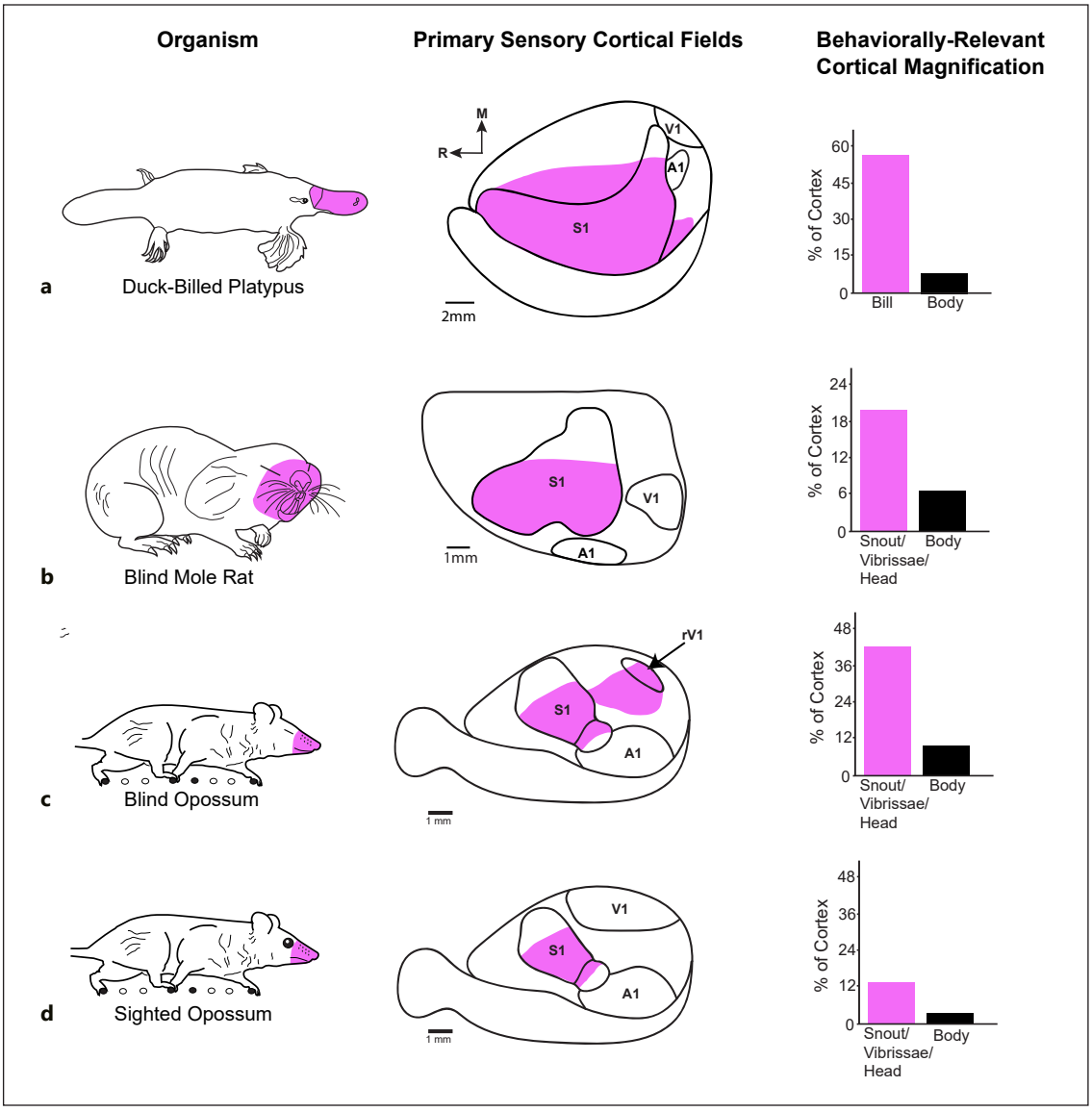

Fig. 3. Experimental manipulations can generate cortical phenotypes that resemble those produced naturally in evolution. **a** Image of the duck-billed platypus (left) and flattened cortex showing the approximate size and location of primary sensory cortical fields (middle). A disproportionately large portion of the cortex is occupied by somatosensory cortex. A large portion of the cortex is devoted to processing the bill (pink). Bar graph (right) shows the percentage of cortex (*y*- axis) occupied by the bill and body representation (*x*-axis), illustrating cortical magnification of the behaviorally relevant sensory organ. **b** Image of blind mole rat (left) and illustration of flattened cortex (middle) showing that S1 occupies a large proportion of the entire cortex and contains and enlarged representation of the snout vibrissae and head (pink). V1 in these animals has been co-opted by the auditory system. Bar graph (right) shows the percentage of cortex devoted to processing inputs from the snout head, and vibrissae. **c** Image of an early blind opossum (left) and corresponding illustration of flattened cortex showing architectonically defined primary sensory fields. Like the platypus and blind mole rat, a large proportion of cortex is devoted to processing the snout, vibrissae, and head, compared to sighted animals (pink). Like the blind mole rat, V1 in blind opossums has been co-opted by another sensory system (the somatosensory system). The bar graph to the right shows the percentage of cortex that represents the head, vibrissae, and snout. **d** Image of a sighted opossum (left) and flattened cortex with the location of V1, S1, and A1 (middle). Compared to early blind opossums, sighted animals have much less neocortex devoted to processing inputs from the snout, head, and vibrissae (bar graph; right). Illustrations and bar graphs were constructed with data from Krubitzer et al. [1995], Karlen et al. [2006], Kahn and Krubitzer [2002], Necker et al. [1992]. S1, primary somatosensory cortex; V1, primary visual cortex; A1, primary auditory cortex.

have reached the diencephalon (P5–P7) and thalamocortical axons have reached the developing cortex (P7 – P10; Molnár et al. [1998]).

After animals reached adulthood, we examined the size of cortical fields and thalamic nuclei, the functional organization and connections of the cortex, and sensory mediated behavior. We found that despite the complete removal of all visual inputs, we could still identify a primary visual area (V1) by its architecture, although it was extremely small [Kahn and Krubitzer, 2002). Functional mapping using electrophysiological recording techniques revealed that what would normally be V1 was co-opted by the somatosensory and auditory systems [Kahn and Krubitzer, 2002; Karlen et al., 2006]. Interestingly, neurons in this reorganized V1 responded almost exclusively to stimulation of the snout, face, vibrissae, and head. More recent studies in bilaterally enucleated opossums reveal functional changes response properties of neurons in the primary somatosensory area (S1) as well. For example, neurons in S1 have smaller receptive fields and greater discriminability compared to sighted animals [Ramamurthy and Krubitzer, 2018]. Together, these alterations in the size and functional organization are reminiscent of what evolution has produced in the platypus and blind mole rat (Fig. 3). Specifically, like the platypus, bilaterally enucleated opossums have a huge swath of cortex that represents a behaviorally relevant sensory surface (the whiskers; Fig. 3c). The reduced size of V1 that is co-opted by the spared sensory systems in bilaterally enucleated opossums is also reminiscent of blind mole rats, in which V1 is reduced in size and has been co-opted by the auditory system [Bronchti et al., 1989].

As observed in comparative studies, our experimental studies show that alterations in the size and function of a structure are not limited to the cortex but are observed in the dorsal thalamus. To quantify these observations, we measured the volume of principal sensory nuclei in the thalamus: the dorsal lateral geniculate (LGNd: visual) and ventral posterior nucleus (VP: somatosensory), of early blind and sighted opossums by measuring the surface area of each nucleus across coronally sectioned tissue stained for either cytochrome oxidase, acetylcholinesterase, or NISSL substance. This investigation first confirmed previous work from our laboratory that the size of LGNd is dramatically decreased in early blind opossums both in absolute and relative size when scaled by brain weight [Karlen and Krubitzer, 2009]. On the other hand, in agreement with recent work in embryonically enucleated mice, we found no difference in the absolute volume of VP between early blind and sighted opossums (Fig. 4a). However, when scaled by brain weight, thalamic and brainstem volume, or by the size of another nucleus (mediodorsal), VP was significantly larger in early blind opossums compared to sighted controls (Fig. 4b). Interestingly, for individuals whose VP and S1 were measured, we found a similar scaling relationship for the volume of VP and the surface area of S1 for both early blind and sighted opossums (Fig. 4c). Likewise, LGNd and V1 scaled similarly in blind and sighted opossums (Fig. 4d). This was intriguing, as recent work has shown that higher-order cortical areas scale in size with primary cortical fields, suggesting that thalamic nuclei, primary and higher order cortical fields all share a specific scaling relationship [Zembrzycki et al., 2015]. Viewed through an evolutionary lens, our thalamic and cortical measurement data in short-tailed opossums shows that we can mimic evolutionary phenotypes by tweaking particular neural structures at particular developmental stages. In this case, we altered the ratio of sensory inputs experimentally. However, evolution has done this over the long timescale by altering peripheral morphology and receptor arrays (e.g., duck billed platypus, star-nosed mole, and blind mole rat). Importantly, our experimental manipulation demonstrates that dramatic phenotypic changes to the cortex and thalamus are possible by simply altering incoming sensory input during early development, although this is unlikely to be the sole driver of phenotypic change to the cortex and thalamus.

In addition to alterations in cortical field/thalamic nuclei size and functional organization, there are significant alterations in cortical and thalamocortical connections of both the targeted system and the spared sensory systems. V1 in bilaterally enucleated opossums still received input from cortical fields and thalamic nuclei associated with visual processing, as in sighted animals, but the density of those inputs was decreased. This retention of visual pathways in the absence of functional vision is also observed in naturally evolved mammals, such as the blind mole rat [Cooper et al., 1993]. In addition to retained connections, V1 in early blind animals had a variety of aberrant connections from cortical and thalamic nuclei of the spared sensory systems. For example, V1 received input from somatosensory (S1), auditory (A1) cortex, and frontal cortex [Dooley and Krubitzer, 2019; Karlen et al., 2006). V1 also received input from thalamic nuclei associated with somatosensory (ventral posterior nucleus) and auditory processing (medial geniculate nucleus). These same changes in subcortical inputs to V1 have also been reported in anophthalmic mice [Chabot et al., 2008; Charbonneau et al., 2012]. Interestingly, the cortical connec-

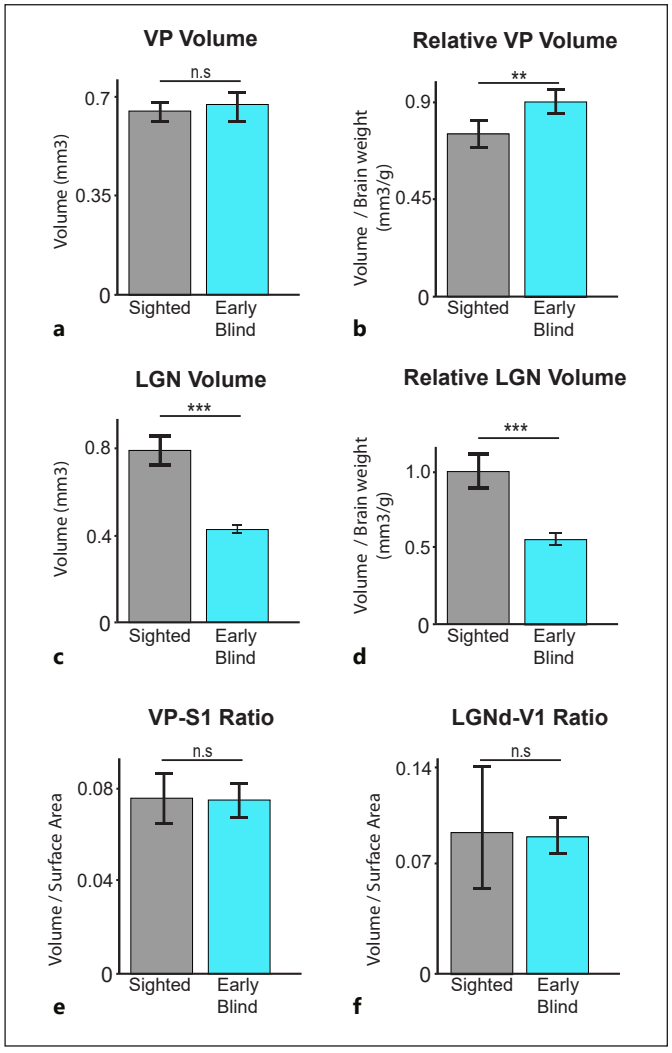

Fig. 4. Measurements of thalamic nuclei in early blind and sighted opossums. Bar graphs show that early blind opossums (blue) have a similar VP volume compared to sighted controls (gray) when measured in absolute size (**a**) ($p(14) = 0.505$), but have a relatively larger VP volume when scaled by brain weight (**b**) ($p(14) = 0.01$). **c**, **d** Early blind opossums exhibit a reduction in the size of LGN when measured in absolute ($p(24) < 0.001$) or relative terms ($p(24) < 0.001$). **e** Bar graphs showing that the size of VP scales with the size of S1 equally in early blind and sighted animals ($p(8) = 0.922$). **f** Similarly, LGN volume scales with the area size of V1 in both groups ($p(8) = 0.893$). These results suggest a tight scaling relationship between the volume of thalamic nuclei and the size of cortical fields. Bar graphs are shown as mean with 95% confidence intervals. VP, ventral posterior nucleus; LGN, lateral geniculate nucleus; S1, primary somatosensory cortex; V1, primary visual cortex.

tions of spared sensory systems were also altered in that S1 received projections from auditory cortex, multimodal cortex and architectonically defined visual areas. While the corticocortical connections of V1 in the blind mole rat have yet to be directly studied, 2-deoxyglucose and subcortical tracing experiments have shown that auditory activation of visual cortex appears to be mediated by projections from the inferior colliculus to the dLGN [Bronchti et al., 2002; Doron and Wollberg, 1994]. Interestingly, in anopthalmic mice and early enucleated hamsters, the LGN also receives input from the inferior colliculus, a structure associated with auditory processing [Bronchti et al., 2002; Izraeli et al., 2002; Piché et al., 2004]. The true similarities and differences in thalamic and cortical connections between experimentally and evolutionarily produced phenotypes will need to be elucidated with anatomical tracing experiments in blind mole rats.

Taken together, our experimental manipulations (tweaks) in developing animals are consistent with the types of changes naturally produced over longer time scales. This leads to two conclusions. First, altering the ratio of sensory input through genetically mediated changes to sensory organs (e.g., eyes, cochlea, skin) that have occurred over the long time scale of evolution could induce massive changes to the neocortex and dorsal thalamus without direct genetic alterations to these structures. Second, large alterations could occur over short timescales if the sensory inputs and environmental context are altered (e.g., movement towards nocturnality, cave dwelling, burrowing). The conditions under which these short timescale alterations could occur have been previously discussed [Krubitzer and Seelke, 2012].

What about Behavior?

While genes are heritable and are passed on through generations, and have a causal effect linked to characteristics of development and the ultimate phenotype that emerges, genes are not the direct targets of selection. Rather, genes co-vary with the targets of selection. It is the behavior an animal generates, its morphological phenotype and even its extended phenotype that are the targets of selection [Krubitzer and Seelke, 2012]. Thus, our laboratory embarked on a series of experiments in which we examined behavior mediated by the spared sensory systems in bilaterally enucleated animals. First, we trained early blind and sighted opossums to perform a two-alternative force choice texture discrimination task and found that early blind animals outperformed sighted animals in discrimination accuracy (i.e., blind animals were more sensitive to small differences in textures) [Ramamurthy et al., 2021] (Fig. 5 a, b). Second, we used a variable ladder rung paradigm to study un-trained, naturalistic naviga-

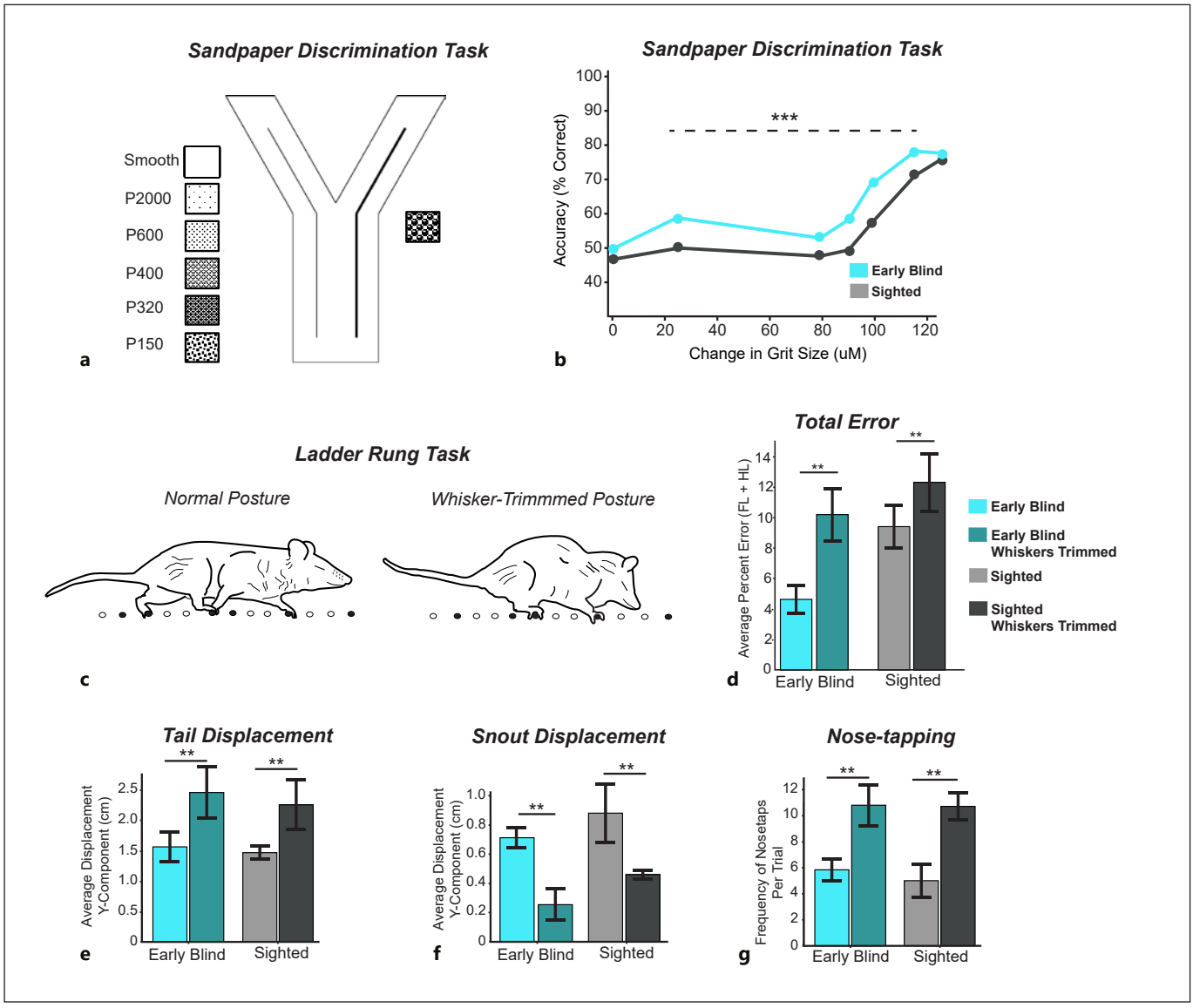

Fig. 5. Altering the ratio of sensory inputs alters behavior. **a** Illustration of the two-choice Y-Maze task. Opossums were trained to discriminate between different grits of sandpaper and rewarded for correct decisions. **b** Line graphs showing accuracy in determining changes in grit size. Early blind opossums (blue) can discriminate between finer changes in texture than sighted opossums (gray) (two-way ANOVA: $p < 0.001$). **c** Illustrations of opossums on the ladder rung task. When the whiskers are present, animals show a standard posture, with a raised snout and long strides (left). When the whiskers are trimmed, both early blind and sighted opossums show a hunched posture (right). **d** Bar graph showing total error on the ladder task before and after whisker trimming. Darker colors denote whisker-trimming scores. A main effect was found for the presence of whiskers on performance ($p = 0.004$) and for early blind opossums performing better than sighted controls ($p = 0.007$). **e**–**g** Bar graphs showing aspects of body posture during ladder crossing, indicating that both animals adopted changes in strategy when the whiskers were trimmed (**e**: $p = 0.042$, **f**: $p = 0.004$, **g**: $p = 0.002$). Bar graphs are shown as mean with bootstrapped 95% confidence intervals. Figures reprinted with permission [Englund et al., 2020, Ramamurthy et al., 2021].

tion in early blind and sighted opossums (Fig. 5c). We found that early blind opossums outperformed sighted animals and had increased limb placement accuracy compared to sighted controls, while showing similarities in kinematics and crossing time [Englund et al., 2020] (Fig. 5d). Moreover, in both of these studies, whisker trimming decreased accuracy and altered the strategies animals employed to complete the tasks. In the discrimination task,

whisker-trimmed opossums closely contacted the walls of the apparatus to gain sensory information. In the navigation task, animals compensated for the lack of whiskers by holding their snout closer to the rungs and tapping the rungs significantly more times to gain sensory information. Also, in the ladder rung task, whisker trimming affected early blind opossums to a greater extent than sighted animals and forced smaller forelimb trajectories during crossing and a more cautious approach to navigating the ladder (Fig. 5e, f). These studies, along with those conducted in other animal models and congenitally blind humans show that the loss of one sense leads to enhanced performance on tasks involving the spared senses [Ricciardi et al., 2014]. These enhanced tactile behaviors are reminiscent of other mammals with specialized tactile behaviors such as the blind mole rat, mouse, and rat. Thus, experimentally or naturally altering the ratio of sensory inputs allows for specialized behavior, which can then be selected on by the environment.

Conclusions

Above, we presented data from our own and other laboratories showing how manipulations made to the developing nervous system can mirror evolutionary-produced phenotypes in brain and behavior. By making these manipulations and comparing how they alter development and ultimately the adult phenotype, we can learn where and when evolution has tinkered with the developmental program to create species-level variation. Yet the extent to which these developmental tweaks recapitulate evolutionary processes is still unknown. However, it is clear from both comparative and developmental studies that there is no single factor that contributes to phenotypic change. Rather, there are multiple mechanisms that operate at multiple levels of organization (e.g., sensory epithelium, body morphology, dorsal thalamus, neocortex) that can produce similar phenotypic outcomes, and the environmental context in which an animal develops can impact these mechanisms and in turn the cortical phenotype. Any animal is a combination of these different factors that contribute to the phenotype of the brain, the body and behavior, and this "combinatorial creature" can emerge over the longer time scale of evolution and the shorter timescale of an individual lifetime [Krubitzer and Prescott, 2018].

Conflict of Interest Statement

The authors declare that they have no competing interests.

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Author Contributions

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References

Adam MA, Harwell CC. Epigenetic regulation of cortical neurogenesis; orchestrating fate switches at the right time and place. Curr Opin Neurobiol. 2020;63:146–53.

Albert M, Huttner WB. Epigenetic and transcriptional pre-patterning: an emerging theme in cortical neurogenesis. Front. Neurosci.. 2018; 12:359.

Antón-Bolaños N, Sempere-Ferràndez A, Guillamón-Vivancos T, Martini FJ, Pérez-Saiz L, Gezelius H, et al. Prenatal activity from thalamic neurons governs the emergence of functional cortical maps in mice. Science. 2019;364:987–90.

Arai Y, Pierani A. Development and evolution of cortical fields. Neurosci Res. 2014;86:66–76.

Ashwell KW. Development of the dorsal and ventral thalamus in platypus (*Ornithorhynchus anatinus*) and short-beaked echidna (*Tachyglossus aculeatus*). Brain Struct Funct. 2012; 217:577–89.

Baldwin MK, Wong P, Reed JL, Kaas JH. Superior colliculus connections with visual thalamus in gray squirrels (Sciurus carolinensis): evidence for four subdivisions within the pulvinar complex. J Comp Neurol. 2011;519:1071–94.

Bales KL, Witczak LR, Simmons TC, Savidge LE, Rothwell ES, Rogers FD, et al. Social touch during development: long-term effects on brain and behavior. Neurosci Biobehav Rev. 2018;95:202–19.

Beurdeley M, Spatazza J, Lee HH, Sugiyama S, Bernard C, Di Nardo AA, et al. Otx2 binding to perineuronal nets persistently regulates plasticity in the mature visual cortex. J Neurosci. 2012;32(27):9429–37.

Bronchti G., Heil P., Sadka R., Hess A., Scheich H., Wollberg Z. Auditory activation of "visual" cortical areas in the blind mole rat (*Spalax ehrenbergi*). Eur J Neurosci. 2002;16:311–29.

Bronchti G, Heil P, Scheich H, Wollberg Z. Auditory pathway and auditory activation of primary visual targets in the blind mole rat (*Spalax ehrenbergi*): I. 2-deoxyglucose study of subcortical centers. J Comp Neurol. 1989;284: 253–74.

Brown AR, Coughlin GM, Teskey GC. Seizures alter cortical representations for complex movements. Neuroscience. 2020;449:134–46.
Campi KL, Collins CE, Todd WD, Kaas J, Krubitzer L. Comparison of area 17 cellular composition in laboratory and wild-caught rats including diurnal and nocturnal species. Brain Behav Evol. 2011;77:116–30.
Cárdenas A, Villalba A, de Juan Romero C, Picó E, Kyrousi C, Tzika AC, et al. Evolution of cortical neurogenesis in amniotes controlled by robo signaling levels. Cell. 2018;174:590–606.e21
Catania KC, Kaas JH. The unusual nose and brain of the star-nosed mole: a star in the brain. BioScience. 1996;46:578–86.
Catania KC, Kaas JH. Organization of the somatosensory cortex of the star-nosed mole. J Comp Neurol. 1995;351:549–67.
Catania KC, Remple MS. Somatosensory cortex dominated by the representation of teeth in the naked mole-rat brain. Proc Natl Acad Sci U S A. 2002;99:5692–7.
Chabot N, Charbonneau V, Laramée ME, Tremblay R, Boire D, Bronchti G. Subcortical auditory input to the primary visual cortex in anophthalmic mice. Neurosci Lett. 2008;433:129–34.
Chalfin BP, Cheung DT, Muniz JA, de Lima Silveira LC, Finlay BL. Scaling of neuron number and volume of the pulvinar complex in new world primates: comparisons with humans, other primates, and mammals. J Comp Neurol. 2007;504:265–74.
Charbonneau V, Laramée ME, Boucher V, Bronchti G, Boire D. Cortical and subcortical projections to primary visual cortex in anophthalmic, enucleated and sighted mice. Eur J Neurosci. 2012;36:2949–63.
Cho KK, Khibnik L, Philpot BD, Bear MF. The ratio of NR2A/B NMDA receptor subunits determines the qualities of ocular dominance plasticity in visual cortex. Proc Natl Acad Sci U S A. 2009;106(13):5377–82.
Cholfin JA, Rubenstein JL. Frontal cortex subdivision patterning is coordinately regulated by Fgf8, Fgf17, and Emx2. J Comp Neurol. 2008;509:144–55.
Cooper HM, Herbin M, Nevo E. Visual system of a naturally microphthalmic mammal: the blind mole rat, *Spalax ehrenbergi*. J Comp Neurol. 1993;328:313–50.
Cretekos CJ, Wang Y, Green ED, Martin JF, Rasweiler JJ, Behringer RR. Regulatory divergence modifies limb length between mammals. Genes Dev. 2008;22:141–51.
Dooley JC, Donaldson MS, Krubitzer LA. Cortical plasticity following stripe rearing in the marsupial Monodelphis domestica: neural response properties of V1. J Neurophysiol. 2017 Feb;117(2):566–81.
Dooley JC, Krubitzer LA. Alterations in cortical and thalamic connections of somatosensory cortex following early loss of vision. J Comp Neurol. 2019;527:1675–88.
Doron N, Wollberg Z. Cross-modal neuroplasticity in the blind mole rat *Spalax ehrenbergi*: a WGA-HRP tracing study. NeuroReport. 1994;5:2697–701.
Duffy KR, Mitchell DE. Darkness alters maturation of visual cortex and promotes fast recovery from monocular deprivation. Curr Biol. 2013;23:382–6.
Elsen GE, Bedogni F, Hodge RD, Bammler TK, MacDonald JW, Lindtner S, et al. The epigenetic factor landscape of developing neocortex is regulated by transcription factors Pax6→ Tbr2→ Tbr1. Front Neurosci. 2018;12:571.
Englund M, Faridjoo S, Iyer CS, Krubitzer L. Available sensory input determines motor performance and strategy in early blind and sighted short-tailed opossums. iScience. 2020;23:101527.
Erzurumlu RS, Gaspar P. Development and critical period plasticity of the barrel cortex. Eur J Neurosci. 2012;35(10):1540–53.
Finlay BL, Uchiyama R. Developmental mechanisms channeling cortical evolution. Trends Neurosci. 2015;38(2):69–76.
Florio M, Albert M, Taverna E, Namba T, Brandl H, Lewitus E, et al. Human-specific gene ARHGAP11B promotes basal progenitor amplification and neocortex expansion. Science. 2015;347:1465–70.
Fukuchi-Shimogori T, Grove EA. Neocortex patterning by the secreted signaling molecule FGF8. Science. 2001;294:1071–4.
Gezelius H, Moreno-Juan V, Mezzera C, Thakurela S, Rodríguez-Malmierca LM, Pistolic J, et al. Genetic labeling of nuclei-specific thalamocortical neurons reveals putative sensory-modality specific genes. Cereb Cortex. 2017;27:5054–69.
Halley AC, Krubitzer L. Not all cortical expansions are the same: the coevolution of the neocortex and the dorsal thalamus in mammals. Curr Opin Neurobiol. 2019;56:78–86.
Heide M, Haffner C, Murayama A, Kurotaki Y, Shinohara H, Okano H, et al. Human-specific ARHGAP11B increases size and folding of primate neocortex in the fetal marmoset. Science. 2020;369(6503):546–50.
Hill J, Inder T, Neil J, Dierker D, Harwell J, Essen DV. Similar patterns of cortical expansion during human development and evolution. PNAS. 2010;107:13135–40.
Ishikawa AW, Komatsu Y, Yoshimura Y. Experience-dependent emergence of fine-scale networks in visual cortex. J Neurosci. 2014;34:12576–86.
Izraeli R, Koay G, Lamish M, Heicklen-Klein AJ, Heffner HE, Heffner RS, et al. Cross-modal neuroplasticity in neonatally enucleated hamsters: structure, electrophysiology and behaviour. Eur J Neurosci. 2002;15:693–712.
Jacobs KM, Donoghue JP. Reshaping the cortical motor map by unmasking latent intracortical connections. Science. 1991;251:944–7.
Kahn DM, Krubitzer L. Massive cross-modal cortical plasticity and the emergence of a new cortical area in developmentally blind mammals. Proc Natl Acad Sci U S A. 2002;99:11429–34.
Karlen SJ, Kahn DM, Krubitzer L. Early blindness results in abnormal corticocortical and thalamocortical connections. Neuroscience. 2006;142:843–58.
Karlen SJ, Krubitzer L. Effects of bilateral enucleation on the size of visual and nonvisual areas of the brain. Cereb Cortex. 2009;19:1360–71.
Kaschube M, Schnabel M, Löwel S, Coppola DM, White LE, Wolf F. Universality in the evolution of orientation columns in the visual cortex. Science. 2010;330:1113–6.
Kaskan PM, Franco ECS, Yamada ES, de Lima Silveira LC, Darlington RB, Finlay BL. Peripheral variability and central constancy in mammalian visual system evolution. Proc Biol Sci. 2005;272(1558):91–100.
Kawaguchi A. Temporal patterning of neocortical progenitor cells: how do they know the right time? Neurosci Res. 2019;138:3–11.
Krubitzer L. The magnificent compromise: cortical field evolution in mammals. Neuron. 2007;56:201–8.
Krubitzer L, Manger P, Pettigrew J, Calford M. Organization of somatosensory cortex in monotremes: in search of the prototypical plan. J Comp Neurol. 1995;351:261–306.
Krubitzer L, Stolzenberg DS. The evolutionary masquerade: genetic and epigenetic contributions to the neocortex. Curr Opin Neurobiol. 2014;24:157–65.
Krubitzer LA, Prescott TJ. The combinatorial creature: cortical phenotypes within and across lifetimes. Trends Neurosci. 2018;41:744–62.
Krubitzer LA, Seelke AM. Cortical evolution in mammals: the bane and beauty of phenotypic variability. Proc Natl Acad Sci U S A. 2012;109 Suppl 1:10647–54.
Liu J, Liu W, Yang L, Wu Q, Zhang H, Fang A, et al. The primate-specific gene TMEM14B marks outer radial glia cells and promotes cortical expansion and folding. Cell Stem Cell. 2017;21:635–49.e8
Liu Y, Vannuscorps G, Caramazza A, Striem-Amit E. Evidence for an effector-independent action system from people born without hands. Proc Natl Acad Sci U S A. 2020;117:28433–41.
Lunghi C, Emir UE, Morrone MC, Bridge H. Short-term monocular deprivation alters GABA in the adult human visual cortex. Curr Biol. 2015;25:1496–501.
Manger PR, Pettigrew JD. Electroreception and the feeding behaviour of platypus (ornithorhynchus anatinus: monotremata: mammalia). Philos Trans R Soc Lond B Biol Sci. 1995;347:359–81.
Mazziotti R, Baroncelli L, Ceglia N, Chelini G, Sala GD, Magnan C, et al. Mir-132/212 is required for maturation of binocular matching of orientation preference and depth perception. Nat Commun. 2017;8:15488.
Mikula S, Manger PR, Jones EG. The thalamus of the monotremes: cyto- and myeloarchitecture and chemical neuroanatomy. Philos Trans R Soc Lond B Biol Sci. 2008;363:2415–40.

Molnár Z, Knott GW, Blakemore C, Saunders NR. Development of thalamocortical projections in the South American gray short-tailed opossum (*Monodelphis domestica*). J Comp Neurol. 1998;398:491–514.
Moreno-Juan V, Filipchuk A, Antón-Bolaños N, Mezzera C, Gezelius H, Andrés B, et al. Prenatal thalamic waves regulate cortical area size prior to sensory processing. Nat Commun. 2017;8:14172.
Moreno-Juan V, Martini FJ, Pérez-Saiz L, Herrero-Navarro Á, Valdeolmillos M, López-Bendito G. Thalamic spontaneous activity coordinates the timing of corticothalamic innervation in the visual system. bioRxiv. 2020.
Necker R, Rehkämper G, Nevo E. Electrophysiological mapping of body representation in the cortex of the blind mole rat. Neuroreport. 1992;3:505–8.
Nott A, Cho S, Seo J, Tsai LH. HDAC2 expression in parvalbumin interneurons regulates synaptic plasticity in the mouse visual cortex. Neuroepigenetics. 2015;1:34–40.
Pantev C, Oostenveld R, Engelien A, Ross B, Roberts LE, Hoke M. Increased auditory cortical representation in musicians. Nature. 1998;392:811–4.
Petit F, Sears KE, Ahituv N. Limb development: a paradigm of gene regulation. Nat Rev Genet. 2017;18:245–58.
Pettigrew JD. Electroreception in monotremes. J Exp Biol. 1999;202:1447–54.
Piché M, Robert S, Miceli D, Bronchti G. Environmental enrichment enhances auditory takeover of the occipital cortex in anophthalmic mice. Eur J Neurosci. 2004;20:3463–72.
Ramamurthy DL, Dodson HK, Krubitzer LA. Developmental plasticity of texture discrimination following early vision loss in the marsupial *Monodelphis domestica*. J Exp Biol. 2021;224(9):jeb236646.
Ramamurthy DL, Krubitzer LA. Neural coding of whisker-mediated touch in primary somatosensory cortex is altered following early blindness. J Neurosci. 2018;38(27):6172–89.
Reh RK, Dias BG, Nelson CA, Kaufer D, Werker JF, Kolb B, et al. Critical period regulation across multiple timescales. Proc Natl Acad Sci U S A. 2020;117:23242–51.
Rebsam A, Mason CA. Otx2's incredible journey. Cell. 2008;134(3):386–7.
Rehkämper G, Necker R, Nevo E. Functional anatomy of the thalamus in the blind mole rat *Spalax ehrenbergi*: an architectonic and electrophysiologically controlled tracing study. J Comp Neurol. 1994;347:570–84.
Ricciardi E, Bonino D, Pellegrini S, Pietrini P. Mind the blind brain to understand the sighted one: is there a supramodal cortical functional architecture? Neurosci Biobehav Rev. 2014;41:64–77.
Robson JA, Hall WC. The organization of the pulvinar in the grey squirrel (*Sciurus carolinensis*). I. Cytoarchitecture and connections. J Comp Neurol. 1977;173:355–88.
Shulha HP, Crisci JL, Reshetov D, Tushir JS, Cheung I, Bharadwaj R, et al. Human-specific histone methylation signatures at transcription start sites in prefrontal neurons. PLoS Biol. 2012;10(11):e1001427.
Smaers JB, Rothman RS, Hudson DR, Balanoff AM, Beatty B, Dechmann DKN, et al. The evolution of mammalian brain size. Sci Adv. 2021;7(18):eabe2101.
Sugiyama S, Di Nardo AA, Aizawa S, Matsuo I, Volovitch M, Prochiantz A, et al. Experience-dependent transfer of Otx2 homeoprotein into the visual cortex activates postnatal plasticity. Cell. 2008;134(3):508–20.
Sur M, Rubenstein JL. Patterning and plasticity of the cerebral cortex. Science. 2005;310:805–10.
Suzuki IK, Gacquer D, Van Heurck R, Kumar D, Wojno M, Bilheu A, et al. Human-specific NOTCH2NL genes expand cortical neurogenesis through Delta/Notch regulation. Cell. 2018;173:1370–84.e16.
Tognini P, Putignano E, Coatti A, Pizzorusso T. Experience-dependent expression of miR-132 regulates ocular dominance plasticity. Nat Neurosci. 2011;14:1237–9.
Tomasello U, Klingler E, Niquille M, Mule N, de Vevey L, Prados J, et al. MiR-137 and miR-122, two outer subventricular zone-enriched non-coding RNAs, regulate basal progenitor expansion and neuronal differentiation. bioRxiv. 2021.
Tropea D, Kreiman G, Lyckman A, Mukherjee S, Yu H, Horng S, et al. Gene expression changes and molecular pathways mediating activity-dependent plasticity in visual cortex. Nat Neurosci. 2006;9:660–8.
Van Essen DC. Scaling of human brain size. Science. 2018;360:1184–5.
Van Essen DC, Dierker DL. Surface-based and probabilistic atlases of primate cerebral cortex. Neuron. 2007;56:209–25.
Wong P, Kaas JH. Architectonic subdivisions of neocortex in the gray squirrel (*Sciurus carolinensis*). Anat Rec. 2008;291:1301–33.
Young NA, Vuong J, Teskey GC. Development of motor maps in rats and their modulation by experience. J Neurophysiol. 2012;108:1309–17.
Zembrzycki A, Stocker AM, Leingärtner A, Sahara S, Chou SJ, Kalatsky V, et al. Genetic mechanisms control the linear scaling between related cortical primary and higher order sensory areas. Elife. 2015;4:e11416.