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Review

Genetic and epigenetic contributions to the cortical phenotype in mammals☆

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Abstract

One aspect of cortical organization, cortical field size, is variable both within and across species. The observed variability arises from a variety of sources, including genes intrinsic to the neocortex and a number of extrinsic and epigenetic factors. Genes intrinsic to the cortex are directly involved in the development and specification of cortical fields and are regulated from both signaling centers located outside of the neocortex, which secrete diffusible molecules, and the expression of transcription factors within the neocortex. In addition, extrinsic factors such as the type, location and density of sensory receptor arrays and how these receptor arrays are utilized, are also strongly related to cortical field size. Epigenetic factors including the relative activity patterns generated by the different types of physical stimuli in a given environment also contribute to differences in cortical organization, including cortical field size. Since both genetic and epigenetic factors contribute to cortical organization, some aspects of the cortical phenotype evolve, while other aspects of the cortical phenotype persist only if the environment in which an individual develops is relatively stable.

Keywords: Evolution; Cortical organization; Cortical development; Visual cortex; Auditory cortex; Somatosensory cortex

Contents

1. Introduction

For some time we have known that brains not only vary in size, but in their size relative to the size of the body, and that in some lineages, portions of the brain have expanded dramatically, such as the neocortex (Fig. 1). The expansion of the neocortex is one of the hallmarks of evolution of the primate brain, and the human brain in particular, and is believed to be associated with a number of complex behaviors such as perception, cognition and volitional motor control.

The increase in the size of the cortical sheet in some lineages is accompanied by a number of organizational changes that together are believed to account for a number of the sophisticated behaviors observed in mammals. Comparative studies indicate that the types of systems level alterations made to the neocortex are restricted and include changes in the relative size of cortical fields, the number of cortical fields, the internal organization of cortical fields, the connectivity of cortical fields, and in the addi-

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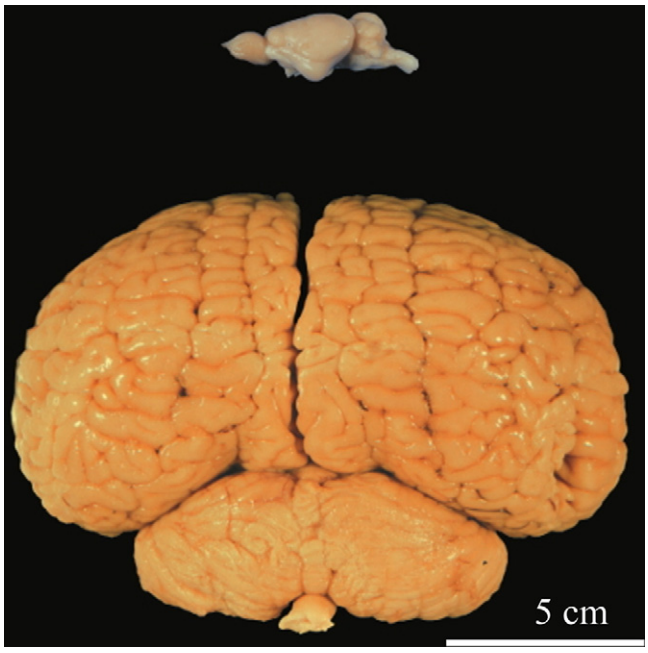

Fig. 1. The brain of the Australian quoll (top), which is a carnivorous marsupial, and the bottlenosed dolphin (bottom). These brains are radically different in overall size and in the size of their neocortex. In the quoll, the neocortex is small and smooth and in the dolphin the cortex is highly fissured, and greatly expanded. In the lateral view of the quoll brain, rostral is to the left and dorsal is to the top. In the caudal view of the dolphin brain, dorsal is to the top and lateral is to the left and right.

tion of modules to cortical fields. A cortical field is defined using a variety of criteria including architectonic distinctions, topographic organization, neuronal response properties, and cortical and subcortical connections [28,29,34]. One of these alterations, that of the size of cortical fields, is associated with differences in the functional organization of a cortical field, and with differences in behavior associated with a particular sensory system. The aim of this review is to examine the factors that contribute to changes in cortical field size both within a species and across species.

The observed differences in the size of a cortical field between species is either linear, and directly scales with the overall size of the body and the entire brain (Fig. 2) or non-linear and is related to the encephalization of the brain [6,25,50]. Encephalization is an increase in the size of the brain beyond what is expected for an animal of a given body size. With a non-linear increase in brain size, cortical fields do not directly scale with the size of the brain, but occupy varying percentages of the neocortex. With encephalization, more cortical fields are present.

Comparative studies also indicate that cortical field size is highly variable across species, and recent evidence demonstrates that cortical field size is variable within a species as well. Since cortical field size is a feature of neocortex that has been modified during evolution, both linearly and non-linearly, an important question to answer is what factors contribute to cortical field size differences within and across species? Are these differences genetically mediated, or due to differences in sensory driven activity that occur during the development of cortical fields? For example, does the expression of genes that are responsible for the patterning of the neocortex and ultimately the emergence of cortical fields during development, vary within and across species and correlate with changes in cortical field size? Or do factors extrinsic to the neocortex, such as alterations in sensory receptor arrays or sensory driven activity present during development, account for differences in cortical field size? Both comparative studies and studies of neural development have begun to address this question.

2. Comparative studies indicate that primary cortical fields vary in their relative size within and across groups of mammals

There is a wealth of data from comparative studies on neocortical organization in a variety of mammals that indicate that the different primary cortical fields assume different proportions of the cortical sheet both within a species and across species. For example, in rats, measurements of the primary somatosensory area (S1), demonstrate that it varies across individuals [48]. Studies in our own laboratory in the South American marsupial *Monodelphis domestica* demonstrate that all primary cortical areas vary in size across individuals, but this variability is minimal between hemispheres in the same individual [32]. This type of intraspecies variability in cortical field size has also been observed for humans and a number of other species [13,19,24,36,41,46,48,53]. Variability in the size of cortical fields across mammals appears to be associated with lifestyle, morphological specialization, and species-specific behaviors. One of the best examples of cortical field size magnification associated with morphology and lifestyle is the duck-billed platypus. In the platypus, S1 assumes 50% of the cortical sheet, which is substantially more than the small fraction of the cortical sheet occupied by A1 and V1 [39]. This enlarged representation of S1 is dominated by the representation of the bill which contains interdigitated multiple rows of electrosensory and mechanosensory receptors. The platypus uses these receptors on the bill for making fine tactile discriminations, navigation, prey detection, and prey capture. These differences in the relative size of cortical fields within a species and their relationship to behaviorally relevant body parts and behaviors have been described in a number of other mammals as well ([7–9,22,36], see [26,34,38] for review).

We have recently begun to quantify the differences in the relative size of primary sensory areas in the mouse, the short-tailed opossum, and the prairie vole [5,23,32], and have found significant differences in cortical field size in each species which appear to be related to morphology and lifestyle (Fig. 3). This relationship between specialized peripheral morphology, unique behaviors associated with morphology and cortical field size indicates that factors extrinsic to the neocortex must play a large role in development when cortical fields are forming. However, the extent to which these extrinsic factors contribute to cortical field size is unknown.

While the relationship between body morphology, use of sensory receptor arrays, and cortical organization is well established, it is clear that intrinsic factors to the neocortex, such as signaling molecules and transcription factors (see below),

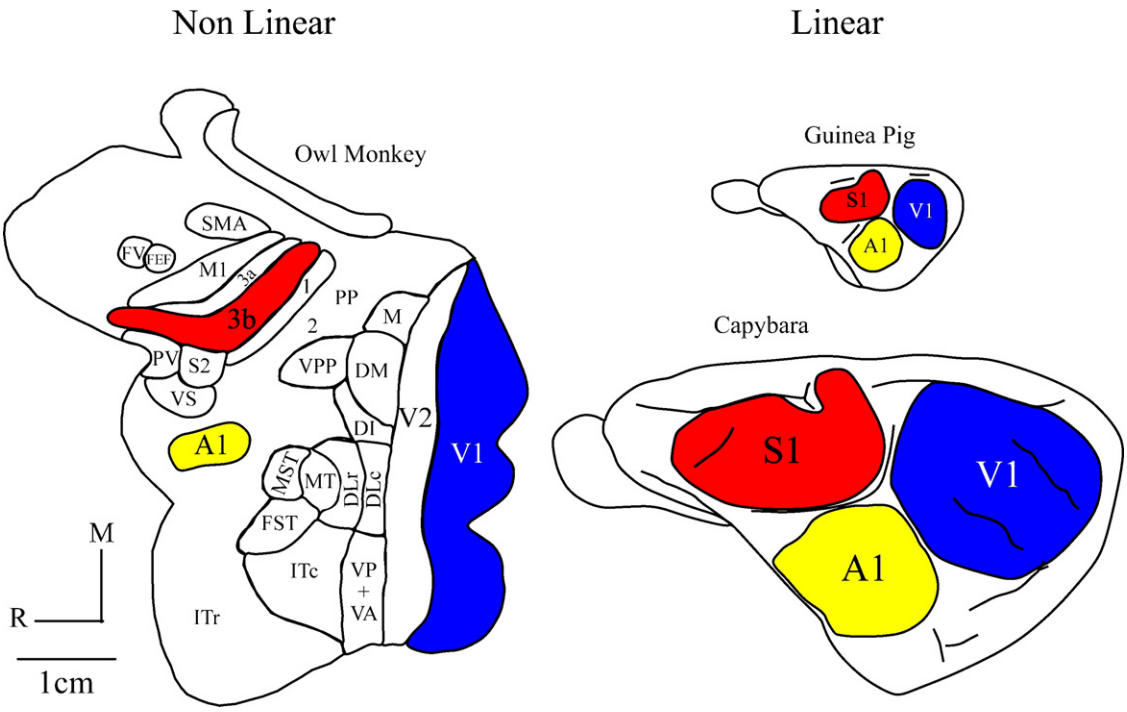

Fig. 2. Tangential views of three species of mammals with differences in the size of their cortical sheet and the relative size of cortical fields. When one compares the brains of the small guinea pig to the brain of the large capybara, it is clear that the increase in the size of the cortex and cortical fields (V1, A1, S1), scales in a linear fashion with increases in the size of the body and brain. Non-linear changes in the size of cortical fields are also observed. For example, the brain of the relatively small owl monkey is larger than that of the capybara, whose body size is at least eight times that of the owl monkey. The cortical sheet and some of the cortical fields have increased in size in a fashion that is not scaled directly to the size of the body. The increase in the size of the neocortex in the owl monkey is accompanied by an increase in the number of cortical fields. This is not observed with linear increases in brain size, such as that observed in the capybara. 3b (S1): the primary somatosensory area; A1: the primary auditory area; V1: the primary visual area; r: rostral; m: medial. The other abbreviations in the monkey brain indicate the names of individual cortical areas. All brains are drawn to scale. Adapted from [6,35,37].

must also contribute to the presence, location and organization of cortical fields. For example, in the subterranean blind mole rat, the eyes have been greatly reduced in size (microophthalmic) and skin has grown over the eyes. These animals are considered to be completely blind, and use their visual system only for circadian functions [10]. Despite the fact that these animals are blind, they still possess a cortical field that can be architectonically defined as V1, and receives inputs from the main "visual" nucleus of the thalamus, the lateral geniculate nucleus (LGN). However, the size of "V1" in these animals is very small, and the LGN receives abnormal inputs from the inferior colliculus [12], a structure normally associated with auditory processing. Similar observations have been made in mice completely lacking eyes (anophthalmic mice). In these mice, V1 (defined architectonically) is still present and receives input from the LGN. However, the LGN receives abnormal input from the dorsal column nucleus, a structure associated with somatosensory processing [1]. These two examples demonstrate that even in the absence of use, or in the absence of the sensory receptor array itself, aspects of cortical organization are still present, suggesting that intrinsic influences (genes) constrain cortical field evolution.

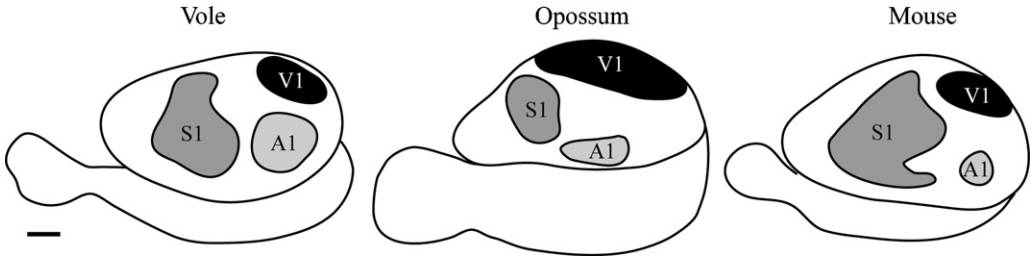

Fig. 3. Tangential views of three different species of mammals with a similar size cortex but with differences in the relative size of their cortical fields. In the auditory vole, A1 assumes a large portion of the cortical sheet compared to A1 in other mammals. In the visual opossum V1 occupies a relatively large portion of the cortical sheet, and in the mouse S1 occupies a relatively large portion of the cortical sheet. Each of these species has a different reliance on each of its sensory systems and this is reflected in the relative size of the different primary cortical areas. Rostral is to the left and medial is to the top. S1: the primary somatosensory area; A1: the primary auditory area; V1: the primary visual area. Scale bar = 1 mm. Adapted from [5].

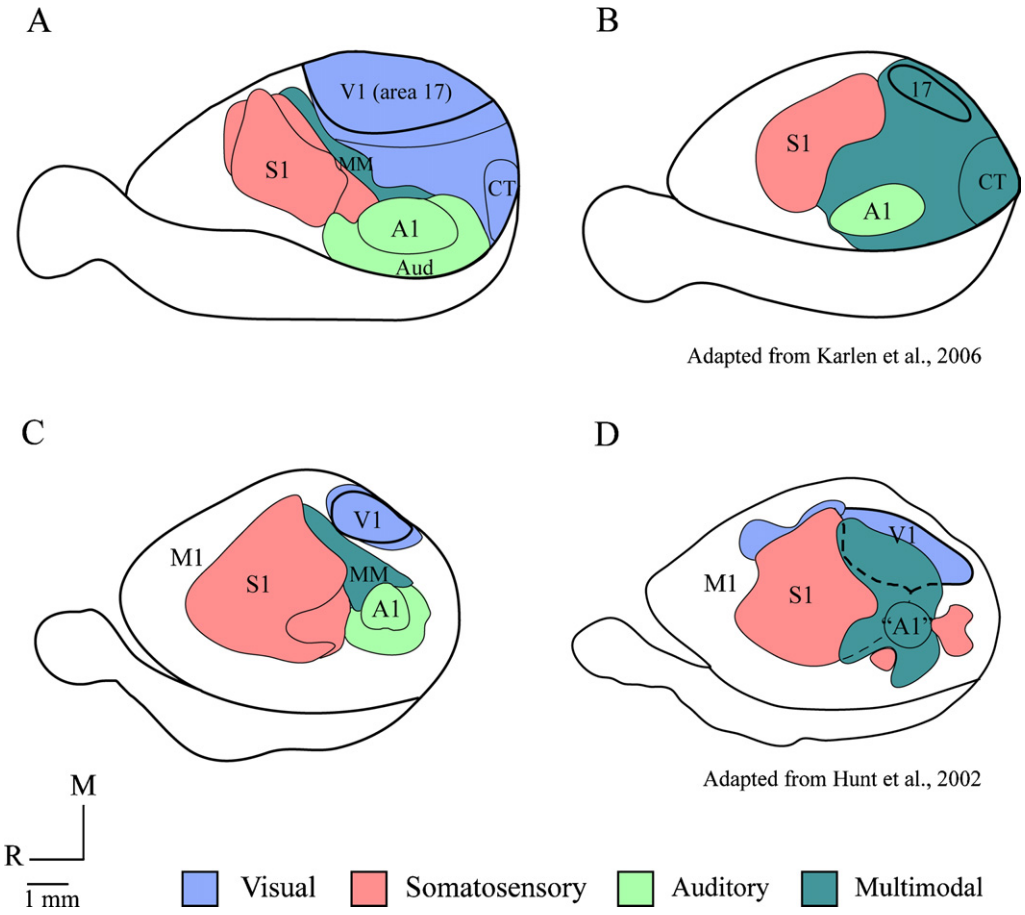

Fig. 4. Tangential view of normal (A) and bilaterally enucleated opossum (B), and the normal (C) and congenitally deaf (D) mouse. The amount of cortex assumed by a particular sensory system changes with alterations in sensory driven activity that arise with loss of a sensory receptor array (bilaterally enucleated animals) or with loss of sensory driven activity (congenitally deaf mouse). These alterations are accompanied by changes in the size of cortical fields. V1 becomes smaller in the bilaterally enucleated opossum. With loss of auditory driven activity, A1 becomes smaller and V1 becomes larger in the congenitally deaf mouse. These deprived areas in each species are taken over by the remaining sensory systems. Conventions as in Fig. 3.

3. Genes are involved in the determination of cortical field size and location within a population

A number of recent studies have demonstrated the important role of specific genes in the generation of cortical fields during development. For example, very early in the developing telencephalon, well before cortical fields have emerged, early signaling centers secrete molecules such as Fgf8, Wnt3a, Shh and Bmp4, which direct the graded expression of transcription factors, or regulatory genes, such as *Emx2*, *Pax6* and *Lhx2*, which in turn regulate patterning in the developing cortex (see [16,43,45,51] for review). These signaling centers are regionally organized, and alterations in their pattern of expression result in alterations in cortical field size and location (e.g. [14,15]). Transcription factors such as *Emx2* and *Pax6*, are graded in their expression in the caudorostral (*Emx2*) and rostrocaudal (*Pax6*) axis and regulate the region-specific expression of other genes which encode cell adhesion molecules such as the cadherins (e.g. *Cad 6, 8* and *11*), other transcription factors such as *Tbr1*, and axon guidance molecules such as *ephrinA-5*. As with the signaling centers, disruption of these transcription factors alters the size and relative location of emerging cortical fields (e.g. [2,17]).

Genes regulated by early transcription factors (e.g. *Cad 6, 8, 11, Tbr1*; and *ephrinA-5*) are regionally expressed in the neocortex and localized to one or more cortical fields, although a direct link has not been established. These genes are involved in a variety of functions in the developing neocortex and establish the histological, functional, neuroanatomical, and molecular identities of individual cortical fields [4,20,21,40,44,52,54]. The expression of many of these genes is intrinsically mediated and can persist in the absence of thalamocortical input, at least until birth [42,44].

This brief description of the series of genetic events that establish cortical field identity is certainly not exhaustive, and without exception, most of what we know about the genetic and molecular development of the neocortex comes from studies of mice. However, it is clear that genes act in a sequential and combinatorial fashion, and that an alteration in the spatial and temporal pattern of expression at any stage could result in dramatic changes in the resulting cortex. While our understanding of these events has crystallized in the last decade, we know very little about how the expression of these genes at different stages of development varies across species to produce differences in cortical field size and location.

4. Factors extrinsic to the cortex are involved in the determination of cortical field size

There are several studies that have examined the role of extrinsic factors, such as patterned activity, on the size of a cortical field. Many of these studies have examined the effect of the loss of a sensory system or sensory driven activity on the size of cortical fields. For example, studies in which prenatal monkeys were bilaterally enucleated and examined after development was complete demonstrate that V1 was dramatically reduced when compared to normal animals (e.g. [47]). A similar finding was demonstrated in bilaterally enucleated short-tailed opossums [30]. In addition, we also examined the functional organization of "V1" in these animals and described the connections of this field. Our data demonstrate that cortex that was architectonically defined as V1 contained neurons that responded to auditory and somatosensory stimulation, and that V1 not only received thalamic inputs from the LGN, as in normal animals, but also from nuclei such as the ventral posterior nucleus, associated with somatosensory processing, and the medial geniculate nucleus, associated with auditory processing (Fig. 4) [31]. This change in cortical field size, function and connectivity with loss of a sensory receptor array during development appears to be a general feature of mammalian sensory cortex. This idea is substantiated in studies of congenitally deaf mice (due to abnormal ion transport in the cochlea), which lack auditory driven activity from the cochlea. Examination of the neocortex in these mice indicates that A1, as architectonically defined, was reduced in size and that V1 increased in size (Fig. 4) [23]. Further, neurons in A1 of these mice respond to visual and somatosensory stimulation. Together, these studies demonstrate that extrinsic factors such as patterns of activity from a particular sensory receptor array also contribute to cortical field size in the developing brain. The series of events and the mechanisms involved that leads to these changes in the size of cortical fields are not well understood.

5. Epigenetic factors contribute to the size of a cortical field

Factors, such as alterations in peripheral morphology and sensory receptor arrays, contribute to aspects of cortical organization (see [38] for review). While these factors are extrinsic to the developing neocortex, they are intrinsic to the animal and, to a large extent, are genetically regulated. However, these specialized sensory receptor arrays transduce particular types of physical stimuli such as photons, displacement of skin and hairs, and movement of molecules within a particular medium, such as air or water. The physical stimuli can be considered epigenetic, but the combination of activity patterns that they generate within a particular organism is dependent on the type, density, and distribution of sensory receptors present within any given animal. While they can be termed epigenetic, their unique influence on any given neocortex cannot be completely separated from the genes that construct both neural and non-neural tissue. Thus, the boundary between intrinsic genetic contributions to the phenotype and activity-dependent or environmental contributions is often fuzzy.

In fact, the genes involved in setting up the body plan organization (e.g. *Hox* genes), do not exclusively determine the final morphology of a particular body part, nor, indirectly, the resultant cortical organization. For example, use of the structure during development also can affect the morphology of the structure itself (which in turn may affect some aspect of cortical organization). Several studies have shown that alterations in mastication behavior in development, brought about by changes in diet, have a direct effect on craniofacial morphology [18], skull dimensions [33], mandibular morphology [3], and bone density [11]. The types of diet that produce such alterations during development are associated with hard versus soft food sources and the presence or absence of particular nutrients. Other epigenetic factors that directly contribute to the development of body morphology and indirectly to cortical organization are temperature, salinity, humidity (see [27] for review) and even gravity (e.g. [49]). The observation that body plan morphology can be altered by epigenetic factors is analogous to the observations made for the neocortex. That is, despite the very large constraints imposed by regulatory genes on fundamental aspects of body morphology or cortical organization, a large degree of phenotypic variability is still possible, and alterations to the body plan can indirectly alter cortical organization.

6. Conclusions

Our brief review on the factors that contribute to cortical field size, only one aspect of the overall cortical phenotype, indicates that this particular phenotypic characteristic, and likely that of a number of neural and non-neural phenotypic characteristics, can be altered by both genes that regulate aspects of the brain and body, and neural activity generated in specific sensory environments. It is likely that these intrinsic, extrinsic and epigenetic factors do not act in isolation to produce a particular size of a cortical field, but rather work as an integrated network that includes the brain, the body, the physical environment, and for higher order cortical areas, conspecifics, and other species which inhabit the same niche.

We know that genes intrinsic to the developing neocortex can have a direct effect on cortical field size and location. In addition, genes that regulate aspects of body morphology and sensory receptor array type, distribution and density can affect cortical field size. The fact that genes function in a combinatorial and sequential fashion during development to construct a nervous system, and that single genes often perform a number of functions (pleiotropy), constrain the evolution of the nervous system.

The unique combination of sensory driven activity that occurs during development can also influence cortical field size. Energy within a given environment is transduced through an adapted filter system, the sensory receptor arrays, associated with different sensory systems. These filters differ in type, location, and sensitivity across different mammals. Energy (e.g. photons) and the laws of physics are invariant, and thus impose another set of constraints that influence the evolving sensory receptors and cortical field size.

Despite the different constraints imposed by genes and the physical environment, the cortical phenotype can be highly variable both within and across species. This phenotypic flexibility comes about in several ways. The first source of phenotypic flexibility is from variability in both the spatial and temporal expression of genes intrinsic to the neocortex. The second source of phenotypic flexibility is variability in peripheral morphology and receptor distribution. This variability in the peripheral morphology is also influenced by variability in expression of genes involved in patterning of the body early in development, as well as variability in use of the structure, and epigenetic factors such as diet, temperature, and pH. The last source of phenotypic flexibility is the unique pattern of activity present in any given environment which impinges on the developing sensory receptors and ultimately the neocortex. All of these factors combine to produce great diversity in size, internal organization, connections and function of cortical fields in the face of the serious constraints imposed by genes and the physical parameters of the environment. This cortical diversity generates a wide range of behaviors, which are the target of selection. Given that the cortical phenotype that generates this diverse behavior is determined through genetic and epigenetic interactions, this would suggest that only some aspects of the cortical phenotype, those controlled by genes, can be inherited and evolve, while other aspects of the cortical phenotype, those shaped by epigenetic factors, are context-dependent and persist only if the environment in which an individual develops is relatively stable.

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