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The evolutionary masquerade: genetic and epigenetic contributions to the neocortex

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The neocortex is a defining feature of the mammalian brain and its expansion is one of the hallmarks of human evolution. Given the complexity of human behavior, it is tempting to think that as a species humans are exclusive compared to other animals. However, comparative studies indicate that human brains follow the same rules of construction and that alterations to the human neocortex take a similar form as in other mammals. Studies from a number of disciplines indicate that many of the morphological specializations associated with the vocal tract, ear and hand were present in early hominins and thus our ancestors had the capacity for speech, language and sophisticated manual abilities, yet much of modern human behavior evolved very recently. In this review, we discuss the possibility that phenotypic changes in modern human brains and behavior may have been mediated by epigenetic mechanisms that allowed for context dependent changes to the cortical phenotype. Further, we consider whether these epigenetic mechanisms may be more readily engaged in humans than in other species in order to rapidly meet the demands of a dynamic environment. We suggest that perhaps it is the extent to which the neocortex incorporates these context dependent alterations that distinguishes humans from other mammals.

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Introduction

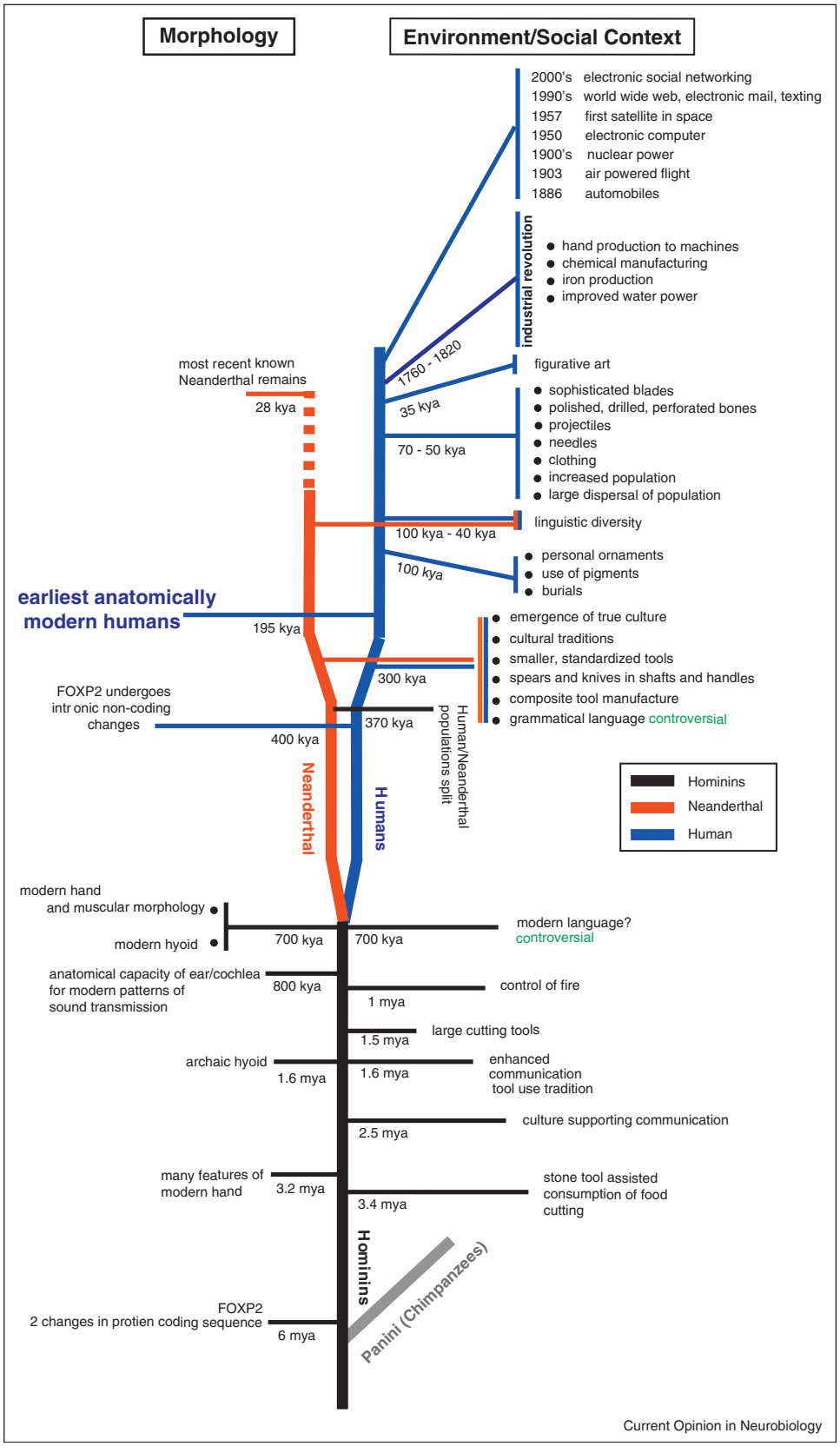
When considering the evolution of the neocortex it is crucial to take into account the morphological features of the body and its sensory effectors, the environmental context in which an individual brain develops, and for mammals like humans, the social milieu in which an individual brain must behave. Simply put, the brain does not evolve in isolation, but in a larger context that at a minimum contains the elements described above. Further, in our urgent quest to decode as many genomes as possible with the promise of gaining some deep understanding of species differences... of what makes humans... human, we overlook a fundamental tenet of biology. Body morphology and behavior are the targets of natural selection, not genes or brains (for review see [1•]). Further, the actual evolution of the brain is a relatively slow process that often takes tens of thousands to millions of years, while dramatic alterations in behavior can occur very rapidly within the lifetime of an individual and within a species over time without invoking evolution by natural selection (i.e. the differential transmission of alleles across generations).

An excellent case in point is *Homo sapiens*. Using ancient DNA, paleogeneticists determined that modern humans evolved some 195 thousand years ago (kya). Despite the split from Neanderthals approximately 700 kya [2], Neanderthal and human genomes are at least 99.5% identical [3•], and their brain size and encephalization quotient are comparable [4]. Further, although genetically modern humans have existed for close to 200 thousand years, complex human behaviors reflected in art, modern culture, and science emerged less than 40 kya years ago, and there is considerable evidence that Neanderthal culture developed similarly and in parallel until this point in time (Figure 1; [5]). From these points we draw three conclusions. First, a relatively large neocortex may be necessary but not sufficient to generate all of the complex behaviors associated with humans, and certainly is no guarantee of survival. Second, if our assumption is that the neocortex generates the behaviors associated with the human condition, it follows that other mechanisms that control expression of the genotype and allow for flexible responses to context must play a powerful role in creating the neocortical phenotype and shaping the behavior that the brain generates. Third, if we are interested in how complexity in cognitive capacity and motor behavior emerges in species over time, understanding only the genetic contributions to brain organization while ignoring the environmental and social context that may affect how genes function will tell us only part of the story.

What aspects of the neocortical phenotype have actually evolved and how can we tell?

Of course there are aspects of the brain that have evolved that depend on specific genes and their deployment during development. This is known through two important methods of inquiry, comparative and developmental

Figure 1


Morphology
Environment/Social Context
2000's electronic social networking
1990's world wide web, electronic mail, texting
1957 first satellite in space
1950 electronic computer
1900's nuclear power
1903 air powered flight
1886 automobiles
industrial revolution
hand production to machines
chemical manufacturing
iron production
improved water power
1760 - 1820
most recent known Neanderthal remains
28 kya
figurative art
35 kya
sophisticated blades
polished, drilled, perforated bones
projectiles
needles
clothing
increased population
large dispersal of population
70 - 50 kya
linguistic diversity
100 kya - 40 kya
personal ornaments
use of pigments
burials
100 kya
earliest anatomically modern humans
195 kya
emergence of true culture
cultural traditions
smaller, standardized tools
spears and knives in shafts and handles
composite tool manufacture
grammatical language controversial
300 kya
FOXP2 undergoes intronic non-coding changes
370 kya
400 kya
Human/Neanderthal populations split
Neanderthal
Humans
Hominins
Neanderthal
Human
modern hand and muscular morphology
modern hyoid
700 kya
700 kya
modern language? controversial
anatomical capacity of ear/cochlea for modern patterns of sound transmission
800 kya
control of fire
1 mya
large cutting tools
1.5 mya
archaic hyoid
1.6 mya
1.6 mya
enhanced communication tool use tradition
culture supporting communication
2.5 mya
many features of modern hand
3.2 mya
stone tool assisted consumption of food cutting
3.4 mya
Hominins
Panini (Chimpanzees)
FOXP2
2 changes in protien coding sequence
6 mya
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neurobiology, both of which demonstrate that there are particular features of neocortical organization that are immutable regardless of the environmental context in which they develop. Comparative studies on a variety of species in our own and other laboratories demonstrate that regardless of habitat, lifestyle, morphological, and behavioral specializations there is a constellation of cortical fields that are present in all mammals investigated, even in the absence of use (Figure 2; for review see [6,7•]). These fields include primary visual, auditory and somatosensory areas (V1, A1 and S1 respectively; see Table 1), as well as several additional sensory areas (e.g. V2, S2/PV, R, SR and SC), and in eutherian mammals at least one motor area (M1). These cortical fields posses a basic six-layered organization, are located in a relatively similar position on the cortical sheet, and have a common and basic pattern of thalamocortical connectivity. Finally, there appears to be a default functional organization in which sensory receptor arrays from a particular sensory system are represented in an orderly, topographic fashion within the cortical fields associated with that sensory system (e.g. V1, S1 and A1). However, this last feature is variable and can be radically altered to the extent that individual cortical fields normally associated with one sensory system (e.g. visual) are capable of supporting different types of sensory maps (e.g. auditory; [8,9]).

The ubiquity of this plan indicates that genes that co-vary with aspects of this basic organization and connectivity were inherited from the common ancestor of all mammals. The alternative and less parsimonious explanation is that these aspects of cortical organization arose independently in different lineages. Thus, even without knowing the specific genes associated with aspects of cortical organization, comparative studies have for many decades provided important insights into cortical evolution.

As noted above, the other means by which we can appreciate the features of neocortical organization that have evolved is to examine genes expressed during development, determine how they are deployed, and which aspect of the phenotype they co-vary with. Although it is beyond the scope of this review to discuss molecular development, there is a wealth of evidence that indicates that some features of the cortical phenotype can be controlled by genes intrinsic to the developing neocortex. For example, early morphogens set up an anterior–posterior axis of the neocortex and regulate transcription factors, which in turn regulate downstream genes associated with establishing cortical field boundaries and thalamocortical connections [10•]. Disruption at any stage of this cascade of events can alter the size and relative position, connections, and even laminar organization of cortical fields [11]. Further, recent studies have demonstrated that altering the location and magnitude of expression of early morphogens can actually induce the formation of new, duplicate cortical fields in mice [12••]. What is not known is the extent to which these experimentally induced genetic alterations occurred naturally in the course of mammalian evolution, and thus to what degree these genetic changes account for species differences in cortical organization and the behavior that the neocortex generates.

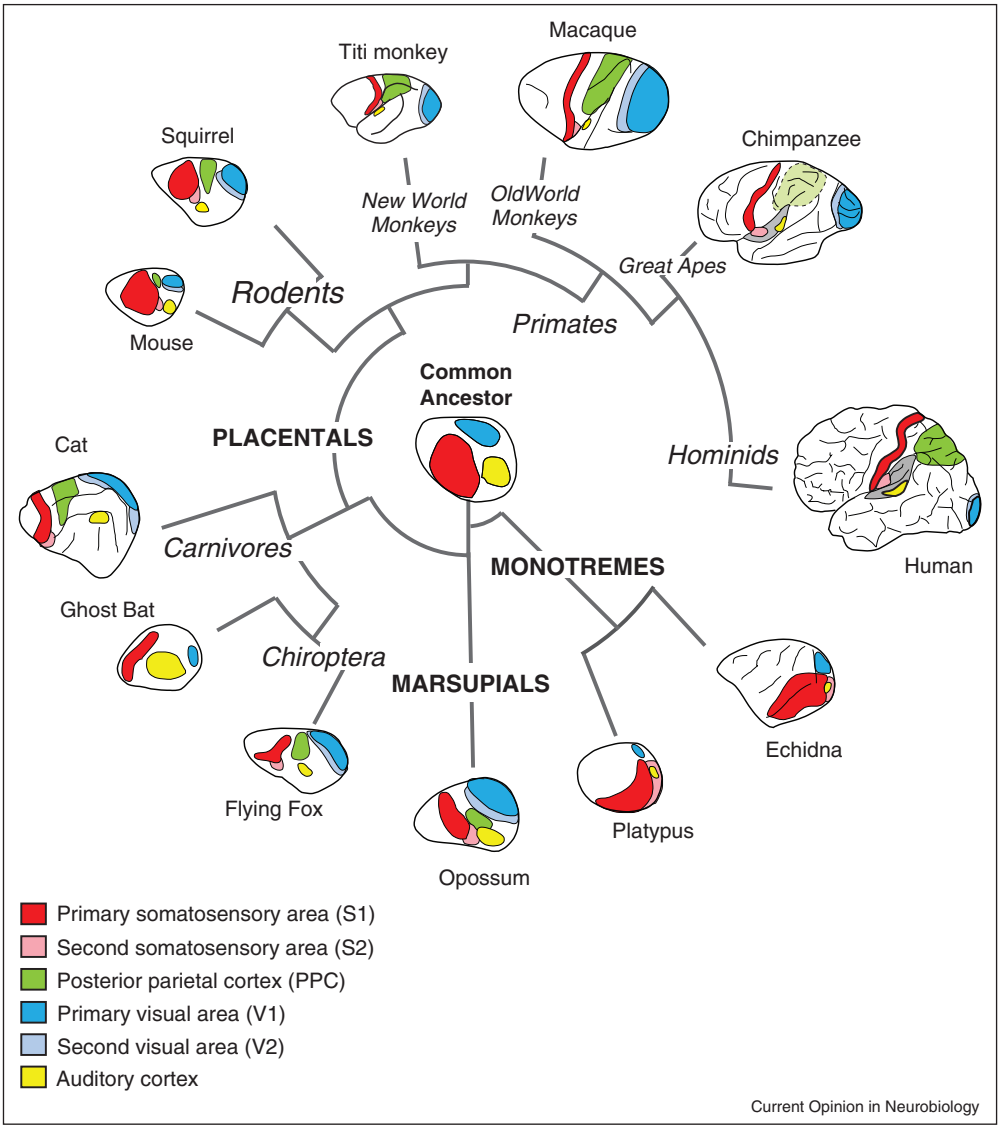
What aspects of the cortical phenotype can be altered?

The very presence of this plan of organization that is shared by all species, even in the absence of use, demonstrates that there are large constraints imposed on evolving nervous systems. One of these constraints is genes, and the genetic regulatory networks that control their deployment, and the other is the immutable laws of matter and energy that govern our planet. All animals must contend with these physical constraints. On the other hand a number of features of this plan of cortical organization can be altered and these include: (1) the absolute and relative size of the cortical sheet, (2) the amount of cortex devoted to processing inputs from a particular sensory system (sensory domain allocation), (3) cortical field size, (4) cortical field number, (5) connections; and (6) neural response properties. Changes in any or all of these will in turn generate changes in behavior (for review see [6]).

Although it has been repeatedly demonstrated that genes intrinsic to the neocortex co-vary with these features of the cortical phenotype, often it is overlooked that genes involved in the construction of body morphology and the generation of sensory effector arrays also have profound affects on the cortical phenotype. For example, in primates a transition from a nocturnal to a diurnal lifestyle led to adaptive changes in the eyes, including their physical enlargement and location on the head (frontally placed eyes with a large binocular overlap), an all cone fovea with a macula lutea, and for catarrhine primates the addition of a cone pigment for trichromatic vision [13,14]. These changes, and the visually mediated behaviors they subserve contribute to the disproportionate amount of

(Figure 1 Legend) A simplified cladogram illustrating the relationship between chimpanzees, humans and Neanderthals, and some of the morphological (left) and environmental/social contextual changes (right side) that occurred in the last 6 million years. It is notable that while morphological changes to the body were relatively few (and likely due to changes in the genome), the social and technological behavior of humans (and Neanderthals) changed relatively rapidly. Although the anatomically modern human emerged about 200 kya, the explosion of culture, art, technology, and possibly language occurred within the last 50,000 years. This suggests that non-evolutionary mechanisms play a significant role in shaping the portions of the brain (the neocortex) largely associated with modern human behavior. Information for this figure was obtained from the following references: [3•,5,26,36••,37,38,40•,41,55,56].

Figure 2



A cladogram illustrating the phylogenetic relationships of mammals and the basic plan of cortical organization shared by all mammalian species due to inheritance from a common ancestor (homology).
Source: Modified from [1•].

Table 1

List of abbreviations.

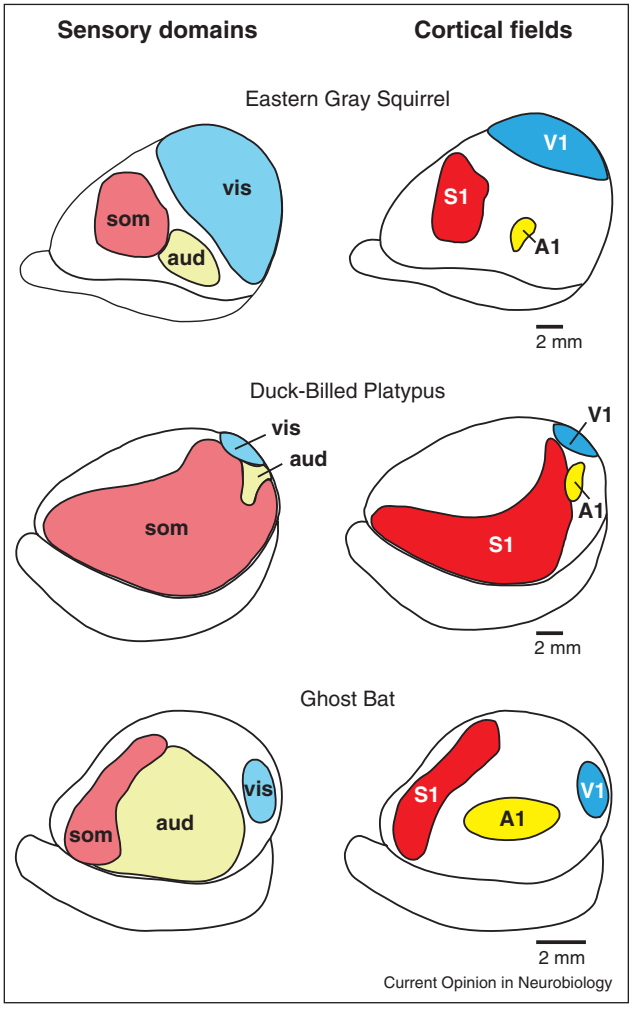
Cortical areas	
A1	Primary auditory area
PV	Parietal ventral area
R	Rostral auditory area
S1	Primary somatosensory area
S2	Second somatosensory area
SC	Caudal somatosensory area
SR	Rostral somatosensory area
V1	Primary visual area
V2	Second visual area

cortex devoted to visual processing (changes in sensory domain allocation) particularly the expansion of the temporal lobe [7•]. On the other hand, the nocturnal, areal and predatory lifestyle of michrochiropteran bats led to alterations in facial morphology associated with echolocation and prey capture [15], an enlargement of the ears, dramatic changes in pinna morphology, and alterations in the cochlea associated with ultrasonic hearing [16]. These changes in morphology and the reliance on auditory mediated prey capture contribute to the disproportionate expansion in the amount of cortex devoted to auditory processing (Figure 3; sensory domain allocation). Similar types of expansions of behaviorally relevant sensory

effector arrays are observed within a cortical field (cortical magnification; Figure 4), and these types of alterations linked to sensory receptor array, body morphology and use are also associated with changes in cortical connectivity [6].

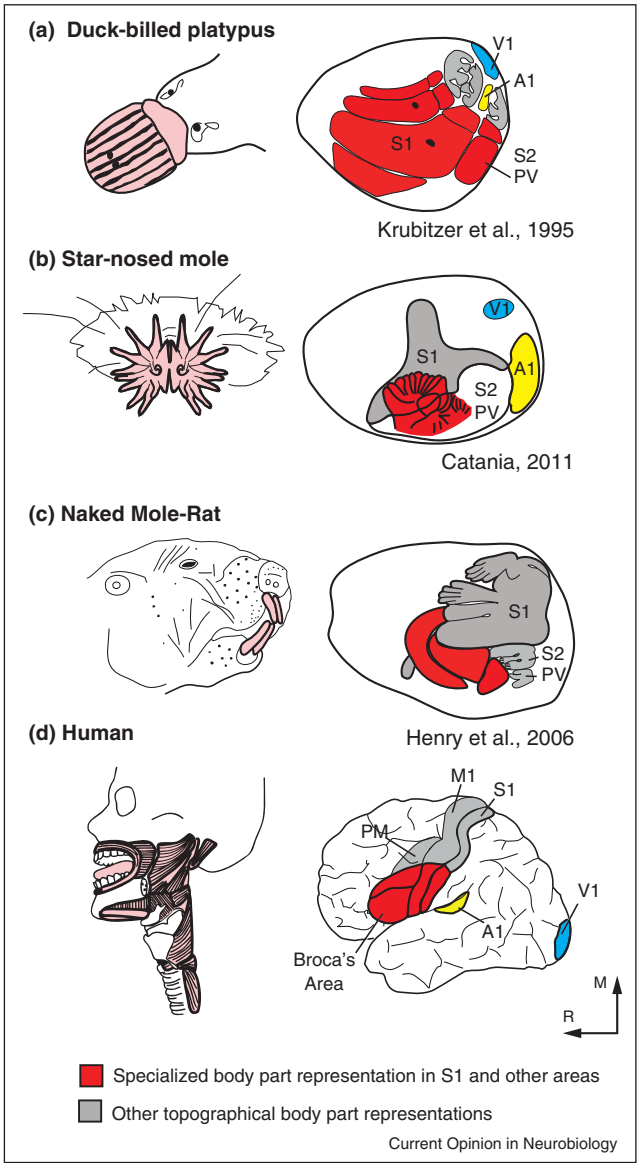
Changes to the neocortex associated with these morphological specializations are due to both innervation density of the receptor array [17] as well as use of the specialized body part [18]. The role of sensory driven activity in shaping both the function and structure of cortical fields has been well established and their impact is particularly strong during early development. For example, the formation of direction and orientation maps within the visual cortex is dependent on early visual experience [19], the formation of frequency maps and temporal processing in auditory cortex relies on early acoustic experience [20],

Figure 3



Sensory domain allocations (left) and cortical field organization in three species of mammals. Each species has a reliance on a different sensory system and both peripheral morphology and cortical organization reflect this. Eastern gray squirrels (top) rely heavily on vision, the duck-billed platypus relies on somatosensation and electrosensory reception, and ghost bats rely on audition. In each, the amount of cortex devoted to the specialized sensory system (sensory domain allocation) and the relative size of primary cortical fields associated with each system assume a relatively large amount of cortical space. See Table 1 for abbreviations.

Figure 4



Cortical magnification in morphologically and behaviorally specialized peripheral morphology (left) and enlargement of cortical fields in somatosensory (and motor) cortex (right). In duck billed platypus **(a)**, the bill has interdigitated stripes of electrosensory and mechanosensory receptors and most of somatosensory cortex (and most of cortex) is devoted to processing input from the bill (cortical magnification). In the star-nosed mole **(b)** and naked mole rat **(c)** different portions of the face/oral morphology are specialized and related to unique orofacial behaviors. Corresponding representations in somatosensory areas are greatly modified. In humans the supralaryngeal tract, tongue and lips have undergone alterations, and these changes are associated with specialized oral behaviors. Like other mammals, corresponding representations in somatosensory, motor and premotor cortex are magnified.

and early differential stimulation of the whiskers of the rat affects the organization of both somatosensory [21] and motor cortex [22]. Thus, differential, early and pervasive activation of sensory receptor arrays (and the motor programs that ensure that these arrays maximally interface with the physical stimulus to be explored) continuously feeds back onto the system to dynamically alter the neocortex throughout a lifetime; and this can occur over generations without invoking evolutionary mechanisms.

What is not known is if or how these alterations to the neocortex due to changes in body morphology and/or experience become encoded by genes associated with neocortical development and evolve. Considering that neocortical development is shaped by experiences that occur after genes have been inherited, how could stochastic changes emerge from inflexible DNA? Further, how would an inflexible genome allow for the adaptations necessary for an organism to survive long enough to reproduce? The adaptive responses needed for survival, and the adaptive responses that are in fact present in mammals could only occur if the genome was flexible and could be modified by the environment. Developmental biologists have tackled a similar issue: if there is really a one to one correspondence between DNA and phenotype, then every somatic cell in the body, which contains exactly the same genotype, would be identical. Instead, of course, the phenotypes of somatic cells are widely varied. With this issue in mind, Conrad Waddington proposed that discovery of the causal mechanisms through which genotype brings about phenotype might be called 'Epigenetics' [23•]. Considering that cellular phenotypes undergo dramatic plasticity during development while the genotype of these cells remains stable, implicit in Waddington's definition is the idea that phenotype can be modified without changes to the genotype [24]. Thus, during the course of development, epigenetic mechanisms allow cells with the same DNA to differentiate and divide, passing on those alterations in gene function, not explained by alterations in DNA sequence, to daughter cells. If we expand this concept to take into account the fact that the phenotype of an organism does not remain static throughout the lifespan, rather it dynamically responds to social and environmental contexts, it seems fitting that epigenetic mechanisms might also mediate the adaptability of brain and behavior to environment. Indeed, we now know that the same epigenetic processes that mediate this 'cellular memory' also occur in mature, non dividing cells in the central nervous system (for review see [25•]). How these epigenetic mechanisms operate to produce changes to the phenotype will be discussed below.

The general rules of how the basic plan of cortical organization is modified, gleaned from other mammals, should be applied when considering specializations of humans, such as language. For example, key changes in human orofacial morphology, including alterations in the hyoid bone (allowing for multiple configurations of tongue, pharyngeal and laryngeal structures [26]), and changes to the supralaryngeal vocal tract [27,28] allow for speech production in humans. Such alterations in peripheral morphology are likely linked to an expansion of sensory, motor, and premotor areas associated with speech production (Figure 4d; Brodmann's area). Likewise, alterations in the outer ear, middle ear and cochlea have evolved such that acoustic information in frequencies associated with human speech (2–4 kHz) are amplified, and linked to expansions in corresponding tonotopic regions of auditory cortex. Like numerous other examples in mammals, these morphological alterations affect the size, organization and connectivity of neocortical areas associated with speech production (Brodmann's area) and comprehension (Wernicke's area). Although these regions of the neocortex are specialized in humans, when considered in light of what we know about other mammals, they follow the same rules of construction.

What is the genetic contribution to these neocortical alterations? Genes associated with specification of orofacial morphology and the supralaryngeal vocal tract obviously contribute to the emergence of speech and language. There is also evidence that the genes intrinsic to the neocortex, such as FOXP2 are, in part, responsible for a number of aspects of speech including the ability to make rapid articulatory movements; and FOXP2 is proposed to be a key gene in human evolution (for review see [29•]). These alterations in vocal tract configuration and FOXP2 were present in the common ancestor of humans and Neanderthals, but modern language and speech production in their current form, do not appear to have been present in these hominins that existed some 800 kya (although when language emerged is contentious; see [5,30] for review). The evolution of both peripheral morphology and cortical organizational features, which were likely adaptations for behaviors other than modern speech, had an unforetold impact on their ultimate use several hundreds of thousands of years after they actually emerged. This use, in turn, had an extraordinary influence on the neocortex. Given the temporal lag between the evolution of concrete biological changes to the body, the emergence of modern language and the dynamic changes to the brain that this specialized use engenders (Figure 1), it would appear that non-evolutionary, epigenetic mechanisms play a key role in the emergence of these behavioral and brain phenotypes. Further, the individual must be immersed in a very specialized context for particular features of neocortical organization to emerge.

An important caveat is that there are features of the environment which are ubiquitous that alter aspects of body morphology such as bone density, craniofacial morphology, and sex determination [6]. These physical

factors include, but are not limited to, gravitational stress, diet (which affects mastication behavior), salinity, humidity and temperature. However, the mechanisms by which these environmental factors generate these changes are not known.

How are these non-evolutionary changes accomplished?

'*We certainly need to remember that between genotype and phenotype, and connecting them to each other, there lies a whole complex of developmental processes. It is convenient to have a name for this complex: 'epigenotype' seems suitable.*' Conrad H. Waddington, 1942 [23•].

DNA is not 'naked' in the nucleus, but rather supercoiled around octomers of histone proteins [31]. Epigenetic marks, or modifications to the DNA and/or histone proteins, affect the way that this chromatin is packaged in the nucleus, which in turn affects the accessibility of regulatory regions in the DNA to transcriptional machinery. The two most commonly studied epigenetic modifications are histone acetylation and DNA methylation. Histone acetylation refers to the addition of acetyl groups to the lysine residues of histone proteins, a process that increases the ease with which genes are transcribed. In contrast, the conversion of cytosine nucleotides to 5-methylcytosines, referred to as DNA methylation, is associated with gene silencing.

It is important to emphasize that neuronal activity can dynamically drive epigenetic modifications [32,33]. Cell surface signals can be translated into long lasting changes in gene expression via the activation of intracellular signaling cascades that result from neurotransmitter binding and subsequent Ca^{2+} influx at the neuronal membrane. Once activated, these signaling cascades can ultimately remodel chromatin through the activation of enzymes that add epigenetic marks and/or interact with subcellular proteins to dissociate corepressors or methyl binding proteins from gene promoters [32,33]. Given that cortical field emergence is associated with the activation of complex transcriptional networks during development, and sensory driven neural activity can modulate these networks via chromatin modifications, a number of the systems level changes in organization described in the above section can be mediated by epigenetic mechanisms. The possibility that epigenetic modifications generate systems level alterations to what are considered human neocortical specializations (e.g. Brodmann's and Wernicke's areas) is an enticing one. Epigenetic mechanisms might also govern the tight spatial and temporal regulation needed for functional and adaptive development of cortical connectivity, explaining why sensory driven activity is critical for cortical development in general. For example, conditional knockout of enzymes associated with DNA methylation in excitatory dorsal forebrain neurons results in a dysregulation of peripheral-related anatomical patterns in somatosensory barrel cortex in mice [34]. Functional thalamocortical connections develop in these mice, but the inability of these connections to show long-term potentiation suggests that these connections are not functionally plastic.

How do epigenetic modifications drive cortical development? Recent data show that visual stimulation during critical periods in development activates intracellular cascades that increase histone acetylation [35]. Thus, during these developmental time points sensory stimulation induces alterations in neuronal activity that direct features of cortical organization (such as ocular dominance plasticity) by turning on/off regulatory factors that affect the accessibility of transcriptional machinery to gene promoters, even after the sensory stimulus has ceased. Importantly, critical periods in neocortical development may be defined by the ability of sensory inputs to activate epigenetic modifications, suggesting that epigenetic mechanisms mediate flexible responses of the genome to the environment. In support of this idea, inducing these epigenetic modifications experimentally in adulthood, after the window for visual plasticity has closed, reinstates the same flexibility that is observed during the critical periods in development [35]. Therefore, when the same molecular players that guide cortical development are activated in adulthood the window for cortical plasticity is reopened.

Conclusions

The notion that alterations to the epigenome rather than the genome may have played a more vital role in making modern humans the cultural and social creatures that we have become is an intriguing possibility. It is clear that our search for genes that distinguish humans from other species can provide only limited information on the remarkable transformation from ancient to modern humans. Both Neanderthal and humans had 'cultural capacity' including FOXP2, modifications to vocal morphology associated with speech (e.g. size and location of hyoid bone; [26,36••], control of fire [37] and tool use [38] (Figure 1)). In fact some of these characteristics predate the Neanderthal/human split over 700 kya. In addition, early hominins had morphological specializations of the hand associated with tool use (e.g. [39,40•]), as well as modifications to the outer and middle ear which amplified frequencies associated with speech ([41]; see [5] for review). Although oral communication was likely to be present early in human evolution (however this issue has not been resolved), modern and complex language and cultural systems are proposed to have emerged more recently in humans (and in our extinct Neanderthal cousins; [5]), and technological advancement as we know it today only occurred in the last few hundred years (Figure 1). Thus, the biological underpinnings necessary for culture and language existed well before modern culture emerged. Specific features of

connectivity and function of unique cortical areas in humans including Brodmann's area, Wernicke's area, prefrontal cortex, posterior parietal cortex and tool action areas [42,43•] may have been primarily transmitted by non-evolutionary epigenetic mechanisms. This is supported by the appropriation of speech and language areas for different functions in congenitally deaf individuals (e.g. [44,45]).

Interestingly, this type of non-evolutionary transmission of behaviors (and associated brain organization) does not occur only in humans. Recent evidence indicates a cultural transmission of tool use in non-human primates such as cebus monkeys and chimpanzees [46,47], both of which have evolved hand morphology necessary for precise manual control [48]. Further, there is archeological evidence that cultural transmission of tool use has been occurring for over 4000 years in chimpanzees [46,49]. If we define culture more broadly to include behaviors such as maternal care, mate selection and foraging techniques, there is a plethora of data that indicates that such non-evolutionary transmission of behavior and brain phenotype occurs in all mammals [50•,51,52,53]. In this respect, it should be noted that although we have focused on epigenetic processes that occur in mature, nondividing cells in the central nervous system, the term epigenetics has traditionally been defined as 'the study of mitotically and/or meiotically heritable changes in gene function that cannot be explained by changes in DNA sequence' [25•]. Some of these heritable changes depend on the social or environmental context, whereas others are incorporated into the germ-line and transmitted to future generations independently of social or environmental context. For example, when gestating rat dams are exposed to the endocrine-disrupting fungicide, vinclozolin, altered DNA methylation and decreased sperm cell death occurs in the 4th generation of male offspring that were never directly exposed to the compound [54]. Therefore, the effects of chemical exposure at critical periods in development can be transmitted to future generations through a reprogramming of the epigenome of the germ cells.

Taken together, converging data from a number of different disciplines including comparative and developmental neurobiology, paleogenomics, paleontology and archeology demonstrate that to understand how aspects of the cortical phenotype emerge and persist across generations, we must consider culture as a key constituent. We contend that phenomena such as culture and social learning should be defined as complex, and persistent patterns of physical energy generated by ourselves, conspecifics and heterospecifics, the physical environment in which we develop and behave, and ultimately groups of brains acting as an emergent entity which continually shape aspects of the cortical phenotype. Some features of the cortical phenotype are driven by what are considered traditional evolutionary mechanisms, and others by epigenetic mechanisms, but the latter can masquerade as evolution if the context in which individuals develop remains static across generations. In our opinion, perhaps the critical difference in humans and other mammals is their extraordinary capacity to evoke these epigenetic mechanisms to develop a cortical phenotype that generates optimal and highly variable behaviors in the dynamic environment generated in part by our own ever-changing phenotype.

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- •• of outstanding interest

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