Report

Current Biology

Exceptional Evolutionary Expansion of Prefrontal Cortex in Great Apes and Humans

Highlights

- Great ape and human prefrontal expansion are evolutionarily derived features
- Great apes and humans are specialized to favor executive cognitive function
- This exceptional prefrontal expansion is likely related to heterochronic remodeling

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In Brief

Smaers et al. report that great ape and human prefrontal cortex expansion are evolutionarily specialized features of cortical organization, favoring executive cognitive function within distributed networks. This pattern of cortical reorganization is likely related to heterochronic changes that prolong prefrontal development.

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Exceptional Evolutionary Expansion of Prefrontal Cortex in Great Apes and Humans

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SUMMARY

One of the enduring questions that has driven neuroscientific enquiry in the last century has been the nature of differences in the prefrontal cortex of humans versus other animals [1]. The prefrontal cortex has drawn particular interest due to its role in a range of evolutionarily specialized cognitive capacities such as language [2], imagination [3], and complex decision making [4]. Both cytoarchitectonic [5] and comparative neuroimaging [6] studies have converged on the conclusion that the proportion of prefrontal cortex in the human brain is greatly increased relative to that of other primates. However, considering the tremendous overall expansion of the neocortex in human evolution, it has proven difficult to ascertain whether this extent of prefrontal enlargement follows general allometric growth patterns, or whether it is exceptional [1]. Species' adherence to a common allometric relationship suggests conservation through phenotypic integration, while species' deviations point toward the occurrence of shifts in genetic and/or developmental mechanisms. Here we investigate prefrontal cortex scaling across anthropoid primates and find that great ape and human prefrontal cortex expansion are non-allometrically derived features of cortical organization. This result aligns with evidence for a developmental heterochronic shift in human prefrontal growth [7, 8], suggesting an association between neurodevelopmental changes and cortical organization on a macroevolutionary scale. The evolutionary origin of non-allometric prefrontal enlargement is estimated to lie at the root of great apes (~19–15 mya), indicating that selection for changes in executive cognitive functions characterized both great ape and human cortical organization.

RESULTS

Phylogenetic analysis of covariance [9] reveals that a multi-grade isometric model (dividing humans, great apes, and other primates) provides a significantly better statistical fit to prefrontal scaling than a one-grade allometric model (Figures 1, 2 and 3, Tables S1 and S2). This applies to the comparison of prefrontal cortex with several other cortical areas that are functionally and neurobiologically linked to it. Comparing cortical areas that are neurobiologically linked ensures that the measure of relative prefrontal size accounts for the hierarchical nature of neural information processing (see [10] and Supplemental Information for more details). We consider only datasets of prefrontal cortex size in primates that have been collected based on cytoarchitectonic criteria and comprise information for more than five species [5, 11] (Figure 1, Table S1; see Supplemental Information for more details). These criteria lead to the selection of two datasets, designated as Brodmann and Smaers datasets hereafter. Phylogenetic ANCOVA was performed by generalizing the standard generalized least-squares procedure to including phylogenetic variance-covariance in combination with additional indicator variables that describe group membership (even when a group consists of a single species; see [9] and Supplemental Information for a detailed description of this approach). Because this implementation of phylogenetic ANCOVA uses standard least-squares procedures only, it provides unbiased results irrespective of sample size (see Supplemental Information for more details). Because statistical power is a simple function of the observed p value, the significant results denote that the tests presented here have high observed power (see Supplemental Information for more details).

To elucidate when in evolutionary time episodes of enlargement in prefrontal cortex occurred, we further used three different evolutionary modeling approaches. These methods explore differences among groups directly from the data (i.e., without a priori group allocation). Results demonstrate that prefrontal cortex exhibits separate instances of exceptional expansion in the hominoid (~30–19 mya), hominid (i.e., great ape and human) (~19–15 mya), human-chimpanzee (~8–6 mya), and human (~6–0 mya) ancestral lineages when compared to different brain structure scaling variables. Ancestral state and rate estimation results (Figures 2 and 3) visualize best estimates of how prefrontal cortex has changed along individual lineages of the primate tree, and best-fit regime configurations highlight sets of lineages ("regimes") that indicate similar trait values for relative prefrontal cortex size in addition to where shifts between regimes occurred in phylogenetic space. These results demonstrate that exceptional prefrontal expansion relative to frontal

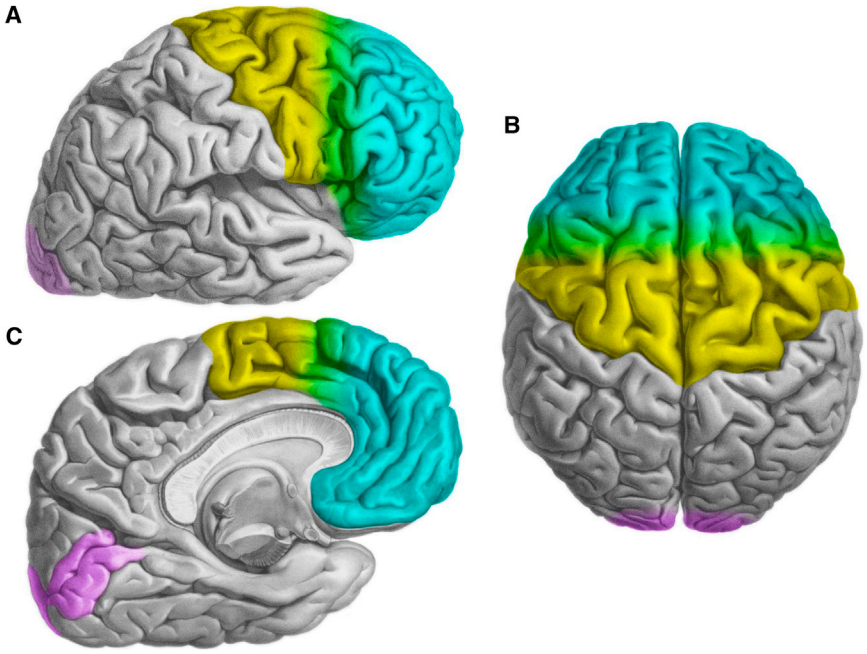

Figure 1. Overview of Brain Regions

Lateral (A), dorsal (B), and medial (C) views of the human brain illustrating the regions under consideration. Red illustrates the primary visual cortex, yellow the frontal motor areas, and blue the prefrontal cortex. The green area depicts a margin of uncertainty in the location of the cytoarchitectonic border between frontal motor areas and prefrontal cortex when using the prefrontal delineation approach proposed by Smaers et al. [11]. This approach considers a series of cumulative volumes along the frontal pole as a proxy for prefrontal cortex volume. This approach allows for the collection of a valid proxy for prefrontal cortex volume in a wide sample of species but results in an underestimation of putative prefrontal expansion in great apes and humans (see Supplemental Information for more details). The Brodmann data provide a more accurate measure of prefrontal cortex size but comprise a more limited comparative sample. Figure adjusted from Foville [40]. See also Tables S1 and S3.

motor areas is estimated to have occurred in the ancestral hominoid lineage, expansion of prefrontal cortex relative to primary visual cortex is estimated to have occurred in the ancestral lineages of great apes and humans, and prefrontal expansion relative to other heteromodal association areas is estimated to have occurred in the human lineage. The statistical effect size of these evolutionary models is high ($\sqrt{\eta}\,\phi \gg 1$, $\beta/\sqrt{\gamma} \gg 2$), rendering strong support for the occurrence of these evolutionary shifts in relative prefrontal enlargement (see more details in Supplemental Information). Bootstrap analysis further supports this conclusion by demonstrating high support for the estimated trait shifts (Figures 2, 3, and S1, see Supplemental Information for more details). High effect size is also supported by the fact that the same result is obtained using four different methods (phylogenetic ANCOVA, ancestral estimation, rate estimation, and multi-regime OU model fitting) and five different model assumptions (see Supplemental Information for more details).

DISCUSSION

Whether or not human prefrontal cortex expansion is predictable from common rules for primate brain allometric scaling bears on the fundamental question of the extent to which human cortical organization can be accounted for solely by genetic and developmental patterns shared with other primates. Although many biological systems are primarily integrated (i.e., different elements of the system change in a coordinated manner), deviations from integration are common and are tied to genetic, developmental, and/or functional shifts in a species' bauplan (e.g., heterochronies [12]). These modifications shape the direction of trait variation on a macroevolutionary scale [12] and are thus fundamental drivers of biological diversity. To understand whether an event aligns with or deviates from integration, a standard approach has been to investigate allometric conservation of traits [13]. Species' adherence to the allometric relationship hereby suggests conservation through phenotypic integration, while species' deviations from the allometric relationship points toward a genetic or developmental shift.

Our results support the conclusion that great ape and human prefrontal expansion are evolutionary specializations of cortical organization that cannot be explained solely by allometric trends. These results align with studies demonstrating that human prefrontal cortex is relatively specialized compared to other primates. Human prefrontal neurons are characterized by higher dendritic branch complexity and synaptic spine density compared to other heteromodal association regions and nonhuman primate prefrontal cortex [14], and regions of the human prefrontal cortex contain more neuropil space than in other great apes [15]. Such neuroanatomical differences may be linked to human-specific increased transcriptional complexity [16] and alterations in the regulation of gene expression [17]. These gene regulatory changes have been suggested to have arisen through heterochronic remodeling of the developmental patterns that underpin human prefrontal growth [7, 8]. In general, across different biological systems, heterochrony (i.e., changes in the rate and timing of developmental patterns) has been shown to underlie deviations from phenotypic integration by altering genetic, developmental, and/or functional effects and leading to changes in the direction of trait variation on a macroevolutionary scale [12]. Indeed, heterochrony has previously been suggested to be an important driver of volumetric reorganization in the mammalian brain [18]. In the case of human prefrontal cortex, developmental changes in mRNA expression have been characterized as comparatively prolonged, or neotenic [8], and shown to have evolved at an accelerated rate relative to chimpanzees, macaques, and human non-cortical regions [7]. In particular, peak expression for synapse-associated genes is delayed to approximately 5 years after birth in humans, compared to a few months after birth in chimpanzees and macaques [19].

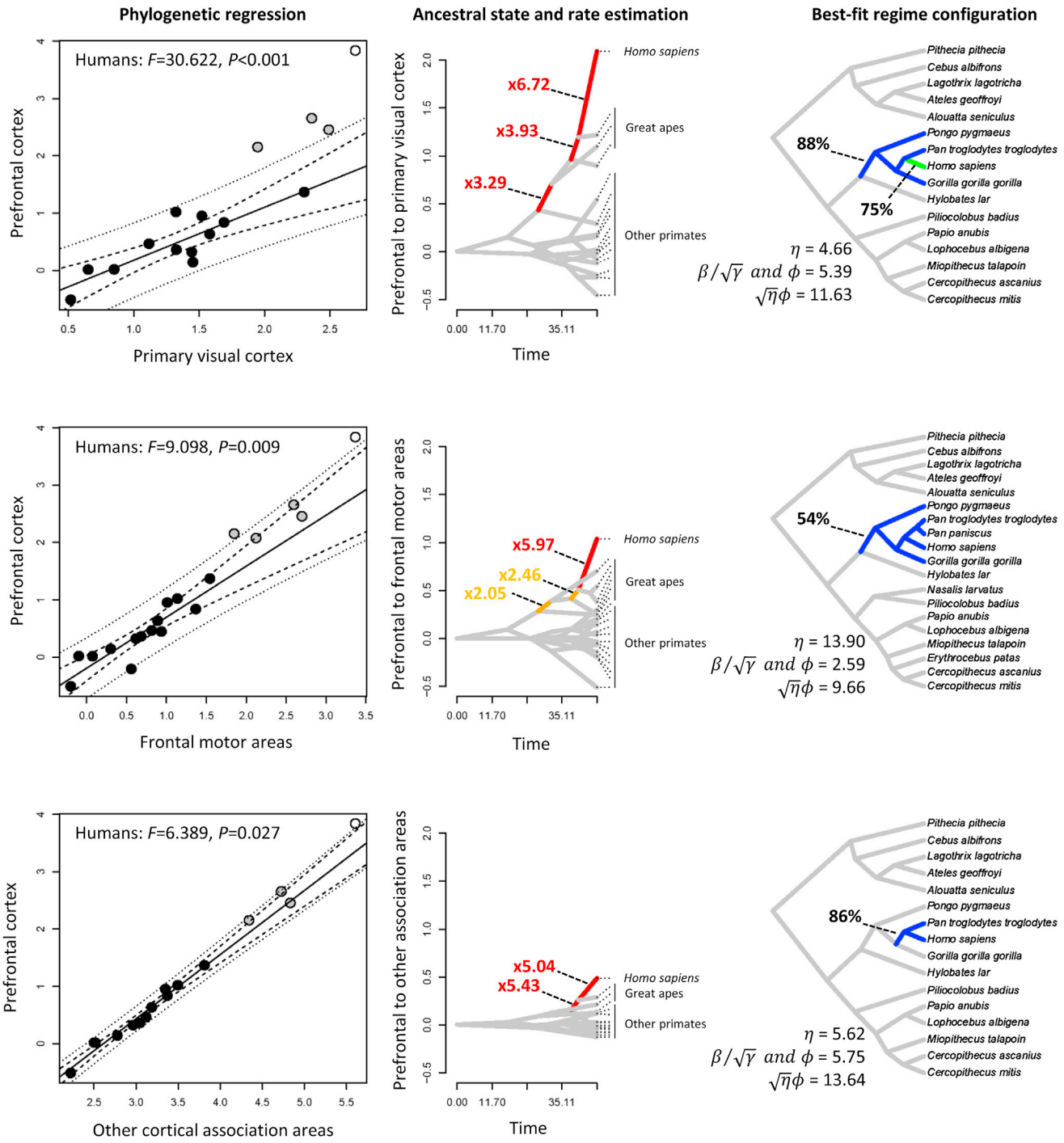

Figure 2. Evolutionary Modeling of Prefrontal Expansion using the Smaers Data

Phylogenetic regressions of log prefrontal cortex size against log size of other cortical areas. Prefrontal data from Smaers et al. [11]. Slopes, confidence intervals (dashed line), and prediction intervals (dotted line) [9] are depicted based on the non-great ape sample. Data points with a white background represent human values, those with a gray background great ape values. *F* and p values indicate the significance of a phylogenetic ANCOVA testing for intercept differences between humans and other primates (see also Smaers and Rohlf [9], Supplemental Information on the use and interpretation of phylogenetic ANCOVA, and Table S2 for more detailed results). Ancestral state and rate estimation plots visualize lineage-specific phenotypic change across time in an ancestral phenogram. Branches are colored according to the extent to which their rate of evolution is larger than expected based on a neutral constant-rate model of evolution (orange = 2–3 times larger; red = more than 3 times larger). Best-fit regime configurations highlight branches with a similar trait value as estimated by a least-squares lasso procedure using a phylogenetic Bayesian information criterion (BIC) [37]. Colors differentiate between significantly different regimes ("regime" is here defined as a

(legend continued on next page)

Furthermore, cortical myelination is completed at the age of sexual maturity for chimpanzees and macaques, while human axonal maturation extends well into the third decade of life [20]. Genetic and developmental studies thus provide evidence for a heterochronic shift in human prefrontal growth. Our results are consistent with these findings, suggesting that such neurodevelopmental changes are associated with cortical reorganization on a macroevolutionary scale.

In addition to exceptional prefrontal expansion in humans, we also demonstrate that great apes show prefrontal enlargement that deviates significantly from the expected allometric scaling pattern of cortical integration in other primates. This result is congruent with the general consensus from comparative psychology and primatology that the level of cognitive abilities in great apes (e.g., higher levels of self-control [21] and cultural traditions [22]) is distinct from that in other primates. Such evolutionary changes in brain organization of great apes relative to other primates provides a possible springboard for future broad comparative genetic and developmental investigations into the mechanisms that shape these neurobiological changes over time.

These results also align with previous suggestions that great ape and human neocortical expansion is primarily due to enlargement of cortical association areas, whereas koniocortex (e.g., primary sensory cortices) scales more closely with body size [6, 23]. Previous assertions that "the size of human frontal lobes, and of specific frontal regions, is as expected relative to the size of other brain structures" [24] do not have support according to our analyses. To further underline this issue, Figure 4 plots size measurements of prefrontal cortex relative to other brain structures for the Brodmann dataset. The isometric relationship of prefrontal cortex to primary visual cortex and frontal motor areas is evident in the proportional size changes in the non-great ape sample. In the human brain, however, prefrontal cortex expands exponentially, while primary visual cortex and frontal motor areas remain in line.

Previous conclusions that human prefrontal cortex size or neuron numbers are only as large as predicted for a scaled-up monkey brain [24, 25] can be explained by three fundamental factors. First, previous studies have not employed statistical procedures to test for significant differences in the intercept among subgroups before interpreting allometry [9]. Second, previous allometric studies have used datasets that are not adequate for the interpretation of comparative differences in prefrontal volumes or neuron numbers. Although cortical areas are defined by functional, connectional, and cytoarchitectonic criteria [5], not by gross anatomical or external morphological characteristics [26], previous allometric studies have used datasets that define prefrontal cortex as all cortex anterior to corpus callosum [24, 25], likely because it is a proxy that is simple and easily applied. However, human prefrontal cortex extends further along the caudal axis of the frontal pole than in chimpanzees and other primates [6], making this delineation result in a disproportionate underestimation of prefrontal cortex in humans relative to that in non-human primates, thus rendering the measure inaccurate for the purposes of volumetric comparison across species. Third, the investigation of putative expansion of a cortical area is commonly evaluated relative to the size of the rest of the cerebral cortex or the rest of the brain [24]. This approach does not account for the functional and anatomical underpinnings of neural information processing [10]. Information ascends initially through primary sensory areas, after which it is integrated in supplementary sensory and temporo-parietal association areas to form mental representations. Prefrontal cortex subsequently exerts control over the manipulation of and changes in these mental representations [4]. Here we show that an evaluation of prefrontal cortex size that accounts for this hierarchical nature of information processing unequivocally indicates the exceptional expansion of prefrontal cortex in great apes and humans (Figures 2 and 3, Table S2). Nonetheless, when using the phylogenetic statistics and evolutionary modeling methods employed in the current study, even the more coarse comparison of prefrontal size to the size of the rest of the cortex (used in previous work to argue that human prefrontal cortex size is as expected for a scaled-up monkey brain [24, 25]) yields a marginally significant result for gray matter ($F = 4.104$, $p = 0.061$) and a significant result for white matter ($F = 5.981$, $p = 0.027$) for the Smaers dataset (which by design provides an underestimate of human prefrontal expansion, see details in Supplemental Information) and a strongly significant result for the Brodmann dataset ($F = 18.921$, $p = 0.007$).

The functional implications of exceptional human prefrontal expansion has previously been interpreted as a potential neural basis for human behavioral and cognitive distinctiveness. One possibility is that extraordinary prefrontal enlargement in great apes and humans is due to the evolution of novel cortical areas. Although an impressive body of work suggests that the basic map of prefrontal areas is largely homologous in Old World monkeys and humans [27], some evidence suggests that the human prefrontal cortex may contain new regions. Brodmann [5] found no nonhuman homologs for areas 45, 46, and 47 (but see work by Petrides and Pandya [28]), and recent research indicates the possibility of major changes in neurogenesis and neural migration that may underpin changes in the distribution of cell types in human prefrontal cortex [29]. More research is needed to provide a definitive answer in this regard. It is, however, a distinct possibility that, rather than being characteristic of human prefrontal cortex evolution, the addition of novel cortical areas may be more characteristic of early primate evolution. The dorsolateral prefrontal cortex, for example, together with a suite of other cortical (superior temporal sulcus, inferior temporal, posterior parietal, ventral and dorsal premotor) and thalamic (dorsal pulvinar) areas have been shown to be functionally and cytoarchitectonically distinct in primates compared to other mammals [30].

Another, though not mutually exclusive, possibility is that new specializations of the great ape and human prefrontal cortex comprise a shift in their network organization with other regions by means of connectional invasion. This evolutionary-developmental process occurs when hypertrophied areas invade targets they do not typically innervate in other species and/or increase

cluster of branches with a similar trait value). Bootstrap support is indicated at the ancestral branch of each regime. Effect size is indicated using different measures. Ho and Ané [38] suggest $\beta/\sqrt{\gamma} > 2$ as a valid indicator of high effect size, whereas Cressler et al. [39] propose $\sqrt{\eta}\phi \gg 1$. According to every proposed measure, analyses presented here demonstrate high effect size, and thus high observed power. See Tables S2–S6 and Figures S1 and S2 for more details and supplemental results. Figure S1 and Table S5 demonstrate that similar results are obtained for the analysis of white matter.

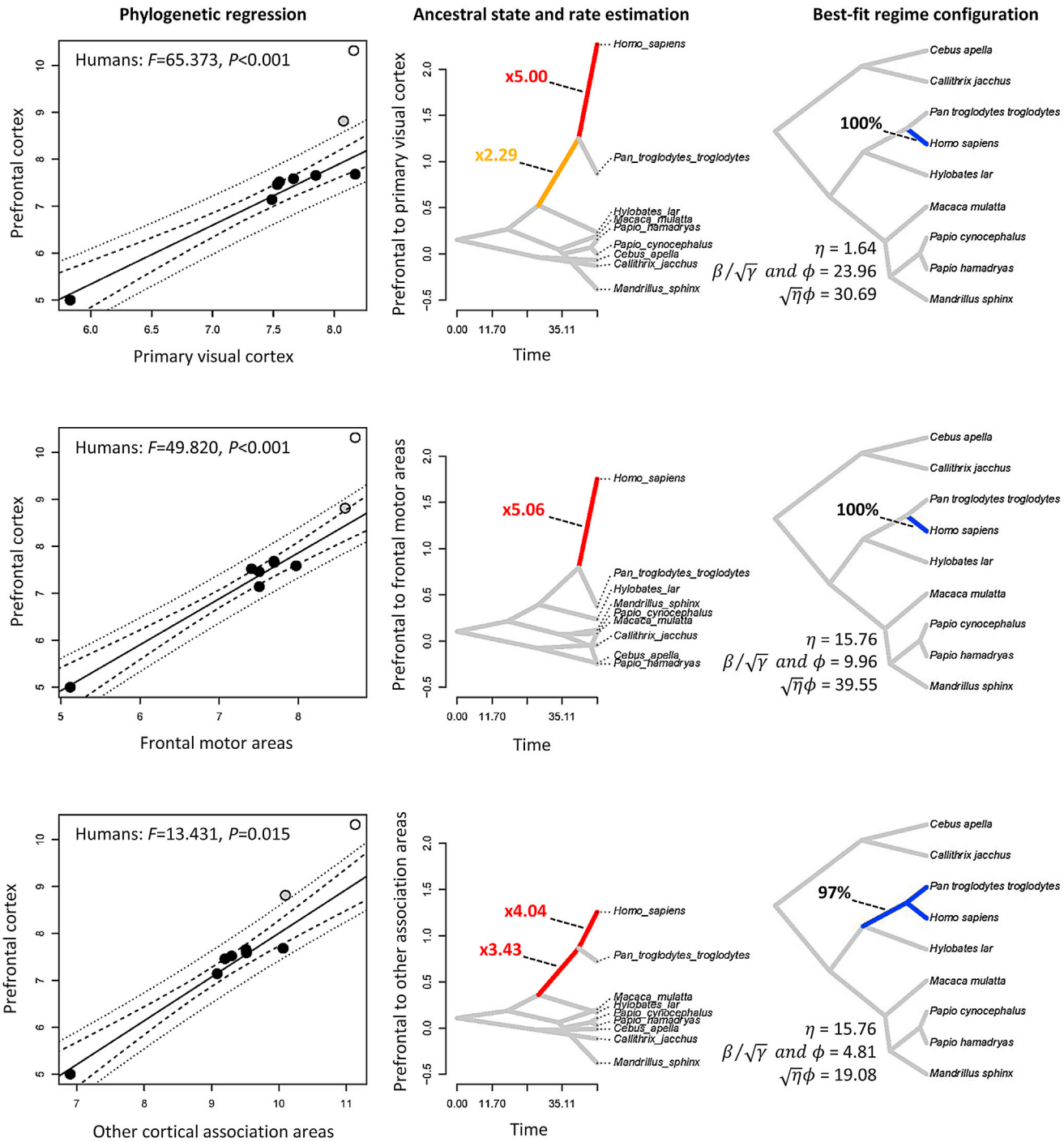

Figure 3. Evolutionary Modeling of Prefrontal Expansion using the Brodmann Data
As in Figure 2, data from Brodmann [5]. See also Figure S1 and Tables S2–S6.

target innervation relative to the ancestral condition [31]. Such new connections may displace others, causing the hypertrophied areas to exert more influence over information processing. This possibility refocuses the characterization of human brain uniqueness toward a distributed neural network in which the prefrontal cortex plays a dominant role. A likely candidate for such a distributed network is the prefronto-cerebellar system. Prefrontal projecting cerebellar lobules have been shown to demonstrate a hominoid/hominid grade shift in size [32] similar to that observed in the prefrontal cortex, to have co-evolved with the prefrontal cortex in great ape and human lineages [33], and to underlie a range of behaviors often associated with human behavioral distinctiveness (e.g., language and executive function [34]). Other distributed networks that may be of particular

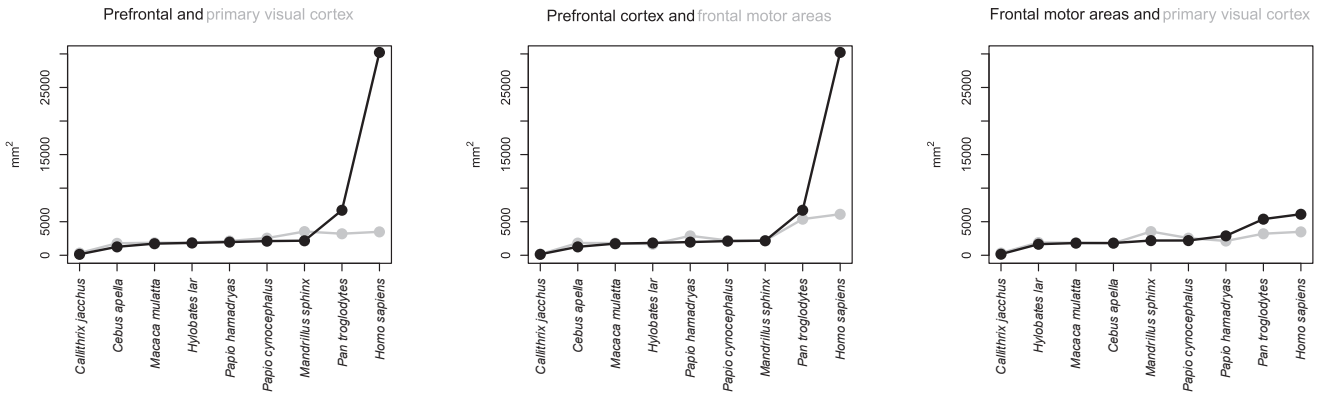

Figure 4. Expansion of Prefrontal Size in the Human Lineage

Plot of prefrontal size and the size of other brain structures. Species are rank ordered according to the size of the first variable in the comparison (highlighted in black). Data from Brodmann [5]. See also Figure S2.

interest in this context are the prefronto-parietal [35] and prefronto-temporal [36] pathways. Considering the exceptional enlargement of prefrontal cortex in great apes and humans, this would suggest that cortical organization in humans and great apes is evolutionary specialized to favor prefrontal cortex function within distributed networks.

We conclude that both human and great ape brain evolution is characterized by non-allometrically derived changes in cortical organization comprising the exceptional expansion of prefrontal cortex. This expansion should be contextualized as part of the elaboration of a large-scale network that involves prefrontal cortex, temporo-parietal cortex [6, 10], and cerebellar hemispheres [32]. Considering that this network is thought to have arisen early in primate evolution [30], great ape and human brains can be considered as extreme (non-allometrically derived) versions of a primate template of cortical organization. The expansion of human prefrontal cortex significantly exceeds the enlargement in other heteromodal association areas, suggesting that human evolution has been characterized by selection for changes in executive functions meditated by this cortical region. The congruence between evidence for heterochronic remodeling of human prefrontal growth with the macroevolutionary expansion of human prefrontal cortex further suggests that the same developmental mechanisms that have been shown to be fundamental drivers of diversity across different biological systems in mammals (e.g., heterochrony) [12] shape primate neurobiological diversity in a similar way.

EXPERIMENTAL PROCEDURES

Data

We consider only the available datasets of prefrontal cortex size in primates that have been collected based on cytoarchitectonic criteria and comprise information for more than five species [5, 11]. These datasets, collected by Brodmann and by Smaers and colleagues, differ in the breadth of the comparative sample (13 versus 19 species, respectively), the nature of the measurement (mm^2 versus mm^3), and the cytoarchitectonic criteria that were employed (granular and agranular cortex versus volumetric bootstrapping along the frontal pole [11] relative to the cytoarchitectonic border between areas 3 and 4). These differences are such that the Brodmann data provide a more accurate delineation of prefrontal cortex size but a more modest comparative sample, whereas the Smaers data provide a larger comparative sample but a proxy for prefrontal cortex volume that underestimates any putative prefrontal expansion in great apes and humans (see Supplemental Information for more details).

Analysis

Phylogenetic ANCOVA was used to test for differences in intercepts and slopes among subgroups (humans versus great apes versus other primates). Such formal tests are required to evaluate whether slopes and intercepts are homogeneous in all subgroups of the sample before interpreting allometry. We used an implementation of phylogenetic ANCOVA that uses standard least-squares procedures only [9], thus ensuring unbiased calculation of regression parameters irrespective of sample size. This method further uses the standard approach of degrees of freedom to penalize for model parameterization to guard against overfitting (see Supplemental Information for more details and additional tests that exemplify this feature).

Best-fit evolutionary scenarios were obtained with least-squares multi-regime Ornstein-Uhlenbeck modeling procedures in combination with a conservative model selection criterion (phylogenetic BIC) to avoid overfitting [37, 38] (see Supplemental Information for more details and additional tests that exemplify results are robust against overfitting). When data indicate a high effect size, this approach has been shown to provide a high power even for sample sizes as few as ten taxa [39]. All analyses presented here indeed show high effect size (see Figures 2 and 3 and Supplemental Information for more details). Ancestral estimates and branch-specific rates were obtained using two different multi-rate models of evolution, both of which yielded equivalent results (see Supplemental Information for more details).

SUPPLEMENTAL INFORMATION

Supplemental Information includes two figures, six tables, and Supplemental Experimental Procedures and can be found with this article online at http://dx.doi.org/10.1016/j.cub.2017.01.020.

AUTHOR CONTRIBUTIONS

Research Design, J.B.S. and C.C.S.; Statistical Analyses, J.B.S. and A.G.-R.; Writing – Original Draft, J.B.S. and A.N.P.; Writing – Review and Editing, all authors.

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Exceptional Evolutionary Expansion of Prefrontal Cortex in Great Apes and Humans

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In this article, we unintentionally omitted to expand on a citation of previously published results. In the caption of Figure 2, we stated that "*F* and p values indicate the significance of a phylogenetic ANCOVA testing for intercept differences between humans and other primates (see also Smaers and Rohlf [9], Supplemental Information..., and Table S2 for more detailed results)" (p. 716). We would like to clarify that in this statement, "see also Smaers and Rohlf" refers, specifically and exclusively, to the phylogenetic ANCOVA of primate prefrontal cortex to primary visual cortex and frontal motor areas using the Smaers dataset in [9]. These results were depicted in a subsection of our Figure 2 (the two top left regression plots) and were numerically presented in a subsection of our Table S2. Smaers and Rohlf presented these results as an empirical example when describing the least-squares solution of phylogenetic ANCOVA and did not discuss the wider biological implications of these results for primate brain evolution. The presentation of the previous results was discussed openly during the review process of this manuscript. The authors apologize for any confusion this oversight may have caused.

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The Evolution of Fangs, Venom, and Mimicry Systems in Blenny Fishes

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In Figure 4D of this article as originally published, two labels relating to control samples were erroneously interchanged: "control buffer" was mislabeled as "forskolin alone," and "forskolin alone" was mislabeled as "control buffer." This error has been rectified in the article online and in the corrected figure shown below. Please note that this error is solely typographical and has no bearing on our results or conclusions. The authors apologize for any confusion that the error may have caused.

In addition, we mistakenly omitted our co-author Karine Mardon from the author list of the article as originally published. This error has also been rectified in the article online. We apologize to Dr. Mardon for the omission.