Exceptional evolutionary expansion of prefrontal cortex in great apes and humans

Smaers JB[1], Gómez-Robles A[2], Parks AN[3]& Sherwood CC[2]

[1]Department of Anthropology, Stony Brook University.
[2]Department of Anthropology and Center for the Advanced Study of Human Paleobiology, The George Washington University.
[3]Interdepartmental Doctoral Program in Anthropological Sciences, Stony Brook University.

Correspondence to: jeroen.smaers@stonybrook.edu

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 towards the occurrence of shifts in genetic and/or developmental mechanisms. Here we investigate prefrontal cortex volumetric 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 genetic and developmental heterochronic shift in human prefrontal growth [7, 8], suggesting an association between neurodevelopmental changes and a shift in the direction of cortical organization on a macroevolutionary scale. The evolutionary origin of non-allometric prefrontal enlargement is estimated to lie at the root of great apes (~19-15Mya), indicating that selection for changes in executive cognitive functions mediated by this cortical region 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 2-3, detailed results in SI). This applies to the comparison of prefrontal cortex with several other cortical areas that are functionally and neurobiologically linked to prefrontal cortex. 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 SI for more details). We consider only data sets of prefrontal cortex volumes in primates that have been collected based on cytoarchitectonic criteria and comprise information for more than 5 species [5, 11] (Figure 1; see SI for more details). 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 SI for a detailed description of this method). Because this implementation of phylogenetic ancova uses standard least-squares procedures only, it provides unbiased results irrespective of sample size (see SI for more details). Considering that results are significant, and that the observed power of a test is a simple function of the observed *P*-value [12], it follows that the tests presented here have high observed power (see SI for more details).

To elucidate when in evolutionary time episodes of enlargement in prefrontal cortex occurred, we further used three different evolutionary modelling 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 (~30-19Mya), hominid (~19-15Mya), human-chimpanzee (-8-6Mya), and human (~6-0Mya) ancestral lineages when compared to different brain structure scaling variables. Ancestral state and

rate estimation results (Figures 2-3) 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 primary visual cortex is estimated to have occurred in the ancestral lineages of great apes and humans, expansion of prefrontal cortex relative to frontal motor areas is estimated to have occurred in the ancestral ape lineage, 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 SI). Bootstrap analysis further supports this conclusion by demonstrating high support for the estimated trait shifts (Figures 2-3, SI Figure 1, see SI 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, multi-regime OU model fitting) and five different model assumptions (see SI 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 13]. These genetic and/or developmental shifts shape the direction of trait variation on a macroevolutionary scale [13] and are thus fundamental drivers of biological diversity. To understand if an event aligns with or deviates from integration, a standard approach has been to investigate allometric conservation of traits [14]. Species' adherence to the allometric relationship hereby suggests conservation through phenotypic integration, while species' deviations from the allometric relationship points towards a genetic or developmental shift.

Our results provide strong support for 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 a higher dendritic branch complexity and synaptic spine density compared to other heteromodal association regions and nonhuman primate prefrontal cortex [15], and regions of the human prefrontal cortex contain more neuropil space than in other great apes [16]. Such neuroanatomical differences may be linked to human-specific increased transcriptional complexity [17] and alterations in the regulation of gene expression [18]. These gene regulatory changes have been suggested to have arisen through heterochronic remodeling of the developmental patterns that underpin human prefrontal growth [19]. In general, across different biological systems, heterochrony [i.e. changes in the timing and/or rate of developmental patterns; 20] 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 [13]. Indeed, heterochrony has previously been suggested to be an important driver of volumetric reorganization in the mammalian brain [21]. 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 [22]. 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 [23]. 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 volumetric reorganization on a macroevolutionary scale.

In addition to exceptional prefrontal expansion in humans, we also demonstrate that great apes show a shift in 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 [24], and cultural traditions [25]) is distinct from that in other primates. The shift in the direction of evolutionary change in brain organization in 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 brain expansion is primarily associated with enlargement of cortical association areas, whereas koniocortex scale more closely with body size [6, 26]. 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" [27] 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 data set. 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 striate 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 [27, 28] can be explained by three fundamental factors. First, previous studies have not employed statistical procedures to check for significant differences in the intercept among subgroups before interpreting allometry [9]. Second, previous allometric studies have used data sets 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 [29], previous allometric studies have used data sets that define prefrontal cortex as all cortex anterior to corpus callosum [27, 28], 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 [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 [27]. This approach, however, 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 [30]. 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 (SI Table 2, Figures 2-3). 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 indeed as expected for a scaled up monkey brain [27, 28]) yields a marginally significant result (P=0.06) for gray matter and a significant result for white matter (P<0.05) for the Smaers data set (which by design provides an underestimate of human prefrontal expansion, see details in SI), and a strongly significant result for the Brodmann data set (P<0.01).

The functional implications of exceptional human prefrontal expansion has previously been interpreted as a potential neural basis for human behavioral and cognitive distinctiveness [31]. 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 prefrontal architectonic plan is largely homologous in Old World monkeys and humans [32], some evidence suggests that the human prefrontal cortex may comprise novel areas. Brodmann [5] found no nonhuman homologues for areas 45,46, and 47 (but see work by Petrides & Pandya [33]), 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 [34, 35]. 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 [36].

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 to increase target innervation relative to the ancestral condition [37]. 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 towards 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 [38] similar to that observed in the prefrontal cortex, to be the target of increased prefrontal input [39], to have co-evolved with the prefrontal cortex in great ape and human lineages [40], and to underlie a range of behaviors often associated with human behavioral distinctiveness (e.g., language [41] and executive function [42]). Other distributed networks that may be of particular interest in this context are the prefronto-parietal [43] and -temporal [44] 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 [38]. Considering that this network is unique to primates and thus thought to have evolved early in primate evolution [36], 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) [13] shape primate neurobiological diversity in a similar way.

Materials and methods

Data

We consider only the available data sets of prefrontal cortex volumes in primates that have been collected based on cytoarchitectonic criteria and comprise information for more than 5 species [5, 11]. These data sets differ in the breadth of the comparative sample (19 versus 13 species, respectively), the nature of the measurement (mm^3 versus mm^2), and the cytoarchitectonic criteria that were employed (volumetric bootstrapping along the frontal pole [11] relative to the cytoarchitectonic border between areas 3 and 4 versus granular and agranular cortex). These differences are such that the Brodmann data provides a more accurate delineation of prefrontal cortex volume but a more modest comparative sample size, whereas the Smaers data provides a larger comparative sample but a proxy for prefrontal cortex volume that underestimates any putative prefrontal expansion in great apes and humans (see SI 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 homogenous 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 that regression parameters are correctly calculated irrespective of sample size. This method further uses the standard approach of degrees of freedom to penalize for model parameterization, hereby adequately guarding against overfitting (see SI for more details and additional tests that exemplify this feature).

Best-fit evolutionary scenarios were obtained with least-squares multi-regime Ornstein-Uhlenbeck modelling procedures that ensure uniqueness of parameter estimation and adequately guard against overfitting [45, 46]. When data indicate a high effect size, this approach has been shown to provide a high power even for samples as low as 10 [47]. All analyses presented here indeed show high effect size (see Figures 2-3, and SI for detailed information). Ancestral estimates and branch-specific rates were obtained using two different multi-rate models of evolution [48, 49], both of which yielded equivalent results (see SI for more details).

Figure 1

Lateral (a), dorsal (b), and medial (c) view 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 SI for more details). The Brodmann data provides a more accurate measure of prefrontal cortex size, but comprises a more limited comparative sample. Figure adjusted from Foville [50].

Figure 2

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 & Rohlf [9], SI for more information, SI Table 2 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 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 BIC criterion [45]. Colors differentiate between significantly different regimes ('regime' is here defined as a 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 meaures. Ho & Ané [46] suggest $\beta/\sqrt{\gamma} > 2$ as a valid indicator of high effect size, whereas Cressler et al. [47] propose $\sqrt{\eta}\phi \gg 1$. According to every proposed measure, analyses presented here demonstrate high effect size, and thus high observed power. See SI for more details.

Figure 3

As in Figure 2, data from Brodmann [5].

Figure 4

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].

Acknowledgements

We thank F.James Rohlf for insightful suggestions, comments and discussion, and Stephen Nash and Luci Betti-Nash (Department of Anatomical Sciences, Stony Brook University) for help with illustrations. JBS was supported by the Wenner Gren Foundation (Gr. 9209). CCS was supported by the James S. McDonnell Foundation (Grant number: 220020293).

Author contributions

Research design, JBS and CCS; Statistical analyses, JBS and AGR; Writing-Original draft, JBS; Writing-Review and editing, all authors.

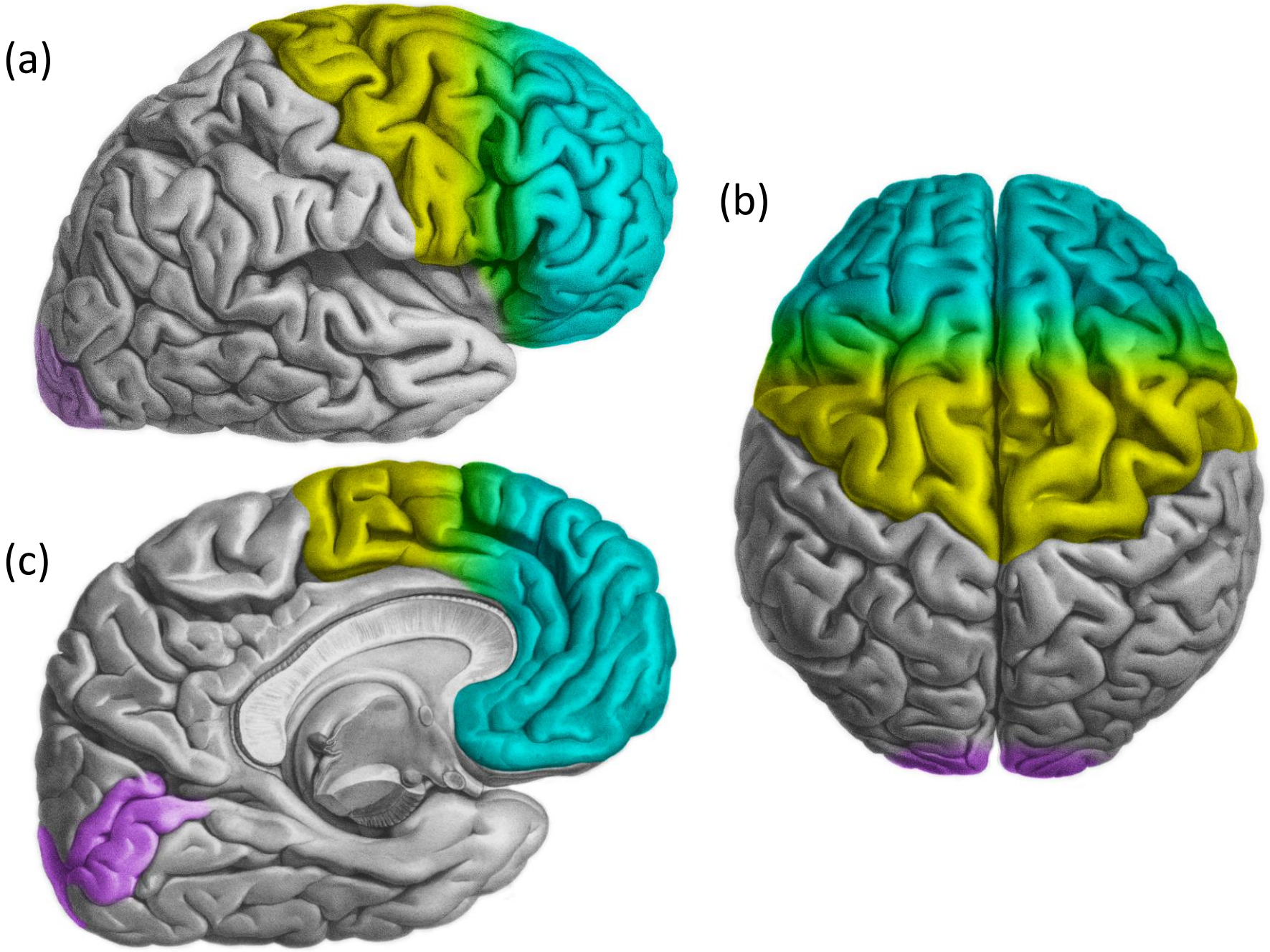
Additional information

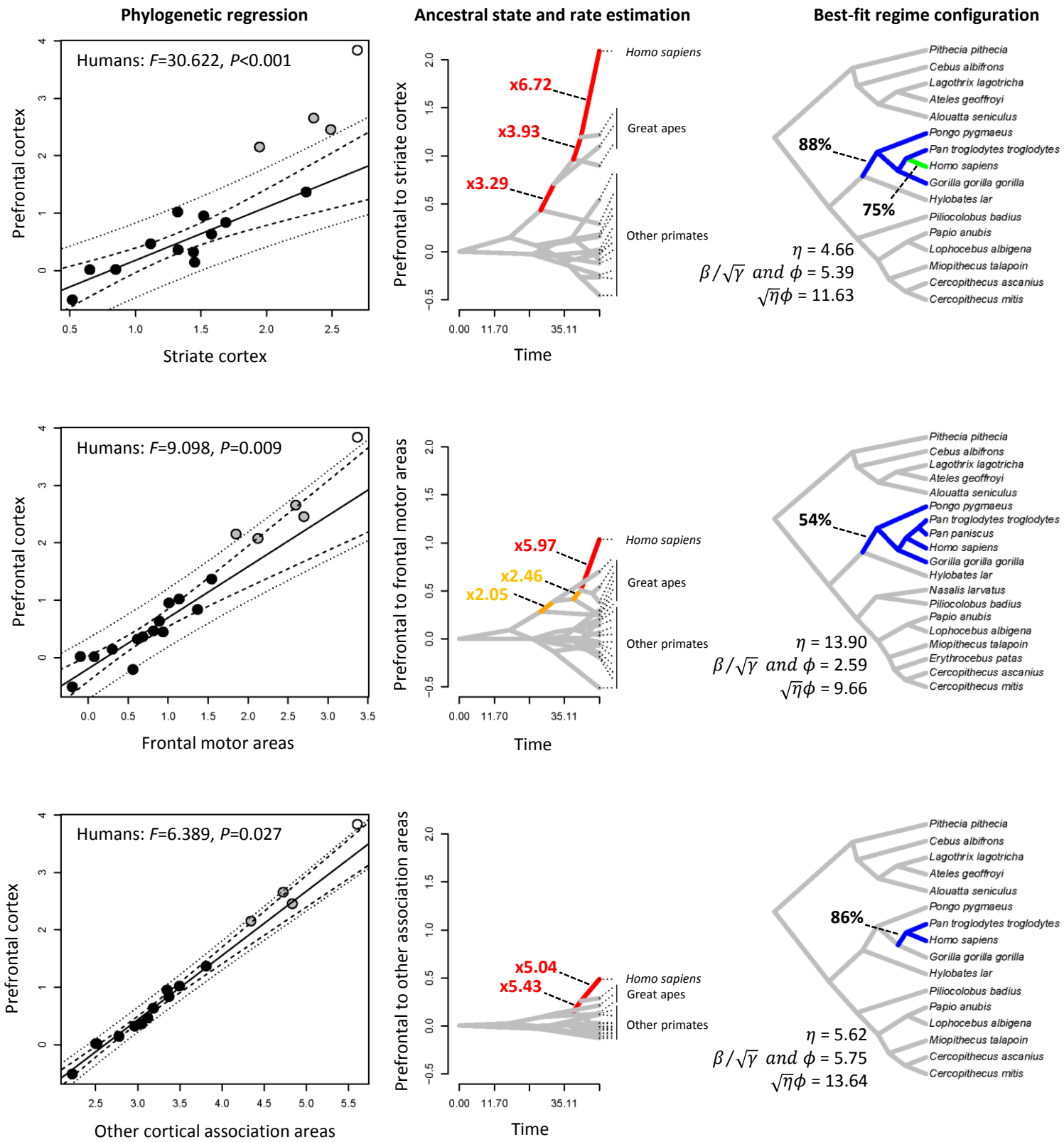
Competing financial interests: The authors declare no competing financial interests.

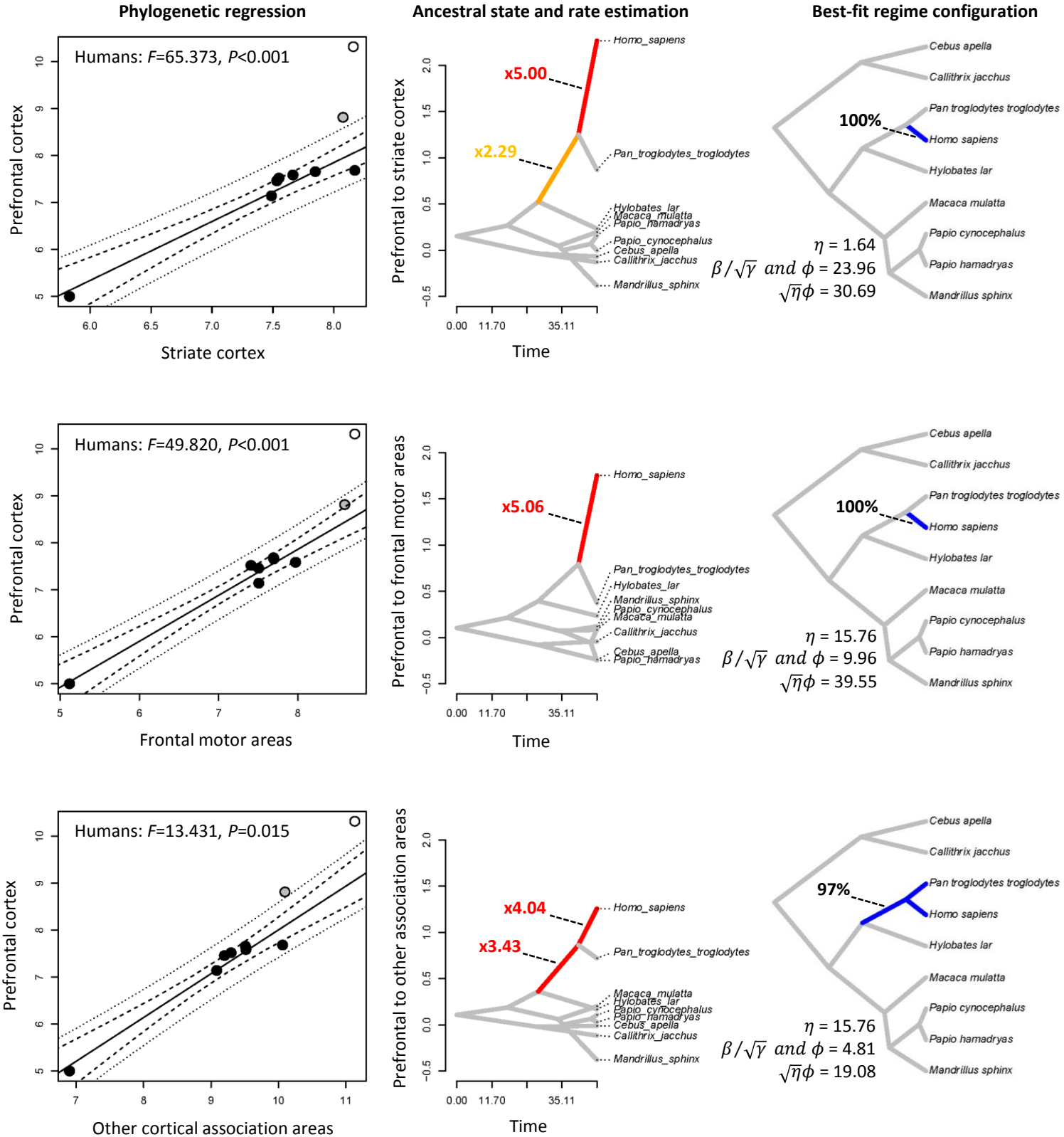
1. Sherwood, C.C., and Smaers, J.B. (2013). What's the fuss over human frontal lobe evolution? Trends in Cognitive Sciences *17*, 432-433.
2. Gabrieli, J.D.E., Poldrack, R.A., and Desmond, J.E. (1998). The role of left prefrontal cortex in language and memory. Proceedings of the National Academy of Sciences of the United States of America *95*, 906-913.
3. Schacter, D.L., Addis, D.R., and Buckner, R.L. (2007). Remembering the past to imagine the future: the prospective brain. Nature Reviews Neuroscience *8*, 657-661.
4. Miller, E.K., and Cohen, J.D. (2001). An integrative theory of prefrontal cortex function. Annual Review of Neuroscience *24*, 167-202.
5. Brodmann, K. (1909). Vergleichende lokalisationslehre der grosshirnrinde in ihren prinzipien dargestellt auf grund des zellenbaues, (Leipzig: Barth).
6. Glasser, M.F., Goyal, M.S., Preuss, T.M., Raichle, M.E., and Van Essen, D.C. (2014). Trends and properties of human cerebral cortex: correlations with cortical myelin content. Neuroimage *93*, 165-175.
7. Somel, M., Liu, X., Tang, L., Yan, Z., Hu, H., Guo, S., Jiang, X., Zhang, X., Xu, G., and Xie, G. (2011). MicroRNA-driven developmental remodeling in the brain distinguishes humans from other primates. PLoS Biol *9*, e1001214.
8. Somel, M., Franz, H., Yan, Z., Lorenc, A., Guo, S., Giger, T., Kelso, J., Nickel, B., Dannemann, M., and Bahn, S. (2009). Transcriptional neoteny in the human brain. Proceedings of the National Academy of Sciences *106*, 5743-5748.
9. Smaers, J., and Rohlf, F. (2016). Testing species' deviation from allometric predictions using the phylogenetic regression. Evolution *70*, 1145-1149.
10. Passingham, R.E., and Smaers, J.B. (2014). Is the prefrontal cortex especially enlarged in the human brain? Brain, behavior and evolution *84*, 156-166.
11. Smaers, J.B., Steele, J., Case, C.R., Cowper, A., Amunts, K., and Zilles, K. (2011). Primate prefrontal cortex evolution: human brains are the extreme of a lateralized ape trend. Brain, Behavior and Evolution *77*, 67-78.
12. Hoenig, J.M., and Heisey, D.M. (2001). The abuse of power: The pervasive fallacy of power calculations for data analysis. The American Statistician *55*, 1-6.
13. Goswami, A., Smaers, J.B., Soligo, C., and Polly, P.D. (2014). The macroevolutionary consequences of phenotypic integration: from development to deep time. Philosophical Transactions of the Royal Society B-Biological Sciences *369*, 20130254.
14. Finlay, B.L., and Darlington, R.B. (1995). Linked regularities in the development and evolution of mammalian brains. Science *268*, 1578-1584.
15. Bianchi, S., Stimpson, C.D., Bauernfeind, A.L., Schapiro, S.J., Baze, W.B., McArthur, M.J., Bronson, E., Hopkins, W.D., Semendeferi, K., and Jacobs, B. (2012). Dendritic morphology of pyramidal neurons in the chimpanzee neocortex: regional specializations and comparison to humans. Cerebral cortex, bhs239.
16. Spocter, M.A., Hopkins, W.D., Barks, S.K., Bianchi, S., Hehmeyer, A.E., Anderson, S.M., Stimpson, C.D., Fobbs, A.J., Hof, P.R., and Sherwood, C.C. (2012). Neuropil distribution in the cerebral cortex differs between humans and chimpanzees. The Journal of Comparative Neurology *520*, 2917-2929.
17. Konopka, G., Friedrich, T., Davis-Turak, J., Winden, K., Oldham, M.C., Gao, F., Chen, L., Wang, G.-Z., Luo, R., and Preuss, T.M. (2012). Human-specific transcriptional networks in the brain. Neuron *75*, 601-617.

18. Muntané, G., Horvath, J.E., Hof, P.R., Ely, J.J., Hopkins, W.D., Raghanti, M.A., Lewandowski, A.H., Wray, G.A., and Sherwood, C.C. (2015). Analysis of synaptic gene expression in the neocortex of primates reveals evolutionary changes in glutamatergic neurotransmission. Cerebral Cortex *25*, 1596-1607.
19. Somel, M., Liu, X., and Khaitovich, P. (2013). Human brain evolution: transcripts, metabolites and their regulators. Nature Reviews Neuroscience *14*, 112-127.
20. Gould, S.J. (1977). Ontogeny and phylogeny, (Harvard University Press).
21. Workman, A.D., Charvet, C.J., Clancy, B., Darlington, R.B., and Finlay, B.L. (2013). Modeling Transformations of Neurodevelopmental Sequences across Mammalian Species. Journal of Neuroscience *33*, 7368-7383.
22. Liu, X., Somel, M., Tang, L., Yan, Z., Jiang, X., Guo, S., Yuan, Y., He, L., Oleksiak, A., and Zhang, Y. (2012). Extension of cortical synaptic development distinguishes humans from chimpanzees and macaques. Genome research *22*, 611-622.
23. Miller, D.J., Duka, T., Stimpson, C.D., Schapiro, S.J., Baze, W.B., McArthur, M.J., Fobbs, A.J., Sousa, A.M., Šestan, N., and Wildman, D.E. (2012). Prolonged myelination in human neocortical evolution. Proceedings of the National Academy of Sciences *109*, 16480-16485.
24. Osvath, M., and Osvath, H. (2008). Chimpanzee (Pan troglodytes) and orangutan (Pongo abelii) forethought: self-control and pre-experience in the face of future tool use. Animal cognition *11*, 661-674.
25. van Schaik, C.P., Ancrenaz, M., Borgen, G., Galdikas, B., Knott, C.D., Singleton, I., Suzuki, A., Utami, S.S., and Merrill, M. (2003). Orangutan cultures and the evolution of material culture. Science *299*, 102-105.
26. Passingham, R.E. (1975). Changes in size and organization of brain in man and his ancestors. Brain Behavior and Evolution *11*, 73-90.
27. Barton, R.A., and Venditti, C. (2013). Human frontal lobes are not relatively large. Proceedings of the National Academy of Sciences *110*, 9001-9006.
28. Gabi, M., Neves, K., Masseron, C., Ribeiro, P.F., Ventura-Antunes, L., Torres, L., Mota, B., Kaas, J.H., and Herculano-Houzel, S. (2016). No relative expansion of the number of prefrontal neurons in primate and human evolution. Proceedings of the National Academy of Sciences, 201610178.
29. Sherwood, C.C., Broadfield, D.C., Holloway, R.L., Gannon, P.J., and Patrick, R.H. (2003). Variability of Broca's area homologue in African great apes: Implications for language evolution. Anatomical Record Part a-Discoveries in Molecular Cellular and Evolutionary Biology *271A*, 276-285.
30. Tanaka, K. (1993). Neuronal mechanisms of object recognition. Science *262*, 685-685.
31. Deacon, T.W. (1990). Rethinking Mammalian Brain Evolution. American Zoologist *30*, 629-705.
32. Petrides, M., Tomaiuolo, F., Yeterian, E.H., and Pandya, D.N. (2012). The prefrontal cortex: Comparative architectonic organization in the human and the macaque monkey brains. Cortex *48*, 46-57.
33. Petrides, M., and Pandya, D.N. (1994). Comparative cytoarchitectonic analysis of the human and the macaque frontal cortex. In Handbook of neuropsychology, Volume 9, F. Boller and J. Grafman, eds. (Amsterdam: Elsevier), pp. 17-58.
34. Paredes, M.F., James, D., Gil-Perotin, S., Kim, H., Cotter, J.A., Ng, C., Sandoval, K., Rowitch, D.H., Xu, D., and McQuillen, P.S. (2016). Extensive migration of young neurons into the infant human frontal lobe. Science *354*, aaf7073.
35. Letinic, K., and Rakic, P. (2001). Telencephalic origin of human thalamic GABAergic neurons. Nature neuroscience *4*, 931-936.

36. Preuss, T.M. (2007). Evolutionary specializations of primate brain systems. In Primate origins: adaptations and evolution. (Springer), pp. 625-675.
37. Striedter, G.F. (2005). Principles of brain evolution, (Sinauer Associates).
38. Balsters, J.H., Cussans, E., Diedrichsen, J., Phillips, K.A., Preuss, T.M., Rilling, J.K., and Ramnani, N. (2010). Evolution of the cerebellar cortex: The selective expansion of prefrontal-projecting cerebellar lobules. Neuroimage *49*, 2045-2052.
39. Ramnani, N., Behrens, T.E.J., Johansen-Berg, H., Richter, M.C., Pinsk, M.A., Andersson, J.L.R., Rudebeck, P., Ciccarelli, O., Richter, W., Thompson, A.J., et al. (2006). The evolution of prefrontal inputs to the cortico-pontine system: Diffusion imaging evidence from macaque monkeys and humans. Cerebral Cortex *16*, 811-818.
40. Smaers, J.B., and Soligo, C. (2013). Brain reorganization, not relative brain size, primarily characterizes anthropoid brain evolution. Proceedings of the Royal Society B-Biological Sciences *280*, 20130269.
41. Stoodley, C.J., and Schmahmann, J.D. (2009). The cerebellum and language: Evidence from patients with cerebellar degeneration. Brain and Language *110*, 149-153.
42. Koziol, L.F., Budding, D.E., and Chidekel, D. (2012). From movement to thought: executive function, embodied cognition, and the cerebellum. The Cerebellum *11*, 505-525.
43. Genovesio, A., Wise, S.P., and Passingham, R.E. (2014). Prefrontal–parietal function: from foraging to foresight. Trends in cognitive sciences *18*, 72-81.
44. Rilling, J.K., Glasser, M.F., Preuss, T.M., Ma, X., Zhao, T., Hu, X., and Behrens, T.E. (2008). The evolution of the arcuate fasciculus revealed with comparative DTI. Nature neuroscience *11*, 426-428.
45. Khabbazian, M., Kriebel, R., Rohe, K., and Ané, C. (2016). Fast and accurate detection of evolutionary shifts in Ornstein–Uhlenbeck models. Methods in Ecology and Evolution *7*, 811-824.
46. Ho, L.S.T., and Ané, C. (2014). Intrinsic inference difficulties for trait evolution with Ornstein-Uhlenbeck models. Methods in Ecology and Evolution *5*, 1133-1146.
47. Cressler, C.E., Butler, M.A., and King, A.A. (2015). Detecting adaptive evolution in phylogenetic comparative analysis using the Ornstein-Uhlenbeck model. Systematic biology, syv043.
48. Venditti, C., Meade, A., and Pagel, M. (2011). Multiple routes to mammalian diversity. Nature *479*, 393-396.
49. Smaers, J.B., Mongle, C.S., and Kandler, A. (2016). A multiple variance Brownian motion framework for the estimation of ancestral states and rates of evolution. Biological Journal of the Linnean Society *118*, 78-94.
50. Foville, M. (1864). L'anatomie de la physique et de la pathologie du système nerveux cérébro-spinal., (Paris: Fortin, Masson et Companie).


(a)
(b)
(c)


Phylogenetic regression
Ancestral state and rate estimation
Best-fit regime configuration
Humans: F=30.622, P<0.001
Prefrontal cortex
Striate cortex
Prefrontal to striate cortex
x6.72
x3.93
x3.29
Homo sapiens
Great apes
Other primates
Time
88%
75%
η = 4.66
β/√γ and ϕ = 5.39
√ηϕ = 11.63
Pithecia pithecia
Cebus albifrons
Lagothrix lagotricha
Ateles geoffroyi
Alouatta seniculus
Pongo pygmaeus
Pan troglodytes troglodytes
Homo sapiens
Gorilla gorilla gorilla
Hylobates lar
Piliocolobus badius
Papio anubis
Lophocebus albigena
Miopithecus talapoin
Cercopithecus ascanius
Cercopithecus mitis
Humans: F=9.098, P=0.009
Prefrontal cortex
Frontal motor areas
Prefrontal to frontal motor areas
x5.97
x2.46
x2.05
Homo sapiens
Great apes
Other primates
Time
54%
η = 13.90
β/√γ and ϕ = 2.59
√ηϕ = 9.66
Pithecia pithecia
Cebus albifrons
Lagothrix lagotricha
Ateles geoffroyi
Alouatta seniculus
Pongo pygmaeus
Pan troglodytes troglodytes
Pan paniscus
Homo sapiens
Gorilla gorilla gorilla
Hylobates lar
Nasalis larvatus
Piliocolobus badius
Papio anubis
Lophocebus albigena
Miopithecus talapoin
Erythrocebus patas
Cercopithecus ascanius
Cercopithecus mitis
Humans: F=6.389, P=0.027
Prefrontal cortex
Other cortical association areas
Prefrontal to other association areas
x5.04
x5.43
Homo sapiens
Great apes
Other primates
Time
86%
η = 5.62
β/√γ and ϕ = 5.75
√ηϕ = 13.64
Pithecia pithecia
Cebus albifrons
Lagothrix lagotricha
Ateles geoffroyi
Alouatta seniculus
Pongo pygmaeus
Pan troglodytes troglodytes
Homo sapiens
Gorilla gorilla gorilla
Hylobates lar
Piliocolobus badius
Papio anubis
Lophocebus albigena
Miopithecus talapoin
Cercopithecus ascanius
Cercopithecus mitis


Phylogenetic regression
Ancestral state and rate estimation
Best-fit regime configuration
Humans: F=65.373, P<0.001
Prefrontal cortex
Striate cortex
Prefrontal to striate cortex
x5.00
x2.29
Homo_sapiens
Pan_troglodytes_troglodytes
Hylobates_lar
Macaca_mulatta
Papio_hamadryas
Papio_cynocephalus
Cebus_apella
Callithrix_jacchus
Mandrillus_sphinx
Time
100%
Cebus apella
Callithrix jacchus
Pan troglodytes troglodytes
Homo sapiens
Hylobates lar
Macaca mulatta
Papio cynocephalus
Papio hamadryas
Mandrillus sphinx
η = 1.64
β/√γ and ϕ = 23.96
√ηϕ = 30.69
Humans: F=49.820, P<0.001
Prefrontal cortex
Frontal motor areas
Prefrontal to frontal motor areas
x5.06
Time
η = 15.76
β/√γ and ϕ = 9.96
√ηϕ = 39.55
Humans: F=13.431, P=0.015
Prefrontal cortex
Other cortical association areas
Prefrontal to other association areas
x4.04
x3.43
Time
97%
η = 15.76
β/√γ and ϕ = 4.81
√ηϕ = 19.08

Prefrontal and striate cortex

Prefrontal cortex and frontal motor areas

Frontal motor areas and striate cortex